Advances in exercise therapy in pre-dialysis CKD, hemodialysis, peritoneal dialysis and kidney transplantation

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Abstract

Purpose of review

Chronic kidney disease (CKD) is characterized by poor levels of physical activity which contribute to increased morbidity across the disease trajectory. The short nature, small samples, and poor methodology across most studies have failed to translate the role of exercise in CKD into its adoption as a frontline adjunct therapeutic option. This review focuses on recent advances surrounding the benefits of exercise interventions across the CKD spectrum.

Recent findings

Key recent advances in exercise studies have focused on the efficacy of novel intervention strategies across the CKD spectrum. These include high-intensity interval training, virtual reality gaming, intradialytic yoga, electrical stimulation of muscles, blood flow restriction training, and protocols combining exercise with nutritional supplementation. Research is also beginning to explore the role of prehabilitation for patients prior to dialysis and kidney transplantation.

Summary

Studies continue to demonstrate wide-ranging benefits of exercise across CKD; however, implementation of exercise remains scarce. Future research needs include evaluating the efficacy of larger and/or more comprehensive interventions on clinically important outcomes. It is hoped with increasing global evidence, high-quality clinical studies, and sustained clinician and patient engagement, exercise programs will become better prioritized in the nephrology field.

Keywords

Exercise; Physical activity; Intradialytic exercise; Physical function, Chronic kidney disease, Dialysis

Introduction

Individuals with chronic kidney disease (CKD) are characterised by poor levels of physical activity and exercise behaviours [1]. Low levels of physical activity adversely impact quality of life (QoL), functional status, and are strongly related with mortality and morbidity across the disease trajectory [2, 3]. For decades, exercise interventions in CKD have been shown to have favorable effects on patient health and QoL. However, owing to the consistent short nature, relatively small samples, and poor methodological quality, these studies have failed to translate to the adoption of exercise in routine practice [4]. The lack of clinical exercise programmes is often attributed to a lack of robust research evidence [5] resulting in the low priority of physical activity and exercise in the nephrology field [6, 7], especially in comparison to established cardiac or respiratory programmes. Furthermore, despite many nephrologists considering exercise and physical activity counselling as within their scope of practice and beneficial, due to competing priorities, they do not regularly counsel patients [8]. As a result, the use of exercise as a frontline adjunct therapeutic option in CKD remains unlikely for now, and physical inactivity and poor functional status stands to remain a detrimental feature of the disease.

This review will focus on the recent advances in evidence surrounding the benefits of exercise interventions to patients across the CKD spectrum: non-dialysis dependent CKD, hemodialysis (HD), peritoneal dialysis (PD), and kidney transplant recipients (KTRs).

Non-dialysis dependent CKD

Exercise-based rehabilitation programmes in individuals with CKD not requiring dialysis are not yet standard treatment. However, given these patients often have reduced disease burden and increased functional capacity compared to those with later disease stages, there is a great opportunity for appropriate and timely exercise-based interventions. Given the popularity over the last decade in high-intensity interval training (HIIT), it is perhaps unsurprising that studies employing this form of novel training are now appearing in clinical trials. Beetham et al. [9**] found that whilst 12-weeks of HIIT (4x4 minutes at 80-95% peak heart rate) provided a feasible and safe option for n=14 patients with CKD stage 3-4, no additional benefits of HIIT were observed when compared to typical moderate-intensity continuous training for cardiorespiratory fitness and markers of skeletal muscle metabolism. As such, in some patients, HIIT may be a suitable alternative to conventional exercise prescription. Findings from the RENEXC study conducted in Sweden, which involved n=151 patients exercising 5 days per week for 12-months, found that both the strength and balance groups increased their aerobic capacity, strength, and physical function [10]. Interestingly, in addition to aerobic exercise, strength training was not superior to balance training, and changes occurred without notable changes in muscle mass [11]. This suggests sufficient stimulus from any form of exercise may elicit beneficial improvements in physical performance and reductions in fat mass.

A key characteristic of CKD, and thus a modifiable target of exercise, is reduced cardiorespiratory fitness. However, mechanisms that contribute to this are not clearly defined but may involve reductions in mitochondrial function, mass and biogenesis. In a study of n=16 individuals, Watson et al. [12*] found that CKD patients exhibit reduced skeletal muscle mitochondrial mass and gene expression of transcription factors involved in mitochondrial biogenesis compared to a non-CKD control group. Interestingly, these reductions were not restored following 12-weeks of combined aerobic and resistance exercise training, implying that some patients may exhibit a form of 'exercise resistance' that blunts improvements in cardiorespiratory fitness, and may explain the variable changes in VO_2peak sometimes observed in CKD exercise trials.

Endothelial dysfunction and arterial stiffness are non-traditional risk factors of CKD-related cardiovascular disease (CVD) that could be targeted with exercise. A study from the USA in 36 patients showed that 12-weeks moderate to vigorous aerobic exercise 3x/week improved microvascular function and maintained conduit artery function, although no changes were observed in central arterial hemodynamics and arterial stiffness [13**]. With trial outcomes often focusing on physiological parameters, there remains limited evidence on the effect on self-reported symptom burden. A trial conducted in n=36 UK CKD patients found that 12-weeks combined aerobic and resistance exercise resulted in a 14% reduction in symptom number, substantial improvements in fatigue, and reductions in primarily muscle-focused symptoms such as stiffness and weakness [14].

An important absence in many exercise interventions is the association and study of long term follow up on clinical outcomes. An increasing number of recent studies have shown positive effects of exercise on different hard and surrogate outcomes. Greenwood et al. [15**] showed that in a cohort of n=757 patients (including non-dialysis patients), completion of a 12-week renal rehabilitation programme was associated with increased survival, with a 'dose-response' effect seen; 'improvers' (defined as an increase of 50m in the incremental shuttle walk) had a 40% independent lower risk of a combined event (e.g., death, hospitalization). Whilst this data comes from a non-randomized study, it does provide support of a rehabilitation model in CKD. In a meta-analysis of 11 RCTs and n=362 patients CKD stage 3-4, Vanden Wyngaert et al. [16] showed favorable effects on estimated glomerular filtration rate (+2.16 ml/min per 1.73m^2) and exercise tolerance (+2.39 ml/kg/min) following an 8-month aerobic training program when compared to standard care.

Exercise is increasingly being advocated for patients preparing for dialysis transition. In particular, to increase cephalic vein diameter that may optimise arteriovenous fistula maturity. An RCT showed that 8-weeks of handgrip exercises (e.g., squeeze ball) may increase cephalic vein diameter in n=34 patients with stage 3 and 4 [17]. This effect was also exhibited by Barbosa et al. [18**] in n=26 patients undergoing training whilst utilising blood flow restriction (BFR) (artery occlusion at 50% maximum systolic blood pressure). Although, BFR did not offer any superiority than exercise plus non-occlusion.

Hemodialysis (HD)

Numerous studies have been published describing the benefits of exercise in HD patients [19-21], yet implementation of exercise programs in HD clinics is low and patient adherence is poor. To address these issues, some recent studies have implemented novel interventions that aim to improve exercise adherence and/or provide more robust evidence of clinical benefits of exercise in HD. Examples of some of these novel intervention strategies include virtual reality gaming (VR), intradialytic yoga, electrical stimulation of muscles, BFR training, HIIT, and protocols combining exercise with nutritional supplementation. VR gaming as an adjunct to an intradialytic exercise (IDE) program proved to be feasible in two separate studies [22**, 23] and Birdee et al. [24] recently demonstrated the feasibility of a novel intradialytic yoga program. In addition, Suzuki et al. demonstrated improvements in muscle strength and physical function using intradialytic electrical stimulation of leg muscles, suggesting this may be an adjunct to physical exercise, especially for highly deconditioned patients [25]. Though more work is needed to determine the efficacy of these interventions, they are good examples of novel strategies that can be used during to get patients more physically active, or at least contracting their muscles, during dialysis.

Another significant concern in the exercise literature in HD is that most interventions have included an extremely low volume and/or intensity of exercise, and this may be contributing to the modest benefits that are often seen [26]. As stated previously, whilst seen in non-dialysis groups (e.g., [9, 18]), BFR and HIIT are examples of training protocols that can be used to increase exercise intensity but had not previously been evaluated in HD patients. Nilsson et al. recently demonstrated the feasibility of a

HIIT intradialytic cycling protocol as an alternative to traditional moderate-intensity intradialytic cycle training [27]. Similarly, both Clarkson et al. and Cardoso et al. have demonstrated that BFR during intradialytic cycling appears safe and tolerable [28, 29]. Data in healthy populations indicates that BFR training may improve muscle mass and strength at lower exercise intensities than is normally required for these adaptations, so is an intriguing exercise modality in deconditioned individuals. While more research is needed, these studies provide examples of novel approaches that could be considered to improve physical functioning in HD patients willing to consider them.

Another approach that can be used to improve the effectiveness of exercise is to include it as a component of a multifactorial intervention strategy. Several recent studies provided examples of this by combining exercise interventions with concomitant nutritional support [30**, 31]. Unfortunately, both studies failed to demonstrate that exercise (either intradialytic cycling or resistance training) enhanced the benefits or oral nutritional supplementation on physical function and related outcomes. These findings highlight the fact that improving HD patients' physical function is a significant challenge, and that novel and more comprehensive intervention strategies need to be evaluated.

Several recent studies have improved our understanding of the cardiovascular benefits of IDE. While there are few reports of adverse events from exercise in HD patients, there are theoretical concerns that IDE may exacerbate hemodynamic instability (e.g., intradialytic hypotension), especially if performed in the later stages (3rd or 4th hour) of dialysis [32, 33]. However, a recent study by Jeong et al. found no difference in the hemodynamic effects of exercise performed during the 1st or 3rd hour of dialysis [34**], suggesting that exercise at any time during treatment is safe. Moreover, two separate studies by Penny et al. [35**] and McGuire et al. [36] both found that IDE reduced myocardial stunning. This important new finding improves our understanding of the potential clinical benefits of IDE and should help encourage clinicians to promote exercise programs in their clinics.

Peritoneal dialysis (PD)

Not unlike the HD population, the majority of people receiving PD are physically inactive, contributing to decreased physical function and poor QoL [1]. Although guidelines recommend physical activity in PD, dialysis professionals lack the knowledge, skill and scope of practice to expertly prescribe and coordinate optimal and personalized exercise regimens [37]. Furthermore, PD patients have been discouraged from participating in exercise programs because of concerns relating to the PD catheter, abdominal pressure and infection [38]. This clinical approach is in contrast to PD patient's attitudes who believe exercise improves mood, self-care abilities, QoL and decreases muscle wasting [39, 40]. Considering a PD patient's sedentary behaviour and added glucose load [41], physical activity is vital in this population.

Recent exercise studies are scarce in PD compared with HD [42]. The largest RCT to date (n=47), conducted in Japan, reported a significant improvement in incremental shuttle walking test following 12-weeks of combined resistance and aerobic exercise program [43**]. Similarly, a USA 12-week combined aerobic and resistance intervention improved the timed-up-and-go performance and appetite of the exercise group compared with usual care [44**]. A non-controlled study in Thailand, measuring the effect of a resistance exercise program using traditional resistance bands, demonstrated improvement in blood pressure, muscle strength and QoL [45*]. The results of this study should be interpreted with caution due to the lack of a control group, however, larger studies are expected from Thailand given their high prevalence of PD.

Recently, exercise programs have been proposed for PD patients to improve physical function [38] and to counteract the increased glucose load [41]. A USA exercise physiologist coordinated program has been described consisting of upper body, lower body, core and aerobic exercises, with exercises categorized for low, medium and high physically functioning PD patients [38]. A novel approach using aerobic cycling and walking has been proposed to counteract the caloric load associated with glucose absorption [41]. Similar to HD exercise programs, it is likely that a combined resistance and aerobic design that fits into PD patient's lifestyle [46] would have the greatest success in preventing the PD patients decreased physical function and QoL [47].

Transplantation

Kidney transplant (KT) candidates

Prehabilitation seeks to enhance a patient's functional capacity before surgery and improve their tolerance for an upcoming physiologic stressor through intensive exercise therapy [48]. This intervention has arisen as an appealing strategy for KT (kidney transplant) candidates because it optimizes a patient while they wait for transplantation, rather than rehabilitate them after surgery [49]. In a recent survey, both clinicians (97%) and patients (94%) agreed that pre-KT prehabilitation would benefit patients undergoing KT and make them less frail [50]. A recently completed pilot involving prehabilitation among n=24 adult (aged 18 and older) KT candidates [51**], suggests that physical activity improves by 64% after 2 months. Furthermore, KT candidates who participated in prehabilitation had a shorter KT length of stay (5 vs. 10 days) compared to age-, sex-, and race-matched controls. However, a multi-transplant center RCT of prehabilitation is needed to confirm the efficacy of this intervention in preventing long-term outcomes and associated costs.

Kidney transplant recipients

In contrast, there are several studies of physical activity and exercise training among KTRs [52]. Previous studies have suggested that physical activity declines in the first month post-KT due to surgical recovery but then increases throughout the first year and plateaus by 5 years [53, 54]. Recent data using actigraphy to measure physical activity and sedentary time among KTRs (n=133) who were on average 9.5 years post-KT found that on average recipients spend 9.4 hours sedentary time and 20.7 minutes in moderate/vigorous physical activity per day [55]. Given these findings, it is not surprising that sarcopenia, measured by handgrip strength and bioelectrical impedance, is common among KTRs and associated with mortality and hospitalization as well as poor QoL [56].

The previously published RCT of exercise interventions among KTRs had different prescribed exercise interventions, duration of the interventions, and sample sizes [52]. A recent meta-analysis of 11 RCTs found that structured exercise improves small arterial stiffness, VO_2 peak, and QoL among KTRs; however, exercise did not improve blood pressure, lipid profile, blood glucose, kidney function, or bodyweight/BMI [57]. A recent RCT of n=99 KTRs (n=85 completing the study), found that recipients who were randomized to 12-months of supervised exercise training three times/week were associated with an increased maximum workload, VO_2 peak, strength, and decreased BMI as well as health-related QoL as compared to recipients randomized to 12-months of general recommendations about physical activity [58]. However, a 12-month intervention is a longer intervention period than in many other studies. Furthermore, the LIFT study of n=61 KTRs and liver transplant recipients (median 9-months post-transplantation) randomized recipients to standard of care or one of two intervention arms: increasing the number of steps by 15% using either accelerometer with and without financial incentives and health engagement questions [59]. This study found no differences in weight change at 3-months across all three arms but did find that those randomized to either intervention arm were more likely to achieve 7,000 steps or more compared to standard of care.

One promising study of n=37 KTRs combined exercise with intensive nutrition but found that this intervention did not prevent weight gain in the first year after KT compared to standard nutritional care [60*]. Finally, a study of n=24 KTRs and n=15 patients with CKD found that an individualized, structured physical activity intervention was associated with an improved metabolic profile, body composition, QoL, and eGFR (only among recipients) as well as reduced inflammation [61-63]. The review of the previous and current literature suggests that structured resistance exercise training for 3-6 months may be beneficial in adult KTRs who are healthy enough to exercise; however, changes of BMI may only be observed after 12-months of intervention. One challenge is identifying the right time post-KT for exercise interventions.

Conclusion

There is an ever-increasing number of clinical studies showing the beneficial role of exercise across the CKD spectrum. However, whilst examples of successful programmes do exist, implementation and recognition of exercise as a safe and adjunct therapeutic option in nephrology remain limited across the globe. Beyond clinical studies, one key and notable advancement in the field of renal exercise was the recent establishment of the Global Renal Exercise Working Group (GREX), an international collaborative group of researchers, patients, and clinicians. This group, facilitated by the ISRNM, has an overarching objective to increase the uptake of exercise and lifestyle interventions into routine clinical care and provides a multidisciplinary network to help address the key global research priorities in the area [64**]. It is hoped with increasing evidence, high-quality clinical studies, and better clinician and patient engagement, exercise programs will become prioritized in nephrology resulting in substantial benefits in patient healthcare across the globe.

Key points

1) Published studies demonstrate benefits of exercise across the spectrum of CKD; however, implementation of exercise programs remains scarce.

2) Recent studies have focused on examining the efficacy of novel intervention strategies across the spectrum of CKD, including higher intensity training in CKD and renal failure, and prehabilitation for patients before kidney transplantation.

3) Future research needs include evaluating the efficacy of larger, more global and/or more comprehensive interventions on clinically important outcomes.

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Table 1 – Summary of key recent studies of interest and their main findings

Reference	Population	Study design	Key outcomes	Main findings
Non-dialysis dependent CKD				
Beetham et al. 2019 [9] Australia	n=14 CKD (stage 3-4)	RCT. 12-weeks of high-intensity interval training (HIIT) or moderate exercise	Feasibility and safety; exercise capacity (VO_2peak); body composition; muscle protein synthesis	No adverse outcomes; ↑exercise capacity; ↑protein synthesis; ↔body composition. No difference between HIIT and moderate groups
Kirkman et al. 2019 [13] USA	n=36 CKD (stage 3-5)	RCT. 12-weeks of supervised aerobic exercise training or control	Exercise capacity (VO_2peak); microvascular function; conduit artery endothelial function; hemodynamics and arterial stiffness; oxidative stress	↑exercise capacity; ↑microvascular function; ↔conduit artery endothelial function; ↔hemodynamics and arterial stiffness; ↔oxidative stress
Greenwood et al. 2019 [15] UK	n=757 CKD (all stages)	Retrospective 12-year longitudinal analysis of s in-centre 12-week renal rehabilitation programme	Time to combined event including death, cerebrovascular accident, myocardial infarction and hospitalisation for heart failure	Patients who did not complete the programme had a 1.6-fold greater risk of a combined event. Dose-response

				was seen with those 'improving' more showing lower risk
Barbosa et al. 2018 [18] Brazil	n=26 CKD (stage 4-5)	RCT. 8-weeks of exercise with restriction blood flow restriction (BFR) or control (no BRF)	Cephalic vein diameter; cephalic vein distensibility; radial artery diameter; systolic flow peak and mean velocity in the upper limbs; forearm circumference; handgrip strength	↑diameter of cephalic vein (control group only); ↑diameter of radial artery (BFR group only); ↑handgrip strength (control group only)
Hemodialysis (HD)				
Segura-Orti et al. 2019 [22] Spain	n=36 HD	RCT. 20-weeks strength + aerobic training (Ex) OR 16 weeks of aerobic and strength training + 4 weeks virtual reality (VR) gaming.	Physical function tests, including normal gait speed, sit-to-stand (STS) 60, one-legged heel raise (OLHR), and 6-minute walk test (6MWT); and exercise adherence	↑physical function and exercise adherence were similar between groups. This suggests intradialytic VR is feasible and reasonable alternative to traditional intradialytic exercise programs

Jeong et al. 2019 [30] USA	n=138 HD	RCT. 3 groups, 12-month intervention: 1) control; 2) oral protein supplementation (OPS, 30g whey); 3) OPS + intradialytic cycling	ISWT; muscle strength; gait speed; cardiovascular function (PWV, systolic and diastolic function)	↔ISWT or most secondary outcomes. Trends for ↑gait speed and diastolic function in OPS + exercise group only
Jeong et al. 2018 [34] USA	n=12 HD	Cross-over design. 3 treatments: control day; intradialytic exercise (IDE) cycling in 1st hour (30 min); 3) IDE in 3rd hour (30 min)	Intradialytic hemodynamic variables, including blood pressure, autonomic function, cardiac output, stroke volume, and TPR	During 1st and 3rd hour exercise, there were transient ↑blood pressure and cardiac output, but ↔ in variables at end of dialysis with or without ICE.
Penny et al. 2019 [35] Canada	n=19 HD	Cross-over design; 2 days: 1) control; 2) IDE cycling (30 minutes)	Myocardial stunning (regional wall motion abnormalities; RWMA) at 3 time points during dialysis (pre-exercise,	At peak HD stress, the number of stunned cardiac segments was ↓

			post-exercise, and peak stress (15 minutes before the end of dialysis)	
Peritoneal dialysis (PD)				
Uchiyama et al. 2019 [43] Japan	n=47 PD (n=13 APD, n=34 CAPD)	RCT. 12-weeks of a combined resistance and aerobic exercise program	Exercise capacity (ISWT); HRQOL; anthropometry; biochemistry; baPWV	↑exercise capacity; ↔handgrip strength; ↔quadriceps; ↑HRQOL; ↔anthropometry; ↑albumin; ↔baPWV
Bennett et al. 2020 [44] USA	n=26 APD	RCT. 12-weeks of a combined resistance and aerobic exercise program	Feasibility and safety; physical Function; PROMs	63% Recruitment; 72% Retention; 77% Sustained exercise following study; ↑TUG; ↑Appetite
Aramrussameekul et al. 2019 [45] Thailand	n=20 CAPD	Pre-Post. 12-weeks home-based rubber rope exercise	BP; hand, leg, back strength; HRQOL	↓SBP & DBP; ↑hand, leg, back strength; ↑HRQOL
Transplantation				
McAdams-DeMarco et al.	n=24 KT candidates	Non-RCT. Average of 28 weekly prehabilitation	Feasibility; physical activity; length of stay; patient feedback	↑physical activity; ↓length of stay. High level of satisfaction with the

2020 [51] USA	active on the waitlist within 3-6 months of transplantation	sessions (1 hour supervised physical therapy) (matched KT control group)		prehabilitation intervention. No adverse events.
Roi et al. 2018 [58] Italy	n=99 KT recipients at least 6-months after KT	RCT. 12-month 3 times/week supervised aerobic and resistance training	Renal function; lipid values; blood chemistry; exercise capacity (VO_2peak); muscle strength (plantar flexor) and power (countermovement jump height); BMI; HRQOL	↑exercise capacity; ↑muscular strength; ↑power; ↓BMI; ↑HRQoL (physical function, physical-role limitations, and social functioning scales)
Serper et al. 2020 [59] USA	n=61 KT recipients and n=66 liver transplant recipients (9-months post-transplantation)	RCT. 12-weeks. 3 arms: arm 1: Standard of care plus wearable physical activity trackers, access to an online portal; arm 2: arm 1 plus step goals and health engagement questions with financial incentives.	Change in patient weight (after 4-months); proportion of days at the target of 7,000 steps per day	↔weight change; those in either intervention arm was more likely to achieve >7,000 steps compared to controls

		Enrolled in a physical activity program with individualized goals; control group		
Henggeler et al. 2018 [60] New Zealand	n=37 KT recipients	RCT. 12-months. Intensive nutrition intervention (individualized nutrition and exercise counselling; 12 dietitian visits; 3 exercise physiologist visits over 12 months) or to standard nutrition care (guideline based; 4 dietitian visits)	Body weight at 6-months post-KT; change in body weight; anthropometric measures; body composition; resting energy expenditure; physical function; physical activity; serum biochemistry; HRQOL	↔body weight; ↔secondary outcomes between groups

RCT randomized controlled trial, PD peritoneal dialysis, APD automated peritoneal dialysis, CAPD continuous ambulatory peritoneal dialysis, HRQOL health-related quality of life, baPWV brachial-ankle pulse wave velocity, ISWT incremental shuttle walk test, TUG timed up and go test, BP blood pressure, SBP systolic blood pressure, DBP diastolic blood pressure, PROMs patient-reported outcome measures, BFR blood flow restriction, IDE intradialytic exercise, 6MWT 6-minute walk test, STS sit-to-stand test, RWMA regional wall motion abnormality, OPS oral protein supplementation

Table 2 – Summary of key points/findings with areas for future research

Key findings and areas for future research
• Urgent research is required to determine how we decrease physical deterioration prior to renal replacement therapy to improve RRT outcomes.
• In particular, the role of prehabilitation needs additional investigation in those being prepared for a KT or dialysis to elucidate is long term effects.
• Further research is needed to clarify upon the optimal dose, timing, and frequency of exercise, particularly in those requiring a KT, HD and PD.
• There is increasing use of novel interventions, such as BFR or HIIT, that aim to improve exercise adherence, however, further research is needed to clarify whether these provide greater clinical benefits.
• Despite an increase in high-quality evidence, there also remains an important role of the healthcare provider in the promotion of exercise. There is a need for the evaluation of effective and efficient counselling strategies and a role for the routine involvement of exercise specialists in kidney care.

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**** Detailed overview of the Global Renal Exercise (GREX) network, its aims, and goals for advancing future research in the field of physical activity and exercise in kidney patients.**