Chapter

Sarcopenia in Older Adults

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Abstract

Sarcopenia has become of great interest and focus of many studies since this phenomenon affects many people. Moreover, sarcopenia is associated with two more pandemic phenomena: frailty and obesity. These health-related conditions are increasing in western countries in general and in the older population in particular. Each of such health conditions relates to functional decline, yet the combination of two or three of them in one person severely affects quality of life and longevity. Aged individuals who are less physically active are more likely to develop sarcopenic obesity, and those who are obese with muscle weakness and inactive are disposed to become frail individuals. Hence, frailty and obesity overlap profoundly with the physical manifestations of sarcopenia of aging. These "unhappy" triads encompasses a wider range of geriatric decline that also includes cognitive, psychology and social deterioration associated with adverse outcomes. Nevertheless, this chapter focuses only on sarcopenia and will review the pathophysiological background of age-related decline in muscle mass and strength.

Keywords: sarcopenia, elderly, strength, muscle mass, physical performance, radicals, cytokines

1. Introduction

1.1 The "unhappy triad"

The end of the last century and the beginning of the first two decades of the present century were characterized by the rise of three medical or health pandemic phenomena, each of which has a serious impact on public health and especially among older people. These three conditions are frailty, sarcopenia, and obesity. When sarcopenia or frailty is also accompanied by obesity, a sarcopenic/frail-obese phenotype is established [1]. Moreover, the presence of these "unhappy triads" of health conditions, in one person, poses a significant threat to one's quality of life and longevity. The prevalence of each of such conditions (i.e., frailty, sarcopenia, and obesity) is widely estimated within different countries; however, with no one single best outcome measure for these diagnoses, there is highly wide range of manifestation and diagnoses in each of these health phenomena [2].

A "cycle of sarcopenia" may be created in which in the presence of one or two factors such as frailty and or obesity, sarcopenia status is likely to continue to deteriorate unless there is outside intervention. It is extremely difficult to overcome this "unhappy triad" when the affected people do not have the resources necessary to get out of muscle weakness and fatigue, such as lower cardiac function (myocardial infraction, angina, chronic heart failure, metabolic state (hypertension, diabetes, and obesity) and arthritis.

Longevity steadily increased over the past several decades. Life expectancy in 65 year Western country subjects is ~20 years, and the proportion of people over age 60 is increasing faster than any other groups (2). Obesity is also worldwide growing [3] and is also accompanied by significant alterations in body composition, with a decline in lean body mass and muscle strength and with an increase in fat mass. This phenomenon known as sarcopenic obesity [4].

The concept of frailty syndrome is basically a geriatric syndrome, which is recently becoming one of the dominant concepts in advanced age. Frailty is a dynamic condition with the presence of several components. There are two major operational definitions for frailty. The most widely used concept is the Fried physical frailty phenotype, which defines frailty based on three or more of the following five symptoms: unintentional weight loss, slowness, weakness, exhaustion, and low physical activity [5]. Yet, functional decline due to sarcopenia is in the core of frailty syndrome [6].

This chapter focuses on sarcopenia. Aged skeletal muscles can be induced to die through different mechanisms mainly via two systems, apoptosis or autophagy; both systems can be activated through different molecules such as free radicals, inflammatory molecules, hormones, and others [7].

2. Sarcopenia

There are currently over 10,000 articles published in referee journals dealing with the phenomenon of Sarcopenia, which was first proposed by Irwin Harold Rosenberg in 1989 at the annual conference of the American Society for Clinical Nutrition. Sarcopenia is age-related myopenia (decrease of muscle mass) and dynapenia (decrease in muscle strength) [8]. More specifically, sarcopenia is a health problem of old people characterized by a slow, progressive skeletal muscle disorder involving the accelerated loss of muscle mass and strength followed by the functional decline that is associated with falls, obesity, frailty, frequent hospitalization, and mortality [9]. Sarcopenia has become of great interest and focus of many studies and since this phenomenon affects many people, the number of older population with sarcopenia is expected to increase all over the world, and it is becoming one of the important and interests, and causes a great deal of financial burden, a private and a public concern, from the individual level to the state and various institutions that deal with welfare and health [10]. It predisposed by genetic profile and lifestyle factors occurring across the life course [11]. The expression of Let-7b and Let-7e microRNA precursors (regulating muscle apoptosis) is significantly higher in older versus younger subjects. Ingenuity pathway analysis identified that the Let-7 family predicted gene targets were related to pathways and biological functions associated with macrophages activity.

Therefore, a great deal of knowledge about the nature of the phenomenon was accumulated, from a biological and clinical point of view, different means to diagnose it, and with particular ways to treat it such as nutritional interventions and drugs to augment the beneficial effects of resistance exercise.

2.1 Definition of sarcopenia

Sarcopenia (Greek "sarx" or flesh + "penia" or loss) is a geriatric syndrome which is described as a progressive decline in skeletal muscle mass and muscle strength from approximately the fifth decade of life.

The European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia in 2010 as a quote: "a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with the risk of adverse

outcome such as physical disability, poor quality of life, and death" [12]. The EWGSOP proposed that age-related muscle weakness is considered as "primary sarcopenia" when no other reason is evident except aging itself. EWGSOP also suggests a concept of three phases of sarcopenia: pre-sarcopenia (there is low muscle mass without low muscle strength or decline in physical performance); sarcopenia (low muscle mass, accompanying either low muscle strength or low physical performance); and severe sarcopenia (when all three criteria are detected).

Another consensus definition of primary sarcopenia done by the International Working Group for Sarcopenia (IWGS) as "an individual presents functional and mobility decline, history of recurrent falls, recent unwanted body weight loss, recent-hospitalization, and chronic metabolic diseases (e.g., diabetes, hypothyroid) malnutrition, low protein intake, and cancer" [13].

2.2 Prevalence and epidemiology of sarcopenia

It is well known and extensively documented that as an older person reaches his sixth decade of life, there is a progressive decline in muscle mass (~1% per year) and strength (~2.5–3% per year) [14]. Sarcopenia is more prevalent in men than in women. It is more prevalent in large muscle groups such as tight, more in untrained individuals and more in people with poor health background [15]. There is a strong association between, muscle strength, age, gender, and disability. In general, there is a decrease in muscle mass at an annual rate of 1.5% after about 50 years old, reaching to 3% per year in their eight decade [16].

Public health planners, physicians and researchers are needed to come up with the consensus of criteria for estimating the prevalence of sarcopenia. Moreover, at present time, there are lacking data for developing any consensus on what constitutes poor muscle mass, and what is the optimal, valid, and reliable tool to measure and to diagnose sarcopenia.

The prevalence of sarcopenia needs to be investigated in multiethnic population, and to explore association with obesity, socioeconomic status, mental and cognitive function, morbidity, quality of life, and life style. Previous studies have been demonstrated associations between muscle mass and function, whereas other studies have established associations between the following:

a. sarcopenia and physical activity [17],

b. muscle mass and BMI [18];

c. muscle performance and certain minerals [19];

d. muscle mass and strength and depressive symptoms and [20];

e. sarcopenia and cognitive impairment [21];

f. muscle strength and falls [22];

g. muscle mass and osteoporosis [23], thus those with sarcopenia possessed approximately 13 times higher risk of having osteoporosis [24], and there is a significant association between osteoporosis and deterioration of the skeletal microarchitecture [25]. The prevalence of osteosarcopenia increases with aged men and women [26]; and

h. sarcopenia and meat intake in male and milk intake in female [27].

3. Biological mechanisms of sarcopenia: from molecular to histological level

There are several molecular mechanisms that may be involved, in some degree, in the commencement and development of sarcopenia. Although the molecular and cellular mechanisms underlying sarcopenia still remain to be clarified, certain common biological mechanisms have been suggested to be involved in sarcopenia. This section will include, in brief, the most common mechanisms related to sarcopenia: oxidative stress [reactive oxygen and nitrogen species (ROS and RNS)]; a-without clinical symptoms of muscle fiber inflammation (due to presence of myokines/cytokines like TNF-α and IL-6); hormonal regulation impairment (such as testosterone, growth hormone, IGF-1, glutathione 4, insulin resistance, and vitamin D); vitamin E deficiency; proteolysis pathway [the lack of responsiveness of the ubiquitin-proteasome system and alterations in the regulation of autophagy and apoptotic pathway (Bcl2 signaling and NF-*K*b)]; and finally, the role of adult stem (satellite) cells. Identifying these mechanisms and their underlying origins is expected to facilitate strategy of intervention programs [28].

From a physiology and histology point of view, the skeletal muscle comprises several types of fibers. The most prominent types are type I and type II fibers. Type II fast twitch muscle fibers characterized by high glycolytic potential, lower oxidative capacity, and faster response, are aimed at muscle strength and short-duration anaerobic activities, whereas type I slow twitch muscle fibers are known as fatigue-resistant due to their characteristics such as large density of capillary bed and myoglobin and being abundant with mitochondria, to better supply oxygen and nutrients to the muscle, thus to improve muscular endurance and aerobic activities [29].

Sarcopenia is characterized by more hypotrophy and less fiber activation of the lower extremity muscles than upper limbs. Moreover, the lower limb muscles of old people are smaller and have significantly more fats and connective tissues than lower limb muscles in young individuals. Sarcopenia is characterized by a reduction in both the number and size of muscle fibers, mainly of type II, and is to some extent caused by a slowly progressive myogenic process, which is stem cells dependent. Therefore, these changes affect not only in energy production, poor muscle repair, and deprived fiber regeneration, but also practically in decline in physical performance and in functional capacity such as walking (stairs), running, and early onset of fatigue which all associate with poor quality of life and more dependency [30].

Of course there is a connection and interdependence between the various factors. Sometimes one of them is a cause or effect, and sometimes it is a result of or outcome from. Some of the mechanisms have a positive correlation and others have a negative correlation. In general, skeletal muscle can "die" in different molecular pathways. Sarcopenia, as a normal physiological process, is associated with a significant rise in the levels of inflammatory molecules both in blood serum and intra- and extracellular. The aging process induced oxidative stress (OS) and degradation of damaged mitochondria promotes the accumulation of lipofuscin, which is one histological marker of fiber oxidative damage. The accumulation of lipofuscin, is recognized as the hallmark pigment of aging muscle. Lipofuscin is an intralysosomal, composed of cross-linked protein residues and lipid per oxidized molecules. This intracellular waste material interferes with muscle metabolism and muscle contraction [31].

Oxidative stress resulted due to imbalance between the production of reactive oxygen/nitrogen species and antioxidants/nitrogen defense molecules. Consequently

and practically, a chain response of inflammatory molecules appears within the fibers with the release of myokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1) that lead to a predisposition to age-related sarcopenia afterward through the activation of the ubiquitin-protease system and the activation of myofiber signaling pathway that leads to muscle apoptosis. It is also suggested that cytokines also contributes to anabolic resistance through provoking the anabolic effect mediated by insulin growth factor-1 (IGF-1), involving in growth hormone resistance which limits IGF-I availability. Some other potential factors and mechanisms are suggested leading to sarcopenia such as TGF-β-activated kinase (TAK)-1; C-reactive protein; a significant reduction of dihydropyridine (DHP)-sensitive Ca^{2+} (the decrease of Ca^{2+} available for mechanical responses in aged skeletal muscle is due to DHP receptor (DHPR)-ryanodine receptor (RyR) uncoupling); and the stress of sarcoplasmic reticulum due to accumulation of unfolded or misfolded proteins like heat shock proteins.

3.1 Oxidative stress and sarcopenia

Sarcopenia is a multifactorial event, thus redox signaling and oxidative stress have a key role play, due to an increase in reactive oxygen and nitrogen species (ROS/RNS) levels, a decrease in enzymatic antioxidant protection and followed by myofiber "quiet" inflammation (i.e., the presence of myokines). Therefore, the oxidative stress is more extensively described in the below section of this chapter.

3.1.1 Endogenous sources of reactive oxygen species, reactive nitrogen species, and antioxidant systems

Reactive oxygen species (ROS) are mainly and normally produced by the mitochondria, and a normal ROS level is indispensable for myofiber functions.

The mitochondrial electron transport chain transfer of a single electron to molecular oxygen gives rise to a monovalent reduction of oxygen, which leads to the formation of superoxide ions (O_2.–). It is the first step in the chain of events to create more free radicals such as hydrogen peroxide (H_2O_2), hydroxyl radical (OH.), and hydroxyl ion (OH^-) [32]. Another source of ROS in skeletal muscle is a large NOX family enzymes (NOX_1, NOX_2, and NOX_4) located in the sarcoplasmic reticulum, transverse tubule, and also in the sarcoplasma membrane [33]. These enzymes have the capacity to transport electrons across the sarcoplasma membrane and generate superoxide and other downstream reactive oxygen species (ROS). Since these enzymes play an important role in excitation contraction coupling, hyperexpression or overproduction of NOXs inhibits muscle contractions. Another mechanism that can explain the crosstalk between NOXs and ROS production is the rise of intracellular Ca^{2+} levels by NOX-derived ROS, which, increasing mitochondrial Ca^{2+} load, induces the ROS production by these organelles.

Reactive nitrogen species (RNS) derived from nitric oxide (•NO) and superoxide ions is produced via the enzymatic activity of inducible nitric oxide synthase 2 (NOS_2) and nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) [34]. NOS_2 is also expressed after induction of cytokines [26]. In skeletal muscle, there are three different isoforms of this isoenzyme: endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible isoform (iNOS). RNS arise from several sources and the levels increase with contractile activity. Nitric oxide (NO) is formed from L-arginine in a reaction catalyzed by the nitric oxide synthase (NOS) enzyme, and it is an important cell signaling molecule [35].

The intrinsic and extrinsic antioxidant systems inhibit oxidation [36, 37]. The intrinsic system includes enzymes such as superoxide dismutase, catalase, peroxidase, and glutathione. Manganese superoxide dismutase (MnSOD) is synthesized by a mitochondrion that catalyzes the breakdown of the superoxide anion into oxygen and hydrogen peroxide. Catalase catalyzes the conversion of hydrogen peroxide to water and oxygen, peroxidase catalyzes the reduction of hydrogen peroxide, and glutathione is a very efficient scavenger of hydrogen peroxide, while glutathione peroxidase 4 is most active with lipid hydroperoxides. The extrinsic system includes dietary supplements such as Ubiquinone-10, coenzyme Q10, creatine, and others, and the combination with physical exercise is even better for muscle atrophy prevention and/or treatment of sarcopenia [38].

The levels of ROS and RNS inside the fibers are firmly controlled by the balance between the rate of endogenous synthesis by ROS/RNS generating systems and the rate of removal through the nonenzymatic and enzymatic antioxidant systems [39]. In aged muscles, there is an excessive ROS/RNS production or diminishing of antioxidant production which interrupts the myofiber metabolism and physiological function, both in resting and in force production [40]. There is plenty of evidence that sarcopenia is caused by an increase of endogenous ROS and/or RNS formation, on the one hand, and decrease in quantity, quality, and antioxidant system efficiency, on the other hand [41, 42]. Sarcopenia is also characterized by mitochondrial dysfunction; mitochondrial morphological changes, lacking fusion and fission; less mitochondria mobility, leading to the accumulation of damaged mitochondria that induces a catabolic process; muscle loss; and fiber inflammation [43, 44].

In conclusion, age-related ROS and RNS overproduction not only generates damage of muscle but also plays a role in regulating intracellular signal transduction pathways that are directly or indirectly involved in skeletal muscle inflammation and apoptosis.

3.1.2 The role of cytokines in sarcopenia

Sarcopenia is definitely associated with inflammatory cytokines/myokines, which prompt a serious negative consequence as a loss of muscle mass and strength with concomitant increase in fat mass, eventually stimulating protein catabolism and muscle degeneration. As such, an excepted catabolic inflammatory process is often observed in older adults, and it can enhance and deteriorate the status of sarcopenia [45].

Skeletal muscle tissue is an vital source of inflammatory molecules, known as "myokines" (e.g., IL-6, IL-1b, TNFα, and IL-1ra) which are overexpressed in aged skeletal muscles, related to the slow, non symptomatic, slowly progressed, inflammation process demonstrated in elderly individuals. Myokines are secreted in response to muscle contraction or strength training [46]; however, their activation as inflammatory signal pathways happen due to aging, which reveals their critical impact on sarcopenia [47]. Several inflammatory myokines, especially interleukin-1 6, and 10 (IL-1, Il-6, IL-10), tumor necrosis factor-alpha (TNF-α), and myostatin play crucial roles in the modulation of inflammatory signaling pathway during the aging-related loss of skeletal muscle [48, 49].

3.1.2.1 Interleukin

The relationship between sarcopenia and the inflammatory cytokines interleukin-1 and 6 (IL-1, IL-6), and the anti-inflammatory cytokine interleukin-10 (IL-10) in an elderly population is well reported [50, 51]. IL-6 within the muscle fibers

promotes glucose uptake and fat oxidation via the phosphoinositide 3-kinase (PI3K) and AMP-activated protein kinase (AMPK) signaling pathways, respectively, and improves insulin sensitivity by blocking the proinflammatory signaling pathways in the muscle. High levels of IL-6 (>40 pg./ml) and IL-10 (>4 pg./ml) are associated with lower physical performance, muscle strength, and muscle mass [52]. Hospitalized geriatric patients with inflammation represented significantly weaker muscle function, shoulder extension strength, and a worse fatigue resistance [53]. Old people living in nursing homes and long-term-assisted living facilities presenting high IL-6 levels were associated with the higher prevalence of frailty [54]. The significant role of IL-6 levels on depressive symptoms in older women in the year after hip fracture may represent a sickness syndrome that is chronic in some individuals [55]. A recent study in community-dwelling older men suggested that the high levels of interleukin-1 (IL-1) is associated with a low grip strength [56]. The ratio of proinflammatory cytokine IL-6 to anti-inflammatory cytokine IL-10 (IL-6/IL-10 ratio) >9.5 pg./ml has been used as a reliable marker for measuring inflammatory status [57].

IL-10 is an anti-inflammatory myokine, mostly produced by macrophages, T-helper 2 cells (also known as CD4+ cells), B-lymphocytes, and monocytes. These cells either secrete antibodies or suppress and destroy any immune response. IL-10 is responsible for destroying the proinflammatory response in various tissues, including skeletal muscle, by suppressing the activation of phagocytes such as macrophages and releasing and activating the inflammatory cytokines such as IL-6, TNFα, and IL-1β. Increased IL-10 was associated with poor physical performance [58, 59].

In summary, inflammatory and proinflammatory interleukin cytokines have both been linked with a number of age-related outcomes, including sarcopenia, chronic morbidity, functional decline, and mortality [60].

3.1.2.2 Tumor necrosis factor-α (TNF-α)

The appearance of sarcopenia is accompanied by the increased levels of inflammation factors such as TNF-α. TNF-α inhibits the synthesis of muscle proteins, accelerates protein decomposition, and upregulates the expression of muscle growth inhibitory factor myostatin and muscle atrophy proteins, F-box-1 Atrogin-1, etc., so as to accelerate protein catabolism and promote skeletal muscle consumption. TNF-α and its soluble receptors showed the most consistent associations with decline in muscle mass and strength [61]. TNF-α is also reported to suppress the Akt/mTOR pathway [62], promoting muscle catabolism, oxidative stress, and nitric acid production [63].

3.1.2.3 C-reactive protein (CRP)

Elevated levels of these proteins, reflecting the conditions of chronic inflammation, have been associated with reduced muscle mass and strength [64], decreased physiology capacity, and more difficulties in performing the activities of daily living [65]. The levels of CRP are negatively associated with appendicular lean body mass [66]. In addition, the increased levels of lipid peroxidation result in the breakdown of biological phospholipids in sarcolemma and mitochondrial membrane, thus preventing the mitochondria to break down and converting fatty acid molecules (β-oxidation) to acyl-CoA chains in order to produce energy. Damage to mitochondria also increases the formation of reactive oxygen species such as superoxide anion [$O_2 \cdot -$], hydroxyl radical [OH−]), and hydrogen peroxide [H_2O_2], complemented by the increased production and secretion of proinflammatory

cytokines such as tissue necrosis factor (TNF)-α and IL-1, 6, and 8 that trigger a cytokine cascade of the inflammatory cytokines that worsen the insulin resistance in skeletal muscle, resulting in the decrease of aerobic capacity [67].

3.2 Hormones and sarcopenia

A variety of other hormones appear to play roles in the age-related alterations in muscle mass, strength function, and in the regulation of muscle metabolism [68].

Testosterone appears to be the central hormone involved in the development of sarcopenia. Testosterone is an important physiologic steroid hormone in muscle mass maintenance. Endogenous testosterone which naturally produced within the endocrine system in both men and women decline gradually with age, correlating with decreased muscle strength it increases both muscle mass and activates adult stem cells (i.e., satellite cells) leading to improved muscle function [69].

Normal growth hormone (GH) level is associated with notable protection from age-related disease in general, and more specifically against sarcopenia. The levels of GH and GH binding proteins declines upon aging. Growth hormone deficiency leads to the loss of muscle mass but not muscle strength [69, 70].

Skeletal muscle is the major organ in which the insulin-mediated glucose uptake by glucose transporter 4 (GLUT4) takes place. Lack of insulin, or IGF-1, or insulin resistance leads to accelerated development of sarcopenia. The muscle IGF-I level declines in aged population.

The primary action of insulin in skeletal muscle is to stimulate glucose uptake and metabolism. In physiological condition as insulin resistance, there is a gradual muscle wasting by several mechanisms such as the following: (a) suppression of PI3K/Akt signaling leading to the activation of caspase-3 and the ubiquitin-proteasome proteolytic pathway causing muscle protein degradation; (b) beta-adrenergic stimulation increases the lipolysis of the cell membrane, breaking down G-proteins that lead to interfering with growth hormone/insulin growth factor-1 receptor bind and diminished muscle regeneration; (c) advancement of gluconeogenesis metabolic pathway; (d) upregulation of sterol regulatory element-binding protein 1c (SREBP-1c); and (e) altering triglyceride and cholesteryl esters transport in the core of plasma lipoproteins, which causes triglycerides to accumulate in skeletal muscle [71, 72]. It has been reported that IGF-I drops 1.88 ng/ml/year in men and 2.13 ng/ml/year in women [73]. Circulating IGF-I level was found to be significantly reduced in sarcopenia patients [74]. mTOR signaling is a significant factor in sarcopenia, and mTOR signaling is altered by the change of IGF-I level [75].

Various medical problems and health conditions such as muscle weakness reduced the muscle mass that is predominantly a type II muscle fiber, bone pain, and systematic oxidative stress linked to 1,25-dihydroxyvitamin D [1,25(OH)2D]/vitamin D deficiency. The vitamin D deficiency expands the sarcomeres space that allows the infiltration of irregular connective tissue and fat tissue. As such, the vitamin D deficiency resulting in reducing physical performance such as gait speed and cognitive performance (such as sustained attention and speed of information processing), mental well-being (e.g., depression), falls and leading to bone deformities. The vitamin D deficiency is a serious medical condition that drastically affects the quality of life of older adults. There are a number of reasons that play a role in vitamin D deficiencies in older adults. Since the majority of the time they spend indoors, they get minimal exposure to sunlight, lacking resistance exercise which is well known to preserve muscle function, and their skin is less exposed to the synthesis of vitamin D [76, 77].

3.3 Vitamin E

Vitamin E, which is a group of eight fat soluble compounds, four tocopherols (α, β, γ, and δ) and four tocotrienols (α, β, γ, and δ), is a lipid soluble vitamin, with potent antioxidant properties and has a role in the modulation of signaling pathways. The vitamin E molecules deficiency, due to malabsorption or malnutrition, worsens age-associated skeletal dysfunction and enhances muscle degeneration, thus increasing sarcopenia [78, 79].

4. Conclusions

This chapter reviewed the possible mechanisms that are linked to sarcopenia. The etiology of sarcopenia is multifactorial, including a wide range of both intramuscular and extra muscular factors. This chapter focuses only on the intramuscular factors that include oxidative stress, inflammation, lack of vitamins, and hormones. Extra muscular factors include adult stem cells, extra cellular matrix (e.g., the function of matrix metaloproteinases), capillary bed, and neuronal activity.

Conflict of interest

The author declares no conflicts of interest, financial or otherwise.

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References

[1] Buch A, Keinan-Boker L, Kis O, Carmeli E, Izkhakov E, Ish-Shalom M, et al. Severe central obesity or diabetes can replace weight loss in the detection of frailty in obese younger elderly - a preliminary study. Clinical Interventions in Aging. 2018;**13**:1907-1918

[2] Buch A, Carmeli E, Shefer G, Keinan-Boker L, Berner Y, Marcus Y, et al. Cognitive impairment and the association between frailty and functional deficits are linked to abdominal obesity in the elderly. Maturitas. 2018;**114**:46-53

[3] Pizzol D, Smith L, Fontana L, Caruso MG, et al. Associations between body mass index, waist circumference and erectile dysfunction: A systematic review and META-analysis. Reviews in Endocrine & Metabolic Disorders. 2020;**31**. [Epub ahead of print]

[4] Batsis JA, Villareal DT. Sarcopenic obesity in older adults: Aetiology, epidemiology and treatment strategies. Nature Reviews. Endocrinology. 2018;**14**(9):513-537

[5] Fried LP, Tangen CM, Walston J, Newman AB, et al. Frailty in older adults: Evidence for a phenotype. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2001;**56**(3):M146-M157

[6] Michel JP, Ecarnot F. Integrating functional ageing into daily clinical practice. Journal of Frailty, Sarcopenia and Falls. 2019;**4**(2):30-35

[7] Carmeli E, Aizenbud D, Rom O. How do skeletal muscles die? An overview. Advances in Experimental Medicine and Biology. 2015;**861**:99-111

[8] Rosenberg IH. Diagnosis, treatment, and prevention of sarcopenia. The American Journal of Clinical Nutrition. 1989;**50**(5):1231-1233

[9] Papadopoulou SK. Sarcopenia: A contemporary health problem among older adult populations. Nutrients. 2020;**12**(5). pii: E1293

[10] Beaudart C, Zaaria M, Pasleau F, Reginster JY, Bruyère O. Health outcomes of sarcopenia: A systematic review and meta-analysis. PLoS One. 2017;**12**(1):e0169548

[11] Drummond MJ, McCarthy JJ, Sinha M, Spratt HM, Volpi E, Esser KA, et al. Aging and microRNA expression in human skeletal muscle: A microarray and bioinformatics analysis. Physiological Genomics. 2011;**43**(10):595-603

[12] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European working group on sarcopenia in older people. Age and Ageing. 2010;**39**:412-423

[13] Fielding RA, Vellas B, Evans WJ, Bhasin S, et al. Sarcopenia: An undiagnosed condition in older adults. Current consensus definition: Prevalence, etiology, and consequences. International Working Group on Sarcopenia. Journal of the American Medical Directors Association. 2011;**12**:249-256

[14] Daly RM, Rosengren BE, Alwis G, Ahlborg HG, Sernbo I, Karlsson MK. Gender specific age-related changes in bone density, muscle strength and functional performance in the elderly: A-10 year prospective population-based study. BMC Geriatrics. 2013;**13**:71

[15] Ligthart-Melis GC, Luiking YC, Kakourou A, Cederholm T, Maier AB, de van der Schueren MAE. Frailty,

sarcopenia, and malnutrition frequently (co-)occur in hospitalized older adults: A systematic review and meta-analysis. Journal of the American Medical Directors Association. 2020; pii: S1525-8610(20)30251-30256

[16] Sehl ME, Yates FE. Rates of senescence between ages 30 and 70 years in healthy people. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2001;**56**:198-208

[17] Steffl M, Bohannon RW, Sontakova L, Tufano JJ, Shiells K, Holmerova I. Relationship between sarcopenia and physical activity in older people: A systematic review and meta-analysis. Clinical Interventions in Aging. 2017;**12**:835-845

[18] Iannuzzi-Sucich M, Prestwood KM, Kenny AM. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2002;**57**(12):M772-M777

[19] van Dronkelaar C, van Velzen A, Abdelrazek M, et al. And physical performance in older adults: A systematic review. Journal of the American Medical Directors Association. 2018;**19**(1):6-11.e3

[20] Taani MH, Siglinsky E, Kovach CR, Buehring B. Psychosocial factors associated with reduced muscle mass, strength, and function in residential care apartment complex residents. Research in Gerontological Nursing. 2018;**11**(5):238-248

[21] Chang KV, Hsu TH, Wu WT, Huang KC, Han DS. Association between sarcopenia and cognitive impairment: A systematic review and meta-analysis. Journal of the American Medical Directors Association. 2016;**17**(12):1164.e7-1164.e15

[22] Zhang XM, Cheng ASK, Dou Q, Zhang W, Zeng Y. "Sarcopenia and its association with falls and fractures in older adults: A systematic review and meta-analysis" by Yeung et al. Journal of Cachexia, Sarcopenia and Muscle. 2020;**11**(1):330-331

[23] Nielsen BR, Abdulla J, Andersen HE, Schwarz P, Suetta C. Sarcopenia and osteoporosis in older people: A systematic review and meta-analysis. European Geriatric Medicine. 2018;**9**:419-434

[24] Sjöblom S, Suuronen J, Rikkonen T, Honkanen R, Kröger H, Sirola J. Relationship between postmenopausal osteoporosis and the components of clinical sarcopenia. Maturitas. 2013;**75**:175-180

[25] Locquet M, Beaudart C, Reginster J-Y, Bruyère O. Association between the decline in muscle health and the decline in bone health in older individuals from the SarcoPhAge cohort. Calcified Tissue International. 2019;**104**:273-284

[26] Kirk B, Al Saedi A, Duque G. Osteosarcopenia: A case of geroscience. Aging Medicine (Milton). 2019;**2**(3):147-156

[27] Lim HS. Association of dietary variety status and sarcopenia in Korean elderly. Journal of Bone Metabolism. 2020;**27**(2):143-149

[28] Riuzzi F, Sorci G, Arcuri C, Giambanco I, Bellezza I, Minelli A, et al. Cellular and molecular mechanisms of sarcopenia: The S100B perspective. Journal of Cachexia, Sarcopenia and Muscle. 2018;**9**(7):1255-1268

[29] Carter CS, Justice JN, Thompson L. Lipotoxicity, aging, and muscle contractility: Does fiber type matter? Geroscience. 2019;**41**(3):297-308

[30] Lexell J. Human aging, muscle mass, and fiber type composition.

The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 1995;**50**:11-16

[31] Hütter E, Skovbro M, Lener B, Prats C, Rabøl R, Dela F, et al. Oxidative stress and mitochondrial impairment can be separated from lipofuscin accumulation in aged human skeletal muscle. Aging Cell. 2007;**6**(2):245-256

[32] Sakellariou GK, McDonagh B. Redox homeostasis in age-related muscle atrophy. Advances in Experimental Medicine and Biology. 2018;**1088**:281-306

[33] Sullivan-Gunn MJ, Lewandowski PA. Elevated hydrogen peroxide and decreased catalase and glutathione peroxidase protection are associated with aging sarcopenia. BMC Geriatrics. 2013;**13**:104

[34] Nemes R, Koltai E, Taylor AW, Suzuki K, Gyori F, Radak Z. Reactive oxygen and nitrogen species regulate key metabolic, anabolic, and catabolic pathways in skeletal muscle. Antioxidants (Basel). 2018;**7**(7). pii: E85

[35] Hall DT, Ma JF, Marco SD, Gallouzi IE. Inducible nitric oxide synthase (iNOS) in muscle wasting syndrome, sarcopenia, and cachexia. Aging (Albany NY). 2011;**3**(8):702-715

[36] Fougere B, van Kan GA, Vellas B, Cesari M. Redox systems, antioxidants and sarcopenia. Current Protein & Peptide Science. 2018;**19**(7):643-648

[37] Di Meo S, Napolitano G, Venditti P. Physiological and pathological role of ROS: Benefits and limitations of antioxidant treatment. International Journal of Molecular Sciences. 2019;**20**(19). pii: E4810

[38] Guescini M, Tiano L, Genova ML, Polidori E, Silvestri S, Orlando P, et al. The combination of physical exercise with muscle-directed antioxidants to counteract sarcopenia: A biomedical rationale for pleiotropic treatment with creatine and coenzyme Q10. Oxidative Medicine and Cellular Longevity. 2017;**2017**:7083049

[39] Ji LL. Antioxidant signaling in skeletal muscle: A brief review. Experimental Gerontology. 2007;**42**(7):582-593

[40] Ji LL. Modulation of skeletal muscle antioxidant defense by exercise: Role of redox signaling. Free Radical Biology & Medicine. 2008;**44**(2):142-152

[41] Liguori I, Russo G, Curcio F, Bulli G, Aran L, Della-Morte D, et al. Oxidative stress, aging, and diseases. Clinical Interventions in Aging. 2018;**13**:757-772

[42] Belenguer-Varea Á, Tarazona-Santabalbina FJ, Avellana-Zaragoza JA, Martínez-Reig M, Mas-Bargues C, Inglés M. Oxidative stress and exceptional human longevity: Systematic review. Free Radical Biology & Medicine. 2020;**149**:51-63

[43] Azuma K, Ikeda K, Inoue S. Functional mechanisms of mitochondrial respiratory chain supercomplex assembly factors and their involvement in muscle quality. International Journal of Molecular Sciences. 2020;**21**(9). pii: E3182

[44] Abrigo J, Simon F, Cabrera D, Vilos C, Cabello-Verrugio C. Mitochondrial dysfunction in skeletal muscle pathologies. Current Protein & Peptide Science. 2019;**20**(6):536-546

[45] Beenakker KG, Ling CH, Meskers CG, de Craen AJ, Stijnen T, Westendorp RG, et al. Patterns of muscle strength loss with age in the general population and patients with a chronic inflammatory state. Ageing Research Reviews. 2010;**9**(4):431-436

[46] Raschke S, Eckardt K, Bjorklund Holven K, Jensen J, Eckel J. Identification and validation of novel contraction-regulated myokines released from primary human skeletal muscle cells. PLoS One. 2013;**8**(4):e62008

[47] Beyer I, Mets T, Bautmans I. Chronic low-grade inflammation and age-related sarcopenia. Current Opinion in Clinical Nutrition and Metabolic Care. 2012;**15**:12-22

[48] Lee JH, Jun HS. Role of myokines in regulating skeletal muscle mass and function. Frontiers in Physiology. 2019;**10**:42

[49] Coelho-Junior HJ, Picca A, Calvani R, Uchida MC, Marzetti. If my muscle could talk: Myokines as a biomarker of frailty. Experimental Gerontology. 2019;**127**:110715

[50] Lambernd S, Taube A, Schober A, Platzbecker B, Gorgens SW, Schlich R, et al. Contractile activity of human skeletal muscle cells prevents insulin resistance by inhibiting pro-inflammatory signalling pathways. Diabetologia. 2012;**55**:1128-1139

[51] Rong YD, Bian AL, Hu HY, Ma Y, Zhou XZ. Study on relationship between elderly sarcopenia and inflammatory cytokine IL-6, anti-inflammatory cytokine IL-10. BMC Geriatrics. 2018;**18**(1):308

[52] Raj DS, Dominic EA, Pai A, Osman F, Morgan M, et al. Muscle, cytokines, and oxidative stress in end-stage renal disease. Kidney International. 2005;**68**(5):2338-2344

[53] Lustosa LP, Batista PP, Pereira DS, Pereira LSM, Scianni A, Ribeiro-Samora GA. Comparison between parameters of muscle performance and inflammatory biomarkers of non-sarcopenic and sarcopenic elderly women. Clinical Interventions in Aging. 2017;**12**:1183-1191

[54] Bautmans I, Njemini R, Lambert M, Demanet C, Mets T. Circulating acute phase mediators and skeletal muscle performance in hospitalized geriatric patients. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2005;**60**(3):361-367

[55] Langmann GA, Perera S, Ferchak MA, Nace DA, Resnick NM, Greenspan SL. Inflammatory markers and frailty in long-term care residents. Journal of the American Geriatrics Society. 2017;**65**(8):1777-1783

[56] Matheny ME, Miller RR, Shardell MD, Hawkes WG, Lenze EJ, Magaziner J, et al. Inflammatory cytokine levels and depressive symptoms in older women in the year after hip fracture: Findings from the Baltimore hip studies. Journal of the American Geriatrics Society. 2011;**59**(12):2249-2255

[57] Patel HP, Al-Shanti N, Davies LC, Barton SJ, Grounds MD, Tellam RL, et al. Lean mass, muscle strength and gene expression in community dwelling older men: Findings from the Hertfordshire sarcopenia study (HSS). Calcified Tissue International. 2014;**95**(4):308-316

[58] Sun J, Su J, Xie Y, Yin MT, Huang Y, Xu L, et al. Plasma IL-6/IL-10 ratio and IL-8 LDH, and HBDH level predict the severity and the risk of death in AIDS patients with pneumocystis pneumonia. Journal of Immunology Research. 2016;**2016**:1583951

[59] Dong B, Sun B. Inflammatory markers and disability in Chinese older adults. Journal of Gerontology & Geriatric Research. 2016;**5**:275

[60] Wilson D, Jackson T, Sapey E, Lord JM. Frailty and sarcopenia: The

potential role of an aged immune system. Ageing Research Reviews. 2017;**36**:1-10

[61] Rong YD, Bian AL, Hu HY, Ma Y, Zhou XZ. Study on relationship between elderly sarcopenia and inflammatory cytokine IL-6, anti-inflammatory cytokine IL-10. BMC Geriatrics. 2018;**18**:308

[62] Schaap LA, Pluijm SM, Deeg DJ, Harris TB, et al. Health ABC study. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2009;**64A**(11):1183-1189

[63] Ziaaldini MM, Marzetti E, Picca A, Murlasits Z. Biochemical pathways of sarcopenia and their modulation by physical exercise: A narrative review. Frontiers in Medicine (Lausanne). 2017;**4**:167

[64] Hall DT, Ma JF, Marco SD, Gallouzi IE. Inducible nitric oxide synthase (iNOS) in muscle wasting syndrome, sarcopenia, and cachexia. Aging (Albany NY). 2011;**3**(8):702-715

[65] Schaap LA, Pluijm SM, Deeg DJ, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. The American Journal of Medicine. 2006;**119**(6):526.e9-17

[66] Cesari M, Penninx BW, Pahor M, Lauretani F, Corsi AM, Rhys Williams G, et al. Inflammatory markers and physical performance in older persons: The in CHIANTI study. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2004;**59**(3):242-248

[67] Bano G, Trevisan C, Carraro S, Solmi M, Luchini C, Stubbs B, et al. Maturitas. 2017;**96**:10-15

[68] Kob R, Bollheimer LC, Bertsch T, Fellner C, Djukic M, Sieber CC, et al. Sarcopenic obesity: Molecular clues to a better understanding of its pathogenesis? Biogerontology. 2015;**16**(1):15-29

[69] Morley JE. Hormones and sarcopenia. Current Pharmaceutical Design. 2017;**23**(30):4484-4492

[70] Shin MJ, Jeon YK, Kim IJ. Testosterone and sarcopenia. World Journal of Men's Health. 2018;**36**(3):192-198

[71] Nass R. Endocrinology and Metabolism Clinics of North America. 2013;**42**(2):187-199

[72] Bartke A. Growth hormone and aging: Updated review. World Journal of Mens Health. 2019;**37**(1):19-30

[73] Cleasby ME, Jamieson PM, Atherton PJ. Insulin resistance and sarcopenia: Mechanistic links between common co-morbidities. The Journal of Endocrinology. 2016;**229**(2):R67-R81

[74] Sato K, Iemitsu M. Exercise and sex steroid hormones in skeletal muscle. The Journal of Steroid Biochemistry and Molecular Biology. 2015;**145**:200-205

[75] Chen LY, Wu YH, Liu LK, Lee WJ, Hwang AC, Peng LN, et al. Association among serum insulin-like growth factor-1, frailty, muscle mass, bone mineral density, and physical performance among community-dwelling middle-aged and older adults in Taiwan. Rejuvenation Research. 2018;**21**(3):270-277

[76] Zembron-Lacny A, Dziubek W, Wolny-Rokicka E, Dabrowska G, Wozniewski M. The relation of inflammaging with skeletal muscle properties in elderly men. American Journal of Men's Health. 2019;**13**(2):1557988319841934

[77] Barclay RD, Burd NA, Tyler C, Tillin NA, Mackenzie RW. The role of the IGF-1 signaling cascade in

muscle protein synthesis and anabolic resistance in aging skeletal muscle. Frontiers in Nutrition. 2019;**6**:146

[78] Garcia M, Seelaender M, Sotiropoulos A, Coletti D, Lancha AH Jr. Vitamin D, muscle recovery, sarcopenia, cachexia, and muscle atrophy. Nutrition. 2019;**60**:66-69

[79] Chung E, Mo H, Wang S, Zu Y, Elfakhani M, et al. Potential roles of vitamin E in age-related changes in skeletal muscle health. Nutrition Research. 2018;**49**:23-36