Sarcopenia

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Second Edition

Edited by

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WILEY Blackwell

This edition first published 2021

Edition History
First edition published 2012 by John Wiley & Sons Ltd

Registered Office(s)
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
9600 Garsington Road, Oxford, OX4 2DQ, UK

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The CIP date for ISBN: 9781119597872 has been applied.

Cover design: Wiley
Cover image: © Choksawatdikorn/Shutterstock

Set in 10/12pt TimesNewRomanMTStd by SPi Global, Pondicherry, India

10 9 8 7 6 5 4 3 2 1

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Preface

Since the original coining of the term sarcopenia in 1988, there has been a rapid increase in the development of scientific approaches to its pathophysiology, definition (together with ethnic appropriate cut-offs), and management. This was highlighted when sarcopenia was established as a muscle disease with its own ICD-CM diagnosis code (ICD-10-CMM62.84). Primary sarcopenia (age related) is of central interest to geriatricians, nutritionists, gerontologists, epidemiologists, biologists, physical and occupational therapists, and all health professionals who provide care for older persons. Secondary sarcopenia has become an increasingly important, treatable side effect of chronic diseases, e.g. congestive heart failure or chronic obstructive pulmonary disease, in many persons.

Since the first edition of *Sarcopenia* some eight years ago, there have been major advances in the understanding of the basic science concepts of how aging interacts with muscles to alter its function. This has been coupled with an increased knowledge in methodology to measure muscle mass and function. There has been a realization that the decline in function due to muscle loss is the hallmark in the development of sarcopenia. This has led to more sophisticated definitions of the disease and a recognition that these definitions require ethnic-specific definitions. While the primary treatment of sarcopenia relies on resistance and other exercises together with nutritional approaches, a large number of pharmacological agents to treat sarcopenia are under development. These exciting and rapid changes have led us to produce a second edition of this book.

This new edition remains a clear and precise reference work for all those health professionals, exercise physiologists, and researchers interested in understanding the complexity of sarcopenia. This book provides the state of art of the complexity involved in the biological aspects of age-related muscle wasting alongside the direct effects of disease on muscles. It explores the rapidly increasing epidemiological knowledge demonstrating the devastating effects of sarcopenia on health outcomes and quality of life of individuals. It explores in detail the modern diagnostic and management approaches to recognizing and improving outcomes in individuals with sarcopenia. To do this we have assembled a wide range of authors from around the world, who are experts in this topic area. We also focus on primary and secondary prevention of sarcopenia as important approaches to enhance the quality of life in older persons.

This book represents a state-of-the-art textbook, with a comprehensive approach to sarcopenia. We hope it will be a valuable reference tool to all those who are interested in this topic. Our authors have taken complex topics and written about them in a clear way allowing access to the knowledge for those starting out in the field, as well as expert researchers and clinicians who are interested in recognizing and treating sarcopenia.

Alfonso J. Cruz-Jentoft and John E. Morley

CHAPTER 1

Definitions of Sarcopenia

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SARCOPENIA: BIRTH AND FIRST STEPS

Irving Rosenberg is credited to have coined the term sarcopenia (from the Greek roots – *sarx* = flesh and *-penia* = low, meaning "poverty of flesh") in 1988 to describe the striking age-related decline in lean body mass and its potential functional significance [1].

Methods to estimate muscle mass (or lean body mass) were increasingly available, as were epidemiological studies using such techniques. Based on these parameters, sarcopenia was operationally defined as a gradual loss of muscle mass. For instance, Baumgartner used a definition based on appendicular skeletal muscle mass estimated by dual-energy x-ray absorptiometry (DXA), corrected for height, and defined sarcopenia as being two standard deviations below sex-specific means of healthy young persons (18–40 years) of a reference population [2]. Longitudinal studies confirmed that a progressive reduction in muscle mass was present in both males and females [3]. Muscle mass declines at approximately 1–2% per year after the age of 50 years. Sarcopenia, when defined as a severe muscle mass loss (two standard deviations below healthy young populations), is present in 5–13% of persons of 60–70 years old and 11–50% of those over 80 years [4].

While the definition of sarcopenia based on a reduced muscle mass alone served the scientific community fairly well, it was less satisfying for clinicians, the pharmaceutical industry, and regulatory agencies. Unlike bone mineral density, measures of muscle mass have not been widely adopted by clinicians. Regulatory agencies have failed to accept that restoration of muscle mass is a valid reason to allow a drug to be approved for use. Also, many crucial aspects of sarcopenia are missed by the simplistic use of muscle mass as a measure, which has shown to be a weak predictor of outcomes; and the link between muscle mass, muscle function (defined by muscle strength and power),

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

physical performance, and other downstream outcomes is not linear [5–8]. The fact that all clinical measures of muscle mass are in fact estimations and have a wide range of measurement error may partially explain this situation [9]. Research has also showed that loss of muscle strength is two to five times faster than loss of muscle mass and is associated with changes in muscle quality (defined as intramuscular fat) and is more predictive of outcomes [3, 8].

GROWTH AND ADOLESCENCE OF SARCOPENIA

In the first decade of the twenty-first century, the relevance of muscle function was so clear that different lines of action were proposed, including the use of different terms to name the condition. *Dynapenia* and *kratopenia* were suggested as alternative terms to describe the loss of muscle strength and power [8, 10], and *myopenia* as an alternative for universal skeletal muscle wasting [11]. However, six different international consensus definitions published at the end of the decade all proposed redefining sarcopenia by adding the loss of muscle mass to the loss of muscle function, with slightly different approaches [10, 12–16].

European Working Group on Sarcopenia in Older People and Asian Working Group on Sarcopenia

To date, this is the most widely cited definition and the only definition that was endorsed by a range of international scientific societies (European Geriatric Medicine Society [EuGMS], European Society for Clinical Nutrition and Metabolism [ESPEN], International Association of Geriatrics and Gerontology-European Region [IAGG-ER], International Academy on Nutrition and Aging [IANA]) [13]. The European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, with a risk of adverse outcomes such as physical disability, decreased quality of life, and increased mortality. According to the EWGSOP criteria, diagnosis of sarcopenia required documentation of low muscle mass plus documentation of either low muscle strength or low physical performance. With the aim of encouraging the assessment of sarcopenia in all patients and all health-care settings, the EWGSOP provided a wide range of tools that made the assessment feasible even in settings with limited resources, including a suggested algorithm for case finding based on physical performance (usual gait speed) as the easiest and most reliable first step to begin sarcopenia screening in clinical practice. However, the EWGSOP found no evidence to recommend cut-off points for each of the parameters used in the definition. The EWGSOP also suggested dividing sarcopenia into categories (primary or age-related and secondary sarcopenia), and sarcopenia staging to reflect the severity of the condition.

The EWGSOP initiative was strongly supported by the Asian Working Group on Sarcopenia (AWGS) [15]. This group collected the best available evidence of sarcopenia research from Asian countries to establish the consensus for sarcopenia diagnosis

and take an extra step forward by proposing gender-specific cut-off values for muscle mass estimation with DXA or bioimpedance analysis, handgrip strength, and usual gait speed. In addition to sarcopenia screening for community-dwelling older people, the AWGS recommended sarcopenia assessment in certain clinical conditions and health-care settings to facilitate implementing sarcopenia in clinical practice.

European Society for Clinical Nutrition and Metabolism Special Interest Groups

A special interest group on cachexia–anorexia in chronic wasting diseases was created in ESPEN, and the definition, assessment, and staging of cachexia were identified as a priority [12]. In the first consensus paper published by this group on the definition of cachexia and pre-cachexia, the need of criteria for the differentiation between cachexia and other conditions associated with low muscle mass lead to a cooperation with the ESPEN special interest group on nutrition in geriatrics. Diagnosis of sarcopenia was defined by the combined presence of a low muscle mass (a percentage of muscle mass ≥2 standard deviations below the mean measured in young adults of the National Health and Nutrition Examination Survey [NHANES] population) and low gait speed.

Society for Sarcopenia, Cachexia and Wasting Disorders (SSCWD)

This organization conveyed American and European researchers to develop a definition of sarcopenia that could be a meaningful surrogate for clinically useful endpoints, allow for treatments, include only measurements longitudinally linked to meaningful outcomes, and have definable cut-off points based on the data [10]. Deviating from the other groups, it was decided that "*sarcopenia with limited mobility"* would be the preferred term to define persons with a need for therapeutic interventions. Sarcopenia with limited mobility was defined as a muscle loss associated with a slow walking speed, with an approach that mirrored that proposed by ESPEN. The limitation in mobility should not be clearly attributable to the direct effect of specific diseases such as peripheral vascular disease, or central or peripheral nervous system disorders, dementia, or cachexia. This group left the question open of whether sarcopenia as a term should be limited to use in older persons or used as a general term for adults of any age.

International Working Group on Sarcopenia (IWGS)

A group of American and European geriatricians and scientists from academia and industry, some of them involved in other definitions, met in Italy at the end of 2009, to arrive at a consensus definition of sarcopenia. Sarcopenia was defined as the age-associated loss of skeletal muscle mass and function [14]. It should be considered in all older patients who present with observed declines in physical function, strength, or overall health, and especially in those who are bedridden, cannot independently rise from a chair, or who have a slow gait speed. A reduced muscle mass would confirm sarcopenia in this clinical setting.

Foundation for the National Institutes of Health

A few years later, an American initiative led by the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium used a different approach, mostly based on the pooled analysis of epidemiological studies, to define sarcopenia [16]. This initiative compiled data from nine studies in community-dwelling older persons, with a pooled sample of 26 625 participants, to identify sex-specific cut-off points for low muscle mass (estimated by the appendicular lean mass adjusted for body mass index) and low muscle strength (measured as grip strength). These cut-off points were shown to be associated with functional limitations (including slow gait speed, used as a component of other definitions).

Both the AWGS and the FNIH tried to overcome a major limitation of the EWGSOP definition – it did not recommend explicit cut-off points for the parameters included in the definition – by proposing precise references to define normality for each variable. However, all definitions at this time agreed on the overall concept of sarcopenia as a compound of low muscle mass and reduced muscle function, defined by muscle strength, reduced physical performance, or both. The role of muscle quality, although mentioned in some initiatives, was still quite unclear.

Some important milestones derived from these definitions have been, among others, the recognition of sarcopenia as an independent condition with an ICD-10-CM code in 2016 [17], the development of the first clinical guideline for the condition [18], and the involvement of the European Medicines Agency in initiatives to develop a framework for drug development [19].

MATURITY OF SARCOPENIA: RECENT DEFINITIONS

A decade later, the EWGSOP met again, with a wider academic support (adding the endorsement of International Osteoporosis Foundation [IOF] and European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases [ESCEO] to ESPEN and EuGMS) to review and update the 2010 definition and reflect the advances in scientific, epidemiological, and clinical knowledge, and to facilitate the implementation of sarcopenia in mainstream clinical practice [20]. The updated consensus definition, named EWGSOP2, states that a person with low muscle strength and low muscle mass or quality will be diagnosed with sarcopenia. When sarcopenia impairs physical performance measures, it will be staged as severe sarcopenia. Sarcopenia is now understood as an organ (skeletal muscle) failure or insufficiency [21] that may appear acutely (in the setting of an acute disease or sudden immobility) or have a more chronic course. It aligns with the new function-centered model proposed by the World Health Organization that focuses on intrinsic capacity (defined as a composite of all physical and mental capacities of an individual) [22].

The three main advances of the EWGSOP2 definition result from new insights: (i) sarcopenia is no longer considered primarily as a geriatric syndrome but as a muscle condition with an ICD-CM diagnosis code (ICD-10-CM M62.84); (ii) loss of muscle quality is introduced as a new diagnostic criterion; and (iii) muscle strength is

recognized as the best predictor of health outcomes. This definition intends to introduce sarcopenia in wide-stream clinical practice as well, by offering a simple diagnostic algorithm. The AWGS has also published and updated definition [23]. Australia and New Zealand have opted to endorse the EWGSOP definitions [24]. Similar definitions focusing on the loss of strength or function in combination with a loss of lean mass have been published by the Society of Sarcopenia, Cachexia and Muscle wasting [25] and by the International Conference of Frailty and Sarcopenia Research [18]. Both also strongly recommended resistance exercise and the major treatment modality.

On the American side, the Sarcopenia Definition and Outcomes Consortium (SDOC) was funded by the National Institute on Aging (NIA) in 2015 with additional support of the FNIH. The SDOC aim is to develop evidence-based diagnostic cut-off points for lean mass and/or muscle strength that enable identification of people at risk or mobility disability as a target population of potential function-promoting therapies [26]. As in the FNIH initiative, the SDOC is again using an epidemiological approach using several cohorts, mostly in the United States but also in Europe, in order to accumulate data from a large number of subjects and be able to calculate an algorithm predictive of sarcopenia outcomes. The project was completed in August 2019, and the final document with recommendations published in 2020 [27].

Sarcopenia is now extending well beyond older age, with recent initiatives trying to define sarcopenia within organ diseases [28] and even in pediatrics [29].

A global (European, Asian, American, and Australia/New Zealand) initiative is now in process to try to come to a consensus on an operational definition of sarcopenia that would finish this long trip.

NEW PLAYERS: BONE, FAT, AND MUSCLE

There are specific aspects not contemplated in current definitions of sarcopenia, as the role of fat, bone, or both which are still far to be settled [30]. They are discussed in detail in other chapters of this book. However, it seems pertinent to mention some aspects that are related to general definitions here.

Osteoporosis is a skeletal condition closely linked to sarcopenia, a condition that has been named osteosarcopenia. The coexistence of both conditions seems to increase the risk of falls and other outcomes associated with each condition alone [31]. There is still some discussion if osteosarcopenia should be defined by body composition (i.e. low muscle mass and low skeletal mass) or if muscle function should be part of the definition [32, 33].

Sarcopenia and obesity also coexist frequently in the so-called sarcopenic obesity [34–37]. Increases in muscle fat and body weight have a strong influence in the accuracy and adjustment of most methods that estimate skeletal muscle mass. As in osteosarcopenia, a body composition approach (i.e. low muscle mass plus obesity defined as increased fat or by anthropometry) has coexisted in research with an approach that defines sarcopenia using functional measures, and efforts to refine the definition are under way.

THE FRONTIERS: FRAILTY, CACHEXIA, MALNUTRITION

Frailty, cachexia, and malnutrition are conditions that share some elements with sarcopenia: they are frequent in old age, predict adverse outcomes, and include in some way low muscle mass within their definitions, which may lead clinicians into problems when trying to sort out which condition predominates in a given patient [38, 39].

The Global Leadership Initiative on Malnutrition (GLIM) has proposed a definition of malnutrition that includes reduced muscle mass as one of the three phenotypic diagnostic criteria [40]. Thus, the finding of a low muscle mass with normal muscle function may suggest that malnutrition is present, although this may well be the start toward a malnutrition-related sarcopenia.

Low muscle mass is also included in the most widely used definitions of cachexia, which also consider the role of low muscle strength [12, 41]. The border between disease-related sarcopenia and cachexia (a time-honored term used to describe severe weight loss and muscle wasting associated with severe inflammatory conditions) is quite blurred, usually depending on the degree of inflammation, the underlying pathophysiology, the triggering condition, and even the discipline the practitioner comes from [42].

The links between physical frailty and sarcopenia are addressed in a different chapter. However, it is relevant that the frailty phenotype includes unintentional weight loss (usually associated with muscle wasting), weakness (defined by a low grip strength), and reduced physical performance (slow walking speed) [43], all of them part of the definition of sarcopenia. Both conditions are closely linked, sarcopenia being a player in a relevant portion of cases with physical frailty [44, 45]. International and Asian definitions of physical frailty exist [46, 47].

THE RESEARCH ARENA

The definition of sarcopenia is rapidly evolving, as is true for many other common conditions and specialties [48–50].

Among the most relevant areas of research and debate that are needed to further improve the definition of sarcopenia some may worth mentioning, in no particular order [25, 45]:

- Muscle mass measurements need to be improved from the present estimations to real measures, in order to decide how this parameter is best included in the definitions of sarcopenia [9].
- The role of physical performance (as part of the definition, measure of severity, or upstream outcome) should be clarified [51].
- Cut-off points that are ethnically appropriate need to be developed.
- Epidemiological studies enriched with complex populations (i.e. those living in nursing homes) are still needed to define the best cut-off points for each parameter and technique used to define sarcopenia in their capacity to predict outcomes.
- A practical way to separate cachexia, sarcopenia, and malnutrition in clinical practice, in order to improve clinical management, is needed, but may not be feasible in many cases.

- The definition of sarcopenia when it comes as a comorbidity of other major diseases (i.e. liver disease, renal diseases, cancer, major surgery) is currently being addressed by many studies, but still many use the muscle mass paradigm not including function.
- Agreement on which of the many adverse outcomes are more relevant to address sarcopenia both in clinical practice and research would increase the number of patients with the diagnosis and foster research of a wide range of therapies.
- The need and role of simple screening tools [52] compared with muscle mass and function measures need to be established.
- Finally, the concept of sarcopenia within a life course approach needs further refinement. Is sarcopenia an old-age condition, or should the threshold be moved and extended to younger populations? If so, are the same definitions valid across the life span?

SUMMARY

Sarcopenia was originally defined as age-related muscle mass. Recent definitions have extended this to include muscle function and muscle quality using different approaches. Current definitions have confirmed the concept that sarcopenia is relevant, frequent, and linked with adverse outcomes, but have not yet been able to extend the diagnosis and management to current clinical practice. The definition of sarcopenia is still work in progress.

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CHAPTER 2

Epidemiology of Muscle Mass Loss with Age

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INTRODUCTION

The development of new body composition methods in the early 1970s and 1980s led to more research on this topic, including the study of differences in body composition between young and older persons. These initial studies were followed by much larger studies covering a wide age range investigating how body composition varied across the life span. Variations in lean body mass and fat-free mass were described between age groups. These studies served as the important scientific basis for developing the concept sarcopenia. Sarcopenia was originally defined as the age-related loss of muscle mass [1]. The term is derived from the Greek words *sarx* (flesh) and *penia* (loss). The development of this concept further stimulated research in this specific body composition area. More recently, large-scale studies among older persons have included accurate and precise measurements of skeletal muscle mass. Moreover, these measurements have been repeated over time, enabling the sarcopenia process to be studied.

This chapter will discuss the results of epidemiological studies investigating the age-related loss of skeletal muscle mass. First, several cross-sectional studies will be presented comparing the body composition between younger and older persons. Then prospective studies will be discussed investigating the change in body composition with aging. The chapter will conclude with the results of more recent, prospective studies that precisely measured change in skeletal muscle mass in large samples of older persons.

MUSCLE MASS DIFFERENCES AMONG AGE GROUPS

Comparisons among young and older men and women with regard to muscle size have been made in several small studies starting in the 1980s. The results showed that

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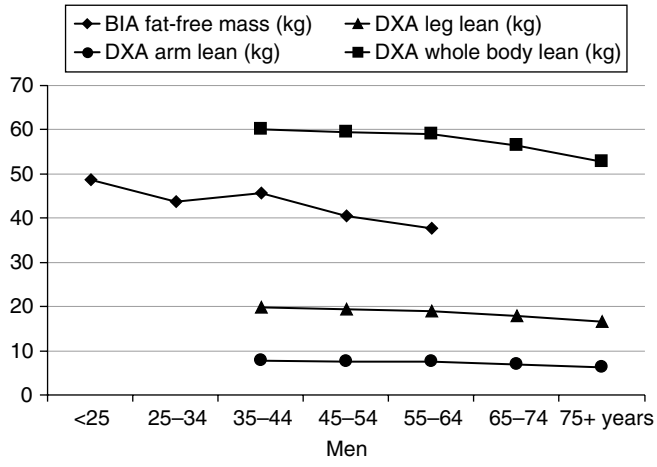

Figure 2.1 Differences in fat-free mass and lean mass using different body composition methodologies between men of different age groups. BIA = bioelectrical impedance; DXA = dual-energy x-ray absorptiometry. *Source*: Based on references [7, 8].

healthy women in their 70s had a 33% smaller quadriceps cross-sectional area as obtained by compound ultrasound imaging compared with women in their 20s [2]. Using the same methodology and age groups, healthy older men had a 25% smaller quadriceps cross-sectional area [3]. In a study investigating thigh composition using five computed tomography (CT) scans of the total thigh, smaller muscle cross-sectional areas were observed in older men compared with younger men even though their total thigh cross-sectional area was similar. The older men had a 13% smaller total muscle cross-sectional area, 25.4% smaller quadriceps, and 17.9% smaller hamstring cross-sectional area [4]. Using magnetic resonance imaging of the leg anterior compartment, muscle area was measured in young and older men and women [5]. The older persons had a smaller area of contractile tissue, 11.5% less in women and 19.2% less in men, compared with the young persons. These data, obtained by different body composition technologies, clearly showed a smaller muscle size in older persons compared with young persons. The observed differences in muscle size between age 20 and age 70 suggested a loss of skeletal muscle mass of about 0.26–0.56% per year.

The amount of non-muscle tissue within the muscle was also assessed using five CT scans of the thigh in 11 older men and 13 young men [4]. Older men had 59.4% more non-muscle tissue within the quadriceps and 127.3% within the hamstring muscle. In a similar study, the amount of non-muscle tissue in older men was 81% higher in the plantar flexors as compared with young men [6]. Thus, apart from the smaller muscle size in old age, these studies suggested that the composition of the muscle also changed with aging, leading to less "lean" muscle tissue in old age.

With the greater availability of body composition methods such as bioelectrical impedance and dual-energy x-ray absorptiometry (DXA) over time, cross-sectional data on muscle size in large study samples including a broad age range have been collected. Examples of these studies using lean mass from DXA (the non-bone, non-fat soft tissue mass) and fat-free mass from bioelectrical impedance, presented by 10-year age groups of men, are presented in Figure 2.1 [7, 8]. Older age groups had a lower

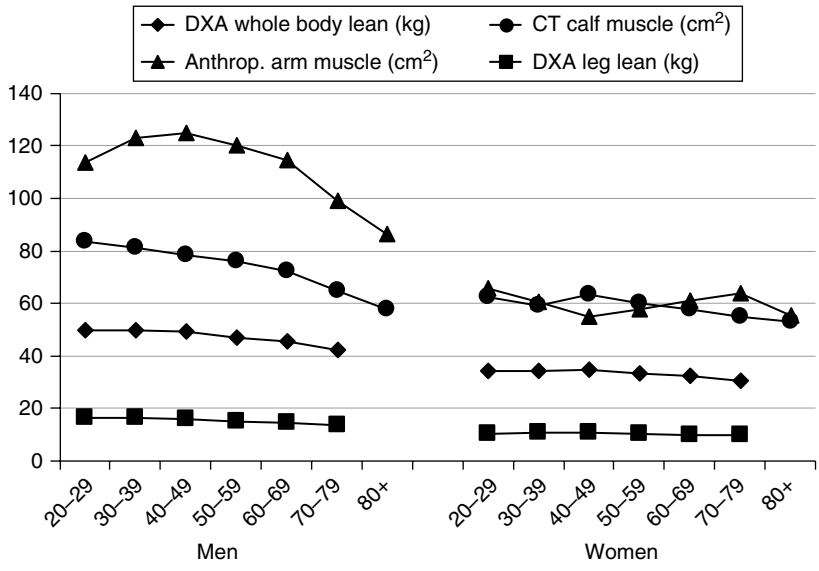

Figure 2.2 Differences in muscle cross-sectional area and lean mass using different body composition methodologies between men and women of different age groups. DXA = dual-energy x-ray absorptiometry; CT = computed tomography; Anthrop. = anthropometry, using arm circumference and triceps skinfold. *Source*: Based on references [9–11].

total body fat-free mass, lower total body lean mass, and lower arm and leg lean mass. Figure 2.2 presents the differences in muscle size between 10-year age groups in men and women. With increasing age group, the data suggested a lower whole-body lean mass and leg lean mass as assessed by DXA [9], a smaller arm muscle cross-sectional area (from anthropometric measures [10]), and a smaller calf muscle cross-sectional area (from peripheral qualitative CT [11]). These cross-sectional data derived from samples from Italy, Australia, India, Japan, and the United States consistently suggested a decline in muscle size with aging. These data also suggested a steeper decline in muscle size with aging in men compared with women.

Cross-sectional data from a sample of 72 women aged 18–69 years suggested a strong correlation between age and the amount of low-density lean tissue as assessed by a CT scan of the mid-thigh. The density of muscle tissue as assessed by CT is indicative of the amount of fat infiltration into the muscle [12]. Higher age was associated with greater amounts of low-density lean tissue (correlation coefficient = 0.52 [13]). This result again suggested a greater fat infiltration into the muscle with the increasing age.

These cross-sectional data, however, should be interpreted carefully as cohort and period effects, and not aging per se, may have caused the observed differences in muscle size and muscle composition between the age groups. For example, well-known cohort differences in body height, a strong determinant of muscle size, may partly explain the lower muscle mass in older persons compared with younger persons. In addition, period differences in lifestyle (e.g. sports participation, diet, and obesity status) and job demands may have differentially affected muscle size and muscle composition between age groups. Therefore, prospective data are needed within the same individuals to investigate the true change in muscle mass with aging.

CHANGE IN MUSCLE MASS WITH AGING

Forbes was among the first researchers to report prospective data on the age-related decrease in lean body mass in a small group of adults using potassium^{40} counting data [14]. The reported decline was −0.41% per year as observed in 13 men and women aged 22–48 years.

Many prospective studies followed using body composition techniques such as bioelectrical impedance, isotope dilution, skinfolds, and underwater weighing to study change in fat-free body mass and total body water with aging [15–21]. However, due to the body composition methodologies used in these studies, no precise measurement of skeletal muscle mass could be obtained because fat-free mass and total body water also include lean, non-muscle tissue such as the visceral organs and bone. Therefore, these studies only provide a crude estimate of the sarcopenia process with aging.

More recent prospective studies have measured the decline in appendicular lean mass using DXA [22–25] and the decline in muscle cross-sectional area by CT in relatively large samples of older men and women [26, 27]. The characteristics of these studies are presented in Table 2.1. From these studies a precise and accurate estimation of the sarcopenia process can be obtained. The relative annual decline in skeletal muscle mass was estimated to be between −0.65 and −1.39% per year for older men and between −0.61 and −0.80% per year for older women (Figure 2.3). Even in weight-stable older persons, a decline in appendicular lean mass was observed [24, 25]. In older persons the absolute as well as the relative decline of skeletal muscle mass with aging was generally larger in men compared with women.

Table 2.1 Characteristics of prospective studies investigating the age-related change in skeletal muscle mass in older men and women as assessed by dual-energy x-ray absorptiometry (DXA) or computed tomography (CT).

Reference	*N* and sex	Country	Age (mean [SD]) or range (*y*)	Mean follow-up time (*y*)	Body composition method	Muscle measurement
22	1129 men 1178 women	United States	70–90	7	DXA	Leg lean mass
23	114 man 95 women	Japan	70–79	6	DXA	Leg lean mass
24*	24 men 54 women	United States	60–90	4.7	DXA	Appendicular lean mass
25*	60 men 101 women	Italy	68–78	2	DXA	Appendicular lean mass
26	869 men 934 women	United States	70–79	5	CT	Mid-thigh muscle cross-sectional area
27	188 men 166 women	United Kingdom	68.9 (2.5) 69.2 (2.6)	7	Peripheral quantitative CT	Arm muscle area

*Weight-stable sample.
SD = standard deviation.

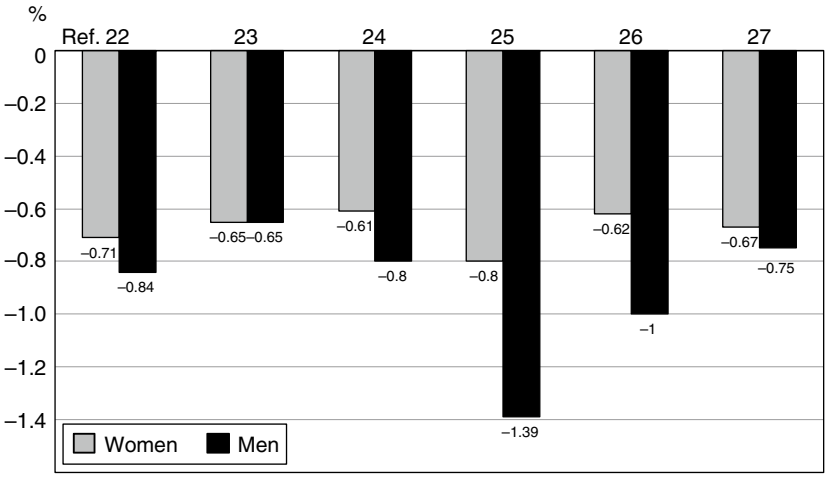

Figure 2.3 Annual decline (%) in skeletal muscle mass in older men and women from prospective studies with follow-up times from 2 to 7 years.

Moreover, prospective studies show that the relative annual decline in skeletal muscle mass increases with higher age group between the ages 40 and 90 years [23, 28]. For example, the relative 6-year change in leg lean mass increased from −0.33% in women in their 40s to −0.65% in women in their 70s. For men, these percentages increased from −0.07 to −0.65% [23].

Limited data are available on the prospective change in muscle fat with aging. Data from the Health, Aging and Body Composition Study showed an increase in intermuscular fat at the mid-thigh of 3.1 cm^2 in older men and 1.7 cm^2 in older women during the 5-year follow-up [29]. This is translated to an annual increase of 9.7% in men and 5.8% in women. This increase was paralleled by a decline in subcutaneous fat at the mid-thigh and shows specifically the increasing fat infiltration into the muscle tissue with the increasing age. Moreover, data from 99 adult male twins with a mean age of 47.3 years at baseline, showed a decline in the ratio of muscle cross-sectional area/functional cross-sectional area over 15 years as assessed by magnetic resonance imaging (MRI) at the L3–L4 level, indicative of greater fat infiltration into the paraspinal muscles with aging [30].

From these body composition studies it can be concluded that the amount of skeletal muscle mass declines substantially with aging. At the same time, the composition of the muscle changes and a greater fat infiltration into the muscle occurs. It is important to understand the potential impact of these changes on healthy aging.

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CHAPTER 3

The Role of Mitochondria in Age-Related Sarcopenia

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MUSCLES TRANSFORM CHEMICAL ENERGY INTO MECHANICAL ENERGY

Skeletal muscle, one of the largest organs in the human body, undergoes major biological, phenotypic, and functional changes during the aging process. The whole muscle mass declines with aging with a faster rate than the overall fat-free mass. The decline starts already around the fourth decade of life and accelerates after the age of 70 [1]. The parallel decline of strength exceeds the rate expected from the decline in mass, and this is consistent with profound biological and architectural changes observed in muscles during the aging process both in animal models and in humans [2].

The primary function of muscles is to generate mechanical force, which is essential for the movement of different body parts while accomplishing fundamental functions such as walking, manufacturing and handling objects, moving the eyes, expanding and compressing the lungs, controlling the opening and closing of larynx among many others. Production of mechanical force requires energy that is provided by the hydrolysis of a high-energy transfer phosphate bond in adenosine 5′-triphosphate (ATP) to produce adenosine diphosphate (ADP) and inorganic phosphate. The flow of energy continuously matches the energy demand through the phosphocreatine (PCr) shuttle, a system that facilitates transfer of high-energy phosphate from muscle cell mitochondria to myofibrils (Figure 3.1). Interestingly, more than 95% of creatine in the body is located in striate muscle, where the fluctuation of energy utilization is the highest [3]. Beyond contraction, skeletal muscle health also requires a constant flux of energy to maintain the activity of the sodium/potassium pumps and ensure calcium transport and sequestration in compartments. The energy for these activities is a substantial

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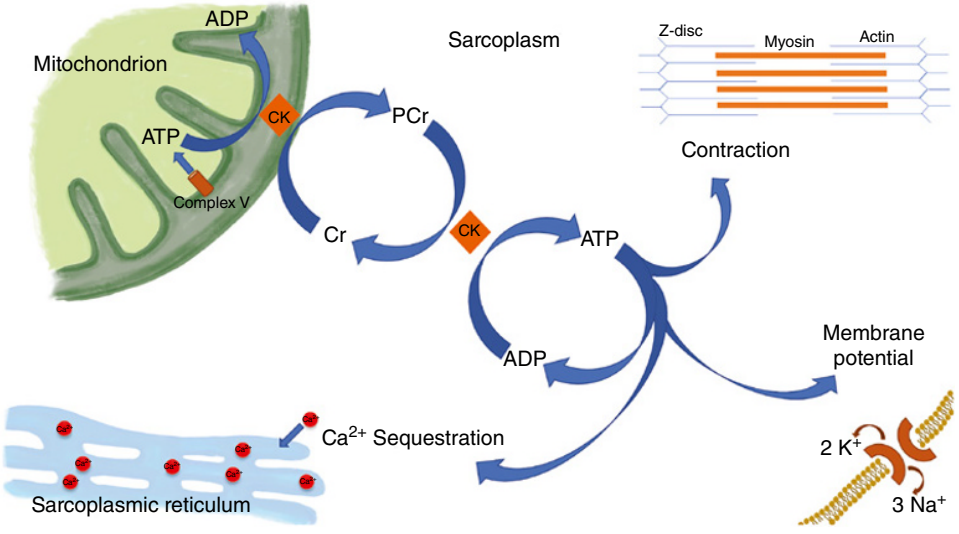

Figure 3.1 Phosphocreatine (PCr) shuttle: the ATP generated by the complex V of the electron transport chain converts creatine into PCr in mitochondrial matrix, which in turn allows ADP phosphorylation in the sarcoplasm. The ATP generated will fuel the muscle contraction through interaction with the myosin chains of the sarcomere, the maintenance of membrane, and calcium (Ca^{2+}) sequestration in the sarcoplasmic reticulum. ADP = adenosine diphosphate; ATP = adenosine 5′-triphosphate; CK = creatine kinase; K^+ = potassium; Na^+ = sodium.

portion of the total energy consumption in resting muscle, but accounts only for a small percentage of energy utilization during intense contraction [4].

The concentration of ATP in human quadriceps muscles is ~5.5 mM (expressed per 1 kg of whole muscle tissue) [5] and during contraction the rate of ATP hydrolysis increases to ~18 mM/min (moderate intensity) to 55–80 mM/min for submaximal isometric contraction, and as high as 160 mM/min for a dynamic contraction generating maximal power. Thus, in the absence of a fresh supply, the ATP already present could only support 5.5/80 = 0.0685 minute or ~4 seconds of contraction. Hence, efficient and intense production of force in skeletal muscle requires continuous ATP regeneration, which occurs through the hydrolysis of PCr. During a brief exercise the decline of PCr and increase of inorganic phosphorous are the only evident biochemical changes in muscle tissue [6]. Of note, even though PCr functions as an accumulator of chemical energy, its concentration is only fourfold greater than that of ATP and, therefore, could only support contraction for a few more seconds if not continuously recharged by ATP produced by mitochondria. At low levels of exercise, the system can stay stable for prolonged time, but when the exercise becomes intense it overcomes the capacity of energy generation, both aerobically and anaerobically [6]. This is the reason why intense and repeated contractions can be sustained only for a short time, and as the rate of energy production slows down with aging, the time prior to fatigue becomes progressively shorter. Of note, when the contraction ceases, the ATP generated by mitochondria fully recharges PCr that rises back to its pre-exercise concentration. The rate of PCr recovery is assessed by ^{31}phosphorous magnetic resonance spectroscopy to estimate maximal mitochondrial function [7].

Given the critical role of energy availability for the proper functionality of skeletal muscle, it is not surprising that mitochondrial dysfunction has been hypothesized to be the primary cause of age-related sarcopenia [8]. This hypothesis is consistent with the fact that several maternally inherited mutations in mitochondrial DNA (mtDNA) genes and some mutations that affect nuclear genes that code for mitochondrial proteins are associated with impaired energetic metabolism and cause different degrees of myopathy with some similarities with age-associated sarcopenia and often associated with brain impairments [9]. In addition, a gene expression study recently performed in a multiethnic population strongly suggested that a decline in mitochondrial integrity and mass is the biological hallmark of frailty and age-related sarcopenia [10].

EVIDENCE THAT MITOCHONDRIAL FUNCTION DECLINES WITH AGING AND ITS CONSEQUENCES ON MUSCLE HEALTH AND FUNCTION

Several lines of research suggest that skeletal muscle mitochondrial volume and function decline with aging even in healthy individuals, and that the magnitude of this decline is larger in individuals with severe multimorbidity and those who are sedentary [8, 11]. Moreover, chronic exercise robustly increases mitochondrial capacity within muscles in older adults [12, 13], and exercise appears to more strongly correlate with mitochondrial content and performance than aging [14, 15]. However, the causal role of mitochondrial dysfunction in the genesis of sarcopenia has not been definitively established, with conflicting results across studies, remaining an area of intense investigation.

Animal studies have shown a decline in mitochondrial mass and number in skeletal muscle with aging, findings that have been confirmed in aging humans [16–21]. Most although not all studies conducted on muscle tissue using both confocal microscopy and electron microscopy have demonstrated that the number and shape of mitochondria, as well as the overall mitochondrial mass, decline with aging [22]. This is consistent with the discovery studies showing that mitochondrial transcripts and proteins are the most underrepresented classes of transcripts and proteins with older age in skeletal muscle [23]. Of note, proteomic studies indicate that the entire class of mitochondrial proteins becomes underrepresented with aging even in very healthy individuals, including structural proteins, proteins that are part of the electron transport chain (ETC) complexes, as well as critical enzymes for glycolysis and Krebs cycle (Figure 3.2) [24]. This is consistent with the idea that the whole mitochondrial mass declines with aging as percentage of muscle mass (or more precisely percentage of muscle proteins).

The decline of mitochondrial mass and function have important consequences for muscle health. Studies conducted with ^{31}P MRI spectroscopy have shown that maximal ATP production (or maximal oxidative capacity) declines with aging even in relatively healthy individuals [25]. The decline of mitochondrial oxidative capacity with aging has been also confirmed "ex vivo;" by conducting respirometry on permeabilized muscle fibers from human biopsies [23, 26]. Such decline accounts for a significant percentage of the decline of muscle strength and walking speed observed with aging [27], is associated with fatigability [28] and sarcopenia [29, 30], and is a strong correlate of cardiorespiratory fitness [23, 26] and the development of insulin resistance [31].

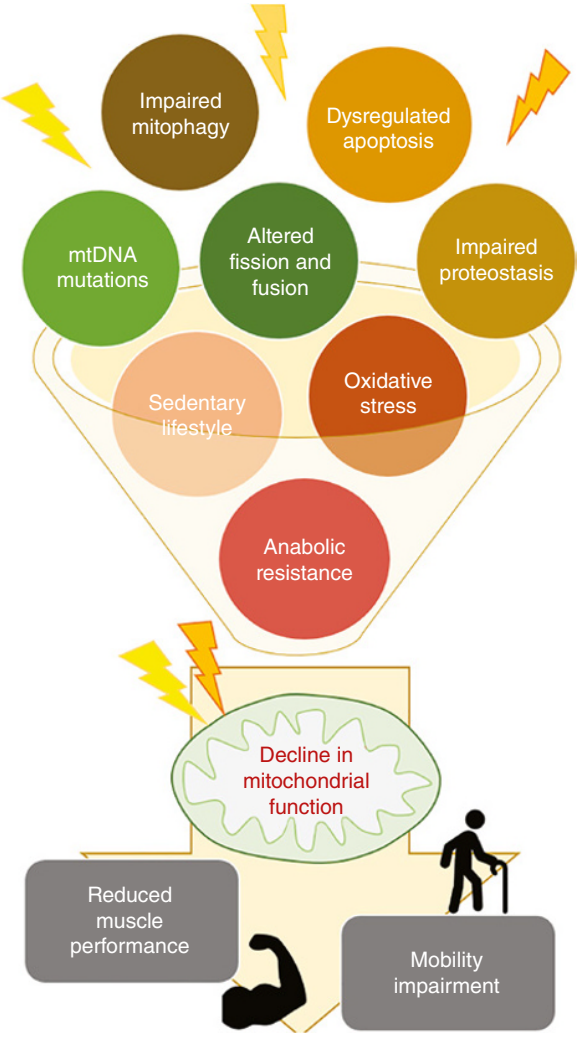

Figure 3.2 Hypothesized mechanisms leading to mitochondrial dysfunction, decline in muscle performance, and mobility impairment.

CAUSES OF THE DECLINE OF MITOCHONDRIAL MASS AND OXIDATIVE CAPACITY IN AGING SKELETAL MUSCLE

In spite of some inconsistencies in the literature, there is enough evidence to conclude that mitochondrial volume and function in skeletal muscle decline with aging. However, there is substantial disagreement on possible causal mechanisms that lead to such decline. Here, we review briefly the main theories and mention some of the supportive evidence.

It is important to recognize that most of the available evidence is based on studies conducted on animal models or human studies with a cross-sectional design, and substantial work still needs to be conducted to better identify the molecular changes that are associated with the decline of muscle mitochondrial health with aging.

Decline of physical activity with aging

It is generally acknowledged that a substantial portion of the decline of mitochondrial function with aging is attributable to the decline of physical activity, observed even in very healthy aging individuals [32]. The level of physical activity is by far the strongest predictor of muscle function with aging and has been linked with the preservation of mitochondrial function. Indeed, the discovery proteomic studies conducted on muscle biopsies from healthy individuals have found a strong association between the levels of self-reported physical activity and increased representation of all mitochondrial proteins, both structural and functional [33]. A reduced physical activity, however, does not exhaustively explain the decline of mitochondrial function, since skeletal muscle oxidative capacity declines even after the effect of age is estimated after adjusting for physical activity [23, 26]. Although observational studies assessing changes of mitochondrial function with aging in individuals who maintain a high level of physical activity are lacking, randomized clinical trials have shown that regular physical activity and resistance exercise prevent age-related sarcopenia [34–36]. The beneficial effect of physical activity on mitochondrial function is mostly mediated by mitochondrial biogenesis, driven by the upregulation of the peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1α), [37, 38]. PGC-1α modulates the biological activity of several transcription factors including the nuclear respiratory factors (NRF1 and NRF2) and mitochondrial transcription factors (TFAM and TF2B) [39], and its concentration in skeletal muscle has been associated with the degree of oxidative capacity and shown to decline with aging [29]. PGC-1α also inhibits the Forkhead box O3a (FoxO3a) and nuclear factor κB (NF-κB), both of which enhance muscle catabolism [40, 41]. In mice, the overexpression of PGC-1α levels in skeletal muscle prevents age-dependent sarcopenia [42]. Thus, increasing mitochondrial biogenesis or enhanced quality control processes by exercise or exercise mimetics is considered one of the possible strategies for sarcopenia prevention.

Oxidative stress

The generation of ATP from ADP in mitochondria requires a perfectly tuned and coordinated activity of metabolic mechanisms that process different substrates to ultimately produce highly charged spared electrons, which are transported through a respiratory chain composed of five proteins complexes. The energy released by these electrons drives the accumulation of hydrogen ions (H^+) against a concentration gradient into the intermembrane space. H^+ returns to the mitochondrial matrix through the fifth complex (ATP-synthase), and releases the energy accumulated to produce ATP and, if oxygen is available, water. Even in ideal conditions, the electron transport system (ETS) is imperfect and some leakage of highly charged electrons occurs at complex I and III and through a partial reduction of oxygen to form superoxide ($^{\bullet}O^{-}_{2}$) that is quickly transformed into hydrogen peroxide (H_2O_2) by two dismutases, superoxide dismutase 2 (SOD2) in the mitochondrial matrix and superoxide dismutase 1 (SOD1). Small amounts of reactive oxygen species (ROS) are now considered essential signaling molecules and beneficial to mitochondrial health, probably through the modulation of mitophagy (explained later in the text) [43]. However, conditions that impair and slow down the normal flux of electrons through the ETC

facilitate the production of ROS above the physiologic quantity and this excess of ROS causes substantial damage to cell membranes, organelles, DNA, and proteins, leading to mitochondrial damage, in an hypothetical vicious cycle where mitochondrial damage facilitates the production of ROS and increased ROS production further damages mitochondria integrity. There is substantial evidence that ROS production increases with aging and it is not adequately buffered by increased level of scavenging enzymes, such as manganese superoxide dismutase (MnSOD or mitochondria-specific SOD2), catalase (CAT), and glutathione peroxidase (GPx). Consistently, aging is associated with increased oxidative damage to macromolecules, especially DNA and proteins [44]. However, a direct link between ROS production, oxidative damage to macromolecules, and mitochondrial dysfunction has not been definitively established.

An important emergent target for ROS-induced mitochondrial damage are cardiolipins. Cardiolipins are glycerophospholipids specific to the mitochondria with a unique dimeric structure of two phosphatidic acid moieties connected to a glycerol backbone. Although the variety of phosphatidic acids found in cardiolipin is extremely large, cardiolipin containing 18-carbon fatty alkyl chains with two unsaturated bonds (18:2), the most frequent form, has probably the highest affinity to the inner membrane proteins of mammalian mitochondria, and is important to the structural integrity of the inner mitochondrial membrane and the preservation of the proper shape of the mitochondrial cristae. This is consistent with findings that show how low circulating levels of lysophosphatidylcholine 18:2 are strongly associated with the risk of losing mobility [45–47]. In eukaryotes, cardiolipins are only synthesized in the mitochondrion, where they remain throughout the mitochondrion lifespan. Functionally, cardiolipin binds to the complexes of the ETC to stabilize their reciprocal positioning and regulate their activation. In particular, cardiolipins interact with NADH-dependent Coenzyme Q oxidoreductase (complex I), succinate dehydrogenase (complex II), ubiquinol cytochrome oxidoreductase (complex III), cytochrome c oxidase (complex IV), and complex V [48]. Cardiolipins are also responsible for anchoring to the mitochondrial membranes two important enzymes: the creatine kinase, which produces PCr from Cr, and the nucleoside diphosphate kinase, which catalyzes the exchange of terminal phosphate between different nucleoside diphosphates (NDPs) and triphosphates (NTPs), such as ATP, in a reversible manner. Cardiolipins participate in the induction of apoptosis by interacting with cytochrome c [48], and are essential for mitochondrial fission and fusion [49]. Excessive, unopposed oxidative stress may determine peroxidation of the cardiolipin, whose structure and proximity to the ETC makes it particularly vulnerable to ROS, leading to structural and functional changes in mitochondria that strongly affect oxidative phosphorylation (OXPHOS) capacity. Of note, to recycle oxidized cardiolipins and newly resynthesize them may be energetically challenging in an environment where energy production is already scarce. The interaction between oxidized cardiolipin and cytochrome c could be responsible for the substantial upregulation of the apoptotic pathways that is often detected in sarcopenic muscle. Indeed, while the cardiolipin content of mitochondria has been shown to decrease with aging, changes in different species of oxidized cardiolipins have not been studied in depth because of the lack of quantitative, reliable, and sensitive measurement methods. Because of its potential therapeutic implications, the study of cardiolipins is an active area of research.

It is important to remember that oxidative stress may also affect structures outside the mitochondria. In particular, the less reactive hydrogen peroxide may cross the mitochondrial membrane and attack molecules in the cytoplasm, nucleus, and other organelles, particularly in the presence of heavy metals, such as iron or copper, which react with hydrogen peroxide to generate highly reactive hydroxyl radicals (Fenton reaction). In muscles, this may involve damage to the contractile apparatus, ion channels, and signaling receptors that may impair muscle function.

Anabolic resistance

Discovery metabolomic studies that compared pairs of individuals with low and high muscle quality matched by age, sex, and body size found that plasma levels of branched-chain amino acids (BCAAs) were higher in individuals with low compared with high muscle quality, operationalized as the ratio between muscle mass and muscle strength [50]. Interestingly, opposite to what had been found in blood, level of BCAAs in the muscle of participants with low muscle quality were higher than that in those with high muscle quality. While the reason behind these findings is not clear, these results are consistent with the notion that the administration of BCAAs, such as leucine, in the diet may prevent age-related decline of muscle strength, decrease muscle fatigue, and alleviate muscle soreness, although there is some indication that this effect could be blunted in older persons [51, 52]. The scarcity of BCAAs within myofibers has important consequences. In myofibers, BCAAs have been shown to stimulate the Pi3K/Akt/mTOR cell signaling pathway; in particular, the mTORC1 controls protein synthesis by activating S6 kinase 1 (S6K1) and inhibiting 4E-binding protein 1 (4EBP1) [53]. Low BCAAs lead to reduced protein synthesis and over time protein damage accumulation and lower muscle mass. Low BCAA availability also directly impacts mitochondria through at least two main mechanisms. Deficient mTORC1 activation and reduced SIRT1 biological activity, secondary to low BCAA availability in myofibers, contribute to a deficit in mitochondrial metabolism by underexpression of PGC1α, a master regulator of mitochondrial biogenesis. In addition, BCAAs undergo transamination by branched-chain aminotransferases (BCATs) to form branched-chain alpha-ketoacids (BCKAs), and oxidative decarboxylation by the mitochondrial branched-chain alpha-ketoacid dehydrogenase (BCKDH) complex. This last step is highly modulated by factors that affect energy availability and consumption, such as nutrition, exercise, and inflammation [54]. Ultimately, carbons that stem from the BCAA catabolism enter the tricarboxylic acid (TCA) cycle as either acetyl-CoA or succinyl-CoA, getting completely oxidized. In summary, impaired BCAA entry in skeletal myofibers appears to be associated with reduced muscle quality, impaired mitochondrial biogenesis, and decreased mitochondrial substrate delivery.

Accumulation of somatic mutations in mitochondrial and nuclear DNA

It has been speculated that the accumulation of somatic mutations in mtDNA over time contributes to mitochondrial dysfunction observed with aging in skeletal muscle [55]. Human mtDNA is a small circular double-stranded DNA molecule of approximately

16.5 thousand base pairs that encodes 37 genes, including two ribosomal RNAs, 22 transfer RNAs, and 13 proteins that are subunits of respiratory chain complexes. It has been suggested that mtDNA is particularly susceptible to oxidative stress damage because of its proximity to the locus of ROS generation, but most recent theories suggest that these mutations are caused by errors in replication fidelity of the mtDNA polymerase, POLGγ [56]. Thus, damage progressively accumulates through the aging process but, as there are hundreds or thousands of mitochondria in a single myofiber, and multiple mtDNA in each mitochondrion, a low rate of random accumulations across the genome is probably compatible with normal functioning [55]. In contrast to this theory, it has been suggested that even small percentages of mutated mtDNA molecules (micro-heteroplasmy) may have functional consequences [57]. The role of mtDNA somatic mutations in the genesis of age-related decline of muscle strength remains controversial [58, 59]. The strongest evidence on the matter comes from a mouse model that contains a mutated proofreading-deficient form of POLGγ, which leads to a severe and rapid accumulation of mtDNA mutations and early development of severe sarcopenia [60].

Both in the nucleus and in mitochondria, the integrity of DNA is continuously challenged by ROS and other damaging agents, such as radiation and chemical mutagens. Endogenous DNA damages occur frequently, estimated as more than 10 000 oxidative damages per day per nucleus, are much higher in mtDNA than in nuclear DNA, especially in high-energy-demanding tissues such as skeletal muscle. Different types of DNA damage are continuously repaired by a very complex and sophisticated repair machinery. However, if the mutational rate is higher than the repair capacity, damage accumulates over time and may determine genomic instability, with severe consequences for the cell's fate. If the unrepaired damage in the coding and control regions of the DNA becomes pervasive, the chance of impairment of critical cell functions may become substantial [61]. Indeed, there is evidence that somatic mutations accumulate with aging and may contribute to important pathologies [62].

Accelerated DNA repair draws energy from the available pool and directly reduces the availability of ATP used by myocytes to produce mechanical force or for maintenance/repair of macromolecules and organelles. In addition, and perhaps more importantly, DNA repair and mitochondrial energetic metabolism compete for the use of nicotinamide adenine dinucleotide (NAD+) as an essential metabolite [63]. In the mitochondrion, NAD+ is a critical electron acceptor during the OXPHOS. Thus, a decrease of cellular NAD+ levels or NAD+/NADH ratio leads to a decrease in the rate of ATP production. In addition, NAD+ is also an essential co-factor of Poly [ADP-ribose] polymerase 1 (PARP-1), a protein that plays a key role in the early phase of the cellular response to different forms of DNA damage. DNA repair consumes large quantities of NAD+, consumption that may overcome the rate of NAD+ synthesis, leading to NAD+ depletion and impaired OXPHOS. In addition, since NAD+ is a co-factor for Sirtuin1, a protein that by de-acetylating the PGC1-alpha/ERR-alpha complex modulates energetic metabolism, mitochondrial biogenesis, and mitophagy, scarcity of NAD+ may compromise these functions leading to further mitochondrial impairment. This hypothesis is consistent with studies that found a downregulation of mitochondrial biogenesis with aging in human cardiac muscle [64]. Finally, the activation of the NAD+ salvage synthesis pathway in response to the decline in intracellular NAD+ consumes large quantities of ATP, thus contributes to the energetic crisis. However, there is evidence showing that the efficiency of this pathway may be improved

by physical activity [65]. Although the precise nature of these complex interactions has not been fully established, there is consensus that NAD+ deficiency is a potential cause of mitochondrial dysfunction and sarcopenia during aging. As the administration of NAD+ and/or NAD+ precursors or PARP inhibitors can increase NAD+ levels, these seem promising therapeutic approaches to prevent sarcopenia.

Fission, fusion, and mitochondrial recycling

The many different types of damage accumulated in mitochondria over time probably underlie the decline of mitochondrial mass and function observed with aging in skeletal muscle. Noteworthy, the rate of damage accumulation is blunted by several resilience mechanisms, but unfortunately the efficiency of this resilience declines with aging.

A primary mechanism aimed at maintaining mitochondrial integrity is the alternation of constant cycles of fission and fusion. **Fission** is the mechanism by which mitochondria divide and duplicate, while through **fusion** two or more smaller mitochondria form a unique larger structure. The conceptualization of fission and fusion is usually referred to mitochondria as single organelles, but how mitochondrial fission and fusion occur in skeletal muscle mitochondria that form a highly connected network is not understood. Thus, our knowledge of these mechanisms in humans is scant, although it is evident that the functionality of fission and fusion is essential to the preservation of mitochondrial health and energetic metabolism [66]. Mitochondria exert a tight quality control on protein integrity, they can repair misfolded proteins or eliminate them through chaperon-mediated autophagy and proteasome proteolysis, without the need of activating other mechanisms [67]. However, when the severity of damage is overt, damaged mitochondria may fuse with other mitochondria in the same myofiber, share undamaged components and, as long as the mtDNA mutation load remains below a certain threshold, maintain a good level of function [68]. If mitochondrial functionality cannot be restored through these mechanisms, damaged and dysfunctional mitochondria can be eliminated though mitophagy (mitochondrial autophagy, see later). In particular, distressed mitochondria undergo fission and segregate most of the damaged components into small mitochondrial vesicles with partially depolarized membranes. These smaller vesicles can either be targeted for autophagy or fuse with other healthy mitochondria. However, if the level of damage is overt and above a certain threshold, both fission and fusion are inhibited to avoid the transfer of damaged material to healthy mitochondria. Under these conditions, the whole mitochondrial membrane would become depolarized and ATP production declines below a critical threshold, activating autophagy (mitophagy), a process that consists in the sequestration of a mitochondrion in an autophagic vacuole (autophagosome) and the hydrolytic degradation of its cargo by fusion with lysosomes (autolysosome) [69].

Profound alterations in mitochondrial fusion and fission proteins have been associated with many age-related conditions, including obesity, neurodegenerative diseases, cardiovascular diseases, type 2 diabetes, and age-related sarcopenia. Although most of these studies were conducted in animal models, they suggest that a dysregulation of mitochondrial dynamics may play an important role in age-related sarcopenia and other age-related chronic conditions in humans [70]. Supporting evidence for this theory comes from the fact that "in vivo;" genetic manipulations of proteins involved in fission accelerated muscle mass decline with aging in mice, while the inhibition of

fission prevented sarcopenia. Moreover, overexpression of dynamin-like 120-kDa protein (OPA1), an essential protein for mitochondrial fusion, is protective against denervation-induced muscle atrophy [71]. The expression of mitochondrial fusion and fission proteins is reduced during aging in human skeletal muscle [72, 73]. Reduced levels of Mitofusin-2 (MFN-2), an outer membrane mitochondrial protein essential for mitochondrial fusion, have been found in sarcopenic older individuals, as compared to age-matched controls [74]. In addition, several lines of research suggest that autophagy becomes defective with aging, including some evidence regarding human skeletal muscle.

The persistence of severely damaged mitochondria jeopardizes attempts to replace them with new, healthy mitochondria. Stressed mitochondria also release non-methylated mtDNA and formyl peptides, that are viewed by the immune system as damage-associated molecular patterns (DAMPs) and detected by Toll Like Receptor 9 (TLR9) and the NLRP3 Inflammasome [75]. The latter triggers caspase-1 activation and the production of interleukin (IL)-1β and IL-18 [76]. A third recently identified pro-inflammatory pathway triggered by released mtDNA involves recognition by the cytosolic sensor cGAS, which activates the adaptor protein STING and the kinase TKB1 leading to the production of type 1 interferons (IFN) [77]. Based on these mechanisms, it is not surprising that the slow, continuous release of mtDNA has been proposed as one of the potential causes of the pro-inflammatory state that is often recognized in older individuals and that has been associated with cardiovascular diseases and other chronic diseases [78]. Interestingly, a pro-inflammatory state witnessed by high levels of pro-inflammatory markers, such as C-Reactive protein and, less consistently, IL-6, has been associated with age-related sarcopenia and recognized as a risk factor for sarcopenia development [79]. It has been suggested that this association is caused by inflammatory mediators that enhance protein catabolism and inhibit protein synthesis, both directly and through interference with the production and biological activity of Insulin-like growth factor-1 [75]. However, the specific mechanism by which inflammation affects muscle protein metabolism has not been fully elucidated. Attempts to prevent or reverse sarcopenia by reducing inflammation in humans have had limited success [79].

Apoptosis

There is strong evidence that apoptosis, the process of programmed cell death, plays a primary role in the pathogenesis of the age-associated decline of muscle mass and strength. Studies that compared skeletal muscle tissues from younger and older rats reported high levels of apoptosis and connected the degree of muscle mass decline with the severity of apoptotic DNA fragmentation [80–82]. Apoptosis appears to be more frequent among type II fibers, possibly consequently to the higher susceptibility to TNF-alpha signaling pathway. In skeletal muscle fibers, apoptosis can be induced either through a mitochondria-independent or a mitochondria-dependent mechanism, and it is not established which one of these pathways contributes to the accelerated decline of muscle mass and strength that eventually leads to sarcopenia. In mitochondria, apoptosis is initiated by mitochondrial matrix accumulation of Ca^{2+} which leads to the opening of the permeability transition pore (MPTP), a large non-selective channel in the inner mitochondrial membrane. The opening of the MPTP

increases concentrations of ROS, elicits membrane depolarization, and releases cytochrome c into the cytosol, activating the apoptotic program through a number of intermediate steps, including the activation of caspase-9 and caspase-3. Apoptosis includes reorganization of the cytoskeleton, arrest of cell replication, fragmentation of the nuclear membrane and the DNA, and eventually cell death. There is some but not concluding evidence that the threshold for apoptosis activation is increased in aging skeletal muscle, especially in humans. Further research is needed in this field. Interestingly, exercise and dietary restriction attenuate apoptosis with aging [81, 82]. Targeting apoptosis might be an effective intervention to counteract age-related muscle wasting. However, more mechanistic studies are required before potentially effective treatment strategies can be developed.

Mitochondrial proteostasis mechanisms

A perfectly tuned control of the protein concentrations, quality control and recycling are essential for mitochondrial health. Such control is exerted by the ubiquitin-proteasome system (UPS) and the autophagy–lysosome system. These catabolic mechanisms are modulated by the AMP-Kinase and the FOXO transcription factor family, which inhibit MTORC1, the master regulator of protein synthesis and degradation. However, whether a dysregulation of this proteostasis mechanism leads to accelerated protein breakdown with aging, which results into a decline of muscle mass, or rather a failure of protein synthesis in replacing the degraded proteins, is currently unknown. Discovery proteomics studies in human muscle have found a substantial underrepresentation of ribosome proteins with older age, suggesting that failing anabolic mechanisms are probably preponderant. On the other hand, studies have found UPS-related proteins and transcription factors overrepresented in quadriceps muscle of older compared with younger persons, while other studies failed to confirm these findings [83, 84]. In conclusion, the mitochondrial quality control system is altered at several levels. While it is reasonable to hypothesize that proteostatis mechanisms play an important role in the maintenance of integrity and efficiency of mitochondria, whether these mechanisms eventually contribute to age-related sarcopenia remains unknown.

ARE AGE-RELATED CHANGES IN MITOCHONDRIAL FUNCTION AT THE ROOT OF SARCOPENIA?

As outlined above, there is substantial evidence that mitochondrial function in skeletal muscle declines with aging, and that such decline has important functional consequences on mobility performance. We have examined several possible causes of mitochondrial dysfunction with aging, including a progressive decline of physical function, oxidative stress, anabolic resistance, accumulation of somatic mutations, and alterations of mitochondrial quality control mechanisms including proteostasis, fusion/fission, and mitophagy. Although we have attempted to be as comprehensive as possible in our review of the literature, we are fully aware that this chapter cannot exhaustively explore the enormous literature on the complex relationship between mitochondria, skeletal muscle, and aging. For example, there is evidence that part of the decline in

muscle strength with aging is due to a dysfunction of neurological control, both at the central and the peripheral level, and mitochondrial aging presumably contributes to this important cause of sarcopenia. Since the neurological prospective to sarcopenia is addressed in another chapter of this book, we are confident that these aspects will not be ignored in this publication.

Importantly, many of the changes in mitochondria described in this chapter occur in the majority of aging individuals, and not only in those who develop sarcopenia. **Thus, the question remains: "Is mitochondrial dysfunction the cause of age-related sarcopenia?".** In spite of extensive and sophisticated research in this field, a solid answer to such question is still lacking. Of course, if the age-associated changes described here are overt, the structure and function of mitochondria would be damaged with serious consequences on muscle oxidative capacity, and ultimately on the anatomic integrity and the ability to produce contractile force. Arguably, the lack of success in this field is due to a substantial disagreement between investigators about the appropriate definition of sarcopenia (also addressed elsewhere in this book), and to the fact that few studies have performed muscle biopsies in older persons affected by sarcopenia, which is often associated with poor health status and disability. As mentioned earlier, perhaps the best evidence that sarcopenia is associated with poor mitochondrial function is a gene expression study recently conducted in a multiethnic population where transcripts related to sarcopenia were substantially underrepresented in people with sarcopenia compared with controls [10]. In addition, a metabolomic study conducted in a relatively large population found that carnitine, a mitochondrial lipid transporter essential for the entry of fatty acids, potential fuel and synthetic precursors for the mitochondria, as well as vitamin E, a strong antioxidant important for mitochondrial function, are underrepresented in the serum of frail compared to non-frail individuals [85]. Indeed, randomized controlled trials are currently in the field that target mitochondrial health to prevent sarcopenia. Ultimately, the results of these studies should provide an answer of whether changes in mitochondrial function are the root causes to sarcopenia.

ACKNOWLEDGMENTS

Supported in part by the Intramural Research Program of the National Institute on Aging, NIH - Baltimore, MD, USA.

The authors would like to thank Miguel Aon and Sonia Cortassa for reading the manuscript and providing very useful suggestions.

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CHAPTER 4

Motor Unit Remodeling

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OVERVIEW OF THE NEUROMUSCULAR SYSTEM

To fully appreciate the contribution of motor unit (MU) remodeling to sarcopenia, a reminder of the basic structure and function of the neuromuscular system is described. The human body is made up of over 500 skeletal muscles [1]. Each individual MU consists of a neuron, its axon and the muscle fibers it innervates. Wrapping around the axon are Schwann cells to form a myelinated sheath and promote the conduction of motor nerve action potentials. In the limited space between the motor neuron terminal and the muscle fiber, sits the neuromuscular junction. This junction, or chemical synapse, allows signals to be translated from neurons to muscle cells via neurotransmitter release and receptor binding.

At the structural level, there are three types of muscle fibers involved in contraction: type I, type IIa, and type IIx. These phenotypes contain differing physiological properties; for example, type I fibers (slow-twitch) are highly oxidative and possess a low capacity to generate adenosine triphosphate (ATP). In comparison, type IIa fibers are fast-twitch, carry high ATP and glycolytic capacity, and are fatigue resistant. Type IIx fibers (also fast-twitch) have the highest ATP generating capacity but lowest glycolytic capacity and fatigue rapidly [2]. Notably, many fibers can express more than one isoform of myosin heavy chain (MHC) and are referred to as hybrid fibers. Stacks of muscle fibers (known as myofibrils), contain sarcomeres and are made up of two main contractile proteins: actin (thin) and myosin (thick). Each myosin is made up of two myosin heads arranged longitudinally with ATP and actin binding sites. Actin, like myosin, has a double helix structure; however, it has additional protein structures, namely troponin and tropomyosin. The former enables calcium (Ca^{2+}) to bind, while the latter blocks the binding site of actin.

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

The nervous system regulates MU recruitment and allows an older adult to carry out a range of movements from fast and powerful (i.e., stairs climbing) to small and subtle (writing). To enable this energy dependent process, action potentials are first generated in the motor cortex of the brain and are then transmitted via the spinal cord into the MU pool. At the peripheral level, this action potential further propagates down motor axons to the neuromuscular junction (NMJ), then throughout muscle fibers down into the transverse tubular system, which in turn, activates ryanodine receptors causing the release of Ca^{2+} ions from the sarcoplasmic reticulum and enables structural proteins to contract. These electrophysiological processes are highly energy dependent and any disruption to the structure or function of MU will impede force production.

AGE-RELATED MU REMODELING

Loss of MUs

Adaptations to the neuromuscular system are marked by aging and are evidenced by direct quantification of MUs from human cadavers or indirectly by estimating MU numbers via electrophysiological techniques.

Early postmortem work shows a substantial reduction in the number of motor neurons (around 30–50%) in the lumber spine of older (>60 years) compared with younger adults [3]. Around the same time, two more cadaver studies demonstrated a decrease in motor neurons serving muscle fibers in the lower spinal region [4, 5]. Myoelectrical examination of various anatomical muscles have added to this body of knowledge. The estimated number of MU in the tibialis anterior, a key dorsiflexor, progressively decreases from young (~25 years [150 MUs]) to old (~65 years [91 MUs]) men, and further declines in the oldest men (~85 years [59 MUs]) [6]. Numerous other studies corroborate this loss of MU in upper (biceps brachii) [7] and lower limb (vastus lateralis) [8] muscles when comparing older adults with their younger counterparts. Although MU numbers have been reported with clear differences between young and old, MU number estimate techniques are limited by muscle size and electrode detection area, likely explaining the remarkably similar MU numbers reported for muscles of vastly different sizes (e.g. 138 in the first dorsal interosseous [9] and 195 in the VL [8]). Therefore, these methods should be viewed as an index rather than a true anatomical count.

A recent review of the literature also noted that by the seventh decade of life, healthy older adults have around 40% fewer MUs [10] than young. Of note, these studies have been conducted in healthy older adults, which demonstrates that neuromuscular remodeling is, to some degree, an unavoidable physiological consequence of aging. A recent review [11] further discusses the neuromuscular adaptions that occur even in states of healthy aging.

Until recently, the direct role of MU remodeling in the pathophysiology of sarcopenia was unknown. Although findings from immunosenescent studies of animal models showed that apoptosis of motor neurons and subsequent denervation of muscle fibers leads to muscle weakness in diseases which overlap with sarcopenia [12].

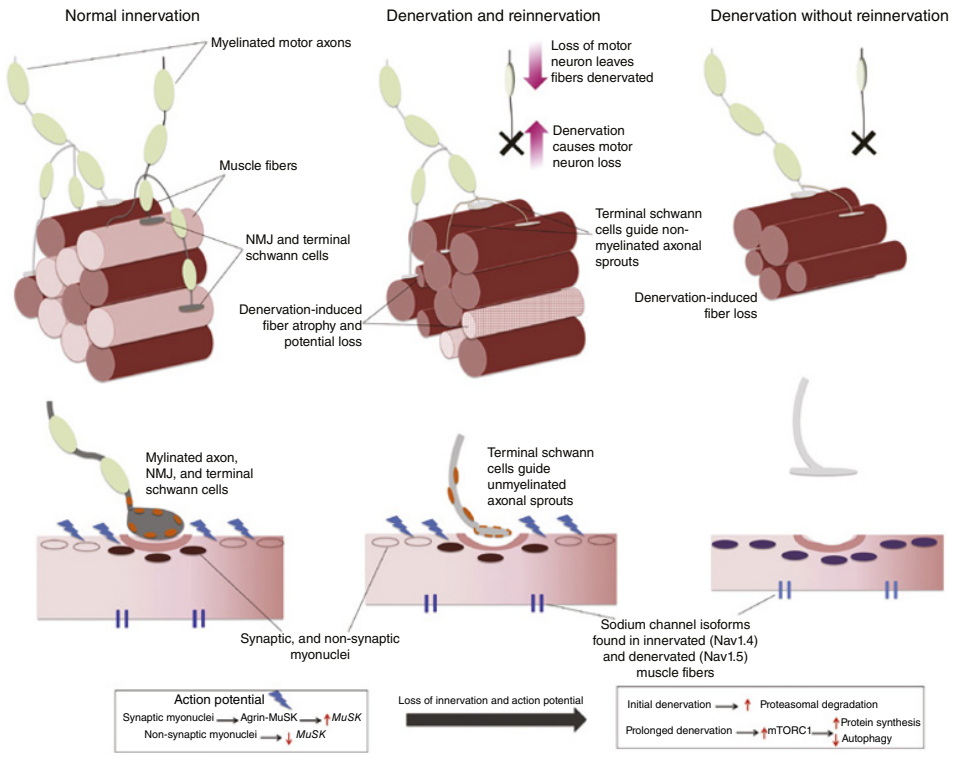

Figure 4.1 Motor unit remodeling and the denervation–reinnervation phenomenon. *Source*: Wilkinson and colleagues [14].

Compelling work by Piasecki and colleagues [13] was the first to quantify MUs across healthy young, non-sarcopenic old, pre-sarcopenic older, and sarcopenic older men. Unsurprisingly, muscle mass (8, 30, 44%), MU number (33, 47, 50%), and maximal strength (34, 39, 49%) were significantly lower in non-sarcopenic old, pre-sarcopenic older, and sarcopenic older men, respectively, in comparison with the younger reference group [12]. Moreover, MU potentials recorded with intramuscular needle electrodes were larger by 26 and 41% in non-sarcopenia and pre-sarcopenic older men, respectively, and were similar to young in the sarcopenic older men. Taken together this suggests "healthier" older men can reinnervate larger bundles of muscle fibers to counteract the loss of motor neurons with age, but this process may fail and contribute to the sarcopenic condition via muscle fiber loss [13]. This phenomenon, known as the denervation–reinnervation cycle, or MU remodeling (Figure 4.1), is a likely explanation for the increased size of MU observed in upper-and lower-limb locomotory muscles [15–19] of previous studies in older adults. Others have also noted that the remaining MUs in an aged muscle are enlarged by around 50% [10]. Indeed, this MU remodeling process is thought to preferentially affect fast-twitch fibers, which via compensatory mechanisms are reinnervated by the smaller earlier recruited MU, or undergo apoptosis [11]. This may result in two scenarios, (i) the smaller MUs adopt control of the muscle resulting in conversion to a "slower" phenotype or (ii) there is a

reduction of muscle fibers in a single MU, both of which may reduce force output required to perform activities of daily living (ADL) (Figure 4.1). More recent work among 86 older men demonstrated that a greater MU potential size of the vastus lateralis muscle was associated with a reduced risk of frailty ($\beta = -0.10$, 95% CI: −0.18, −0.02, $p = 0.013$ [adjusted for age and body mass index]) when utilizing the frailty index as a diagnostic tool [20]. These finding are of particular relevance given both sarcopenia and frailty share overlapping characteristics, with the former condition also a risk factor for the latter [21].

LOSS OF MUSCLE FIBERS

The loss of MU largely correlates with the loss of muscle fibers in aging [22]. Autopsy work comparing the quadriceps muscle of younger and older men demonstrate a substantial reduction in the number of muscle fibers (~214 000) in the latter cohort [23]. A 12-year longitudinal trial of older men also found a 14.7% decrease in the cross-sectional area of the quadriceps muscle [24]. Regarding muscle fiber phenotypes, comparison of males and females between 15 and 83 years found a 25–35% loss in muscle mass with senescence [25]. Others have documented the same, by the sixth decade of life, the number of type II muscle fibers declined from ~60 to 30% in two separate studies [26, 27]. It should be noted that total muscle atrophy may not be specific to the loss of type II fibers alone; in the abovementioned longitudinal trial [24] there was a ~40–60% loss of type I fibers at age 75 compared with age 65. In saying this, the loss of type II fibers is suggested to occur at a more rapid rate, which is likely a direct consequence of the neuromuscular remodeling phenomenon.

REDUCED FIRING CAPACITY OF MUs

The firing rate of MU (measured by action potential activity) has received great attention due to the apparent high level of plasticity and number of older adults presenting with functional limitations. MU firing rates have been documented to be 30–35% less in older compared with younger adults during various sub- and maximal-intensity contractions [28, 29], with a number of additional lower-limb studies reporting reduced discharge rates in older compared with younger adults [8, 30–32]. This reduction in firing rates is thought to stem from the remodeling of MU; the loss of the larger muscle fibers which exhibit the greatest force potential and fastest discharge rates [11] and the shift toward a slower type 1 fiber phenotype, with evidence to suggest this may be sex dependent [33].

The decline in MU firing capacity can significantly impede an older adult's ability to carry out ADL. For instance, the maximal effort required to perform chair rises (old 80%, young 42%) and ascend (old 78%, young 54%) and descend (old 88%, young 42%) stairs is markedly higher in older adults [34]. During these tasks, muscle activation of the knee extensors and flexors were 2- and 1.6-fold higher in older vs younger adults, respectively [34]. Given there is an increased prevalence of hybrid fibers in the

old compared with the young [35], greater denervation of MUs in sarcopenic older adults [13], as well an established link between MU remodeling and frailty [20], logic would dictate that MU firing rates would be even more compromised in sarcopenic individuals, although further studies are needed to examine this in diagnosed populations using a consensus definition.

MECHANISMS OF MU REMODELING

Role of resistance and endurance exercise in preserving MU function

Animal models have provided insights into the role of physical activity in maintaining the functioning of MUs. Older rats exposed to chronic exercise (10 months of swimming, 3 times/week) mitigated the loss of motor neurons, axon diameter, and fiber density in the gastrocnemius muscle when compared with sedentary age-matched rats [36]. Another study in rats showed an 12.9% increase in fast fatigue-resistant MUs after 8 weeks of endurance training (5 times/week of treadmill running) in the same muscle group as the previous study [37]. Of note, these MUs demonstrated faster twitch duration and increased ability to potentiate force after just 2 weeks of training [37]. Investigations involving spinal cord sections of aged mice revealed microglia content can be manipulated with endurance-type exercise and prevent motor neuron loss [38]. However, how these findings translate to human neuromuscular physiology is unclear.

The only research elucidating the effects of age and exercise on the structure and function of MUs in humans has stemmed from masters athletes, who are typically described as individuals above 35 years old training and competing in intense athletic endeavors [39], although it is common to only include those aged over 60 years in this field of research. In a study from 2010 [40], the number of intact MUs in the tibialis anterior of masters runners (~65 years old) were compared with MU number (data published in 2005 [6]) in recreationally active controls (~25 years), and healthy age-matched controls (~65 years) [40]. While MU number did not differ between the young and masters runners, there was a significant decline in the number of MUs in the old (~91 MU) compared with the masters runners (~140 MU) and younger (~150 MU) cohort [40], demonstrating a benefit of chronic exercise. However, these findings could not be repeated in a subsequent study, where the same anatomical muscle was examined for MU number using similar methods in healthy young (~ 26 years), master runners (~69 years), and older adults (71 years), and found both groups of old had fewer MUs than young, with no difference between older athletes and non-athletes [19].

The most recent study on this subject differed from the previous two in that endurance (distance runners) and power (sprinters) trained masters athletes were included along with a larger muscle group, the vastus lateralis [18]. Again, there were no differences in the estimated number of MUs between healthy old and highly active masters athletes of either discipline. Comparisons showed MU potential size was greater in all older groups compared with young; however, this affect was augmented in both groups of masters athletes compared with the older controls. The authors suggested this benefit may be related to the ability of axonal sprouting and reinnervating of denervated fibers with advancing age [18], as previously described. This notion was further

supported with recent biopsy data from older female masters athletes (~80 years) who demonstrated fewer markers of denervation and greater reinnervation capacity than age-matched sedentary women (~77 years) [41].

While considering the dearth number of studies available, the abovementioned data suggest that regular endurance- or physical-based exercise can offset some of the deleterious effects of aging on MU remodeling. Notwithstanding, further studies are needed to investigate the benefits of lifelong exercise in older adults, and particularly, the effect of exercise on rescuing MU structure and function in sarcopenic populations.

FUTURE DIRECTIONS

The loss of muscle mass with age is entirely explained by the atrophy *and* loss of individual muscle fibers [14], with further loss of function explained by altered neural mechanisms [42]. The evidence presented here clearly highlights the peripheral motor system as a key component of sarcopenia; however, the issue of MU plasticity in relation to muscle fiber loss is disproportionately underexplored in comparison with that of fiber atrophy; the former should be considered as an interventional target in future research, be that lifestyle, nutritional, or pharmaceutical. Moreover, the study of the combining factors of fiber loss and fiber atrophy would yield yet greater insight into total muscle loss, inclusive of the inter-connectivity of the two processes, that is, is fiber atrophy a *cause* or a *consequence* of denervation and subsequent MU remodeling?

Longitudinal data are invaluable in answering these questions and have provided much with regards to the response of older muscle to a number of interventions; however, data relating to the structural and functional reorganization of older human MUs are less apparent. Critical among this are the effects of short-term (>6 weeks) exercise interventions; while we know those who have exercised throughout adulthood have inferred some neuromuscular benefits [18, 43], it is not clear if more acute exercise (resistance or endurance) interventions can exhibit similar outcomes. Moreover, as axonal sprouting, the compensatory process of reinnervating denervated fibers, involves the synthesis and transport of a number of proteins, nutritional and pharmaceutical interventions should also be explored.

Crucially, all of the above should be approached with a multitude of in/ex vivo; techniques, combining recent electrophysiological advances such as intramuscular and high-density electromyography (iEMG, HD-sEMG), and molecular biology markers of denervation–reinnervation such as alterations in gene expression, production of exercise-induced myokines, and fiber type morphology.

CONCLUSIONS

A healthy neuromuscular system is paramount to maintaining ambulation into old age. Any compromise to the integrity of MUs, including, apoptosis of motor neurons, denervation–reinnervation, muscle fiber atrophy and shifts in fiber type, may reduce the functional capacity of MUs and subsequently affect the force output of skeletal

muscles. If MU remodeling persists, and reaches a threshold whereby sarcopenia occurs, the risk of frailty, disability, and premature mortality is high. Evidence from masters athletes highlights the benefits of lifelong exercise in both endurance- and strength-type exercises; however, clear mechanistic evidence is lacking. Finally, future work is required to investigate the mechanisms which precede neuromuscular remodeling. Identifying these aspects may help to develop therapeutic drugs for those who cannot exercise (i.e., bed-bound, post hip fracture) or those who are not willing to engage in physical activity regimens.

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CHAPTER 5

Nutrition, Protein Turnover and Muscle Mass

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INTRODUCTION

Muscle erosion, which begins after the age of 50 years, is one of the most important factors of disability in older people, but it may also occur early in life in case of chronic disease [1]. The cumulative decline in muscle mass reaches 40% from 20 to 80 years. The magnitude of this phenomenon as a public health problem is now well established as there has been a lot of epidemiological studies and meta-analysis focusing on the decrements of strength and muscle mass with advancing age. So, sarcopenia has been recognized as a specific disease with an International Classification of Diseases (ICD) code (M62.84) [2]. The reduction in muscle mass and strength provokes an impaired mobility and increased risk for falls and fall-related fractures. In addition, muscle loss is associated with a decrease in overall physical activity levels with subsequent metabolic alterations such as obesity, insulin resistance, and a reduction in bone density in older persons. Sedentary individuals, subjects with poor protein intakes, low vitamin D and low testosterone levels, and those suffering from debilitating or inflammatory diseases are at greater risks of sarcopenia. As older person population increases around the world, the involuntary loss of muscle mass with aging will become a major health problem in years to come, from a European prevalence of 10.9 million in 2016 to 18.7 million in 2045 [3].

Sarcopenia is due predominantly to the atrophy of skeletal muscle fibers, mainly type II fibers [4]. This results in a relative elevation in type I fiber density related to a supposed preservation of muscle endurance and a reduction in muscle strength. On a metabolic point of view, muscle size, function, and composition are closely regulated by muscle protein turnover rate. Consequently, the age-related loss of

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

muscle proteins is a consequence of an imbalance between protein synthesis and degradation rates (Figure 5.1); whereas, basal muscle protein synthesis and breakdown rates appear to be unaffected by age [5, 6], the muscle protein synthetic response to the main anabolic stimuli, i.e. food intake and physical activity, appears to be blunted in older individuals [7–9]. This anabolic resistance is now considered to be a key factor contributing to progressive loss of skeletal muscle mass throughout our lifespan. Other factors such as neurodegenerative processes with loss of alpha motor neurons in the spinal column, dysregulation of anabolic hormone (insulin, growth, and sex hormones) and cytokine productions, modifications in the response to inflammatory events, inadequate nutritional intakes, and sedentarism also participate in muscle loss during aging.

The determinants of sarcopenia include likely both genetic and environmental factors, with a complex series of poorly understood interactions [10]. Likewise it is possible that epigenetic events may influence muscle fiber type evolution [11]. In fact, it is still unknown whether muscle loss of aged people is an inevitable condition of aging per se, or if illnesses, inappropriate nutrition, sedentarism, and other lifestyle habits are major causes of sarcopenia. Currently, as the pathophysiology of sarcopenia is still poorly understood and identified in clinical practice, interventions to either prevent, retard, or reverse this condition are still limited: physical exercise has a positive impact on muscle mass, function, and performance in healthy subjects aged over 60 years with very large variations in response to the dietary supplementation protocols [12–14].

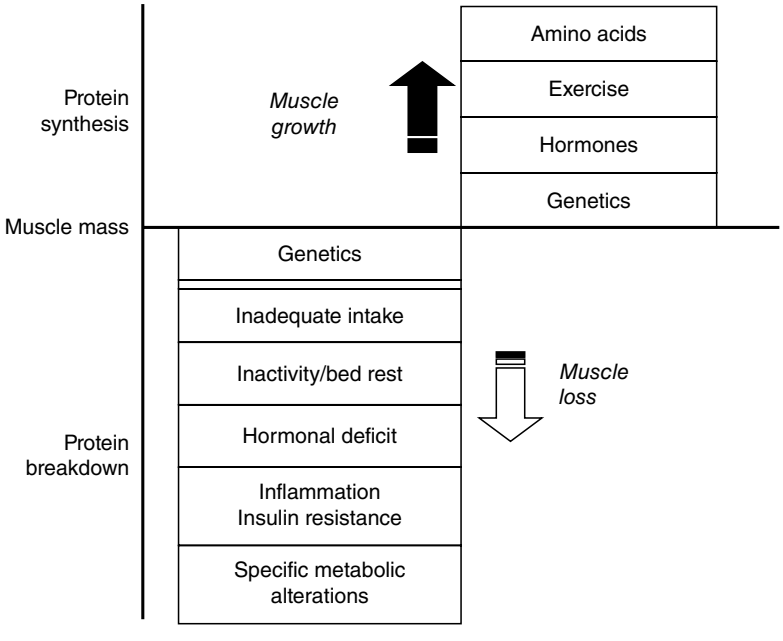

Figure 5.1 Regulation of muscle protein mass.

EVIDENCES FOR A ROLE FOR NUTRITION IN SARCOPENIA

"Anabolic resistance" of skeletal muscle to nutrition in older persons

Many authors have argued that muscle loss in older persons partly depends upon inadequate nutritional intake and/or an impaired response of skeletal muscle to nutrients, e.g. amino acids [13, 15]. By using femoral arterio-venous balance and biopsies of vastus lateralis, the rates of muscle protein synthesis and breakdown have been measured in response to oral or intravenous infusions of amino acid mixture in young and older persons [16, 17]. When amino acids are infused intravenously, a significant increase in amino acid delivery to the leg, amino acid transport, and muscle protein synthesis is reported irrespective of age [16]. So, although protein breakdown was not modified during amino acid infusion, a positive net balance of amino acids across the muscle was achieved. These data suggest that despite an age-related decline in muscle mass, muscle protein anabolism can be stimulated by high amino acid availability in older persons [16]. Muscle protein turnover and amino acid transport in healthy young and older people were also determined during an oral administration of an amino acid mixture. As already shown by Boirie et al. for leucine [18], amino acid first-pass splanchnic extraction of phenylalanine was significantly higher in older persons during ingestion of amino acids, but the delivery to the leg increased to the same extent in both groups. In addition, amino acid transport into muscle cells, muscle protein synthesis, and net balance increased similarly in both the young and older persons [17]. Thus, despite an increased splanchnic extraction, muscle protein anabolism can be stimulated by oral amino acids in older as well as in young subjects as far as the dietary protein intakes or the amount of amino acid mixture administered is high enough to induce a sufficient amino acid availability for skeletal muscles. Interestingly, muscle protein synthesis increased to the same extent after an oral intake of either balanced amino acids or essential amino acids (EAAs) only in healthy older persons [19], suggesting that nonessential amino acids may not be required to stimulate muscle protein anabolism in older adults, although specific studies on which and how much of these EAAs has to be performed. From these studies it seems that the amount of amino acids/protein intake is crucial for triggering protein synthesis. Indeed, it was demonstrated that a smaller amount of protein during meal intake was not able to stimulate muscle protein synthesis as efficiently as higher doses [20]. This concept of a limited response to feeding was already demonstrated in animal studies involving old rodents [21, 22]. When amino acids and glucose are administered either orally or intravenously during an euglycemic hyperinsulinemic clamp [8, 23] an increased amino acid delivery and transport into the muscle and a decreased muscle protein breakdown occurs in both groups. However, the stimulation of muscle protein synthesis in the young subjects was not depicted in older persons despite the elevation in plasma amino acids and an even higher insulinemia [8, 23]. More recently, an impaired capacity to increase muscle protein synthesis rates in response to protein intake was confirmed in large cohorts of healthy young and older men [9]. Interestingly, the response of whole body protein breakdown was lower in older persons in response to insulin or to the meal [24–26]. The adaptation of muscle protein anabolism to hyperaminoacidemia and hyperinsulinemia seems to be due to an impaired response to insulin as demonstrated by direct infusion into the arterial side of the muscle area [27]. When specific

muscle protein fractions within the skeletal muscle were separated, it was shown that the mitochondrial proteins were particularly affected by the age-related insulin resistance [8, 28]. Investigations from Elena Volpi's group have indicated that the blunted response of protein synthesis in healthy older persons was the result of a decreased adaptation of leg blood flow to insulin [29]. Indeed blood flow is a crucial determinant of amino acid delivery and of the protein synthesis process through amino acids transport [30]. When blood flow was restored by using nitroprussiate in older persons, muscle protein synthesis was also normalized [31]. These studies lead us to open the question of muscle sensitivity to hormones like insulin or to substrates like amino acids, suggesting that a threshold needs to be reached to induce muscle protein synthesis and that this threshold may be higher in the case of inflammation (Figure 5.2). Previous studies have shown that reducing inflammation by using anti-inflammatory agents is able to restore muscle protein synthesis in old rats [32]. It also demonstrates that substrates delivery has to be controlled by acting on the plasma availability or the blood flow. In addition, it is known that lipid intakes modulate insulin sensitivity of glucose metabolism and inflammation. In an animal study, an oleate-enriched diet decreased inflammation markers in the plasma and in the adipose tissue of old rats [33]. However, the major effect of feeding old rats a high-oleate diet was to restore muscle protein synthesis in response to amino acid and insulin.

Therefore, the lack of anabolic response to a complete meal in skeletal muscle is likely to contribute to the development, over the long term, of sarcopenia in older persons. The consecutive issue is whether nutrition, i.e. an adapted protein intake, could reverse the phenomenon.

Apart from dietary protein, other nutrients can play a key role in protein anabolism in older people. Mechanistically, these nutrients could help the anabolic effectors of

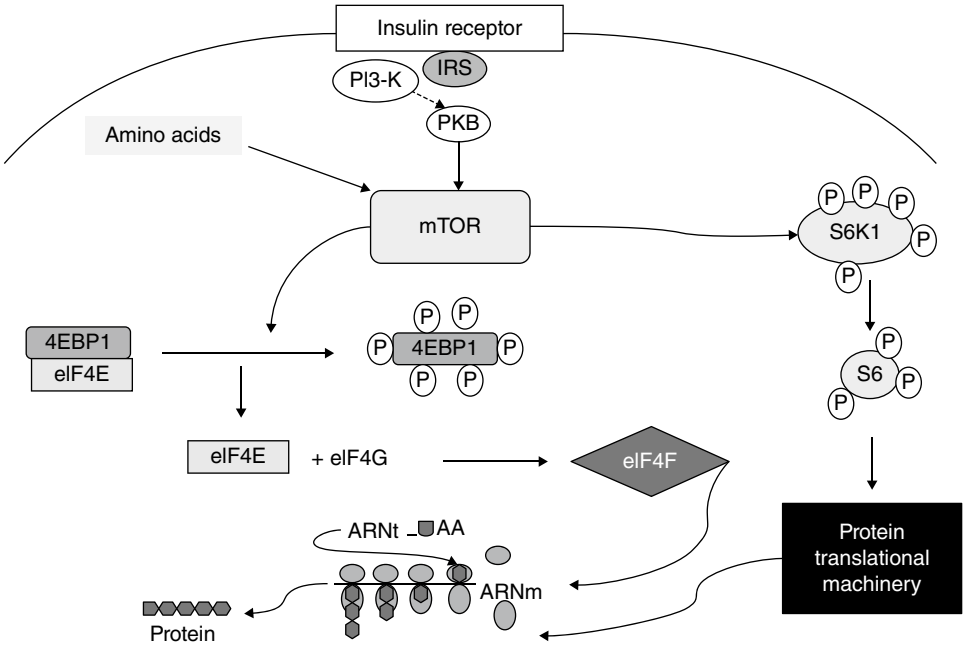

Figure 5.2 Activation of insulin signaling pathway by amino acids.

the meal to stimulate protein anabolism. For example, vitamin D is able to increase the effects of insulin and amino acids on the rate of muscle protein synthesis. Vitamin D deficiency is very common in older population living in institutions or in the community, reaching up to 90% of older adults. The clinical relevance is that hypovitaminosis D is accompanied by adverse health events. For instance, hypovitaminosis D is associated with poorer physical performance in older adults [34]. The explanation most commonly offered is based on the possible involvement of vitamin D in muscle health and function [35]. In animals, i.e. old rats, a long-term vitamin D deficiency resulted in decreased skeletal muscle mass and increased adiposity with a subsequent intramyocellular lipid depot, suggesting that vitamin D deficiency could exacerbate the effects of aging on muscle, i.e. sarcopenia [36]. The related lipotoxicity was shown to be detrimental for type II muscles at least, with a significant decrease in fasted muscle protein synthesis. Interestingly, vitamin D supplementation in old vitamin D-deficient rats prevented these changes. In addition, it was recently reported that a six-month treatment with vitamin D showed beneficial effects on appendicular muscle mass in pre-sarcopenic older men and women [37]. With regard to the cellular mechanism, as revealed in murine C2C12 skeletal myotubes, vitamin D sensitizes the Akt/mTOR-dependent pathway to the stimulating effect of leucine and insulin, resulting in a further activation of protein synthesis [38].

What is the basis of protein requirement during aging?

Protein requirement is defined as the lowest dietary protein intake able to compensate for the obligatory losses of nitrogen from the body and to preserve bodily functions [39]. The current mean dietary requirement for healthy adult men and women of all ages, was set by the 1985 joint FAO/WHO/UNU expert consultation, and estimated to be 0.6 g protein/kg/d, with a suggested safe level of intake set at 0.75 g protein/kg/d [40]. However, because of many changes in body organs functions and metabolism with age, such as body composition, insulin resistance, altered protein metabolism especially in skeletal muscle, some authors [41–44] have suggested that the utilization of dietary proteins and amino acids may differ between the young and the older adults. Consequently, the same authors, using various methodologies, i.e. nitrogen balance and tracer procedures, have tried to define the modifications of protein requirement with advancing age [41–44]. Taken together, studies based on nitrogen balance using the same formula, showed that protein requirement increases in older people, especially in aged individuals during compulsory inactivity such as bed rest [45].

It is generally difficult to establish firm recommendations for protein intake for this population, but it is safe to consider that protein requirement can be slightly increased in older people to limit loss of lean body mass and preserve a better response to any critical stress like sepsis or trauma. Recommendations for dietary protein intake in older persons have been reviewed in 2013 by the PROT-AGE study group [46, 47]. According to these experts in geriatrics and nutrition, older people should consume an average daily intake of 1.0–1.2 g/kg/d in healthy condition and 1.2–1.5 g/kg/d in disease states, respectively.

This current recommendation is reflected by data from the Health ABC study showing that despite adequate intakes of dietary protein, appendicular muscle mass (reflecting whole body muscle mass) was lost during a three-year follow-up and that the less

protein is eaten the more muscle is lost [48]. Thus, it is possible that nitrogen balance may not exactly reflect the small changes in protein metabolism that happen every day at a low scale, but cumulating for months can result in a significant decline in muscle protein mass. In this case, it is hypothesized that adaptation of older persons to protein restriction may be inadequate as already reported by Castaneda et al. [49]. This is the reason why most of the research should also focus on the incomplete recovery of muscle mass following stress also called "the catabolic crisis model" [50]. For instance in hospitalized older persons, nitrogen balance studies indicate that a daily intake of 1.3–1.6 g protein /kg/d should be applied [51].

How to improve protein retention in older persons: beyond protein quantity?

What is the response to increasing protein intakes?

Surprisingly, only a few experiments were designed to study the effect of increased or decreased protein intake in an older population. When the protein amount in the diet increases from 12 to 21% of total energy, whole body protein turnover was enhanced in older men and women [52]. Following a low protein intake (50% of usual intake), no modification of whole body protein synthesis and breakdown was noticed in a group of aged women [53]. However, whole body protein oxidation, nitrogen balance, muscle mass and function, and immune response were significantly affected in the group fed a low-protein diet [49]. Collectively, these observations highlight the importance of maintaining adequate protein intakes in older people to counteract the negative effect of aging on protein metabolism. These previous observations were repeated indicating some adaptations using muscle-specific transcript profiles [54]. Of course, the other important question is about the upper limit of protein intakes in older persons, knowing that a reduced glomerular filtration capacity is occurring. To address this issue, we demonstrated [55] that a high-protein ingestion, i.e. 3 g/kg fat-free mass/d for 10 days, was inefficient to enhance protein synthesis at whole body as well as the skeletal muscle levels in healthy older persons in the postabsorptive state. Interestingly, although a high protein diet normally enhanced glomerular filtration rate in young adults, it reduced renal function in the aged group [55]. Other data have shown long ago that the maximal adaptive capacity of ureagenesis in adults (for a mean weight of 70 kg) was about 22 mg of urea nitrogen/kg body weight/h [56]. These data correspond to a maximal protein consumption of ~3.3 g/kg/d, so that the safe upper limit for protein intake has been fixed to less than 2.2 g/kg/d by the French group on protein recommendation for older persons [57]. In addition, reports have highlighted that the amount of protein consumed per meal is important for muscle mass and function. In fact, consuming frequent meals containing 30–45 g of protein was associated with greater leg lean mass and knee extensor muscle strength [58]. The above mentioned nutritional strategy was also associated with higher appendicular lean body mass (an index of muscle mass) in both older men and women at baseline and after a two-year follow-up period [59]. Besides the quantity of protein consumed, the source of protein, the quality of protein, i.e. its digestibility and its composition in EAAs, can modulate protein metabolism and be beneficial for muscle quality.

Is there an effect of the protein source?

The consumption of different protein sources and its effect on protein metabolism has been assessed in older women [60]. One diet was composed half of animal proteins and half of vegetable proteins, whereas one-third of the proteins consumed in a second diet were from vegetable and two-thirds from animals, and inversely in a third diet. Nitrogen balance was not modified in this study, but whole body protein breakdown was not inhibited to the same extent by the meal when the protein source was from vegetables in comparison with meat [60]. This study showed that intake of high-quality proteins may be an important issue in older people, suggesting also that aging may be associated with more specific amino acid requirements especially for the EAAs. The quality of dietary proteins and its impact on muscle protein synthesis may be less important when protein intake is sufficient. In a previous study, we compared milk and soy proteins were compared for their potential impact on muscle protein synthesis using a classical steady-state approach [61]. No differences could be found between the different sources of dietary proteins despite changes in leg amino acid uptakes. However, there is not enough data in the field of aging regarding the issue of EAAs especially at low protein intakes.

Several studies have evaluated the effect of consuming plant-based proteins on muscle protein metabolism in young, adult, and old rats, pigs, and humans, compared to animal proteins, i.e., meat, milk, and its constitutive proteins (casein and whey proteins) [62]. A few of these studies have focused on the impact of plant-based foods [60], soy protein [63, 64], or wheat protein [65] ingestion on protein synthesis at the whole body or skeletal muscle level in older individuals. The majority of these studies have reported that good-quality animal proteins have a greater ability to enhance muscle protein synthesis rate and to support muscle mass than plant-based proteins. Therefore, although plant-based protein sources that are rich in fiber and micronutrients may be valuable to improve nutritional density of diet, they have lower anabolic potential than animal-based proteins. Strategies to improve these properties by increasing protein quality (i.e., their amino acid composition and digestibility) including selective breeding, fortifying plant-based proteins with specific EAAs, mixing several plant proteins, and mixing plant- with animal-based protein sources can support a healthier life, notably to prevent chronic disease, such as sarcopenia, in aging.

Optimizing protein digestion rate to improve amino acid availability?

By analogy with carbohydrates, the concept of "fast" and "slow" proteins was established according to the speed at which protein are digested and absorbed from the gut [18]. The two main milk proteins, i.e. casein and whey protein, have different metabolic fates in the intestinal tract. Whey protein, a soluble protein, is considered as a "fast" protein since the plasma appearance of its constituting amino acids after its digestion and absorption is high, fast, but transient. On the contrary, casein clots in the stomach, which delays its gastric emptying and therefore results in a slower, lower but prolonged release and absorption of amino acids. This concept was applied to study the response of postprandial protein metabolism during aging [66]. In this population, the duration and magnitude of elevated plasma amino acids are key factors

to counteract the decrease in muscle sensitivity to amino acids. Accordingly, whole body protein gain was higher after a meal containing "fast" protein, i.e. whey protein, than "slow" protein, i.e. casein, in older persons, when considering either isonitrogenous or isoleucine (as leucine is a well-known anabolic factor) meals. In addition, postprandial protein utilization by the body was significantly higher with the fast protein than with the slow one [66]. We also demonstrated that postprandial protein retention due to an increase in protein was greater in older men when a fraction of the dietary proteins is provided by soluble milk proteins, i.e. whey proteins, rather than caseins [67]. Precisely, in this study, a daily administration of a drinkable dairy product containing large amount of proteins was able to promote an increase in protein intake and postprandial protein anabolism in older men. However, protein retention was better achieved when soluble milk proteins were provided rather than caseins. Consequently, improving the quality of protein by combining digestion rate and leucine content may be a more attractive option than simply increasing the quantity of protein intake (whatever their biological value) to improve protein retention in older persons. A report from Paddon-Jones et al. showed that whey proteins were able to stimulate muscle protein synthesis rate in a group of healthy older individuals as well as the free amino acid mixture but the EAA content of the two diets was not similar [68]. We also measured the postprandial muscle protein synthesis in response to a bolus of either whey protein, casein or casein hydrolysate in healthy older persons [69]. It was clearly demonstrated that not only the speed of protein absorption, but also the leucine content were key factors for the stimulation of muscle protein anabolism. In another study, we reported that whey proteins improved postprandial muscle protein synthesis, especially mitochondrial muscle proteins and myosin, in older persons [70]. As myosin is an important protein of the contractile apparatus and mitochondrial muscle proteins are essential for energy production in order to achieve muscle contraction, these results may ultimately have positive consequences on muscle function in older men. Thus, fast-digesting proteins administrated as a bolus could limit muscle protein loss and speed up muscle recovery after a disease-related immobilization in older humans. Hence, supplementing breakfast with a vitamin D and leucine-enriched whey protein medical nutrition drink stimulated postprandial muscle protein synthesis and increased muscle mass after six weeks of intervention in healthy older adults and may therefore be a way to support muscle preservation in older people [71].

Whey protein is efficient not only on muscle mass but also on muscle function, notably after physical exercise. Aged rats supplemented with rapidly digestible soluble milk proteins for two months in association with moderate physical activity displayed an increase in spontaneous locomotor activity and improved dynamic and static gait parameters without increase in muscle mass [72]. In 60-year-old participants, significant increases in muscle mass and strength and a reduction in muscle fatigue have been observed following a four-month training coupled with the daily consumption of 10 g of soluble milk proteins [73]. In another study by Chale et al., whey protein concentrate supplementation for six months did not increase the beneficial effect of resistance training on muscle mass strength and power, and physical function in older persons [74].

These data clearly suggest that a dietary protein mixture which can be quickly digested and absorbed might be more efficient to limit protein loss during aging than a mixture yielding slower kinetics. Age-related anabolic resistance could be overcome by a better availability of dietary amino acids especially EAAs. For instance, muscle

function is improved in older persons during bed rest after EAAs supplementation [45]. Another way to optimize amino acid availability from solid foods is to improve chewing capacity since it may influence postprandial amino acid kinetics. Indeed, it has been demonstrated that chewing alterations induced by dental prosthesis could modulate postprandial AA kinetics following meat ingestion [75].

Is there a specific daily protein feeding pattern?

A "pulse" protein feeding pattern that combines meals rich and low in proteins during the day may improve protein retention in older persons [24, 76]. A "spread" diet composed of four meals, spreading daily protein intake over 12 hours was compared with a pulse diet providing 80% of daily protein intake concentrated at midday. The pulse protein pattern was more efficient at improving nitrogen balances and whole-body protein retention in aged people after 15 days. Concerning the potential explanation, it can be argued that the pulse protein diet is characterized by a couple of advantages: (i) the midday protein pulse meal may stimulate whole body synthesis by highly increasing amino acid concentration, (ii) high carbohydrate and low protein meals, i.e. at dinner, are known to limit protein loss by reducing protein breakdown rate via postprandial hyperinsulinemia, and (iii) the midday meal is combined with the daily physical activity associated with everyday life. Interestingly, the beneficial effect of the pulse protein pattern on protein accretion still persisted several days after the end of the diet [76]. The pulse protein diet also restored a significant anabolic response of skeletal muscle protein synthesis to feeding without affecting protein breakdown in old rats [77]. These studies suggest that the use of a "pulse" protein pattern increases body protein retention, in particular in skeletal muscle. This concept has been applied to malnourished and at-risk hospitalized old patients [78] and clearly the protein pulse feeding strategy improves lean mass and skeletal muscle mass in this population. Thus, this nutritional strategy represents an attractive and safe approach rather than a simple increase in protein intake in older persons subjects since it may be difficult to achieve a high amount of dietary protein in this population. Nevertheless, according to a recent study in community-dwelling older people, the protein pulse feeding does not induce any better effect on muscle strength, physical function, or quality of life than protein spread diet [79].

Improvement of protein retention by amino acids?

Animal and human studies have focused on the potential mechanism of the decreased skeletal muscle sensitivity to amino acids in older individuals. A defect in branched chain amino acid (BCAA) pathway activation may be responsible for this alteration [8]. Consequently, the alteration of muscle protein synthesis response to anabolic signals may be counteracted by nutritional strategies aiming at improving BCAA availability. For example, in vitro or in vivo high leucine administration is able to stimulate muscle protein synthesis rate in aged rodents [21, 80, 81]. In these models, leucine acts as an actual mediator able to drive specific intracellular pathways linked with the stimulation of protein translation [82]. Interestingly, when given to old rats

for 10 days, the beneficial effect of leucine supplementation persisted, indicating that a long-term utilization of leucine-enriched diets may limit muscle wasting in aged individuals [83]. In addition, these data suggest that nutritional manipulations increasing the availability of leucine into skeletal muscle, such as the utilization of a leucine-rich fast protein, i.e. whey protein, could be beneficial to improve protein retention during aging. The beneficial effect of such a diet on muscle protein synthesis in aged humans has been determined in several studies [68, 84–86]. It is concluded that leucine is able to stimulate muscle protein synthesis in the short term but may not on a longer term [87].

Special attention has also been focused on the impact of citrulline on muscle protein synthesis. This AA is not incorporated in the protein matrix during protein synthesis but it has been shown to stimulate muscle protein synthesis in malnourished animals [88]. Other amino acids, like glutamine, may be helpful to preserve skeletal muscle in older persons, especially in stressed conditions [89].

ANABOLIC RESPONSE TO PHYSICAL EXERCISE IN OLDER PERSONS

The anabolic effect of resistance exercise should be used to amplify the anabolic action of dietary proteins on muscle protein synthesis. Yarasheski et al. determined the rate of vastus lateralis muscle protein synthesis by using the in vivo incorporation of intravenously infused ^{13}C-leucine into mixed muscle protein in both young and older men before and at the end of two weeks of resistance exercise training [90]. Although the muscle fractional synthesis rate was lower in older persons before training, it increased to reach a comparable rate irrespective of the age of the subjects after two weeks of exercise. In contrast to these results, Welle et al. found no improvement in myofibrillar protein synthesis rate in either young or old men who completed 12 weeks of resistance training [91]. The discrepancy between these observations could be explained by the different experimental designs used in these studies. The training stimulus may not have been powerful enough to affect protein turnover in the investigation by Welle et al. [91]. In addition, the timings of muscle protein synthesis determination relative to the last bout of exercise were also different in these investigations. Further, other measurements of synthesis rate of individual muscle proteins showed that a two-week weightlifting program increased MHC synthesis rate in 23–32 and 78- to 84-year-old subjects [92]. However, the protein synthesis rate of actin was increased after exercise only in the younger group, showing that the anabolic effect of resistance exercise in older persons is protein-dependent. Age-related lowering of the transcript levels of MHC IIa and IIx is not reversed by three months of resistance exercise training [93], whereas exercise resulted in a higher synthesis rate of MHC in association with an increase in MHC I isoform transcript levels [94]. Other results showed that the stimulation of MHC synthesis rate by resistance exercise is mediated by more efficient translation of mRNA [95]. Furthermore, the effect of a 16 weeks endurance exercise session on MHC isoform protein composition and mRNA abundance was tested [96]. The regulation of MHC isoform transcripts remained robust in older muscle after endurance exercise, but this did not result in corresponding changes in MHC protein expression [96].

Few data are currently available concerning the rate of muscle protein breakdown after exercise in older people. A session of 45 minutes of eccentric exercise produced a similar increase in whole body protein breakdown irrespective of the age of the subjects [97]. However, myofibrillar proteolysis, based on 3-methylhistidine (3-MH)/creatinine measurements, did not increase until 10 days post-exercise in the young group but remained high through the same period in the older men [97]. In addition, the urinary 3-MH-to-creatinine ratio was not affected at the end of two weeks of resistance exercise in either the younger or older volunteers [92].

Moreover, the increasing frequency of brief bouts of muscle disuse often experienced with advancing age (e.g. owing to being hospitalized, injured, or confined to the home due to adverse weather conditions) has been postulated as a contributing factor to the sarcopenic process [50]. It has been illustrated in young adults in which just five days of muscle disuse impairs the ability of skeletal muscle tissue to utilize dietary protein-derived amino acids for de novo muscle protein synthesis [9]. In contrast, resistance-type exercise enhances the anabolic response of skeletal muscle to nutrients, improving the capacity of skeletal muscle tissue to use dietary protein-derived amino acids for de novo muscle protein synthesis in young and older adults [98].

From this section, it may be concluded that aging muscle still responds to exercise but there are no clear-cut recommendations for any specific type of physical activity.

COMBINATION OF NUTRITIONAL AND TRAINING STRATEGIES

Most of the studies failed to show any beneficial effect of nutritional supplementations on muscle anabolic properties in exercising older persons. For example, Welle et al. reported that high-protein meals (0.6–2.4 g protein/kg/d) did not enhance the myofibrillar protein synthesis rate in vastus lateralis muscle following three sessions of resistance exercise in 62- to 75-year-old men and women [99]. In very old frail people (87 years old), high-intensity resistance exercise training with or without concomitant multinutrient supplementation had the same efficiency on muscle weakness reversibility [99]. Of note, reports showed that ingestion of oral pre- or post-exercise amino acid supplements can improve net muscle protein balance in young subjects [100, 101]. The response to amino acid intake with concomitant exercise is dependent upon the composition and amount, as well as the pattern and timing of amino acid ingestion in relation to the performance of exercise [102]. The response of net muscle protein synthesis to consumption of an EAA–carbohydrate supplement solution immediately before resistance exercise is greater than when the solution is consumed after exercise, primarily because of an increase in muscle protein synthesis as a result of increased delivery of amino acids to the leg [103]. Whether amino acid and carbohydrate intakes immediately before or after resistance exercise can enhance the anabolic effect of training in older individuals as shown in the younger group is still controversial. It was shown that dietary protein digestion and absorption kinetics were not impaired after exercise at an older age. Moreover, exercising before protein intake allows for a greater use of dietary protein-derived amino acids for de novo muscle protein synthesis in both young and older men, likely contributing to improve muscle function [98]. We investigated changes in muscle strength and fatigue of 60-year-old men following a 16-week

multicomponent exercise training program combined with whey proteins or total milk proteins supplementation [73]. We observed significant increases in muscle mass and strength and a reduction in muscle fatigue following training coupled with the daily consumption of 10 g of whey proteins, as compared with total milk proteins, in these subjects. Obviously, it is most important to optimize the anabolic response to resistance exercise in these participants with the aim of preserving muscle mass and function. As people are considered to prefer well-known nutrient products that are accessible and palatable, the recommendation of exercise-timed soluble milk protein consumption appears to be especially well suited to older individuals involved in training programs.

CONCLUDING REMARKS AND FUTURE DIRECTION

Loss of muscle mass involves a number of underlying mechanisms including intrinsic changes in the muscle and central nervous system, humoral, and lifestyle factors. However, nutrition is the key regulator of muscle maintenance through its numerous biological actions on protein synthesis machinery. Many data demonstrate that nutritional means to counter sarcopenia exist. These strategies aim at improving amino acid availability since postprandial elevation of plasma AA is the main determinant of muscle anabolism. Other metabolic aspects can modulate sensitivity of skeletal muscle to nutrients, like the quality and the pattern of daily protein intakes rather than simply increasing the amount of proteins which should be cautiously used in an aged population with a potentially reduced kidney function. Inactivity also induces anabolic resistance and regular exercise could reverse this phenomenon. The combination of specific nutritional and physical activity programs may have a significant effect on muscle protein balance in young subjects. This strategy has to be tested in older people. Furthermore, the possibility of therapeutic approach to enhance protein synthesis and to limit sarcopenia has been emphasized by studies in the care management of heart failure [104], hypertension [105, 106] or COPD [107]. Other approaches using angiotensin-converting enzyme inhibitors have resulted in a reduction of strength and walking speed decline in comparison with other antihypertensive agents [108]. This evidence of pharmacological approaches is able to help to reduce age-related weakness and dependence. So, interventional strategies using nutritional advices, drugs, and/or exercise need to be studied in large groups of subjects before being applied to the general public. The ultimate objective of such investigations is to restore mobility and to limit physical dependence of older people in order to improve their quality of life.

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CHAPTER 6

Recognizing Persons at Risk for Sarcopenia

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Sarcopenia is recognized as a disease with its own International Classification of Disease. However, sarcopenia is rarely recognized or diagnosed by primary care health professionals. The average general practitioner has between 7 and 10 minutes for each patient visit. To make the diagnosis of sarcopenia requires either measuring grip strength or walking speed together with a measure of lean mass. For a primary care clinician to consider making a referral for the diagnosis and treatment for sarcopenia they need to recognize that there is a likelihood that the person may be sarcopenic. This may be particularly difficult in persons with sarcopenic obesity [1]. For this reason there is a need for a rapid screening test for sarcopenia. The need for such a test is particularly important as persons with sarcopenia are at high risk for deleterious outcomes such as falls, hip fractures, disability, hospitalizations, nursing home admissions, and mortality [2, 3]. Lack of knowledge of the average clinician of the existence of sarcopenia as a disease further increases the likelihood of the diagnosis not being considered [4].

SARC-F

In 2013, SARC-F was developed by the group at Saint Louis University to provide a rapid screening test to allow the recognition of the possible diagnosis of sarcopenia [5] (Table 6.1). This screener was developed with the recognition that functional deterioration of activities requiring muscle activity is the hallmark of sarcopenia. The screener can either be self-administered or administered by the person responsible for rooming the patient. It takes less than 30 seconds to complete.

The original validation of SARC-F was completed in 230 persons in China [6]. SARC-F was correlated with impaired physical performance and grip strength as well as hospitalizations. Woo et al. [7, 8] compared SARC-F to working definitions for sarcopenia (Asian,

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Table 6.1 SARC-F screen for sarcopenia.

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 pounds?	None = 0 Some = 1 A lot or unable = 2
Assistance in walking	How much difficulty do you have walking across a room?	None = 0 Some = 1 A lot, use aids, or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None = 0 Some = 1 A lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None = 0 Some = 1 A lot or unable = 2
Falls	How many times have you fallen in the past year?	None = 0 1–3 falls = 1 ≥4 falls = 2

European, and International) in 4000 community dwellers in Hong Kong. SARC-F had good specificity and poor sensitivity. Equivalent predictive ability of functional measures at four years was compared to working definitions. It also predicted mortality.

Malmstrom et al. [9] evaluated SARC-F in the St. Louis African American Health Study (AAH), the Baltimore Longitudinal Study of Aging (BLSA) and in the National Health and Nutrition Examination Survey. They found that SARC-F had internal consistency and good criterion and construct validity. In all three groups it had a good correlation with functional performance and mortality at six years. In the BLSA it predicted mortality.

Tanaka et al. [10] studied a group of patients with cardiovascular disease. They found that an elevated SARC-F score was associated with lower handgrip and leg strength, respiratory muscle strength, poorer standing balance, slow gait speed and six-minute walking distance, and lower short physical performance battery (SPPB) score.

A meta-analysis of seven studies including 12 800 subjects showed that SARC-F has a high specificity but poor sensitivity, suggesting it is a reasonable screening test for sarcopenia [11]. SARC-F has been validated in China [6], Hong Kong [7, 8, 12], United States [9, 13], Japan [10, 14–17], Taiwan [18], Mexico [19], Germany [20], France [21], Singapore [22], Korea [23], Austria [24], Turkey [25, 26], Spain [16, 27], and Belgium [28] (Table 6.2).

Woo et al. [30] reported that a three-item scale (strength, ability to climb stairs, and need for assistance in walking) had a better diagnostic area under the curve and better predictive value of bad outcomes compared with the five-item SARC-F. Lim et al. [31] studied 200 participants in Singapore and felt that the shorter version was not superior to the full SARC-F. They did suggest that the falls item was not an important factor in making the diagnosis. Yang et al. [32] found that the three-item questionnaire had a worse area under the curve than the SARC-F.

Barbosa-Silva et al. [33] found that calf circumference together with SARC-F had greatly improved sensitivity when compared with SARC-F alone with the European Working Group on Sarcopenia in Older People (EWGSOP) as a gold standard.

Table 6.2 Validations of SARC-F.

Author	Country	*n*	Outcomes
Cao et al. [6]	China	230	Predicts poor function, grip strength, and hospitalization
Woo et al. [7, 8]	Hong Kong	4000	Good specificity compared with Asian and European working definitions – predictive of function (gait speed, grip strength, and repeated chair stand) at 4 years and mortality at 10 years
Malmstrom [9]	United States: St. Louis	998	Instrumental activities of daily living (IADL) deficits, slower chair stands, lower grip strength, lower short physical performance battery scores (cross-sectionally) and predicted poor IADL deficits, poor physical performance and 6-year hospitalization
	United States: Baltimore	1053	IADL deficits, lower grip strength at baseline, and mortality at two-month follow-up
	United States: NHANES	3288	Slower walk speed, knee extensor strength at baseline, and mortality at 27-month follow-up
Tanaka [10]	Japan	235	Lower grip, leg and respiratory muscle strength, poorer gait speed and walking distance, and poorer balance and SPPB
Wu [18]	Taiwan	670	Low grip strength and lean mass, poor quality of life, and hospitalization and mortality
Parra-Rodriguez [19]	Mexico	487	Reliability. ADL deficits, low gait speed, poor grip strength, lower SPPB
Ida [14]	Japan	207	Specificity (85.8% men and 72.4% women); sensitivity (14.8 and 33.3%) to EWGOS
Kemmler [20]	Germany	74	Diagnostic overlap equivalent for SARC-F to EWGSOP, FNIH, IWGS
Rolland [21]	France	504	Specificity 85% versus FNIH; lower physical performance
Tan [22]	Singapore	115	More than two hospitalization in a year; higher rate of falls
Kotiarczyk [13]	United States	141	Specificity versus EWGSOP 78.7% and versus FNIH 81.1%, low sensitivity
Kim [23]	Korea	1222	High specificity versus Asian sarcopenia. Poor grip strength, slow walking speed, lower quality of life, poor cognitive performance
Ida [15]	Japan	140	High specificity (90.89–95.5%) and predictive value (81.5%) in chronic liver disease
Peball [24]	Austria	434	High prevalence in Parkinson disease compared with the controls
Bahat [25]	Turkey	207	High specificity and low sensitivity versus EWGSOP, FNIH, IWGS, Society of sarcopenia, cachexia and wasting disorders (SCWD). High specificity for muscle mass, handgrip, SPPB, and sit to stand

(*Continued*)

Table 6.2 (Continued)

Author	Country	*n*	Outcomes
Su [12]	Hong Kong	4000	SARC-F with FRAX has an increased ability to predict hip fracture
Ida [16]	Japan	318	SARC-F associated with sleep disorder
Requena-Calleja [29]	Spain	596	SARC-F increases mortality in persons with atrial fibrillation
Nozoe [17]	Japan	183	SARC-F predicts severe stroke
Sanchez-Rodriguez [27]	Spain	208	SARC-F is useful to identify sarcopenic patients in outpatients
Tuna [26]	Turkey	56	Correlates with poor sleep quality
Hajaoui [28]	Belgium	306	Specificity of 87.1% and sensitivity of 36.0% compared with EWGSOP1

ADL, activities of daily living; EWGSOP, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health; IWGS, International Working Group on Sarcopenia; SPPB, short physical performance battery.

Bahat et al. [34] found that SARC-F plus calf circumference improved specificity but not sensitivity when compared with SARC-F. In 120 participants in Indonesia, SARC-F plus calf circumference had good diagnostic performance for sarcopenia [35]. Mo et al. [36] in a meta-analysis found that SARC-CalF has excellent accuracy with moderate sensitivity as a diagnostic tool for sarcopenia.

Overall, these studies support the concept that SARC-F or SARC-CalF is a good screening tool for sarcopenia. Adding age and body mass index may further enhance its accuracy [37].

OTHER SCREENING TESTS FOR SARCOPENIA

The short portable sarcopenia measure (SPSM) consists of lean muscle mass by bioimpedance, grip strength adjusted for height and five chair stands [38]. The SPSM compares well to DEXA measurements of lean mass. It is more sensitivity but no more specific than the SARC-F [5].

The Mini-Sarcopenic Risk Assessment (MRSA-5) (age, activity, food intake, weight loss, and hospital admission) has good sensitivity but poorer specificity. The three-item MRSA has similar diagnostic accuracy to the SARC-F [39, 40], but not as good as the SARC-CalF [32].

Age, grip strength, and calf circumference in combination has good specificity and sensitivity for sarcopenia [41]. However, at this stage there is only one study.

CONCLUSION

Both SARC-F and SARC-CalF have been shown to be excellent, quick-to-use screening tools for sarcopenia. SARC-F is now recommended for screening by the European Working Group on Sarcopenia in Older People 2 [42], the International Conference on

Sarcopenia and Frailty Research [43], and the Society of Sarcopenia, Cachexia and Wasting Disorders [44]. This rapid screen should be done yearly as part of the Annual Medicare Wellness examination in the United States [45] and included in the primary care physician's armamentarium to screen all persons 65 years or older at least once a year. Persons who screen positive should be encouraged to become involved in an exercise program.

DISCLOSURES

The author declares there are no conflicts.

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CHAPTER 7

Adverse Outcomes and Functional Consequences of Sarcopenia

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INTRODUCTION

Since the publication of the first edition of this book, major changes have occurred in the definition of sarcopenia, to include some are the consequences of sarcopenia previously described in the chapter of adverse outcomes and functional consequences.

This chapter provides a summary of the current state of research on these topics, to cover mortality, functional decline, rate of falls, fracture incidence, quality of life, metabolic consequences, and use of health services. The chapter will also cover the term "secondary sarcopenia" associated with disuse, malnutrition, and inflammation.

MORTALITY

Systematic reviews on prospective studies of people aged 60 years and over as well as individual population studies have shown that sarcopenia increases the odds ratio of mortality between 1.6 and 3.6 [1–3], and that the effect was higher in people aged 79 years or older [1]. Individual constituent definition of sarcopenia, such as grip strength, and body composition among community-living older people aged 65 years and over also predicted all-cause mortality [4, 5], while grip strength and other physical performance measures in mid-life predicted late-life mortality [6–8].

With respect to secondary sarcopenia in the clinical setting, other than increased mortality (with odds ratio much higher than those for community-living older people), depleted muscle mass is also associated with infection, increased duration of mechanical ventilation, longer hospitalization, readmission rates, and rehabilitation needs [9]. Worse outcomes are observed among patients with liver failure.

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MOBILITY LIMITATIONS

Functional decline, or mobility limitations, initially classified as one of the adverse consequences, has been incorporated into the definition and diagnosis of sarcopenia. For example, a prospective study of Hong Kong Chinese older people proposed that sarcopenia may be defined in terms of risk of physical limitations [10] and other adverse outcomes [11], and anthropometric cut points based on incident mobility and physical limitation have been proposed [12]. Similarly, the Foundation of National Institute of Health (FNIH) also proposed a data-driven approach in deriving cut points that is associated with slow walking speed (<0.8 m/s) [13]. Other consensus panel definitions used a combination of muscle mass, muscle strength, and physical performance measures in the diagnosis of sarcopenia [14, 15]. Systematic reviews show that sarcopenia is associated with increased odds ratio of functional decline between 2.5 and 3.0 [1, 3].

FALLS AND FRACTURES

Sarcopenia has been reported to increase the rate of falls in two community-living populations, with an hazard ratio (HR) between 2.38 and 3.23 [16, 17]. Reduced strength and poor balance would contribute directly to occurrence of falls. As expected, there is also an association between sarcopenia and fractures, not only mediated by occurrence of falls, but also through the hormonal interaction between muscle and bone, with a common factor giving rise to both muscle weakness and low bone mineral density, giving rise to the term osteosarcopenia [18]. The use of sarcopenia screening tool SARC-F [19] combined with the fracture risk prediction tool FRAX improves fracture risk prediction in older Chinese men aged 65 years and over at 10 years [20] and in both men and women at 14 years [21].

QUALITY OF LIFE

Quality of life represents an important patient-related outcome measure in the management of sarcopenia. Generic quality-of-life instruments such as the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) have been widely used, and association examined in relationship to individual components included in the diagnosis of sarcopenia. A decline in these components is associated with poorer physical component of health-related quality of life. Physical, psychological, and social factors may all contribute to poorer quality of life [22]. Specific tools for musculoskeletal health have also been proposed, including one for sarcopenia [23] (SarQol).

METABOLIC CONSEQUENCES

Skeletal muscle mass accounts for 40–50% of lean body mass in adults, and therefore the majority of whole-body postprandial glucose disposal. Muscle mass is lost with age, leading to insulin resistance at the tissue level, with an adverse effect on glucose

and energy homeostasis. The term "anabolic resistance" has been used to describe the reduced muscle protein synthesis in response to nutrients and the reduced insulin-mediated suppression of proteolysis that occurs with sarcopenia [24]. It is known that people with type 2 diabetes mellitus (T2D) have a higher prevalence of sarcopenia, resulting in mobility limitations [25]. Increase in body fat in T2D may be one of the factors contributing to muscle dysfunction, by direct muscle fat infiltration or indirectly through upregulation of inflammatory cytokines. The coexistence of sarcopenia and obesity results in adverse cardiometabolic as well as functional outcomes [26, 27], although it is uncertain whether the process is sarcopenia leading to obesity or obesity leading to sarcopenia, and the term obese sarcopenia instead of sarcopenia obesity has been proposed to reflect the pathological sequence [28]. Current literature continues to use the term sarcopenic obesity, although there is no universal consensus definition to capture both conditions. Nevertheless, composite measures of both total body fat as well as sarcopenia measures predict mortality, incident mobility limitations, as well as cardiovascular diseases. However, the threshold values are different for different outcomes [29–31].

SECONDARY SARCOPENIA

The term secondary sarcopenia refers to loss of muscle mass as a result of disuse (for example, stroke or prolonged bedrest), and/or the presence of chronic diseases with varying degrees of upregulation of inflammatory cytokines, but distinct from the condition of cachexia. For example, the prevalence of sarcopenia in patients with heart failure (HF) is 20% higher compared with healthy subjects of the same age, and not confined only to the older age groups. There is increased catabolic stress in the skeletal muscle of HF patients, presenting clinical as reduced exercise tolerance, ventilator inefficiency, as well as inefficient chronotropic response. Malnutrition as a result of anorexia caused by inflammatory cytokines also aggravates muscle loss. Both malnutrition and sarcopenia are commonly observed among patients undergoing rehabilitation, the prevalence of both conditions ranging from 40 to 67% [32].

The relationship between secondary sarcopenia and cachexia is not distinct and may be viewed as a transition between the two states. While muscle loss occurs in cachexia, the underlying disease state plays a prominent role with its associated anorexia, weight loss, fatigue, and reduced physical activity. Anorexia, inflammation, insulin resistance, and increased muscle breakdown are more marked in cachexia, while inflammatory cytokines such as interleukin-6 and tumor necrosis factor are highly elevated compared with sarcopenia [33].

CONTROVERSIES

Recently, there are ongoing discussions examining the role of functional outcomes of sarcopenia and muscle mass in the definition of sarcopenia itself. If the purpose of diagnosis of sarcopenia is to predict adverse outcomes so that interventional measures may be implemented (non-pharmacological or pharmacological), then measures that

actually predict adverse outcomes should be used. A community study of older adults with a mean age of 81.2 years showed that strength measures are better than muscle mass measures in predicting health-related outcomes in older people [34]. Similarly, the Sarcopenia Definitions and Outcomes Project (supported by the National Institute on Aging and the Foundation for the National Institute of Health United States) analyzed pooled data from 10 prospective studies of community-living older people in United States, Sweden, Amsterdam, and Hong Kong concluded that lean mass measured by dual energy x-ray absorptiometry was not predictive of physical function, falls, or mortality, whereas more accurate estimation of muscle mass by isotope dilution method (D_3Cr) was predictive (unpublished data presented at the SDOC conference in Boston in November 2018). However, use of this method would be difficult in community and clinical settings. Furthermore, some measures currently proposed to be incorporated into the definition of sarcopenia such as grip strength, may actually influence outcomes not via muscle but through neurological pathways that represent brain health [35].

CONCLUSION

Multiple pathways lead to age-related muscle loss, which include poor nutrition, physical inactivity, oxidative damage to mitochondrial energy metabolism, upregulation of inflammatory cytokines, hormone resistance syndromes, protein anabolic failure, neurodegeneration, and changes in muscle fiber structure and the neuromuscular junction. Sarcopenia in turn leads to reduction in VO2 peak, reduced physical activity, mobility limitations, and consequent downstream adverse outcomes such as falls and fractures, disability and dependency, poor quality of life, use of hospital services, as well as mortality, contributing to a downward spiral of decline.

Strategies for early detection and intervention would be of public health and clinical importance.

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CHAPTER 8

A Lifecourse Approach to Sarcopenia

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INTRODUCTION

Sarcopenia is the loss of skeletal muscle mass and function with age. It is a common condition and its association with serious future disability, morbidity, and mortality, as well as its significant health-care costs, are well documented. The last decade has seen a rapid expansion in research activity related to sarcopenia [1]. An area of growing interest is taking a lifecourse approach to sarcopenia, for two main reasons. First, there is growing awareness that sarcopenia does not solely affect older people and may also occur at younger ages in the setting of long-term conditions (LTCs) [2]. Secondly, a lifecourse approach recognizes that a range of exposures from conception onwards may have important effects on the development of sarcopenia [3].

Factors at older ages associated with sarcopenia have been extensively described. However, there remains considerable unexplained variation in skeletal muscle between older individuals which might be explained in part by the observation that muscle mass and function in later life reflect not only the rate of loss but also the peak attained earlier in life. In terms of etiology, a lifecourse approach includes identifying the determinants of peak muscle mass and function as well as the determinants of loss. Birth and other lifecourse cohorts are a key resource for such studies. These cohorts can also be used to investigate the adverse health consequences of sarcopenia. A lifecourse approach to sarcopenia therefore has important clinical relevance regarding the prediction, prevention, and development of novel therapeutic agents for sarcopenia.

This chapter will provide background to the lifecourse approach and describe the value of lifecourse cohorts, including those beginning at birth. It will present the epidemiological evidence linking sarcopenia to a range of adverse health consequences. Then, with regard to etiology, it will provide an overview of lifecourse influences including early nutrition and growth, lifestyle risk factors, and current understanding

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

about underlying cellular and molecular mechanisms. The final section will summarize how a lifecourse approach to sarcopenia is of relevance to clinical practice.

A LIFECOURSE APPROACH

The impetus for a lifecourse approach has come from a series of epidemiological studies demonstrating the relationship between small size at birth and an increased risk of age-related disease in later life, including a landmark study showing that differences in rates of death from coronary heart disease in different parts of England and Wales paralleled previous differences in death rates among newborn babies [4]. This led to the Barker developmental origins of health and disease hypothesis that adverse environmental influences in utero and during infancy, permanently change the body's structure, physiology, and metabolism, increasing susceptibility to disease in later life. This link between early environmental influences, growth and development, and long-term consequences for human health, aging and disease is called programming; a process whereby a stimulus or insult acting at a critical period of development has lasting or lifelong significance.

In mammals, an adverse intrauterine environment, including suboptimal nutrition, results in an integrated range of responses, suggesting the involvement of a few key regulatory genes that reset the developmental trajectory in expectation of poor postnatal conditions. A mismatch between the anticipated and the actual mature environment exposes the organism to risks of adverse consequences. For humans, it is suggested that prediction is inaccurate for many individuals because of changes in the postnatal environment toward energy-dense nutrition and low energy expenditure, contributing to the epidemic of age-related disease [5].

The lifecourse approach has subsequently been extended beyond prenatal and infant life to encompass influences through childhood and adolescence, as well as those operating subsequently in adult life. This lifecourse approach uses a multidisciplinary framework to understand the importance of time and timing in inter-relationships between exposures and outcomes at the individual and population levels [6]. This approach is helpful for the testing of different lifecourse hypotheses, such as whether risk factors have cumulative adverse effects across life or whether they exert their main effects during particular stage(s) of the lifecourse.

USE OF COHORT STUDIES ACROSS THE LIFECOURSE

Grip strength is a simple measure of muscle strength that is recommended as a first stage in the assessment of sarcopenia. It has been incorporated into numerous cohort studies spanning all stages of the lifecourse. We previously used 12 British cohort and cross-sectional studies to produce the first set of lifecourse normative data for grip strength, spanning ages 4–90 years, as shown in Figure 8.1. These data suggested three overall periods: growth to peak grip strength in early adult life, broad maintenance in midlife, and then decline [7]. This highlights how the development of

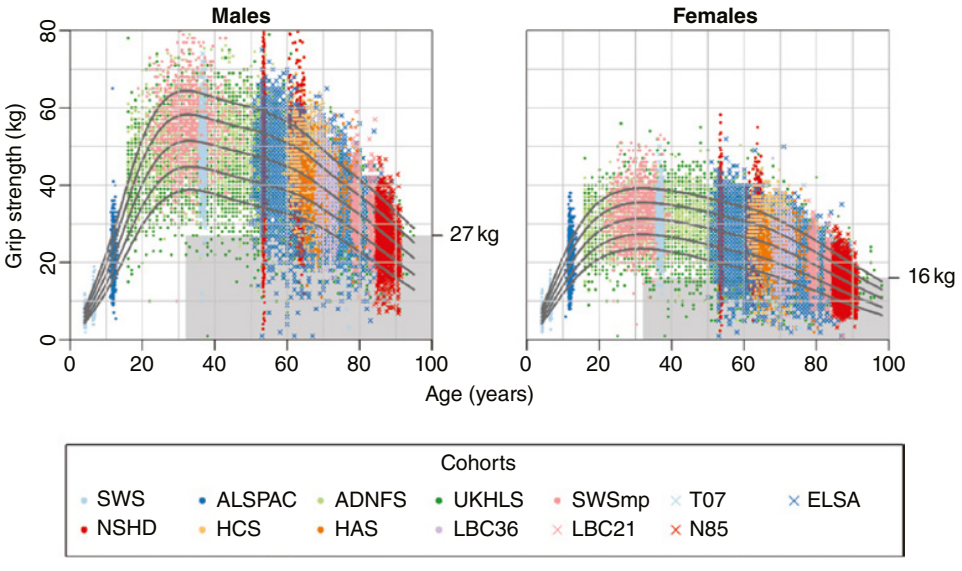

Figure 8.1 Lifecourse normative data for grip strength from 12 British studies. Centiles shown are 10th, 25th, 50th, 75th, and 90th. Cut points based on a *T*-score ≤ −2.5 are shown for males and females (≤27 and 16 kg, respectively). ADNFS = Allied Dunbar National Fitness Survey; ALSPAC = Avon Longitudinal Study of Parents and Children; ELSA = English Longitudinal Study of Ageing; HAS = Hertfordshire Ageing Study; HCS = Hertfordshire Cohort Study; LBC1921 and LBC1936 = Lothian Birth Cohorts of 1921 and 1936; N85 = Newcastle 85+ Study; NSHD = Medical Research Council National Survey of Health and Development; SWS = Southampton Women's Survey; SWSmp = mothers and their partners from the SWS; T-07 = West of Scotland Twenty-07 Study; UKHLS = Understanding Society: the UK Household Panel Study. *Source*: From Dodds et al. [7]. Public Domain.

sarcopenia may result from both (i) lower peak muscle mass and function in early adult life and (ii) more rapid decline in later life. Birth and other lifecourse cohorts can be used to explore the determinants of both these processes. In such studies, muscle mass and function are typically analyzed as continuous variables. This is especially relevant at younger ages where only a small proportion of the population fall below cut points used in the diagnosis of sarcopenia (as highlighted for grip strength in Figure 8.1).

Birth cohort studies

Birth cohorts are key to studies involving a lifecourse approach. They include retrospective and prospective longitudinal study designs and can encompass the collection of information on individuals from birth to death as well as information across generations. For example, some birth cohorts include description of individuals during gestation as well as description of their mothers prior to and during pregnancy. The use of prospective and retrospective birth cohorts allows influences on skeletal muscle growth, development, and aging to be studied across the lifecourse.

Retrospective birth cohorts involve the use of historical records of information from early in life. The Barker hypothesis was established with the use of data from the county of Hertfordshire, United Kingdom, where a large set of historical records were discovered. In the early twentieth century, there was widespread concern about the physical deterioration of the British people. In 1911, Ethel Margaret Burnside (Hertfordshire's first "chief health visitor and lady inspector of midwives") assembled a team of midwives and nurses charged with improving the health of children in Hertfordshire. A midwife attended women during childbirth and recorded the birth weight of their offspring on a card. A health visitor subsequently went to each baby's home throughout its infancy and recorded its illnesses, development, and method of infant feeding. The baby was then weighed again at one year of age. This information was transcribed into ledgers at the Hertfordshire county office. The ledgers cover all births in Hertfordshire from 1911 until the National Health Service was formed in 1948.

The Hertfordshire Ageing Study was established in 1995 to examine the developmental origins of aging, utilizing the historical records of early growth and collecting longitudinal data on aging phenotypes across a range of body systems in men and women born in 1920–1930 [8]. Subsequently, the larger Hertfordshire Cohort Study (HCS) was set up to evaluate the combined effects of genetic and early environmental influences as well as adult diet and lifestyle on health, aging, and disease in people born in 1931–1939 [9]. Both studies have included characterization of skeletal muscle in older people allowing a lifecourse approach to the study of sarcopenia.

The United Kingdom also has a number of national prospective birth cohorts with younger individuals. The Medical Research Council National Survey of Health and Development (NSHD) is a socially stratified sample of all births that occurred during one week in March 1946 across England, Scotland, and Wales. This cohort of 5362 men and women has been followed up prospectively across life from birth onwards, the most recent data collection being completed with the participants aged 69 years [10].

A more recent development in prospective birth cohorts is the description of individuals during gestation as well as description of the mothers prior to conception. An excellent example of this is the Southampton Women's Survey (SWS) which has recruited over 12 500 women aged 20–34 years living in the city of Southampton, United Kingdom, and interviewed them to assess health, body composition, lifestyle, and diet [11]. They have been followed in subsequent pregnancies and their offspring were followed through childhood, with the aim of prospectively identifying the influence of the pre-conceptional and antenatal environment on the growth and development of the fetus, infant, and child. The Avon Longitudinal Study of Parents and Children is another major prospective population study including over 11 000 infants followed through pregnancy and born at term in 1991–1992, although data on maternal characteristics prior to conception is not available in this study [12].

Other lifecourse cohorts

Birth cohorts are complemented by cohorts with recruitment later in the lifecourse which can provide useful information on representative samples of older people. An example is the English Longitudinal Study of Ageing, a cohort of adults aged 50+ when first assessed in 2002–2003 with additional refreshment samples recruited at

later study waves [13, 14]. We recently used data from this cohort to show a slight secular decline in the mean grip strength of older English adults between 2006 and 2012–2013 [15]. Such a decline, if present in the wider population, is important given the consequences of sarcopenia described in the next section.

LIFECOURSE CONSEQUENCES OF SARCOPENIA

Sarcopenia and its components have a range of adverse consequences, most strikingly increased all-cause mortality rates but also disability, reduced quality of life, LTCs and hospitalization. This section describes some of the evidence for each of these consequences.

All-cause mortality rates

We previously showed in community-dwelling men of mean age 75 years that weaker grip strength was associated with mortality from all-causes, from cardiovascular disease, and from cancer over 24 years of follow-up [16]. This study was included alongside 13 others (for a total of 53 476 participants) in a systematic review and meta-analysis showing that women and men with the weakest quarter of grip strength were at over one-and-a-half times the risk of death during the follow-up compared with those in the highest quarter (summary hazard ratio 1.67 [95% CI: 1.45, 1.93], including adjustments for age, sex, and body size) [17]. Most of these studies had a mean age above 60 years at baseline.

Subsequent research has extended the grip–mortality relationship to younger ages, such as the finding that Swedish male conscripts aged 16–19 years with weaker grip strength are at increased risk of death in young adulthood [18]. There is also evidence that more rapid loss of grip strength over time [19] and inability to complete a grip strength test [20] are associated with an increased risk of death. Lower levels of physical performance using tests such as gait speed, chair rise, and standing balance have also been linked to mortality [17]. In contrast, there is no clear evidence of a relationship between low muscle mass and mortality [21, 22].

Disability

The components of sarcopenia have a similar relationship with disability as they do for all-cause mortality, namely that poor muscle function shows a stronger relationship than does reduced muscle mass [23]. Weak grip strength and measures of physical performance such as walking speed have been associated with incident or progressive disability in 22 studies as summarized in a systematic review [24]. Such studies have typically used baseline assessments at older ages with relatively short periods of follow-up.

We recently used data from the NSHD to investigate if worse performance in grip strength, chair rise, and standing balance time at age 53 were associated with the development of mobility and/or personal care disability 16 years later. All three measures were associated with the development of disability, independent of LTCs, and body

mass index (BMI) [25]. These findings highlight the possibility that assessments of sarcopenia in midlife could be used to identify those at risk of poor health in old age, who could then benefit from early intervention.

Quality of life

Work from the HCS has established a link between grip strength as a marker of sarcopenia and health-related quality of life (HRQoL), as assessed by the eight domain scores of the Short Form 36 questionnaire, including general health and physical functioning [26]. Subjects in the lowest sex-specific fifth of the distribution were classified as having "poor" status for each domain. Lower grip strength was associated with reduced HRQoL in both men and women. This did not appear to be explained by age, size, physical activity, or comorbidity. More recently, a quality-of-life questionnaire that can be self-administered has been developed specifically for patients with sarcopenia [27].

Long-term conditions and hospitalization

There is growing evidence that the sarcopenia is more common among those with LTCs such as those affecting the respiratory and cardiovascular systems [1]. There is also cross-sectional evidence that the number of LTCs a person has is inversely related to their grip strength [28]. It is likely that the relationship between LTCs and sarcopenia operates in both directions. An example of this is the development of type 2 diabetes and the known metabolic functions of muscle. We were able to test the hypothesis that glucose tolerance, muscle strength, and physical function would be linked in people with and without type 2 diabetes utilizing data from 1391 community-dwelling men and women aged 59–73 years participating in the HCS [29]. A graded association was demonstrated between increased glucose level, weaker muscle strength, and impaired physical function, not only in older people with diabetes or impaired glucose tolerance, but also in those without either diagnosis (Figure 8.2).

Sarcopenia has also been linked to length of hospital stay. We previously carried out a small clinical study looking at whether admission grip strength predicted length of stay in hospitalized older patients in an acute medical setting [30]. One hundred and twenty male and female patients aged over 75 years were recruited within 48 hours of admission. A single investigator measured grip strength and collected information on age, gender, comorbidity, medication, and nutritional, functional and case-mix scores. Lower grip strength was significantly associated with worse nutritional status, impaired functional status, and a reduced likelihood of discharge home. Similarly, we have previously shown that weak grip strength is associated with a reduced likelihood of discharge to a patient's usual place of residence following a period of inpatient rehabilitation [31].

More recently, we have been able to link data from 2997 participants of the HCS to their hospital episode statistics over the following decade. We have shown that weaker grip strength was associated with both elective and emergency admissions in women, and in emergency admissions in men, as shown in Figure 8.3. These findings remained after adjustment for age, height, weight, smoking status, alcohol consumption, and social class.

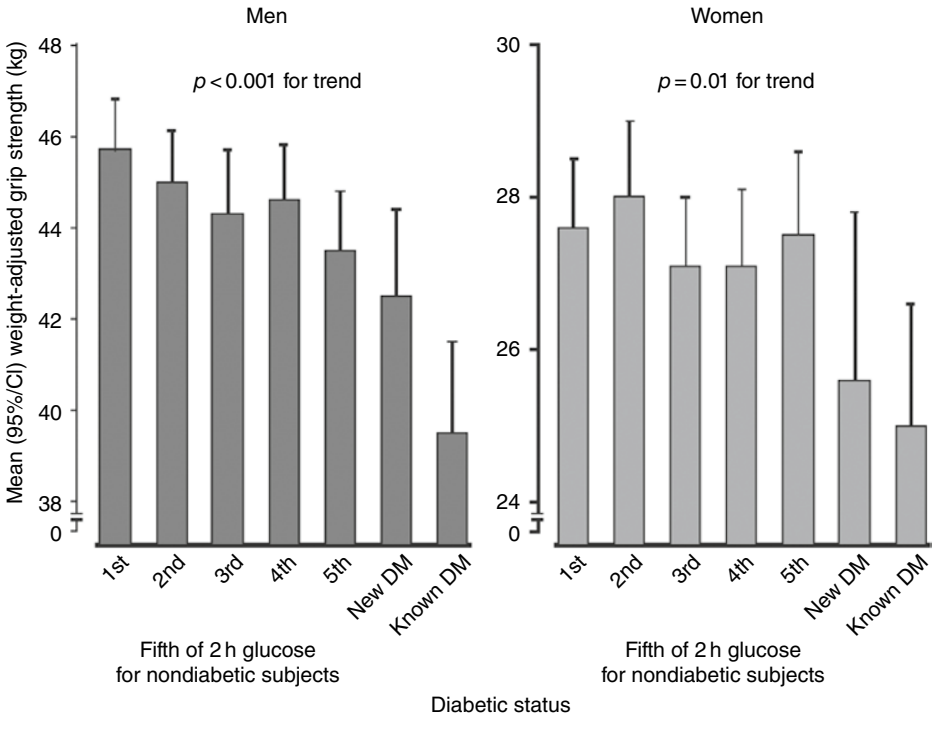

Figure 8.2 Relationship between grip strength and diabetic status in older men and women [29]. *Source*: From Aihie Sayer et al. [29]. © 2005 American Diabetes Association.

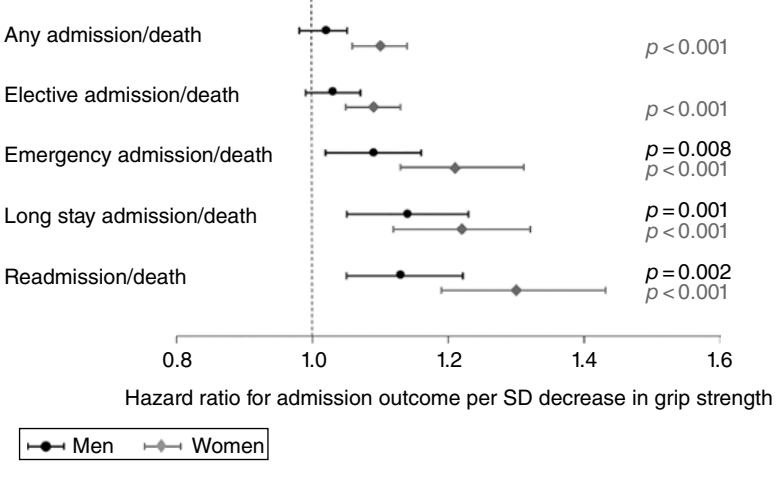

Figure 8.3 Association of grip strength with admission outcomes per standard deviation decrease in grip strength in men and women [32]. *Source*: From Simmonds [32]. © 2015 Oxford University Press.

LIFECOURSE DETERMINANTS OF SARCOPENIA

Determinants of sarcopenia at older ages including body size, LTCs, and level of physical activity have been described. The beneficial effect of exercise interventions, to slow the age-related loss of muscle, has been well documented. However, sarcopenia becomes increasingly prevalent with age and hence the opportunities for prevention in old age may be more limited. A lifecourse approach significantly broadens the window for intervention by considering both the peak muscle strength and mass achieved in early adulthood and the subsequent decline.

The potential relevance of genetic and developmental factors in sarcopenia is highlighted by the differences in mean grip strength among countries. In a recent systematic review and meta-analysis, we investigated the difference between mean grip strength in developed and developing country settings. Those in developing countries had on average a grip strength 0.85 standard deviations lower than that in our British normative data (Figure 8.4). At the same time, midlife provides an opportunity to intervene within a shorter timescale in a way that is already done for conditions such as cardiovascular disease. This section therefore begins by reviewing the evidence linking sarcopenia to early size and nutrition. It then goes on to examine the role of midlife risk factors.

Each point represents the mean value of grip strength for each item of normative data, plotted against the midpoint of the age range it relates to. Values from the same sample are connected.

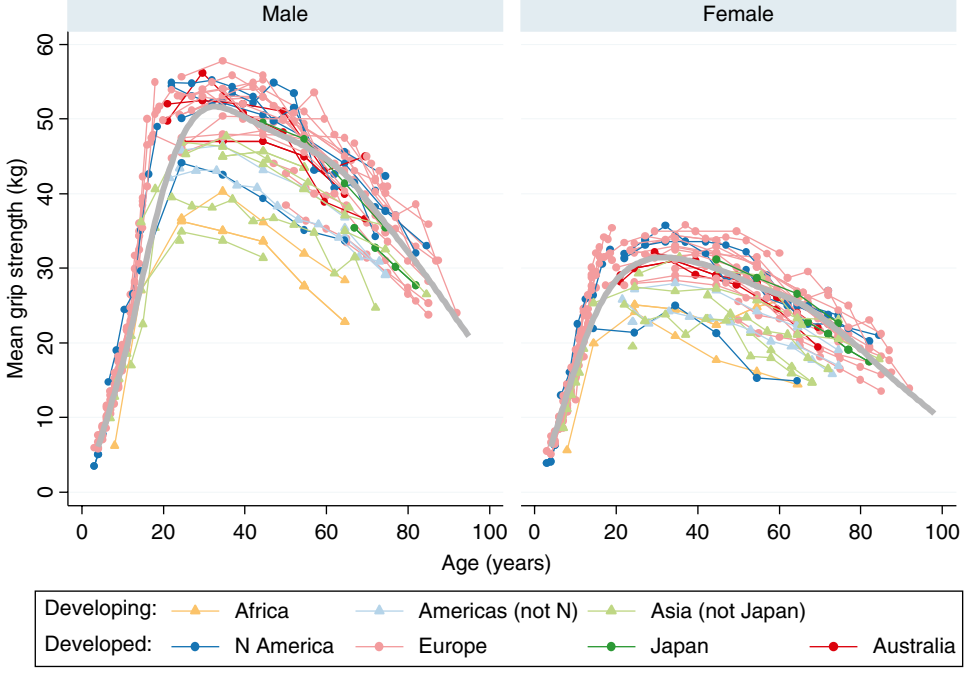

Figure 8.4 Grip strength mean values from included samples, by region [33]. *Source*: From Dodds et al. [33]. Public Domain.

Data from developing and developed regions are shown with triangles and circles, respectively.

For comparison, the gray line shows the mean values from our normative data for 12 British studies.

Early growth and nutrition

The link between birth weight and muscle strength in older people was first observed in the Hertfordshire Ageing Study, a retrospective cohort study of men and women born in Hertfordshire, United Kingdom, between 1920 and 1930 and still living there 60–70 years later [34]. They had historical health visitor records of weight at birth and one year and were traced through the National Health Service Central Registry in Southport, United Kingdom. Following a home interview, 717 people attended a local clinic for measurement of current size and markers of aging in different body systems including grip strength. Lower birth weight and weight at one year were significantly associated with lower grip strength in later life, independent of adult size.

This finding was then replicated in the HCS where participants were born in 1931–1939 [35] and also in the National Survey of Health and Development where the participants were born in 1946 [36]. Subsequent work has demonstrated a similar effect size of birth weight on adult muscle strength in young women aged 20–34 years taking part in the SWS, suggesting an association with peak muscle strength [37]. A positive relationship has also been shown in the children born in the SWS between birth weight and grip strength at age 4 years [38].

A systematic review and meta-analysis of the published evidence for an association between lower birth weight and reduced grip strength in later life has allowed the derivation of a pooled estimate for the association between birth weight and grip strength in absolute terms [39]. Sixteen independent articles were found describing the relationship between birth weight and grip strength in later life. Three of these studied small groups of low birth weight versus normal birth weight individuals and only followed participants to childhood or early adulthood; all demonstrated lower grip strength among lower birth weight individuals. The remaining 13 studies considered the full range of birth weight with follow-up ages ranging from 9 to 68 years of age. Authors provided additional results to allow meta-analysis of the birth weight–grip strength relationship after adjustment for age and height.

The resulting forest plot shows the pooled estimate of a 0.86 kg (95% CI: 0.58, 1.15) increase in grip strength per 1 kg increase in birth weight (Figure 8.5). There was some evidence of heterogeneity present, especially at younger ages. However, no individual study unduly influenced the pooled estimate.

It has been possible to add to these findings with a more detailed lifecourse approach using the longitudinal data collected in the National Survey of Health and Development [40]. Grip strength and body size were measured in 1406 men and 1444 women who were 53 years old and had prospective childhood data on weight, height, motor milestones, and cognitive ability, and information on lifetime social class, current physical activity, and health status. Birth weight and pre-pubertal height gain were associated with midlife grip strength, independently of later weight and height gain. Pubertal growth was also independently associated with midlife grip

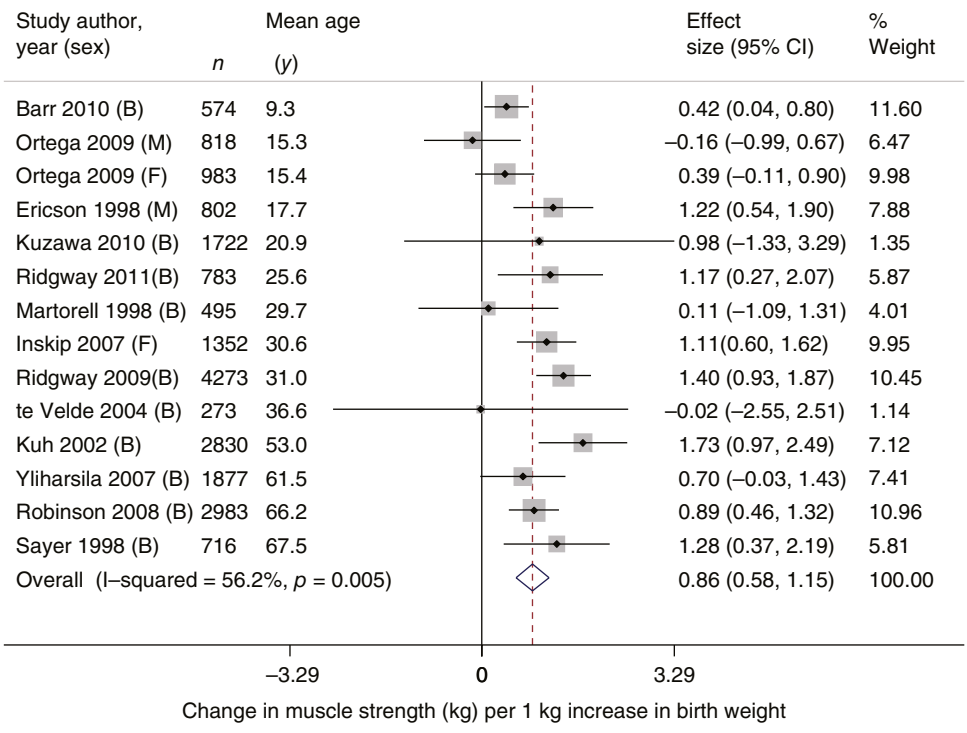

Figure 8.5 Forest plot of studies assessing the association between birth weight (kg) and later muscle strength (kg), after adjustment for age and height. Studies ordered by mean age at time of strength measurement. B = both males and females; M = males only; F = females only included in study [39]. *Source*: From Dodds et al. [39].© 2012 Springer Nature.

strength. For men, weight gain during puberty was beneficial, whereas for women it was height gain. Those participants with earlier infant motor development had better midlife grip strength which was partly explained by the growth trajectory. This suggests that components of prenatal, prepubertal, and pubertal growth have long-term effects on midlife grip strength.

Studies investigating the relationship between growth in early life and muscle mass have demonstrated consistent findings linking low birth weight with reduced muscle mass. A study of older men participating in the HCS showed that birth weight was significantly positively associated with fat-free mass but not with measures of adult fat mass [41]. In contrast, weight at one year was associated with fat-free mass and adult fat mass estimated using anthropometry. Similar findings were observed in studies of men and women using urinary creatinine excretion [42] and dual x-ray absorptiometry (DXA) [43] to estimate muscle mass. A study on the Helsinki Birth Cohort Finland has replicated the relationships between small size at birth, lower muscle mass, and reduced grip strength in older people [44]. Studies of birth weight and muscle mass in earlier stages of life demonstrate similar findings for children, teenagers, and young adults.

It is also possible to measure muscle size directly using peripheral quantitative computed tomography (pQCT) and we were able to assess this in 313 men and 318 women

from the HCS [45]. Birth weight was strongly positively related to forearm muscle area in the men and women and there were similar but weaker associations between birth weight and calf muscle area. These relationships were all attenuated by adjustment for adult size. The findings are consistent with the tracking of muscle size across the lifecourse.

The effect of early nutrition on long-term human health is challenging to ascertain but one approach is to use historical records of infant feeding as there is a growing literature that links greater duration and exclusivity of breastfeeding to beneficial effects on adult health outcomes. Muscle growth in the neonatal period may be sensitive to variations in early nutrition but little is known about long-term effects of infant feeding on muscle strength. The relationship between type of milk feeding in infancy and muscle strength in adult life was examined in 2983 community-dwelling older men and women participating in the HCS [46]. Information about milk feeding for each participant was abstracted from the historical records. In all, 60% (1783) of the participants were breastfed only, 31% (926) were breast and bottle-fed, and 9% (274) were bottle-fed only. There were no differences in type of milk feeding between men and women, or according to social class at birth. In men but not women, grip strength was related to the type of milk feeding, such that greater exposure to breast milk in infancy was associated with greater grip strength in adult life ($p = 0.023$). These data suggest that differences in nutritional exposure in the early postnatal period may have lifelong implications for muscle strength in men.

Midlife risk factors

Midlife provides an important opportunity to make assessments of future health, for example as is routinely carried out in primary care in the United Kingdom with respect to risk of cardiovascular disease. It also represents a period when sarcopenia is uncommon and hence provides an opportunity for preventive strategies. Modifiable risk factors that have been examined in this period include physical activity, diet, and body size.

Leisure time physical activity has been assessed at ages 36, 43, 53, and 60–64 in the NSHD. We were able to relate this to grip strength at age 60–64 years. There was evidence of a cumulative benefit of physical activity, with those in the most active third across the four time points being on average 2.11 kg (95% CI: 0.88, 3.35) stronger than those in the least active third [47]. Leisure time physical activity across midlife has also been shown to have benefits for appendicular lean mass as assessed by DXA at age 60–64 [48]. Finally, there is evidence from the Mini-Finland Health Examination Survey that becoming sedentary in midlife, between mean ages 43 and 64 years, is associated with more rapid decline in grip strength [49].

There is considerable literature which suggests that several aspects of diet may be important in the development of sarcopenia [50]. Food intake falls by approximately 25% from 40 to 70 years of age, and particularly if combined with a tendency toward a restricted diet, may lead to inadequate nutrient intake. Components of diet that have shown significant associations with sarcopenia in observational studies include protein, vitamin D, and antioxidants. However, these components have typically not shown benefit in intervention studies and this may reflect the fact that such components tend to be correlated with one another. It may therefore be that the overall pattern of diet is more relevant. Findings from the NSHD support this hypothesis.

A healthier diet pattern across adulthood, characterized by higher consumption of fruit, vegetables, and wholegrain bread, was found to be associated with improved performance in chair rise time, timed up and go, and standing balance at age 60–64 [51].

Increased body size, as assessed with BMI, has been linked to poor physical performance such as slower walking speed, both in cross-sectional [52] and longitudinal studies [53]. The relationships for grip strength have been more mixed, with either no association shown [54] or the finding of higher grip strength in men with higher BMI [52]. It is recognized that midlife risk factors such as low physical activity, poor diet, and raised BMI tend to cluster within individuals, and there is evidence that having greater numbers of these risk factors is associated with worse physical function [55].

CELLULAR AND MOLECULAR MECHANISMS

This chapter has highlighted the significant health consequences of sarcopenia and evidence regarding its determinants across the lifecourse. An improved understanding of the mechanisms underpinning the development of sarcopenia is needed if progress is to be made in the prevention and treatment of this condition. This section considers the roles of fiber number, epigenetics and microRNAs, mitochondrial function, and the extracellular matrix (ECM) surrounding skeletal muscle.

Fiber number

Muscle fiber number is a critical determinant of muscle mass and strength at all stages of life. For human skeletal muscle, it appears that fiber number is set at 24 weeks of gestation. Hence subsequent growth, maintenance, and repair is believed to occur through muscle fiber hypertrophy rather than hyperplasia, achieved by recruitment of myoblasts derived from embryonic stem cells at approximately six weeks of gestation. Fiber hypertrophy appears to be particularly important for muscle growth in the neonatal period when skeletal muscle is the fastest growing protein mass due to accelerated rates of protein synthesis accompanied by the rapid accumulation of muscle nuclei. These observations suggest that key periods during early life may influence the formation of myofibers and recruitment of myoblasts with long-term consequences for muscle mass and strength [56].

This work is now being taken forward in studies of older adults to investigate mechanisms underlying the developmental origins of sarcopenia. We found in the Hertfordshire Sarcopenia Study [57] that it is both feasible and acceptable to carry out muscle biopsy in older men taking part in an established epidemiological study [58]. This study was able to investigate whether low birth weight was associated with altered skeletal muscle morphology in older men. It involved 99 men with historical records of birth weight aged 68–76 years who consented for detailed characterization of muscle, including a biopsy of the vastus lateralis [59]. Tissue was processed for immunohistochemical studies and analyzed to determine myofiber density, area, and score.

Muscle fiber score was significantly reduced in those with lower birth weight. In addition, there was a trend for reduced myofiber density and increased myofiber area in those with lower birth weight although these differences were not statistically significant. These findings provide preliminary evidence that developmental influences on human muscle morphology may be similar to those demonstrated in animal models and explain the widely reported associations between lower birth weight and sarcopenia. Larger studies including older women as well as older men are now ongoing and understanding of mechanisms can be taken forward with detailed molecular as well as cellular characterization.

Epigenetics and microRNAs

Epigenetics refers to heritable changes in gene expression that do not require a change in genetic sequence, such as the process of DNA methylation. Epigenetic changes have emerged as a promising marker of biological aging, although to date the changes in skeletal muscle with aging and in sarcopenia are poorly understood. There is evidence that genes encoding components of the respiratory chain undergo increased methylation with age [60].

Developments in transcriptomics are improving our understanding of short noncoding RNA sequences, microRNAs, which affect the translation of other genes and thereby have the potential to regulate many of the processes suggested to contribute to the development of sarcopenia [61]. Their relevance from a lifecourse perspective comes from the fact that they have also been shown to have a key role in the embryonic development of skeletal muscle, and also that the finding of marked differences in microRNA profiles between young and old subjects.

Mitochondrial function

Impairments in skeletal muscle mitochondrial function and content have been implicated in the development of sarcopenia, although there is debate as to whether mitochondrial changes occur as an intrinsic part of aging or due to the associated reduction in physical activity [62].

We recently established that it is feasible to carry out an assessment of mitochondrial function and content in healthy 85-year-olds, using phosphorous magnetic resonance spectroscopy after exercise and immunofluorescence of muscle biopsy samples. We found that function and content were preserved in this active sample, supporting the idea that physical activity can prevent age-related changes [63].

Extracellular matrix

As well as changes within skeletal muscle fibers, it is important to consider the role of the ECM which is responsible for the transmission of force from the sarcomeres to tendons. A study showed that there are distinct changes in ECM expression across different stages of the mouse life course [64]. The components of ECM also undergo complex post-translational modifications with age, such as the formation of advanced

glycation end products [65]. Such changes can lead to increased stiffness of the ECM and impaired force transmission. Similarly, those with obesity and diabetes have been found to have increased amounts of collagen surrounding muscle fibers [66]. This may in part account for the observation (as described in the section on lifecourse determinants) that those exposed to obesity for a greater proportion of adulthood have lower physical performance in early old age.

CONCLUSIONS AND RELEVANCE TO CLINICAL PRACTICE

Taking a lifecourse approach to sarcopenia is relevant to clinical practice for several reasons. It provides an opportunity to assess individuals' risk of future sarcopenia, and indeed to recognize groups such as those with LTCs who may develop sarcopenia earlier in the lifecourse. It also suggests that the window for instituting beneficial interventions such as increasing physical activity or optimizing nutritional intake should be widened to include all stages of life. This could be particularly relevant in midlife, when assessment of future cardiovascular disease risk is already undertaken in primary care. Furthermore, knowledge of underlying mechanisms, particularly at the cellular and molecular level, has the potential to inform the development of novel therapeutic agents to treat sarcopenia.

In conclusion, there is growing support for a lifecourse approach to understanding sarcopenia both in terms of identifying major health consequences and in terms of recognizing important influences operating from conception to death. There is consistent evidence that sarcopenia is associated with increased disability, morbidity and mortality, as well as significant health-care costs. In terms of etiology, a lifecourse approach includes identifying the determinants of peak muscle mass and function as well as the determinants of loss; birth and other cohorts are a key resource for such studies. A lifecourse approach to sarcopenia has important clinical relevance with regard to the prediction, prevention, and development of novel therapeutic agents for sarcopenia.

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CHAPTER 9

Acute Sarcopenia

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DEFINITION

Sarcopenia is an age-related syndrome characterized by generalized loss of skeletal muscle mass and strength which is associated with an increased risk of adverse outcomes, such as physical disability, poor quality of life, and death ([1]). Reduction in skeletal muscle mass and strength is a progressive condition that begins in adulthood and continues through aging [2], and it is regarded as a key component of frailty. Sarcopenia lasting ≥6 months is considered a chronic condition, while it is defined as an acute condition when its duration is lower than six months ([3]). Other authors proposed a different definition of acute sarcopenia, highlighting the role of acute stressors. Acute sarcopenia has been defined as a change in muscle mass and muscle function within 28 days of a significant physiological stressor event, such as an acute illness, surgery, trauma, or burns, to such an extent to newly meet the criteria for sarcopenia [4].

While chronic sarcopenia is associated with chronic and progressive diseases, acute sarcopenia usually arises during an acute illness or injury [3]. Indeed, acute sarcopenia is usually related to hospitalization or a surgical procedure that triggers the acute loss of muscle mass and function due to an increased inflammatory burden in combination with muscle disuse [4, 5].

EPIDEMIOLOGY

In order to describe the incidence of acute sarcopenia, a rapid reduction in muscle mass and muscle function should be demonstrated. This definition implies that at least two measurements of muscle mass and muscle function are available ([4]). For this reason, reliable data concerning the incidence of acute sarcopenia are very scarce [1].

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

On the other hand, more data have been published concerning the prevalence of sarcopenia in acute situations, such as hospitalization, surgery, or in intensive care unit (ICU) setting. Table 9.1 summarizes epidemiological findings about incidence and prevalence of acute sarcopenia in different settings.

Acute sarcopenia in medical units

The incidence of sarcopenia was investigated in the GLISTEN study. Sarcopenia at hospital admission was diagnosed in 227 (34.7%) patients. Among patients without sarcopenia at hospital admission (n = 394), 58 participants (14.7%) met the European Working Group on Sarcopenia in Older People (EWGSOP)-1 sarcopenia diagnostic criteria at hospital discharge. More than 50% of those who developed sarcopenia during hospital stay showed over 10% muscle mass loss compared with baseline values [6].

The prevalence of sarcopenia in older subjects hospitalized in medical wards varies between 10 and 34.7% [7–11]. Severe sarcopenia, defined as the presence of low muscle mass, low strength, and impaired physical function, has been found in between 17.5 and 21.0% of patients [10, 12–13].

Women have a higher prevalence of sarcopenia and severe sarcopenia than men, whereas pre-sarcopenia is equally distributed in both genders [9–10, 14].

Sarcopenia increases with age and it is inversely correlated with body mass index [7] and albuminemia [9], but not with polypharmacy [15].

It should be noted that until recently the EWGSOP-1 criteria have been the most used diagnostic criteria for sarcopenia. A recent study that used EWGSOP-2 criteria considered retrospectively 144 geriatric inpatients hospitalized in a single center in Salzburg. The Authors applied both version 1 and 2 criteria. Sarcopenia prevalence according to the EWGSOP-1 algorithm (n = 41, 27.7%) was significantly higher than that with EWGSOP-2 (n = 26, 18.1%, $p < 0.05$), demonstrating a low concordance rate [16]. Furthermore, a recent analysis of the GLISTEN study compared sarcopenia prevalence and diagnostic agreement between the EWGSOP-2 criteria and the operational definition proposed by the Foundation for the National Institutes of Health Sarcopenia Project. In this study, among 220 participants who were classified as sarcopenic by at least one definition, agreement was obtained in only 65 (10.7%) [17].

Another recent study compared different criteria for sarcopenia in a sample of older (>70 year) inpatients. The authors compared nine commonly used diagnostic criteria for sarcopenia in hospitalized older patients, considering medical and surgical wards. Among older inpatients, prevalence rates of sarcopenia were high, especially in male inpatients and varied substantially depending on the diagnostic criteria, ranging between 12.0 and 75.9% in males and 3.1 and 75.3% in females [18]. Overall, these recent studies reinforce the fact that sarcopenia epidemiology is strongly affected by the criteria used.

Acute sarcopenia in surgical units

A recent pilot study from Welch and colleagues described the incidence of sarcopenia in older adults before and after colorectal surgery (mean age 74.7 years). Serial measurements of bilateral anterior thigh thickness and handgrip strength were performed

Table 9.1 Studies that described the incidence and prevalence of acute sarcopenia.

Author, year	Setting	Study design	Population	Age	Measurement of muscle mass	Results
Incidence						
Martone, 2017	Medical units	Multicenter observational prospective study	394 older subjects admitted to 12 acute medical wards	Mean age 81.0± 6.8 years (82.3± 6.6 years in women and 79.6± 6.0 years in men)	Bioelectrical impedance analysis (BIA)	14.7% of subjects met the European Working Group on Sarcopenia in Older People (EWGSOP) sarcopenia diagnostic criteria at discharge. The incidence of sarcopenia was associated with the number of days spent in bed (5.1 days in bed compared with 3.2 days for those with no sarcopenia at discharge, $p = 0.02$) and body mass index compared with non-sarcopenic patients ($25.0 \pm 3.8\,kg/m^2$ vs $27.6 \pm 4.9\,kg/m^2$, respectively; $p = <0.001$).
Welch, 2019	Surgical unit (colorectal)	Pilot observational prospective study	7 older adults	74.7 years (SD 4.1).	Quadriceps muscle thickness was measured using B-mode ultrasonography	Bilateral anterior thigh thickness (BATT) and gait speed declined at one week postoperatively (median BATT 4.17 cm, 3.47 cm, $p = 0.028$; median gait speed 0.89 m/s, 0.83 m/s, $p = 0.043$). Baseline hsCRP correlated with change in BATT ($\tau b = 0.73$, $p = 0.04$) and baseline DHEA-S correlated with change in gait speed ($\tau b = 0.87$, $p = 0.02$).
Prevalence						
Gariballa, 2013	Medical unit	Observational cohort study	432 randomly selected older inpatients patients	Sarcopenic 79±7 years, not sarcopenic 77±6 years	Mid-arm muscle circumference (MAMC).	44 (10%) subjects were sarcopenic. They were more likely to be older, have more depressive symptoms and lower serum albumin concentration. The length of hospital stay (LOS) was significantly longer in patients

(*Continued*)

Table 9.1 (Continued)

Author, year	Setting	Study design	Population	Age	Measurement of muscle mass	Results
						diagnosed with sarcopenia compared with patients without sarcopenia [mean (SD) LOS 13.4 (8.8) vs 9.4 (7) days respectively, $p = 0.003$]. The risk of nonelective readmission in the six months follow-up period was significantly lower in patients without sarcopenia compared with those diagnosed with sarcopenia (adjusted hazard ratio (HR) 0.53; 95% confidence interval [CI]: 0.32–0.87, $p = 0.013$). The death rate was also lower in patients without sarcopenia 38/388 (10%), compared with those with sarcopenia 12/44 (27%), p-value = 0.001
Vetrano, 2014	Medical unit	Multicenter observational prospective cohort study	770 in-hospital patients.	80.8 ± 7 years	BIA.	Sarcopenia was present in 214 (28%) patients. 22 participants died during hospital stay, and 113 in the year after discharge. Participants with sarcopenia had a significantly higher in-hospital (6% vs 2%; $p = 0.007$) and 1-year mortality (26% vs 14%; $p < .001$) as compared with participants without sarcopenia. After adjusting for potential confounders, sarcopenia resulted significantly associated with in-hospital (HR: 3.45; 95% CI: 1.35–8.86) and 1-year mortality (HR: 1.59; 95% CI: 1.10–2.41).
Cerri, 2015	Medical unit	Observational prospective study	103 patients admitted to the acute geriatric clinic	total sample: 84.2 ± 7.1; sarcopenic 83.1 ± 7.9; non sarcopenic 87.4 ± 4.8, uncertain 84.2 ± 5.9 ($p = 0.05$)	BIA.	Sarcopenia was diagnosed in 22 patients (21.4%). Eleven (10.7%) patients died within the three months post-discharge period. Kaplan–Meier survival curves showed that sarcopenic patients died significantly more frequently than others (log-rank $p \leq 0.001$).

Jacobsen, 2016	Medical unit	120 patients, 44 men and 76 women	Observational multicentric cross-sectional study (two acute geriatric hospital wards in Norway)	Mean age 82.5±8.0 years	MAMC	Sarcopenia was present in 30% of the patients. Significant independent associations was found with short physical performance battery (SPPB) score (β 0.64, 95% CI: 0.38–0.90), sarcopenia (β −3.3; 95% CI: −4.9 to −1.7), pulmonary disease (β −2.1; 95% CI: −3.7 to −0.46), cancer (β −1.7; 95% CI: −3.4 to −0.033) and nutritional status.
Bianchi, 2017	Medical unit	655 older adults (51.9% women) admitted to 12 acute hospital wards in Italy	Cross-sectional analysis of multicenter observational GLISTEN study	Mean age 81.0±6.8 years	BIA	The overall prevalence of sarcopenia at hospital admission was 34.7% (95% CI: 28–37) and it was associated with increasing age (p <0.001).
Rossi, 2014	Medical unit	Observational cohort study	119 acutely ill persons (34.4% female)	Mean age 80.40±6.9 years	BIA	1 in 4 patients was sarcopenic.
Smoliner, 2014	Medical unit	Cross-sectional study	198 acute geriatric patients	Mean age 83 years, range 79–87	BIA	Thirteen patients (6.6%) were defined as sarcopenic and 37 (18.7%) were defined as severely sarcopenic. In a group comparison, patients with sarcopenia had a poorer nutritional status.

(*Continued*)

Table 9.1 (Continued)

Author, year	Setting	Study design	Population	Age	Measurement of muscle mass	Results
Ghaffarian, 2019	Surgical unit (vascular)	Retrospective observational study	415 patients	Mean age: non-sarcopenic non frail 59.1 ± 15.4 years, frail 62.7 ± 15.3 years, sarcopenic 65.5 ± 14.0 years; both 64.9 ± 16.8 years	Single axial computed tomography (CT) image at the caudal end of the third lumbar vertebra	27% were sarcopenic and 13% were both sarcopenic and frail. Long-term survival was significantly decreased for patients diagnosed with either frailty alone or frailty and sarcopenia who underwent surgical or nonsurgical management (log-rank, $p < 0.001$ for both comparisons). In multivariate regression models, however, frailty was the only independent variable (HR: 7.7; 95% CI: 3.2–18.7; $p < 0.001$) that predicted mortality
González-Montalvo, 2016	Surgical unit (orthopedic)	Observational prospective	509 consecutive patients admitted for hip fracture	Mean age was 85.3 (SD 6.8 years).	BIA	The prevalence of sarcopenia was 17.1% (12.4% in men, 18.3% in women). Sarcopenia was associated with residence in nursing homes (30.5% vs 19.6%, $p = 0.030$), older age (86.8, SD 6.2 vs 85.1, SD 6.9 years, $p = 0.038$), and lower body mass index (23.1, SD 3.6 vs 25.6, SD 4.23, $p < 0.001$). In the multivariate analysis, only low body mass index was predictive of sarcopenia (odds ratio [OR]: 0.85; 95% CI: 0.80–0.91).
Díaz de Bustamante, 2018	Surgical unit (orthopedic)	Observational prospective study	509 patients	Mean age was 85.6 ± 6.9 years	BIA	The prevalence of sarcopenia was 17.1%.

Steihaug, 2017	Surgical unit (orthopedic)	Multicenter cross-sectional study.	202 patients	Mean age was 79.4 ± 8.2	Anthropometry using gender, height, arm circumference and triceps skinfold.	74 (37%) were diagnosed as sarcopenic. Sarcopenia was associated with age, OR 1.4 per 5 years, 95% CI: 1.1, 1.8, ASA Physical Status Classification System score, OR 2.3 per point, 95% CI: 1.3, 4.3 and number of medications at discharge, OR 1.2 per medication, 95% CI: 1.0, 1.3 and inversely associated with body mass index (BMI), OR 0.8, 95% CI: 0.7, 0.9 and serum albumin, OR 0.9, 95% CI: 0.8, 1.0.
Sheean, 2014	Intensive care unit (ICU)	Cross-sectional study	56 patients	Mean age: normally nourished 58.5 ± 14.6; under nourished 60.0 ± 17.0	Single transverse CT slice located at the mid-point of the third lumbar (L3) region	Sarcopenia was assessed at three time points: within 14 days (group 1), 10 days (group 2), and 7 days (group 3) after admission. Sarcopenia was prevalent in 60% (n = 34/56) of patients in group 1, 60% (n = 29/48) of patients in group 2, and 56% (n = 20/36) of patients in group 3. The prevalence of sarcopenic obesity was also similar among the groups with 24% (n = 8/34) in group 1, 24% (n = 7/29) in group 2 and 25% (n = 5/20) in group 3.
Churilov, 2018	Post-acute Reha bilitation units	Systematic review and meta-analysis	Inpatients rehabilitation after hip fracture (five studies), general decond itioning (one study)	–	–	Sarcopenia prevalence ranged from 28 to 69%. Pooled sarcopenia prevalence obtained with random effect meta-analysis: 56% (95% CI: 46–65), with high heterogeneity I^2 = 92.9%. Main quality shortcomings: lack of reporting of inter- and intra-rater reliability, lack of generalizability to other rehabilitation populations

Mean age and muscle mass assessment were not available in the meta-analysis by Churilov et al.

prior to, within 24 hours of surgery, and one week postoperatively. At baseline, the prevalence of sarcopenia was 28.6%. One week after surgery 75% of subjects met the criteria for sarcopenia [19].

The prevalence of sarcopenia in surgical patients is higher than that in patients in medical wards, ranging from 17 to 40% of patients [19–22]. It is often associated with frailty [21], female sex [20, 22], older age, and lower serum albumin concentration [23].

Acute sarcopenia in intensive care

Available data in the ICU setting suggest a prevalence of sarcopenia between 60 and 71% in older adults admitted to the ICU for major trauma or for acute respiratory failure [54]. This prevalence is very high in comparison with the data collected in medical and surgical wards. In this respect, it should be pointed out that, while studies assessing sarcopenia in medical and surgical wards have been obtained using diagnostic criteria for sarcopenia, ICU studies are based only on the assessment of the muscle mass obtained through the computed tomography (CT) scan, without an evaluation of muscle function.

Acute sarcopenia in rehabilitation and post-acute care

A review in the rehabilitation setting found a prevalence of sarcopenia ranging from 28 to 69% of patients. Sarcopenia may be present in approximately half of rehabilitation patients and its prevalence may vary based on the admission diagnosis [25] and it is strongly associated with malnutrition.

PATHOGENESIS

Several mechanisms might contribute to the development of acute sarcopenia. Immobilization and disuse play a fundamental role in accelerating muscle loss, in association with an imbalance between protein synthesis and degradation, inflammation, hormones deregulation, and acute malnutrition [26]. Of note, these mechanisms are also involved in the development of chronic sarcopenia, with the possible exception of immobilization, which is more typical of an acute condition. In non-acutely ill subjects, a similar role in promoting muscle mass and function loss is played by a sedentary lifestyle [27].

Acute sarcopenia secondary to hospitalization is associated with an acute rapid decline in muscle mass and muscle function. This decline may be partially recovered after discharge from hospital and recovery from illness, but the muscle may not return to pre-illness baseline, resulting in chronic sarcopenia [4].

Immobilization

A pilot study carried out on healthy older volunteers ($n = 8$) showed that five days of limb immobilization already lead to a 1.5% loss of quadriceps cross-sectional area, which would correspond to about 1 kg of muscle tissue lost in the whole body. This effect seems to be less evident in young adults [28].

It is well known that after 7–10 days of bed rest, 3–12% of muscle mass can be lost [29–32]. Considering a longer time frame, i.e. between 10 and 42 days of immobilization, there is a decline of muscle mass of 0.5–0.6% per day, with a reduction in muscle strength of 0.3–4.2% per day [33]. In keeping with these results, in the GLISTEN study Martone et al. [6] reported that every day of bed rest was associated with a 5% increase in likelihood of developing sarcopenia during hospital stay.

Imbalance between protein synthesis and degradation

Drummond and colleagues demonstrated a decline of about 35% in muscular protein synthesis response to essential amino acid (EAA) ingestion in older individuals following seven days of bed rest [34]. This phenomenon is called "anabolic resistance" to food intake and it is mediated by a reduced activation of mammalian target of rapamycin complex (mTORC1) signaling by the amino acid ingestion [35]. On the other hand, the degradation of proteins is sustained by the ubiquitin proteasome pathway, which induces proteolysis through the degradation of myofibrils [31–33]. Furthermore, during an acute illness there is an increase in the myocyte apoptosis, mediated by caspase proteases system [34] and an increased rate of autophagy via cathepsins pathway [35] and calcium-dependent calpain system [36].

Inflammation

The development of sarcopenia is associated with oxidative stress and inflammation ([37, 38]). Increased levels of interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) are related with sarcopenia or reduced muscle strength in older adults without acute medical conditions and they are mentioned as causal factors associated with muscle loss during the aging process [39, 40]. In addition, studies performed in chronic conditions associated with high levels of pro-inflammatory cytokines, such as chronic obstructive pulmonary disease, rheumatoid arthritis (RA) and inflammatory myopathies, show a higher prevalence of sarcopenia [41]. During acute illness, the levels of these cytokines increase exponentially, due to an increased level of endotoxin, related to septic status, trauma, or surgery. In animal models, the administration of endotoxins activates muscle proteolysis via the ubiquitin–proteasome pathway and inhibits protein synthesis [42]. In animal models, surgery-induced sepsis produces an increase in inflammatory cytokines and subsequent muscle damage within 24 hours [43].

Endocrine stress responses

Cortisol is a mediator of protein catabolism and its serum levels rise significantly with acute illness. Hypercortisolemia exacerbates loss of muscle mass and muscle strength. Experimental studies demonstrate that an increase in the cortisol levels during bed rest determine a loss of muscle in healthy volunteers higher than bed rest alone [44].

In addition, the serum levels of the androgen precursor dehydroepiandrosterone sulfate (DHEAS) decline during aging, producing an increased cortisol:DHEAS ratio, and a state of relative cortisol excess. This ratio increases during acute illness or stress further impairing muscle anabolism [45]. Furthermore, during acute illness there is an insulin resistance that determine a defective insulin signaling. This condition increases muscle proteolysis, due to the inability to the mTOR system to inhibit autophagy-induced lysosomal proteolysis [46]. In one study, although circulating levels of glucocorticoid were not associated with muscle strength or size in older subjects, muscle strength was associated with enzyme 11beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) mRNA muscle levels. This enzyme converts inactive cortisone to active cortisol. Therefore, higher levels indicate increased cortisol generation within muscles [47]. An example of acute sarcopenia due to increased endocrine stress response can be observed in the surgical setting. Surgery is characterized by pain and inflammatory reaction that in turn stimulate the hypothalamic–pituitary–adrenal axis with important homeostatic and metabolic imbalance. Increased catecholamine levels might lead to cardiovascular complications, whereas increased cortisol levels have been associated not only with protein catabolism but also with acute cognitive disfunction. All together these biological mechanisms might trigger cardiovascular deconditioning that along with prolonged bed rest and malnutrition facilitate the onset of sarcopenia (Figure 9.1).

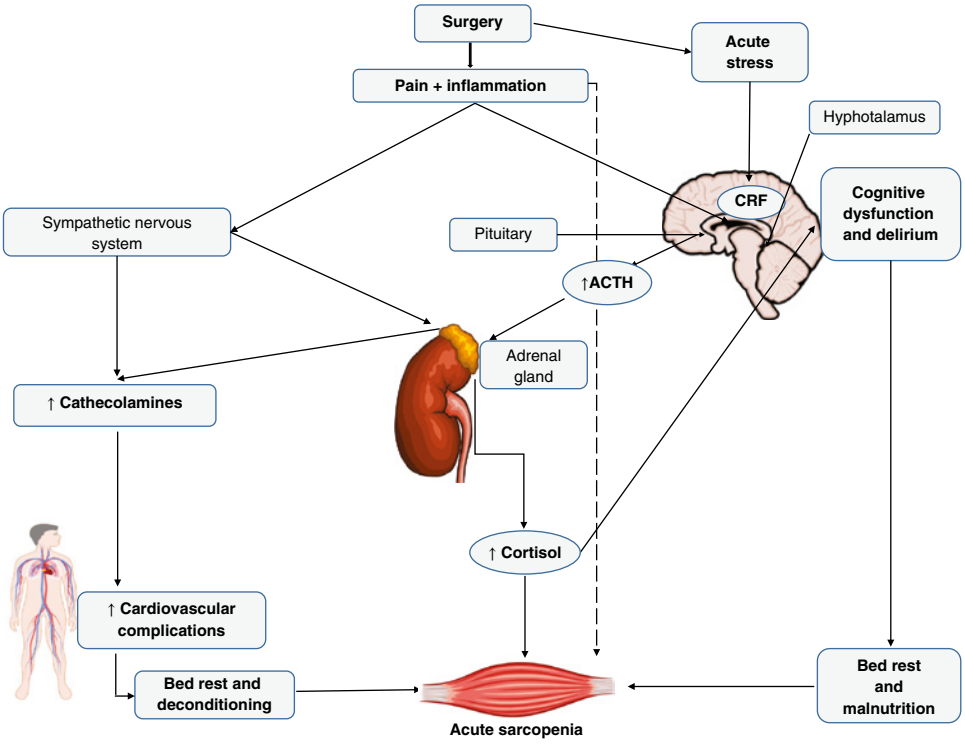

Figure 9.1 Pathogenesis of acute sarcopenia following surgical interventions.

Nutritional deficits

One in three patients admitted to the hospital is malnourished [48]. During acute illnesses, inflammation contribute to exacerbate this condition, causing the so-called "disease-related malnutrition". Indeed, the combined action of high pro-inflammatory cytokine activity, increased corticosteroid and catecholamine release, resistance to insulin and other growth hormones, bed rest, and reduced food intake determine a fast decline of body energy and nutrient stores [49]. Inflammatory pathways lead to anorexia, reduced food intake, aggravated weight loss, and increased muscle catabolism, and these phenomena are often interconnected with the pathophysiological mechanisms of diseases. In addition, anabolic resistance is closely related with the availability of amino acids after meals, which is decreased during reduced food intake.

OUTCOMES

Medical wards

In hospitalized patients, sarcopenia is associated with an increased length of stay (LOS) [6, 8, 50, 51]. Martone et al. described a 18% longer LOS in subjects who developed sarcopenia [6]. The EMPOWER study demonstrated an association among lower muscle strength at admission with being at risk of geriatric conditions, such as delirium, falls, malnutrition, and functional disability [52]. Furthermore, hospitalized sarcopenic subjects have an increased rate of in-hospital [11] and post-discharge [17, 53] mortality. The risk of death increases by up to four times if sarcopenia is associated with malnutrition [54], Sarcopenic subjects have also an increased risk of readmission compared with the subjects without sarcopenia (hazard ratio [HR]: 1.81; 95% confidence interval [CI]: 1.17–2.80) and of mortality (HR: 2.49; 95% CI: 1.25–4.95) within three years after discharge [55].

Surgical wards

In patients who undergo major surgery, sarcopenia is associated with poorer outcomes, i.e. lower probability of short-term and long-term survival and higher risk of postsurgical complications.

Du et al. carried out a retrospective analysis in older subjects (mean age 84 years) who underwent an emergency surgical procedure. The overall in-hospital mortality was 18%. Sarcopenia was present in 73% of patients. There were no differences in duration of hospital stay (13 [8–25] vs 10 [5–19] days, $p = 0.15$) and requirement for ICU care postoperatively (33% vs 19%, $p = 0.22$) between sarcopenic and nonsarcopenic patients. However, sarcopenic patients had more postoperative complications (45% vs 15%, $p = 0.005$) and higher risk of in-hospital death (23 vs 4%, $p = 0.037$) [56].

In 201 older adults admitted for hip fracture assessed longitudinally in three Norwegian hospitals, the LOS was significantly longer in patients diagnosed with sarcopenia compared with patients without sarcopenia (mean (SD) 13.4 (8.8) vs 9.4 (7) days, respectively, $p = 0.003$) [57].

Following colorectal surgery, an increased rate of postoperative infections, higher frequency of need for rehabilitation and longer length of stay were observed in older patients [58].

A review by Shen et al. examined the relationship of sarcopenia and frailty with in-hospital mortality and postsurgical complications in older adults who underwent gastrectomy for gastric cancer. They pooled data from eight studies. Six studies reported the association between sarcopenia and postoperative complications. The odds ratio (OR) of sarcopenic gastric cancer patients for negative postoperative outcome was 3.12 (95% CI: 2.23–4.37). However, these studies did not consider the onset of sarcopenia, but they measured sarcopenia before surgery [59].

Another observational study considered adult patients with cirrhosis who had CT scans of the abdomen with pelvis before and after liver transplantation. Sarcopenia was present in 33 (62.3%) cirrhotic patients before transplantation. After liver transplantation, 46 (86.8%) patients had sarcopenia. Of the 33 patients who had pretransplant sarcopenia, in only 2 (6.1%) patients a reversal of sarcopenia was observed, while the remaining patients (n = 31; 93.9%) had persistent sarcopenia post transplantation. Of the 20 patients who did not have sarcopenia pre-orthotopic liver transplantation (OLT), the majority (n = 15, 75%) developed sarcopenia after OLT [60].

Intensive care

Sarcopenia may impair the function of respiratory muscles, which influences the weaning process [61, 62]. In critically ill patients, sarcopenia is a prognostic factor for less ventilator-free days, longer LOS, and mortality.

A retrospective study in 84 adults demonstrated that the LOS of sarcopenic patients was significantly longer than that of the non-sarcopenic patients (18.7 vs 6.4 days, respectively; $p < 0.001$) and the mean ICU stay and ventilation-free days of the sarcopenic patients were approximately three times longer than that of the non-sarcopenic patients. Sarcopenic patients were older than non-sarcopenic patients (mean age 56.7 ± 18.4 years and 43.2 ± 14.2 years, respectively) [63].

Another retrospective cohort study carried out on 96 ICU patients (median age 73 years, 67.8% older than 64 years) showed that sarcopenia is an independent predictor for difficult-to-wean (DtW) in critically ill surgical patients [61].

TREATMENT

Sarcopenia recognizes a multifactorial etiology. Therefore, different treatment strategies have been proposed to reduce muscle loss in acutely ill hospitalized patients.

Physical exercise

Exercise training, both aerobic and resistance, is effective in preventing and ameliorating sarcopenia [64].

Although the effects of exercise on acute sarcopenia have not been investigated until now, a trial in very old hospitalized patient assessed the efficacy of twice-a-day sessions (morning and evening, of 20 minutes duration during 5–7 consecutive days including weekends) versus the usual-care group (habitual hospital care, with physical rehabilitation when needed) on muscle strength, gait speed, and short physical performance battery (SPPB) score. A total of 370 subjects were enrolled. The exercise group showed a mean increase of 2.2 points (95% CI: 1.7–2.6 points) on the SPPB scale versus 0.2 points (95% CI: −0.1 to 0.5 points) in controls. Handgrip strength test, assessed as a secondary outcome, decreased in the control group and increased in the intervention group ($p < 0.001$) [65].

Nutritional intervention

EAAs stimulate mTORC1 signaling, amino acid transporter expression, and muscle protein synthesis, but in older adults the normal anabolic response to a dose of EAAs is blunted after seven days of bed rest [34]. In this respect, some studies assessed the efficacy of amino acid supplementation and, specifically, the role of leucine supplementation in bed rest conditions. There are many studies focused on the effect of nutritional supplementation in older hospitalized patients, but there is still a lack of consensus about the composition of supplements that should be administered.

A review by Wandrag et al identified different studies that demonstrated the efficacy of EAA supplementation [66]. Ferrando et al examined whether 15 g EAAs in addition to a standard diet during 10 days of bed rest would maintain muscle mass and function in older subjects [67]. In a further bed rest study, a supplement containing 49.5 g/day EAA with carbohydrate was examined as anabolic stimulus during 28 days of bed rest. Although muscle wasting, measured using dual-energy X-ray absorptiometry (DXA) appeared to be minimized with EAA supplement, muscle strength (single-leg, one-repetition maximum (1RM) leg extension strength) was not fully preserved [68].

A review by Thalacker-Mercer examined metabolic challenges in hospitalized older adults, providing some suggestions for an effective nutritional intervention against muscle wasting associated with bed rest in older adults. They proposed a balanced diet to maintain muscle health during hospitalization of older adults composed of 30 g high-quality protein: 3 g leucine and fast absorbing protein with high leucine content, equal meal protein distribution (30: 30: 30), and appropriate timing of protein supplementation (between meals) [69]. The authors concluded that more evidence is necessary to produce a strong recommendation. Indeed, it is still unclear if the protein intake should adjust for body weight or lean muscle mass rather than absolute dose, the effects of gastric emptying of a mixed macronutrient meal on protein synthesis rates and the relationship of protein supplementation and the onset of diabetes mellitus.

A recent review analyzed the effect of protein and amino acid supplements in older adults with acute or chronic conditions. Thirty-nine randomized controlled trails ($n = 4274$) were included. Eight studies considered older hospitalized patients, especially malnourished and admitted for hip fractures. The studies used a range of protein or EAA supplements. The authors concluded that protein and EAA

supplements may improve fat-free mass, muscle strength, and physical function (standardized mean difference = 0·21–0·27, all $p < 0.005$), and that undernourished older subjects benefitted most. In conclusion, due to the heterogeneity and low quality of studies, no definitive conclusions can be made regarding the effects of specific supplements ([70]).

Neuromuscular electrical stimulation

Neuromuscular electrical stimulation (NMES) has been proposed as a potential strategy to prevent targeted muscle atrophy and loss of muscle strength ([70]). It consists of the induction of muscle contraction by means of electrical stimuli. It has been proposed for patients unable to perform physical activity due to acute illness, i.e. ICU patients or postsurgical patients [71].

Despite this is a promising strategy, data come from small randomized trials that involved adult patients. Nonetheless, an improvement in muscle mass is demonstrated using biopsies [72] and CT scan [73], but there is a lack of data about gains in muscle strength and performance.

Combined interventions

Miller et al performed a 12-week intervention in subjects hospitalized for hip fracture. Intervention started within seven days after surgery. Participants were randomized to receive daily multinutrient energy-dense oral supplement (6.3 kJ/mL) individually prescribed for six weeks (n = 25), tri-weekly resistance training for 12 weeks (n = 25), combined treatment (n = 24), or attention control plus usual care (home visits only, general nutrition, and exercise advice) (n = 26). The outcomes were muscle strength (quadriceps), gait speed, weight change, quality of life, and health-care utilization at completion of the 12-week intervention. At 12 weeks, all groups lost weight, especially those receiving resistance training alone. Significant weight loss was prevented if supplement was consumed for at least 35 days. The groups were not different at 12 weeks for any other outcome [74].

A randomized trial in 200 patients >78 years admitted to an internal medicine ward compared patients who received a nutritional supplementation in addition to an exercise program with exercise alone. The intervention consisted of nutritional supplements (600 kcal, 20 g/day protein) added to a standard diet and a simultaneous intensive rehabilitation program. The tolerance of supplements and their influence on spontaneous food intake, self-sufficiency, muscle strength, and body composition were evaluated during the study period. Both groups of patients experienced decreases in body weight and BMI during their hospital stay. At admission, lean mass value was similar in both groups (30.9 ± 10.9 and 30.6 ± 9.1 in the control group and the intervention group, respectively), but significant differences appeared at follow-up, at 3, 6, 9, and 12 months after discharge. (control group: 27 ± 6.4; 27.4 ± 7.6; 26 ± 8.1; 28.3 ± 7.5; intervention group 31.9 ± 8.5; 30.2 ± 8.8; 29.6 ± 8.5; 31.9 ± 9.9). Nutritional supplementation and the rehabilitation program in the study group prevented the loss of lean body mass and a decrease in autonomy at six months after discharge [75].

Takeuchi et al. [76] studied the effects of branched-chain amino acids (BCCA) and vitamin D supplementation on physical function, muscle mass and strength, and nutritional status in sarcopenic older adults during hospital-based rehabilitation. A multicenter randomized parallel group controlled trial was performed during eight weeks including 68 patients. The intervention group received BCAA and vitamin D supplementation. The supplement comprised 10.0 g protein (BCAA, 2500 mg) and 12.5 µg vitamin D, and provided 200 kcal/125 mL. Beginning on the first day of the study, the supplement was ingested once a day, within 30 minutes after the end of the resistance training. Both groups underwent low-intensity resistance training in addition to the post-acute rehabilitation program. Handgrip strength, calf circumference, and BMI increased significantly in both groups over time ($p < 0.05$), with significantly greater improvements in the intervention group (p = 0.041, 0.033 and 0.035, respectively).

CONCLUSION

Although acute sarcopenia is common and it is associated with negative health outcomes, particularly in older adults admitted to the hospital, the current literature on this topic is scanty. To further limit the current evidence, the majority of studies did not perform two consecutive measurements of muscle mass and strength, which would be needed to demonstrate acute sarcopenia, but rather relied on a single measurement in patients suffering from acute conditions, thus including both acute and chronic sarcopenia.

The literature is therefore essentially limited to studies performed in older adults with acute conditions admitted to the hospital. In this population, there is limited evidence that physical exercise and nutritional support based on amino acid supplements might improve muscle performance. This condition urgently needs more research to improve knowledge of its physiopathology and allow the design and testing of more effective preventive and therapeutic interventions.

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CHAPTER 10

Sarcopenia, Frailty, and Intrinsic Capacity

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Most experts in this field will agree that sarcopenia and frailty are closely related entities, but that nevertheless one should regard them as truly distinct. The aim of this chapter is therefore to present the characteristics that are shared by them, but also to identify the conceptual differences.

INTRODUCING THE FRAILTY CONCEPT

As a prerequisite, it has to be stated that the format of this chapter does not allow to describe all aspects of the frailty syndrome in detail. Instead, the following paragraphs will provide a condensed overview on the topic and the reader is kindly referred to several recently published reviews for deeper insight [1, 2].

The term frailty had been used among laymen for decades before a conceptual basis was developed by geriatricians. In English dictionaries, frailty has been described as physical weakness and poor health, while geriatric medicine and gerontology consensus conferences agreed that frailty is characterized by a decline in functioning across multiple physiological systems and that it is associated with an increase of an individual's vulnerability for developing dependency when exposed to a stressor [3, 4]. Frailty has originally been understood as a multidimensional syndrome which involves physical, psychological, and sociological components as well. While in most older individuals the development of frailty is closely linked to comorbidity, it may also be regarded as an extreme consequence of the normal aging process. Frailty is a dynamic entity which implies that transitions between the various degrees of frailty can be

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observed [2]. From a conceptual point of view frailty is seen as chronic or at least subacute condition, while the existence of acute frailty has been seriously debated.

As a consequence of the ongoing demographic shift, the relevance of frailty for most societies across the world will persistently grow over the next decades. Its prevalence increases with age, but not all older individuals finally will become frail. Frailty is more common in females than in males and its prevalence is also influenced by socioeconomic factors. In community-dwelling older individuals beyond age 65 the frailty prevalence has been reported between 12 and 16% depending on the applied diagnostic criteria [5, 6]. Much higher frailty rates around 50% have been reported for nursing home residents [7] and when serious chronic comorbidities were present as, for example, end-stage renal disease or hematological malignancies. At the moment, it is still not clear, whether frailty prevalence has been decreasing or increasing in successive birth cohorts.

Frailty is an important risk factor for negative health outcomes like declining functionality, falls, fractures, hospitalization, disability, nursing home admission, and mortality [8–10]. It is also associated with lower quality of life and increased health-care costs [11].

While the clinical relevance of frailty has not been debated in recent years, there is still no general agreement which instruments should be used for its diagnosis. As a consequence of this absence of an international consensus there has been also no universally agreed set of diagnostic criteria for this syndrome. During the past two decades, more than 50 frailty tools have been developed and the number is still growing, as medical specialties, e.g. cardiology and abdominal surgery, have started to develop frailty tools for their specific patient populations. The decision which tool may be most appropriate will also be influenced by the setting in which frailty should be diagnosed. The amount of time that can be spent on a frailty diagnosis will differ in most cases between a GP's office and a hospital setting as the consequences of a frailty diagnosis will possibly also be different. In the first case, it will be most likely a screening effort which may be followed by a complete geriatric assessment, while in non-geriatric hospital setting the frailty diagnosis will in most cases assist to calculate the risk for a planned intervention, diagnostic or therapeutic, in a vulnerable older individual. The choice may also be different if a frailty diagnosis is needed for research purposes.

THE PHYSICAL PHENOTYPE ACCORDING TO FRIED AND THE DEFICIT MODEL ACCORDING TO ROCKWOOD

The two most widely utilized approaches are the phenotypic definition of frailty developed by Fried and co-workers based on data from the Cardiovascular Health Survey [12] and the Frailty Index developed by Rockwood and co-workers [13].

The Fried definition proposes five items (Table 10.1): weight loss, exhaustion, weakness, slow walking speed, and low levels of physical activity. Frailty is diagnosed when at least three criteria are met. An individual is categorized as pre-frail when one or two of these criteria are present. Based on the results of several recent studies, the criterion weight loss may be regarded as one-sided, as high body mass index (BMI) values above

Table 10.1 Criteria for the phenotypic definition of frailty developed by Fried et al. [12].

• Weight loss:	>5 kg/a
• Exhaustion:	depression scale CES-D (2 points)
• Weakness:	grip strength (lowest 20%)
• Gait speed:	5 m (slowest 20%)
• Low physical activity:	kcal/week (lowest 20%)
Diagnosis of frailty:	3 or more criteria met.
Diagnosis of pre-frailty:	1–2 criteria met.

Source: Modified from Fried et al. [12].

30 kg/m^2 are also associated with a loss of functionality and independence, both of which are closely related to frailty. Furthermore, weight loss thresholds given in the Fried criteria may be too high for the European population, as shown in a study on community-dwelling older persons [14]. This is corroborated by the act that in most trials using the Fried criteria, small adaptations of the original definition have been utilized [15]. While the Fried criteria show good applicability in the research setting, it is highly unlikely that they will gain wider acceptance in clinical routine. For example, in older hospital patients and especially those admitted to geriatric departments it may prove difficult to assess frailty according to Fried as the majority of patients may not be able to perform the gait speed test. With regard to the hospital population, one should also consider that in many instances any physical testing may be overshadowed by the symptoms and complications of acute disease and the results may not represent a person's pre-admission frailty level. In addition, general practitioners will most likely regard the application of the Fried criteria too time consuming. The use of a questionnaire like the validated FRAIL scale may therefore be considered a valuable alternative that can be completed in the vast majority of patients with only a limited investment of resources [16].

For the calculation of the Frailty Index by Rockwood, it is necessary to tick off a number of prespecified deficits that are present in an individual [17]. In the most extensive variant provided by Rockwood and co-workers, 70 deficits were used for the evaluation of frailty (Table 10.2). These included active diseases, ability to perform activities of daily living, and physical signs from clinical and neurological examinations. The presence of each deficit scored one point. Theoretically, but not practically, a maximum score of 70 was possible. The Frailty Index is calculated by the sum of scores of present deficits divided by 70. The highest number of deficits the authors found in any setting was 47 [17]. In more stripped-down version of the Frailty Index, the number of deficits has been reduced to 40. However, it will prove very unpractical to apply the Frailty Index under clinical conditions, as it will too time consuming. However, several research groups have recently demonstrated that routine data sets that are available in electronic form may be used to calculate Frailty Indexes that are not identical with those established by Rockwood but that are based on the same concept and that were prove to have adequate prognostic validity. Under these circumstances the concept of Rockwood will most probably retain major relevance for specific applications, e.g. among community-living individuals for screening purposes and in public health in the context of resource estimations.

Table 10.2 List of variables used for the 70-item Frailty Index by Rockwood et al. [13].

Changes in everyday activities	Mood problems	Others
Head and neck problems	Feeling sad, blue, depressed	Seizures, generalized
Poor muscle tone in neck	History of depressed mood	Syncope, blackouts
Bradykinesia, facial	Depression	Headache
Bradykinesia, limbs	(Clinical impression)	Cerebrovascular problems
Problems with getting dressed	Sleeping changes	History of stroke
Problems with bathing	Restlessness	History of diabetes mellitus
Problems carrying out personal grooming	Memory changes	Arterial hypertension
	Short-term memory impairment	Peripheral pulses
Urinary incontinence		Myocardial infarction
Toileting problems	Long-term memory impairment	Arrhythmia
Poor muscle bulk		Congestive heart failure
Rectal problems	Changes in general mental functioning	Lung problems
Gastrointestinal problems		Respiratory problems
Problems with cooking	Onset of cognitive symptoms	History of thyroid disease
History of Parkinson's disease	Clouding or delirium	Thyroid problems
Problems with going out alone	Paranoid features	Malignant disease
Impaired mobility	History relevant to cognitive impairment or loss	Breast problems
Musculoskeletal problems		Abdominal problems
Tired all the time	Family history relevant to cognitive impairment or loss	Presence of snout reflex
Abnormal muscle tone in limbs		Palmomental reflex
Impaired limb coordination	Impaired vibration	Cardiac problems
Impaired coordination, trunk	Tremor at rest	Other medical history
Poor standing posture	Postural tremor	
Irregular gait pattern	Intention tremor	
Skin problems	Suck reflex	
	Family history of neurodegenerative disease	
	Falls	

Source: From Rockwood et al. [13]. © 2005 Canadian Medical Association.

Another frailty tool that has gained wider acceptance is the semi-quantitative Clinical Frailty Scale (CFS) (Figure 10.2), which was developed as an outcome of the Canadian Study of Health and Aging and which offers nine categories covering the spectrum from "very fit to terminally ill." The CFS relies on accurate clinical judgement only, but in most cases, it only needs very little time for completion. Some

research groups advocated the use of function tests only for frailty assessment. In this regard the gait speed test and the short physical performance battery have received the most attention up to now [18, 19].

At the moment, it is still very much debated whether individuals that have been identified as being frail or pre-frail should be targeted directly by an intervention program or whether this diagnosis should lead to a more thorough analysis of individual etiologic factor that should be specifically targeted. Puts et al showed in their systematic review on interventions that intended to prevent or reduce the level of frailty in community-dwelling older adults that only programs that included physical activity were proven effective in this population [20].

SARCOPENIA AND FRAILTY – OVERLAP AND DIFFERENCES

Also, with regard to the growing awareness of the two syndromes beyond geriatric medicine it is important to underline the existing differences but also to acknowledge shared traits. It is obvious that the diagnostic criteria for the physical phenotype of frailty which include handgrip strength and gait speed overlap with the diagnostic criteria for sarcopenia. From a theoretical point of view, sarcopenia is a main contributing factor in the pathogenesis of frailty according to Fried (Figure 10.1). In addition, both syndromes share several etiologic factors that are related to the aging process itself and also to comorbidities, for example inflammatory processes, reduced physical activity, endocrine factors, and nutritional deficits.

However, the two syndromes differ with regard to certain diagnostic traits that are included in the frailty criteria of Fried and especially in the list of Rockwood, but that are absent among the diagnostic criteria for sarcopenia. For example, the physical phenotype addresses weight loss, fatigue, and physical activity, and the Rockwood

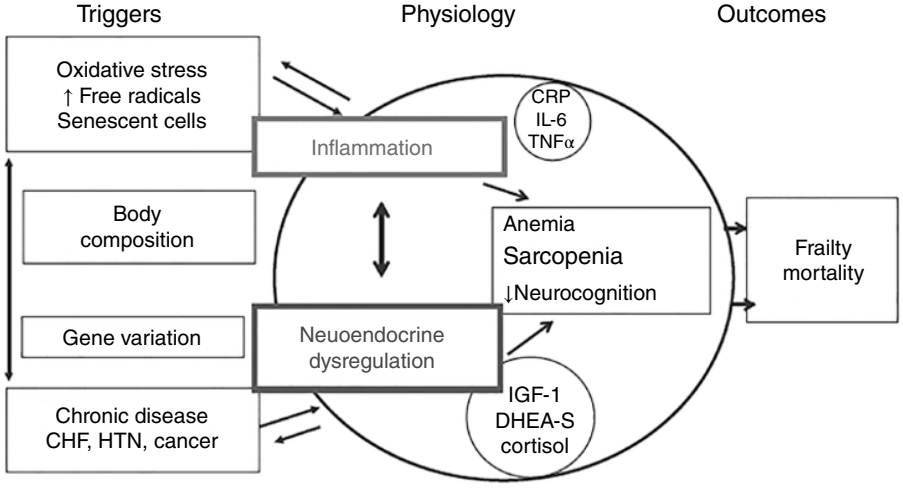

Figure 10.1 Modal pathway to adverse outcomes in older persons. *Source*: Adapted from Walston J 2007 (personal communication).

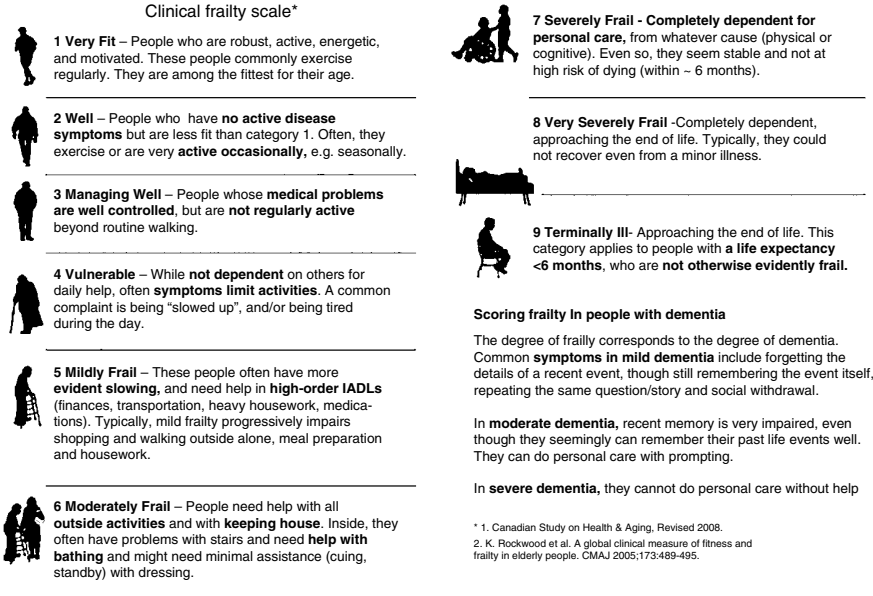

Figure 10.2 Clinical frailty scale. *Source*: From Geriatric Medicine Research, Dalhouse University, Halifax, Canada 2007–2009. Version 1.2. All rights reserved.

index goes far beyond mere physical aspects of this syndrome as it includes a wide array of deficits, e.g. cognitive deficits, and comorbidities. How do these differences affect studies on the prevalence of the two syndromes?

In a study from the United States that included medical outpatients between age 50 and 90 and that applied the FRAIL scale for the diagnosis of frailty and the SARC-F for the diagnosis of sarcopenia, 32.3% were non-frail, 38.9% pre-frail, and 28.8% frail, while 29.3% of the sample were identified to have sarcopenia [21]. In a recent Japanese study in cardiologic and diabetic outpatients, a frailty prevalence of 24% was reported when modified Fried criteria were applied, while the prevalence of sarcopenia according to the Asian Working Group for Sarcopenia (AWGS) was 31%. The authors observed a relevant overlap between these two syndromes. Approximately, 60% of the frail subjects were also sarcopenic and 40% of those with sarcopenia were also frail [22].

In general, it has to be acknowledged that the overlap between the two syndromes varies widely as a consequence of the diagnostic tools that are applied and of the population which is investigated. Reijnierse et al. applied different tools for the diagnosis of sarcopenia and frailty in a geriatric outpatient population [23]. They found that the prevalence rates for sarcopenia varied between 17 and 22% and that those for frailty varied between 29 and 33%. They reported only little concordance with regard to intraindividual prevalence rates of the two syndromes. In their geriatric outpatient population sarcopenic patients showed a greater overlap with frailty than frail patients with sarcopenia. This observation may be interpreted as being supportive of the general observation that sarcopenia is an essential contributing factor to frailty, while frailty may be regarded as a much boarder, multidimensional concept. The latter is reflected especially by the concept of the frailty index which was developed by Rockwood and co-workers.

THE FUTURE RELEVANCE OF FRAILTY

The relevance of the sarcopenia concept has already been acknowledged far beyond the field of geriatric medicine which is especially true for the application of this concept in oncology, nephrology, and cardiology. More medical specialties will surely follow. However, an even wider scope of applications has been developed for the frailty concept which includes among others

- the identification of etiologic factors for accelerated functional decline during the aging process,
- the stratification of patient populations according to risk for diagnostic and therapeutic interventions,
- public health issues in the context of health care and nursing costs in older populations [24].

To gain wider acceptance in the medical community of routine frailty screening it may prove necessary to distinguish the two geriatric syndromes more than was done so in the past and to avoid significant overlap as much as possible.

In the context of risk stratification of patient populations, the frailty concept allows to integrate functional decline and already existing deficits across multiple systems with special emphasis on the musculoskeletal and the cognitive system. The concept of the Rockwood Frailty Index includes traits of functional decline up to disability and comorbidity as well. Thereby it offers higher prognostic validity than the more limited approach of Fried. However, even in its 40-item version the Rockwood index will not be suitable instrument for clinical routine and less so even among general practitioners in the community. Less time-consuming instruments are required to guarantee wider acceptance in both settings. At the moment, it has not yet been clear whether different medical specialties have to develop specific frailty instruments for their patient populations or whether already established instruments can be shared across different patient populations.

Another concept for the application of frailty that has been adopted especially in France and in the United Kingdom introduced the screening for frailty in the community to target vulnerable older individuals who should receive a comprehensive geriatric assessment. The latter will identify the individual deficits which should be targeted by specific interventions. In the process of the identification of vulnerable older individuals who are pre-frail or frail among community-living older persons electronic frailty scores that are derived from routine electronic data sets in the hospital and from general practitioners may prove valuable [25, 26].

INTRINSIC CAPACITY

A drawback of both the diagnosis of sarcopenia and the frailty syndrome is due to the fact, that they concentrate on deficits. Older adults, both with normal aging or chronic illnesses adding up to multimorbidity, can only partly be captured when concentrating only on deficits. An approach more focused on remaining resources would therefore help when planning and implementing adaptive therapies in this older vulnerable population.

Resilience as a counterpart to frailty would here serve as a counterbalancing approach. Nevertheless, resilience historically focuses more on psychological resources of humans. A construct also involving the physical domain including muscle function and mass – including the diagnosis of sarcopenia – of older adults would therefore be of substantial help. The Clinical Consortium on Healthy Ageing (CCHA) within the World Health Organization (WHO) has started to develop such a diagnostic tool some years ago. Integrated Care for Older People (ICOPE) is a community-based approach. ICOPE represents a shift from earlier approaches that targeted on specific – mainly single and organ-oriented – diseases to address the person as a whole by using a person-centered integrated approach [27]. Such a tool also emerges as an important attempt when patient value-based care becomes a key domain within the health systems of a global scale. The ICOPE screening tool is called “intrinsic capacity” (IC) [28, 29]. The IC screening tool has emerged out of this project. In 2019, it has been pilot-tested globally (China, France, India, Japan, Mexico, Spain, and Thailand) [30].

The ICOPE screening tool – intrinsic capacity – captures six key domains:

- Cognitive decline
- Limited mobility
- Malnutrition
- Visual impairment
- Hearing loss
- Depressive symptoms

IC includes muscle function and by that possible sarcopenia from two different angles:

- limited mobility
- malnutrition

IC can therefore help health and social services to provide a more person-centered and coordinated model of care to support the functional status and abilities of older adults.

The ICOPE screening approach is built up by different steps:

- Screen
  - for losses in intrinsic capacity
- Person-centered assessment in primary care
  - Assess in greater depth for conditions associated with loss in IC
  - Assess and manage underlying diseases
  - Assess and manage social and physical environments
- Personalized care plan
  - Person-centered goal setting
  - Multidisciplinary team
  - Design a care plan including multicomponent interventions, management of underlying diseases, self-care and self-management, and social care and support
  - Referral and follow-up
- Ensure referral pathway and monitoring of care plan
- Engage communities and support caregivers

Taken together, muscle function more than muscle mass, is a cornerstone for functionality and intrinsic capacity of older adults. Both preventive and therapeutic measures to prevent muscle function and loss until sarcopenia becomes overt is therefore of upmost importance.

Whereas sarcopenia has given an ICD code recently, both frailty and Intrinsic capacity has not yet gained such a classification note. This for the time being renders sarcopenia in the forefront of research including the development of specific pharmacological treatment strategies in addition to optimizing exercise and nutritional interventions. Nonetheless, a more integrated approach as aimed by the WHO would more capture the multifaceted functional problems many older adults face. To this respect, the newly published international definition of sarcopenia pointing more on muscle function

than muscle mass opens new diagnostic and therapeutic opportunities. It is hoped that IC by including functional aspects of muscle is a good step ahead.

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CHAPTER 11

Osteosarcopenia

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INTRODUCTION

The musculoskeletal system, like all bodily systems, deteriorates with age. Once a threshold has been reached whereby there is a simultaneous loss of muscle and bone mass, as well as muscle strength and functional capacity, osteosarcopenia occurs [1]. The addition of sarcopenia to osteopenia/osteoporosis was first coined in 2009 (by Binkley and Buehring) as "sarco-osteopenia" [2]. Since then, concomitant muscle and bone wasting has evolved to "osteosarcopenia" [3], and has been identified as a case of geroscience [1]. The socioeconomic burdening of osteoporosis and sarcopenia are significant [4], and are markedly greater when these diseases collide. The impact on health-care systems and an older person's mobility and quality of life is monument [5], stressing the need for a dual preventive approach. Considering this, in addition to the increase in the aging population of which one-third of older adults (≥65 years) suffer from an injurious fall each year [6], there is a drastic need to educate researchers and health-care professionals on the pathophysiological processes underpinning osteosarcopenia, as well as its epidemiology, clinical assessment, and treatment. This chapter aims to provide an overview of the aforementioned pertaining to the latest scientific evidence.

PATHOPHYSIOLOGY

Genetics

Hereditary factors are involved in the pathology of numerous diseases, and osteoporosis and sarcopenia are no exception to this. Along with lifestyle factors, genetics determine the muscle and bone homeostasis [1]. Among 1757 Danish twins, roughly

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

52% [confidence interval (CI): 48–55%] of the variation in grip strength could be attributed to genetics [7]. The contribution of whole-body muscle mass (estimated by bioimpedance analysis) also associates with genetic phenotypes among Danish men and women [8]. Similarly, around 50–80% of bone mineral density (BMD) was accounted by genetic factors [9]. Recent work from the UK Biobank found 518 genetic loci that were linked to BMD attained from the heel ultrasounds of 426 824 adults [10].

These advancements in the field have resulted in larger, genome-wide association studies, which have identified multiple pleiotropic genes linked to muscle and bone. For instance, a meta-analysis of 10 414 children estimated the shared genetic component between lean mass and BMD at 43% (95% CI: 29–56%) with the single nucleotide polymorphism (SNP) heritability estimated at 39% (95% CI: 30–48%) [11]. Among this bivariate analysis, variants in the *sterol regulatory element binding transcription factor 1 (SREBF1)*, which regulates fat metabolism, was strongly associated with both BMD and lean mass [11]. Another gene *METTL21C*, known to regulate protein degradation, is thought to have pleiotropic effects on muscle and bone [12]. This protein reduces the number and size of myocytes and induces apoptosis of osteocytes in cell lines [12], seemingly via upregulation of the nuclear factor NF-κB inflammatory pathway [13]. Several other genes involved in the structure and function of muscle and bone have been identified which include, but are not limited to, the genes *MC4R, FTO, MGMT, TCF4, TMEM18, LINC01104, PEX14, SLC8A1*, and *TGFA* [14].

Mechanical

Muscle and bone are connected anatomically and form a large portion of the musculoskeletal unit. Like muscle mass [15], bone accrual begins from birth until the third decade of life and is stable until around the fourth decade, and decreases thereafter [16]. The size, shape, architecture, and composition of these tissues are highly responsive to lifestyle factors. For instance, both tissues adapt in response to physical loading (i.e. mechanical forces and gravity) [17, 18] and unloading (i.e. bed rest) [19], and deteriorate across the life span [15, 20]. Along with advancing age, physical inactivity is a major risk factor for both osteoporosis and sarcopenia, and lean body mass is strongly associated with bone mass [21]. Due to this parallel, research has investigated whether a bidirectional relationship exist between these two diseases.

In older men and women, low muscle mass, strength and function associates with low BMD [22]. Likewise, among the SarcoPhAge cohort, clinically relevant declines after one year were observed between appendicular lean mass and bone density (at the hip and neck) [23], while reductions in muscle strength were also associated with loss of bone density over the same time period. A four-year trial of older Koreans also found the incidence of osteoporosis was predictive of sarcopenia [24], while in the opposite direction sarcopenia increases the risk of osteoporosis [23]. It should be noted that muscle anabolism is more rapid than bone formation during early life [25], and as such, some posit that the external forces placed on muscle during physical loading are transferred to the skeleton to drive BMD [17]. While this theory holds merit, the abovementioned cross-sectional and longitudinal studies suggest a two-way link between osteoporosis and sarcopenia.

Further longitudinal trials are required to better identify the bio-mechanical mechanism(s) contributing to muscle and bone wasting. One method which may aid in identifying this is to explore the molecular mechanism by which lifestyle factors such as resistance exercise (RE) can simultaneously increase muscle and bone mass. In turn, this may unravel the muscle–bone mechanical link contributing to the pathophysiology of osteosarcopenia.

Metabolic

Muscle and bone are constantly being turned over which is dependent, in part, by the ability of mesenchymal stem cells (MSC) to proliferate and differentiate into myoblasts and osteoblasts. In muscle, myotubes are formed by the ability of satellite cells to initiate myogenesis. Likewise, the number and activity of osteoblasts are paramount to bone formation. Aging of both tissues results in an impaired MSC response. This presents as a reduction of satellite cells in myofibers [26], as well as a decrease in the number and proliferation rates of osteoprogenitor cells [27]. With senescence, MSC are also prone to differentiate into adipocytes resulting in fat infiltration of both tissues which may confer lipotoxic effects on surrounding tissues [28]. This infiltration of adipose tissue is independent of any increase in visceral fat.

Nutritional factors, particularly protein intake, also play a key role in muscle and bone remodeling. Dietary protein facilitates the accretion of contractile proteins such as actin and myosin in muscle, as well as ~50% of the structural proteins (collagen) located in the bone matrix. Given that protein utilization rates decrease in both organs with age, it is unsurprising that low protein intake associates with lower lean (muscle) [29], and bone mass [30], and has been identified as an overlapping risk factor for both osteoporosis and sarcopenia thus of osteosarcopenia [1]. While the mechanistic effects of amino acids on increasing muscle protein synthesis rates are clear, the beneficial effects of a higher intake of protein on bone formation (other than aiding collagen synthesis) are still being investigated. Various pleiotropic mechanisms have recently been suggested such as stimulation of anabolic hormones and growth factors (IGF-1) or by indirectly increasing muscle mass which, in turn, may act favorably on bone formation [31]. It was recently shown that nonagenarian men with osteosarcopenia, but not women, exhibited lower IGF-1 values than non-osteoporotic or non-sarcopenic controls [32].

There is a myriad of other pathological conditions which contribute to muscle and bone wasting, including abnormal hormonal profiles (i.e., menopause and male hypogonadism), hyperthyroidism, malnutrition, diabetes mellitus, glucocorticoid treatment, and low calcium and vitamin D status [3, 33]. Considering the latter, there is now strong evidence from various models indicating that the vitamin D receptor (VDR) plays a role in muscle and bone loss. In postmenopausal women, associations between VDR genotypes and upper- and lower-limb strength have been observed [34]. In addition, vitamin D deficiency [35] or complete deletion of the VDR [36] results in impaired myogenesis and sarcopenia. Likewise, the biologically active form of vitamin D and its receptor are essential for bone growth and health [37], and three-year supplementation with a vitamin D analogue eldecalcitol prevents fractures in osteoporotic patients [37]. More recently, in vivo and vitro works have shown that expression of

receptor activator of nuclear factor kappa-B ligand (RANKL) is expressed in not only bone, but muscle too [13]. RANKL inhibits osteoclastogenesis [38] and activates the nuclear factor NF-κB inflammatory pathway inhibiting myoblast differentiation [13], resulting in osteoporosis in postmenopausal women [39], as well as muscle dysfunction in humans and rodents [13]. Taken together, these findings highlight a possible avenue by which drug treatments may act to curb osteosarcopenia via upregulation of IGF-1 and VDR or inhibition of RANKL.

Muscle and bone interactions

Muscle and bone were previously viewed as distinct mechanical organs; however, there is now established evidence of biochemical cross talk between these tissues [40] (Figure 11.1).

Myokines, a family of cytokines which are formed, expressed, and circulated by myocytes, have shown to exhibit effects on bone via endocrine and paracrine signaling [41]. Examples of such myokines include myostatin, IGF-1, fibroblast growth factor-2 (FGF-2), interleukin (IL)-6, IL-15, and irisin [3] (Table 11.1). Of these, myostatin, also known as growth and differentiation factor 8, has consistently shown to be catabolic to

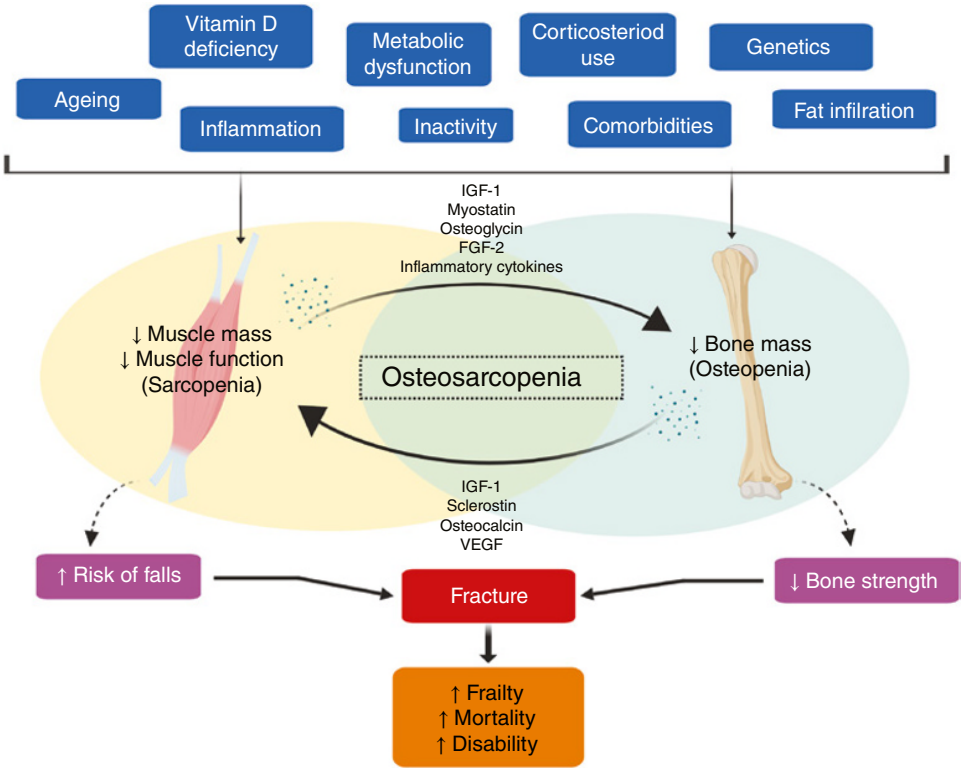

Figure 11.1 Muscle and bone cross talk, pathophysiology, and clinical outcomes in osteosarcopenia. *Source*: Adapted from Kirk et al. [1].

Table 11.1 Factors released by muscle and bone.

Muscle–bone effects	
Myostatin	Catabolic
IGF-1	Anabolic
FGF-2	Anabolic
IL-6	Catabolic
IL-15	Anabolic
Irisin	Anabolic
Osteonectin	Anabolic
Osteoglycin	Anabolic
Bone–muscle effects	
Osteocalcin	Anabolic
Sclerostin	Catabolic
Present in muscle and bone	
Fatty infiltration	Catabolic

IGF-1: Insulin-like growth factor 1; FGF-2: Fibroblast growth factor 2; IL-6: Interleukin-6; IL-15: Interleukin-15.

muscle and bone [42]. In the presence of myostatin, osteoblast activity is impeded [43], while inhibition of myostatin increases lean mass and bone strength in rodents [44]. Growth factors too, such as IGF-1 and FGF-2, secreted by myokines positively increase bone remodeling via proliferation and differentiation of osteoblasts in human bone [45, 46]. More evidence of cross talk between muscle and bone comes from interleukins, which are secreted in response to muscular contractions. IL-6 inhibits osteoblast differentiation and increases osteoclast activity [47]. In contrast, irisin, upregulated during endurance exercise, acts to increase energy expenditure by stimulating adipose tissue from white to brown in muscle [48], while preventing osteoclastogenesis via the inhibition of RANKL [49]. Of note, irisin as a therapy in mice exposed to hind-limb unloading enhanced cortical and trabecular bone density, and prevented muscle atrophy [50], suggesting a possible role for osteoporosis and sarcopenia treatment. Other myokines displaying cross talk with bone include the following: IL-15, capable of reducing adipose tissue accumulation and promoting bone mineral formation [51]; osteonectin with its anabolic effects on bone [47]; and osteoglycin, which may regulate bone formation by matching it to energy homeostasis [52].

In regards to factors released by bone, osteocalcin produced by osteoblasts has endocrine effects on various tissues including muscle, where it has shown to increase beta-cell proliferation [53]. Moreover, in a study of postmenopausal women (>70 years), normative levels of osteocalcin were strongly associated with lower limb strength [54]. in vivo work on mouse models have also established a role of osteocalcin in preserving muscle mass by promoting muscle protein synthesis in myotubes [55]. Meanwhile, sclerostin, a glycoprotein produced by osteocytes promotes the differentiation and proliferation of myoblasts, with long-term deficiency suggested to be detrimental to muscle [47].

In more recent times, our laboratory has discussed the role of ectopic fat infiltration in muscle and bone [3, 28]. Indeed, intramuscular and bone marrow fat creates a lipotoxic environment, which is characterized by increased circulating inflammatory markers such as IL-6 and tumor necrosis factor alpha [56]. In bone, the accumulation of marrow fat associates with declines in density and increases fracture risk [57], while

intramuscular fat is linked to frailty and declines in mobility [58]. Our laboratory has recently investigated the impact of palmitic acid, the most abundant saturated fatty acid in intramuscular fat and bone marrow. Our findings demonstrate a lipotoxic effect of palmitic acid, with this fatty acid shown to decrease osteoblast differentiation [59], and osteocyte survival [60]. These findings open a possible avenue by which a palmitic acid may act as a future diagnostic marker or therapeutic target for osteosarcopenia [28].

EPIDEMIOLOGY

Prevalence

The prevalence of osteosarcopenia is dependent upon the population examined and the definition applied. Prevalence estimates increase if osteopenia is included in the definition, and the association of osteosarcopenia with negative outcomes remains with this inclusion [61]. More dramatic is the variability of osteosarcopenia prevalence estimates when different sarcopenia definitions are applied [62]. A recent systematic review and meta-analysis identified 17 studies examining osteosarcopenia prevalence and outcomes across both inpatient and community settings [62]. Five different definitions for the sarcopenia component were applied [63–67] and the prevalence of osteosarcopenia ranged from 5 to 40% [62]. Prevalence is greatest among high-risk groups such as those who fall or have fractured (27.2–40%) but remains significant among community-dwelling older adults (10.4–28%) [5, 68–71].

Clinical outcomes

Key clinical outcomes by which geriatric syndromes can be measured include associations with falls, fractures, and mortality [72]. Perhaps the most important feature of osteosarcopenia is its association with adverse outcomes. Associations of osteosarcopenia with negative outcomes have been mixed in mostly cross-sectional, and some longitudinal, studies [62]. However, similar to the variability of osteosarcopenia prevalence estimates, associations of osteosarcopenia with negative outcomes are dependent on the population studied and the definition applied. Older adults with sarcopenia have a greater relative risk (RR) of fracture than those without sarcopenia (RR 1.37, 95% CI: 1.18–1.59; $p<0.05$) [62]. BMD is also lower in those with sarcopenia than those without sarcopenia [62]. A recent cross-sectional study in a high-risk population of community-dwelling older adults found a strong association with falls and fractures when applying the EWGSOP2 definition for sarcopenia [61]. In contrast, two recent longitudinal studies of community-dwelling older men did not find an association of osteosarcopenia with falls, fractures, or mortality, beyond the association of osteosarcopenia's component parts with these outcomes [73, 74]. However, one of these studies did not use a current definition of sarcopenia [75]. A one-year follow-up study of older adults with hip fracture showed that those with osteosarcopenia had a significantly greater mortality risk at one year (15.1%), than those with sarcopenia (10.3%)

or osteoporosis alone (5.1%) [70]. Until consensus is achieved on the operational definition of sarcopenia, and accurate determinations of muscle mass are applied in longitudinal studies, questions of the true impact of osteosarcopenia on older adults will remain unanswered.

CLINICAL ASSESSMENT

Assessment for osteosarcopenia is an integral component of the comprehensive geriatric assessment [76]. A clinician assessment for osteosarcopenia is far more than mere diagnosis; it includes a thorough medical history, risk-factor (including falls) identification, physical examination, functional assessments, and person-specific investigations [77]. Accepted definitions of osteoporosis, osteopenia [78], and sarcopenia [75] need to be applied. Unlike sarcopenia, the reference values for low BMD are globally accepted. Indeed, osteopenia and osteoporosis are defined as equal to or less than −1 and −2.5 standard deviations (respectively) below the peak bone mass of a young healthy population, with diagnosis of osteoporosis also made in the presence of a minimal trauma fracture [78].

History

Clinicians should consider the possible causes, symptoms, and impact of osteosarcopenia when taking a history. Given the frequency of concomitant sensory or cognitive deficits in older comorbid adults, collateral history from next of kin, carers, and involved health-care professionals may be required. Secondary causes of osteosarcopenia may be activity-related, disease-related, or nutrition- and medication-related (Figure 11.2). Examining these factors may guide management focused on optimizing individual characteristics contributing to osteosarcopenia. If there is a history of falls, clinicians should be highly suspicious that osteosarcopenia may be present. Falls are a major risk factor for fractures, and falls may also be a sign of sarcopenia. A comprehensive falls assessment involves a thorough history and physical examination, aimed at addressing modifiable falls risk factors [77].

While there is no risk-calculation tool yet available for osteosarcopenia, numerous screening- and risk-calculation tools are available for osteoporosis and sarcopenia. The SARC-F is a five-item questionnaire and is recommended [75, 79, 80] to assist in sarcopenia case-finding. There are numerous tools available for fracture risk calculation, the most common of which is the FRAX © [81]. The FRAX © can be used with or without BMD assessment, and has been validated across global populations [81].

Physical assessments

A variety of physical assessments are at the clinician's disposal when assessing for osteosarcopenia. The choice of physical assessment(s) is largely dependent on the clinician's preferred definition of sarcopenia. The two most useful physical assessments are the measurement of hand grip strength (kg) using a hand-held dynamometer, and

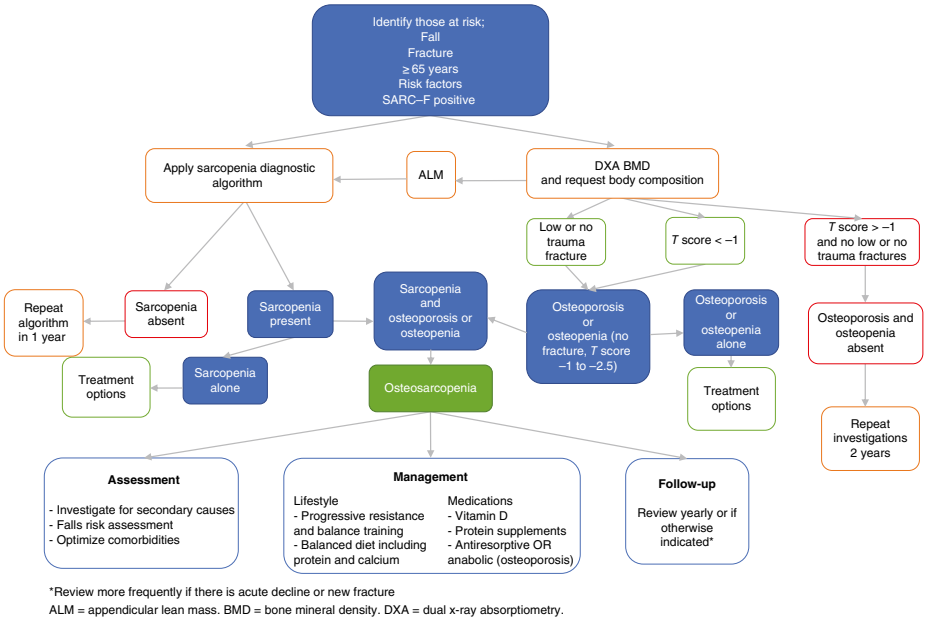

Figure 11.2 Algorithm for the clinician's approach to osteosarcopenia.

calculation of walking speed (m/s) over 4 m [77]. Handgrip strength is a key measure of muscle strength, and is a component of the most commonly cited definitions of sarcopenia [66, 75, 82, 83]. Walking speed is the most well-studied indicator of physical performance, and is measured over a 6-m course with 1-m lead-in and -out [84]. Walking speed of less than less than 0.8 m/s is a strong predictor of physical limitation and mortality risk [63]. An alternative measure of muscle strength contained within the EWGSOP2 definition is the time take to complete five chair sit-to-stands [75]. Other measures of physical performance include the short physical performance battery (SPPB), the timed up and go test (TUG), and the 400-m walk test [75]. While these alternative measures offer the clinician a greater number of assessment options, clinicians should be aware that the interchangeable application of these measures can result in markedly varied prevalence estimates within the same population [85].

Investigations

The key parameters of interest in osteosarcopenia relate to muscle mass/quantity, or quality, and BMD. Multiple diagnostic tools are available to assess these parameters, with various levels of accuracy and application. The most commonly used tool is dual-energy x-ray absorptiometry (DXA). DXA has the advantage of being able to accurately determine BMD, but also measures body composition including fat and lean mass. Appendicular lean mass (ALM) approximates muscle mass and is a component of recent sarcopenia definitions [67, 75].

DXA-determined BMD is a key tool for assisting in the prediction of fracture risk, in addition to monitoring individual response to antiresorptive and anabolic therapies. Other tools that can be used in the diagnosis of low BMD include peripheral DXA (pDXA), quantitative computed tomography (QCT), quantitative ultrasound (QUS), and radiographic absorptiometry. A majority of people who sustain minimal trauma fractures have BMD in the normal or osteopenic range, due to the distribution of BMD across the population [77]. Thus, techniques for BMD assessment have high specificity but low sensitivity in fracture prediction [86].

The indications for BMD assessment include:

- Women ≥65 years, and men aged ≥70 years;
- Younger postmenopausal women and women in menopausal transition;
- Men aged 50–69 years with risk factors for fracture;
- Adults who have a fracture at, or after the age of 50 years; and
- Adults with a condition (e.g. rheumatoid arthritis) or taking medications (e.g. glucocorticoids greater than 5 mg per day for three months) associated with low bone mass or bone loss [86].

Whole body magnetic resonance imaging is the only clinically available diagnostic tool that accurately measures muscle mass or volume. However, this is certainly not practical or feasible in application. Current diagnostic methods include surrogates or approximations of muscle mass, such as ALM for DXA, and fat-free mass using bioelectrical impedance (BIA). Current definitions of sarcopenia incorporate DXA and BIA approximations of muscle mass in their definitions [75], with various adjustments

[including for height^2, weight and body mass index (BMI)]. Another diagnostic technique of interest is peripheral QCT, which can also measure intramuscular adipose tissue (IMAT). IMAT may be a measure of muscle quality, and is unrelated to obesity [28].

More recently, the creatinine D_3 dilution method (D_3Cr muscle mass) has been a focus in the sarcopenia field. Labeled creatine is taken orally by persons and converted to creatinine in a steady, non-enzymatic process within skeletal muscle. A morning urine sample is collected three to five days later and the ratio of labeled to unlabeled creatinine is measured via mass spectrometry, which through a correction algorithm can accurately estimate muscle mass [87]. D_3Cr muscle mass has a strong relation with falls, fractures, and mortality risk [88, 89] in older men. However, further study is required in representative longitudinal samples to determine its application, and currently the technique is not clinically available.

TREATMENTS

Non-pharmacological

RE promotes increases in lean body mass [90], strength [91] and functional capacity [92] in older adults, even in the oldest old residing in nursing homes [93]. Reductions in fat mass [29], and IMAT [94], are also achievable with prolonged interventions in sarcopenic elders. Therefore, it is recommended as the primary prevention strategy for sarcopenia by international working groups [79]. Similarly, RE has an osteogenic effect on bone mass evident from multiple clinical trials [95, 96] and meta-analyses [97–100] in aged men and postmenopausal women, although its feasibility and efficacy in reducing fracture risk in those with severe osteoporosis warrants further investigation [101]. The intensity of exercise appears to be an important factor, with high-intensity RE [96] or impact exercise (hopping and jumping) needed to elicit clinical gains in BMD [101]. Daily activities and other cardiovascular based-exercises (swimming, walking, gardening) are not sufficient to stimulate osteoblastogenesis [102], and should not be recommended as an osteoporosis treatment.

The benefits of RE can be augmented by increasing the intake of dietary protein [103, 104], creatine [105] and vitamin D [106], all of which have a modulating effect on muscle and bone. Regarding the former, animal proteins are superior to plant proteins due to the amino acid leucine [107]. Maintaining sufficient levels of calcium is also critical for the preservation of BMD [108]. These non-pharmacological recommendations for mitigating osteoporosis, sarcopenia, and osteosarcopenia are discussed in further detail elsewhere [31, 101, 109].

Pharmacological

Despite the promising effects of myostatin antibodies in increasing muscle and bone mass, as well as decreasing fat mass [110–112], these findings have not translated into improvements in muscle strength or functional capacity. Likewise, the development of

selective androgen receptor modulators, which do not increase the risk of cardiac events or prostate cancer [113], have shown equivocal results in aging muscle and sarcopenia [114].

To date, the most promising pharmacotherapy for the treatment of osteosarcopenia is denosumab, a human monoclonal antibody, which inhibits RANKL expression in muscle and bone. Three recent trials have shown compelling evidence in favor of denosumab to increase lean (muscle) and bone mass [13], grip strength [13], gait speed, and dynamic balance [115], as well as a reduction in falls [116] in older adults. With a direct mechanism identified, further double-blind clinical trials are underway to confirm these results. Other pharmacological targets such as marrow fat and IMAT are being explored. Overall, the future looks bright for a possible drug treatment for osteosarcopenia, which could potentiate the beneficial and dual effect of exercise and nutritional interventions on muscle and bone, or may aid those who are non-ambulatory (i.e. bed bound, post-hip fracture, etc.).

SUMMARY

Osteosarcopenia is a multifaceted, musculoskeletal syndrome, which warrants a comprehensive geriatric assessment. The pathology of osteosarcopenia encompasses genetic, mechanical, and metabolic traits, with sedentarism and malnutrition exacerbating its existence. Overlapping risk factors are shared between osteoporosis and sarcopenia, and multiple growth factors are involved in the cross talk between muscle and bone, which may manifest as osteosarcopenia. The complexity of the syndrome makes biomarkers for osteosarcopenia challenging, yet a possible pharmacotherapy with dual effects on muscle and bone is emerging. Denosumab, historically a bone-forming antibody, has now shown promise in the sarcopenia field. While excitement ensues, further double-blind clinical trials are warranted to test its efficacy. In combination with current osteoporosis treatments, for now, RE along with increased protein intake, vitamin D, calcium, and creatine are the most effective treatments to alleviate osteosarcopenia. Finally, further research is needed to investigate the synergistic effects of RE, nutritional supplementation, and muscle and bone anabolic agents to identify a hierarchy of treatment options for osteosarcopenic patients.

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CHAPTER 12

Sarcopenic Obesity

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INTRODUCTION

In humans, muscle mass and fat mass usually grow in parallel to body weight: the higher the fat mass, the higher the fat-free mass. However, this harmony can be lost in several conditions, leading to sarcopenic obesity (SO).

Age-related body composition changes (i.e. muscle loss coupled with visceral fat increase as well as deposition of fat inside muscles) may predispose to SO, in particular in people with weight gain [1–3]. Obesity itself predisposes to SO, due to decline in physical activity, subclinical inflammation, and insulin resistance [4]. Further, SO has been observed to be frequent in subjects with cancer [5], diabetes [6], and rheumatoid arthritis [7]. Weight cycling (i.e. number of cycles of weight regain after weight loss in obese subjects) has been also found to be associated with SO [8].

DEFINITION OF SARCOPENIC OBESITY

A lack of consensus on SO definition still persists. Years ago, Baumgartner et al. introduced the term SO. According to Baumgartner et al. [9], SO was defined by the concurrence of sarcopenia and high amount of fat mass (i.e. percentage of body fat greater than 27% in men and 38% in women). Sarcopenia was defined by dividing appendicular skeletal muscle mass, as assessed by dual-energy x-ray absorptiometry (DXA), by height squared (ASM/h^2), thus obtaining a relative skeletal muscle index. Individuals were defined as having class I sarcopenia when ASM/h^2 was within −1 and −2 standard deviations (SD) of the sex-specific mean of a young reference group, and sarcopenia class II when ASM/h^2 was below −2 SD of the sex-specific

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

mean of a young reference group. However, almost 15% of men and women enrolled in the New Mexico Elder Health Survey were considered to be sarcopenic obese when using this definition [9].

Later, Newman et al. [10] observed that the prevalence of SO among overweight and obese older subjects differed depending on the method used to define sarcopenia. Two different criteria for sarcopenia were used: ASM/h^2 and ASM relative to height and total fat mass computed from the residual of the linear regression used to model the relationship between ASM on height and fat mass, where a positive residual was meaning relatively muscular individual and negative a relative sarcopenic individual. Using the Baumgartner definition of sarcopenia, 8.9% of overweight men and 7.1% of overweight women were classified as sarcopenic and none of the subjects with a body mass index (BMI) >30 kg/m^2 were sarcopenic using ASM/h^2, while 11.5% of men and 14.4% of obese women were defined as being sarcopenic using the residual method. Newman et al. results clearly showed that obesity could mask the presence of sarcopenia and that Baumgartner et al. definition [9] may underestimate sarcopenia in overweight and obese subjects, thus leading to underestimation of SO. Davison et al. [11] and Zoico et al. [12] defined SO individuals as those in the upper two quintiles of body fat and in the lower three of muscle mass.

The ratio between ASM/h^2, as evaluated by DXA, and visceral abdominal adipose tissue, as evaluated by computed tomography (CT), has been suggested as a tool for SO definition [13].

In patients with solid cancer, SO has been identified by using CT scan: by choosing third lumbar vertebrae, as a standard landmark, two consecutive CT images have been selected from L3 to the iliac crest to measure cross-sectional of psoas muscles, paraspinal muscles, and abdominal wall muscles [5].

As it stands, none of above cited SO definitions are able to take into account quality of muscle, in term of fat infiltration (so-called myosteatosis) or fibrosis. They are also missing muscle function, in terms of strength and performance. It seems possible to argue that a better definition of SO should be in line with the concept extensively considered by the European Working Group on Sarcopenia in Older People [14], which developed a definition of sarcopenia that focused on low muscle strength as a key characteristic of sarcopenia, recommending detection of low muscle quantity and quality to confirm a sarcopenia diagnosis, and identifying poor physical performance as indicative of severe sarcopenia. Adjustment for BMI of the sex-specific cut-off points for muscle mass as well as of muscle function, has been also suggested [15]. Finally, the term dynapenic abdominal obesity (DAO) has been coined to define subjects with both central fat distribution and low muscle strength [16].

Debate is also still open about the most appropriate indices and cut-off of overweight and obesity in older persons, abdominal circumference measurements, widely considered a good surrogate of fat distribution and, in particular, of visceral abdominal adipose tissue, seem to be more adequate than BMI [17]. In conclusion, no consensus has yet to be found on SO in terms of definition and diagnostic criteria.

The prevalence of SO ranges, depending on the definition used, between 4.4 and 17% for males and between 3 and 14% for females in different studies [18]. For DAO the prevalence ranges from 6.1 to 12% in males and from 11 to 12.6% in females [19]. Moreover, no matter what definition is used, SO prevalence increases with aging.

PATHOGENESIS OF SO

Several mechanisms may be responsible for SO (Figure 12.1). Association between aging and SO can be explained by the fact that aging is characterized by progressive decline in muscle mass, decreased physical activity and, consequently, decline in total energy expenditure, events leading to weight gain, especially increase in visceral abdominal fat. In fact, it must be kept in mind that muscle and fat have been considered endocrine organs, as they are capable of secreting molecules that communicate with cells in autocrine and paracrine pathways and that they could share common pathways of damage [20].

Skeletal muscle, through the secretion of myokines, may mediate some positive consequences on physical activity. Irisin, a peptide produced by muscle cells during exercise, may control fat gain by stimulating transdifferentiation of white adipocytes into brite adipocytes and also by promoting the increase of UCP-1, thus increasing energy expenditure. Irisin may also determine myocite differentiation and growth, thereby promoting the expression of elevated levels of IGF-1 and reducing levels of myostatin [21]. Thus, it is possible to hypothesize that in older people reduction in physical exercise (PE) may negatively influence the production of irisin by myocytes, which leads to an increase in fat mass and to SO [22].

It is currently well known that adipocytes produce several peptides, called adipokines and that the secretory profile of adipocytes depends on their size (the greater the diameter, the higher the pro-inflammatory profile) [23]. Therefore, weight gain, thus inducing an increase in adipose cell size, may determine a discrepancy between

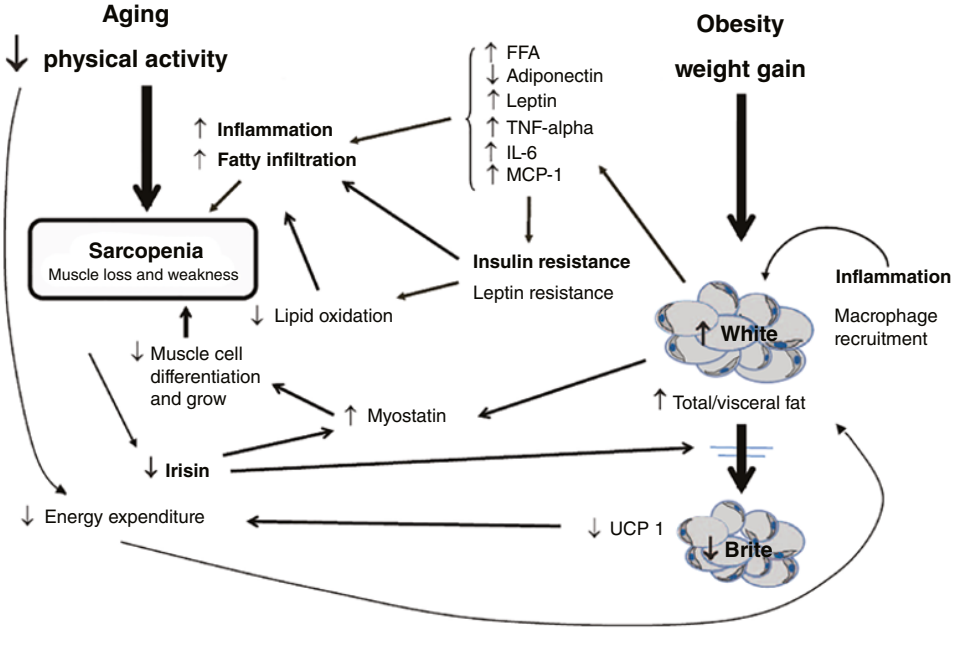

Figure 12.1 Mechanisms leading to sarcopenic obesity: interplay between adipocytes and myocytes. *Source*: From Zamboni et al. [20]. © 2018 Wolters kluwer.

pro-inflammatory and anti-inflammatory adipokines. It has also been found that aging itself may increase inflammatory profile of adipocytes. However, subclinical inflammation, derived both by aging and weight gain, may represent an important connection between sarcopenia and obesity [24].

Increased leptin levels, frequently observed in obesity and also in old subjects, may determine leptin resistance and thus decrease fatty acid oxidation in muscles, leading to fat deposition in ectopic tissues (pancreas, liver, heart, muscle), contributing to alteration of muscle quality in older obese people and lead to SO [2, 25].

Insulin resistance may also induce greater decline in protein synthesis, increase in muscle catabolism, and thus may be involved in the pathogenesis of SO [26]. Moreover, hypertrophic adipocytes produce excessive free Fatty Acids (FAs) that accumulate intra- and inter-myocytes ectopically, which determines mitochondrial dysfunction, beta-oxidation of FA alteration with increased reactive oxygen species production [27]. Coupled with the presence in older subjects of dysfunctional preadipocytes that may determine reduced adipogenesis and compromise capacity of fat cells to store FA, and excess of fat "over spilled" to non-adipose tissues. In this case, excess energy is redirected toward peripheral organs, aimed at facilitating their storage in the form of triacylglycerol [28].

However, since buffer ability of triacylglycerol becomes soon saturated, surplus lipids enter alternative non-oxidative pathways, which determines the production of toxic reactive lipids species, leading organ-specific toxic response and apoptosis. Reactive lipids can infiltrate tissues of metabolically relevant organs, such as skeletal muscle, inducing lipotoxicity, phenomenon that largely participates in pathophysiology of insulin resistance and sarcopenia [29].

Finally, increased gene expression and myostatin protein, an inhibitor of satellite muscle cell differentiation and proliferation, have been found in muscle biopsies of obese patients and may contribute to skeletal muscle damage [30].

CLINICAL IMPLICATIONS

Evidence indicates that when obesity and muscle impairment coexist, they act synergistically on the risk of developing multiple unfavorable health-related outcomes. For instance, in the New Mexico Aging Process Study cohort [9], the odds ratios for disability in sarcopenic, obese, and SO groups, relative to the group of seniors with a normal body composition, were 2.07, 2.33, and 4.12, respectively. Rolland et al. [31] confirmed these findings by showing that compared with women with a healthy body composition, those with SO had 2.60 higher odds of having difficulty climbing stairs, 2.35 higher odds of having difficulty going downstairs, and 1.54 higher odds of having moving difficulties. Baumgartner et al. [32], in eight-year follow-up of the New Mexico Aging Process Study, showed that subjects with SO at baseline were two or three times more likely to develop instrumental disability than lean sarcopenic or non-sarcopenic obese subjects.

In a cross-sectional study of 2039 men and women aged 55 years and older, where leg extension strength was measured with a dynamometer, 12% of the non-dynapenic and non-obese group had walking disability, compared with 18% of those with obesity

alone, 24% of those with dynapenia, and 36% of those with dynapenic obesity [16]. Interestingly [16] dynapenic obese subjects had a walking speed of approximately 0.14 m/s lower than the non-dynapenic and non-obese subjects, determining a difference of 2.8 seconds every 20 m distance. Furthermore, in the InCHIANTI study [19], dynapenia was found to be associated with risk of death, independently of the presence of abdominal obesity, whereas DAO was significantly associated with the risk of hospitalization and disability. We observed similar results in a study sample of men and women older than 70 years evaluated with a 10-year follow-up [33].

Some studies evaluated the association between SO and metabolic alterations and their findings are not conclusive. Aubertin-Leheudre et al. [34], in a small study sample of postmenopausal women, did not observe any difference in cardiovascular and metabolic risk factor profile between obese old women with or without sarcopenia. A longitudinal follow-up study of over 3000 older adults reported that the combination of low muscle mass and abdominal obesity was not associated with an increased risk for the development of cardiovascular disease over an eight-year follow-up [35]. However, opposite results were observed in the Korean Sarcopenic Obesity Study, an ongoing prospective observational cohort study [13]. In this population, association among SO, evaluated as ASM to visceral abdominal fat ratio, metabolic syndrome, and arterial stiffness was observed in 526 apparently healthy adults. In line with these findings are those of Lee et al. [36] who observed that the relative risk of metabolic syndrome in people with or without SO were, respectively, 1.31 in men (95% confidence interval [CI], 1.10–1.56, $p = 0.003$) and 1.17 in women (95% CI, 1.10–1.25, $p < 0.001$).

A few studies evaluated the joint effects of both sarcopenia and SO on pulmonary function. In a longitudinal study involving 77 older men and women with BMI ranging from 19.8 to 37 with a seven-year follow-up period, we observed that combination of fat free mass (FFM) loss and fat gain had additive negative effects on pulmonary function [37]. A negative relation between SO and lung function has been also observed in other studies [38–40].

Some evidence links SO to mortality. In the National Health and Nutrition Examination Survey (NHANES) 1999–2004, it was demonstrated that SO increased risk of mortality in people aged between 50 and 70 years old, but not in people aged 70 years old or older [41]. Similar results were reported in the English Longitudinal Study of Ageing [42]. Studies considering muscle strength, instead of muscle mass, demonstrate a much stronger relationship between SO and mortality. Indeed, Sanada et al. [43], in a population of 2309 Japanese American men followed up for 24 years, demonstrated that all-cause mortality increased in men with SO. It has also been demonstrated that SO is independently associated with higher mortality and higher number of complications across multiple cancer types and different treatment regimen probably because sarcopenic patients are more vulnerable to stress, or because increased fat mass could enlarge drug dosage, thereby inducing a higher rate of dose toxicity [5]. Consequently, SO screening has been suggested as a useful tool for the identification of greater risks for complications and worse outcomes in cancer patients undergoing surgical or chemotherapy treatment for several tumor types (pancreatic cancer, rectal cancer, hepatocellular carcinoma, lymphoblastic leukemia) [5].

Moreover, DAO has also been shown to be associated with increased risk of mortality: in fact, recently higher mortality risk was observed in DAO patients than non-dynapenic abdominal obese subjects (2.46 and 1.57, respectively) [19, 33].

TREATMENT

There was a debate in the past about the hazard of obesity in older persons and thus about the need for its treatment. However, since SO is associated with poor outcomes, its treatment should be considered carefully. Weight loss is usually associated with a decline in fat mass, as well as a decline in fat-free and bone mass. However, it seems crucial that any treatment of SO should cause a reduction in fat mass, in particular abdominal fat mass, preserving muscle mass quality and function. Nutritional intervention and PE remain the cornerstone of both therapy and prevention of SO. It is important to notice that SO is still an undertreated condition, despite its relatively high prevalence, in particular, among the old population.

Management of weight loss in older persons has raised concerns for years, due to the possible associated loss in lean body mass [44] and the risk of inappropriate nutritional intake. However, it has been demonstrated that appropriate weight loss, if combined with exercise, improved sarcopenia and frailty in obese older subject [45]. Treatment must be reserved only for weight-stable subjects, with life expectancy longer than at least one year, and must be carried out only by a team of expert physicians, nurses, dieticians, and physical therapists.

Energy restriction prescribed in order to induce weight loss in SO patients should be moderate, no greater than a 500 kcal/d [17]. Sarcopenic obese older adults seem to have higher protein needs due to the so-called "anabolic resistance" [46]; as a result, a dietary protein intake of 1.0–1.1 g proteins/kg of body weight should be prescribed. Accordingly, it has been recently demonstrated that a protein-enriched diet improved both body composition and muscle strength in SO women [47]. Whey protein, derived from milk, has been shown to preserve postprandial myofibrillar protein synthesis in overweight and obese adults who underwent a hypocaloric diet [48, 49]. As well as the specific amino acids content, the different protein source may also be determinant, as animal-derived ones seem to be more effective in driving muscle protein synthesis [50]. Combination of proteins and amino acids, such as leucine with vitamin D and omega-3, may enhance postprandial protein synthesis and muscle mass both in healthy older men as in obese older subject [51]. Furthermore, timing of protein intake seems important, as a more evenly distribution of dietary protein intake during the day was associated with higher muscle strength score, physical performance, and skeletal muscle mass in older adults, in both sexes [52].

PE has been shown to determine greater to reduction in fat mass, preserving fat-free mass loss and improving physical performance parameters [53]. In fact, PE determines amplified anabolic response from endogenous amino acids [54], it improves insulin resistance by increasing intramuscular IGF-1 and muscle sensitivity to blood flow glucose [52], and may activate differentiation and proliferation of skeletal muscle satellite cells, by increasing the irisin secretion.

Strategies that combine hypocaloric diet in SO subjects together with PE in order to prevent the muscle mass loss seem to be the best practice. Different types of PE should be combined in the treatment. Resistance exercise [55] has been shown to determine an increase in skeletal muscle mass as well as muscle strength [55]. Both resistance exercise and aerobic training improve physical capacity, in terms of handgrip strength [45], gait speed, and aerobic endurance (Table 12.1).

Table 12.1 Treatment of sarcopenic obesity in older adults.

Treatment of sarcopenic obesity		
Nutrition	**Physical exercise (multicomponent program)**	**Behavior**
Avoid severe hypocaloric diets	Resistance training	Group activity for nutrition and exercise implementation
250–500 kcal energy deficit	Aerobic training	Social support
Up to 1.1 g/kg high-quality protein and amino acids	Balance training	Self-monitoring techniques
Calcium and vitamin D supplementation	Flexibility	Relapse prevention

CONCLUSION

Loss of muscle mass and gain in fat seem to be linked to each other and contribute, in the presence of positive energy balance, to the development of SO. Several conditions such as aging, chronic disease, cancer, obesity, and weight cycling may be responsible for SO.

Recently, great effort has been made to improve the definition of sarcopenia, in order to get it used in clinical practice. Similar effort seems to be mandatory for SO definition. Based on more recent findings, improvements in SO definition should consider age-associated quality changes in muscles, including myosteatosis, as well as strength and function loss.

Evidence shows that SO is associated with higher risk of physical disability, morbidity, and mortality. Identification of older subjects with SO could help in the selection of a group of subjects with a particularly high health risk, and the concept of SO may help to clarify the relation between obesity, morbidity, and mortality in older persons.

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CHAPTER 13

Sarcopenia and Cognitive Impairment

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INTRODUCTION

Aging is an ongoing process with various complex characteristics, and the interplay between multimorbidity and disability poses major health challenges in later life [1–3]. Along with advanced aging, disability or functional impairment gradually outweighs multimorbidity in association with adverse outcomes in older adults [4–6]. Although functional impairments in the literature have been more commonly referred to as physical function, functional impairments may include physical, cognitive, or sensory domains. Functional impairments in these domains may occur individually or synergistically, which further jeopardizes the health of older adults [7–9]. However, functional impairments have often been examined separately and subsequently linked to different or common adverse outcomes. These functional impairments are not only highly interrelated with each other but also the cause or the consequence of each other [10]. In particular, the interaction between physical and cognitive impairments has gained extensive research attention. Physical disability and dementia are two major adverse outcomes in aging research and are of great importance to the quality of life of older people.

In cross-sectional and longitudinal studies, both associations and sequential relationships of physical and cognitive impairments have been shown, and these impairments also showed synergistic effects that increase the health risk of older adults [7, 10]. However, the occurrence of physical and cognitive impairments usually insidiously develops over time. Longitudinal studies have shown that declines in physical function may occur earlier than declines in cognition [11]; physical prefrailty and frailty have been recognized as risk factors for dementia of all types [12]. However, cognitive impairment may be divided into different processes, such as memory, executive function, language,

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

and others, although most previous studies have used decreases in global cognitive function to define cognitive impairment. Early cognitive impairment other than memory domain were usually overlooked in evaluating the sequential relationship in the development of physical and cognitive impairment in previous studies.

Sarcopenia, defined as the age-related loss of muscle mass plus the loss of muscle strength and/or reduction in physical performance, is usually considered to occur earlier than physical frailty [13–15]. The development of sarcopenia is multifactorial and involves genetic factors, developmental factors, nutritional status, chronic conditions, lifestyle factors, and many others. The development of sarcopenia overlaps with various chronic conditions, as a consequence of physical inactivity related to chronic conditions, or reflects the wasting nature of uncontrolled diseases [13, 14]. Hence, the coexistence of sarcopenia with chronic conditions, especially neurodegenerative disease or cerebrovascular disease, is not uncommon and presents a great challenge for determining the causality. Despite the difficulties in defining the causal relationships between sarcopenia and these conditions, the interrelationship between sarcopenia and cognitive impairment may play certain roles in preventing physical disability and dementia through an integrated approach. Among older adults with multimorbidity, the presence of coexisting sarcopenia and cognitive impairment complicates their care needs, which requires a comprehensive approach for assessment and care planning. Therefore, this chapter will explore the epidemiology of the coexistence of sarcopenia and cognitive impairment, as well as their development in the aging process and the potential cross talk between them.

AGING AND COGNITIVE DECLINES

Aging may be described as the gradual decline in the physiological function of individual organs or multiple organs, changes in body composition, and functional declines over time. In the assessment of physical function, muscle strength and physical performance were common indicators to define early declines in physical function as well as to provide a link to physical disability. Regarding cognitive impairment, clinicians are more familiar with that defined by global cognitive function, but global dysfunction may represent a late manifestation of cognitive declines that has limited reversibility. Clinicians usually simplify cognitive dysfunction to only declines in the memory domain and overlook declines in nonmemory domains. However, declines in nonmemory domains have been reported to appear earlier than those in memory domains and predict further cognitive impairments and adverse outcomes.

Cognitive functioning typically refers to multiple mental abilities in human beings, including learning, thinking, reasoning, remembering, problem-solving, decision-making, and attention [16]. In developmental psychology, basic constructs of cognitive functioning include general intelligence, fluid intelligence, and crystalized intelligence [16]. Crystalized intelligence is also called the "acquired knowledge" that represents the accumulation of a lifetime intellectual knowledge and achievements and may continue to increase over time. Crystalized intelligence remains stable or gradually improves at a rate of 0.02–0.004 standard deviations per year after the sixth and seventh decades of life [17]. On the other hand, fluid cognitive ability is independent of

crystallized intelligence and refers to reasoning or thinking, the speed of processing and the ability to solve problems in novel situations. In neuropsychological assessments, executive function, processing speed, memory, and psychomotor ability are referred to fluid intelligence, and these domains, especially psychomotor ability and processing speed, peak in the third decade of life and gradually decline at an estimated rate of 0.02 standard deviations per year [17]. Processing speed is the speed at which cognitive activities and motor responses are performed. Many reported cognitive changes in healthy older adults are related to the slowing of processing speed, and these changes may negatively impact neuropsychological performance in other cognitive domains, such as language and verbal fluency.

Memory may be the most common cognitive complaint of older adults, and older adults usually do not perform as well as younger adults on various learning and memory tests. Age-related memory changes may consist of slowed processing speed [18], reduced ability to ignore irrelevant information [19], and less use of strategies to improve learning and memory [20]. Memory can be categorized into two major entities, i.e. declarative (explicit) and nondeclarative (implicit) memory. Declarative memory is the conscious recollection of facts and events and may be further categorized into semantic memory and episodic memory. Semantic memory involves the use of information, language, and practical knowledge; episodic memory involves memories of personally experienced events. Declines in semantic and episodic memory may be part of normal aging, but the timing of these declines may differ. In particular, episodic memory shows declines over the lifetime, but semantic memory mainly declines in the late life [21]. On the other hand, nondeclarative memory is outside of personal awareness, such as how to ride a bicycle, and it remains unchanged across the lifespan [22].

The formation and maintenance of memory can be divided into several different stages. Acquisition refers to the ability to encode new information into memory, and this ability declines over time [21]. Memory retrieval is the ability to access newly learned information, and this ability also declines over time in the aging process [23]. Language is a complex cognitive domain involving both crystallized and fluid cognitive abilities that remains relatively intact with normal aging. Visual confrontation naming remains stable until age 70 and declines later on [24]; verbal fluency, the ability to perform a word search and generate words for a certain category in a certain amount of time, also shows age-related declines [25]. Executive functioning is the capacity that allows a person to successfully engage in independent, appropriate, purposive, and self-serving behavior, including self-monitoring, planning, organization, reasoning, mental flexibility, and problem-solving [22]. Executive functioning involves rapid motor responses, which are more significantly susceptible to age effects [26], and reasoning with unfamiliar material also declines with age. However, other types of executive function, such as the ability to appreciate similarities, describe the meaning of proverbs, and reason about familiar materials, remain stable throughout life. In addition, concept formation, abstraction, and mental flexibility decline with age, especially after age 70; hence, older adults tend to think more concretely than younger adults [27, 28].

In summary, not all cognitive abilities decline with age. Processing speed and verbal fluency both show age-related declines, but declines in memory and executive function are determined by multiple factors instead of a simple age-related condition. The results of a longitudinal study showed that the decline in executive function occurred earlier than declines in other cognitive domains.

PHYSICAL AND COGNITIVE DECLINES

Knowing the components of cognitive functioning and their age-related declines may improve the understanding of the complex interrelationship between sarcopenia, physical declines, and cognitive declines because different studies may use different neuropsychological assessments in defining cognitive performance. Several previous studies have shown that declines in physical function occur earlier than declines in cognitive function, and frailty was a strong risk factor for incident dementia of all types [11, 12]. In a longitudinal study, the prevalence of physical frailty and cognitive impairment both increased over time and synergistically increased the risk for adverse outcomes of study participants [10]. However, cognitive impairment was defined by using the Mini-Mental State Examination in some studies, which may not be sensitive to detect early cognitive declines.

Sarcopenia might occur earlier than physical frailty in the early stage of aging, and it may occur in late life with multiple comorbid conditions [13, 14]. In different scenarios, associations between sarcopenia and cognitive impairment defined in various ways, e.g. declines in only executive function or language or impairment in global cognition, may coexist. Currently available studies evaluating the associations between sarcopenia and cognitive impairment showed different results due to the differences of assessments of cognitive functioning (Table 13.1) [29–48]. A cross-sectional study examined the associations between physical frailty status and cognitive function, which revealed that frailty in older adults was significantly associated with global cognitive impairment, but prefrailty was associated with cognitive impairment in non-memory domains instead of memory domains [49]. In addition, a Japanese 10-year longitudinal study showed that declines in handgrip strength predicted incident global cognitive declines, and declines in gait speed predicted incident declines in processing speed [50]. Therefore, reduced muscle strength and low physical performance, the important components in the diagnosis of sarcopenia, eventually predict subsequent cognitive declines that further strengthened the linkage between sarcopenia and cognitive impairment in late life.

"Cognitive frailty" was proposed to explore the synergistic effect of the concomitant physical and cognitive impairments and was operationally defined as the presence of both physical frailty and mild cognitive impairment [51]. This operational definition identified a low prevalence of cognitive frailty in the community-dwelling older adults. A longitudinal study showed that slowness plus mild cognitive impairment was superior to cognitive frailty in predicting adverse outcomes. Ruan et al. modified the operational definition of cognitive frailty into "reversible cognitive frailty" and "potentially reversible cognitive frailty" [52]. "Reversible cognitive frailty" was defined as physical prefrailty plus subjective cognitive decline, and "potentially reversible cognitive frailty" was defined by physical prefrailty plus mild cognitive impairment [53]. The modifications increased the prevalence of cognitive frailty with a stronger emphasis on reversibility. However, the reversibility of potential cognitive frailty has not yet been validated, although epidemiological studies have confirmed its prognostic role [53, 54]. On the other hand, "motoric cognitive risk syndrome" had been proposed using slow gait speed plus subjective memory complaints, and several longitudinal studies have reported its associations with adverse outcomes [55, 56].

Table 13.1 Studies Evaluating Associations Between Sarcopenia and Cognitive Impairment.

Author (Year)	Country	Study design	Sample	Participants	Measurement	Cognition measurement	Prevalence of sarcopenia	Main Results
Tuna F et al. [29]	Turkey	Cross-sectional study at a physical medicine and rehabilitation clinic	56 adults	Mean age: 69.7±4.0 years (range: 65–80 years); 59% women	Rapid geriatric assessment, SARC-F	Rapid cognitive screen (RCS), Pittsburgh sleep quality index	sarcopenia: 35.7%; dementia: 33.9%; poor sleep quality: 53.6%	Sarcopenia was positively correlated with poor sleep quality and negatively correlated with RCS cognition score ($r = -0.314$, $p < 0.05$) and physical activity
Franzon K et al. [30]	Sweden	The Uppsala Longitudinal Study of Adult Men	287 men; 5 years later, 127 men were re-evaluated	Mean age: 86.6 ± 1.0 years	EWGSOP • SMI < 7.26 kg/m^2 • gait speed ≤0.8 m/s • HGS < 30 kg later updated definition • SMI < 7.0 kg/m2 • HGS < 27 kg • chair stand test >15 s	Independent aging: -MMSE ≥25 points, absence of diagnosed dementia, community dwelling, independency in personal care and ability to walk outdoors alone.	21% and 20% based on different definitions Independent aging was 83% (239/288) at baseline and 69% (87/127) 5 years later	Sarcopenia measured with two different definitions and SMI alone not associated with independent aging.
Szlejf C et al. [31]	Brazil	cross-sectional study	5038 (ELSA-Brasil Study)	mean age: 62.5±5.8 (age ≥55 years); 53.7% women	FNIH • MM: BIA ALM_{BMI} < 0.789 for men and < 0.512 for women • HGS < 26 kg for men and < 16 kg for women	Delayed word recall test (DWRT), semantic verbal fluency test (VFT), Trail making test B	Sarcopenia: 1.8%; low muscle mass: 23.3%; low muscle strength: 4.4%	Sarcopenia was associated with poorer performance on the VFT (β=-0.20; 95% CI= -0.38 to −0.01; p = 0.03); low muscle strength was associated with poorer performance in all cognitive tests

(*Continued*)

Table 13.1 (Continued)

Author (Year)	Country	Study design	Sample	Participants	Measurement	Cognition measurement	Prevalence of sarcopenia	Main Results
Tamura Y et al. [32]	Japan	3-year prospective observational study at a frailty clinic	323	Mean age: 78 (range: 50–95 years); 37.8% men	AWGS • MM: BIA (kg/m2) • handgrip strength • walking speed: middle 4 m from 6 m walk	Cognitive impairment: MMSE score ≤ 27, or MoCA-J ≤ 25 Suspected dementia: MMSE score ≤ 23 or HDS-*R* ≤ 20 or DASC-21 ≥ 31	31.4% (male: 33.1%, female: 30.4%)	90% of sarcopenic patients revealed cognitive impairment; approximately 20% with suspected dementia
Ogawa et al. [33]	Japan	Cross-sectional study at a memory clinic	352	285 with AD (35.8% men; mean age, 82.0 ± 5.3; range: 67–96 years); 67 with normal cognition (NC) (44.8% men; mean age: 81.1± 4.7; range: 71–94 years)	AWGS	DSM-5, MMSE	Female early AD, 36%; mild AD, 45%; moderate AD, 60% vs. (NC), 11% Male early AD, 41%; mild AD, 47%; and moderate AD, 47% vs. NC, 13%	Older age, lower BMI and lower MMSE score were associated with sarcopenia in patients with AD

Tolea MI et al. [34]	FL, USA	Cross-sectional study	353 with a clinic visit and valid cognitive assessment	Mean age: 69 years; 65.4% female Sarcopenia group: mean age, 73.02±0.90; 67% female; Sarcopenic obesity group: mean age, 71.17±2.21; 83.3% female	Short portable sarcopenia measure (SPSM): bottom two quintiles Obesity: BMI ≥30 kg/m^2	MoCA<26/30, Trail making tests A and B, clock drawing test, naming, sentence repetition, word fluency -finger tapping to letter, serial subtraction, and digits forward and backward, orientation, short-term memory, animal naming test		Sarcopenic obesity was associated with the lowest performance on global cognition ($Est._{Definition1}$=−2.85 ± 1.38, p = 0.039), followed by sarcopenia ($Est._{Definition1}$=−1.88 ± 0.79, p = 0.017) Subdomain-specific analyses revealed executive function ($Est._{Definition1}$=−0.76 ± 0.26 for sarcopenia, p<0.05) and orientation ($Est._{Definition1}$=−0.36 ± 0.15 for sarcopenia, p<0.05) as the individual cognitive skills likely to be impacted.
Kamo T et al. [35]	Japan	Cross-sectional study	250 residents who were eligible to receive long-term care insurance in three nursing homes in two different cities	Mean age: 86.4 ± 7.7 years; 81.6% women Sarcopenia group: mean age, 85.6 ± 7.4 years No sarcopenia group: mean age, 87.1 ± 7.8 years (p = 0.12)	AWGS • MM: by near-infrared spectroscopy (NIRS) • Appendicular muscle mass (kg)=[(0.17xheight]+(0.17xweight)+(8.45xOD1))-28.97 • SMI: kg/m2 • walking speed: 4 m walking test	MMSE	45.2%	Sex and BMI were associated with sarcopenia, but not MMSE

(*Continued*)

Table 13.1 (Continued)

Author (Year)	Country	Study design	Sample	Participants	Measurement	Cognition measurement	Prevalence of sarcopenia	Main Results
Hao Q et al. [36]	China	Cross-sectional study	407 in three acute geriatric wards in 2012	Mean age: 81.0 ± 8.0 years	AWGS • MM: CC <31 cm	Cognitive impairment was defined as an MMSE score of ≤17 for unschooled people, ≤20 for those primary school education and ≤24 for those with high school or higher education	Overall, 31%; female, 44% vs. male, 26%	Cognitive impairment more common in the sarcopenic group than in the nonsarcopenic group (41% vs. 25% p = 0.002); female, smoking, cognitive impairment (OR 2.08, 95% CI: 1.10–3.95) and polypharmacy were risk factors for sarcopenia, but higher BMI was a protective factor (OR 0.75, 95% CI 0.68–0.83
Samper-Ternent et al. [37]	Colombia	Cross-sectional study, SABE Bogotá Study in 2012	1442 community-dwelling adults aged ≥ 60 years		EWGOSP, Fried phenotype	MMSE	11.5%	MMSE scores were **not** associated with sarcopenia; factors associated with sarcopenia were older age, female, smoking
Landi F et al. [38]	Italy	ilSIRENTE Aging and Longevity Study, a prospective cohort study	332 aged ≥80 years	Mean age: 86.1±1.4 years; 67.7% women Sarcopenia group: age, 87.5 ± 5.4 years No sarcopenia group: age, 85.1±4.3	EWGSOP • LMM: lower tertile of MAMC, <21.1 cm in men; <19.2 cm in women • walking speed: 4-m course <0.8 m/s	six-item cognitive performance scale (CPS): a 7-point ordinal scale, with higher scores indicative of worse cognitive performance	30.8%	Sarcopenia was associated with higher mean CPS score(1.2±1.8 in sarcopenia vs. 0.6±1.3 in nonsarcopenia, p=0.002)

Nishiguchi et al. [39]	Japan	One-year longitudinal prospective study	131 community-dwelling individuals, aged ≥ 60 years		AWGS	MMSE	7.6%	Sarcopenia was an independent risk factor for cognitive deterioration during the 1-year study period (normal group, −0.32±8.39%; sarcopenia group, −5.86±5.16%; p=0.002)
Huang et al. [40]	Taiwan	Cross-sectional study	731 community-dwelling individuals	Sarcopenia: 76.7 ± 5.3 years; 72% men Controls: 73.1 ± 5.4 years; 51.4% men	AWGS	MMSE <16 for illiterate, <21 for those ≤ 6 years of education, <24 for those had > 6 years education; Verbal learning test; Boston naming test; verbal fluency test; Taylor complex figure test; digits backward test; clock drawing test	6.8%	Sarcopenia was not significantly associated with overall cognitive function but was significantly associated with impairment in the verbal fluency test.
Sugimoto et al. [41]	Japan	Cross-sectional study	418 (sarcopenia, 88; control, 330) aged ≥ 60 years who attended a memory clinic (October 2010 to July 2014)	Sarcopenia: 80.0 ± 5.9 years Controls: 76.9±6.0 yeas	EWGSOP • SMI by BIA: male <7.0 kg/m^2; female <5.7 kg/m^2 • HGS: male <26 kg; female <18 kg • TUGT <13.56 s	National Institute of Neurological and Communicative Disorders and Stroke; Alzheimer's Disease and Related Disorders Association; MMSE	Overall, 21.1% (no impairment = 8.6%, amnestic MCI = 12.5%, AD =23.3%)	In both sexes, age and BMI were both factors associated with sarcopenia with cognitive declines

(*Continued*)

Table 13.1 (Continued)

Author (Year)	Country	Study design	Sample	Participants	Measurement	Cognition measurement	Prevalence of sarcopenia	Main Results
Papachristou et al. [42]	England	Cross-sectional study, British Regional Heart Study (BRHS)	1570 elderly men		EWGSOP • SMI by BIA FNIH	Test-Your-Memory (TYM)	2.7%	41 % with MCI, 8% with severe cognitive impairment (SCI) and SCI were more likely to have higher visceral fat and sarcopenia; No independent association was noted in sarcopenia and SCI.
Gao et al. [43]	China	Cross-sectional study	612	Mean age: 70.6 ± 6.7 years; range 60–91 years	AWGS	MMSE Chinese version	Overall, 9.8% (women, 12.0%; men 6.7%) 13.1% in rural area; 7.0% in urban population	Participants with sarcopenia had lower MMSE scores.
Tolea et al. [44]	USA	Cross-sectional study	223 community-dwelling adults aged ≥ 40 years	Mean age: 68.1 ± 10.6 years; 65% female	LMM by BIA: male <7.26 kg/m^2; female: <5.45 kg/m^2	MoCA <26; Ascertaining Dementia 8 score ≥ 2		Individuals with sarcopenia are not only more likely to have single but also to have dual impairments in cognitive and physical function.

Kim et al. [45]	Republic of Korea	Cross-sectional study	95 ESRD patients aged ≥ 50 years (sarcopenia: 32; controls: 63)	Mean age: 63.9 ± 10.0 years, 56.8% men Sarcopenia: 63.4 ± 11.7 years Controls: 64.1 ± 9.3 years	EWGSOP • LMM by BIA: male <8.87 kg/m^2; female <6.42 kg/m^2	MMSE <24	37.0% in men and 29.3% in women with ESRD	Sarcopenia was highly prevalent in elderly patients with ESRD and is closely associated with subjective global assessment (SGA), inflammatory markers, β2-microglobulin, depression and cognitive dysfunction (OR = 6.35, 95% CI = 1.62–34.96).
Hsu et al. [46]	Taiwan	Cross-sectional study	353 men aged ≥65 years	Mean age: 82.7 ± 5.3 years Sarcopenia: 83.7 ± 5.7 years Controls: 82.2±5.0 years	EWGSOP • LMM by BIA <8.87 kg/m^2 • Low muscle strength <22.5 kg • Slow walking speed ≤0.8 m/s	MMSE <24	30.9%	Sarcopenia was significantly associated with cognitive impairment (adjusted OR: 3.03, 95% CI: 1.63–5.65, P < 0.001) and depressive symptoms (adjusted OR: 2.25, 95% CI: 1.03–4.89, P = 0.04)
Alexandre et al. [47]	Brazil	Cross-sectional study, SABE study from 2006	1149 community-dwelling older adults	Sarcopenia: male: 74.8 ± 1.0 years; female: 75.8 ± 1.0 years Controls: male: 68.1 ± 0.6 years; female: 68.9 ± 0.6 years	EWGSOP • SMI ≤8.90 kg/m^2 for men and ≤6.37 kg/m^2 for women • walking speed <0.8 m/s	Modified MMSE <12 points	16.1% in women, 14.4% in men	Advanced age, cognitive impairment, lower income, smoking, malnutrition and risk for malnutrition were associated with sarcopenia.

(*Continued*)

Table 13.1 (Continued)

Author (Year)	Country	Study design	Sample	Participants	Measurement	Cognition measurement	Prevalence of sarcopenia	Main Results
Abellan van Kan et al. [48]	France	Cross-sectional study, EPIDOS cohort	3025 elderly women aged over 75 y/o		Six criteria to evaluate sarcopenia (Baumgartner, Delmonico, Newman, IWGS, SIG, and EWGSOP) • LMM by DEXA: appendicular lean mass (ALM/ $h^2 \leq 5.67$ kg/m^2)	-Short portable mental status questionnaire <8 points	3.3–18.8%	None of the six instruments had a significant association with cognitive impairment.

AD, Alzheimer's Disease; AWGS, Asian Working Group for Sarcopenia; BIA, bioelectrical impedance; BMI, body mass index; CC=calf circumference; DASC-21=Dementia Assessment Sheet in Community-based Integrated Care System-21 items; DXA, Dual X-Ray Absorptiometry; ESRD, End-Stage Renal Disease; EWGSOP, European Working Group on Sarcopenia in Older People; FNIH, Foundation for the National Institutes of Health; HDS-*R*=Hasegawa's Dementia Scale-Revised; HGS=hand grip strength; IWGS, International Working Group on Sarcopenia; LMM, Lean Muscle Mass; MAMC=mid-arm muscle circumference-(3.14xtriceps skin fold thickness); MM=muscle mass; MCI, Mild Cognitive Impairment; MMSE, mini mental state examination; MoCA= Montreal Cognitive Assessment; SABE=Salud Bienestar y Envejecimiento; MoCA-J, Japanese version of Montreal Cognitive Assessment; SIG, Special Interest Group; SMI=skeletal muscle index.

However, both cognitive frailty and motoric cognitive risk syndrome may not sufficiently satisfy the optimal definition for the state of concomitant physio-cognitive decline, especially in regard to potential reversibility. First, not all five components of physical frailty were independently present in the development of physical frailty, and the components of slowness and weakness were highly clustered, but no other components [57]. Hence, using physical prefrailty and frailty in the definition of physio-cognitive declines may introduce different pathoetiological factors into the same entity and confound the outcome prediction of reversibility. The results of a longitudinal study showed that the mobility type of frailty (weakness and slowness as the core) differed from the nonmobility type of frailty (mainly malaise and weigh loss) in clinical characteristics and outcomes [57]. On the other hand, studies have shown that declines in executive function appear earlier than declines in the memory domain and are closely related to the neurodegenerative process [58]. The Alzheimer's Disease Neuroimaging Initiative reported that subjective cognitive complaints may result in misdiagnosis of mild cognitive impairment [59]. Subjective cognitive complaints were not associated with objective cognitive functioning and were more closely associated with depressive symptoms [59]. Therefore, a new definition for this physio-cognitive decline phenomenon has been proposed using the mobility component of physical frailty only (slowness and/or weakness) plus cognitive declines assessed by objective assessments (1.5 standard deviations below the matched population in any cognitive domain), and the prevalence was approximately 10–15% among community-dwelling older adults [60–62]. Moreover, longitudinal studies have shown associations of this physio-cognitive decline phenomenon with cardiovascular mortality, all-cause mortality, and incident dementia [60–62].

SARCOPENIA AND COGNITIVE IMPAIRMENT

Although the linkage between physical and cognitive declines, as well as their synergistic effects, in the aging process has been demonstrated [7, 10], the pathophysiology remains unclear. Since reduced muscle strength and/or low physical performance is the required component in the diagnosis of sarcopenia [13–15], musculoskeletal and neurological factors may individually or in combination contribute to the development of sarcopenia. Positive associations between sarcopenia and cognitive impairment have been reported in studies from different places and across ethnicities (Table 13.1). However, studies have also suggested that the associations were mainly related to muscle function but not muscle mass [30, 40]. A previous study in Taiwan showed that reduced muscle strength and/or low physical performance was significantly associated with cognitive impairment, but sarcopenia or low muscle mass only was not [31]. The findings were echoed by another study from Sweden [40]. The results suggested that associations between sarcopenia and cognitive impairment were resulted from neurological factors, and the loss of muscle mass may be a consequence of these factors. It is unsurprising that neurodegenerative processes, either in the central nervous system, in the peripheral nervous system, at the neuromuscular junction, or in all of these systems, may result in subsequent physical function decline. However, the peripheral organs may also provide feedback to the nervous systems and modify the whole process. The cross talk between muscle and brain has been reported in animal and human studies [63, 64].

The associations between sarcopenia and cognitive impairment have been reported in two systematic reviews, but the included studies were mostly cross-sectional or using a cross-sectional sample in the prospective cohorts [65, 66]. Most published studies have identified positive associations between sarcopenia and cognitive impairment among community-dwelling older people, as well as individuals who visited frailty clinics or memory clinics or even older people with dementia. However, some studies did not identify positive associations between sarcopenia and cognitive impairment. Based on recent studies, cognitive assessments are recommended for older adults with sarcopenia or physical functional decline, and older adults with cognitive impairment also recommended to receive further evaluation about physical function and sarcopenia. Despite the positive associations in epidemiological studies, the patho-etiological links between sarcopenia and cognitive impairment remain to be determined. Studies have shown that exercise plays an important role in preventing physical and cognitive declines, which also highlights the potential interaction between muscle and brain [67, 68].

Repeated muscle contractions are the key feature of exercise, and those contractions may result in the secretion of various myokines that interact with different organs [64, 65]. Based on the current evidence, the secretion of brain-derived neurotrophic factor (BDNF) and irisin are increased after exercise; both BDNF and irisin play protective roles against cognitive declines [64]. In addition, the negative regulator of skeletal muscle mass, myostatin, has been identified as a potential therapeutic target for sarcopenia [69]. Both neutralizing antibodies and activin IIB receptor blockade reversed skeletal muscle loss but did not significantly improve muscle strength or physical performance. Although it remains uncertain whether myostatin will fulfill therapeutic potential for treating sarcopenia, its negative regulation of muscle mass has helped to characterize the balance in skeletal muscle mass maintenance. An animal study identified the presence of myostatin mRNA in neurons of the hippocampus, the parahippocampus, and the olfactory bulb [70], but the physiological function of myokine mRNA in neurons remains unclear. Another study reported that myostatin significantly delayed neurodifferentiation in the developmental process and triggered apoptosis of neurons [71, 72]. The negative regulation of myostatin in neurons is similar to that in skeletal muscle. Owing to the molecular weight of myostatin, muscle-secreted myostatin may not penetrate the blood–brain barrier, so it may be hypothesized that neuron-secreted myostatin plays a certain role in neurodegeneration. Based on these discoveries, it seems that myostatin secreted by muscles and neurons have similar physiological actions on skeletal muscles and neurons, respectively, but there may be some unreported biomarkers linking the myostatin activity in the muscles and neurons for the synchronized action. Through circulation, there may be an extraspinal pathway for myokines or other biomarkers to facilitate muscle–neuron communications. On the other hand, muscle contractions may communicate with neurons through afferent fibers of the spinal cord. However, currently, these pathways remain hypothetical except for the biological actions of BDNF and irisin. It is still far from possible to draw conclusions regarding the mechanisms of the cross talk between muscle and brain, but it is likely that muscle contractions generate some signals, either spinal or extraspinal, to the brain and may synergistically act in the same direction.

CONCLUSIONS

Both sarcopenia and cognitive impairment are common conditions in older adults, and their coexistence has been reported among community-dwelling older adults, as well as those who attended frailty clinics or memory clinics or have dementia. However, there is a lack of results from longitudinal studies and intervention studies that evaluate the sequential relationships in the development of sarcopenia and cognitive impairment. Potential muscle–brain cross talk may exist through spinal or extraspinal pathways that facilitates communications between muscle and brain in the aging process.

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CHAPTER 14

Sarcopenia and Other Chronic Organ Diseases

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This chapter will focus on several chronic diseases that are associated with sarcopenia and discuss how each chronic disease affects the development of sarcopenia and how sarcopenia affects the outcome of older people with each chronic disease. In addition, considering the risk of sarcopenia in each disease, it is important to manage the patients from the point of view of sarcopenia prevention. Therefore, when we take care of patients with chronic disease, screening, prevention, and intervention of sarcopenia is important for the disease management to prevent age-related disability and poor quality of life.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow limitation and exacerbation of respiratory distress as the disease progresses. Because shortness of breath limits the physical activity in patients with COPD, especially in older patients, muscle mass and function decrease due to impaired physical activity, resulting in a vicious cycle of deteriorating exercise capacity [1]. In addition to decreased activity due to limited respiratory function, problems such as inflammation, oxidative stress, malnutrition, and hypoxemia may also cause skeletal muscle dysfunction in COPD patients [2]. These are the main causes of sarcopenia in COPD and the complication of sarcopenia in COPD patients leads to poor health outcomes.

Although the prevalence of sarcopenia is less than 10% in the general population, the prevalence of sarcopenia in patients with stable COPD was 15–25% when applying the European Working Group on Sarcopenia in Older People (EWGSOP) criteria, and no sex differences were found in a British study [3].

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

To improve the outcome of COPD patients, prevention and intervention of sarcopenia are mandatory and pulmonary rehabilitation should be provided for COPD patients to improve outcomes in sarcopenic patients. Pulmonary rehabilitation has been shown to improve the symptoms and quality of life of patients with COPD. It relieves dyspnea and fatigue, as well as increasing exercise tolerance, emotional function, and patient's feeling of control over their illness [3, 4]. Because poor appetite and associated malnutrition affect the muscle health, pulmonary rehabilitation along with appropriate nutritional supplementation should be also considered. Two studies compared the effect of aerobic training alone, resistance training alone, and the combination of aerobic and resistance training in COPD patients with mixing results [5, 6]. However, considering the etiology of sarcopenia due to aging (type II fiber impaired) and COPD (type I fiber impaired), the combination of aerobic and resistance training would be desirable when the patient condition allows both kinds of interventions. Recently, neuromuscular electrical stimulation can also improve functional exercise capacity in patients with severe COPD by enhancing quadriceps muscle mass and function, supporting the use of electrical stimulation in patients who are unable to perform conventional pulmonary rehabilitation [7]. Thus, health-care professionals who take care of COPD patients should be aware of the importance of preventing sarcopenia along with appropriate disease management considering their longer life expectance due to improved medical management. However, more evidence is needed how early interventions should be started in patients with COPD.

CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is associated with noncommunicable diseases such as diabetes, hypertension, dyslipidemia and obesity and is more prevalent in older people, because renal function shows an age-dependent decline. CKD is a risk factor for several key outcomes, such as cardiovascular disease, stroke, renal failure, and mortality, and prospective studies have shown that CKD increases the risk for physical disability and cognitive decline in older adults by approximately twofold [8, 9].

The loss of muscle mass is common in CKD, which is mainly caused by a negative balance of protein homeostasis and the effect of various CKD-associated catabolic changes may explain why sarcopenia is common in CKD patients [10]. These changes can be attributed to a number of factors, such as accumulation of uremic toxins, chronic inflammation, insulin resistance, hormonal imbalance, malnutrition, vitamin D deficiency, oxidative stress, and increased ubiquitination [11]. In terms of chronic inflammation, some inflammatory markers such as interleukin 6, CRP, and tumor necrosis factor (TNF) alpha are associated with sarcopenia [12], and in CKD patients, these markers are higher than that in individuals with normal renal function and are associated with unfavorable outcomes [13]. Upregulation of the renin–angiotensin–aldosterone system can also impair muscle regeneration in CKD [14, 15]. CKD is further associated with impaired regeneration in the muscle tissue due to increase plasma myostatin levels in CKD patients [16].

Cross-sectional studies have shown that sarcopenia is more prevalent in patients with CKD stage 3 than in individuals with normal renal function. The prevalence of

sarcopenia in patients with predialysis stage CKD (G3–G5) has been reported to be between 5.9 and 15.4% [17–19]. The proportion of patients with sarcopenia is higher as CKD progresses to more severe stages. The prevalence of sarcopenia in patients in the dialysis stage has been reported to be between 12.7 and 33.7%, which can be attributed to the differences in the mean subject age and in the method and criteria for evaluating sarcopenia [20–22].

The loss of muscle mass in this population is correlated with greater morbidity and mortality, particularly due to an increase in cardiovascular outcomes [23]. Therefore, the early identification of sarcopenia and evaluation of the modifiable factors associated with the patient are essential. In terms of the interventions for sarcopenia in CKD patients, Wilkinson et al. [24] report that 12 weeks (3 times/week) of aerobic exercise alone or in combination with resistance training in non-dialysis CKD patients resulted in a reduction in the total number of health-related quality-of-life symptoms by 17%. As expected, aerobic exercise reduced the frequency of shortness of breath, and other symptoms. The addition of resistance exercise further decreased loss of muscular strength/power. However, no changes were seen in subjective physical function or physical activity levels. In patients with stage 3 CKD, 16 weeks of moderate-intensity aerobic exercise three times per week led to a mild improvement in VO_2 peak [25]. Thus, providing an appropriate resistance and aerobic training program would be able to improve the outcome of CKD patients. In terms of the nutritional supplementation higher protein intake can deteriorate renal function in CKD; therefore, care is needed to limit the protein intake of severe CKD patients, although a long-term outcome study is needed to determine the appropriate protein intake to prevent and treat sarcopenia and frailty in CKD patients.

CHRONIC HEART FAILURE

Chronic heart failure (CHF) is a serious and frequent disease with high mortality, whose prevalence is affected by aging [26]. Reduction in mortality and, more importantly, increased life expectancy has been attained in CHF patients by different therapeutic options. In spite of the progress of heart failure treatment, skeletal muscle loss is frequently observed in patients with CHF and may contribute to fatigue, dyspnea and low physical activity, leading to adverse health outcomes [27]. The high incidence of sarcopenia in CHF patients may be due to mitochondrial dysfunction combined with an abnormal energy metabolism and a transition of type I to type II myofibers [28, 29]. In addition, malnutrition, an increase of proinflammatory cytokines, a decrease of anabolic hormones, increased myostatin expression, aponuclear apoptosis, and oxidative stress are also involved in muscle dysfunction in heart failure [30]. Due to these detrimental influences to skeletal muscle in CHF, approximately 20% CHF patients are suffering from sarcopenia, which is significantly higher than the general population [31].

How can we prevent muscle loss in CHF patients? Indeed, exercise training not only can have cardio-protective effects and slow down the transition from cardiac dysfunction to heart failure but also can induce anti-catabolic signaling in skeletal muscle [32]. In spite of lack of evidence to show the effect of resistance training in CHF patients, the combination of aerobic and resistance training would be a standard approach for

the prevention of sarcopenia in CHF patients. The use of neuromuscular electrical stimulation also seems to be safe and to improve functional capacity, muscle strength and quality of life compared with conventional aerobic exercise in CHF patients [33]. Sarcopenia in CHF may ultimately progress to cardiac cachexia [34], which is associated with an extremely poor prognosis [35]. Cachexia is also complicated with CKD, COPD, and rheumatoid arthritis (RA) in addition to cancer.

DIABETES MELLITUS

The prevalence of type 2 diabetes mellitus has been increasing in most of the countries. Due to the improvement of medical management of type 2 diabetes, patients are getting older and older, facing various age-related problems; geriatric syndromes such as sarcopenia and frailty. Bidirectional links exist between type 2 diabetes and sarcopenia, and the existence of one condition can increase the risk of developing the other [36]. Factors such as insulin resistance, inflammation, increased oxidative stress, and macrovascular complications can affect muscle health; and impaired muscle health can also contribute to development and progression of type 2 diabetes [36]. Considering the interaction between diabetes and sarcopenia, it is conceivable that appropriate lifestyle interventions such as diet and exercise can improve and maintain functional and metabolic health in patients with type 2 diabetes and sarcopenia. In the treatment of diabetes, we should keep in mind that muscle function may be negatively affected by intensification of anti-diabetic drug treatment. Especially in older people, preserving mobility should be more important than a tight blood sugar control. Although reduction of dietary energy intake and weight loss are recommended for the treatment, such interventions may worsen muscle loss in older patients; therefore, appropriate exercise and nutritional supplementation should be advised for the prevention of sarcopenia [37, 38].

There are many drugs available for blood sugar control. So far there is no drug that has been proven to be effective for the prevention of sarcopenia among the drugs for type 2 diabetes. Although insulin is an anabolic hormone that increases muscle protein synthesis and limits protein degradation [39], its therapeutic potential for the prevention of sarcopenia remains unclear. Metformin is the first line drug for the treatment of type 2 diabetes even in older individuals and activates AMP-activated protein kinase (AMPK) [40], which can protect against age-related functional and mitochondrial impairment [41]. However, AMPK also stimulates myofibrillar protein degradation [42] and stimulate myostatin expression [43]. Clinical studies indicate a lack of evidence to show the definite effect of metformin on muscle mass and strength in human. Thus, the net effect of metformin on muscle function and its clinical impact on sarcopenia remain to be determined. Other anti-diabetic drugs have not been shown to be beneficial for muscle health except thiazolidinediones. In the MrOS study, men with diabetes treated with metformin alone and metformin plus thiazolidinediones over 3.5 years had an attenuated loss of total lean mass compared to men with diabetes that were not treated with insulin sensitizers, and men with untreated diabetes [44]. However, we should keep in mind that thiazolidinediones can increase the risk of osteoporotic fractures in women. Currently available data stress the importance of an early detection of muscle deterioration in diabetic patients to prevent progression of sarcopenia and type 2 diabetes.

There are several epidemiological data to show the prevalence of type 2 diabetes in older people. In both cross-sectional and longitudinal studies, accelerated loss of muscle mass and strength is shown in diabetic patients, which is dependent on the duration of diabetes and HbA1c levels. In a cross-sectional study of Indian patients, type 2 diabetic patients had 3.48-fold higher odds ratio compared with the nondiabetic control for pre-sarcopenia by the EWGSOP definition [45]. A Dutch group reported that reduction in skeletal muscle mass and muscle strength was observed in patients with type 2 diabetes even after adjusting for confounding factors [46]. In Japan, the relationship between metabolic syndrome and sarcopenia diagnosed based on the EWGSOP criteria was studied among 1971 community-dwelling older people. Among patients with metabolic syndrome, the prevalence of sarcopenia was fivefold higher in men aged between 65 and 74 years [47]. Among American older adults, diabetic patients showed significantly slower gait speed than nondiabetic controls. The relationships among sarcopenia, sarcopenic obesity, and metabolic syndrome have been also investigated in people living in Taiwan who were diagnosed with sarcopenia based on skeletal muscle index (SMI) estimated from bioelectrical impedance analysis (BIA) or sarcopenic obesity based on body mass index (BMI). Compared with healthy subjects, the odds ratio for development of metabolic syndrome among patients with sarcopenic obesity and nonobese patients with sarcopenia was 11.59 (95% confidence interval (CI): 6.72–19.98) and 1.98 (95% CI: 1.25–3.16), respectively [48]. Approaches for the patients with sarcopenic obesity and type 2 diabetes and/or metabolic syndrome are quite challenging because these patients are usually complicated with frailty and have a higher risk for falls and fracture. Complications of osteoarthritis would be another concern to make an appropriate intervention for this kind of patients.

RHEUMATOID ARTHRITIS (RA)

Patients with RA have a higher risk for developing sarcopenia due to chronic inflammation, decreased physical activity caused by pain and deformity of the joints, and concomitant treatments such as the use of glucocorticoids. Although several studies have reported that RA patients have low lean mass, or low muscle strength compared with the general population, none of them had defined sarcopenia based on the EWGSOP or AWGS [49–51]. However, recently Torii et al. have shown that the prevalence of sarcopenia was 37.1% (14.7%, severe sarcopenia; 22.4%, sarcopenia), with 49.0% classified as having low muscle mass by the AWGS criteria [52]. Age, disease duration, disease activity, and malnutrition are positively associated with sarcopenia, whereas the use of biological disease-modifying anti-rheumatic drugs was negatively associated with sarcopenia. Mochizuki et al. also showed that the prevalence of sarcopenia was 29.6% by the AWGS criteria in Japanese patients with RA aged 65 and over [53]. Further studies should be done to show how anti-rheumatic medications affect the development of sarcopenia in RA patients. Because of the increase of older RA patients, more attention should be paid for the prevention and treatment of sarcopenia. However, pain and deformity of the joints can affect the exercise intervention. Therefore, a multidisciplinary approach should be taken in addition to the treatment by rheumatologist.

CONCLUSIONS

Chronic diseases such as COPD, CKD, CHF, type 2 diabetes mellitus, and RA are associated with sarcopenia. When treating these patients, screening of sarcopenia is one of the important strategies to manage the patients. Although disease management is important for the prevention of sarcopenia, we need to be aware of the importance of sarcopenia prevention during the disease management and when sarcopenia is present appropriate interventions should be provided on the basis of multidisciplinary approach.

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CHAPTER 15

Imaging of Skeletal Muscle

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INTRODUCTION

Modern definitions of sarcopenia describe it as the loss of physical function secondary to loss of muscle quantity. The quantity of muscle may be assessed using dual X-ray absorptiometry (DXA), computed tomography (CT), or magnetic resonance imaging (MRI). DXA is a two-dimensional (2D) measurement which assesses the masses of lean, fat, and osseous components in the body. CT and MRI are 3D modalities that can assess muscle cross-sectional area or volume, depending on whether the acquisition techniques involve single section or volumetric imaging. In addition to muscle mass, CT, MRI, and magnetic resonance spectroscopy (MRS) can be employed to assess the composition of skeletal muscle, in particular the extent of adipose infiltration of skeletal muscle tissue and the distribution of the adipose content between and within specific muscle groups, as well as the partition of intramuscular triglyceride between adipocytes, and the skeletal muscle fibers themselves. MRS and positron emission tomography (PET) may be utilized to study the metabolic activity of skeletal muscle tissue, including production of ATP/ADP as well as glucose and amino acid metabolism.

DUAL X-RAY ABSORPTIOMETRY

Dual X-ray absorptiometry (DXA) is an accurate, clinically available method of assessing body composition at any anatomic site [1]. Originally developed to assess bone mineral density (BMD), DXA was introduced in the late 1980s and has become the mainstay of osteoporosis diagnosis and clinical evaluation worldwide. In the DXA concept, X-rays with a bimodal energy spectrum, obtained either by

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

rare-earth filtration [2] of an X-ray tube, or rapid switching of kVp [3], are passed through the body. The DXA scanner has a detector system which measures the attenuation of the "high" and "low" energy X-rays by the object being scanned, determining the difference in attenuation of the two X-ray energies. With this technique, bone can readily be differentiated from soft tissue on the basis of this attenuation differences. By relating these measurements to calibration standards, it is possible to measure the mass of bone in grams at each point or pixel of the projectional image. An areal bone density in g/cm^2 is obtained by determining a region of interest, such as the lumbar spine or the femoral neck and dividing the total mass in gram summed across all the pixels in the region by the region's area in cm^2. Starting in the early 1990s, prospective studies have documented the association of areal BMD with incident osteoporotic fracture and have documented therapy responses to anti-resorptives and other osteoporosis medications [4]. DXA has been widely adopted in the clinical setting due to its low cost, high reliability, and a radiation dose which is close to daily background radiation and much smaller than that received during a transatlantic flight.

In those regions of the image that have no bone, it is possible to use the differential X-ray absorption measurement described above to separate lean from fat tissue. This composition measurement is used both to correct BMD values for the variability introduced by the adipose content of soft tissue which overlies bone, as well as to generate quantitative image maps of the composition of soft tissue [1, 5]. For correction of BMD measurements, the ratio of adipose/lean tissue adjacent to the bone is extrapolated to the region directly above the bone, where only the total mass of soft tissue has been quantified. Applying this ratio to the soft tissue mass allows for the estimation of adipose, lean and bone tissue mass in skeletal regions. When this three compartment estimate is joined to the adipose and lean tissue measurements from the non-bone regions, a full three compartment body composition estimate can be made. Body composition measurements require a whole body scan. Analytic software is then used to partition the bone, adipose, and lean content into anatomic segments, including the trunk, pelvis limbs, etc. (Figure 15.1). Generally, the precision for body composition measurements by commercial scanners is quite good, with values of roughly 1% for bone content and 2–3% for lean and adipose content. The algorithms to accomplish these partitions, the precision, and the sources of error vary between DXA manufacturers, and the reader is referred to recent technical papers that describe this approach, along with its strengths and limitations [6–11].

Constant hydration is an assumption common to all DXA body composition measurements [12]. DXA systems assume that the hydration of fat-free mass is constant at 73%, although there is a small amount of normal variation in this property which does not appear to introduce clinically significant errors into the measurement. However, pathologic over- or under-hydration can introduce errors into the percentage fat estimates. Clinically, such conditions can be caused by excessive water retention or edema. DXA software enables one to determine bone mineral and soft-tissue composition in different regions of the body.

DXA body composition measurements have been widely employed to track the changes in lean and fat mass associated with sarcopenia [13–24]. In the limbs, the lean tissue mass is employed as a surrogate for muscle mass, and these appendicular mass measurements have been employed in early attempts to establish the definition and

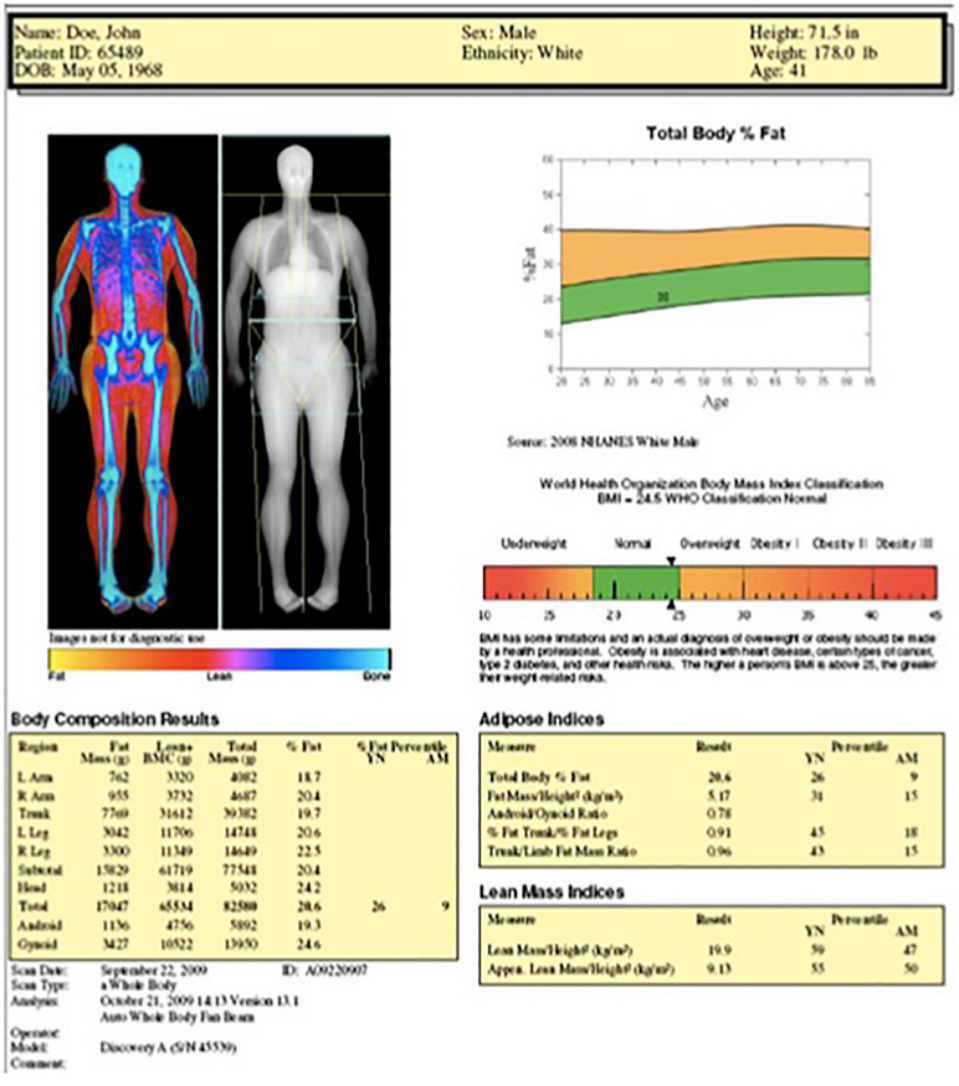

Figure 15.1 Patient image from a whole body composition measurement made by a Hoiogic Discovery A DXA scanner.

prevalence of sarcopenia, to track the loss of skeletal muscle with age, and to estimate the association of low skeletal mass with prevalent and incident functional impairments, with falls and with sarcopenia-related skeletal conditions such as osteoporosis and skeletal fracture. However, as shown in the following sections, an estimate of skeletal muscle mass alone is of limited value in understanding the relationship between the status of skeletal muscle tissue and the functional impairments associated with sarcopenia [25]. Other image-based techniques can be used to combine a mass estimate with measures of tissue composition and metabolism which greatly improve the detail in the clinical portrait of sarcopenia.

COMPUTED TOMOGRAPHY

CT is a 3D X-ray absorptiometric measurement which provides the distribution of linear attenuation coefficient in thin cross-sections of tissue [26]. In the transverse plane, the object being scanned is contained within a fan of X-rays defined between the individual elements of the detector array and the X-ray source. The detector array consists of multiple rows of detectors, which depending on the model of CT scanner, typically ranges from 16 to 256 rows that extend in the direction of the table axis. Modern CT scanners are typically based on "helical" acquisitions, where the detector array and X-ray tube rotate while the table continuously translates the subject along the z-axis [27]. At distinct intervals (typically 360 per gantry rotation), the attenuation of the X-ray beams between the X-ray spot and the individual X-ray detectors is measured by the system. This attenuation measurement is the logarithm of the measured intensity of the X-ray beam with the subject in place to the intensity measured in air. The rotation of the X-ray tube and detector thus acquire a helix of data around the subject and interpolative techniques which employ data from the multiple rows of detector arrays are employed to fill in the gaps between the arms of the helices and generate a fully cylindrical volume of encasing the subject. The volume of data is reconstructed into cross sections of varying thickness, ranging from 0.5 to 10 mm depending on the specific clinical imaging requirements. These cross sections are sampled into square matrices of picture elements, or "pixels." Because the image represents a slice of tissue, the picture elements have a thickness, and thus are volume elements, or "voxels." The dimensions of the voxels may be adjusted depending on the size of the organ being imaged. Depending on the type of scanner, the voxel dimensions range from the micrometer level to roughly 1 mm "in plane" and up to several millimeter in slice thickness. In the resulting CT image, the voxel values map to linear attenuation coefficient, a measure of density and electron density of the tissue. Because these linear attenuation coefficients depend on the effective X-ray energy (which varies between CT scanner models and different kilovoltage peak (kVp) settings of the same scanner), a simple scale, known as the Hounsfield scale, is used to standardize them. The gray-scale value of each voxel is represented as a Hounsfield Unit, which is defined as the difference of the linear attenuation coefficient of a given voxel from that of water, divided by the linear attenuation coefficient of water. The Hounsfield Unit (HU) scale is a linear scale in which air has a value of – 1000, water 0, muscle 30, with bone typically ranging from 300 to 3000 units.

The value of the Hounsfield unit for a given tissue type depends on several technical factors. First, if the sizes of the structures in the tissue are smaller than the dimensions of the voxel, the HU value is subject to partial volume averaging, in which the HU value is the average HU of the constituent tissues of the voxel, weighted by their volume fractions. For example, a 0.78 mm × 0.78 mm × 10 mm voxel of trabecular bone is a mixture of bone, collagen, cellular marrow, and fatty marrow, and HU is the volume-weighted average of these four constituents. Beam hardening is a second source of variation in HU. In a CT image, the result of this is that for the same tissue, attenuation coefficients at the outside of the patient are systematically higher than those in the interior. Although manufacturers of CT equipment have implemented beam-hardening corrections, the efficacy of these corrections varies between manufacturers and between technical settings on different machines. Modern CT systems have multiple

arrays of detectors, and some machines feature X-ray systems producing dual-energy X-ray beams [28], allowing to separation of voxels into three constituent components. A technical review of modern CT systems is provided in a paper by Seeram [29].

CT imaging may be employed to quantify bulk characteristics of muscle and body composition that are highly related to muscle strength and to overall functional ability in older persons. In particular, CT imaging is widely used to study muscle and fat in epidemiologic studies of body composition. Typically, acquisitions have included single cross sections at the L1/2 or L4/5 intervertebral space to image body fat or volumetric measurements obtained in the abdomen and in the thigh, usually relating to the midthigh or to a bony landmark [30–36]. As shown in Figure 15.2, the key variables quantified include the total muscle cross sectional area (CSA) of the midthigh, the CSA values of the quadriceps and hamstrings, the total CSA of subcutaneous fat, and the attenuation coefficients of the total thigh muscle and the hamstrings and quadriceps separately. The CSA values of the total thigh muscle and quadriceps muscle are positively associated with increasing knee extensor strength.

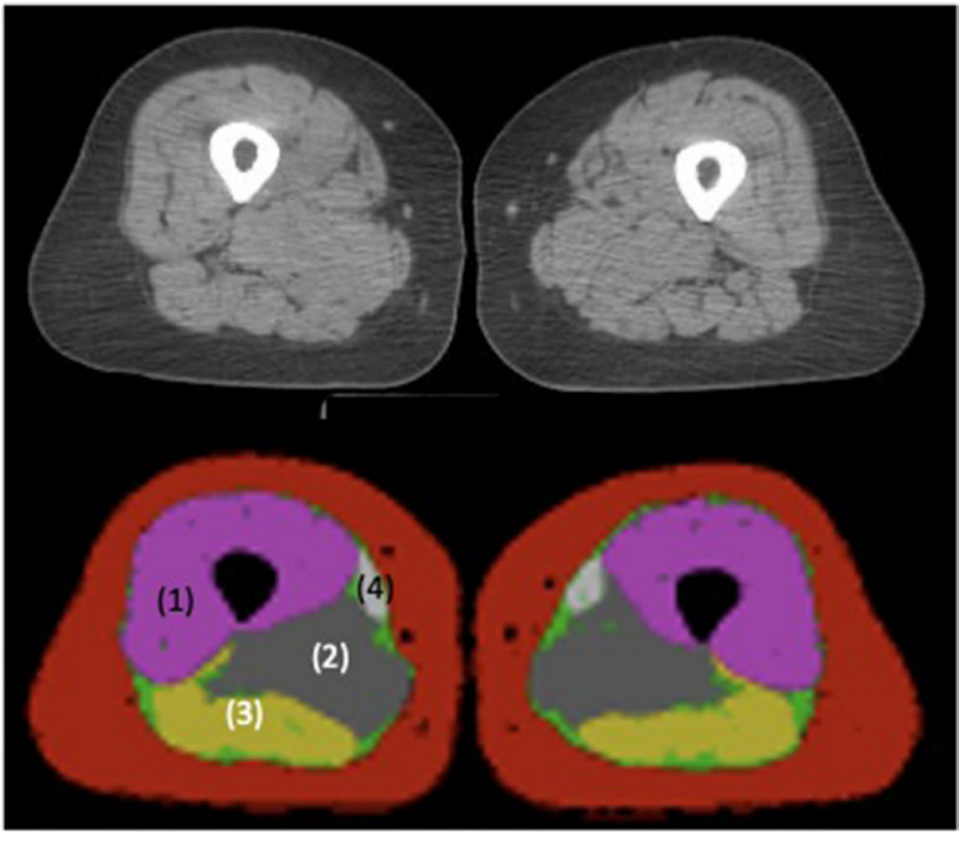

Figure 15.2 Mid thigh CT scans and segmentation of muscle groups using analytic software. Top row: CT scans of mid thigh. Bottom row: Segmentation of main muscle groups, including quadriceps (1), adductors (2), hamstrings (3) and Sartorius (4).

The CSA declines with age, as does the muscle strength, and is smaller in females than in males [30–32]. Another property of great interest to the study of sarcopenia is the mean attenuation coefficient, which is computed within all of the muscle regions after a threshold is applied to exclude depots of fat embedded within each muscle group. In older subjects, the mean attenuation coefficient, when calculated in this manner, has been shown histologically to correspond to fat accumulation within and between the muscle cells. The increasing fat infiltration into the muscle with aging may be an important, if not central, aspect of sarcopenia [30–32, 37]. Lower values of the mean thigh muscle attenuation coefficient correspond to increasing fattiness of muscle tissue. Decreasing thigh muscle attenuation is correlated to decreasing muscle strength, a relationship which is independent of the muscle CSA and the total amount of adipose tissue in the thigh. Measures of CSA and muscle attenuation assessed at multiple skeletal sites are associated with indices of functional capacity in older adults, including chair stand and leg strength measurements which have been shown to be strongly predictive of falls [34–36]. Several studies based on the Health, Aging, and Body Composition Study, a large NIH-funded population study, have related measures of body composition derived by CT to indices of functional ability and quality of life in independently living older people. Visser et al. examined the relationship between measures of thigh composition and lower-extremity performance (LEP), assessed by two timed tests: a series of five chair stands without use of arms and a 6-m walk [36]. Reduced thigh CSA was associated with poorer LEP, as was reduced thigh muscle attenuation coefficient, even after the adjustment for muscle area. The attenuation coefficient of thigh muscle is not only related to current physical performance but is also related to incident functional decline. Analyzing longitudinal data from the Health ABC study, Visser et al. observed that low baseline values of thigh muscle attenuation predicted incident mobility limitation, defined as inability to walk one-quarter mile or climb 10 steps [35]. These data on mobility limitations are consistent with later studies that examined association of muscle attenuation with incident fracture. Lang et al. showed that reduced attenuation of the thigh muscle was associated with incident hip fracture [38], and Schafer et al. showed that reduced thigh muscle attenuation was associated with clinical fractures in older subjects with diabetes [39]. Reduced thigh muscle attenuation coefficient is also associated with increased insulin resistance and the presence of metabolic syndrome in older persons. Diabetes and other weight-related health conditions are associated with poor vision, musculoskeletal pain, and other conditions which are themselves indicators of increased fall risk [30]. Recently, investigators have developed new approaches to characterize skeletal muscle using volumetric CT, with novel image processing metrics to describe the muscle lipid distribution in three dimensions [40]. In a subsequent study, these parameters were shown in multivariate models to associate with hip fracture in a case–control study, improving the ability of CT to discriminate fracture risk compared with bone parameters alone [41].

MAGNETIC RESONANCE IMAGING

MRI is an imaging technique that is based on using radio waves to excite protons in the presence of an external magnetic field. The resonance frequency at which protons maximally absorb the radio energy is based on their local chemical environment. Because

musculoskeletal tissues are rich in proton-containing molecules such as muscle proteins and lipids, MRI is an inherently powerful tool at depicting the anatomy of muscle tissues, particularly in the delineation of lean and adipose components of muscles. While some investigators have used 3D MRI acquisitions to determine lean tissue and intermuscular fat volumes in a range of applications, the true advantage of MRI is the ability to obtain spectroscopic data that can probe in vivo the ATP-generating functions within skeletal muscle and the storage of important nutrients such as lipid and glycogen.

Proton magnetic resonance spectroscopy (1H-MRS) is a technique that can differentiate lipids stored within adipocytes (extramyocellular lipid, EMCL) from intramyocellular lipid (IMCL) stored as droplets on the border of the myoplasm [42–45]. This differentiation is based on the variance in resonance frequency between protons contained in relatively cylindrical deposits of EMCL in adipocytes and protons contained in IMCL deposits which are spherical in shape. These resonances show up as different peaks on the proton spectrum of skeletal muscle (Figure 15.3). Probing IMCL is of clinical importance because IMCL stores represent lipid which borders mitochondria, and which represent an energy supply of free fatty acids for oxidation. IMCL intensity determined by 1H-MRS has been found to correlate with insulin resistance and obesity. The risk of insulin resistance is known to increase with age, and aging skeletal muscle is characterized by decreasing oxidative capacity that may lead to increased IMCL. MRS may also be used to detect resonances of 31P and 13C nuclei contained in ATP, ADP, inorganic phosphate, glycogen, and other chemical forms in skeletal muscle estimate the

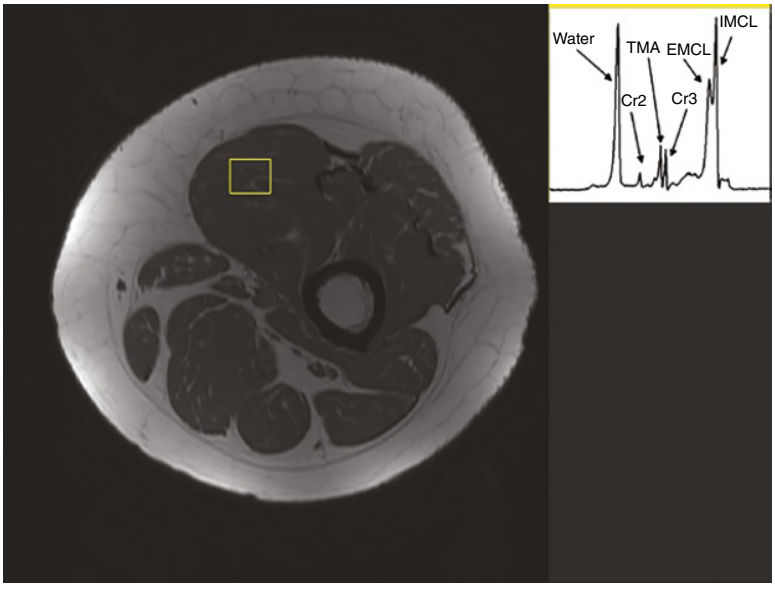

Figure 15.3 MRI image of distal femur at left showing yellow box indicating location of spectroscopic acquisition of the quadriceps muscle. Proton spectroscopy studies may be used to assess the relative amounts of intra and extramyocellular lipid. At right, a proton spectrum corresponding to the soleus muscle shows 1H resonances associated with creatinine (CR2 and CR3), water, extramyocellular lipid (EMCL), intramyocellular lipid (IMCL), and trimethylamines (TMA).

intracellular pH, as well as the free concentrations of ADP, and Mg^{2+} ions. These measurements allow the technique to be used to estimate rates of ATP synthesis under ischemic (glycogenolytic) conditions or aerobic (oxidative) conditions. Other applications in skeletal muscle studies include estimates of the oxidative capacity of skeletal muscle, as well as the proton efflux and buffer capacity, which provide insight into the recovery of skeletal muscle from exercise. The wide chemical shift of the 13C resonance allows 13C-MRS to assess the relative abundances of a wide range of molecules related to glycogen synthesis and glycogenolysis. Using the natural abundance (1.1%) of 13C, it is possible to detect resonances of 13C in glycogen and triglyceride. This allows for estimates of glycogen turnover in skeletal muscle and for studies of insulin resistance and type 2 diabetes. By administration of 13C glucose, it is possible to enrich 13C, allowing for more advanced determinations, such as examining glycogen synthesis rate and quantifying organelle and mitochondrial activity during the tricarboxylic acid (TCA) cycle. cells, shedding important light on muscle metabolism. 31PMRS can be used to directly analyze relative abundances of 31P contained in compounds of interest to energetics of skeletal muscle, including ATP, inorganic phosphate, and phosphocreatine [42, 46–50]. Continued improvements in MRI signal-to-noise ratio have led to recent advances in spectroscopic imaging of skeletal muscle, allowing for multiple P31 [51, 52] and 13C spectra [53, 54] to be acquired throughout a region of interest and for these studies to be acquired in muscle subregions with distinct biochemical compositions and physical function. Other physiologic measurements that can be obtained with MRI include fiber microstructure, blood flow, and ion fluxes. Diffusion-weighted tensor imaging (DTI) was developed to study the microstructural ordering of the white matter tracts of the central nervous system. DTI images are based on the anisotropy of the diffusion of water and tissues that have distinctly ordered microstructures, such the white matter of the brain, display anisotropic diffusion properties. Recently, improved clinical scanners and acquisition methods have permitted this approach to be extended to the study of skeletal muscles. Studies have examined the potential application to fiber tracking to measure fiber length, cross-sectional area, and pennation angles [55–59]. Arterial spin labelling (ASL) and blood oxygen level-dependent (BOLD) imaging can be used to study blood flow in skeletal muscle. ASL imaging provides a signal which is proportional to perfusion [60–63], whereas the signal in BOLD imaging depends on a combination of microvascular density, blood flow and volume, and rate of oxygen extraction [64–69]. ASL has been employed to study changes in perfusion during and after exercise, and BOLD imaging has been applied to study impaired blood flow in degenerative muscle disorders. 23Na imaging has been applied to study disorders of muscle associated with impairment of ion channel function [70, 71]. In this application, increases in the 23Na signal intensity are associated with muscle membrane depolarization in muscle myotonia and paramyotonia, indicating that MRI imaging can be used to image cellular changes in muscle function.

POSITRON EMISSION TOMOGRAPHY

PET is an imaging technique which is employed to image the biodistribution of a compound of interest labeled with a positron-emitting atom, for example an 18F or 11C. The most commonly employed PET imaging agent is 18F-fluorodeoxyglucose (FDG), a glucose analog which is widely employed to study glucose metabolism across

multiple tissue types. 18FFDG penetrates the cell membrane and is phosphorylated to FDG-6-phosphate and is no longer metabolized and thus is trapped within the cell. It builds up in the cell in proportion to the rate of glucose transport across the cell membrane and also in relation to the activities of hexokinase and glucose-6-phospotase within the cell. In skeletal muscle, FDG imaging has been employed to study glucose utilization. When used in conjunction with compartmental modeling, this approach has been employed to dissect the rate of glucose utilization in terms of the components of cell membrane transport and phosphorylative activity in insulin resistance associated with both obesity and diabetes [72, 73]. 11C-acetate imaging has been employed to measure perfusion and oxygen utilization of skeletal muscle tissue [74]. Another application of PET which is relevant to skeletal muscle is the use of 11C-methyl-methionine to estimate the rate of protein synthesis (Figure 15.4). This agent accumulates in skeletal muscle as 11C-labeled protein, and the use of this methylated agent has advantages over radiolabeled leucine in that the latter accumulates in the blood as 11C-labeled CO_2. Fischmann and others have validated this technique against skeletal muscle necropsy in an animal model [75] and have used it to outline the rate of skeletal muscle protein synthesis in healthy young volunteers [76]. Recently, Arentzon-Lantz et al. validated this technique in humans by conducting a study in volunteers comparing 11C-methyl-methionine PET/CT to skeletal muscle biopsies obtained after 13C-phenylalanine infusion [77]. They carried out imaging and biopsy studies before and after ingestion of a whey protein supplement, a well-characterized model for elevating skeletal muscle protein synthesis. They observed that both 13C-phenylaline-based fractional synthesis rate and protein synthesis rate by 11C-methyl-methionine PET/CT were elevated after the meal, and that the percent elevation was correlated between the two modalities.

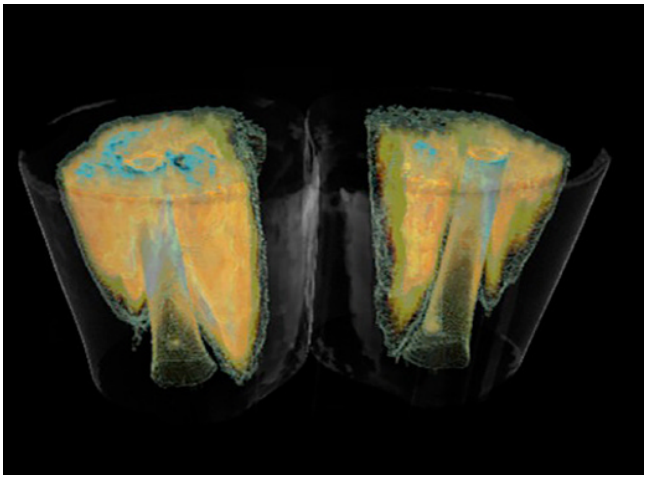

Figure 15.4 Three dimensional reconstruction fan image from the mid-thigh from a PET/CT acquisition using 11C-L-Methyl Methionine (11C-MET) to estimate protein synthesis rate of skeletal muscle. Solid pixels represent uptake of 11C-MET and transparent greyscale represents the delination of the thigh anatomy. This image was obtained of a female subject one hour after completion of unilateral leg resistance exercise of the right leg (left leg on the image). Note increased uptake in exercised leg.

CONCLUSION

In summary, imaging can be used to derive skeletal muscle tissue properties of relevance to aging and sarcopenia. While DXA may be used to characterize skeletal muscle mass at appendicular sites, 3D techniques such as CT, MRI and PET allow direct characterization of skeletal muscle tissue at multiple anatomic sites, including both central and peripheral anatomy. These characterizations not only include muscle mass, a parameter which is clinically important, but which has limited value to predict deleterious outcomes of sarcopenia, but also muscle metabolism measures which may have the potential to improve our ability to predict outcomes and to better understand the mechanisms underlying clinical interventions. The advent of multi-modality imaging such as PET/CT and PET/MRI, allow for the ability to improve our mapping of functional measures to anatomy, as well as to spatially correlate multiple metabolic measures of skeletal muscle.

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CHAPTER 16

Measurements of Muscle Mass, Equations and Cut-off Points

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INTRODUCTION

This chapter will describe different methods that can be used to measure or estimate muscle mass. Furthermore, several sarcopenia cut-off points based on these methods will be discussed. In the first paragraph, the estimation of muscle mass by anthropometric methods such as arm and calf circumference will be explained as well as prediction equations based on anthropometric measures to predict appendicular skeletal muscle mass (ASMM). Second, the bioelectrical impedance method will be described including the currently available muscle mass prediction equations. Then, the use of dual-energy X-ray absorptiometry (DXA) will be described and finally the use of the imaging techniques computed tomography (CT) and magnetic resonance imaging (MRI). The focus of this chapter will be on the single assessment of muscle mass rather than on multiple muscle mass assessments, because a single measurement of muscle mass is more clinically feasible. Advantages and disadvantages of each method and of the developed sarcopenia cut-off points, when available, will be discussed.

ANTHROPOMETRY – METHOD DESCRIPTION

Efforts have been made in examining the use of anthropometric measurements to estimate muscle size and to define sarcopenia. Assessment of a single anthropometric measurement as well as a combination of anthropometric measurements have been used as indicators of skeletal muscle mass or have been used to predict skeletal muscle mass. A potential advantage of this approach is the greater feasibility of simple anthropometric measures in clinical practice although these measurements will provide

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

a less precise estimate of the amount of muscle mass and the inter-observer variability of the measurement may be large.

Anthropometric measurements at the mid-upper arm have been frequently used as indicators of muscle mass. The following standard formulae [1] are being used: *Arm muscle circumference (cm) = arm circumference − (π * triceps skinfold thickness)* and *Arm muscle cross-sectional area (cm²) = (arm circumference − (π * triceps skinfold thickness))² /4*π*. The latter formula assumes that the arm and muscle within it are circular and that the skinfold thickness represents the average thickness between skin and muscle. Skinfold thickness is relatively more important in calculating muscle cross-sectional area in obese individuals. In young adults the latter equation was shown to overestimate arm muscle area as assessed by CT by 20–25%. This was due to the assumption of a circular mid-arm muscle compartment and due to inclusion of mid-arm cross-sectional bone area [1].

Arm circumference and arm muscle area have been related to total body muscle mass as determined by urinary creatinine excretion method, showing a rather low explained variance of 52 and 38% in younger persons [2]. This low explained variance, together with the large standard error of estimation (2.91 and 3.29 kg), shows their limited use to assess muscle mass. In a sample of 617 Chinese persons aged 69–82 years, arm circumference and arm muscle area were correlated with arm lean mass as assessed by DXA in older men (r = 0.60 and r = 0.61 [3]). In older women, these correlations were much lower; r = 0.28 and r = 0.39. Other studies also confirm that single anthropometric measurements at the arm are insufficiently correlated with ASMM as determined by DXA [4].

The correlation between calf circumference and ASMM from DXA is generally stronger as compared with the correlation between arm circumference and ASMM [4]. This was confirmed in a sample of 158 older men from the Longitudinal Aging Study Amsterdam (Table 16.1). However, in women the correlations of arm circumference and calf circumference with ASMM were similar (Table 16.1). In both men and women, the correlation between body weight and ASMM was highest: r = 0.62 in men and r = 0.69 in women. In 1458 French women aged 70 years, the correlation between different anthropometric measurements and ASMM from DXA was examined [5]. Of the anthropometric measures, including waist circumference, hip circumference, calf circumference, and grip strength, the calf circumference was most strongly associated with ASMM (r = 0.63, 95% CI 0.60–0.66). Similar as in the Longitudinal Aging Study Amsterdam, body weight was more strongly associated with ASMM (r = 0.83, 95% CI 0.71–0.76) than any other anthropometric parameter. High correlations between calf circumference and ASMM were also seen in a more recent Japanese study among 526 older men and women between the age of 40 and 89 years (r = 0.81 in men, r = 0.73 in women) [6].

Another approach to estimate skeletal muscle mass from anthropometry is to perform multiple circumference measurements across a body segment to estimate the total muscle volume in that segment. The estimated muscle volume is then validated against the muscle volume based on multiple MRI scans [7, 8]. Muscle volume of the thigh segment, based on three estimates of muscle area across the thigh, was 40% (SD 21) higher as compared to MRI. For the calf segment the overestimation was 18% (SD 14) [7, 8]. These studies show the limited use of multiple anthropometric measurements to estimate segmental muscle volume.

Table 16.1 Correlation between individual anthropometric parameters and appendicular skeletal muscle mass (ASMM) from dual-energy X-ray absorptiometry in 303 men and women aged 68–90 years from the Longitudinal Aging Study Amsterdam.

	Men	**Women**
Characteristics (mean (SD))		
Age (y)	76.5 (5.9)	76.2 (6.2)
Body height (cm)	174 (7)	161 (6)
Body weight (kg)	79.5 (11.8)	69.7 (12.0)
Body mass index (kg/m^2)	26.0 (3.4)	26.7 (4.7)
Mid-upper arm circumference (cm)	29.6 (2.8)	30.0 (3.8)
Calf circumference (cm)	36.4 (2.7)	35.8 (3.1)
Waist circumference (cm)	100.2 (10.6)	92.4 (11.6)
Hip circumference (cm)	101.7 (6.3)	104.0 (9.5)
ASMM (kg)	22.1 (2.7)	14.9 (2.3)
Pearson correlation coefficients with ASMM*		
Height (cm)	0.59	0.53
Body weight (kg)	0.76	0.69
Body mass index (kg/m^2)	0.54	0.45
Mid-upper arm circumference (cm)	0.58	0.49
Calf circumference (cm)	0.66	0.45
Waist circumference (cm)	0.54	0.51
Hip circumference (cm)	0.59	0.53

*All p-values < 0.0001.

Apart from single anthropometric indicators of muscle mass, prediction equations based on a set of different anthropometric measurements have been developed and cross-validated. Cadaver studies showed that total body skeletal muscle mass could be predicted based on equations including at least six different anthropometric measurements [9, 10]. The percentage of variance in total body skeletal muscle explained by the anthropometric variables was 96–97% but the standard error of estimation was substantial (1.49–1.53 kg). In 1998, Baumgartner et al. developed and validated a prediction equation to predict ASMM from DXA using three anthropometric measurements, grip strength, and sex [11]. This equation was developed in a random sample of the New Mexico Elder Health Survey, including 199 older men and women and was used to propose the first cut-off points to define sarcopenia. The following equation was developed in 149 persons: *ASMM (kg) = (0.2487 * body weight) + (0.0483 * body height) − (0.1584 * hip circumference) + (0.0732 * grip strength) + (2.5843 * sex) + 5.8828* (explained variance 91%, standard error of estimation 1.58 kg). The validity of this equation was then tested in the other 50 persons of the sample. Predicted muscle mass was highly correlated with measured muscle mass: the explained variance was 86% with a standard error of estimation of 1.72 kg. It should be noted that individual prediction errors in the total sample ranged from +4.2 to −5.1 kg, and that in 17% of the sample the prediction error was larger than 2 kg. In 2003, Rolland and others also developed a prediction equation to estimate ASMM as assessed by DXA in a large sample of French women aged 70 and older (5). The following equation was developed: *ASMM (kg) = (0.31 * calf circumference (cm)) + (0.05* waist circumference (cm)) + (0.08* hip circumference (cm)) + (0.02* grip strength (kPa)) − (0.16* body mass index (kg/m^2)) − 5.1*. The reported explained variance was 48%, which is rather

low, and the standard error of estimation was not reported. These two studies suggest that predicted ASMM based on a set of anthropometric variables, combined with a grip strength assessment, should always be interpreted very carefully, especially when this is done on an individual level.

ANTHROPOMETRY – CUT-OFF POINTS IN SARCOPENIA RESEARCH

Anthropometric measures of muscle mass in older persons have been related to different health outcomes in observational studies. Most of these studies have used mortality as an outcome but some studies investigating functional status are available. These studies may provide some insight into a potential cut-off point for sarcopenia.

A study among 357 older Italian men and women showed that persons in the lowest tertile of arm muscle circumference (<21.1 cm in men and <19.2 cm in women) had a poorer four-year survival compared with those with high arm muscle circumference [12]. A lower arm muscle area (lowest tertile <23.5 cm^2) was associated with two-year mortality risk in 957 Japanese frail older persons [13]. An arm muscle area of <21.4 cm^2 (men) and <21.6 cm^2 (women), corresponding with the lowest quartile, was also associated with an almost twofold higher risk of death during a four-year follow-up among 1376 community-dwelling men and women aged 70 years and older living in Australia [14]. Follow-up data from the same study, the Australian Longitudinal Study of Ageing, showed that these cut-off points were also predictive of eight-year mortality [15] while no significant associations were observed for body mass index (BMI). A study among 219 geriatric patients also confirmed the strong association between lower arm muscle area and 4.5-year mortality risk [16]. Recent findings from the Longitudinal Aging Study Amsterdam showed, after excluding (ex)smokers, cancer patients and persons with obstructive lung disease, an inverse, J-shaped association between upper-arm circumference and 15-year mortality in both older men and women [17]. Based on the dose–response plots, the mortality risk already started to increase at values below 30 cm. These studies consistently show that a smaller arm circumference, arm muscle circumference, and arm muscle area are related to an increased mortality risk in older men and women. However, none of the studies specifically developed a cut-off value below which this risk was increased. Therefore, no consistent cut-off value can be established as a criterion for the presence of sarcopenia based on anthropometric measurements at the arm.

Studies have also investigated the association between arm anthropometric measurements and functional decline in older persons. In a cross-sectional study among 357 older Italian men and women, persons those in the lowest tertile of arm muscle circumference (<21.1 cm in men and <19.2 cm in women) showed a poorer functional performance and poorer grip strength compared with those with high arm muscle circumference (>23.4 cm in men and >21.3 cm in women) [12]. A recent prospective study among 543 community-dwelling, frail Japanese older persons showed that a single measurement of arm circumference or arm muscle area was not an indicator of future decline in activities of daily living scores during a two-year follow-up [18]. However, a decline in arm circumference equal or greater than 1.6 cm was associated

with a decline in activities of daily living scores, although cause and effect cannot clearly be distinguished.

Rolland et al. [5] examined the potential use of the calf circumference as an indicator of sarcopenia. Using receiver operating characteristic (ROC) curves, the optimal cut-off point for calf circumference to determine sarcopenia was investigated among 1458 older French women [5]. Sarcopenia was defined based on DXA measurements using the cut-off point of Baumgartner et al. which was based on a young sample from the Rosetta Study [11]. A calf circumference cut-off point of 32 cm was optimal based on the combination of sensitivity and specificity; however, the authors decided to set the cut-off point at 31 cm to maximize specificity without reducing the sensitivity too much. Women with a calf circumference below 31 cm were 2.5 times more likely to have activity of daily living disabilities and were twofold to threefold more likely to have physical function difficulties. A low calf circumference was not associated with fall history of the previous six months. Although the calf circumference cut-off point resulted in a good specificity (91.4%), its sensitivity was rather low (44.3%). Kawakami et al. [6] investigated the use of calf circumference as a surrogate marker of muscle mass for diagnosing sarcopenia in middle-aged and older men and women. Also in this study DXA measurement cut-off points based on the Rosetta Study were used [11]. ROC curves showed that the optimal cut-off point for predicting class I and class I/II sarcopenia were 34.1 cm (sensitivity 88%, specificity 91%) and 36.8 cm (sensitivity 66%, specificity 74%) in men, and 32.8 cm (sensitivity 76% and specificity 73%) and 33.6 cm (sensitivity 66%, specificity 74) in women, respectively. The association between the observed cut-off point with health outcomes such as falls or functional limitations was not investigated. In a cross-sectional Korean study among 657 older adults aged 70–84 years optimal cut-off points were explored and the association with low calf circumference with physical function was investigated [19]. Optimal cut-off points were 35 cm for men and 33 cm for women. The correlation between calf circumference and DXA muscle mass was rather weak ($r = 0.55$ for both men and women), but a low calf circumference was associated with lower grip strength and physical performance. In a cross-sectional Italian study among 266 older men and women with a mean age of 86 years, a small calf circumference (<31 cm) was associated with poor physical performance and a higher score on the frailty index [20].

All in all, there seems to be limited usefulness of anthropometric measurements to assess sarcopenia. However, if no other muscle mass diagnostic methods are available, calf circumference may be used as a surrogate measure of muscle mass.

BIOELECTRICAL IMPEDANCE – METHOD DESCRIPTION

Bioelectrical impedance analysis (BIA) is a relatively simple, quick and noninvasive method for estimating body water and fat-free mass (FFM). The use of BIA in studies of body composition has grown rapidly over the past two decades. FFM as predicted by BIA has traditionally been used as a surrogate measure of skeletal muscle in the absence of better instruments. FFM, however, not only consists of skeletal muscle mass (~51%) [21], but also includes other organs, bone, and water of which the latter can show great variation.

BIA is based on the principle that lean body mass, which consists largely of ions in a water solution, conducts electricity far better than fat tissue. Therefore, the resistance of the body to an electrical current is inversely related to the lean body mass. The two main determinants of impedance, resistance and reactance, respond differently at any given frequency to intracellular and extracellular fluids. The reciprocal of the impedance is proportional to total body water for a current frequency ≥50 kHz or, to extracellular fluid, for frequencies below 5 kHz. Impedance values are then converted into values specific for total body water or extracellular fluid and then into FFM by means of prediction equations that are population specific. Prediction of lean mass can be improved by accounting for sex as well as height and weight. Most BIA measurements are made at a single frequency (50 kHz), although instruments that can measure at multiple frequencies become more available nowadays. The BIA method is very simple in practice. Electrodes (either two or four) are attached to a person's extremities (usually wrist and ankle) (Figure 16.1). A weak radio frequency signal is applied to the electrodes, and the impedance is measured. Usually several measurements are made, but the whole procedure takes less than a minute. Because the BIA method is simple, quick, safe, and noninvasive, it is potentially useful in clinical practice.

Many researchers have investigated the applicability of BIA prediction equations in various populations. BIA results have been shown to be confounded by fluid retention, as found in patients with chronic obstructive pulmonary disease (COPD) [22]. Hydrostatic disturbances, peripheral edema, and the use of diuretic medication may affect the validity of BIA measurements in older age groups [23]. As shown by Visser et al. [24] and Deurenberg et al. [25], BIA measurements are affected

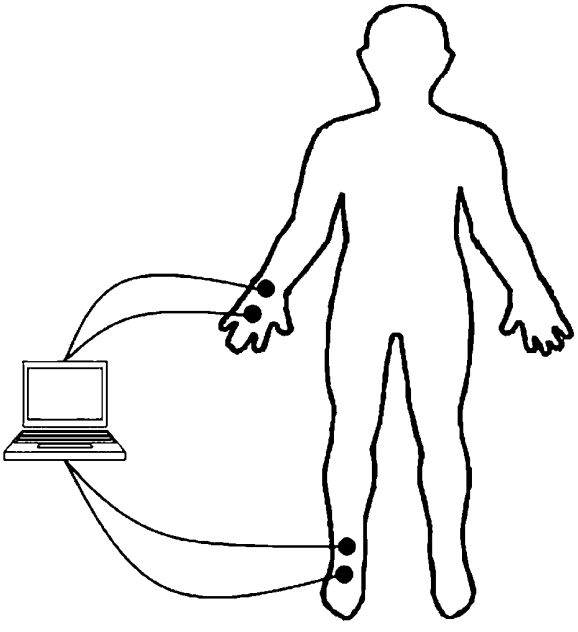

Figure 16.1 Schematic representation of the bioelectrical impedance measurement. Two electrodes are placed on the hand and foot.

by an increase in extracellular fluid in skeletal muscle of older persons. Therefore, Pietrobelli et al. [26] explored BIA prediction equations for ASMM at increasing electrical frequencies in 49 healthy men and women by using segmental BIA (measurement of the arms and legs). The hypothesis of this study was that ASMM prediction equations would no longer include age as an independent predictor at frequencies greater than 50 kHz (which is the standard electrical frequency used). It was shown, however, that age was a significant predictor in the prediction equation at all frequencies under study, suggesting other age-related changes in the skeletal muscle besides fluid increase that influence BIA measurement in older persons. In this study, it was also found that the prediction equation for ASMM improved at higher frequencies, which implies that multiple frequency BIA systems may offer an advantage over the conventional 50-kHz BIA method when evaluating muscle mass. Indeed, in a Japanese study involving 405 older adults (aged 65–90 years) it was shown that skeletal muscle mass measured with multiple frequency BIA was stronger associated with muscle strength compared with skeletal muscle mass measured by single-frequency BIA. However, more research in other populations is needed to confirm these findings [27].

Unfortunately, BIA methods that have been validated for the prediction of FFM in young individuals have been found to be inadequate when used in older populations [23]. Visser et al. [24] found that existing prediction equations for BIA that were based on young and middle-aged subjects overestimated lean mass and underestimated the percentage of body fat in an older (aged 60–87 years) population. Other studies have suggested that the errors in BIA equations are not related to age, but to the specific populations under study [28, 29]. In contrast, Genton et al. [30] compared four equations specific for BIA analysis in older persons and found only the equations derived by Kyle et al. [31] to accurately predict FFM in a group of persons with an age range of 65–94 years. The BIA equations developed by Deurenberg et al. [32] (age range 60–83 years) and Roubenoff et al. [28] (average age 78) were not found to be valid by Dey et al. [33].

More recently, several new equations have been developed in specific ethnic groups and age groups [34–38]. Rangel Peniche et al. [34] have developed the first, validated Latin American equation from a sample of Mexican older adults (60 years and over). The best fitted model was: ASMM = −0.005376 + (0.2394 × height^2 / resistance) + (2.708 × sex) + (0.065 × weight). In a cross-validation it was shown to perform better than the BIA equations by Kyle and Sergi.

Kim et al. [35] developed a BIA equation from a sample of 720 Korean older adults aged 65–80 years from the Ansung cohort. The generated prediction model was: ASMM = [(height^2 /resistance × 0.104) + (age × −0.050) + (sex × 2.954) + (weight × 0.055)] + 5.663. This equation was validated against DXA in another Korean cohort (KLoSHA) which included 189 men and 285 women of similar age as the development cohort. Furthermore, the muscle mass estimation was also analyzed in relation to mean peak torque of the leg muscles which was found to be similar compared to DXA muscle mass (all correlations between 0.39 and 0.49). Sex-specific BIA equations have been developed and cross-validated in a Japanese sample of 250 older adults aged 65 and over [36]. The equation for men: ASMM = 0.197 × (impedance index) + 0.179 × (weight) – 0.019 and for women: ASMM = 0.221 × (impedance index) + 0.117 × (weight) + 0.881.

Sergi et al. [37] developed and validated a BIA equation against DXA in 296 healthy older Caucasian men and women aged 60 years and older. Therefore, this equation is currently recommended by the European Working Group on Sarcopenia in Older People (EWGSOP) for use in older European populations [39]. The BIA equation was found to be more reliable than the equation derived by Kyle et al. [31], which is probably due to the fact that Kyle et al. used a sample with a larger age range (22–94 years).

The performance of several of the abovementioned equations was compared against DXA-derived skeletal muscle mass in a sample of 195 Australian older adults [40]. The equation by Sergi [37] showed the greatest predictive accuracy in women and overweight persons, while the equation by Kyle et al. [31] performed best in men. The equations of Kim [35] and Yoshida [36] performed worse, which is to be expected as these equations were derived from Asian samples [40]. Vermeiren et al. [38] developed a BIA equation for adults of 80 years and over which showed higher agreement with DXA appendicular lean mass compared with the equation of Sergi.

Both the equation of Kyle et al. [31] and the equation of Sergi et al. [37] were developed using Hologic DXA machines, Therefore, in 2017, new BIA equations were derived from 291 older Caucasian men and women with functional limitations, based on the data from Hologic DXA machines and GE Lunar machines separately [41]. Stepwise multiple linear regression analyses revealed that impedance index, weight, and sex were predictors to be included in both equations. Cross-validation showed no large differences in DXA appendicular lean mass versus BIA-derived appendicular lean mass, with a mean bias lower than 100 g [41].

In conclusion, when determining body composition in older persons, one should keep in mind that BIA equations are subject to errors, either due to age-related changes in hydration or population-specific characteristics. Therefore, BIA equations should be validated in the population in which they are to be applied, which of course hampers the use of BIA as a fast and simple method [42] and its use in clinical practice. The equation developed by Sergi et al. [37] is recommended for use in European populations [39].

BIOELECTRICAL IMPEDANCE – CUT-OFF POINTS IN SARCOPENIA RESEARCH

In the past years, BIA prediction equations have been developed to estimate total or appendicular muscle mass. In general, equation models include height squared, the BIA resistance, sex, and age as independent predictors of muscle mass. Janssen et al. developed a prediction equation for estimating whole-body skeletal muscle [43]. Whole-body skeletal muscle mass, determined by MRI, was compared with BIA measurements in a multiethnic sample of 388 men and women, aged 18–86 years, at two different laboratories. Within each laboratory, equations of skeletal muscle mass were developed using the impedance measured with BIA, body height squared, sex, and age in the Caucasian subsample. Second, both equations were cross validated and pooled to create one final equation: $skeletal\ muscle\ mass\ (kg) = (height^2 / (R \times 0.401)) + (sex \times 3.825) + (age \times -0.071) + 5.102$, where height is in centimeters, R is the BIA resistance in ohms, men = 1, women = 0, and age is in years. This (Caucasian-derived) equation was then applied to Hispanics, African Americans, and Asians which resulted

in a reasonable prediction of skeletal muscle in Hispanics and African Americans (explained variance 74%, standard error of estimation 2.7 kg (9%)), but showed an underestimation of skeletal muscle mass in Asians. The average difference between MRI-measured and BIA-predicted skeletal muscle mass was 2.45 kg (SD 1.61, $p < 0.001$). These results indicate that the Caucasian-derived equation is not applicable to Asian populations and that individual prediction errors can be substantial.

In a second cross-sectional study [44], the prevalence of sarcopenia was investigated using the data from the Third National Health and Nutrition Examination Survey (NHANES III). The predicted amount of muscle mass was expressed as the percentage of total body weight (termed skeletal muscle index, SMI) to adjust for stature and the mass of non-skeletal muscle tissues (fat, organ, bone). A potential disadvantage of the used index is that the ratio of whole-body skeletal muscle mass divided by total body weight is largely dependent on the amount of body fat since the between-person variation in total body fat is much larger compared with the between-person variation in skeletal muscle. The mean SMI in 3116 young men aged 18–39 years was 42.5% (SD 5.5%). The mean SMI in 3298 young women aged 18–39 years was 33.1% (SD 5.5%). An index within one to two standard deviations from the sex-specific mean value was considered class I sarcopenia. An index less than two standard deviations from the young reference group was considered to indicate class II sarcopenia. This led to the following cut-off points: a normal SMI in men was defined as an index greater than 37%, class I sarcopenia as an index between 31 and 37%, and class II sarcopenia as an index of less than 31%. In women, the cut-off points for normal SMI, class I sarcopenia, and class II sarcopenia were 28% or greater, between 22% and 28%, and less than 22%, respectively. Using this approach, 45 and 59% of the older (≥60 years) men and women were classified as having class I (moderate) sarcopenia, and 7 and 10%, respectively, of the older men and women were classified as having class II (severe) sarcopenia.

In the same cross-sectional study [44], class II sarcopenia based on the SMI was associated with functional impairment and disability in men and women. However, after adjustment for age, race, BMI, health behaviors, and comorbidity, some of the associations disappeared. Of the 12 items, class II sarcopenia in men was only related to the tandem stand performance and self-reported limitations stooping/crouching/kneeling. In women, class II sarcopenia was associated with five items.

In another study by the same author, cut-off points were determined for identifying persons with increased risk of physical disability (difficulty performing activities of daily living) using data from NHANES III [45]. ROC analysis was used to develop skeletal muscle cut-off points associated with physical disability. An SMI of ≤6.75 kg/m^2 was selected as the moderately increased risk cut-off point (class I sarcopenia), and an SMI of ≤5.75 kg/m^2 was selected as the high-risk cut-off point (class II sarcopenia) for physical disability in women. For men, an SMI of ≤10.75 kg/m^2 was selected as the moderately increased risk cut-off point, and an SMI of ≤8.50 kg/m^2 was selected as the high-risk cut-off point for physical disability. It should be noted that the skeletal muscle cut-off points determined in this study are similar to the arbitrary cut-off points based on two standard deviations below the mean of young adults determined in previous studies [11, 46]. See paragraph on DXA cut-off points for more details. Also, the cut-off points determined in this study were for physical disability and might have been different if another outcome measure such as mobility

limitations had been used. Furthermore, the cut-off points derived from the ROC analyses are population dependent and may be different in less healthy or institutionalized older persons.

Kyle et al. [47] developed a BIA prediction equation for ASMM in a study sample of 444 healthy persons aged 22–94 years and 326 heart, lung, or liver transplant patients aged 18–70 years which was validated against DXA. The correlation between ASMM obtained by the BIA prediction equation and the DXA measurement was 0.95 in healthy persons and 0.91 in patients. The standard error of estimation was 1.1 kg (5%) in healthy persons and 1.5 kg (7.6%) in patients. The best fitted model to estimate skeletal muscle mass was: ASMM = −4.211 + (0.267 * height ^{2} /(−0.012 × age) + (0.058 × reactance).

In a small cross-sectional study among older people in Taiwan, the BIA equation developed by Janssen to estimate skeletal muscle mass was used to investigate sarcopenia prevalence rates [48]. Despite the findings of Janssen that the BIA-derived equation underestimates skeletal muscle mass in Asians, this study found only small differences between MRI-measured and BIA-estimated skeletal muscle in a small group of 41 volunteers (aged 22–90 years). The differences ranged from +2.84 kg to −2.81 kg, $p = 0.15$. Sarcopenia was defined as the SMI of two standard deviations or more below the normal sex-specific mean for young persons ($n = 200$, mean age 27 years). In this study, an SMI of 8.87 kg/m^2 in men and 6.42 kg/m^2 in women or lower was considered as sarcopenia. The study shows a prevalence of sarcopenia of 23.6% in men and 18.6% in women. The sarcopenia prevalence rates found in this study are difficult to compare with other studies due to several issues. First, the current study only included community-dwelling volunteers without activities of daily living difficulties. Second, the cut-off points selected in this study are lower compared with the cut-off points in other studies [44, 45], which obviously leads to lower prevalence rates of sarcopenia.

The equations by Janssen and Kyle were both validated against DXA in 98 noninstitutionalized 75-year-old people [49]. The equation developed by Janssen overestimated total body skeletal muscle mass compared with DXA (mean difference of 1.02 (SD 1.39) in women, 4.05 (SD 2.22) in men, $p < 0.03$ in both groups). Also, the equation by Kyle overestimated ASMM (mean difference 0.64 (SD 1.41) in women, 1.23 (SD 1.63) in men, $p = 0.01$ and $p < 0.03$, respectively). It was suggested that these differences may be due to the fact that the equations by Janssen and Kyle were developed to include a wide range of ages, perhaps at the cost of less accuracy among older persons. Therefore, Tengvall developed a new age-specific equation to predict total body skeletal muscle mass by bioelectrical impedance spectrometry (BIS), which measures intracellular water, extracellular water, total body water, and FFM. This equation could predict total body skeletal muscle mass (correlation with DXA 0.91), although with great individual variation and therefore needs to be validated in other populations. Cut-off points for sarcopenia were not selected in this study.

In 2009, the relationship between sarcopenia and cardiovascular disease risk was investigated [50] using skeletal muscle mass calculated with the equation developed by Janssen. Muscle mass was adjusted for height using a regression-based residual technique. Sarcopenia was defined as the lowest sex-specific tertile of muscle mass (mean muscle mass 18.9 kg [SD 4.5]) and was not significantly associated with increased risk of cardiovascular disease.

Vermeiren et al. [38] developed a BIA equation for the oldest old (80 year and over) which was: appendicular lean mass = 0.827 + (0.19 × impedance index) + (2,101 × sex) + (0.079 × weight). Compared with DXA, this equation overestimated appendicular lean mass. Sarcopenia prevalence according to different definitions was calculated based on this new equation and was compared with DXA and the equations by Kyle, Sergi, and Scafoglieri. Regardless of the sarcopenia definition and cut-offs used, a higher prevalence of sarcopenia was established, ranging from 29 to 32%, compared with 13 to 17% based on the equations of Kyle, Sergi, or Scafoglieri. Sarcopenia prevalence rates based on DXA appendicular lean mass ranged from 34 to 44% depending on the cut-off points used. ROC analysis were performed to search for sex-specific cut-off points. For women, a cut-off point of 5.49 kg/m^2 was found, with an area under the curve (AUC) of 0.77, a high sensitivity of 95%, but a low specificity of 40%. For men, the cut-off point was 6.98 kg/m2, with an AUC of 0.86, a sensitivity of 95%, and a specificity of 47%. Due to the low specificity, these cut-off points are currently not useful to establish sarcopenia.

In conclusion, there are several BIA prediction equations and sarcopenia cut-off points in the current literature (see Table 16.2 for an overview). In recent years equations have been developed for specific populations. Researchers should consider all options carefully with respect to the population under study. For older Caucasian populations the equation by Sergi et al. [37] currently seems to be the best option for estimating ASMM.

DXA – METHOD DESCRIPTION

The DXA method was originally developed to measure bone mineral density of the proximal femur, lumbar spine or forearm to allow a diagnosis of osteoporosis. Because of this application, the method is widespread and well-known in the clinical setting. The tissue attenuation of photons transmitted by the two X-ray beams with different energy levels also provides information on the composition of soft tissue. Whole-body DXA therefore enables the precise derivation of the none-bone tissue into fat mass and FFM. This can be determined for the total body as well as of specific regions of interest (such as the limbs) (Figure 16.2). The duration of the measurement depends on the type of DXA scanner, but can be less than five minutes for a whole-body scan which enhances its feasibility in the clinical setting [51, 52]. A detailed description of the DXA method can be found in Chapter 14.

Heymsfield et al. were among the first to show that the bone-free, FFM of the arms and legs provides an accurate assessment of ASMM [53]. Using data from 44 healthy persons with a mean age of 52 (SD 20) years, they showed that ASMM was highly correlated with total body potassium as measured by whole-body counting (r = 0.94) and total body nitrogen as estimated from prompt gamma-neutron-activation analysis (r = 0.78). Several years later, a high correlation between ASMM from DXA and total body skeletal muscle from CT was shown in 17 healthy persons and 8 AIDS patients [54].

DXA measurements of the amount of muscle mass of the leg only have also been validated against MRI and CT. Shih et al. [55] showed that the bone-free, fat-free soft

Table 16.4 Overview of methods to assess muscle mass in older persons.

Method	Frequently used muscle mass measures	Regional muscle	Whole-body muscle	Low cost	Availability	Radiation exposure	Precision	Accuracy
Anthropometry	Upper-arm muscle circumference	+++	+	+++	+++	+++	+	+
	Upper-arm muscle cross-sectional area	+++	+	+++	+++	+++	+	+
	Predicted ASMM	+	++	+++	+++	+++	+	+
Bioelectrical impedance	Predicted FFM	+	+	+++	+++	+++	+	+++
	Predicted ASMM	+	++	+++	+++	+++	+	+++
Dual-energy X-ray absorptiometry	ASMM	+++	++	++	++	++	++	++
Computed tomography	Mid-thigh cross-sectional muscle area	+++	+	+	+	+	+++	+++
Magnetic resonance imaging	Mid-thigh cross-sectional muscle area	+++	+	+	+	+++	+++	+++
	Total body muscle volume	+	+++	+	+	+++	+++	++

ASMM = appendicular skeletal muscle mass, FFM = fat-free mass. +++ Indicates a very positive feature of the method, while + indicates a less positive feature.

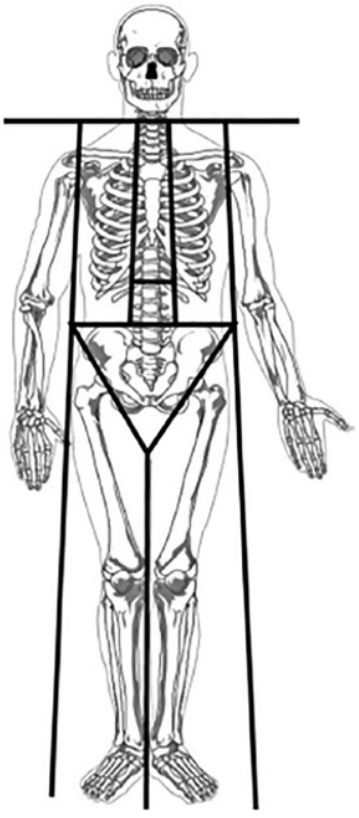

Figure 16.2 Schematic representation of the regions of interest commonly used in dual-energy X-ray absorptiometry. The tissue composition of the arms and legs is used to assess appendicular skeletal muscle mass.

tissue of the leg as determined by DXA in 207 adults was highly correlated with skeletal muscle mass as determined by multiple MRI scans of 1.0 cm thickness with a 4.0 cm space between scans (explained variance 89%). Age and BMI also explained a small, but statistically significant, part of the variance and increased the total explained variance to 90.4%. The validity of leg muscle mass by DXA was validated in 60 men and women aged 70–79 years using multi-slice CT of the legs [56]. The explained variance was 96% with a standard error of estimation of 0.7 kg. However, a study comparing a 1.3 cm mid-thigh slice by DXA with a 1.0 mm CT slice in 30 older women recovering from a hip fracture, showed a much lower explained variance (73%) [57]. In addition, the 8- to 12-month change in mid-thigh muscle mass by DXA was poorly correlated with the change assessed by CT, with an intraclass correlation coefficient of 0.51. In 50 sedentary older men and women, the increase in total thigh skeletal muscle mass caused by single leg exercise training was measured by multi-slice CT as well as DXA [58]. Muscle mass at baseline and muscle mass after exercise training were highly correlated between the two methods ($r = 0.88$ and $r = 0.90$). The increase in thigh muscle mass due to exercise training was 3.9% by CT and 2.6% by DXA, with a poor correlation between the two methods ($r = 0.52$).

Based on these examples and other validation studies, DXA is currently considered a valid and accurate methodology to measure ASMM in humans. The method is being used in clinical as well as research settings. Although CT and MRI are more precise alternatives to detect small changes in muscle mass over time, DXA is frequently being used to test the effect of a specific intervention on muscle.

DXA – CUT-OFF POINTS IN SARCOPENIA RESEARCH

Baumgartner and colleagues were the first to develop a definition of sarcopenia based on DXA measurements [11]. Analogous to the BMI, the ASMM was divided by height squared to adjust for the strong association between body height and ASMM. The cut-off points for low ASMM were developed using a similar approach as for the cut-off points for osteoporosis. Older persons with an ASMM less than two standard deviations from the mean of a young reference population were considered sarcopenic. DXA data from a young (aged 18–40 years) volunteer sample of 229 non-Hispanic white men and women participating in the Rosetta Stone Study in New York; [59] were used to determine the sarcopenia cut-off points. The developed ASMM cut-off points were 7.26 kg/m^2 for men and 5.45 kg/m^2 for women [11]. Although these cut-off points are limited by the fact that the young reference group was a volunteer sample and might not have been representative for young US men and women (it was actually the first young sample with available DXA measurements) they are widely being used in sarcopenia research.

The Baumgartner cut-off points for sarcopenia were first applied to the New Mexico Elder Health Survey in which ASMM was predicted using an equation including sex, several anthropometric measures, and grip strength [11]. After adjustment for age, income, ethnicity, obesity, comorbidity, current smoking, physical activity, and alcohol intake, sarcopenic men and women were more likely to have ≥3 physical disabilities on an Instrumental Activities of Daily Living scale. In men, but not in women, sarcopenia was also associated with >1 balance abnormality, the use of a cane or walker, and falling in the past year.

Using the same approach, based on two standard deviations below the mean of a young reference sample, sarcopenia cut-off points have also been developed in 111 young, healthy Chinese persons aged 20–39 years [60]. The mean reported ASMM was 7.4 (SD 0.84) for men and 6.4 (SD 0.79) for women, which would translate to ASMM cut-off points of <5.72 kg/m^2 for men and <4.82 kg/m^2 for women to indicate sarcopenia. These values are substantially lower than previously defined in young Caucasian persons [11] which suggested that sarcopenia cut-off points might be race-specific. After this study, several other Asian studies were conducted using the same approach with slightly higher estimated cut-off points compared with Lau et al. [61-64] Based on the results of these studies, the Asian Working Group for Sarcopenia (AWGS) currently recommends using height-adjusted skeletal muscle mass with cut-off points of 7.0 kg/m2 for men and 5.4 kg/m2 for women [65].

In 2003, a second approach was used to derive sarcopenia cut-off points [66]. This approach was initiated based on the finding in the Health, Aging and Body Composition Study that the sarcopenia prevalence using the original Baumgartner

sarcopenia cut-off points was very high in normal weight older persons (>50%) but not present in obese older persons. In theory, obese older persons can also be sarcopenic and the term sarcopenic obesity was developed to describe this condition [67]. The new method incorporated both body height and total body fat. The lowest 20th percentile of the residuals of the regression of total body height and body fat on ASMM derived in the older men and women separately was used to define sarcopenia. The percentile cut point was chosen arbitrarily. The residuals of the regression were thus used to identify those whose ASMM was much lower than the predicted value and had a negative residual. Separate models were fit for men: $ASMM\ (kg) = -22.48 + (24.14^{*}\ height\ (m)) + (0.21^{*}\ total\ fat\ mass\ (kg))$ and for women: $ASMM\ (kg) = -13.19 + (14.75^{*}\ height\ (m)) + (0.23^{*}\ total\ fat\ mass\ (kg))$. This new definition was compared with the lowest 20th percentile of the ratio of ASMM divided by height squared (7.23 kg/m^2 in men, 5.67 kg/m^2 in women). These cut-off points turned out to be very similar to the original Baumgartner cut-off points [11]. In men, sarcopenia according to both definitions increased the risk of having a low function. The risk of a low function score almost doubled in women with sarcopenia based on the residuals. In contrast, women with sarcopenia based on the ratio had a *lower* risk for having a low function. This is explained by the fact that the non-sarcopenic group includes obese women who have a low function score because of their excess body fat. A similar approach was used in the study of Kim et al. [62] in older Korean adults aged 60 and over. Sex-specific models were created: for men: ASMM (kg) = −31.23 + (32.84 × height (m)) + (0.24 × total fat mass (kg)) for men and ASMM (kg) = −19.10 + (21.65 × height (m)) + (0.20 × total fat mass (kg)) for women. The prevalence of sarcopenia based on these models was 15.4% in men and 22.3% in women, which was much higher when compared with the sarcopenia prevalence based on the lowest 20th percentile of the ASMM/height^2 from a young reference group (7.40 kg/m^2 for men and 5.14 kg/m^2 for women, resulting in a sarcopenia prevalence of 6.3 and 4.1%, respectively) [62].

The association between sarcopenia using both abovementioned definitions and a five-year change in physical function was also examined in the Health Aging and Body Composition Study [68]. Again, sarcopenia based on the residual method was better for predicting incident lower-extremity mobility limitations compared with the ratio ASMM/height^2 method. In fact, men and women with sarcopenia based on the ratio method had a *lower* risk of developing incident mobility limitations which was attenuated after adjustment for total body fat. Based on these studies we can conclude that the amount of ASMM can only be correctly interpreted when considering not only body height but total body fat mass as well.

A third approach has been described to define a potential cut-off value for sarcopenia [69]. ROC curves were used to determine the optimal cut-off point for ASMM/height^2 based on the relationship with physical limitations in 3153 community-living, Chinese men and women aged 65 years and older [69]. A U-shaped association was observed between ASMM/height^2 and physical limitations for both men and women. However, the area under the ROC curve (AUC) was low (0.528), showing a very limited predictability of sarcopenia for the presence of physical limitations. ASMM/height^2 values below the range of 7.25–7.75 kg/m^2 in men and below the range of 6.00–6.25 kg/m^2 in women were associated with an increased risk of physical limitations. However, no clear, single cut-off value gave best sensitivity and specificity.

DXA data obtained in the National Health and Nutrition Examination Survey, collected from 1999 through 2004 in a representative sample of the US population, have been recently used to determine reference values for body composition [70]. Mean values for ASMM/height^2 obtained in, for example, young persons aged 20–25 years could potentially be used to determine a cut-off value for sarcopenia using the approach of two standard deviations below the mean. This would result in the following cut-off points: <6.19 kg/m^2 for Caucasian men, <6.12 kg/m^2 for African American men, <6.46 kg/m^2 for Mexican American men, <4.73 kg/m^2 for Caucasian women, <5.29 kg/m^2 for African American women, and <4.70 kg/m^2 for Mexican American women. Gould et al. [71] developed reference ranges for total and appendicular muscle mass in a population-based sample of Australian older men and women aged 20–93 years. Cut-off points for ASMM/height^2 were 6.94 kg/m^2 for men and 5.30 kg/m^2 for women which are slightly lower than the cut-off values found by Baumgartner. However, as explained before in this chapter, these cut-off points do not consider the amount of total body fat and may underestimate sarcopenia in obese persons. Furthermore, since this young NHANES sample also includes obese persons, the cut-off points might be overestimated.

In 2014, the Foundation for the National Institutes of Health Sarcopenia Project used data from nine data sets including 11 270 older men and women to create cut-off values for low muscle mass associated with muscle weakness using a data-driven approach [72]. Classification and regression tree (CART) analyses identified cut-off values for low appendicular lean mass (ALM<19.75 kg in men and <15.02 kg in women). Other muscle parameters such as ALM divided by height were not identified as important discriminators of muscle weakness, with the exception of ALM divided by BMI. Cut-off values for ALM/BMI were 0.789 for men and 0.512 for women. In 2017, the Sarcopenia Definition and Outcomes Consortium was formed [73] and is currently the largest effort to define sarcopenia, using data from 8 epidemiological cohorts, 10 clinical samples, and 2 nationally representative samples from the United States. The results of this effort are expected soon.

Based on this literature overview, it can be concluded that there is no consensus on DXA-derived sarcopenia cut-off points (Table 16.3). Even though the original cut-off points by Baumgartner are widely being used, these values have several drawbacks as discussed above and cannot be applied to other race groups. A careful interpretation of ASMM from DXA, incorporating at least sex, race, body height, and total body fat, is necessary to determine whether muscle mass is too low for an individual patient. This has unfortunately complicated the quick and easy determination of sarcopenia by DXA in clinical practice. A simple algorithm to interpret ASMM and high-quality research showing that sarcopenia according to this algorithm is clinically relevant with regard to future health and functioning of the older patient, are two important prerequisites for the future.

CT AND MRI – METHOD DESCRIPTION

Nowadays, CT and MRI are more and more used for measurement of body composition and are considered the reference methods for studying skeletal muscle. The use of CT and MRI as reference methods is based on the main assumption that measured

cross-sectional muscle area (CSA) is equivalent to actual skeletal muscle CSA. Information about the specific methods and usage of CT and MRI are discussed in detail in Chapter 14. In short, the principle of CT is based on the use of a scanning an X-ray beam that passes through the participant/patient. The X-ray exit transmission intensity is monitored by a series of detectors, which results in the visual production of cross-sectional slices of about 10 mm thick. The average attenuation coefficient along the length of the X-ray beam is then calculated and expressed in Hounsfield units (HU).

The principle of MRI involves a cylindrical magnet with an internal diameter large enough to enclose a human body to allow for an external magnetic field. The presence of gradient coils creates a smaller identification field, known as a gradient field. The radio frequency coil generated by these magnetic fields provides the force necessary to rotate nuclear spin away from the direction of the external magnetic field. Radio frequency signals are emitted, which are combined to form an image. Variations in the radio frequency pulse sequence are used to specific tissues, such as adipose tissue or skeletal muscle. Although multi-slice whole-body imaging is generally considered the reference for measuring total body adipose tissue or skeletal muscle volumes, most researchers over the past two decades measured a single cross-sectional image of the abdomen. In a study by Shen et al., the correlation between single-slice abdominal CSAs and total body compartment volumes were examined in 328 healthy adults [74]. The highest correlation between a single-slice skeletal muscle area (SMA) and total body SMA was about 5 cm above the L4–L5 level ($r = 0.924$). Regression models based on this cross-sectional image accurately predicted total body SMA. Effects of sex, age, ethnicity, body scanning position, BMI, and waist circumference on the strength of the association were small, suggesting that a single slice image may be used to represent total body skeletal muscle mass across a wide range of healthy subjects.

CT and MRI are the most accurate imaging methods to assess muscle cross-sectional area, muscle volume, and muscle quality (muscle density and intramuscular fat infiltration). The assessment of muscle density using MRI or CT provides a reliable and valid measure of the fatty degeneration of muscle tissue [75]. A lower muscle density indicates more intramuscular fat, which is associated with lower muscle functioning/strength [76].

Caution should be taken with regard to using CT as an assessment of muscle mass in some patient populations. There is a variation of +30 to +80 HU in the attenuation of normal muscle. There can be wide variation in the size or volume of muscles on each side of the body. Because of the variation in muscle size associated with physical training and nutrition status, general reductions in muscle size may be difficult to determine in the early stages of disease without baseline measurements [77]. The effect of energy restriction and exercise on appendicular skeletal muscle volume was examined recently with MRI [78]. Obese women treated with diet only showed a significant decrease in skeletal muscle volume in arms and legs compared with women treated with diet and aerobic exercise. This finding shows the ability to detect small changes in skeletal muscle mass by MRI. Another study by Song et al. [79] showed a significant loss of skeletal muscle mass (mean −0.72 [SD 0.71]) measured by MRI after two years of follow-up in 29 African American women aged 65 years and older. MRI and CT are costly, time consuming, and are technically difficult to perform. CT also involves exposure to radiation. Therefore, their use is mostly restricted to body composition research and their use in clinical practice to assess sarcopenia is limited.

Table 16.3 Characteristics of studies that developed sarcopenia cut-off points based on DXA measurements.

Reference	Study sample	N	Age range	Sex	BMI mean (SD)	Ethnicity	Country	Muscle mass index		Cut-off points
Baumgartner et al. [11]	Rosetta Study	229	18–40	M, F	24.6 (3.8) 24.1 (5.4)	Non-Hispanic whites	United States	ASMM/ht^2	M: F:	<7.26 kg/m^2 <5.45 kg/m^2
Newman et al. [66]	Health ABC Study	2984	70–79	M, F	Whites: M: 27.0 (3.7) F: 26.0 (4.6) Blacks: M: 27.1 (4.3) F: 29.7 (5.7)	Whites, blacks	United States	Residual of ASMM regressed on ht and total body fat ASMM/ht^2	M: F: M: F:	≤–2.29 kg ≤–1.73 kg <7.23 kg/m^2 <5.67 kg/m^2
Lau et al. [60]	Chinese community	111	20–39	M, F	M: 22.5 (9.5) F: 23.5 (3.9)	Asian	Hong Kong	ASMM/ht^2	M: F:	<5.72 kg/m^2 <4.82 kg/m^2
Woo et al. [69]	Chinese community	3153	65+	M, F	M:23.5 (3.1) F: 24.0 (3.4)	Asian	Hong Kong	ASMM/ht^2	M: F:	<7.25–7.75 kg/m^2 <6.00–6.25 kg/m^2
Based on Kelly et al. [70]	NHANES 1999–2004	558	20–25	M, F	—	Non-Hispanic whites, non-Hispanic blacks and Mexican Americans	United States	ASMM/ht^2	Non-Hispanic (NH) whites NH blacks Mex. Americans	M: <6.19 kg/m^2 F: <4.73 kg/m^2 M: <6.12 kg/m^2 F: <5.29 kg/m^2 M: F: <6.46 kg/m^2 <4.70 kg/m^2
Kim et al. [62]	Korean community	526	20–88	M, F	M: 25.2 (3.1) F: 23.9 (3.7)	Asian	Korea	ASMM/ht^2 Residual of ASMM regressed on ht and total body fat (ASSM/weight)×100	M: F: M: F: M: F:	<7.40 kg/m^2 <5.14 kg/m^2 < - 1.87 < - 1.62 <35.71% <30.70%
Sanada et al. [61]	Japanese community	529	18–40	M, F	M: 23.0 (3.0) F: 20.8 (2.6)	Asian	Japan	ASMM/ht^2	M: F:	<6.87 kg/m^2 <5.46 kg/m^2

Kim et al. [63]	Fourth Korean National Health and Nutritional Examination (KNHANES IV)	2513	20–39	M, F	M: 24.0 (3.4) F: 22.1 (3.5)	Asian	Korea	ASMM/ht^2 (ASMM/weight)×100	M: F: M: F;	<6.58 <4.59 <29.1% <23.0%
Lee et al. [64]	I-Lan Longitudinal Ageing Study (ILAS)	100	20–40	M, F	24.2 (3.8) 22.3 (3.7)	Asian	Japan	ASSM/ht^2	M: F:	7.27 5.44
Studenski (2014) and Cawthon et al. [72]	Multiple cohorts participating in the FNIH sarcopenia project	11 270	65+	M, F	26.9 (5.2)	Whites, blacks, Hispanics	United States	ASSM	M: F:	<20 kg <15 kg
Gould et al. [71]	Geelong Osteoporosis Study	2371	20–93	M, F	—	Caucasian	Australia	ASSM/ht^2	M: F:	<6.94 kg/m^2 <5.30 kg/m^2

M = male; F = female; BMI = body mass index; DXA = dual-energy X-ray absorptiometry; SD = standard deviation; ASMM = appendicular skeletal muscle mass; ht = body height; FNIH = Foundation for the National Institutes of Health.

CT AND MRI – CUT-OFF POINTS IN SARCOPENIA RESEARCH

Several studies have used CT or MRI to investigate consequences of sarcopenia [80–86], and most of these studies did not use cut-off points but used rather population-specific tertiles or quartiles. Lauretani et al. [80] investigated calf muscle area, measured by peripheral quantitative CT (pQCT), in relationship to poor mobility in the InChianti study. The CSAs obtained at 66% of the tibia length was used in the analyses, as this has been suggested to be the region with the largest outer calf diameter, with little variability across individuals [87]. Sarcopenia cut-off points were developed in the participants aged 20–29 years. Persons were considered sarcopenic when their values were less than two standard deviations of the mean of the young reference group (83.3 cm^2 [95% confidence interval (CI) 78.9–87.8] in men, 62.6 cm^2 [58.5−66.7] in women). Calf muscle area was divided into quintiles to investigate the relationship with poor mobility, but only showed weak associations. The AUC was 0.64 and 0.57 in women for the relationship between calf muscle area and walking slower than 0.8 m/s and unable to walk without difficulty for 1 km, respectively. For men these values were 0.84 and 0.69. The optimal cut-off value for low calf muscle area, yielding the highest sensitivity and specificity, was 54.97 and 56.67 cm^2 in women and 63.05 and 68.82 cm^2 in men for both these outcomes. However, after adjustment for age, low calf muscle area according to these cut-off points was not associated with an increased risk for poor mobility in women. In men, a low calf muscle area was only associated with a walking speed slower than 0.8 m/s and not with self-reported difficulty.

Several studies based on the Health, Aging, and Body Composition Study have related measures of body composition derived by CT to indices of functional ability, quality of life and mortality in the well-functioning older persons. Visser et al. [81] used sex- and race-specific quartiles of mid-thigh muscle CSA and intramuscular fat infiltration to investigate the association with incident mobility limitations in 3075 well-functioning people aged 70–79 years. Persons in the lowest quartile (<230 cm^2 in white men, <245 cm^2 in black men, <152 cm^2 in white women, <181 cm^2 in black women) were more likely to develop mobility limitations compared with persons with a CSA in the highest quartile. In a study by Newman et al. [82], mid-thigh CSA (analyzed as a continuous measure) was weakly associated with mortality in the same study population. This is in concordance with a study performed by Cesari et al. [83]. In this study, skeletal muscle mass was measured by pQCT of the calf and was then related to mortality in data from 934 participants (mean age 74.5 years [SD 7.0]). Sarcopenia was defined according to the lowest sex-specific tertile of the residuals of a linear regression model that predicted muscle mass from height (in cm) and fat mass area (log value of cm^2). Sarcopenia was not associated with an increased risk of mortality.

Recently, reference values for CT muscle mass have been provided in several studies. Using data from 420 healthy Caucasian kidney donors aged 20–60 years, distributions of SMA, SMI (SMA/$height^2$), and muscle radiation attenuation (MRA in HU, a measure of muscle quality taking fat mass into account) were investigated for CT scans at the third lumbar vertebra (L3) [84]. The fifth percentile was used to define low SMA, SMI, and MRA, which corresponded with an SMA of 134 cm^2, an SMI of 41.6 cm^2/m^2, and an MRA of 29.3 HU in men, and 89.2 cm^2, 32.0 cm^2/m^2, and 22.0 HU in women, respectively. The authors also provided percentiles for different age and BMI categories within the sexes.

In a US study among 604 healthy kidney donors (aged 18–40), skeletal muscle cut-off values were defined using CT scans of several levels, including L3 (skeletal muscle), L4 (psoas muscle), and T12 (skeletal muscle and dorsal muscle group area) [85]. Sarcopenia cut-offs based on two standard deviations below the mean. Compared with the study of van der Werf et al. [84], the cut-off values for low SMA and SMI were slightly higher (SMA: 141.7 cm^2 for men and 91.2 cm^2 for women; SMI: 44.6 cm^2/m^2 for men and 34.0 cm^2/m^2 for women).

An Asian study has reported reference values and cut-off values for L3 psoas muscle based on data from 541 Japanese healthy liver donors aged 20 years and older that can be used to determine low muscle mass in Asian populations [86]. Sex-specific cut-off points for low skeletal muscle mass were 6.36 cm^2/m^2 for men and 3.92 cm^2/m^2 for women. Studies to investigate the association between low CT muscle mass based on the reported cut-off values and health outcomes are needed to validate these cut-off values.

In conclusion, although CT and MRI are considered the reference methods for assessment of skeletal muscle mass, not many studies have yet used these methods to determine sarcopenia and its long-term consequences. Studies relating muscle mass by CT or MRI to specific outcomes mainly used population specific cut-off points like quartiles or tertiles or defined sarcopenia as muscle mass below two standard deviations of the mean muscle mass in a reference population. Recently, reference values and cut-off values have been reported in Caucasian and Asian samples, which need further research.

EMERGING METHODS

In the past years, new promising methods to assess muscle mass have become available. The first method is ultrasonography or ultrasound. Ultrasound is a cheap, portable, noninvasive technique that produces images of the body through high-frequency sound waves [88]. The method itself is not new; it is effectively used for the diagnosis of neuromuscular disorders with positive predictive values of up to 90% [89]. However, the method has only recently gained interest from researchers to be used for sarcopenia diagnosis [90, 91]. In a recent systematic review including studies that used ultrasound in older persons aged 60 years and over, it was concluded that ultrasound is a valid method to assess muscle mass when compared with DXA, MRI, or CT [92]. Ultrasound is highly correlated with DXA measurements of muscle mass and has a good intra- and inter-reliability [92]. A protocol has recently been proposed for using ultrasound in sarcopenia research [91]. Several research steps need to be taken before ultrasound can be implemented in sarcopenia research and practice, including the creation of reference values and equations to diagnose sarcopenia.

Another emerging method is deuterated creatine (D_3-Creatine) dilution, which is a direct measure of muscle mass as opposed to other measures of muscle mass such as DXA. D_3-Creatine is a stable isotope that can be given orally and subsequently distributes to the muscle compartment. The creatine is turned over in the muscle through conversion into creatinine, which is excreted in urine. Enrichment of labeled creatinine in the urine is related to skeletal muscle labeled creatine enrichment and thus whole-body creatine pool and skeletal muscle mass. The test is simple and cheap. A study

Table 16.4 Overview of methods to assess muscle mass in older persons.

Method	Frequently used muscle mass measures	Regional muscle	Whole-body muscle	Low cost	Availability	Radiation exposure	Precision	Accuracy
Anthropometry	Upper-arm muscle circumference	+++	+	+++	+++	+++	+	+
	Upper-arm muscle cross-sectional area	+++	+	+++	+++	+++	+	+
	Predicted ASMM	+	++	+++	+++	+++	+	+
Bioelectrical impedance	Predicted FFM	+	+	+++	+++	+++	+	+++
	Predicted ASMM	+	++	+++	+++	+++	+	+++
Dual-energy X-ray absorptiometry	ASMM	+++	++	++	++	++	++	++
Computed tomography	Mid-thigh cross-sectional muscle area	+++	+	+	+	+	+++	+++
Magnetic resonance imaging	Mid-thigh cross-sectional muscle area	+++	+	+	+	+++	+++	+++
	Total body muscle volume	+	+++	+	+	+++	+++	++

ASMM = appendicular skeletal muscle mass, FFM = fat-free mass. +++ Indicates a very positive feature of the method, while + indicates a less positive feature.

from Clark et al. have shown good correlations of D_3-creatine dilution tests with MRI-based muscle mass measurements, with less bias compared with DXA muscle mass [93], but also revealed high intra-individual variability [93]. Recent data have shown that men with the lowest muscle mass as measured by D_3-creatine dilution had a higher risk of mobility limitations and injurious falls, worse physical performance, and lower muscle strength compared with men with higher muscle mass [94]. Details about the method can be found in Chapter 17.

OVERVIEW OF METHODS

In Table 16.4, an overview is provided of the discussed body composition methods to assess muscle mass in older persons. The most frequently used measures of muscle mass assessed by these methods are listed as well as the ability of the methods to measure regional and/or whole-body muscle mass. Furthermore, a rating of the costs of the method, the general availability of the method and the patient radiation exposure are provided. Also, the precision (validity) and accuracy (reproducibility) of each method are rated.

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CHAPTER 17

Deuterated Creatine Dilution to Assess Muscle Mass (D3-Cr Muscle Mass) in Humans: Methods, Early Results, and Future Directions

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Disclosures: PMC is a consultant to BioAge Labs and has research grants to her institution from Nestle and Abbott for work unrelated to this chapter. GlaxoSmithKline provided in-kind support by providing the D3-Cr dose and analysis of urine samples in the MrOS study; the MrOS project was otherwise funded by the National Institute on Aging and the National Institute of Arthritis and Musculoskeletal and Skin Diseases. WJE is listed as an inventor on the issued patents for the D3-cr dilution method; he derives no income from this intellectual property.

INTRODUCTION

The assessment of total body skeletal muscle mass has, until recently, been problematic, as many published studies have relied on an assessment of lean body mass (LBM) as a proxy for skeletal muscle mass. Skeletal muscle is a significant, but not the only, component of LBM. Lean mass is frequently incorrectly referred to as muscle mass. The assumption that lean mass is synonymous with muscle mass has resulted in incorrect conclusions regarding the relationship between skeletal muscle mass and functional

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

capacity in older people [1]. As a result, the definition of sarcopenia has evolved from an age-related decrease in skeletal muscle mass [2] to an age-related decrease in strength [3] and/or functional capacity along with a of loss of LBM [4].

A new approach to measure muscle mass (the deuterated creatine (D3-Cr) dilution method) has recently been implemented in large clinical studies [5]. In this chapter, we will first describe the operational aspects of the D3-Cr dilution protocol including the methods for administering the timed dose and urine collection and calculation of creatine (Cr) pool size and muscle mass. Then, we will review the published literature for studies that have implemented this measure. Finally, we will discuss the next logical steps needed for research in this area.

METHODS AND OPERATIONAL APPROACH

Overview of Dilution Method

The D3-Cr dilution method relies three aspects of Cr metabolism: (i) about 98% of the total body Cr pool is sequestered in skeletal muscle, (ii) Cr is synthesized in the liver and kidneys and transported into muscle against a large concentration gradient and (iii) Cr is turned over in muscle through the non-enzymatic, irreversible (in vivo) conversion of Cr to creatinine (Crn), which is rapidly excreted. These are the main assumptions of the 24-hour urine Crn method to estimate muscle mass described by Heymsfield et al. [6] where the amount of Crn excreted in a 24-hour period is directly related to skeletal muscle mass. However, use of 24-hour urine collection requires dietary control during the collection period. This is because any Crn ingested as part of the diet is rapidly excreted and leads to an erroneously high calculation of muscle mass. In addition, the method also requires collection of all urine produced during a 24-hour period as missing a single micturition will result in an erroneously low determination of muscle mass.

The D3-Cr dilution method provides a direct measurement of Cr pool size which is used to calculate muscle mass (and assumes a concentration of 4.3 g of Cr/kg muscle). An oral dose of a tracer quantity of D3-Cr is 100% bioavailable and once absorbed is transported across the sarcolemma and sequestered in sarcomeres. The excretion of Crn and measurement of D3-Crn enrichment in urine provides an opportunity to "sample" the intra-myocellular enrichment of D3-Cr and, thus, determine the dilution of the oral D3-Cr label in the whole-body Cr pool in skeletal muscle. Importantly, the D3-Cr measurement does not require dietary control and relies on a single spot, fasted urine sample taken 48–96 hours after dosing. The enrichment of urine D3-Crn reaches isotopic steady state at about 48 hours after dosing and remains stable for at least another 48 hours [7]. Because we determine urine Crn enrichment (D3-Crn/Crn ratio), subjects with compromised renal function can be measured as long as even a small amount of urine is produced. Cross-sectional [8] and longitudinal [9] validation studies of this method were performed in rats and in humans. As described below, the method has been validated in men and women of all ages [7, 10]. A cartoon illustrating the D3-Cr dilution method is provided in Figure 17.1.

A cross-sectional study in rats of different ages demonstrated a strong relationship between D3-Cr muscle mass and lean mass measured by quantitative magnetic

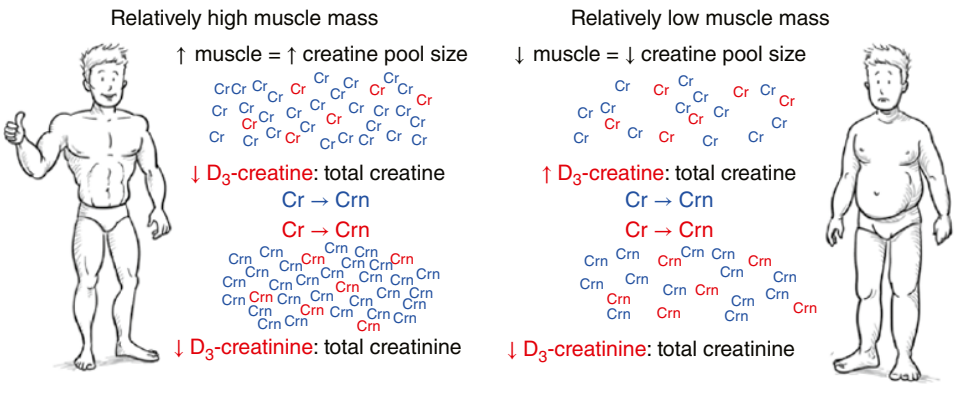

Figure 17.1 Creatine pool size and muscle mass estimation in humans.

resonance (QMR) ($r = 0.959$, $P < 0.0001$) and muscle mass of the lower limbs (weighed after dissection) ($r = 0.929$, $P < 0.0001$) [8]. A subsequent, longitudinal validation study of muscle mass accrual of growing animals and loss of muscle mass due to dexamethasone treatment demonstrated a strong relationship between change in QMR lean mass and change in D3-Cr muscle mass ($r = 0.9629$, $P < 0.0001$) [9]. A cross-sectional, clinical validation study was performed in young and older men and women [7]. D3-Cr muscle mass was strongly associated with whole-body magnetic resonance imaging (MRI) of muscle mass ($r = 0.868$, $P < 0.0001$) and dual-energy X-ray absorptiometry (DXA) ($r = 0.745$, $P < 0.0001$). The line of identity passed through the origin for whole-body MRI versus D3-Cr muscle, while whole-body DXA overestimated muscle mass compared.

Importantly, the D3-Cr dilution method measures a parameter, the Cr pool, or the total amount of Cr present in the body. In the sarcomere, Cr and Cr phosphate are located adjacent to the Z-disc and the A-band [11] and are not associated with non-contractile components. This strongly suggests that assessment of the Cr pool size provides an indicator of functional muscle mass independent of lipid and fibrotic tissue, both of which increase with advancing age [12]. These components (lipid and fibrotic tissue) also may reduce the accuracy of the measurement of purely anatomic muscle mass using radiographic imaging or using indirect methods like DXA.

Although the D3-Cr dilution method provides a direct measure of Cr pool size and muscle mass, there are two potential methodological sources of variability: sampling urine prior to isotopic steady sate or when a subject is not fasting. Data from Clark et al. [7], representing young and older men and women and, demonstrate the urine enrichment of D3-Crn for the entire period of time after ingestion of a dose of D3-Cr. During this period of time all subjects were consuming a controlled diet. Urine was collected in batches (not as a single sample). By approximately 48 hours after ingestion, urine D3-Crn enrichment was stable, an indication that the enrichment of urine D3-Crn was the same as the enrichment of the precursor, D3-Cr, and is in isotopic steady state. If a urine sample is collected during the period between taking the dose and 48 hours, the sample enrichment will be low compared with the intramyocellular enrichment of D3-Cr and the resulting calculation for muscle mass will not be correct. Urine enrichment of D3-Crn displays a cycle (increases and decreases) that corresponds to

consumption of food. While ingestion of Cr is low for most humans (cooking of meat results in the almost complete conversion of Cr to Crn), Crn is a normal component of a diet that contains meat or fish and, because Crn is not stored, it is excreted rapidly, and can dilute the enrichment of urine D3-Crn. This dietary effect can be eliminated by collection of a fasting urine sample. The additional assumption of this method is that an oral dose of a tracer quantity of D3-Cr is 100% bioavailable and once absorbed is transported across the sarcolemma and sequestered in sarcomeres. In some subjects, a small amount of the oral tracer dose is "spilled" into urine and not transported into muscle. This "spillage" of label into urine is greater in adult women compared with men and is likely due to a higher rate of production of endogenous Cr than uptake by muscle. It appears that the fasting urine Cr/Crn ratio is constant and, as a result, the amount of spillage can be estimated and corrected with an algorithm based on urine levels of Cr and Crn [10].

Reproducibility of the D3-Cr dilution measure

Clark et al. also published a reproducibility study about D3-Cr muscle mass and DXA lean mass in humans [13]. In 33 older adults, D3-Cr dilution estimates of muscle mass estimates were correlated with MRI muscle volume ($r = 0.88$, $P < 0.0001$), with less bias compared with total LBM assessment by DXA, which overestimated muscle mass versus MRI ($+22.5 \pm 3.7$ kg). The D3-Cr muscle mass, magnetic resonance (MR) muscle volume, and DXA lean mass measures were repeated in 14 of these participants three to four months later (1 participant had congestive heart failure.) This study that intra-individual variability over timeframe was high with the D3-Cr dilution method, with intra-subject SD for estimated muscle mass of 2.5 kg versus MRI (0.5 kg) and DXA (0.8 kg). However, the long time period (three to four months) between assessments have led to erroneous conclusions. As described below, data from the Osteoporotic Fractures in Men (MrOS) study demonstrated that over a period of 1.6 years, D3-Cr muscle mass, walking speed, and DXA lean mass all decline with age (about 4–5% during this time period) [14]. No changes in lean mass by DXA were observed over this time period. Only change in D3-Cr muscle mass, and not DXA lean mass, was associated with declines in walking speed. Thus, the time period for assessment of "repeatability" may have been too long; it is possible that these older adults, and especially the participant with heart failure, lost D3-Cr muscle mass (but not DXA lean mass or MR muscle volume) during this time frame. Under these conditions, the variability in the D3-Cr muscle mass measure would be spuriously inflated relative to DXA lean and MR muscle volume. A reproducibility study with a shorter time interval between assessments (that accounts for any remaining dose from the initial assessment) should be conducted.

Implementation of the D3-Cr dilution method in research settings

The D3-Cr-dilution method been implemented recently in a number of studies, although only two have published results available as of the writing of this chapter [5, 14, 15]. As this method relies of use of an isotopically labeled dose, the D3-Cr dilution

measure of muscle mass can only be obtained prospectively. Participants must be dosed with D3-Cr prior to urine collection; archived samples without dosing cannot be used. The largest study to date to implement the measure is the multicenter MrOS study, in which 1425 older, community-dwelling men had complete, valid assessments of D3-Cr muscle mass at the Year 14 study visit [5]. The MrOS study presented a number of challenges to implementing the measure: the participants were older with limited mobility. The men were assessed at six different academic medical centers in the United States, each with separate institutional review board procedures and requirements. The nature of the test required tracking and reminder calls to ensure accurate timing of the dose and urine collections. Collection of the fasting sample also necessitated reminder contacts. Listed below are several hurdles encountered during the implementation of the D3-Cr dilution protocol and how these were overcome in MrOS.

Mitigating concerns about safety of the D3-Cr dose

One of the most important components of determination of muscle mass is the accurate delivery of a dose as this is a dilution method. A mass spectrometer is used for urine sample analysis so the use of tracer quantities of D3-Cr provides measurable enrichment of urine D3-Crn. The actual dose used is less important than absolute certainly of the amount of the dose. We have used 30–60 mg doses of encapsulated D3-Cr and these doses provide sufficient and measurable enrichment of urine D3-Crn. It should be stressed that this tracer quantity of Cr is 30- to 60-fold less than the average Cr consumption of most adults. We have used a quick internet search for "side effects creatine," and this generates numerous warnings about possible dangers of Cr supplementation including weight gain, stomach upset, kidney damage, and other conditions [16]. This literature refers to Cr supplementation as a nutritional intervention where doses of 5–10 g per day – and up to 20 g per day – are common [17]. These doses are orders of magnitude larger than the dose included in the D3-Cr dilution test (that is 5000–20 000 mg from dietary sources versus 30 mg used in the D3-Cr dilution test). Cr also found in the diet of meat eaters; those who consume meat ingest up to 2 g of Cr a day [18]. Furthermore, deuterium is a nonradioactive stable isotope that is nontoxic and safe. In MrOS, sites were provided with a "frequently asked questions" handout that could be shared with participants who raised concerns about the measure.

Implementing the Timed Dose and Fasting Morning Urine Collection

The most challenging part of the D3-Cr dilution protocol is the timing of the dose and subsequent fasting urine collection. As described, above, collecting urine too soon after the dose will not allow sufficient time for urine D3-Crn enrichment to come into equilibrium with the body Cr pool and reach isotopic steady state. Thus, measures made too soon after the dose is ingested will result in overestimation of the Cr pool size and thus D3-Cr muscle mass. Collecting urine too late after the dose is ingested will result in decreased urine D3-Crn enrichment as a result of turnover of D3-Cr

(about 1.7%/d) that would result in overestimation of the Cr pool size and D3-Cr muscle mass. Finally, dietary control before and after the dose is ingested is not required. However, as dietary Crn is rapidly absorbed and excreted in urine and, as a result, will dilute the enrichment of urine D3-Crn, a fasting urine sample is need. This is most easily obtained by requesting the second void after an overnight fast and prior to consumption of any food. To ensure that clinical centers were using the correct days and times for dosing and urine collection, charts were shared with the clinics that listed when reminder calls and dose ingestion should occur for each weekday when clinic visits could occur.

Given the constraints about the timing of the dosing and collection of urine, the optimal approach for use in clinical research studies is to observe the dosing of the participant, and then have the participant produce a urine sample under controlled conditions (such as in a clinical lab or at home with a research staff member available to transport the urine back to the central processing facility.) Options for dosing and collection are provided in Figure 17.2. However, this can be costly to implement, and in MrOS, we used a number of approaches. The most successful and cost-effective approach was to mail the dose of D3-Cr to participants ahead of their scheduled clinic visit with detailed instructions. A reminder phone call was then made that repeated about the timing of the dose and the requirement for fasting on the day of the clinic visit. The ingestion of the dose was thus timed to be with 72–144 hours of the participant's scheduled clinic visit. Then, when participants came to the clinic for their visit, they produced a urine sample which was then aliquoted by the lab and kept frozen at −20 °C until shipment on dry ice to the central laboratory. In this scenario (mail dose and then collect urine in the clinic), initially consent was obtained orally from MrOS participants over the phone before the dose was ingested. Participants then confirmed consent to the urine D3-Cr dilution procedure in writing at the clinic visit before the urine sample was collected. The institutional review board at one institution initially did not allow for oral consent to the D3-Cr dilution procedure, meaning the "mail dose and collect urine in the clinic" option could not be used. In this clinic, the participants were received the D3-Cr dose at the clinic visit, and the urine was collected at home (with phone calls placed to remind participants about the specimen collection). In most situations, urine specimens were collected by clinic staff and driven back to the clinic processing. In a handful of instances, the urine sample was mailed back to the clinic using self-freezing gel packs. This was the least successful approach, as it required completed shipping instructions and mailing of liquid urine.

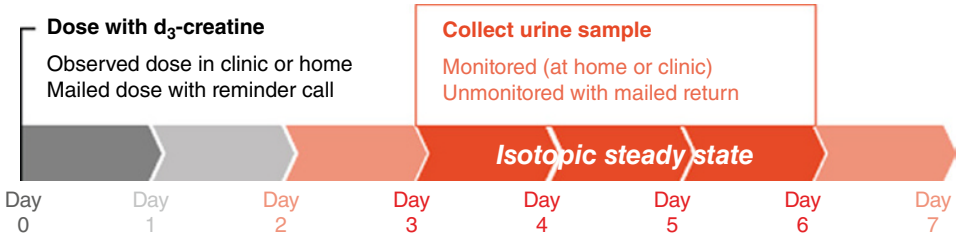

Figure 17.2 Options for dosing adult participants and collecting urine in clinical research studies.

In this population of older men, not all were able to easily mail packages (many lived in residences without access to postage-paid package pick-up), and occasionally the gel packs would warm during shipment. A number of samples were useable after the mail-in approach.

CONSIDERATION OF BODY SIZE IN ANALYSIS OF MUSCLE MASS

Absolute values of muscle mass without consideration of total body size are difficult to interpret, because body size (weight and height) vary widely, and as a result, whether or not a given amount of muscle is "enough" for function, how large or how small a person is must be considered. A slender and short woman needs a lower absolute amount of muscle mass to function in her daily environment than a tall, obese man. We assert that the most important consideration of body size in this setting is body weight. Analogies can be drawn from the obesity literature on this point. While body weight scaled to height squared (or body mass index [BMI]) is often used as a measure of obesity; however, BMI does not prove an assessment of body composition. Percent body fat (i.e. total body fat scaled to body weight) may a more appropriate measure of adiposity than is BMI [19]. Thus, we recommend the primary approach to analyze D3-Cr muscle mass is to standardize it to body weight (D3-Cr muscle mass/weight). If this is the case, then why DXA-based analyses of lean mass relied of scaling to height squared [20] to standardize for body size? This has to do with the fact that DXA is a three-compartment model: DXA directly measures bone mineral content and body fat, and by subtraction of lean mass. The amount of bone mineral in the body is somewhat negligible compared with fat and lean mass. Therefore, mathematically, the ratio of total body lean mass to body weight is nearly directly inversely proportional to the ratio of total body fat to body weight (i.e. percent fat). Thus, the ratio of total body lean mass to weight from DXA would be difficult to interpret: would this be the amount of lean mass present, or the absence of fat? Use of height [2] to standardize lean mass measure to body size avoids these problems particular to DXA and other compartment models. The D3-Cr muscle mass approach is not a compartment model; therefore, the absence of fat does not mathematically equate to the presence of muscle, and the ratio of D3-Cr muscle mass to weight is both reasonable and interpretable. D3-Cr muscle mass/weight is therefore the recommended approach to analyze data. Figure 17.3 provides a graphical representation of body composition components assessed by DXA and by D3-Cr dilution.

SUMMARY OF OBSERVATIONAL HUMAN STUDIES THAT HAVE IMPLEMENTED THE D3-Cr DILUTION METHOD

The MrOS study is a large, multicenter prospective cohort study designed to study healthy aging with a particular focus on osteoporosis and fractures. At the Year 14 clinic visit, all surviving participants were invited to complete a clinic visit that included assessment of muscle mass by D3-Cr dilution, DXA body composition,

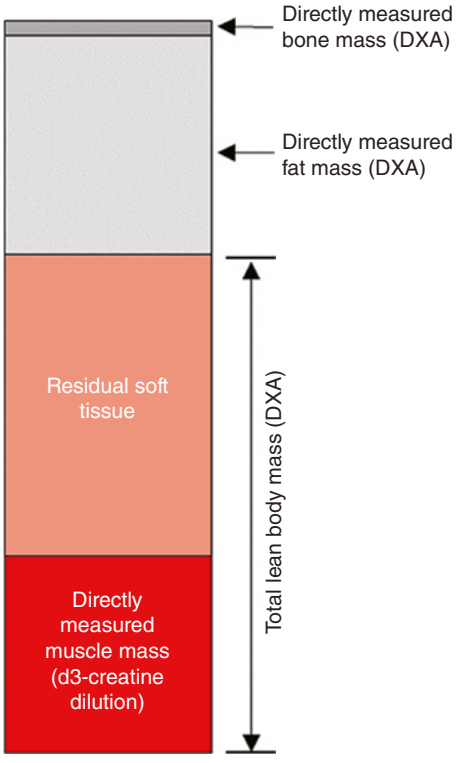

Figure 17.3 Schematic of body composition components as measured by dual energy x-ray absorptiometry (DXA) and D3-Cr dilution. DXA directly measures bone and fat mass, but not muscle mass.

physical performance, strength, and self-reported function. We assessed muscle mass by D3-Cr dilution in 1369 men (mean age, 84.2 years). As seen in previously completed validation studies, in MrOS, DXA-derived measures of total body lean mass and total muscle mass by D3-Cr dilution were moderately correlated ($r = 0.67$, $p < .001$), but the relationship does not fall along the line of identity, demonstrating that these two methods are measuring different things. Of note, measurement error of this magnitude can strongly bias the observed relative risk [21]. For example, in a simulation where the true relative risk (RR) between an exposure measured without error (i.e. the gold standard) and an outcome is RR = 1.5, when the exposure is measured with error (and modestly correlated with the gold standard at $r = 0.65$), the resulting observed RR is attenuated to only RR = 1.17. This assumes that this measurement error is non-differential with regard to the outcome. Differential error can bias toward the null or induce spurious associations. Our data from MrOS imply that the measurement error inherent to DXA could explain the lack of association between DXA ALM/ht^2 and outcomes. In fact, the MrOS data support this notion.

In MrOS, we have shown that D3-Cr muscle mass has a broad and strong relationship with physical performance, mobility limitation, and serious injurious falls [5]. MrOS men completed the short physical performance battery (SPPB), usual walking

speed over 6 m. Men self-reported any mobility limitations (any difficulty walking 2–3 blocks or climbing 10 steps), and serious injurious falls during the year after the exam. Across quartiles of D3-Cr muscle mass/weight, multivariate linear models calculated adjusted means for SPPB and gait speed; multivariate logistic models calculated adjusted odds ratios for incident mobility limitation or falls. All models were adjusted for age, strength, comorbidities and other confounders. Men in the lowest quartile of D3-Cr muscle mass/weight were slower and had worse performance on the SPPB than those with the highest values of D3-Cr muscle mass/weight (walking speed mean, Q1: 1.04 m/s vs. Q4: 1.17 m/s, $p<.001$; SPPB mean, Q1: 8.4 points vs. Q4: 10.4 points, $p<.001$). Lower DXA lean mass was not associated with slower walking speed or worse SPPB performance. If anything, lower DXA lean mass was associated with faster walking speed. Associations were generally similar for other measures of strength and function. Further, men in lowest quartile of D3-Cr muscle mass/weight were twofold to sixfold more likely to have serious health outcomes than men in the highest quartile of D3-Cr muscle mass/weight, including a sixfold increased likelihood of prevalent mobility limitation (odds ratio [OR]: 6.2, 95% confidence interval [CI]: 3.7, 10.5); a 2.4-fold increased risk of serious injurious fall (OR: 2.4, 95% CI: 1.4, 3.3) and a 2.1-fold increased risk of incident mobility limitation (OR: 2.1, 95% CI: 1.4, 3.3). DXA lean mass was unrelated to falls. Lower DXA ALM/h^2 was associated with a *lower* likelihood of prevalent mobility limitation (OR, Q1 vs. Q4: 0.4, 95% CI: 0.3, 0.6) and a *lower* likelihood of incident mobility limitation (OR, Q1 vs. Q4: 0.6, 95% CI: 0.4, 1.0). (These DXA results suggest, counterintuitively, that less lean mass is better for physical function outcomes.) Analyses are underway regarding associations between D3-Cr muscle mass or DXA lean mass and risk of other incident outcomes such as fractures, disability and mortality. From these data, we conclude that unlike DXA lean mass, low D3-Cr muscle mass is strongly related to poor outcomes in older men.

MrOS has also published data regarding change in D3-Cr muscle mass. A convenience sample of 40 men (mean age 84.9 years) from the MrOS study repeated assessment of DXA lean mass, D3-Cr muscle mass, walking speed and grip strength on average 1.6 years after the Year 14 clinic visit. These data show a striking ~4–5% loss of D3-Cr muscle mass while there was no change in DXA lean mass (total body, ALM, or ALM standardized to body size) during this time [14]. This suggests that the loss of muscle mass has been underestimated in previous studies which have shown that strength and lean mass decline with age [22–24], with declines in strength occurring more rapidly than declines in DXA lean mass [24] (or cross-sectional muscle area (CSA) by CT) [24]. Furthermore, decline in D3-Cr muscle mass is correlated with decline in walking speed. Declines in D3-Cr muscle mass over 1.6 years mirror declines in strength and walking speed, while changes in lean mass by DXA do not: the only measure that was correlated with change in performance (gait speed) was the decline in D3-Cr muscle mass ($r = 0.33$, $p = 0.037$) [14]. These data suggest that magnitude of the change in muscle mass may in fact mirror the magnitude of the change in performance and strength. Importantly, in this study, without an independent measurement of muscle mass, a change in muscle "quality" would be a logical explanation of the observed decrease in strength and gait speed with not reduction in lean mass.

A limitation of the MrOS study is that the cohort is only men, who report mostly White race. It is unknown whether the MrOS results would generalize to other populations such

as women or other race and ethnic groups. Further, the number of men with repeat D3-Cr muscle mass assessment is small. Therefore, more work needs to be completed, including new studies of D3-Cr muscle mass and adding this measure to existing studies in which participants are being characterized.

A small cross-sectional study by Buehring et al. [15] examined body composition in 112 community-dwelling older subjects (23 men and 89 women, mean age 80 years) using DXA, bioelectric impedance spectroscopy (BIS) and the D3-Cr dilution method. Similar to MrOS and other validation studies, D3-Cr muscle mass was significantly correlated with DXA total lean mass (with DXA lean mass overestimating muscle mass). D3-Cr muscle mass and DXA total body lean mass were both related jumping power, but associations with other measures of function varied. However, in these analyses, D3-Cr muscle mass was not standardized to body size (e.g. expressed as D3-Cr muscle mass/body weight). The correction for body mass is critical to any examination of function; using weight adjustment in MrOS revealed a strong association of muscle mass on clinical outcomes. Thus, the lack of strong associations with function in this small study could be due to failing to account for body size and the relatively narrow range of values of muscle function. Nevertheless, the authors concluded that "this study further establishes the D3-Cr dilution method as an easy to use and accurate assessment of whole-body skeletal muscle mass. The method . . . [could] . . . be used in large clinical and cohort studies, and, potentially, as a diagnostic tool."

NEXT STEPS

The compelling data from the MrOS study supports the use of the D3-Cr muscle mass measure in research settings. In fact, we posit that the D3-Cr muscle mass measure should be tested in any population where muscle is postulated to impact health and disease. This suggests that its use is not limited to studies of sarcopenic older adults but could also illuminate other fields such as research on wasting conditions such as cancer cachexia and HIV as well as studies of growth (such as babies in children) In fact, a number of these projects are currently underway. Should this future research in older adults support the initial MrOS findings, the D3-Cr muscle mass measure may become the standard approach for assessing muscle mass in research settings. Once established as a research tool, a reasonable next step would be to evaluate how the D3-Cr muscle mass measure could be used to diagnose sarcopenia and other wasting conditions in clinical settings, including whether or not this test should be added or, or even entirely replace, current definitions of sarcopenia. Current definitions of sarcopenia do not include a direct measure of muscle mass; instead they rely primarily on DXA lean mass. Only more data and time will provide answers to these unknowns.

In those with relatively high muscle mass, relatively less of the total Cr pool is comprised of labeled Cr (D3-Cr, noted as Cr in red). As Cr is converted to Cr, and D3-Cr is converted to D3-Crn, relatively less of the Crn excreted in the urine is labeled (D3-Crn, noted as Crn in red.) Thus, the ratio of D3-Crn to total Crn is relatively low in those with high muscle mass. In those with relatively low muscle mass, the opposite is

true: relatively more of the total Cr pool is comprised of labeled Cr, resulting in relatively more of the Crn excreted in the urine to be labeled. Thus, the ratio of D3-Crn to total Crn is relatively high in those with lower muscle mass.

For this timed test, participants ingest a dose, either at home or in clinic, and then provide a urine sample three to six days later once the labeled creatine has reached isotopic steady state.

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CHAPTER 18

Measurement of Muscle Strength and Power

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INTRODUCTION

As shown in other chapters, loss of muscle mass is not inevitably associated with loss of muscle strength. In fact, a correlation of the two parameter amounts can only be found between 0.3 and 0.6 [1]. Consequently, also the revised European Consensus definition of sarcopenia includes physical performance instead of relying solely on muscle mass as in older definitions [2]. (Chapter 6: Definition of Sarcopenia). Besides muscle strength also muscle power shows an age-related decline. Furthermore, it could be shown that muscle power declines faster than muscle strength [3]. These observations are of practical relevance, as lower power of the lower extremities has been shown to be associated with a two to three times higher risk for the development of functional deficits. This association is much stronger than between muscular strength and future functional deficits [4]. In addition, increases in muscle power have a higher impact on improvements of functionality when compared with increases of muscle strength [5]. These findings have a strong influence on exercise concepts which are developed for the therapy of sarcopenia (see Chapter 18: Exercise Interventions to Improve Sarcopenia).

The above introduction underlines the relevance of measuring muscle strength and muscle power. In this chapter, the different options of measurement that are applicable in science and in clinical routine will be presented. First, the terminology of physical parameters that are relevant in this context will be outlined. These parameters differentiate from those measured for the evaluation of physical performance. The latter will be discussed in Chapter 18. In the second part the different methods of measurement that are relevant for research and clinical practice will be presented.

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

TERMINOLOGY

Muscular activity

The interaction between muscle-generated strength and external forces can lead to dynamic or isometric activity. Isometric activity is characterized by a pure increase of tension while the distance between muscle origin and muscle attachment remains constant. Strength is generated, but no outside work is performed, as no muscle shortening occurs. In contrast, all muscle activity that is associated with changes of muscle length – not taking into account the direction – is described as dynamic.

Dynamic activity is always associated with changes of joint angles, whether increases or decreases. They are described as concentric if they cause muscle shortening, and as eccentric if despite muscle activity muscle lengthening is observed which is caused by external factors, e.g. weights. When defining a specific dynamic muscle activity, the type of change of length (muscle shortening or muscle lengthening), the speed of the respective change, and the movement of involved body parts against each other have to be mentioned. In principal, the muscle`s operating strength is never constant; when changing joint angles, the conditions under which the muscle is working do not stay constant and its ability to generate strength is changing. Therefore, isotonic muscle activity with constant tension is not found in everyday movements. Likewise, one does not normally come across isokinetic muscle activity with constant speed of contraction. Even if a certain movement would be realized with constant velocity – which would mean isokinetically – maybe with the help of a specifically constructed power machine or an ergometer this would not imply that the individual muscle would contract with constant velocity. Furthermore, in practice conditions rarely occur, under which pure concentric, eccentric, or isometric activities are realized. In fact, combinations of all these actions are observed in the context of everyday movements.

Quantification of muscular action

In the context of muscular actions several physical parameters can be measured. Strength describes the capacity to alter the passive and/or motion state of an object (standard unit = newton, N). Moment of force or torque describes the rotary impact of a force exerted on an object. It is calculated by multiplying the operating force and the vertical distance of the force vector to the axis of rotation (standard unit = newton × meter). Work is defined as the product of strength and distance without taking into account the time factor (standard unit = Joule, J). Power describes the velocity, by which a certain work is performed (standard unit = Watt, W).

Strength and power

Muscular strength is globally defined as the physical force that a muscle can exert on specific parts of the body. Here, the muscle may develop different sized forces, depending on the realized form of action (isometric, concentric, eccentric, etc.).

Therefore, it is necessary to specify the form of action under which the force was measured. Besides the form of action, information on the initial muscle length or joint angle must also be available.

Another form to determine muscular strength was proposed by De Lorme [6]. He assumed that even with known terms and conditions of muscle length and/or joint angle, precise determination of muscle strength and torque can still only be carried out with difficulty. From a practical point of view his method offers clear advantages to the physically based approach for the determination of muscular strength. The basic idea is to define strength by the maximum load that can be lifted once (1RM = one repetition maximum).

Power, however, can be determined for a single movement, a series of movements, or, as in the case of endurance, for a large number of repetitive movements. This can occur continuously at any point in time of the movement sequence or transmitted over certain movement sections. Power (W) is the outcome of work (J) per time, or the product of operating strength (N) and the distance covered (m) divided by time (s). Calculating power is easily possible on strength-training equipment, as it is common in research, since the resistance needed to overcome for the muscular action is known. For measurements in clinical routine this is usually not an option.

METHODS OF MEASUREMENT

In the following section, several methods for measurement of muscle strength and muscle power will be described. These methods represent only a selection and are by no means complete. We will describe both kinds of methods – those that are used almost exclusively for research and also those that can be applied in clinical practice as well.

Methods used for research purposes

Computerized pneumatic strength training equipment

Limb strength and power can be measured using computerized pneumatic strength training equipment. Specific training machines are available for different movements of upper and lower extremities, e.g. arm curl, triceps extension, triceps flexion, leg extension, leg press, leg curl, hip abductor, and hip adductor.

For strength measurement the use of the so-called one repetition maximum (1RM) has become a standard. The 1RM is defined as the maximum load that can be moved one time only throughout the full range of motion while maintaining proper form.

The double leg press may serve as an example to explain how these measurements are actually taken (Graph 1). In the starting position, the seat of the machine is usually positioned to place the knee joint between 90 and 100° of flexion. The hips are kept in a similar degree of flexion. Test persons are instructed to extend both legs fully but without locking the knee joint. They perform the concentric phase, maintain full extension, and perform the eccentric phase of each repetition over 2, 1, and 2 seconds, respectively. The resistance is then progressively increased gradually until the participant is no longer able to move the lever arm one time through the full range of motion.

For measurement of power and velocity the test persons are instructed to perform the lift at each established percentage of 1RM as fast as possible through the full range of motion. Power may be assessed at different percentages of 1RM (40, 50, 60, 70, 80, and 90%). Specifically developed software assists in the calculation of power and velocity. In many studies 40% of 1RM and 70% of 1RM have been chosen as outcome variables as they represent power production at relatively high force and low velocity – 70% 1RM – and at low force and high velocity – 40% 1RM. Similar test protocols have been applied in several well-designed studies on power and velocity in older individuals. Among others Fielding and co-workers have published several highly relevant papers in this field [7–9].

Nottingham power rig

The leg extensor power rig provides a safe and convenient method for assessing explosive power output from the lower limb [10] (Figure 18.2). The measurement of leg extensor power is functionally relevant, as it has been shown to be related to mobility [11] and instrumental activities of daily living [12] and has been identified as a risk factor for falls [13]. This measurement is also thought to be related to functional activities such as stair climbing [10](13). It allows an acceptable and useful measurement of muscle power in older persons, which is not confounded by balance. It is sensitive to the loss of muscle with age and to improvements with training. The equipment was designed in the School of Biomedical Sciences at the University of Nottingham Medical School in 1990. Measurement is made seated using one leg at a time. There is minimal involvement of back muscles. The extension movement takes 0.25–0.40 second in a push through 0.165 m against a flat pedal. At the end of the push the leg is fully extended. As the movement is made seated the forces are contained between the buttocks and the foot. The seat position is adjusted for leg length and the push is transmitted by a lever and chain to spin a flywheel. The gearing is such that resistance to the movement remains nearly constant throughout the extension. The final angular velocity of the flywheel is measured by an opto switch and is used to calculate the average leg extensor power (LEP) in the push.

STS transfer

When compared with the aforementioned methods, power measurement of the sit-to-stand transfer on a force platform represents a movement that is also relevant for everyday practice. Simultaneously, additional capabilities with regard to balance have to be met by test persons. Furthermore, the transfer has to be executed without any support by the arms. The procedure to measure muscular power of the lower limb by the sit-to-stand transfer test was described by Lindemann et al. for the first time in 2003 [14]. According to their protocol, subjects were seated on the front part of a chair with defined height. The arms were crossed over the chest and the eyes were fixed straight ahead while both feet rested on a force plate. The force plate measures the vertical ground reaction force. Test persons were then asked to rise as fast as possible into a standing position and to stand as quiet as possible until the end of data recording. The test should be performed three times with a

Figure 18.1 Double leg press.

Figure 18.2 Nottingham power rig.

one-minute rest between the trials. For all trials the subjects were encouraged by the investigator to ensure the explosive movement. Sit-to-stand transfer power is defined as $P = F \cdot s/t$ and is calculated by using the changes of vertical ground reaction force during the rising phase (time in seconds between peak force and end of

the rising phase: t), vertical ground reaction force during quiet standing ($F = m \cdot g$, m: weight of subject in kg, g: 9,81 m/s^2) and the difference between body height standing and body height sitting in meters (s). The trial that showed the highest power should be used as maximum power. Other studies could show that power measurement based on the sit-to-stand transfer correlated well with power measured by the Nottingham power rig [14].

Vertical jump

Muscle power can be derived from ground reaction force resulting from a vertical jump. For measurement a commercially available mechanographic system may be used. A rather simple jumping paradigm that could be applied in older individuals ranging between senior athletes and frail individuals. The following protocol which has originally been described by Rittweger et al. may be followed [15]. Jumping has to be performed as a counter-movement jump (i.e. brief squat before the jump) with freely moving arms. Subjects are usually allowed to make themselves acquainted with several submaximal jumps. The instruction should be to jump with the head and chest as high as possible, thus producing the maximum elevation of the center of mass. As a variable of interest, the peak power out of three two-legged counter-movement jumps should be identified. The authors noticed in their studies that the peak force is 10% greater if the jumping takes place on one leg only. Therefore, peak force may be assessed as the best of three one-legged jumps on the dominant leg.

This test can be performed on a ground reaction force platform with a personal computer and an integrated analog–digital board and software. Such a system computes the subject's vertical velocity by integrating the ground reaction force. Body mass and starting point are assessed during quiet stance immediately before the jump. Instantaneous power is calculated as the product of force and velocity. For further information, the reader may refer to the original publications [15, 16].

Methods for clinical routine

The methods that have been described in section "Methods Used for Research Purposes" require equipment that will be regarded as too costly and sophisticated for application in clinical practice. Here the ideal approach should be simple and quick. In addition, costs should be low and the method should also be applicable in frail older adults. The following methods do at least partly meet these expectations.

Handgrip strength

The measurement of handgrip strength is a common procedure in the course of geriatric assessments and used in both research and clinical practice. Primarily two measuring methods are used. On the one hand, dynamometers (e.g. Jamar dynamometer,

Figure 18.3 The Jamar dynamometer.

Table 18.1 Standard values of the isometric hand strength on the dynamometer according to [16].

			Handgrip strength			
			Male		Female	
Age	Number	Hand	Mean value [kg]	SD [kg]	Mean value [kg]	SD [kg]
65–69	55	R	41.3	9.3	22.5	4.4
		L	34.8	9.0	18.6	3.7
70–74	55	R	34.2	9.8	22.5	5.3
		L	29.4	8.2	18.8	4.6
75+	51	R	29.8	9.5	19.3	5.0
		L	24.9	7.7	17.1	4.0

Source: Based on Runge et al. [16].

Figure 18.3) are used to measure the isometric handgrip strength. Often the measured values are given in kilograms, although the physical quantity measured is a force. The measurement should be done in a sitting position with the shoulder adducted and neutrally rotated, elbow flexed at 90°, forearm in neutral position, and wrist between 0 and 30° dorsiflexion and between 0 and 15° ulnar deviation to avoid overlapping with other motoric tasks, as is the case when standing. When measuring, make sure a constant muscle length or joint angle by adjustment of the thrust bearing is set depending on the size of the hand. Individuals' ability to use their hand functionally needs to be considered when interpreting handgrip strength (e.g. osteoarthritis, rheumatoid arthritis). Measurement of the maximum strength requires repeated measurements, usually three on each side. The subject should be verbally motivated by a standard command to carry out the contraction with maximum force. The maximum value of these measurements corresponds to the maximum handgrip strength of this person. Table 18.1 shows standard values of the isometric hand strength on the dynamometer [17].

Figure 18.4 Martin Vigorimeter.

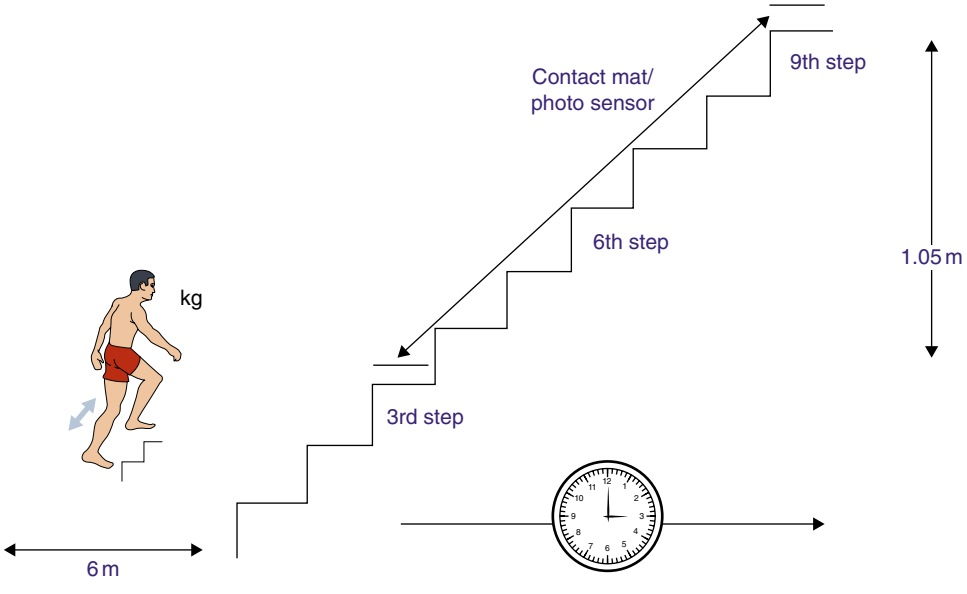

Figure 18.5 Principles of the stair climb test.

On the other hand, the handgrip strength can be measured with a vigorimeter (e.g. Martin Vigorimeter, Figure 18.4). Here the subjects are given a type of rubber ball in their hand to contract. This rubber ball is connected to a manometer. The maximum increased pressure reached in this ball is equivalent to the maximum handgrip strength and is expressed in kilopascals. The instruction on carrying out measurements of isometric handgrip strength outlined above also applies to the vigorimeter. Different ball sizes are used to adapt to different hand sizes, thus enabling uniform pretension of the

Table 18.2 Standard values of the Martin vigorimeter.

Age (yr)	Males Median values (kPa) per age span	Females Median values (kPa) per age span
60–64	106	76
65–69	97	71
70–74	91	67
75–79	82	63
80–84	75	59
≥85	64	64

Source: Based on Mathiowetz et al. [17].

muscles. This form of action is a dynamic contraction process. Therefore, the two measurements are not directly convertible with each other. Comparative studies show a good correlation between the two methods, although the isometric handgrip measurement depends strongly on the hand anthropometry, as it is the case with the vigorimeter [18]. Table 18.2 shows standard values for the Martin Vigorimeter.

The relevance of the measurement of hand strength lies in its high predictive value of mortality, morbidity, and cognitive decline [19].

Chair rise

Often the ability to stand up from a chair is used to gauge the power of the lower extremities. From a practical point of view this is very appealing for use in clinical practice, but also for examinations/assessments outside of the clinic. Generally, it must be stressed that from a biomechanical point of view such an assessment determines far more than just the power of the lower extremities. Similar to the STS transfer on the force plate and the vertical jump, further coordinative and cognitive exertions are needed to perform this activity.

A standard seat height is recommended. In order to confine the power measurement to the lower extremities, it is important that the subject's arms are not used in supporting the upward movement. Therefore, the exercise should be carried out with folded arms. For this purpose, a chair without armrests is recommended. A standard command, that accentuates the explosive movement of standing up is very important. The time span between the command and upright standing of the subject should be determined by the investigator using a stopwatch. In practice, the time of five consecutive sit–stand phases is measured. The calculation of power in watts with the involvement of body weight and height difference is often not done in clinical application. Rather, the immediately measured time value is used to estimate the power. This conclusion also seems feasible as the muscle power measured by the Nottingham power rig correlated well with the chair rise time [20]. The disadvantage of this method is the restriction to those subjects who are able to stand up without using their arms. Nevertheless, the fact alone that those subjects, who cannot get up without assistance, already have an increased risk for a prolonged hospital stay than those who can carry out the exercise is interesting [21].

Stair climbing

The stair climb power (SCP) test can be considered as an inexpensive test which is easy to perform. This test can be completed in less than one minute and requires only access to a flight of stairs, a scale, and a stopwatch. Stair climb power is calculated based on the following formula: power equals force times velocity. Stair climb time and vertical height of stairs are used to calculate velocity (distance/time), while body mass and acceleration due to gravity are used to calculate force (see Figure 18.3). The stairs should be well-lighted and a number around 10 would be appropriate. Test persons are instructed to safely ascend the stairs as fast as they can. For safety purposes they are allowed to use a handrail if they find it necessary. Very clear orders are indicated. Timing starts when the test person begins moving and it is stopped when both feet of the test person reach the top step. Excellent test–retest reliability could be shown for this approach. Stair climb power is usually expressed as SCP/kg. Stair climb power is well correlated with the score of the short physical performance battery (SPPB) [22]. When the components of the SPPB were analyzed separately a much higher correlation could be shown with the results of the chair rise test than for gait speed. Further, similar magnitude of correlation with the double leg press power measured at 40 and 70% of the one repetition maximum were shown.

Inertial measurement unit–based power measurements

Newer technical developments allow the use of accelerometers for power measurements. Accelerometers are often combined with gyroscopes to senor units, called inertial measurement units (IMUs). IMUs are compact, wearable sensors, and since these sensors are inexpensive and easy to use, they offer the opportunity to cover the research field as well as the clinical routine measurements.

Calculation of sensor-based peak power

The sensors are usually placed at the hip to analyze the center of mass (COM) kinematics [23]. In contrast to the presented calculations of the power for stair climbing or sit-to-stand transfers, measurements with IMUs or force platforms allow peak power calculations. The peak power is the highest power generated during the exercise. Besides the acceleration data (standard unit = meter per second squared, m/s^2) calculation of peak power requires the weight of the subject in kilograms. The peak power (P) is defined by the multiplication of the subject's weight (m), the maximal acceleration (a) in vertical direction, and the maximal velocity (v) in vertical direction: $P = F \cdot v = m \cdot a \cdot v$. The subject's vertical velocity is computed by numerical integration of the measured acceleration in vertical direction.

Applications of sensor-based (peak) power measurements

In 2010, Zijlstra et al. [23] introduced the sensor-based measurement of power required to lift the body's COM during the STS transfer. Regterschot et al. [24] found that sensor-based STS peak power has a higher sensitivity to detect effects of training leg

strength and power than standard clinical measures like for example the measurement of the isometric quadriceps' strength.

In principle, the method of peak power calculation can be flexibly used for different functional tests. However, sensor-based peak power measurements have rarely been used so far for vertical jumps and stair climbing. Most studies in IMU-based jump analyses focus on the jump height estimation [25–27] instead of jump power, whereby the jump height can be calculated by numerical double integration, take-off velocity, or flight time [28] and is not an accurate indicator of power [29]. For stair climbing tests IMUs are often used to determine the duration of climbing a specific number of stairs and calculate the (mean) power [30] based on the definition in section "Stair Climbing." Recent studies show first investigations of IMU-based stair climbing peak power [31].

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CHAPTER 19

Measurements of Physical Performance

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INTRODUCTION

In hospitalized and community-dwelling older people, the comprehensive geriatric assessment (CGA) is one of the most effective clinical approaches to prevent functional decline and disability. The first researches on this topic were performed more than 30 years ago [1] and several meta-analyses have confirmed numerous benefits from routinely adopting the CGA in the evaluation of older persons [2–4].

Physical performance can be defined as the degree to which the organism is capable of accomplishing specific and independent physical tasks. It is a function of body shape, sex and age, but also affected by endogenous and exogenous stimuli. Physical performance should be differentiated from physical impairment, which can be considered as an early and preclinical state of disability. Physical performance measures are, among the multiple determinants of functional decline, key predictors of disability. They also represent secondary endpoints (or surrogate markers) for interventions aimed at preventing the onset of major health-related events, including hospitalization, institutionalization, disability, and death.

In both the classical model of disability originally proposed by Nagi [5] and its revision by Jette [6], functional limitations (i.e. the impossibility of performing basic physical tasks such as walking, rising from a chair, climbing stairs . . .) represent relevant early phases of the disabling process. Initial functional impairments may be assessed using physical performance tests in which patients are asked to perform a specific physical task. Physical performance measures are performed in a standardized manner and objectively evaluate the capacity of the individual to accomplish specific

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

physical tasks characterized by different degrees of difficulty. Thus, the adopted test can be chosen according to the functional status of the individual and the objectives of the assessment. This approach limits environmental influences and provides objective estimates which may be more reliable than self- or proxy reports of functional limitations [7].

The interest in the physical performance measures is linked to the reversible nature of the disability process, especially if interventions are promptly put in place at the early phases of it [8]. In fact, early detection of physical impairment may prevent a progression to more severe stages of the disabling process [9]. For example, it has been demonstrated that physical exercise interventions in frail older people can prevent disability and prolong functional independence [10]. On the other hand, once disability appears, it is rarely reversible despite difficult and costly interventions.

During the past years, physical performances measures have growingly been included in longitudinal studies to measure functional limitations [11]. Today, physical performance measures are well-established clinically meaningful outcomes, both in pharmacological and non-pharmacological researches. Although their adoption in the clinical routine is still suboptimal, their use is surely increasing. A recent survey conducted concluded that the majority of clinicians is measuring physical performance in older persons, despite an evident heterogeneity in the choice of instruments and thresholds of normality [12]. The grown attention given to the assessment of physical performance in older persons is probably motivated by multiple reasons. First, preventing the functional decline of the older people is today better recognized as a primary goal of care (even among non-geriatric settings), and is a well-recognized priority for public health. Second, physical performance has repeatedly been indicated as a "sixth vital sign" for older persons [13–15]. Third, the assessment of physical performance has become a crucial step in the diagnostic algorithm of several conditions of advanced age, in particular sarcopenia [16].

WHAT INFORMATION IS PROVIDED TO A CLINICIAN WHEN ADOPTING PHYSICAL PERFORMANCE MEASURES?

Physical performance measures are relevant both in clinical and research settings because they are strong predictors of clinically meaningful adverse health events in older people. In fact, a large body of evidence is demonstrating today that poor results on standardized physical performance measures are able to independently predict adverse outcomes (including falls, physical disability, hospitalization, institutionalization, and death) [7, 17–21]. The validity of physical performance tests for major health-related events has been shown to be remarkably consistent throughout multiple cohorts and in extremely different populations [22].

A paradigmatic example might be found in the gait speed, a parameter that can be assessed over short tracks, as 8 ft, 4 m, or 6 m. Gait speed tests are of special interest because (i) easy to assess and implement in the routine clinical practice, and (ii) able to predict the future onset of disability [17, 18, 23], cognitive decline and dementia [24–26], institutionalization and hospitalization [20, 27], and mortality [27–29]. In nine pooled cohort studies of older people, gait speed was associated with survival

with significant increments per 0.1 m/s, a variation that is considered clinically meaningful [30]. All of this information is relevant to improve clinical decisions in geriatrics as well as in other medical disciplines increasingly involved in the health care of older persons. For example, gait speed has been proposed to screen older patients with aortic stenosis to be referred to CGA in order to define the most adequate intervention (i.e. surgical intervention, transcatheter aortic valve implantation [TAVI], medical treatment) to propose for their cardiac condition [31].

Several reasons can explain the predictive capacity of physical performance measures for adverse outcomes. Prevalence of comorbidity increases with advancing age and affects performances. In patients with congestive heart failure [32, 33] or lung disease [34], the distance covered at the 6-minute walk test (6MWT) is a reliable marker of mortality and commonly used to estimate the aerobic capacity of the individual. The fact that poor physical performance measures are able to predict negative outcomes even among well-functioning older adults [35] and independently of comorbidities [36] suggests they could also capture and represent markers of underlying subclinical disease. It has even been reported that poor physical performance is associated with hidden components of vulnerability (e.g. unfavorable genetic profiles [37]) or psychological components (e.g. mood [38]), thus reflecting and quantifying the capacity of the individual to cope with stressors. It has been estimated that about half of the individual's differences in walking speed might account for both genetic and nongenetic familial effects [39], indirectly extending the value of physical performance measures from the mere quantification of muscle functioning to more general markers of weelbeing [40].

In addition to delivering a reliable and efficient measure to classify performance, the physical performance tests are also responsive to changes over time and might be helpful in monitoring the efficacy of interventions. In fact, these tests are sensible to small changes [41]. The efficacy of a rehabilitation intervention, a physical exercise programs, or a treatment for sarcopenia can thus objectively be assessed with these measures [42]. Interestingly, sarcopenia definitions have been evolving over time from the simple quantification of muscle mass to a more complex evaluation of muscle quantity and quality, whereas this latter is captured by the assessment of physical performance and/or muscle strength.

SARCOPENIA AND PHYSICAL PERFORMANCE

Sarcopenia, that is the age-related decline of skeletal muscle, is considered a major responsible for the functional impairment occurring with aging [43]. Since the first descriptions of sarcopenia exclusively focused on the quantification of the muscle mass [44, 45], several operational definitions of this condition have been proposed over the past years by different panels of experts [46–49]. Despite a certain heterogeneity in the identification of the specific tests to capture the two dimensions of muscle decline (i.e. muscle quantity and quality), there is today a general agreement that physical performance measures have to be included in the diagnostic algorithm of sarcopenia, mainly because (i) they are directly related to skeletal muscle quality [50], and (ii) they provide the clinical relevance to the otherwise sterile and perhaps futile quantification of muscle mass [51].

The operational definition proposed by the *European Working Group on Sarcopenia in Older People* (EWGSOP) [49] in 2010 is, to date, probably the one most commonly found in the literature. It recommends the use of gait speed (and as alternative muscle strength) to identify individuals at risk of sarcopenia and, therefore, candidates for body composition assessment. This operational definition has recently been updated by the Working Group [16]. Differently from the previous version, muscle strength is today considered the main clinical manifestation of sarcopenia. Thus, individuals at risk of being sarcopenic (e.g., because complaining fatigue, losing weight, malnourished . . .) should immediately be evaluated by administering the handgrip strength or chair stand test. According to the new definition, gait speed is not anymore serving as the main entry door to the diagnostic algorithm, but one of the possible measures (together with other physical performance tests, as the short physical performance battery [SPPB] [7, 17, 18] or the Timed Up-and-Go [TUG] [52]) to estimate the severity of the sarcopenic condition. Such evaluation of the sarcopenia severity is suggested to be conducted after the assessment of appendicular lean mass (preferentially via dual-energy X-ray absorptiometry).

Interestingly, the walking speed test is extremely appealing in clinical and research settings because it is a simple, quick, well-tolerated, inexpensive, and highly reliable test [53], in addition to being predictive of disability, institutionalization, falls, and mortality.

The links between physical performance (such as walking speed) and muscle mass and strength are complex [54]. An increase in muscle mass usually results in an increase in muscle strength, but an increase in muscle mass does not automatically result in improved physical performance. Such dyssynergia has been, for example, reported in a recent clinical trial testing a novel pharmacological agent against sarcopenia [55]. Results showed a certain capacity of the intervention to positively modify the body composition, but the effects on the muscular function were null (thus affecting the clinical interest for the product). It is likely that the decline in muscle mass affects physical performance only when such loss falls under a critical threshold. This cut-off point is specific for each single physical function test. In this context, as abovementioned, it is noteworthy that current evidence clearly demonstrates that muscle function is a better predictor of clinical outcomes than muscle mass [56, 57].

MEASURES OF PHYSICAL PERFORMANCE

The short physical performance battery (SPPB)

The SPPB is probably one of the most known physical performance tests. It was originally developed at the National Institute on Aging for use in the Established Population for the Epidemiologic Studies of the Elderly (EPESE) [7]. The SPPB is a composite measure of the physical performance of lower extremities. It is a standardized assessment that can be adopted both in research and clinical practice. The SPPB is based on three timed tests: the balance test, the usual gait speed (performed on a short distance course), and the repeated chair stands test.

For the balance test, the subject is asked to hold three increasingly challenging standing positions for 10 seconds each: (i) a side-by-side position; (ii) semi-tandem position (the heel of one foot beside the big toe of the other foot); and (iii) tandem position (the heel of one foot in front of and touching the toes of the other foot). Balance test score (in seconds) is given by the total time for which positions are held (range from 0 to 30 seconds).

For the usual gait speed test, the subject is asked to walk at his/her usual pace over a 4-m course [11] (originally 8 ft or 2.4 m [7]). He/she is instructed to stand with both feet touching the starting line and to start walking after a verbal command. The subject is allowed to use walking aids (i.e. cane, walker, or other walking aid) if necessary, but no assistance by another person can be provided. Timing begin when the starting command is given, and time (in seconds) needed to complete the entire distance is recorded. The faster of two walks is then considered in computing the SPPB score.

The repeated chair stands test is performed using a straight-backed chair, placed with its back against a wall. The subject is first asked to stand from a sitting position without using his/her arms. If he/she is able to perform the task, he/she is then asked to stand up and sit down five times, as quickly as possible with arms folded across his/her chests. The time to complete five stands is then recorded.

The results of the three physical performance subtasks (all time-based in seconds) are used to calculate a summary score by using predetermined cut-off points identifying different degrees of physical capacity. The resulting score ranges from 0 to 4 for each of the three physical performance subtasks, whereas 4 indicates the best performers and 0 the worst performers. As such, the global summary score ranging from 0 (worst performers) to 12 (best performers) can then be calculated by adding the categorical results derived from the three timed physical performance subtasks.

The instructions (including videos) describing how to administer the SPPB are available for free at the National Institute on Aging website: (https://www.nia.nih.gov/research/labs/leps/short-physical-performance-battery-sppb).

The SPPB has proved its reliability [58] and validity for predicting several negative outcomes, including hospital admission [59], physical disability [60], and mortality [61]. Besides predicting major negative health outcomes, the instrument has growingly been considered as able to mirror the general health status of the individual. Thus, not surprisingly, it is today often used as a marker of physical frailty. Frailty, defined as a state of increased vulnerability to stressors, is a geriatric condition increasingly object of research and clinical evaluation. In the absence of a "gold standard" definition of frailty, the physical domain tends to be the one that more than others is used for measuring the homeostatic exhaustion of the organism. Thus, not surprisingly, the SPPB is frequently been adopted for the assessment of frailty. For example, a recent report published by the European Medicine Agency [62] has recently reviewed the instruments available for including the characterization of frailty in clinical trials. In fact, the so-called evidence-based medicine issue affecting geriatric research has largely been attributed to the lack of assessment of non-nosological conditions affecting the quality of life and risk profile of the individual. In this document, the SPPB is presented as the instrument that more than others is able to better serve for the purpose. It is thus recommended to use the SPPB for the risk stratification and description of the study population, as well as outcome on which judge the effectiveness and safety of interventions.

In the SPRINTT project, the target condition of Physical Frailty & Sarcopenia (PF&S) is defined by the SPPB in its physical frailty component [63]. Aim of the randomized controlled trial included in the project is to test the effect of lifestyle modifications (i.e. mainly physical exercise and nutritional counseling) in the prevention of incident mobility disability. In the study, the concept of physical frailty is operationalized looking at SPPB results ranging between 3 and 9 (i.e. excluding robust [SPPB higher than 9] and disabled [SPPB lower than 3] individuals) [63]. It is noteworthy that this approach is mimicking and replicating what previously done in the Lifestyle Interventions and Independence For Elders (LIFE) study [9], which represents the first phase III randomized controlled trial able to demonstrate the effectiveness of physical exercise in the prevention of disability in older persons. Many other studies are available in the literature that can be mentioned to exemplify the use of the SPPB for stratifying populations according to physical performance and mobility capacity [22, 64]. Last but not least, it is worth to be mentioned the use that the recently updated recommendations by the EWGSOP are giving to a low SPPB result (i.e. <9) as an indicator of severe sarcopenia [16].

As mentioned earlier, the importance of improving the design of clinical trials for obtaining more robust results of pharmacological or non-pharmacological interventions targeting older persons is increasingly felt. In this scenario, the identification of thresholds defining which are the clinically meaningful modification for the SPPB are of special interest [65, 66]. Among all, Gill and colleagues proposed the criteria of responsiveness to an intervention to range between 0.5 (small meaningful change) and 1 (substantial meaningful change) points [11].

In high-functioning older adults, the SPPB (as well as the short distance walk tests) may suffer of a ceiling effect. In other words, high performers might all be flatted at the highest levels with a consequent loss of discrimination capacity of the test. To solve this issue, more challenging tests of physical performance have been developed over time. These measures may better discriminate among higher-functioning study participants. For example, in the Health, Aging and Body Composition (Health ABC) Study, a more challenging version of the SPPB was administered to participants [67]. This approach was aimed at better characterizing the wide range of function at baseline among the fit older participants of the study.

Chair stand test

The chair stand test is a physical performance test aimed at assessing the lower body muscle strength of older adults [7]. It is performed as part of the SPPB, but also independently used as a standalone test. As previously described, in the chair stand test, the amount of time that the person takes to rise five times from a sitting position is recorded. In order to complete the test, the participant cannot use his/her arms to stand up and has to fully sit down every time.

The recent EWGSOP recommendations for the definition of sarcopenia indicate the Chair Stand test as preliminary muscle strength assessment in order to determine the clinical presence of sarcopenia (using a defining cut-point of 15 seconds for both men and women) [16]. Since the chair stand test represents a proxy of both strength and

endurance, it is growingly been used as measure of functional outcome in the rehabilitative settings [68, 69].

In a variant of the chair stand test, the subject is asked to complete as many full stands as possible within the given time (i.e. 30 seconds) [70]. By eliminating the ceiling of the five repetitions, the test includes a larger component of muscle resistance and starts to define the muscular fatigability. In active community-dwelling older adults, a cut-point of 8 stands has demonstrated to be predictive of incident disability [71].

Timed up-and-go test

The TUG test is a physical performance measure that has been mainly used to assess dynamic balance [52]. It is a single test measuring the time a person takes to complete a complex series of motor tasks (i.e. standing up from a standard armchair, walking 3 m, turning, walking back to the chair, and sitting down again). The stopwatch is started on the word "Go" and stopped at the moment the subject sits down. The time to perform the task is compared with normative values for age, gender, and research-based guidelines that measure increased risk of falls and functional decline. The TUG test has been repeatedly used in persons with frailty, Parkinson's disease, cognitive impairment, recent joint surgery, and osteoarthritis.

The test is easy to learn and perform in clinical settings. The TUG test can be performed by physicians, nurses, occupational, or physical therapists. The patient wears his regular footwear, uses his usual assistive device, if needed (it has to be reported on the form), and walks at a usual pace. No physical assistance is given. A practice trial is given first and the averaged times of two following trials are recorded.

A TUG score of 14 seconds is sensitive (87%) and specific (87%) for identifying elderly individuals who are at risk for falls [72]. The test–retest reliability (intraclass correlation 0.97–0.99 and Spearman's = 0.93) and the inter-rater reliability intraclass correlation coefficient (ICC = 0.99) are good [73, 74]. The performance of the patient can also be summarized into a five-point-scaled score [75]. A TUG result equal to or higher than 20 seconds defines a condition of severe sarcopenia, according to the recently updated EWGSOP recommendations [16].

Stair climb power test

The stair climbing exercise tests were developed more than 50 years ago as an anaerobic power test aimed at assessing athletic performance. More recently, the stair climb power test (SCPT) has been proposed as a clinically relevant measure of leg power impairment [76]. The SCPT is a helpful, inexpensive, and simple opportunity to confirm the diagnosis of sarcopenia [49, 77] in community-dwelling older people or nursing home residents [76, 78, 79]. The test requires only a flight of stairs (preventively measured in order to standardize the task). The procedure is simple and can be completed in less than one minute. In fact, the subject is simply asked to climb a 10-stair flight of stairs as fast as he/she can. After command "Ready, set, go" the examiner starts timing when the subject starts to move and stops timing when both feet have reached the 10th step. The average time of two trials is recorded.

The SCPT measure (in watts, W) is calculated by multiplying the vertical height of the 10 steps (in meters) by the body weight of the patient (in kilograms) and the acceleration due to gravity (g = 9.80 m/s^2) divided by the stair climb time (seconds). That is:

$$\mathrm{SCPT} = \mathrm{Strength}(\mathrm{F}) \times \mathrm{Speed}(\mathrm{V}) = \left[\mathrm{Body\ weight}(\mathrm{M}) \times \mathrm{Acceleration}(\mathrm{g}) \times \mathrm{Distance}(\mathrm{d})\right] / \mathrm{Time}(\mathrm{t})$$

This clinically meaningful test may be useful both in clinical and research settings. The test–retest reliability of the SCPT measure has been reported as excellent (r = 0.99) [76].

Gait speed tests

The 6MWT has been widely used in the clinical setting settings because it is a reliable physical performance measure, in particular as marker of aerobic capacity [80–84]. During this test, participants are encouraged to walk at a regular pace for as much as possible over a 6-minute period [85]. The 6MWT captures a hierarchy of functioning in healthy elderly subjects. A 20-m and 50-m change at the 6MWT results are considered the minimum and substantial clinically meaningful variations, respectively [11].

Nevertheless, when the 6MWT is adopted in older persons, some special considerations have to be taken into account. The benefit of the resistance testing is limited in elderly people who may have multiple reasons for poorly performing beyond the simple physical exhaustion. Moreover, the risk of adverse events due to the solicitation of the organism by requesting a major effort might be increased, especially among the frailest persons. In geriatric medicine and research, the 6MWT may instead be found useful for discriminating different categories of risk among older individuals in healthy conditions. In fact, the possible ceiling effect of short-course walking tests might be overcome by demanding more challenging tasks (see the section "Gait speed test").

In these last years, the 400-m walking test has received more attention by the scientific community. The test consists of asking the individual to cover a 400-m track (i.e. 10 laps on a 20-m per segment course, that is 40 m per lap, along a corridor) within 15 minutes. The individual is asked to walk at his/her own pace, with the aim of covering the 400-m distance without running. Although the time to complete the 400 m walk is recorded [86], the test provides a dichotomous result defining the mobility disability of the individual [63]. The primary goal is not to measure the subject's physiological resistance, but to define whether his/her mobility function is suitable for guaranteeing independent life. In fact, the ability to cover the 400-m distance within 15 minutes is assumed as the minimum capacity for allowing the person to independently self-maintain him/herself in the community, thus defining the first stage of the disabling cascade. The 400-m walk test has been repeatedly used in randomized controlled trials (e.g. LIFE, SPRINTT [9, 87]), exploring the effects of preventive interventions against disability as primary outcome of interest.

The usual gait speed is one of the three components of the SPPB, but it can also be used as a single parameter for clinical practice and research settings [88]. This simple assessment tool can easily identify individuals with a high-risk profile for

negative health-related outcomes in the community. Gait speed has a good sensitivity to change and can be used to evaluate effect of pharmacological or non-pharmacological intervention. The estimated minimally significant magnitude of meaningful change of gait speed is 0.05 m/s while a substantial change of gait speed is 0.10 m/s[11].

In the recently updated recommendations for the sarcopenia management released by the EWGSOP, gait speed is indicated as the main indicator for measuring the severity of the condition of interest [16]. For simplicity, a single cut-point of 0.8 m/s (obtained over a short-track course) can be used in the clinical setting and both sexes for defining individuals exposed to a relevant risk of negative outcomes. However, it should never be overlooked the fact that the association between gait speed and outcomes follows a linear pattern, thus requiring a certain flexibility in the interpretation of abnormalities and definition of critical thresholds (Figure 19.1).

Interestingly, gait speed tests can be administered in restrictive areas, such as homes. They are also less time-consuming than long-distance walk tests. The 4-m walk test is

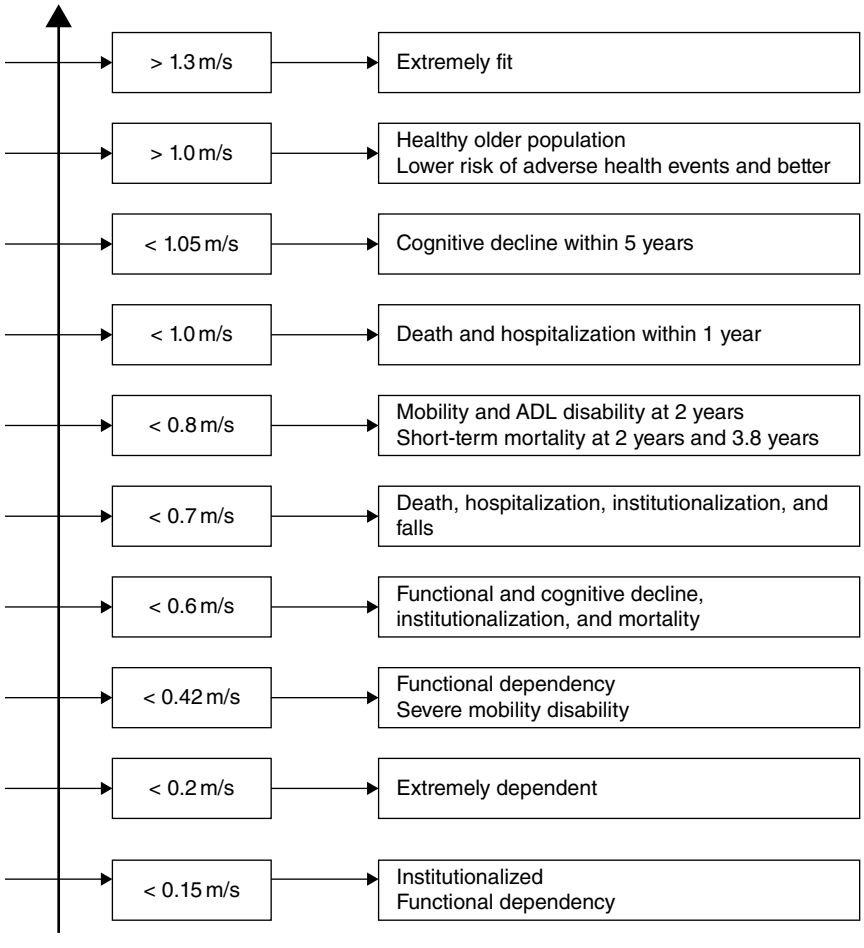

Figure 19.1 Cut-off points of usual gait speed and risk of adverse outcomes. *Source*: Adapted from Abellan van Kan, et al. [53].

currently the most commonly used short-walk test validated in older persons. It has also shown high reliability [80, 88], and its test–retest reliability is also high (intraclass r = 0.9) [89]. Sometimes, the usual gait speed test has been used as a surrogate for the long-distance walk tests and to measure the overall functional status of older persons [89]. On the other hand, the usual gait speed is not a perfect surrogate for the whole SPPB. The balance and the chair stand tests, the other two components of the SPPB, have been reported to add valuable information to the gait speed [19] and to be a similarly strong predictors of adverse health events [90]. It is also possible that the predictive capacity of the three SPPB components might vary according to the tested population (e.g. the gait speed is most predictive in community-dwelling individuals, the chair stand test among those experiencing initial impairments, and the balance test among the frailest and most disabled ones).

Self-reported functional limitation assessment

Several self- or proxy physical function tools have been developed over the years. These tools are practical, safe, not time-consuming, and have a lower cost than the usual physical performance measures. Self-report of difficulty in performing functional activities identifies older persons with physical disability not ascertained by self-report of the need for help [91]. Compared with objective physical performance measures, these questionnaires may capture in their results different aspects of the health status, those that are more related to the feelings and self-perceptions of the individual.

The Late-life Function and Disability Instrument (LLFDI) is currently one of the most validated self-reported functional limitation assessment measure [92]. The LLFDI lists items evaluating 32 physical activities and the capacity to accomplish 16 major tasks of daily life. The basic and advanced lower extremity functional limitation and upper extremity functional limitation are self-reported in questionnaires. The reliability and validity of this comprehensive measure has been demonstrated compared with the SPPB and the 400-m walk test [92]. The LLFDI has been translated into several languages, and a short form of it has been developed. The questionnaire is more sensitive to changes than the Barthel Index [93]. However, its responsiveness to clinically meaningful changes still warrants further research.

Promising technologies have been developed during the past years to measure functional limitations. These approaches rely on a large set of questions related to functional tasks which are hierarchically ordered by a computer-adaptive testing (CAT) system [94, 95]. This tool creates directly an algorithm adapted to the subject's functional level that avoids unnecessary questions (so-called *item response theory* [IRT]). Then, this adaptive testing results in a shorter time of drawing up without losing the precision of the assessment. This approach has been initially supported by the Patient-Reported Outcomes Measurement Information System (PROMIS) initiative, funded by the National Institutes of Health to both improve the precision of physical function assessment and reducing respondent burden [96]. Compared with the LLFDI, using IRT and CAT results in a small loss in accuracy and sensitivity to change but a substantial reduction in time of administration [97]. Apart from the reduction of the amount of time required to complete a functional assessment, this approach is relevant in longitudinal studies on aging because it can be performed across multiple

settings (from community-dwelling to nursing home resident), and because it tends to cover the whole spectrum of functioning. However, a simple instrument that can accurately measure physical performances from bedridden patients to higher levels of independent mobility in hospital or community settings is still lacking [98, 99]. The De Morton Mobility Index (DEMMI) has recently been proposed as a mobility instrument developed in the acute hospital setting to overcome this limitation [100]. This score has been reported to be valid and reliable [100]. The scores ranged from 0 (poor mobility) to 100 (good mobility) relying on clinician observation of performance on 15 hierarchical mobility tasks.

The role of technology

Thanks to technological innovations, powerful tools to measure physical performance (even at global scale) are now available. Smartphones, for example, are routinely equipped with onboard accelerometers, able to detect, and provide a relatively accurate steps count. In a recent study [101], data from a huge number of smartphones worldwide were analyzed. The large-scale data set (including more than 68-million step recordings from 111 countries) provided objective and valuable information on physical activity (i.e. a proxy of physical function) worldwide. Moreover, the data showed a distribution of activity within countries and subpopulations, paving the way for future health policy interventions.

Technological instruments could become part of and support the routine functional performance assessment (for example, through motion sensors included in mobile phones for measuring the 6MWT [102]). They can also be useful for standardizing and minimizing errors in the assessment of functional performance. For example, the Mobility Assessment Tool (MAT-sf) is one of the first examples of a short-form video-animated tool designed for measuring mobility [103]. It consists of 10 animated video clips that test the respondents' level of proficiency in performing mobility tasks. The tool avoids the lack of specificity in item content of the self-report measures that often creates errors and ambiguities in the measurement.

Furthermore, technological devices can not only measure physical performance, but also motivate positive lifestyle changes. Pedometers, for example, have shown to be effective in improving daily physical activity and functional outcomes in older persons [104], by providing an objective goal to the individual and increasing his/her awareness about the own health status (i.e. self-empowerment in the health management). In a paradigmatic study, participants underwent a walking program that included the use of pedometers together with coaching activities. As a result, study participants increased their daily step count by 22% in a 4-week period. The study completion rate was high (81%), showing that a pedometer represents a simple and easy device to use, even in an older population. Moreover, a reduction in the daily step count was observed when pedometers were temporarily removed (4.8% drop in one week). In this context, it is important to remind that pedometers are not only serving as motivators, but may also be useful to clinicians to provide an objective quantification of the physical activity of the individual. In other words, their adoption in the clinical setting might provide extra information for judging the health status of the individual and/or the effectiveness of implemented interventions.

Sensors are not only wearable, but can also be part of the surrounding environment, the so-called "Internet of things." Smart-homes equipped with sensors that can detect the quantity and quality of daily activity of their residents are today already available [105].

These examples are just part of the constantly evolving field of "mobile health" (i.e. application of sensors, devices, and technology for obtaining data pertinent to wellness as well as diagnosis, prevention, and management of diseases) [106]. Although growing and fascinating, mobile health is still facing important regulatory, ethical, and clinical issues. There are still concerns to be solved, including privacy and equity issues as well as how to fit the vast streams of generated data into clinical practice. These aspects will have to be addressed as the use of technologies in the field increases.

CONCLUSIONS

The administration of physical performance measures is crucial for the proper and complete assessment of older people. It allows the heterogeneity of older persons' health status to be captured. Physical performance measures provide clear and objective estimates of the risk of negative health-related events. These measures differently identify high-risk groups from self-reported difficulties, and support the selection and evaluation of older people in both clinical and research settings. The additional information provided by these measures can indeed drive clinical decisions because physical performance/function should not be considered as a mere reflection of the physical domain; physical performance measures have to be considered as markers of well-being. As such, they can perfectly serve as important outcomes when evaluating the efficacy of interventions directed towards the improvement of the individual's health status.

Physical performance can be improved at any age, even in frail elderly populations. Interventional studies have demonstrated that physical activity programs result in better walking ability, balance, and strength. Physical performance measures can be used as surrogate biomarkers of functional decline. Of course, the heterogeneity of the older population may require attention when choosing the most informative physical performance measure. Ceiling and floor effects should always be considered in this context.

The evaluation of physical performance measures in older people is still not always performed in the daily clinical practice, at least not as other clinical or biochemical parameters. Their implementation should be encouraged and promoted as much as possible, also keeping in mind that the maintenance of proper physical function represents one of the priorities for the healthy aging of the person.

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CHAPTER 20

Biomarkers for Physical Frailty and Sarcopenia: A "Two-Body Problem"

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INTRODUCTION

Moving from the assumption that "there is probably no decline in structure and function more dramatic than the decline in lean body mass or muscle mass over the decades of life," Irwin Rosenberg referred to the age-associated decline of muscle mass as "sarcopenia" [1]. Since then, it became clear that both quantitative (i.e. mass) and qualitative (i.e. strength and/or function) declines of skeletal muscle occur during aging [2]. As such, a more a complex construct including these two components has been developed to refer to sarcopenia [2].

Yet, an univocal operational definition has not been agreed upon even though all existing definitions predict negative health-related events in older people [3]. Notably, in September 2016, sarcopenia has been recognized as a "disease entity" with a dedicated ICD-10-CM code [4]. This milestone achievement will foster identification of major factors contributing to this condition and biological targets amenable for interventions, and will support its implementation as part of the clinical routine [5].

Frailty is the term used to refer to the age-related decline in physiologic reserve and homeostatic capacity predisposing individuals to a wide range of negative health-related events (i.e. falls, morbidity, disability, hospitalization, institutionalization, and mortality) [6]. Similar to sarcopenia, the operationalization and clinical implementation of frailty are still debated [6]. Indeed, its phenotypic heterogeneity [7], the multisystem derangements underlying its pathophysiology [8], and the fluctuations of individuals across severity states [9] hamper a comprehensive appraisal of the condition.

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

Physical frailty (PF) represents the domain upon which the most popular assessment tools for frailty are built [10]. At the clinical level, the picture of PF remarkably overlaps with that of sarcopenia [11] in a way that muscle wasting can be envisioned as the "organ failure" underpinning the clinical manifestations of PF [12]. Therefore, the two conditions have been merged into a new entity (i.e. PF & sarcopenia; PF&S) [13] that has been operationalized within the "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) project [14, 15]. Here, PF is translated by means of physical performance measures (i.e. short physical performance battery score ≥3 and ≤9) [14, 15].

When referring to its pathophysiology, PF&S may be viewed as a prototypical geriatric/geroscience condition [16]. Indeed, PF&S has a multifactorial etiology that recapitulates all biological hallmarks of aging (i.e. genomic and epigenetic instability, loss of proteostasis, mitochondrial dysfunction, telomere shortening, dysregulated nutrient signaling, stem cell exhaustion, cellular senescence, and altered intercellular signaling) [16–18]. According to the geroscience hypothesis, perturbations in these mechanisms may represent the biological foundation of the complex picture of age-related conditions, including PF&S [16]. As a corollary to this, the analysis of a single process/pathway in the context of PF&S will inevitably fail at capturing its intrinsic complexity [18–20].

Multi-marker analysis has increasingly been recognized as a complementary and more sophisticated strategy for investigating highly dynamic and complex conditions, including PF&S [20–23]. In this context, a biomarker discovery process is developed according to a more comprehensive, multivariable landscape incorporating as many contributing factors as possible [20–23]. This approach is rooted into the conceptualization of allostatic load, the progressive biological burden to cells and body systems imposed by cumulative environmental demands [24]. In this scenario, biomarkers represent endophenotypes for physiological dysregulation that may support: (i) diagnosis; (ii) tracking of disease/condition progression; (iii) clinical decision-making; and (iv) verification of the efficacy of an intervention before clinical benefits become detectable.

Ad hoc multivariate statistical approaches complete the multistep flow of the biomarker discovery process and allow identifying patterns of mediators that can be applied as a multivariate measure of departure from an individual's "normal operating conditions" (NOCs) [25]. The output of this analysis may complement the clinical appraisal of PF&S and expand existing indeces based on routine clinical/laboratory measures [26].

Here, we present multi-marker biomarker discovery as an approach for capturing the complexity of PF&S, overview candidate biomarkers for PF&S, and discuss relevant pathways involving these mediators.

BIOMARKERS FOR PHYSICAL FRAILTY AND SARCOPENIA: WHERE DO WE STAND?

A great deal of work revealed the involvement of muscle-specific cellular processes in the pathogenesis of sarcopenia [27–31]. For instance, dysregulation of myocyte apoptosis [32], derangements in mitochondrial function and quality control processes [33, 34],

oxidative/nitrosative stress [35], iron dyshomeostasis [36, 37], and alterations in protein synthesis and breakdown are the most studied [38, 39]. The dissection of such pathways has allowed identifying a vast array of potential biomarkers for muscle atrophy and dysfunction and provided valuable information on the pathophysiology of sarcopenia. Measures that require access to tissues or cells isolated from standard blood draw (e.g. CD4/CD8 T-cell ratio, T-cell p16INK4a expression, mitochondrial respirometry) have lower feasibility for large trials due to significant resource burden, need of skilled laboratory personnel and specialized equipment and, in the case of tissue sampling, invasive procedures (i.e. biopsy) that may not be readily available or easily standardized across clinical trial sites. Furthermore, investigations performed in tissue samples carry the downside of lacking indicators of temporal occurrence of events with regard to a specific condition. Indeed, identifying the trigger of dysfunctional processes from a *snapshot*, such as the one provided by this analysis, is challenging at best.

In this scenario, the development of biological markers that can be measured in biofluids at any time point and be used in a cost-effective manner to guide the diagnosis and facilitate the monitoring of PF&S are highly sought after [40]. Several circulating markers have been proposed in the last years as useful parameters to explore more directly skeletal muscle changes in relation to physiological and pathological states. Circulating (plasma or serum) levels of C-terminal agrin fragment (CAF), growth differentiation factor 11 (GDF11), extracellular heat shock protein 72 (eHsp72), high-temperature requirement serine protease A1 (HtrA1), procollagen type III N-terminal peptide (P3NP), and irisin are the most popular mediators that have been associated with low muscle mass, strength, and physical function impairment in older adults (reviewed in [41]).

Moreover, growing evidence indicates perturbations in protein-amino acid metabolism as relevant to the pathophysiology of sarcopenia [42, 43]. Dietary protein intake and circulating amino acids (AAs) are building blocks for muscle proteins and therefore pivotal factors for muscle plasticity and trophism [44]. Recently, results from the Baltimore Longitudinal Study of Aging (BLSA) showed an association between specific patterns of AAs with muscle mass in older adults with functional limitations [45] and low muscle quality [46]. Moreover, reduced non-fasting plasma concentrations of branched-chain AAs (BCAAs), leucine and isoleucine, were reported in Norwegian older community-dwellers with sarcopenia [47]. Also, higher proline concentrations were associated with sarcopenia in older Japanese people [48]. Finally, low levels of essential AAs were found in frail older Japanese persons compared with non-frail peers [49].

Moving from metabolism to inflammation, emerging evidence indicates that circulating levels of mitochondrial DNA (mtDNA) may be a surrogate biomarker of sarcopenia in reason of the tight association with chronic low-grade inflammation and age-related changes in body composition [50–53]. In particular, oxidized cell-free mtDNA as well as nucleoids extruded from damaged mitochondria as damage-associated molecular patterns (DAMPs) are candidate triggers of inflammation in sarcopenia [53]. These DAMPs may induce a powerful innate immune response through hypomethylated CpG motifs resembling those of bacterial DNA via recognition by toll-like receptors (TLRs) and interaction with pattern recognition receptors (PRRs) [50].

Contracting muscles secrete endocrine-like intercellular communication vesicles referred to as exosomes that are conserved delivery systems and allow for peripheral and distal organ crosstalk [54]. These vesicles contain both myokines and nucleic acids, including mtDNA [55]. However, the relationship between exosome composition and sarcopenia is yet unexplored. Hence, whether muscle-derived exosomes may serve as biomarkers for sarcopenia needs to be established. These studies may be particularly relevant for understanding the dynamic response of skeletal muscle and may be instrumental to identify new biological targets for drug development.

Although paving the way for biomarker discovery, all the reported studies have the caveat of investigating single domains of the PF&S condition. Instead, analysis embodying a large number of biological and functional variables and accessing a vast array of physiologic domains are needed. This has set the momentum for the conception of a new generation of more comprehensive studies that are discussed in the next paragraph.

MULTI-MARKER RESEARCH STRATEGIES: MOVING THE FIELD FORWARD

Recently, a multidisciplinary Biomarkers Workgroup convened on an evidence-based panel of biomarkers for the Targeting Aging with Metformin (TAME) trial and a conceptual framework that could be applied to next-generation clinical trials targeting aging [18].

With the aim of promoting the identification of biological markers associated with PF&S, an ad hoc study, the "BIOmarkers associated with Sarcopenia and Physical frailty in ElderRly pErsons" (BIOSPHERE), was designed [41]. In BIOSPHERE, the determination and validation of a panel of biomarkers able to integrate specific biochemical measurements into the assessment of PF&S both in clinical and research settings were specifically addressed. The assessment of clinical, functional, and imaging parameters was used for identifying PF&S. Subsequently, multivariate modeling was applied to an array of circulating mediators pertaining to inflammatory and metabolic pathways together with all the assessed parameters to identify a set of biomarkers able to capture a PF&S fingerprint [41].

Preliminary results from BIOSPHERE showed a gender-specific inflammatory signature in older people with PF&S [22]. In particular, a core "cytokinome" composed of higher levels of C-reactive protein (CRP) and lower concentrations of myeloperoxidase (MPO), interleukin (IL) 8, monocyte chemoattractant protein 1 (MCP-1), and platelet-derived growth factor (PDGF) BB was identified [22].

Furthermore, metabolomics coupled with Partial Least Squares–Discriminant Analysis (PLS-DA) allowed identifying distinct signatures of circulating AAs and derivatives in older adults with and without PF&S [56]. In particular, higher serum levels of asparagine, aspartic acid, citrulline, ethanolamine, glutamic acid, sarcosine, and taurine characterized PF&S participants, while higher concentrations of alpha amino butyric acid and methionine were found in non-PF&S controls [56].

When tracking down the inflammatory/metabolic pathways of the mediators relevant to the PF&S phenotype, a link emerged between the specific patterns of AAs and a generalized decrease in total energy and quality/quantity of dietary protein intake [56].

Similar results were found in the cross-sectional Maastricht Sarcopenia Study (MaSS) in which sarcopenic older adults showed lower levels of metabolic markers related to the nutritional status (i.e. essential AAs, BCAAs, and eicosapentaenoic acid) [57].

Albeit novel and promising, these findings need to be confirmed by large-scale and longitudinal studies. So far, the accrued evidence holds promise toward the integration of specific biochemical measurements into the assessment of PF&S in research and clinical settings.

CONCLUSION

Over the last decades, clinical, functional, and imaging parameters have been instrumental for the clinical assessment of sarcopenia and frailty. However, the pathophysiologic complexity of the two conditions has hampered the development and implementation of a "gold standard" marker that reliably predicts meaningfully outcomes.

PF&S may be considered a prototypical multifactorial geriatric/geroscience condition recapitulating all biological hallmarks of aging whose perturbation may represent the biological foundation of PF&S. In this context, multi-marker analyses coupled with ad hoc multivariate statistical approaches represent complementary and more sophisticated strategies for investigating highly dynamic and complex conditions as PF&S.

This analytical strategy may allow identification and validation of biomarkers that will help (a) integrate specific biochemical measurements into the clinical assessment of PF&S, (b) provide insights into the biological pathways leading to functional impairment in old age, (c) identify novel targets amenable for interventions, and (d) determine surrogate endpoints to be used in clinical and research settings.

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CHAPTER 21

Quality of Life and Sarcopenia

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INTRODUCTION

In everyday conversation, most would instinctively understand what is meant when the term "quality of life" is used but would be hard-pressed to describe what this concept actually entails. In the literature, this dynamic is also present, and there is no consensus on a single definition of the concept [1]. The World Health Organization Quality of Life Group sought to tackle this issue and proposed a broad definition of quality of life, which states that quality of life is *"the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals"* [2]. Three key concepts are integrated into this definition: that quality of life (QoL) is subjective, that it is multidimensional in nature and consists of at a minimum a physical, psychological and social component, and that it takes into account both positive and negative dimensions [3]. However, the constituent parts that make up quality of life can still differ widely depending on the domain in which it is used. For example, quality of life from the perspective of urban planning or international development is not going to be the same as quality of life used in a health context.

Often, the term "health-related quality of life" (HRQoL) is used in the medical literature, and it is often used interchangeably with "quality of life" and "health status" [4, 5]. Many conceptual models for HRQoL have been elaborated, of which the Wilson & Cleary model, the Ferrans et al. model (a revision of the Wilson & Cleary model), and the World Health Organization model are the most commonly used [6]. Looking closer at the Ferrans et al. model, a causal model can be seen, where biological function influences symptoms, which in turn influences functional status, this then influences general health perceptions which ultimately influences overall quality of life. Underpinning this are the characteristics of the individual and the environment,

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

that interact on each of the previously mentioned patient outcomes [7]. However, defining HRQoL remains an ongoing process, with multiple definitions already elaborated, which mostly emphasize the impact of health or disease on a person's self-perceived well-being/quality of life/health state [4].

Considerable attention has been accorded to QoL in aging, and a number of authors have formulated definitions and developed instruments, without reaching a consensus [5]. A recent thematic synthesis provides the most comprehensive view on the dimensions of quality of life in community-dwelling older people. The authors categorized the different aspects of quality of life into nine interconnected domains, which are health perceptions, autonomy, role and activity, relationships, attitude and adaptation, emotional comfort, spirituality, home and neighborhood, and financial security [8].

So far, no theoretical works on the elaboration of a concept of QoL in sarcopenia have been published, although at least two sarcopenia-specific patient-reported outcome measures have been developed, the Sarcopenia Quality of Life (SarQoL®) questionnaire and the Age-Related Muscle Loss Questionnaire (ARMLQ) [9, 10]. Both instruments provide information from the patient's perspective, but only the SarQoL evaluates QoL, while the ARMLQ restricts its domain of interest to the functional impact of reduced muscle strength.

So far, only one systematic review has focused on the association between sarcopenia and quality of life. Woo and colleagues performed a review on the relationship between sarcopenia (or its components: muscle mass, strength, or function) and quality of life in 2016 [11]. However, they identified only one study that had used more than one component to diagnose sarcopenia (in this case the European Working Group on Sarcopenia in Older People, EWGSOP1[12], criteria were used). This study demonstrated an association between sarcopenia and lower scores on the general health and the physical functioning domain of the Short Form – 36-item (SF-36) questionnaire. A further four studies based the diagnosis of sarcopenia solely on low muscle mass, but only two found an association between lower muscle mass and poorer quality of life, and this only in the male participants. From the other 15 included studies, they concluded that physical performance and strength, but not muscle mass, was associated with QoL in cross-sectional studies. But, they also highlight the poor quality of the included studies and the poor uptake of consensus diagnostic criteria for sarcopenia [11]. Because there is a need to complement this systematic review with more recent studies focusing specifically on sarcopenia, and to aid in promoting a better understanding about the potential impact of sarcopenia on QoL, we searched for all studies in the literature that have assessed QoL in sarcopenic populations.

LITERATURE REVIEW OF QOL AND SARCOPENIA

Medline (via Ovid) was searched in July 2019 for studies assessing QoL in sarcopenic individuals. The search was not limited to a particular study design, population characteristic, sarcopenia diagnostic definition or QoL questionnaire used. No limit on date of publication or language was applied. Our search strategy identified 644 potentially relevant references. After a first screening of titles/abstracts of all references, 88 were read in full text, of which 34 met our inclusion criteria and were included in

this review. An additional study [13], comprising results of two different cohorts (Hertfordshire Sarcopenia Study (HSS) cohort and Hertfordshire Cohort Study (HCS) cohort) was identified from the bibliographies of the included studies. Among these 35 references, 17 studies focused on age-related sarcopenia (Table 21.1) and 18 focused on disease-related sarcopenia (Table 21.2).

Age-related sarcopenia and quality of life

QoL in age-related sarcopenia has been studied by 15 cross-sectional studies, one case–control study, and one prospective study, all published between 2012 and 2019. Study samples ranged from 56 [29] to 4937 [14] Asian (six studies), European (six studies) or American (five studies) older adults aged 60 years and older. Sarcopenia was diagnosed either by the presence of low muscle mass only (five studies), by the EWGSOP1[12] definition (five studies), by the presence of low muscle mass and low muscle strength (one study), by the presence of low muscle mass and low physical performance (one study) or by using the SARC-F questionnaire [48] (three studies). Two studies also compared different diagnostic criteria. The prevalence of sarcopenia ranged from 5.7% in a population of Japanese community-dwelling individuals diagnosed with the AWGS criteria [27] to 36.5% in a population of Mexican adults using the EWGSOP1 criteria [26].

Regarding QoL, The SF-36 questionnaire [49], the EuroQoL 5-Dimension (EQ-5D) utility score [50] and the EuroQoL Visual Analogue Scale (EQVAS) were the most popular scales identified across studies to measure QoL in sarcopenic populations, with all three of them being generic scales. Two other specific scales were also used by some authors: the Control, Autonomy, Self-realization and Pleasure (CASP) questionnaire [51], designed to measure QoL in early old age, and the SarQoL [52], a specific QoL questionnaire for sarcopenia developed in 2015.

The association between sarcopenia and lower QoL is supported by the majority of the studies identified in this review. Indeed, in half of the studies [14–20, 53] a strong association between sarcopenia and QoL was observed. Three of these studies [14–16] confirmed this relation even after running multivariate analyses taking into account some of the potential cofounding factors such as age, sex, body mass index, body fat mass, family income, physical activity, and functional dependence. Another study [17] showed a lower global score on the EQ-5D for sarcopenic participants in univariate analyses with only two subscales of the EQ-5D (mobility and usual care) which stayed significant after taking care of cofounding factors. Four other studies [18–21] also provided a significant association with QoL but did not use multivariate analysis.

In 5 out of the 17 studies [13, 22–25], an association between sarcopenia and QoL was found but only in part of the analyses. For the SF-36 questionnaire, for example, which is divided into eight domains of QoL, a significant association with sarcopenia was found only for some of these domains, namely the "physical role functioning" domain in the study of Silva Neto et al. [22], the "social role functioning" domain for the study of Ozturk et al. [23] and the "physical functioning" domain for the study of Beaudart et al. [25], the last one being the only one to use multivariate analyses. The other domains of QoL were not significantly reduced in sarcopenic participants as compared with non-sarcopenic ones in these studies. Another study did not find any

Table 21.1 Studies assessing QoL in age-related sarcopenia.

Author	Study design	Type of population and sample size	Diagnosis of sarcopenia	Prevalence of sarcopenia	Tool for measuring QoL	Main results	Conclusion
D. S. Sun [14]	Cross-sectional study	Korean adults 60 years and older 4937 participants (2777 women, 2160 men)	Only MM Baumgartner	6.6% - 11.2% of men - 3.2% of women	EQ-5D EQVAS	Significant association between sarcopenia and lower EQVAS and EQ-5D index scores in elderly men and women (adjusted on age, BMI and body fat mass)	⬇ ⬇ ⬇ Sarcopenic
. P. Marques [15]	Cross-sectional analyses of a prospective cohort	Brazilian community dwelling older adults 60 years and older 591 participants (389 women, 202 men)	Low GS + low MM EWGSOP1	6.26% - 11.6% of men - 4.88% of women	CASP-16 Brazil	Significant negative association between sarcopenia and quality of life in women and in men (adjusted for age group, family income, physical activity of leisure and transportation, functional dependence, cognitive deficit and depressive symptoms)	⬇ ⬇ ⬇ Sarcopenic
. Beaudart [16]	Cross-sectional study	Belgian community dwelling older adults 65 years and older 387 participants (231 women, 156 men)	Baumgartner Delmonico EWGSOP1 FNIH IWGS SCWD	Baumgartner: 26.5% Delmonico: 34% EWGSOP: 16.7% FNIH: 27.4% IWGS: 12.1% SCWD: 5.9%	SarQoL (total score and seven individual domains)	Lower QoL for the total score of the questionnaire and each individual domain for sarcopenic versus non-sarcopenic (adjusted on age and sex) for the EWSGOP, FNIH, IWGS, SCWD definitions, not for Baumgartner and Delmonico definitions.	⬇ ⬇ ⬇ Sarcopenic

S. W. Go [17]	Cross-sectional study	Korean older adults 50 years and older 1397 participants, all men	Low MM only Baumgartner	15.7%	EQ-5D	The score of the EQ-5D index was significantly lower and the rate of having problems with individual components of health-related quality of life was higher in the sarcopenic group (univariate analysis). The total score as well as the subscales of mobility and usual activity stayed lower for sarcopenic participants after adjustment (age, BMI, calcium intake, regular exercise, smoking, alcohol, and education).	⬇ ⬇ ⬇ Sarcopenic
S. Verlaan [18]	Case–control study	Dutch older adults 65 years and older 132 participants (78 women, 54 men)	Low MM + low SPPB	50% (non-sarcopenic participants matched to sarcopenic participants)	EQ-5D EQVAS	Lower QoL for EQ-5D and EQVAS for sarcopenic participants compared with non-sarcopenic ones (univariate analyses)	⬇ ⬇ Sarcopenic
S. Kim [19]	Cross-sectional study	Korean older adults 70 years and older 1222 participants (645 women, 577 men)	SARC-F AWGS EWGSOP1 IWGS FNIH	4.2% in men, 15.3% in women with SARC-F Varied from 1.7 to 12.8% for men and from 2.0 to 14.6% for women across other definitions	EQ-5D	Significantly lower QoL for sarcopenic diagnosed with SARC-F compared with non-sarcopenic (univariate analysis)	⬇ ⬇ Sarcopenic

(*Continued*)

Table 21.1 (Continued)

Author	Study design	Type of population and sample size	Diagnosis of sarcopenia	Prevalence of sarcopenia	Tool for measuring QoL	Main results	Conclusion
L. Parra Rodríguez [20]	Cross-sectional analyses of a prospective cohort	Mexican seniors 60 years and older 487 participants (390 women, 97 men)	SARC-F EWGSOP1 IWGS AWGS	1/ SARC-F 19.5% 2/ EWGSOP 9.3% 3/ IWGS: 20.8% 4/ AWGS: 11.2%	EQVAS	The SARC-F is moderately negatively but significantly correlated with quality of life. The higher the score is, the higher is the risk of being sarcopenic, the lower the QoL is.	⬇ ⬇ Sarcopenic
T-Y. Wu [21]	Prospective study	Thai community-dwelling seniors 55 years and older 670 participants (330 women, 340 men)	SARC-F	6.11%	CASP-12 score	Lower QoL for sarcopenic compared with non-sarcopenic in two years of follow-up and in year 4 of follow-up (univariate analyses).	⬇ ⬇ Sarcopenic
L. S. Silva Neto [22]	Cross-sectional study	Quilombola older adults 60 years and older 70 participants (39 women, 31 men)	1/ Low MM + low GS or low PP EWGSOP 2/ Low MM only Baumgartner	1/ EWGSOP: 10% 2/ Baumgartner: 15.7%	SF-36 (eight domains separately)	1/ EWGSOP: lower quality of life for sarcopenic participants for the physical role functioning domain – no association with the other domains of the SF-36 2/ Baumgartner: lower quality of life for sarcopenic participants for physical role functioning, bodily pain, social role functioning and emotional role functioning – no association with the other domains of the SF-36 Univariate analyses	⬇ Sarcopenic

Z.A. Öztürk [23]	Cross-sectional study	Turkish geriatric older adults 65 years and older 423 participants (240 women, 183 men)	Low MM + low GS or low PP EWGSOP1	14%	SF-36 (eight domains separately)	For sarcopenic participants versus non-sarcopenic non-obese participants, significantly associated only for social functioning domain of the SF-36 – no association with the other domains of the SF-36	⬇ Sarcopenic
J.J. Moon and Sam-Guk Park [24]	Cross-sectional study	Korean older adults 65 years and older 409 participants (178 women, 231 men)	Low MM only Different criteria	Varied from 6.3 to 42.4% in men and from 12.8 to 42.4% in women, depending on the criteria applied	EQ-5D	No difference for QoL between sarcopenic and non-sarcopenic participants for EQ-5D index except when sarcopenia is diagnosed with LESMI criteria with more problems for sarcopenic participants as compared with non-sarcopenic	⬇ Sarcopenic
C. Beaudart [25]	Cross-sectional study	Belgian community-dwelling senior 65 years and older 534 participants (323 women, 211 men)	Low MM + low GS or low PP EWGSOP1	13.7% - 11.8% in men - 14.9% in women	SF-36 (eight individual domains) EQ-5D EQ-VAS	SF-36: lower QoL for sarcopenic participants as compared with non-sarcopenic participants for the physical function domain (adjusted on age, sex BMI, MMSE, MNA, number of drugs, and number of comorbidities). No significant differences for the other domains. EQ-5D, EQVAS: no difference between groups.	⬇ SF36: Sarcopenic EQ5D-EQVAS: no difference

(*Continued*)

Table 21.1 (Continued)

Author	Study design	Type of population and sample size	Diagnosis of sarcopenia	Prevalence of sarcopenia	Tool for measuring QoL	Main results	Conclusion
Patel [13]	Cross-sectional analyses of a prospective cohort	English community-dwelling participants of HCS and HSS cohorts HCS: mean age of 67 years, 1787 participants (1022 women, 765 men) HSS: mean age of 73 years, 103 participants, all men.	EWGSOP1	HCS: 4.6% in men and 7.9% in women. HSS: From 6.8 to 7.8% according to the criteria used for muscle mass assessment	SF-36 (self-reported general health and physical functioning domain scores derived).	HCS: Lower QoL for sarcopenic compared with non-sarcopenic (univariate analysis) HSC: No difference between sarcopenic and non-sarcopenic.	⬇ Sarcopenic
B. Manrique-Espinoza [26]	Cross-sectional analyses of a prospective cohort	Mexican older adults 70 years and older 543 participants (286 women, 257 men)	Low MM + low GS or low PP EWGSOP1	36.5% of sarcopenic	SF-36 (PCS and MCS)	Only severe sarcopenia was inversely associated with PCS and MCS (adjusted for sociodemographic and health characteristics).	No difference for sarcopenic ⬇ Severe sarcopenic ⬇ ⬇
H. Mori [27]	Cross-sectional study	Japanese community-dwelling adults 60 years and older 331 participants (283 women,93 men)	Low GS or low gait speed + low SMI AWGS	5.7% sarcopenia only 3.6% combined sarcopenia + frailty	SF-36 (PCS and MCS)	Sarcopenia only: no significant difference compared with robust individuals. Sarcopenia + frailty: significant lower PCS and MCS compared with robust individuals (adjusted on age and sex)	No difference
R. Pedrero-Chamizo [28]	Cross-sectional study	Representative sample of Spanish seniors aged 65-92 years. 2747 participants (2102 women, 645 men)	Low MM only	23.9% - 23.4% in men - 24% in women	EQ-5D EQVAS	No significant difference between sarcopenic group and normal group.	No difference

L. S. Silva Neto [29]	Cross-sectional study	Brazilian older women 56 participants, all women	Low MM only Baumgartner	23.2%	SF-36 (eight individual domains)	No difference between sarcopenic and non-sarcopenic. Significant moderate positive correlations found between the amount of appendicular lean mass and PF, RP, Pain, GH, SF and RE subscales of the SF-36.	No difference

AWGS = Asian Working Group on Sarcopenia; BMI = body mass index; EQ5D= EuroQol questionnaire; EQVAS = EuroQoL Visual Analogue Scale; EWGSOP = European Working Group on Sarcopenia in Older People; FNIH = Foundation for the National Institutes of Health Sarcopenia Project; GH = general health perception; GS= grip strength; HCS = Hertfordshire Cohort Study; HSS = Hertfordshire Sarcopenia Study; IWGS = International Working Group on Sarcopenia; MCS = mental component summary; MM= muscle mass; MMSE = mini mental state examination; MNA = mini-nutritional assessment; PCS = physical component summary; PF = physical functioning domain; PP= physical performance; RE = emotional role functioning; RP = physical role functioning; SCWD = Society on Sarcopenia, Cachexia and Wasting Disorders; SF = social functioning; SF-36 = short form 36-item questionnaire; SMI = skeletal muscle index; SPPB = short physical performance battery.

association between sarcopenia and the EQ-5D questionnaire except when sarcopenia is diagnosed with lower extremity skeletal muscle mass index criteria [24]. Finally, the study of Patel et al. [13] is divided into two parts. Investigations were done on the HCS cohort and showed significantly reduced QoL in sarcopenic participants as compared with non-sarcopenic ones, in univariate analysis. Other investigations were done on the HSS cohort and did not show any difference on QoL between sarcopenic and non-sarcopenic.

Finally, in the remaining four studies [26–29], no association was found between sarcopenia and QoL. Across these four studies, heterogeneous sarcopenic diagnostic criteria were found as well as a heterogeneous origin of the population (Mexican, Japanese, Spanish and Brazilian participants). However, in three of these four studies, a relatively high prevalence of sarcopenia was observed, as compared with the other 12 studies presented above. In the study of Manrique-Espinoza et al. [26], for example, a prevalence of 36.5% for sarcopenia was found in a population of rural Mexican older people, which is higher than the prevalence usually observed. In this specific study, the authors reported nevertheless a significantly lower QoL of severely sarcopenic individuals (prevalence of severe sarcopenia of 20.5%) as compared with others.

Disease-related sarcopenia and quality of life

QoL in disease-related sarcopenia has been studied by 10 cross-sectional studies, 6 prospective studies, and 2 randomized controlled studies for which only baseline data have been used, all published between 2009 and 2019. Study samples ranged from 41 [40] to 574 [37] Asian (five studies), European (seven studies), American (five studies), and Austrian (one study) participants. Heterogeneous populations were found: participants suffering from liver, digestive, cardiac, pancreatic or pulmonary diseases, patients suffering from cancer, Parkinson or cerebral palsy, patients recruited following abdominal surgery or before allogeneic hematopoietic stem cell transplantation, or obese participants. Sarcopenia was diagnosed either by the presence of low muscle mass only (11 studies), by the EWGSOP1 definition (2 studies), by the presence of low muscle mass and low muscle strength (4 studies), or by using the SARC-F questionnaire (1 study). The prevalence of sarcopenia ranged from 5.15% in a population of Canadian overweight and obese postmenopausal women [47] to 69% in a population of Norwegian patients recruited after major upper abdominal surgery [42]. In both studies, the diagnosis of sarcopenia was established by the presence of low muscle mass.

A larger sample of different QoL questionnaires was found for studies taking place in the field of disease-related sarcopenia, as compared with studies in the field of age-related sarcopenia. The SF-36 and EQ-5D were found in, respectively, five and four studies but some specific disease-related QoL tools were also used such as a Parkinson disease questionnaire (PDQ [54]), the functional assessment of cancer therapy (FACT) questionnaires, specific to the type of cancer, as well as another cancer-specific QoL questionnaire which is the well-known EORTC QLQ-C30 [55].

Among the 18 studies, slightly more than half demonstrated significantly reduced QoL in sarcopenia. One study [30] showed a strong and significant association between

Table 21.2 Studies assessing QoL with disease-related sarcopenia.

Author	Study design	Type of population and sample size	Diagnosis of sarcopenia	Prevalence of sarcopenia	Tool for measuring QoL	Main results	Conclusion
R. D. Nipp [30]	Baseline data of a RCT	German patients with advanced cancer – with 8 weeks of diagnosis of incurable lung or gastrointestinal cancer (mean age 64 years) 237 participants (109 women, 128 men)	Low MM only	55.3%	FACT-G	Sarcopenia was associated with worse QoL (adjusted on age, sex, marital status, education and cancer type)	⬇⬇⬇ Sarcopenic
Y. Ando [31]	Cross-sectional study	Japanese cirrhotic patients hospitalized (median age 69 years) 88 participants (39 women, 49 men)	Low MM + low GS Japan Society of Hepatology criteria	27.3%	SF-36 (eight individual domains + PCS and MCS)	Significantly lower QoL for sarcopenic compared with non-sarcopenic for all individual domains + for PCS (not significant for MCS) Univariate analysis	⬇⬇ Sarcopenic
I. Jeon [32]	Cross-sectional study	Korean adults with cerebral palsy (mean age 42.8 years) 80 participants (34 women, 46 men)	Low MM + low GS or low PP EWGSOP1	49.3%	EQ-5D-3L	Sarcopenic participants had a significantly lower QoL than non-sarcopenic participants (univariate analysis)	⬇⬇ Sarcopenic
M. Peball [33]	Cross-sectional study	Austrian patients aged 65 years and older with Parkinson disease 104 participants (40 women, 64 men)	SARC-F	55.8% in PD patients, 8.2% in the non-PD controls	PDQ-8 SI	Sarcopenia was associated with decreased quality of life (univariate analysis)	⬇⬇ Sarcopenic
S. S. Olesen [34]	Prospective study	Denmark patients 18-75 years with chronic pancreatitis 182 participants (56 women, 126 men)	Low MM + low GS or low PP EWGSOP1	17%	EORCT QLQ-C30	Sarcopenia was associated with a significant decrease of QoL for the global health and all the functional scales of the EORTC QLQ-C30 except cognitive function. Univariate analysis	⬇⬇ Sarcopenic

(*Continued*)

Table 21.2 (Continued)

Author	Study design	Type of population and sample size	Diagnosis of sarcopenia	Prevalence of sarcopenia	Tool for measuring QoL	Main results	Conclusion
S. Onishi [35]	Cross-sectional study	Japanese patients with digestive diseases, mean age 70 years 303 patients (116 women, 187 men)	Low MM + low GS	32%	SF-8 (eight individual domains + PCS and MCS)	Significant lower QoL for sarcopenic participants for PF, RP, GH, RE, and PCS of the SF-8	⬇⬇ Sarcopenic
A. Emami [36]	Cross-sectional study	German ambulatory men with chronic heart failure 207 participants, all men	Low MM only	14.5%	EQ-5D	Significantly lower quality of life for sarcopenic participants (univariate analysis)	⬇⬇ Sarcopenic
H.K. Koo [37]	Cross-sectional study	Koran male with chronic obstructive pulmonary disease, mean age between 57.8 and 68.3 years 574 participants, all men	Low MM only	29.3%	EQ-5D EQVAS	Lower QoL for sarcopenic participants compared with non-sarcopenic ones for both EQ-5D and EQVAS (univariate analysis)	⬇⬇ Sarcopenic
J. Rodríguez Torres [38]	Prospective study	Spanish older adults with malignant pleural effusion (mean age 66.2 years for non-sarcopenic and 71.7 years for sarcopenic) 86 participants (32 women, 54 men)	Low MM + low MS EWGSOP1	50%	EQ-5D EQVAS	Significant lower QoL for sarcopenia compared with non-sarcopenia for mobility, personal care, pain, and anxiety/depression subscales of the EQ-5D. No difference for daily activity subscale and EQVAS. Univariate analysis. QoL of participants with sarcopenia was significantly poorer three months after discharge.	⬇ Sarcopenic
S. Morishita [39]	Prospective study	Japanese patients before allogeneic hematopoietic stem cell transplantation, median age 50 years 164 participants (64 women, 100 men)	Low MM only	50.6%	SF-36 (eight individual domains)	Patients with sarcopenia showed significantly lower scores in physical functioning, bodily pain, and vitality in health-related QOL than those without sarcopenia.	Sarcopenic ⬇

P. Sheean [40]	Cross-sectional study	American women with estrogen receptor–positive metastatic breast cancer (mean age 59.6 years) 41 participants, all women	Low MM only	34.1%	FACT-B FACT-ES	No difference between groups	No difference
E. H. van Roekel [41]	Cross-sectional study	Dutch stage I–III colorectal cancer survivors, mean age 64.3 years 104 participants (42 women, 62 men)	Low MM only	32%	EORTC QlQ-C30	No significant association between sarcopenia and QoL (adjusted)	No difference
E. K. Aahlin [42]	Prospective study	Norwegian patients after major upper abdominal surgery 385 participants	Low MM only	69%	SF-36 (PCS and MCS)	No significant association between sarcopenia and QoL	No difference
J. Giglio [43]	Prospective study	Brazilian elderly patients on hemodialysis, mean age 70 years 170 participants (60 women, 110 men)	Low MM + low GS EWGSOP1	37%	Kidney disease quality of life KDQoL-SF which includes the specific ESRD questionnaire and generic SF-36	No significant association between sarcopenia and QoL, for any of the QoL questionnaires included in the KDQoL-SF	No difference
S. C. Adams [44]	Baseline data of a RCT	Canadian breast cancer patients receiving adjuvant chemotherapy. 200 participants, all women	Low MM only	25.5%	FACT-An TOI-An Fatigue scale	No significant association between sarcopenia and QoL	No difference
A. Yadav [45]	Cross-sectional study	American liver transplant candidates, mean age 55.3 years 213 participants (84 women, 129 men)	Low MM only	22.2%	SF-36	No significant association between sarcopenia and QoL	No difference

(*Continued*)

Table 21.2 (Continued)

Author	Study design	Type of population and sample size	Diagnosis of sarcopenia	Prevalence of sarcopenia	Tool for measuring QoL	Main results	Conclusion
L. Thoresen [46]	Prospective study	Norwegian patients with advanced colorectal carcinoma, median age 64 years 50 participants (26 women, 24 men) but only 28 for analyses on sarcopenia	Low MM only	35.7%	EORTC QLQ-C30	No significant difference for functional scales of the EORTC QLQ-C30 between sarcopenic and non-sarcopenic. Regarding symptom scales, a difference was only found for financial difficulties, more often observed in sarcopenic population.	No difference
V. Messier [47]	Cross-sectional study	Canadian overweight and obese postmenopausal women 136 participants, all women	Low MM only	5.15%	Medical Outcomes Study General Health Survey	No significant association between sarcopenia and QoL	No difference

EQ-5D= EuroQol questionnaire; EWGSOP = European Working Group on Sarcopenia in Older People; GH = general health perception; GS= grip strength; MCS = mental component summary; MM= muscle mass; PCS = physical component summary; PF = physical functioning domain; PP= physical performance; RE = emotional role functioning; RP = physical role functioning; SF = social role functioning; SF-36 = short form 36-item questionnaire

sarcopenia and decreased QoL using multivariate analyses and taking into account confounding factors in German patients with advanced and incurable cancer. Seven other studies [31–37] also showed reduced QoL in sarcopenic patients, whatever the questionnaire used and the domains of QoL investigated, but did not adjust their analyses on confounding factors. Finally, two studies [38, 39] also showed an association between sarcopenia and QoL but only in a restricted part of the analyses. The eight other studies [40–47] found in the literature did not highlight any reduced QoL in sarcopenic participants. Among these eight studies, seven used reduced muscle mass as the single criterion to diagnose sarcopenia. Since this definition does not restrict the diagnosis of sarcopenia to individuals presenting both a reduced muscle mass and a reduced muscle function, the prevalence of sarcopenia is often higher.

Discussion of results of the review

Since sarcopenia is associated with many health consequences, a reduced QoL in this population seems intuitively evident [56]. Based on the model of Ferrans et al. [7], the association between sarcopenia and QoL is summarized in Figure 21.1. The prospective and generalized loss of muscle mass, muscle strength, physical performance, and muscle quality resulting from sarcopenia could emerge as mobility impairments, malnutrition, disability, and increased sedentary behavior. These symptoms could themselves lead to a loss of independence, a higher risk of falls, fractures, hospital or nursing home admissions, and/or an impaired ability to perform daily activities. All of these factors contribute to a lower QoL in sarcopenia. In age-related sarcopenia studies, there seems to be a general consensus in the literature on the negative impact of sarcopenia on QoL, whether confirmed by multivariate statistics or only univariate, as well as whether global QoL is concerned or only some domains (Figure 21.2a). The

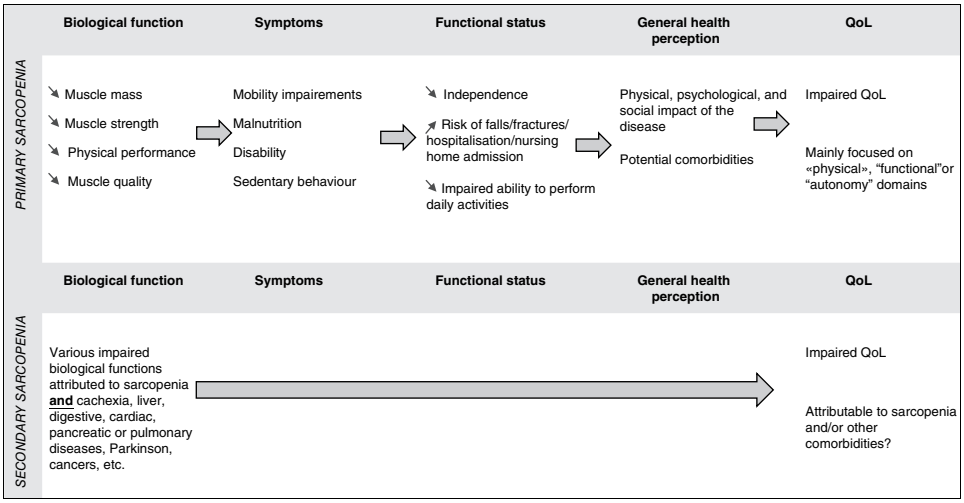

Figure 21.1 Proposition for a conceptual model of quality of life in sarcopenia.

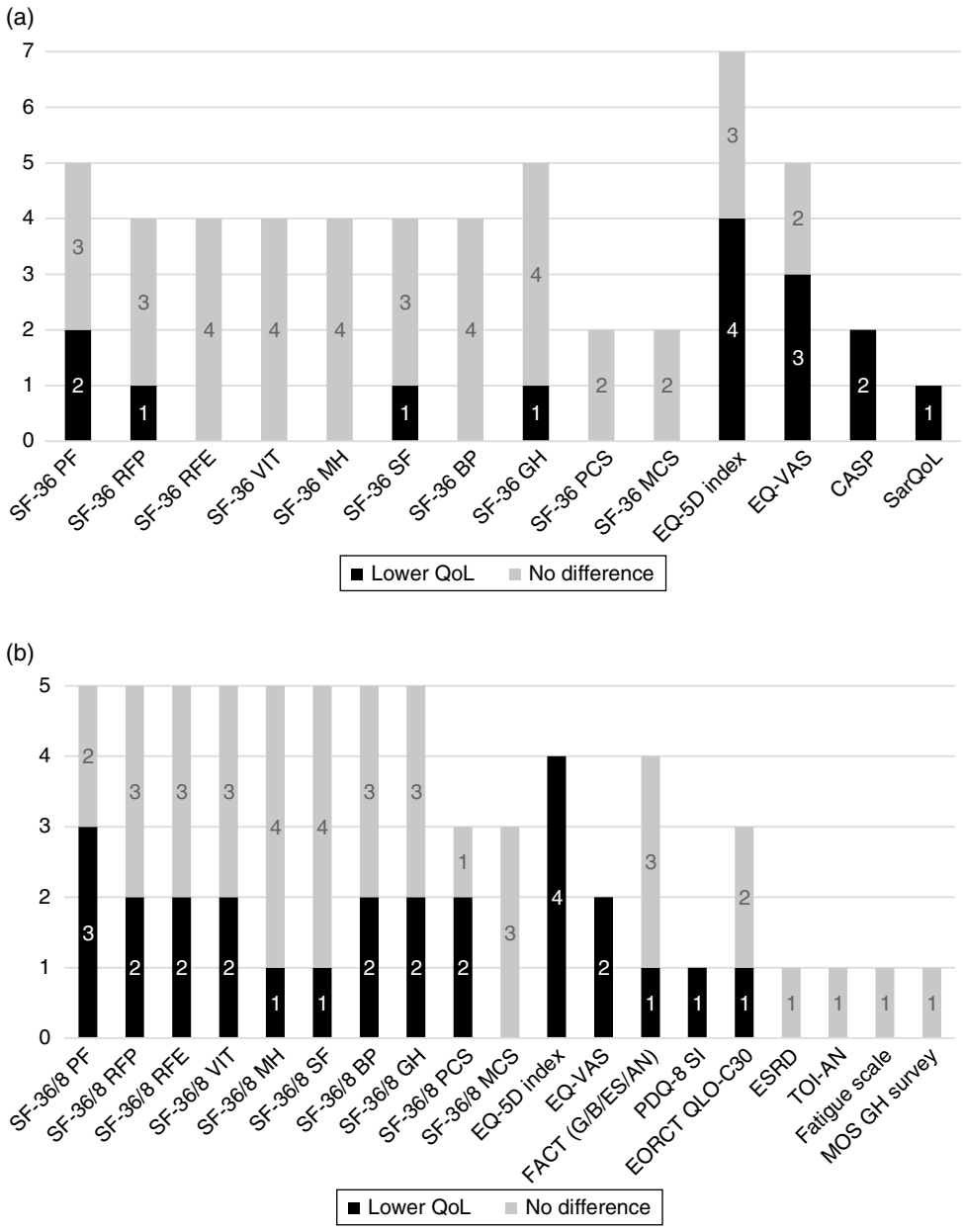

Figure 21.2 (a) Number of studies reporting difference in QoL in primary sarcopenia versus no sarcopenia. (b) Number of studies reporting difference in QoL in secondary sarcopenia versus no sarcopenia.

association between sarcopenia and reduced QoL is more difficult to highlight in individuals suffering from secondary sarcopenia. Indeed, these populations are impacted by heterogeneous health conditions that could impact QoL and decrease directly the potential association between sarcopenia itself and QoL (Figure 21.2b).

In its initial definition in 1989, sarcopenia was characterized by reduced muscle mass alone. But, quickly, this definition was enriched by scientific and technological advances and gradually evolved to incorporate the notions of decreased muscle strength and physical performance. In Europe, the EWGSOP developed a consensus definition of sarcopenia in 2010 and updated it in 2019 (EWGSOP2) based on accumulated evidence [12, 57]. In this definition, sarcopenia is characterized by reduced muscle strength and muscle mass while reduced physical performance is considered as an indicator of severe sarcopenia. Since all of the studies included in this review were published after 2009, it is surprising to observe such an important number of studies using the very initial definition of sarcopenia, and diagnose sarcopenia as reduced muscle mass without measuring muscle strength or physical performance. One hypothesis could be that sarcopenia evaluations are done as an afterthought, with available data, instead of studies being specifically designed around sarcopenia. As much as possible, authors are encouraged to apply recent consensus definitions of sarcopenia in the protocol of their future studies, in order to standardize measurements. In studies involving patients suffering from age-related sarcopenia, the relationship between sarcopenia and QoL does not seem linked to the definition of sarcopenia used. However, in disease-related sarcopenia studies, among the eight studies that did not reach a conclusion of a negative association between sarcopenia and QoL, seven studies used reduced muscle mass as the unique criterion to diagnose sarcopenia. Using muscle mass as the unique criterion usually leads to a higher prevalence of sarcopenia. Globally, in all of the studies included in this review, the relationship between sarcopenia and lower QoL seems less evident in studies with higher prevalence of sarcopenia. Restricting the population of sarcopenic participants to those suffering from reduced muscle mass but also reduced muscle function leads to a lower prevalence of sarcopenia and assumes the identification of individuals suffering from more severe muscle health impacts. Therefore, the likelihood of observing a significant difference of QoL between sarcopenic and non-sarcopenic groups should seemingly rise.

Our results have also brought to light the fact that QoL in sarcopenic participants may be reduced as compared with non-sarcopenic participants, but only for some QoL domains. This observation is particularly true when using the SF-36 questionnaire, where only the "physical functioning" domain seems impacted in participants with age-related sarcopenia. All the other domains, as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS) were almost never impacted by sarcopenia. Our attention was drawn to the large confidence intervals for SF-36 domains found across the different studies that use the SF-36 to measure quality of life. These large confidence intervals may result from heterogeneous populations, small sample sizes or the use of inadequate tools for the outcome measured. So far, the SF-36 questionnaire has not been validated for a population of individuals suffering from sarcopenia or even for older populations and it may not be adapted to the research question. Generic questionnaires, such as the SF-36, are designed for all types of populations and include a broad range of QoL aspects (i.e. for SF-36, physical health, mental health, social health, and functional health). However, since sarcopenia mainly impacts muscle health, it is not surprising to observe reduced QoL focused on physical and functional health and not particularly in other domains such as social health or mental health. What is surprising is that this observation does not seem true for the EQ-5D, also a generic QoL questionnaire. Indeed, as is the case for primary and secondary sarcopenia, this tool seems particularly adapted to highlight a decreased QoL in sarcopenic individuals as compared with healthy population. However, contrary to

the SF-36, the EQ-5D is only composed of five questions, with four of them that could be directly or indirectly negatively impacted by a poor muscle health (mobility, autonomy, activities of daily living, and pain).

Nevertheless, in generic questionnaires, only a part of the questions are relevant to sarcopenia; therefore, it is more difficult to observe a difference between sarcopenic and non-sarcopenic individuals with such a tool than with a specific questionnaire in which all questions are related to QoL as influenced by sarcopenia. After an intervention that increases muscle function, for example, all responses to a specific questionnaire are likely to vary, and the general score of the scale is also likely to be impacted. On the other hand, in generic questionnaires, only a restricted number of questions are likely to be concerned by sarcopenia, and the variation in the global score across time or following a treatment will be lower. A specific tool would thus be better able to accurately assess the impact of sarcopenia on QoL.

THE SARQOL QUESTIONNAIRE

As shown in the previous paragraphs, sarcopenia seems to negatively impact quality of life of affected older people. However, specific and detailed knowledge of the effect of sarcopenia on the lived everyday experience of patients is still scarce because of the use of generic questionnaires. These generic measures lack the specificity and sensitivity needed to capture a detailed and accurate picture of the quality of life of sarcopenic patients.

To address this weakness, the SarQoL questionnaire was developed and made available via the website www.sarqol.org. The instrument was specifically designed to permit prospective evaluation of QoL and to detect changes in QoL pre- and post-intervention. Hereunder, an overview of its development and subsequent investigations of its psychometric properties is given.

Development of the SarQoL questionnaire

As recommended in the literature, the developers sought to catalogue as many items that might be connected to QoL in sarcopenia by conducting a literature review as well as by interviewing sarcopenic individuals and soliciting the opinions of experts. Fifty-five items were selected and categorized into seven domains of health-related dysfunction. These domains cover physical and mental health, locomotion, social relations, body composition, functionality, activities of daily living, leisure activities, and fears. The 55 items were integrated into 22 questions, and response options are presented in the form of Likert scales for intensity or frequency for most questions. The seven domains are scored on a scale from 0 (worst QoL) to 100 (best QoL), and an Overall QoL score, also on a scale from 0 to 100, is calculated based on all items [52].

Psychometric properties

Researchers and clinicians who wish to use a questionnaire, or another tool, should be able to trust that the instrument is reliable, valid and responsive, i.e. it is free from measurement error, it measures what it claims to measure, and it can detect change

over time. In order to provide this information, several studies on the psychometric properties of the SarQoL questionnaire were undertaken. The questionnaire was first administered to a sample of French-speaking older participants from the Sarcopenia and Physical impairment with advancing Age (SarcoPhAge) study [25, 58]. Since then, validation studies have been published for the English version, the Dutch version, the Polish version, the Hungarian version, the Romanian version, the Greek version, the Russian version, and the Lithuanian version [59–66].

An overview of the results of these studies can be found in Figure 21.3, and will be explained in detail hereunder.

The construct validity and the known-groups validity of the questionnaire, two of the benchmarks to evaluate whether an instrument measures the construct it claims to measure (in this case, quality of life in sarcopenia), have been evaluated in eight languages with a total sample of 318 sarcopenic and 1025 non-sarcopenic participants. Hypotheses on the strength of correlation between the SarQoL questionnaire and (parts of) other questionnaires largely confirm that the SarQoL questionnaire measures QoL, although some divergent hypotheses (i.e. no or weak correlation between the SarQoL and parts of other questionnaires is expected) were rejected. Known-groups validity has been consistently confirmed in all eight validation studies, with sarcopenic participants having significantly lower quality of life scores compared with non-sarcopenic individuals [59–66].

A considerable amount is also known on the reliability of the questionnaire. Seven studies have tested the test–retest reliability of the Overall QoL score and found excellent results. A pooled analysis on 278 individuals from these seven studies was also conducted, and found an intraclass correlation coefficient of 0.969 (0.961–0.975) for the Overall QoL score, very close to perfect agreement. The internal consistency, indicating whether all items in the questionnaire evaluate the same construct, has been found to be around 0.9 (range: 0.88–0.96) throughout the eight validation studies, which indicates that a small degree of redundancy may be present in the questionnaire, and it could be shortened. Lastly, the measurement error and the smallest detectable change (SDC) were also examined in the previously mentioned pooled analysis of 278 participants, and a standard error of measurement (SEM) of 2.65 points was found. This means that there is a 95% probability that the "true" QoL of any given patient can be found in the range of ± 5.3 points (or 2 SEM) around the Overall QoL score measured by the SarQoL questionnaire. A Bland–Altman analysis on the Overall QoL score revealed no systematic bias [59–67].

Another element of the SarQoL questionnaire has been studied to help with the interpretation of the obtained QoL scores. The smallest detectable change, indicating the minimum amount of change in the Overall QoL score that needs to be observed before we can be sure that the change is real and not, potentially, a result of measurement error, was evaluated in the same study that also calculated the standard error of measurement. For an individual patient, the Overall QoL score needs to change by at least 7.35 points (on a score between 0 and 100 points) between two observations to be able to confidently consider that the patient's QoL has changed [67].

Lastly, the ability of the questionnaire to detect changes in quality of life, known as the responsiveness of a questionnaire, was examined in 42 sarcopenic participants followed over a period of two years. Responsiveness was evaluated by two methods: first by the testing of hypotheses on the correlation of changes in quality of life measured by the SarQoL questionnaire and changes measured by the SF-36 questionnaire and

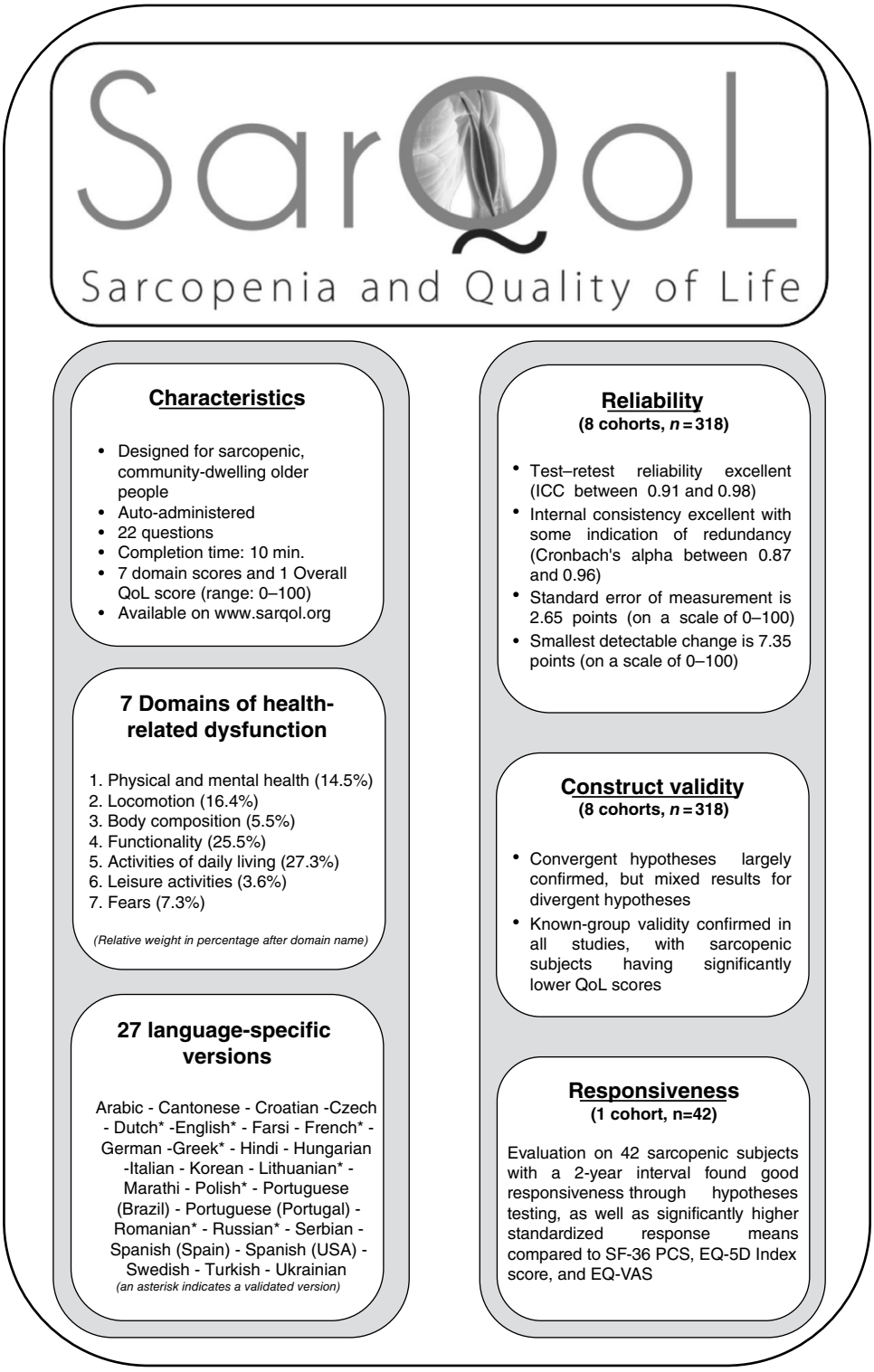

Figure 21.3 The Sarcopenia Quality of Life (SarQoL), a specific questionnaire for QoL in sarcopenia.

the EQ-5D questionnaire. Secondly, by calculating the standardized response means (SRM, a form of effect size) of the different questionnaires (SarQoL, SF-36, and EQ-5D), and comparing the magnitude of the effect between them. This study found that the SarQoL questionnaire has good responsiveness as established by the confirmation of eight out of the nine prespecified hypotheses, backed up by the observation that the SRM of the Overall SarQoL score was significantly larger than the SRM of the SF-36 physical component score (−0.72 vs. −0.20), the EQ-5D utility score (−0.72 vs. 0.18) and the EQVAS (−0.72 vs. −0.09) [68].

Applicability with different diagnostic criteria

The applicability of the SarQoL questionnaire when used with different diagnostic criteria for sarcopenia was evaluated in 387 participants participating in the SarcoPhAge study in Liège, Belgium. Six different sets of diagnostic criteria (Baumgartner [69], Delmonico [70], EWGSOP1[12], FNIH [71], IWGS [72], SCWD [73]) were applied to the sample, resulting in big swings in the prevalence of sarcopenia, from 4.39 to 32.8%. Despite this, the SarQoL questionnaire was able to discriminate between the sarcopenic and non-sarcopenic participants for the four definitions that are based on the combination of muscle mass and muscle function (EWGSOP1, FNIH, IWGS, SCWD), but not the two definitions that only look at muscle mass (Baumgartner, Delmonico)[16]. The applicability of the SarQoL questionnaire with the revised EWGSOP2 criteria was also verified and confirmed, both in the validation study of the Lithuanian version of the SarQoL questionnaire as well as in the SarcoPhAge cohort.

Future perspectives

The SarQoL questionnaire has demonstrated in several studies that it is a valid and reliable instrument to assess quality of life in sarcopenic older people. While more information on quality of life in sarcopenia has become available in recent years, as detailed in the preceding literature review, the instruments used are generic questionnaires that can only tell part of the story. By incorporating the SarQoL questionnaire in combination with a generic questionnaire, researchers could get the best of both worlds: the generalizability of a generic questionnaire and the precision and comprehensiveness of a specific questionnaire.

To facilitate the uptake of the SarQoL questionnaire in situations where time is rationed, such as clinical practice and large studies with multiple questionnaires, an effort is underway to shorten the SarQoL questionnaire, and to validate this short form SarQoL questionnaire.

CONCLUSION

The association between sarcopenia and quality of life became a topic of high interest in the past 10 last years, highlighted by the identification of no less than 35 observational studies presenting such results, identified through our literature search. Evidence

from the literature underlines that age-related sarcopenia seems to be related to poorer quality of life with a large majority of studies showing a lower quality of life, in specific domains or as a whole, for sarcopenic individuals compared with non-sarcopenic ones. Quality of life seems mainly to be impacted on physical and functional domains, suggesting that specific QoL questionnaires for sarcopenia could be of interest. The potential impact of disease-related sarcopenia on quality of life is less clear, likely because patients suffering from secondary sarcopenia are impacted by heterogeneous health conditions that impact QoL themselves. Despite the publications of consensus definitions of sarcopenia, characterizing the disease by reduced muscle mass coupled to reduced muscle function, in almost half of the identified studies, sarcopenia diagnosis is based on the presence of low muscle mass only and does not take into account muscle function. Authors should be encouraged to apply consensus definitions of sarcopenia in their study samples in order to offer a correct and clinically relevant diagnosis of sarcopenia. This first step could help to draft stronger evidence on the research questions under investigation in the field of sarcopenia. The second step could be to combine the use of a generic QoL questionnaire with the use of a specific QoL questionnaire for sarcopenia, for example the SarQoL questionnaire, to obtain more accurate values of QoL in this population and be able to follow sarcopenic individuals across time with more sensitivity.

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CHAPTER 22

Exercise Interventions to Prevent and Improve Sarcopenia

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INTRODUCTION

Although the term "sarcopenia" has taken on various definitions since the original use by Rosenberg [1], it has evolved into a general designation of vulnerability to weakness, atrophy functional loss, and diminished independence among aging adults. Research on sarcopenia has become an intense topic of study, and it has even been recognized with a 10th-revision of the International Statistical Classification of Diseases (ICD-10) code (M62.84) [2]. Decreases in muscle tissue quantity and quality may begin to occur prior to the fourth decade of life [3] and gradually worsens after age 60 [4]. The age-related changes in morphological and functional characteristics of skeletal muscle are often accompanied by other comorbid conditions which may cluster and serve to worsen the severity of sarcopenia, risk for frailty, and disability. In particular, various factors such as chronic inflammation [5] and oxidative stress [6], insulin resistance [7], skeletal muscle fibrosis [8], myosteatosis (i.e. intramuscular and intermuscular adipose tissue infiltration), reduced mitochondrial area density and function [9–11], and increased overall fat mass (i.e. "sarcopenic obesity") [12–14] are known to be coincident with, caused by, or exacerbated through the trajectory of aging, disuse, and sarcopenia. Thus, despite the ongoing debate and conjecture regarding its classification as a disease state versus a normal process of aging, sarcopenia represents a *very* complex phenotype with a multifactorial etiology.

The contribution of age-related sarcopenia to functional decline is mediated largely by reductions in muscle strength [15–17]. In fact, the rate of age-related declines in muscle strength is two to five times greater than declines in muscle size [13]. The European Working Group on Sarcopenia in Older People recently updated their recommendations

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

to focus on low muscle strength as the key characteristic of sarcopenia and use detection of low muscle quantity and quality to confirm the sarcopenia diagnosis [18]. Thereafter, a Foundation for the Institutes of Health (FNIH)-funded initiative published cut-points for grip strength (grip strength of <26 kg in men and <16 kg in women [19]) and appendicular lean mass divided by body mass index. These strength thresholds have been shown to be strongly related to incident mobility limitations and mortality [17].

Even more recently, the FNIH funded the Sarcopenia Definitions and Outcomes Consortium, a collaboration among content experts and many cohort studies and clinical populations, to further develop evidence-based cut-points for lean mass and strength to identify persons at risk for mobility disability and other adverse health outcomes, such as falls, self-reported mobility limitation, hip fractures, and death [20]. A large body of evidence links muscular weakness to a host of negative age-related health outcomes including diabetes [21], disability [22, 23], cognitive decline [24–27], osteoporosis [28], and early all-cause mortality [22, 29–31]. Given these links and the recognition of weakness as a hallmark feature of sarcopenia, grip strength (a robust proxy indicator of overall strength) [32] has been labeled a "biomarker of aging" [33].

There is also a growing consensus that the low-grade chronic inflammation in aging ("inflammaging") is a strong risk factor for both morbidity and mortality in older adults [34], and may represent a strong mechanism linking age-related increases in adiposity and metabolic dysregulation with sarcopenia and muscle weakness [35, 36]. Central to the pathophysiology of sarcopenia, weakness, and related comorbidities, physical *inactivity* is consistently recognized as a predominant and perennial "cause [37]." Thus, since sarcopenia is robustly associated with weakness, frailty, and mobility disability [38, 39], failure to prevent its progression with behavioral interventions including strategic physical activity (PA), exercise, and lifestyle modification may significantly impede optimal quality of life (QOL) [40], and lead to early mortality [41–43].

DEFINITION OF TERMS

Several potent behavioral factors are recognized to independently contribute to onset and progression of sarcopenia, weakness, and related comorbidities, including obesity, physical inactivity, smoking, and malnutrition. Of these factors, physical inactivity is perhaps the most detrimental for inciting functional loss and disability throughout late adulthood, and along with insufficient dietary provisions, is the risk component that has received the most research attention for treating age-related atrophy and weakness. Indeed, ample evidence exists to confirm a robust, independent association between sedentary behavior (SB) and disease, disability, and shortened life span among older adults [44]. Despite this rather simplistic and predictable trajectory of age-related *decline*, substantial debate persists regarding the optimal strategy to slow or reverse the downward spiral of muscle tissue integrity and function. At the center of this debate, there is currently no consensus recommendation for PA and exercise among older adults with sarcopenia. However, the National Strength and Conditioning Association (NSCA) has recently issued a Position Statement pertaining to resistance training recommendations in older adults [45], which is highlighted in the text below.

Concerns of elevated risk associated with activity for this population have prompted a minimalistic paradigm, and a general trend of nonprogressive, yet "safe" activity suggestions. However, and as an important point of clarification, "activity participation" should not be interpreted as merely the antonym of "inactivity." Rather, in order to appreciate the extent to which various lifestyle, PA and exercise strategies contributes value to the spectrum of health and physical fitness among older adults with sarcopenia and weakness, the unique attributes of each must be distinguished. Although maintenance or increases in leisure time PA is known to support preservation of function and longevity [44], there are also well-recognized health benefits associated with structured and progressive exercise including resistance exercise (RE). Thus, for the purpose of this chapter, a clear distinction is made between (a) lifestyle strategies to reduce SB and related chronic health risks, (b) PA strategies that confer preservation of function and basic cardiometabolic health, and (c) structured exercise strategies that are intended to induce specific physiologic and morphologic adaptations.

Sedentary behavior

SB may be defined as time spent sitting or lying down [46], and is known to increase with age [47]. This modifiable risk factor has received significant attention as a robust predictor of chronic disease and mortality among adults [48–50], and moreover, is acknowledged to accelerate sarcopenia [51]. Importantly, SB should not be regarded as synonymous with extremely low PA levels, as these factors are each *independently* associated with diabetogenic and atherogenic profiles [48, 49, 52]. SB is generally defined as a range of behaviors that coincide with an energy expenditure less than or equal to 1.5x resting energy expenditure [53]. In using this definition, it is actually plausible to have a potentiated risk profile if someone is both physically inactive and also engages in extended bouts of SB. Conversely, it is also possible to become deficient in only one, as these behaviors represent two viable targets of intervention. Although decrements in muscle mass and function have been considered the primary contributing factors of functional deficits among aging adults [54], it is conceivable that such changes are also the principal drivers of increased SB in this population. Thus, it is logical to presume that sarcopenia precedes functional deficit, but it is also quite likely that SB itself may lead to sarcopenia and weakness. Generally, both weakness and obesity precipitate SB, which ultimately results in a diminished volume and frequency of stimulus to the cardiometabolic, neuromuscular, and musculoskeletal systems. Although sarcopenia is considered a readily preventable and treatable condition, it is rarely diagnosed early, and in turn may lead to decreases in functional capacity, and gradual yet significant muscle wasting over time. Clearly, the associated outcomes of functional deficit and chronic SB may also serve as a contributing risk factor for other chronic disease processes (e.g. the metabolic syndrome [55]). This circular cause and consequence of events has made the treatment of age-related comorbid conditions an exceedingly difficult directive; however, a simplistic and yet central preventive strategy from a clinical context is to encourage a lifestyle characterized by replacing SB with light PA [56].

Physical activity

PA is an umbrella term loosely defined by the Institute of Medicine as body movements that are produced through contraction of skeletal muscles, and that increase energy expenditure. Thus, baseline activity is operationalized as the smallest increments of body movements that increases energy above SB (e.g. standing, slow walking, lifting very light objects) [57]. Consistent with this definition, individuals who do only baseline activity are not sedentary, per se, but are *still* considered to be inactive. It is well known that older populations are less active than young adults, and this trend is coincident with various secondary effects of aging (i.e. those resulting from environment, behaviors, and/or disease). Conversely, and from a holistic perspective, regular PA involvement is associated with significant attenuation of these secondary consequences, and thus can serve to mediate longevity. Toward that end, recent evidence reveals that increasing or maintaining PA is related to greater survival in older adults, even among those with obesity or functional limitations [44]. Thus, health-enhancing PA may be defined as any body movement that is distinct from baseline activity, and that is expected to add benefit for *enhanced* health. In 2007, the American College of Sports Medicine (ACSM) and American Heart Association (AHA) published joint PA and public health recommendations for older adults [58], in which specific modes and doses of activity were sanctioned to promote maintenance and/or improvement of health. In 2009 the ACSM extended those recommendations in a position stand to provide an overview of issues critical to both exercise and PA in the older adult population [59]. Consistent with the recently released Physical Activity Guidelines for Americans, 2nd edition (PAGA) [60], the combined message is clear – PA can make people feel better, function better, sleep better, and reduce the risk of many chronic diseases [61]. Specific emphasis throughout each publication was placed on accumulation of daily PA volume as a general panacea for age-related comorbidities.

Indeed, regular PA is considered necessary for health maintenance, and is recommended to sustain a healthy body composition and/or body mass index (BMI), lipid/lipoprotein profile, glucose tolerance, blood pressure, ambulatory balance, and psychological well-being among older adults [58, 59]. Lifestyle PA or leisure-time PA may be generally defined as aerobic in nature and can take the form of any popular leisure activity (e.g. walking, gardening, biking, golf). In addition to avoiding SB, some lifestyle PA is certainly better than no activity at all, and for most outcomes there is a dose–response relationship between volume, frequency, and intensity of PA, and respective health benefit [59]. In an effort to provide quantifiable parameters of PA prescription, a focal point of the current guidelines [59] also includes recommendations of mode- and dose-dependent PA. Therefore, since the majority of older adults prefer short bouts of lower-intensity leisure activity [62], it is deemed necessary to operationalize, and provide rationale for inclusion of moderate- and vigorous-intensity PA. In remaining consistent with the ACSM/AHA nomenclature, moderate-intensity PA may be defined as PA that involves a moderate level of effort relative to an individual's aerobic capacity [58]. This type of PA is further characterized by noticeable increases in heart rate and respiration and may be most easily performed using repetitive modalities such as brisk walking, biking, and aqua-based aerobic activity. Although baseline activity, lifestyle PA, and moderate-intensity PA are all very appropriate suggestions for many of the comorbidities associated with sarcopenia, none of these is particularly effective for preservation of skeletal muscle quantity or quality (i.e. strength/muscle mass).

Exercise

Conversely, **exercise** is a type of PA that is associated with distinctive adaptations to a given physiological system and is typically prescribed with the intent for weight loss, health, physical fitness, and/or athletic/performance improvement. Whereas lifestyle PA can be accomplished at random and accumulate throughout the day, exercise is generally referred to as planned, structured, and repetitive. Further, whereas lifestyle PA may contribute to maintenance or improvements in global health and enhanced QOL among older adults, only certain types of exercise are known to have profound benefits for sarcopenia-specific mechanisms and outcomes. In particular, tailored exercise is necessary for targeting components of health-related physical fitness, which include cardiorespiratory fitness, muscular strength and endurance, body composition, flexibility, and balance [63]. Each of these components either indirectly mediates risk of sarcopenia-related comorbidities (e.g. cardiorespiratory fitness), or is directly associated with prevention or reversal of sarcopenia itself (e.g. strength training). **Table 1** offers the type of exercise needed to accommodate each of these health-related physical fitness outcomes, the mechanism(s) through which the adaptation occurs, and the nature of this contribution to directly or indirectly influence health and/or function.

BENEFITS OF PA AND AGING

Since the seminal work of Morris in the early fifties [64], there is a huge scientific evidence about the benefits of PA in the primary and secondary prevention of several chronic diseases, disability, and premature death [65–68]. However, there is still skepticism among older persons, health professionals, and policy makers about the potency of exercise for disease prevention and treatment in the older, particularly in frail adults. Although PA cannot stop the aging process, exercise can minimize the physiological effects of a SB and increase active life expectancy by limiting the development and progression of chronic disease and disabling conditions.

There is no doubt that regular PA is good for health in all populations including the older [61]. Indeed, regular PA has been associated with a decreased risk of: all-cause mortality (including cardiovascular disease), cardiovascular disease (including heart disease and stroke), hypertension, type 2 diabetes, adverse blood profile, cancers (bladder, breast, colon, endometrium, esophagus, kidney, lung, stomach), dementia (including Alzheimer's disease), depression, falls (including fall-related injury). In addition, regular PA improved cognition, sleep, bone health, and physical function, reduced anxiety, and overall improved QOL.

Response to exercise

The physiological, cardiovascular, and neuromuscular adjustments to exercise of healthy sedentary older are qualitatively similar to those of young adults [69, 70]. Although improvements tend to be less in older versus young people, the relative increases in many variables, including VO_2 max, submaximal metabolic responses, exercise tolerance, muscle strength, endurance, and size are generally similar [71].

Table 22.1 Type of exercise and its influence on sarcopenia.

Type of exercise	Health-related component of physical fitness	Example modality options	Mechanism(s) of adaptation	Influence on sarcopenia	Influence on related comorbidities
Moderate and vigorous PA: Aerobic exercise	Cardiorespiratory fitness, Body composition, Muscular endurance, and Balance	Brisk walking, Cycling, Jogging, Recumbent stepping, Swimming and aqua aerobics, Hiking, Elliptical training, Group aerobic classes	*Central:* (i) Improved aerobic capacity (VO_2 max) through increases in cardiac output and stroke volume; and (ii) decreased heart rate at rest and during exercise. *Peripheral:* (i) Increased capillarization of type I muscle fibers (arteriovenous oxygen difference); (ii) Increased mitochondrial size, density, and function (fatty acid oxidation); (iii) Increased stores of metabolic energy (e.g. creatine phosphate, glycogen, triglycerides); and (iv) increased aerobic enzyme activity (e.g. myokinase).	*Direct:* Significant improvement in muscle function (i.e. muscular endurance and fatigue resistance) *Indirect:* Modest improvement in balance, and thus reduction of slip-and-fall risk.	Improvement in all risk factors for cardiometabolic diseases, i.e. body composition (reduced adiposity), decreased blood pressure, improved insulin sensitivity, improved cholesterol/triglyceride profile, and reduction in chronic inflammation.
Resistance exercise	Muscular strength and endurance, Body composition, Flexibility, and Balance	Free weights, Selectorized machines, Pneumatic resistance equipment, Body-weight movements (e.g. pushups, squats), Alternative resistive implements (e.g. kettlebells, medicine balls, elastic bands)	*Morphological/Architectural:* (i) Increases in single fiber physiological cross-sectional area and whole muscle hypertrophy and thickness; (ii) Increases in fascicle length (sarcomeres in series); and (iii) Increases in pennation angle. *Neuromuscular:* (i) Increased force production capacity and rate of force development through greater recruitment capacity of Type II fiber and increased rate coding (motor unit discharge frequency); and (ii) Improved neuromuscular efficiency through increased intra- and intermuscular coordination, and decreased antagonist coactivation.	*Direct:* Significant improvements in muscle size and function (i.e. hypertrophy, strength, power, and endurance) *Indirect:* Significant improvements in balance and flexibility. Modest improvements in cardiorespiratory fitness, particularly for previously sedentary older adults.	(i) Decreases risk of slip-and-fall accident; (ii) Improvement in glucose homeostasis and insulin sensitivity; (iii) Increases in bone-mineral density and tendon strength; and (iv) Improvement in mobility.

Stretching/ Range of motion exercise	Flexibility, Balance	Static stretching, Passive stretching, Dynamic range-of-motion exercise, Tai-Chi, Yoga, Pilates, Active-isolated stretching	(i) Decreased stiffness of musculotendinous unit; (ii) Decreased passive resistive force; (iii) Increased stretch tolerance.	None	(i) Improvement in mobility, and (ii) Decreased risk of slip-and-fall accidents.
Balance exercises	Balance	Single-leg stance exercises, Lateral weight-shift exercises, Unstable surface walking and isometric poses	(i) Small increases in strength capacity of ankle, knee, hip, and spinal stabilizer muscles, and (ii) Improved proprioception and kinesthetic awareness.	None	Decreased risk of slip-and-fall accidents.

Optimization of body composition

The patterns of change in body composition seen in usual aging include increase in adipose mass, decrease in skeletal muscle mass, and decrease in bone mass, which may negatively impact metabolic, cardiovascular, and musculoskeletal function [72]. Physically active older adults compared with sedentary have less total and abdominal body fat a greater muscle mass in the limbs and higher bone mineral density [73].

Decreases the risk of developing many chronic diseases

The relative risk of developing many chronic diseases (cardiovascular disease, type 2 diabetes, hypertension, obesity, and certain cancers), the prevalence of degenerative musculoskeletal conditions (osteoporosis, arthritis, sarcopenia) and disability increases with advancing age [61]. The mechanisms of the preventive exercise effect are varied and not completely known, and include: decrease in body weight, maintenance of muscles and tendons strength, decrease in estrogens levels, decrease in blood pressure, decrease in low-density lipoprotein (LDL) cholesterol, decrease in insulin resistance and hyperinsulinemia.

Treatment of chronic diseases

Traditional medical approach usually does not address disuse and deconditioning accompanying some chronic disease (congestive heart failure, chronic obstructive pulmonary disease, intermittent claudication, and chronic renal failure), which may be responsible for much of their associated disability. Moreover, PA is a main therapeutic intervention for the treatment and management of many chronic diseases including coronary heart disease, hypertension, peripheral vascular disease, type 2 diabetes, obesity, hypercholesterolemia, osteoporosis, osteoarthritis, chronic obstructive pulmonary disease, depression and anxiety, dementia, pain, congestive heart failure, syncope, stroke, back pain, and constipation [61] .

Exercise may also lower the risk for recurrences of disease such as cardiovascular disease. REs that improves skeletal muscle mass in patients with congestive heart failure counteracts the catabolic effects of cytokines [74]. Quadriceps exercises in patients with arthritis improve joint stability and may add benefits to analgesics [75]. Also exercise may counteract undesirable side effects of medications such as myopathy and osteopenia in patients receiving corticosteroid treatment [76].

Decreases falls and injuries

More than one-third of community-living older adults fall each year. Approximately 10% of falls result in a major injury such as a fracture, serious soft tissue injury, or traumatic brain injury. Falls are not only associated with morbidity and mortality, but are also linked to poorer overall functioning and early admission to long-term care facilities [77]. PA reduces risk of falls and injuries from falls [78, 79] even in the oldest

old [80]. Effective approaches include multidimensional risk factor assessment tied to targeted interventions, exercise programs (balance, strength, and endurance training), and environmental assessment and modification

Decreases disability

The expansion of the aging population has led to a diversification of noncommunicable disease morbidity, including increased prevalence of aging-related mobility impairments and a substantial reduction in the number of healthy, nondisabled years [81–83]. Adults with disabilities comprise nearly 15% of the population, and growing by 0.15% per year [84]. The health-care burden associated with disability is nearly twice that of individuals without disabilities, and is likely owing to a higher risk for chronic disease in these individuals [85]. Early screening and continued health promotion efforts are vital to reduce the escalating burden associated with multimorbidity and disability in the growing aging population. Epidemiological studies have demonstrated a dose–response pattern for PA that is associated with a lower risk of physical limitations [86]. Additionally, studies have reported the benefits of PA on physical capacity and precursors of physical disability (increasing muscle strength, aerobic capacity, and bone density) [87], even in frail older persons [88, 89].

Physically active adults are more likely to survive to age 80 or beyond and had approximately on half risk of dying with disability compared with their sedentary counterparts [90]. There is a clear overlap between the risk factors for disability and the consequences of inactivity: decreased exercise capacity, gait instability, and impaired lower extremity function and mobility characterized both populations.

Improves psychological health

Physically active older have more positive psychological attitude and a lower prevalence and incidence of depressive symptoms. Exercise can improves psychological health and well-being including anxiety, depression, overall well-being, and QOL [91]. There is strong evidence that high-intensity RE training is effective in the treatment of clinical depression [92]. Both aerobic and RE produce clinically improvements in depressed older persons, with response rates ranging from 25 to 88%. Most well-controlled exercise training studies result in significant improvements in both physical fitness and self-efficacy for PA in older adults [93].

Mental and social health

Regular PA is associated with better mental health and social integration. Different studies have linked participation in regular PA with a reduced risk for dementia or cognitive decline in older adults [94, 95]. The mechanism for this relationship is not well understood; it has been suggested that enhanced blood flow, increased brain volume, elevations in brain-derived neurotrophic factor, and improvements in neurotransmitter systems and IGF-1 function may occur in response to behavioral and

aerobic training [96], Also it is well demonstrated that exercise training increases fitness, physical function, cognitive function, and positive behavior in people with dementia and related cognitive impairments [97].

Increases life expectancy

There is a clear evidence of an inverse relationship between the volume of PA in a lifetime and all-cause mortality rates in both men and women and older and younger [98]. Volumes of energy expenditure doing exercise of at least 1000 kcal/week reduce mortality by 30%; volumes closer to 2000 kcal/week reduce the risk by 50%. Also older adults with chronic diseases experience a long-term beneficial mortality effect from participation in exercise programs [99]. It is important to know that despite the increasing likelihood of comorbidity, frailty, dependence, and ever-shortening life expectancy, remaining and even starting to be physically active increases the likelihood of living longer and staying functionally independent [100]. There is also a robust link between weakness and early mortality [101, 102], and thus promoting early exercise habits that promote muscular fitness to reduce the risk of frailty and longevity.

Improves quality of life (QOL)

QOL is a psychological construct, which has commonly been defined as a conscious judgment of the satisfaction an individual has with respect to his/her own life. PA was positively and consistently associated with some QOL domains among older individuals, supporting the notion that promoting PA in older people may have an impact beyond physical health [103].

TYPES OF EXERCISE

Aerobic exercise

AE is a form of structured PA characterized by rhythmic and repetitive movements of large muscles, for sustained periods. AE is thus any continuous PA that depends primarily on the use of oxygen to meet energy demands through aerobic metabolism, and that is structured and intended to generate improvements in cardiorespiratory fitness, body composition, and/or cardiometabolic health. Since aerobic metabolism is needed for a continuum of physiologic processes spanning from basic energy needs at rest, to elite endurance-sport performance, specific cut-offs have been derived for apparently healthy adults to distinguish between *very light intensity* AE (<30% VO_2R or heart rate reserve [HRR]), *light intensity* AE (30% to 39% VO_2R or HRR), *moderate intensity* AE (40% to 59% VO_2R or HRR), *vigorous intensity* AE (60- 89% VO_2R or HRR), and *near-maximal to maximal intensity* AE (≥90% VO_2R or HRR) [104]. Despite these cut-offs, there is no accepted "threshold" or minimum level of intensity that is needed for cardiorespiratory fitness. Indeed, most research has demonstrated that improvement in cardiorespiratory fitness (i.e. improvement in VO_2 max) is highly contingent upon initial

fitness capacity, such that more highly fit individuals require greater relative intensities [105]. However, since the primary focus of aerobic activity and exercise for older adults has been to encourage initial participation and sustainable PA involvement, very little emphasis has been devoted to recommending specific exercise dosages for fitness improvement. Rather, current ACSM/AHA guidelines suggest that aerobic PA for older adults be prescribed to "promote and maintain health," and in accordance with a 0-to-10 rating scale of perceived physical exertion (RPE) for moderate-intensity (5 to 6 out of 10) and vigorous-intensity (7 to 8 out of 10) exercise [58, 59]. Moreover, in order to meet the criterion definition of "aerobic exercise," aerobic PA must be performed at a *minimum* of moderate intensity (i.e. 40 to 59% VO_2R or HRR; or 5–6 RPE out of 10), and continuously for a sufficient duration of time (≥10 minutes) [58, 59, 104]. The updated physical activity guidelines for Americans (PAGA) recommendations [60], suggest that all adults (including older adults) should do at least 150 minutes (2 hours and 30 minutes) to 300 minutes (5 hours) a week of moderate-intensity, or 75 minutes (1 hour and 15 minutes) to 150 minutes (2 hours and 30 minutes) a week of vigorous-intensity AE, or an equivalent combination of moderate- and vigorous-intensity AE. However, additional health benefits are gained by engaging in PA beyond the equivalent of 300 minutes (5 hours) of moderate-intensity PA a week. However, the updated PAGA recommendations further clarify that when older adults cannot do 150 minutes of moderate-intensity AE a week because of chronic conditions, "they should be as physically active as their abilities and conditions allow" [60].

Notwithstanding the value of AE for health promotion and cardiorespiratory fitness among older adults, its impact on sarcopenia is generally recognized as an indirect mediator of chronic comorbidities. Considering that sedentary older adults are at risk for simultaneous reduction in lean body mass and gradual increases in adiposity [12–14], presence of normal BMIs may actually conceal the extent of cardiometabolic risk, i.e. "normal weight obesity [106, 107]" (Figure 22.1).

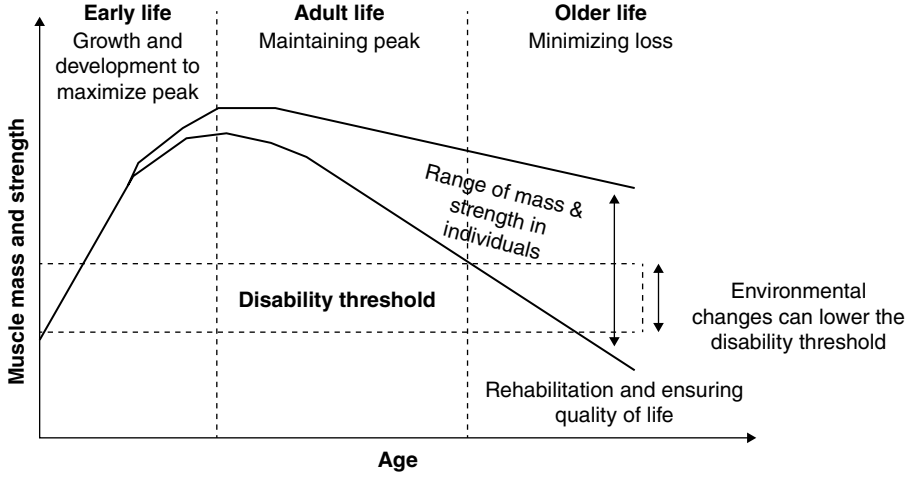

Figure 22.1 Scatter plot depicting the correlation between body mass index (BMI) and percent body fat (%BF) for the whole sample, by sex. The vertical line represents the standard BMI cut-off for obesity (BMI ≥ 30). The horizontal lines represent the sex-specific %BF cut-offs for obesity in men (≥25%) and women (≥35%). *Source*: From Peterson et al. [128].

Further, considering the increased prevalence of the metabolic syndrome and type 2 diabetes among older adults [109–113], public health and clinical efforts must continue to bolster support for regular aerobic activity as a means to circumvent undue chronic health risk and early mortality in this population. The positive benefits of AE on cardiometabolic health are multifaceted, and can be explained by three phenomena [114]. During the acute phase, a single bout of exercise can significantly increase whole-body glucose disposal and thus, temporarily attenuate hyperglycemia. For several hours after the bout of exercise, insulin sensitivity is increased. Lastly and most importantly, repeated bouts of AE leads to a chronic adaptive response, and is characterized by enhanced cardiorespiratory fitness and global improvements in insulin action [115, 116]. AE is also effective for improving blood pressure and lipid profiles, decreasing visceral adiposity, enhancing fatty acid oxidation, increasing mitochondrial function and content, and attenuating the proinflammatory state [117–119].

High-intensity interval training (HIIT)

HIIT consists of utilizing similar modes of exercise as used during traditional AE (e.g. cycling, running); however, with alternating short periods of intense exercise and recovery periods of passive or mild-intensity exercise. The intense intervals typically last between 15 seconds and 4 minutes and can approach 80% to 95% of an individual's maximum heart rate. The recovery (i.e. lower intensity) intervals are typically equal to or slightly longer than the intense work intervals and consist of passive rest or mild exercise at 40 to 50% of the maximum heart rate. The combined work/rest interval are commonly repeated 6–15 times and should depend on the duration and intensity of the work intervals. Thus, the total HIIT exercise time ranges from 10 to 40 or more minutes depending on the actual duration of the work and rest periods. There is now a clear evidence supporting the potential value of HIIT in managing many age-related chronic diseases, as well as reducing indices of cardiometabolic risk in healthy adults (including older adults) [56, 120, 121]. In fact, in a recent study, 12-weeks of HIIT enhanced insulin sensitivity and lean mass, improved aerobic capacity and skeletal muscle mitochondrial respiration, revealed a robust increase in gene transcripts than other exercise modalities in older adults, and reversed many age-related differences in the proteome, particularly of mitochondrial proteins in concert with increased mitochondrial protein synthesis [121].

Resistance exercise

RE is a form of structured PA that is generally defined as exercise through which muscles must work against or resist the force of an applied load. Structured RE relies on anaerobic metabolism to meet energy demands and is typically prescribed with the intent to improve muscular strength and endurance, or to induce skeletal muscle hypertrophy. Since muscle weakness and atrophy are predictive of functional deficit, disability, and early all-cause mortality among older adults [39, 101, 102, 122–124], RE may be considered the primary preventive or treatment strategy in the battle against sarcopenia [45, 125, 126]. However, at present only 27% of the population [US]

is estimated to participate in leisure time RE, and these rates are dramatically less for individuals over the age of 50 years [127]. Moreover, although the effectiveness of RE for older adults has been deemed to be supported by the highest category of evidence (i.e. "Evidence Category A.") [59], the overall reported value of RE for strength and hypertrophy among aging persons is inconsistent across investigations. Debate concerning the appropriateness of RE among older individuals has cultivated questions regarding general efficacy and safety for this population, particularly as applies to progression of training. There are very few published accounts that have examined the overall benefit of RE in aging persons while considering a continuum of dosage schemes, treatment durations, and/or age ranges on longitudinal adaptation. As a result, previous PA recommendations for older adults included guidelines for RE [58, 59], albeit at minimal dosages and not specific to sarcopenia treatment/prevention.

The extent of sarcopenia and weakness is widely variable among older adults, which is suggested to be attributable to the peak in mass and strength attained earlier in life [108] (Figure 22.2). Thus, even though significant adaptation is possible in the "oldest old" [129], it may be expected that the benefits of early intervention will translate to preservation of long-term health and independence. Previous studies have documented a disproportionate decline of strength and muscle mass, which suggests that these age-related phenomena are somewhat independent [130, 131]. Further, there is a robust association between strength deficit and diminished functional capacity [132, 133], and although the rate of decline is largely an individual phenomenon [134], further decrement may be mitigated with early diagnosis and RE participation [135]. Several investigations have reported that after even short durations of RE, protein synthesis rate and neuromuscular adaptive responses among older adults were similar to that of young subjects, despite a much lower pre-exercise rate [136–139].

The guidelines for RE are very different between young and middle-aged healthy adults [140, 141], and those sanctioned for older populations [58, 59, 142]. Most notably,

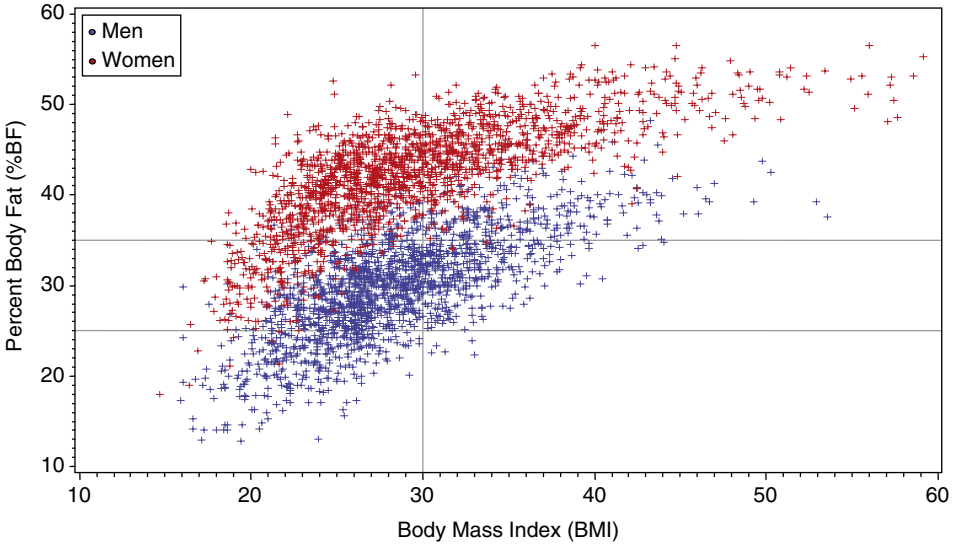

Figure 22.2 A life course model of sarcopenia. *Source*: From Sayer et al. [108].

and in spite of a significant body of literature to support the safety and effectiveness of higher-dose training, previous recommendations for older adults did not endorse progression to accommodate long-term adaptation. However, evidence from two meta-analyses [143, 144] has revealed that RE is effective for eliciting significant strength adaptation and increases in lean body mass among older adults, and that there is a robust dose–response relationship such that volume and intensity are strongly associated with both hypertrophy and strength improvements. These findings reflect and support the viability of progression in RE dosage to accommodate a hierarchical muscular adaptive response to training [145]. Progressive RE should thus be encouraged among healthy adults, regardless of age, to minimize degenerative muscular morphology and dysfunction. In fact, the NSCA very recently issued a Position Statement pertaining to resistance training recommendations in older adults [45], which greatly expanded on the previous recommendations. In general, the new recommendations suggest that a properly designed resistance training program for older adults should include an individualized and periodized approach working toward 2–3 sets of 1–2 multi-joint exercises per major muscle group, achieving intensities of 70–85% of one repetition maximum (1 RM), 2–3 times per week [45].

Volume of RE may be defined as the total number of sets performed per unit of time (i.e. not including warm-up sets). There has been substantial debate concerning the appropriate operational definition of training volume within the literature, which has made this a difficult parameter to control in research. A widely accepted definition for this is volume load (VL), which takes into account the total number of performed sets, repetitions, and weight (kg) lifted (i.e. total repetitions [no.] x external load [kg]); however, since most published RE studies for older adults do not include VL as a prescription entity, it is difficult to draw conclusions regarding the dose–response relationship. Therefore, total number of sets performed may be considered an appropriate surrogate index of the absolute volume of physiologic stress, through which RE can be prescribed. Training *frequency* is defined as the occurrence, per unit of time (e.g. calendar week) that a full body RE regimen is completed. In many instances, published interventions that incorporated higher-volume training are partitioned to accommodate greater overall time requirements. As an example, full body training may be divided into two upper- and two lower-body training sessions per week (four total sessions). Thus, even though training has manifested over four days, the frequency of training is two days (i.e. the full body was trained twice, in a given week). *Intensity* of training is commonly defined as the percentage of maximal ability for a given exercise (i.e. 1 RM). Although this operational definition for intensity provides a more objective, quantifiable unit than training fatigue or rating of perceived exertion, current recommendations for older adults still rely on a 0-to-10 RPE for moderate-intensity (5–6 out of 10) and vigorous-intensity (7–8 out of 10) RE [58, 59]. Alternatively, intensity of RE may be modified based on a targeted number of repetitions, or by increasing loading within a prescribed repetition-maximum range (e.g. 8–12 RM) [140]. Since it is often challenging or unsafe to ascertain a true 1 RM among older adults, using these latter methods to assign intensity is likely the most feasible, effective strategy.

Power training

The NSCA Position Statement also recommends power exercises to be performed at higher velocities in concentric movements c [45]. Resistance training performed at

maximal velocity during the concentric phase (i.e. explosive resistance training where muscles exert maximum force in short intervals of time) may promote greater functional improvements than resistance training performed at slower velocities in older adults [146, 147]. This may reflect the ability to perform activities of daily living, which may be more dependent of the capacity to apply force quickly than the capacity to exert maximal strength [148–151]. It may also help with prevention of slip and fall accidents, as power training can improve rate of force development during both concentric and eccentric contractions. Some studies have even shown greater functional enhancements comparing explosive resistance training and traditional resistance training in older adults [146, 147, 152, 153]. In a recent meta-analysis of randomized clinical trials assessing lower-body muscular power (only 1 out of 12 randomized controlled trials [RCTs] included individuals less than 60 years of age), Straight et al. [154] showed that explosive resistance training was more effective than traditional resistance training for increasing lower-body muscular strength and power. One interesting characteristic of explosive resistance training prescription in older adults is that maximal strength and power, as well as muscle size and functional performance enhancements can be achieved at low-to-moderate intensities (i.e. 40–60% of 1 RM) [147, 155].

Flexibility exercises

Flexibility, the ability to move a joint through a complete range of motion (ROM), declines with aging. Depends, mainly, by muscles, tendons, and bones [156]. Limited ROM in the joints, especially hip, knee, and ankle increase the risk of falls and contribute to age-related gait changes that could affect mobility and physical independence [157]. Flexibility or stretching exercise refers to exercise that lengthens muscles to increase a joint's capacity to move through a full ROM. Stretches can be static (assume position, hold stretch, then relax), dynamic (fluid motion [e.g. tai chi]), active (balance while holding stretch, then moving [e.g. yoga]), or a combination (proprioceptive neuromuscular facilitation). Flexibility measurements include flexion and extension movements, but there are no current tests available that can provide representative values of total body flexibility [68].

Balance training

Balance is the ability to maintain the body's center of mass (COM) within the limits of the base of support [68]. Older populations are at high risk for balance problems more often of multifactorial origin: weakness in the core stabilizing muscles, altered muscle activation patterns, loss of proprioception, and an inability to control normal postural control. Joint stability depends on static (bones, capsules, and ligaments) and dynamic (neuromuscular control of the skeletal muscle affecting a joint to maintain its center of rotation in response to perturbation) components [156]. There are different types of balance exercises:

- Progressively difficult postures that gradually reduce the base of support (e.g. two-legged stand, semi tandem stand, tandem stand, one-legged stand).

- Dynamic movements that perturb the center of gravity (e.g. tandem walk, backward walking, sideways walking, heel walking, toe walking circle turns, standing from a sitting position, walking on compliant surface such as foam mattresses, maintaining balance on moving vehicles such as bus or train).
- Stressing postural muscle groups (e.g. heel stands, toe stands).
- Reducing sensory input (e.g. standing with eyes closed).

Multicomponent physical exercise (MPE)

MPE programs include a combination of aerobic, resistance, flexibility, balance exercise, and other types of training (gait, coordination). Recent evidence reported significant effects of MPE programs on all dimensions of sarcopenia in healthy and frail older adults [158]. In view of these evidences, the Belgian Society of Geriatrics and Gerontology recommend MPE therapy to improve muscle mass, muscle strength, and physical performance in older people [125]. There is evidence to demonstrate that MPE may be effective at improving physical and cognitive health in older healthy adults living in the community [159–164]. This type of exercise intervention seems to have a great adherence and satisfaction among elders, and can be incorporated in clinical settings, for and not-for-profit recreational facilities/fitness gyms, and institutional settings.

Other types of exercise

There are some relatively novel training methods that are been testing in different older populations including frail and sarcopenic However, they are presently confined to research or clinical contexts [71].

Blood flow restriction (BFR) is defined as REs with maintaining arterial blood inflow and restricting venous blood outflow of the trained muscle [165]. As a result, this metabolic stress stimulates anabolic signaling pathways. A recent meta-analysis of eight studies reported that the combination of BFR and low-intensity RE is more effective that RE alone in increasing muscle strength in clinical populations at risk of muscle wasting, such as older people [166].

Neuromuscular electrical stimulation (NMES) uses a device that sends electrical impulses to nerves and generates involuntary muscle contractions and is able to stimulate the same signaling pathways as those activated by voluntary exercise. NMES has been recently been used to counteract age-related muscle and functional decline in older people [167].

Vibration is the application, using a vibration platform, of a mechanical oscillation to the whole body or some parts of it, and thus elicits involuntary muscle contractions. This strategy can help to prevent age-related loss of muscular strength in older individuals [168].

EXERCISE INTERVENTIONS AND SARCOPENIA

General recommendations

As a general recommendation, adults should move more and sit less throughout the day. Thus, some PA is better than none. Adults who sit less and do any amount of moderate-to-vigorous PA gain some health benefits [61], Several areas should be emphasized in promoting PA in older adults [58, 59, 65]:

- Consider some issues like personal preferences, cultural norms, exercise history, readiness, motivation, self-discipline, and short- and long-term goals and logistics.
- The plan should be tailored according to chronic conditions and activity limitations, risk for falls, individual abilities, and fitness. Muscle strengthening activities and/or balance training may need to precede aerobic training activities among very frail individuals.
- Identify specific objectives and tasks. Care should be taken to identify, how, when, and where each activity will be performed. For example, "Take a 10-minute walk, three times a day, every day of the week. Choose a speed that allows you to talk but that is moderately hard work. The distance is not important, but make sure to walk for the entire 10 minutes."
- Initiate activity at modest duration and intensity and progress gradually to minimize the risk of injury. Many months of activity at less than recommended levels is appropriate for very deconditioned older adults as they increase activity in a stepwise manner. In addition, activity plans need to be re-evaluated when there are changes in health status.
- Before and after PA there are necessary warm-up and cool-down activities at a slower speed or lower intensity. These exercises allow a gradual increase or decrease in heart rate and breathing. A warm-up with aerobic activity usually consists of short intervals of low-intensity movement (e.g. walking for five minutes).
- Sensory impairments, such as hearing loss, can make it difficult to instruct older adults. Therefore, speaking loudly and slowly, using visual aids, and demonstrating exercises are all techniques that help older adults become active.

Lifestyle modifications

It is extremely important to encourage older adults to do the daily living as active as possible limiting sedentary activities. There are different ways to incorporate physical exercise in the daily routine

- Performing PA accompanied by a friend or relative, as this helps to maintain in the PA program.
- Avoiding watching television for extended periods and instead using some of this time to exercise
- Walking instead of driving when traveling short distances
- Using the stairs instead of the elevator, at least some floors.

- When going shopping, parking the car far from the entrance and walk.
- Getting off the subway or bus some stops before the destination
- Walking through all the aisles at the supermarket or mall
- When taking care of grandchildren, taking them to the park instead of staying inside
- Having some small weights alongside the couch in order to exercise while watching the television
- While waiting in a line, train the equilibrium by standing on one foot at a time.
- Exercising while talking on the phone, for example by walking or performing other leg exercises.
- Activate the step counter of your mobile and try to increase the number of steps every day

Aerobic exercise

The emphasis behind ACSM/AHA recommendations [58, 59] for older adults is centered on general health promotion, and thus the principal suggestions are related to accumulating habitual aerobic PA and exercise. According to these guidelines, older adults are encouraged to accumulate 30–60 minutes of moderate-intensity PA per day (150–300 minutes per week), or at least 20–30 minutes per day (75–150 minutes per week) of vigorous-intensity. Specifically, continuous or intermittent moderate-intensity (40–59% VO_2R or HRR; or 5–6 RPE out of 10) to vigorous-intensity (60–89% VO_2R or HRR; or 7–8 RPE out of 10) AE should be performed with the explicit goals of improved cardiorespiratory fitness. Exercise should be performed at least 3 days/week, but preferably 5 or more, with no more than 2 consecutive days between bouts. Sessions should be a minimum of 10 minutes for intermittent AE and intended to reach energy expenditure goals of a minimum of 100–250 kcal per session. Gradual progression in duration and intensity may be effective for sarcopenic-obese older adults, and/or for further improvement in cardiorespiratory fitness capacity beyond the baseline requirements for health. However, caution is warranted since progressing sedentary older adults too quickly may exacerbate untoward responses such as musculoskeletal injury. Activities such as brisk walking, swimming, and recumbent cycling/stepping are usually well tolerated by older individuals; however, unless otherwise specified by a primary care physician or cardiologist, individuals may also progress to other modalities such as jogging, hiking, rowing, and stair climbing. HIIT can be incorporated one to three times per week to augment the cardiorespiratory effectiveness of light, moderate, and vigorous AE [56].

Resistance exercise (RE)

The current guidelines suggest that for healthy adults older than 60 years of age, resistance training intensity should achieve 70–85% of 1RM during training periodization to optimize strength gains. Changes in muscle morphology and functional performance may also be achieved at low-to-moderate intensities (approximately 50–70% of 1RM). Although periodized and non-periodized resistance training programs may elicit similar

neuromuscular adaptations, lower (or sometimes higher) intensities may be used to vary the training, prevent boredom, and also promote training adaptations in periodized programs as intensity progresses up to 85% of 1 RM [45]. Although there is indeed sufficient evidence to support the short-term efficacy of light- to moderate-intensity RE for strength improvement among older adults [80], there is also ample evidence to confirm the viability of *progressive* RE for improving strength and muscle mass over the long term [145]. As is generally accepted for any novice trainees, prescription of RE should include a "familiarization" period, in which very low dosage training (i.e. minimal sets and intensity) takes place one to two times per week. Following the familiarization, it may be expected that older adults with sarcopenia can benefit from gradual increases in training dosage to accommodate improvements in strength and muscle hypertrophy. Additional suggestions pertaining to progression in RE include (i) gradual increases in intensity from moderate (i.e. 50–70% of 1 RM [12–15 RM]; or 5–6 RPE out of 10) to vigorous (i.e. 70–85% of 1 RM [6-10 RM]; or 7–8 RPE out of 10), (ii) gradual increases in the number of sets from a single set-, to as many as three or four sets per muscle group, (iii) gradual decreases in the number of repetitions performed (i.e. to coincide with progressively heavier loading), from 12–15 repetitions per set, to approximately 6–10 repetitions per set, and (iv) progression in mode from primarily body weight or machine-based RE to machine plus free-weight RE. After general strength and muscular endurance have been established (8–12 weeks), it is recommended that healthy older adults incorporate explosive concentric power with moderate intensities (i.e. 40–60% of 1 RM).

Due to the disproportionate degree of muscle atrophy and strength decline of the lower limb musculature during aging [169], an RE intervention model for positive effects on lower-extremity strength is recommended to provide enhancement of overall functional capacity. Indeed, lower-extremity weakness in older adults is a primary independent contributor to reduced walking speed [170], decreased lower extremity performance and functional impairment [39, 122], falls [171, 172], physical disability [173, 174], and frailty [175]. RE has also been associated with improvements in various cardiometabolic risk factors in the absence of weight loss, including decreased LDL cholesterol [176, 177], decreased triglycerides [176], reductions in blood pressure [134], and increases in high-density lipoprotein (HDL) cholesterol [177]. Several studies have also documented the superiority of RE over traditional AE for glycemic control and insulin sensitivity among type 2 diabetic adults [178]. [179]. In addition, chronic RE improves bone mineral density and decreases abdominal and visceral fat mass [180–184]; in adults with type 2 diabetes, RE reduces hemoglobin A1c (HbA1c) compared to aerobic training [185]. For these reasons, RE is often considered a "medicine" [181, 186]. Therefore, with careful planning, the application of RE among older adults with sarcopenia is not only feasible for eliciting significant adaptation in both force production capacity and muscular hypertrophy but is also effective for reducing risk of many sarcopenia-related comorbidities. Increased public health and clinical efforts are needed to encourage the provision of this mode of PA.

Flexibility

There are a small number of studies that have documented the effects of flexibility exercises in older populations. There is some evidence that flexibility can be increased in the

major joints by these exercises; however, how much and what types of flexibility exercises are most effective have not been completely established [59]. Recommendations states that flexibility exercise should be done at least 2 days per week, 10 minutes per day at a moderate intensity (5-6) on a scale of 0 to 10 and including exercise for the neck, shoulder, elbow, wrist, hip, knee, and ankle [59]. In older populations, duration of stretching longer than usual (30–60 seconds) may get greater improvements in ROM [104].

Balance

Balance training are exercises that help maintain stability during daily activities [61]. There are no specific recommendations regarding specific frequency, intensity, or type of balance exercises for older adults. Preferably, older adults at risk of falls and stability problems should do balance training three or more days a week. The exercises can increase in difficulty by progressing from holding onto a stable support (like furniture) while doing the exercises to doing them without support.

Safety

Many older adults initiating PA fear precipitating a cardiac event or a musculoskeletal injury. Fears can be mitigated with adequate supervision and education. General recommendations for safety, particularly in the initial stages of exercise, have recently been published [61, 187]:

- Choosing types of PA appropriate for each person' current fitness level and health goals.
- Increasing PA gradually over time. "Start low and go slow".
- Performing PA in a safe environment, exercising with another person and carrying a cell phone to facilitate calling for emergency help.
- Wearing proper footwear and clothing
- Ensuring good nutrition and liquid intake and adequate sleep before PA
- Exercise machines have advantages for older, especially frail, as the ROM is easier to control. Chair- and bed-based exercise should be considered as a starting point and used by frail patients

Healthy older adults generally do not need to consult a health-care professional before becoming physically active. However, it is recommended for people with chronic conditions and symptoms to consult a health-care professional or PA specialist about the types and amounts of activity appropriate for them.

There are some absolute contraindications for PA like recent changes in ECG, acute myocardial infarction, unstable angina, uncontrolled arrhythmias, acute heart failure, severe conduction disease, and acute noncardiac diseases that may be exacerbated by exercise (infection, renal failure, thyrotoxicosis).

Many caregivers recommend that an exercise stress test precede exercise activity, especially for sedentary older adults but not all clinicians feel that this is necessary, especially for patients they deem generally stable based on clinical examination.

If an injury occurs, it interrupts activity and resuming at a lower intensity level. Muscle soreness is common and frequently is innocuous and transient and can be modified with reduced training intensity, cold compresses, and sufficient time and patience to allow spontaneous healing to occur.

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CHAPTER 23

Nutritional Approaches to Treat Sarcopenia

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INTRODUCTION – SARCOPENIA ETIOLOGIES AND EFFECT OF NUTRITIONAL INTERVENTION

Sarcopenia is a condition with interacting multiple causes. The classification of sarcopenia into primary and secondary sarcopenia reflects this variation of underlying mechanisms [1]. A prerequisite for planning and providing the optimal treatment is the understanding of the mechanisms in each case. The effect of for example nutritional interventions will largely depend on the etiology of sarcopenia.

Primary sarcopenia is loss of muscle function and mass due to catabolic mechanisms elicited by aging processes *per se* [1]. Increasing age decrease appetite. Some contributing factors to this so-called "anorexia of aging" [2] are changes in smell and taste perception, hormonal balance between hunger and satiety signals (e.g. cholecystokinin and ghrelin), and ventricular distention capacity. Other contributing factors to primary age-related sarcopenia are less or not susceptible to nutritional interventions; e.g. increased apoptosis, reduced excretion of anabolic hormones (e.g. testosterone and estrogens), motor-neuron degradation, and the occurrence of low-grade inflammation (i.e. inflammaging [3]). Secondary sarcopenia, on the other hand, presents when there are obvious other causes for the loss of muscle mass and function [1]. Of specific interest for this chapter is malnutrition-related sarcopenia due to insufficient intake of energy or protein, malabsorption, and anorexia, but also related to obesity, i.e. sarcopenic obesity (see Chapter 12). Other secondary forms of sarcopenia are disease- and inactivity-related sarcopenia not primarily related to nutrition or insufficient

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

dietary intake. Still nutritional therapy could be a worthwhile complement to other adequate means of treatment. For example, to combine protein supplementation with resistance training to combat a sedentary lifestyle or physical inactivity due to other reasons, or to combine energy and protein supplementation with medical efforts and exercise to limit the muscle catabolism that links to inflammatory-driven weight loss during disease-related malnutrition, i.e. cachexia [4].

This chapter will deal with various nutritional approaches that have the potential to affect muscle function and mass, with a focus on protein intake. Current and coming recommendations and the relevant evidence base for such recommendations is presented. Moreover, other potential nutritional treatment options to combat sarcopenia; vitamin D, essential fatty acids, and muscle protective dietary food patterns will be discussed.

DIETARY PROTEIN INTAKE AND MUSCLE ANABOLISM

Myofibrillar proteins, i.e. actin and myosin, build muscle cells. With a turnover (degradation and synthesis) rate of muscle tissue of up to 2% per day the muscle is highly dependent on a continuous supply of amino acids. Not only is the quantity of the intake, but also the quality according to protein source and amino acid composition important for muscle equilibrium or accretion.

Current dietary protein recommendations

The amount of dietary protein needed daily to keep up muscle homeostasis is a controversial subject discussed intensively over years. Questioned by several international expert groups as well as by official dietary guidelines, still the dominating official protein intake recommendation is 0.8 g/kg body weight(BW)/d for adults [5–7]. Some of these recommendations are soon to be updated. The 0.8-g recommendation originates from Institute of Medicine (IOM) 2006 [8], and based on one meta-analysis [9] of 19 short-term nitrogen balance studies. Only one was on subjects older than 65 years [10]. Due to the result of the meta-analysis, the estimated average requirement (EAR) was set to 0.65 g/kg BW/d, and the subsequently recommended dietary allowance (RDA) of 0.83 g/kg BW/d defined to cover minimum daily needs in all (97%) healthy individuals. No discrimination by age was recommended.

Even by using these conservative cut-offs it is estimated that about one-third of adults over the age of 50 fail to meet the RDA for protein while approximately 10% of older women fail to meet even the EAR for protein.

Is there a need for higher protein recommendation in older adults?

Since the beginning of this century, much evidence has mounted to challenge the recommendations from IOM 2006, and several expert groups recommend higher protein intakes.

The international PROT-AGE Study Group suggested in 2013 that people older than 65 need a protein intake at least in the range of 1.0–1.2 g/kg BW/d. Older adults with acute or chronic diseases were advised 1.2–1.5 g/kg BW/d. It was advised that special attention from this rule is needed in subjects with renal insufficiency, i.e. glomerular filtration rate (GFR) <30 ml/min/1.73 m^2 [11].

One year later an international expert group from European Society for Clinical Nutrition and Metabolism (ESPEN) [12] gave support to these recommendations by stating, "Firstly, for healthy older people, the diet should provide at least 1.0 to 1.2 g protein/kg BW/day. Next, for older people who are malnourished or at risk of malnutrition because they have acute or chronic illness, the diet should provide 1.2 to 1.5 g protein/kg BW/d, with even higher intake for individuals with severe illness or injury. Finally, it was stated that all older people, for as long as possible, should undertake daily physical activity or exercise (resistance training, aerobic exercise)."

The official Nordic Nutrition Recommendations 2012 (Nordic Council of Ministers 2015) [13], that gives macronutrient intake recommendations as proportions of total energy intake (E%) stated that for older (>65) healthy adults the protein intake should account for 15–20 E%, with an average of 18 E% [13, 14]. This corresponds to 1.1–1.3 and 1.2 g protein/kg BW/d, respectively. This reflected an increase in the recommendation of 20% as compared with the corresponding recommendations from 2004.

Subsequently, several expert statements have supported a higher recommendation [15–20] although many still find the evidence base to be vague.

WHO has recently published a document "Integrated care for older people, Guidelines on community-level interventions to manage declines in intrinsic capacity" stating ". . .standard protein intake may not be sufficient for older people," but not giving any more detailed intake recommendations [21].

What is the evidence base for a higher protein recommendation?

Sarcopenia is an insidious process with a slow loss of function and muscle mass, finally evolving into sarcopenia in the older individual. Nitrogen balance studies have been considered the "golden standard" for defining protein needs, but such studies are performed over only three to seven days and are likely not able to discern very small negative balances over a long time. During the last decade, an alternative technique for measuring nitrogen balance by stable isotopes developed [22, 17]. Results from the "indicator amino acid oxidation" (IAAO) technique indicate that previous measurements by conventional nitrogen balance techniques have underestimated the requirement by 30–50% [23].

Although experimental studies show that the protein synthesis capacity of muscle is quite similar in older and younger adults [24–27], there are many observations that older people in general need a higher intake of dietary protein to elicit a maximum synthetic response [28, 29]. This "anabolic resistance" [30, 31] is due to the same factors that are involved in the development of primary (age-related) sarcopenia; for example, increased apoptotic activity, dysfunctional autophagy, increased splanchnic extraction of amino acids, and inflammaging.

Whole diet approaches – observational and interventional studies

Due to the slow process of sarcopenia at old age the evidence grade of well-performed long-term prospective observational studies should likely be upgraded, although high-quality randomized controlled trials (RCTs) are of the highest value. Still, such RCTs need to be long enough to overcome the risks of either miss long-term delayed effects of increased protein exposure or showing acute effects that will level off due to metabolic adaptations or changes in dietary preferences.

Several important observational studies have originated from the Health Aging Body Composition (ABC) Study with somewhat contradicting results. One is providing three-year follow-up data on reported protein intake and muscle mass development, measured by dual-energy x-ray absorptiometry (DXA), in older community-dwelling adults indicating favorable protective effects on muscle mass by higher intakes than 0.8 g/kg BW/d [32] in a dose-dependent manner. Interestingly, a more recent publication from this same cohort on a five-year follow-up on protein intake and mid-thigh muscle volume by computed tomography (CT) scan, could not reproduce the data from the report 2008 [33]. Perhaps even more important, due to the recent focus on function rather than mass, a third study has provided protein-favorable six-year follow-up data on the relation between reported protein intake and risk of developing mobility limitations of walking and stair climbing [34].

The branch-chained essential amino acid leucine enhances muscle protein synthesis in experimental models [35, 36]. In a Danish WHO-MONICA cohort, dietary leucine intake was calculated from dietary interviews, and the result was related to lean body mass (LBM) by bioelectrical impedance analysis (BIA) and physical function six years later. In contrast to the younger population (<65 years), who maintained their LBM irrespective of protein or leucine intake, the older subjects (>65 years) were able to maintain their lean body mass if they were in the highest quartile of leucine intake (7.1 g/d). High leucine intake linked to the highest total protein intake (1.26 g/kg BW/d) [37]. Long-term prospective studies are mainly of interest for understanding the preventive value of certain nutrients in the whole diet.

Smaller short-term RCTs have indicated that maintenance of 0.8 g protein/kg BW/d leads to decreased thigh muscle volume and decreased urinary nitrogen excretion in older subjects [38].

Animal or vegetable protein sources

Animal products provide a greater per gram quantity and quality of protein compared with plant-based sources. However, plant-based diets are also well equipped to meet protein requirements for essential amino acids, but meal size needs to enlarge. Plant-based diets also provide a mix of other potentially muscle protective nutrients (see below about dietary patterns), not found in animal-based diets.

Figure 23.1 provides data on the protein content of some general foods. Differences in the ability of different protein sources to promote muscle protein synthesis are typically attributed to two key factors, i.e. amino acid composition of the protein, and the digestion and absorption kinetics.

Food 100 g	Protein (g)
Lean beef	25
Chicken breast	25
Salmon	22
Tuna in water	24
Milk (1%)	3
Yoghurt (low fat)	5
Hard cheese	25
Eggs (one egg)	7
Peanuts	26
Almonds	20
Nuts (various)	13–20
Soybeans (cooked)	11
Lentils (cooked)	9
White beans (cooked)	7
Green peas (cooked)	5
Quinoa	5
Pasta	3–11
Rice (cooked)	3
Potatoes	3
Avocado	2
Banana	1

Figure 23.1 Protein content in various foods.

Protein supplementation studies – whole protein approach

When sarcopenia has already developed, as in the very old community-dwelling individual, chronically ill, or nursing home resident, liquid protein supplementation is usually the major tool for enhancing the protein intake. Although there are many clinical protein supplementation studies from such settings, only few are in populations identified as sarcopenic according to the most recent definitions. Still it is of interest to review the important intervention studies targeting muscle effects in general.

One meta-analysis [39] summarized 36 RCTs of altogether close to 4000 patients (one-third had had a hip fracture, average treatment period of three months), and evaluated multiple effects of high protein oral nutritional supplementation (>20 E% from protein). Of sarcopenia relevance was improved handgrip strength, together with reduced complications and re-admissions. Most of the included studies provided whole proteins without particular emphasis on protein quality or amino acid distribution.

Two Dutch studies in older frail adults reported that 30 g of concentrated milk protein alone for six months improved leg strength and short physical performance

battery (SPPB), a combination of gait speed, chair-stand capacity, and balance [40]. The same protein supplementation combined with exercise did not enhance the exercise induced improved leg strength, but it resulted in a clinically relevant gain of muscle mass [41].

A Korean RCT [42] in 120 frail or pre-frail [43] older subjects tested the effects of supplemental protein powder to increase protein intake from 0.8 g/kg BW/d (placebo) to either 1.2 or 1.5 g/kg BW/d, respectively. After three months the highest intake, i.e. 1.5 but not 1.2 g/kg BW/d, were associated with increased appendicular skeletal muscle mass and improved gait speed.

Protein supplementation studies – fast and slow proteins, essential amino acids, leucine, hydroxyl methylbutyrate

The rate of muscle protein synthesis in the muscle, especially the acute response, clearly varies with the kind and quality of protein exposing the muscle.

Kinetics of dietary protein digestion and absorption varies, and the speed of this process may influence postprandial amino acid availability and the protein synthesis response in muscle. Thus, dietary proteins classify as *"fast"* or *"slow" proteins* [44]. "Fast" digestive proteins, e.g. whey give a faster and stronger stimulation of muscle protein synthesis when compared with "slow" proteins, e.g. casein [45]. Supplements with whey protein and essential amino acid mixtures appear in the plasma within 15 minutes of ingestion and denote as "fast" proteins. Conversely, proteins from most regular food sources (e.g. beef, chicken, dairy products) take considerably longer to appear and considered "slow" proteins. Fast proteins may improve muscle function in older patients and contribute to limit "anabolic resistance" of aging [46].

The *essential amino acid* (EAA) content and composition of a protein is perhaps the most important determinant of its anabolic potential. EAA are especially effective in providing a strong acute protein synthesis response [47]. But, does this translate into similar effects in the clinical long-term situation? One clinical study randomized older patients that underwent knee arthroplasty to 20 g of EAA or placebo for six weeks post-operatively. Interestingly, EAA protected lean mass, quadriceps strength as well as mobility, i.e. timed-up-and-go (TUG) test [48].

Leucine, which is a branch chained EAA, has particular protein synthesis augmenting effects also shown in experimental studies [35, 49]. Again, the question is whether such short-term observations translates into long-term efficacy. The outcome of clinical leucine studies is not unanimous but appears under certain prerequisites to be an important additive to nutritional approaches.

The PROVIDE Study provides some support for this statement. In a three-month study close to 400 sarcopenic mostly community-dwelling older adults were randomized to a leucine, vitamin D- and protein-enriched liquid supplement or an isocaloric placebo. Although the primary outcomes of SPPB and handgrip strength were negative, the secondary outcomes of chair-stand capacity and appendicular muscle mass came out in favor of the active treatment [50]. As for most nutritional intervention studies it is difficult to clearly say which of the provided nutrients that were responsible for the effect (or if it was a combined effect).

Hydroxy methylbutyrate (HMB) is an active metabolite of leucine with similar anabolic effects as leucine. HMB is hypothesized to be even more effective than leucine in the clinical context [51–53]. In a similar study to the PROVIDE study, 330 sarcopenic and malnourished older people were randomized to two energy-rich (iso-caloric) high-protein oral nutrition support (ONS) (28 and 40 g of protein, respectively) with and without HMB. Six months later, both groups improved their leg and handgrip strength. There were some additive effects attributed to HMB for leg strength in the subgroup with mild–moderate sarcopenia [54].

Do all older than 65 years benefit from higher protein intake?

In this era of improving health and function among older people, in parallel with the global obesity epidemic also affecting the older population, it might be questionable to give the same protein recommendation to everybody beyond 65 years of age.

A study in overweight non-sarcopenic American healthy males older than 65 years with mobility impairments, and protein intakes below the RDA of 0.8 g/kg BW/d, may cast light on this issue [55]. The study tested, among other hypotheses, two levels of protein intake (0.8 vs. 1.3 g/kg BW/d) on muscle mass and strength over six months. The body weight among the participants averaged 92 kg (BMI approximately 30 kg/m^2). Subsequently the "low" protein intake group ingested a quite high absolute protein intake, amounting to 74 g of protein (equal to daily beef intake of 340 g). Accordingly, the "high" protein intake group took 120 g of protein per day (corresponding to 540 g of beef). There were no differences in muscle mass or strength after six months according to protein intake. Perhaps this outcome reflected the fact that in sufficient ranges of absolute protein intake, a further increase does not augment protein synthesis in healthy moderately old adults. A previous experimental study in young and old subjects showed that a single "moderate" serving of 113 g of beef (equal to 30 g of protein) was equally effective in eliciting a protein synthesis response as a larger serving of 340 g of beef (90 g of protein) [56].

Lessons learned from this [55] and other studies are that protein recommendations, beyond age and protein intake, may also consider weight, muscle, and health status.

Absolute or proportional protein intake recommendations?

In 2006, IOM [8] suggested to use an Acceptable Macronutrient Distribution Range (AMDR) given as energy percent (E%) of the total energy intake. IOM stated in 2006 that the AMDR for proteins could be 10–35 E% which in contrast to the RDA of 0.8 g/kg BW/d provides a much broader recommendation, permitting a greater flexibility with meal planning and consideration of individual needs. The practicability of this AMDR (10–35 E%) is limited by the generous quantity of protein accepted by the upper end of the range (up to 2.5 g/kg BW/d in older populations). With a narrower range, protein recommendations by an AMDR of for example 10–20 E% (like suggested in the NNR2012 [13]) could provide more flexibility. Moreover, the protein recommendation would relate to desirable physical activity levels (PAL) and energy intakes, and sex, rather than to the actual body weight only. Thus, an AMDR model may moderate high protein intake recommendations for overweight and obese populations.

COMBINING PROTEIN SUPPLEMENTATION WITH EXERCISE

Resistance exercise is the key treatment to combat sarcopenia across all ages and clinical conditions [57–59]. A Cochrane systematic review in 2009 covering 121 studies of resistance exercise clearly confirm beneficial effects on muscle strength [60] in older adults.

Intuitively, the combination of resistance exercise with protein supplementation appears logical. Still it has to be accounted that the anabolic signal of resistance training is strong. Consequently, many studies indicate that addition of extra proteins not always add beneficial effects. The overall data indicate that addition of proteins is mainly effective when the habitual protein intake and amino acid exposure to muscle is insufficient, and when the recipient is sarcopenic or undernourished.

For older people who are sarcopenic or at risk of becoming sarcopenic it is safe to recommend a combination of resistance training and additional proteins. For this matter, timing of the protein intake could be important (see Section "TIMING OF PROTEIN CONSUMPTION").

What is the evidence base for combining exercise and protein supplementation?

A meta-analysis in 2012 [61] summarized 22 RCTs of combined exercise and protein supplementation. Both young and old study populations were included. Studies were selected to provide exercise to all participants and protein ONS versus placebo was randomized. The protein supplementation added (in both young and old) a significant increase in fat-free mass (FFM) and improved quadriceps strength.

Sarcopenic older Japanese women were randomized to resistance exercise (two times per week) alone or in combination with EAA supplementation, EAA supplementation alone or to a fourth group that was provided health education. Three months later walking speed had improved in all three intervention groups, leg muscle mass in the exercise only and the combined exercise and EAA groups, while knee extension strength improved only in the combined exercise and EAA group [62].

Another positive study on combining exercise and nutrition also selected only sarcopenic old (80 years) adults [63]. Exercise for 20 minutes five times per week was prescribed to all and a combination of whey protein, EAA, leucine, and vitamin D versus placebo was randomly allocated. Twelve weeks later FFM had increased by 1.6 kg and handgrip strength by 3.7 kg in the intervention group compared with the placebo. A small study in post-stroke patients with sarcopenia, indicated as well that adding a leucine-rich supplementation to low-intensity resistance training increased muscle mass, handgrip strength and, the functional independence measure (FIM) score [64]. Two other Japanese RCTs over 8 and 12 weeks, respectively, in sarcopenic older adults, reported beneficial effects of leucine or protein supplementation, respectively, combined with resistance training on handgrip strength, muscle mass and knee extension [65, 66]. Whey supplementation and resistance exercise in combination with exercise over 14 weeks in frail elderly improved handgrip strength and TUG, with no additional effect by creatine supplement [67].

As hinted, not all studies show beneficial effects of protein supplementation when added to exercise. This was, for example, the case in one Dutch study of healthy non-sarcopenic old men doing resistance exercise over 12 weeks randomized to receive 20 g of proteins after each session three times per week [68]. The VIVE2 study from the United States and Sweden, prescribed for half a year exercise three times per week, with a randomly allocated high-protein, high-leucine, and high-vitamin D supplement to mobility-limited, but not undernourished or sarcopenic older subjects [69]. There were small positive effects on 400-m walk test and quadriceps strength, with no added effect of the supplementation (except reduced intramuscular fat accretion [70]).

TIMING OF PROTEIN CONSUMPTION

Two aspects of timing of the protein intake will be discussed: i.e. distribution of the dietary intake over the day and intake in relation to exercise.

It is unresolved if an even distribution of protein over the three main meals daily is promoting muscle accretion and function. Still, it is advisable to ensure a high-protein content of all meals in order to reach the recommended levels. Resistance exercise facilitates protein synthesis; however, this window is open for quite a long time. Still, it appears wise to ensure a high amino acid exposure to the muscle by a protein intake in timely conjunction with the exercise session.

Distribution of protein intake over the day

Many individuals consume the majority of their daily protein during one of the daily meals, i.e. lunch or dinner [71]. Meal distribution data from NHANES indicate that average protein intakes are about 15, 15, and 30 g during breakfast, lunch, and dinner, respectively. Experimental studies point to a requirement of dietary intake of 25–30 g of proteins (8–10 g of EAA) for a maximum protein synthesis response [25, 72]. A Canadian 3-year observational study in >1500 older adults reported that a more even distributed protein intake was associated with a greater strength (handgrip and leg) but not with mobility (e.g. TUG and gait speed) [73].

Consequently, some suggest evenly distributed protein intakes of at least 25–30 g per meal, to enable an optimal muscle protein synthesis. Stronger interventional data supporting this suggestion is still missing, and there are reports that contradict the relevance of evenly distributing the protein intake [74].

Timing of protein ingestion with exercise

During resistance exercise the protein synthesis in the muscle is limited, but within an hour restored and increased during a period of up to 48 hours [75–77]. It is advisable to ensure amino acid exposure to the muscle when exercise facilitates protein synthesis [78].

Fast proteins, i.e. whey and EAA solutions, appear in the circulation about 15 minutes post ingestion and accordingly they should be administered in close proximity to the exercise session. Conversely, proteins from regular foods like beef, chicken or dairy products take longer to appear and for this particular reason they should be ingested 60–90 minutes before the exercise session.

OTHER NUTRITIONAL APPROACHES

Vitamin D and sarcopenia

The role of vitamin D for muscle performance in older people is elusive. Muscle cells express abundant vitamin D receptors (VDR). Early observations show that severe vitamin D deficiency goes with myopathies that respond to vitamin D therapy [79, 80]. Experimental studies show that exposure of vitamin D to muscle cells affect VDR gene expression and other cellular functions [80]. In short-term smaller intervention studies, vitamin D improves muscle fiber area [81]. A much-cited meta-analysis [82] indicated that vitamin D supplementation prevented falls in older individuals. Several RCTs evaluating vitamin D effects on muscle mass and function has been performed and subjected to repeated meta-analyses.

Due to the current knowledge, it appears safe to recommend vitamin D supplementation in medium daily or weekly doses to older people under certain circumstances. Correct manifest hypovitaminosis. Vitamin D concentrations should at least be kept above 20 ng/l, equal to 50 nmol/l. Older subjects with sarcopenia or at risk of sarcopenia are usually also at risk of osteoporosis, as well as of vitamin D deficiency, which increases the safety of prescribing vitamin D. For treatment of sarcopenia combine vitamin D with protein supplementation (and exercise).

What is the evidence base for vitamin D recommendations?

Since 2011 at least three larger meta-analyses have been published [83–85]. The reports present different major outcome measures. Stockton and co-workers [83] combined 17 RCTs of adults >18 years. Altogether, the intervention provided no effects on handgrip or lower limb strength. However, two studies in vitamin D–depleted participants (25(hydroxi)vitamin D [25(OH)D] <25 nmol/l) indicated improved hip muscle strength by the supplementation. The meta-analysis by Beaudart and co-workers [84] compiling 30 RCTs could detect a small positive effect on global muscle strength by the vitamin D supplementation. Supporting the previous meta-analysis, results were stronger in older subjects with low 25(OH)D values (<30 nmol/l). The third meta-analysis [85] combined 15 RCTs with handgrip strength or TUG test as outcome variables. There were no effects on any of the two outcomes.

A recent RCT selected community-dwelling men and women over 60 years with 25(OH)D<20 ng/ml (equal to <50 nmol/l), and supplemented vitamin D to reach levels of >32 ng/l within a year. The intervention did not affect lower-extremity power, strength or lean mass [86]. Six months of vitamin D supplementation to frail or

prefrail adults >65 years with baseline serum concentrations of 20–50 nmol/l did not change muscle mass or physical performance [87]. Likewise, high monthly doses of vitamin D to 380 older adults >70 years for one year did not affect handgrip strength or TUG test [88]. In contrast to these negative studies, a Japanese study in community-dwelling older adults on the combination of daily resistance exercises and 1000 IU vitamin D/day showed that exercise and vitamin supplementation improved physical function, including lower limb muscle strength, separately, but the combined treatment was most effective [89].

Essential fatty acids

The polyunsaturated fatty acids (PUFA): i.e. omega-3 FA found mainly in marine and green leaf foods, and omega-6 FAs that are mainly of non-tropical vegetable origin, are essential in the sense that they are necessary for survival, and we have to eat them to cover our needs. Among many capacities, these FAs enter the cell nucleus and affect gene expression relevant for muscle protein synthesis [90]. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have gained most interest.

The 1990s saw several reports on positive effects by EPA administration on muscle mass in patients with cancer cachexia [91]. These observations paved the way for a large RCT with 2 g of EPA randomly allocated to 200 patients with weight losing pancreatic cancer [92]. ITT analyses could not show any effects on muscle mass. However, EPA levels increased also in the controls, and per-protocol and post-hoc analyses indicated positive effects on LBM by the EPA supplementation. Temporarily, the interest for omega-3 FAs and muscle in cancer declined. However, a recent report of six RCTS (2009–2014) on omega-3 FA therapy to patients with various malignancies show general increases in LBM after one to two months of treatment [93].

Whether omega-3 FA supplementation is effective to prevent or combat sarcopenia of old age is unresolved. A 6-month RCT in a small group of older healthy adults provided 3 g of EPA or placebo, and reported improvements in thigh volume and handgrip strength [94]. In contrast, the bigger French MAPT trial concluded "low-dose omega-3 supplementation, either alone or in combination with a multi-domain lifestyle intervention, had no significant effect on muscle strength over three years in elderly people" [95]. This negative report is in line with the randomized addition of omega-3 FAs to resistance exercise for three months to healthy older men that did not have any effects on either performance or expression of inflammatory cytokines [96].

Dietary patterns

Food is a mixture of hundreds of nutrients and chemical substances that have a plethora of functions alone and in combination. In contrast to pharmacological substances, it is seldom useful to evaluate nutrient effects separately, since they mostly interact in networks. Medicine practices tend to assess nutrients as pharmacological substances, and therefore may dismiss potential nutrient effects when efficacy of each nutrient separately is not scientifically proved. The concept of food patterns acknowledges that interactions of nutrients combined may have physiological effects.

Fortunately, the literature indicates that food patterns that are good for health in general are also good for muscles. Plant-based diets, founded mainly on vegetables and fruits, combined with unsaturated non-tropical vegetable oils, fish, and poultry (i.e. like traditional Mediterranean dietary pattern) appear to be best for long-term muscle function.

What is the evidence base for plant-based diets and muscle fitness?

Health effects by food and food modifications usually take long time to appear. Consequently, well-performed long-term observational studies are reliable sources of evidence. There is a scarcity of long-term RCTs on healthy diets and sarcopenia outcomes. The major diet studied is the traditional Mediterranean diet and the compliance is usually assessed according to the Mediterranean Diet Score (MDS) ranging from 0 to 8 points [97].

MDS calculated from food frequency questionnaires (FFQ) in a cohort of 690 community-dwelling persons (>65 years) in Tuscany, i.e. the InChianti Study, was inversely related to the development of frailty within six years. Frailty was diagnosed as at least two of poor muscle strength, exhaustion, low gait speed, and low physical activity [98]. A similar Spanish 3-year observational study in 1800 older subjects indicated that the risk of becoming frail halved by high adherence to Mediterranean diet [99]. A Swedish study [100] in 87-year-old men reports inverse relationship between development of sarcopenia [101] and MDS calculated at the age of 71 years. Crude odds ratio (OR) 0.68, 95% confidence interval (CI) 0.46–0.99 for each standard deviation (SD) increment of MDS. An extensive review [102] summarized previous reviews, and reported benefits of Mediterranean diet on muscle function in general as well as in the lower extremities.

Accordingly, one 3-year follow-up in >700 British older adults identified three dietary patterns; the "traditional British" rich in butter, red meat, and potatoes was associated with a doubled risk of developing sarcopenia ("even when overall protein intake was good") [103].

STATE OF THE ART

Summary of nutritional approaches to prevent and treat sarcopenia in older (i.e. >70 years of age) adults:

- Provide 1–1.5 g of protein/kg BW/d; i.e. 15–20 E% of total daily energy intake, from protein, depending on status of health, nutrition and muscle.
- Animal protein sources provide protein of high quality according to EAA distribution, but vegetable protein sources provide, beyond proteins, fiber, good fat quality, and antioxidants.
- Protein supplementation provides high amounts of EAA.
- Leucine or HMB enrichment could be considered to further stimulate protein synthesis, especially in sarcopenic or undernourished older individuals

- Consider combining resistance exercise with protein supplementation, especially in sarcopenic or undernourished subjects. Supplementation probably does not provide any extra benefit beyond the exercise in healthy well-nourished elderly.
- Consider spreading protein intake over the three daily meals, according to some experimental and epidemiologic evidence.
- Resistance exercise facilitate protein synthesis. Ensure sufficient protein administration in conjunction with exercise.
- Whey and protein supplementation are fast proteins that appear in the circulation within 15 minutes.
- Supplement with vitamin D daily or weekly if serum concentrations are low.
- The role of essential fatty acids, in particular omega-3 FA (EPA and DHA), for muscle health is still unclear.
- In a lifetime perspective healthy diets, like the traditional Mediterranean diet, which is plant-based (high in legumes, vegetables, fruits, whole-grain cereals), predominance of unsaturated fat/oil, and moderate in meat and dairy products, appears to be good for prevention of sarcopenia.

FUTURE PERSPECTIVES

- Continuous research fine-tunes the increased protein intake recommendations that likely will be accepted by official regulatory bodies as European Food Safety Authority (EFSA), US Food and Drug Administration (FDA), and World Health Organization (WHO).
- It will clear who benefits most from higher doses of protein as the response likely depends on both biological and chronological age.
- The knowledge on microbiota and muscle interactions will increase; the role for dysbiosis in low-grade systemic inflammation and muscle catabolism will clear. Pro- and prebiotics may take its place in the preventive/treatment arsenal.
- Which components of healthy diets, such as vegetables, fatty acid sources, vitamins, minerals, antioxidants, and much more that contribute to overall as well as muscle health will appear.

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CHAPTER 24

Beta-hydroxy-beta-methylbutyrate (HMB) and Sarcopenia

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INTRODUCTION

Beta-hydroxy-beta-methylbutyrate (HMB) is an active metabolite of leucine, a branched-chain essential amino acid entirely derived from food sources, and it has been studied for many decades (Figure 24.1). HMB per se is present in very small amounts of some foods, such as cauliflower, citrus fruit, avocado, and catfish. HMB is synthesized from leucine in two separate steps occurring in liver and muscle cell [1]. At muscle cells level, leucine has an explicit role in controlling and at the same time regulating protein synthesis, and HMB has an important role as a key active metabolite in this process. Nevertheless, only approximately 5% of leucine that we can eat with the usual diet is converted to HMB, which, in a subject weighing 70–80 kg, ends in the production of 0.2–0.4 g of HMB per day [2].

The HMB supplementation has been generally used as ergogenic supplement usually combined with exercise training. In the past, bodybuilders and athletes have used HMB supplementation to build muscle mass and to increase performance, as it is usually available as nutritional supplement in the form of calcium salt CaHMB monohydrate. Recent studies have conducted to better understand the role of HMB supplementation to preserve or rebuild muscle mass in subjects at risk and/or affected by sarcopenia, mainly the older people in community and in different health-care settings (acute hospital, rehabilitation unit, long-term care). The HMB use in older subjects has gained in interest to reduce sarcopenia and increase muscle function. Some

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

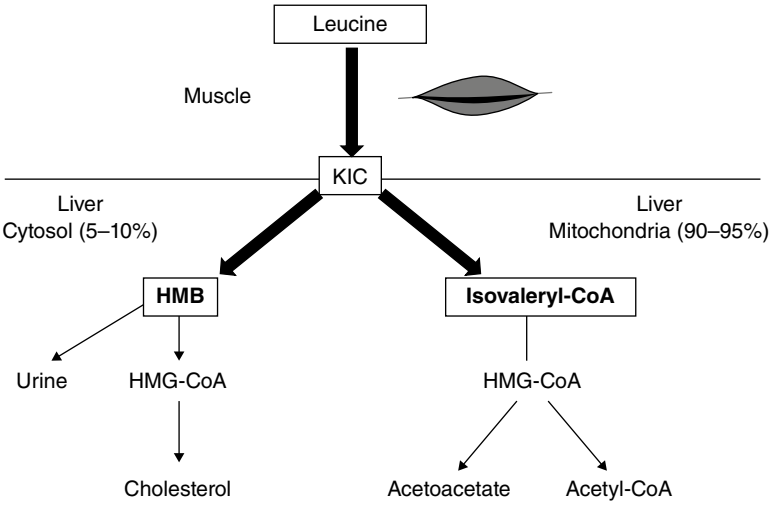

Figure 24.1 Metabolism of beta-hydroxy-beta-methylbutyrate (HMB) in the body.

studies showed the positive effects of HMB supplementation, alone or in combination with other micro- and macronutrients and exercise program, for maintaining and improving lean body mass, muscle strength, and physical performance [3].

BIOLOGICAL ACTIVITY OF HMB ON MUSCLE CELLS

The HMB has important effects (Figure 24.2) in enhancing myofibrillar protein synthesis via the mammalian target of rapamycin (mTOR) pathway and the growth hormone/IGF-1axis, and in avoiding muscle protein breakdown via the ubiquitin proteasome and the autophagy–lysosome systems [4]. Overall, HMB has been demonstrated to stabilize the muscle cell membrane, downregulate the protein degradation, and upregulate the protein synthesis [5].

The HMB increases protein synthesis directly by activating mTOR, the intracellular protein that controls protein synthesis and its effects are boosted by IGF-1. In this way, HMB may help overcome the age-related reduction in tissue response to endogenous growth hormones, such as IGF-1 that contributes to sarcopenia [6].

On the other hand, the HMB hampers muscle cell inflammation pathways reducing the protein degradation process. In particular, the HMB hinders the stimulation of caspase-8, thus inhibiting the downregulation of protein synthesis and increasing the inhibition of protein breakdown started by nuclear factor kappa B (NFκB). Hence, HMB preserves protein synthesis and counteracts additional protein degradation [3].

Muscle protein synthesis rates are regulated largely by anabolic stimuli, such as exercise, physical activity, and specific foods. Proteins from usual diet and/or specific nutritional supplementation, such as HMB, increase muscle protein synthesis rates and are also able to prevent protein breakdown, thus improving the net muscle

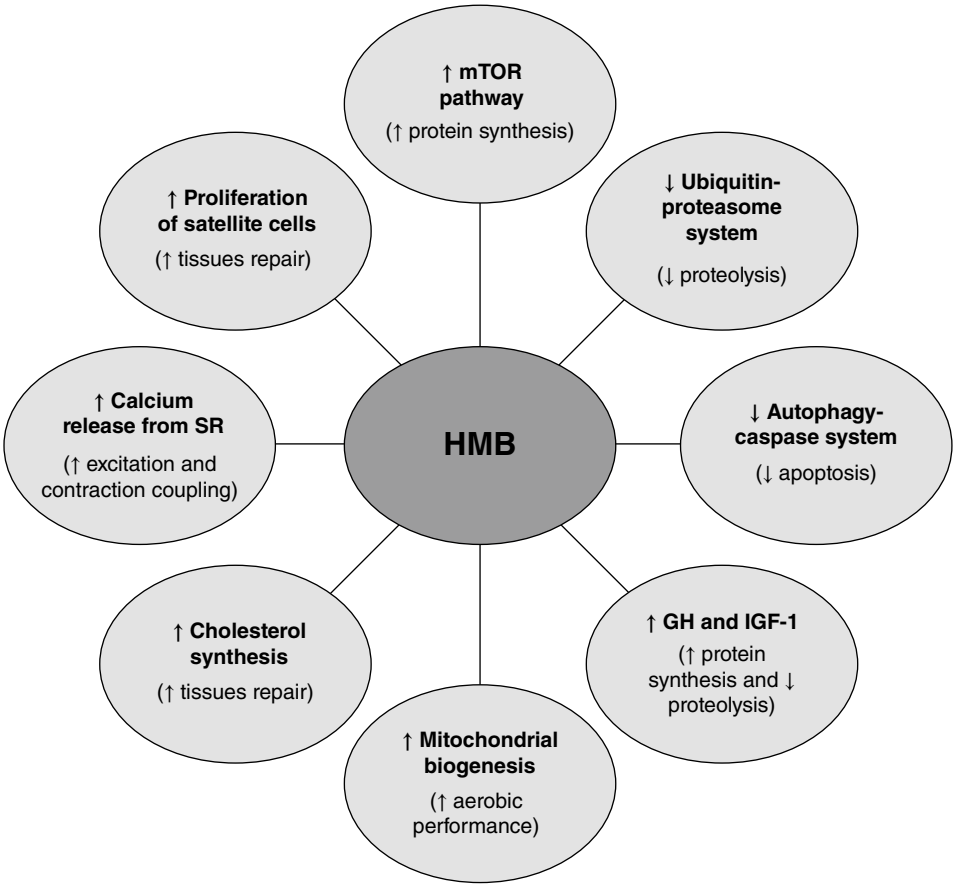

Figure 24.2 An overview of potential pathways of beta-hydroxy-beta-methylbutyrate (HMB).

protein buildup. It is clearly demonstrated that aging process per se has no negative influence on the skeletal muscle protein breakdown rates, autophagy, or the ubiquitin proteasome system [7, 8]. Therefore, targeting the muscle protein synthesis process may hold potential benefits in the preservation of muscle health during the aging process. In fact, even though during the aging process muscle cells have a low rate of anabolic response, higher protein intake (for example, 10–15 g, with at least 3 g of leucine) is able to overwhelmed this anabolic resistance and at the same time to stimulate a protein synthesis response similar to that observed in younger subjects [9].

HMB IN THE DAILY DIET

Recent findings suggested that 2.4 g of HMB per day are useful for the muscle health [10]. Nevertheless, this amount is difficult to obtain from the diet, considering the low quantities of HMB in foods and the low rate of conversion of leucine into

HMB [11]. In addition, the quantity of leucine available from the usual diet is usually insufficient. For healthy subjects to produce 2.4 g of HMB per day (the equivalent of 3 g CaHMB), it is estimated that 60 g of leucine would need to be consumed, which is really hard to reach every day, even for a young individual [12]. According to the USDA Food Composition Databases, black beans are one of the best sources of leucine (~1.7 g of leucine in 100 g of beans), hence an intake of approximately 3.5 kg of beans should be required to obtain 60 g of leucine, which would be really difficult. This means that even consuming high-leucine food sources, such as dairy, meat, eggs, the amount needed to reach 2.4 g of HMB per day is beyond that consumed in a common daily diet. For this reason, the HMB supplementation is an alternative, and may be helpful mainly for persons with or at risk of sarcopenia, such as older subjects or those with disease-related muscle mass and quality problems [3].

HMB INTERVENTION STUDIES IN OLDER ADULTS AND IN DISEASE CONDITIONS

During the last three decades, many studies have documented the effects of HMB supplementation on body composition, muscle mass and strength, and physical performance in adult and older subjects. Since 1990 there have been more than 100 publications on using HMB alone or in combination with other micro and macronutrients, of which some studies were conducted in healthy older people and others included specific clinical conditions [3, 5, 13]. In addition to research studies, many systematic reviews, meta-analyses, and position papers have been published so far [14]. The dose of HMB supplemented into the active groups was usually 3 g per day and most researchers considered it as the optimal dosage. Limited studies tested lower or higher doses (from 2 to 6 g), showing that especially higher doses per day did not make any difference [15].

The review papers highlight the possible relationship between HMB supplementation and specific domains related with the maintenance of muscle mass, strength, and function in older subjects. Nevertheless, the researches conducted so far have some important limitations, comprising sometime the low number of subjects per study group, the heterogeneity of study designs, methodologies, and outcomes. Furthermore, the combination of HMB with other amino acids or nutritional supplements (such as vitamins) limits the ability to determine the direct effect of HMB alone or its positive effect in particular preparations. In this respect, it is critical to underline that nutrition needs to be considered a multimodal intervention that should regularly incorporate other healthy lifestyle factors, such as exercise and healthy diet. Studying the different nutritional intervention, it is always problematic to elucidate the influence of single elements in nutritional formulations. This is because an extensive variety of factors are correlated to the positive results, and combinations of different components may also change these effects. It is usually expected that the positive effects of specific ingredients in nutritional formulations be better obtained as a full product rather than any single element alone [3, 5].

Overall, combined nutritional intervention including supplementation with HMB, vitamin D, and calcium can produce weight gain, decrease physical functional impairments,

and decrease the number of falls, as well as the length of hospital stays, and the incidence of clinical adverse events, which has significant cost implications [11].

HMB in bed rest subjects

Bed rest is one of the most important causes of muscle mass loss in older subjects, especially during the hospital stay. The loss of muscle mass and strength is also correlated with the loss of physical functional capacity after hospital discharge. Deutz and colleagues [16] conducted a randomized controlled trial documenting the positive effect of HMB supplementation in the prevention of muscle loss among 20 healthy women forced in bed rest for 24 hours per day for a period of 10 days. Subjects in the active group received HMB supplementation (3 g per day) starting 5 days before and for all the period in the bed rest, while subjects in the control group received only placebo. At the end of the 10 days in bed rest, participants in the control group showed a meaningful decline in total lean body mass (assessed by dual-energy X-ray absorptiometry [DXA]) of 2.05 kg (−4.9% from baseline value), while those participants treated with HMB supplementation did not suffer significant change (loss of 0.17 kg of lean body mass, −0.04% from baseline value). These findings clearly demonstrate that in healthy older individuals, the HMB supplementation may preserve muscle mass during a long period of bed rest [16]. Even though these results are positive, they need to be confirmed in larger sample and in not experimental setting.

HMB in acute care patients

The HMB supplementation has been extensively studied in hospitalized subjects, highlighting important positive effects in terms of mortality and morbidity. The NOURISH (Nutrition Effect on Unplanned Readmissions and Survival in Hospitalized Patients) [17] study was one of the most important trials utilizing a specialized oral nutritional supplement conducted so far. The study evaluated the effects of nutritional intervention comprising a specific nutritional supplement – 350 kcal, 20 g protein, 1.5 g CaHMB, 11 g fat, 44 g carbohydrate, together with other essential micronutrients – on the incidence of hospital readmission, nutritional status, and mortality among older, malnourished, hospitalized older subjects versus a placebo oral supplement with only vitamin C and carbohydrates. In particular, the primary outcome was the incidence of nonelective readmission within 90 days after discharge and the primary efficacy endpoint was the composite event of death or nonelective readmission within 90 days after discharge. Hospitalized patients were randomized to receive the HMB nutritional supplement or the placebo plus each individual hospital's standard nutritional care (control group). Patients included in the study (n = 622) were 65 years of age and older with primary diagnosis of congestive heart failure, acute myocardial infarction, pneumonia, or COPD and with malnutrition status as assessed by the Subjective Global Assessment (SGA) tool. Although there was no significant difference between groups for the primary composite endpoint, the 90-day mortality rate was significantly lower with the supplement containing HMB, compared with the control supplement (4.8% vs. 9.7%; P = 0.018) [17].

Positive modifications were detected in nutritional status, too; the subjects receiving the HMB supplement showed higher probabilities of reaching a better nutritional status after 90 days from hospital discharge (OR 2.04, 95% CI 1.28–3.25; $P < 0.01$). Similarly, handgrip strength was significantly higher in the active group supplemented with HMB versus the control group ($P = 0.03$). After 90 days, there was a significant positive correlation between handgrip strength and nutritional status; 49% of subjects with improved muscle strength had a better nutritional status compared with 31% with unchanged or declined handgrip strength ($P = 0.003$). Overall, this study clearly showed that high-protein and HMB supplementation reduced post-discharge mortality and improved nutritional status, handgrip strength, dietary intake, and nutritional markers compared with the placebo or the standard of care [17].

An economic analysis of the NOURISH trial used study data on resource use and subject-reported health-related quality of life to evaluate the cost-effectiveness of the study product. Study authors estimated a cost-effectiveness ratio of $33 818 per QALY in the 90 days horizon of the study, which is well below the standard threshold of $50 000 per QALY (suggesting cost-effectiveness). When the time horizon was extended to the remaining life of the patient, the cost-effectiveness ratio fell to less than $1000 per QALY. This study demonstrated that HMB supplementation was highly cost-effective relative to the standard of care.

The HMB supplementation has been demonstrated to reduce immobilization and hospitalization in orthopedic patients with malnutrition through an improvement in wound healing, muscle mass, and muscle strength. Ekinci and colleagues [18] investigated the effects of such supplementation (enteral product containing 3 g of HMB, 36 g protein, minerals, and vitamins) among older female patients with a hip fracture on wound healing, bed rest period, muscle strength, and some biomarkers parameters. The control group received only standard postoperative nutrition. Wound-healing period was significantly shorter in the supplemented group than in the control group. At the same time, the number of subjects in the supplemented group who were mobile on days 15 and 30 (81.3%) was significantly higher than patients in the control group (26.7%) ($P = 0.001$). Finally, muscle strength after one month was significantly higher in the supplemented group with HMB compared with the control group. The study concluded that supplementation with HMB and proteins led to acceleration of wound healing, shortening of bed rest period, and increased muscle strength without changing body mass index in older subjects with hip fracture [18].

HMB in post-acute patients

Olveira and colleagues [19] assessed the effect of Pulmonary Rehabilitation for 12 weeks in normally nourished non-cystic-fibrosis bronchiectasis patients compared with the effect of rehabilitation program plus HMB supplementation on body composition, muscle strength, quality of life, and serum biomarkers. Subjects were randomly assigned to receive only rehabilitation for 12 weeks or rehabilitation plus HBM supplement. Thirty patients were randomized (15 per each group) without differences in clinical and respiratory variables. In the group receiving the specialized nutritional supplement with HMB, bone mineral density, mean and maximum handgrip dynamometry, mid-arm muscle circumference (MAMC), and prealbumin were

significantly increased from baseline at 12 and 24 weeks, and fat-free mass (FFM) and FFM index, at 12 weeks. These results documented that the addition of an oral nutritional supplement enriched with HMB and proteins to pulmonary rehabilitation program improve body composition, muscle strength, and related quality of life in bronchiectasis patients [19].

More recently, a randomized controlled trial by Malafarina and colleagues [20] evaluated the effects of nutritional supplement with HMB, proteins, and vitamins on muscle mass and nutritional markers among older subjects with hip fracture. This study sample (n = 92 with mean age 86 ± 6 years) admitted to rehabilitation units after hip fracture surgery received standard diet plus two portions per day of nutritional supplement with HMB or only usual diet for one month. Body mass index and appendicular lean mass (aLM) were substantially stable in patients receiving the active product, whereas these parameters diminished in the control group, with a significant difference ($p < 0.001$ and $p = 0.020$, respectively). As expected, subjects supplemented with HMB showed higher intake of proteins ($P = 0.007$) and vitamin D ($P = 0.001$). In addition, a greater rate of subjects in the active group showed functional recovery (68%) when compared with the control group (59%), although the difference was not statistically significant ($P = 0.265$). These results showed that adding to the standard diet the HMB supplementation resulted in muscle mass maintenance and enhanced functional recovery and nutritional status in older subjects with hip fracture during the rehabilitation period [20].

HMB in community older people

Berton and colleagues [21] evaluated whether a specialized supplement containing protein, 1.5 g of HMB, and other important micronutrients (minerals and vitamins) for eight weeks could improve physical performance and muscle strength parameters in a group of community-dwelling older women. Eighty healthy women attending a twice-weekly mild fitness program were divided into two groups. The short physical performance battery (SPPB) score was considered as the primary outcome, and changes in the peak torque isometric and isokinetic strength of the lower limbs, and 6-minute walking test (6MWT) as secondary outcomes. After eight weeks, there were no significant differences between the groups SPPB, body composition parameters. The group treated with the HMB supplementation scored significantly better than the control group for peak torque isokinetic flexion (delta = 1.56 ± 1.56, p = 0.03) and extension (delta = 3.32 ± 2.61, p = 0.03), peak torque isometric strength (delta = 9.74 ± 3.90, p = 0.02), 6MWT (delta = 7.67 ± 8.29, p=0.04), and handgrip endurance (delta = 21.41 ± 16.28, p = 0.02). The study concluded that a nutritional supplement containing 1.5 g of HMB for eight weeks in healthy elderly women had no significant effects on SPPB but did significantly improve several muscle strength and physical performance parameters [21].

More recently, Cramer and colleagues [22] assessed the effects of two high-quality oral supplements differing in amount and type of key nutrients (HMB) in community older adult. The study enrolled subjects with malnutrition and sarcopenia, 65 years and older (n = 330). The study sample was randomized to receive the control supplements (330 kcal, 14 g protein, including vitamins and minerals) or the experimental

supplements (330 kcal, 1.5 g of HMB with 20 g protein, including minerals and vitamins) twice a day for six months. Both groups (control and experimental) improved isokinetic peak torque, muscle quality, grip strength, and gait speed from baseline with no treatment differences. In secondary analysis, subjects with severe sarcopenia (44%) showed lower baseline isokinetic peak torque and muscle quality, without differences in strength improvements between treatments. However, subjects with mild–moderate sarcopenia showed higher baseline isokinetic peak torque and muscle quality, with differences in strength improvements at 12 weeks (experimental with HMB > control without HMB, $p = 0.032$) among those subjects with normal grip strength. The authors concluded that nutritional supplements enhanced all the strength outcomes in older adults with malnutrition and sarcopenia; at the same time, in those with mild–moderate sarcopenia (but not severe sarcopenia) consumption of the specialized supplement with HMB (experimental supplement) improved leg muscle strength and quality compared with the standard supplement (control supplement) [22].

HMB WITH EXERCISE

Physical inactivity (sedentary lifestyle) and muscle disuse correlate to the rapid onset of anabolic resistance, both in young and older subjects [23]. Inactivity and sedentary lifestyle are also likely to lower basal muscle protein synthesis rate. As a consequence, it has been hypothesized that a synergistic prescription of HMB supplementation and physical exercise is essential for middle-aged and older subjects, especially for those people suffering from catabolic stressors such as illness, obesity, inflammation, injury, or persistent sedentary. The combination of physical exercise program (in particular, resistance exercise) and HMB intake has been demonstrated to have a positive and synergistic effect on skeletal muscle protein synthesis [24]. Some data clearly demonstrate that specific physical exercises protocols offer the greatest benefits to the muscle cells during the aging process when joined with a correct dietary protein intake (at least 1.0 g per day per kg of ideal body weight) and HMB supplementation [3, 5].

EFFICACY OF HMB IN ATHLETES

Young athletes extensively used the HMB supplementation as an ergogenic performance increment. This is related to some studies that demonstrated that supplement containing HBM when pooled with exercise training protocol, may lead to improve muscle mass and muscle strength, and at the same time to increase endurance in athletes. This positive effect on muscle strength and physical performance may be more marked in specific disorders where proteolysis is more pronounced, as in sedentary subjects that decide to start to do exercise. Nevertheless, there is still not conclusive evidence relate to the high variability in study design and methodological issues. Recently, a meta-analysis of 394 subjects from 9 different studies showed small benefits in the average muscle strength of lower body and these gains were mostly observed in untrained lifters; furthermore, no important changes in body composition were

observed [5, 25]. It is also demonstrated that the HMB supplementation may avoid muscle damage, too. A systematic review established the positive effects of HMB in preventing physical activity- and exercise-correlated muscle damage in well-trained and untrained subjects [26]

A position statement published by the International Society of Sports and Nutrition supported the use of HMB to improve recovery in well-trained and untrained individuals, and to increase skeletal muscle hypertrophy, strength, and power together with the appropriate physical activity and exercise protocol prescription [27]. In particular, this recommendation suggests to consuming the HMB supplement close to the physical workout, starting at least two weeks prior to an exercise session.

SAFETY OF HMB

Overall, the HMB supplementation seems to be safe in humans without any particular side effects. A study examining data from nine studies, using 3 g of HMB per day for two months, did not find any safety concern in blood tests, tolerance, or other adverse events [5]. On the contrary, in addition to the positive effects at muscle cell level, HMB reduced total cholesterol, low-density lipoprotein (LDL) cholesterol, and systolic blood pressure. These results have been confirmed in the clinical trials that included both healthy and frail older subjects and prospectively studied safety parameters; in all these studies there were no specific side effects that could be directly correlated to the use of HMB [5, 28].

HMB IN THE EUROPEAN SOCIETY FOR CLINICAL NUTRITION AND METABOLISM GUIDELINE

The Recommendation 2.2 of European Society for Clinical Nutrition and Metabolism (ESPEN) guideline [29] suggests that in malnourished polymorbid medical inpatients or those at high risk of malnutrition, nutrient-specific oral nutritional supplement should be administered, which may maintain muscle mass, reduce mortality, or improve quality of life (grade of recommendation B, consensus 89% agreement). The ESPEN reported that several specialized nutrients have been tested for their effectiveness on the improvement of outcomes in hospitalized patients. According to the NOURISH study, a multicenter randomized controlled trial (RCT) that included 652 malnourished inpatients, high-protein and HMB supplementation may not yield a difference when compared with the placebo on readmission rates, but may help with the maintenance of muscle mass during hospital stay and result in a significant decrease in post-discharge mortality (90-day mortality was 4.8% in the intervention group [IG] vs. 9.7% in the control group [CG]; relative risk [RR] 0.49 (95% confidence interval [CI] 0.27e0.90), p 1/4 0.018) (level of evidence 1++). The HMB is also cited in recommendation 9.3 [29]: in polymorbid medical inpatients at high risk of malnutrition or with established malnutrition aged 65 and older, continued nutritional support post hospital discharge with either nutritional supplement or individualized nutritional

intervention shall be considered to lower mortality. Finally, recommendation 7.1 suggests that in polymorbid medical inpatients with pressure ulcers, specific amino acids (arginine and glutamine) and HMB can be added to oral/enteral feeds to accelerate the healing of pressure ulcers [29].

CONCLUSION

Experimental research clearly suggests that HMB has many positive effects that may counteract sarcopenia status; these positive effects are confirmed by the use of HMB supplementation in younger athletes, too [30]. Yet, clinical research on the effects of supplement containing HBM in sarcopenia is restricted by the small number of randomized controlled trials, different methods used, lack of agreement on outcome measures, and concerns on the interaction of HMB with other ingredients and with exercise. Overall, findings document that the HMB may avoid muscle mass loss or increase muscle mass, and at the same time enhance muscle strength, physical function, and performance. Even though the limitations in research preclude conclusive conclusions, the evidences provided by recent studies may act as the foundation for future studies examining whether the implementation of nutritional interventions targeting the skeletal muscle (HMB supplementation) improve the clinical outcomes of frail older persons [8]. In this respect it is important to highlight that the ESPEN guidelines on nutritional support for polymorbid internal medicine patients suggests that in malnourished inpatients or in those subjects at high risk of malnutrition, nutrient-specific supplementation (with HMB) should be administered, which may maintain muscle mass, reduce mortality, or improve quality of life [29].

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CHAPTER 25

The Future of Drug Treatments

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INTRODUCTION

The relationship between sarcopenia and negative outcomes has important implications regarding the therapeutic approaches. Lifestyle intervention (i.e. physical activity, in particular resistance exercise training, and nutrition) have shown to have an important impact in preventing and reversing sarcopenia. However, many older people are sedentary and do not want to exercise or cannot exercise. Therefore, several drugs were suggested, with various levels of scientific evidence, to have an impact on muscle mass, strength, and function. With growing understanding of the specific molecular pathways involved in the structural and functional modifications affecting the skeletal muscle during the aging process, many potential targets for pharmacological intervention to prevent and/or to treat sarcopenia have been suggested.

In this chapter, we review the effect of three classes of drugs (cardiovascular, hormone, and metabolic agents) on sarcopenia and muscular outcomes in older adults. For each class of medications, we describe the evidence from clinical studies and the biological plausibility.

CARDIOVASCULAR DRUGS

Angiotensin II converting enzyme inhibitors

In subjects with congestive heart failure (CHF), Angiotensin II converting enzyme inhibitors (ACE inhibitors) have been demonstrated to prevent morbidity, mortality, and hospital admissions, and to reduce the decline in physical function and exercise capacity. The effects of ACE inhibitors on muscle function have been mainly attributed

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

to positive cardiovascular effects. However, it has been hypothesized that ACE inhibitor-induced favorable effects may also be mediated by direct positive actions of these agents on the skeletal muscle [1].

Clinical experience

Firstly, the effect of ACE inhibitors on muscle strength was examined in an observational study among 641 older disabled women without CHF (mean age 79 years) [2]. In this group, continued ACE inhibitor users had a significantly lower average three-year decline in muscle strength (−1.0 kg) than either continued/intermittent users of other antihypertensive drugs (−3.7 kg; $p = 0.016$) or never users of antihypertensive drugs (−3.9 kg; $p = 0.026$).

The cross-sectional associations of antihypertensive medications use with lean body mass (LBM) was examined in a cross-sectional study among 2431 independent older adults [3]. Comparisons between groups demonstrated that lower extremity muscle mass was greater in users of ACE inhibitors (mean ± standard error [SE]: 16.1 ± 0.2), when compared with either users of no drug (mean ± SE: 15.9 ± 0.1, p vs. ACE inhibitors 0.15) or users of other antihypertensive drugs (mean ± SE: 15.7 ± 0.1, p vs. ACE inhibitors = 0.001).

In a double-blind randomized controlled trial, 130 older adults (mean age 78.7 years) with functional impairment were randomly assigned to receive either perindopril or placebo for a period of 20 weeks [4]. Among 95 participants who completed the trial, the mean six-minute walking test was significantly improved in subjects receiving perindopril relative to the placebo group (mean between-group difference 31.4 m). However in a following study, the use of perindopril did not seemed to improve the effect of exercise training on physical function in a group of impaired older people without heart failure [5]. In a prospective double-blind trial, comparing the effects of treatment with enalapril versus nifedipine on physical performances in older subjects with hypertension, no significant differences in muscle strength, walking capacity, or functional measures were observed [6]. TheTrial of Angiotensin-Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors (TRAIN) study, found no beneficial effect on physical performances in the older subjects randomized in the ACE inhibitors group compared with the placebo group after six months of treatment [7]. Another recent and large prospective study of postmenopausal women, found that angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) use was significantly associated with higher LBM in cross-sectional analyses [8]. Finally, a more recent meta-analysis [9], compared the use of three different ACEIs (enalapril, perindopril, and fosinopril). No significant results were obtained, even if a modest positive effect in favor of the intervention groups was reported, suggesting that subgroups of older people might benefit from the treatment with ACEIs in terms of muscular function.

Several genetic studies support the hypothesis that the ACE system may be involved in skeletal muscle function. Among elite athletes, the presence of the ACE II genotype seemed more common among long distance athletes, while the D allele was associated with power oriented performance in athletes such as short distance swimmers and

sprinters [10]. A possible explanation for these findings derives from a genetic study by Zhang and colleagues, which showed that the ACE I allele is associated with an increased percentage of type I muscle fibers [11]. On the contrary, the D allele is associated with the expression of type II fibers that are less fatigue resistant and more efficient in power performance than the type I isoforms. However, there is some contradictory evidence regarding the influence of the ACE gene on endurance and power performance among healthy young adults [12]. Among older adults no association between ACE gene and physical performance has been proved so far [13].

Further evidence is required before recommending ACE inhibitors to counter the effects of sarcopenia.

Mechanism of action

Potential mechanisms responsible for the beneficial effects of ACE inhibitors on skeletal muscle are summarized in Figure 25.1.

In patients with CHF, enalapril and losartan were shown to determine a shift of the myosin heavy chains of leg skeletal muscle gastrocnemius from type II toward type I fibers [14]. This result is in line with the results of the study of Zhang and colleagues demonstrating that the ACE I allele (associated with low ACE activity) is associated with an increased percentage of type I muscle fibers, while the D allele (associated with high ACE activity) is associated with the expression of type II fibers [11].

The renin–angiotensin system may mediate the inflammatory response and therefore influence muscle function. Studies conducted in vitro have shown that angiotensin II increases interleukin (IL)-6 and tumor necrosis factor (TNF)-α production in

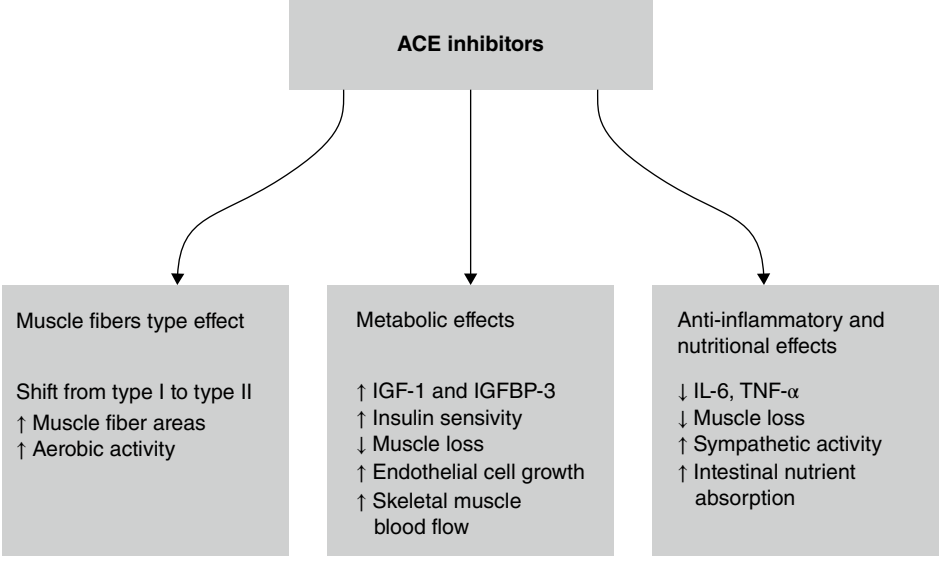

Figure 25.1 Effect of ACE inhibitors on skeletal muscle.

smooth vascular muscle [15]. Kranzhofer and colleagues confirmed this important function of angiotensin in triggering the inflammatory pathway and demonstrated that ACE inhibitors can suppress the pro-inflammatory activities of angiotensin [16]. The anti-inflammatory effect of ACE inhibitors has been confirmed in an observational study conducted among 161 subjects undergoing elective coronary artery bypass surgery. Subjects treated with ACE inhibitors had a significant lower increase in IL-6 concentration post-surgery compared with other participants [17].

ACE inhibitors may favorably impact the nutritional status by regulation of the intestinal absorption of nutrients and may modulate appetite and physical activity by a direct effect on the central nervous system. Furthermore, some studies in animals have shown that treatment with ACE inhibitors increased the natural angiogenesis and enhanced the collateral vessel development in the ischemic limb [18]. In addition, Zimmerman and colleagues demonstrated that the expression of vascular endothelial growth factor was augmented in cardiac tissue following treatment with ramipril [19].

Finally, the ACE inhibitors play an important role in the modulation of the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis [20]. IGF-1 is known to be a potential contributor to sarcopenia. It has been hypothesized that ACE inhibitors may prevent the loss of muscle mass through modulation of the IGF-1 system. This effect may be related to the reduction of the autocrine IGF-1 system. The direct effect of ACE inhibitors on the IGF-1 system has been reported in two different large epidemiological cohort studies in older people. In the ilSIRENTE study [21] and in the InCHIANTI study [22], the older adults treated with the ACE inhibitors showed higher insulin-like growth factor-binding protein-3 (IGFBP-3) levels. On the other hand, overexpression of muscle-specific isoform of IGF-1 reduces the angiotensin II–induced muscle loss [20]. Taken together, these results suggest that medications that inhibit the conversion of angiotensin I to angiotensin II, such as ACE inhibitors, may delay or prevent muscle loss in older adults, possibly through modulation of the IGF-1 system.

Overall, the long-term use of ACE inhibitors may attenuate the decline in muscle strength and walking speed in older people and induce a greater lower limb lean muscle mass when compared with users of other antihypertensives [23]. ACE inhibitors have been shown to improve the exercise capacity in both younger and older people with heart failure but they do not improve the grip strength [24].

Other studies found no positive relationship between the intake of ACE inhibitors and skeletal muscle mass, strength, muscle quality, or function [25]. Further studies will hopefully analyze better the role of the ACEIs in the treatment and prevention of sarcopenia. For example, the LACE trial, a multicenter, placebo-controlled, randomized controlled ongoing trial, will explore the role of leucine and ACE inhibition can improve muscle mass and function in people with sarcopenia as defined by the European Working Group on Sarcopenia (EWGSOP) [26].

Statins

The proteomic analysis performed in animals chronically treated with different hypolipidemic drugs, showed that either statin or fibrate administration is able to modify the expression of specific proteins essential for skeletal muscle function [27]. Based on this experimental evidence, the possible use of statin to treat sarcopenia has been hypothesized.

Clinical experience

The effect of statin on body composition has been tested in a clinical trial among 49 community dwelling subjects – 60- to 69-year-old men and women – who completed two weeks of nutrition education, followed by 12 weeks of high-intensity resistance exercise training, with post-exercise protein supplementation [28]. This trial documented that serum cholesterol and statin treatment were independently associated with greater increases in LBM after training, suggesting that statin may improve muscle response to exercise program. Furthermore, in an observational study among 756 community-dwelling older adults, statin users over a one-year period performed modestly better than nonusers for timed chair stands test (−0.5 seconds; $p = 0.04$) [29]. In another study, the results demonstrated that the use of atorvastatin in older patients did not affect the muscle function and the adaptation of the muscle itself in response to different physical activities, even high-intensity muscle-damaging activities. It also showed some advantages in the performance during resistance exercise [30]. Similar results were found in the LIFE study, a 1635-person multicenter single-blind randomized trial, which evaluated the effect of statin use on older sedentary individuals at high risk of mobility disability. Older adults who required statin medications had a benefit from interventions increasing physical activity [31]. Moreover, statin myalgia was found not to be associated with deficits in muscle strength and lean mass or the dysregulation of muscle protein turnover in older people [32].

However, it is important to highlight that statins have also been recognized to cause adverse effects on skeletal muscle mass. Statins may reduce aerobic exercise tolerance through impaired mitochondrial function, decreased mitochondrial content, and apoptotic pathways. In a longitudinal study performed in community-dwelling older adults, treatment with statin was associated with greater declines in strength and increases the risk of falls [33]. In another study, the use of simvastatin was associated with a decrease in cardiorespiratory fitness and skeletal muscle mitochondrial content when combined with exercise training in overweight or obese patients at risk of the metabolic syndrome [34].

Mechanism of action

The potential positive effects of statins on skeletal muscle and physical performance are summarized in Figure 25.2.

Statins might affect muscle mass and function retarding the negative effects of atherosclerosis on blood vessels of skeletal muscle, ensuring a better perfusion and therefore preventing muscle wasting and reducing muscle weakness and/or fatigue. Statins also increase the production of nitric oxide in the endothelium, which has local vasodilatory properties. Furthermore, Bitto and colleagues have demonstrated that simvastatin improves the rate of wound healing in diabetic mice; this process seems to be mediated by increased vascular endothelial growth factor [35].

Statins may reduce inflammation, which, in turn is an important determinant of sarcopenia. Several studies have pointed out that treatment with statin reduces C-reactive protein and other inflammatory marker levels independently of the effect on cholesterol [36]. This hypothesis is indirectly confirmed by the Heart Prevention Study

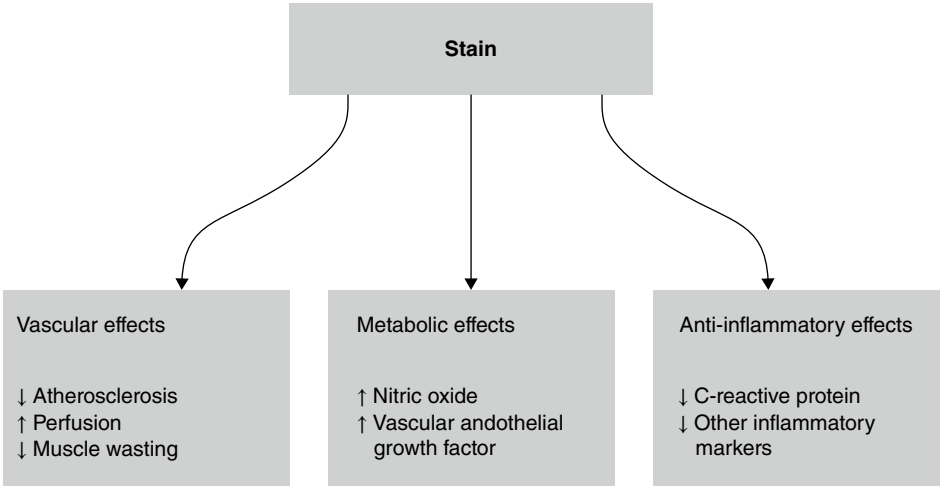

Figure 25.2 Effect of statin on skeletal muscle.

(HPS) [37] and the JUPITER trial [38] which suggested that the reduction of cardiovascular events among pravastatin and rosuvastatin users is independent of baseline cholesterol levels.

The evidence that the use of statins reduces inflammation, together with the recognition of inflammation as an important determinant of muscle mass and function, appears to provide a rationale to hypothesize a direct effect of statins on sarcopenia. However, further studies are required to better define the effects of statins on skeletal muscle mass, strength, endurance, and performance [39].

HORMONE REPLACEMENT

Testosterone

Testosterone is secreted by the ovarian thecal cells in women and by the Leydig cells in men. Testosterone has been associated with higher muscle mass and muscle protein synthesis. It also appears to increase the number of satellite cells in both animal and human studies, which are important for muscle cell function. In older men, epidemiologic studies support the relationship between declines in testosterone levels with age and loss of muscle mass and strength. As a consequence, hormone replacement has received considerable interest as a potential therapy for sarcopenia.

Clinical experience

Several randomized controlled studies have been conducted with testosterone showing a direct effect of this hormone on muscle mass and in several cases on muscle strength, particularly in men with testosterone deficits [39–42]. Studies of

testosterone replacement therapy in men have shown varied results, depending on the age of the subjects and on the plasmatic testosterone level before the treatment. A meta-analysis performed in 2006, including data from 11 randomized clinical trials, suggested that testosterone treatment produced a moderate increase in muscle strength compared with placebo [43]. In an umbrella review of systematic reviews and meta-analyses, testosterone supplementation in older participants (without clear sarcopenia status), was reported to have a significant effect on muscle mass but a modest to minimal effect on muscle strength and physical performance, especially among men with low serum testosterone levels (< 200–300 ng/dl) [9]. Srinivas-Shankar and colleagues documented in frail and intermediate frail older men that administration of 50 mg/day of transdermal testosterone for a period of six months resulted in a significant increase in LBM associated with increased knee extensor strength [44]. Testosterone supplementation showed better results in increasing muscle mass and function in frail older adults when it is combined with nutritional supplements in undernourished subjects [45] or with physical activity programs [46, 47]. Overall, the effects of testosterone therapy in older subjects with normal level of testosterone have not been adequately studied. Furthermore, despite the positive effect of testosterone supplementation on muscle mass, a conclusive evidence of a direct effect of this treatment on disability and physical performance is still lacking. Inconsistency of the results of the randomized clinical trials administering testosterone replacement therapy on muscle mass and muscle strength responses in older men may be explained by the administration route. Indeed, intramuscular testosterone replacement therapy was recently reported in a meta-analysis to be more effective than transdermal formulations [48]

When considering testosterone replacement therapy, the potential benefits of treatment must be weighed against the possible side effects. The Baltimore Longitudinal Study on Aging involving 781 subjects showed a direct correlation between prostate cancer and the testosterone levels. The likelihood of acquiring a high-risk prostate cancer in men 65 years or older doubled for every 0.1 unit increase in free testosterone level [49]. This, along with other potential side effects of testosterone treatment, such as peripheral edema, gynecomastia, polycythemia, and sleep apnea, limits its use as a safe treatment for sarcopenia [50]. Application of testosterone gel was associated with an increased risk of cardiovascular adverse events in older men with limitations in mobility and multimorbidity [51]. In the Testosterone Trials (TTrials), a coordinated set of seven randomized controlled trials (788 men with a mean age of 72 years), testosterone increased the coronary artery noncalcified plaque volume. Testosterone was not associated with more cardiovascular or prostate adverse events than placebo. However, larger trials and longer follow-up are required to determine whether testosterone increases cardiovascular or prostate risks [52]. Therefore, at present, the most prudent course of action is to treat only older men with repeatedly low serum testosterone levels and symptoms and signs consistent with androgen deficiency.

Mechanism of action

Anabolic effects and effects on motor neurons have been suggested for the role of testosterone in muscle function (Figure 25.3).

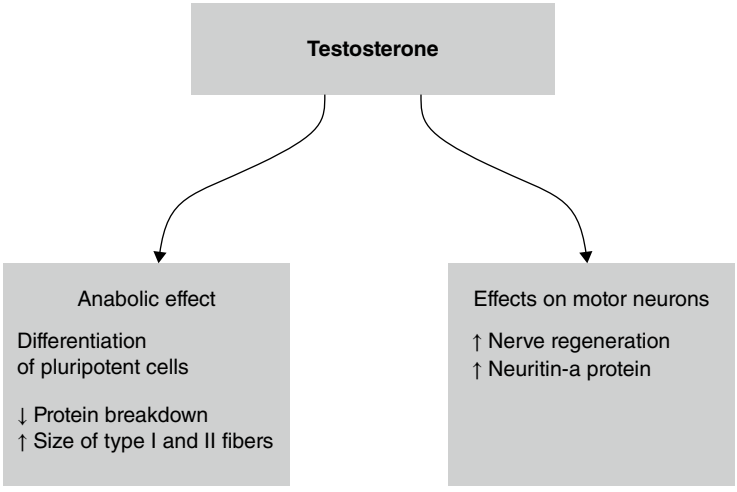

Figure 25.3 Effect of testosterone on skeletal muscle.

Some data suggest that testosterone induces muscle fiber hypertrophy by acting at multiple steps in the pathways regulating muscle protein synthesis and breakdown. A study conducted in older men showed that testosterone administration promotes muscle anabolism by reducing protein breakdown [53]. Testosterone does not provide additional stimulation of muscle anabolism when combined with amino acid supplementation.

Testosterone administration is associated with an increase in the cross-sectional areas of both type I and II muscle fibers [54]. In young men, testosterone-induced gains in muscle size were associated with a significant increase in muscle fiber cross-sectional area and the cross-sectional areas of both type I and II fibers increased in proportion to testosterone concentrations [55]. The observation that differentiation of pluripotent cells is testosterone dependent gives a unifying explanation for the shared effects of testosterone on muscle and fat mass. In this respect, it is important to highlight that some studies demonstrated that testosterone controls and regulates the lineage determination in mesenchymal pluripotent cells, by promoting their commitment to the myogenic lineage and inhibiting their differentiation into the adipogenic lineage through an androgen receptor–mediated pathway.

Motor neurons have androgen receptors and are potential sites of testosterone action. The importance of androgens in motor neurons is confirmed by the fact that a particular mutation in the androgen receptor gene may cause a degenerative disorder known as Spinal and Bulbar Muscular Atrophy, which is characterized by the death of motor neurons expressing high levels of androgen receptors, which are mainly located in the anterior horns of the spinal cord and in the bulbar region [56]. Finally, it has been shown that testosterone may enhance peripheral nerve regeneration following injury by stimulating the production of neuritin, a protein that is involved in the re-establishment of neuronal connectivity following traumatic damage to the central nervous system [57].

Estrogens and tibolone

Women experience an accelerated loss of muscle mass and strength after menopause [58]. Modifications in lifestyle habits (low level of physical activity) and hormonal changes may be the two main causes of both loss muscle mass and strength [58]. Some evidences demonstrating the association between hormonal replacement treatment and muscle mass and muscle strength have been documented. Nevertheless, disagreement still exists regarding the role of estrogen on skeletal muscle in women.

Clinical experience

Three of seven clinical trials on estrogens showed a significant positive effect on muscle strength [59–61]; on the contrary, four other randomized controlled trials did not find any effect on muscle mass [62] and strength [63–65]. Plausible explanations for these controversial results may be related to the duration of the observation period and the different mean age of participants; in this respect, it is important to highlight that older women included in these studies showed no effects related to treatment with estrogens.

The only clinical trial on tibolone, a synthetic steroid with estrogenic, progestagenic, and androgenic activity, showed a significant positive effect on muscle strength [66]. At the same time, tibolone seems to be associated with significant and positive effects on muscle mass [67]. In particular, tibolone increases fat-free mass and total body water content and reduces fat mass. Positive effects of tibolone were confirmed even if used in combination with estrogens. Hanggi and colleagues documented that tibolone treatment had no impact on muscle mass, suggesting that this treatment may play a role only in fat distribution [68].

The effect of estrogens on body composition is more controversial, with studies suggesting that this drug can either increase LBM or decrease fat mass and other studies showing no effects [58].

Overall, only a few of the described clinical studies on estrogens and on tibolone included older women [64].

Considering also the well-known side effects associated with the use of these drugs (breast cancer, endometrial cancer, ovarian cancer, venous thromboembolic risk, stroke), estrogens or tibolone treatment should not be recommended as a primary line of treatment for sarcopenia. Further researches are needed to better clarify the effects of these drugs on muscle mass and strength and their long-term safety in older subjects.

Mechanism of action

Estrogen and tibolone may both react with intra-nuclear receptors in muscle fibers, and tibolone may also act by binding androgen receptors in muscle fibers and increase free testosterone and GH. Tibolone was shown to directly increase serum IGF-1 levels [69] and also to increase the amount of free testosterone. Estrogen is converted to

testosterone, which has an anabolic effect on muscle protein synthesis. Moreover, both sex hormones may suppress inflammatory cytokines that have catabolic effects on skeletal muscle.

Tibolone may have another positive effect on muscle strength, increasing the plasma levels of nitric oxide that mediates satellite cell activation [70]. In postmenopausal women, estrogen therapy results in a higher myogenic regulatory factor gene expression, a greater myogenic response to physical exercise, and a lower muscle damage after maximal eccentric exercise [71]. Finally, estrogen replacement treatment has been reported to improve insulin response during physical activity training programs [72].

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a hormone precursor which is converted to testosterone/estrogen hormones at specific target tissues [73]. Since DHEA is a precursor in the biosynthesis of these hormones, DHEA supplementation in both males and females could potentially help in enhancing muscle mass and strength.

Clinical experience

In most human observational studies, a weak correlation between circulating levels of DHEA and muscle strength or muscle mass is reported. There are few studies assessing the effects of DHEA supplementation in older adults, and the effects on muscle mass and function have been found to be variable. In 2011, a systematic review found only eight studies that investigated the effect of DHEA supplementation on body composition and physical performance in older adults. [74] The authors of this review concluded that the benefit of DHEA on muscle strength and physical function in older adults remains inconclusive. Some studies conducted in aged men and women demonstrated that supplementation of DHEA increases the bone density, testosterone and estradiol levels, but has no effects on muscle size, strength, or function [73]. Kenny and colleagues conducted a randomized trial in 99 women (mean age 76.6 ± 6.0) to investigate the effects of DHEA combined with exercise on bone mass, muscle strength, and physical function [46]. It has been documented that DHEA supplementation improved lower extremity strength and function in older, frail women involved in an aerobic exercise program. Another study showed improvement in strength in a group of healthy older adults only after adding high-resistance training to DHEA supplementation [75]. Improvement in strength and function may require a combination of DHEA and exercise, although this result was not seen in all studies. Christiansen and colleagues investigated the effects of DHEA supplementation in women with adrenal failure [76]. After six months, treatment with DEHA had no effects on muscle mass, fat mass, and bone tissue; only a small increase in LBM was observed while a high frequency of side effects was documented. Researchers evaluating DHEA use in aging adults suggest that its effects should be evaluated over a longer period of time, and it might be more efficacious if the DHEA dosage administered resulted in circulating androgen levels exceeding those of young, healthy adults [73]. Finally, in a systematic review Baker and colleagues [74] showed that the benefit of DHEA on muscle strength

and physical function in older adults remains inconclusive. DHEA does not appear to routinely benefit measures of physical function or performance. Some measures of muscle strength may improve, although consensus was not reached. Even though DHEA supplementation may give other benefits such as increased bone density and sex hormone levels, it has not yet been proven to counter sarcopenia.

Mechanism of action

In the inChianti study, Valenti and colleagues demonstrated that in men aged 60–79 years, circulating DHEA is an independent correlate of muscle strength and calf muscle area [77]. There are several mechanisms by which DHEA may influence muscle mass and strength, including the ability of skeletal muscle to convert DHEA to active androgens and increases in IGF-1. The importance of DHEA in older subjects is that almost all of the total androgens are derived from these adrenal precursor steroids [74]. Studies conducted in animal models have demonstrated that skeletal muscle contains specific enzymes able of converting circulating DHEA to testosterone and further to dehydrotestosterone, an androgen that acts on the local steroid receptors [78]. Moreover, DHEA supplementation increases IGF-1 levels that stimulates the proliferation and migration of myogenic or muscle precursor cells.

Growth hormone

Extensive interest has been devoted to study the effects of GH on sarcopenia. Levels of GH are usually lower in older subjects and the amplitude and frequency of pulsatile GH release are significantly reduced; thus it was hypothesized that GH would be useful in preventing the age-related muscle mass loss. However, despite the large number of studies which have assessed the effects of GH supplementation on muscle mass, strength, and physical performance, there is still an ongoing debate whether or not to use GH to prevent and/or to treat sarcopenia. Noteworthy, controversial findings have been reported in healthy or moderately frail, non-GH-deficient older adults following GH treatment.

Clinical experience

Many studies reported only marginal effects of GH supplementation. Brill and colleagues demonstrated that one month of GH supplementation improved balance and, in combination with testosterone, ameliorated physical function, but was unable to enhance muscle strength [79]. Papadakis and colleagues documented that among healthy subjects older than 69 years of age, GH treatment for six months increased muscle mass and decreased fat mass, without improving physical performance [80]. Blackman and colleagues found no significant effect on muscle strength among healthy older women after supplementation with GH and reported only a marginal significant increase of muscle strength in men treated with GH and testosterone [81]. For instance, some other studies reported an increase of muscle mass and strength in healthy older

persons after GH supplementation [50, 73]. In a group of older men, those who received the highest doses of combined supplementation of GH with testosterone for four months increased their muscle mass by at a mean of 3 kg and their muscle strength by 30%, while the mean fat mass decreased [82]. In 2009, a meta-analysis [83] reported that GH replacement in GH-deficient adults was associated with a significant positive effect on aerobic exercise capacity and muscle mass. However, one year later, another meta-analysis, restricted to high-quality studies, did not supported a beneficial effect of GH replacement on strength in GH deficiency adults [84].

Most studies have documented that GH supplementation is ineffective in older subjects, both considering muscle mass and muscle strength. Taaffe and colleagues showed that treatment with recombinant human GH to older men performing regularly an exercise program did not increase muscle mass or tissue IGF-1 expression [85]. Yarasheski and colleagues demonstrated in a small sample of sedentary men that resistance exercise training improved muscle strength and metabolism, but these improvements were not augmented when exercise training was combined with GH supplementation [86]. Similarly, Thompson and colleagues failed to show in moderately obese postmenopausal women any effect of GH supplementation on muscle strength [87]. Lange and colleagues conducted a randomized clinical trial examining the effects of GH alone, exercise alone, and GH combined with exercise [88]. This trial showed that GH alone had no effect on muscle mass, strength, and power; the exercise-induced improvements were not further augmented by GH supplementation.

These contrasting findings may be explained by methodological differences between the studies, the short-term of these controlled studies and by the small number of subjects enrolled. Numerous causes may explain the ineffectiveness of GH supplementation to improve muscle mass and strength, such as the failure of exogenous GH administration to mimic the pulsatile pattern of natural GH secretion or the induction of GH-related insulin resistance [50]. Furthermore, it is important to consider that the majority of the trials conducted on GH supplementation have reported a high incidence of adverse effects, such as fluid retention, soft tissue edema, orthostatic hypotension, diabetes, carpal tunnel syndrome, arthralgias, and gynecomastia. In conclusion, based on the current evidence, GH treatment should not be considered as a safe strategy to improve body composition and functionality in older individuals.

Mechanism of action

Two important mechanisms of action – anti-inflammatory and anabolic – have been suggested for the role of GH on skeletal muscle function (Figure 25.4).

The effect of GH on the muscle is mainly mediated by IGF-1. In response to GH, the liver and the skeletal muscle produces IGF-1 for systemic release. IGF-1 has hyperplastic and hypertrophic effects on the skeletal muscle. The hyperplastic effect results in the proliferation of muscle satellite cells, while the hypertrophic effect results in increased synthesis of contractile proteins. In addition, IGF-1 suppresses proteolysis, promotes the delivery of amino acids and glucose to myocytes, and stimulates myoblast proliferation and differentiation. Systemic IGF-1 administration enhances the rate of muscle functional recovery after injury and improves endurance and contractile muscle function.

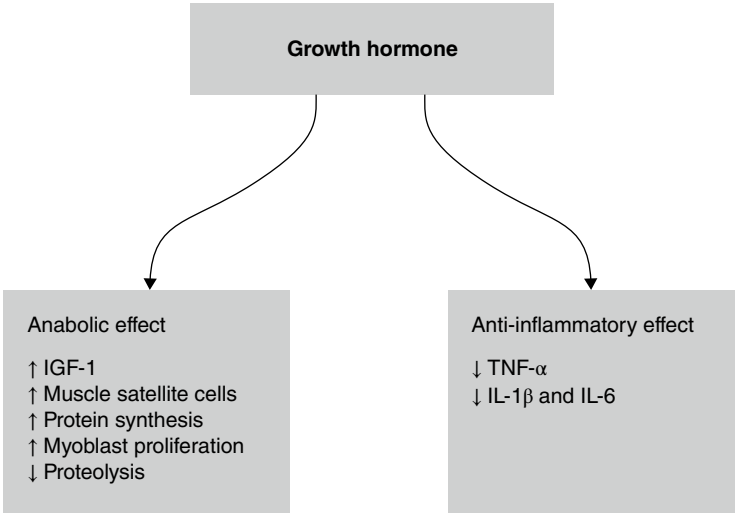

Figure 25.4 Effect of GH on skeletal muscle.

Some studies have demonstrated that muscle expression of IGF-1 accelerates the regenerative process after injury modulating the inflammatory response and limiting the onset of fibrosis [89]. The IGF-1 expression significantly downregulates pro-inflammatory cytokines, such TNF-α and IL-1β. Administration of IGF-1 has been shown as a promising strategy to improve cardiac function and reduce infarct size after acute myocardial injury [90]. Mechanisms hypothesized for this effect include the reduction of inflammatory response (e.g. IL-6 and IL-1β) and the severity of cardiomyocyte apoptosis.

Ghrelin

Ghrelin is a peptide hormone secreted by the stomach in response to fasting. An enhanced blood ghrelin concentration results in an increased sensation of hunger and food intake. Considering that anorexia and malnutrition are important causes of sarcopenia, it has been hypothesized that ghrelin supplementation could be effective in preventing age-related muscle mass loss.

Clinical experience

Some promising effects of ghrelin supplementation have been reported [91]. In a sample of 25 subjects with chronic obstructive pulmonary disease, subcutaneous injections of a synthetic ghrelin analogue tended to increase the lean mass and the physical performances [91]. In this population with cachexia related to chronic obstructive pulmonary disease (COPD), GH administration was reported, in a small sample size randomized controlled trial of 33 participants, to improve respiratory symptoms and strength [92]. Furthermore, ghrelin concentrations have been reported to be strongly

correlated with the amount of skeletal muscle mass [93]. However, very few clinical studies on synthetic ghrelin or ghrelin agonist treatment have been conducted in older subjects. In healthy older adults, without sarcopenia, two years of an oral ghrelin mimetic agent increased the GH and IGF-1 blood levels and muscle mass but without significant changes in strength or physical function [94].

Mechanism of action

Ghrelin stimulates the release of GH through an activation of the GH secretagogue-receptor (GHS-R 1a) present in the hypothalamus; moreover, ghrelin mimetic re-establish the pulsatile GH secretion in older adults. Subsequently, in older adults GH secretagogue or GH secretagogue-receptor agonist may be involved in the metabolism of muscle mass. This effect, partially related to melanocortin receptor antagonism that modulates food intake, has led to exploring ghrelin as a potential therapy to reduce wasting in cachexia and sarcopenia [91].

METABOLIC AGENTS

Creatine

Creatine plays an important role in protein and cellular metabolisms. The benefit of creatine supplementation on exercise performances has been reported in young adults and creatine has been proposed as a potential therapy for the prevention and management of sarcopenia [95].

Clinical experience

Several studies have assessed the effects of creatine supplementation in middle-aged and older adults with conflicting results. Brose and colleagues have shown a significant increase in muscle mass and muscle strength in older adults after a creatine supplementation combined with 14 weeks of resistance training [96]. Similarly, other studies have documented a significant increase in muscle mass after following 2–12 weeks of creatine supplementation and resistance training in older men [40]. In contrast to these findings, Rawson and colleagues found that one month of creatine supplementation did not enhance fat-free mass, total body mass, or upper extremity strength gains, yet it reduced leg fatigue [97]. Bermon and colleagues failed to find an increase in lower limb muscle mass after eight weeks of creatine supplementation and resistance training in older men and women [98]. In a group of 46 middle-aged to older adult men ([54–73] years), no differences were found in response to six months of resistance training with creatine supplementation [99]. In other studies, creatine supplementation in older males did not improve muscle mass or neuromuscular fatigue [39, 40]. In 2017, a meta-analysis including 53 studies reported that creatine supplementation improved upper and lower limb strength performance for exercise with short duration (less than

three minutes) whatever the characteristics of the participant included, the training protocols, and the supplementary doses or duration [100]. However, other studies reported no beneficial effects of long-term low-dose dietary creatine supplementation in older women on muscle mass or muscle strength [101].

There is substantial controversy over whether creatine supplementation increases the benefits of resistance training alone in older subjects and whether the creatine supplementation should be given before or after the training session. In 2014, a systematic review and meta-analysis investigated whether creatine supplementation in addition to resistance training increased muscle mass, muscle strength, and function in older adults. The results of this works support a positive effect of creatine supplementation on muscle mass gain, muscle strength, and functional performance during resistance training over resistance training alone. This meta-analysis was performed in only 357 participants and the authors also highlighted the limited number of studies [102]. In a 24-week randomized controlled trial that investigated the efficacy of creatine supplementation in 60 vulnerable older women, associated with or without resistance training, creatine supplementation combined with resistance training significantly improved appendicular lean mass and muscle function.[103]. In a small sample size randomized controlled trial, creatine supplementation in association with resistance training improves muscle strength compared with resistance training alone whatever the timing of the supplementation. However, a greater gain in lean tissue mass was observed when creatine supplementation was taken after the resistance training than before[104]. Another study found that changes in muscle mass or strength were similar when creatine supplementation was taken before or after the resistance training in older adults [105]. No definitive conclusion can be made from current works.

Based on these conflicting results and considering that creatine may increase the risk of interstitial nephritis, creatine supplementation cannot be recommended as routinely treatment for sarcopenia in older adults [40]. The benefit of creatine supplementation on muscle mass gain, strength, and functional performance during resistance training reported in healthy older adults is encouraging. However, the limited number of studies and the small sample size of the randomized controlled trial suggest further research is still needed.

Mechanism of action

Anabolic, antioxidant, and neuroprotective effects have been suggested for the role of creatine on muscle function (Figure 25.5).

It has been hypothesized that creatine increases the expression of myogenic transcription factors and facilitates the upregulation of muscle-specific genes such as myogenin and myogenic regulatory factor-4 (MRF-4), thereby facilitating an increase in muscle mass and strength.

A study conducted in young healthy volunteers demonstrated that creatine supplementation during two weeks of leg immobilization followed by 10 weeks of rehabilitation training significantly increased the expression of myogenic transcription factor MRF-4, which in turn was correlated with an increase in muscle cross-sectional area [106]. In another study, creatine supplementation combined with 12 weeks of resistance training significantly increased mRNA and protein expression of myogenin

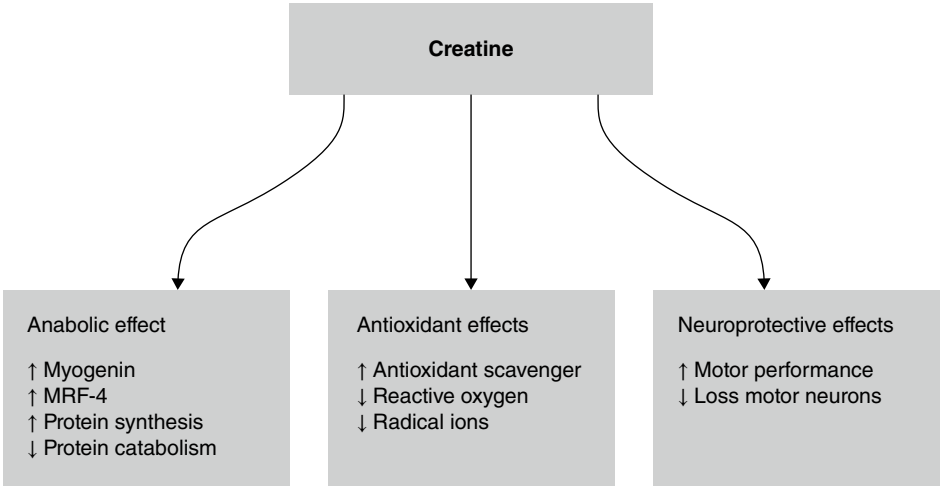

Figure 25.5 Effect of creatine on skeletal muscle.

and MRF-4 [107]. Creatine may also increase the muscle-specific protein synthesis in skeletal muscle and/or decrease the rate of protein catabolism.

Some authors demonstrated that creatine has a role as antioxidant scavenger, mainly against radical ions. Creatine exerts a significant antioxidant activity, via a mechanism depending on direct scavenging of reactive oxygen and nitrogen species. This antioxidant role of creatine seems to lead also to a neuroprotective effect. In an animal model of amyotrophic lateral sclerosis, creatine was demonstrated to have a dose-dependent enhancement in motor performance and protect from loss of motor neurons.

Vitamin D

It is known that vitamin D plays an important role in bone and muscle metabolism. One of the characteristic clinical symptoms of vitamin D deficiency is the muscle weakness. Prevalence of low level of vitamin D has been documented to be high in older people [108]. For this reason, the nutritional recommendations for the management of sarcopenia proposed to evaluate plasma 25(OH) vitamin D level in all subjects at risk of sarcopenia and to supplement all persons with low values [95].

Clinical experience

Vitamin D has the potential to improve muscle strength. A recent systematic review of vitamin D and its impact on physical performance in older people showed conflicting evidence from cross-sectional studies, which also demonstrated inconsistent cross-sectional associations between 25(OH) vitamin D level and muscle strength [109]. Kyoung Kim and colleagues found a strong inverse association between 25(OH) vitamin D level and sarcopenia in the older Korean population [110]. Prospective analyses of the Longitudinal Aging Study Amsterdam (LASA) have shown that 25(OH) vitamin D

level is predictive of increased muscle mass and strength over three years [111]. In the Tasmanian Older Adult Cohort Study, a prospective study of community-dwelling older adults, the higher 25(OH) vitamin D is modestly but significantly associated with greater muscle mass, and also predictive of improved muscle strength in older adults [110].

In three different randomized controlled trials, vitamin D supplementation has been reported to increase muscle strength [112–114]. Furthermore, in adults aged 65 years and older, the supplementation with 800 IU of vitamin D significantly improve by 4–11% lower extremity strength or function [115] after 2–12 months. The positive effects of vitamin D supplement on muscle mass and function has been hypothesized as the mechanism behind a fall reduction in older nursing home residents given vitamin D [50]. A meta-analysis has documented that 700–1000 IU per day of vitamin D reduces the risk of falling by 19% in older people [116]. Verschueren and colleagues documented in a randomized clinical study of 113 institutionalized older females aged over 70 years an increase by 6.4% in knee extensor strength after six months of vitamin D supplementation [117]. The combined effect of resistance exercise training and vitamin D3 supplementation on muscle functioning in older adults was also investigated in a recent meta-analysis on seven studies including a total of 792 participants. This work support a small additive effect of vitamin D in combination with resistance training for the improvement of muscle strength in older adults. No additional benefit beyond exercise was reported for physical performance tests such as the short physical performance battery (SPPB) or the timed up and go (TUG). [118] On the other hand, some studies failed to find significant benefits on physical function, falls risk, or quality of life with vitamin D supplementation in subjects with vitamin D deficits [50, 91]. In community-dwelling older persons, a meta-analysis from 15 studies including 2866 participants aged of 65 years and older, reported no significant improvement in muscle strength after the administration of vitamin D [119]. The difference in muscle mass and strength response between studies may in part be attributed to differences in the dose of vitamin D used (with better outcomes seen when higher doses are used), the differences in measurement techniques (handgrip dynamometer vs. leg press), age, and serum vitamin D level at baseline [39, 40, 50]. Response to vitamin D supplementation may also depend on baseline levels of 25(OH)D and protein intake. A sufficient baseline levels of 25(OH) D and protein intake may be required to increase muscle mass[120].

Taking into account the high prevalence of vitamin D deficiency (more than 70%) among institutionalized subjects, vitamin D supplementation has to be considered as a possible approach to prevent sarcopenia and to improve the effects of sarcopenia in terms of morbidity and mortality in this population. Vitamin D plasmatic levels should be measured in frail older people and in particular in institutionalized individuals. Vitamin D oral supplementation should be provided to subjects with vitamin D plasmatic levels lower than 40 nmol/l [121]. The recommended daily intake of vitamin D is between 400 and 600 IU per day which may be insufficient to raise serum vitamin D levels to a desirable level of 75–100 nmol/l [50]. Some studies have demonstrated that in order to achieve optimal levels of 25(OH) vitamin D, doses between 700 and 1000 IU would be needed [50]. In the United States, fortification of some foods – such as milk and orange juice – is mandatory, whereas in European countries only a few foods are fortified with vitamin D. However, the question of whether it should be obligatory for food products to be added with vitamin D remains controversial [50].

Mechanism of action

Several mechanisms of action have been suggested for the role of vitamin D on muscle function (Figure 25.6). The activation of the vitamin D receptors in skeletal muscle results in protein synthesis and subsequent muscle cell growth. Muscle anabolism decreases when vitamin D plasma level is low [39, 91]. Low levels of vitamin D influences muscle protein turnover through reduced insulin secretion and increase myofibrillar degradation [39]. Some authors have observed histological muscle atrophy – predominantly type II fibers – in the presence of vitamin D deficiency [122].

Vitamin D supplementation for three months in a small, uncontrolled study resulted in significant increases in the relative number and size of type II muscle fibers in older women [123]. Similarly, it is observed that a supplementation of 1000 IU of vitamin D per day in older stroke survivors increased type II muscle fiber mean diameter by 2.5-fold over a two-year period [124].

Nuclear vitamin D receptors have various genetic polymorphisms which have been associated with muscle mass. Vitamin D and vitamin D receptors have a direct effect on both the metabolic processes and the transcriptional regulation of skeletal muscle. In combination with other factors, vitamin D linked with its nuclear receptor can modulate gene expression of proteins such as protein involved in the metabolism of calcium or IGFBP-3. Muscle function may also be influenced by vitamin D membrane receptors through the ability to modulate the membrane calcium channels of the muscle fibers.

Finally, recent researches indicate that vitamin D supplementation is associated with decreases in pro-inflammatory and increases in anti-inflammatory cytokines. Given that inflammation has been proposed as a cause of sarcopenia onset and progression, improved vitamin D status may prevent functional declines through lowering inflammation levels [125].

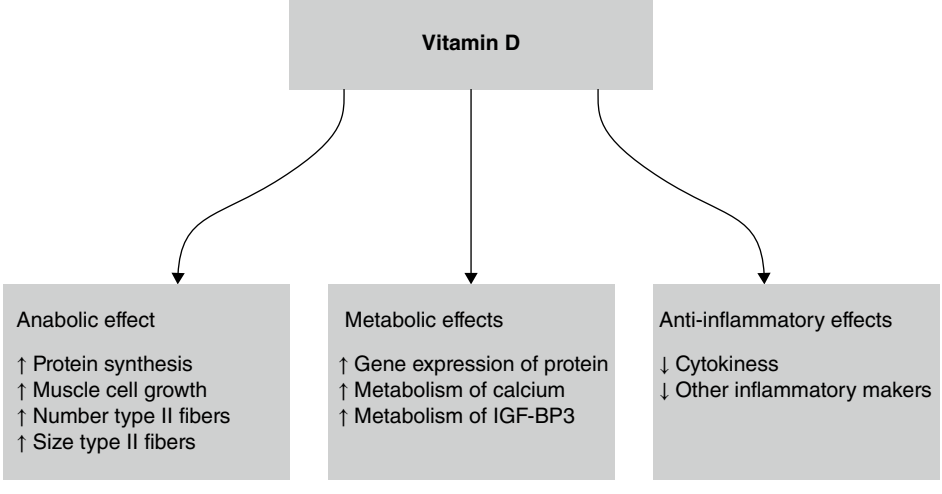

Figure 25.6 Effect of vitamin D on skeletal muscle.

B-HYDROXY B-METHYLBUTYRATE

The β-hydroxy β-methylbutyrate (HMB) is an active metabolite of leucine, a branched-chain essential amino acid, and it is synthesized from leucine in muscle and liver cells. HMB [126] is found in very small amounts in some foods, such as avocado, citrus, fruit, cauliflower, and catfish. Traditionally used by athletes and bodybuilders in the form of calcium salt HMB monohydrate (CaHMB) to enhance performance and build muscle mass, its use seems to play an important role in preserving or rebuilding muscle mass in populations in whom loss of LBM would increase risk for injury, disability, or mortality. Proteins, essentials amino acids or specific HMB supplementations, are able to increase muscle protein synthesis rates and to inhibit protein breakdown. Aging process per se does not impact skeletal muscle protein breakdown rates [127]. Targeting muscle protein synthesis could be promising in the prevention of muscle loss and sarcopenia during aging [126].

Clinical experience

HMB has been widely studied in healthy adults, alone and in combination with other amino acids, as an adjunct to exercise to help improve body composition and physical performance. Several studies support the effectiveness and the safety profile for HMB supplementation at the daily dose of 3 g [128] per day, in decreasing delayed onset of muscle soreness and markers of muscle damage, increasing LBM without fat gain, increasing various markers of physical performance, including muscle mass and strength.

A randomized, double-blind, placebo-controlled study demonstrated that 12 weeks of HMB supplementation in combination with arginine and lysine increased the rate of protein synthesis approximately of 20%, significantly improved the body composition and physical performance ("get-up-and-go" test performance improved 17% vs. no change with placebo), and significantly enhanced the muscle strength (knee flexor and extensor force, and handgrip) in older women [129]. In a randomized, double-blind, placebo-controlled study, Vukovich and colleagues evaluated the effects of adding 3 g of HMB per day (n = 14) or placebo (n = 17) to a five-days/week program of weight training in healthy men and women (mean age 70 years) [130]. After eight weeks, older adults taking HMB alone showed significant improvement from baseline in body composition compared with those who were taking placebo (change in LBM +0.8 kg with HMB, –0.2 kg with placebo) [95]. The HMB plus arginine and glutamine supplementation improved nitrogen balance in severely ill trauma patients, indicating increased protein synthesis. A randomized trial examined the effects of HMB supplementation on inflammation, protein metabolism, and pulmonary function in patients requiring mechanical ventilation for chronic obstructive pulmonary disease. After seven days, patients who received HMB had significant reductions in C-reactive protein and in white blood cell counts from baseline [131]. In addition, 56% of subjects in the HMB group had improved pulmonary function compared with only 25% of the subjects in the control group. More recent studies supported those findings and underlined the possible key role of HMB supplementation in increasing protein synthesis in older and critical care patients. A randomized, double-blind pilot trial demonstrated

in Phase I that, in men and women aged over 65, prolonged supplementation with CaHMB improved total lean mass, strength, function, and muscle quality without resistance exercise. In Phase II, similar results were obtained with the high-intensity resistance training protocol with or without CaHMB, but this second group showed a significant decreased total fat mass along with the increased total lean mass and arm muscle quality [132]. Again, a randomized, controlled, double-blind, parallel-group design study carried out in 24 healthy older adult subjects, confirmed that the HMB supplementation preserved muscle mass during 10 days of bed rest [133]. Another parallel-group, randomized, controlled, open-label trial, demonstrated that the oral supplement of 1.5 g of calcium HMB for eight weeks, did significantly improve several muscle strength and physical performance parameters in a group of community-dwelling healthy older women, but had no significant effects on the SPPB [134]. In another study, the authors found that a HMB-enriched diet improved muscle mass and functional performance overall preventing the onset of sarcopenia in older patients with hip fractures [135]. A very recent double-blind placebo controlled trial, analyzed the incremental effect in relation to muscle hypertrophy found in older aged men subjected to a HMB-free acid supplementation adjunct to resistance exercise training [136].

A recent review underlined how the administration of high-protein HMB-enriched oral nutritional supplements could be a tool to mitigate the decline connected with sarcopenia by maintaining and improving in muscle mass, preserving muscle function and ameliorating clinical outcomes in hospitalized patients [137]. Finally, a very recent systematic review and meta-analysis of randomized controlled trials showed that HMB, and supplements containing HMB, increased muscle mass and strength in a variety of clinical conditions characterized by loss of muscle mass and skeletal muscle weakness, including aging and critical illness or particular conditions such as in the case of older care home residents receiving tube feeding, hospitalized older people with malnutrition/sarcopenia or undergoing orthopedic intervention, in patients with cancer or rheumatoid cachexia, HIV, maintenance hemodialysis, and bronchiectasis [138].

Mechanism of action

The HMB exerts its effects through protective, anticatabolic mechanisms and has been shown to directly influence protein synthesis. The HMB has been shown to stabilize the muscle cell membrane, to modulate protein degradation, and to up-regulate protein synthesis [139]. As a substrate for cholesterol synthesis in the muscle cell, HMB contributes to the strengthening of the cell membrane. In this way, HMB helps to stabilize the muscle cell membrane to keep the muscle cell intact. Furthermore, it selectively inhibits intracellular inflammation to attenuate protein degradation pathways. A prospective, randomized, double blinded, placebo-controlled investigation, for 10 weeks studied the effect of HMB supplementations in older adults who underwent 10 days of bed rest followed by eight weeks progressive resistance training rehabilitation program of the upper and lower extremities three times per week and consumed a placebo or calcium HMB. Results showed that HMB stimulated an increase in triacylglycerol fatty acid pool, which may protect the muscle from other bioactive lipid species known to stimulate ROS and inflammatory pathways. Moreover, during the rehabilitation phase, HMB increased mitochondrial oxidative phosphorylation content and dynamics compared with the

placebo control, preserving muscle mass during bed rest time and enhancing muscle strength during exercise recovery [140]. The HMB inhibits the activation of caspase-8, thereby preventing the downregulation of protein synthesis and increasing inhibition of protein degradation initiated by nuclear factor kappa B (NFκB) [141]. Thus, by inhibiting caspase-8 activation on the cell membrane, HMB maintains protein synthesis and prevents additional protein degradation. In addition, the HMB increases protein synthesis directly by activating mammalian target of rapamycin (mTOR), an intracellular protein that controls protein synthesis. It is the active leucine metabolite that consistently activates the mTOR signal pathway. IGF-1 is one of the growth factors that activates mTOR in muscle cells. The HMB also activates mTOR, and its effects are boosted by IGF-1. In this way, HMB may help overcome the age-related reduction in tissue response to endogenous GHs such as IGF-1 that contributes to sarcopenia [142]. Moreover, HMB-treatment was found to enhance the proliferation of muscle stem cells, increasing the number of satellite cells fast twitch plantaris muscles of aged rats. Also, HMB increased the nuclear protein abundance of proliferation markers such as inhibitor of differentiation-2 and cyclin A. The proliferation of satellite cells leads to an increased number of differentiated myonuclei which eventually is able to support muscle hypertrophic changes and functional changes in sarcopenic muscles[143].

OTHER POSSIBLE PHARMACOLOGIC APPROACHES

Selective androgen receptor modulators

Synthetic androgen modulators such as selective androgen receptor modulators (SARMs) are potential alternatives to testosterone. SARMs have the same anabolic effect on muscle tissue as testosterone, without its undesirable side effects of treatment obtained by improving the tissue selectivity of this drug. One trial in healthy older men and women has been conducted with the SARM, ostarin. This study demonstrated that a three months treatment with ostarin increased muscle mass and stair climbing power [144]. Another six months randomized controlled study, involving 170 women aged 65 years and older with sarcopenia and moderate physical dysfunction, investigated the benefit of treatment with SARMs (MK-0773) versus placebo. All participants received vitamin D and protein supplementation. A statistically significant increase in LBM was observed in participants receiving the SARMs but no improvement was observed in muscle strength or physical performances [145]. These new drugs may expand the clinical application of androgens in sarcopenia as they enter the clinical phase research. In particular, one of the biggest potential advantages of SARMs is that these drugs might be safe to use in women. With improved tissue selectivity, SARMs that maintain the anabolic actions of androgens without causing the undesirable side effects associated with traditional androgen therapies would really expand the sarcopenia therapeutic options for androgen use in women. Cancer cachexia, a muscle wasting due to cancer, is also an important field of investigation for SARMs. The future of SARMs for the treatment of sarcopenia will depend on results of ongoing trials.

Phytoestrogen supplementation and isoflavones

A potential approach to prevent or to treat sarcopenia might be phytoestrogen supplementation. Isoflavones are produced almost exclusively by the members of the Leguminosae family and most of them act as phytoestrogens. Some clinical studies investigated the effect of soy isoflavone supplementation on muscle mass and physical performance.

Aubertin-Leheudre and colleagues [146] demonstrated that a 70 mg per day of soy isoflavone supplementation for a period of 24 weeks in obese sarcopenic postmenopausal women was associated with a significant increase in fat-free mass (+0.5 kg). In a randomized study conducted in postmenopausal women, Moeller and colleagues have shown that LBM increased to a greater extent in the isoflavone-rich group (+3.4%) than in the isoflavone-poor (+1%) or control (0%) groups [147]. More recently, Maesta and colleagues [104] evaluated the combined effect of soy protein (25 g) with resistance training on body composition in postmenopausal women. This study showed that soy protein combined with 16 weeks of resistance training did not result in greater increases in muscle mass compared with resistance training alone, suggesting that soy protein supplementation had no influence on muscle mass. Similar results were found in a more recent study which showed that adding soy protein to milk resulted in a greater increase in muscle strength but not in muscle gain after 16 weeks of resistance training in healthy postmenopausal women [148].

Phytoestrogens may have a beneficial effect on muscle mass, possibly because of their affinity to estrogen receptor-α, which is found on muscle, or through their effects on reducing inflammation. One animal study demonstrated that chronic high-soy-protein diet was effective to reduce the activation of pathway involved in muscle protein degradation [149]. In particular, isoflavones supplements are found in soy products and exert its effects through a lipid-lowering effect, favor vasodilatation as well as arterial compliance and the regulation of fasting glucose and insulin levels [150]. Some isoflavones, in particular soy isoflavones, when studied in populations eating soy protein, have indicated that there is a lower incidence of breast cancer because of its role in influencing sex hormone metabolism and biological activity through intracellular enzymes, protein synthesis, growth factor actions, and angiogenesis [150].

Melanocortin-4 receptor antagonists

The melanocortin-4 receptor (MC4R) is a G-protein-coupled receptor that is expressed in the hypothalamus. It plays an important role in the regulation of food intake, energy expenditure, and catabolism [39, 91]. The central melanocortin system seems important in the pathogenesis of cachexia. Its effect on feeding behavior and the metabolic rate is mediated by MC4R.

In mice, stimulation of the MC4R has been demonstrated to decrease food-seeking behavior, to increase basal metabolic rate and to decrease LBM [91]. In humans, mutations of the MC4R resulted in severe obesity [151]. On the other hand, blockade of central melanocortin signaling increased both LBM and fat mass in a rat model of cardiac cachexia [152].

Inhibition of the melanocortin system either through antagonism or by an antibody against the MC4R has shown encouraging results in animal models of cachexia. A MC4R antagonist was reported to have beneficial effect in attenuating body composition changes – such as sarcopenia – related to cachexia [91]. Clinical trials in humans are awaiting for this promising candidate for the treatment of sarcopenia.

Ornithine alpha-ketoglutarate

Ornithine alpha-ketoglutarate is a precursor of biologically active amino acids such as glutamine and arginine, and other active compounds that are important in the regulation of protein metabolism in skeletal muscle. Ornithine has a potent effect on the secretion of anabolic hormones, like insulin and GHs; furthermore, it is not only a precursor of active metabolites and hormones but important interactions exist between each component produced after ornithine supplementation [153].

Supplementation of total parenteral nutrition with ornithine alpha-ketoglutarate has been shown to maintain nitrogen balance and to reduce skeletal muscle protein breakdown after abdominal surgery [153]. Ornithine alpha-ketoglutarate has been demonstrated to improve nutritional status when given to older patients soon after discharge from hospital. In a study conducted on 370 free-living malnourished older subjects (mean age 80.0 ± 0.5 years), a significant beneficial effect on weight, body mass index, and plasma albumin and transthyretin was noted after ornithine alpha-ketoglutarate supplementation compared with the control group receiving only a placebo [153].

Ornithine alpha-ketoglutarate by its various direct and indirect potential actions on protein metabolism could be a valuable candidate to limit muscle weakness in older subjects with sarcopenia. However, the possible effect of ornithine supplementation on muscle mass and strength has never been investigated in sarcopenic subjects without nutritional problems.

Leptin

The cytokine-like hormone leptin is an important factor linking food intake with energy expenditure and subsequently body composition. Leptin is an adipokine secreted by the adipose tissue that downregulated satiety and the size of adipose tissue mass, but muscle is also a primary source of leptin, and serum leptin levels increase with increased muscle mass. Leptin has also been reported to regulate several physiological processes including skeletal muscle protein synthesis. Leptin receptors are abundant in both skeletal muscle and bone-derived mesenchymal stem cells [154] and their expression is elevated with disuse atrophy, bone loss, and leptin deficiency increases expression of the muscle-wasting protein myostatin [155]. Central leptin resistance can increase with age, and low circulating levels of leptin have been observed among frail older persons. Leptin treatment in vitro increases the expression of myogenic genes in primary myoblasts, and leptin treatment in vivo increases the expression of microRNAs involved in myogenesis [154].

Leptin-deficient mice are obese and display a reduced skeletal muscle mass [39]. Hamrick and colleagues demonstrated that leptin supplementation increased the relative mass of quadriceps muscle in aged mice as well as the fibers size of skeletal muscle fibers in the extensor digitorum longus [155]. These results are consistent with previous work in leptin-deficient ob/ob mice, where recombinant leptin therapy increased muscle mass in part by suppressing myostatin. Exogenous leptin is capable of inducing a significant anabolic response in skeletal muscle, as well as producing changes in the expression of specific miRNAs. While leptin supplementation plays an important role in metabolism of skeletal muscle of aged mice, leptin is able to regulate 37 miRNA gene expression, but to reverse only three dysregulated miRNAs in aged mice (miR-685, miR-142-3p, and miR-155), suggesting that other therapeutic approaches need to be investigated in order to target certain miRNAs identified in aged muscle [155].

In clinical practice, obese patients may not be the target population to benefit from leptin supplementation as they exhibit leptin resistance [39]. This leptin resistance appears to be due to hypertriglyceridemia and as a consequence lowering triglycerides may overcome the leptin resistance. Moreover, a study by Kohara et al. investigated the relationship among plasma leptin levels, femoral muscle sarcopenia, and visceral obesity in middle-aged to older men and women. Plasma leptin levels were found to significantly, independently, and negatively related to femoral muscle cross-sectional area. Also, leptin levels were higher in subjects with both femoral muscle sarcopenia and visceral obesity than in those with only one condition highlighting the importance of sarcopenia in understanding the pathophysiological aspect of obesity in older populations [156]. Also in osteoarthritis patients with sarcopenic obesity serum leptin levels were significantly higher than those with non-sarcopenic obesity. Furthermore, high serum leptin was negatively associated with vitamin D and physical performance, in particular reduced muscle strength and functional impairment [157]. Overall, aging is associated with bone loss and muscle atrophy, contributing to frailty, postural instability, and falls. Therapeutic interventions such as protein and amino acid supplementation that can increase muscle mass and muscle-derived leptin may have multiple benefits for older patients [157].

Myostatin inhibition

Myostatin, also identified as growth differentiation factor-8, is a member of the transforming growth factor-β (TGF-β). It is expressed almost exclusively in skeletal muscle and it has an important role for the normal metabolism of muscle mass [91]. Myostatin inhibits myoblast proliferation and thus acts as a negative regulator of skeletal muscle mass [91]. Myostatin inhibition may, therefore, represent an interesting therapeutic approach to sarcopenia prevention and treatment. It was originally discovered when mutations of the myostatin gene were found to be associated with muscle hypertrophy [50].

Animal studies demonstrated that antibody-directed myostatin inhibition improves muscle mass and function in aging mice [91]. Murphy and colleagues reported a statistically significant increased muscle mass by 8–18%, muscle fiber size by 12% and muscle strength by 35% after 14 weeks of myostatin antibody treatment. At the same time, the rate of type II fibers increased by 114% and muscle fiber oxidative capacity

improved by 39% [158]. These results also extend those observed in middle-aged (13–16 months) mice, where six-week treatment with a myostatin antagonist enhanced grip strength [159]. In animals and humans, mutations in the myostatin gene result in increased muscle mass. A single gene myostatin inhibitor enhances muscle mass and strength in the mouse. Antagonism of myostatin enhanced muscle tissue regeneration in aged mice.

Different approaches to inhibit the negative effects of myostatin on skeletal muscle are presently under development. Hormones such as follistatin – a myostatin-binding protein – or drugs such as trichostatin-A can antagonize myostatin and are potential new drugs for sarcopenia treatment [160]. Inhibition of myostatin with follistatin may have potential therapeutic benefits on skeletal muscle. The effects of follistatin, originally named FSH-suppressing protein (FSP), are multiple. It induces muscle hypertrophy through satellite cell proliferation by inhibiting both myostatin and activin. Recombinant human antibodies to myostatin are currently tested in human suffering of muscular dystrophy. Phase II trials have been carried out in muscular dystrophy and preliminary results have shown that MYO-29, a recombinant antibody to myostatin, had good safety and tolerability profile [161]. In the future, gene administration of myostatin-inhibitor-proteins may also to be an option to enhance muscle mass and strength. However, it has been reported that muscle tissue may be more susceptible to muscle and tendon injuries in mice with myostatin deficiency [50].

Recently, two Phase II randomized trials investigated the efficacy and safety of myostatin antibody versus placebo in older patients. The first trial [162] assessed the efficacy of a humanized monoclonal antibody targeting myostatin, in patients undergoing elective total hip arthroplasty. Four hundred subjects aged ≥50 years scheduled for elective total hip arthroplasty for osteoarthritis were randomized for placebo or different doses of subcutaneous injections of myostatin antibody (35, 105, or 315 mg) at weeks 0, 4, 8, and 12 with follow-up until week 24. A dose-dependent increase in appendicular LBM and decreases in fat mass were observed in the intervention group. In the second study [163], the aim was to test whether myostatin antibody increases appendicular LBM and improves physical performance in older individuals who have had recent falls and have low muscle strength and power. Ninety-nine participants were randomly assigned to receive placebo and 102 to receive the myostatin antibody. Subcutaneous injections of placebo or 315 mg of myostatin antibody at weeks 0, 4, 8, 12, 16, and 20 were performed. The authors reported an increased in lean mass (between-groups difference = 0.43 kg (95% confidence interval [CI] 0.192–0.660; $p < 0.0001$) and a trend of improvement of functional measures of muscle power. Taken together, these encouraging results suggest that additional studies are required know whether myostatin antibody can reduce the risk of falls or physical dependency in frail older patients.

Bimagrumab is a human monoclonal antibody that binds to type II activin receptors and prevents the binding of its ligands (e.g. myostatin, activin A) which usually act as inhibitors of muscle growth and protein anabolism. Bimagrumab would act blocking these ligands therefore increasing muscle mass in young and older adults 3. A 24-week, randomized, double-blind, placebo-controlled, parallel-arm, proof-of-concept study by Rooks et all. evaluated the effect of pharmacological treatment with Bimagrumab in community-dwelling adults aged 65 and older with sarcopenia and mobility limitations. Participants were randomly assigned (1:1) to receive Bimagrumab 30 mg/kg intravenous or placebo. Body composition with DXA, grip strength, six-minute walk distance,

gait speed and safety of the drug were assessed. After one of two doses of Bimagrumab patients showed increase in thigh muscle volume, LBM, appendicular lean mass, and reductions in body fat mass compared with the placebo group. Also, improvements in mobility-based physical function were showed. Finally, Bimagrumab was safe and well tolerated in older adults 1. [164].

A double-blind, placebo-controlled trial by the same authors, evaluated the clinical potential of Bimagrumab for the recovery of skeletal muscle volume from disuse atrophy in healthy young males. A full-length cast was placed on all participants on one of the lower extremities for two weeks. After cast removal, subjects were randomized to receive a single intravenous (i.v.) dose of either Bimagrumab 30 mg/kg or placebo. Following the two weeks of joint-immobilizing cast, participants who received Bimagrumab safely accelerated the recovery of tight muscle volume and lowered the accumulation of thigh muscle volume and reversal of accumulated intermuscular adipose tissue. Given those findings, further evaluation of Bimagrumab in older adults with lower skeletal muscle mass and impaired physical function are wished 2. [165, 166]

Agents that target the myostatin pathway may be useful in increasing muscle mass and, therefore, play an important role in muscle wasting disorders as well as age-related sarcopenia [50]. At present, no other conclusive data have been reported from human studies [91].

CONCLUSIONS

Some promising results of clinical studies suggest beneficial effects of several drug classes for the prevention and treatment of sarcopenia in older adults. As shown, these medications with various mechanisms may influence muscular outcomes which may contribute to age-related physical decline. However, despite being extremely exciting for the geriatric community, these results are not sufficiently strong to support routine use of these medications to prevent disability and functional impairment in older adults and further studies are needed to confirm the hypothesis that these drugs could provide an effective intervention to prevent physical decline in older persons, leading to greater autonomy in this growing population.

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CHAPTER 26

Sarcopenia: Is It Preventable?

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INTRODUCTION

Sarcopenia is a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality [1]. As befits an age-related trait, the process of sarcopenia is universal with age. Indeed, most human physiologic systems regress with aging, independently of substantial disease effects, at an average linear loss of 0.34–1.28% per year between the age of 30 and 70 [2]. Therefore, sarcopenia can be considered as the effect of aging on muscle mass in every human being. This is true even for athletes who, although they continue to be physically active and perform at levels well above those of sedentary adults, demonstrate a decline in lean tissue with age [3]. Next to the intrinsic, age-related processes, a multitude of extrinsic and behavioral factors can aggravate the development and/or progression of sarcopenia; such as disuse and lack of physical activity, malnutrition, chronic inflammation, and (co-)morbidity. The relative contribution of these factors can show important variability from person to person and, therefore, there is a huge variation in the loss of muscle mass and muscle strength between individuals. Some older people have a muscle mass that is comparable to that of younger adults, whereas other older adults have a muscle mass that is so low that it compromises their functional abilities. Sarcopenia, thus, can be thought of as both a process and an outcome.

AGE-RELATED CHANGES IN BODY COMPOSITION

The age-related changes in body composition develop very gradually. Muscle mass begins to decline at approximately 1% per year after the age of 30. Longitudinal changes in body composition show in men a tendency to gain fat and lean mass

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

through their 40s, followed by a trend toward weight loss, resulting in the loss of both compartments after age 60 years [4]. Studies in women show consistent gains in fat across the age spectrum. Cross-sectional data suggest that whole-body protein declines curvilinearly with age, such that there is an accelerated decline after 65 years of age [5]. Recently, it has been shown that there is an exponential increase in the loss of lean tissue in subjects older than 75 years compared to younger older people [6]. Initially clinical relevance is very low, symptoms being absent. In later stages the loss of muscle mass has been shown to be associated with disability. However, the development of disability is a very complex area and is almost always multifactorial in these subjects. Whether sarcopenia becomes a clinically evident problem depends on many factors, including the starting level of muscle mass and the rate of its decline. There are several mechanisms that may be involved in the onset and progression of sarcopenia. These mechanisms involve, among others, protein synthesis, proteolysis, neuromuscular integrity, and intramuscular adipose tissue [7, 8]. In an individual with sarcopenia, several mechanisms may be involved, and relative contributions may vary over time. It would be interesting if the effects of aging *per se* could be separated from the effects of chronic disease or physical activity, which itself tends to decline with age.

PREVALENCE OF SARCOPENIA

The general trend in prevalence studies of sarcopenia is that in older cohorts prevalence rises both in men and women with an even higher prevalence in men. Several longitudinal studies indicate that muscle mass and size decrease by approximately 6% per decade in the average person beginning at approximately 45 years of age [9]. In the existing literature, a wide variability in prevalence has been reported depending on the criteria used [10, 11]. Some authors estimate the prevalence of sarcopenia at 5–13% in the 60–70-year-olds and 11–50% for the population aged 80 years or older [12–14]. Additionally, the variation in the prevalence of sarcopenia is higher in women compared to men [11]. However, it can be assumed that in a specific age cohort people who do not fulfill criteria for the diagnosis of sarcopenia also have lost muscle both in a qualitative and quantitative way. Indeed, they have been and still are exposed to the same pathophysiological mechanisms as those who actually fulfill the criteria for sarcopenia. So, it can be said that the prevalence of sarcopenia in the older adult population reaches a 100%. The diagnosis, however, based on cut-off values [15], such as two standard deviations below a reference value for age- and gender-adjusted young healthy adults, converts the continuous process of muscle mass loss into a categorical one with categories such as pre-sarcopenia and sarcopenia [16]. This approach is designed for the identification of subjects with an already existing sarcopenia and presenting with a (risk for the development of) functional disability due to muscle weakness. As with other degenerative conditions, it is open to debate whether everybody will eventually develop sarcopenia up to a degree corresponding to the diagnostic criteria proposed.

PREVENTION

Preventing disability involves a wide range of interrelated programs, actions, and activities from different parties. It involves public health policy makers as well as health-care practitioners (physicians, nurses, and allied health professionals) working

Table 26.1 Level of prevention according to the condition of the patient (presenting with or without possibly sarcopenia related symptoms) and the evaluation of the practitioner (based on performance-based evaluation).

		Sarcopenia signs doctor	
		Absent	**Present**
Sarcopenia symptoms patient	**Absent**	Primary prevention	Secondary prevention
	Present	Quaternary prevention	Tertiary prevention

Table 26.2 Preventive intervention system with universal, selective, and indicated prevention levels.

Prevention	Target	Aim	Action
Universal	Entire population	To prevent or delay sarcopenia	Information and skills to prevent sarcopenia
Selective	Groups whose risk of developing sarcopenia is above average	To prevent or delay sarcopenia	• Information about nutritional supplements • Websites for active seniors
Indicated	• To identify individuals who exhibit early signs of sarcopenia • Identifiers may include low muscle functionality and increased falls	Involves a screening process	Specific and personal interventions in nutrition and exercise

at different levels. Preventive strategies are typically described as taking place at the primary, secondary, tertiary, and quaternary levels (Table 26.1). Next to the typical levels of prevention other preventive intervention classification systems have been proposed in the area of disease prevention by Gordon [17]. They consist of a three-tiered preventive intervention system with universal, selective, and indicated prevention levels (Table 26.2). This three-step model overlaps partly with primary and secondary prevention from the more traditional model but it can help with supplying specific prevention strategies in the algorithm for the prevention of sarcopenia. The effectiveness of prevention programs, however, largely depends on the extent to which individuals take personal responsibility for their own health and are willing to follow recommendations regarding healthy lifestyle including nutrition and exercise.

Primary

Primary prevention includes actions to protect against disease and disability before they occur. Today, the most pressing health problems in developed countries are chronic diseases and conditions based on the increasing multimorbidity found in people growing older. This increasing multimorbidity is the cradle of the geriatric syndromes. Primary prevention of such syndromes is more challenging than primary prevention of

well-defined diseases because it requires changing health behaviors. In the case of sarcopenia this includes the basic activities of a healthy lifestyle such as good nutrition and adequate exercise and rest. However, efforts to change deeply rooted and often culturally influenced patterns of behaviors, such as diet and physical inactivity, generally have been less successful than environmental health and immunization programs.

Secondary

The goal of secondary prevention is to identify and detect a disease or a condition in its earliest stages, before noticeable symptoms develop, when it is most likely to be treated successfully. With early detection and diagnosis, it may be possible to reverse a condition, slow its progression, prevent or minimize its complications, and limit ensuing disability. With better insights into the pathophysiology of sarcopenia, more studies are needed using techniques that not only visualize muscle quantity, but also muscle quality, such as computed tomography (CT), magnetic resonance imaging (MRI), or more useful in clinical routine practice, ultrasound [18].

Tertiary

Tertiary prevention programs aim to improve the quality of life for people already affected by a disease or condition by limiting complications and disabilities, reducing the severity and progression of the condition and providing rehabilitation to restore functionality and self-sufficiency. For sarcopenic older adults, medication, nutritional, or exercise interventions could improve quality of life by for improving mobility and independency.

Quaternary

This term describes the set of health activities that mitigate or avoid the consequences of unnecessary or excessive interventions in the health system.

PREVENTION STRATEGY

In the strategy of dealing with sarcopenia, prevention should be distinguished from treatment. However, interventions will target similar underlying pathophysiological processes. The difference lies in the actual support and coaching of the individual. Therefore, an algorithm for management of the sarcopenia process should be developed to guide the actual interventions needed in different stages.

Sarcopenia as "a condition" is a major cause of frailty and disability in older people, but as "an active process" it is present in every person reaching adult life. Given the intrinsic, age-related character of sarcopenia, primary prevention, if possible, should start as early as the onset of the underlying process (i.e. at a young adult age);

at higher ages, secondary and tertiary preventive strategies can be considered in order to avoid excessive progression of sarcopenia (see Table 26.1 for definition of prevention levels).

In the primary prevention strategy, people should be clearly informed about evidence-based approaches in order to preserve muscle mass and performance as long as possible. At the same time their awareness for (often commercial) non-evidence-based anti-aging treatments should be raised. When consulting PubMed (last search on 15 September 2019) for peer-reviewed publications with the keywords SARCOPENIA AND PREVENTION, 482 hits were found (434 hits when limited for reports on humans only). Based on the existing body of knowledge, physical exercise and nutrition seem to be the major elements in all levels of the prevention of sarcopenia.

In order to identify individuals for primary, secondary or higher prevention levels, low-cost, but sensitive assessment tools are necessary. Although a universal consensus definition of sarcopenia is lacking, the actual proposed screening algorithms are focused at identifying subjects corresponding to the diagnostic criteria for sarcopenia (i.e. T-score < -2 for muscle mass and/or strength). In fact, using these criteria, subjects presenting with an (increased risk for) sarcopenia-related disability can be identified. In this context, the European Working Group on Sarcopenia in Older People recently revised their original case-finding algorithm from walking speed to screening with the SARC-F questionnaire and then measuring grip strength [1, 16]. In order to identify subjects susceptible for primary and secondary prevention, the phase corresponding to decreased gait speed is probably too advanced, and suggests already an indication for tertiary prevention and/or treatment. Therefore, muscle performance assessment, using an easy and reliable method, and providing a score on a continuous scale, is probably more suitable to identify persons with sarcopenia-induced muscle weakness without presenting clinical signs of functional disability. Grip strength is easy to measure, and age-related changes in grip strength are well described [19] and run parallel to the strength losses in other muscle groups [20]. Therefore, grip strength was put forward as the preferential screening tool for muscle strength in aging after using a very short screening questionnaire (SARC-F). Because daily activities often require sustained intense muscle contractions (e.g. when bearing shopping bags), sarcopenia could incur a sense of fatigue in older persons. Therefore, muscle fatigue can be proposed as a supplementary factor in the screening for early signs of muscle weakness. Recently, a fatigue resistance test based on grip strength (expressed as the time for grip strength to decrease to 50% of its maximum during sustained contraction) as well as a simple equation to calculate grip work (0.75 × fatigue resistance × maximal grip strength) has been elaborated and validated. This resistance test could be easily integrated in the early assessment [21–25].

Here, we propose a clinical decision-making algorithm for the preventive management of subjects/patients in the stages before sarcopenia-induced disability becomes apparent (see Figure 26.1). Primary prevention targets all subjects of adult age, presenting grip strength corresponding to levels higher or within the gender-matched normal values that can be expected at young age. Secondary prevention targets subjects that show lower grip strength, but still above the statistically defined cut-off points (T-scores or $p < 0.05$ levels)[12, 16, 19, 21] and without signs of sarcopenia-induced functional disability (as proposed in the "diagnosis" of sarcopenia) [12, 16].

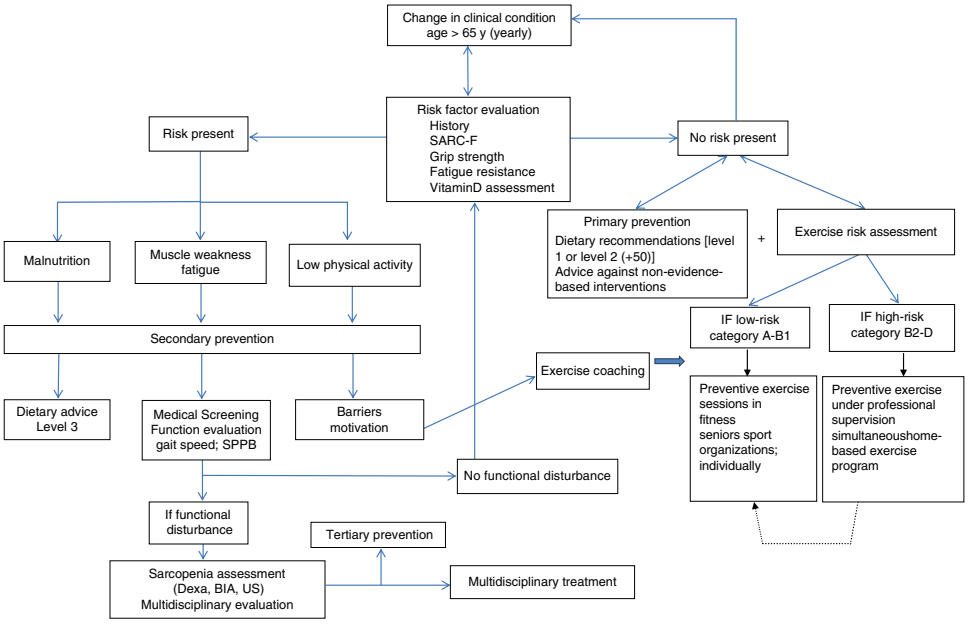

Figure 26.1 Clinical decision-making algorithm for the preventive management of subjects/patients in the stages before sarcopenia-induced disability becomes apparent.

PHYSICAL EXERCISE

Regular physical activity is one of the major elements in general health prevention. In order to obtain significant health benefits, 30 minutes of moderate physical activity on a daily basis is recommended [26]. Physical exercise can be prescribed in a wide variety of modalities, depending on the intensity (load or resistance, number of repetitions, number of series), duration, frequency and type (weight lifting, walking or running, bicycling, etc.). Resistance training, preferentially at higher intensity and higher frequency (i.e. three times per week instead of once or twice a week), appears to be the most appropriate physical exercise modality in order to prevent loss of and/or improve muscle strength in healthy older persons [27–29]. This type of training consists classically of three series of 10–12 repetitions at 70–85% of the one repetition maximum (1 RM = the weight that can be moved maximum once over the whole range of movement). A frequency of one to three exercise sessions per week leads to optimal results [30]. With this training regimen excessive age-related strength loss can, at least partly, be countered and significant gains in muscle strength can be obtained within a short time [27, 31, 32]. For frail older adults, similar resistance exercise interventions are recommended with higher focus on a gradual increase starting from 20 to 30% up to 80% of the 1 RM is recommended. In addition, functional and balance training should be implemented in order to stimulate daily functioning [30]. Very recently, the Belgian Society for Gerontology and Geriatrics published recommendations for exercise interventions in older adults in which high-resistance training interventions at 70–80% of the 1 RM are recommended for improving muscle strength, muscle mass, and physical performance. Multimodal exercises and blood flow restriction resistance training may be considered as well [33].

The mechanisms through which physical activity maintains muscle mass and performance are complex and incompletely understood. Physical exercise (especially resistance exercise) stimulates muscular protein synthesis by activating the insulin-like growth factor-1 (IGF1) signaling pathway (acting via protein kinase B [AKT], mammalian target of rapamycin complex [mTOR], and further downstream signaling), and suppresses protein degradation (via FOXO, and via repression of nuclear factor κB [NF-κB] and the ubiquitin-proteasome pathway) [34].

Interestingly, regular physical activity has also a strong regulating effect on systemic inflammatory processes [35, 36]. In fact, aging, even in healthy persons, is commonly accompanied by slightly elevated concentrations of circulating pro-inflammatory mediators (such as Interleukin [IL]-6 and tumor necrosis factor-α), a phenomenon corresponding to a chronic low-grade inflammatory profile (CLIP) [37]. Older persons presenting more pronounced CLIP show indeed lower muscle mass and muscle strength [38, 39]. Besides providing anabolic stimuli, it is well known that intensive physical training provokes an inflammatory reaction, accompanied by the liberation of pro-inflammatory cytokines (especially IL-6) [40] and complex changes in the cellular components of the immune system. In this context, IL-6 is thought to be mainly released from the contracting muscles and would act as a "myokine," exerting a different function from that seen during e.g. acute infections [40]. The acute phase response to exercise is positively related to the intensity of the muscle work delivered. Recently, it has been shown that older persons, similar to young adults, are able to respond to physical stress by a significant exercise-induced increase of circulating IL-6 [41, 42]. In

fact, the exposure to (repetitive) mild stress has been shown to improve survival and longevity both at the cellular and organism level [43]. In this context, an improved wound healing by physical training has recently been described in old mice [44] and in older humans [45]; the underlying mechanisms, possibly immune-related, have not been elucidated yet. Exercise can probably lower the expression of toll-like receptor 4, thus leading to lower infection-induced cytokine release by peripheral mononuclear blood cells [46]. Physical exercise would thus reduce both CLIP and the acute inflammatory response upon infection in the aged. CLIP fits within the concept of "inflammaging" [47], describing a benefit at young age from a highly responsive immune system (showing good resistance against infections), but a disadvantage when aging by higher CLIP and sarcopenia. Similarly, "anti-inflammaging" corresponds to low inflammatory responses at young age (showing higher susceptibility to infectious diseases), but leading to lower CLIP and less sarcopenia in old age [47]. In this context, physical exercise would shift subjects from an "inflammaging" toward an "anti-inflammaging" profile, with beneficial effects on muscle mass and muscle performance.

In the *primary prevention*, all adult subjects should be advised to adopt an active lifestyle, including at least 30 minutes of moderate physical activity each day. However, given the dose–response relationship, physical exercise stimulating the large muscle groups at an above than average intensity (i.e. inducing muscle fatigue following a limited number of repetitions) can be recommended two to three times a week in order to prevent excessive muscle strength and mass. This type of exercise can be performed either without external guidance or in specific exercise settings (e.g. fitness, seniors sports club). Given the fact that in general far too few people engage in physical activity, clinicians should be aware of potential motivators and barriers for physical activity. It has been shown that in Western European countries such as Belgium, only one in two citizens attains a minimum of 2.5 hours of moderate physical activity per week [48], and that this proportion decreases to one in five at the age of 75 years and over. The same trend can be observed in other European [49] and non-European industrialized countries [50]. Moreover, from the age of 80 years and over, physical activity shows a sharp decrease. Motivators and barriers for physical activity have been described for different age groups including children, middle-aged, and older people [51], as well as for the oldest old [52]. When promoting physical activity in older persons, special attention should be paid to the health benefits of physical activity, to the subject's fears, individual preferences and social support, and to constraints related to the physical environment [52].

Secondary prevention targets subjects with lower muscle performance than on average expected at young adult age, but without showing evidence for sarcopenia-induced functional disability. For these subjects, the exercise recommendations are similar as those for subjects with normal muscle performance. However, special attention to the barriers for physical activity should be identified as well as other factors that can contribute to increased progression of sarcopenia (e.g. episodes of acute inflammation and/or sources of chronic inflammation). When patients show an increased risk for complications due to comorbidity (e.g. chronic heart failure, painful joints) or medication use, higher levels of exercise supervision can be considered, such as adapted exercise classes or physical exercise under supervision of a physical therapist. Recently, a simple classification system has been proposed, which stratifies health categories corresponding to an increasing risk for complications during physical exercise (see

Table 26.3 Health categories for risk stratification of complications during physical exercise in older persons.

Health category	Description	Clinical examples
A A1	Completely healthy; no medication	
A2	Completely healthy; using only preventive medication	Hormonal replacement therapy, aspirin, etc.
B B1	Functioning normally; presence of stabilized, non-cardiovascular disease; absence of cardiovascular abnormalities	Treated hypothyroidism, stable diabetes, etc.
B2	Functioning normally; using medication with cardiovascular effect, no overt cardiovascular disease other than normalized arterial hypertension	Arterial hypertension; β blocking agent, etc.
C	(History of) cardiovascular pathology or abnormal electrocardiogram (ECG).	Bundle branch block; angina, coronary artery bypass graft (CABG), etc.
D	Presenting signs of acute or active disease at the moment of examination.	Bronchospasm, swollen joints, influenza, etc.

Source: From [1].

Table 26.3), and which can be used by clinicians in the context of exercise prescription [10, 53]. The classification system was primarily designed to allow the establishment of recommendations concerning the exercise schedule (type, duration, and intensity) of older persons in the absence of direct medical supervision. Therefore, the classification system is rather conservative and it is easy to use for an individual considered at risk for complications. Roughly, participants in category A (completely healthy) will have no particular limitations for exercising; for those in category B1 (functioning normally, but presenting chronic non-cardiovascular disorders) the instructions will vary with the nature of the health problem; those in category B2 will only exercise at higher intensity (e.g. up to 80% of maximal heart rate or higher) when guided by an instructor qualified for training elderly persons; those in category C will only be allowed to exercise under supervision of an instructor and with medical guidance of the training program; and those in category D will not exercise unless cleared by a physician.

NUTRITIONAL BASICS

Protein

Skeletal muscle mass is relatively constant during young to middle-aged adulthood, suggesting that there is an equilibrium between protein synthesis during absorptive states (i.e. postprandial, following feeding) that is balanced by the catabolism during fasting states. However, this equilibrium in healthy muscle between protein synthesis and breakdown is getting progressively disrupted with aging. In older people,

synthesis rate of mixed muscle proteins including myofibrillar and mitochondrial proteins decreases with 30% [54]. Muscle protein synthesis is stimulated by dietary intake of both essential and nonessential amino acids. There is a substantial body of research suggesting that over 80% of the stimulatory effect on protein synthesis observed after a meal can be attributed to amino acids [55]. In older people compared with younger individuals this stimulatory effect is being blunted but not absent. It can be overruled by increasing the amount of protein. In addition to their role in protein synthesis, amino acids also play a role in the regulation of protein breakdown [56]. Nitrogen balance studies in aging populations (56–80 years of age) have indicated greater protein needs for the elderly (1.14 g/kg/d) relative to the young (0.8 g/kg/d)[57]. The same research group, however, showed in a short-term nitrogen balance study that the requirement for total dietary protein was not different for healthy older adults than for younger adults and that the allowance estimate does not differed statistically from the recommended dietary allowance (RDA)[58]. On the other hand, older individuals whose consumption levels approach the RDA are at greater risk for disease than those consuming more than 1.2 g/kg/d [59]. This provides critical information in terms of inadequate protein intake as a possible mechanism underlying sarcopenia, particularly because protein intake has been reported as inversely proportional to age. In 2013, the PROT-AGE study group summarized recommendations for older adults (65+ years), creating three large subgroups: healthy sedentary older adults, healthy active older adults, and adults with chronic diseases [60]. For healthy sedentary older adults, a protein intake of 1–1.2 g/kg/d is recommended. For healthy active older adults, a protein intake of at least 1.2 g/kg/d is recommended supplemented with 20 g protein when specific exercise sessions are included. For older adults with chronic disease, a protein intake of 1.2–1.5 g/kg/d is recommended, with intake up to 2.0 g/kg/d in case of severe illness or injury. Randomized controlled trial data indicate that it is more important to ingest a sufficient amount of high-quality protein (25–30 g) with each meal rather than one large bolus, because greater than 30 g in a single meal may not further stimulate muscle protein synthesis [61]. Moreover, a sufficient high baseline level of proteins and vitamin D might be required to increase muscle mass in older adults presenting sarcopenia [62]. Of course, the efficiency of protein supplementation on achieving an anabolic state may be dependent on total daily protein intake or the distribution of protein intake throughout the day [63]. Also, the quality of the protein is important: "slow" proteins (e.g. casein) do not seem to stimulate muscle protein synthesis as much as "fast" proteins (e.g. whey) [64–66]. Last, the source of the proteins such as animal or vegetable proteins could be of importance. Only few studies have investigated this so far, but have shown that protein breakdown was smaller in those consuming animal proteins compared with those consuming vegetable proteins [67–69]. Also, essential amino acids seem to stimulate muscle protein synthesis more than nonessential amino acids [70]. Furthermore, Paddon-Jones reported that aging does not inevitably reduce the anabolic response to a high-quality protein meal, rather it is the presence of carbohydrates that blunts this response due to the effects of insulin resistance on muscle protein synthesis [65]. These data would suggest that high-quality protein should be consumed in smaller quantities, but not together with carbohydrates.

Table 26.4 Nutritional interventions in the prevention strategy for sarcopenia.

Primary prevention
Level 1
Balanced Mediterranean type of diet
High-quality protein divided over several meals: 1.0–1.2 g/kg/d protein 400–1000 IU vitamin D
Level 2
Balanced Mediterranean type of diet
High-quality protein divided over several meals: 1.0–1.2 g/kg/d protein 800–2000 IU vitamin D
Secondary prevention
Level 3
Dietary history/dietitian's advice
Personalized Mediterranean type of diet
High-quality protein divided over several meals: 1.0–1.2 g/kg/d protein 800–2000 IU vitamin D
Tertiary prevention
Level 4
Dietary history/dietitian's advice
Personalized Mediterranean type of diet
High-quality protein divided over several meals: 1.2–1.5 g/kg/d protein 800–2000 IU vitamin D
Level 5
Dietary history/dietitian's advice
Personalized Mediterranean type of diet
High-quality protein divided over several meals: 1.2–1.5 g/kg/d protein 800–2000 IU vitamin D
Nutritional supplements containing essential amino acids, such as leucine
Quaternary prevention
Parallel advice together with all preceding levels of prevention

Low nutrient intake secondary to the "anorexia of aging" is considered an important risk factor in the development and progression of sarcopenia [71]. Morley reviewed the phenomena of the anorexia of aging and reported that early satiety, secondary to decreased relaxation of the fundus, increased the release of cholecystokinin in response to fat intake, and that increased leptin levels and neurotransmitters may all play a role in the anorexia of aging. It is also reported that 15% of those older than 60 years eat less than 75% of the recommended daily allowance for protein [72]. Thus, although poor overall nutritional intake may play a role in sarcopenia, low protein intake appears to be a significant problem for older adults and may be a potential target for an intervention strategy.

In summary, from the nutritional point of view a balanced diet with a protein intake of 0.8 g/kg/d is appropriate for younger and middle-aged adults. However, with the progressive blunting of the anabolic response to a high-quality protein meal protein requirements may be higher. In normal older adults and in those with chronic illnesses, 1–1.5 g/kg/d is recommended. In older adults with severe illness, it is recommended to increase the amount of protein intake to 2.0 g/kg/d. So in accordance with the clinical situation, advice should be given to increase protein intake with aging as suggested in the algorithm (Figure 26.1, Table 26.4).

Vitamin D

Vitamin D has recently received recognition as another potential intervention strategy for sarcopenia. Although our understanding of the relationship between vitamin D and muscle function has advanced over the past decade, a complete understanding of the vitamin D action on muscle tissue and how this translates into improvements in muscular performance are yet to be elucidated. One possible explanation is the role of the Vitamin D receptor (VDR) gene, which has a key regulatory role in calcium homeostasis and skeletal muscle function [73]. Although genetic variation in the VDR appears to impact muscle strength and the risk for sarcopenia, the influence seems limited [74]. Older adults are at increased risk of developing vitamin D insufficiency and supplementation may be indicated in those older people with low vitamin D levels to combat sarcopenia, functional decline, and falls risk [75]. As people age, skin cannot synthesize vitamin D efficiently and the kidney is less able to convert vitamin D to its active hormone form. The consensus position is that the available evidence of safety and the potential benefits for adults justify recommending that optimal vitamin D status represents a serum 25-hydroxyvitamin D level of at least 75 nmol/l [76]. When considering this cutoff, a prevalence of about 81% is vitamin D inadequacy in women aged 80 years and older [77]. People may try to meet their vitamin D needs through exposure to sunlight, but exposure to sunlight and dietary intake are insufficient to maintain this level, and use of vitamin D supplementation is therefore indicated for most adults. The clinical approach can take into account three "settings," based on suspicion for vitamin D insufficiency [78]. The first group is adults below age 50 years without comorbid conditions affecting vitamin D absorption or action who are at low risk for vitamin D insufficiency. For these people, supplementation at 10–25 μg (400–1000 IU) is appropriate, and serum 25-hydroxyvitamin D should not be measured. People with moderate risk for vitamin D insufficiency are adults 50 years of age or older without comorbid conditions that affect vitamin D absorption or action. For these people, routine supplementation with vitamin D is appropriate, and this should be at a dose of 20–50 μg (800–2000 IU). Serum 25-hydroxyvitamin D should not be measured routinely in initial assessment of these individuals, but if pharmacologic therapy is prescribed, 25-hydroxyvitamin D should be measured after three to four months of an adequate supplementation dose. People at high risk for adverse outcomes from vitamin D insufficiency include those with recurrent fractures, bone loss, sarcopenia, and/or comorbid conditions that affect vitamin D absorption or action. In these cases, serum 25-hydroxyvitamin D should be measured as part of the initial assessment, and supplementation with vitamin D should be based on the measured value. Supplementation dose requirements above the current definition of tolerable upper intake level (50 μg [2000 IU]) may be identified by measuring serum 25-hydroxyvitamin D levels. Vitamin D3 is the preferred supplementary form for humans, with vitamin D2 being available for large-dose preparations. Calcitriol and its analogs are prescription products with narrow margins of safety. They are not synonymous with vitamin D and are not advised for prevention or routine treatment of osteoporosis. For most adults given a supplement, an initial dose of vitamin D3 of 20–25 μg (800–1000 IU) daily, is likely to raise serum 25-hydroxyvitamin D by approximately 15–30 nmol/l. To achieve desirable vitamin D status (>75 nmol/l) many individuals will require doses greater than this minimum dose. A weekly dose of 250 μg (10 000 IU) vitamin D3 may be more convenient for some patients if available.

However, it should be kept in mind that one yearly dose of 300 000–500 000 IU of vitamin D could increase risk of falls and fractures, especially in the first three months after the vitamin D bolus and therefore, it is suggested to prescribe a daily, weekly, or monthly dose of vitamin D [79].

Antioxidants

As a possible large contributing factor in muscle decline [80], both the process of oxidative damage and antioxidants have been the target of increasing interest during the last decades. Since antioxidants can be acquired through a normal diet, theoretically, this specific nutritional support could prevent the onset of age-related conditions such as sarcopenia [81]. There are different types of antioxidants which have a different effect on the oxidative process, according to the lipophilicity of the molecule. The most studied compounds are vitamin E and vitamin C [82]. However, there are no large-scale studies clearly defining the link between these antioxidants and sarcopenia, the data being rather scarce and even conflicting at that. Therefore, although theoretically interesting, at this moment no recommendations can be made regarding the intake of antioxidants in the prevention of sarcopenia.

Minerals

Minerals such as sodium, potassium, and calcium play an important role in normal muscle functioning. Other minerals such as magnesium, phosphor, zinc, and selenium give way to muscle disfunction when deficiencies are present. However, their link with sarcopenia is unclear. There are some data, although mostly from observational studies [83]. Sarcopenia prevalence numbers were associated to intake of selenium [84, 85], phosphorus [85], calcium [86], and magnesium [84, 85]. Muscle mass is associated with intake of calcium [86] and serum selenium levels [87]. Physical performance was positively associated with selenium [88], zinc [89], iron [89], and magnesium [90] levels in older adults. However, the referenced studies were observational and for some minerals conflicting data exist. Therefore, although theoretically interesting, at this moment no recommendations can be made regarding the intake of minerals in the prevention of sarcopenia.

Diets

Many specific compounds are being researched, but in practice these are mostly consumed within the ranges of a diet instead of through supplementation. In this regard, two specific diets should be mentioned: the Mediterranean diet and the Baltic diet. An adherence to the Mediterranean diet was positively associated with fat-free mass, explosive leg power, physical performance, lower body performance, and negatively associated with the odds of having sarcopenia in older men and women [91–93]. Since exporting this diet to non-Mediterranean countries could pose difficulties in regards of food availability and preference, for Nordic countries the Baltic diet was developed [94]. It must be noted that definitions of both diets can vary according to the

study or region where it is applied, and that this is often combined with a large variability in outcomes measured. Still, there seems to be a role for these kinds of diet in sarcopenia prevention, as a lower adherence to both diets was associated with a lower relative skeletal muscle index and a lower lean body mass. More studies are needed to strengthen the level of evidence for concrete recommendations of these diets regarding the prevention of sarcopenia. For other nutrients, the Belgian Society for Gerontology and Geriatrics, based on an umbrella review of previously published reviews, recommends leucine supplementation for increasing muscle mass in sarcopenic older adults. Additionally, adding proteins to a resistance training program is recommended to increase muscle strength and muscle mass. For obese older adults, the intervention should be performed for at least 24 weeks [95].

QUATERNARY PREVENTION: WARNING AGAINST NON-EVIDENCE-BASED INTERVENTIONS

One weakness of most pharmacological studies is that sarcopenia as a construct is often very poorly described, making it very difficult to draw clear conclusions. A recent review did not show sufficient evidence to justify pharmacological intervention in clinical practice to *prevent* sarcopenia except for vitamin D and testosterone [96]. Vitamin D is already extensively reviewed elsewhere in this chapter. Testosterone should only be used in very specific indications given the possible side effects. In this regard, patients should be warned against the use of other anabolic agents (such as dehydroepiandrosterone [DHEA], growth hormone, growth hormone–releasing hormone, and insulin-like growth factor), given the lack of clear data and, just as testosterone, their risk for harmful side effects. The search for pharmacologic drugs that could prevent sarcopenia is going on. The new drugs being studied will have to show their efficacy on physical performance outcomes in addition to muscle mass and strength, and target populations will have to be defined [97]. For the detailed discussion of this topic the reader is referred to the specific chapter in this book dealing with the pharmacologic treatment options of sarcopenia.

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CHAPTER 27

Financial Impact of Sarcopenia

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INTRODUCTION

Sarcopenia is the combination of age-related loss of skeletal muscle mass [1] and loss of physical capacity [2]. Loss of physical capacity in particular is associated with increased risk of falls and fractures, loss of physical independence, and prolonged convalescence [3]. But also the loss of muscle mass and quality specifically has distinct consequences which have recently been discovered as muscle is being established as an endocrine organ. A reduction in muscle has metabolic implications such as increased insulin resistance and changes in myokine production [4, 5] which results in an altered reaction to disease and treatment [6]. It is well established that morbidity as well as mortality are increased in individuals with sarcopenia [7]. The prevalence of sarcopenia increases with age and obviously depends on setting and methodology but studies indicate a prevalence ranging from 10% in healthy adults aged between 60 and 70 years [8] to 33% in long-term care populations [9], making it a clinically relevant problem.

The impairment in physical capacity, the loss of independence, extended recovery; all have the potential to increase both the length of hospital stay (LOS) and health-care utilization, which undeniably puts an increased strain on the health-care system (see Figure 27.1 and Table 27.1). Moreover, the relationship between sarcopenia and hospitalization is most likely mutual and might turn into a vicious circle (see Figure 27.2, which depicts the mutual relationship between sarcopenia and hospitalization). Hospitalization is associated with the so-called post-hospital syndrome [10], which is described as an "acquired, transient period of vulnerability" following hospital discharge with profound effect on the recovery of the patients, in particularly old patients. The main characteristic of the post-hospital syndrome are acute unplanned readmissions within a month of hospital discharge which are frequently not due to the primary illness

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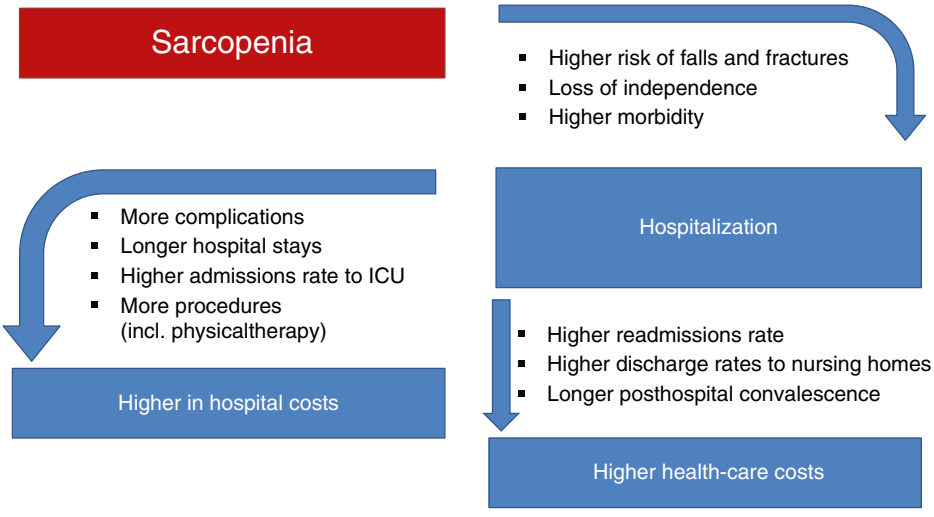

Figure 27.1 Relationship between low muscle mass and/or strength and health-care expenditure and costs.

Table 27.1 Summary of factors relating to low muscle mass associated with higher costs.

Factors associated with higher costs	Findings
Community dwelling setting	
Higher risk for disability	Higher average total annual costs (direct medical care and indirect costs)
Higher living costs (home care, assisted living)	Higher health-care utilization
Perioperative setting	
More postoperative complications	Higher payer costs
Longer LOS	Higher hospital costs
Higher admission rate to ICU	Low to negative margin of gain
Higher admission rate to nursing institutions after hospital discharge	Higher outpatient cost while waiting for transplantation
Higher likelihood of blood transfusion	Higher laboratory costs
Higher use of diagnostic imaging	Emergency department costs
Higher use of medication	Higher payer and patient costs
General hospital setting	
Longer length of stay	Higher hospital costs

ICU = intensive care unit; LOS = length of hospital stay.

preceding the hospitalization. Factors leading to the post-hospital syndrome are hospital related, and include i.a. poor nutritional intake in the hospital, bed rest or low physical activity, sleep disruption with effect on circadian rhythm, medication with effect on cognition or physical status, anxiety, pain, and discomfort, all of which have the potential to increase the risk for developing or advancing sarcopenia.

There have been several attempts to define age-related sarcopenia and determine the most suitable diagnostic criteria, with the most recent and accepted being the definition by the European Working Group on Sarcopenia in Older People (EWGSOP)

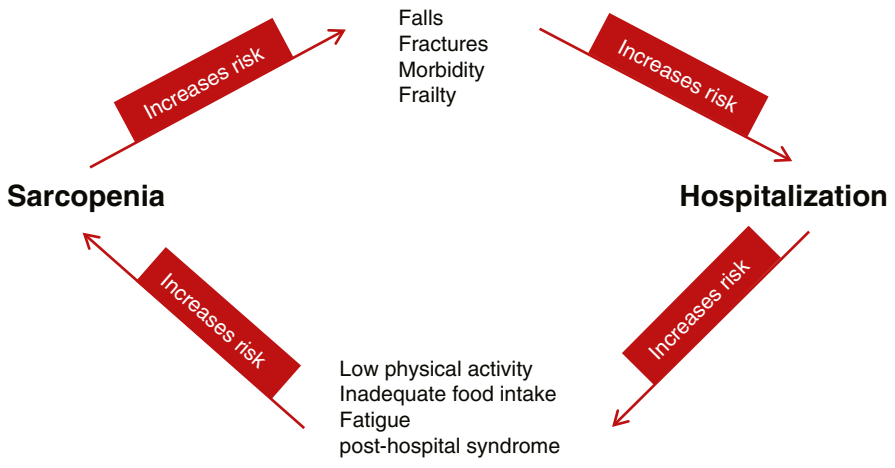

Figure 27.2 Vicious circle between sarcopenia and hospitalization.

which was updated in 2018 [11]. It focuses on the loss of strength/function as the primary phenomenon. However, with all the attention that sarcopenia has gained in the last years and the introduction of an ICD-CM code (M62.84) for age-related sarcopenia in the United States in 2016, which represents increased awareness and recognition of sarcopenia as a prevalent and relevant syndrome and provides the urgently needed incentive to screen for and treat sarcopenia, there has been increasing interest in investigating the effect of loss of muscle mass in disease-related settings, outside the purely age-related content.

Reduced muscle mass in chronic disease and immobility or obesity with low physical activity have been referred to as secondary sarcopenia by some authors in order to distinguish it from the age-associated, or primary, sarcopenia [12, 13]. Ultimately, although different criteria might have been used in the various settings and publications, there is most likely frequently an overlap of the two phenotypes as, for example, in older, obese patients with cancer.

Both the financial impact of age-related sarcopenia, as defined by then current standards or more recent consensus criteria, as well as the impact of low muscle mass in clinical conditions, which does not necessarily indicate but neither precludes age-related sarcopenia, have been studied. The impact of low muscle mass on the postoperative outcome, in particular, has been extensively assessed.

This chapter will look at age-associated sarcopenia and low muscle mass in hospital settings separately, as it is difficult to combine studies from predominantly clinical settings with studies performed in community-dwelling older adults.

DATA FROM COHORT STUDIES: AGE-ASSOCIATED SARCOPENIA IN COMMUNITY-DWELLING OLD

In 2004, Janssen et al. carried out a first rough estimation of costs resulting from age-associated loss of skeletal muscle mass depletion [14]. Their calculations were based on the relative risk of developing disability with low muscle mass and prevalence of

low muscle mass in subjects over 60 years of age. Using data from two representative health surveys, the third National Health and Nutrition Examination Survey (NHANES) and the National Medical Care and Utilization Expenditure Survey (NMCUES), the contribution of low muscle mass to the risk of disability was estimated (population-attributable risk) and combined with the economic cost of disability. Estimated direct costs attributable to low muscle mass amounted to approximately 18.5 billion US$ (10.8 billion US$ in men and 7.7 US$ billion in women) which represented 1.5% of the total national health-care expenditure. Taking variations in the population-attributable risk of low muscle mass and cost of disability into account, sensitivity analyses revealed that costs could vary between 11.8 billion US$ and 26.2 billion US$. The excess expenditure was slightly higher in women at 860 US$ and 933 US$ per male and female patients with low muscle mass, respectively. Reduction in the prevalence of low muscle mass by 10% were estimated to lead to potential cost savings of 1.1 billion US$ (figures adjusted for the year 2000).

A recent analysis using the data from the National Health and Nutrition Examination Survey ($n = 4011$, adults aged over 40 years) by Goates and colleagues [15], showed that sarcopenic persons had a nearly twofold higher likelihood of hospitalizations (odds ratio (OR) 1.95, $p < 0.001$) and an annual marginal increase in cost of 2315.7 US$ per person compared with non-sarcopenic individuals. The total estimated cost of hospitalizations associated with sarcopenia was 40.4 billion US$ whereof approximately half occurred in older individuals (over the age of 65, 19.12 billion US$). The average per person cost was highest for Hispanic women showing ethnic disparity.

Lo and colleagues determined annual expenditure associated with low muscle mass in the Elderly Nutrition and Health Survey, a prospective study with an eight-year follow-up. Nearly 25% of the large sample of community-dwelling old persons aged 65 years and over had low muscle mass at baseline. After eight years, duration and costs of hospitalization as well as total medical costs were highest in the participants with a low muscle mass with total annual costs estimated at 2802.7 ± 945.2 versus 1852.0 ± 917.8€, $p < 0.001$. The authors also assessed dietary diversity and physical activity at baseline and found that these factors attenuated the effects of low muscle mass on health-care utilization and expenditure [16]. Interestingly, individuals with higher muscle mass had fewer hospital stays and hospital emergency visits but higher outpatient, preventive, and dental care service utilization than those with lower muscle mass.

While the previous studies used muscle mass as an indicator of sarcopenia in the economic analyses, the economic effect of low muscle strength has also been investigated. Steffl et al. employed a cost-of-illness approach to analyze the costs associated with muscle weakness in older adults aged over 70 without severe chronic disease, using the Czech data set from the Survey of Health, Ageing and Retirement in Europe (SHARE) [17]. According to the authors' estimations, low strength alone which occurred in 9.4% in this study population was associated with significantly higher direct, e.g. medical care, and indirect costs, e.g. replacement costs for caregivers, amounting to 1125.3 ± 1367.2€ in subjects with low muscle strength versus 561.4 ± 762.6€ in subjects with normal strength, $p = 0.001$. Moreover, old adults with low grip strength had around 30% higher risk of being hospitalized. Even when adjusted for significant risk factors such as age and body mass index, low handgrip strength was associated with the risk of significantly higher direct costs (OR 2.11, 95% confidence interval (CI): 1.43–3.09) in a general linear regression model.

Using data from the Maastricht Sarcopenia Study (MaSS), Mijnarends and colleagues reported significantly higher mean health-care costs in the sarcopenic participants ($n = 53$) compared with non-sarcopenic participants. These health-care utilization costs were self-reported and regarded costs occurred in the preceding three months such as visits to a general practitioner and hospital paramedical staff and costs such as medication, purchase of medical aids, in hose adjustment, food service, or nutritional supplements. The main driver of the higher costs (4325€, 95% CI: 3198–5471€) versus those of non-sarcopenic participants; 1533€, 95% CI: 1153–1912€) was the living situation with home care, assisted living, or residential living. However, when comparing the sarcopenic patients with age- and sex-matched participants, these differences were no longer significant [18]. In another analysis using data from MaSS, the authors were able to show that lower gait speed and slower chair stand were the main predictors of disability in the activities in daily living and as such associated with significantly higher health-care costs [19].

RETROSPECTIVE DATA FROM SURGICAL SETTINGS ON THE FINANCIAL IMPACT OF LOW MUSCLE MASS

The majority of studies on the financial impact of low muscle mass stem from the surgical setting. Cost analyses in the perioperative setting are available in the form of retrospective analyses of routinely collected data, clinical data registries, or for other study end points. They are largely limited to hospital-related costs and include health-care utilization in the year following surgery. Also, the data sets are usually restricted to patients who received a computer tomography (CT) scan which was also suitable for the determination of skeletal muscle mass. This of course limits transferability to other settings or cohorts.

The Michigan Surgical Quality Collaborative (MSQC) is a collaborative of Michigan hospitals which in 2016 included 72 hospitals. The clinical data registry is intended for population-based analyses of the quality of surgical care, offering the opportunity for economic analyses as well. Two publications analyzed the difference regarding length of stay, hospital costs [20], and health-care utilization in the postoperative year [3] between patients with and without low muscle mass who had undergone elective surgery. Low skeletal muscle mass was defined using preoperative CT scans as reduced lean psoas muscle area (LPA, defined as under lowest sex-specific tertile at L4). Sheetz and colleagues analyzed 1593 patients with elective major general or vascular surgery. Patients with low muscle mass were significantly older (66.4 ± 14.4 years) than patients with adequate muscle mass (48.5 ± 14.8 years, $p < 0.001$). The authors observed longer length of stay in patients with low versus normal muscle mass (seven vs. four days, $p < 0.001$) and hospital costs as well as payer (reimbursement) costs were higher in patients with low muscle mass. Payer costs amounted to 6989.17 US$ per 1000 mm^2 LPA, $p < 0.001$, which further increased with postoperative complications (26,988.41 US$ per 1000 mm^2 LPA, $p < 0.001$). Following adjustment for important confounders, low muscle was independently associated with increased payer costs, which increased further when postoperative complications occurred. Costs associated with low muscle mass, even without complications were comparable with the

costs of patients with complications but normal muscle mass. Treatment of patients with low muscle mass even lead to a negative average hospital margin (payer costs–hospital costs) (−873 US$ per patient) compared with the average margin in all patients (1806 US$ per patient) and to the costs in patients with normal muscle mass (3170 US$ per patient).

Kirk and colleagues studied LOS as well as the subsequent utilization of health-care resources in the year following surgery and analyzed differences in patients with and without low muscle mass as well as corresponding costs [3]. Costs included hospital expenditure within one year of surgery and were higher in patients with low compared with normal muscle mass (unadjusted; 67525 US$ vs. 39720 US$, $p < 0.001$). Patients with low muscle mass had a significantly higher rate of postoperative complications (33.3% vs. 17.6%, $p < 0.001$). Adjusted in multivariate analyses, low muscle mass predicted admission to the intensive care unit (OR 2.24, CI: 1.38–3.64, $p < 0.001$), prolonged LOS (OR 3.47, CI: 1.91–5.02, $p < 0.001$) as well as postoperative one-year mortality (OR 3.26, CI: 1.73–6.15, $p < 0.001$). Although the postoperative acute readmission rate was not significantly higher in patients with low muscle mass, the likeliness of being discharged to an institution instead of back to their homes was significantly higher for patients with low muscle mass, even when adjusted for multiple covariates (OR 4.42, CI: 2.28–8.55, $p < 0.001$). The costs for care homes were not included in analyses study but represent a substantial financial expense, especially when considering that the likelihood of not being released home independently was four times in patients with low muscle mass.

Gani et al. assessed 1169 patients who underwent major hepatobiliary, pancreatic, or colorectal resection [21] in a retrospective analysis from routine hospital data. Based on psoas muscle volume (below the lowest sex-specific quartile of L3 total psoas volume assessed by CT), 293 of patients had low muscle mass. Low muscle mass was associated with significantly higher total hospital costs (38804 US$ vs. 24482 US$ in patients with normal muscle mass, $p < 0.001$) in a multivariable regression analysis. When stratifying the study population into subgroups of patients who did or did not develop postoperative complications, the costs remained significantly higher in patients with low muscle mass (for patients with complications: low vs. normal muscle: 65856 US$ (interquartile range (IQR) 43730–70784) vs. 59609 US$ (IQR 40527–63291), $p < 0.001$, for patients with complications, low vs. normal muscle mass: 26282 US$ (IQR 24530–39802) vs. 23763 US$ (IQR 22220–35254), $p < 0.001$). Similarly, when looking at costs for length of stay, low muscle mass was associated with higher costs irrespective of whether LOS was longer than expected (length of stay shorter than expected: low vs. normal muscle mass: 25038 US$ (IQR 24106–26358) vs. 22827 US$ (IQR 21768–23972), $p < 0.001$) or not (length of stay longer than expected: low vs. normal muscle: 43283 US$ (IQR 39818–66145) vs. 38679 US$ (IQR 35563–58015), $p < 0.001$).

Van Vugt and colleagues have looked at hospital costs in patients undergoing abdominal cancer surgery [22] and in patients listed for liver transplantation [23]. The first retrospective analysis included patients over 18 years of age with cancer of the gastrointestinal or hepatopancreatobiliary tracts undergoing elective curative surgery and who had a preoperative CT scan within 90 days. Low muscle mass was identified in 45.6% of patients. These patients experienced more postoperative

complications and longer hospital stays than patients with normal muscle mass. Total costs included surgical and postoperative costs during the hospital stay. While total costs varied between cancer type and major versus minor surgery, they were 12.7% higher in patients with low (17 144€ (IQR 12 694–25, 02)) vs. normal muscle mass (14 961€ (IQR 10 744–21 200), $p < 0.001$). Muscle mass was independently associated with an increase in costs in a multivariable linear regression analysis, and total expenditure decreased with incremental increase of muscle mass. In the subgroup of patients 65 years and older, total costs remained higher for patients with low muscle mass (18 256€ (IQR 12 808–25 131) vs. 15 490€ (IQR 11 060–21 098), $p = 0.041$).

The second retrospective analysis from Van Vugt et al. included 224 patients with cirrhosis and listed for liver transplantation [23]. Fifty-five patients had low muscle mass based on the lowest sex-specific quartile of muscle mass at L3 assessed with CT scans. Total costs included both hospital and outpatient costs during the time on the waiting list. Costs were significantly higher in liver transplant candidates with low muscle mass independent of the total waiting time and corresponded to 68€ (IQR 16–503) per day on the waiting list for patients with low muscle mass versus 40€ (IQR 10–108) per day for patients with normal muscle mass ($p = 0.013$). Again, an incremental increase in muscle mass was associated with decreased health-care expenditure in a multivariable regression analysis adjusted for confounders.

Bokshan and colleagues conducted a retrospective analysis on the cost of low muscle mass in a small group of patients over 55 years of age who underwent elective orthopedic (thoracolumbar spine) surgery [24]. Thirty-two percent of patients had low muscle mass based on preoperative CT scans of psoas muscle volume (i.e. below the lowest sex-specific tertile of L4 total psoas area for the definition). Patients with low muscle mass incurred nearly twice as high total hospital-related costs compared with patients with normal muscle mass. Moreover, likelihood of requiring blood transfusion was twice as high (43.8% vs. 20.6%, $p = 0.04$) and need of diagnostic imaging 2.6-fold greater (68.8 vs. 26.5%, $p = 0.002$) which resulted in corresponding higher costs (2452 US$ vs. 801 US$, $p = 0.01$). Furthermore, patients with low muscle mass had a higher use of medication and higher laboratory and emergency department costs. However, these results are limited due to the small sample size.

Combined muscle mass and strength and/or physical performance corresponding to the EWGSOP criteria to define sarcopenia have also been used in a prospective study in 470 gastric cancer patients undergoing gastrectomy [25]. Huang et al. differentiated between sarcopenia (low muscle mass and low handgrip strength or gait speed) and severe sarcopenia (low muscle mass, low handgrip strength, and low gait speed). The prevalence of sarcopenia and severe sarcopenia together was 16.8% ($n = 79$). Patients with sarcopenia and severe sarcopenia had a longer length of stay (11 (IQR 7), $p = 0.001$, 14 (IQR 7), $p < 0.001$ vs. 12 (IQR 6) days) and severe sarcopenia was an independent predictor of postoperative complications in a multivariate analysis (OR 8.957, CI: 3.876–20.697, $p < 0.001$). Hospital costs were also higher in patients with sarcopenia and severe sarcopenia compared with patients without sarcopenia (sarcopenia: 8206.7 (IQR 4032.9), severe sarcopenia 8462.3 (IQR 3657.8) vs. 6975.5.30 (IQR 2260.2) in non-sarcopenic patients).

FINANCIAL IMPACT OF LOW SKELETAL MUSCLE MASS AND STRENGTH – SARCOPENIA – IN A GENERAL HOSPITAL SETTING

Two cross-sectional studies which included patients from various hospital departments and used both muscle mass and strength to characterize sarcopenia have also analyzed corresponding costs. The study by Sousa and colleagues analyzed costs associated with sarcopenia in a general, hospitalized, adult population [26]. They included all ages (18 years and older) and found that 24% were sarcopenic. Hospital costs were based on the diagnosis-related group codes at discharge and were higher in patients with versus without sarcopenia in the entire population as well as when stratified according to age (under and over 65 years).

The study performed by Antunes et al. included 201 patients aged 65 years and over and also from various hospital departments [27]. Sarcopenia, as defined by low muscle mass and low handgrip strength, was identified in approximately 10% of patients. Hospitalization costs were calculated based on weighted diagnosis-related group codes. After adjustment for confounders, both sarcopenia and low muscle strength alone were associated with higher hospitalization costs compared with the mean cost of an average patient. Sarcopenia (OR 5.70, 95% CI: 1.57–20.71, $p = 0.008$) and low muscle strength alone (OR 2.40, 95% CI: 1.12–5.15, $p = 0.025$) were associated with hospital costs exceeding mean cost of an average patient.

CRITICAL DISCUSSION

As age-related sarcopenia is increasingly being acknowledged as a major public health concern, efforts have been undertaken to define its economic burden. However, although the majority of the studies find proof for the economic impact of low muscle mass, the few studies available differ remarkably with regard to setting, population, different methods, and partly un-validated diagnostic criteria for classification of low muscle mass, rendering a systematic approach to analyze costs impossible at this point in time. A recently published meta-analysis failed to combine the available studies due the high heterogeneity and methodological bias. [28] This is in part due to the fact that older studies precede the current criteria for age-related sarcopenia and that analyses are retrospective in nature using available data from e.g. clinical data registries. This is in particular true for most studies in the perioperative setting. Although it is very probable that the majority of patients with low muscle mass indeed exhibit age-related sarcopenia, these studies do not follow the diagnostic criteria for age-related sarcopenia. They frequently rely on available CT scans which represents a population selection such that the data cannot be extrapolated to all hospital patients. Also, they use the psoas muscle instead of the more validated cross-sectional area at L3 which is not accepted as sentinel muscle for sarcopenia [29] due to the high frequency of regional atrophy in the lower back; and lastly, low muscle mass is not combined with low function or strength as recommended. As studying the effect of age-related sarcopenia was not the primary intent in these studies, potential confounders are frequently not

accounted for which substantially blurs the results. The studies in the perioperative setting e.g. include cancer patients. While cancer does not preclude age-associated sarcopenia, loss of muscle mass undeniably is a hallmark symptom of cancer cachexia, which makes disentangling the effects on outcome and thus costs difficult; particularly because costs were frequently driven by LOS which is already increased in malnutrition or cachexia [30].

Nevertheless, the data show that low muscle mass and sarcopenia are associated with increased health-care utilization outside of the hospital as well as during a hospital stay in the form of extended length of stay and increased complications, especially in the postoperative setting.

Despite the different methodology used for the evaluation of muscle mass, including diagnostic criteria as well as thresholds to define sarcopenia, the diverse settings, and partly small sample size numbers, the findings of these studies indicate that direct and indirect health-care costs are increased in patients with low muscle mass or age-related sarcopenia. Thus, the prevention of muscle loss and treatment of sarcopenia are expected not only to improve prognosis and convalescence of patients but also lead to cost savings for the health care. In order to facilitate public health-care decisions, however, more standardized research is necessary.

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CHAPTER 28

Sarcopenia Management for Clinicians

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MANAGEMENT OF SARCOPENIA IN CLINICAL PRACTICE

Although sarcopenia is now recognized as a medical disease with an ICD-10-CM code (M62.84) [1], we must not fall into the trap of being disease focused, but instead continue to offer comprehensive management of sarcopenia as a complex and chronic health condition that can exacerbate other prevalent geriatric syndromes, such as falls, undernutrition, and frailty. There is currently no magic elixir, no operation, or pill available that will cure sarcopenia. The condition remains manageable only through healthy nutrition and physical activity, and treatment requires a clinician's time, patience, and at times creative thinking.

Research has demonstrated that the loss of muscle mass and strength begins in middle age, but that debilitating sarcopenia becomes more prevalent as age increases in a percentage of the population. The condition may, in fact, seriously compromise the health of one in three older adults over the age of 80 years [2]. Other geriatric syndromes, such as frailty, are also more prevalent in adults aged 80 years and older, the fastest growing age demographic globally [3]. These statistical realities give impetus to a continued comprehensive and proactive approach to the management of sarcopenia across the lifespan.

Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.

Table 28.1 *Meals on wheels* mnemonic for treatable factors accompanying or contributing to sarcopenia.

Medications
Emotional (depression)
Alcoholism, anorexia tardive, abuse (elder)
Late-life paranoia
Swallowing problems
Oral problems
Nosocomial infections, no money (poverty)
Wandering/dementia
Hyperthyroidism, hypercalcemia, hypoadrenalism
Enteric problems (malabsorption)
Eating problems (e.g. tremor)
Low-salt, low-cholesterol diet
Shopping and meal preparation problems, stones (cholecystitis)

Source: Developed by J.E. Morley. Copyright is held by the US government.

IDENTIFYING REVERSIBLE FACTORS

It is rare for sarcopenia to be present in isolation when a patient is initially assessed. A thorough examination of the individual, therefore, will frequently find remediable factors, including inappropriate prescribing and suboptimally managed comorbidities. Because of the many factors that need to be considered as possible contributors to the patient's poor health other than sarcopenia, a mnemonic guide, such as *meals on wheels* is particularly useful for the clinician (Table 28.1) [4]. Immediately treatable conditions require diagnosis and attention, and many measures can be undertaken to improve an individual's well-being even before treatment for sarcopenia is initiated. Often, a multidisciplinary approach is beneficial.

Using the meals on wheels mnemonic, a clinician can identify a whole suite of interactions. For example, when someone is depressed as well as sarcopenic, the obvious symptoms might be those of anorexia and poor motivation when it comes to preparing and eating meals. In combination, these features would result in a reduction in food intake, culminating in muscle mass and strength loss. Failure to recognize and treat the underlying depression would make it impossible to ensure the effectiveness of other treatment strategies, such as healthy meal provision and exercise. Successful treatment of sarcopenia is unlikely to be achieved in a poorly motivated person.

Thus, for any management strategy for sarcopenia to be effective, the clinician must begin with a comprehensive assessment to identify potentially remediable conditions which should then be addressed.

Physical activity

The International Clinical Practice Guidelines for Sarcopenia (ICFSR) provide a conditional recommendation for resistance training for the effective improvement of muscle strength, muscle mass and overall physical function [5], observing at the same time the need for further rigorous methodological research focused on patient-related outcomes.

With appropriate prescription, resistance training is thought to be safe, including in older people [6], and older adults may gain up to 1.1 kg in lean body mass by performing full-body resistance training for an average of 20.5 weeks [7]. Stabilizing other health conditions supports participation in resistance training, which should be individualized, particularly in relation to repetitions and intensity, and involve multiple muscle groups [6].

Clearly, some conditions would preclude exercise or dictate that only certain types of activity should be undertaken. Valsalva maneuvers, for example, could negatively affect blood pressure or hernias [6]. Absolute contraindications to exercise include unstable coronary heart disease, decompensated heart failure, uncontrolled arrhythmias, severe pulmonary hypertension, severe and symptomatic aortic stenosis, acute myocarditis, endocarditis, uncontrolled hypertension (>180/110 mmHg), aortic dissection, Marfan's syndrome, and active proliferative retinopathy [6].

However, age and frailty should not be a barrier to resistance training for most patients and has long been shown to have a beneficial effect on skeletal muscle mass, even in those aged 85 years and older [8]. In a seminal paper published in 1994, Fiatarone and colleagues confirmed that it was feasible to provide high-intensity resistance exercise in residential aged care settings, such as nursing homes, even among the very elderly [9]. One hundred frail residents participated in the 1994 study, which achieved a 94% adherence rate.

A recent position statement from the National Strength and Conditioning Association recommends that resistance training programs can be introduced for older people in residential aged care facilities using portable equipment and seated exercise alternatives [6]. Increasing levels of exercise and multicomponent exercise should ideally be performed at least three times per week for 45−60 minutes per session at a moderate to high intensity [10]. Variety may be important in improving adherence.

Clinicians should keep in mind when organizing a program of exercise that there are many barriers both they and their patients have to face. Apart from motivation, community-based patients may face a lack of funds or transport. Others may be experiencing poorly controlled pain. Successful participation may require steps be put in place to ensure that progress is sure and gradual. This takes us back once again to the importance of the initial assessment.

The benefits from exercise extend beyond that seen in relation to the treatment of sarcopenia. Exercise can contribute also to improved mood, and prevent or reduce cognitive decline [11, 12], while improving appetite and oral intake [13]. Group exercise promotes social interaction and has a beneficial effect on cognition, mood, and levels of motivation [14].

Unfortunately, human beings are becoming increasingly sedentary. Using technology to both entertain and transport us, many of us rarely engage in demanding physical activity and certainly not resistance training. We are well aware that sedentary behavior is associated with increased mortality risk [15], while any activity, at any intensity, is associated with reduced risk[16]. In a very recent study, the mortality risk was clearly attenuated when physical activity recommendations were met (i.e. ≥150 moderate to vigorous physical activity minutes/week) [17].

The public health message is clear. Physical activity across the life span is critical to good health. Just as one should save for one's retirement, there is a need to invest also in muscle and bone health earlier in life to set oneself up for a healthier life at an older age.

Nutrition

When it comes to nutritional strategies for poorly nourished individuals, attention immediately turns to protein, a major structural and functional nutrient found in all cells, essential for growth and the maintenance of all body tissues, including the heart and blood.

Some people are persistently unable to meet the required dietary protein requirement because as they have aged, they have lost their interest in food and reduce their food intake, referred to as the *anorexia of aging*. This behavior is often associated with a reduction in the senses of taste and smell, perhaps the side effects of prescription drugs, poor oral health, age-related depression, or acute or chronic diseases [18]. In terms of sarcopenia, if the daily intake of protein becomes insufficient, muscle growth and repair will decrease precipitously, and muscle function will be impaired [19]. This could affect balance and movement.

Prior to the development of undernutrition or weight loss, screening for risk factors for weight loss is possible utilizing the Simplified Nutritional Assessment Questionnaire [20]. Data from the questionnaire analysis can assist with identifying the underlying conditions influencing the progression of sarcopenia and possible management strategies. Using the *meals on wheels* paradigm, as previously noted, the clinician will need to consider all of the possible factors influencing the development of sarcopenia in order to address them as part of a holistic treatment plan that could include protein supplementation.

The loss of taste and smell is a feature of well-being that should be considered whenever a strategy to boost nutrition is planned. Restrictive diets should be avoided, particularly for residents in aged care facilities, as restrictions in the timing and type of meals and snacks may contribute inadvertently to reduced caloric intake, resulting in weight, strength, as well as muscle mass loss [21]. Flavor enhancement is a strategy that should be considered to improve caloric intake, and smaller, but more frequent meals and snacks, as well as the physical setting.

Protein requirements are much higher for older people, reaching 1–1.2 g/kg body weight per day in contrast to previous recommendations of 0.8 g/kg body weight per day [22, 23], but it remains unclear as to how best to consume protein. Planning for protein consumption to occur evenly during the day or to be delivered through pulse feeding are areas for further research. There is already evidence to support the consumption of protein two to three hours following exercise [24, 25], but realistically, for logistical or adherence purposes, exercise strategies may need to introduce protein supplementation in close proximity to the activity.

It is important to note, however, that while there is expert consensus on the importance of meeting daily protein requirements in older people, there is still limited evidence to confirm the benefits of protein supplementation [6]. While the effectiveness of protein supplements is reasonably clear in terms of muscle function and strength, results of tests on the recovery of muscle mass are largely inconclusive [26].

Research into disordered muscle anabolism, as evident in sarcopenia, has included investigations into the amino acid, *leucine*. Leucine can be obtained from ingesting either plant or animal protein, although animal protein is regarded as more anabolic, possibly because of the lower content of leucine in plant protein [27].

It has been reported that at least 3 g of leucine is required to overcome anabolic resistance in older people [28]. Most recently, through a secondary analysis, twice daily supplementation for 13 weeks with vitamin D (800 IU) and leucine-enriched whey

protein (20 g whey protein, 3 g leucine) in sarcopenic individuals aged 65 years and over ($n = 288$) was shown to reduce chronic low-grade inflammation [29]. Vitamin D while currently not an ICFSR recommendation, may be useful for bone health.

This research built on a primary study ($n = 380$), the results of which indicated that nutritional supplementation without exercise may be of benefit in supporting appendicular muscle mass [30], but not grip strength or short physical performance battery scores.

There is increasing interest in the treatment of sarcopenia during the perioperative period. In a recently published study out of the United States, for example, patients undergoing radical cystectomy were provided a nutritional supplement throughout the whole of their surgical stay, from admission to discharge. Compared with another group provided only with multivitamins and minerals, those taking the nutritional supplement lost less weight and the proportion of the group with sarcopenia remained unchanged. In the vitamin and mineral group, the number of individuals with sarcopenia increased by 20% [31].

Other interventions

The benefits of pharmacological interventions in the treatment of sarcopenia remain uncertain. A recent systematic review has pointed out that introducing a selective androgen receptor modulator (SARM) in older adults with sarcopenia did not benefit strength or function, both of which are vital for independence in older age [32]. The trial of pharmacological agents continues. There have been several trials investigating the use of myostatin antibodies, given the links between myostatin and muscle wasting [33]. Angiotensin-converting enzyme inhibitors (ACEi) have been proposed as a support for muscle strength and walking speed, but at this point in time, research findings are inconclusive [34].

CONCLUSION

In conclusion, there is increasing research into how best to treat sarcopenia, including the exploration of novel protein supplementation and pharmacological strategies. In the meantime, clinicians who have diagnosed sarcopenia should take a comprehensive approach to the management of the condition and address reversible factors that are contributing to a decline in nutritional (especially protein) intake, and loss of lean muscle mass and strength. Currently, physical activity and healthy nutrition continue to be the cornerstone of sarcopenia management, neither of which come in pill form, and each of which can demand patience and creativity from the clinician.

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Sarcopenia, Second Edition. Edited by Alfonso J. Cruz-Jentoft and John E. Morley.