Sarcopenia in Chronic Kidney Disease

ABSTRACT
Sarcopenia is a chronic condition associated with physiological aging process and is defined by the reduction of the mass, muscle strength and function. In Chronic Kidney Disease (CKD), sarcopenia is prevalent and is associated with increased morbidity and mortality and the occurrence of cardiovascular complications. By analyzing sarcopenia in patients with renal insufficiency, complex mechanisms that contribute to loss of muscle mass are highlighted, such as activation of mediators that stimulate the ubiquitin-proteasome system (SUP) ATP-dependent, inflammation, metabolic acidosis, angiotensin II and some hormonal factors. The therapeutic approach to sarcopenia in CKD includes exercises, correction of metabolic acidosis, hormone replacement therapy and insulin resistance. Thus, it is of paramount importance early recognition of sarcopenia in this population, in order to establish effective therapeutic interventions, thus avoiding the full range of complications associated with muscle wasting in CKD.

Keywords: kidney failure, chronic; malnutrition; muscle strength; sarcopenia.

The loss of muscle mass in Chronic Kidney Disease (CKD) is considered an important complicating factor, contributing to a sedentary lifestyle and compromising cardiovascular health due to increased morbimortality.1 This is of great relevance because CKD is a serious public health problem. In Brazil, it is estimated that the prevalence and incidence of end-stage renal disease (ESRD) is 405 and 144 patients per one million inhabitants, respectively.2

Aging is associated with sarcopenia and increased CKD prevalence. It is important to emphasize that both sarcopenia as uremia are progressive diseases, which contribute to maximizing morbidity and raise healthcare costs. The term uremic sarcopenia seems more appropriate to describe the process of progressive and cumulative loss of muscle mass that occurs in CKD, thus becoming a priority therapeutic target towards prevention and treatment of muscle wasting in these patients.3

Sarcopenia occurs in all CKD stages and the more severe the loss of renal function, the greater the risk of sarcopenia. Foley et al.,4 assessed patients in the Third National Health and Nutrition Examination Survey (NHANES III), and they found an
Sarcopenia and CKD

Assessment of sarcopenia and CKD stages, and such association was influenced by aging; low socioeconomic status; lack of physical activity; low carbohydrate, fat and protein intake; hypercalcemia; vitamin D deficiency; blood hypertension and insulin resistance.

Sarcopenia may bring about greater functional impairment for patients in the advanced stages of CKD, as proved by McIntery et al., comparing CKD patients in stages 4 and 5 in hemodialysis (HD) and peritoneal dialysis (PD). Data showed a significant difference in the cross-sectional area of the examined muscles and in the functional capacity of patients in stages 4 and 5; however, there was no difference between patients in HD and PD, which shows that the dialysis modality may not have a different impact on sarcopenic patients.

**Skeletal Muscle Abnormalities in CKD**

Muscle weakness and fatigue are frequently reported by patients with CKD and there are several mechanisms responsible for these symptoms, such as hormonal imbalance, malnutrition, ATP and glycogen depletion, inadequate oxygen transport as a consequence of anemia, metabolic acidosis and electrolyte disorder, lifestyle changes, muscle wasting and weakness due to muscle fiber atrophy.

The most common abnormality in muscle biopsies of uremic patients is type II muscle fiber atrophy, which have a smaller cross-sectional area, and muscle fiber grouping.

**Muscle Protein Loss Mechanisms**

Muscle wasting etiology in renal patients is multifactorial and similar to that of sarcopenia in general, involving hormonal and immunological causes; myocellular changes; inflammation; metabolic acidosis; protein intake reduction; physical inactivity; excess angiotensin II; abnormalities in insulin/IGF-1 signaling and in myostatin expression; and reduced function of satellite cells (Figure 1). Most of these mechanisms stimulate the ATP-dependent SUP pathway, which is recognized as one of the most important forms of muscle loss.

**Progenitor Cells and Satellite Cells**

After muscle injury, satellite cells are activated and express MyoD and myogenin transcription factors on their surfaces, which leads to myoblast formation and proliferation, and they differentiate to form new muscle fibers to repair the damaged muscle. In CKD, the function of satellite cells is impaired, producing low levels of myogenin and MyoD proteins, hampering muscle regeneration.

**Inflammation**

In CKD there are high circulating levels of inflammatory markers such as C reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α); and inflammation is a major cause of muscle wasting in this population. Several mechanisms may explain the role inflammation plays in this context, such as NFκB path induction, inhibition of insulin-induced protein synthesis, and changes in the insulin/IGF-1 pathway signaling. Inflammation also causes muscle loss through the activation of SUP.

**ATP-Dependent UPS**

The ATP-dependent proteolysis via the ubiquitin-proteasome system (UPS) is characterized as the primary cause of muscle mass degradation in CKD. Inflammation and metabolic acidosis play key roles in UPS activation (Figure 2).

Inflammation activates UPS, which cleavages the 14-kD actin fragment - the hallmark of CKD-related muscle proteolysis. The density of this actin fragment may serve as a marker to detect muscle loss in early stages.

Metabolic acidosis - common in CKD patients, can also stimulate UPS, which causes amino acid oxidation in skeletal muscles.

**Metabolic Acidosis**

Metabolic acidosis stimulates the UPS pathway and causes muscle protein loss and calorie and protein loss (CPL) through protein degradation and protein synthesis reduction.
Suitable serum vitamin D levels are associated with the proliferation and differentiation of various cells including skeletal muscle cells. Vitamin D supplementation is associated with muscle function improvements, reduced falls, and it may impact muscle fiber composition and morphology in the elderly. CKD patients have more prolonged muscle contraction phases, regardless of calcium, phosphorus and PTH serum levels. These
observations suggest a possible vitamin D role in patients with CKD.

**Changes in Angiotensin II**
The renin-angiotensin system is activated in various catabolic conditions, including CKD, which leads to activation of caspase-3 in skeletal muscles, resulting in actin cleavage. Angiotensin II can increase muscle proteolysis by reducing circulating levels of IGF-1 and activating the TGF-β pathway, which is a major mechanism of muscle mass loss.

**Changes in Appetite**
Anorexia is a common and complex change in CKD. The main causes reported in the literature are disorders of hormones that act in the regulation of appetite, such as leptin and ghrelin, reduced ability to distinguish flavors, gastrointestinal symptoms associated with uremia, depression, hemodynamic instability resulting from exposure to antihypertensive agents or hemodialysis, and feeling of fullness during peritoneal dialysis.

**Changes in Sex Hormones**
More than 60% of patients with advanced CKD have low serum levels of testosterone, which could contribute to muscle mass loss. Potential mechanisms by which low testosterone levels could lead to muscle catabolism include altered IGF-1 signaling and an increase in myostatin levels.

Women with CKD usually have oligomenorrhea and estrogen deficiency in the early stages of the disease, which could lead to reduced muscle strength.

**Changes in Growth Hormone**
CKD is associated with GH resistance, being considered a potential cause of increased protein catabolism and skeletal muscle loss. This can be explained by an IGF-1 anabolic hormone resistance to protein turnover in skeletal muscle and reduction in IGF bioactivity in ESRD, which would lead to a reduction of free IGF-1 in proportion to the degree of kidney failure.

**Changes in Insulin**
CKD is associated with insulin resistance from the early stages of the disease, when glomerular filtration is still normal. Vitamin D deficiency and anemia may contribute to increased insulin resistance in these patients. Insulin resistance is also associated with muscle protein loss, mainly by means of the UPS pathway.

**Calorie and Protein Loss (CPL)**
The cause of CPL in CKD is complex, including inflammation; diseases associated with increased catabolism, which may occur together with CKD; loss of nutrients through the dialysate, metabolic acidosis, insulin resistance, GH and IGF-1; hyperglucagonemia, hyperparathyroidism and blood loss in the hemodialysis machine, feces or blood drawing.

In a recent consensus of the International Society of Renal Nutrition and Metabolism (ISRNM), the authors stressed that CKD-related malnutrition, lack of appetite and food restrictions, contribute to the etiology of CPL, but other highly prevalent factors are necessary for the complete syndrome to develop. These include uremia-induced alterations, such as increased energy expenditure, physical inactivity and frailty.

Serum inflammatory markers such as CRP and IL-6 may be persistently high in the CPL process, but were not included as part of the diagnostic criteria of this syndrome. Other factors besides inflammation, seem to be crucial in the etiology of CPL. The loss of muscle mass constitutes the main criterion for CPL in CKD, contributing thus to the development of sarcopenia. Hypoalbuminemia, low BMI, low protein and low calorie diets are also involved.

In Brazil, a study carried out by the Brazilian Society of Nephrology Nutrition Commission evaluated 2,622 patients with CKD and showed that 37.4% had serum levels consistent with hypoalbuminemia. In another Brazilian study, Piratelli & Telarolli Junior observed moderate or severe malnutrition ranging from 22 to 54% of 48 patients from a dialysis center and, of those, 29% had weight 75% below normal.

Araújo et al. performed a prospective study that followed 344 patients in HD for 10 years. The authors concluded that smaller middle arm circumference and low calorie intake at the start of dialysis were risk factors for mortality.
SLEEP AND PHYSICAL INACTIVITY

CKD patients undergoing dialysis have a reduced level of physical activity, which may lead to loss of muscle proteins and muscle atrophy via a complex mechanism that includes physical inactivity and lack of training.35

CHANGES IN MYOSTATIN AND FOLLISTATIN

Myostatin and follistatin are members of the TGF-β family. Myostatin expression is increased in uremic cachexia, representing a negative impact on skeletal muscle mass and growth, leading to muscle atrophy.3

Follistatin, a regulatory glycoprotein previously recognized as an FSH-suppressing protein, is a powerful myostatin antagonist, and experimental evidence suggests that its exacerbated expression induces a significant improvement in muscle mass.36,37 However; the mechanisms involved in the effects related to follistatin are still unknown. A study by Gilson et al.38 demonstrated that satellite cell proliferation contributed significantly to follistatin-induced muscle mass gain and probably to increased protein synthesis.

In a recent publication, Miyamoto et al.39 reported that follistatin levels were not altered in patients with CKD, except in those very much wasted and with more inflammatory activity, and, in these patients, there was a negative association with muscle strength and bone mineral density. Strategies to increase muscle mass and strength by follistatin-induced myostatin inhibition may represent a potential therapeutic approach in muscle atrophy that occurs in uremia, and in other conditions.

POTENTIAL THERAPEUTIC PREVENTION AND INTERVENTION FOR MUSCLE LOSS

STRENGTH EXERCISES

Storer et al.40 reported that strength exercises performed on a cycle ergometer immediately before the start of hemodialysis, improved patients’ strength, fatigue and physical performance.

In a controlled, randomized study of 26 patients in pre-dialysis, inflammatory markers (IL-6 and CRP) decreased after 12 weeks of training with strength exercises.41

These findings suggest beneficial effects of aerobic and resistance training on muscle mass in patients in pre-dialysis and dialysis.

NUTRITIONAL SUPPLEMENTS

There is evidence that nutritional support can improve CPL in adults with ESRD. Caglar et al.42 evaluated 55 patients with CPL in HD, who received conventional nutritional counselling for 3 months and, in the subsequent 6 months, received a specific nutritional supplement for patients on dialysis three times a week, during hemodialysis. They reported a significant increase in serum albumin and prealbumin.

Some randomized studies using serum albumin levels as an endpoint showed significant improvements in hipoalbuminemia.43-51

In Brazil, Ripe et al.52 carried out a pilot study and reported that high levels of intradialytic protein supplementation was not associated with inflammation, but may have beneficial effects in HD.

METABOLIC ACIDOSIS CORRECTION

Stein et al.53 evaluated the effects of correcting metabolic acidosis in patients on continuous outpatient peritoneal dialysis. Correction of acidosis led to about 2 kg of weight gain and evidence of increased muscle mass based on anthropometric measurements.

TESTOSTERONE

The weekly administration of 100mg of nandrolone, for 24 weeks, increased the appendicular lean mass in about 2 fold.54 Additional information is necessary for testosterone replacement to be widely recommended, especially in women.

INSULIN RESISTANCE CORRECTION

In animal models of CKD, there is a strong association between the altered signaling in the insulin/IGF-1 ratio and muscle loss.28 Thus, mechanisms that impair the insulin/IGF-1 ratio signaling should be identified in an attempt to develop treatment strategies.3

SARCOPENIA AND CKD

Some studies have addressed the issue sarcopenia and CKD in the world literature, as depicted on Table 1. However, there is still a gap concerning this issue, and further studies are needed for a better understanding of the pathophysiology, clinical implications, diagnosis and therapeutic approach.
CONCLUSION

Uremic muscle loss is complex, progressive, and its pathogenesis is similar to sarcopenia. This devastating complication not only contributes to a sedentary lifestyle and poor quality of life, but also increases the incidence of cardiovascular complications, morbidity and mortality. CKD patients must undergo preventive measures and be assessed for the presence of sarcopenia at early stages, when the institution of therapeutic measures may be capable of reversing the process of muscle loss and thereby reduce the range of complications that can occur as a result of sarcopenia in renal patients.

REFERENCES


TABLE 1

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>CKD stage</th>
<th>Conclusion</th>
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<tbody>
<tr>
<td>Kim et al.,55 2013</td>
<td>95</td>
<td>ESRD</td>
<td>Sarcopenia is associated with a global subjective assessment, inflammation markers, β2 microglobulin, depression and cognitive decline</td>
</tr>
<tr>
<td>Chang et al.,56 2011</td>
<td>128</td>
<td>Predialysis</td>
<td>Hand grip was an independent predictor of mortality and progression to ESRD.</td>
</tr>
<tr>
<td>Kato et al.,57 2011</td>
<td>161</td>
<td>Hemodialysis</td>
<td>Sarcopenia is associated with systemic arteriosclerosis changes</td>
</tr>
<tr>
<td>Noori et al.,58 2010</td>
<td>792</td>
<td>Hemodialysis</td>
<td>A larger mid-arm circumference was equivalent to lean body mass and was an independent predictor of better mental health and survival</td>
</tr>
<tr>
<td>Honda et al.,59 2007</td>
<td>328</td>
<td>ESRD</td>
<td>Calorie and protein loss is associated with inflammation and mortality in sarcopenic patients</td>
</tr>
<tr>
<td>Foley et al.,60 2007</td>
<td>13.770</td>
<td>Predialysis</td>
<td>Association between sarcopenia and glomerular filtration decline</td>
</tr>
<tr>
<td>Johansen et al.,61 2003</td>
<td>38</td>
<td>Hemodialysis</td>
<td>Muscle atrophy and a larger number of non-contractile fibers are present in the muscles of patients in hemodialysis. Muscle atrophy is associated with a worse physical performance.</td>
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Sarcopenia and CKD


