REVIEW

The Necessity for Renal Rehabilitation

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ABSTRACT

Chronic kidney disease negatively impacts the lives of a significant number of Americans. Unlike patients who suffer from chronic illnesses such as cardiovascular disease and pulmonary disease, renal patients currently do not have access to rehabilitation services specifically tailored to their ailments. Implementing renal rehabilitation services has the potential to attenuate further progression of kidney disease and improve the quality of life of patients. Providing properly structured renal rehabilitation services to kidney patients should be a future goal of the medical community. *Journal of Clinical Exercise Physiology*. 2020;9(3):118–130.

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INTRODUCTION

Chronic kidney disease (CKD) is characterized by damaged or malfunctioning kidneys, which results in the accumulation of uremic toxins, electrolyte abnormalities, acid-base imbalances, and edema (1,2). CKD is classified primarily by glomerular filtration rate (GFR), a measure of the ability of nephrons to appropriately filter molecules (3). As kidney function deteriorates (Table 1), patients move progressively from stage 1 (which signifies a normal GFR) to stages 2, 3a, 3b, 4, and finally 5, which signifies kidney failure (2). The most progressive stage, end-stage renal disease (ESRD), is characterized by extreme kidney damage and low function, necessitating dialysis or a transplant (1). A diagnosis of CKD is concomitant with an increased cardiovascular disease (CVD) risk (2). In fact, 50% of patients with CKD die from CVD before progressing to ESRD (3). Vascular stiffness associated with calcification (4), diabetes (5), hypertension (5), dyslipidemia (5,6), and systemic inflammation (7) are compounding comorbidities that lead to an increased risk of CVD in patients with CKD. While pharmacological treatments for alleviating symptoms associated with CKD are improving, few with the ability to provide nephroprotection are prescribed (3). Additional treatments must be implemented in conjunction with medications to prevent the progression of the pathologies plaguing patients with CKD (8,9). One such proposed supplemental remedy is exercise.

Historically, some clinicians have been wary about exercising patients with CKD due to the perceived risk of adverse events, such as myocardial infarction, hypoglycemia, and hypertension (10). However, several researchers have indicated that no adverse events occurred while exercising patients with CKD when appropriate exercise prescriptions were implemented (8,10–15). Furthermore, sedentary behavior predisposes these patients to poor health outcomes and further increases the risk for adverse events during exercise compared to nonsedentary patients (10). Patients with CKD exhibit lower-than-normal aerobic capacities compared with healthy individuals and diminished aerobic capacities are related to increased mortality (13,16). Low aerobic capacities and reduced exercise tolerance are associated with sedentary behavior or physical inactivity, muscular dysfunction, cardiovascular complications, anemia, and inflammation observed in those with CKD (17). Endothelial dysfunction, prevalent in those with CKD, is also thought to reduce exercise tolerance (18–20). A reduced peak oxygen consumption ($\dot{V}O_{2peak}$) may also lead to difficulties in performing necessary daily activities essential to living (10), thereby decreasing the quality of life

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TABLE 1. Glomerular filtration rate (GFR) categories. Adapted from (2).

GFR category	GFR (mL·min^{-1}·1.73m^{-2})	Terms
1	$\geq$90	Normal or high
2	60–89	Mildly decreased
3a	45–59	Mildly to moderately decreased
3b	30–44	Moderately to severely decreased
4	15–29	Severely decreased
5	<15	Kidney failure

(QOL) for those with CKD at any stage. Exercise increases QOL, aerobic capacity, and muscular strength in those with CKD (21), among other benefits. Increasing the physical activity of various diseased populations has been shown to rehabilitate and positively impact the lives of patients (13). Patients with CKD respond similarly and should be exposed to exercise rehabilitation programs as individuals with other chronic diseases such as cancer (22), CVD (23), or peripheral arterial disease (PAD) (24,25). The following review supports the justification for the development and implementation of a renal rehabilitation program with goals of attenuating disease progression and improving QOL while potentially reducing healthcare costs.

Epidemiology

Approximately 15% (37 million) of adults in the United States are afflicted with CKD (1). A silent disease, only 1 in 10 adults suffering from CKD are cognizant of their illness. CKD more commonly afflicts women (15%) than men (12%), and individuals 65 years and older (38%) than middle-aged individuals 45 to 64 years (13%) and younger adults aged 18 to 44 years (7%). Non-Hispanic blacks display a slightly higher prevalence of CKD (16%) compared with Hispanics (14%), non-Hispanic whites (13%), and non-Hispanic Asians (12%) (1). In 2017, roughly \$120 billion was spent treating CKD (\$84 billion) and ESRD (\$35.9 billion) patients on Medicare (26). According to the United States Renal Data System (USRDS), halting the progression of CKD and reducing the prevalence of comorbidities such as CVD and diabetes would greatly reduce Medicare expenses (27). In 2013, Honeycutt et al. (28) calculated that while having stage 1 CKD did not impose an appreciable amount of Medicare spending, stages 2, 3, and 4 annual expenses per patient were \$1,700, \$3,500, and \$12,700, respectively. Exponentially higher is the individual cost associated with ESRD and hemodialysis treatment, estimated at \$91,795 in 2017 (27). For this population, implementing exercise and physical activity programs in the form of renal rehabilitation may thwart disease progression and reduce the costs associated with the latter stages of CKD.

In the face of extenuating circumstances, such as the COVID-19 pandemic, hemodialysis treatments for ESRD patients may be disrupted (29). Roughly 20% to 30% of COVID-19 patients may require hemodialysis due to kidney damage inflicted by the virus. An increase in emergent COVID-19 cases and diminishing supplies during the pandemic likely prevented some ESRD patients in some affected locations from receiving optimal care. ESRD patients still receiving dialysis were placed in compromising situations in which exposure to infectious diseases was heightened (29). Preventative measures, such as exercise, improve the already dwindling health of ESRD patients during times of crises and may make these individuals more resilient.

Pathophysiology

CKD predominantly develops secondarily to diabetes and hypertension (1,8,13,30). Cardiovascular disease, obesity, genetic predisposition, renal injury, age, and dyslipidemia comprise other risk factors for developing CKD (1,30). Kidney dysfunction must persist for more than 3 months and exist in conjunction with abnormalities in GFR and albuminuria to be classified as CKD (2). CKD is classified by 6 GFR categories and further subdivided by albuminuria range (2). Individuals void of signs of kidney disease who are classified as stages 1 or 2 with an albuminuria classification of A1 do not meet the diagnostic criteria for CKD (2). The progressive worsening of proteinuria and GFR are indicative of the progression of CKD (30).

Comorbidities include anemia, cardiovascular disease, hypertension, edema, depression, elevated phosphorus and potassium levels, and low calcium levels (1). Chronic inflammation also plagues patients with CKD (7). Elevated levels of tumor necrosis factor alpha (TNF-α), interleukin (IL-1, IL-6), and C-reactive protein (CRP) are common. These inflammatory agents are implicit in the development of CVD and muscle dysfunction (7). Patients with CKD are prone to developing vascular stiffness due to dysfunctions in calcium metabolism, hypertension, and diabetes, which contributes to CVD (8). Endothelial dysfunction is another prevalent occurrence in patients with CKD, resulting from increases in reactive oxygen species (ROS) and decreases in nitric oxide production (19). Not only does CKD itself induce poor health in patients, but comorbidities associated with CKD further complicate the treatment of patients. Numerous pharmacological treatments are often required to treat these comorbidities. Some patients with CKD with hypertension may require at least 3 medications to control their blood pressure alone (31). While most drugs target one or a few ailments in patients with CKD, exercise serves as a more holistic approach to the management of renal disease. Exercise may also aid in the reduction of the numerous medications patients with CKD must take to manage their symptoms, which could reduce the number of drug-related side effects experienced.

WHO IS APPROPRIATE FOR RENAL REHABILITATION?

Patients with CKD with markers of kidney damage and a GFR < 60 mL·min^{-1}·1.73 m^{-2} for more than 3 months constitute high risk patients with CKD (2). Therefore, patients classified as stages 3a through 5 should be the focus of renal rehabilitation programs (2). Exercise may slow the progression of the disease and positively impact overall health outcomes for these patients (7). However, patients with CKD often lack knowledge regarding the implementation of exercise and resources available to them (32). That said, with appropriate guidance and support from clinical professionals (32), it seems as though renal patients are willing to exercise.

Predialysis Patients: Training Responses and Safety

The benefits of exercising predialysis patients with CKD outweigh the risks associated with sedentary behavior. Sedentary behavior is common in the CKD population (33). Being sedentary exacerbates CKD progression as sedentary behavior gives rise to obesity, hypertension, dyslipidemia, glucose intolerance, inflammation, and CVD (21). As a result, patients with CKD often concurrently suffer from obesity, type 2 diabetes, and hypertension (8). Skeletal muscle dysfunction and the subsequent loss in strength and mobility is common in patients with CKD (32). Patients with CKD also exhibit lower $\dot{V}O_{2peak}$ values compared with normal patients, and an inverse relationship exists between $\dot{V}O_{2peak}$ and CKD stage (34–36).

Implementing an exercise regimen during the early stages of CKD may attenuate the loss of functional capacity (35). Increases in functional capacity associated with aerobic and resistance training have been shown in research on nondialysis patients with CKD (37). Moderate-intensity exercise performed at 50% to 60% of $\dot{V}O_{2peak}$ for an average of 129.2 ± 8.6 min per week for 16 weeks induced favorable increases in aerobic capacity in stage 3 patients with CKD (38). Following a 12-week at-home aerobic exercise regimen of 30 min of moderate intensity walking 3 times per week, stage 3 and 4 patients with CKD exhibited significant increases in $\dot{V}O_{2peak}$ (12). Therefore, moderate-intensity exercise may be beneficial for patients with CKD for improving aerobic functioning (12).

Combining resistance training with aerobic exercise may provide further benefits. The attenuation of muscle wasting in patients with CKD is necessary for the maintenance of muscular strength and physical activity (36). Stage 3 and 4 patients with CKD who walked at home and, under supervision by a clinician, engaged in resistance exercise for one year and displayed an increase in physical activity and muscular strength without negatively impacting kidney functioning (39). Walking was performed for 30 min per day, and patients were aiming for 8,000 to 10,000 steps per day. Resistance exercises performed by patients included 20 to 30 repetitions of hand dynamometer training, squats, and calf raises completed 3 times per week (39). In a similar study by Watson et al. (36), after supplementing aerobic exercise with resistance training for 12 weeks, stages 3b through 5 predialysis patients with CKD showed more improvements in muscular strength and hypertrophy compared with a group who only performed aerobic exercise. All patients with CKD performed supervised aerobic exercise at 70% to 80% of maximum heart rate 3 times per week for 12 weeks. The aerobic exercise group performed 30 min of aerobic exercise during all sessions, while the group that combined aerobic exercise with resistance training performed 30 min of aerobic exercise when not resistance training and performed 20 min of aerobic exercise when adding resistance training to the daily session. The group that resistance trained performed 3 sets of 12 repetitions of leg extensions and leg presses 2 times per week for the 12-week intervention. While both the aerobic and combined exercise groups increased muscular strength in the legs, the group that included resistance training showed significantly larger strength increases than the aerobic-only group. Similarly, exercise increased quadriceps muscle volume in all patients with CKD, but the resistance trained group showed significantly larger increases (36).

Howden et al. (8) implemented a 12-month supervised combined aerobic and resistance exercise regimen in nondialysis patients with CKD to determine the effectiveness of exercise on $\dot{V}O_{2peak}$, cardiac function, vascular stiffness, and ventricular-vascular interaction. Continuous patient progress was monitored by the supervising clinicians via telephone and e-mail. Dieticians and psychologists also provided 4 weeks of lifestyle intervention to enhance dietary and behavioral practices. Vascular stiffness was not significantly different among groups after the intervention. Compared with a control group who declined by 1%, the exercise group displayed an 11% increase in $\dot{V}O_{2peak}$. The exercise group showed a significant decrease in weight, waist circumference, and body mass index after training. Diastolic functioning and ventricular-vascular interaction were also improved in the exercise group. Therefore, the notion was supported that chronic combined exercise training improves cardiorespiratory fitness in patients with CKD and improves CVD risk factors (8).

Patients with CKD often present with dysfunction of the vascular endothelium due to the high comorbidity with diabetes and hypertension (20). Vascular dysfunction further predisposes the CKD population to CVD. Endothelial dysfunction is indicative of undesirable alterations in nitric oxide release, blood flow, coagulation, fibrinolysis, inflammation, dyslipidemia, plaque formation, and ROS (20). Exercise may improve vascular dysfunction in predialysis patients (40). Mustata et al. sought to examine how exercise impacted physical impairment, arterial stiffness, and QOL of 20 sedentary predialysis (stage 3 or 4) patients. Measures of $\dot{V}O_{2peak}$ and endurance time (ET) were used to study physical impairment via cardiopulmonary exercise training (CPET), augmentation index (AI) was used to measure arterial stiffness, and 2 questionnaires were used to assess QOL. Patients with CKD completed baseline testing and then were randomized into the control group or the exercise group. For 1 year, the exercise group completed supervised and followed at-home training programs. Two times per week, patients completed supervised exercise on a treadmill, cycle ergometer, or elliptical machine. Three days per week, patients walked at home. For both exercise modalities, durations began at 5 to 20 min and progressed to 60 min. Exercise intensity was set at 40% to 60% of $\dot{V}O_{2peak}$, with surrogate measures being heart rate and rating of perceived exertion (RPE) of 12 to 15 on the Borg scale. However, the median weekly exercise time was 43.4 min; therefore, most patients did not achieve the recommended exercise duration (40).

Despite not achieving the recommended exercise prescription for duration, significant differences in changes in $\dot{V}O_{2peak}$, ET, and AI values between groups from baseline to one year were identified (40). The exercise group averaged larger increases in $\dot{V}O_{2peak}$ (3.59 $mL \cdot kg^{-1} \cdot min^{-1}$) and ET (10.97 min) and decreases in AI (−11.7%) than the control group, who only received standard care. No significant differences in QOL were observed. The improvement in AI values was a unique finding in the study, suggesting that arterial stiffness and possibly endothelial functioning improve with exercise (40). However, the finding of Mustata et al. (40) regarding AI conflicts with the results of Howden et al. (8). This is possibly due to the fact that supervised exercise sessions persisted for only 8 weeks in the Howden study. Therefore, more studies on the impact of exercise on direct measures of endothelial functioning in patients with CKD are necessary (18).

One such randomized controlled trial (RCT) directly assessing endothelial function in stages 3 to 5 predialysis patients with CKD was performed by Kirkman et al. (41). For 12 weeks, 19 patients exercised while 17 patients served as controls and received only standard care. The exercising patients performed 3 bouts of cycling, walking, jogging, or elliptical exercise per week under the supervision of a clinician. The target time and duration of exercise were 45 min at 60% to 85% of heart rate reserve. At baseline and after 12 weeks, CPET to assess cardiorespiratory fitness, laser-Doppler flowmetry with microdialysis to assess microvascular function, brachial artery flow-mediated dilation (FMD) to assess arterial endothelial function, SphygmoCor (ATCOR, Naperville, Illinois) measures to assess central blood pressure (CBP) and AI, and urine analysis to examine oxidative stress markers were completed. The intervention group displayed an increase in cardiorespiratory fitness, improved microvascular functioning, the maintenance of redox balance, and the maintenance of endothelial functioning compared with the control group. No between group differences were observed regarding CBP and AI (41).

Van Craenenbroeck et al. (42) examined endothelial functioning and arterial stiffness in stage 3 to 4 patients with CKD in an RCT. For 3 months, patients used a stationary cycle to exercise at home 4 times per day in 10-min increments at an intensity that elicited 90% of maximal heart rate. Initially, patients also completed at least 3 clinician-supervised exercise sessions for the first 2 weeks followed by 1 supervised session for 2 weeks. Patient adherence to at-home exercise was assessed on a monthly basis. Baseline and post-intervention measures included CPET for cardiorespiratory fitness, FMD for endothelial function, SphygmoCor for AI (ATCOR), a venous blood sample to assess vascular function, and a questionnaire to assess QOL. After 3 months, patients in the exercise group exhibited improved measures of cardiorespiratory fitness, notably a 27% increase in $\dot{V}O_{2peak}$, and QOL compared with the control group. However, endothelial function, arterial stiffness, and vascular function were not significantly improved in the exercise group compared with the control group. As a result, the researchers concluded that the underlying improvement in $\dot{V}O_{2peak}$ may not be related to improved vascular function (42). Once again, a longer exercise intervention may be necessary to improve endothelial and vascular function in patients with CKD. Additionally, the impact of resistance training on vascular measures should also be evaluated.

Hamada et al. demonstrated that combining moderate-intensity walking with resistance training has been shown to improve physiological measures and physical activity in patients with CKD of all stages (43). An exercise program was performed in a class setting but structured so that patients could replicate the exercise at home. Group exercise, performed for 90 to 120 min 6 times per month for 6 months, included walking at a moderate intensity of 12 to 14 on the 20-point Borg scale and resistance training at 3 to 4 metabolic equivalents (METs). The results showed that not only is exercise not detrimental to renal functioning, but supervised moderate-intensity aerobic and resistance exercise combined with nutritional and psychological counseling positively improves functional capacity, body weight, waist circumference, blood pressure, and proteinuria. Six months of supervised combined exercise also significantly improved self-reported physical activity and daily number of steps taken (43). Therefore, supervised exercise sessions may positively change the physical activity and exercise habits of patients with CKD.

High-intensity interval training (HIIT) may be a viable method of cardiopulmonary training for stage 3 and 4 patients with CKD (11). Beetham et al. compared the effectiveness and safety of HIIT with moderate-intensity continuous training (MICT). All exercise sessions were supervised by an accredited exercise physiologist. Overall, the patients had a high level of adherence to both exercise participation and prescribed exercise intensity. Exercise did not result in any adverse events and the patients enjoyed both types. No group differences existed between HIIT and MICT, making both viable exercise options for patients with CKD. However, only patients with CKD deemed healthy enough to participate completed the study, so HIIT may not be suitable for all patients with CKD. The findings of Beetham et al. (11) do support clinical supervision of exercising patients with CKD to enhance adherence to exercise and reduce the risk of adverse events regardless of the exercise protocol implemented. A 95.7% adherence rate to aerobic exercise when supervised by an exercise professional was also determined by other researchers (38). Therefore, patients with CKD may simply need and feel more comfortable exercising with guidance and supervision than trying to implement an exercise regimen on their own. A summary of additional

TABLE 2. Research benefits of exercise for predialysis patients with chronic kidney disease (CKD).

Study	CKD stage(s)	Exercise type	Intervention length	Benefits
Aoike et al. (12)	3–4	Moderate-intensity aerobic training	12 weeks	↑ $\dot{V}O_{2peak}$ (9.5%) & functional capacity ↑ maximal ventilation ↑ treadmill speed at VT & $\dot{V}O_{2peak}$ ↑ $\dot{V}O_{2peak}$, HR, & treadmill speed at RCP ↓ SBP & DBP no adverse events
Aoike et al. (13)	3–4	Moderate-intensity aerobic training	24 weeks	↑ $\dot{V}O_{2peak}$ & functional capacity ↑ QOL & sleep no adverse events
Barcellos et al. (37)	2–4	Aerobic and resistance training	16 weeks	↓ hs-CRP ↓ fasting blood glucose ↑ functional capacity eGFR not impacted by exercise
Beetham et al. (11)	3–4	HIIT and moderate-intensity aerobic training	12 weeks	high adherence to HIIT & moderate intensity no adverse events ↑ exercise capacity ↑ protein synthesis
Hamada et al. (43)	1–5	Aerobic and resistance training	6 months	↑ physical activity & functional capacity ↓ weight & waist circumference ↓ SBP & DBP ↔ eGFR ↓ proteinuria
Headley et al. (38)	3a, 3b	Moderate-intensity aerobic training	16 weeks	↑ $\dot{V}O_{2peak}$ (8.3%)
Howden et al. (8)	3–4	Moderate-intensity aerobic and resistance training lifestyle intervention	12 months	↑ $\dot{V}O_{2peak}$ (11%) ↓ weight, waist circumference, BMI ↑ diastolic functioning ↔ systolic functioning no adverse events
Santana et al. (34)	1–4	30-min moderate-intensity aerobic exercise	1 acute bout	eGFR not significantly ↓ by exercise
Watson et al. (36)	3b–5	Moderate-intensity aerobic and resistance training	12 weeks	↑ muscular strength ↑ hypertrophy
Zhang et al. (108)	2–5	Meta-analysis using aerobic and resistance exercise RCTs	6 weeks–12 months	↑ eGFR ↓ SBP & DBP ↓ BMI

$\dot{V}O_{2peak}$ = peak oxygen consumption; VT = ventilatory threshold; HR = heart rate; RCP = respiratory compensation point; SBP = systolic blood pressure; DBP = diastolic blood pressure; QOL = quality of life; hs-CRP = high-sensitivity C-reactive protein; eGFR = estimated glomerular filtration rate; HIIT = high-intensity interval training; RCTs = randomized controlled trials; BMI = body mass index

benefits of exercise for patients with CKD can be seen in Table 2.

When following ACSM guidelines for aerobic exercise, researchers have shown that no patients with CKD experienced any injuries or adverse events (12,13). Similarly, other researchers have reported that aerobic and resistance exercise were safe and beneficial for patients with CKD (44). To increase safety during exercise, clinicians must remember that patients with CKD are at an increased risk of falls; therefore, certain modalities of exercise (such as cycling) may be more appropriate for higher-risk patients (Figure 1). Monitoring blood pressure and electrocardiogram tracings during exercise may be prudent in high-risk patients (21). Consideration of patient medications is also imperative.

FIGURE 1. A dialysis patient cycling during treatment. Photograph provided by the Manitoba Renal Program with permission.

With the use of blood pressure-lowering drugs and drugs used to treat diabetes, those with CKD are at risk for hypotension (32) and hypoglycemia (10) during and after exercise. Therefore, exercise professionals trained to work with special populations should be training kidney patients. As with any exercising individual, predialysis patients with CKD should not participate if presenting contraindications to exercise. An in-depth analysis of exercise prescription for patients with CKD will be presented at the end of this review.

Based upon a recent internet search (45), currently there are few functioning renal rehabilitation exercise programs (RREPs); one such RREP is conducted by Active Body Physiotherapy in Australia. For 6 weeks, patients with CKD are taught how to incorporate exercise into their daily lives following guidelines provided by The National Kidney Foundation of Australia. Personalized programs consisting of aerobic exercise, resistance training, and stretching are performed 3 times per week for 60 min. The outcome goal of the Active Body RREP is to educate patients with CKD about exercise so that patients can continue an exercise regimen at home or under the supervision of a clinician upon the completion of the program (45). Researchers at the University of Delaware have also implemented an RREP in an effort to attenuate the development of CVD in patients with CKD (46). The clinician-supervised RREP provides individualized exercise programs for patients with CKD of all stages as well as those who have received a kidney transplant (46). The RREP at Guy's and St Thomas' Hospitals in London consists of 12 weeks of supervised training designed to educate kidney patients on appropriate ways to exercise (47). Two times a week for 60 min, patients complete a circuit-style exercise program. Unfortunately, examples of exercises performed are not listed in the leaflet on the Guy's and St Thomas' website. After the completion of the RREP, kidney patients should be able to complete 3 exercise bouts per week on their own. Kidney patients do not incur an additional fee for the RREP (47).

A RCT performed by Rossi et al. (48) closely mimicked the RREP implemented at Guy's and St Thomas' hospitals. For 12 weeks, stage 3 and 4 patients with CKD performed supervised exercise twice weekly. Patients with a history of cardiovascular complications exercised at cardiac rehab centers, while those without CVD exercised at physical therapy centers. All professionals exercising patients with CKD were trained regarding exercise implementation. The exercise program consisted of aerobic exercise, resistance training, and stretching. Aerobic exercise was comprised of walking on a treadmill or cycling on a stationary cycle. Patients progressively increased their aerobic exercise times by 2 to 3 min each session and aimed to reach 60 min of continuous exercise. No patient exercised above 60% to 65% of their maximal heart rate. Unsupervised walking was also suggested, with patients aiming to reach 5,000 to 10,000 steps per day. Resistance training consisted of upper and lower body free weight exercises. Patients began by performing one set of 10 repetitions of each exercise using 1 to 10-lb free weights and aimed to progress to 3 sets of 15 repetitions, increasing the weight as tolerated (48). The RREP at Guy's and St Thomas' Hospitals and the RCT conducted by Rossi et al. serve as models, but medical professionals should also collaborate on constructing a single universal RREP that can be implemented at most hospitals to ensure an optimal standard of care.

Dialysis Patients: Training Responses and Safety

Numerous studies have shown benefits of exercise training in ESRD. These include improvements in muscle strength, function, cardiovascular structure and function, and QOL (15,49,50). However, the literature shows significant inconsistencies, and the benefits seen in many studies are modest. For example, two of the largest studies examining the effects of endurance exercise on physical function in dialysis patients were published recently by Manfredini et al. (51) and Koh et al. (52). In both studies, the primary outcome related to physical function was performance on the 6-minute walk test (6MWT). While both showed numerical increases in average walking distance following the intervention period (+ 39m and + 49m, respectively), this change was only statistically significant in the Manfredini et al. trial. This was likely due to the larger sample size in the Manfredini trial (n = 227) compared with the Koh trial (n = 70), as opposed to any methodological difference between the studies. Importantly, other research suggests that changes of at least 54 to 80 meters on the 6MWT are needed to be clinically meaningful, in part due to the inherent variability in performance on this test (53), submitting that changes in both studies on 6MWT performance were modest.

Data regarding the effects of endurance exercise on CVD risk are encouraging yet also inconsistent. A recent meta-analysis demonstrated that intradialytic exercise improves cardiorespiratory fitness, and the effect appears to be greatest in studies that combined endurance and resistance training (54). A number of small studies have demonstrated a modest beneficial effect of exercise training on traditional CVD risk factors (e.g., blood pressure and serum cholesterol) in HD patients (49,50,55). For example, the effects of exercise on cardiac function, endothelial function, and arterial stiffness have been rather inconsistent. Several small pilot studies suggest that markers of arterial stiffness are reduced following 3 to 6 months of endurance exercise training (56,57). However, two of the larger RCTs involving exercise in HD patients failed to show improvement in arterial stiffness after 6 or 12 months of endurance training (52,58).

Recent systematic reviews of resistance training in HD patients generally indicate increases in muscle hypertrophy, strength, and objective measures of physical function following progressive resistance training (50,55,59). But, again, the benefits appear to be modest or inconsistent. Several resistance training interventions in HD patients with the largest sample sizes and longest intervention periods have failed to demonstrate significant increases in muscle hypertrophy (60–62) and a recent meta-analysis concluded that while muscle strength seems to improve with resistance training, muscle mass does not (59). Moreover, several recent interventions that improved muscle size or composition following resistance training failed to improve physical function (60,63,64).

Taken together, it appears that both resistance and endurance training have modest, albeit inconsistent, benefits. It also appears to make little difference whether the exercise is performed during dialysis, which is most common, or out of the clinic (55,65). The most important consideration for exercise prescription appears to be getting patients to move more. However, there are many concerns in the literature. Most studies published to date have significant shortcomings, including small sample sizes, short intervention periods, and low volume and intensity of exercise (66–68). The primary reason for this is that the poor health and physical function in dialysis patients makes it extremely difficult to recruit and maintain patients in studies. There are also limited data on hard outcomes such as hospitalizations and mortality. Future studies need to address these limitations.

Several unique risks are associated with exercise in hemodialysis (HD) patients, especially if the exercise is performed during dialysis. These include hemodynamic instability, muscle cramping, and dialysis access complications (66). Cardiovascular concerns are especially important to consider with intradialytic exercise due to the large amounts of fluid removed during treatment. For this reason, it is often recommended that exercise not be performed in the later stages of dialysis (21,69). However, recent data from Jeong et al. (70) indicate that hemodynamic instability during dialysis is not exacerbated when exercise is performed in the third hour of treatment. This suggests that optimal timing for intradialytic exercise should be individualized to ensure what is best for the patient.

Another concern related to hemodynamic instability and intradialytic exercise is the potential exacerbation of myocardial stunning. Intradialytic myocardial stunning is a frequent complication of dialysis that occurs due to a reduction in blood flow to the myocardium due to the removal of blood volume from ultrafiltration (71). Though exercise redistributes blood flow to the working muscle, two recent studies both demonstrated that intradialytic cycling reduced—as opposed to exacerbated—myocardial stunning (41,42). Intradialytic muscle cramping is another concern that could theoretically be mitigated or exacerbated by exercise. Dialysis-induced muscle cramps are likely caused by changes in plasma osmolality and extracellular fluid volume, though their exact origin is uncertain (74). While some have suggested that exercise training may reduce cramping during HD, there is little published data on this topic (75,76). Additional studies are needed to clarify the impact of exercise mode, timing, and intensity on myocardial stunning and muscle cramping.

A dialysis patient's access type and site are another important factor that must be considered when prescribing exercise in dialysis patients. It is recommended for dialysis patients with an arteriovenous fistula (AVF) or graft (AVG) to avoid upper limb activity with their access arm during dialysis (21). However, the nonaccess arm could be exercised during dialysis while the access site arm can be exercised at home or in the waiting room. Some researchers have recommended only light weights with the access arm, but there is no evidence to suggest, once the AVF/AVG matures, that the arm cannot lift heavy weights (66,77,78). Indeed, a study by Cheema et al. that included upper body progressive resistance training at a high intensity (RPE 15–17) in both access and nonaccess arms during dialysis treatment days showed no adverse effects on patients' vascular access sites (60).

Another controversy in the literature involves what blood pressure should be considered a contraindication to exercise in HD patients. American Heart Association (AHA) guidelines state that exercise is contraindicated for any individual who has a resting blood pressure of 180/110 mmHg (79). However, dialysis patients often have exceedingly high blood pressure compared with the general population (in part due to chronic volume overload), so strictly following the AHA guidelines would preclude many HD patients from consistently exercising. Moreover, data from the Dialysis Outcome and Practices Patterns Study (DOPPS) indicate that a systolic blood pressure of 140 to 160 mm Hg (stage 2 hypertension) is associated with reduced mortality in HD patients (80). This suggests that higher blood pressures during exercise may be safely tolerated in dialysis patients, though this question has not been thoroughly evaluated.

In summary, there are many hypothetical concerns with exercise in dialysis patients, including risks related to hemodynamic instability, muscle cramping, and the AV access. However, these concerns do not appear to manifest into adverse events; there is little evidence of such in the literature (15,53,73). A systematic review by Heiwe et al. (15) analyzed 45 studies that included data from more than 1,800 patients participating in aerobic and resistance exercises during dialysis treatments or at home. The review concluded that exercise did not cause cardiac or other adverse events leading to hospitalization or mortality. Despite the overwhelming data to address safety concerns, clinicians are still reluctant to prescribe exercise to their patients. Without a recommendation from nephrologists or the support from nurses and caregivers, implementing exercise or physical activity programs as a means of promoting a lifestyle change will be a challenge (81). Given the extremely poor function and low physical activity in many ESRD patients, contraindications to exercise need to be carefully considered such that they do not provide additional barriers to physical activity than are necessary. This is especially important considering that most patients are engaging only in low-moderate intensity exercise if they do anything at all.

FUNCTIONAL TESTING AND STRESS TESTING

Assessing patients with CKD via functional or stress testing before implementing an exercise regimen is important for many reasons. Perhaps of most importance, performing a stress test enables the exercise professional to observe the cardiovascular responses (i.e., electrocardiogram, hemodynamic) during exercise and determine safe limits for the CKD patient. Due to the excessive prevalence of cardiovascular comorbidities, some have suggested that all stage 5 and HD patients should undergo an exercise stress test prior to exercise (82,83). However, the intensity at which most HD patients exercise is typically very low, so this requirement is likely unnecessary and would only provide another barrier to exercise for an already excessively sedentary population. Others have suggested that medical clearance should only be required for patients participating in vigorous exercise activities (84). As a result, functional tests are recommended. Additionally, preliminary functional and stress testing serve as a baseline so that clinicians can monitor patient progress throughout the exercise program and more accurately prescribe effective exercise.

As previously stated, functional testing should be performed when a patient is deemed unable to complete a CPET or graded exercise test (GXT). When possible, a CPET or GXT may be used to assess the aerobic capacity of predialysis patients with CKD (12,85). A lower-intensity protocol—the Modified Bruce—has been successfully used by researchers to test renal patients (85). Exercise can be prescribed using CPET and GXT results so that patients with CKD can benefit from an exercise regimen (12,85). Ventilatory threshold (VT) and respiratory compensation point (RCP) during submaximal exercise can also be used to assess fitness and prescribe exercise (12). Viable functional tests that may be used with the CKD population are the 6MWT (12,51,86,87), sit-to-stand tests (12,37,51,87), the 2-min step test (12,37), the time up-and-go test (12), the 8-foot up-and-go test (37), balance tests (86,87), and leg and handgrip strength tests (86,87). While dialysis patients may not be able to perform such functional tests at initial assessment (51), using functional tests post-training may be possible to assess improvement if tolerated. Additionally, the timing of functional testing may be important for assessing dialysis patients, with optimal testing occurring when patients are not feeling fatigued (88). Functional tests that are shorter in duration and lower in intensity, such as gait speed (88), may be a more viable option for assessing dialysis patients.

EXERCISE PRESCRIPTION

Deficiencies in access to guidelines for exercising and adequate support from healthcare providers often preclude patients with CKD from exercising (32). However, guidelines for exercising patients with CKD do exist and can be tailored to fit the needs of each patient (32). An exercise program should be preceded by a full medical history and examination, including a cardiovascular screening, pharmacological history, and bloodwork (21). The cardiovascular screening should include a blood pressure evaluation and a CPET supplemented by an electrocardiogram evaluation when tolerated by patients (21). ESRD patients may want to avoid a CPET; therefore, functional tests as tolerated may be more appropriate in assessing functional capacity. However, if ESRD patients are cleared by a physician to exercise, their inability to perform an exercise test should not prevent them from training. Clinicians trained in exercising special populations should oversee exercising patients with CKD (21). Howden et al. (44) support the notion that the exercise regimens of patients with CKD should be supervised by trained clinicians to increase adherence. Not only must clinicians consider potential risks that may occur when exercising patients with CKD, risks associated with other comorbidities must be acknowledged (21). Managing risks is especially pertinent in patients with ESRD (21). With appropriate supervision, the risk of adverse events occurring during exercise can be diminished (10).

Predialysis Exercise Recommendations

An exercise program consisting of aerobic exercise, resistance training, and flexibility training is recommended for patients with CKD with no contraindications to exercise (21). Exercise modalities, such as walking, jogging, or cycling, that used large muscle groups are preferred methods of aerobic exercise to increase $\dot{V}O_{2peak}$ (89). Ideally, patients with CKD should complete a total of 150 min of aerobic exercise per week (2). The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend 30 min of aerobic exercise 5 times per week (2). Based on a review by Johansen and Painter (10), the ACSM suggests patients with CKD perform aerobic exercise 3 to 5 d per week for 20 to 60 total min (either continuous or broken up into tolerable time increments) at a moderate intensity of 40% to 59% of reserve $\dot{V}O_2$ or an RPE of 12 to 13 on the 6 to 20 scale (90). Progressive increases in exercise time should be implemented as tolerable and based on an individual basis (90). For example, an individual who cannot tolerate aerobic exercise for 30 consecutive minutes can break-up the exercise bouts into smaller time increments, such as 3 10-min bouts of walking, until longer exercise periods are achievable. The ACSM recommends that patients with CKD begin aerobic exercise at a low-to-moderate intensity and increase intensity as aerobic fitness improves. However, the exercise program should be tailored to the needs of the individual and necessary alterations should be made to increase exercise safety and tolerance (90).

Resistance training to improve muscular strength is also highly recommended (89). In conjunction with Johansen and Painter (10), the ACSM recommends that patients with CKD resistance train 2 to 3 d per week at resistances equal to 65% to 75% of an estimated 1-RM (90). Each resistance training session should incorporate 8 to 10 exercises that work major muscle groups (10,90). At least one set of 10 to 15 repetitions should be performed for each exercise, but multiple sets may be performed if tolerated (10,90). Based on the RCT of exercise in chronic kidney disease (RENEXC) trial, predialysis patients with CKD who may initially be unable to perform resistance training at the start of an exercise program may incur similar benefits by performing balance training (91). Finally, based on the work of Johansen and Painter (10), the ACSM (90) supports the inclusion of flexibility training 2 to 3 d per week.

Dialysis Exercise Recommendations

There are many challenges when it comes to prescribing exercise to ESRD patients. First, most clinics do not employ exercise specialists, and nephrologists and other clinic staff have limited training with regard to exercise and therefore are unsure what to prescribe (92). In addition, most renal programs do not have clear exercise policies or physical activity guidelines. The KDIGO recommends individuals with CKD/ESRD participate in 150 min of physical activity per week, including at least 30 min/d, 5 d a week. Nevertheless, specifics regarding the frequency, intensity, type, and timing of PA guidelines for ESRD patients remain unclear (93). Several exercise guidelines that may help in prescribing exercise have been published in recent years (21,94,95). While these guidelines differ, some similarities include a focus on endurance, resistance, balance, and flexibility training. The UK Renal Association clinical practice guidelines on hemodialysis provided the best evidence available to promote the availability of intradialytic exercise for every patient and suggest that exercise regimens be designed by appropriately trained staff (95). Unfortunately, this suggestion is not advocated globally.

Despite these recommendations and guidelines, physical activity levels in HD remain extremely low, and few clinics around the world offer exercise programs (67,68,69). Furthermore, in 2015, the US Kidney Disease Outcomes Quality Initiative (K/DOQI) removed exercise recommendations as part of their clinical practice guidelines for hemodialysis (99). To address these issues, several groups have recently begun to advocate for a paradigm shift toward implementing more personalized exercise or physical activity prescriptions in which patients are provided the autonomy to select the type of exercise most important to them (100–102). This type of prescription may include combinations of intradialytic and out-of-clinic exercise, including light-intensity activities (e.g., walking dogs, grocery shopping, taking the stairs rather than the elevator), and high-intensity exercise as an individualized approach to conform to the needs of individual patients (65,100). Future research is needed to demonstrate the feasibility and efficacy of this approach.

SUPPLEMENTAL SERVICES

To ensure a holistic approach, renal rehabilitation patients would benefit from the implementation of psychological and nutritional counselling in addition to exercise training. Patients with CKD are at risk for suffering from major depressive disorder or symptoms of depression (103). ESRD patients may be especially prone to depression, being four times more likely to develop the mental disorder compared to the general population (104). The risk of negative outcomes increases when CKD is comorbid with depression (103). Antidepressants can be used to combat depression but may further complicate treatment due to the numerous drugs patients already take for CKD and other comorbidities (104). One suggested supplemental treatment that may alleviate depression or depressive symptoms in patients with CKD is cognitive behavioral therapy (CBT) (104). The integration of CBT in renal rehabilitation programs would be beneficial for patients without the need to incorporate yet another pharmacological therapy (104). However, CBT is more time consuming than the use of antidepressants. Therefore, CBT should only be used for patients with CKD diagnosed with depression or depression symptoms. The option of psychological counseling should, however, be present for all patients with CKD. Even shorter meetings with a mental health professional may provide psychological benefits and attenuate declines in QOL for patients with CKD. Additionally, research regarding mental health treatment in the CKD population is sparse and warrants further investigation before implementation (105).

CKD progression can be prevented by following dietary guidelines to avoid foods high in kidney damaging contents. Patients with CKD must be prudent with their dietary intake of sodium, potassium, and phosphorus (106). Elevated sodium levels are associated with hypertension and CKD progression. Diets rich in potassium and phosphorus predispose patients with CKD to hyperkalemia and hyperphosphatemia, respectively. Proper protein intake must also be monitored to ensure patients receive enough protein to attenuate muscle wasting without ingesting excessive amounts of protein that further reduce GFR. Iron and vitamin D deficiencies in patients must be monitored and treated appropriately (106). Finally, patients with CKD should be encouraged to increase fiber intake as necessary as fiber deficiencies have been identified in this population (107). Patients with CKD consuming high fiber diets have been shown to have reduced serum urea and creatinine levels (107). Due to the complex dietary needs of renal patients, dieticians and nutritionists should consult with patients regarding proper dietary guidelines. Patients should be assessed by dieticians and nutritionists so that individualized dietary guidelines can be prescribed (106). Additionally, patients should be provided with a list of foods high in sodium, potassium, and phosphorus that should be avoided or eaten in moderation based on individualized programs. Patients with CKD are likely unaware of foods that are potentially hazardous, so supplemental nutritional counseling provides patients with lifestyle changes that can be easily implemented and positively impactful.

CONCLUSIONS

Resistance training and cardiorespiratory exercise are essential to the maintenance of a healthy lifestyle for patients with CKD. However, patients with CKD often lack knowledge in exercise programming. With the proper guidance and supervision of a clinician trained to exercise special populations, patients with CKD can engage in exercise in the best and most appropriate manner to prevent disease progression and improve physiological and psychological functioning. Without a proper exercise program to follow, patients with CKD may continue their sedentary lifestyles, which only compounds the dysfunction associated with CKD and related comorbidities. Additionally, as renal disease progresses, so does the associated cost of medical care. Based on research outcomes, an exercise prescription of aerobic training combined with resistance training seems to result in the most positive benefits for patients with CKD in terms of cardiometabolic and musculoskeletal function. A combined exercise prescription implemented at home may be as beneficial as supervised exercise training, provided renal patients are given instructions and guidance by a trained clinician. Renal rehabilitation programs would serve to bridge the gap between the knowledge clinical professionals have for exercising patients with CKD and the actual incorporation of exercise into the daily lives of patients. For renal patients, exercise may be an economical form of medicine.

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