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REVIEW ARTICLE

Sarcopenia in critically ill patients

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Abstract Sarcopenia occurring as a primary consequence of aging and secondary due to certain medical problems including chronic disease, malnutrition and inactivity is a progressive generalized loss of skeletal muscle mass, strength and function. The prevalence of sarcopenia increases with aging (approximately 5–13 % in the sixth and seventh decades). However, data showing the prevalence and clinical outcomes of sarcopenia in intensive care units (ICUs) are limited. A similar condition to sarcopenia in the ICU, called ICU-acquired weakness (ICU-AW), has been reported more frequently. Here, we aim to examine the importance of sarcopenia, especially ICU-AW, in ICU patients via related articles in Medline.

Keywords Sarcopenia · Intensive care unit-acquired weakness · Intensive care unit · Critical illness

Introduction

Sarcopenia is a progressive generalized loss of skeletal muscle mass, strength and function occurring as a primary consequence of aging and secondary due to certain causes including diseases, malnutrition and inactivity [1, 2]. Sarcopenia may cause impairment of functional status, and eventually lead to a loss of independence. Prevalence of sarcopenia increases with aging and is approximately 5–13 % in the sixth and seventh decades [1]. Its prevalence may be as high as 50 % for people aged >80 years [3].

Major associated factors causing development of sarcopenia may be summarized as interactions of environmental and hormonal factors, underlying diseases, activation of inflammatory pathways, mitochondrial dysfunction, reduced satellite cell numbers, and loss of neuromuscular junctions [4].

Sarcopenia can be classified as primary (age-related) or secondary sarcopenia (inactivity, malnutrition and disease-related sarcopenia such as intensive care unit-acquired weakness [ICU-AW]) [5]. Although it is seen in elderly people, it may be also be present in different clinical settings including critical illnesses. In particular, patients in ICUs encounter an increased risk of muscle weakness, loss of function and sarcopenia. Skeletal muscle weakness is prevalent in ICU patients who are immobilized or need critical care.

However, data showing the prevalence and clinical outcomes of sarcopenia in ICUs is limited. Here, we aim to examine the importance of sarcopenia in ICU patients via related articles in Medline.

Definition and prevalence of sarcopenia in ICU

Sarcopenia is a term reflecting of the loss of muscle mass and strength or function [5]. Although this term is used especially in geriatric patients, it has not previously been well described in ICU patients. A similar condition to sarcopenia, especially secondary sarcopenia, has been reported in ICU patients, called ICU-acquired weakness (ICU-AW) [6–9]. However, knowledge about primary sarcopenia or age-related sarcopenia, in ICU patients is limited due to the lack of the studies in this area.

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Table 1 Risk factors for ICU-AW

Age
Female gender
Protein and energy malnutrition
Severity and duration of systemic inflammatory response
Length of ICU stay
Severity of underlying disease and multiorgan failure
Duration of mechanical ventilation
Immobilization–inactivity
Hyperglycemia
Hypoalbuminemia
Parenteral nutrition
Corticosteroid usage
Neuromuscular-blocking agents usage

ICU-AW (defined as bilateral symmetrical limb weakness) is a result of axonal polyneuropathy (critical illness polyneuropathy), myopathy (critical illness myopathy) or frequently a combination of both (critical illness neuromyopathy) [10, 11]. ICU-AW primarily affects the lower limbs and may extend to tetraplegia in more severe cases [12]. It is associated with respiratory muscle weakness, delaying of weaning from mechanical ventilation, prolonged ICU and hospital stay and mortality [13]. Studies have reported a prevalence rate for ICU-AW ranging from 25−100 %, depending on the different defining criteria [10, 14]. ICU-AW may be included as one of the causes of secondary sarcopenia.

Studies showing short-term outcomes of sarcopenia in ICUs

A prospective cohort study of 64 critically ill septic patients demonstrated that polyneuropathy associated with critical illness developed in 34 patients and length of mechanical ventilation (median 34 vs. 14 days, $p < 0.001$), duration of weaning period (median 15 vs 2 days, $p < 0.001$), length of stay in ICU (median 46.5 vs 22.5 days, $p < 0.001$) and hospital stay (median 85 vs 33 days, $p < 0.001$) were significantly higher in patients with polyneuropathy [15]. This study also found that critical illness polyneuropathy was the only risk factor independently associated with weaning failure (OR 15.4, 95 % CI 4.55–52.3, $p < 0.001$) in multivariate analysis [15].

Another study investigating the relationship between ICU-acquired paresis (ICU-AP), hospital stay and mortality in a prospective multicenter cohort study showed that patients with ICU-AP had longer ICU stay (median 19 vs. 10 days, $p < 0.001$), longer hospital stay (median 28 vs 16 days, $p < 0.001$) and required longer mechanical ventilation (median 12 vs 6 days, $p < 0.001$) [16]. On the other hand, handgrip strength was lower and hospital mortality was higher (31.4 vs 6.0 %, $p < 0.001$) in subjects with ICU-AP [16]. It was also emphasized that ICU-AP was independently associated with hospital mortality (OR 7.8, 95 % CI 2.4–25.3, $p = 0.001$) and handgrip strength was independently associated with hospital mortality (OR 4.5, 95 % CI 1.5–13.6, $p = 0.007$) [16].

Studies showing long-term outcomes of sarcopenia in ICUs

In a study evaluating 109 survivors of acute respiratory distress syndrome at 3, 6, and 12 months after discharge from the ICU, it was demonstrated that survivors had persistent functional disability at one year after discharge [17]. Another prospective, observational cohort study of 817 patients investigating factors related to mortality rate and quality of life at one year after prolonged mechanical ventilation showed that 57 % of survivors required caregiver assistance after a 1-year follow-up period [18].

Risk factors for ICU-AW

Major risk factors for ICU-AW are thought to be related to severity and duration of systemic inflammatory response, length of ICU stay, duration of mechanical ventilation and immobilization. On the other hand, age, female gender, hyperglycemia, hypoalbuminemia, parenteral nutrition, corticosteroid administration and neuromuscular-blocking agents are considered as possible risk factors for ICU-AW (Table 1) [12, 19, 20]. Moreover, some of these risk factors such as length of ICU stay and duration of mechanical ventilation may be consequences of ICU-AW. Therefore, it appears that there is a vicious cycle between certain risk factors and ICU-AW.

Muscle loss related to inactivity caused by critical illness in ICUs may cause a decline in functional status. Almost all patients in ICUs are at risk of skeletal muscle wasting because of prolonged bed rest. As the prevalence of primary age-related sarcopenia increases with aging, it may also be thought that elderly patients with primary sarcopenia are more at risk for development of ICU-AW than patients without primary sarcopenia. Muscles are exposed to lower mechanical loads and sustain loads for less time. This cumulative decrement in force and power output causes changes in skeletal muscle morphology, muscle catabolism, aerobic capacity and the electromechanical relationship of the nerve−muscle interface, and depresses contractile function. Bed rest may be a natural consequence of illnesses and after 4 h of bed rest, muscles deteriorate,

sarcomeres reduce, muscle fibers and total muscle length shorten, and contractile force decreases [21]. Approximately 10 % of total body muscle mass may be lost in hospitalized elderly patients during 3 days of immobility, and there may be >10 % reduction in postural muscle strength after one week of complete bed rest in healthy individuals [21, 22]. Deconditioning can lead to disuse syndromes, including cardiovascular vulnerability, musculoskeletal fragility, depression and premature aging; contractures of muscles can begin to form after 8 h of immobility in patients with disuse syndromes [21, 23].

Assessment methods for sarcopenia

Both muscle mass and muscle function should be assessed for diagnosis of sarcopenia [5]. However, there is no gold standard assessment method in ICU patients. The most commonly used diagnostic criteria for sarcopenia were defined by Cruz-Jentoft et al. [5] According to these criteria, patients having decreased muscle mass should also have at least one of the following—(1) loss of muscle strength and/or (2) impaired muscle performance. Generally, muscle mass is assessed by using the following methods—bioelectrical impedance analysis, dual X-ray absorptiometry, computed tomography, and ultrasonography or anthropometric measurements. Muscle strength is usually assessed by handgrip strength and muscle performance is assessed by gait-speed tests.

Some volitional tests for determining muscle strength, for example handgrip strength test, are easier to perform. Values of <11 kg force for men and <7 kg force for women have been reported to identify ICU-AW in previously healthy individuals but these are not suitable for ICU patients because of immobilization, life-threatening illnesses and cooperation and consciousness problems from sedative medications [24]. Some non-volitional neurophysiologic and muscle strength assessment tests using electrical and magnetic stimulation techniques of peripheral nerves are available [25]; however, these tests are primarily research tools, and widespread use can be difficult in ICUs, as well as the need for experienced staff and expensive equipment. Muscle mass should also be assessed for diagnosis of sarcopenia; however, as there is no gold standard examination, cross-sectional muscle area and fat-free mass measurements seem to be valid, suitable and commonly used methods [26]. Ultrasonographic measurements of the rectus femoris muscle is sensitive and can demonstrate changes in muscle thickness during ICU stay [27, 28]. Seymour et al. demonstrated that the rectus femoris muscle cross-sectional area in patients with chronic obstructive pulmonary disease (COPD) measured by ultrasound is lower than healthy individuals and is linearly related with maximum voluntary contraction strength of quadriceps [27]. Another recent study by Cartwright et al. investigated ICU-AW in 16 patients with acute respiratory failure (ARF) using serial muscle ultrasound for thickness and gray-scale assessment of the tibialis anterior, rectus femoris, abductor digiti minimi, biceps, and diaphragm muscles over 14 days. They found that tibialis anterior and rectus femoris muscles had significant decreases in gray-scale standard deviation but no muscles showed significant changes in thickness. Consequently, they suggested that this technique should be examined further for diagnosing and tracking those with ICU-AW [29]. Bioelectrical impedance analysis (BIA) is not suitable in patients with electrolyte abnormalities and hypervolemia in ICUs. Some studies suggested that BIA is a good method for evaluating and monitoring nutritional status in ICU patients and BIA-derived active cell mass is a good indication of malnutrition and poor outcome in COPD patients with ARF; however, there is insufficient data for the evaluation of muscle mass by BIA in ICU patients [30–32]. Thus, diagnosing sarcopenia in ICU patients is still under debate.

Mechanisms of sarcopenia in critically ill patients

In critically ill patients, muscle weakness is related to immobility and systemic inflammation. Muscle atrophy is most commonly associated with decreased protein synthesis and increased protein degradation. All steps of protein synthesis (transcriptional, translational, and post-translational) are affected by immobilization, but the most commonly affected step is the translational step. Mammalian target of rapamycin (mTOR) and insulin-like growth factor-1 (IGF-1) are two intracellular regulator proteins which play an important role in translational control mechanisms [12]. mTOR interacts with extracellular stimuli including nutrients and growth factors, such as IGF-1 and modulates skeletal muscle growth through activation of translational factors of protein synthesis [12]. Recent studies demonstrated that immobilization transiently reduces IGF-1 mRNA levels and adenosine monophosphate-activated protein kinase activity in mouse and rats and causes severe muscle atrophy [33]. Catabolism of proteins increases in critically ill patients causing increased amino acid uptake by rapidly turning over central proteins, which is constrained by the maximum rate of amino acid release from muscle, and acute central protein deficiency occurs. In this state, sufficient amino acid or protein provision can improve clinical outcome by increasing central protein synthesis, regulating the inflammatory response and alleviating the muscle protein loss in the short term and minimizing the muscle atrophy of critical illness in the long term [34, 35].

Prolonged immobilization also stimulates degradation of muscle protein by using different proteolytic pathways such as (1) the nuclear factor-kappaB (NF-κB) pathway, (2)

the ubiquitin–proteasome pathway, (3) calcium-dependent calpains, (4) the caspase-3 system, and (5) lysosomal proteases [36].

Activation of NF-κB by infections, pro-inflammatory cytokines, oxidative stress and mitogens causes muscle atrophy [37]. The ubiquitin–proteasome pathway, a member of the family of protein-dissolving enzymes, may be activated after sarcomere damage and is particularly related with rapid muscle atrophy [38]. Additionally, calpains play a role in the activation of the NF-κB pathway and as sarcolemma is damaged, calpain-induced NF-κB activates and results in cell death [39, 40]. The caspase-3 system has certain functions in the early stage of protein degradation and this system is activated by reactive oxygen radicals [41]. In critically ill patients, the lysosomal pathway is activated and regulated by the ubiquitin and calpain pathways [20]. It has been shown in mice models that lysosomal activity increases following muscle denervation [42]. Complex mechanisms and interactions also play an important role by using these five pathways in muscle protein breakdown.

Management of sarcopenia

Increasing protein intake

Evidence for the protein requirements of critically ill patients is still limited, but some studies suggest that at least 1.2 g/kg protein should be given to ICU patients [43]. We also know that inadequate energy intake in ICU patients is associated with complications, such as acute respiratory distress syndrome, infections, renal failure, pressure sores and mortality.

In a prospective observational cohort study, it was demonstrated that successfully reaching a predefined energy target and protein target (at least 1.2 g/kg of preadmission body weight) was associated with a decrease in 28-day mortality by as much as 50 % [44]; however, reaching only the energy targets does not appear to be sufficient in this study [44]. Another prospective observational cohort study of 113 ICU patients aimed to investigate the relationship between mortality and energy and protein requirements. In these severely ill ICU patients, a higher provision of protein and amino acids was associated with a lower mortality (0.79 ± 0.29, 1.06 ± 0.23 and 1.46 ± 0.29 g protein/kg per day correlated with a 10-day survival of 50, 78 and 87 %, respectively) [45].

Additionally, some guidelines (Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition) recommend 2.0 g protein/kg ideal body weight as the minimum amount to provide to severely burned and multi-trauma patients and a minimum of 2.5 g/kg ideal body weight for critically ill morbidly obese patients [46]. The American Burn Association guideline recommends 1.5–3.0 g/kg protein for severely burned patients [47]. The European Society for Enteral and Parenteral Nutrition recommends from 1.3−1.5 g/kg for almost all critically ill patients, and the European Society of Intensive Care Medicine recommends protein intakes of 1.8 g/kg [48, 49]. Although different recommendations are available in the clinical literature, most critically ill patients should receive at least 1.5 g/kg/day protein, and clinical studies also strongly suggest that 2–2.5 g/kg/day protein is safe and beneficial for critically ill patients [47, 50, 51].

Vitamin D supplementation

Although vitamin D deficiency has been implicated in chronic diseases such as osteoporosis, cardiovascular diseases, malignancies, cognitive dysfunction, etc. and found to be associated with increased overall mortality, its role in critically ill patients is not well described. Furthermore, studies showing a relationship between sarcopenia and vitamin D deficiency suggest that use of vitamin D may improve clinical outcomes of sarcopenia treatment as well as prevention of sarcopenia [52–55]. In an observational study, Braun et al. investigated the relationship between 25-hydroxyvitamin-D (25(OH)D) deficiency at critical care initiation and all-cause mortalities in 1,325 critically ill patients. They demonstrated that 25(OH)D deficiency was predictive for short-term and long-term mortality. The odds ratio for mortality rate was found to be 1.85 for 25(OH)D deficiency (≤15 ng/mL) and 1.31 (16–29 ng/mL) for insufficiency. The number of patients with sepsis and organ failure were greater in the 25(OH)D deficiency group ($p < 0.001$ and $p = 0.009$, respectively) [56]. Another study by Higgins et al. demonstrated that 25(OH)D insufficiency was very common in ICUs (82 %) and was significantly associated with longer time-to-alive ICU discharge; they also reported that 25(OH)D levels continued to significantly decrease throughout the duration of ICU stay [57]. Another retrospective study found that ICU survivors had a significantly lower rate of vitamin D deficiency compared with non-survivors (28 vs 53 %) and that patients with vitamin D deficiency stayed in ICUs for ≥3 days and had a significantly higher death risk (RR 1.81) compared to the non-deficiency group. Consequently, they recommended in their study that 25(OH)D levels should be routinely checked and deficiencies treated in ICU patients [58].

Increasing exercise

Recent literature demonstrated that critically ill patients who survive had poor physical, functional, and cognitive

outcomes after ICU discharge, referred to as 'post-intensive care syndrome' [59]. We know that exercise in other populations improves strength and function of muscles, and decreases inflammation and oxidative stress, so early physical therapy in ICUs may prevent or reverse physical impairments. In a review article, Kayambu et al. investigated the effect of exercise in critically ill patients to show clinical outcomes by using randomized controlled trials, meta-analyses, and systematic reviews [60]. In summary, there were significant positive effects favoring physical therapy in ICUs to improve peripheral and respiratory muscle strength, quality of life, physical function, increasing ventilator-free days, and reducing hospital and ICU length of stay. However, there was no significantly positive effect on mortality. Physical therapy in ICUs must be an important component of critical care management [60].

One study aimed to analyze the concept of mobilization within the context of the critical care setting and searched 61 suitable articles from 1966−2012. Their major finding was that mobilization has an effect on both physical and psychosocial components [61]. Mobilization decreases bone demineralization, enhances insulin sensitivity, increases gastrointestinal motility, improves mood and quality of life, and increases well-being and functional ability. Although this analysis revealed that mobilization might improve patient outcomes, further studies are required to identify the efficacy of mobilization in the critical care setting [61].

Nowadays, electrical muscle stimulation in the ICU setting is used to preserve muscle mass and strength. In a systematic review, Parry et al. investigated nine studies concerning electrical muscle stimulation in the ICU and found that this intervention is a promising way to preserve the muscle of ICU patients; however, there is no evidence regarding this intervention in acute settings [62]. Further studies are needed for using electrical muscle stimulation in ICU settings.

Conclusion

Sarcopenia is an important cause of morbidity and mortality in older people. There is also a growing concern in ICUs regarding ICU-AW, but not enough is known about sarcopenia in ICUs. Further studies are needed in this area to improve the clinical outcomes in ICU patients, and also to show the exact impact of sarcopenia with regard to prevalence and association with morbidity and mortality on ICU patients.

Compliance with ethical standards

Conflict of interest None.

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