Review Article

Uremic Sarcopenia

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Abstract

"Uremic sarcopenia" refers to a progressive decrease in muscle mass, strength, and function despite normal skeletal muscle physiology in patients with chronic kidney disease (CKD). Sarcopenia involves multiple risk factors, comprising immunological changes, hormonal, metabolic acidosis, reduced protein intake, and physical inactivity. All these risk factors, along with complex pathophysiological mechanisms including ubiquitin, insulin/IGF-1, myostatin, and indoxyl sulfate, activate downstream pathways that ultimately increase muscle degradation while reducing muscle regeneration. Uremic sarcopenia not only affects the quality of life but also increases the risk of morbidity and mortality in patients with CKD. Of all the treatment modalities, aerobic and resistance exercise have shown prevention and reduced rate of muscle degeneration. A variety of pharmacological agents have been tried to target different steps in the known pathogenetic pathways, including the use of androgens and anabolic steroids, correction of vitamin D deficiency, use of growth hormone supplementation, and suppression of the ubiquitin pathway. Though some of these techniques have had beneficial results in animal experiments, human trials are still sparse. This review article relates to recent publications that describe the abnormalities in skeletal muscle that primarily leads to muscle wasting and its consequences in patients with CKD.

Keywords: *Emergent therapies, exercise, metabolic acidosis, sarcopenia, ubiquitin–proteasome pathway, uremia*

Introduction

The skeletal muscle compartment, constituting 40% of body weight and 50% of body protein, is a major physiological reserve that gets depleted as renal function deteriorates.[1] Each component of the protein, which forms the skeletal muscle mass, plays a critical role in survival and is tightly regulated. When there is a dire need for proteins and amino acids, the muscles get broken down as excess protein does not get stored in the body, thus making continuous and adequate daily dietary intake of protein mandatory. Protein is an essential component of every cell in the human body, including viscera, blood cells, enzymes, antibodies, and connective tissue.[1] All these critical functions in which proteins are an essential part get deranged when there is accelerated protein catabolism as in chronic kidney disease (CKD). As a consequence, there is increased morbidity and mortality in CKD patients with uremic sarcopenia.[2-4]

Risk factors predisposing to sarcopenia:[5] [Figure 1]

Pathophysiology of sarcopenia

The literature uses the term "sarcopenia" for the loss of muscle mass, and the term "dynapenia" refers to loss of muscle strength, both of which occur concurrently in patients with CKD but at different rates; the muscle strength declines at a faster than the muscle mass. Thus, in CKD, reduced physical activity leads to accelerated muscle loss, which leads to further reduced physical activity, and the cycle continues.

The ubiquitin–proteasome system

Studies in humans and rodents have identified the ubiquitin–proteasome system[6] (UPS) as the major pathway degrading protein in skeletal muscle. Although lysosomal cathepsins and calcium-dependent calpains can be upregulated in catabolic conditions, their role in the degradation of myofibrillar proteins in CKD is substantially below that of the UPS. The biochemical processes degrading proteins in the UPS are tightly regulated to avoid uncontrolled degradation of cellular proteins. Proteins destined for

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degradation in the UPS are first conjugated to ubiquitin, a highly conserved protein member of the heat shock protein family [Figure 2]. Ubiquitin is joined to lysine residues by the E1 enzyme, an ATP-mediated process. Activated ubiquitin is then transferred to an E2 carrier protein before being joined to the substrate protein in a reaction catalyzed by an E3 enzyme. Each of the large number of E3 enzymes recognizes specific proteins, thereby providing specificity to the process. This process is repeated until five ubiquitin molecules form a ubiquitin chain that marks the protein substrate for degradation in the 26S proteasome. This large complex of subunit proteins is composed of a 20S core proteasome and 19S complexes, forming a barrel-shaped structure with a 19S complex at each end. These 19S caps cleave ubiquitin molecules from the protein by processes that include ATPases and recognition sites. The 19S complex also catalyzes the unfolding of substrate proteins and facilitates the transport of the unfolded protein into the 20S core of the proteasome, which contains protease activities. Inside the 26S proteasome, proteins are cleaved into small peptides. The peptides are released and rapidly hydrolyzed to amino acids by cytoplasmic peptidases; the amino acids are then transported out of the cell.

Myostatin pathway

Myostatin is a protein that blocks the expression of MyoD (which enhances myogenesis), thus inhibiting skeletal muscle growth. It has been demonstrated that there is increased myostatin expression in the muscle of rats with end-stage renal disease.[7]

Impaired insulin/IGF-I signaling

Impairment in insulin/IGF-1 signaling leads to reduction in forkhead transcription factor (FOXO) phosphorylation, which, in turn, causes synthesis of certain enzymes of the UPS pathway that plays a key role in muscle degradation that recognizes and targets specific muscle proteins for degradation. Thus, pharmacological agents that target FOXO may find a place in the treatment of sarcopenia in the future.[8]

Growth hormone resistance

Growth hormone resistance is observed in CKD, which plays a role in increasing protein catabolism and muscle wasting. Experimental data also suggest that growth hormone supplements had encouraging results in animal and preliminary human trials.[9]

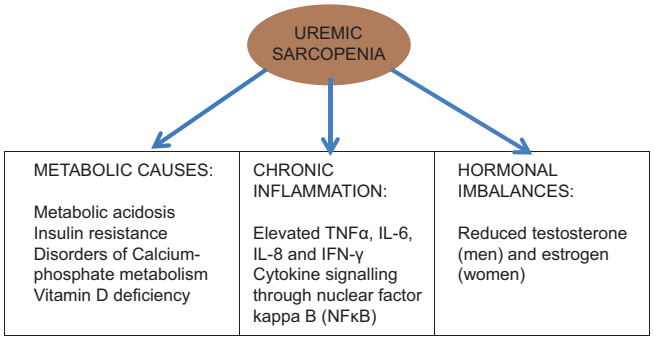

Figure 1: Molecular pathways involved in proteolysis

Renin- Angiotensin-aldosterone system (RAS)

RAS system, which is also upregulated in CKD, impairs muscle regeneration and further upregulates the UPS proteolytic pathway.

Indoxyl sulphate

Recent clinical studies have established an inverse association between plasma indoxyl sulfate and skeletal muscle mass in patients with CKD. This indoxyl sulfate, which is one of the uremic toxins, accumulates in the muscle that downregulates the production of ATP from the tricarboxylic acid cycle; thus, myocytes undergo death[10] [Figure 3].

Assessment of skeletal muscle loss in CKD

The prevailing methods to assess muscle mass are either imprecise or expensive, which poses difficulty in developing effective treatment strategies against muscle loss and strength. The lack of precise definitions for muscle wasting poses yet another problem in determining the degree of wasting.[11]

Some of the common assessments used are

- Assessment of skeletal muscle mass

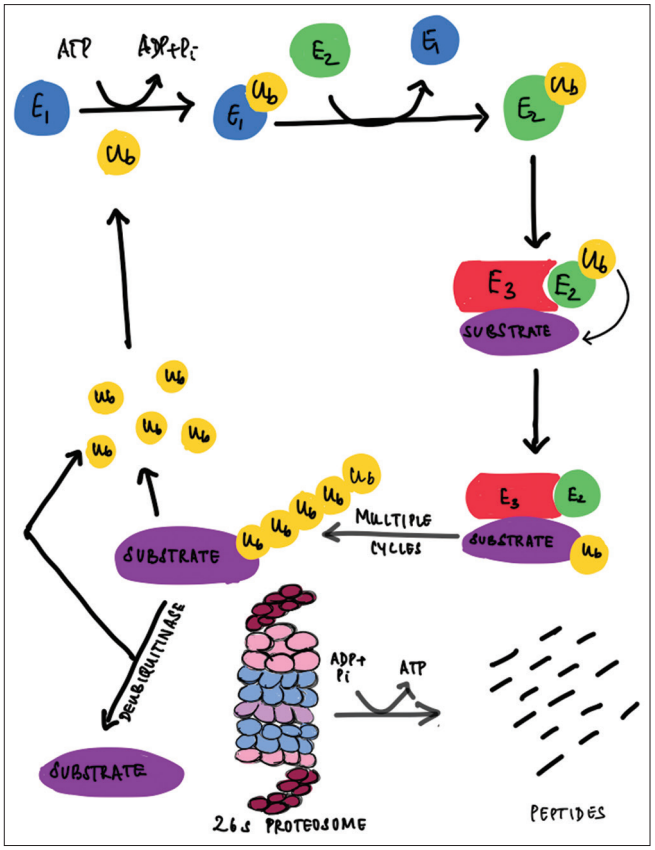

Figure 2: Ubiquitin–proteosome pathway of protein degradation. Abbreviations: E1 (2,3)- Enzyme 1 (2,3); Ub- Ubiquitin

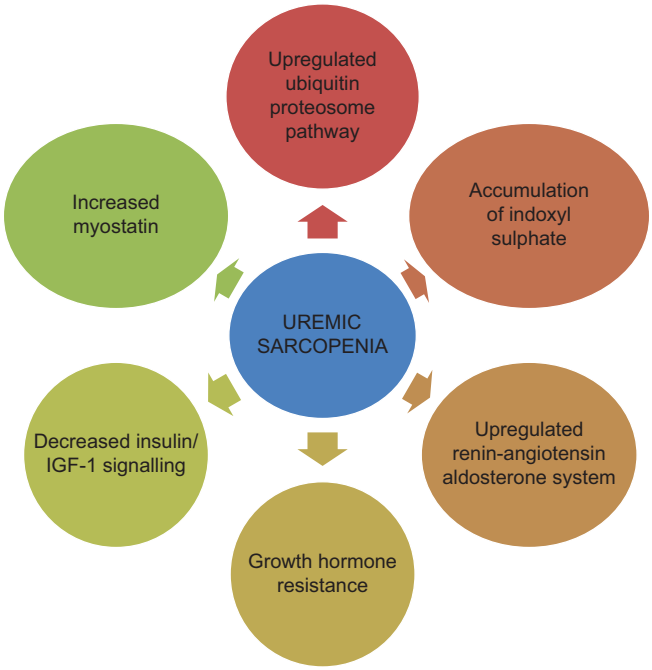

Figure 3: Pathophysiology of uremic sarcopenia

- Body mass index (BMI)
- Circumferential or caliper-based methods
- Bioelectrical impedance analysis (BIA)
- Whole-body dual-energy X-ray absorptiometry (DEXA)

- Measurements of isometric, isokinetic, or isotonic muscle strength.

Clinical methods to estimate sarcopenia:[12]

- **4-m gait speed**
  - The patient is instructed to walk at a comfortable pace for a distance of 4 m. As the patient performs this twice, the fastest time is recorded, and patients with faster baseline gait have lesser disability.[5]
- **30-s sit-to-stand**
  - The patient is seated in the middle of an armless chair with feet shoulder-width apart and arms crossed at the chest. The patient is then encouraged to complete as many full stands as possible within 30 s.
- **Grip strength**
  - Three consecutive efforts are made with the patient's dominant hand, with a minimum of 1-min rest between efforts, while ensuring that the arm position is consistent (flexed or extended at the elbow).
  - The mean from these three efforts is used for consideration.

Serological markers of sarcopenia

The other approach to determine the balance in muscle metabolism is by evaluating serum biomarkers. Serum creatinine may serve as an appropriate marker to assess changes in muscle mass in end-stage renal disease (ESRD) patients with nil or minimal residual renal function. The drawback in using serum creatinine is that the reference values depend on individual muscle mass, though it may be of use in assessing short-term muscle mass loss for that individual. The N-terminal propeptide of type III procollagen (P3NP) is of current interest, as it is released into circulation during collagen synthesis and needs to be studied further extensively before application.[13]

Aging: A major confounder when loss of muscle mass is evaluated in CKD

After the third decade of life, the muscle mass decreases at a rate of about 1.0%–1.5% per year with the total body fat increasing in parallel, which is called "sarcopenia of aging."[14,15] Because much of the CKD patients on dialysis are of older age, how much of this sarcopenia is due to kidney disease primarily and due to uremia remains questionable. A recent National Health and Nutrition Examination Survey (NHANES) report of 11,643 individuals who underwent DEXA studied the association between sarcopenia and CKD stages. They found an almost linear crude association between sarcopenia and renal function, but the association flattened out when standardized for age. It has been proposed that intramuscular fat infiltration may explain the loss of muscle function with age. Intramuscular adipose tissue infiltration, as evidenced by magnetic resonance imaging was greater. Altogether, this evidence may indicate that risk factors for the loss of muscle mass may not be the same as those for the loss of muscle functionality.[16]

Established treatments for loss of muscle mass in CKD

In a recent study by Dubey *et al*.,[17] the prevalence of sarcopenia in CKD stages 3 and 4 was found to be in 69.1%. With such high prevalence, prevention and treatment of uremic sarcopenia must be based on optimal nutritional support and correction of acidosis, with the cornerstone being physical exercise.

Nutritional approach[18]

Dietary interventions in patients with CKD must aim at providing adequate energy and protein load that is essential for health, considering the fact that the processes of muscle mass reduction have already set in. Current recommendations for CKD (stages III-VND) include a low-protein diet (LPD) of 0.6–0.8 g/kg body weight (b.w.)/ day and an energy intake of 30–35 kcal/kg b.w./day. However, studies have shown that energy supplements of 200 kcal/day (40 g of maltodextrin together with 5 g of oil creamer) facilitate better adherence to nutritional therapy. For patients on hemodialysis, the recommended intake of protein is 1.0–1.2 g/kg/day and an energy intake of 35 kcal/kg/day, considering the hypercatabolic state induced by dialysis. All these protein and energy supplements are initially catered by oral supplements to start with and aimed at nutritional goals of serum albumin >4 g/dL and serum pre-albumin >30 mg/dL.

Ketoanalogs (KAs) are essential amino acid nitrogen-free analogs, which when combined with a low-protein diet have shown that KAs improve protein synthesis, inhibit ubiquitin-proteasome mechanisms, and reduce DNA fragmentation in muscle cells, thus providing a supportive therapeutic strategy to counteract muscle atrophy.

Intradialytic parenteral nutrition (IDPN) is the administration of amino acids, glucose, and lipids mixture through the venous line of the dialysis circuit during each session of HD. An ideal IDPN for a 75-kg individual should consist of no more than 1 L of infusion fluid (to avoid water overload) and a maximum of 1000 kcal and 50 g of amino acids. However, the maximum nutrient intake that can be achieved with IDPN is approximately 3000 kcal and 150 g of amino acids. IDPN can provide only up to a maximum of 25% of the ideal nutritional intake. Thus, it may be administered only if the patient has a spontaneous protein intake of 0.8–0.9 g/kg b.w./day and an energy intake of 20 kcal/kg/day. IDPN can be stopped if any of the following criteria is fulfilled: serum albumin stable >3.8 g/dL for more than 3 months, improvement in the subjective global assessment (SGA) score up to stage A (well-nourished) or B (moderation malnourished), positive clinical examination for effective nutritional improvement, or increased protein intake >1 g/kg b.w./day and energy >30 kcal/kg b.w./day.

In patients who suffer from severe malnutrition and with spontaneous energy intake of less than 20 kcal/day, oral supplementation and IDPN may not be sufficient for calorie and protein supplementation. Under such conditions, as well as in the presence of impaired swallowing capacity, daily nutritional support, enteral nutrition (EN), or total parenteral nutrition (TPN) is required. It is preferable to use EN than TPN. ESPEN (European Society for Clinical Nutrition and Metabolism) guidelines[137] state that EN must be taken into account in severely malnourished patients with a BMI of <20 kg/m^2, a reduction in body weight of >10% in the last 6 months, albumin values of <3.5 g/dL, and pre-albumin values of <300 mg/L. EN via nasogastric or nasojejunal route is less expensive in addition to having a trophic action toward the gastrointestinal mucosa improving its integrity. Parenteral administration, on the contrary, requires good vascular access, which can have an irritating effect on the vascular district itself. TPN becomes mandatory in the case of severe gastrointestinal dysfunction such as intestinal ischemia, gastrointestinal obstruction, or peritonitis and is the last possible choice in the event of failure of adequate nutritional intake through oral supplements, EN, and IDPN.

Other supplements

Omega-3 polyunsaturated fatty acids also have been shown to reduce glucose plasma fasting, serum insulin levels, homeostasis model of assessment (HOMA)-IR, and improve the quantitative insulin sensitivity check index. The use of fiber as a nutritional supplement has also shown benefits in reducing uremic toxins produced by the gut microbiota such as indoxyl sulfate and p-cresol, which would reduce mortality in patients with CKD.

Effects of physical exercise

Among the established treatment options to prevent muscle wasting in ESRD patients, resistance exercise (RE) training appears to be the most effective. However, CKD patients with other comorbidities such as osteoporosis, cardiac failure, and anemia generally resort to a sedentary lifestyle.[19] Nevertheless, RE training does prove to be safe and possible in both outpatient settings and at home, and those on concomitant dialysis. For example, leg cycling during hemodialysis (HD) improves not only cardiopulmonary fitness and endurance but also muscle strength, power, fatigability, and physical function. Similarly, a 12-week/24-session combined cardiovascular and RE program in CKD stage 3–4 patients, improves physical capacity and quality of life. Moreover, a recent study provides compelling evidence that regular moderate-intensity aerobic exercise is safe with regard to immune and inflammatory responses and has the potential to be an effective anti-inflammatory therapy in CKD. In accordance, Gielen *et al*.[20] showed that exercise training significantly reduced the local expression of tumor necrosis factor (TNF), interleukin (IL)-1β, IL-6, and inducible nitric oxide synthase (iNOS) in skeletal muscle of congestive heart failure (CHF) patients.

Irisin is a peroxisome proliferator-activated receptor-activator 1-α (PGC-1α)-dependent and exercise-responsive myokine with the potential to induce murine brown-fat-like development of white adipose tissue.[21,22] Though chronic training enhances irisin production in mice, the results have been conflicting in humans. As irisin serum concentrations decrease with reduced renal function, further studies should elucidate the role of this elusive myokine in uremic muscle loss and whether exercise and/or exercise mimetics can normalize irisin levels in patients with CKD. However, the characterization of irisin remains unresolved, and its role as a potential exercise hormone is unsettled. As the emerging field of exercise epigenomics is expected to prosper and delineate mechanisms by which exercise confers a healthier phenotype and improves performance, this field may also add to treatment possibilities in dialysis patients.

Correction of metabolic acidosis

Metabolic acidosis frequently occurs in CKD, impairs growth in children, and stimulates muscle wasting in adults. Clinically, it has been known for many decades that correcting metabolic acidosis in children with renal tubular acidosis improves their growth. In patients with CKD, their nitrogen balance significantly improved when the plasma bicarbonate concentration was corrected by providing alkali supplements. Stein *et al*.,[23] who conducted a year long, randomized trial, reported that correcting metabolic acidosis

in continuous ambulatory peritoneal dialysis patients led to a 2-kg weight gain and evidence of an increase in muscle mass based on anthropometric estimates. Similarly, in hemodialysis patients, correction of metabolic acidosis blocked the increase in muscle protein breakdown. The consensus is that alkali therapy should be given to achieve a plasma HCO3 concentration of 22 mmol/L for patients with metabolic acidosis of any cause.

Testosterone

More than 60% of men with advanced CKD have low plasma concentrations of testosterone, which might contribute to muscle wasting. Potential mechanisms by which a low testosterone concentration might cause muscle catabolism include altered IGF-I signaling and an increase in myostatin (a protein that suppresses muscle growth). Regardless, 100 mg nandrolone/week given for 24 weeks increased appendicular lean mass twofold based on DEXA scanning.[24] Additional information is needed before testosterone replacement therapy can be widely recommended because of its side effects, especially in women.

Correction of insulin resistance

The db/db mouse was studied as a model of insulin resistance and activation of caspase-3, in which the mechanism of the UPS was revealed, providing an explanation for the loss of muscle mass.[25] Also, administration of a thiazolidinedione improved insulin resistance and increased insulin receptor substrate-1 (IRS-1)–associated phosphatidylinositol 3-kinase activity and p-Akt in muscle along with suppression of protein breakdown in muscle. Though investigations to find the influence of insulin sensitizers on changes in muscle protein turned out to be futile, there is enough evidence that diabetes mellitus is the strongest predictor of lost lean body mass (independently of variables such as age, sex, serum albumin, inflammation markers, and dialysis modality). In non-diabetic hemodialysis patients, increased muscle breakdown has been associated with increased insulin resistance, indicating that there is a close relation between abnormal insulin/IGF-I signaling and muscle wasting. Consequently, mechanisms that impair insulin/IGF-I signaling should be identified to maximize the likelihood of developing treatment strategies.[26]

Emerging treatments for loss of muscle mass in CKD

Vitamin D

Alteration in vitamin D metabolism is almost always present in patients with CKD and promotes the risk of bone mineral disease. Garcia *et al*.[27] identified key vitamin D-related molecular pathways that are responsible for muscle regulation. He stated that the addition of 1,25-vitamin D to myoblasts increased the expression and nuclear translocation of the vitamin D receptor. The addition of vitamin D also promoted myogenic differentiation by increasing IGF-2 and follistatin expression and decreasing the expression of myostatin. Sanders *et al*.[28] showed that vitamin D insufficiency in the elderly was associated with reductions in both bone mineral density and type-2 muscle fibers. Therefore, a less strong skeleton in combination with reduced muscle power may increase the risk of falls and fractures. Thus, as active vitamin D treatment was associated with increased muscle mass in HD patients; therefore, supplementing vitamin D should be considered in sarcopenic CKD patients.

Growth hormone

GH, IGF-1, and insulin are anabolic factors that result in an increase in muscle mass.[29] Abnormalities in the physiological axis of GH and IGF-1 have been thought to be associated with the development of protein energy wasting in CKD.[30] Acquired resistance to GH is a potential cause for increased net protein catabolism in ESRD patients. GH exerts anabolic actions in children and even in adults; protein synthesis, reduced protein degradation, increased fat mobilization, and increased gluconeogenesis, with IGF-1 being the major mediator of these actions. Evidence suggests that uremia and the inflammatory milieu in patients with CKD are associated with the development of resistance to GH at cellular levels.[31] Recombinant human GH administered at pharmacological doses not only improved net muscle protein balance but also improved inflammation, cardiovascular status, lipid profile, and erythropoiesis.[32]

Potential future treatments for loss of muscle mass in CKD

Stimulation of mitochondrial biogenesis

Resveratrol,[33] an activator of sirtuins (SIRT), has been shown to ameliorate metabolic disorders and muscle wasting in diabetic rats. Sirtuins contribute to the stimulation of peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α), which leads to mitochondrial biogenesis in the setting of uremia. In dialysis-dependent patients, the expression of PGC-1α is low, and skeletal muscle PGC-1α was recently shown to modulate kynurenine metabolism and mediate resilience to depression in rats. Thus, the association between muscle wasting, low expression of PGC-1α, and depression need further consideration in ESRD.

Myogenic stem (Satellite) cells

As life progresses, there is an increased accumulation of toxic uremic metabolites, which results in the process of aging. As we age, there is decreased regenerative potential and impaired myogenic stem cell or satellite cell function along with a decrease in their number. Elabd *et al*.[34] demonstrated that systemic administration of oxytocin increases the activation and proliferation of even the aged satellite cells. Such a demonstration again needs to be further studied in the setting of uremia in CKD patients.

Conclusion

Decreased muscle mass is almost a constant feature in renal failure patients and serves to be a strong predictor for morbidity and mortality, especially in dialysis-dependent CKD patients. Uremic sarcopenia results from an imbalance between muscle regeneration and degeneration due to various hormonal and physical factors. Because time-established treatments such as physical exercise and correction of metabolic acidosis and testosterone have proven to be insufficient, emerging treatment modalities involving satellite cells and mitochondrial biogenesis needs to be studied further in detail to provide a better quality of life in patients with CKD.

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Conflicts of interest

There are no conflicts of interest.

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