



Sarcopenia from Pathophysiology to Clinical : Literature Review

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ABSTRACT

The causes of sarcopenia are thought to be *multifactorial* including: environmental factors, illness, activation of inflammatory pathways, mitochondrial dysfunction, loss of neuromuscular junctions, reduced number of satellite cells and changes in the quality of hormonal function. The mechanism of sarcopenia occurs because the aging process coupled with reduced physical activity can cause the formation of cytokines to increase so that inflammation is easy, insulin resistant, anabolic resistance and neuromuscular impairments.

1. Introduction

Physiological and muscle morphological changes that appear with increasing age include a decrease in the number and size of muscle fibers, especially in type 2 (fast-twitch muscle) muscles, accompanied by infiltration of fatty tissue and fibrous tissue into muscle mass.¹⁻⁴ Besides, there is a degenerative change of the satellite and myoblast cells and become inactive. However, Sneijder et al (2009) reported that myoblasts and satellite cells can become active again (myogenesis process) if the muscles are given a physical workload with the appropriate intensity.³ Some researchers have found that obesity and infiltration of fat tissue into muscle aggravate sarcopenia. This phenomenon is referred to as *sarcopenic obesity*, although looking obese is usually considered a *subgroup* of sarcopenia. Koster et al (2011) in a longitudinal study found that the lower the quality of the muscle, the increased the amount of fat infiltration in the muscle.⁵

Risk Factors and Mechanisms for Sarcopenia

The causes of sarcopenia are thought to be *multifactorial* and include: environmental factors, illness, activation of the inflammatory pathway, mitochondrial dysfunction, loss of neuromuscular junctions, reduced number of satellite cells and changes in the quality of hormonal function (Figure 2.3.). The mechanism of sarcopenia occurs due to the aging process (*aging*) coupled with reduced physical activity which can cause the formation of cytokines to increase so that inflammation, insulin resistance, *anabolic resistance* and neuromuscular *impairments* are easy (Figure 2.3).⁶

Sarcopenia refers to age-induced decline in skeletal muscle quality, strength, and mass, which reaches 1% annually after age > 50 years. Sarcopenia can be considered as an analogue of osteoporosis (characterized by bone loss) occurring only in skeletal

muscle tissue. This disorder threatens physical performance, independent life, and quality of life. An age-related definition of sarcopenia based on low muscle and muscle mass has been produced by the European Working Group on Sarcopenia in Indonesian Parents. According to the European Working Group on the Approach to Sarcopenia in the Elderly, a study reported that the prevalence of sarcopenia was 4.6% in men and 7.9% of women in adults living in communities with a mean age of 67 in Great Britain.⁷⁻⁸

Inflammation and Nutrition

The *low-grade* state of inflammation has been defined as inflammation due to aging or inflammaging and, to some extent, can be beneficial for healthy aging, stimulating normal tissue *remodeling*.⁹ However, in most cases, the combination of an active inflammatory state with reduced antioxidant defenses is detrimental to health. *Inflammaging* is closely related to immunosenescence, a reduced or altered immune response to antigenic stimulation, which has been shown in animal and human models.¹⁰ Age is associated with a decrease in age in T and B cells, particularly at the levels of CD8 and CD95 "*virgin cells*", and a concomitant increase in *Natural Killer* (NK) cells is a distinctive feature of this process.¹¹

Interleukin-1 β (IL-1 β), Tumor Necrosis Factor- α (TNF- α) and Interleukin-6 (IL-6) have been identified as key roles in inflammation.¹² In the physiological acute phase response, IL-6 modulates synthesis reactants, including C-reactive protein (CRP), and promote immune cell activation.¹³ Aging is associated with changes in the trans-signaling of the IL-6 system with a decrease in soluble IL-6 receptor (sIL-6r) and IL-6 inhibitor sgp130. Thus, increased signaling due to reduced inhibition induces improper activation of the receptors. Cellular IL-6, promotes an inflammatory cascade independently of the presence of antigenic stimulation or tissue damage.¹³⁻¹⁴

These physio-pathological changes have profound clinical implications. In a large group of community-dwelling elderly subjects, elevated serum IL-6 and IL-1RA concentrations have been associated with decreased physical performance in a follow-up period of six years.¹⁵ A recent translational study has shown

that telomere friction may be a genetic substrates linking low-grade chronic inflammation with altered cell function, and with decreased muscle performance.¹⁶ In a large, *cross-sectional*, population-based study conducted on women living in the community over 65 years of age, IL-6 levels were also independently associated with a higher prevalence of weakness. In addition, inflammation can be prodromic to the onset of disability, cognitive and multimorbidity. All chronic diseases with high prevalence in the older population, including cancer, are associated with altered immune and inflammatory responses. Finally, inflammation also impacts survival, contributing to cognitive symptoms, depression and poor physical performance to determine a high risk profile for death.

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The role of nutrition in this process is very important. Low-grade chronic inflammation is a major determinant of "aging anorexia," while acute inflammation can contribute to increased energy requirements, leading to the development of "disease-related malnutrition". The resulting anabolic imbalance between nutritional intake and demand has been linked to weakness, loss of mass, muscle, reduced muscle strength, and functional dependence that causes disability. Decreased food intake and increased energy requirements create a vicious cycle with worse prognostic predictions. This catabolic state is greatest during critical illness conditions characterized by poor response to nutritional interventions. In older individuals hospitalized for acute disease or chronic disease reactivation, the degree of inflammation has a greater influence on prognosis related to status, nutrition. More importantly, the low-grade catabolic state that exists outside the acute phase is strongly associated with inflammation. This phenomenon, defined as "anabolic resistance", implies suboptimal synthesis of skeletal muscle protein in response to physiological stimuli and is one of the main determinants of sarcopenia.²⁰⁻²⁴ In healthy, active elderly men, the level of inflammation is measured by a mild increase in CRP, causes decreased aerobic fitness and insulin resistance in skeletal muscle and stimulates protein synthesis after dietary intake which is less effective than in younger men.^{25,26}

Hyperphosphorylation of mTOR and effectors downstream of S6K1, with consequent downregulation of the mTORC1 signaling pathway, may be the molecular substrate involved.²⁷ In chronic disease subjects with higher levels of "basal" inflammation, this mechanism is enhanced which can lead to cachexia. Reduced physical activity also contributes to "anabolic resistance", which causes a vicious cycle to be very difficult to break.²⁸⁻³⁰

Nutritional interventions can help inhibit "anabolic resistance". There are two pathways that contribute to restoring normal protein synthesis, namely increasing the intake of protein / amino acids that can overcome the increased anabolic threshold, and / or increasing the intake of nutrients that have anti-inflammatory properties. The first approach in several observational studies and clinical trials investigating the role of nutritional interventions in sarcopenia. Surprisingly, most of the evidence claims that protein or amino acid supplements are unable to increase muscle mass, muscle strength and physical performance in parallel.

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The second approach focuses on key nutrients that are able to reduce inflammatory status as an actor of endocrine nutritional networks. The pathway linking nutrition to inflammation is *insulin growth factor-1* (IGF-1), which is positively modulated by diet and the anabolic hormone system and is negatively affected by inflammation and oxidative stress. IGF-1 levels tend to decrease with age, concurrently with an increase in subclinical inflammatory status. Interestingly, in a large population-based study of women, Cappola et al, have shown that low IGF-1 levels and high IL-6 levels synergistically contribute to limited mortality and mobility.³²⁻³³

Molecular studies have shown that many nutrients may be able to modulate systemic inflammation. These include long-chain saturated fatty acids, oleic acid, *poly unsaturated fatty acid* n-3 (PUFA n-3), vitamin D, magnesium, calcium, whey protein, casein and amino acids such as cysteine, histidine, glycine, and leucine. However, at present insufficient clinical data are present on older individuals only for vitamin D, PUFA n-3 and *whey protein*.³⁰

Vitamin D, n-3 PUFA and *whey protein* as anti-inflammatory nutrients, the current state of the scientific literature makes it possible to state that only n-3 PUFAs have a documented, albeit mild, anti-inflammatory effect in elderly subjects. There is no strong evidence to support the anti-inflammatory effects of vitamin D or whey supplements in older people. Epigenetic mechanisms have been proposed to significantly influence the relationship between diet and inflammatory response individually, and hence may represent one reason for the gaps that exist between physio-pathological and clinical studies. The gut microbiome and diet-microbiome interactions may also have a role in promoting or controlling inflammation in the elderly. Future research should better address all of these issues, clarifying the molecular and clinical reasons for combination nutritional interventions especially with vitamin D, n-3 PUFAs and whey protein.³⁴⁻³⁵

The 1989 definition

Sarcopenia comes from the Greek sarx (muscle) and penia (loss) which means loss of muscle mass. The term was first introduced by Irvin Rosenberg in 1988. Sarcopenia is a syndrome characterized by a progressive and overall reduction in skeletal muscle mass and muscle strength. Sarcopenia is generally accompanied by physical inactivity, decreased mobility, slow gait, and low physical ability (stamina). Although sarcopenia mainly occurs in the elderly, there are other conditions that can cause sarcopenia in young adults, such as malnutrition, lifestyle, malignancy, and cachexia. Sarcopenia begins at the age of 40-50 years and increases by about 0.6% each following year.³⁶

Sarcopenia is a complex phenomenon with a multifactorial etiology. The process of sarcopenia involves the interaction of the peripheral nervous system, central nervous system, hormonal, nutritional status, immunology, and inadequate physical activity. At the molecular level, sarcopenia is caused by a disproportionate decrease in muscle protein synthesis rate and / or an increase in muscle protein breakdown. The neuropathic process is most influential because it is responsible for the degeneration of the alpha motor nerves that supply the muscle fibers and cause loss of

motor units.³⁷ The aging process causes structural and functional changes in skeletal muscles, especially in the first 40 years.

Definition of Sarcopenia 2010

In 2010 The *European Working Group on Sarcopenia in Older People* (EWGSOP) linked sarcopenia with geriatric syndrome. Geriatric syndrome is a health disorder in the elderly, resulting from the interaction of various diseases and an increase in age which is displayed in the form of various signs and symptoms. Some examples of geriatric syndrome are delirium, easy falls and incontinence.³¹ In general, sarcopenia represents a health condition that results in impaired mobility, decreased muscle function and muscle mass, increased risk of falls and fractures, decreased ability to perform daily activities, the occurrence of physical disabilities, loss of independence and an increased risk of death.³¹ In 2010, the diagnosis of sarcopenia was seen from low muscle mass, low muscle strength and low physical activity. This 2010 definition of sarcopenia has caused controversy because several studies have found no relationship between muscle strength and muscle mass.³²

The mechanism of sarcopenia involves several things such as protein synthesis, proteolysis, neuromuscular integrity and levels of muscle fat. A person with sarcopenia can have several factors, with contributions that vary and develop over time. Figure 2. shows the basic mechanism of sarcopenia.³²

Based on the mechanism of sarcopenia as depicted in Figure 2, the categories of sarcopenia are categorized into primary sarcopenia and secondary sarcopenia. Primary sarcopenia is only related to age, secondary sarcopenia is related to length of rest, sedentary lifestyle, *zero-gravity* conditions, diseases accompanied by organ failure (heart, lung, liver, kidney and brain), inflammatory disease, malignancy or endocrine disease, lack of intake of nutrients that results in a lack of energy or protein production such as *malabsorption*, *gastrointestinal disorders* or medications that can cause anorexia.³²

The diagnosis of sarcopenia according to the 2010 EWGSOP can be confirmed if at least two of the following three criteria are obtained: low muscle mass,

poor muscle strength, and poor physical performance. Decreased muscle mass is muscle mass less than 2 times the standard deviation of the reference population of male or female healthy young adults in the area. This diagnostic criterion is difficult to apply in Indonesia because there is no normative data on the amount of muscle mass in the young adult population as well as data on muscle strength retention in various age groups and sexes. In addition, until now there is no standard technique for measuring the amount of muscle mass for the elderly.³³

The supporting examinations to determine the diagnosis of sarcopenia are as follows:

The European working group sarcopenia in the elderly (EWGSOP) in 2010 also recommended an assessment of low muscle size with low muscle mass and strength or performance that can be utilized in any clinical definition.³⁴ Several studies have adopted these criteria and definitions such as Bian et al (2017) who combine criteria for sarcopenia according to the EWGSOP (2010) and the Asian Working Group for Sarcopenia (AWGS) in 2015.^{32,34}

- Muscle mass was assessed by measuring the extremity muscle mass (ASM = appendicular skeletal muscle mass) using the Janssen formula:
 - $ASM \text{ mass (kg)} = [(Ht^2 / R \times 3 \times 0.401) + (\text{gender} \times 3 \times 3.825) + (\text{age} \times -0.071)] + 15.102$
- $ASM \text{ index (ASMI)} = ASM \text{ (kg)} / \text{height}^2 \text{ (m}^2\text{)}$. Cut-off value:
 - Male : $ASM \text{ index} < 7.0 \text{ kg} / \text{m}^2$
 - Female : $ASM \text{ index} < 5.7 \text{ kg} / \text{m}^2$
- Muscle strength by assessing the strength of the grip (hand grip)
 - Male : $HG < 26 \text{ kg}$
 - Female : $HG < 18 \text{ kg}$
- Walking speed, according to EWGSOP using a walking test of 4 m completed in seconds (t).
Walking speed = $4 \text{ (m)} / t \text{ sec}$
 - Low gait speed $< 0.8 \text{ m} / \text{sec}$

Muscle quantity and quality are both important for muscle function. Between the ages of 20 and 70 years, skeletal muscle mass decreases by 40%.³⁸⁻⁴⁰ The decrease in muscle mass and muscle quality that occurs with the aging process clinically results in weakness, disability, hospitalization and death.⁴⁰

Definition of Sarcopenia 2018

In 2018 EWGSOP conducted further research and development on sarcopenia. Based on the times, the treatment and management of sarcopenia and previous findings, EWGSOP2.⁹ According to the definition of EWGSOP2 sarcopenia is a progressive and comprehensive skeletal muscle disorder that has the impact of increasing the likelihood of falls, fractures, physical disabilities and death⁴. The original EWGSOP definition of sarcopenia was only associated with large changes in muscle function decline over time, and low muscle mass as the main criterion. EWGSOP 2 recommends the SARC-F questionnaire that patients can easily fill out and understand based on the following criteria: ⁹

1. Low muscle strength,
2. Low quantity and quality of muscles
3. Low physical performance.

Functional status can be assessed by measuring grip strength or walking speed. Muscle mass can be evaluated with a variety of diagnostic modalities including ultrasound, dual-energy X-ray absorptiometry, or MRI. The SARC-F questionnaire is a simple and well-validated screening tool for sarcopenia where a score of ≥ 4 is positive for sarcopenia.^{4,38} In addition to SARC-F, EWGSOP2 also recommends using *sarcopenia quality of life* (SARQOL). SARQOL contains questions based on muscle quantity, muscle quality, physical performance, and mental age. Table 2.1. present data on simple screening to detect sarcopenia.

The *cut off point* for sarcopenia according to EWGSOP 2 of 2018 can be seen in Table 2.2. In addition to the *cut off point* value above, there are several variables that must be filled in such as age (years), gender, BMI, comorbidity, number of diseases currently being suffered, the number of types of drugs

consumed, alcohol consumption, smoking, Mini Mental State Examination. and depression.

Sarcopenia Categories and Conditions

- Primary and secondary sarcopenia

Primary and secondary sarcopenia in everyone is associated with aging, in most cases it cannot be identified. The primary category is *age related*, the secondary category is related to clinical factors such as systemic disease, inflammatory processes, malignancy or organ failure. Physical activity contributes to the development of sarcopenia, as well as *sedentary life* or immobility and disability. Sarcopenia also correlates with anorexia, malabsorption, limited intake of healthy foods or limited ability to eat.⁹

- Acute and Chronic Sarcopenia

Acute sarcopenia usually occurs due to illness or injury for ≤ 6 months, while chronic conditions > 6 months.⁹

- Sarcopenia obesity

Sarcopenia obesity is a condition of reduced lean body mass in the context of excess adiposity. Sarcopenia obesity is most commonly reported in the elderly, because risk and prevalence increases with increasing age. Obesity worsens sarcopenia, increases fat-to-muscle infiltration, decreases physical functioning and increases the risk of death.⁹

- Sarcopenia malnutrition

The sarcopenia phenotype is also associated with malnutrition, regardless of whether the malnutrition is rooted in low food intake (hunger, inability to eat), reduced bioavailability of nutrients (e.g. with diarrhea, vomiting) or high nutritional requirements (e.g. with inflammatory diseases such as cancer or organ failure with cachexia).⁹

Degree of sarcopenia

Assessment of the degree of sarcopenia can be seen in Table 2.3. below⁹:

Sarcopenia Assessment Algorithm Based on EWGSOP2

Figure 4. presents the algorithm for sarcopenia assessment based on EWGSOP2. The first step that must be done is to determine the case, can use the SARC-F questionnaire and continue to assess muscle strength through *grip strength* and *chair stand tests*, if the assessment of muscle strength is low then it is likely that this is sarcopenia. Confirmation is done by measuring the quantity and quality of muscles through DXA, BIA, CT and / or MRI. After it was confirmed that the subject had sarcopenia, physical measurements were taken⁹

Bioelectrical Impedance Assessment (BIA)

One of the methods used to measure body fat is bioelectrical impedance analysis (BIA). The BIA is able to determine the level of body fat by measuring the impedance of the human body. This method is done by passing an alternating current (AC) at a certain frequency into the human body. The amount of the body impedance value can be determined by measuring the voltage generated from the alternating current that is constantly flowed into the human body. This body impedance value will later be used as a reference in determining a person's body fat.³⁶

Several studies on body fat measurement have been conducted before, one of which is the measurement of body fat using the two-electrode hand-to-hand method.⁴⁵ In other studies, there are also four electrodes used. Also research was conducted using four electrodes, but what was measured was the impedance between the right and left feet (*foot-to-foot*).⁴⁰ In another study, measurements of body fat using four electrodes were also developed using the *whole body measurement* method but the user had to move the electrode connector manually according to the body part to be measured.³³

The composition of the human body can be modeled in the form of two compartments, namely the non-fat mass (*fat free mass*) and the fat mass (*fat mass*). Figure 2.6. shows the composition of the human body in which the non-fat mass (fat free mass, FFM) is composed of approximately 73% fluid, 20% metabolic tissue, and 7% minerals in bone.³⁸

One of the equations used to determine FFM and FM is the result of an experiment conducted by Elliot Mylloot et al as shown in the formula below. After knowing the fat mass value, the body fat percentage value can be known by comparing the value of fat mass to body weight.⁴⁰

$$\mathbf{FFM} = 0.360 \left(\frac{\mathbf{height}^2}{\mathbf{impedance}} \right) + 0.162(\mathbf{height}) + 0.289(\mathbf{weight}) - 0.134(\mathbf{age}) + 4.83(\mathbf{sex}) - 6.83$$

$$\mathbf{FM} = \mathbf{weight} - \mathbf{FFM}$$

$$\mathbf{BF} = \frac{\mathbf{FM}}{\mathbf{weight}} \times 100\%$$

Information :

FFM = Fat Free Mass (Kg)

Height = Height(cm)

Impedance = impedance (Ω)

Gender Male = 1 and Female = 0

FM = Fat Mass

Weight = weight (kg)

Age = Age (years)

BF = Body Fat

The variables commonly used in calculating BIA are:

FFM = Fat Free Mass (Kg)

Height = Height(cm)

Impedance = impedance (Ω)

Gender Male = 1 and Female = 0

FM = Fat Mass

Weight = weight (kg)

Age = Age (years)

BF = Body Fat

VFA = Visceral Fat Analysis

SMI = Skeleton Mass Index

AC = Arm circumference

ICW = Intracellular Water

AMC = Arm Muscle Circumference

ECW = Extra Cellular Water

WC = Waist Circumference

In research on sarcopenia, the BIAs used were BMI, SMI, WC in BIA, FFM, FM, BF and age.⁴¹

Table 1. Sarcopenia Screening Questionnaire using the SARC-F9,43 Questionnaire^{9,43}

Component	Question	Appraisal
<i>Strength</i> (Power)	Do you feel too heavy lifting objects weighing 5 kg (10 pounds)?	No = 0 Slightly Heavy = 1 Very Heavy / Can't = 2
<i>Assistance in walking</i> (Help While Walking)	Do you have problems walking or entering the room?	No = 0 Slightly Heavy = 1 Very heavy / need help / can't alone = 2
<i>Rise from a chair</i> (Standing from the chair)	Do you have problems moving / moving to a chair or bed?	No = 0 Rather heavy = 1 cannot alone = 2
<i>Climb stairs</i> (Climbing up the stairs)	Do you have problems climbing 10 stairs?	No = 0 Rather heavy = 1 Very heavy / not ias = 2
<i>Falls</i> (Fell)	How often did you fall during this year?	Never = 0 falls about 1-3 = 1 fall ≥ 4 = 2

* If the value is ≥ 4 , sarcopenia is diagnosed

Table 2.2. Cut Off Point of Sarkopenia based on EWGSOP2 and AWGS⁹

Variable	Cut Off Point			
	EWGSOP		AWGS	
	Male	Female	Male	Female
Strength holds grip strength and stands up from the chair				
Hand Grip Strength	<30kg	<20kg	<26 kg	<18kg
Get up from the chair	>15 sec			
Muscle Quantity (Muscle Mass)				

DXA	<7.2kg/m ²	<5.5 kg/m ²	<7 kg/m ²	<5.4 kg/m ²
BIA	-	-	<7 kg/m ²	<5.7kg/m ²
Physical performance				
Gait speed	<0,8 m/detik			
Short physical performance battery (SPPB)	8 point			
4m walk test	Unable to finish / unable or able to complete ≥ 6 minutes			

Table 2.3. Assessment of Degree of Sarcopenia ⁹

Stage	Muscle mass	Muscle strength	Performance
Sarcopenia	Decreased	Normal	Normal
Severe Sarcopenia	Decreased	Decreased	Decreased

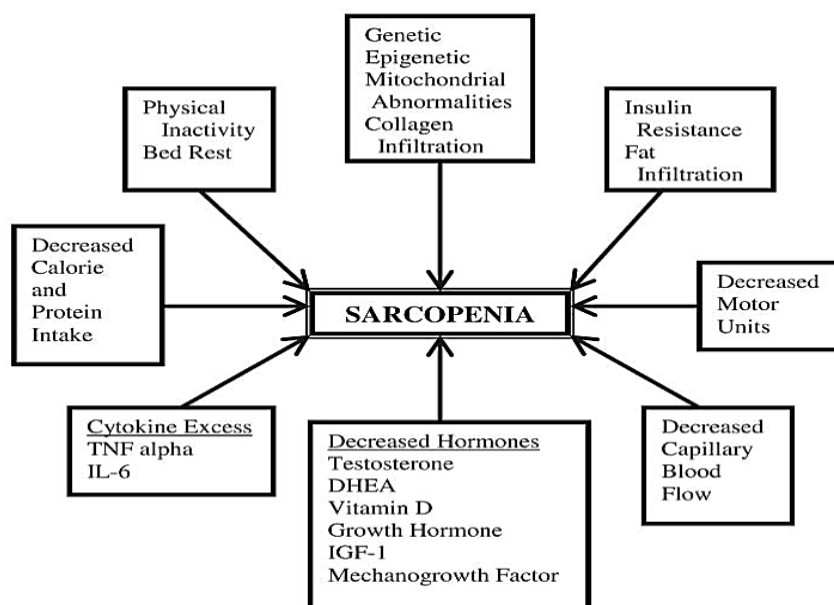


Figure 1. Factors causing sarcopenia.²³

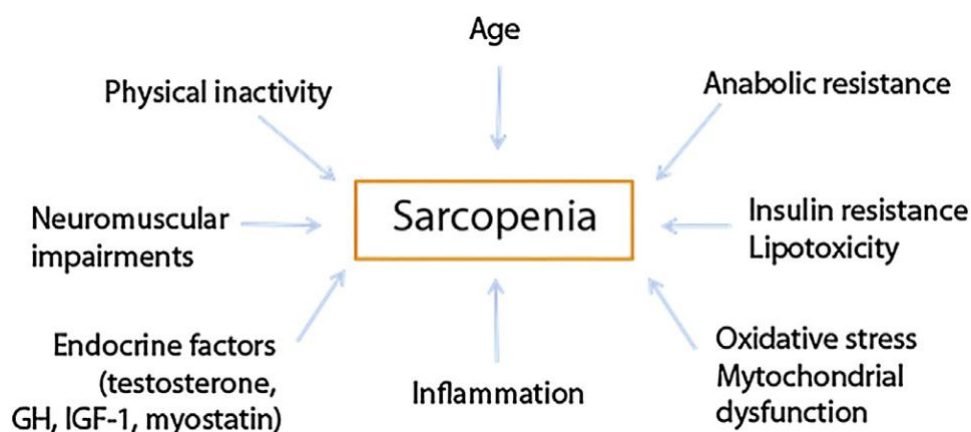


Figure 2. Mechanism of occurrence of sarcopenia.²¹

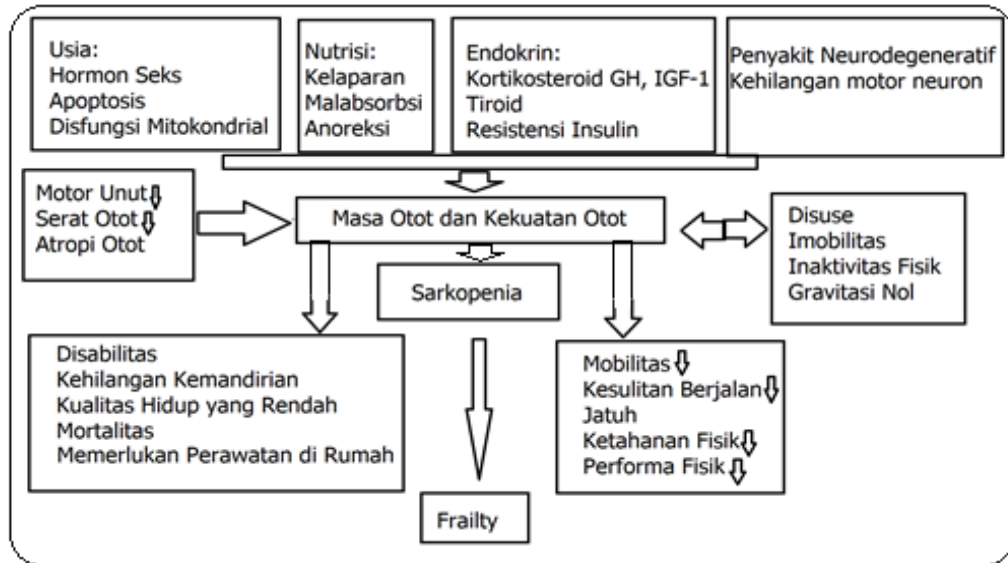


Figure 3. Conditions that have the potential to cause sarcopenia.²⁹

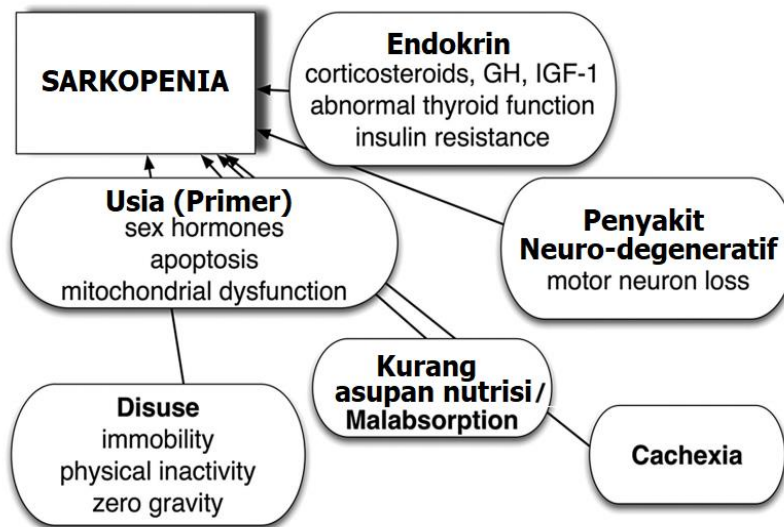


Figure 4. Mechanism of Sarcopenia 2010³²

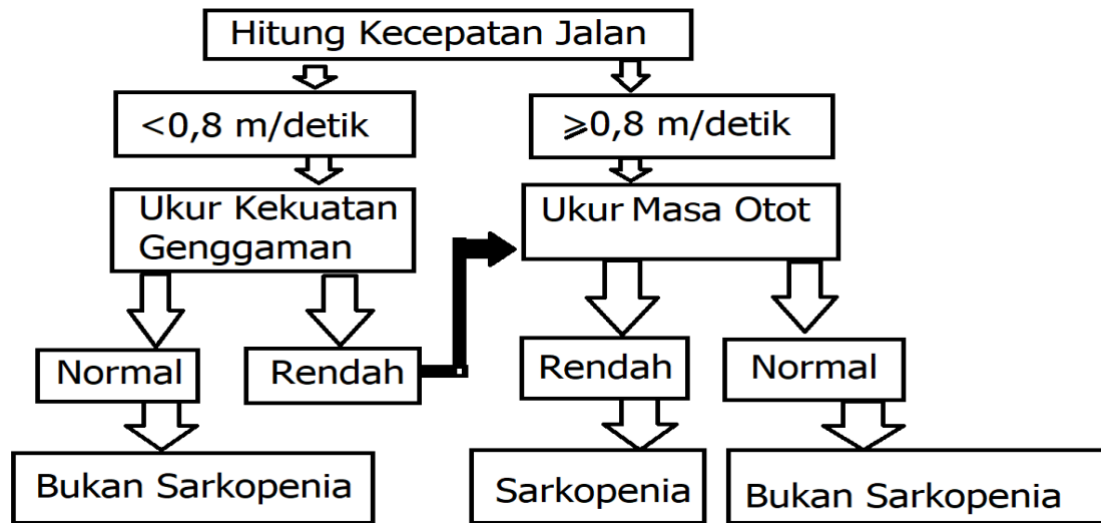


Figure 5. Algorithms suggested by the EWGSOP for screening and finding cases of Sarcopenia³⁰

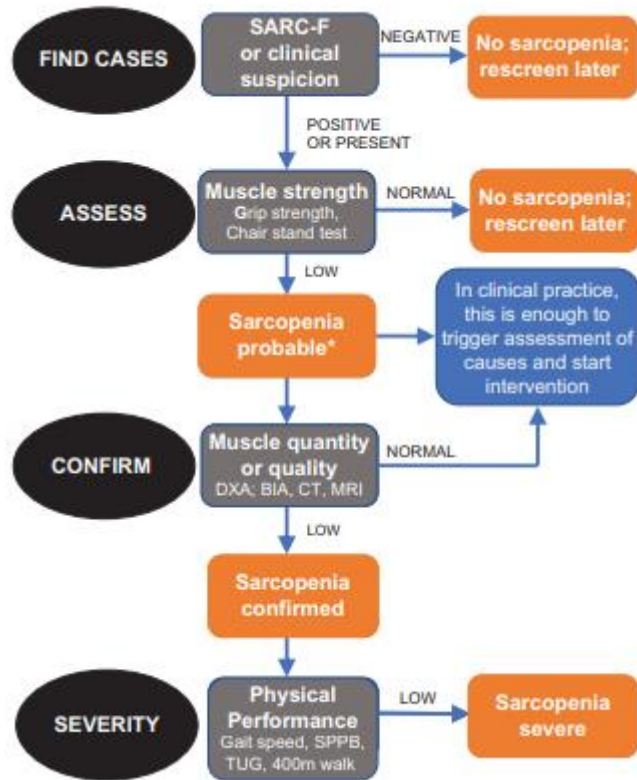


Figure 6. Algorithm for Sarcopenia Assessment in EWGSOP2⁹

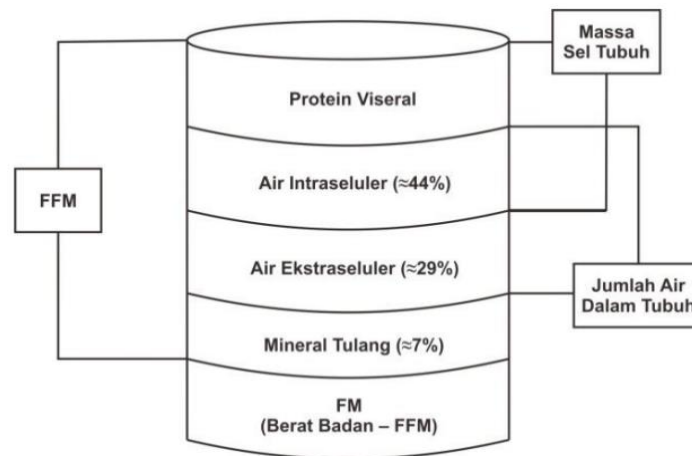


Figure 7. Human Body Composition

2. References

1. Setiati S, Seto E, Sumantri S. Frailty profile of elderly outpatient in Cipto Mangunkusumo Hospital Jakarta. In press. 2013
2. Sudarma V, Halim L. High skeletal muscle mass is associated with increased serum 25 (OH) D levels in elderly. *Universa Medicina*, 2017;36(3):236–42.
3. Yazar, Tamer; Yazar, Hülya Olgun. Prevalance of sarkopenia according to decade. *Clinical nutrition ESPEN*, 2019, 29: 137-141.
4. Scimeca M, et al. "Vitamin D receptor in muscle atrophy of elderly patients: a key element of osteoporosis-sarkopenia connection." *Aging and disease* 9.6, 2018: 952.
5. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357 :266–281.
6. Cruz-Jentoft, Alfonso J., et al. "Sarkopenia: revised European consensus on definition and diagnosis." *Age and ageing* 48.1 (2018): 16-31.
7. Conzade, Romy, et al. "Vitamin D in Relation to Incident Sarkopenia and Changes in Muscle Parameters Among Older Adults: The KORA-Age Study." *Calcified tissue international*, 2019, 1-10.
8. Liberman, Keliame, et al. "Thirteen weeks of supplementation of vitamin D and leucine-enriched whey protein nutritional supplement attenuates chronic low-grade inflammation in sarcopenic older adults: the PROVIDE study." *Aging clinical and experimental research*, 2019, 1-10.
9. Garcia M, et al. "Vitamin D, muscle recovery, sarkopenia, cachexia, and muscle atrophy." *Nutrition* 60 (2019): 66-69.
10. El-Hajj C, et al. "Vitamin D supplementation and muscle strength in pre-sarcopenic elderly Lebanese people: a randomized controlled trial." *Archives of osteoporosis*, 2019, 14.1: 4.
11. Fedarko, Neal S. "Theories and mechanisms of aging." *Geriatric Anesthesiology*. Springer, Cham, 2018. 19-25.
12. Blundell A, Masud T. "Teaching and learning the content of geriatric medicine." *Learning Geriatric Medicine*. Springer, Cham, 2018. 7-15.
13. Naseeb, M. A., Volpe, S. L. Protein and exercise in the prevention of sarkopenia and aging. *Nutrition research*, 2017, 40, 1-20.
14. Boirie, Yves, and Christelle Guillet. "Fast digestive proteins and sarkopenia of aging." *Current Opinion in Clinical Nutrition & Metabolic Care* 21.1 (2018): 37-41.
15. Skaaby, Tea, Betina H. Thuesen, and Allan Linneberg. "Vitamin D, Sarkopenia and Aging." *Vitamin D in Clinical Medicine*. Vol. 50. Karger Publishers, 2018. 177-188.
16. Calvani, Riccardo, et al. "Biomarkers for physical frailty and sarkopenia: state of the science and future developments." *Journal of cachexia, sarkopenia and muscle* 6.4 (2015): 278-286.
17. Bianchi, Lara, et al. "Prevalence and clinical correlates of sarkopenia, identified according to the EWGSOP definition and diagnostic

- algorithm, in hospitalized older people: The GLISTEN Study." *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* 72.11 (2017): 1575-1581.
18. Cruz-Jentoft, Alfonso J., et al. "Sarkopenia: European consensus on definition and diagnosis Report of the European Working Group on Sarkopenia in Older People A. J. Cruz-Gentoft et al." *Age and ageing* 39.4, 2010: 412-423.
 19. Bian, Ai-Lin, et al. A study on relationship between elderly sarkopenia and inflammatory factors IL-6 and TNF- α . *European journal of medical research*, 2017, 22.1: 25.
 20. McKee, Alexis, and John E. Morley. "Hormones and Sarkopenia." *Current Opinion in Endocrine and Metabolic Research*, 2019.
 21. Bruce, Bonnie, and James F. Fries. "The health assessment questionnaire (HAQ)." *Clinical and experimental rheumatology* 23.5, 2005: S14.
 22. Phaniendra, Alugogu; Jestadi, Dinesh Babu; Periyasamy, Latha. Free radicals: properties, sources, targets, and their implication in various diseases. *Indian journal of clinical biochemistry*, 2015, 30.1: 11-26.
 23. Patel HP, Syddall HE, Jameson K, Robinson S, Denison H, Roberts HC, et al: Prevalence of sarkopenia in community-dwelling older people in the UK using the European Working Group on Sarkopenia in Older People (EWGSOP) definition: findings from the Hertfordshire Cohort Study (HCS). *Age Ageing* 2013;42:378–384.
 24. Brown JC, Harhay MO, Harhay MN: Sarkopenia and mortality among a population-based sample of community-dwelling older adults. *J Cachexia Sarkopenia Muscle* 2016;7:290–298.
 25. Ryall JG, Schertzer JD, Lynch GS: Cellular and molecular mechanisms underlying age-related skeletal muscle wasting and weakness. *Biogerontology* 2008; 9:213–228.
 26. Brioché T, Pagano AF, Py G, Chopard A: Muscle wasting and aging: experimental models, fatty infiltrations, and prevention. *Mol Aspects Med* 2016;50: 56–87.
 27. Bauer JM, Verlaan S, Bautmans I, Brandt K, Donini LM, Maggio M, et al: Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarkopenia in older adults, the PROVIDE study: a randomized, double-blind, placebo-controlled trial. *J Am Med Dir Assoc* 2015;16:740–747.
 28. Walsh S, Ludlow AT, Metter EJ, Ferrucci L, Roth SM: Replication study of the vitamin D receptor (VDR) genotype association with skeletal muscle traits and sarkopenia. *Aging Clin Exp Res* 2016;28:435–442.
 29. Boonen S, Bischoff-Ferrari HA, Cooper C, Lips P, Ljunggren O, Meunier PJ, et al: Addressing the musculoskeletal components of fracture risk with calcium and vitamin D: a review of the evidence. *Calcif Tissue Int* 2006;78:257–270
 30. Meehan M, Penckofer S: The role of vitamin D in the aging adult. *J Aging Gerontol* 2014;2:60–71.
 31. Annweiler C, Beauchet O: Questioning vitamin D status of elderly fallers and nonfallers: a meta-analysis to address a “forgotten step.” *J Intern Med* 2015; 277:16–44.
 32. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, et al: Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA* 2010;303:1815–1822.
 33. Annweiler C, Montero-Odasso M, Schott AM, Berrut G, Fantino B, Beauchet O: Fall prevention and vitamin D in the elderly: an overview of the key role of the non-bone effects. *J Neuroeng Rehabil* 2010;7: 50.
 34. Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, et al: Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2009;169:551–561.
 35. Bischoff-Ferrari HA, Willett WC, Orav EJ, Lips P, Meunier PJ, Lyons RA, et al: A pooled analysis of vitamin D dose requirements for fracture prevention. *N Engl J Med* 2012;367:40–49.
 36. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al: Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006;354:669–683.

37. Avenell A, Gillespie WJ, Gillespie LD, O'Connell D: Vitamin D and vitamin D analogues for preventing fractures associated with involutional and postmenopausal osteoporosis. *Cochrane Database Syst Rev* 2009;2:CD000227.
38. Gonzalez, Maria Cristina, and Steven B. Heymsfield. "Bioelectrical impedance analysis for diagnosing sarkopenia and cachexia: what are we really estimating?." *Journal of cachexia, sarkopenia and muscle* 8.2 (2017): 187-189.
39. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al: Vitamin D3 and calcium to prevent hip fractures in elderly women. *N Engl J Med* 1992;327:1637–1642.
40. Manoy, Pacharee, et al. "Elevated serum leptin levels are associated with low vitamin D, sarcopenic obesity, poor muscle strength, and physical performance in knee osteoarthritis." *Biomarkers* 22.8 (2017): 723-730.