



EDITORIAL COMMENT

Sarcopenia in CKD: a roadmap from basic pathogenetic mechanisms to clinical trials

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ABSTRACT

Sarcopenia and frailty are recognized as key risk factors for adverse outcomes in patients on renal replacement therapy or with non-dialysis chronic kidney disease (CKD). However, there is still debate about their pathogenesis and, thus, about the best therapeutic approaches, as well as the impact on outcomes of current approaches based on different exercise programmes. In the past two issues of *Clinical Kidney Journal*, several manuscripts address the issue of sarcopenia in CKD from the point of view of pathogenesis and new therapeutic approaches, monitoring of results, implementation of exercise programmes and specific potential benefits of exercise programmes in dialysis and non-dialysis CKD patients, as assessed by clinical trials.

Keywords: chronic kidney disease, exercise, frailty, inflammation, protein-energy wasting, sarcopenia, satellite cell, TWEAK, osteosarcopenia

The frailty syndrome has been defined as the presence of three or more of the following criteria: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed and low physical activity [1]. Frailty is associated with high mortality [1]. The prevalence of frailty is much higher in dialysis-dependent chronic kidney disease (CKD) patients than in the older adult population (60 versus 11% in one study) [2]. Even among non-dialysis CKD patients, a whopping 81% reported excessive tiredness [3]. There are several frailty scores associated to markers of inflammation, hospitalization and protein-energy wasting [4, 5]. Sarcopenia is a clinical correlate of frailty, which is common in CKD and is associated with lower quality of life and physical functioning, as well as with an increased risk of major adverse cardiovascular events and mortality. Sarcopenia may be associated with bone disease (osteosarcopenia). In recent issues of *Clinical Kidney Journal* (ckj), several manuscripts address the issue of sarcopenia in CKD from the point of view of pathogenesis [6], monitoring and its clinical significance [7, 8], implementation

and impact of exercise programmes [7, 9] and specific potential benefits of exercise programmes in dialysis and non-dialysis CKD patients, as assessed by clinical trials [10, 11].

A better understanding of the pathogenesis of sarcopenia and, specifically, of CKD-associated sarcopenia may facilitate the development of novel therapeutic approaches. Recent advances have focused on skeletal muscle renewal, the role of mitochondrial pathophysiology and exercise mimetics. Skeletal muscle progenitor cells are termed satellite cells and provide new nuclei to myofibres, thus contributing to increase and maintain muscle mass. O'Sullivan et al. [6] review the impact of CKD on satellite cells and the contribution of these cells to the altered myogenic response to exercise.

An acquired mitochondrial myopathy has been described in CKD [12]. Multiple abnormalities of mitochondrial structure, function and composition are present in experimental and clinical CKD. Skeletal muscle biopsies from patients with advanced CKD show lower mitochondrial volume density and

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mitochondrial DNA copy number than controls. In mice, CKD induces autophagy and mitochondria dysfunction in skeletal muscle. Muscle overloading to mimick resistance exercise increased mitochondrial copy number, and reversed the CKD-induced decrease in the master regulator of mitochondrial biogenesis peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) [13]. Both skeletal muscle and kidney PGC-1 α are downregulated by inflammatory mediators such as TNF-like weak inducer of apoptosis (TWEAK), contributing to sarcopenia and kidney injury, respectively [14, 15]. Interestingly, outside the CKD context, the beneficial effect of exercise on PGC-1 α may be mediated by modulation of TWEAK [16]. In this regard, CKD is a pro-inflammatory state and anti-inflammatory strategies may be explored to reverse sarcopenia [17].

Based on an improved understanding of pathogenesis, one therapeutic approach being explored for sarcopenia is the use of exercise mimetics, drug treatments that may result in similar molecular adaptations to those elicited by exercise [18]. Recent reports have addressed whether microRNA, such as the miR-23a/miR-27a cluster, may be used as exercise mimetics for muscle wasting in CKD [18]. The beneficial effect was associated with improvements in proteolysis, muscle regeneration and inflammatory cytokines. However, miR-23a also maintains mitochondrial integrity, although dosing considerations may be important, as it also suppresses PGC-1 α [19, 20].

Gollie et al. [7] review the available tools to monitor skeletal muscle composition and function in the CKD context. Specifically, they review the strengths and limitations of dual-energy X-ray absorptiometry and bioelectrical impedance to estimate body composition and of proxy measures of skeletal muscle quality using ultrasound. Another approach is the analysis of self-reported measures. Clarke et al. [8] report that the self-reported measures of physical performance Duke Activity Status Index (physical function) and General Practice Physical Activity Questionnaire (habitual activity regarding walking behaviour) were independently associated with survival in non-dialysis CKD [8]. These measures could be added to the use of imaging or more conventional studies [21].

Finally, several recent *ckj* manuscripts address therapy for sarcopenia and frailty, and randomized clinical trials (RCTs) addressing this issue. A 2015 systematic review on the effects of exercise in CKD patients concluded that most RCTs included small samples, were of short duration and applied aerobic exercises. The strongest evidence was for the effects of aerobic exercise on improving physical fitness, muscular strength and quality of life in dialysis patients, but the evidence base was missing for non-dialysis CKD [22]. A more recent 2018 systematic review and meta-analysis disclosed favourable effects of aerobic exercise on estimated glomerular filtration rate (eGFR) and exercise tolerance, following an on average 35-week aerobic training programme when compared with standard care in CKD G3–4 [23]. Despite this, Gollie et al. [7] review evidence that progressive resistance exercise improves skeletal muscle mass and strength and health-related quality of life and report that most evidence still derives from end-stage renal disease studies and limited evidence is available in earlier stages of CKD [7].

One of the issues of exercise programmes is implementation. Staff knowledge, patient motivation and equipment problems had been identified as barriers to exercise on dialysis. An increase in the uptake of exercise on dialysis from 23% to 74% was achieved by an intervention focused on patient and nursing staff education, equipment modification and patient motivation schemes [24]. More recently, Young et al. [9] identified patient and staff barriers to intradialytic exercise implementation

through a quality improvement project focused on interventions designed to increase patient and staff engagement based on the Theoretical Domains Framework, using a series of 'Plan, Do, Study, Act' cycles. Patient participation dropped to 48% and adherence to 63% by 12 months. Only patients that completed the programme benefited from it, displaying significant improvements in functional ability and a reduction in depression [9].

Only RCTs will provide the required level of evidence to influence clinical practice. Aragoncillo et al. [10] describe the PHYSICALFAV RCT (NCT03213756) that will evaluate the usefulness of preoperative isometric exercise for 8 weeks in pre-dialysis or dialysis patients on a main endpoint of rate of primary failure of a new arteriovenous fistula. This study addresses a key point in need of clarification as identified by recent vascular access guidelines [25]. Wilkinson et al. [11] report that 12 weeks (3 times/week) of supervised aerobic exercise alone or in combination with resistance training in non-dialysis CKD patients resulted in a reduction in the total number of health-related quality of life symptoms reported by 17%. Aerobic exercise reduced the frequency of 'shortness of breath', and the intrusiveness of 'sleep disturbance', 'loss of muscular strength/power', 'muscle spasm/stiffness' and 'restless legs'. The addition of resistance exercise further decreased 'loss of muscular strength/power'. No changes were seen in subjective physical function or physical activity levels.

This information adds to recent RCTs in dialysis or non-dialysis patients. In patients with Stage 3 CKD, randomization to 16 weeks of supervised moderate-intensity aerobic exercise three times per week led to a mild improvement in VO₂ peak, but did not induce changes in high density lipoprotein (HDL) particle size or favourable lipid profile modifications [26]. In another RCT in non-dialysis CKD patients, the addition of resistance exercise to aerobic exercise conferred greater increases in muscle mass and strength than aerobic exercise alone [27]. In 111 patients with moderate-to-severe CKD, the combination of 4-month dietary calorie restriction and aerobic exercise had significant, albeit clinically modest, benefits on body weight, fat

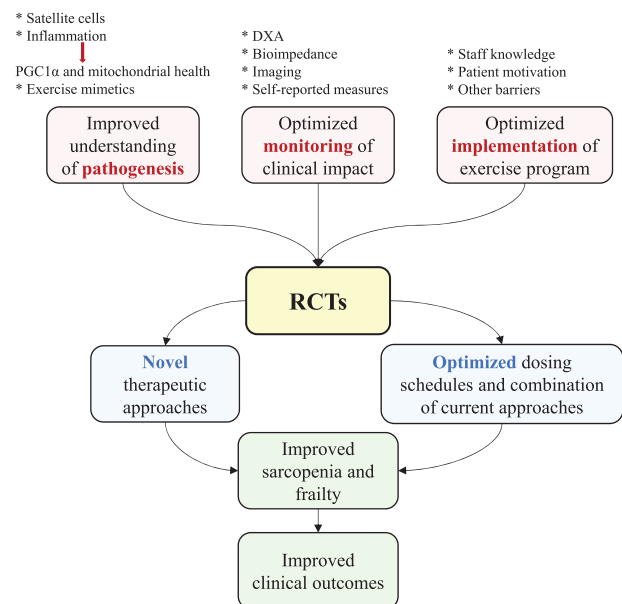


FIGURE 1: A roadmap to improve sarcopenia and CKD: from bench to bedside. Drawn based on information from Refs [6–11]. DXA, dual-energy X-ray absorptiometry.

mass and markers of oxidative stress and inflammatory response [28]. A 14-week intradialytic training programme induced significant improvements on physical performance. However, the rate of clinically meaningful responders was low and the level of responsiveness depended on baseline physical status, highlighting the need to individualize exercise prescription [29].

In summary, there is increasing interest in actively addressing sarcopenia and frailty. However, clinical success will depend on identifying novel avenues of therapy through a better understanding of pathogenic pathways, optimizing the tools to monitor the impact of therapy, individualizing the therapeutic approaches, including the optimal dose and combination of different exercise modalities, and addressing barriers to implementation in both healthcare staff and patients (Figure 1).

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CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

- Fried LP, Tangen CM, Walston J et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56: M146–M156
- Nixon AC, Bampouras TM, Pendleton N et al. Frailty and chronic kidney disease: current evidence and continuing uncertainties. *Clin Kidney J* 2018; 11: 236–245
- Brown SA, Tyrer FC, Clarke AL et al. Symptom burden in patients with chronic kidney disease not requiring renal replacement therapy. *Clin Kidney J* 2017; 10: 788–796
- Johansen KL, Dalrymple LS, Delgado C et al. Factors associated with frailty and its trajectory among patients on hemodialysis. *Clin J Am Soc Nephrol* 2017; 12: 1100–1108
- Gracia-Iguacel C, González-Parra E, Barril-Cuadrado G et al. Defining protein-energy wasting syndrome in chronic kidney disease: prevalence and clinical implications. *Nefrologia* 2014; 34: 507–519
- O'Sullivan TF, Smith AC, Watson EL. Satellite cell function, intramuscular inflammation and exercise in chronic kidney disease. *Clin Kidney J* 2018; 11: 810–821
- Gollie JM, Harris-Love MO, Patel SS et al. Chronic kidney disease: considerations for monitoring skeletal muscle health and prescribing resistance exercise. *Clin Kidney J* 2018; 11: 822–831
- Clarke AL, Zaccardi F, Gould DW et al. Association of self-reported physical function with survival in patients with chronic kidney disease. *Clin Kidney J* 2019; 12: 122–128
- Young HML, Jeurkar S, Churchward DR et al. Implementing a theory-based intradialytic exercise programme in practice: a quality improvement project. *Clin Kidney J* 2018; 11: 832–840
- Aragoncillo I, Ligerio JM, Hevia C et al. Rationale and design of the PHYSICALFAV trial: a randomized controlled trial to evaluate the effect of preoperative isometric exercise on vascular calibre and maturation of autologous arteriovenous fistulas. *Clin Kidney J* 2018; 11: 841–845
- Wilkinson TJ, Watson EL, Gould DW et al. Twelve weeks of supervised exercise improves self-reported symptom burden and fatigue in chronic kidney disease: a secondary analysis of the “ExTra CKD” trial. *Clin Kidney J* 2019; 12: 113–121
- Rao M, Jaber BL, Balakrishnan VS. Chronic kidney disease and acquired mitochondrial myopathy. *Curr Opin Nephrol Hypertens* 2018; 27: 113–120
- Su Z, Klein JD, Du J et al. Chronic kidney disease induces autophagy leading to dysfunction of mitochondria in skeletal muscle. *Am J Physiol Renal Physiol* 2017; 312: F1128–F1140
- Hindi SM, Mishra V, Bhatnagar S et al. Regulatory circuitry of TWEAK-Fn14 system and PGC-1 α in skeletal muscle atrophy program. *FASEB J* 2014; 28: 1398–1411
- Ruiz-Andres O, Suarez-Alvarez B, Sánchez-Ramos C et al. The inflammatory cytokine TWEAK decreases PGC-1 α expression and mitochondrial function in acute kidney injury. *Kidney Int* 2016; 89: 399–410
- Padrão AI, Figueira ACC, Faustino-Rocha AI et al. Long-term exercise training prevents mammary tumorigenesis-induced muscle wasting in rats through the regulation of TWEAK signalling. *Acta Physiol (Oxf)* 2017; 219: 803–813
- Castillo-Rodríguez E, Pizarro-Sánchez S, Sanz AB et al. Inflammatory cytokines as uremic toxins: Ni Son Todos Los Que Estan, Ni Estan Todos Los Que Son. *Toxins (Basel)* 2017; 9: 114
- Mak RH, Cheung WW. MicroRNA as novel exercise mimetic for muscle wasting in CKD. *J Am Soc Nephrol* 2017; 28: 2557–2559
- Zhang B, Liu SQ, Li C et al. MicroRNA-23a curbs necrosis during early T cell activation by enforcing intracellular reactive oxygen species equilibrium. *Immunity* 2016; 44: 568–581
- Russell AP, Wada S, Vergani L et al. Disruption of skeletal muscle mitochondrial network genes and miRNAs in amyotrophic lateral sclerosis. *Neurobiol Dis* 2013; 49: 107–117
- Sergi G, Trevisan C, Veronesi N et al. Imaging of sarcopenia. *Eur J Radiol* 2016; 85: 1519–1524
- Barcellos FC, Santos IS, Umpierre D et al. Effects of exercise in the whole spectrum of chronic kidney disease: a systematic review. *Clin Kidney J* 2015; 8: 753–765
- Vanden Wyngaert K, Van Craenenbroeck AH, Van Biesen W et al. The effects of aerobic exercise on eGFR, blood pressure and VO₂ peak in patients with chronic kidney disease stages 3–4: A systematic review and meta-analysis. *PLoS One* 2018; 13: e0203662
- Abdulnassir L, Egas-Kitchener S, Whibley D et al. Captivating a captive audience: a quality improvement project increasing participation in intradialytic exercise across five renal dialysis units. *Clin Kidney J* 2017; 10: 516–523
- Ibeas J, Roca-Tey R, Vallespín J et al. Spanish Clinical Guidelines on vascular access for haemodialysis. *Nefrologia* 2017; 37 (Suppl 1): 1–191
- Miele EM, Headley SAE, Germain M et al. High-density lipoprotein particle pattern and overall lipid responses to a short-term moderate-intensity aerobic exercise training intervention in patients with chronic kidney disease. *Clin Kidney J* 2017; 10: 524–531
- Watson EL, Gould DW, Wilkinson TJ et al. Twelve-week combined resistance and aerobic training confers greater benefits than aerobic training alone in nondialysis CKD. *Am J Physiol Renal Physiol* 2018; 314: F1188–F1196
- Ikizler TA, Robinson-Cohen C, Ellis C et al. Metabolic effects of diet and exercise in patients with moderate to severe CKD: a randomized clinical trial. *J Am Soc Nephrol* 2018; 29: 250–259
- Valenzuela PL, de Alba A, Pedrero-Chamizo R et al. Intradialytic exercise: one size doesn't fit all. *Front Physiol* 2018; 9: 844