Uraemic sarcopenia -pathophysiology and implications

Dr Tanuj Moses Lamech, Madras Medical College

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Abstract

Sarcopenia has been defined as low muscle mass together with low muscle function (strength or performance). It has a complex pathophysiology, involving a host of mediators including (but not limited to) ubiquitin, insulin/IGF-1, myostatin and indoxyl sulfate, which activate downstream pathways that ultimately increase muscle degradation and reduce muscle regeneration. Alterations in the renin-angiotensin-aldosterone system and vitamin D deficiency have also been implicated in the pathogenesis. Uremic sarcopenia has important clinical implications as it has been recognised as an important indicator of poor long-term outcomes. Several clinical studies have linked sarcopenia with a significantly higher risk of mortality and disability. Aerobic and resistance exercise is known to prevent or delay the development of sarcopenia, and numerous pharmacological agents have been devised to target different steps in the known pathogenetic pathways. Some of these interventions include pharmacological manipulation of the myostatin pathway, use of androgens and anabolic steroids, correction of vitamin D deficiency, use of growth hormone supplementation and suppression of the ubiquitin pathway. Several of these techniques have had encouraging results in animal experiments, and exploratory human trials are underway. It is imperative that further research be undertaken to attempt to identify novel interventions that can reverse the inexorable decline that sarcopenia is currently associated with.

Introduction

"Whilst meagre Phthisis deals a silent blow,

Her strokes are sure, but her advances slow;

No loud alarms, nor fierce assaults are shown:

She starves the fortress first, then takes the town"

The above lines were penned by the 18th century physician/poet Samuel Garth, alluding to the relentless wasting syndrome seen in tuberculosis (or "phthisis" as it was once called). Nephrologists will immediately recognise the unmistakable parallels to the emaciating ravages of chronic kidney disease.

The term sarcopenia (or sarcomalacia) was first proposed by Irwin H. Rosenberg in 1988, to describe the age-related decline in lean body mass, along with its wide-ranging implications on ambulation, mobility and independence. The word comes from Greek roots, where “sarx” means flesh and “penia” means loss.

Loss of muscle is a normal phenomenon of aging, and adults without chronic kidney disease should expect a loss of muscle mass of about 1% per year. However, this process is greatly accelerated in chronic kidney disease. Furthermore, during hemodialysis, there is enhanced proteolysis of muscle. It has been calculated that about 10 g of amino acids are irreversibly lost to the dialysate during each session of hemodialysis.[1]

Definitions: What’s in a name?

While the phenomenon of muscle wasting is already widely known, a unifying definition remains elusive.

The European Working Group on Sarcopenia (2010) defined sarcopenia as low muscle mass together with low muscle function (strength or performance).[2]

Sarcopenia has been recognised as a disease entity with the awarding of an ICD-10-CM (M62.84) code in September 2016[3]. This is an important step, as it is hoped that it will accelerate interest in drug development and targeted therapeutic interventions (as was the case earlier, with the recognition of osteoporosis as a disease state).

Clinical assessment of sarcopenia

In the absence of a clear unambiguous universal definition that can be used for clinical trials and research, there has been a plethora of operational definitions used to define the syndrome of uremic sarcopenia. Some of the common assessments used are:

- Assessment of skeletal muscle mass
    - Bioelectrical impedance analysis (BIA)
    - Whole body dual-energy X-ray absorptiometry (DEXA)
    - Body mass index (BMI)
    - Circumferential or calliper-based methods
- Measurements of isometric, isokinetic, or isotonic muscle strength

Clinically relevant measures of sarcopenia:[4]

- **Short Physical Performance Battery (SPPB)**
    - This is a composite score of standing balance, 4 metre gait speed and sit-to-stand
- **Usual gait speed**
    - A distance of 4 m is measured, and the patient is instructed to walk at a comfortable pace. The patient performs this twice, and the fastest time is recorded.
    - The seemingly simple evaluation of gait speed is of such importance that it has been termed the “fifth vital sign” in the elderly, as it has been found to be predictive of disability and even mortality. Patients with faster baseline gait have lower rates of incident disability.[5]
- **30s 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 seconds.
- **Grip strength**
    - The patient's dominant hand is used, and three consecutive efforts are made, with a minimum of 1-minute 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.
- **Timed-up-and-go (TUAG)**
    - The patient rises from a chair on command, walks at a comfortable pace for 3 m, turns, walks back, and sits back on the chair.

Terminologies related to sarcopenia

There is no dearth of phrases used to describe the various alterations in the functioning of the musculoskeletal system – dynapenia, protein-energy wasting (PEW), frailty and cachexia have all been used, often erroneously and interchangeably. However, it is important to note the subtle differences between these seemingly similar terms.

Dynapenia is defined as a loss of muscle strength ("dyna" in Greek means power or force), regardless of the presence or absence of muscle wasting.[6] Muscle strength depends on a variety of factors, including fibre type, quality, innervation and pennation (muscle fibre angle), in addition to size. Hence dynapenia can occur even in the presence of preserved muscle mass. Size, it would seem, doesn't matter.

Protein-energy wasting (PEW) is defined by the existence of three of four criteria – biochemical indicators (low albumin and cholesterol), low body weight, decreased muscle mass, and low protein-energy intake. It thus comprises the nutritional and metabolic abnormalities that are often seen in end-stage renal disease, and is associated with high mortality and morbidity.[7]

Frailty describes the generalised decline in physical function that occurs in the setting of various stressors, including illness or hospitalisation. Strictly speaking it is defined by the presence of three of five components – low body weight for height (<18.5 kg/m^2), slowness in walking, subjective or objectively demonstrable weakness, a sense of exhaustion and decreased physical activity.

Cachexia has been defined as "a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass), that cannot be reversed by conventional nutritional support and leads to progressive functional impairment".[8] The weight loss in cachexia is specific to the inciting etiology, and is not related to age, malabsorption or hyperthyroidism. Cachexia is a term frequently used in relation to cancer; in fact the definition above was created by an international consensus committee which aimed to specifically describe *cancer* cachexia. In the setting of chronic kidney disease, cachexia is not a term that is in widespread use, given its overlap with the definitions of sarcopenia and PEW.

To the uninitiated, taking the trouble to individually define these seemingly overlapping phraseologies would seem to be an exercise in semantics, but this is not so, as they have therapeutic implications. For

example, the patient with sarcopenia will benefit from physical therapy, whereas the patient with PEW or cachexia will benefit more from nutritional therapy. The devil is in the detail, as they say.

Pathophysiology of sarcopenia

Uremic sarcopenia results in a vicious cycle of reduced physical activity, which accelerates muscle loss, which in turn further reduces physical activity. This loss of muscle mass is mediated by an increase in muscle degradation and a decrease in muscle regeneration and growth.

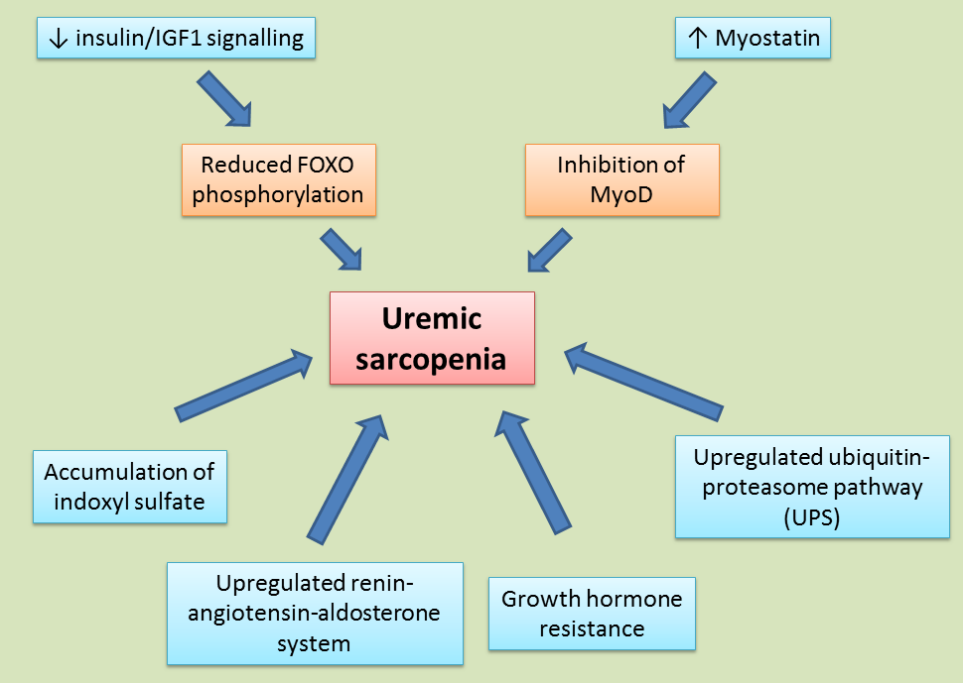
Risk factors predisposing to sarcopenia:

- Factors associated with kidney disease[9]
    - Nutritional deficiencies
    - Metabolic acidosis
    - Insulin resistance
    - Calcium-phosphate metabolism disturbances
    - Vitamin D deficiency
    - Significant proteinuria, which can rarely be a cause of severe protein losses
- Factors associated with the developing inflammatory process[9]
    - TNFα, IL-6, IL-8 and IFN-γ are frequently elevated
    - Cytokine signalling through nuclear factor kappa B (NFκB) results in muscle proteolysis
- Effect of gender[10]
    - Testosterone is associated with increased muscle mass, while deficiency, which is common with CKD, is associated with reduced muscle mass
    - Similarly oestrogen is associated with increased muscle strength, but most female patients with CKD are oligomenorrhoeic and oestrogen-deficient at an early stage
    - In general, male gender is associated with a more rapid rate of progression of sarcopenia

Molecular mechanisms of proteolysis:

- **Myostatin** is a protein that blocks the expression of MyoD (which enhances myogenesis). It therefore inhibits skeletal muscle growth. It has been demonstrated that there is increased myostatin expression in the muscle of rats with end-stage renal disease.[11]
- **Ubiquitin** is a member of the heat shock protein family. Polyubiquitination of proteins targets the molecule to proteasomes for degradation to peptides, which are then hydrolysed to amino acids. This ubiquitin-proteasome pathway (UPS) is upregulated by various stimuli including inflammation, metabolic acidosis, and vitamin D deficiency, leading to increased muscle proteolysis.
- **Impaired insulin/IGF-I signalling** is another important pathway causing muscle degradation. It leads to reduction in forkhead transcription factor (FOXO) phosphorylation. This results in synthesis of certain enzymes of the UPS pathway that recognise and target specific muscle proteins for degradation. It has been demonstrated experimentally that FOXO1 plays a role in CKD-related muscle-wasting and this in turn may serve as a future therapeutic target.[12]
- Thus, myostatin and the insulin-like growth factors (IGF-I and IGF-II) play inhibitory and stimulatory roles, respectively, in the development of skeletal muscle mass, forming a kind of yin-and-yang system in uremic sarcopenia.[13]

- Given the close physiological relationship between IGF-I and growth hormone, it is unsurprising to note that **growth hormone resistance** at the skeletal muscle level has also been noted be associated with increased protein catabolism and wasting in chronic kidney disease. Furthermore, growth hormone supplementation has had encouraging results in animal experiments and early human trials.[10]
- The **renin-angiotensin-aldosterone system** is also up-regulated in CKD, and this pathway also impairs muscle regeneration and further accentuates the UPS proteolytic pathway.
- Recently it has been suggested that the uraemic toxin **indoxyl sulfate** which accumulates in muscle tissue results in a host of metabolic alterations eventually culminating in the downregulation of the tricarboxylic acid cycle which starves muscle cells of ATP. Clinical studies have shown a significant inverse association between plasma indoxyl sulfate and skeletal muscle mass in patients with chronic kidney disease.[14]



*[**Fig. 1** – Pathophysiology of uremic sarcopenia. FOXO – O subclass of the Forkhead family of transcription factors; UPS – ubiquitin-proteasome system; IGF1 – insulin-like growth factor 1]*

Muscle biopsy studies:

Type II muscle fibre atrophy is one of the most common histological finding in muscles of patients with sarcopenia, with greater atrophy of type IIB fibres, than type IIA fibres. There has also been some recent data suggesting that Type I fibres also have smaller cross-sectional areas, as compared with healthy controls.

Ultrastructurally, it has been noted that while there are no structural alterations in the mitochondria of patients undergoing dialysis, there are significant biochemical perturbations, including increased glycogen and lipofuscin content, and reduced mitochondrial enzymes (such as cytochrome c oxidase).[10]

Animal models to study sarcopenia:

Sprague-Dawley rats, the senescence-accelerated mouse P8 (SAMP8) and the hind limb unloading rodent model, are some of the animals models that were initially used to study the entity of sarcopenia.

Clinical implications of sarcopenia

Pereira et al[15] studied 287 non-dialysis-dependent CKD patients who were in stages 3-5. Sarcopenia was defined as as

- Reduced muscle function (as assessed by handgrip strength)
  [plus]
- Diminished muscle mass as assessed by any of the following
  A. Mid-arm muscle circumference
  B. Muscle wasting by global subjective assessment
  C. Reduced skeletal muscle mass index estimated by bioelectrical impedance analysis (BIA)

It was found that the prevalence of sarcopenia varied by the method used to assess muscle mass, with the prevalence being 9.8% for A, 9.4% for B, and 5.9% for C. This is probably because BIA (C) is affected by volume expansion that is seen with chronic kidney disease (CKD), while the other measurements are not. This variability further highlights the need for uniformity in definitions of sarcopenia. The study also found that during the 40 months of follow-up period, sarcopenia diagnosed by any of the three methods was associated with a significantly higher hazard for all-cause mortality [HR 3.02 (95% CI: 1.30-7.05)].

Roshnanravan B et al[16] evaluated 385 CKD patients who were in stages 2-4, who were assessed for sarcopenia with handgrip strength, usual gait speed, timed up and go (TUAG), and 6-minute walking distance. Patients were followed up for 3 years. It was found that each 0.1 m/s decrease in gait speed was associated with a 26% higher risk of death, and each 1-second longer timed up and go (TUAG) was associated with an 8% higher risk of death. In fact, 3-year mortality was better predicted by gait speed and TUAG than even kidney function and commonly measured serum biomarkers.

Chang YT et al[17] studied 128 patients with non-dialysis-dependent CKD, who were assessed at baseline and followed up for 33.8 ± 9.2 months. The renal composite endpoint of pre-dialysis mortality or dialysis-dependent ESRD was used. It was found that hand grip strength was an independent predictor of renal outcome in patients with non-dialysis-dependent CKD.

Thus, sarcopenia in the setting of CKD must be recognised as an important indicator of poor long-term outcomes.

Interventions for sarcopenia in chronic kidney disease

"Knowing the diagnosis is good; Knowing the cause is better; Knowing the cure is best."

Aerobic and resistance exercise:

A prospective cohort study of 5812 male veterans, who were followed-up for a median of 7.9 years, found that individuals with higher exercise capacity had a lower risk of developing CKD. It was calculated that the risk of CKD was 22% lower for every one metabolic equivalent increase in exercise capacity.[18]

A Cochrane review from 2015[19] which included primarily patients on hemodialysis, suggested that aerobic exercise significantly improves physical fitness, muscle strength and quality of life in dialysis patients. The best exercise protocol, however, remains to be established.

While the benefits of exercise in dialysis patients are well established, there is still insufficient data to support the role of exercise in mitigating CKD progression in the pre-dialysis population. However, a

systematic review of seven RCTs in stages 3-5 CKD suggested an increase in both muscle strength and quality of life with resistance training.[20]

Pharmacological interventions:

Myostatin has been targeted pharmacologically in an attempt to reverse or forestall the sarcopenic effects of uremia.

- Experimental injection of myostatin antibodies into laboratory mice has been shown to increase protein synthesis and reduce protein degradation.
- Activin receptor type IIB, which binds myostatin, has been tried in postmenopausal healthy volunteers in an exploratory study, and was shown to improve lean mass.[21] However, the same compound, when used in an RCT for patients with Duchenne muscular dystrophy, resulted in epistaxis and telangiectasias, despite a trend towards improvement in lean mass, forcing the trial to be stopped early.[22]
- A humanised monoclonal antibody against myostatin (LY2495655) was studied in a phase 2 placebo-controlled RCT in post-operative patients who have undergone a total hip arthroplasty for end stage osteoarthritis. It was found that the drug increases appendicular lean body mass and decreases fat mass.[23]
- An antimyostatin peptibody called PINTA 745, was tried in a phase II proof-of-concept clinical trial in patients undergoing hemodialysis. However the trial did not meet its primary endpoint, and the development of the molecule was subsequently suspended by its parent company, Atara Bio. Disappointingly, this was the only trial of myostatin antagonism that involved the CKD population.

Androgens and anabolic steroids have also been tried in various studies. The rationale is that testosterone is important to maintain skeletal muscle mass through effects on muscle protein synthesis.

- Nandrolone decanoate therapy has been tried in dialysis patients, and has been found to improve skeletal muscle mass.[24]
- Oxymetholone, which is an anabolic steroid with lower androgenic effect, has also been shown to have beneficial effects in a small RCT involving hemodialysis patients. However, it was found to increase liver enzymes.[25]
- Selective androgen receptor modulators have been of interest, as they improve muscle anabolism, but have less systemic side effects. GTx-024 (enobosarm) has been shown to improve lean body mass and physical function in healthy elderly men and postmenopausal women in a phase II RCT.[26] This drug has also been tried in cancer-associated sarcopenia (the POWER trials). However, these trials are yet to report.[27]

A few other agents have also been explored in small-scale trials.

- Correction of vitamin D deficiency in peritoneal dialysis patients improved muscle strength and functional ability.[28]
- Growth hormone supplementation has also been found to improve skeletal muscle mass in dialysis patients[29], but there is as yet no data on the generalisability of these results to the pre-dialysis CKD population.
- The appetite-stimulating agent, megestrol acetate has been tried, but in some small studies in ESRD patients, the risks of adverse effects exceeded the putative benefits.[30]

- Suppression of the UPS pathway that is central to the pathogenesis of sarcopenia has also been suggested with the proteasome inhibitor bortezomib. However, such therapies are yet to be formally investigated.

Hemodialysis:

Patients on hemodialysis are particularly vulnerable to the development of sarcopenia due to the strong stimulation of the inflammatory response induced by the blood-dialyser interaction. Some of the pro-inflammatory cytokines that have been implicated include interleukin-1 beta, tumour necrosis factor-alpha and IL-6.

Therefore, attempts have been made to shorten the exposure of blood to the dialyser membranes, by reducing the time of hemodialysis, in exchange for increasing their frequency. Small-scale studies seemed to demonstrate benefit from this technique, but more definitive evidence is probably required before widespread implementation.[9]

Conclusion

Chronic kidney disease is an affliction that possesses a vast armamentarium to slay its victims. Acute pulmonary oedema and hyperkalemia-induced arrhythmias are rapidly lethal, often killing the patient even before they reach medical attention. Uremic sarcopenia, on the other hand, lies on the other extreme of the spectrum; it remains a smouldering cause of progressively worsening disability – slowly but surely draining the vitality out of its host.

Though we have begun to uncover pieces of the puzzle, its pathophysiology, for the most part, remains mysterious. Our numerous attempts at treating it have had marginal benefits at best. Despite the development of several complex pharmacological agents targeting various steps in known pathogenetic pathways, the intervention with the clearest benefit remains the simplest of all – physical exercise.

Even as we attempt to surmount one of the most debilitating complications of chronic kidney disease, we remain conscious of the fact that our progress thus far has been limited. Nevertheless, novel therapies and innovative therapeutic targets are continually being investigated, and a breakthrough may perhaps be right around the corner. However, for the time being at least, sarcopenia remains the monstrosity that Samuel Garth described three centuries ago:

“Her strokes are sure, but her advances slow;

No loud alarms, nor fierce assaults are shown:

She starves the fortress first, then takes the town.”

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