Bone is Not Alone: the Effects of Skeletal Muscle Dysfunction in Chronic Kidney Disease

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Abstract

Chronic kidney disease (CKD) is associated with a decline in muscle mass, strength, and function, collectively called "sarcopenia." Sarcopenia is associated with hospitalizations and mortality in CKD and is therefore important to understand and characterize. While the focus of skeletal health in CKD has traditionally focused on bone and mineral aberrations, it is now recognized that sarcopenia must also play a role in poor musculoskeletal health in this population. In this paper, we present an overview of skeletal muscle changes in CKD, including defects in skeletal muscle catabolism and anabolism in uremic tissue. There are many gaps in knowledge in this field that should be the focus for future research to unravel pathogenesis and therapies for musculoskeletal health in CKD.

Keywords

Skeletal muscle; Myogenesis; Myostatin; Sarcopenia; Atrophy

Muscle and Its Effect on the Bone in CKD

Chronic Kidney Disease (CKD) is common, affecting more than 26 million Americans [1]. CKD has striking similarities with aging; both carry increased burden of falls, fractures, immobility, loss of functional independence, and frailty that leads to hospitalizations and mortality [2–5]. Bone changes in CKD have been described in detail by others in this series. Associated with these bone abnormalities is also significant skeletal muscle loss, termed "sarcopenia" in CKD. Sarcopenia is widely prevalent in patients undergoing dialysis and is associated with increased hospitalizations and mortality [6, 7•, 8, 9, 10•]. Skeletal muscle is attached to the bone, and forces arc transmitted from the altered muscle to the altered bone

in CKD. Tests of muscle function have been shown to be associated with increased fracture risk in dialysis patients [11], as well as in earlier stages of CKD [12]. These biomechanical relationships are not yet fully characterized in CKD.

Both the muscle and bone are subjected to the uremic environment in CKD, with its attendant inflammation, insulin resistance, metabolic acidosis, and alterations of mineral metabolism. Further, there are various muscle-derived factors such as insulin-like growth factor (IGF-1), myostatin, etc. that have effects on bone metabolism and form part of the bone-muscle connection in aging [13•, 14•]. Additionally, loss of skeletal muscle (due to CKD and its comorbid conditions) also predisposes a person to a more sedentary lifestyle [15] and increased risk of falls and frailty that in turn leads to more fractures, hospitalizations, and poorer quality of life [16], There-fore, sarcopenia in CKD is not a benign consequence of uremia, and skeletal muscle and bone loss are interrelated by both biomechanics and common exposure to uremic toxins to cause adverse outcomes in CKD. In this review, we present an over-view of changes in skeletal muscle in CKD (see Fig. 1) and their assessment. The goal of understanding sarcopenia in CKD is to eventually develop and test interventions for sarcopenia that improve immobility, disability, falls, fractures, and mortality.

Assessment of Skeletal Muscle Loss in Chronic Kidney Disease

The definition of sarcopenia is very variable in the literature. Whereas sarcopenia literally translates to paucity of muscle, others in the literature use the term "sarcopenia" for loss of muscle mass and the term "dynapenia" for loss of muscle strength. Both of these may occur concurrently in CKD, though these losses may occur at different rates. Strength can diminish at a greater rate than muscle mass [17] and vice versa [18], and the interplay between these two concepts is important. In CKD, the term "protein-energy wasting" (PEW) has been proposed to represent a combination of poor nutritional status (low serum levels of albumin, transthyretin, or cholesterol), decreased body mass (low or reduced body or fat mass or weight loss with reduced intake of protein and energy), and decreased muscle mass (muscle wasting or sarcopenia, reduced mid-arm muscle circumference) [19]. In this review, we will use *the term sarcopenia to refer to changes in muscle mass, strength, or physical function.*

In the aging population, operational definitions for sarcopenia include various cutoffs for lean muscle mass, muscle strength, and physical function (see Table 1). There are three major definitions currently in use: the Foundation of the NIH, the International Working Group on Sarcopenia. and the European Working Group [10•, 20, 21, 22•]. There are no comprehensive operational definitions or specific cutoffs for these measures that have been validated longitudinally in CKD, but declining trends in individual parameters are associated with poor outcomes. In a prospective study of 323 patients with mean GFR of 41.3 ± 19.3 ml/min per 1.73 m^2 at the start, Roshanravan et al. showed that a 0.1 m/s decrease in gait speed is associated with a 26 % increased risk of mortality over 3 years [23•]. This is consistent with the data in the general population showing increased risk of mortality with lower values on measures of physical function (gait speed) [24]. A study in 103 incident peritoneal dialysis patients from China similarly demonstrated that lean body mass assessed by creatinine kinetics decreased over 12 months, and low lean mass predicted poor ability to

self-perform peritoneal dialysis and decreased patient survival [25]. A recent study from the UK evaluated 60 patients with CKD 4–5 and 74 prevalent patients on dialysis (28 peritoneal and 46 hemodialysis, with average duration on dialysis of 3 years). They assessed serial measures of both muscle mass (muscle cross-sectional area on CT) and physical performance (sit-to-stand testing) and demonstrated that 35 % of patients lost muscle mass in the first year [26]. A study of 128 patients with pre-dialysis CKD followed for a mean of 33 months showed that hand-grip strength is a significant predictor of poor renal outcomes (pre-dialysis mortality or dialysis-dependent end-stage renal disease) [27]. Therefore, patients with kidney disease progressively lose skeletal muscle mass, strength, and function, and this loss is associated with poor outcomes.

There are multiple ways to assess each component of sarcopenia, as shown in Table 1. Considerations in CKD for these measures are listed. Urine creatinine excretion in 24 h urine collections is a measure of skeletal muscle mass in those with normal kidney function, but is not as useful in CKD where tubular excretion and handling of creatinine are altered or urinary output decreased. Patients with kidney disease have reduced values for all of these muscle measures, and cutoffs established in the literature for aging elders may not apply.

Pathophysiology of CKD-Associated Sarcopenia

CKD-associated sarcopenia is the result of an altered balance among catabolic and anabolic processes to control muscle homeostasis (Fig. 2). Controlling homeostasis is an extraordinarily complex process made up of hormonal, immunologic, progenitor cell function, mitochondrial dysfunction, inflammation, metabolic acidosis, malnutrition, physical inactivity, excess angiotensin II, and growth factors (insulin/insulin-like growth factor 1 (IGF-I), myostatin), all of which are altered to variable extents from early CKD to dialysis.

Skeletal Muscle Regeneration

The ability of an aging system absence of comorbidity to regenerate or maintain skeletal muscle mass is quite complex. In response to a stressor (i.e., muscle injury, inflammation), myogenic regulatory factors (MRFs) alter expression to activate satellite cells (aka. muscle stem cells (MuSCs)), differentiate into myotubes, and eventually form a myofiber [28]. The ability of MuSCs to respond in the "normal" aging system has demonstrated contrasting results with a reduced [29] or normal/no change [30] in number of MuSCs. Some have shown impaired function is associated with decreased or delayed expression of myogenic regulatory factors, which regulate satellite cell proliferation and differentiation. Clinically, there is little known regarding myogenic regulation in the CKD population. Studies in CKD (5/6 nephrectomy) animal model demonstrated impaired MuSC activation and reduced MRFs in CKD (as compared to normal aging) both at basal level and in response to injury [31]. To date, little is known regarding how the satellite cell functions in CKD and whether progression of diseases correlates with progressive changes in cell function. However, many of the factors known to regulate MuSCs are abnormal in CKD.

Androgens

The ability to maintain muscle mass through protein formation may be mediated though testosterone. Testosterone may influence skeletal muscle formation/regeneration as it has been shown to increase the number of satellite cells [32•] and stimulate muscle protein synthesis [33]. In CKD, hypogonadism is common and may be exacerbated by other common CKD comorbidities (i.e., obesity, diabetes mellitus, and hypertension) [34]. Serum testosterone levels have been associated with reduced muscle mass and strength in CKD [34, 35]. In randomized controlled trials in dialysis patients, nandrolone decanoate alone has been associated with improvements in skeletal muscle mass [36], as well as when combined with resistance exercise [37]. Longer term studies in CKD are needed, especially to establish the risk benefit ratio with androgen supplementation, given adverse events have been noted with testosterone replacement for other indications [38].

Vitamin D

Although vitamin D is largely thought of as a regulator of the bone, recent studies indicate that vitamin D may also be important in skeletal muscle maintenance and regeneration. In C_2C_{12} myoblasts, treatment with 1,25 Vitamin D resulted in increased myogenesis [39], protein synthesis [40], and myotube diameter [41]. Conversely, vitamin D deficiency can induce muscle wasting acting primarily through the ubiquitin-proteasome pathway [42]. Overcoming vitamin D deficiency with supplementation increased muscle size and strength in patients on hemodialysis [43]. Further, supplementation increased mobility and function (i.e., the timed up and go test, gait velocity test, timed chair stand test, and stair climb test) in both CKD and dialysis patients [44]. Therefore, the prevalence of vitamin D deficiency in CKD may contribute to skeletal muscle atrophy and impaired muscle performance.

Renin-Angiotensin System

The renin-angiotensin (RAS) is upregulated in CKD [451 as well as in sarcopenia in aging [46]. This is important as angiotensin peptides (i.e., angiotensin I (Ang I), angiotensin II (Ang II)) are produced by skeletal muscle [47], but there is little to no expression of Ang I and II receptors in the muscle [48]. Despite the poor expression of Ang II receptors in adult muscle fibers, Ang II contributes directly and indirectly to muscle atrophy. Increased Ang II expression reduces the satellite cell pool and muscle regenerative capacity [49•] and upregulates caspase-3 and the ubiquitin-proteasome proteolytic pathways [50, 51]. Indirect effects of Ang II on skeletal muscle atrophy occur through intermediate molecules such as interleukin-6 that impair insulin/IGF-1 signaling and decreased Akt phosphorylation [48].

IGF/Insulin

A simplistic take upon a complex system is that, in skeletal muscle, insulin and insulin-like growth factor (IGF) interact with anabolic (extracellular response kinases (ERKs) and phosphatidylinositol 3-kinase (P13K)), and catabolic (ubiquitin-proteasome) pathways to regulate skeletal muscle mass and subsequent muscle performance. Activation of the ERK and PI3K pathways has been shown to increase proliferation [52], differentiation [53], and maintenance of muscle fiber growth [54]. In end-stage renal disease, patients develop resistance to insulin/IGF that modulates protein metabolism [55]. Protein metabolism,

impaired regeneration, and increased fibrosis were demonstrated in a mouse model of CKD [31]. Growth hormone supplementation increases serum IGF-1 levels; it is used in children with CKD to normalize linear growth, and it is associated with increase in muscle mass [56]. The muscle anabolic effect of growth hormone with IGF-1 in CKD has been shown [57], including the benefits on lean muscle mass increase and fat mass reduction [58]; however, the use of growth hormone in adults with CKD and sarcopenia has not been adequately studied.

Ubiquitin-Proteasome Pathway

The ubiquitin-proteasome pathway (UPP) may interact with the IGF pathway via insulin resistance activating the UPP to promote catabolic conditions that lead to muscle atrophy in CKD [59]. In the UPP target, proteins are ubiquitinated and fed into the proteasome to be digested and degraded. Protein degradation (i.e., muscle atrophy) occurs when activated (i.e., dephosphorylated) nuclear forkhead box member (FOXOs) increases the expression of atrogin-1 and MuRF1 E3 ligases [60]. The FOXO proteins are a subgroup of the forkhead family of transcription factors; the "O" distinction indicates regulation by the insulin/PI3K/Akt pathway [61]. Of the four FOXOs (i.e., 1, 3, 4, 6), FOXO1 was identified to be the primary mediator of muscle wasting in an animal model of CKD [62]. The process degrading actomyosin complexes occurs through when caspase-3 is cleaved, then in turn is removed though the UPP. Caspase-3 is identified by the presence of an insoluble, 14 kDa remnant of actin. This biomarker has been found to increase in a number of catabolic conditions including osteoarthritis, burns, and in patients on dialysis [63].

Myostatin

Myostatin is a myokine that acts as a negative regulator of skeletal muscle mass through the upregulation of atrogenes (atrogin-1 and MuRF1) and downregulation of myogenesis genes (i.e., MyoD, myogenin) [64]. Myostatin levels are elevated in a number of diseases that demonstrate skeletal muscle wasting, including, liver disease [65], chronic obstructive pulmonary disease [66], and in CKD patients [67]. In a 5/6 nephrectomy mouse model of CKD mice, anti-myostatin treatment, a) increased body weight, muscle mass, and protein synthesis; b) reduced protein degradation; and c) improved satellite cell function [31]. In humans, drugs that bind to the myostatin receptor activin IIB have been shown to increase muscle mass and are currently in early-phase clinical trials in the elderly, offering a novel potential pharmacologic therapy to improve muscle mass [68, 69]. A trial of an anti-myostatin peptibody in CKD is currently enrolling (NCT01958970 www.clinicaltrials.gov).

Conclusion

There appears to be disruption of skeletal muscle homeostasis in CKD, with increased catabolism and decreased anabolism: the sum of these phenomena is the sarcopenia that occurs in CKD and progresses with time. Studies to unravel the pathogenesis of sarcopenia in animal models of CKD and in humans are extremely important, especially if targets for future interventions are to be identified. Clinical biomarkers of sarcopenia, i.e., measures of muscle mass, strength, and function, need to be validated overtime in CKD and related to patient-centered outcome measures such as disability, quality of life, and mortality.

Ultimately, therapies that are developed will be useful and widely accepted only if they improve patient-centered outcomes of sarcopenia in CKD.

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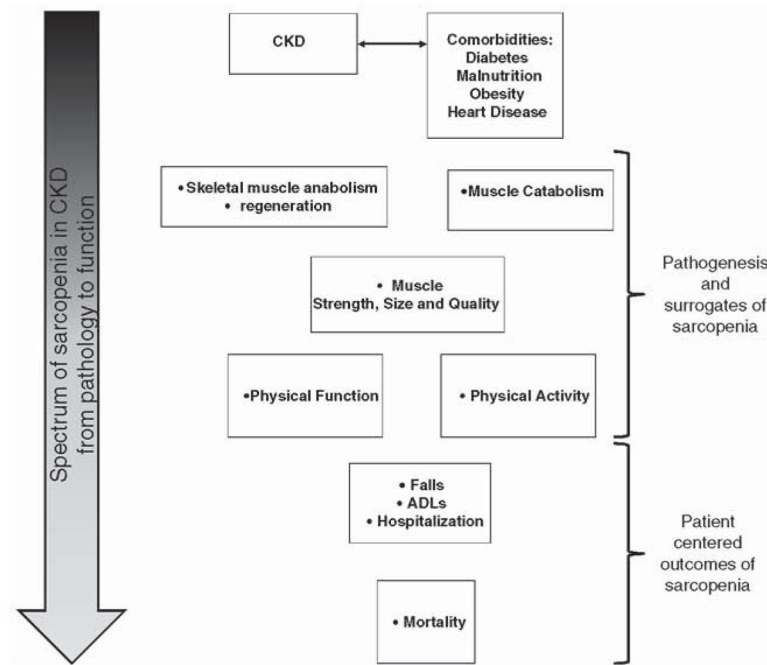
Fig. 1.
Spectrum of sarcopenia in CKD— The spectrum of C KD and associated comorbidities can ultimately influence mortality. This is evident by increased muscle catabolism and decreased regeneration that leads to reduced muscle strength, size, quality (i.e. collectively known as sarcopenia), and consequently limiations in function and activity. Key consequences of sarcopenia in patients with CKD are increased falls, fractures, immobility, disability, and hospitalizations. These ramifications ultimately will influence mortality
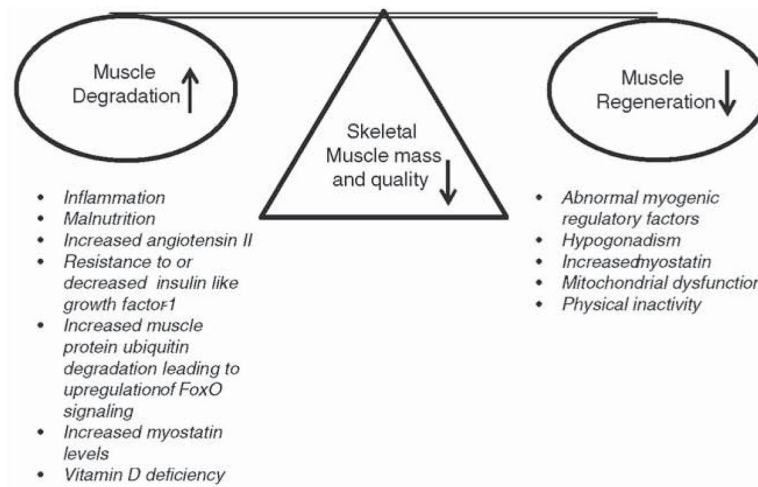
Fig. 2.
Skeletal muscle loss in CKD is a result of increased muscle degradation and impaired regeneration

Table 1

Objective assessment of muscle mass, strength, and function

		CKD[a]/dialysis considerations
Muscle mass	Bioelectrical impedance (BIA)	BIA—measured after midweek session (in dialysis)
	Dual X-ray absorptiometry (DXA)	Significant atrophy of skeletal muscle may interfere with measurements in some patients
	Computerized tomography (CT)	
	Magnetic resonance imaging (MRI)	
Strength	Isotonic (constant load) Dynamometry, free weights	Using limb contralateral to dialysis access
	Isometric (constant angle) Hand-held dynamometry, computerized dynamometry, manual testing	Timing test with dialysis (pre-or post-dialysis)
	Isokinetic (constant velocity) Computerized dynamometry	
Function	Gait Speed (4 m walk)	Vascular complications, amputations, and neuropathy in CKD patients may limit use of certain tests.
	6 min walk test	
	Repeated chair stand	
	Timed up and go	
	Upper body ergometer	

[a]Reference values/cutoffs from healthy populations are likely different from those from CKD patients