

Influence of sarcopenia focused on critically ill patients

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A systemic review was performed to evaluate the epidemiological, pathophysiological, and clinical features of sarcopenia, the relationship of sarcopenia with critical illness and its impact on mortality, and diagnostic methods and treatment modalities. Generally, in the presence of critical illness, sarcopenia is not included in the treatment approach strategies. An intensivist should be aware that sarcopenia may be present in critically ill patients. Although the main modalities against sarcopenia are early mobilization and nutritional support, they can only prevent its development and may have positive effects on prognosis rather than treating the existing sarcopenia.

Key Words: critical illness; intensive care unit; mortality; sarcopenia

INTRODUCTION

Although sarcopenia was first described by Irwin Rosenberg in 1989 as an age-related decrease in muscle mass (“sarx” or flesh and “penia” or loss) [1], the first definition suitable for clinical use was created by Baumgartner et al. [2] in 1998 as loss of appendicular skeletal muscle mass (ASMM). ASMM is the sum of skeletal muscle mass in the four extremities by two standard deviations or more in healthy young individuals. However, neither Rosenberg [1] nor Baumgartner et al. [2] mentioned muscle strength in these definitions. Finally, the European Working Group on Sarcopenia in Older People (EWGSOP) described sarcopenia in 2010 as undesired loss of skeletal muscle mass and strength and a decrease in physical performance, resulting in increased vulnerability and mortality especially in the elderly [3]. In the pathophysiology-based definition, sarcopenia can be considered a type of organ failure (muscle insufficiency) that can develop mostly chronically (with aging) or infrequently acutely (i.e., during hospitalization or long-term bed rest) [3,4]. In this review, the epidemiological, pathophysiological, and clinical features of sarcopenia are discussed along with the influence of sarcopenia on critically ill patients and their mortality as well as current diagnostic methods and treatment modalities.

EPIDEMIOLOGY OF SARCOPENIA

ASMM and strength reduction begins in the 4th decade of life. The frequency of sarcopenia in the normal population has been reported by EWGSOP to be 5%–13% between the ages of 60–70 years and 11%–50% above the age of 80 years [3]. With increasing frequency, it is expected to affect approximately 1.2 million people by 2025 and 2 million people by 2050 [5]. Its

Review Article

Received: September 16, 2020

Revised: November 25, 2020

Accepted: November 25, 2020

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prevalence is twice as high in men than in women especially in sedentary individuals [6].

With the increase in the aging population, the number of patients hospitalized in the intensive care unit (ICU) has been increasing every year. These patients may be admitted to the ICU for chronic diseases such as heart failure, renal failure, or cancer or for acute conditions such as sepsis, fall injuries, trauma, and postoperative care. There may be decreases in physiological reserves and muscle mass and strength, as well as nutritional deterioration. As there is no practical method that can be performed bedside, it is difficult to evaluate the incidence of sarcopenia in patients in the ICU. In a study using computed tomography (CT) in the ICU, the frequency of sarcopenia was 15%–50% in cancer patients, 30%–45% in patients with liver failure, and 60%–70% in critically ill patients [7].

PATHOPHYSIOLOGY OF SARCOPENIA

Reduction in innervation and capillary density of skeletal muscle and selective atrophy of type II muscle fibers are possible mechanisms of sarcopenia. In various studies, it has been reported that a relationship exists between sarcopenia and age-related changes in quality, mass, and strength of muscles, as well as metabolic, physiological, and functional disorders that lead to increased morbidity and disability in the elderly [8]. Sarcopenia is thought to be associated with changes in testosterone, estrogen, growth hormone, and angiotensin II levels. Insulin resistance or low insulin level is a common characteristic of diseases that cause extreme muscle wasting. This can promote muscle atrophy due to diminished response to insulin and insulin-like growth factor 1, which enhances muscle protein synthesis and inhibits proteolysis. In addition, in the presence of proinflammatory cytokines (such as tumor necrosis factor α and interleukin-6), muscle breakdown is triggered and causes sarcopenia in the elderly [9].

CLINICAL CHARACTERISTICS OF SARCOPENIA IN THE CRITICALLY ILL PATIENT

Staging sarcopenia is important in terms of planning the treatment as well as in determining the severity of the disease and predicting its course. There are three stages of sarcopenia. In the “presarcopenia” stage, there is a reduction in muscle mass without change in muscle strength or physical performance. In the “sarcopenia” stage, there is a decrease in muscle strength or physical performance in addition to a decrease in muscle

KEY MESSAGES

- An intensivist should be aware that sarcopenia can be present in critically ill patients.
- Early mobilization and nutritional support can prevent its development and can have positive effects on prognosis rather than treating existing sarcopenia.

mass. In the presence of “severe sarcopenia,” muscle mass, muscle strength, and physical performance are decreased [3]. Knowing the stages of sarcopenia can help determine treatment modalities and recovery goals [10].

Sarcopenia as classified by EWGSOP is either primary or secondary. Primary sarcopenia is only associated with advancing age, with no other reason. Secondary sarcopenia is related to other causes like non-use of muscles, inflammatory disease, malnutrition, and malignancy as well as chronic diseases like cardiac, pulmonary, or renal diseases. In many elderly people, the etiology of sarcopenia is multifactorial, and its classification as primary or secondary might not be possible [3]. EWGSOP classified sarcopenia as acute or chronic in its 2019 version. Acute sarcopenia develops rapidly in the last 6 months of hospitalized elderly patients and is usually associated with an acute illness or injury. Chronic sarcopenia, which takes more than 6 months to develop, is associated with chronic and progressive conditions [11].

Patients are admitted to the ICU with various diagnoses. Patients with sarcopenia are particularly vulnerable in the presence of major physiologic stressors including trauma, major surgery, and critical illness. Due to advanced age and presence of chronic comorbidities, some patients may already have sarcopenia when admitted to ICU [12]. In the presence of primary or secondary sarcopenia, the response to sepsis may be impaired, and mortality has been shown to be higher in patients with sepsis [13]. Patients requiring surgery are often admitted to the ICU. In addition to comorbidities, stress factors related to major surgical intervention negatively affect the short- and long-term prognoses in sarcopenic patients. All these are factors that can prolong ICU and hospital stays [14–17]. Likewise, major postoperative complications and the consequent length and cost of hospital stay are five times higher in major surgeries in sarcopenic patients [12].

In the ICU, patients should be stabilized quickly, and mechanical ventilation should be ended as soon as possible. Although intensive care departments have very successful weaning protocols, weaning difficulties are 10%–30% higher compared to those in the ward [17]. The pathophysiology of

weaning failure is often multifactorial, including comorbidities with dysfunction of the lung, heart, and diaphragm/respiratory muscles. Thus, weaning failure is expected to be high in sarcopenic patients since sarcopenia impairs the function of the diaphragm/respiratory muscles [18]. Once connected to a ventilator, sarcopenic patients show higher mortality than non-sarcopenic patients [19-22]. Recently, reports are increasing on high mortality in patients with low skeletal muscle mass when they arrive at the ICU [21,22].

DIAGNOSIS

EWGSOP reported that decrease in muscle mass and function must be exhibited for diagnosis of sarcopenia. Muscle function can be measured through several physical performance tests and use of specific devices. Difficulties in cooperation and mobilization of these tools can make it difficult to diagnose sarcopenia in the ICU. EWGSOP reported that reduction in muscle mass can be detected through the total or appendicular skeletal muscle mass index (SMMI) [23].

Baumgartner et al. [2] suggested using dual-energy X-ray absorptiometry to measure muscle mass and using the ratio of muscle mass to patient height squared (kg/m^2) to measure lean body mass, amount of adipose tissue, and bone mineral density separately and noninvasively. However, the main disadvantages of this method involve the effect of hydration state of the patient and its two-dimensional properties [24]. Lean body mass can be measured through the bioelectrical impedance method. Due to its noninvasive features, this method is easy to apply. However, it cannot measure muscle mass directly and instead measures the electrical transmission of the entire body based on muscle mass. This method is affected by the body's fluid balance, standardization of which can be difficult in the ICU [25].

CT and magnetic resonance imaging (MRI) methods are considered the gold standards for evaluation of muscle mass [25]. However, there are limitations due to high cost and difficulty in application especially in the presence of critical illness. With these methods, lean muscle mass, adipose tissue, and even fat infiltrations in the muscle can be evaluated. Both CT and MRI use cross-sectional measurement of body compositions. The user performs the measurements after marking fat or muscle components in the software [25,26]. In this technique, the subcutaneous fat/muscle ratio and visceral/subcutaneous fat tissue ratio are used. Cross-sectional analysis with CT at the L3 vertebral level correlate with all body tissue measurements. In this method, the total cross-sectional area in-

cluding adipose tissue, psoas, paraspinal muscles (erector spinae, quadratus lumborum), and abdominal wall muscles (transversus abdominis, external and internal oblique, rectus abdominis) is evaluated [27]. Due to the difference in body composition in men and women in abdominal CT, the sex-specific SMMI threshold value is $52.4 \text{ cm}^2/\text{m}^2$ in men and $38.5 \text{ cm}^2/\text{m}^2$ in women [28].

When performing bedside evaluation in critical patients, assessment of skeletal muscle by ultrasound (USG) can be useful [26]. However, it has yet to be included in the diagnostic algorithm due to uncertainties such as type of USG probe (linear or convex), anatomical region to be measured (abdomen, lower, or upper extremity), and patient position during examination (supine, prone, or standing). Additionally, it has difficulties such as maintaining immobility of the patient, standardizing the pressure to be applied with the probe, and determining how the probe will be inclined [29].

PROGNOSIS

The ICU population is very heterogeneous; a large proportion of patients is of advanced age and suffering from chronic comorbidities such as cancer and cardiovascular or renal failure. These comorbidities and presence of sarcopenia are an effective predictor of weaning difficulty, prolonged hospital and ICU stay, and increased mortality and morbidity [30]. The presence of sarcopenia during hospitalization in the ICU contributes to sepsis, resistant infections, neuropathy, and ventilator-associated pneumonia. It is important to reveal the cause of sarcopenia in terms of treatment planning. It remains unknown whether the close relationship between sarcopenia and increased mortality arises from the sarcopenia itself or the muscle destruction resulting from concomitant disease [31,32]. In the current pandemic, acute sarcopenia can coexist with coronavirus disease 2019 (COVID-19) and might have a negative effect on duration of mechanical ventilation and prognosis [33].

DIFFERENTIAL DIAGNOSIS

It is especially important to distinguish sarcopenia from cachexia, a metabolic syndrome characterized by loss of muscle mass with or without loss of fat mass due to underlying disease. Similar mechanisms, such as mitochondrial dysfunction, insulin resistance, changes in protein metabolism, and the presence of inflammation play a role in both sarcopenia and cachexia. Cachexia differs from sarcopenia primarily

through loss of body weight [34]. In sarcopenia, loss of muscle mass can be accompanied by morphologic traits such as normal weight, overweight, or even obesity and fat infiltration [6]. Cachexia is a multi-organ syndrome with underlying diseases such as cancer, chronic infection, chronic obstructive pulmonary disease, and chronic heart failure. It is characterized by a decrease in body weight, destruction of muscle and adipose tissue, and often anorexia. Most cachectic patients can be sarcopenic, but not all sarcopenic patients are cachectic [35]. This shows that the physical appearance of the patient can be misleading when predicting sarcopenia.

Frailty and sarcopenia are clinical syndromes that can occur with general weakness due to aging. Frailty can be defined as a reduction in the ability to react physically and psychosocially to stress. The importance of early diagnosis of frailty in the elderly is increasing. Early diagnosis is important to protect patients from negative consequences such as falling, hospitalization, and death. Most frail older people may be sarcopenic, and some older people with sarcopenia also are frail [35].

TREATMENT

Awareness of sarcopenia has recently increased. Since it is related to age, preventive efforts should be performed for the target community. Insufficient energy intake, limitation of physical activity due to prolonged bed rest, and accompanying depression are additional risk factors for sarcopenia and functional decline in hospitalized individuals. In coexistence of sarcopenia with critical illness, there is currently no systematic treatment protocol. However, the following measures and practices have been found to be useful in reducing the severity of disease.

Exercise

By stimulating protein synthesis in muscles with exercise, muscle mass formation increases and allows faster adaptation to the effort. Early mobilization in the ICU prevents destruction of muscles and increases quality of life by creating a positive effect on the mood of the patient in the recovery process [36]. The number of skeletal muscle fibers can be increased with resistive exercises like weight lifting and stretching [37]. Sarcopenia is a reversible condition when diagnosed early. For patients hospitalized in the ICU, exercise and mobilization as early as possible are critical. In cases of inability to exercise, passive exercise can be used. Although there is not enough knowledge on their long-term effects, nutrition and

exercise have a strong additive or synergistic effect with different methods of action in sarcopenic patients [38].

Nutritional Support

Since nutrition has an important role in the pathophysiology of sarcopenia, it is important in prevention and treatment of sarcopenia. In middle age, cellular and molecular changes reduce the response to nutrition and physical activity, resulting in greater muscle breakdown [38]. Consumption of food decreases by 25% among older people, and the quality of the food eaten is impaired. Malnutrition plays a role in the pathogenesis of sarcopenia and leads to a decrease in muscle function in many elderly individuals, especially individuals with low body weight [39,40]. Malnutrition and significant skeletal muscle mass loss arise from the low amount of protein intake with aging and increased catabolism due to accompanying chronic diseases. The presence of more than one disease accompanying aging and the use of multiple medications can disrupt nutrition significantly. At the same time, with aging, the response to anabolic stimulation decreases and protein requirement increases compared to those of younger people. Fifty percent or more of the elderly patients admitted to the ICU are malnourished [41].

Nutritional status should be measured with indirect calorimetry in the ICU. In long-term starvation, fat and muscle experience breakdown. Aggressive nutrition protocols can be applied in ICU patients. Dietary proteins provide the amino acids needed for synthesis of muscle proteins and function as an anabolic stimulant. If kidney functions are not impaired, it is recommended that protein be given in high doses in the elderly in the ICU [41,42]. Proteins, essential amino acids (EAA), β -hydroxy β -methyl butyrate (HMB), vitamin D, calcium, antioxidants, and omega-3 fatty acids are important for skeletal muscle health [43].

Protein provides amino acids required for muscle synthesis. Protein malnutrition impairs immune system function. In addition, it also causes the increased risk of infection, delay in wound healing, increased risk of pressure ulcer formation, and prolonged hospitalization with increased morbidity and mortality [44]. Leucine is an EAA that plays an important role in muscle mass and function by increasing the use of amino acids and proteins in the muscles. There is evidence that leucine can activate signaling pathways that lead to protein synthesis [45]. When EAA and HMB are given together, they improve muscle mass and function more than protein given alone. There are studies reporting that it is more effective to apply nutritional support with exercise [38]. HMB is a leucine

metabolite that helps to increase muscle tension and mass and is increasingly used as a nutritional supplement in sarcopenic patients [43]. HMB increases protein synthesis while preventing its breakdown, with increased effect when combined with exercise. When nutritional support is initiated in the ICU, the enteral route is the preferred option. However, in cases where enteral nutrition does not reach the target dose, it is combined with total parenteral nutrition. In critical illness, macro- and micronutrients must be added during feeding. Calorie and protein intake should be 25–35 kcal/kg/day and 1.2–1.5 g/kg/day, respectively, in elderly and critically ill patients hospitalized in the ICU [46–48]. Protein support, especially that enriched with leucine, stimulates protein synthesis in muscle. The greater is the amount of leucine used, the stronger is the protein synthesis enhancing effect. However, with aging, sensitivity to leucine decreases. Whey is the preferred protein in the diet because it is easy to digest and is rich in leucine. The use of EAA enriched with leucine is particularly useful in patients on mechanical ventilators [39].

In recent years, it has been emphasized that vitamin D deficiency is responsible for the pathophysiology of many diseases. It is a common health problem especially among older people. In addition to other benefits, vitamin D regulates the function and physiology of skeletal muscles. It can stimulate the proliferation and differentiation of skeletal muscle fibers, maintaining and improving muscle strength and physical performance [46–48]. Vitamin D supplements are beneficial for increasing muscle tension. Reduced protein intake and low vitamin D level have been found to correlate with diminished muscle strength. With aging, serum vitamin D level decreases due to reduced dietary intake, decreased synthesis due to less sunlight exposure, and reduced conversion to 1-25-hydroxy vitamin D in the kidneys. Serum vitamin D level should be kept at 40 ng/mL using at least 800 IU/day [48]. When vitamin D was administered with leucine and protein complex, improvement in muscle parameters was shown in elderly sarcopenic patients [39]. Omega-3 fatty acids can prevent age-related loss of muscle mass and improve physical performance by mediating cell signaling function and inflammation-related oxidative damage. Therefore, its use is recommended in elderly critical patients in the ICU [49,50].

Muscle Electrical Stimulation

It is important to begin physical activity early in the ICU to preserve muscle mass. Neuromuscular electrical stimulation is recommended as an alternative therapy in the early period when conventional physiotherapy and mobilization cannot

be performed. If possible, it should be applied together with exercise [51].

CONCLUSION

An intensivist should be aware that sarcopenia can be present in the critically ill patient. The patient can be admitted to the ICU with sarcopenia or can develop it acutely in the ICU. Although the main modalities against sarcopenia are early mobilization and nutritional support, these only prevent its development and may have positive effects on prognosis rather than treating the existing sarcopenia.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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