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Exercise Training in Chronic Kidney Disease Patients

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Contents

Abstract

Chronic kidney disease (CKD) is a major public health problem that affects an estimated 1.7 million Australians. Patients with CKD commonly progress to end-stage kidney disease (ESKD) requiring dialysis and/or kidney

transplantation. They are at high risk of cardiovascular disease and many die from this prior to reaching ESKD. Few therapies are available to slow CKD progression and reduce cardiovascular morbidity and mortality. The benefit of exercise training has been well demonstrated in a range of disease conditions including ESKD and was recently highlighted by a systematic review in haemodialysis patients and a recent Cochrane review of all stages of CKD. However, the effects of exercise training in patients with CKD have not been extensively investigated. Our systematic search of the literature found only ten clinical trials in this area. The aim of this review is to review these studies, and to discuss the findings, safety considerations and suggest future areas of research. Overall, the majority of the studies are small, non-randomized, non-controlled trials. They have found that exercise training can increase exercise capacity, improve muscle strength and function, decrease blood pressure, and improve inflammation and oxidative stress biomarkers. The effects of exercise training on kidney function, cardiovascular disease and quality of life are unknown. Studies are needed to answer these questions and develop evidence-based exercise training guidelines for individuals with CKD.

1. Introduction

Physical inactivity resulting in poor exercise capacity is a common consequence of chronic kidney disease (CKD) and is associated with increased mortality in the general population.[1] The benefits of exercise training in patients with end-stage kidney disease (ESKD) have been investigated for 30 years with studies consistently demonstrating improvements in cardiorespiratory fitness (e.g. peak oxygen uptake [$\dot{V}O_{2peak}$]), physical functioning and cardiovascular risk.[2,3] A recent meta-analysis by Segura-Ortí[4] in ESKD patients found that aerobic exercise or a combination of aerobic and resistance training improves exercise capacity. Furthermore, resistance training alone increases functional capacity, lower limb strength and quality of life. The review was unable to determine the effect of exercise training on blood pressure, inflammation and risk of falls through pooling of previous data. Whilst a Cochrane review reporting on all stages of kidney disease concluded that there is enough scientific evidence to suggest that exercising regularly will have benefits across all stages of the disease.[5] There has been less focus on patients with mild-to-moderate kidney disease, where potentially the benefits of exercise training may prevent loss of physical function and independence, and improve risk factors such as blood pressure, which contribute to both the progression of kidney disease and cardiovascular risk.[1]

Exercise capacity has been found to have an independent association with mortality risk in both healthy and chronic disease populations.[6-10] Specifically, in ESKD, $\dot{V}O_{2peak}$ was the strongest predictor of survival and is thought to provide additional incremental prognostic information,[11] as $\dot{V}O_{2peak}$ can be modified through exercise training. It is unknown if this relationship extends to patients with CKD, although it is likely. Evidence also exists in both healthy and clinical populations to suggest that exercise training can reduce blood pressure[12] and inflammation,[13] improve muscle function and therefore reduce the risk of falls,[14] and improve quality of life.[15,16] In addition, regular exercise can reduce the risk of developing a large number of chronic diseases and conditions,[15] which are relevant to CKD patients due to the high number of co-morbidities associated with this disease.[17-19] The aim of this review is to systematically review the available literature in CKD patients, and to discuss the findings of the studies, the safety considerations and suggest future areas of research.

1.1 Chronic Kidney Disease

Kidney disease is defined by the Kidney Disease Outcomes Quality Initiative (K/DOQI) as either (i) kidney damage for ≥3 months, as confirmed by kidney biopsy or markers of kidney damage such as proteinuria or albuminuria, with or without a reduced glomerular filtration rate (GFR); or (ii) GFR <60 mL/min/1.73 m^2 for ≥3 months, with or without kidney damage.[20] The guidelines further classify kidney disease into five stages: stage I CKD has signs of kidney damage with normal kidney function (≥90 mL/min/1.73 m^2), stage II GFR of 60–89 mL/min/1.73 m^2, stage III GFR 30–59 mL/min/1.73 m^2, stage IV CKD GFR of 15–29 mL/min/1.73 m^2 and finally stage V CKD GFR of <15 mL/min/1.73 m^2.[20] Due to the asymptomatic nature of the condition, until the later stages of the disease, it has been difficult to ascertain the true prevalence within the population. It has been estimated that in Australia, over 1.7 million individuals have a GFR of <60 mL/min/1.73 m^2.[21]

2. Methods

We performed this systematic review and reported it in accordance with Cochrane[22] and PRISMA guidelines.[23] A review of the literature was conducted to identify exercise training studies that had assessed either physiological or functional outcomes in CKD patients. The search included MEDLINE (PubMed), CINAHL®, Web of Science and EMBASE databases, and was completed on 31 December 2010. The search utilized the MeSH database, with the concepts of kidney disease and exercise training searched, which included 'chronic kidney disease', 'renal disease', 'pre-dialysis kidney disease'; and 'aerobic exercise', 'resistance exercise', 'combination exercise training', 'exercise', 'physical activity' and 'lifestyle intervention'. Articles were then further reviewed for relevance to the topic and studies were considered suitable if they met the following criteria: exercise training in non-dialysis CKD patients with pre- and post-outcome measures. The search was limited to those in the English language and adult human trials. Studies that met the following criteria were included: (i) participants had CKD, as classified by the K/DOQI guidelines; (ii) use of aerobic, resistance or combined aerobic and resistance training; (iii) outcome measures included measurement of exercise capacity (aerobic interventions) or maximal muscle strength.

Ten trials were identified as suitable with 13 articles published from these.[24-35] Men and women were included in all trials and the sample sizes ranged from 8 to 54 patients, enrolling in total 217 participants, which included 139 exercising CKD participants, 78 CKD controls and 32 healthy controls. Mean ages ranged from 47[29] to 76[27,28] years. The aetiology of kidney disease was only reported in six studies.[25-28,30,31] A variety of outcome measures have been evaluated including exercise capacity, kidney function, blood pressure, muscular strength, functional capacity, left ventricular function, pulmonary function, cardiovascular function, blood chemistry, change in body weight and composition, skeletal muscle fibre type and oxidative stress parameters.

2.1 Quality Assessment

The methodological quality of included studies was rated by two investigators using a scale from the Physiotherapy Evidence Database (PEDro). Disagreement was resolved by a third. Table I shows the 11 criteria used to assess each trial, with 1 point awarded for each criteria met. Due to the low number of studies in the field, we did not exclude studies from this review based on their score.

3. Aerobic Exercise Training

Six studies have been conducted using only aerobic exercise training programmes.[30-33] Exercise capacity was the most commonly evaluated outcome.[6,10,37] The modes of exercise prescribed were walking,[33] a combination of walking and stationary cycling,[30] aquatic exercises,[32] a combination of all of these[31] or a combination of treadmill walking, stationary cycle, elliptical trainer and home walking.[36] Table II shows the differences in exercise session durations and the quality of the studies demonstrated in table I. Intensity was progressively increased from 50%

Table I. Methodology quality of the aerobic and resistance exercise training studies conducted in chronic kidney disease patients

Study (year)	PEDro criteria											
	1[a]	2[b]	3[c]	4[d]	5[e]	6[f]	7[g]	8[h]	9[i]	10[j]	11[k]	Total
Aerobic studies												
Mustata et al.[36] (2010)	+	+	+	+	–	–	–	+	+	+	+	8
Leehey et al.[33] (2009)	+	+	–	–	–	–	–	–	+	+	+	5
Eidemak et al.[31] (1997)	–	+	–	+	–	–	–	–	–	+	+	4
Resistance studies												
Castaneda et al.[26] (2001)	+	+	–	+	–	–	–	+	+	+	+	7

a Eligibility criteria were specified.

b Subjects were randomly allocated to groups.

c Allocation was concealed.

d The groups were similar at baseline regarding the most important prognostic indicators.

e There was blinding of all subjects.

f There was blinding of all therapists who administered the therapy.

g There was blinding of all assessors who measured at least one key outcome.

h Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.

i All subjects for whom outcome measures were available received the treatment or control condition as allocated, or where this was not the case, data for at least one key outcome was analysed by 'intent to treat'.

j The results of between-group statistical comparisons are reported for at least one key outcome.

k The study provides both point measures and measures of variability for at least one key outcome.

to 60% of heart rate reserve (HRR) to 70% of HRR in one study[30] and between 25% and 84% of maximal exercise capacity in the others.[31,33] Designs included randomized controlled trials,[31,33] a non-randomized trial[32] and a crossover design study.[30]

3.1 Exercise Capacity

Four of the six studies showed significant, albeit modest improvements in exercise capacity. Eidemak et al.[31] reported that $\dot{V}O_{2peak}$ was improved by 8% from 25 to 27 mL/kg/min, whilst the control group decreased by 10% from 21 to 19 mL/kg/min. The study by Toyama et al.[35] also reported similar increases in exercise capacity; specifically, a 10% increase in the anaerobic threshold (AT-$\dot{V}O_2$) after training, whilst the control group decreased by approximately 14%. In a crossover study, Boyce et al.[30] found a 12% increase in exercise capacity following 4 months of training. Subsequent detraining of this group resulted in a significant reduction in $\dot{V}O_{2peak}$ over 2 months by 9%.

Although, four of these studies showed statistically significant improvements in exercise capacity as a consequence of the exercise interventions, it is not clear whether these are substantial enough to be of clinical relevance.[30,31,35,36] An increase in exercise capacity by one metabolic equivalent (MET) or 3.5 mL/kg/min is associated with a reduction in the risk of mortality by 17% in females[7] and 12% in males in the general population.[8] Additionally, ESKD patients have an increased mortality rate if exercise capacity is below 17.5 mL/kg/min.[11] Given that exercise capacity is generally reported to be below age predicted normative values, even maintenance of this measure may in itself prove protective and of value in this population. However, the current literature is unable to provide evidence to confirm this and is an area requiring further study. Furthermore, CKD patients are at an increased risk of death associated with cardiovascular causes;[38] however, the relationship between exercise capacity and mortality has not been reported in this population.

In contrast, Pechter et al.[32] stated that $\dot{V}O_{2peak}$ did not significantly increase following their

Table II. Summary of studies investigating the effect of aerobic exercise training

Study (year)	Design	No. of patients, (exercise/control)	Exercise training/modality	Duration	Outcomes
Eidemak et al.[31] (1997)	RCT	15/15	Unsupervised home based for 30 min/day Stationary bike, running, swimming, walking at approximately 60–75% $\dot{V}O_{2max}$	18 mo (range 8–28 mo), 20 mo in the control group (range 10–30)	↑ $\dot{V}O_{2peak}$ ↔ GFR ↔ Lipids
Boyce et al.[30] (1997)	Crossover	8/NC	Supervised for 60 min, 3 × wk 30 min walking + 30 min stationary cycling at 70% HRR	4 mo	↑ $\dot{V}O_{2peak}$ ↑ BP ↔ LV function ↑ Strength ↓ CrCl ↓ GFR ↔ Hb ↔ Lipids
Pechter et al.[32] (2003)	Non-randomized, self-selecting control group	17/9	Supervised for 30 min, 2 × wk Vertical aerobic aquatic exercise, 10 min warm-up gentle stretching, 10 min cardiovascular exercises increasing intensity, 10 min cool-down stretching	12 wk	↔ $\dot{V}O_{2peak}$ ↑ Peak oxygen pulse ↑ Ventilation ↑ Peak load ↑ Proteinuria ↑ Cys-C ↑ eGFR ↑ BMI ↔ BP ↑ TC ↑ Oxidative stress
Leehey et al.[33] (2009)	RCT	7/4	Supervised + home based 30–40 min, 3 × wk, 3–5 min or warm-up, range of motion exercises, interval training (walking), cool-down and post-exercise range-of-motion exercise	6 wk (supervised) + 18 wk (home based-telemedicine)	↔ $\dot{V}O_{2max}$ ↔ Exercise duration ↔ Proteinuria ↔ BP ↔ HR ↔ Weight loss ↔ BMI ↔ Glucose ↔ Lipids ↔ Inflammation
Musata et al.[36] (2010)	RCT	10/10	Supervised + home based 5–60 mins, 3 × wk Supervised treadmill, stationary cycle, elliptical trainer. Home-based walking	1 mo (supervised) + 11 mo (supervised + home based)	↑ $\dot{V}O_{2peak}$ ↑ ET ↓ AIx ↔ QOL
Toyama et al.[35] (2010)	Non-randomized	10/9	Supervised + home based 30 mins, 2 × wk 30 min stationary bike or walking	12 wk	↑ AT-$\dot{V}O_2$ ↓ Triglycerdies ↓ LDL-C ↑ HDL-C ↑ eGFR

AIx = augmentation index; **AT** = anaerobic threshold; **BMI** = body mass index; **BP** = blood pressure; **CrCl** = creatinine clearance; **Cys-C** = cystatin-C; **eGFR** = estimated glomerular filtration rate; **ET** = endurance time; **GFR** = glomerular filtration rate; **Hb** = haemoglobin; **HDL** = high-density lipoprotein; **HR** = heart rate; **HRR** = HR reserve; **LDL** = low-density lipoprotein; **LV** = left ventricle; **NC** = no control specified; **QOL** = quality of life; **RCT** = randomized controlled trial; **TC** = total cholesterol; $\dot{V}O_2$ = oxygen uptake; $\dot{V}O_{2max}$ = maximal $\dot{V}O_2$; $\dot{V}O_{2peak}$ = peak $\dot{V}O_2$; ↑ indicates increase; ↔ indicates no change; ↓ indicates decrease.

exercise intervention. This study was of similar duration to the other two,[29,30] but exercise prescribed was described as low intensity and exclusively performed in water. The investigators used peak oxygen pulse, which is defined as the amount of oxygen consumed by the body from the blood in one systolic discharge of the heart to determine the effect of the intervention on exercise capacity. Peak oxygen pulse has been reported to be a significant predictor of mortality[39] and extensive myocardial ischaemia[40] in the general population. It has not been validated in the CKD population. Care would need to be taken in using this measure in patients who have an AV fistula, as this is likely to significantly alter the validity of the results. In this study, the intervention significantly increased peak oxygen pulse from 11 to 13 mL O_2/beats/min. In addition, peak ventilation was increased from 51 to 56 L/min and peak workload from 97 W to 111 W. Despite the low-intensity training, failing to improve $\dot{V}O_{2peak}$, peak power output did significantly improve. Loss of peak power has been reported to reflect loss of type II motor units, reduction in nerve conduction and intrinsic changes in skeletal muscle force and power production.[41] Therefore, the finding that the low-intensity aquatic exercise significantly improved peak power may indicate that there have been other physiological adaptations as a consequence of training, irrespective of change in exercise capacity as measured by $\dot{V}O_{2peak}$.

Finally, Leehey et al.[33] also found no significant change in maximal oxygen uptake ($\dot{V}O_{2max}$) as a result of the exercise intervention (table II). This was likely due to the high dropout of study participants. Twenty patients were recruited to the study; of these, one person failed the prescreening laboratory tests and six were removed from the study, two due to a positive stress test, two due to the investigators decision, one as a result of the patient's choice and one commenced haemodialysis treatment, leaving 13 patients randomized. Following randomization, but before any testing, a further two of the six control patients were removed due to investigator decision and patient's wish, meaning that only four subjects remained in the control group. In light of this, it is difficult to determine whether these results are reflective of the CKD population. This study highlights the importance of the prescreening of patients prior to commencement of exercise training with 10% of the study participants having a positive stress test, and provides further evidence on the difficulty in engaging patients in these types of interventions.

3.1.1 Meta-Analysis

Only two of the three aerobic training studies contained the necessary mean and standard deviation $\dot{V}O_{2peak}$ data to conduct a meta-analysis.[33,36] The corresponding author from the other study was contacted to provide the additional information required.[31] Data from the three studies was analysed using Review Manager (RevMan) version 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration, Denmark). Mean differences and 95% confidence intervals were calculated along with heterogeneity using the I^2 statistic to determine whether studies could be pooled. Statistical significance was set at $p < 0.05$. In two studies,[32,33] differences in baseline $\dot{V}O_{2peak}$ values between control and exercise-trained groups resulted in significant heterogeneity ($I^2 = 80\%$; $p = 0.002$) that excluded them from the meta-analysis. This resulted in only one remaining study[36] being eligible for analysis, meaning the meta-analysis was not performed.

3.2 Blood Pressure

Changes in blood pressure as a result of aerobic exercise training were assessed in three of the six studies.[30,32,33] The evaluation of this indicator of cardiovascular health is important in the CKD population as cardiovascular disease is the most common cause of death at all stages of kidney disease. Reduction in blood pressure to 125/75 mmHg has been shown to improve the outcome in patients with CKD by slowing the loss of renal function.[42] Boyce et al.[30] were able to show a substantial reduction in both systolic and diastolic blood pressure from 145/90 to 125/75 mmHg following exercise training. The authors noted that these changes were evident despite no change to medication usage, body

weight or sodium intake. However, these results should be interpreted with caution in view of the small study sample size and lack of additional supportive studies. Pechter et al.[32] also showed a similar magnitude of reduction in resting blood pressure in their training group from 147/87 to 139/84 mmHg, whilst the control group remained unchanged. Medication usage was also left unchanged throughout the exercise intervention, as was diet. Aquatic exercise, as utilized by Pechter et al.,[32] has previously been reported to be effective in lowering blood pressure in hypertensive patients[43] and is recommended by the American Heart Association as a therapy for the prevention and treatment of hypertension.[44] The authors suggest that this modality of exercise training is useful, as it decreases plasma renin activity, lowers renal sympathetic nerve activity and levels of catecholamine, and prostaglandin levels,[45] which contribute to renal vascular pressure and sodium excretion.[32,46]

Blood pressure remained unaffected by exercise training in the remaining studies.[31,33,35,36] Whilst Eidemak et al.,[31] Toyama et al.[35] and Mustata et al.[36] all observed an improvement in exercise capacity, this did not translate to improvement in blood pressure. Leehey et al.[33] did observe a mean lowering in resting systolic and diastolic blood pressure, which they suggested was a training effect they were unable to determine the statistical significance of due to the small sample size of the study. In addition, three of the studies utilized exercise programmes that involved patients exercising unsupervised, meaning adherence to training is difficult to assess.[31,33] Mustata et al.[36] did assess adherence. They reported that in their study adherence was as high as 80% for the supervised exercise sessions but only 20% for the home sessions. In the study by Toyama et al.[35] of a supervised exercise programme, adherence was unreported.

3.3 Kidney Function

The major focus of treating kidney disease is to slow the deterioration of kidney function primarily through good control of blood pressure, using medications such as angiotensin converting enzyme inhibitors and other aggressive cardiovascular risk factor management. Early research in animal models has revealed that exercise does not negatively influence the loss of renal function.[47] Studies in humans evaluating the effect of exercise on renal function are scarce, and the current evidence is poor. The main issue in completing a study with kidney function as the outcome measure is the number of patients required. We performed sample size calculations using data from a trial we have conducted evaluating the effects of atorvastatin on kidney function in a heterogeneous group of CKD patients.[48] Assuming a rate of decline in controls (mean ± standard deviation) -1.47 ± 3.4 mL/min/1.73 m^2/year we would need 1870 patients to detect a 30% improvement in kidney function (α-0.05, 95% CI 1-β, 0.8). Choosing a more homogenous group of CKD patients (e.g. similar cause of CKD and similar medications) with well defined decreases in kidney function (from a pre-trial phase) is likely to lessen the number of patients needed by decreasing the within-group variability in the decline in kidney function. However, it would also diminish the ability to generalize the findings.

Five of the studies conducted have described the effect of aerobic exercise training on a change in kidney function.[30-33,35] Pechter et al.[32] found encouraging results with their aquatic exercise reporting to improve kidney function. Whilst the authors observed a decrease in protein creatinine ratio and cystatin-C, the reported improvement in kidney function must be interpreted with care due to the low numbers in the trial. Similarly, the recent study by Toyama et al.[35] reported a large significant improvement in estimated GFR (eGFR). However, as with the previous study, the intervention numbers were small and the study duration short. Overall, the studies suggest that there is no indication of harm in performing cardiorespiratory exercise training in CKD patients. Specifically, Eidemak et al.[31] was able to demonstrate no effect on the decline in kidney function following their exercise intervention. The authors found that the rate of loss of function was similar in the exercise (–0.27, range 95% CI +0.57, –1.31 mL/[min/1.73 m^2/month]) and the control group (–0.28, range 95% CI +0.18,

–0.93 mL/[min/1.73 m^2/month]). The authors acknowledge that the study numbers of 15 per group were likely to be too small to exclude an effect of exercise on disease progression. Boyce et al.[30] and Leehey et al.[33] both observed reductions in renal-function parameters. This is likely a consequence of the low sample size and follow-up period. A further limitation is that both studies used outcome measures that included the measurement of creatinine. Exercise training may result in the depletion of fluid volume, which in turn can increase creatinine levels. There is no evidence of this in CKD patients, creatinine levels have been observed to fluctuate as a consequence of exercise in healthy subjects.[49] This is an important area that requires further investigation in CKD patients, as it may indicate that the eGFR based on serum creatinine is not an appropriate measure of renal function if patients have just exercised. Creatinine-based outcome measures can also be altered as a consequence of increasing muscle turnover,[50,51] thus resulting in an increase in serum creatinine, whilst eGFR would decrease. Furthermore, timing of samples should be considered when interpreting results, with exercise-induced proteinuria, a common consequence of physical activity. High levels of serum cystatin C indicate that glomerular filtration rate has declined. Cystatin C levels provide an estimate of GFR that is independent of muscle mass and does not require adjustments for age, sex or race, suggesting that this may be a more optimal measure of kidney function in exercise studies.[52] However, plasma cystatin C will be subject to the same hydration limitations as serum creatinine.

3.4 Blood Lipids

Five studies have looked at the effects of aerobic exercise training on blood lipids.[30-33,35] Eidemak et al.[31] is the only study to report a significant change with total cholesterol increasing in the exercise group from 5.0 to 5.6 mmol/L. This is an unusual finding and not reflective of the usual changes in this parameter with exercise training.[53] As there were no changes in blood lipid in the other three studies,[30,32,33] it is possible that this effect was due to a dietary or medication change. Unfortunately, the authors did not report on these factors. Toyama et al.[35] found that the exercise training group showed a significant decrease in triglycerides and low-density lipoprotein cholesterol (LDL-C), whilst high-density lipoprotein cholesterol (HDL-C) significantly increased. The authors noted that two patients in the exercise group showed a large increase in HDL-C levels, suggesting that the interpretation of these results should be with caution due to the low sample size. Toyama et al.[35] also reported that in adjusted multiple regressions, HDL-C had a positive relationship with an increase in eGFR levels. We believe that further investigation is required to substantiate this relationship and, again, must be interpreted with care due to the small sample size.

3.5 Oxidative Stress

In patients with CKD, the balance between anti- and pro-oxidant systems is impaired, resulting in increased oxidative stress.[54] This is then thought to contribute to endothelial dysfunction and atherosclerosis, and the increased morbidity and mortality in CKD patients.[55] The exact mechanisms behind the increased oxidative stress and the consequence in CKD are not fully elucidated. The effect of aerobic water-based exercise on markers of oxidative stress was investigated in one study.[32] Products of lipid peroxidation; malondialdehyde and 4-hydroxyalkenals, were measured along with conjugated dienes and reduced and oxidized glutathione. Aquatic exercise was found to decrease markers of oxidative stress. The authors suggest that this is indicative of increased antioxidant activity, although it was not established.[32] The effects of exercise training on oxidative stress in CKD patients needs further investigation, as there is some evidence that it contributes to cardiovascular disease morbidity and mortality in these individuals.[55]

3.6 Arterial Stiffness

Arterial stiffness is an important marker of cardiovascular risk and is a predictor of survival in patients with ESKD.[56] One study has explored the effect of aerobic exercise training on arterial

stiffness.[36] The authors reported that arterial stiffness, as measured by augmentation index, was improved after 1 year of exercise training. Although not measured in this study, pulse wave velocity is a more accurate measure of arterial stiffness than augmentation index, but this latter measure is a good surrogate indicator of resistance. As this was a pilot study, data must be interpreted with caution due to the lack of power to detect difference between groups; however, these results are promising.

4. Resistance Exercise Training

Resistance training is beneficial as it increases skeletal muscle mass, strength and endurance, assists in maintaining basal metabolic rate, and improves functional capacity and mobility independence.[57] Two trials have been conducted utilizing resistance training alone in CKD patients, one of which was a randomized controlled design. From these two trials there have been five published studies, which are summarized in table III.[25-28,34] As methodology was similar between the studies, the only initial publication was assessed. The trials varied in their prescription of exercise intensity with one conducting training sessions at 80% of one-repetition maximum (1-RM)[25,26,34] and the other using a dynamic strength and endurance training regimen of 60% 1-RM.[27,28] Both trials were supervised and resistance was adjusted throughout the intervention to facilitate progression. In the trial by Castaneda et al.,[25,26,34] participants were required to perform three sets of eight repetitions on each machine per session with a total of five machines (chest and leg press, latissimus pull-down, knee extension and knee flexion). This took approximately 45 minutes. In the other trial, patients performed three sets of 20 repetitions of knee extensions with each leg, and static endurance was trained by extending the knee and keeping it horizontal to the floor, holding the knee position for five seconds with a 15 second rest in between each hold for five sets of one repetition with each leg.[27,28] Following this, the participants completed a low-intensity group exercise programme for 30 minutes. Change in skeletal muscle strength is the most commonly assessed outcome along with measures of cellular muscle function.

4.1 Muscular Strength and Function

Loss of muscle mass or sarcopaenia is a common consequence of kidney disease, as CKD is a catabolic state. Castaneda et al.[26] conducted a study with the intervention consisting of a low-protein diet plus a resistance training programme, as described in section 4, or a low-protein diet alone. The intervention resulted in a significant increase in total body potassium and hypertrophied type I and II muscle fibres. These results suggest that this type of exercise training can ameliorate the effects of a low-protein diet and the catabolic nature of kidney disease. The increased hypertrophied muscle fibres were accompanied by large and significant increases in both upper and lower body strength, whilst the low-protein diet group decreased in strength. In the study by Heiwe et al.,[28] the training led to an increase of quadriceps strength by 60% in the CKD group and 70% in the healthy comparison group. Dynamic muscular endurance also significantly improved in response to the exercise training by 53% in the CKD group and 79% in the healthy exercise group. The authors concluded that the skeletal muscle of CKD patients responds to resistance training in a similar way to healthy muscle.

In another study by Heiwe et al.,[27] the molecular response in the skeletal muscle to the resistance training programme was investigated. There were no statistical differences in muscle fibre-type proportion between the CKD patients and healthy controls at baseline. The exercise training did not change muscle fibre proportions in either the CKD patients or healthy controls, despite an improvement in muscular strength. It was suggested that the increase in muscular strength without a change in muscle fibre area or type is likely to be a result of increased neural adaptation only.

4.2 Inflammation and Other Biochemical Changes

Low-grade chronic inflammation, such as increased levels of serum C-reactive protein (CRP),

Table III. Summary of studies investigating the effect of resistance exercise training

Study (year)	Design	No. of patients (exercise/control)	Intervention	Duration	Outcome
Castaneda et al.[26] (2001)	RCT	14/12	Supervised for 45 min, 3×wk Chest and leg press, latissimus pull down, knee extension and knee flexion, 3 sets of 8 repetitions at 80% 1-RM	12 wk	↑ Total body potassium ↔ Thigh CT ↑ Type I muscle fibre CSA ↑ Type II muscle fibre ↑ CSA ↑ Strength ↔ BMI ↓ GFR ↔ Resting EE Protein turnover
Castaneda et al.[25] (2004)	RCT	14/12	Supervised for 45 min, 3×wk	12 wk	↓ Systemic inflammation ↑ Type I muscle fibre CSA ↑ Type II muscle fibre CSA ↔ BMI ↑ Strength
Balakrishnan et al.[34] (2010)	RCT	14/12	Supervised for 45 min, 3×wk 5 min warm-up, chest and leg press, latissimus pull down, knee extension and knee flexion, 3 sets of 8 repetitions at 80% 1-RM, 35 min, 5 min cool-down 5–8 upper and lower body stretches	12 wk	↑ mtDNA copy number ↑ Type I muscle fibre CSA ↑ Type II muscle fibre CSA ↑ Strength
Heiwe et al.[28] (2001)	Non-randomized self-selecting group	16/9 + healthy control 18/5	Supervised, 3×wk Knee extension, 3 sets of 20 repetitions at 60% 1-RM, static quadricep endurance performed by extending knee for 5 sec, 5 sets of 1 repetition, low-intensity group exercise programme followed 30 min	12 wk	↑ Strength ↑ 6MWT ↑ TUG ↔ Muscular endurance
Heiwe et al.[27] (2005)	Non-randomized self-selecting group	7/5 + healthy exercise group 6	Supervised, 3×wk Knee extension, 3 sets of 20 repetitions at 60% 1-RM, static quadricep endurance performed by extending knee for 5 sec, 5 sets of 1 repetition, low-intensity group exercise programme followed 30 mins	12 wk	↑ Strength ↔ Endurance ↔ Type I CSA ↔ Type IIA CSA ↔ Type IIB CSA ↔ Type I proportion ↔ Type IIA proportion ↔ Type IIB proportion

1-RM = one-repetition maximum; **6MWT** = six-minute walk test; **BMI** = body mass index; **CSA** = cross-sectional area; **CT** = computed tomography; **EE** = energy expenditure; **GFR** = glomerular filtration rate; **mtDNA** = mitochondrial DNA; **RCT** = randomized control trial; **TUG** = timed up and go's; ↑ indicates increase; ↔ indicates no change; ↓ indicates decrease.

pentraxin-3 and interlukin-6 (IL-6) are a common occurrence in patients with CKD, and is a predictor of survival.[58-60] Castaneda et al.[25] found that their resistance training programme significantly reduced the amount of circulating CRP compared with the control group (–1.7 vs 1.5 mg/L) and IL-6 levels (–4.2 vs 2.3 pg/mL). The authors also identified an inverse association between longitudinal change in serum IL-6 levels and skeletal muscle fibre size and muscle strength. This suggests that the anabolic stimulus of resistance exercise training may reverse the catabolic state of CKD by decreasing chronic inflammation.

This group has recently published further data from this trial.[34] They reported that the resistance exercise training also enhanced mitochondrial content in skeletal muscle. Prior to training, there was a significant negative association between a mitochondrial DNA (mtDNA) copy number, a measure of mitochondrial content and IL-6 plasma concentrations. No other associations were found with any clinical, metabolic,

dietary or muscle phenotypic variables. Resistance exercise training resulted in a time-by-group interaction with an mtDNA copy number. The resistance exercise training group's median mtDNA copy number value increased from 13 125 to 14 099, and decreased in the control group from 14 762 to 12 094. Following 12 weeks of training, the correlates of the delta of the mtDNA copy number for the group were energy intake, IGF-1 and the type I and II muscle fibre area.[34] This suggests that energy intake and IGF-1 levels are important factors when attempting to increase mitochondrial content and, in turn, skeletal muscle content in patients with CKD. This study provides evidence that in the presence of CKD, exercise can ameliorate mitochondrial loss, which has been shown to be prevalent in CKD.[61] The authors do note that there were individual variations in mtDNA copy number improvement, with a small amount of participants showing a decline similar to that observed in the control group.

4.3 Kidney Function

Castaneda et al.[26] reported that kidney function improved by a small but significant amount in the exercise group (25–26 mL/min per 1.73 m^2) compared with the control group (30–28 mL/min per 1.73 m^2) but this finding must be interpreted with care due to the small subject numbers and duration of the follow-up period.

4.4 Exercise Capacity

Heiwe et al.[28] found that following 12 weeks of supervised resistance training, the CKD patients significantly increased their walking distance by 20% and functional mobility by 13%. This improvement was similar to the changes observed in the healthy comparison group (15% and 37%, respectively). There were no changes in the CKD controls that did not exercise.

In summary, although the evidence supporting resistance exercise training in CKD patients is minimal with only five studies, the data is favourable. The results indicate that supervised resistance exercise training improves muscle function and strength, mobility and walking distance, and lowers inflammation. These studies confirm that in this catabolic state where muscle wastage is common, resistance training may prevent deleterious reduction in skeletal muscle mass, and possibly augment muscle mass and improve skeletal muscular function. This is a promising area for further study.

5. Combination Resistance and Aerobic Exercise Training

A combination of resistance and aerobic training is reported as the most effective in achieving better health and fitness outcomes.[15] Two published studies have used combination exercise training in CKD patients, which is summarized in table IV.[24,29] Neither was conducted as a randomized-controlled trial. The first was published in 1991 and the intervention required participants to exercise at 60–70% of their maximal exercise capacity, although the intensity of the strength training was not reported.[29] The participants performed interval style exercise (jumping and running) in addition to exercises for mobility, strength for large muscle groups, and balance and coordination. Cook et al.[24] conducted the second study with obese participants with CKD stage II–V who had stable or increasing weight (body mass index above 30 kg/m^2 or >28 with co-morbidities, eGFR = 44.8 ± 26 mL/min/1.73 m^2) [table IV]. In the exercise group, 19 subjects were in stages II–IV CKD, three had received a kidney transplant and the others were receiving renal replacement therapy (n = 22). Subjects were tested every 3 months. The intervention involved a combination of individualized home-based exercise and a low fat, calorie-reduced, renal specific diet plus 120 mg/day of Orlistat, which is a weight-loss agent that prevents the absorption of fat. The individualized exercise programmes included aerobic and resistance exercise with hand weights and therabands. Compliance was assessed using exercise diaries, which were reviewed at monthly clinic appointments. Exercise intensity was progressively increased on a monthly basis for the first 6 months, and was reviewed again at 9 and 12 months. Whilst this study included patients with stage V ESKD, mean group GFR suggests that patients who were reported to have completed the study (n = 12) were likely to have been CKD patients as

Table IV. Summary of studies investigating the effect of combination exercise training

Study (year)	Design	No. of patients exercise/control	Intervention	Duration	Outcome
Clyne et al.[29] (1991)	Allocated based on geographical proximity to testing centre, exercise group lived locally	10/9	Supervised for 60 min, 3 × wk 45 min 60–70% max. exercise capacity, interval 3 peaks in HR, jumping and running, with mobility, strength, balance and coordination exercises 15 min stretching	3 mo	↑ Exercise capacity ↑ Muscle strength ↔ Total Hb ↔ Blood volume ↔ GFR ↔ BP
Cook et al.[24] (2008)	Non-randomized	32/22	Unsupervised for 20–30 mins, 3 × wk Walking, sit-to-stand exercises, swimming and cycling, and resistance training with hand weights and theraband	12 mo	↑ Weight ↑ BMI ↑ WC ↔ eGFR ↑ 6MWT ↑ TUG ↑ DASI

6MWT = six minute walk test; **BMI** = body mass index; **BP** = blood pressure; **DASI** = Duke's activity status index; **eGFR** = estimated glomerular filtration rate; **GFR** = glomerular filtration rate; **Hb** = haemoglobin; **HR** = heart rate; **max.** = maximum; **TUG** = timed up and go; **WC** = waist circumference; ↑ indicates increase; ↔ indicates no change; ↓ indicates decrease.

GFR was 35.5 ± 19.6 at 12 months and, therefore, the study was included in this review.

5.1 Exercise Capacity

Exercise capacity and functional capacity was found to be improved by both studies.[24,29] In the study by Clyne et al.,[29] combination exercise training was found to significantly increase peak power from 159 at baseline to 174 W, whilst there was no significant change in the peak power of the control group. They reported that, compared with previously published healthy comparison data,[62] the exercise intervention was successful in restoring exercise capacity back to normative values in the exercise group. However, prior to the commencement of training, the participant's exercise capacity was already at 91% of the expected norm and was at 99% once the study was complete,[62] suggesting that this was a very healthy group of CKD patients. Cook et al.[24] found that a 6-minute walk time improved by 45%, sit-to-stand time by 30%, timed up and go by 37%, and Duke's activity status index by 50%. No control group follow-up data was reported, nor was any subgroup analysis performed to differentiate the states of kidney disease.

5.2 Muscular Strength

Muscular strength was investigated in one of the combination studies.[29] Clyne et al.[29] reported that muscle function significantly increased as a result of the intervention. This was assessed by measuring the knee extensors and hip flexors static and dynamic endurance. The exercise group significantly improved static muscular endurance from a median of 77 to 113 seconds, while dynamic endurance improved from 41 to 93 repetitions. The control group remained unchanged.[29]

5.3 Kidney Function

Kidney function was unchanged in the exercise training study by Clyne et al.[29] Cook et al.[24] reported that kidney function significantly decreased following the intervention from eGFR of 44.8 mL/min to 35.5 mL/min. This data, however, was reported on only 12 of the patients to undergo the intervention. The authors indicated that the observational control group's kidney function declined as well, from baseline values of 38.8 mL/min to 33.6 mL/min, although this was not statistically significant. Also, the authors did not indicate how many participants this data was based on in the control group.

5.4 Blood Pressure

The effect of combination exercise training on blood pressure was examined by Clyne et al.[29] There was no significant change in blood pressure as a result of the exercise intervention. However,

the average resting blood pressure in the exercise group was significantly higher than that of the control group, 157/96 versus 137/84 mmHg after the observation period. Clyne et al.[29] suggested that the failure to observe a change in blood pressure as a result of the intervention is likely due to the 3-month study duration being too short.

6. Pre-Exercise Screening

The studies to date have reported no serious adverse advents as a consequence of exercise training, which is a similar finding to studies conducted in the haemodialysis population.[2] Adverse events have been reported in only one study of haemodialysis patients.[63] This study included exercise-induced injuries as an outcome, and reported one muscular supraspinalus tear. One other study in the dialysis population reported that there were no dropouts as a result of the exercise intervention.[64] Mortality has not been assessed. The authors suggest that further work is required to evaluate the risks to the wider CKD population, as studies have included highly selected patient groups; however, given the low adverse events reported, we suggest that exercise is safe. In addition, work on the most appropriate screening method is also required. As such, we would recommend that prior to the initiation of supervised exercise training, patients should be thoroughly assessed by an individual who is qualified and experienced with pathophysiology, pharmacology and exercise. The screening process should involve a detailed review of available medical records and a comprehensive medical history, clinical examination and, when indicated, additional physiological testing. Using the standard American College of Sports Medicine (ACSM) risk stratification[65] may be limiting, as most patients will be identified as high risk according to their criteria. Consideration must be given when interpreting the risk level to the type of exercise individuals intend to perform, be it supervised or self-guided. Prescription of non-supervised exercise programmes should be tailored appropriately based on this assessment and used with care.

In the study by Leehey et al.,[33] 10% of recruited patients were excluded based on a positive exercise stress test result. In light of this and the known high levels of CVD in CKD patients, if patients are intending to undertake moderate-to-high level exercise, then they should undergo exercise stress testing. This would provide useful information regarding sub-clinical ischaemia and would be able to safely guide exercise prescription.

We recommend that medical clearance should be sought for patients with CKD prior to prescription of an exercise programme. However, primary healthcare providers may see fit to recommend gentle exercise, such as low-intensity walking for aerobic fitness, and stair climbing to improve muscular endurance and function to patients without undertaking detailed pre-exercise screening. This may assist in encouraging physical activity behaviour to lead to the adoption of more intense (e.g. moderate) exercise that has more evidence for health benefits. We acknowledge that further research is required to fully ascertain the risks of exercise in this population.

6.1 Exercise Training Safety Considerations

Safety considerations should be a priority before initiating an exercise programme in this population due to the high number of co-morbidities and general lack of physical condition of the participants. One study was completed in diabetics with CKD but the study numbers are small (seven participants in the exercise group).[33] It is now well established that diabetes mellitus is the leading cause of CKD. We suggest that patients who initiate exercise training should receive counselling about the effect of exercise on blood sugar control and insulin use to minimize the risk of concurrent hypoglycaemic episodes. A larger study (n = 54) by Cook et al.[24] included obese participants. This study was also completed without mention of adverse events as a consequence of the exercise training. Musculoskeletal and joint issues are likely to be a common consequence of the initiation of exercise training due to the high prevalence of co-morbidities in most CKD patients. Education about minimizing the risk of soft tissue and joint injury should be

included in the prescription of exercise to the patient. Specifically, patients should be advised that the use of non-steroidal, anti-inflammatory drugs may harm the kidneys, and therefore are not recommended. Patients should also be counselled about the effect of exercise on blood pressure control; in particular, postural hypotension.

7. Recommendations for Future Research

Further research is necessary to effectively establish the optimal exercise prescription for CKD patients. At present, exercise physiologists and other health professionals prescribe exercise based on recommendations for other chronic disease and the general population. Consideration when developing future studies should be given to the physiological and functional adaptations to exercise training, which will promote improved cardiovascular risk profiles, quality of life and will delay the onset of renal-replacement therapy. With the growing burden of cardiovascular and metabolic disease in this population, further studies should include patient groups who are more reflective of the CKD population. Furthermore, no studies have investigated the effect of exercise on endothelial and vascular dysfunction, which are thought to strongly contribute to disease progression and cardiovascular risk in patients with CKD. Whilst exercise capacity has been shown to be an important indicator of survival in other disease populations, including patients with ESKD, it is unclear if this relationship exists in CKD. Moreover, it is unknown if improvements in exercise capacity will confer improved outcome in terms of reduced morbidity and mortality. Finally, it is essential that long-term follow-up studies, which have prospectively followed patients for more than 12 months, are conducted.

8. Conclusion

The effect of exercise training in patients with CKD has been studied in ten different trials including 217 participants.[24-30,32-34] The quality of the majority of these studies is low, with most being non-randomized, non-controlled trials. The studies have excluded participants who have significant co-morbidities or pre-existing coronary heart disease, and some do not report inclusion or exclusion criteria. This limits the ability to generalize the findings of these studies. Despite combination exercise training being the preferred training modality,[66] only two studies have used this form of training.[24,29] From the evidence reviewed, we would suggest that exercise training will lead to an improvement in $\dot{V}O_{2peak}$, and this will be of therapeutic benefit to this population. It is not clear from the available evidence whether exercise training improves muscle strength, function and quality of life, or reduces falls risk, inflammation and blood pressure. However, it is recommended that, to achieve improvements in health-related outcomes, patients perform both aerobic and resistance exercise training in combination and should, ideally, include flexibility training, according to ACSM guidelines for older adults/clinical populations.[15] It is still unknown whether exercise training has an effect on kidney function, diabetes status, quality of life, development of cardiovascular disease, morbidity and mortality.

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