

## Full Reviews

# Uraemic sarcopenia: aetiology and implications

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### ABSTRACT

The term uraemic myopathy has been used loosely to describe the skeletal muscle abnormalities in uraemic patients. However, it does not fully explain the observed abnormalities as recent research has documented a normal skeletal muscle physiology in the presence of reduced muscle force, selective structural changes and significant muscle wasting. Ageing is associated with sarcopenia (muscle wasting) and an increase in the prevalence of chronic kidney disease (CKD), which accelerates the normal physiological muscle wasting. Similar to sarcopenia, muscle wasting in uraemic patients appears to be the hallmark of the disease and its aetiology is multifactorial with hormonal, immunologic and myocellular changes, metabolic acidosis, reduced protein intake and physical inactivity. Uraemic sarcopenia presents a high probability for morbidity and mortality and consequently a high priority for muscle wasting prevention and treatment in these patients. Perhaps, the use of the term 'uraemic sarcopenia' would provide recognition by the renal community for this devastating problem. The purpose of this review is to relate the findings of the recent publications that describe abnormalities in uraemic skeletal muscle to the possible pathogenesis of muscle wasting and its consequences in patients with CKD.

**Keywords:** muscle wasting, pathophysiology, sarcopenia, uraemia

### INTRODUCTION

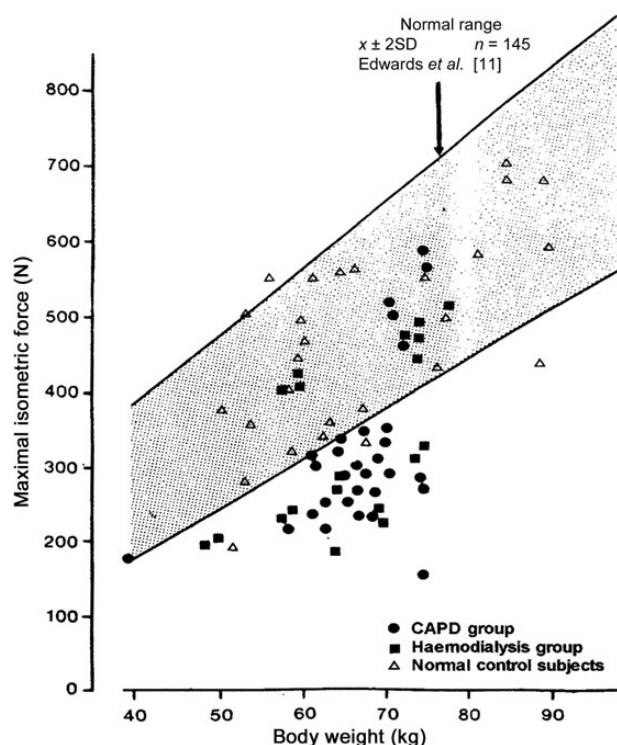
Skeletal muscle abnormalities in chronic kidney disease (CKD) have been described over half a century ago under the loose term uraemic myopathy [1]. The early literature reported two patterns of muscle weakness in dialysis patients; one

affecting predominately distal muscles and associated with neuropathy and the other affecting predominantly proximal muscles [2, 3]. A recent report has suggested that uraemic myopathy is common with an overall prevalence of ~50% in dialysis patients [4]. However, in general, physical examination, electromyographical studies and muscle enzymes are normal in these patients. A more recent research has documented reduced muscle force, selective structural changes and significant muscle wasting in the presence of normal skeletal muscle physiology [5, 6]. Although the term uraemic myopathy raised awareness of the problem, it did not fully explain the pathophysiology of the disease.

It is important to emphasize that both uraemia and sarcopenia are progressive diseases. Uraemia is a clinical syndrome associated with fluid, metabolic abnormalities, electrolyte and hormone imbalances, which develop in parallel with deterioration of renal function. Some of these abnormalities start earlier in the course of the uraemia and others appear late. However, by using the term uraemic sarcopenia, the progressive and cumulative effect of the CKD on the skeletal muscles is implied.

### SKELETAL MUSCLE ABNORMALITIES IN CKD

Muscle weakness, defined as a failure to generate force [7], is common in CKD patients. Several studies have confirmed reduced muscle strength in these patients [6, 8, 9]; however, only two studies analysed objectively the contractile properties of skeletal muscle of dialysis patients. Berkelhammer *et al.* [10] assessed the function of the adductor pollicis muscle in terms of force and speed of relaxation and concluded that skeletal muscle function is unaffected by uraemia, but provides a functional measure of nutritional status in chronic renal failure. In a more recent study, our group investigated the quadriceps



**FIGURE 1:** Reproduced with permission from Fahal *et al.* [6]. Force (N) of maximum voluntary isometric contractions of quadriceps in all dialysis patients and controls. Shaded area represents the normal range of 84 males (aged 6–63 years) and 61 females (aged 5–46 years) from Edwards *et al.* [11].

femoris and adductor pollicis muscles force and contractile properties in a group of dialysis patients. Objective measurement of quadriceps force revealed unequivocal force reduction in 71% of the patients (Figure 1), particularly, in malnourished patients. We also demonstrated no evidence of impaired neuromuscular transmission or impaired excitation–contraction coupling as demonstrated by percutaneous electrical stimulation studies; however, skeletal muscle relaxation characteristics were slowed in all patients particularly in the malnourished group [6].

## MUSCLE FATIGUE

Fatigue, defined as the failure to sustain force or power output [7], is often reported by patients on dialysis. Two types of fatigue are recognized based on an anatomical subdivision, central and peripheral [7, 11].

In patients with CKD, the mechanisms responsible for the perceived fatigue remain poorly understood. In theory, hormonal imbalances [12], malnutrition [10], ATP and glycogen depletion [13], impaired oxygen transport due to anaemia, metabolic acidosis, alterations in electrolytes [14], altered life style [15] and muscle wasting and weakness due to muscle fibres atrophy [16] could all lead to peripheral fatigue development during exercise. However, there is little objective evidence of impairment in peripheral muscle function itself that contributes to fatigue in these patients. Many studies have

examined exercise capacity relying on measures of  $\text{VO}_2$  max [17, 18] or voluntary contractions lifting loads. Few studies have examined the electrophysiological response of muscle during fatiguing activity. Berkelhammer *et al.* [10] examined the frequency, force and relaxation characteristics of adductor pollicis on the stimulation of the ulnar nerve in patients with chronic renal failure and were able to show no abnormality, although the 10–100 Hz force ratio was increased and relaxation characteristics slower in a group of malnourished patients. In a more recent study, our group reported that the fatigability of dialysis patients muscle is the same as in normal subjects. Fatigue of adductor pollicis during electrically evoked contractions was similarly demonstrated in both patient and control groups, the changes in physiological parameters measured (force, excitation and relaxation characteristics) were similar in both the groups [5] and frequency dependence of force generation, 20:50 Hz tetanic force ratio and relaxation characteristics were not significantly different between the patient and control groups. However, subdividing the patients by nutritional status using the Subjective Global Assessment questionnaire revealed greater fatigue at 10 Hz in the malnourished compared with the well-nourished group [5]. Although these findings have been attributed to ‘malnutrition’, more recent evidence documented that muscle abnormalities in uraemia can occur despite adequate nutritional intake and feeding does not improve the abnormalities. Instead, there are complex mechanisms that stimulate loss of skeletal muscle which will be discussed in this review.

## MUSCLE BIOPSY STUDIES

The earliest histological studies of the skeletal muscles of haemodialysis patients were at variance reporting electromyographical and morphological abnormalities with or without neuropathic changes [16, 19]. However, there is firm evidence that the most common abnormalities in uraemia are Type II fibre atrophy, small cross-sectional area (CSA) and type grouping [20, 21]. Recently, we found Type II fibre CSA ( $\mu\text{m}^2$ ) of uraemic patients to be smaller than that of healthy controls ( $3883 \pm 557$  versus  $5213 \pm 1288$ ) and also found a suggestion that Type I fibres CSA ( $\mu\text{m}^2$ ) are smaller ( $4011 \pm 458$  versus  $4627 \pm 1112$ ) in the uraemic patients compared with the healthy controls. Considering the subtypes of Type II fibres, we found greater atrophy of Type IIB fibres (Type X using the myosin heavy chain-based classification) than of Type IIA fibres ( $2335 \pm 473$  versus  $3533 \pm 956$ ) and a significantly smaller Type IIB fibre area ( $2335 \pm 473$  versus  $4346 \pm 1496$ ) in the malnourished uraemic patients compared with the well-nourished patients [5].

Electron microscopy studies showed no significant structural abnormalities in the mitochondria of dialysis patients. However, the glycogen content was increased possibly reflecting reduced physical activity, and lipofuscin increased possibly due to muscle atrophy [19, 22]. However, the mitochondrial enzymes (cytochrome *c* oxidase, succinate reduction of cytochrome, palmitate oxidation and citrate synthase) were low in the quadriceps muscle biopsy of dialysis patients compared

with normal controls and chronic fatigue patients [5]. A more recent study using muscle biopsies of patients with CKD has also reported a decrease in muscle mitochondrial oxidative enzymes (muscle cytochrome *c* oxidase activity and citrate synthase) and a decrease in the synthesis of muscle contractile mixed muscle proteins, myosin heavy chain and mitochondrial proteins. The synthetic rates of muscle proteins and activity of mitochondrial enzymes were negatively correlated to the severity of renal failure [23]. In another study, the same group demonstrated an age-related selective decline in the synthesis rate of the muscle proteins myosin heavy chain [24] and a similar decline in the rate of muscle mitochondrial protein synthesis with ageing, which was associated with a decline in skeletal muscle oxidative capacity and mitochondrial function [25]. The mechanism by which uraemia contributes to the decrease in the synthetic rate of several muscle proteins is complex and will be discussed in the following sections.

## MUSCLE PROTEIN WASTING

Muscle wasting is common [26] and is progressive in patients with CKD [27]. The decrease in muscle mass involves both a decrease in muscle fibre size (atrophy) and number (hypoplasia). This is attributed to muscle protein wasting and its multifactorial aetiology with hormonal, immunologic and myocellular changes, inflammation, metabolic acidosis, reduced protein intake, physical inactivity, excess angiotensin II, abnormalities in insulin/insulin-like growth factor I (IGF-I), myostatin expression and reduction in satellite cells function (Figure 2). Most of these stimulate the ATP-dependent ubiquitin-proteasome system (UPS), which has been identified as the most important pathway for muscle wasting. The potential intracellular signalling processes involved in uraemic muscle wasting are depicted in Figure 3 and although certain regulatory pathways are emphasized other mechanisms are probably involved as well.

Similar to sarcopenia, the loss of muscle mass (wasting) in CKD patients appears to be multifactorial and the different mechanisms contributing to uraemic sarcopenia are reviewed below.

## MYOGENIC PROGENITOR AND SATELLITE CELLS

Satellite cells are skeletal muscle-specific stem cells known for their robust myogenic potential and self-renewal properties. They are located between the basal lamina and sarcolemma of muscle fibres [28, 29]. 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 fibres to repair injured muscle [30]. Transplantation of a single muscle fibre, with resident satellite cells intact, is sufficient not only to support significant regeneration of the host limb muscle but also to replenish the satellite cell pool [31].

Wang *et al.* [32] reported decreased MyoD protein and myogenin expression with impaired regeneration of injured muscle in mice with CKD. These abnormalities suggested that satellite cells function is impaired in CKD; however, the abnormalities were corrected in the muscle by resistance exercise. Recently, the same group reported a new mechanism for CKD-induced muscle atrophy linking impaired satellite cell function to decreased IGF-1R signalling leading to reducing satellite cell proliferation and differentiation [33].

## INFLAMMATION

Low-grade inflammation is common in CKD even in early stages as evident from increased circulating levels of inflammatory markers (CRP and interleukin-6—‘IL-6’, and tumour necrosis factor- $\alpha$ —‘TNF- $\alpha$ ’). Recent evidence suggests that inflammation is an important cause of muscle wasting in patients with CKD [34–36]. Further research has shown that muscle mass in dialysis patients is inversely correlated to circulating levels of IL-6 and CRP [37]. There are several mechanisms for the role of inflammation in muscle wasting. TNF- $\alpha$  enhances muscle wasting via induction of the NF $\kappa$ B pathway [38] and treatment with TNF- $\alpha$  attenuates insulin-stimulated protein synthesis [39] and inhibits myocyte differentiation through NF $\kappa$ B activation, causing muscle wasting [40]. Zhang *et al.* [41] uncovered a new role for an acute phase reactant protein. Infusion of angiotensin II increases hepatic production of IL-6 and SAA acting synergistically to impair insulin/IGF-1 signalling, thus promoting muscle proteolysis. Cheung *et al.* showed that infusion of cytokines (TNF- $\alpha$ , IL-6, IL-1 $\beta$ , interferon- $\gamma$ ) enhanced muscle protein degradation via the NF $\kappa$ B pathway, whereas neutralization of these factors by genetic or pharmacological approaches attenuates muscle wasting [42]. Inflammation also leads to muscle wasting through the activation of the UPS. This system is thought to be the major cause of muscle wasting in CKD and will be discussed in the following section.

## ATP-DEPENDENT UPS

Regulation of muscle protein balance in uraemia is complex and involves several mechanisms [42]. The ATP-dependent ubiquitin-proteasome proteolysis is singled out as the major cause of increased skeletal muscle degradation in CKD [43]. Inflammation and metabolic acidosis play a major role in activating the UPS. 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 [44]. Metabolic acidosis, which is common among CKD patients, can similarly induce UPS up-regulation and increased branch amino acid oxidation in skeletal muscle [45]. 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. The same group also noted that



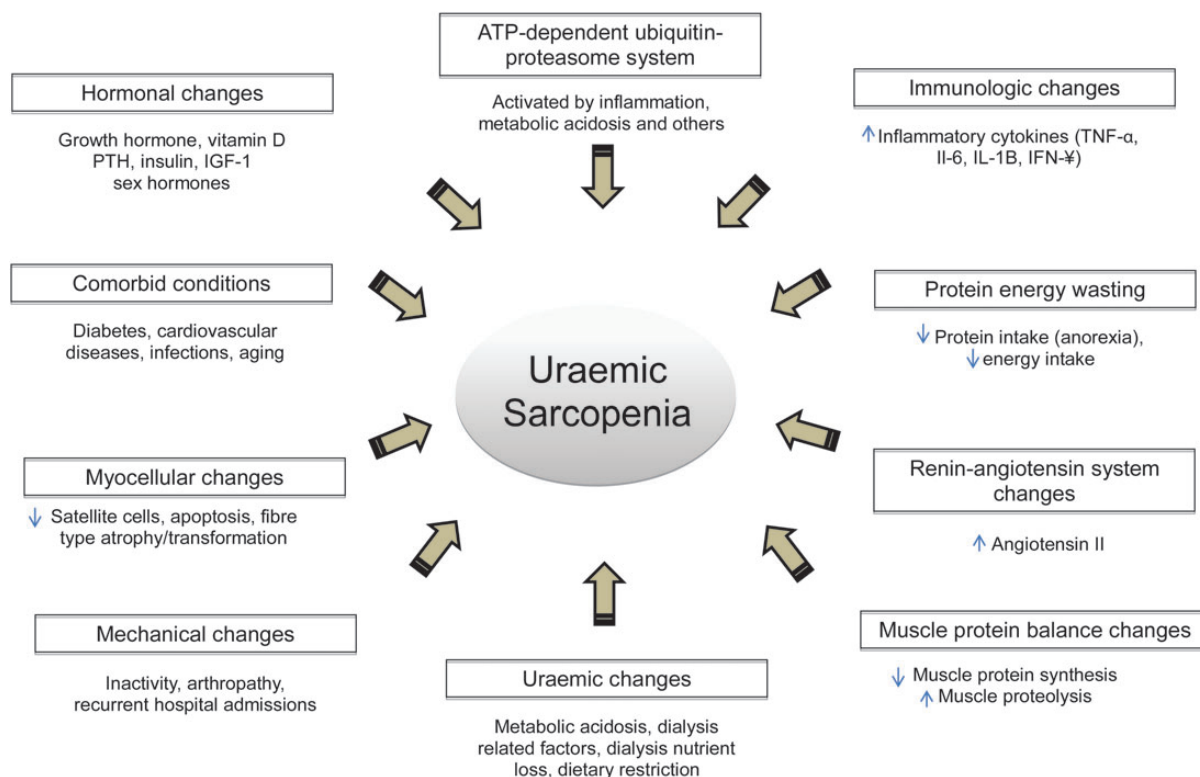


FIGURE 2: Possible aetiology of uraemic sarcopenia.

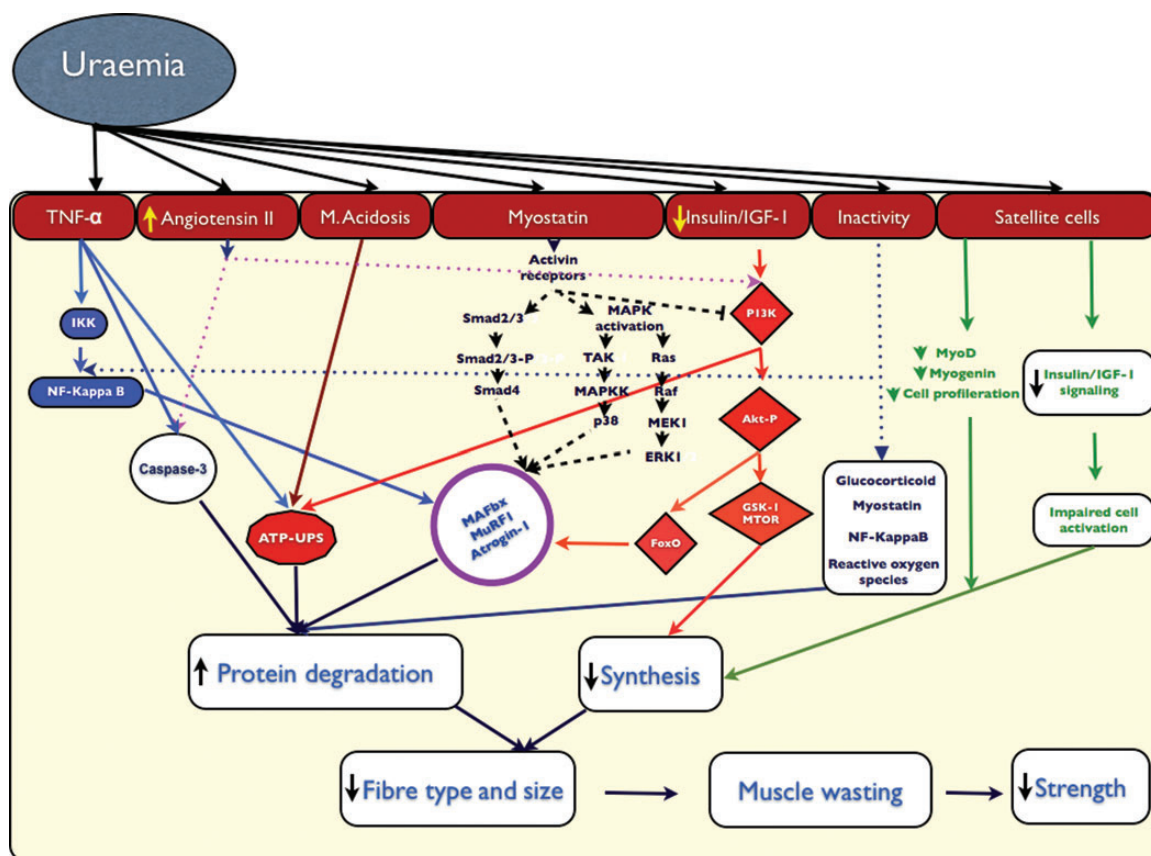


FIGURE 3: Potential intracellular signalling processes involved in uraemic muscle wasting (sarcopenia). Although certain regulatory pathways are emphasized other mechanisms are probably involved as well.

the skeletal muscle of dialysis patients exhibited augmented apoptosis [46].

## METABOLIC ACIDOSIS

Metabolic acidosis is prevalent among CKD patients, particularly those in stage 4 [47]. It promotes muscle protein wasting and protein-energy wasting (PEW) [48] by increasing protein degradation [49] and reducing protein synthesis [50]. As a result, maintenance of muscle mass is impaired in CKD patients with altered protein turnover rates, Type II fibre atrophy manifested clinically in muscle wasting [51]. Muscle protein degradation and excessive oxidation of branched-chain amino acids in skeletal muscle [52] are achieved through up-regulation of the ubiquitin-proteasome pathway [42].

Stein *et al.* [53] randomly assigned 200 peritoneal dialysis patients with metabolic acidosis to treatment with a dialysate solution of 35 mmol/L lactate or to a dialysate of 40 mmol/L lactate. After 1 year, both the groups of patients had higher serum bicarbonate, had gained weight and had an increase in mid-arm muscle circumference compatible with an increase in muscle mass. Pickering *et al.* [54] 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 and also found an increase in plasma branched-chain amino acids consistent with a decrease in their degradation. A recent study from our group using sodium bicarbonate supplementation in patients with pre-dialysis CKD reported a slower decline in renal function as well as increase in dietary protein intake and reduction in normalized protein nitrogen appearance, reflecting a lower protein breakdown leading to an increment in the lean body mass as assessed by mid-arm muscle circumference [55]. Other studies of bicarbonate supplementation were also associated with the reduction of protein degradation in both peritoneal [50, 56] and haemodialysis [57] patients as well as in elderly pre- end-stage renal disease (ESRD) patients [58]. Correction of acidosis may, therefore, help to preserve muscle mass and improve the health of patients with CKD.

## CHANGES IN VITAMIN D

Vitamin D status is positively associated with muscle strength [59], physical performance [60] and inversely associated with the risk of falling [61] and it also plays an important role in other metabolic pathways, such as immune regulation, inflammation, insulin resistance, hypertension, thrombosis and the proliferation and differentiation of several cells including skeletal muscle [62]. Vitamin D supplementation has shown to improve tests of muscle function [63], reduce falls [64], and possibly impact on muscle fibre composition and morphology in vitamin D-deficient older adults [65]. In addition, the identification of the vitamin D receptor on muscle cells [66] has provided further support for a direct effect of vitamin D on muscle tissue.

As in individuals with normal renal function and vitamin D deficiency [67], patients with CKD have prolongation of the

relaxation phases of muscle contraction, independent of serum calcium, parathyroid hormone or serum phosphorus levels [6, 9]. These observations suggested a possible role for vitamin D in the myopathy of CKD and early clinical descriptions recognized a potential association between vitamin D and muscle in CKD patients [68]. In addition, muscle biopsies in adults with profound vitamin D deficiency have shown predominantly Type II fibre atrophy and enlarged interfibrillar spaces and infiltration of fat, fibrosis and glycogen granules [69]. These morphological features are not dissimilar from those found in patients with CKD with Type II muscle fibre atrophy, lipofuscin and glycogen deposition [2, 5].

## CHANGES IN THE ANGIOTENSIN II

The reninangiotensin 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 [70]. Brink *et al.* [71] demonstrated that infusion of angiotensin II in the rat produced increased muscle proteolysis and decreased circulating and skeletal muscle IGF-1 leading to a marked reduction in body weight. While the administration of losartan, an angiotensin II Type 1 receptor blocker, inhibits canonical transforming growth factor- $\beta$  (TGF- $\beta$ ) signalling activity and promotes muscle remodelling in mouse models of Marfan syndrome and dystrophin-deficient Duchenne muscular dystrophy [72]. Increased TGF- $\beta$  signalling is among the mechanisms of the skeletal muscle wasting [73]. It is a known inhibitor of skeletal muscle regeneration and remodelling, impaired myocyte differentiation [74], inhibits satellite cell activation, [73, 75] and leads to the formation of fibrotic tissue in response to skeletal muscle injury [75]. Furthermore, treatment with losartan after infliction of muscle injury also improved regeneration in normal adult murine skeletal muscle by reducing fibrotic tissue formation [76]. Another study demonstrated that losartan facilitated the remodelling of sarcomeric skeletal muscle after injury and protected it from disuse atrophy during immobilization in an ageing mouse model [77].

## CHANGES IN APPETITE

Anorexia, defined as the loss of desire for food, is common and complex in CKD. Disturbances in appetite-regulating hormones, decreased ability to distinguish flavours, altered taste, uraemia-related gastrointestinal symptoms [78], depression [79], haemodynamic instability as a result of exposure to anti-hypertensive medications or haemodialysis, and a sensation of fullness during peritoneal dialysis are among the causes cited in the literature.

Disturbances in appetite-regulating hormones such as leptin, a potent appetite inhibitor [80], and ghrelin, an appetite stimulant [81], have been reported in CKD. Leptin, a potential mediator of inflammation-induced anorexia [82] is elevated in

CKD patients [83] due to impaired renal clearance [84]. Reports on the total circulating ghrelin levels in CKD are inconsistent [85, 86]. However, recent studies have shown that only plasma des-acyl ghrelin levels were elevated in CKD patients and suggested that elevated des-acyl ghrelin levels could be involved in the anorexia of CKD patients [87].

## GENDER AND CHANGES IN SEX HORMONES

Experimental and clinical studies have shown gender differences in disease presentation and severity of symptoms. The influence of sex hormones on muscle function has been previously investigated. Testosterone, an anabolic steroid, administration is associated with an increase in muscle mass and strength [88], while testosterone deficiency causes reduced muscle mass. In men with CKD, testosterone deficiency is common [89]. It is due to reduce prolactin clearance [90] and uraemic inhibition of luteinizing hormone signalling at the level of the Leydig cells [91].

Female with CKD are usually oligomenorrhoeic and oestrogen deficient at an early stage. Oestrogen is responsible for changes in strength and investigations of force production during the menstrual cycle in healthy women reported greater force generation of the adductor pollicis [92] and the quadriceps femoris muscle group [93] around ovulation when oestrogen levels are at their height. Phillips *et al.* [94] in another study found that muscle weakness in women occurs at an earlier age than in men, but strength is preserved by hormone replacement therapy.

Male gender is associated with a more rapid rate of progression and a worse renal outcome in patients with chronic renal disease [95, 96]. Inflammation-induced anorexia is more severe among male rats, while progesterone injections decreased the severity of anorexia among female rats [97]. Nephrectomized male rats develop anaemia and malnutrition, whereas matched female rats are not significantly affected [98]. Moreover, a recent study suggests that sex may determine the severity of symptoms, such as handgrip strength, among patients who report a poor appetite.

All of 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 [99] and consequently skeletal muscle abnormalities.

## CHANGES IN GROWTH HORMONE

CKD is associated with growth hormone (GH) resistance [100] and, in skeletal muscle, it is a potential cause of increased protein catabolism and wasting. Several mechanisms for GH resistance have been reported in CKD [101, 102]. 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 [103]. IGF bioactivity has been found to be reduced in end-stage renal failure leading

to the reduction in free IGF-1 in proportion to renal failure [104].

Studies have shown that recombinant human growth hormone (rhGH) administered at pharmacologic doses induces a net anabolic action and also improves food utilization in uraemic animal models [105] and in patients with advanced CKD [106]. Anabolic effects of rhGH in haemodialysis patients have also been noted on the muscle compartment, with increases of up to 3–4 kg in lean body mass with short and mid-term administration [107]. rhGH improves whole-body protein homeostasis. It significantly reduces essential amino acid and muscle loss in chronic haemodialysis patients [108]. A 6-week administration of 50 µg rhGH in cachectic haemodialysis patients has significantly improved the net muscle protein balance [109] and increased lean body mass and quality of life with no significant side effects [110].

## CHANGES IN INSULIN

CKD is associated with insulin resistance from an early stage [111] and even when the GFR is normal [112, 113]. Insulin resistance correlated linearly with the decline in renal function [114] and is established in almost all patients at ESRD [115]. Several explanations for the presence of insulin resistance in CKD patients have been proposed, such as deficiency of vitamin D, anaemia or putative uraemic toxins [116–118].

Insulin resistance in CKD patients has been related to the development of uraemic myopathy and diabetic dialysis patients have a higher prevalence and more severe forms of uraemic myopathy [119]. This is because insulin resistance decreases the use of glucose as an energy source [115], increases hepatic gluconeogenesis not normally suppressible following insulin release, reduces hepatic and/or skeletal muscle glucose uptake and impairs intracellular glucose metabolism [116]. It is strongly associated with increased muscle protein breakdown, primarily mediated by the ubiquitin-proteasome pathway [44, 120]. Recently, the link between impaired insulin/IGF-I signalling in muscle leading to a decrease in P-Akt and muscle wasting was unrevealed under several conditions, including excess angiotensin II, inflammation and CKD with acidosis [45, 121] 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 atrogin-1/muscle atrophy F-box (MAFbx) and muscle ring finger 1 (MuRF1) [121]. It is important to emphasize that sarcopenia is a progressive disease and the effects of insulin resistance is a cumulative effect starting early in the course of the 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 [58]. The aetiology of PEW in CKD

**Table 1. Aetiology of muscle wasting in sarcopenia and CKD**

Sarcopenia	CKD
<ul style="list-style-type: none"> <li>• Increase in proinflammatory cytokines</li> <li>• Decreased protein intake</li> <li>• Decline in exercise</li> <li>• Decrease sex hormones</li> <li>• Decreased Growth hormone</li> <li>• Decreased insulin</li> <li>• Decrease vitamin D</li> <li>• Decline in satellite cells</li> </ul>	<ul style="list-style-type: none"> <li>• Increase in proinflammatory cytokines</li> <li>• Muscle protein imbalance</li> <li>• Inactivity</li> <li>• Decrease sex hormones</li> <li>• Growth hormone resistance</li> <li>• Insulin resistance</li> <li>• Vitamin D abnormalities</li> <li>• Decline in satellite cells</li> <li>• Metabolic acidosis</li> <li>• Angiotensin II</li> <li>• PEW</li> <li>• Myostatin overexpression</li> </ul>

is complex and includes inflammation, transient intercurrent catabolic illnesses [122], nutrient losses into dialysate [123], metabolic acidosis [124], resistance to insulin [125], GH [126] and IGF-I [127], hyperglucagonemia [128], hyperparathyroidism [129] and loss of blood into the haemodialyser, into faeces or by blood drawing [130].

### PHYSICAL INACTIVITY AND EXERCISE

The benefits of exercise in the general population are well documented [131–134] as is the reduced physical activity in dialysis and CKD patients [135, 136]. Recent research suggested that CKD can induce muscle protein wasting and muscle atrophy due to complex mechanisms including physical inactivity and deconditioning [137]. 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 [138–140] and by reducing low-grade inflammation and increasing IGF-I and IGF-II [141, 142].

### CHANGES IN MYOSTATIN AND FOLLISTATIN

Myostatin and follistatin are members of the TGF- $\beta$  family. Myostatin levels are overexpressed in uraemic cachexia and negatively impact on skeletal muscle mass and growth leading to muscle atrophy through a complex signalling mechanism which involves the activation of the canonical pathway of Smad, mitogen-activated protein kinase pathway and inhibition of Akt signalling [32, 143]. Strategies to correct uraemic sarcopenia may be mediated, at least, in part, by inhibition of myostatin expression [144].

Follistatin, a regulatory glycoprotein, previously known as FSH-suppressing protein is a potent myostatin antagonist and experimental evidence has shown that overexpression of follistatin induces a dramatic increase in muscle mass [145, 146]. However, the mechanisms involved in the follistatin effect are relatively unknown and Gilson *et al.* [147] have recently shown that satellite cell proliferation significantly contributes to the follistatin-induced muscle growth and probably

increased protein synthesis. The same authors also reported that activin is as well a crucial player in the regulation of muscle mass.

In a recent publication, Miyamoto *et al.* [148] reported that follistatin levels were not affected in patients with CKD, except in wasted and inflamed patients when it is negatively associated with muscle strength and bone mineral density. The authors speculated in line with the above-reported experimental evidence that follistatin is activated to counter regulate the effects of myostatin and activin in uraemia. Strategies to increase the skeletal muscle size and strength through myostatin inhibition by follistatin would represent a potential therapeutic approach to muscle atrophy in uraemia and other conditions.

### 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 [148–155] and poor survival in dialysis patients with a low body size [156, 157] and reduced serum creatinine [158]. However this phenomenon of the reverse epidemiology of obesity is not unique to the dialysis population. Patients with chronic heart failure [159], elderly patients [160] and patients with malignancy [161] or AIDS [162] also exhibit a risk factor reversal and all share a degree of muscle wasting.

Several studies investigated whether lean body mass or fat mass confers this survival advantage. Kalantar-Zadeh *et al.* [163] 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.* [164] also reported that higher fat mass in both sexes and higher lean body mass in women appear to be protective, and in a different study the same group reported that the mid-arm muscle circumference is a surrogate of larger lean body mass and an independent predictor of better mental health and greater survival in dialysis patients [165]. Other recent studies have suggested that higher lean body mass, but not fat mass, is associated with greater survival in CKD patients [166].

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 [167]. Importantly, low exercise capacity as a consequence of muscle wasting is also a powerful, independent predictor of mortality in patients with CKD [168].

### CONCLUSIONS

As in sarcopenia, uraemic muscle wasting is complex (Figure 2), progressive and its pathogenesis is similar (Table 1). Older persons are particularly susceptible to renal failure and this accelerates the physiological muscle wasting in this patient group. This devastating complication not only promotes a sedentary lifestyle and decreased quality of living,



but also increases cardiovascular complications, morbidity and mortality.

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 therapeutic strategies to maintain skeletal muscle homeostasis and repair at a time which may lead to a meaningful preventive response. Perhaps, the use of the term uraemic sarcopenia would provide recognition by the renal community for this devastating problem.

## CONFLICT OF INTEREST STATEMENT

None declared.

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Received for publication: 3.10.2012; Accepted in revised form: 26.2.2013