Chapter

Clinical Relations of Sarcopenia

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Abstract

Sarcopenia is one of geriatric syndromes, characterized by decreased muscle mass accompanied by decreased muscle strength and/or performance. It is more prevalent with increase in age, and the prevalence depends on the criteria applied and the characteristic of the elderly. Sarcopenia has a higher risk of morbidity and mortality in elderly patients. The definition criteria of sarcopenia are still controversial, but diagnostic criteria from the Asian Working Group for Sarcopenia and the European Working Group on Sarcopenia in Older People (EWGSOP) are the most used criteria for clinical practice. Pathogenesis sarcopenia involved a multifactorial process and is divided into intrinsic and extrinsic factors. Risk factors for sarcopenia include constitutional factors, aging, lifestyle, changes in body condition, and chronic diseases. Based on that, sarcopenia is divided into primary and secondary sarcopenia. There are three stage of sarcopenia, which are presarcopenia, sarcopenia, and severe sarcopenia. Nutrition and exercise are the two main pillars to manage sarcopenia.

Keywords: sarcopenia, elderly, clinical, muscle, morbidity

1. Introduction

The consequences of sarcopenia due to aging are often not getting noticed. Sarcopenia, which is characterized by decreased muscle mass accompanied by decreased muscle strength and/or performance, is often regarded as an ordinary physiological change due to aging. Muscles that have a mass of nearly 50% of the body mass are very important because besides serving as a body movement tool, they also are endocrine organs (secrete proteins called myokines that affect the metabolism of bodies systematically) and protective organs (counteract the negative effects of body fat). If muscle mass decreases, then the protective function of the body will be disrupted.

As age increases, the prevalence of sarcopenia also increases, where at an age of 65–70 years, the prevalence is between 13 and 24%, and at the age of more than 80 years, it is more than 50% [1]. The prevalence of sarcopenia based on gender at the age of 60–69 years is found in 10% of men and 8% of women, while in those over 80 years, it is in 40% of men and 18% of women [2]. The prevalence also differs based on the health-care setting. In acute care hospitals (age > 65 years), the prevalence is 10%. In long-term care facilities (age > 70 years), it is 33%, and in community-dwelling elderly (age ≥ 60 years), it is 29% [3]. It is difficult to obtain the typical prevalence of sarcopenia because it depends on the definition applied and characteristics of the elderly, but in the results from large-scale studies involving 1000 or more participants, the prevalence rate is estimated to be between 6 and 12% [4].

Sarcopenia is a risk factor for adverse outcomes in the elderly, including frailty, fractures, falls, and mortality. Sarcopenic elderly patients have a higher risk of cardiovascular death, especially patients with obesity. In cancer patients, sarcopenia reduces the survival rate [4, 5]. Sarcopenia is also associated with a large health expenditure which, in the USA (in 2000), is reported to be approximately $18.5 billion ($10.8 billion for men and $7.7 billion for women) [6].

This chapter will discuss mainly about the clinical relations of sarcopenia as well as its definition, pathogenesis, risk factors, diagnosis, stage, and its management.

2. Definition and terminology of sarcopenia

Sarcopenia is a syndrome characterized by progressive, complete loss of mass, strength, and/or skeletal muscle performance that is at risk of causing physical disability, low quality of life, and death [7]. Based on the Asian Working Group for Sarcopenia (AWGS), elderly with low muscle mass coupled with low grip strength and/or low walking speed are diagnosed with sarcopenia [8]. The rationalization of the use of muscle mass and strength separately on sarcopenia criteria is because muscle strength does not depend solely on muscle mass and the relationship between strength and muscle mass is not linear. Therefore, defining sarcopenia only from muscle mass considered is to be narrow and of limited clinical value [9].

Another opinion states that there is another term for stating muscle assessment, dynapenia. Dynapenia can be defined as a syndrome of loss of muscle strength related to age but not caused by neurological or muscular disease. In determining the mechanism of dynapenia, it is different from the mechanism of sarcopenia. The incidence of sarcopenia is determined by multifactorals characterized by a decrease in muscle mass, strength, and/or performance, while dynapenia is determined by only one factor, namely muscle weakness.

Muscle weakness is one of the factors involved in the etiology of dynapenia which causes functional limitations or physical disabilities. The determination of dynapenia starts with screening individuals over 60 years of age. For groups with high risk, knee extension strength assessment should be carried out to establish the diagnosis of dynapenia, while in the low-risk group it is recommended to take grip strength assessment measurements to confirm the results of the previous screening. Nevertheless, sarcopenia is more widely studied and discussed than dynapenia [10].

3. Pathogenesis of sarcopenia

There are several mechanisms involved in the progression of sarcopenia (**Figure 1**). These mechanisms involve protein synthesis, proteolysis, neuromuscular integrity, and mobility of nutritional status. In individuals with sarcopenia, various mechanisms may be involved and their contribution varies relative to time [7]. Walston also believes that there is a multifactorial process that triggers sarcopenia. These triggers include chronic illness, fat infiltration, physical inactivity, hormonal changes, energy, protein intake, oxidative stress, and inflammatory processes. The inflammatory process is recognized as a basic mechanism that results in the stimulation of muscle protein catabolism [11].

When viewed from simpler pathogenesis, sarcopenia is divided into two factors, namely intrinsic and extrinsic factors. Intrinsic factors consist of accumulation of pro-inflammatory cytokines, oxidative stress, mitochondrial dysfunction, insulin resistance, and disorders of motor neuron endplates. While extrinsic factors consist of radiation, nutrition, drugs consumed, smoking

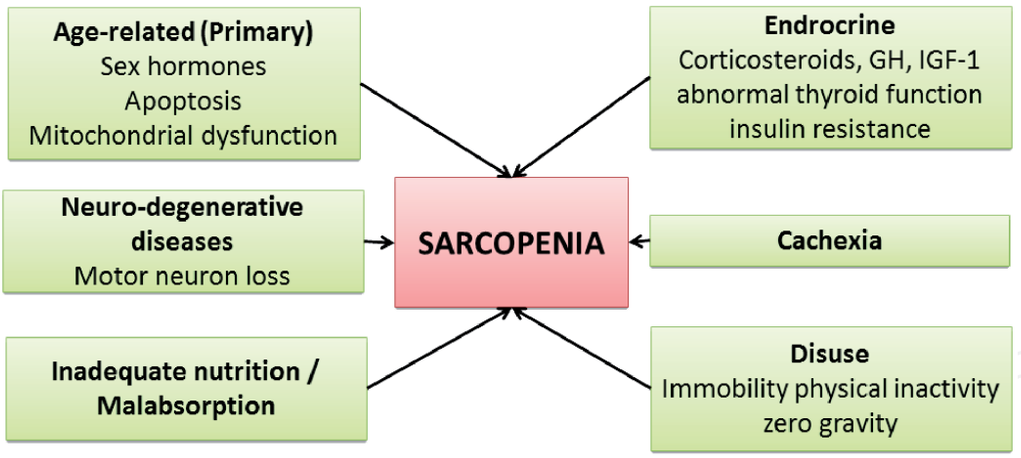

Figure 1.
Mechanisms of sarcopenia [7]. Note: Growth hormone (GH); insulin-like growth factor 1 (IGF-1).

behavior, infection, social environment, and physical activity. The interaction of intrinsic and extrinsic factors occurs in a complex, simultaneous, and dynamic manner. Every elderly person who experiences sarcopenia will have specific and individual interactions. In the end, the condition occurs as an imbalance of protein metabolism between degradation/catabolism and protein synthesis/anabolism. Sarcopenia occurs due to high protein catabolism accompanied by low protein anabolism [12]. High catabolism often results from chronic inflammation in the elderly. The elderly experience an immunosenescence condition that causes chronic inflammatory conditions of a low degree. In this condition, the body will be exposed to long-term pro-inflammatory cytokine mediators. Pro-inflammatory cytokines such as TNF-α will trigger muscle cell apoptosis in the elderly [13]. While protein metabolism decreases due to decreased protein intake and physical activity as well as decreased IGF-1 and growth hormone due to the process.

4. Risk factors for sarcopenia

Sarcopenia is a geriatric syndrome that is influenced by various factors including the following [7].

4.1 Constitutional factor

Constitutional factors are factors that are inherently closely related to humans, such as age, sex, and genetics. Age affects the occurrence of sarcopenia. The prevalence of sarcopenia increases with age, and even more than 45% of people over 80 years of age experience sarcopenia [14]. Decreased estrogen levels during menopause can cause a decrease in bone density, muscle mass, and muscle strength. In this case, the hormonal role of menopause is related to sarcopenia [15]. A study of 1971 elderly people in Kashiwa City, Chiba, Japan, showed differences in the prevalence of sarcopenia by sex, where in men it was 14.2%, while in women it was 22.1% [16]. Reverse results can be obtained elsewhere due to the differences in habits, activities, and nutritional intake. Several genes are related to lower limb muscle strength such as the growth differentiation factor 8 (GDF8) gene, cyclin-dependent kinase inhibitor 1 A (CDKN1A), and myogenic differentiation antigen 1 (MYOD1). Besides that, ciliary neurotrophic factor gene variant (CNTF A allele) is associated with loss of muscle strength [17].

4.2 Aging factor

The consequences of the aging process cause changes in the body system that is different for every human being. The aging process causes several changes in the human body system associated with sarcopenia, such as loss of neuromuscular function, changes in endocrine function, increased production of pro-inflammatory cytokines, and mitochondrial dysfunction. The aging process causes a decrease in the coordination of muscle work and a decrease in muscle strength due to a decrease in the number of alpha motor neurons and motor units. The aging process also results in atrophy of type II muscle fibers. Type II muscle fibers are found in large muscles that are important for basic activities such as getting up, going upstairs, and balance. Also, there is structural damage and decreased neuronal function at the motor center to the neuromuscular junction. Good muscle contraction requires the optimal functioning of the neuromuscular system because muscle tissue and nerve tissue are closely related to form motor neurons [18–20].

4.3 Lifestyle

The current lifestyle affects the incidence of sarcopenia in the elderly. Decreased food intake, especially protein, accompanied by less physical activity increases the risk of sarcopenia. Physical activity in the elderly experiences setbacks due to technological advancements such as elevators, escalators, vehicles, and others. Food consumption in the elderly is also changing, which tends to increase the consumption of fast food that is high in calories and fat. Optimal nutrition, especially protein, is needed to maintain muscle mass. Geriatric patients require a minimum of 1.2–2.0 g of protein/kilogram of body weight per day [21].

4.4 Changes in body condition

Prolonged bed rest increases the risk of sarcopenia. This is due to the lack of physical activity and mobility; immobility and underweight increase the risk of sarcopenia due to increased protein catabolism.

4.5 Chronic disease

Chronic diseases such as diabetes, advanced organ failure, cognitive impairment, and mood disorders cause chronic inflammation that can cause sarcopenia.

5. Diagnosis of sarcopenia

The diagnosis of sarcopenia is based on various risk factors reinforced by muscle weakness, fatigue, low endurance associated with decreased walking speed, impaired movement, and inability to perform daily tasks. The problem of diagnosis arises due to the variety of these sizes when viewed from age, race, and gender. There has not been much great research and precise accuracy to get a normal cutoff point. These sizes differ based on race and gender. Some researchers and research working groups also issued mixed figures.

Based on the European Working Group on Sarcopenia in Older People (EWGSOP), a criterion for sarcopenia is a loss of muscle mass coupled with one of the two conditions, namely loss of muscle strength and or loss of performance [7, 22]. In 2014, AWGS also issued a consensus with the same criteria with only changes in the size of the normal value. The other criteria for defining sarcopenia from the international society are listed in **Table 1**.

Study group	Definitions	Criteria		
		Muscle mass	**Muscle strength**	**Performance**
European Working Group on Sarcopenia in Older People [7]	Loss of muscle mass and strength	Low muscle mass (<2 SD below the mean of healthy young adults, aged 19–39 years)	Low handgrip strength (<2 SD below the mean of healthy young adults, aged 19–39 years)	Low gait speed (<2 SD below the mean of healthy young adults, aged 19–39 years)
Foundation for the National Institutes of Health Sarcopenia Project [23]	Loss of muscle mass and muscle weakness	Appendicular lean mass adjusted for body mass index <0.789 in men and < 0.512 in women	Handgrip strength <26 kg in men and < 16 kg in women	Gait speed ≤0.8 m/s
European Society for Clinical Nutrition and Metabolism (ESPEN) Special Interest Groups [24]	Loss of muscle mass and muscle strength	Low muscle mass (<2 SD below the mean in young adults, aged 19–39 years)	None	Reduced gait speed (<0.8 m/s in 4-min test) or reduced performance in any functional test used for comprehensive geriatric assessment
International Working Group on Sarcopenia [25]	Loss of muscle mass and function with age	Reduced muscle mass (appendicular lean mass relative to height squared ≤7.23 kg/m^2 in men and ≤ 5.67 kg/m^2 in women)	None	Gait speed <1 m/s
Society of Sarcopenia, Cachexia and Wasting Disorders [26]	Loss of muscle mass with reduced mobility	A lean appendicular mass relative to height squared (<2 SD below the mean of healthy young adults, aged 20–30 years)	None	Walking speed ≤1 m/s

Table 1.
Diagnostic criteria for sarcopenia from various international societies.

Sarcopenia measurement parameters consist of measurements of muscle mass, muscle strength, and function or physical performance (physical performance). In clinical practice, diagnosis can follow the algorithm set by AWGS in 2014, as shown in **Figure 2**. The normal threshold check requirements are clearly explained in **Table 2**. Experts often experience differences of opinion for difficulty in getting a normal value or cutoff and determining the best inspection technique to get the most accurate results.

5.1 Muscle mass

Measurement of muscle mass can be done by using computed tomography (CT), magnetic resonance imaging (MRI), and dual energy X-ray absorptiometry (DXA). The use of CT and MRI in muscle mass measurement is the measurement method that has the best accuracy because the measurement can distinguish fatty tissue from other soft tissues, but this measurement requires expensive costs [27]. Other measurements using DXA can provide results of body fat composition, bone

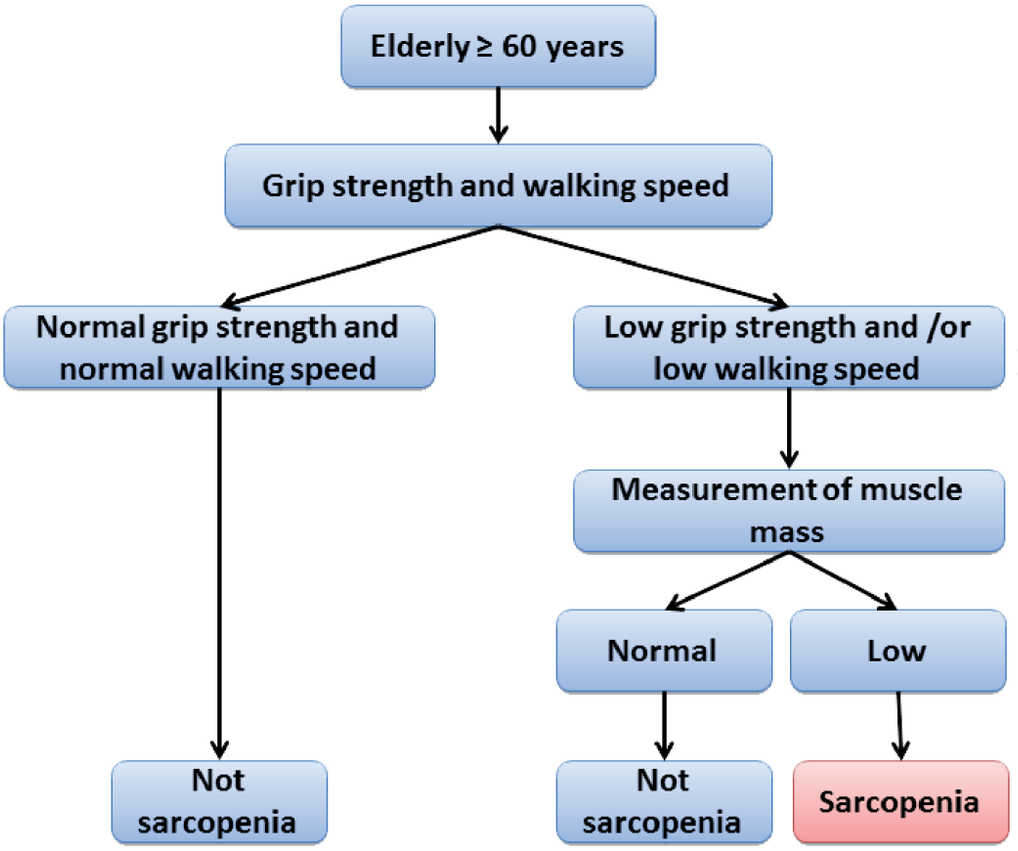

Figure 2.
Sarcopenia diagnosis algorithm based on the Asian working Group for Sarcopenia [8].

Criteria	Measuring instrument	Threshold
Muscle mass	DXA	
	• Man	<7.0 kg/m^2
	• Woman	<5.4 kg/m^2
	BIA	
	• Man	<7.0 kg/m^2
	• Woman	<5.7 kg/m^2
Muscle strength	Grip strength tests	
	• Man	<26 kg
	• Woman	<18 kg
Physical performance	Walking speed	<0.8 m/s

Table 2.
Measurement of sarcopenia according to the Asian working Group for Sarcopenia [8].

mineral, and fat-free body mass. The disadvantages of this technique are that the tools used are not portable [28]. While anthropometric measurements are very easy to do, it is not recommended to diagnose sarcopenia because it has a very high error rate. Anthropometric measurements are performed by measuring the circumference of the upper arm (LLA) or the circumference of the calf [27, 29]. Measurement of muscle mass is made using bio-impedance analysis (BIA), which is chosen for both research and clinical practice. Measurement using BIA has a good correlation value with MRI measurement in measuring body fat mass and body fat-free mass.

The most ideal muscle mass calculation for sarcopenia is based on the skeletal mass index (SMI), which is formulated by the appendicular skeletal mass (in kg) divided by height (in m^2). If there is a decrease in two deviations of muscle mass index/skeletal mass index (SMI) from the mean SMI population of young men and women, then it can be categorized as a decrease in muscle mass [7].

5.2 Muscle strength

Muscle strength can be measured in several ways, namely the grip strength test, knee extension test, and peak expiratory flow (PEF). The grip strength test is a simple examination so it is both used for clinical practice and research. Studies show this examination has a good correlation with inferior limb strength, mobility, and daily living activities (ADL). Examination of the knee extension is as good as a grip strength test, but this examination requires equipment and training in advance so it is not good for clinical practice. In peak expiratory flow (PEF) tests, it is very good for measuring respiratory muscle strength but cannot be used to measure the overall muscle strength [7]. The criterion for decreasing muscle strength according to the AWGS is less than 20 percentile of the mean population of grip strength tests [8].

5.3 Physical performance

An examination of physical performance is an examination of muscle function by performing physical activity. There are several ways of checking physical performance, such as the Short Physical Performance Battery (SPPB), walking speed, a 6-min walk test, time up and go test, and the strength of climbing stairs. Inspection with Short Physical Performance Battery (SPPB) is a standard inspection for physical performance. This check is carried out to evaluate balance, path, strength, and endurance. SPPB is done by assessing the ability to stand on both legs, in semi-tandem and tandem positions, the time needed to walk 8 ft, and the time

No	Component	Question	Answer
1	S = *Strength*	How difficult it is for the patient to lift or carry objects weighing 5 kg?	0 = No difficulties 1 = A little difficult 2 = Very difficult or cannot do without help
2	A = *Assistance walking*	How difficult is it for sufferers to walk across the room and do they need help?	0 = No difficulties 1 = A little difficult 2 = Very difficult, need help, or cannot do without help
3	R = *Rise from a chair*	How difficult it is for the sufferer to get up and move from a chair or bed?	0 = No difficulties 1 = A little difficult 2 = Very difficult, need help, or cannot do without help
4	C = *Climb stairs*	How difficult it is to the sufferer to climb 10 stairs?	0 = No difficulties 1 = A little difficult 2 = Very difficult or cannot do without help
5	F = *Falls*	How many times has the patient fallen in the past year?	0 = Not dropped in the past year 1 = Fell 1–3 times in the past year 2 = Fell 4 times in the past year

Table 3.
Strength, assistance walking, rise from a chair, climb stairs, and falls [34].

needed to get up from a seat and get back to sitting for as much as five cycles [30]. Based on AWGS recommendations, physical performance can be measured by a test of running as far as 5 m. Walking speed provides predictive value for the condition of disability and predicts the course of the disease [31, 32]. Time to get up and go test is a method of measuring physical performance in the elderly by using subjects rising from a chair, walking at a close range, returning, and sitting as before [33]. Stair climb power test is used as a method for assessing foot impairment. But the stair climb power test is only used for research [7].

Currently, there is a questionnaire for Strength, Assistance walking, Rise from a chair, Climb stairs, and Falls (SARC-F), which can be used to detect early sarcopenia quickly and it has high specifications. This is because the diagnosis of sarcopenia using the SARC-F questionnaire does not require certain other measurement tools. This criterion is subjective only by conducting careful and thorough interviews. The SARC-F questionnaire has a good specificity and sensitivity in identifying the presence of sarcopenia. The sarcopenia category is defined if the SARCF score > 4, as shown in **Table 3** [34].

6. Category and stage sarcopenia

Sarcopenia is a condition with many different causes and outcomes. In some individuals, a single cause of sarcopenia can be identified, but in other cases, clinicians can fail to identify the cause of sarcopenia. To facilitate clinical practice, sarcopenia is categorized into primary and secondary sarcopenia (**Table 4**). The etiology of sarcopenia can be multifactorial in the elderly, so there is a possibility that a person belongs to the primary, secondary, or both types of sarcopenia [7].

Sarcopenia stage is divided into three types based on the condition of muscle mass, muscle strength, and physical performance. The division of sarcopenia is seen in **Table 5**.

Primary sarcopenia • **Age-related sarcopenia**	No other cause evident except aging
Secondary sarcopenia • **Activity-related sarcopenia**	Can result from bed rest, sedentary lifestyle, deconditioning, or zero-gravity conditions
• **Disease-related sarcopenia**	Associated with advanced organ failure (heart, lung, liver, kidney, and brain), inflammatory disease, malignancy, or endocrine disease
• **Nutrition-related sarcopenia**	Results from inadequate dietary intake of energy and/or protein, as with malabsorption, gastrointestinal disorders, or use of medications that cause anorexia

Table 4.
Category of sarcopenia by cause [7].

Stage	Muscle mass	Muscle strength	Performance
Presarcopenia	Decreased		
Sarcopenia	Decreased	Decreased or normal	Decreased or normal
Severe sarcopenia	Decreased	Decreased	Decreased

Table 5.
Stage of sarcopenia [7].

7. Management of sarcopenia

Sarcopenia is a condition caused by a variety of complex factors. Therefore, a Geriatric Patient Full Assessment (P3G) for the management of sarcopenia should be carried out interdisciplinary with a focused and comprehensive intervention. P3G aims to improve physical and psychological patients, optimize drug administration to reduce the incidence of hospitalization and the risk of mortality, and increase patient satisfaction. P3G is carried out with an interdisciplinary team consisting of geriatric doctors, nurses, social workers, pharmacists, and physiotherapists who make plans for integrated care [17].

Diet control and physical training such as resistance training and stretching have a positive impact on sarcopenia associated with chronic diseases such as diabetes mellitus, hypertension, and coronary heart disease. Besides, psychological supportive therapy is needed for the management of sarcopenia because psychological factors of patients with sarcopenia are important in both prevention and recovery. Here are some recommendations for the management of sarcopenia [35]:

a. Multimodal therapy can be carried out with balanced energy and protein supplementation for the prevention and recovery of sarcopenia. The recommended total protein intake is 1–1.5 g/kg/day.

b. The recommended protein consumption is of good quality such as the amino acid leucine.

c. Creatine supplementation to enhance the physical exercise effects of sarcopenia patients.

d. Vitamin D supplementation with doses above 100 nmol/L. A dose of vitamin D is given up to 50,000 IU per week.

e. Resistance and aerobic exercise are done for 20–30 min, 3 times a week.

A protein diet is an important key needed to prevent a progressive reduction in muscle mass. Its mechanism of action is by preventing a negative nitrogen balance. The recommended diet for healthy people is 0.8 g/kg/day (RDA = recommended diet allowance). In the elderly >70 years, 40% of the protein diet is less than the RDA. In elderly patients with sarcopenia, the minimum recommended diet is according to the RDA (0.8) and will be increased to 1–1.5 g/kg/day by the increase in physical activity and comorbidities. Adequate protein intake in the elderly over 70 years has a positive effect on the ability to maintain muscle reserves and prevent sarcopenia. The positive effect is because the protein diet stimulates insulin-like growth factor 1 (IGF-1). Increased levels of IGF-1 as a result of this diet have an impact on preventing decreased protein synthesis and decreased muscle mass [36].

The use of creatine as a treatment for sarcopenia is still controversial because several studies have different results. In one study, the results showed that the elderly who took creatine supplements followed by endurance training experienced an increased muscle mass and strength. However, other studies show conflicting results, where creatine supplementation does not affect the muscle mass and strength [37].

Vitamin D levels can affect the incidence of sarcopenia. Some data show that inadequate levels of vitamin D can reduce muscle function and are associated with

sarcopenia. Low levels of 25 (OH) D are associated with lower muscle mass, lower functional test results and can be used to predict muscle mass loss which will be one of the causes of disability. Lack of vitamin D is associated with poorer muscle function and loss of muscle mass [17].

Important physical activity becomes a pillar of conventional management that is very profitable. Large observational studies such as the British Regional Heart Study (BRHS), the Third National Health and Nutrition Examination Survey (NHANES III), and the Cardiovascular Health Study (CHS) show an inverse relationship between CRP concentration and physical activity in the elderly. The Health Aging and Body Composition (Health ABC) Study also found a linear tendency to decrease TNF with increased physical activity [9]. Therefore, physical activity is very necessary for the management of sarcopenia. The management of sarcopenia through physical activity must be designed with specific guidelines so that it gradually burdens muscles and makes positive adaptations. This should also be noted in physiology related to age and aging to avoid injury. Physical exercise in sarcopenia patients is focused on dynamic movements that target the major or major muscle groups such as knee and hip extensors through intrinsic and eccentric movements. The period of heating and cooling in the elderly is sought to last 15–20 min when heating and 10–15 min when cooling [38].

Management of other sarcopenia is still under studies, such as the therapeutic approach of using testosterone, estrogen, dehydroepiandrosterone (DHEA), and angiotensin-converting enzyme inhibitors (ACE inhibitors) [17].

8. Conclusions

Sarcopenia is more prevalent in older patients, especially men, and is defined by decreased muscle mass with decreased muscle strength and/or performance. Sarcopenia can cause multiple morbidities in the elderly, including frailty, fractures, falls, and even death. There are multifactorial factors (divided into intrinsic and extrinsic factors) that trigger sarcopenia, but the inflammatory process is recognized as a basic mechanism. Constitutional factors, aging, lifestyle, changes in body condition, and chronic diseases are considered as risk factors for sarcopenia in the elderly. Diagnostic criteria for sarcopenia are still under controversy since there is a variety of the component because it differs based on race and gender. Criteria from EWGSOP and AWGS are the most widely used. Currently, SARC-F questionnaires can detect early sarcopenia and have high specifications. In clinical practice, sarcopenia is categorized into primary and secondary sarcopenia and is divided into three stadiums, which are pre-sarcopenia, sarcopenia, and severe sarcopenia. Management of sarcopenia should be interdisciplinary with a focused and comprehensive intervention. Nutrition and physical training are the most important therapies for sarcopenia in the elderly.

Conflict of interest

The authors declare no conflict of interest.

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