

# Clinical Manifestations and Pathophysiology of Sarcopenia

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**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<sup>1</sup>, and high mortality<sup>2</sup>. The number of elderly population with sarcopenia is increasing all over the world, and it is becoming an important public concern<sup>3</sup>.

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<sup>4</sup>. 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”<sup>5</sup>. 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<sup>6</sup>. As the result, the average reported age-related decreases in knee extensor strength are 20–40%<sup>7</sup>, and even greater losses (50% or over) have been reported for those in their ninth decade and beyond<sup>8,9</sup>. Immobility and malnutrition, especially low protein intake,

could deteriorate sarcopenia<sup>10</sup>, and influence of multiple factors leading to aging-related sarcopenia is demonstrated in Figure 1.

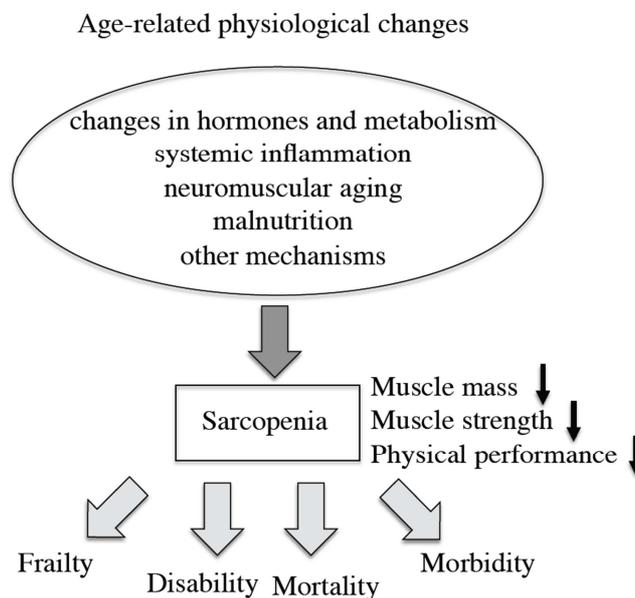


Figure 1. Influence of multiple factors leading to aging-related sarcopenia.

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<sup>11</sup>.

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<sup>12</sup>. 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 protein-1 (MuRF1) and Muscle Atrophy F-Box (MAFbx), which stimulate protein degradation<sup>13</sup>. 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.<sup>14</sup>

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

1,25(OH)<sub>2</sub>D, 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<sup>20</sup>. Vitamin D levels decline in older persons<sup>21</sup>. Lower 25-hydroxyvitamin D (25[OH]D) levels increase the risk of sarcopenia in older men and women<sup>22</sup>. 25(OH)D levels were positively associated with skeletal muscle index (SMI)<sup>23</sup>.

### 2.2. Systemic Inflammation

As humans age, serum level of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), interleukin-1 (IL-1) and C-reactive protein (CRP) elevate<sup>24</sup>. 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<sup>25,26</sup>. In a Korean study, high-sensitivity CRP levels were significantly and independently associated with sarcopenic obesity<sup>23</sup>. Inflamm-aging might be involved in sarcopenia<sup>27</sup>.

### 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<sup>3</sup>. 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<sup>10</sup>.

### 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<sup>28</sup>. Another study showed that genetic ablation of satellite cells affected cross-sectional areas of myofibers in all adult muscles, although the extent and timing differed according to muscles<sup>29</sup>.

Other studies have indicated the involvement of apoptosis in muscle<sup>30</sup> and mitochondrial dysfunction<sup>31,32</sup>. 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<sup>33</sup>. 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<sup>5</sup>. 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<sup>34</sup>. 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)<sup>33</sup>. FNIH analyzed data from nine sources of community-dwelling older persons and proposed the cutoffs<sup>35</sup>.

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<sup>36</sup>. 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<sup>35</sup>. The EWGSOP and AWGS and FNIH recommend 0.8m/sec as the cut-off<sup>5</sup>. However, AWGS implies that the cut-off for Asians might be higher than 1.0 m/sec according to most Asian studies<sup>37</sup>. IWGS recommends 1.0m/sec<sup>33</sup>.

### 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<sup>2</sup> (kg/m<sup>2</sup>)<sup>38,39</sup>. 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<sup>2</sup> for men and 5.5kg/m<sup>2</sup> for women<sup>38</sup>, or SMI (by BIA) 8.87kg/m<sup>2</sup> for men and 6.42kg/m<sup>2</sup> for women<sup>39</sup>. AWGS recommends 7.0kg/m<sup>2</sup> for men and 5.4kg/m<sup>2</sup> for women (DXA), or 7.0kg/m<sup>2</sup> for men and 5.7kg/m<sup>2</sup> for women (BIA)<sup>37</sup>. IWGS recommends 7.23kg/m<sup>2</sup> for men and 5.67kg/m<sup>2</sup> for women (DXA)<sup>33</sup>. FNIH criteria contain ASM per BMI instead of SMI<sup>35</sup>.

### 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<sup>5</sup>. Asians generally have lower grip strength than Caucasians, so AWGS defines low grip strength as <26 kg for men and <18 kg for women<sup>37</sup>. In IWGS criteria, the cutoff value is not specified<sup>33</sup>. In FNIH criteria, <26 kg for men and <18 kg for women<sup>35</sup>.

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<sup>5</sup>. 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<sup>38</sup>. 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<sup>40</sup>. The prevalence of sarcopenia in Japanese elderly men and women diagnosed using Asian criteria was 9.6% and 7.7%, respectively<sup>41</sup>.

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<sup>42</sup>.

## 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<sup>43</sup>. 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<sup>44</sup>. 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<sup>45</sup>. Other groups have also established frailty assessment tools<sup>46,47</sup>.

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<sup>48</sup>.

### 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<sup>49</sup>. According to a cross-sectional study, the prevalence rates of sarcopenic obesity are 6.1% in men and 7.3% in women<sup>50</sup>. Sarcopenic obesity is a risk of hypertension<sup>51</sup>, arteriosclerosis<sup>52</sup>, and high mortality<sup>53</sup>.

## 6. Interventions

### 6.1. Pharmacological Interventions

#### 6.1.1. Vitamin D

Low serum vitamin D is suggested to be associated with sarcopenia<sup>54,55</sup>, sarcopenic obesity<sup>50</sup>, falls, hip fracture and mortality<sup>56,57</sup>. 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<sup>58-61</sup>. The therapy might be considered if a plasma level of 25-hydroxyvitamin D is less than 30 ng/ml (70 nmol)<sup>62,63</sup>.

#### 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<sup>64-66</sup>.

#### 6.1.3. Testosterone

Some studies have suggested that testosterone supplementation attenuated several sarcopenic symptoms including decrease in muscle mass<sup>67-69</sup> and grip strength<sup>70,71</sup>. Oral low-dose testosterone administration induced whole-body protein anabolism in postmenopausal women<sup>72</sup>. A recent study reported that testosterone administration increased muscle fiber diameter and peak power in community-dwelling older men<sup>73</sup>. However, testosterone therapy in older men is associated with various risks, such as sleep apnea, thrombotic complications and prostate cancers<sup>74</sup>, 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<sup>75</sup>.

#### 6.1.5. Estrogen

Menopause is associated with a natural decline in estrogen, which decreases muscle mass and strength<sup>76</sup>. Estrogen supplementation increases lean body mass or muscle strength when administered to postmenopausal women<sup>77,78</sup>. However, some studies failed to show a positive effect of estrogen on muscle mass<sup>79-81</sup>. Estrogen is related to various adverse effects, such as breast cancer, thromboembolism, cholecystitis, stroke and coronary events<sup>78</sup>, 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<sup>82</sup>. However, most studies have shown that administration of GH alone failed to improve muscle strength despite amelioration of the detrimental somatic changes of aging<sup>83</sup>. 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<sup>84</sup>. However, there was no consistent effect of protein supplementation on muscle mass, strength or function<sup>85</sup>.

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<sup>85</sup>.

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<sup>86</sup>. In several studies of the elderly, improvement of physical performance, strength and muscle mass was observed by administering of 2-3 g HMB<sup>87,88</sup>. HMB was also effective for the loss of muscle caused by cancer-related cachexia<sup>89</sup>. However, larger well-controlled studies are required to clarify the effects of HMB on sarcopenia<sup>85</sup>.

#### 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<sup>90</sup>. 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<sup>91</sup>. Frequent aerobic exercise might

ameliorate sarcopenia by increasing skeletal muscle insulin sensitivity and inducing proliferator activated receptor gamma co-activator 1- $\alpha$  (PGC-1 $\alpha$ )<sup>90</sup>.

The combination of exercise and nutrition might be better<sup>84</sup>, because protein acts synergistically with exercise to increase muscle mass<sup>1</sup>. 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<sup>92</sup>.

## 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.

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