Muscle-bone crosstalk in chronic kidney disease: the potential modulatory effects of exercise

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Abstract

Chronic kidney disease (CKD) is a prevalent worldwide public burden that increasingly compromises overall health as the disease progresses. Two of the most negatively affected tissues are bone and skeletal muscle, with CKD negatively impacting their structure, function and activity, impairing the quality of life of these patients and contributing to morbidity and mortality. Whereas skeletal health in this population has conventionally been associated with bone and mineral disorders, sarcopenia has been observed to impact skeletal muscle health in CKD. Indeed, bone and muscle tissues are linked anatomically and physiologically, and together regulate functional and metabolic mechanisms. With the initial crosstalk between the skeleton and muscle proposed to explain bone formation through muscle contraction, it is now understood that this communication occurs through the interaction of myokines and osteokines, with the skeletal muscle secretome playing a pivotal role in the regulation of bone activity. Regular exercise has been reported to be beneficial to overall health. Also, the positive regulatory effect that exercise has been proposed to have on bone and muscle anatomical, functional, and metabolic activity has led to the proposal of regular physical exercise as a therapeutic strategy for muscle and bone-related disorders. The detection of bone- and muscle-derived cytokine secretion following physical exercise has strengthened the idea of a cross communication between these organs. Hence, this review presents an overview of the impact of CKD in bone and skeletal muscle, and narrates how these tissues intrinsically communicate with each other, with focus on the potential effect of exercise in the modulation of this intercommunication.

Keywords: muscle, bone, ckd, exercise, myokines, osteokines.

Declarations

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1. Introduction

Chronic kidney disease (CKD) has recently been defined as a 'model of accelerated aging', influencing the human body in a patently comparable fashion to aging, with an elevated liability for locomotor disorders, specifically fractures, falls, and limited mobility, loss of function, and frailty [1, 2]. CKD patients often develop mineral and bone disorders (MBD), which include disturbances in the homeostasis of calcium (Ca^{2+}), phosphorus (P^{+}), vitamin D, and parathyroid hormone (PTH); abnormalities in bone turnover, mineralization, and volume; or vascular or other soft tissue calcifications [3]. With these impairments potentially contributing to increased fracture occurrence [4], and with CKD patients having a higher prevalence of cardiovascular disease [5], the combination of these significantly increases the rate of morbidity, hospitalizations and mortality [1, 2].

Despite earlier research on skeletal health focusing upon bone and mineral abnormalities, recently it has been recognized that sarcopenia also has a major role in reduced musculoskeletal health in CKD [6, 7]. CKD patients suffer severe skeletal muscle wasting [8], with CKD being pathologically associated with a gradual and severe deterioration in overall skeletal muscle mass, function and strength [6, 9–11]. This is particularly evident in advanced stages of the disease [10], with this compromised skeletal muscle health increasing the risk of mortality in CKD.

Skeletal muscle is attached to bone both anatomically and physiologically, as they cooperate to allow movement and locomotion. Muscle and bone act in parallel to support and regulate the muscles' functions in order to produce strength and exert forces to allow for functional independence [7, 12]. This led to the development of the term 'bone-muscle unit' in the late 90's, strengthened by the linear association between total body mineral content and lean mass reported in a large study of individuals (n = 1450) ranging from 2 to 87 years of age [13]. However, it is currently known that the bone-muscle crosstalk is not solely a mechanism for bone formation through the application of mechanical load to skeletal muscle, but an ongoing communication between myokines and osteokines that act together to activate muscle metabolism [12, 14, 15]. Whilst movement and locomotion are enabled through the skeletal muscle's contractile properties (sliding filaments in the sarcomeres) [16], whole-body metabolism is facilitated by the continuous crosstalk between these tissues at a molecular, endocrine and substrate level [12, 17–19]. Indeed, the homeostatic regulation of muscle and bone is influenced by both endogenous and exogenous factors, that intrinsically collaborate to allow for the regulation of structure and function [15, 19, 20].

The growing knowledge about the interactions between bone and muscle, and the influence of exercise on both these tissues has important implications for clinical practice, especially when targeting a reduction of the burden of co-morbidities in CKD patients. This review focuses on the cross communication between muscle and bone, seeking to highlight the potential modulatory effect of exercise on these tissues, highlighting its usefulness as a novel therapeutic strategy to improve muscle and bone parameters, and consequently overall health and quality of life in patients with CKD.

2. Skeletal muscle and bone metabolism in CKD

2.1 Bone metabolism in CKD

Epidemiologically, as treatments have improved CKD patients now are able to live longer lives with survival rates much improved. However, the incidence of skeletal fractures has been higher in recent years. Older CKD patients have especially high fracture rates, in part because the incidence of skeletal fractures increases with aging [4], and also because fracture risk is exacerbated as CKD progresses [21]. The loss of bone tissue observed in CKD is caused in part by a disturbed replacement of bone tissue, referred to as bone remodelling. Physiological bone remodelling is a process that coordinates the relation between bone formation and resorption by constantly eliminating old bone and replacing it with resynthesized protein-rich, mineralization of the matrix [22]. Indeed, the rate of bone remodelling (influenced by exogenous and endogenous factors) regulates the quality of bone extracellular matrix, which in turn may alter bone strength. In CKD patients, the systemic mineral metabolism and the overall composition of bone tissue is altered in parallel with the progression of the disease [23], with studies showing a direct correlation between declines in glomerular filtration rate (GFR) and deteriorating bone microarchitecture (which may estimate bone quality) and remodelling [24]. This scenario has been described as a broader systemic disorder associated with CKD that includes extra-skeletal calcifications, termed CKD-MBD [3]. Despite most CKD patients showing histologic signs of elevated bone turnover alongside high concentration levels of PTH [25, 26], low bone turnover has been reported as the predominant MBD in both pre-dialysis and haemodialysis patients [27, 28]. Alongside this deterioration in bone turnover, mineralization and strength, CKD-MBD is characterised by an abnormal metabolism of Ca^{2+}, P^{+}, and vitamin D, soft-tissue calcifications, as well as an overactivity of PTH [24], with the latter mediating a significant loss in cortical bone in this population [29].

Moreover, the process of bone remodelling, is regulated through the action of certain osteogenic proteins, such as the receptor activator of nuclear factor-κB ligand (RANKL) [22]. The presence of the myogenic Interleukin (IL)-6 drives the occurrence of osteoclastogenesis by activating the secretion of osteoblast- and osteocyte-induced receptor activator of nuclear factor κ-B (RANK). This triggers an elevated expression of RANKL [30], following loss of brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1 (BMAL1) [31], a transcription factor that when absent in osteoblasts, increases the ability to support osteoclastogenesis [31]. However, while the activation of RANKL induces osteoclastogenesis, an elevation in osteoprotegerin (OPG) inhibits this process. The binding of RANKL to its receptor RANK, triggers a cascade of signalling events that induce differentiation, activity and survival of osteoclasts [32]. However, OPG may bind to RANKL as well, which prevents the latter binding to RANK [33]. This action of OPG may be important in restraining osteoclastogenesis, and therefore preventing bone loss [33]. However, reports on RANKL and OPG levels in CKD, especially in haemodialysis patients, have shown conflicting outcomes. While OPG concentrations are consistently reported as pathologically high in haemodialysis patients [34–36], reports on RANKL levels are inconsistent, with higher [37], lower [34], or similar [38] levels, when compared with healthy individuals. In pre-dialysis patients, serum OPG was observed to be progressively elevated with reductions in creatinine clearance [39].

An important bone-derived endocrine pathway that influences certain tissues systemically is osteocalcin (OCN), which signals through sclerostin (Sost). OCN is secreted by osteoblasts and then activated by osteoclasts during the process of bone resorption. High levels of OCN are commonly found in CKD patients [40], potentially due to decreased renal clearance, increased bone metabolism or even a combination of these two factors, with the progressive increase in circulating OCN correlating with intact PTH and Bone Alkaline Phosphatase (BALP) levels [41]. Moreover, the increase in OCN levels may reflect the severity of the bone lesion [42]. Yet, serum levels of OCN's uncarboxylated form (ucOCN) were observed to be considerably lower in pre-dialysis patients compared with healthy individuals, with close associations with subclinical atherosclerosis in CKD found [43]. Despite the utility of OCN and BALP as indicators of bone formation, these molecules alone cannot provide sufficient evidence to determine the underlying histologic variants of skeletal diseases [40]. Furthermore, osteocyte- and osteoblast-derived fibroblast growth factor (FGF)-23 has been proposed as one of the main bone-derived endocrine markers involved in the regulation of systemic phosphate and vitamin D [44]. In the presence of the co-receptor klotho, FGF-23 binds to the FGF receptor, with its expression being activated by osteocyte-derived PHEX and Dmp1 [45]. In CKD, FGF-23 has been observed to be associated with muscle atrophy through inhibition of insulin/IGF signalling in skeletal muscle [46]. However, its influence in bone metabolism is still being investigated, as *in vitro* studies observed no alteration in C2C12 myotube function, and *ex vivo* FGF-23 treatment did not alter Soleus muscle contractility [47].

2.2 Muscle metabolism in CKD

Several terms associated with muscle wasting in chronic diseases such as protein-energy wasting (PEW), cachexia and sarcopenia have been used interchangeably [48]. In CKD, the catabolic state induced by this condition has been proposed to be associated with elevated uraemia and PEW [49]. This is a consequence of underlying complications such as acidosis, systemic inflammation, insulin resistance, and increased levels of myostatin, eventually leading to a reduction in muscle protein synthesis [50–52] and an increase in protein degradation. Indeed, PEW has been suggested as an adequate predictor of mortality in some cohorts of CKD patients [53, 54], with PEW being also proposed as the initial state of a continuous process leading to cachexia, as both have comparable catabolic pathways and physiopathology [48], with the noticeable clinical feature of cachexia being further associated with inflammation and weight reduction in adults [55]. Therefore, cachexia has been described as an underlying cause of sarcopenia [55], the latter defining the loss of muscle mass and function [56] and relating with dynapenia (loss of muscle strength [57]), which in CKD patients increase with disease progression [58]. Given that muscle metabolism influences many metabolic pathways [18, 59–62], the maintenance of skeletal muscle mass, strength and force production in this population is highly clinically significant. Indeed, a longitudinal study completed on 103 patients undergoing peritoneal dialysis who were followed for an 8-year period found that higher lean body mass (assessed by creatinine kinetics) predicts longer overall patient survival, while low lean body mass is associated with increased mortality and morbidity rates [63].

The regulation of skeletal muscle mass is modulated by continuous changes in the rate at which muscle protein synthesis and breakdown occur, with turnover rates in healthy adults averaging ~1% to 2% muscle protein per day [64], equating to approximately 300-600g of remodelled protein every day. Yet, the balance between muscle mass synthesis/breakdown, which is known to be disturbed in many catabolic diseases, such as CKD, is regulated by a network of signalling pathways which transmit external stimuli to intracellular pathways leading to gene transcription activation/deactivation [65, 66]. This ongoing protein turnover occurring in muscle tissue facilitates the continuous replacement of aged or damaged proteins, therefore contributing to the maintenance of healthy skeletal muscle [67]. Thus, skeletal muscle wasting in CKD may be explained by a dysregulated protein synthesis and degradation. Contrarily

to commonly held notions, it has been reported that in the basal state both synthesis and catabolism are elevated in maintenance haemodialysis patients [68], which therefore leads to dialysis patients having a rapid turnover of unhealthy muscle, with protein dysfunction in dialysis patients recently proposed to be mediated by integrin [69]. In pre-dialysis patients, mRNA expression markers of protein degradation were observed to be elevated, with the myogenic Pax7 and MyoD expression being lower, when compared with age-matched healthy controls [70].

There are several possible mechanisms that may be involved in the initiation of skeletal muscle wasting in these patients. This sarcopenia-related protein degradation may be explained by several systems, such as the ubiquitin-proteasome system, where multiple ubiquitin molecules attach to specific proteins marking them for rapid degradation following enzymatic activation, with these polyubiquitinated proteins being subsequently degraded by the proteasome [71]. Another mechanism of sarcopenia-related protein degradation is lysosomal proteolysis, which despite the low presence of lysosomes in adult skeletal muscle, these organelles have been observed to be stimulated in a variety of pathological conditions, specifically through the action of the protease cathepsin known to regulate extracellular matrix homeostasis, autophagy, apoptosis, glomerular permeability, and inflammation in CKD [72]. More recently, the role of autophagosomes in muscle pathology, double-membrane vesicles formed from intracellular lysosomal degradation, has also been described [73]. In mice, CKD has been observed to induce autophagy and mitochondrial dysfunction in skeletal muscle [74]. Excessive activation of this proteolytic- and lysosomal-dependent degradation leads to skeletal muscle loss of mass and strength [75]. Moreover, given the large inter-individual variability relating to length of disease, differences in co-morbidities and medications, predominating factors are likely to vary between individuals. Broadly these factors include inflammation, metabolic acidosis, myostatin and oxidative stress acting upon protein balance, but also function of skeletal muscle satellite cells (MuSc) [50, 76]. Systemically, this relationship between protein synthesis and degradation is manipulated by myokines such as myostatin and IL-6, respectively. Myostatin, a member of the transforming growth factor-β (TGF-β) superfamily of cytokines, is known as a suppressor of skeletal muscle tissue growth, with elevated concentrations showing to be correlated with muscle disuse, injury and sarcopenia [77]. Myostatin secretion to the circulation signals as an endocrine cytokine [78], with both plasma and intramuscular levels of myostatin known to be elevated in early stage CKD [79, 80]. Myostatin affects muscle wasting by disrupting MuSc function and an up regulation of E3 ligases instigating protein breakdown by the proteasome [50]. Interesting, in murine CKD models an anti-myostatin peptibody normalised protein metabolism, alleviating atrophy and systemic inflammation [81], highlighting this as a potentially important candidate to be considered for therapies to alleviate skeletal muscle wasting. Interestingly, activated signal transducer and activator of transcription 3 (p-Stat3) was found in CKD-induced mice, leading to the hypothesis that CKD-derived muscle wasting is initiated by this mechanism [81]. Following this, Zhang *et al.* observed in C2C12 myotubes that p-Stat3 muscle wasting may stimulate myostatin [82]. Their team also observed a robustly elevated muscle p-Stat3 and an increased expression of IL-6 and tumor necrosis factor-alpha (TNF-α) in CKD compared with healthy subjects, associating a p-Stat3 activation with muscle damage in human CKD patients as well [82].

Chronic systemic inflammation is common in CKD and IL-6 signalling has been associated with myogenesis and subsequent skeletal muscle growth through the regulation of the proliferative capability of muscle stem cells [83]. IL-6 knockout mice were shown to have an impaired hypertrophic response to overloading [84], with this hypertrophic mechanism requiring both an elevation in net protein synthesis and accretion of new nuclei from MuSc. Interestingly, the impaired hypertrophy detected in IL-6 null rodents has been attributed to a reduced accretion of myonuclei, while protein synthesis pathways remain unchanged [84]. This blunted myonuclei sensitivity may therefore be observed as a consequence of the faulty proliferation and migration of MuSc in the absence of IL-6 [84]. In CKD, IL-6 is commonly observed to be chronically elevated [85], which is largely caused by an increased oxidative stress and a potentially reduced clearance due to impaired renal function. In addition, skeletal muscle expression of TNF-α and IL-6 have been reported to be higher in CKD patients [80, 86] strongly suggesting that an inflammatory environment also exists within skeletal muscle which has important implications for increasing protein degradation.

3. Skeletal muscle-bone crosstalk

3.1 Myokines and bone metabolism

Beyond its negative effect on skeletal muscle growth, myostatin has been reported to be involved in poor bone metabolism, by negatively impacting bone remodelling, eliciting osteoclastogenesis, and reducing bone formation [77]. Inhibition of myostatin in the osteogenic differentiation of bone marrow stem cells elicited an elevation in the expression of osteogenic growth factors, such as insulin-like growth factor 1 (IGF-1) [87]. In myostatin-inhibited mice, elevated osteogenesis was observed, with a general increase in bone density, strength and mineralization [77]. However, despite the well-defined influence of myostatin in bone remodelling, the mechanism by which it occurs is still unclear. It has

been proposed that myostatin supresses miRNA-128 in osteocyte-derived exosomes, as well as stimulating the production of Sost, RANKL and Dickkopf Wnt signalling pathway inhibitor 1 (DKK1) [88]. This has been proposed due to the influence that miRNA-128 has on inhibiting Wnt signalling, and the rapid extent to which osteocyte-derived exosomes are taken up by osteoblasts, leading to reduced osteoblastogenesis and impaired bone formation [89].

Whereas myostatin has been clearly defined as a catabolic myokine on bone tissue remodelling, the muscle-derived IGF-1, FGF-2, and IL-15 exert clear anabolic effects in bone metabolism. Both IGF-1 and FGF-2 elicit similar anabolic mechanisms in osteoblasts, increasing osteoblast proliferation and accelerating bone formation [14]. While IGF-1 regulates bone anabolism as a response to an elevation in osteoblast survival and proliferation [90], FGF-2 has been proposed to be secreted following disruption of plasma membrane in response from either injury or mechanical muscle contraction, rather than exocytosis [14]. Recently, FGF-2 has also been observed to attenuate glucocorticoid-mediated bone resorption through inhibition of Sost signalling [91], reinforcing its anabolic effects on bone metabolism. Additionally, higher circulating levels of muscle-derived IL-15 have been associated with increased bone mineral content in mice models [92]. In human CKD patients, increased circulating levels of IL-15 have been observed, despite lower levels of IL-15 in Staphylococcus enterotoxin A-stimulated and in influenza A vaccine-stimulated supernatants [93]. Low levels of IGF-1 have been associated with increased muscle wasting [94], and lower bone mineral density in CKD patients [95]. Additionally, previous research observed an association between low levels of IGF-1 and mortality, with lower IGF-1 concentrations detected in haemodialysis patients who died, compared with survivors [96]. However, FGF-2 concentrations are poorly described in CKD and remain uncertain, despite FGF-2 mRNA expression being significantly upregulated in interstitial and tubular cells in end-stage kidney disease [97].

Another myokine involved in bone metabolism is irisin. Irisin is an endocrine myokine secreted from skeletal muscle in response to an increased expression of peroxisome proliferator-activated receptor γ co-activator-1 α (PGC1α). Irisin's primary target organ has been proposed to be bone tissue, based on compelling evidence on its influence in improving cortical bone mass and geometry, without affecting the transdifferentiation of adipose tissue in in male mice. This highlights irisin's role as the molecular transducer responsible for the cross-talk in the muscle-bone unit during physical activity [98]. Interestingly, irisin and its precursor FNDC5 expression in skeletal muscle were reported to be elevated in myostatin knockout rodents [99]. Plasma levels of irisin have been reported to be lower in CKD patients, with previous research observing approximately 59% lower resting concentration levels in stage 5 CKD patients, when compared with age- and sex-matched healthy individuals [100]. Moreover, irisin levels were reduced as renal function declined in a sample of 532 patients across stages 1-5 CKD, even after adjustment for adjusted for age, gender and body mass index [101].

3.2 Osteokines and muscle metabolism

A converging body of evidence suggests there is crosstalk within a bone-muscle unit [102], with both these organs being impacted by CKD. The influence of elements such as reduced bone density (commonly referred to as bone quantity), and low bone microarchitecture, when taken together, may lead to a significant reduction in mechanical strength. The relationship of these factors with fall risk and reduced neuromuscular strength may consequently lead to accelerated skeletal fractures [4]. In addition to providing structure, protecting organs, and enabling movement, bone tissue is the main reservoir of minerals such as $Ca^{2+}$and K^{+}, which are fundamental for muscle contraction.

The homeostatic regulation of bone and skeletal muscle is dependent on endogenous and exogenous factors which act intrinsically to regulate structure and function. Dietary protein, vitamin D and Ca^{2+} modulate bone metabolism, with protein and perhaps also vitamin D downregulating catabolic mechanisms. These also activate anabolic signalling pathways such as OCN, IGF-1, and phosphorylated mammalian target-of-rapamycin (mTOR) [103], which in turn are associated with increased bone density [104], lean mass, strength and function [103, 105]. The signalling of OCN in myofibers has been shown to be necessary for muscle mass maintenance, following observation of increased protein synthesis both in old and 10-month-old female mice muscle cells [106]. In this study [106], a reduction in myofibers cross-sectional area was observed, but muscle strength was unchanged in OCN-deleted mice compared to control littermates, suggesting OCN favours muscle mass maintenance, yet does not affect strength. Additionally, 12-month-old mice lacking the receptor GPRC6A in all cells were observed to have considerably low skeletal muscle mass and body weight, when compared to control littermates [107]. Despite *Gprc6a* gene being expressed in myofibers and OCN signalling through this receptor to regulate muscle function during exercise [108], a similar reduction in muscle weight was observed in 12-month-old compound mutant mice lacking one allele of *Osteocalcin* and one allele of *Gprc6a*, specifically in myofibers. This provides direct genetic evidence that OCN may be an important modulator of muscle mass [106, 108]. Furthermore, the influence of OCN in regulating muscle mass through regulation of protein synthesis in myofibers has been strengthened, following detection of OCN-induced phosphorylation of S6K1, an mTOR target

protein [106]. Interestingly, S6K1 was interrupted by Torin1, through its inhibitory action on the mTOR complex [106], highlighting the effects of OCN in promoting myotube-derived protein synthesis.

Recently it has been observed that the anti-anabolic Sost acts to induce osteoblastogenesis [109]. This mechanism occurs following inhibition of Wnt signalling upon binding with the receptors LRP5 and LRP6, therefore inhibiting osteogenesis [109]. Following identification of these two receptors in myocytes [109], it has been reported that *in vitro* and *ex vivo* evidence suggest that cultured osteocytes may potentially elicit myogenesis and contractile force, proposing that Wnts could be mediators of bone to muscle signalling, likely via modulation of intracellular Ca^{2+} signalling and the Wnt/β-Catenin pathway [110], which is antagonistic to its known action in bone tissue. However, a recent cross-sectional study in elderly Koreans with sarcopenia had contrasting results, with serum Sost concentrations inversely correlated with muscle mass [111], denoting an identical catabolic effect as occurs in bone. Studies of the role of Wnt signalling in CKD have been increasing in recent years, with immunohistochemical evidence of kidney biopsy samples emphasising the presence of several common Wnt proteins in CKD [112]. These are commonly associated with renal tubule specific inhibition of Wnt secretion, resulting in the inhibition of fibroblast gene expression activation and exacerbation of kidney fibrosis [112], with its influence in CKD muscle poorly described.

Another bone marker that exerts its influence on skeletal muscle metabolism is RANK. RANK may be expressed in skeletal muscle, and activation of the NF-κB pathway induces an inhibition of myogenic differentiation, leading to skeletal muscle dysfunction and loss [113]. In mouse models, mRNA expression of RANK-RANKL was indeed observed to occur highly in both muscle and bone, with the overexpression of RANKL being reported as the cause for decreased muscle mass and force [114]. An increased expression of RANKL and reduced expression of OPG following osteoblast-exposure to PTH in hyperparathyroidism has been observed [115]. These authors [115] cultured mouse primary bone marrow stromal osteoblasts with bovine PTH peptide [bPTH (1-34)] for up to 28 days, and observed that PTH significantly up-regulates RANKL mRNA, and inhibits OPG expression at all stages of osteoblast differentiation. This suggests exposure to PTH is associated with elevated osteoclastogenesis. However, despite the antagonistic reports on RANKL concentrations reported in CKD [34, 37, 38], the effect of PTH on the up-regulation of RANKL mRNA leading to elevated bone resorption has been confirmed to occur in haemodialysis patients [37]. Fig. 1 depicts the skeletal muscle-bone crosstalk through the influence of the myokines and osteokines described in this review.

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4. The potential effects of exercise in the modulation of the skeletal muscle-bone communication in CKD

4.1 Effects of exercise on osteokines in CKD

Highlighting the noteworthy progress in understanding bone and skeletal muscle disease in CKD in recent years, physical exercise has been advised as a preventative and therapeutic method against bone disorders such as osteoporosis [116]. The majority of studies report exercise has significant effects on bone mass [117, 118] and mineral density [119], through the inhibition of bone resorption [117] and promotion of bone formation [120]. Additionally, regular exercise has been reported to improve the metabolic activity for contraction [121] and regulation of skeletal muscle mass and function [122–125], making it a promising novel therapeutic strategy for muscle-related disorders.

The demonstration that the bone-derived hormone osteocalcin favours muscle functions during exercise raises the question of whether this hormone may also regulate muscle mass. On a functional level, reduced muscle mass was observed in OCN-deleted mice [108], with this condition being reversed following administration of OCN's uncarboxylated form (ucOCN) in older mice [106]. Moreover, ucOCN was also shown to elevate in response to exercise of different types and durations [126–128], which in turn has been observed to be associated with certain cellular and metabolic effects such as the promotion of the survival and function of pancreatic β-cells, increase in insulin secretion and sensitivity, and in glucose uptake. These data support the perspective that ucOCN is involved in muscle hypertrophy and strength, as observed in adult mice, following its signalling through its receptor GPRC6A [107]. Indeed, elevations of both ucOCN and muscle-derived IL-6 levels have been observed in mice following endurance exercise (treadmill-run for 4 days, 17 min/day with increasing speed from 10 to 30 cm/s), with these changes being dependent of one another [129]. The expected exercise-induced elevated response of OCN has not been observed in IL-6-deficient rodents, with this effect being corrected following injection of IL-6 [129].

In a recent systematic review we have observed a positive relation of resistance exercise interventions on bone health in CKD patients, suggesting however that a greater focus on conducting prospective studies and long-term randomized controlled trials to examine the influence of different exercise modalities on bone parameters is necessary [130]. A study

completed on 39 stage 3-4 CKD patients reported no chronic influence of exercise in markers of bone metabolism (including ucOCN) following 24 weeks of low to moderate intensity aerobic training (30 min, 3x/week, with 10-min increments at weeks 4 and 8) [131]. However, a three-month aerobic exercise program (three sessions weekly), where haemodialysis patients completed a total 30 minutes of self-paced, intradialytic cycling elicited an elevation in bone mineral density and skeletal muscle functional capacity (i.e. greater six-minute walk distance covered), when compared to before the exercise program [132]. Also, six months of intradialytic resistance exercise using elastic bands (72 sessions in total) did not influence OCN concentrations. However, there was an elevation in OPG (~15%), which was hypothesized to contribute to bone loss prevention in haemodialysis patients [133].

In line with and corroborating the therapeutic effects of exercise in bone metabolism, an eight-week period of intradialytic resistance exercise has induced robust elevations in resting concentrations of BALP and serum 1,25-dihydroxyvitamin D in haemodialysis patients [134]. Regular exercise has been shown to potentially prevent bone loss through improvements in bone mineral density as a result of an increased expression of bone markers such as BALP [135] and OPG [136]. Moreover, resistance exercise has shown more promising osteogenic effects compared with aerobic exercise [130], though research comparing modes of exercise are limited, and more research is needed.

There is increasing research highlighting exercise as an appropriate therapeutic strategy to reduce the chronic impact of diseases [137]. A study completed on healthy male individuals has observed increased concentrations of OPG following eight days of acute, weight-bearing endurance exercise [138]. Elevated levels of OPG, despite unchanged RANKL, have also been observed after one year of aerobic (fast walking) exercise in postmenopausal women [139], whereas a significant reduction in RANKL was reported to occur following eight weeks of resistance training in male rats [140]. Furthermore, mechanical strain imposed by a flexcell bioflex instrument on murine bone stromal cells induced a significant reduction in RANKL [141], highlighting the potential positive effects of resistance exercise in the maintenance of bone and muscle quality and strength. However, increased RANKL was observed 5 minutes, 1 hour and 24 hours after high-intensity, low impact exercise in young adult males [142], but no change was observed in RANKL or OPG following eight months of either resistance or aerobic exercise in older women [143]. These contrasting results highlight the need for more research examining the effects of exercise on these bone-muscle markers, with the existing data showing promising results as to the applicability of exercise interventions as an important therapeutic strategy in fighting bone and muscle loss of quality and function.

4.2 Effects of exercise on myokines in CKD

CKD patients undergoing haemodialysis are known to be considerably less physically active than age-matched healthy individuals [144]. Moreover, a study performed on CKD patients separated into two groups depending on the severity of the disease (stage 3-4 CKD and haemodialysis patients) highlights similarly low physical activity levels among pre-dialysis patients (i.e. stages 3-4) and patients undergoing HD [145]. Despite the multifactorial causes for muscle wasting and reduced muscle quality in CKD, physical inactivity has been extensively proposed to be a major contributor [146–148]. A 2-year observational study completed on 134 patients (60 on haemodialysis, 28 on peritoneal dialysis, 46 CKD 4-5) reported a 35% reduction in skeletal muscle mass determined by thigh cross-sectional area on computed tomography in the first year of treatment, with muscle loss being more pronounced in pre-dialysis patients [149].

Myokines such as irisin, IL-15, and IL-6 have been consistently shown to be released by skeletal muscle in response to exercise [150–152], with these biomarkers exerting beneficial physiological and metabolic effects in both skeletal muscle and bone, and even in immune cells, directly driving a systemic anti-inflammatory effect in the body [82, 153]. The skeletal muscle secretome connects with bone through the influence of several molecules, such as IGF-1, FGF-2 and myostatin. Interestingly, it has been reported that splice variants of muscle IGF-1 mRNA expression are increased to the same extent after five months of endurance, resistance, or combined exercise programs in haemodialysis patients, despite unchanged lean mass when comparing before to after the training period [154]. The authors [154] suggested that the design of the exercise program may not have been appropriate to elicit a skeletal muscle adaptive response due to the patients' low physical capacity and function. However, an exercise-induced overexpression of IGF-1 was observed in healthy muscle from aging individuals, which was speculated to be a compensatory mechanism to overcome the aging-associated anti-anabolic effect of muscle protein synthesis [155]. This exacerbated IGF-1 signalling in haemodialysis patients may not necessarily be indicative of an anabolic mechanism, but instead may be an aberrant response in overstimulated skeletal muscle tissue. Therefore, caution should be taken when interpreting results from exercise interventions (with focus on modality, duration and intensity) and thoroughly define how these may influence IGF-1 signalling to appropriately account for the influence of inter and intradialytic regulation of skeletal muscle activity.

There is some evidence that skeletal muscle's osteo-inducible cellular populations may directly influence bone formation and its capability to regenerate [156]. Interestingly, a study completed in rodents observed that high-intensity muscle

contractions during hindlimb unloading (defined as resistance exercise) performed during disuse promoted cortical bone geometry and formation rate restoration, and suppressed unloading-induced elevations in Sost-positive osteocytes [157], with Sost promoting osteoblast apoptosis through inhibition of certain signalling pathways, leading to reductions in bone formation [158]. Corroborating these authors [157], an elevation in myocyte-released FGF-2, a signalling protein with osteogenic properties involved in tissue repair and cell growth, was shown to have a significant positive influence on bone formation in mice with oestrogen deficiency [159], with this myokine known to be released in response to mechanically-induced plasma membrane disruption and mechanical stretching [160]. The mechanically-induced release of FGF-2 in response to eccentric muscle contraction and plasma membrane disruption may therefore be a pathway by which physical activity/exercise and bone formation are connected [14, 159].

We have shown compelling evidence of the anti-inflammatory effects of exercise in CKD [161]. Macrophages are a type of leucocytes present in skeletal muscle tissue that are central in muscle repair and pathogen clearance, mechanism regulated through a myofibers-immune cells crosstalk [153]. It has been proposed that macrophages may induce a calcifying phenotype, mainly via BALP expression in human vascular smooth muscle cells in the presence of interferon-γ [162]. However, evidence of the effects of exercise in the crosstalk between immune cells (such as macrophages), bone and skeletal muscle in CKD patients is limited, with the few existing studies examining this interaction being conducted in rodents due to the invasiveness of sampling procedures. In CKD patient muscle biopsy samples, we have observed a reduced inflammatory IL-6 and TNF-α response was observed to an acute bout of exercise following a period of resistance exercise training, but neither unaccustomed nor accustomed exercise resulted in a change in myogenin or MyoD mRNA expression, observing that exercise creates a large inflammatory response within the muscle, no longer present following regular training [163]. Nonetheless, genomic associations have been reported to be predictive of peak bone density and lean body mass [164], and single-nucleotide polymorphisms in the genes that regulate myostatin and the vitamin D receptor showing direct associations with the reduction of muscle and bone mass [19], with CKD altering the circulating concentrations and cellular responses of these markers. Importantly, a study applied two different exercise protocols (a resistance, muscle overload protocol, and a treadmill-run) to examine muscle protein metabolism and progenitor cell function in CKD-induced mice (by subtotal nephrectomy) [165]. Both reduced the CKD-associated muscle proteolysis and improved phosphorylation of Akt and the transcription factor FoxO1 [165]. Interestingly, the authors observed that two weeks of resistance exercise elicited an increase in levels of mTOR (a mediator of protein synthesis), normalising protein synthesis in the muscles of CKD-induced mice [165]. Moreover, this exercise intervention increased muscle progenitor cellular activity and numbers, determined by the amounts of MyoD and myogenin mRNAs [165]. As pharmacological myostatin inhibition reversed muscle mass loss, suppressed inflammatory cytokines, increased protein synthesis and enhanced satellite cell function in mice [81], these information may boost the possible application of exercise as a therapeutic strategy, with myostatin mRNA shown to gradually decrease in the 24 hours after moderate exercise in healthy subjects [166]. Recently, it was proposed the bone-derived osteocalcin signalling in myofibers is required for exercise adaptation, which is linked with improved muscle function, promoting muscle IL-6 secretion during exercise [108].

Of note, it is known that the influence of IL-6 in bone tissue occurs through osteoblast signalling resulting in elevated RANKL expression and osteoclastogenesis [129]. Additionally, these authors [129] have observed that IL-6-deficient mice have repeatedly shown compromised exercise-induced muscle activity, whereas those lacking IL-6 receptor in myofibers did not show compromised muscle function. However, those lacking the IL-6 receptor in osteoblast instead have mirrored the effect of total IL-6 deficiency, indicating the regulatory effect of OCN in muscle function. This suggests that the benefits of IL-6 in muscle function are regulated through the skeleton, with exercise (muscle contraction) playing a pivotal role in the modulation of this mechanism.

With exercise being known for its beneficial effects on new bone formation and bone mineral density [167], irisin (known to be released into the circulation in response to physical activity and exercise [168]) has been suggested as a major molecular modulator on increasing the protective effect that skeletal muscle may yield on bone tissue [98]. In fact, conditioned medium from primary myoblasts (obtained from exercised muscle and cultured *ex vivo*) were observed to boost the amount of BALP positive colonies in a culture of undifferentiated bone marrow stromal cells, with the conditioned medium-differentiated osteoblasts from exercised muscle expressing higher levels of BALP and collagen type I mRNA, yet a reverted effect was observed when conditioned medium were spiked with a neutralizing antibody against irisin [169]. A period of six months of intradialytic resistance exercise did not elicit any changes in resting levels of irisin in haemodialysis patients, despite an increase in muscle mass as a result of the program was observed [170]. Indeed, a 12-month period of exercise completed in 151 pre-dialysis CKD patients robustly increased leg and whole-body lean mass, with an elevation in myostatin levels observed [171]. The authors [171] randomly divided the participants into two groups to complete either 90 minutes of strength or balance training. Both groups also completed an additional 60 minutes of endurance exercise (150 minutes/week in total). These data may suggest that, despite lower levels of irisin observed in CKD patients compared with healthy controls [170], an exercise-induced increase in muscle mass may have potentially occurred due to the increased myostatin responsiveness [171]. As a reminder, myostatin is a

negative regulator of muscle mass. This is in contrast with what has been observed elsewhere [171], where plasma myostatin was significantly correlated with muscle mass and physical performance at baseline, yet these relationships were blunted after 12 months of training, in pre-dialysis patients with healthy-like C-reactive protein and albumin levels. Myostatin expression is known to be intrinsically related with IL-6 activity and upregulated in an inflammatory status [82, 172], suggesting this as a major cause for protein wasting in CKD. Interestingly, in non-inflamed individuals, myostatin levels have been observed to be within normal range, when compared with healthy individuals [173]. Therefore, an exercise-induced elevation in myostatin levels in CKD patients as observed elsewhere [171], may be interpreted as an expected physiological response to increased muscle mass, since myostatin is primarily expressed in skeletal muscle [77]. Contrastingly, a study completed on 60 patients on maintenance haemodialysis have reported that higher myostatin levels were associated with lower muscle function, measured via handgrip strength on the dominant upper limb [174]. It may be suggested that these contrasting results may be clarified by the different stages of the disease, with haemodialysis patients suffering from more severe inflammatory states than pre-dialysis patients. Still, this highlights the need for further research, and for caution when using exercise interventions to examine myostatin responsiveness in this population. Additionally, despite irisin being proposed to be an exercise-dependent myokine, to the authors' knowledge, there are very limited studies examining this relationship in CKD.

5. **Final remarks**

While countless dialysis patients may appear too frail to engage in moderate to vigorous exercise sessions, those who can undertake such programs experience considerable benefits [175]. Less vigorous exercise (aerobic, resistance or other alternative forms), may also be valuable, challenging the concern clinicians have about the application of resistance exercise to fight skeletal muscle loss of mass and function, and disproving the gradually less common conviction of exercise as a contraindication to the patients' health [175]. Indeed, a recently published prospective cohort study on 89 patients with CKD stages 3b-5 with a follow-up period of 3.3 years reported that each 1 cm^2 increase in muscle size (quadriceps) and 10-meter improvement on the incremental shuttle walk test was associated with a 38% and 3% reduction in risk of mortality, respectively [176].

Naturally, CKD patients who undergo dialysis treatment, either peritoneal dialysis or haemodialysis, experience an imposed reduction of physical activity due to inevitable sedentary time during treatment. Recognised as key risk factors for unfavourable outcomes in both pre-dialysis patients and those undergoing renal replacement treatment, there is still debate about the best therapeutic strategies to reduce sarcopenia and frailty. The intrinsic communication between muscle and bone tissues has been comprehensively narrated in this review. It arises that by therapeutically acting on one of these organs (e.g. to treat a metabolic dysfunction), one can get beneficial results on the other, with the net result possibly being potentiated when acting holistically [177]. This may be the case of exercise interventions, recently described as a "polypill" to aid in the treatment of morbidity and to improve overall health status, given its encouraging pleiotropic outcomes on all organs and systems [137].

The outcomes from this review on the potential influence of exercise on the attenuation of the detrimental impact of CKD in bone and skeletal muscle tissues and its metabolism and cross communication, highlights the urgent need for the massive implementation of worldwide exercise programs, as it has been thoroughly promoted by multi- national organizations such as the Global Renal Exercise (GREX) network. The influence of formalized groups demonstrates increased global interest in this area, which may in turn positively influence the prevention of the physical dysfunction associated with CKD, but especially with patients undergoing dialysis treatment. This is the case of the ongoing intradialytic exercise programs implemented in Mexico, Portugal, Canada and Germany which highlight the importance of demonstrating that, in addition to improving overall patient health, exercise programs need to be cost-effective, possibly through reduction of medications, improving dialysis compliance or even reducing hard outcomes such as hospitalizations and mortality [178].

The authors consider the most important take-home message from this review is the importance of implementing exercise as a therapeutic strategy to reduce muscle and bone impairments, aiming to ameliorate physical function and improve the overall quality of life across the spectrum of CKD. Effective counselling and advice on the implementation of physical activity and exercise, and the rising influence of the interdisciplinary communication between kidney health providers and specialised exercise physiologists is essential to guide an effective and crucial implementation of exercise programs worldwide.

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Figure captions:

Fig. 1 Relationship between anabolic signalling pathways, myokines and osteokines in bone and skeletal muscle metabolism in Chronic Kidney Disease. CKD is associated with dysregulated myokine and osteokine activity, and increased circulating cytokines. Myostatin correlates with sarcopenia and is elevated in CKD. It induces an increased expression of ActRIIB from osteoblasts and is therefore associated with increased osteoclastogenesis and consequently reduced bone formation. Muscle-derived IL-6 elicits increased RANKL expression, which in turn increases osteoclastogenesis and reduces myogenic differentiation. However, the bone derived OPG (abnormally high in CKD) may bind to RANKL to reverse this catabolic effect. Increased OCN is observed in CKD, directly correlating with increased protein synthesis (S6K1 and mTOR phosphorylation), with exercise playing a pivotal role in upregulating *Gprc6a* eliciting an adequate muscle mass regulation. Exercise also has a positive regulatory effect on increasing bone density, lean mass and muscle strength, by eliciting elevated FGF-2 responses and anabolic signalling pathways such as mTOR and IGF-1, as well as increased ucOCN.

Figure

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