

Essay: Uraemic Sarcopenia – Pathophysiology and implications

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Abstract

Sarcopenia was a term coined by Irwin Rosenberg to mean ‘paucity of flesh’ . The underlying mechanisms of sarcopenia in the context of CKD revolve around the loss of muscle mass. The current state of knowledge indicates that the factors predisposing patients with chronic kidney disease to the development of sarcopenia in fact can be divided into two groups, associated with the developing inflammatory process and associated with the kidney disease. Major factors involved in pathophysiology are inflammation, acidosis, hormonal factors ,insulin resistance and ATP-dependent ubiquitin-proteasome system Sarcopenia is a powerful predictor of morbidity and mortality in CKD patients Considering the impact of muscle wasting on the well-being of patients with CKD and the healthcare system in general, it makes logical sense to identify and introduce therapeutics strategies to maintain skeletal muscle homeostasis and repair at a time which may lead to a meaningful preventive response..

Introduction

Sarcopenia was a term coined by Irwin Rosenberg to mean ‘paucity of flesh’ (in Greek ‘sarx’ or flesh + ‘penia’ or loss). It refers to age-related decline in skeletal muscle .To date; the term sarcopenia is primarily a research term. However, the recent development of an International Classification of Diseases, (ICD-10) code for sarcopenia highlights the need for uniformity and recognition of the underlying constructs by practicing clinicians. Therefore, the definition of sarcopenia was adapted to include any loss of muscle tissue and function due to aging, chronic diseases, low protein-energy intake and physical inactivity. Chronic kidney disease (CKD) is a catabolic state, known to be associated with protein wasting , there may also be decreased muscle synthesis in the uremic milieu ^[1]. Perhaps, the use of the term ‘uraemic sarcopenia’ would provide recognition by the renal community for this devastating problem. It is important for practicing nephrologists to be able to identify and quantify sarcopenia in their patients, as well as familiarize themselves with interventions to diminish its progression

Sarcopenia is diagnosed with some measure of lean mass (i.e. DEXA dual-energy x-ray absorptiometry and bioelectrical impedance analysis (BIA) and/or physical function [Table 1] For many clinical situations, DEXA and/or BIA are not clinically feasible due to time and/or cost.

Pathophysiology of Sarcopenia in Chronic Kidney Disease

The underlying mechanisms of sarcopenia in the context of CKD revolve around the loss of muscle mass. This is a ‘chicken-or-the-egg’ conundrum, as it is unknown whether reduced physical activity causes muscle loss or loss of muscle causes reduced activity. Regardless of the initiating factor, the loss of muscle mass in CKD may be attributed to a negative balance of protein homeostasis, that is increased catabolism and decreased synthesis of muscle. (Figure 1)

The current state of knowledge indicates that the factors predisposing patients with chronic kidney disease to the development of sarcopenia in fact can be divided into two groups, associated with the developing inflammatory process and associated with the kidney disease^[3]

Inflammation

Inflammatory markers (CRP and interleukin-6—‘IL-6’, and tumour necrosis factor- α —‘TNF- α ’). Cause muscle wasting in patients with CKD. Infusion of an acute phase reactant protein angiotensin II by Zhang et al^[5] showed increased hepatic production of IL-6 and SAA acting synergistically to impair insulin/IGF-1 signaling, thus promoting muscle proteolysis.

Metabolic acidosis

Metabolic acidosis promotes muscle protein wasting and protein-energy wasting by increasing protein degradation and reducing protein synthesis. Muscle protein degradation and excessive oxidation of branched-chain amino acids in skeletal muscle are achieved through up-regulation of the ubiquitin-proteasome pathway^[6]. Pickering et al. found that a small increase of the serum bicarbonate level in CAPD patients leads to a down-regulation of proteolysis via the UPS in muscle.

Myogenic progenitor and satellite cells

Satellite cells are skeletal muscle-specific stem cells known for their robust myogenic potential and self-renewal properties. After muscle injury, satellite cells are activated and express the MyoD and myogenin transcription factors leading to proliferation and formation of myoblasts, and then differentiate, forming new muscle fibers to repair injured muscle. Wang et al.^[7] reported decreased MyoD protein and myogenin expression with impaired regeneration of injured muscle in mice with CKD.

Changes in myostatin and follistatin

Muscle regeneration and size have been shown to be effected by myostatin, a negative regulator of skeletal muscle mass. Myostatin and follistatin are members of the TGF- β family. Myostatin levels are over expressed in uraemic cachexia and negatively impact on skeletal muscle mass and growth leading to muscle atrophy through a complex signaling mechanism which involves the activation of the canonical pathway of Smad, mitogen-activated protein kinase pathway and inhibition of Akt signaling^[8]. Follistatin, a regulatory glycoprotein, previously known as FSH-suppressing protein is a potent myostatin antagonist and experimental evidence has shown that over expression of follistatin induces a dramatic increase in muscle mass^[9].

Changes in the angiotensin

The rennin angiotensin system is activated in many catabolic conditions including CKD leading to down-regulation of phospho-Akt and activation of caspase-3 in skeletal muscle, resulting in actin cleavage, an important component of muscle proteolysis and to increased apoptosis^[10]. Brink et al demonstrated that infusion of angiotensin II in the rat increased muscle proteolysis and decreased circulating and skeletal muscle IGF-1 leading to a marked reduction in body weight.

ATP-dependent ubiquitin-proteasome system (UPS)

The ATP-dependent ubiquitin-proteasome proteolysis is singled out as the major cause of increased skeletal muscle degradation in CKD. Inflammation activates the UPS leading to cleavage of a characteristic 14 kDa actin fragment in the soluble fragment of muscle which is the hallmark of increased muscle proteolysis in CKD. Metabolic acidosis, which is common among CKD patients, can similarly induce UPS up regulation. Boivin et al. observed increased caspase-3 activity in the skeletal muscle of dialysis patients leading to increased generation of 14 kDa actin as well as ubiquitinated C-terminal actin fragment^[11].

Hormonal changes

Role of vitamin D :Patients with CKD have prolongation of the relaxation phases of muscle contraction, independent of serum calcium, parathyroid hormone or serum phosphorus levels, suggesting a possible role for vitamin D in the myopathy of CKD^[12]. In addition, muscle biopsies in adults with profound vitamin D deficiency have shown predominantly Type II fiber atrophy and enlarged interfibrillar spaces and infiltration of fat, fibrosis and glycogen granules.

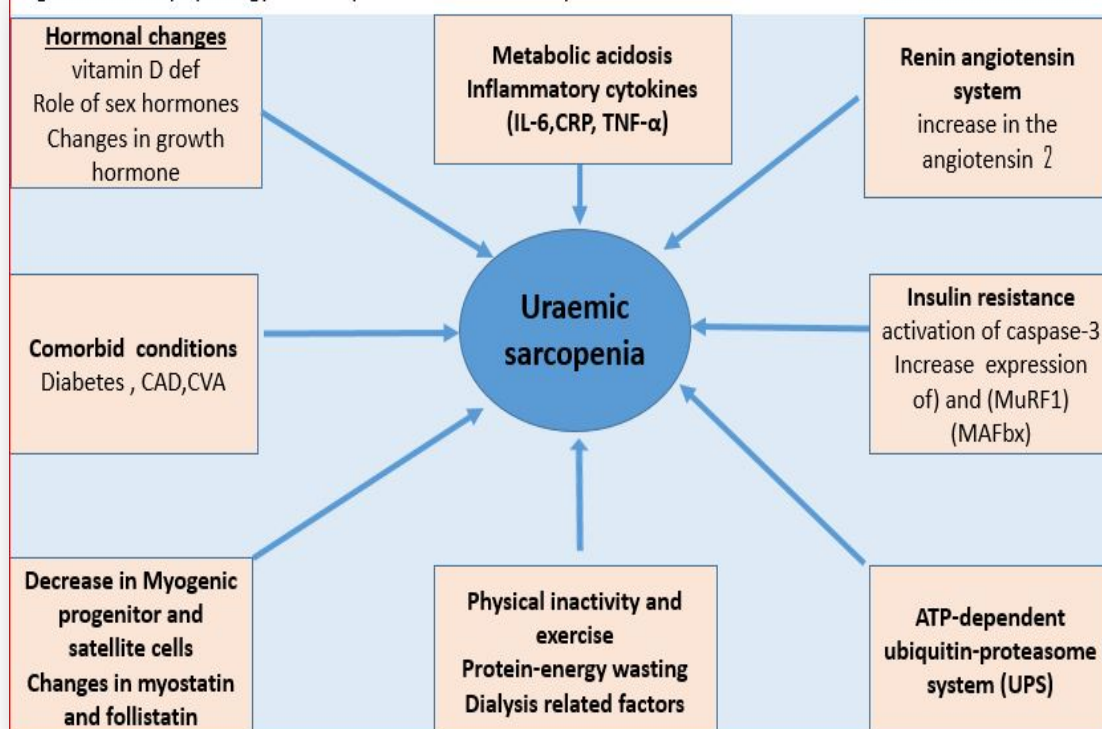
Role of sex hormones Inflammation-induced anorexia is more severe among male rats, while progesterone injections decreased the severity of anorexia among female rats. These observations suggest that gender and sex hormones may contribute to the different symptomatology associated with poor appetite in men and women and support the hypothesis that uraemic men may be more susceptible than women to inflammation-induced anorexia^[13] and consequently skeletal muscle abnormalities.

Changes in growth hormone CKD is associated with growth hormone (GH) resistance and, in skeletal muscle, it is a potential cause of increased protein catabolism and wasting.. The resistance of the anabolic hormone IGF-1 to protein turnover in skeletal muscles in CKD has been proposed as one of the mechanisms leading to muscle wasting^[14]

Insulin resistance

CKD is associated with insulin resistance from an early stage and even when the GFR is normal. It is strongly associated with increased muscle protein break down, primarily mediated by the ubiquitin-proteasome pathway. Recently, the link between impaired insulin/IGF-I signaling in muscle leading to a decrease in P Akt and muscle wasting was unveiled under several conditions, including excess angiotensin II, inflammation and CKD with acidosis^[15] and results in activating two pathways causing muscle protein wasting. First, there is activation of caspase-3 that breaks down the complex protein structure of muscle. Second, a low P-Akt decreases phosphorylation of the forkhead transcription factor, which permits its translocation into the nucleus, where it stimulates the expression of atrogen-1/muscle atrophy F-box (MAFbx) and muscle ring finger 1 (MuRF1)^[16]

Figure 1 : Pathophysiology of sarcopenia in chronic kidney disease



Protein-energy wasting

PEW is not uncommon in patients with CKD. It is characterized by reduced circulating body protein, reduced body mass and reduced muscle mass. Disturbances in appetite regulating hormones such as leptin, a potent appetite inhibitor, and ghrelin, an appetite stimulant, have been reported in CKD^[17]

Physical inactivity and exercise

Recent research suggested that CKD can induce muscle protein wasting and muscle atrophy due to complex mechanisms including physical inactivity and deconditioning^[18]. Resistance training in animal models has been shown to reduce muscle protein catabolism and improves the muscle wasting associated with CKD, both by increasing the muscle size and strength

IMPLICATIONS OF URAEMIC SARCOPENIA

Sarcopenia is a powerful predictor of morbidity and mortality in dialysis patients. Several studies suggested that a larger body size in maintenance dialysis patients has survival advantages^[19] and poor survival in dialysis patients with a low body size v. Kalantar-Zadeh et al.^[20] reported that low baseline body fat percentage and fat loss over time are independently associated with higher mortality in maintenance dialysis patients even after adjustment for demographics and surrogates of muscle mass and inflammation. Noori et al.^[21] also reported that higher fat mass in both sexes and higher lean body mass in women appear to be protective. There are a limited number of studies that have examined consequences of sarcopenia in predialysis CKD. In the Pereira et al.^[22] study sarcopenia

measured by muscle mass index, using BIA and hand grip strength, was associated with a Hazard Ratio (HR) for mortality of 3.02 (95% CI: 1.30–7.05, n = 287) and an independent predictor of better mental health and greater survival in dialysis patients

Muscle wasting is a devastating complication because it leads to decreased quality of life, increases cardiovascular complications and increases morbidity and mortality associated with CKD. Importantly, low exercise capacity as a consequence of muscle wasting is also a powerful, independent predictor of mortality in patients with CKD ^[23]. Although we know a lot of hormonal and molecular mechanisms, in every day practice, the arsenal for the prevention and treatment still remains relatively poor. we can safely apply the method, which has been successfully used for many years in elderly people with or without kidney disease: a proper nutrition to ensure an adequate intake of calories and protein combined with skillfully matched and regular exercise may act both as prevention and treatment. In a recent Cochrane review, exercise interventions were administered in patients on dialysis in 45 of 59 randomized controlled trials (RCTs), whereas a smaller proportion included patients with CKD predialysis (11 of 59 RCTs) ^[24]. In the predialysis population, the following exercise types were used: aerobic (six studies), resistance training (three studies), and aerobic and resistance (two studies). The conclusion was that there were insufficient data to support a role of exercise mitigating CKD progression but there was evidence for aerobic exercise improving aerobic capacity and health-related quality of life. Myostatin is a myokine and an inhibitor of skeletal muscle growth ^[25]. In a 5/6 nephrectomy mouse model, subcutaneous myostatin antibody injections (5 mg/kg) had multiple beneficial effects upon skeletal muscle, including reduced protein degradation, increased protein synthesis and improved satellite cell function

Role of nephrologists

A recent survey showed that though 61.2% of polled nephrologists felt that their patients' physical activity was poor, 53% did not prescribe exercise to dialysis patients. As would be expected, the majority did not receive training regarding exercise in their medical school or residency ^[26]. Another survey of nephrologists also showed that a lack of time while rounding in dialysis units and a significant number believed that other 'medical' issues were more important than the lack of physical activity. Once sarcopenia is identified it is important to combat it with interventions lead by exercise and nutrition professionals. In patients undergoing dialysis, a structured physical therapy program has been shown to increase distance walked on the 6-min walk test and in quadriceps strength ^[27]

Conclusion

Sarcopenia in CKD, though not well defined, is very important with respect to its relationship with patient-centered outcomes of mobility limitations, functional limitations in activities of daily living, hospitalizations, fractures and mortality. Specific cutoffs for assessments that define sarcopenia in the CKD population are unknown, but individual patient trends may be of similar importance. There are many simple physical function and muscle function tests that can be performed in the nephrologist's office without adding more than a few minutes to patient encounters. Despite this excessive risk of muscle wasting, CKD patients are treated with much less intensity, suggesting that clinicians have concentrated on complications in patients with ESRD, when pathology is already too advanced or irreversible. Considering the impact of muscle wasting on the well-being of patients with CKD and the

healthcare system in general, it makes logical sense to study patients with mild-to-moderate renal impairment at a stage when the skeletal muscle complications may still be reversible and to identify and introduce therapeutics strategies to maintain skeletal muscle homeostasis and repair at a time which may lead to a meaningful preventive response.

Operational definitions of sarcopenia ^[2,4]

Author	Appendicular lean mass	Gait	Physical performance
International Working Group on Sarcopenia	Appendicular skeletal muscle mass/height ² categorized by sex-specific lowest 20% of the health aging and body composition study	Gait speed ≤1 m/s	
European Working Group on Sarcopenia in Older People	Low appendicular skeletal muscle mass (ASM) using the Baumgartner's criteria (ASM/height ² ≤5.45 kg/m ²)	Gait speed ≤0.8 m/s	Grip strength cutoff of 20 kg (via dynamometer)
Foundation of NIH Sarcopenia Project	Appendicular lean mass Men: <0.789 Women: <0.512	Gait speed ≤0.8 m/s	Grip strength Men: <26 women: < 16 kg

Conflict of interest statement

None declared.

Disclosures - none , no source of funding

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