Biomedical Sciences
2015; 1(2): 10-17
http://www.sciencepublishinggroup.com/j/bs
doi: 10.11648/j.bs.20150102.11

Clinical Manifestations and Pathophysiology of Sarcopenia

Mitsutaka Yakabe, Sumito Ogawa*, Masahiro Akishita

Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Email address:
suogawa-tky@umin.ac.jp (S. Ogawa)

To cite this article:
Mitsutaka Yakabe, Sumito Ogawa, Masahiro Akishita. Clinical Manifestations and Pathophysiology of Sarcopenia. *Biomedical Sciences*. Vol. 1, No. 2, 2015, pp. 10-17. doi: 10.11648/j.bs.20150102.11

Abstract: Sarcopenia is an age-related condition characterized by low muscle mass and low physical performance. Several groups have established diagnostic criteria for sarcopenia, which include usual gait speed, skeletal muscle mass and grip strength. In this article, we summarize these criteria, pathogenesis, epidemiology, related conditions and possible interventions for sarcopenia.

Keywords: Sarcopenia, Frailty, Vitamin D, Testosterone, Nutrition, Inflammation

1. Introduction

Sarcopenia is characterized by loss of muscle mass, strength and function. This debilitating condition is common in the elderly and results in frailty, disability [1], and high mortality [2]. The number of elderly population with sarcopenia is increasing all over the world, and it is becoming an important public concern [3].

The word "sarcopenia" is derived from Greek **'**sarx**'** (flesh) and **'**penia**'** (loss). This term was first proposed by Rosenberg in 1988, originally indicating muscle mass loss caused by aging [4]. The range of muscle decrease included in sarcopenia was controversial, and there was no conclusive definition of sarcopenia. In 2010, 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, poor quality of life and death" [5]. Then sarcopenia have gradually come to be known to clinicians and researchers.

2. Pathogenesis of Sarcopenia

As humans age, significant changes in muscle mass and quality take place. After about age 50, muscle mass decreases at an annual rate of 1–2%. The decline in muscle strength is even higher, amounting to 1.5% per year in their sixth decade, and 3% per year thereafter [6]. As the result, the average reported age-related decreases in knee extensor strength are 20-40% [7], and even greater losses (50% or over) have been reported for those in their ninth decade and beyond [8, 9]. Immobility and malnutrition, especially low protein intake, could deteriorate sarcopenia [10], and influence of multiple factors leading to aging-related sarcopenia is demonstrated in Figure 1.

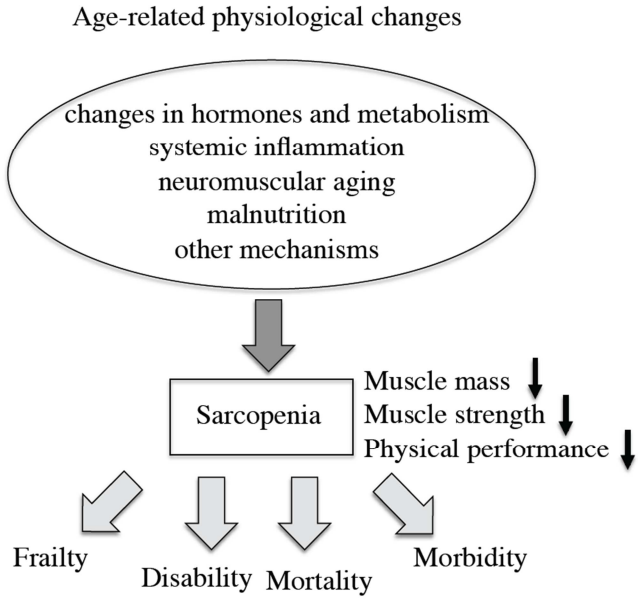

Figure 1. *Influence of multiple factors leading to aging-related sarcopenia.*

Skeletal muscle consists of two types of fibers: Type I and Type II. Type II fast fibers have a higher glycolytic potential, lower oxidative capacity, and faster response as compared to type I slow fibers. Type I fibers are known as fatigue-resistant fibers due to their characteristics that include greater density of mitochondria, capillaries and myoglobin content. With age, atrophy almost only affects type II fibers [11].

Molecular mechanisms of sarcopenia are not fully understood. Some factors have been suggested to be involved as described below.

2.1. Changes in Hormones and Metabolism

As humans age, serum concentration or activity of several hormones decreases. Growth hormone (GH)/ insulin-like growth factor-1 (IGF-1), androgens and vitamin D could be involved in sarcopenia.

GH is released from the pituitary gland and promotes IGF-1 secretion. IGF-1 binds to IGF-1 receptor and activates its downstream Akt/ *mammalian* target of rapamycin (mTOR) pathway [12]. mTOR induces muscle hypertrophy by promoting protein synthesis. Akt inhibits FOXO transcriptional factors and blocks the upregulation of E3 ubiquitin ligases, or muscle RING-finger protin-1 (MuRF1) and Muscle Attrophy F-Box (MAFbx), which stimulate protein degradation [13]. Therefore, decrease of GH and IGF-1 might be involved in sarcopenia. Insulin is also an anabolic hormone and activates Akt/mTOR pathway. Skeletal muscle protein synthesis is resistant to the anabolic action of insulin in older subjects, and this could be involved in the development of sarcopenia. [14].

Androgens are physiologic anabolic steroid hormones, and testosterone is necessary to maintain muscle mass. Its concentration declines with age [15]. In males, levels of testosterone decrease by 1% per year, and those of bioavailable testosterone by 2% per year from age 30 [16, 17]. In women, testosterone levels drop rapidly from 20 to 45 years of age [18]. Testosterone increases muscle protein synthesis [19], and its effects on muscle are modulated by several factors including genetic background, nutrition, and exercise.

1,25(OH)2D, an active form of vitamin D, binds to VDR (vitamin D receptor) and activates it. VDR regulates transcription of genes involved in calcium handling and muscle cell differentiation and proliferation at the genomic level [20]. Vitamin D levels decline in older persons [21]. Lower 25-hydroxyvitamin D (25[OH]D) levels increase the risk of sarcopenia in older men and women [22]. 25(OH)D levels were positively associated with skeletal muscle index (SMI) [23].

2.2. Systemic Inflammation

As humans age, serum level of tumor necrosis factor-a (TNF-), interleukin-6 (IL-6), interleukin-1 (IL-1) and C-reactive protein (CRP) elevate [24]. Adipose tissues are supposed to secrete these cytokines. A theory called inflamm-aging (inflammation +aging) proposes that, as humans age, systemic low-grade inflammation is one of the causes of various diseases such as atherosclerosis, dementia, type 2 diabetes and osteoporosis [25, 26]. In a Korean study, high-sensitivity CRP levels were significantly and independently associated with sarcopenic obesity [23]. Inflamm-aging might be involved in sarcopenia [27].

2.3. Neuromuscular Aging

Neuron loss is a progressive, irreversible process that increases with age. Multiple levels of the nervous system are affected by age, including the motor cortex, the spinal cord, peripheral neurons, and the neuromuscular junction [3]. Age-related changes have been noted in the neuromuscular junction. A motor unit is made up of a single alpha motoneuron and all the muscle fibers connected with it. If alpha motoneuron is lost, denervated muscle fibers join to connect to surviving alpha motoneurons. This determines that a single alpha motoneuron must connect with more muscle fibers, constituting bigger motor units. This leads to loss of efficacy and could be the cause of sarcopenia [10].

2.4. Other Mechanisms

Though loss of satellite cells has been attributed to the development of sarcopenia, their roles are still controversial. One recent study showed that depletion of satellite cells in adult sedentary mice did not affect sarcopenia although it impaired muscle regenerative capacity [28]. Another study showed that genetic ablation of satellite cells affected cross-sectional areas of myofibres in all adult muscles, although the extent and timing differed according to muscles [29].

Other studies have indicated the involvement of apoptosis in muscle [30] and mitochondrial dysfunction [31, 32]. However, the pathogenesis of sarcopenia remains to be elucidated, and further study is needed.

3. Diagnostic Criteria

Sarcopenia still lacks definite criteria. Proper selections for cutoff values with full considerations of sex and ethnic differences are important to reach the universal diagnostic criteria for sarcopenia internationally [33]. Some markers have been adopted in research and practice. Especially, gait speed, muscle mass and muscle strength are supposed to be useful. Each indicator might be considered low when it is over -2SDs below the mean of young male and female reference group.

Here we show criteria by the EWGSOP, Asian Working Group for Sarcopenia (AWGS), International Working Group for Sarcopenia (IWGS) and the Foundation for the National Institutes of Health (FNIH).

The EWGSOP suggests an algorithm for sarcopenia case finding and screening among community-dwelling people aged 65 years and older [5]. In the algorithm, (i) lower skeletal muscle mass plus (ii) lower gait speed and/or low grip strength are essential for the diagnosis. AWGS recommends using 60 or 65 years as the age for sarcopenia diagnosis according to the conditions of each country in Asia [34]. IWGS specifies several conditions for sarcopenia assessment, including (1) noted decline in function, strength, “health” status, (2) self-reported mobility-related difficulty, (3) history of recurrent falls, (4) recent unintentional weight loss (>5%), (5) post-hospitalization, and (6) other chronic conditions (e.g. type 2 diabetes, chronic heart failure, chronic obstructive pulmonary disease, chronic kidney disease, rheumatoid arthritis, and cancer) [33]. FNIH analyzed data from nine sources of community-dwelling older persons and proposed the cutoffs [35].

In these criteria, usual gait speed, muscle mass and handgrip strength are adopted as the markers.

3.1. Usual Gait Speed

Usual gait speed identifies autonomous community-dwelling older people at risk of adverse outcomes and can be used as a single-item assessment tool [36]. Usual gait speed without deceleration is commonly used, and walking courses are 4 or 6 m long in most studies, because they are considered equivalent [35]. The EWGSOP and AWGS and FNIH recommend 0.8m/sec as the cut-off [5]. However, AWGS implies that the cut-off for Asians might be higher than 1.0 m/sec according to most Asian studies [37]. IWGS recommends 1.0m/sec [33].

3.2. Muscle Mass

Bioimpedance analysis (BIA) and Dual energy X-ray absorptiometry (DXA) can be performed in evaluating muscle mass. The muscle mass of the four limbs is summed from a DXA scan or BIA as appendicular skeletal muscle mass (ASM), and a skeletal muscle mass index (SMI) is defined as ASM/height^2 (kg/m^2) [38, 39]. The EWGSOP defines low muscle mass as -2SDs below the mean of young reference group. Two exemplary cutoff values are: SMI (by DXA) 7.26kg/m^2 for men and 5.5kg/m^2 for women [38], or SMI (by BIA) 8.87kg/m^2 for men and 6.42kg/m^2 for women [39]. AWGS recommends 7.0kg/m^2 for men and 5.4kg/m^2 for women (DXA), or 7.0kg/m^2 for men and 5.7kg/m^2 for women (BIA) [37]. IWGS recommends 7.23kg/m^2 for men and 5.67kg/m^2 for women (DXA) [33]. FNIH criteria contain ASM per BMI instead of SMI [35].

3.3. Handgrip Strength

Handgrip strength is considered the most practical marker of muscle strength. The EWGSOP recommends 30kg for men and 20kg for women as the cut-off [5]. Asians generally have lower grip strength than Caucasians, so AWGS defines low grip strength as <26 kg for men and <18 kg for women [37]. In IWGS criteria, the cutoff value is not specified [33]. In FNIH criteria, <26 kg for men and <18 kg for women [35].

In EWGSOP consensus, the diagnosis of sarcopenia doesn't depend on its cause, and the term 'primary sarcopenia' or 'secondary sarcopenia' is used depending on the cause. The categories of 'primary sarcopenia' and 'secondary sarcopenia' proposed by the EWGSOP may be useful in clinical practice [5]. Sarcopenia can be considered 'primary' (or age-related) when no other cause is evident except aging itself, while sarcopenia can be considered 'secondary' when one or more other causes are evident. However, in many old persons, the etiology of sarcopenia is multi-factorial, so it might not be possible to identify a single cause of sarcopenia.

EWGSOP also suggests a conceptual staging as 'presarcopenia', 'sarcopenia' and 'severe sarcopenia'. The 'presarcopenia' stage is characterised by low muscle mass without low muscle strength or low physical performance. The 'sarcopenia' stage is characterised by low muscle mass, plus low muscle strength or low physical performance. 'Severe sarcopenia' is the stage identified when all three criteria (low muscle mass, low muscle strength and low physical performance) are met. Recognizing the stage of sarcopenia might help in selecting treatments and setting appropriate recovery goals.

4. Epidemiology

The prevalence of sarcopenia is different according to the diagnostic criteria in studies. Baumgartner *et al.* used an SMI cutoff of -2SDs below the mean of young reference group, and the prevalence of sarcopenia ranged from 13 to 24% in persons aged 65 to 70 years and was over 50% for those older than 80 years [38]. Another study reported that sarcopenia was prevalent in 10% of men and 8% of women (>60 years old), and that reduced skeletal muscle was independently associated with functional impairment and disability, particularly in older women [40]. The prevalence of sarcopenia in Japanese elderly men and women diagnosed using Asian criteria was 9.6% and 7.7%, respectively [41].

The number of people aged over 60 around the world was estimated to be 600 million in 2000. It is expected to rise to 1.2 billion by 2025 and 2 billion by 2050. Sarcopenia is estimated to affect over 50 million people today and will affect over 200 million in the next 40 years [42].

5. Related Conditions

5.1. Cachexia

Cachexia is widely recognized in older adults as severe wasting that accompanies disease states such as cancer, congestive cardiomyopathy and end-stage renal disease. Cachexia is defined as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass [43]. Thus, most cachectic individuals are also sarcopenic, but most sarcopenic individuals are not considered cachectic. Sarcopenia is one of the elements of the proposed definition for cachexia.

5.2. Frailty

Frailty is a geriatric syndrome resulting from age-related cumulative declines across multiple physiologic systems, with impaired homeostatic reserve and a reduced capacity of the organism to withstand stress. A statement defined frailty as a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death [44]. Fried *et al.* developed a phenotypic definition of frailty based on physical aspects; three or more of the following characteristics support a frailty diagnosis—unintended weight loss, exhaustion, weakness, slow gait speed and low physical activity [45]. Other groups have also established frailty assessment tools [46, 47].

Frailty and sarcopenia overlap; most frail older people

exhibit sarcopenia, and some older people with sarcopenia are also frail. The general concept of frailty encompasses psychological and social dimensions as well, including cognitive status, social support and other environmental factors [48].

5.3. Sarcopenic Obesity

Sarcopenic obesity is a condition in which lean body mass is lost while fat mass is preserved or even increased. The relationship between age-related reduction of muscle mass and strength is often independent of body mass. Changes in muscle composition are also important. For example, **'**marbling**'**, or fat infiltration into muscle, lowers muscle quality and work performance [49]. According to a cross-sectional study, the prevalence rates of sarcopenic obesity are 6.1% in men and 7.3% in women [50]. Sarcopenic obesity is a risk of hypertention [51], arteriosclerosis [52], and high mortality [53].

6. Interventions

6.1. Pharmacological Interventions

6.1.1. Vitamin D

Low serum vitamin D is suggested to be associated with sarcopenia [54, 55], sarcopenic obesity [50], falls, hip fracture and mortality [56, 57]. The effectiveness of vitamin D supplementation remains controversial, but in several studies, this has been shown to increase muscle strength and performance, or to reduce the risk of falling [58-61]. The therapy might be considered if a plasma level of 25-hydroxyvitamin D is less than 30 ng/ml (70 nmol) [62, 63].

6.1.2. Creatine

Creatine is supposed to have anti-catabolic and antioxidant properties that could benefit aging muscle. In some studies, creatine supplementation was effective in the augmentation of muscle mass and strength, especially combined with resistant exercise [64-66].

6.1.3. Testosterone

Some studies have suggested that testosterone supplementation attenuated several sarcopenic symptoms including decrease in muscle mass [67-69] and grip strength [70, 71]. Oral low-dose testosterone administration induced whole-body protein anabolism in postmenopausal women [72]. A recent study reported that testosterone administration increased muscle fiber diameter and peak power in community-dwelling older men [73]. However, testosterone therapy in older men is associated with various risks, such as sleep apnea, thrombotic complications and prostate cancers [74], so these side effects might outweigh the benefits.

6.1.4. Dehydroepiandrosterone (DHEA)

DHEA is a hormone precursor which is converted into sex hormones in specific target tissues, and some clinical studies with DHEA have been performed. However, its effect on muscle strength in the elderly is yet to be proven [75].

6.1.5. Estrogen

Menopause is associated with a natural decline in estrogen, which decreases muscle mass and strength [76]. Estrogen supplementation increases lean body mass or muscle strength when administered to postmenopausal women [77, 78]. However, some studies failed to show a positive effect of estrogen on muscle mass [79-81]. Estrogen is related to various adverse effects, such as breast cancer, thromboembolism, cholecystitis, stroke and coronary events [78], so further research is needed to confirm its benefits and to determine its safety.

6.1.6. GH

In a study targeted for older persons, growth hormone increases nitrogen retention, body mass and muscle mass [82]. However, most studies have shown that administration of GH alone failed to improve muscle strength despite amelioration of the detrimental somatic changes of aging [83]. Further studies are needed to assess the long-term efficacy and safety of GH replacement therapy.

6.2. Non-pharmacological Interventions

6.2.1. Nutrition

Increased intake of high-quality proteins from foods might be an easier and more cost-effective strategy for improving muscle health in older adults than pharmacological approaches. Especially, milk-based proteins might be an effective protein source for stimulating muscle protein synthesis and promoting gains in muscle mass over time [84]. However, there was no consistent effect of protein supplementation on muscle mass, strength or function [85].

Essential amino acids (EAA), especially leucine, are an anabolic stimulus for muscle synthesis. However, there is no agreement on what mixture of EAA may provide the best stimulus. There are two studies which have used such a mixture, providing very limited evidence that there may be some effect on muscle mass and function through amino-acid supplementation [85].

Approximately 5% of leucine taken is metabolized into beta-hydroxy-beta-methylbutyrate (HMB). This metabolite has several ergogenic benefits, such as anti-catabolic, anabolic, and lipolytic effects, and these benefits can be generalized to the elderly [86]. In several studies of the elderly, improvement of physical performance, strength and muscle mass was observed by administrating of 2-3 g HMB [87, 88]. HMB was also effective for the loss of muscle caused by cancer-related cachexia [89]. However, larger well-controlled studies are required to clarify the effects of HMB on sarcopenia [85].

6.2.2. Exercise

Slow-velocity resistance exercise (i.e., performing the concentric and eccentric phase of each muscle contraction in 2–3 sec) is a safe, feasible, and effective intervention to induce muscle hypertrophy and increase strength in older adults [90]. A systematic review reported that most resistance training programs last 8–12 weeks, using 2–3 sets of 8–10 repetitions at 65% of 1-repetition maximum (1 RM), and are performed 2–3 days per week [91]. Frequent aerobic exercise might

ameliorate sarcopenia by increasing skeletal muscle insulin sensitivity and inducing proliferator activated receptor gamma co-activator 1-α (PGC-1α) [90].

The combination of exercise and nutrition might be better [84], because protein acts synergistically with exercise to increase muscle mass [1]. According to a review of seventeen studies in which combined nutrition and exercise interventions were performed for the elderly, improvement of muscle strength, mass and physical performance were observed, and enhanced benefits of exercise training, when combined with dietary supplementation, have been shown in some trials [92].

7. Conclusions

Sarcopenia is becoming a major threat to aging society. However, causes for sarcopenia remain unclear. Several criteria for sarcopenia have been proposed, but there is no definite criteria. Moreover, therapeutic methods have not been established. Further study is needed to tackle sarcopenia.

Acknowledgements

This study was supported by the Research Funding for Longevity Sciences (25-11) from National Center for Geriatrics and Gerontology (NCGG), Japan.

References

[1] Morley JE. Sarcopenia in the elderly. Fam Pract. 2012;29 Suppl 1:i44-i48.

[2] Kemmler W, von Stengel S, Engelke K, Haberle L, Mayhew JL, Kalender WA. Exercise, body composition, and functional ability: a randomized controlled trial. Am J Prev Med. 2010;38:279-287.

[3] Kim TN, Choi KM. Sarcopenia: definition, epidemiology, and pathophysiology. J Bone Metab. 2013;20:1-10.

[4] Rosenberg IH. Sarcopenia: origins and clinical relevance. J Nutr. 1997;127:990S-991S.

[5] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinkova E, Vandewoude M, Zamboni M. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412-423.

[6] von Haehling S, Morley JE, Anker SD. An overview of sarcopenia: facts and numbers on prevalence and clinical impact. J Cachexia Sarcopenia Muscle. 2010;1:129-133.

[7] Doherty TJ. Invited review: Aging and sarcopenia. J Appl Physiol. 2003;95:1717-1727.

[8] Murray MP, Duthie EH, Jr., Gambert SR, Sepic SB, Mollinger LA. Age-related differences in knee muscle strength in normal women. J Gerontol. 1985;40:275-280.

[9] Murray MP, Gardner GM, Mollinger LA, Sepic SB. Strength of isometric and isokinetic contractions: knee muscles of men aged 20 to 86. Phys Ther. 1980;60:412-419.

[10] Malafarina V, Uriz-Otano F, Iniesta R, Gil-Guerrero L. Sarcopenia in the elderly: diagnosis, physiopathology and treatment. Maturitas. 2012;71:109-114.

[11] Evans WJ, Campbell WW. Sarcopenia and age-related changes in body composition and functional capacity. J Nutr. 1993;123:465-468.

[12] Sonntag WE, Ramsey M, Carter CS. Growth hormone and insulin-like growth factor-1 (IGF-1) and their influence on cognitive aging. Ageing Res Rev. 2005;4:195-212.

[13] Glass DJ. Skeletal muscle hypertrophy and atrophy signaling pathways. Int J Biochem Cell Biol. 2005;37:1974-1984.

[14] Rasmussen BB, Fujita S, Wolfe RR, Mittendorfer B, Roy M, Rowe VL, Volpi E. Insulin resistance of muscle protein metabolism in aging. FASEB J. 2006;20:768-769.

[15] Basualto-Alarcon C, Varela D, Duran J, Maass R, Estrada M. Sarcopenia and Androgens: A Link between Pathology and Treatment. Front Endocrinol (Lausanne). 2014;5:217.

[16] Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab. 2002;87:589-598.

[17] Morley JE, Kaiser FE, Perry HM, 3rd, Patrick P, Morley PM, Stauber PM, Vellas B, Baumgartner RN, Garry PJ. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. Metabolism. 1997;46:410-413.

[18] Morley JE, Perry HM, 3rd. Androgens and women at the menopause and beyond. J Gerontol A Biol Sci Med Sci. 2003;58:M409-416.

[19] Urban RJ, Bodenburg YH, Gilkison C, Foxworth J, Coggan AR, Wolfe RR, Ferrando A. Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. Am J Physiol. 1995;269:E820-826.

[20] Ceglia L, Harris SS. Vitamin D and its role in skeletal muscle. Calcif Tissue Int. 2013;92:151-162.

[21] Perry HM, 3rd, Horowitz M, Morley JE, Patrick P, Vellas B, Baumgartner R, Garry PJ. Longitudinal changes in serum 25-hydroxyvitamin D in older people. Metabolism. 1999;48:1028-1032.

[22] Visser M, Deeg DJ, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. J Clin Endocrinol Metab. 2003;88:5766-5772.

[23] Kim TN, Park MS, Lim KI, Choi HY, Yang SJ, Yoo HJ, Kang HJ, Song W, Choi H, Baik SH, Choi DS, Choi KM. Relationships between sarcopenic obesity and insulin resistance, inflammation, and vitamin D status: the Korean Sarcopenic Obesity Study. Clin Endocrinol (Oxf). 2013;78:525-532.

[24] Thomas DR. Sarcopenia. Clin Geriatr Med. 2010;26:331-346.

[25] Castelo-Branco C, Soveral I. The immune system and aging: a review. Gynecol Endocrinol. 2014;30:16-22.

[26] Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000;908:244-254.

[27] Curtis E, Litwic A, Cooper C, Dennison E. Determinants of Muscle and Bone Aging. J Cell Physiol. 2015.

[28] Fry CS, Lee JD, Mula J, Kirby TJ, Jackson JR, Liu F, Yang L, Mendias CL, Dupont-Versteegden EE, McCarthy JJ, Peterson CA. Inducible depletion of satellite cells in adult, sedentary mice impairs muscle regenerative capacity without affecting sarcopenia. Nat Med. 2015;21:76-80.

[29] Keefe AC, Lawson JA, Flygare SD, Fox ZD, Colasanto MP, Mathew SJ, Yandell M, Kardon G. Muscle stem cells contribute to myofibres in sedentary adult mice. Nat Commun. 2015;6:7087.

[30] Tower J. Programmed cell death in aging. Ageing Res Rev. 2015;23:90-100.

[31] Das S, Morvan F, Jourde B, Meier V, Kahle P, Brebbia P, Toussaint G, Glass DJ, Fornaro M. ATP citrate lyase improves mitochondrial function in skeletal muscle. Cell Metab. 2015;21:868-876.

[32] Marzetti E, Calvani R, Cesari M, Buford TW, Lorenzi M, Behnke BJ, Leeuwenburgh C. Mitochondrial dysfunction and sarcopenia of aging: from signaling pathways to clinical trials. Int J Biochem Cell Biol. 2013;45:2288-2301.

[33] Lee WJ, Liu LK, Peng LN, Lin MH, Chen LK. Comparisons of sarcopenia defined by IWGS and EWGSOP criteria among older people: results from the I-Lan longitudinal aging study. J Am Med Dir Assoc. 2013;14:528 e521-527.

[34] Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, Chou MY, Chen LY, Hsu PS, Krairit O, Lee JS, Lee WJ, Lee Y, Liang CK, Limpawattana P, Lin CS, Peng LN, Satake S, Suzuki T, Won CW, Wu CH, Wu SN, Zhang T, Zeng P, Akishita M, Arai H. Sarcopenia in Asia: consensus report of the asian working group for sarcopenia. J Am Med Dir Assoc. 2014;15:95-101.

[35] Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, Ferrucci L, Guralnik JM, Fragala MS, Kenny AM, Kiel DP, Kritchevsky SB, Shardell MD, Dam TT, Vassileva MT. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci. 2014;69:547-558.

[36] Abellan van Kan G, Rolland Y, Andrieu S, Bauer J, Beauchet O, Bonnefoy M, Cesari M, Donini LM, Gillette Guyonnet S, Inzitari M, Nourhashemi F, Onder G, Ritz P, Salva A, Visser M, Vellas B. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. J Nutr Health Aging. 2009;13:881-889.

[37] Arai H, Akishita M, Chen LK. Growing research on sarcopenia in Asia. Geriatr Gerontol Int. 2014;14 Suppl 1:1-7.

[38] Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, Garry PJ, Lindeman RD. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998;147:755-763.

[39] Chien MY, Huang TY, Wu YT. Prevalence of sarcopenia estimated using a bioelectrical impedance analysis prediction equation in community-dwelling elderly people in Taiwan. J Am Geriatr Soc. 2008;56:1710-1715.

[40] Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc. 2002;50:889-896.

[41] Yuki A, Ando F, Shimokata H. [Transdisciplinary Approach for Sarcopenia. Sarcopenia : definition and the criteria for Asian elderly people]. Clin Calcium. 2014;24:1441-1448.

[42] Santilli V, Bernetti A, Mangone M, Paoloni M. Clinical definition of sarcopenia. Clin Cases Miner Bone Metab. 2014;11:177-180.

[43] Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, Jatoi A, Kalantar-Zadeh K, Lochs H, Mantovani G, Marks D, Mitch WE, Muscaritoli M, Najand A, Ponikowski P, Rossi Fanelli F, Schambelan M, Schols A, Schuster M, Thomas D, Wolfe R, Anker SD. Cachexia: a new definition. Clin Nutr. 2008;27:793-799.

[44] Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, Cesari M, Chumlea WC, Doehner W, Evans J, Fried LP, Guralnik JM, Katz PR, Malmstrom TK, McCarter RJ, Gutierrez Robledo LM, Rockwood K, von Haehling S, Vandewoude MF, Walston J. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013;14:392-397.

[45] Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:M146-156.

[46] Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging. 2012;16:601-608.

[47] Vellas B, Balardy L, Gillette-Guyonnet S, Abellan Van Kan G, Ghisolfi-Marque A, Subra J, Bismuth S, Oustric S, Cesari M. Looking for frailty in community-dwelling older persons: the Gerontopole Frailty Screening Tool (GFST). J Nutr Health Aging. 2013;17:629-631.

[48] Bauer JM, Sieber CC. Sarcopenia and frailty: a clinician's controversial point of view. Exp Gerontol. 2008;43:674-678.

[49] Visser M, Kritchevsky SB, Goodpaster BH, Newman AB, Nevitt M, Stamm E, Harris TB. Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the health, aging and body composition study. J Am Geriatr Soc. 2002;50:897-904.

[50] Hwang B, Lim JY, Lee J, Choi NK, Ahn YO, Park BJ. Prevalence rate and associated factors of sarcopenic obesity in korean elderly population. J Korean Med Sci. 2012;27:748-755.

[51] Park SH, Park JH, Song PS, Kim DK, Kim KH, Seol SH, Kim HK, Jang HJ, Lee JG, Park HY, Park J, Shin KJ, Kim D, Moon YS. Sarcopenic obesity as an independent risk factor of hypertension. J Am Soc Hypertens. 2013;7:420-425.

[52] Kohara K, Ochi M, Tabara Y, Nagai T, Igase M, Miki T. Arterial stiffness in sarcopenic visceral obesity in the elderly: J-SHIPP study. Int J Cardiol. 2012;158:146-148.

[53] Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. Sarcopenic obesity and risk of cardiovascular disease and mortality: a population-based cohort study of older men. J Am Geriatr Soc. 2014;62:253-260.

[54] Scott D, Blizzard L, Fell J, Ding C, Winzenberg T, Jones G. A prospective study of the associations between 25-hydroxy-vitamin D, sarcopenia progression and physical activity in older adults. Clin Endocrinol (Oxf). 2010;73:581-587.

[55] Park S, Ham JO, Lee BK. A positive association of vitamin D deficiency and sarcopenia in 50 year old women, but not men. Clin Nutr. 2013.

[56] LaCroix AZ, Kotchen J, Anderson G, Brzyski R, Cauley JA, Cummings SR, Gass M, Johnson KC, Ko M, Larson J, Manson JE, Stefanick ML, Wactawski-Wende J. Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial. J Gerontol A Biol Sci Med Sci. 2009;64:559-567.

[57] Zittermann A, Iodice S, Pilz S, Grant WB, Bagnardi V, Gandini S. Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies. Am J Clin Nutr. 2012;95:91-100.

[58] Sakuma K, Yamaguchi A. Sarcopenia and age-related endocrine function. Int J Endocrinol. 2012;2012:127362.

[59] Annweiler C, Schott AM, Berrut G, Fantino B, Beauchet O. Vitamin D-related changes in physical performance: a systematic review. J Nutr Health Aging. 2009;13:893-898.

[60] Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, Wong JB, Egli A, Kiel DP, Henschkowski J. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. Bmj. 2009;339:b3692-b3692.

[61] Ito S, Harada A, Kasai T, Sakai Y, Takemura M, Matsui Y, Hida T, Ishiguro N. Use of alfacalcidol in osteoporotic patients with low muscle mass might increase muscle mass: An investigation using a patient database. Geriatr Gerontol Int. 2014;14 Suppl 1:122-128.

[62] Morley JE. Vitamin d redux. J Am Med Dir Assoc. 2009;10:591-592.

[63] Chung JY, Kang HT, Lee DC, Lee HR, Lee YJ. Body composition and its association with cardiometabolic risk factors in the elderly: A focus on sarcopenic obesity. Arch Gerontol Geriatr. 2013;56:270-278.

[64] Chrusch MJ, Chilibeck PD, Chad KE, Davison KS, Burke DG. Creatine supplementation combined with resistance training in older men. Med Sci Sports Exerc. 2001;33:2111-2117.

[65] Candow DG, Chilibeck PD, Chad KE, Chrusch MJ, Davison KS, Burke DG. Effect of ceasing creatine supplementation while maintaining resistance training in older men. J Aging Phys Act. 2004;12:219-231.

[66] Candow DG, Vogt E, Johannsmeyer S, Forbes SC, Farthing JP. Strategic creatine supplementation and resistance training in healthy older adults. Appl Physiol Nutr Metab. 2015;40:689-694.

[67] Morley JE, Perry HM, 3rd. Androgen deficiency in aging men: role of testosterone replacement therapy. J Lab Clin Med. 2000;135:370-378.

[68] Ferrando AA, Sheffield-Moore M, Yeckel CW, Gilkison C, Jiang J, Achacosa A, Lieberman SA, Tipton K, Wolfe RR, Urban RJ. Testosterone administration to older men improves muscle function: molecular and physiological mechanisms. Am J Physiol Endocrinol Metab. 2002;282:E601-607.

[69] Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Lenrow DA, Holmes JH, Dlewati A, Santanna J, Rosen CJ, Strom BL. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Clin Endocrinol Metab. 1999;84:2647-2653.

[70] Bakhshi V, Elliott M, Gentili A, Godschalk M, Mulligan T. Testosterone improves rehabilitation outcomes in ill older men. J Am Geriatr Soc. 2000;48:550-553.

[71] Bhasin S, Calof OM, Storer TW, Lee ML, Mazer NA, Jasuja R, Montori VM, Gao W, Dalton JT. Drug insight: Testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging. Nat Clin Pract Endocrinol Metab. 2006;2:146-159.

[72] Birzniece V, Umpleby MA, Poljak A, Handelsman DJ, Ho KK. Oral low-dose testosterone administration induces whole-body protein anabolism in postmenopausal women: a novel liver-targeted therapy. Eur J Endocrinol. 2013;169:321-327.

[73] Fitts RH, Peters JR, Dillon EL, Durham WJ, Sheffield-Moore M, Urban RJ. Weekly versus monthly testosterone administration on fast and slow skeletal muscle fibers in older adult males. J Clin Endocrinol Metab. 2015;100:E223-231.

[74] Mudali S, Dobs AS. Effects of testosterone on body composition of the aging male. Mech Ageing Dev. 2004;125:297-304.

[75] Dayal M, Sammel MD, Zhao J, Hummel AC, Vandenbourne K, Barnhart KT. Supplementation with DHEA: effect on muscle size, strength, quality of life, and lipids. J Womens Health (Larchmt). 2005;14:391-400.

[76] Maltais ML, Desroches J, Dionne IJ. Changes in muscle mass and strength after menopause. J Musculoskelet Neuronal Interact. 2009;9:186-197.

[77] Sorensen MB, Rosenfalck AM, Hojgaard L, Ottesen B. Obesity and sarcopenia after menopause are reversed by sex hormone replacement therapy. Obes Res. 2001;9:622-626.

[78] Jacobsen DE, Samson MM, Kezic S, Verhaar HJ. Postmenopausal HRT and tibolone in relation to muscle strength and body composition. Maturitas. 2007;58:7-18.

[79] Hansen RD, Raja C, Baber RJ, Lieberman D, Allen BJ. Effects of 20-mg oestradiol implant therapy on bone mineral density, fat distribution and muscle mass in postmenopausal women. Acta Diabetol. 2003;40 Suppl 1:S191-195.

[80] Tanko LB, Movsesyan L, Svendsen OL, Christiansen C. The effect of hormone replacement therapy on appendicular lean tissue mass in early postmenopausal women. Menopause. 2002;9:117-121.

[81] Kenny AM, Dawson L, Kleppinger A, Iannuzzi-Sucich M, Judge JO. Prevalence of sarcopenia and predictors of skeletal muscle mass in nonobese women who are long-term users of estrogen-replacement therapy. J Gerontol A Biol Sci Med Sci. 2003;58:M436-440.

[82] Nass R, Johannsson G, Christiansen JS, Kopchick JJ, Thorner MO. The aging population--is there a role for endocrine interventions? Growth Horm IGF Res. 2009;19:89-100.

[83] Giannoulis MG, Martin FC, Nair KS, Umpleby AM, Sonksen P. Hormone replacement therapy and physical function in healthy older men. Time to talk hormones? Endocr Rev. 2012;33:314-377.

[84] Candow DG, Forbes SC, Little JP, Cornish SM, Pinkoski C, Chilibeck PD. Effect of nutritional interventions and resistance exercise on aging muscle mass and strength. Biogerontology. 2012;13:345-358.

[85] Hickson M. Nutritional interventions in sarcopenia: a critical review. Proc Nutr Soc. 2015:1-9.

[86] Wilson GJ, Wilson JM, Manninen AH. Effects of beta-hydroxy-beta-methylbutyrate (HMB) on exercise performance and body composition across varying levels of age, sex, and training experience: A review. Nutr Metab (Lond). 2008;5:1.

[87] Flakoll P, Sharp R, Baier S, Levenhagen D, Carr C, Nissen S. Effect of beta-hydroxy-beta-methylbutyrate, arginine, and lysine supplementation on strength, functionality, body composition, and protein metabolism in elderly women. Nutrition. 2004;20:445-451.

[88] Baier S, Johannsen D, Abumrad N, Rathmacher JA, Nissen S, Flakoll P. Year-long changes in protein metabolism in elderly men and women supplemented with a nutrition cocktail of beta-hydroxy-beta-methylbutyrate (HMB), L-arginine, and L-lysine. JPEN J Parenter Enteral Nutr. 2009;33:71-82.

[89] May PE, Barber A, D'Olimpio JT, Hourihane A, Abumrad NN. Reversal of cancer-related wasting using oral supplementation with a combination of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine. Am J Surg. 2002;183:471-479.

[90] Iolascon G, Di Pietro G, Gimigliano F, Mauro GL, Moretti A, Giamattei MT, Ortolani S, Tarantino U, Brandi ML. Physical exercise and sarcopenia in older people: position paper of the Italian Society of Orthopaedics and Medicine (OrtoMed). Clin Cases Miner Bone Metab. 2014;11:215-221.

[91] Latham NK, Bennett DA, Stretton CM, Anderson CS. Systematic review of progressive resistance strength training in older adults. J Gerontol A Biol Sci Med Sci. 2004;59:48-61.

[92] Denison HJ, Cooper C, Sayer AA, Robinson SM. Prevention and optimal management of sarcopenia: a review of combined exercise and nutrition interventions to improve muscle outcomes in older people. Clin Interv Aging. 2015;10:859-869.