Clinical Kidney Journal

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LEADING EUROPEAN NEPHROLOGY

Clinical Kidney Journal, 2018, vol. 11, no. 6, 810–821

doi: 10.1093/ckj/sfy052
Advance Access Publication Date: 30 July 2018
CKJ Review

CKJ REVIEW

Satellite cell function, intramuscular inflammation and exercise in chronic kidney disease

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ABSTRACT

Skeletal muscle wasting is a common feature of chronic kidney disease (CKD) and is clinically relevant due to associations with quality of life, physical functioning, mortality and a number of comorbidities. Satellite cells (SCs) are a population of skeletal muscle progenitor cells responsible for accrual and maintenance of muscle mass by providing new nuclei to myofibres. Recent evidence from animal models and human studies indicates CKD may negatively affect SC abundance and function in response to stimuli such as exercise and damage. The aim of this review is to collate recent literature on the effect of CKD on SCs, with a particular focus on the myogenic response to exercise in this population. Exercise is widely recognized as important for the maintenance of healthy skeletal muscle mass and is increasingly advocated in the care of a number of chronic conditions. Therefore a greater understanding of the impact of uraemia upon SCs and the possible altered myogenic response in CKD is required to inform strategies to prevent uraemic cachexia.

Keywords: exercise, intramuscular inflammation, sarcopenia, satellite cells, skeletal muscle

INTRODUCTION

Skeletal muscle wasting in CKD

Chronic kidney disease (CKD) is characterized by a progressive decline in renal function, often in conjunction with structural abnormalities. The prevalence of CKD Stages 3–5 is predicted to be 8.5% in the UK and 10.6% globally, with prevalence greatest at Stage 3, higher among women and increasing with age [1–3]. The number of patients receiving renal replacement therapy (RRT) has increased in the UK from 45 484 to 61 256 between 2007 and 2015 [4, 5].

Cachexia is highly prevalent in CKD (Table 1). It is associated with declining renal function [6–8] and therefore is prominent during the latter stages of the disease [9]. However, wasting is also reported in non-dialysis patients [7, 10, 11] and the rate of decline may be greater compared with patients receiving RRT [12]. Reduced muscle mass and strength is also common in renal transplant recipients [13, 14] and is associated with mortality and graft failure [15, 16].

The prevalence of muscle wasting in CKD varies depending on the method of assessment, with different criteria referring to measures of body composition, functional outcomes or a combination (Table 1) [10, 17–27]. Even when employing the same measure, differing cut-off values are often used. For example, the European Working Group on Sarcopenia in Older People (EWGSOP) and Foundation for the National Institutes of Health (FNIH) determine sarcopenia according to hand-grip strength but with differing cut-offs (<30 kg/20 kg versus <26 kg/16 kg in men and women, respectively). This can significantly influence prevalence statistics. Zhou *et al.* [18] reported 29% of 148 non-dialysis patients fit the EWGSOP classification of sarcopenia, however, according to appendicular lean mass

Received: 21.2.2018. Editorial decision: 18.5.2018

Table 1. Prevalence of sarcopenia in CKD and associations with mortality and physical function

Reference	Population	Criteria	Prevalence (%)	Association
Souza *et al.* [17]	NDD	EWGSOP	11.9	ADL, gait speed, functional capacity, higher BMI
		FNIH	28.7	
Zhou *et al.* [18]	NDD CKD (Stages 3–5)	ASMI < 7.3/5.5 kg/m^2 men/women	36	Measured GFR, functional reach, Berg balance score.
		HGS < 30/20 kg men/women	29	
		ASMI and Handgrip	14	
Pereira *et al.* [10]	NDD CKD (3–5)	HGS < 30th percentile of population, sex-specific reference, plus:		Mortality HR (association between mortality and sarcopenia according to BIA significant after multivariate adjustment)
		MACM < 90% population reference	9.8	
		SGA	9.4	
		BIA < 10.76/6.76 kg/m^2 men/women	5.9	
Lamarca *et al.* [19]	HD CKD	DEXA 20th percentile of young individuals	73.5	
		2 SD below mean of young individuals	32.7	
		BIA 20th percentile of young individuals	51	
		2 SD below mean of young individuals	13.7	
		SKF 20th percentile of young individuals	44.1	
		2 SD below mean of young individuals	3.9	
		MAMC < 90% population reference	34.7	
		CC <31 cm	21.8	
		HGS < 10th percentile of population cohort	85.1	
Kittiskulnam *et al.* [20]	HD CKD	Low MM (2 SD below sex-specific means for young adults) indexed to:		Gait speed (Associations between data and mortality presented in another paper [21]. Significantly higher mortality rate in sarcopenic patients, according to low MM, but not in adjusted models)
		Height	8.1	
		Weight	25.3	
		BSA	32.4	
		BMI	25.0	
		Low MM and SM strength (HGS <26/16 kg men/women) indexed to:		
		Height	3.9	
		Weight	11.4	
		BSA	15.9	
		BMI	14.0	
Gracia-Iguacel *et al.* [22]	HD CKD	ISRMN [23] criteria of PEW at 3 time points		No association between PEW and mortality but loss of MM associated with increased mortality
		Baseline		
		12 months	37	
		24 months	40.5	
			41.1	
Carrero *et al.* [24]	HD	SGA	39	Mortality risk
Kittiskulnam *et al.* [21]	HD	HGS <26/16 kg men/women	29.9	Low HGS and slow gait speed associated with mortality risk
Chang *et al.* [25]	NDD CKD	HGS, SGA, BIA, MAMC, MAMA, MAC, SKF	N/A	Only HGS was significantly associated with composite endpoints of non-dialysis mortality and ESRD
Isoyama *et al.* [26]	Dialysis CKD	ASMI 7.3/5.5 kg/m^2	24%	Low MS associated with PEW, comorbidities, inactivity, old age, low albumin, inflammation. No association of these factors with low MM
		HGS <30/20 kg men/women	15%	
		Combined	20%	
				Both low MS and MM independently associated with mortality risk
Wang *et al.* [27]	NDD CKD	LTI <10% reference value	12.2%	Serum albumin, eGFR, age, IL-6, CVD

ASMI, Appendicular Skeletal Muscle Index; BIA, bioelectrical impedance analysis; BSA, body surface area; CC, calf circumference; DEXA, dual-energy X-ray absorptiometry; SKF, skinfold thickness; HGS, handgrip strength; LTI, Lean Tissue Index.; MAC, mid-arm circumference; MAMA, mid-arm muscle area; MAMC, mid-arm muscle circumference; NDD, non-dialysis dependent; SGA, subjective global assessment; SM, skeletal muscle.

(<7.3 kg/m^2 versus 5.5 kg/m^2 for men and women, respectively) this increased to 36%, whereas 14% satisfied both criteria [18]. Every 1 mL/min/1.73 m^2 decrement in measured GFR was associated with a 0.15 kg loss of lean mass, which was in turn positively associated with physical functioning [18]. Therefore, regardless of the criteria used, sarcopenia appears to worsen with disease progression and is associated with poorer performance of activities of daily living (ADL), slower gait speed, reduced physical functioning and inactivity [17]. Consensus on the definition and methods of assessment of sarcopenia in CKD

are required and should employ multidimensional measures encompassing muscle size and functionality with cut-off points relevant to CKD [28].

The clinical relevance of reduced muscle mass and strength in CKD is exemplified through associations with mortality, depression, quality of life, diabetes and cardiovascular disease (CVD) [10,29–32]. For example, psoas cross-sectional area (CSA) independently predicts major adverse cardiovascular events in non-dialysis patients [33]. Reduced muscle mass is also associated with impaired exercise capacity and physical functioning [9, 11, 12, 34, 35], which likely contribute to reduced rates of physical activity in CKD [11, 36]. Roshanravan *et al.*, [37] recently collated evidence from non-dialysis demonstrating every 0.1 m/s decrement in gait speed is associated with a 26% greater risk of death [37]. Reduced strength and physical capacity may account for the higher fall rates in CKD patients compared with the general population [38]. Falls are a major cause of acute injury and often initiate a decline in functional independence, culminating in greater reliance on health care services [39], which is predicted to cost the National Health Service in excess of £2.3 billion per years [39]. This exemplifies the importance of early detection of skeletal muscle impairment to allow for timely initiation of appropriate therapy in patients with CKD [40].

CKD adversely alters both protein synthesis and degradation, with proposed mechanisms including upregulation of the ubiquitin–proteasome system (UPS), caspase-3 and autophagy in response to factors that include metabolic acidosis, inflammation, mitochondrial dysfunction, oxidative stress and insulin resistance (IR) [40–43]. Satellite cells (SCs) are specialized stem-like cells that regulate skeletal muscle mass by initiating myogenesis, thereby facilitating growth and repair. Altered SC function is a feature of a number of conditions associated with loss of muscle mass, including unloading, denervation and atrophy induced by a number of chronic diseases [44]. Recent evidence indicates that CKD may also impair the functioning of these cells, presenting a novel mechanism contributing to uraemic cachexia [41]. The aim of this article is to review the available literature investigating the role of SCs in uraemic cachexia and to explore the potential for exercise to restore any lost or inhibited function of these cells.

Overview of myogenesis

Skeletal muscle comprises long cylindrical multinucleated fibres that run the length of a tissue longitudinally and are grouped into bundles, referred to as fascicles (Figure 1). Myofibres are composed of numerous myofibrils organized in series, which are in turn composed of sarcomeres, the contractile unit of muscle tissue required for locomotion. Muscle fibres are highly specialized, with specific metabolic capacities to meet distinct contractile demands. As a result, mature muscle is post-mitotic and comprises terminally differentiated cells [45]. However, skeletal muscle is also highly plastic, displaying remarkable capacity to increase in size following hypertrophic stimuli or repair damaged myofibres. This is afforded by the population of SCs that supply new myonuclei to regenerating or expanding myotubes [46].

Individual myofibres are enveloped by an elastic membrane, the sarcolemma, which comprises a plasma and basement membrane. Under homeostatic conditions, SCs reside in a niche between these membranes in a dormant state known as quiescence. Quiescent SCs are undifferentiated and non-proliferative, but upon activation by damage, exercise or growth factors, they are able to re-enter the cell cycle [47]. SC progeny, referred to as myoblasts or myogenic precursor cells (MPCs), proliferate and differentiate, committing to the myogenic lineage (myocytes). A small population of SCs will undergo asymmetric division, with one of their progeny progressing along the myogenic programme, whereas the other retains its stem cell–like capacity and returns to quiescence, maintaining the SC pool [46]. Myoblasts undergoing terminal differentiation will either fuse to each other or to existing myotubes, providing new myonuclei that are phenotypically and functionally indistinguishable from those surrounding them [48].

Myogenesis is regulated by the sequential expression of a number of transcription factors, namely paired-box protein-7 (Pax7) and a group of myogenic regulatory factors (MRFs). Quiescent SCs can be identified by the expression of Pax7 and the absence of myoblast determination protein (MyoD) and myogenin expression [46]. Upon activation, myogenic factor 5 (Myf5) is upregulated and subsequently proliferating MPCs express high levels of MyoD. Following several rounds of proliferation, terminal differentiation is initiated by myogenin and MRF4, whereas differentiated cells are also notable for their absence of Pax7 expression, due to downregulation by myogenin [46–49].

Numerous regulators participate in the orchestration of this complex process, acting via distinct signalling pathways to facilitate MRF expression and cellular progression through each stage of the myogenic program. It is beyond the scope of this review to discuss the many regulatory factors involved in myogenesis, however, interested readers are directed to the following comprehensive reviews [46, 49].

SC FUNCTION IN CKD

Research assessing the effect of CKD on myogenesis is relatively scarce. However, it has been suggested that mice subjected to subtotal nephrectomy exhibit reduced MPC abundance, with 18% fewer myonuclei located outside the sarcolemma of myofibres [50].

When assessed according to MRF expression, CKD mice showed reduced mRNA expression of Pax7, but in the presence of increased MyoD and myogenin, increased mRNA expression [51]. These mice were not subjected to injury and there was no evidence of ongoing regeneration, however, elevated muscle RING-finger protein-1 (MuRF1) and muscle atrophy F-box (MAFbx) mRNA expression supports the notion of elevated proteolysis, previously reported in CKD, potentially providing a stimulus for myogenesis [51].

In contrast, another study reported no difference in Pax7 gene expression or the abundance of $Pax7^{+}$ cells between CKD and wild-type (WT) mice [52]. However, MyoD, Myf-5 and myogenin mRNA were supressed in CKD muscle [50, 52]. Reduced positive staining for MyoD was seen in SCs isolated from CKD mice, together with lower levels of '5-bromo-2'-deoxyuridine (BrdU) incorporation and embryonic myosin heavy chain (eMyHC) staining indicating downregulated SC proliferation and differentiation, respectively, compared with WT-derived SCs. This *in vitro* evidence suggests that CKD does not reduce the number of SCs but impairs their activation and differentiation [52].

The discrepancy of the influence of uraemia on MRF expression may be a product of differing methods, with a genetic model of slow progressive CKD being used by Avin *et al.* [51] compared with the more widely used 5/6 subtotal nephrectomy [52].

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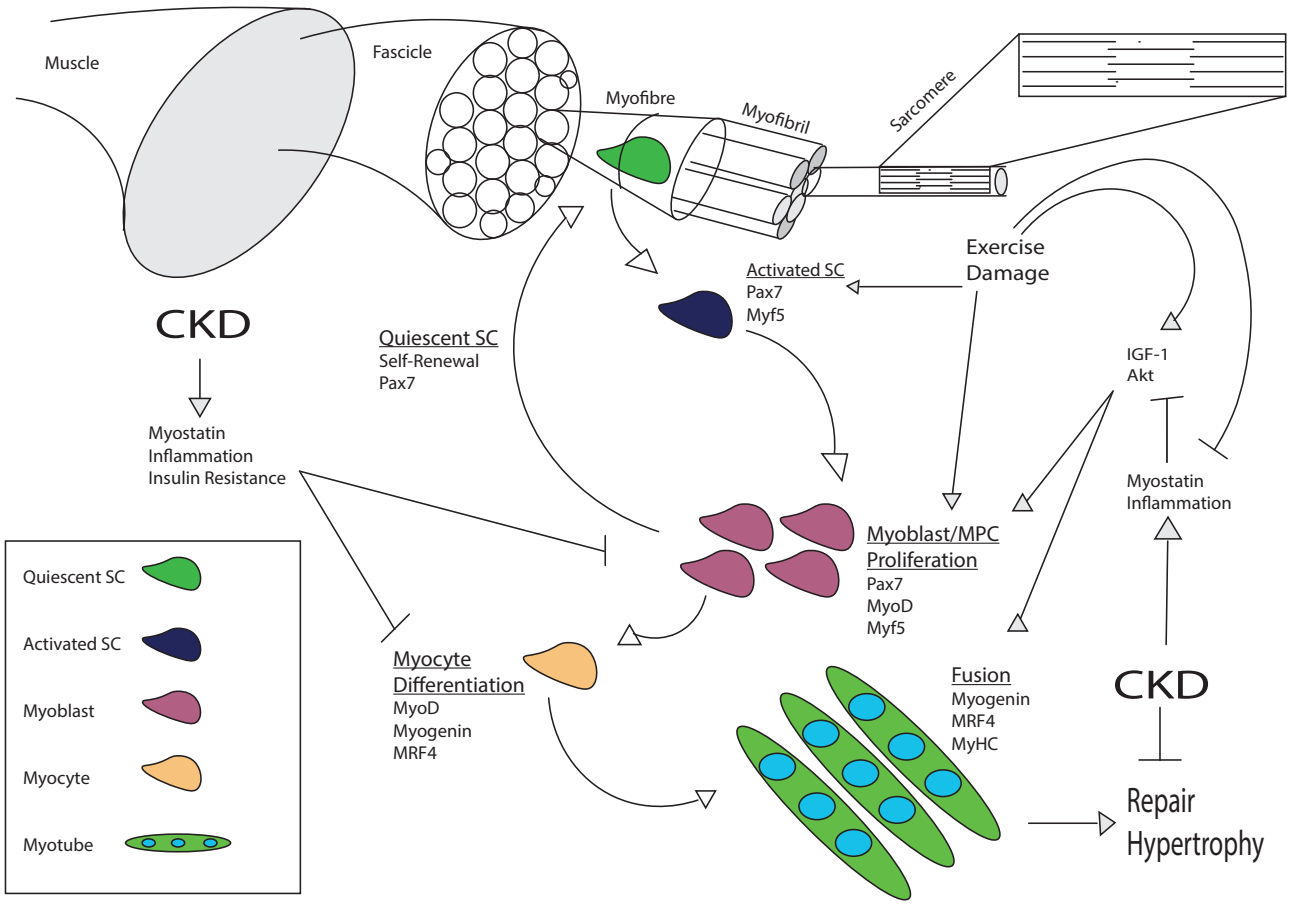

FIGURE 1: Overview of myogenesis and regulatory processes and the possible effect of CKD. Arrows denote stimulatory/upregulatory impact and flat lines indicate negative/suppressive impact. SCs are activated by stimuli such as exercise and damage. Proliferating cells and myoblasts either return to quiescence or differentiate to become myocytes. Mature myocytes fuse to each other or existing myotubes, providing new myonuclei. CKD interferes with both proliferation and differentiation of SCs with factors including inflammation, myostatin signalling and IGF-1/Akt dysregulation proposed as primary mechanisms. See text for details.

Regardless, both studies show CKD induced dysregulation of SCs in mice.

SCs are required to repair muscle after acute injury, indicated by the lack of regenerative myogenesis following ablation of $Pax7^+$ cells [53, 54]. Nephrectomized mice subjected to cardiotoxin (CTX) injury show blunted MyoD and myogenin mRNA expression 72-h post-injury, persisting for 14 days [52]. While WT muscle achieved full repair after 14 days, at this point CKD mice presented expanded interstitial spaces, persistence of mononuclear cells and myofibres remained considerably smaller after a month [52]. Therefore the blunted myogenic gene expression seen in isolated SCs *in vitro* and whole muscle in CKD is replicated in an *in vivo* model of injury, culminating in impaired tissue regeneration. To our knowledge, no data are available assessing the myogenic response of humans with CKD to muscle damage. However, another scenario in which SCs are activated is in response to exercise.

Effects of exercise on SC function in CKD

Generally, exercise activates SCs, with numerous studies showing initiation of myogenesis following a single bout in healthy individuals [55–58]. This has been seen following protocols designed to induce muscle damage, however, SCs also respond to non-damaging and non-hypertrophic exercise [59]. Sedentary obese individuals showed an increase in $Pax7^+$ and $MyoD^+$ cells in type I fibres after a single bout of a resistance exercise protocol relevant to 'real-world' physical activity (8×8 leg extension repetitions at 70% 1 repetition maximum). Although no change in type II fibre–specific SCs was seen [60]. SC activation in the absence of myofibre damage suggests different mechanisms of action, with cytokines and growth factors proposed to play central roles [61].

Exercise has previously been shown to attenuate CKD-induced atrophy in mice [50]. This was due in part to the rescue of depressed protein synthesis and elevated proteolytic rates. Muscle overload, but not treadmill running, increased peripherally located myonuclei by 1.8-fold and increased the expression of MyoD, myogenin and embryonic MyHC [50]. This indicates that a model of resistance exercise can increase MPC abundance and activation compared with non-exercised uraemic mice, alleviating CKD-induced atrophy.

Exercise is increasingly being recognized as an important aspect in the treatment of CKD due to improvements in muscle size and function, physical capacity and CVD risk [40, 62]. However, the effect of CKD on SC function in patients and the myogenic response to exercise has received less attention.

Dialysis patients showed reduced SC content in type II compared with type I fibres [63]. However, when normalized for fibre area, this difference was no longer evident, suggesting this

finding may be a product of disproportionate atrophy in type II fibres common in CKD patients [63]. The abundance of SCs per fibre increased by 15% in type I fibres following 16 weeks of high-intensity resistance training, with no increase in myonuclear content [63]. Interestingly, there was no change in the SC content, but an increase in myonuclear content was reported in type II fibres, indicating fibre-specific SC responses to training. [63].

We have previously reported the molecular response to resistance exercise in non-dialysis patients [64]. We found no change in MyoD or myogenin mRNA expression 24-h after an unaccustomed bout of exercise compared with baseline levels. Similarly, no acute myogenic response was seen following a period of resistance training [64]. This lack of exercise-induced myogenesis could diminish exercise adaptation, contributing to loss of muscle mass. However, these patients did show increases in muscle CSA (8%), volume (10%) and knee extensor strength (13%) after training [65]. SC activation during the early stages of training appears responsive to the degree of damage caused by unaccustomed exercise, which is attenuated with regular exercise [66]. Therefore it is possible the exercise protocol we employed did not cause sufficient tissue damage to stimulate SC activation. With regard to the training-induced hypertrophy, while we did not assess SC and myonuclear content, it is possible to achieve hypertrophy without the accrual of additional myonuclei if the existing pool is capable of supporting the transcriptional capacity of the expanded tissue [66].

Alternatively, the single sample point at 24-h post-exercise missed an effect. Comprehensive determination of the time course of gene expression over a 24-h period following resistance exercise reported upregulation of myogenic genes from 2- to 12-h, with MRF4, MyoD and myogenin peaking within 4–8 h in young healthy individuals [67]. Increases in $Pax7^+$ cells have been reported 24-h post-exercise [56] and even peaking 72-h after and remaining above baseline values 120-h post-exercise [57]. However, these studies have generally employed more extreme protocols of exhaustive eccentric exercise, causing greater damage. The time course of a myogenic response to exercise, both damaging and non-damaging, requires more thorough investigation in CKD.

In summary, SCs are recognized to be essential regulators of skeletal muscle repair [68]. Their role in hypertrophy, however, has been the subject of debate, with some supporting an essential requirement [69], while others show hypertrophy can be achieved in their absence [68, 70]. These differences could be the product of the methods used to deplete SCs (irradiation versus genetic approaches) in animal models and hypertrophic stimuli (overload versus myostatin inhibition). In humans, a wealth of evidence shows SC activation following acute and chronic resistance exercise [57, 58, 60, 63, 66, 67, 71–73]. Indeed, positive correlations between acute SC response and chronic hypertrophic gains support a role for SC in skeletal muscle adaptation [74]. As previously mentioned, non-hypertrophic aerobic exercise also stimulates a myogenic activation, without increasing the SC pool, supporting a role in non-hypertrophic skeletal muscle remodelling [59]. While debate remains on the absolute requirement of SCs to hypertrophy in animal models, the human evidence showing myogenic activation after both resistance and endurance exercise overwhelmingly supports a central role of SCs in skeletal muscle adaptation to exercise [48].

Within the context of CKD, however, there is a shortage of research assessing the effect of CKD on SC function. The studies that have been performed indicate that uraemia impairs SC abundance and/or activation. This has been shown to correspond to blunted myogenic response to muscle injury and exercise, potentially contributing to sarcopenia.

MECHANISMS OF SC DYSFUNCTION IN CKD

Inflammation

SCs are receptive to and indeed reliant on signals from their local environment, mediated by factors such as disease, damage and exercise [46]. The involvement of cells of other lineages, namely haematopoietic, is now recognized as pivotal to SC function in response to exercise and tissue injury [75].

The early inflammatory response to acute injury is well characterized, with neutrophils entering muscle within 1–24 h [76–81] and producing large amounts of oxidative free radicals to remove cellular debris [82, 83]. Following neutrophil accumulation, macrophages become the dominant leucocyte population in regenerating skeletal muscle. An initial population of $Ly6C^+$ monocytes/macrophages infiltrate regenerating muscle, phagocytizing necrotic debris and producing large amounts of pro-inflammatory cytokines before transitioning *in situ* to pro-regenerative Ly6C-macrophages [84–86]. Impaired regeneration following macrophage depletion illustrates their importance [84, 87, 88]. This is due to close interaction between myogenic cells and macrophages throughout myogenesis, with the former facilitating monocyte chemotaxis while macrophages in turn protect MPCs and myotubes against apoptosis [89, 90].

Pro-inflammatory macrophages associate with proliferating MPCs in human muscle [91] and produce soluble factors that stimulate MPC proliferation and cytokine secretion *in vitro* [91, 92]. Tumour necrosis factor α (TNFα) induces a dose-dependent increase in myoblast proliferation [93] but inhibits myogenic differentiation via nuclear factor κB (NF-κB) activation [94–96]. However, macrophages are also a source of insulin-like growth factor-1 (IGF-1) [97] and anti-inflammatory macrophages have been shown to co-localize with myogenin-positive MPCs *in vivo*, promoting differentiation and myotube fusion [91]. In sum, macrophage-derived growth factors and cytokines are involved in both MPC proliferation and differentiation, demonstrating the importance of the local inflammatory milieu in myogenesis.

CKD has a profound effect on this local inflammatory environment, characterized by low-grade inflammation in circulation. For example, systemic concentrations of C-reactive protein (CRP) were independently associated with elevated protein degradation and reduced protein synthesis and protein balance in maintenance haemodialysis (HD) patients [98], while interleukin-6 (IL-6) concentration was associated with reduced lean tissue mass in non-dialysis CKD patients [27].

However, CKD patients also show elevated mRNA expression of intramuscular IL-6, TNF-α, toll-like receptor-4 (TLR4) and myostatin, while NF-κB and p38 mitogen-activated protein kinase (MAPK) signalling is also upregulated [99–101]. Uraemic rodent models show greater cytokine production and macrophage infiltration in adipose tissue, while peritoneal macrophages isolated from partially nephrectomized mice show augmented M1 and blunted M2 polarization [102, 103]. Similar findings were recently reported in humans with end-stage renal disease (ESRD), as patients exhibited greater macrophage presence in adipose tissue [104]. With regard to skeletal muscle, excessive macrophage infiltration and prolonged pro-inflammatory cytokine expression were reported in CKD mice subjected to CTX-induced injury, culminating in delayed regeneration [52]. Therefore uraemia upregulates cytokine expression and inflammatory

signalling pathways in peripheral tissues while also altering inflammatory cell infiltration and function.

This altered immune cell presence and function in peripheral tissues may be a product of circulatory factors, with CKD serum promoting M1 polarization and greater cytokine expression in macrophages derived from WT animals [102]. Serum also promotes a pro-inflammatory response in myogenic cell lines, evidenced by upregulation of TLR4 and TNF-α expression in C2C12 cells [100] and also impairing mitochondrial function [104]. Similarly, indoxyl sulfate, a uraemic toxin, recently reduced proliferation and differentiation of C2C12 while also downregulating both mRNA and protein expression of MyoD, myogenin and MyHC [105]. In sum, uraemia promotes a pro-inflammatory response from both immune and myogenic cells.

As in response to injury, inflammation is part of a normal exercise response and is an important regulator of SC activation [106]. However, recent micro-array analysis showed an overall pattern of blunted gene expression response to an acute bout of exercise in CKD patients before and after transplantation [107]. Enhancement of various gene pathways following exercise increased post-transplant, particularly those related to cytokine and chemokine activity [107]. In addition to investigating the myogenic response to resistance exercise described earlier [64], we have also assessed the intramuscular inflammatory response to an acute bout of resistance exercise in non-dialysis CKD patients before and after 8 weeks of progressive resistance training [65]. A considerable inflammatory response to exercise in the untrained state was reported, with IL-6 (53-fold), monocyte chemoattractant protein-1 (25-fold) and TNF-α (4-fold) all increasing significantly. This suggests a transient worsening of the inflammatory environment within muscle 24 h after a single bout of exercise. Whether this inflammatory cytokine upregulation is greater than that normally seen in healthy individuals is unclear, however, the response was dampened after a period of training [64]. In addition, IL-15 mRNA was suppressed significantly from baseline in the untrained state. IL-15 is another myokine with mitogenic properties [108] and has recently been shown to mitigate the negative influence of TNF-α on human myogenesis [109]. Training corrected this blunted IL-15 expression, which was also combined with the reversal of inflammatory cytokine expression [64]. There was no evidence of overt oxidative stress or protein catabolism following exercise in either the unaccustomed or trained state [64].

Collectively this indicates an altered intramuscular response to acute exercise in CKD patients. The apparent lack of a myogenic response in these patients following exercise has been discussed earlier. Whether this was due to elevated local inflammation is unclear, but evidence suggests that CKD patients were also unable to stimulate a myogenic response after a period of training, despite normalization of cytokine expression [64]. Considering the role of inflammation in myogenesis and the effect of cytokines and immune cells on SCs in culture, future research should address the effect of inflammatory factors present in uraemia on SC function.

IR and diabetes mellitus (DM)

The prevalence of IR in CKD has been reported to range from 10 to 100%, with variance likely due to differences in population and cause of disease, methods of measurement and criteria of IR [110]. Research assessing how IR interferes with myogenesis in CKD is lacking, however, much evidence has assessed its role in SC dysfunction in obesity and type 2 DM.

Large-scale cross-sectional evidence indicates patients with type 2 DM show decreased muscle mass, quality and strength and reduced physical function compared with non-diabetic counterparts [111, 112] and that losses of skeletal muscle mass, quality and strength with age are accelerated in the presence of type 2 DM [113, 114].

Myopathy is common in insulin-resistant states, with SC abundance and function central to this [115]. Lipotoxicity, caused either by high-fat diets or transgenic mouse models, prolongs muscle regeneration via impaired SC functioning [116, 117]. Animal models of type 2 DM show delayed regeneration following CTX injury, with impaired SC activation and proliferation in response to damage, as indicated by reduced BrdU incorporation [118]. Delayed regeneration coincided with impaired inflammatory response with attenuated macrophage accumulation in damaged areas, potentially contributing to persistent necrosis and collagen accumulation [118, 119].

SCs derived from insulin-resistant donors exhibit impaired glucose and lipid metabolism, indicating these cells retain donor characteristics *in vitro* [115, 120]. Interestingly, altered inflammatory signalling is also conserved in primary cell cultures derived from insulin-resistant individuals with evidence of increased NF-κB DNA binding and cytokine production [121] and dysfunctional IL-6-negative regulation [122]. The effect of inflammation on SC function has been discussed previously (see above) and may represent a common mechanism through which CKD and type 2 DM negatively influence myogenesis.

Exercise is routinely used in the management of diabetes. Reduced SC proliferation in obese Zucker rats was counteracted by loading along with protein expression of myogenin, MyoD and Akt [123]. However, no change in SC content was seen after 6 months of endurance exercise in obese male type 2 DM patients [124]. This may be due to the lack of hypertrophy, with patients showing no change in fibre composition, CSA or lean mass. Therefore exercise has the potential to ameliorate the negative influence of type 2 DM and IR on SC function, but further research is needed specifically in the context of CKD and to clarify the optimal exercise mode to use for maximum benefit.

IGF-1

IGF-1 signalling is central to maintaining a healthy muscle mass. Following IGF-1 receptor binding, a cascade of intracellular signalling is initiated that represents a crossroads in protein metabolism, stimulating protein synthesis via downstream targets, such as Protein Kinase B and mammalian target of rapamycin, while suppressing degradation through phosphorylation of Forkhead box O1 (FoxO1) and subsequent inhibition of the UPS [125, 126]. This is relevant to CKD, as rodent models show defective post-receptor insulin/IGF-1 signalling culminating in reduced Akt activation [127].

IGF-1 levels increase both locally and in circulation after exercise. Intramuscular IGF-1 also increases after tissue damage, primarily derived from macrophages [97, 128]. Most mitogens are generally believed to increase proliferation and inhibit differentiation, however, IGF-1 positively regulates both of these mutually exclusive processes through distinct signalling pathways. Early provision of IGF-1 by macrophages mediates MPC proliferation via MAPK signalling, whereas later IGF-1 secretion by macrophages and other cell types, including fibroblasts, supports differentiation via phosphatidylinositol-3-kinase-induced p70 S6 kinase activation [129]. Alternatively, the IGF-1 splice variant mechano-growth factor (MGF) is expressed early after mechanical stretch in rodents, promoting proliferation and

blocking differentiation, whereas IGF-IEa is expressed later and promotes myoblast differentiation [130, 131]. A similar expression time course of these IGF-1 isoforms was replicated in humans after exercise [132].

Numerous studies using *in vivo* transgenic or knock-out models point to a major role of IGF-1 in the regulation of muscle mass [133]. Transgenic mice bearing heterozygous IGF-1 receptor (IGF-1R) mutation in MyoD^{+} cells show reduced muscle mass and myofibre CSA, while myogenic gene expression, proliferation and differentiation rates are also suppressed [52, 133]. IGF-1 signalling intersects with numerous members of other pathways in skeletal muscle [126], including transforming growth factor β1 (TGF-β1), which suppresses MyoD-dependent differentiation via Smad3 signalling [134]. However, IGF-1 prevents nuclear translocation of Smad3 and subsequent impact on gene expression due to cytoplasmic association with p-Akt [133]. Exercise-induced Akt activation has been seen to be blunted in mouse models of CKD and in human CKD patients, suggesting CKD induces an anabolic resistance [50, 64] that may impair SC function and also contribute to fibrosis by failing to regulate TGF-β1 signalling, as seen in IGF-1R$^{+/-}$ models [133]. This appears to be rescued by exercise training [50, 64], which was also associated with increased MRF expression, suggesting that this is one possible mechanism by which regular exercise training might be able to improve SC function.

Muscle overload designed to replicate resistance exercise increased IGF-1 mRNA in CKD mice and corrected atrophy [135]. Similarly, a cycling-based endurance training program increased IGF-1 expression in muscle of maintenance HD patients [136]. This highlights suppressed IGF-1 signalling as a therapeutic target to prevent muscle wasting, which appears can be positively modulated by exercise training. This is an attractive, safe and low-cost intervention that provides numerous other benefits to CKD patients.

Myostatin

Myostatin is a member of the TGF-β protein family and is a negative regulator of muscle mass. It is expressed in SCs and their progeny, where it inhibits G_0-S phase progression and proliferation [137]. Myostatin knock-out myoblasts exhibit prolonged proliferation in differentiation medium due to extended expression of MyoD and myogenin [137].

In a recent publication, myostatin was shown to stimulate fibro/adipogenic precursor (FAP) cell proliferation. FAPs are bipotent progenitor cells capable of differentiating into adipocytes or fibrocytes. Myostatin increases fibrotic gene expression in FAPs, promoting fibrocyte differentiation and potentially accounting for greater FAP content and α-smooth muscle actin expression in CKD muscle following injury [138]. Blocking myostatin was effective in reducing FAP abundance and fibrotic gene expression in injured CKD mice compared with controls, while also decreasing fibrotic gene expression. Therefore it appears myostatin expression simultaneously inhibits myogenesis and promotes fibrosis by pushing FAPs towards fibrocyte differentiation [138].

Myostatin mRNA expression is elevated in CKD muscle, potentially due to TNF-α-induced NF-κB activation [51, 138, 139]. This appears to induce atrophy, as intramuscular antagonism of myostatin corrected rates of protein synthesis and degradation, preventing loss of muscle mass [139]. This was partially due to increased Akt phosphorylation, subsequently increasing phosphorylation of FoxO3a and FoxO1 [139]. In addition, myostatin inhibition also increased MyoD and myogenin expression at rest and in response to CTX injury in CKD mice [139].

The applicability of myostatin inhibition to CKD patients has not been investigated, but a number of clinical trials have been performed in healthy controls [140], elderly participants [141] and other patient populations [142]. These trials demonstrate anti-myostatin treatments to be generally well tolerated and to exert positive effects on muscle mass and functional outcomes [140, 143].

Another method of reducing myostatin expression is through exercise. Muscle overload attenuates declines in MyoD, myogenin and eMyHC expression in CKD muscle [50] and normalized elevated myostatin expression [135]. Regular endurance training also appears to improve myostatin mRNA expression levels in HD patients [136] and resistance exercise suppressed myostatin expression 24 h after a single bout in non-dialysis patients [64]. Therefore exercise may pose a viable therapeutic strategy of improving the effect of altered intramuscular myostatin signalling in CKD.

Nutrient availability

In addition to stimuli such as exercise, tissue damage and growth hormones, nutrient availability has emerged as an additional modulator of SC function. Protein provision, specifically of branched-chain amino acids (BCAAs) such as leucine, may have the potential to augment SC responses *in vitro* and *in vivo* following acute exercise, as comprehensively reviewed recently [144].

Dietary recommendations, especially those concerning protein, are complicated within a uraemic context. Failure to excrete non-volatile acids derived from dietary protein can result in metabolic acidosis, which is implicated in protein catabolism, systemic inflammation and CKD progression [145]. However, protein energy wasting is prevalent in CKD and frequently caused by inadequate dietary protein intake [146]. Low-protein diets are common in non-dialysis CKD patients, and hypertrophic benefits of exercise have been achieved consuming 0.6 g/kg/day [147]. However, considering the impact of protein availability on hypertrophic and specifically SC responses to exercise [144], further research is warranted to determine the optimal dosage and timing of protein intake post-exercise in order to maximize benefits without compromising other aspects of patient care.

Ageing

Another factor relevant to SC dysfunction within the context of CKD is ageing. The decline in skeletal muscle mass starts during the third decade of life, accelerating during the fifth [148] and SC dysfunction has been highlighted as a contributing factor [149]. Increasing age is associated with reduced fibre CSA and SC content [73], which disproportionately effects type II fibres [149, 150]. While 4 weeks of retraining in young participants restored the myofibre area and SC content lost during 2 weeks of immobilization, elderly individuals showed no such recovery [151]. Previous research also reports blunted acute SC responses after resistance exercise in type II–associated SCs, potentially due to delayed downregulation of myostatin [73, 152]. This indicates impaired or delayed SC response to exercise. Promisingly however, age-related declines in type II fibre size and SC content can be corrected following prolonged resistance exercise regimes lasting 12 weeks [149].

As with elderly individuals, dialysis patients reportedly show greater type II–specific fibre atrophy [153] and lower type II SC content [63]. Due to the chronic nature of renal disease, prevalence is high in the elderly. However, with neither study including age-matched controls, it is difficult to disentangle the contributions of aging and CKD to muscle wasting and SC dysfunction.

SUMMARY

Muscle wasting is prevalent in CKD patients and is associated with a number of negative outcomes. Impaired SC functioning has emerged as a novel mechanism of atrophy and muscle dysfunction in CKD. Research on this topic is in its infancy, but a greater understanding of the effect of uraemia on SCs and the mechanisms through which this occurs will allow for more targeted treatment strategies.

This is particularly pertinent as increasingly there are calls for exercise to be implemented into standard renal care due to its favourable impacts on a range of common comorbidities [154]. Despite the wealth of evidence in support of 'exercise as medicine' in CKD, routine prescription is uncommon [155]. More research is required to determine the necessary dose to prescribe to CKD patients, particularly in non-dialysis and transplant populations [156], to increase implementation to that seen in other chronic diseases.

FUNDING

This report is independent research supported by the National Institute for Health Research Leicester Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research Leicester BRC or the Department of Health.

CONFLICT OF INTEREST STATEMENT

None declared.

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