

Sarcopenia in Patients with Chronic Kidney Disease

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ABSTRACT

Sarcopenia is defined as a decrease in muscle mass and muscle strength, and its frequency increases with aging. Since different criteria and methods can be used for its definition, its incidence rates vary. Chronic kidney disease is a progressive process and many systems may be affected in these patients. Studies also show that chronic kidney disease can lead to the development of sarcopenia. Many factors are held responsible for the development of sarcopenia in chronic kidney disease. Age, inflammation, malnutrition, uremic toxins, and hormonal imbalance are the most important ones. In this review, general information about sarcopenia and the development of sarcopenia in patients with chronic kidney disease are discussed in light of the literature.

Keywords: Chronic kidney disease, renal transplantation, sarcopenia

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INTRODUCTION

Sarcopenia is named after a combination of the Greek words “sarcos” (meat) and “penia” (loss). This term was first used by Irwin H. Rosenberg in 1989. Rosenberg¹ defined sarcopenia as the reduction in muscle mass associated with aging. In 2009, the European Working Group on Sarcopenia in Older People (EWGSOP) was established, with the members of many different institutions (EUGMS, ESPEN, IANA, IAGG-ER). In 2018, the definition of sarcopenia was revised by the EWGSOP, and the main parameters were determined as muscle strength and muscle mass (Table 1).²

The incidence of sarcopenia increases with advancing age. In a study, the incidence of sarcopenia was reported to range from 5% to 13% between the ages of 60 and 70 years and from 11% to 50% in those aged 80 years and over.³ Sarcopenia is called “primary sarcopenia” when it occurs due to aging without any other reason and “secondary sarcopenia” when it occurs due to one or more other causes. The risk factors

responsible for the development of sarcopenia are shown in Table 2.

The mechanism of sarcopenia is not clear. Protein synthesis–proteolysis balance is important in its formation. With aging, decrease in anabolic hormones, increase in oxidative stress due to proinflammatory, interleukin-6 (IL-6) and free radical accumulation, and changes in mitochondrial functions of muscle cells may play a role in the development of sarcopenia.⁴

It is thought that the number of satellite cells involved in muscle regeneration decreases with aging and this may contribute to the development of sarcopenia. Insulin-like growth factor-1 (IGF-1) and androgen levels decrease with aging. Low-circulating angiotensin-II is associated with muscle weakness and decreased IGF-1 levels and insulin resistance, which can lead to sarcopenia. Observational studies have shown that proinflammatory cytokines, tumor necrosis factor- α , and IL-6 levels increase in aging muscle.^{5,6}



Table 1. Sarcopenia diagnostic criteria (EWGSOP, 2018)

Probable sarcopenia is identified when criterion 1 was detected.
 Additional documentation of criterion 2 confirms the diagnosis.
 When criteria 1, 2, and 3 are all met; sarcopenia is considered severe.

- (1) Low muscle strength
- (2) Low muscle mass or quality
- (3) Low physical performance

For the diagnosis of sarcopenia, muscle quantity and functionality should be evaluated. The parameters to be measured are muscle mass, muscle strength, and physical performance. Computed tomography (CT), magnetic resonance imaging (MRI), ultrasonographic imaging, or dual-energy x-ray absorptiometry (DEXA) can be used for the measurement of muscle mass. In the evaluation of muscle strength, a handgrip strength (HGS) test is usually applied. For physical performance, gait speed, the timed up and go test can be performed. European working group on sarcopenia in older people 2 (EWGSOP2) has developed an algorithm to detect individuals with sarcopenia (Figure 1).

Sarcopenia has negative consequences such as fragility, decrease in quality of life, deterioration in the immune system, deterioration in respiratory functions, falls, disability, loss of strength, and death.⁷

SARCOPENIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is often called a model of “accelerated aging,” therefore, it is likely that the direction of relationships between loss of lean mass, skeletal muscle strength and physical performance, and patient-centered outcomes such as mobility limitation, disability, and mortality is the same as in the general population. Although some criteria have been developed to date for the definition of sarcopenia, there is no clarity on the applicability of these criteria in CKD patients. The test used in the definition of sarcopenia may also affect the diagnosis of sarcopenia in CKD patients. Hypervolemia seen in CKD patients may affect bioelectrical impedance analysis.⁸

MAIN POINTS

- Chronic kidney disease (CKD) is a risk factor for the development of Sarcopenia and should be evaluated from this point of view.
- Inflammation and hormonal imbalance facilitate the development of Sarcopenia.
- Although some criteria have been developed to define sarcopenia, the feasibility of using such criteria in CKD patients has not yet been clarified yet.
- Increased frequency of sarcopenia in CKD patients has been shown to have negative consequences (cardiovascular events and mortality).

Table 2. Classification of sarcopenia

Primary sarcopenia	
Age-related sarcopenia	
Secondary sarcopenia	
Activity-related sarcopenia	Sedentary lifestyle
Disease-related sarcopenia	Advanced failures of organs (of the heart, lungs, the liver, kidneys), malignancies, endocrine diseases
Nutritional sarcopenia	Malabsorption, diseases, or medicine causing anorexia

The mechanisms underlying sarcopenia in CKD revolve around the loss of muscle mass. This is a "chicken-or-the-egg" conundrum because it is not known whether reduced physical activity causes muscle loss or muscle loss causes decreased activity. The loss of muscle mass in CKD can be attributed to a negative balance of protein homeostasis, with increased catabolism and decreased muscle synthesis.⁹

Muscle regeneration is impaired in CKD. The permanent imbalance between protein breakdown and synthesis in muscle causes muscle loss. During muscle loss, high levels of reactive

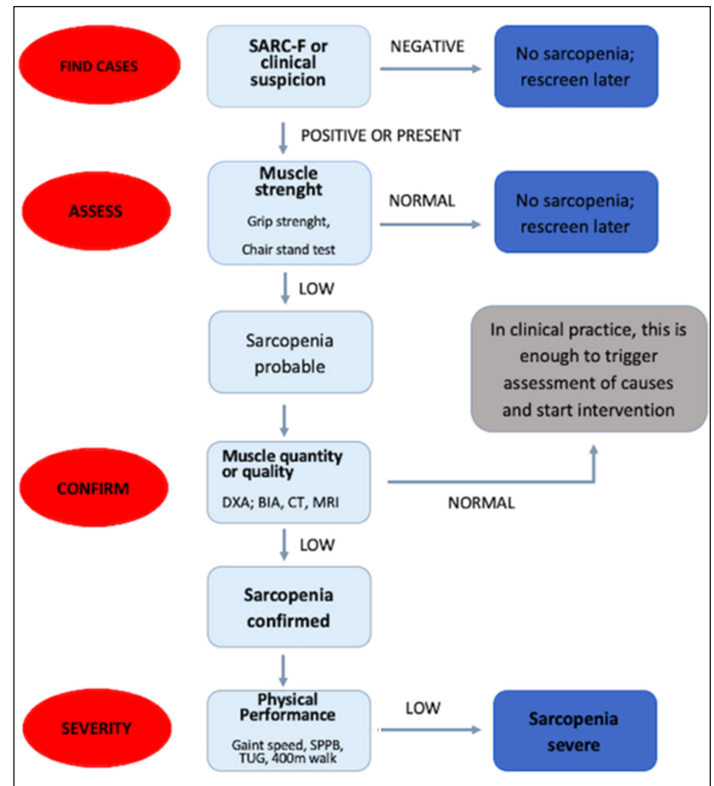


Figure 1. Sarcopenia: EWGSOP2 algorithm for case-finding, diagnosis, and quantifying severity in practice. BIA, bioelectrical impedance analysis; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; MRI, magnetic resonance imaging.

oxygen species (ROS) and inflammatory cytokines are detected in the muscle. These increased ROS and inflammatory cytokine levels induce myostatin expression.¹⁰ Myostatin, a negative regulator of skeletal muscle mass, has been shown to be increased in patients with CKD. Binding of myostatin to activin-A type-IIb receptors stimulates the expression of atrogens, such as atrogin-1 and muscle-ringing factor 1, which are members of the muscle-specific ubiquitin ligase family.¹⁰ Moreover, impaired mitochondrial function contributes to reduced muscular endurance.

The increased catabolic process is also effective in the development of sarcopenia in CKD patients. Chronic inflammation, uremic toxins, malnutrition, and hormonal imbalance (insulin resistance, vitamin D deficiency, and hypogonadism) affect this catabolic process. The renin-angiotensin-aldosterone system is upregulated in CKD, which impairs muscle regeneration and increases uremia potential sarcopenia (UPS) proteolytic pathways (Figure 2).

In the literature, there are various studies examining the incidence of sarcopenia and the factors affecting it in CKD and dialysis patients. In the study conducted by Souza et al,⁹ 100 patients were included and they found the frequency of sarcopenia to be 11.9% according to the EWGSOP criteria and 28.7% according to the Foundation for the National Institutes of Health criteria. It was reported that the frequency of sarcopenia increased in parallel with the stage of CKD. Pereira et al¹¹ found the frequency of sarcopenia to be between 5.9% and 9.8% in 287 non-dialysis CKD patients by using different measurements. It can be said that the frequency is slightly increased in dialysis patients. Kim et al¹² revealed the incidence of sarcopenia in 95 HD patients to be 37% in men and 29.3% in women.

This increased incidence of sarcopenia in CKD patients has been shown to have negative consequences. In the study of

Pereria et al,¹¹ sarcopenia was found to be associated with an HR for mortality of 1.8 (95% CI: 0.78-4.17). In a study on 385 patients with the mean estimated glomerular filtration rate of 41 mL/min/1.73 m², each 0.1 m/s decrement in gait speed was associated with a 26% higher risk for death and each 1-s longer timed up and go was associated with an 8% greater risk for mortality.¹³ In another study performed on 128 predialysis CKD patients followed up for a median period of 2.8 years, decreased HGS was independently associated with the composite outcome of progression to end-stage kidney disease and mortality across different stages of predialysis CKD.¹⁴

In a prospective study by Kim et al,¹⁵ 142 hemodialysis patients were followed up for 4.5 years and sarcopenia was detected in 47 patients. During the follow-up, 28 patients died. HGS, lean tissue index (LTI), and serum prealbumin levels were significantly lower in patients who died. It was determined that low HGS and LTI significantly increased mortality.¹⁵

In a 6-center study by Giglio et al,¹⁶ in which 170 hemodialysis patients were included, the patients were followed up for 36 months in terms of hospitalization and mortality. Sarcopenia was observed in 37% of the patients, and it was found that sarcopenia increased the risk of hospitalization and that sarcopenia was a predictor of mortality.¹⁶

Sarcopenia is also observed in peritoneal dialysis patients. In the study of As'habi et al,¹⁷ 79 peritoneal dialysis patients were included in the study. The prevalences of dynapenic obesity and sarcopenic obesity in Peritoneal dialysis (PD) patients were found to be 11.4% and 3.8%, respectively.¹⁷ In a prospective study conducted by Wu et al,¹⁸ 158 peritoneal dialysis patients were followed. Edema-free lean soft tissue measurement and non-contrast abdominal CT were used to evaluate total skeletal muscle (TSM) and psoas muscle (PM) indices at the level of the third lumbar vertebra. Forty-one of the patients were found to

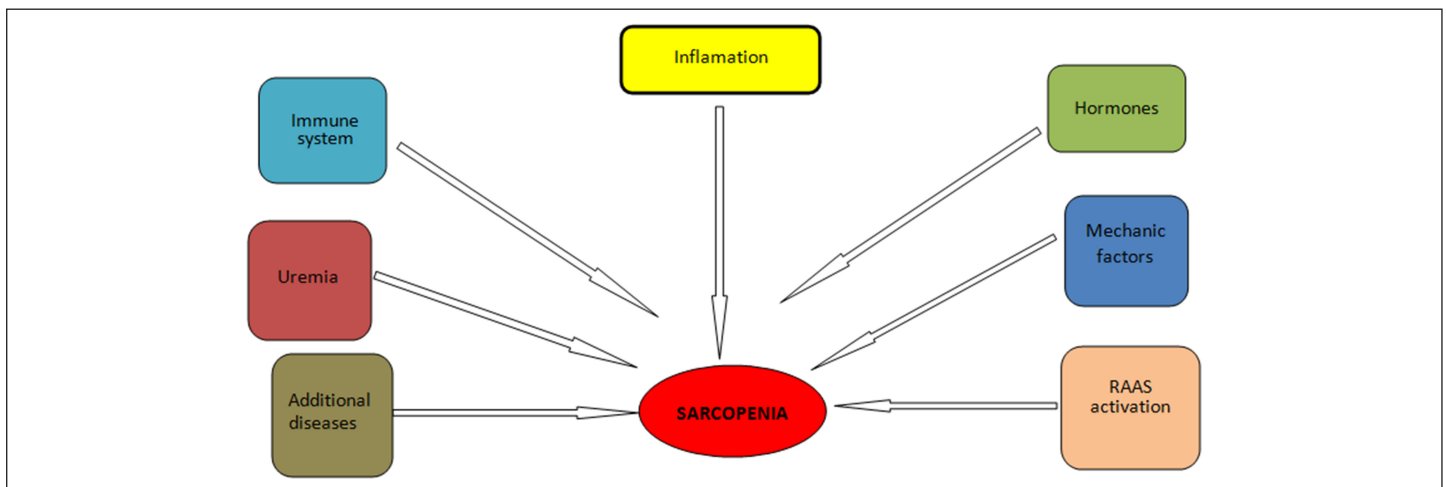


Figure 2. Potential sarcopenia mechanisms in uremia

be sarcopenic according to the TSM and 65 according to the PM indexes.¹⁸

The frequency of sarcopenia has also been investigated in kidney transplant patients. In the study of Ozkayar et al,¹⁹ which was performed on 166 kidney transplant patients, sarcopenia was detected in 34 patients. The findings showed that sarcopenia occurred at a younger age in kidney transplant patients compared to the general population.¹⁹ In a study by Yanishi et al,²⁰ 51 kidney transplant patients were evaluated in terms of sarcopenia. Sarcopenia was found in 6 patients, and pre-sarcopenia was detected in 20 patients. Age and duration of dialysis were reported to be independent variables for sarcopenic status.²⁰

In conclusion, sarcopenia is an important problem in patients with chronic kidney disease, dialysis, and kidney transplant, and it has negative consequences. Patients in this population should be evaluated for sarcopenia and necessary precautions should be taken.

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