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Review

Exercise & Sports Science Australia (ESSA) position statement on exercise and chronic kidney disease

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ABSTRACT

Objectives: Chronic kidney disease (CKD) is prevalent, affecting 13% of adult Australians and poses increased risk for cardiovascular morbidity and mortality. This position article provides evidence-based guidelines on the role of exercise training for CKD patients and provides recommendations for prescribing and delivering exercise training.
Design: Position stand.
Methods: Synthesis of published work within the field of exercise training and chronic kidney disease.
Results: Exercise training likely to provide benefits to CKD patients, including improvements in cardio-respiratory fitness, quality of life, sympatho-adrenal activity, muscle strength and increased energy intake and possible reduction in inflammatory biomarkers. Existing studies generally report small sample sizes, brief training periods and relatively high attrition rates. Exercise training appears to be safe for CKD patients with no deaths directly related to exercise training in over 30,000 patient-hours, although strict medical exclusion criteria in previous studies resulted in 25% of patients being excluded potentially impacting the generalisability of the findings.
Conclusions: Aerobic exercise at an intensity of >60% of maximum capacity is recommended to improve cardio-respiratory fitness. Few data are available on resistance training and it is unclear whether this form of training retards catabolic/inflammatory processes typical of CKD. However, it should be considered important due to its proven beneficial effects on bone density and muscle mass. Due to the high prevalence and incidence of co-morbidities in CKD patients, exercise training programs should be prescribed and delivered by individuals with appropriate qualifications and experience to recognise and accommodate co-morbidities and associated complications.

1. Background

This Position Statement provides evidence-based guidelines for exercise training in patients with chronic kidney disease (CKD). CKD is a complex disease that impacts on multiple organs and systems. CKD is a major public health problem associated with high morbidity, mortality and costs to the community.[1] Kidney Disease Improving Global Outcome (KDIGO) defines CKD as (a) kidney damage $\geq$ three months with structural or functional kidney abnormalities with or without decreased glomerular filtration rate (GFR), or (b) GFR < 60 ml/min/1.73 m^2 present > three months with or without kidney damage.[2] A recent update now also takes into account serum albumin levels when assigning risk of serious events according to eGFR status (see Supplementary Table).[2] Prognosis for people with CKD is poor and reduced GFR is an independent predictor of death, cardiovascular events, and hospitalization.[3,4] CKD has many causes and is associated with metabolic conditions such as obesity, type 2 diabetes and cardiovascular diseases.[5,6] CKD classification has 5 stages according to severity, diagnosis, treatment and prognosis, with stage 5 usually described as end stage kidney disease (ESKD).[7] CKD is estimated to affect 13.4% of Australian adults (aged 25 years or older), with more than half of these in stage 3–5. Moreover, 30% of Australian adults aged over 65 years have CKD stage 3–5.[8]

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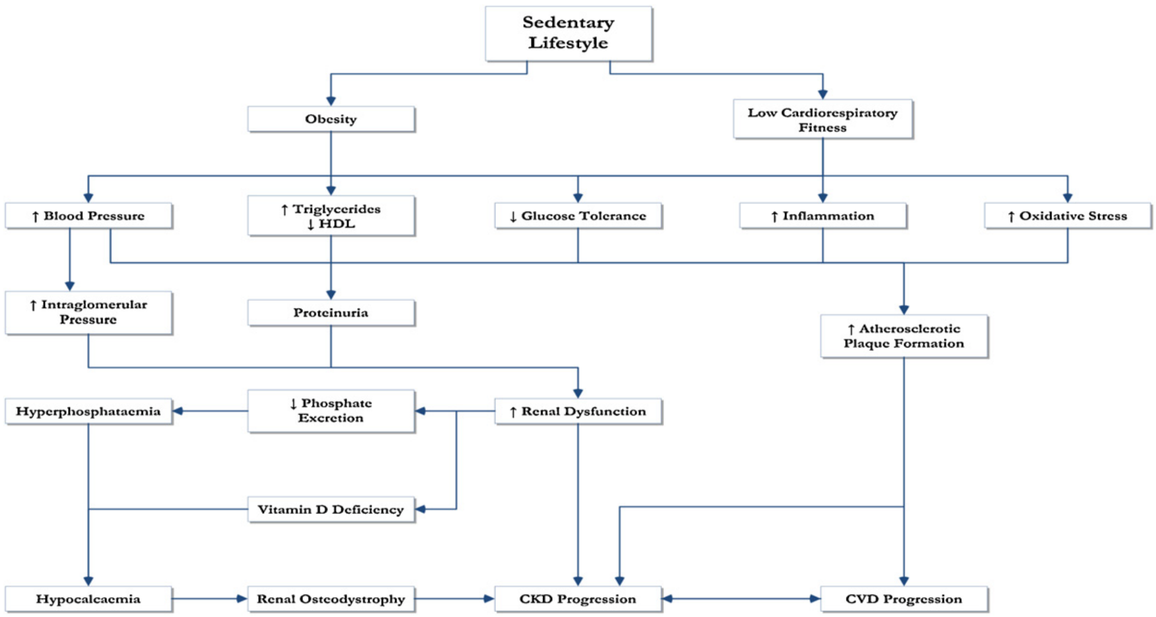

Fig. 1. Lifestyle factors influencing CKD development and progression.

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2. Evidence for benefits of exercise in CKD

As with related chronic diseases, physical inactivity is a major CKD risk factor[9] and a predictor of cardiovascular mortality.[10] In ESKD patients, a peak VO_2 below 17.5 ml kg^{-1} min^{-1} is associated with increased mortality.[11] However, the relationship between exercise capacity and mortality has not been reported in CKD stages 1–4. Nevertheless, a negative relationship between kidney function, anaemia and exercise capacity, measured as peak VO_2 has been described in CKD patients with stages 4 and 5.[12] Fig. 1 illustrates the connection between sedentary lifestyle and CKD.

The importance of modifying lifestyle for medical management of CKD is evident in many exercise training studies.[13] Regular exercisers have better quality of life, physical functioning, sleep quality scores, report fewer physical activity limitations and are less affected by pain or poor appetite. In models adjusted for demographics, co-morbidities and socio-economic indicators, mortality risk was 27% lower among regular exercisers.[14] Several exercise training reviews and meta-analyses for CKD have been published[13,15–19] the consensus is that regular exercise is beneficial for patients in CKD stages 1–4 and stage 5 (ESKD), with the majority of evidence being for ESKD. Furthemore, a recent extensive Cochrane review examined the aerobic and resistance training effects on functional and clinical measures related to CKD.[13] The review highlights that:

- Both low and high intensity aerobic exercise resulted in increased aerobic capacity, but, high intensity exercise produced larger increases.
- Resistance training alone had no significant effect on aerobic capacity.
- Supervised exercise programs are associated with greater benefits than unsupervised exercise.
- Muscle strength is likely to increase with both aerobic and resistance type exercises, but more with resistance training. Muscle endurance (sit-to-stand in 60 s) is not likely to increase with exercise (both resistance and aerobic).
- Exercise training had no significant effects on the capacity to perform activities of daily living.
- Exercise training improves central haemodynamics (reduced blood pressure and resting heart rate). Most benefits were observed in those who performed high intensity exercise.
- The effects of exercise training on serum albumin are unclear.
- Exercise training significantly increased energy intake following exercise training.
- Exercise training did not significantly reduce fat mass or waist circumference.
- Exercise training did not improve lipid profile or fasting glucose levels.
- Exercise training did not improve left ventricular structure or function.
- Dropout rate varied widely amongst studies, ranging from 0 to 70%.
- In most studies the compliance was 70% or greater.

Hence, exercise training can improve aerobic capacity, muscle strength and some psychological measures in CKD patients. Exercise may improve kidney function which is measured by estimated glomerular filtration rate (eGFR). Overall, the optimal "dose" of exercise that will lead to improve clinical measures in this population is unclear. Differences between individual studies illustrate the difficulties translating existing data into practice (see Table 1). About two thirds of published trials are <6 months duration and thus may be sub-optimal for achieving changes in desired outcomes.[20] All but two studies in Table 1 present data in haemodialysis patients.

Only four studies utilised isolated resistance training, so the specific effects of resistance training in CKD patients are poorly understood. Although a greater number of aerobic and combined training studies exist, study duration, intensity, frequency, exercise modality, venue (home versus outpatient versus inter-dialytic) are so varied it is difficult to determine optimal exercise prescription. Nevertheless, the limited existing evidence on exercise intensity suggests greater benefit from moderate or higher intensity rather than low intensity exercise, for a range of markers related to physical function and cardiovascular health.[13] Many ESKD patients exhibit inflammation, muscle wasting and poor

Table 1
Published randomized, controlled studies of exercise training in CKD patients versus sedentary control.

Aerobic training studies	*N* (ExT)	CKD stage	Training	Study duration, delivery method	Data extracted
Chang[47]	71 (36)	HD	AT	2 Months, ID Cycling	↓Fatigue
Cheema[21]	49 (24)	HD	RT	3 Months, Strength ID	↑Strength
Cheema[25]	49 (24)	HD	RT	3 Months RT, ID	Cytokines–no change
Chen J.[48]	50 (25)	HD	RT	4 Months ID	↑Strength, ↑↓ADL
Chen P.Y.[49]	94 (45)	CKD 2–4	AT	3 Months, HD	Biochemistry, no change
Daniilidis[50]	34 (20)	HD	AT	3 Months, ID	↓IL-6
Deligiannis[29]	60 (30)	HD	CT	6 Months, ND	↑Peak VO_2, ↑HRV
Deligiannis[30]	16 (12)	HD	CT	6 Months, ND	↑Peak VO_2, ↑LVEF %
Dong[23]	32 (15)	HD	RT	6 Months Diet plus ExT vs Diet	↓Body Mass and ↑Strength
Frey[26]	11 (5)	HD	AT	2 Months, ID	↑Energy Intake
Johansen[22]	79 (40)	HD	RT	3 Months, ID	↑Muscle size, ↑strength, ↑SF-36[†]
Koh[37]	70 (43)	HD	AT	6 Months, Cycling, ID	↑SF-36
Koufaki[27]	18 (15)	HD	AT	3 Months, Cycling, ID	↑Peak VO_2, ↑Energy Intake
Kouidi[31]	31 (20)	HD	AT	6 Months, various aerobic, ND	↑Peak VO_2, ↓Depression
Kouidi[51]	48 (24)	HD	CT[‡]	4 Years, Aerobic & Strength ND	Home v outpatient ↑Peak VO_2
Kouidi[32]	59 (30)	HD	CT	10 Months, Cycling ID	↑Peak VO_2
Leehey[36]	11 (7)	CKD 2–4	AT	6 Months Home	eGFR, HbA1 C, lipids, calories, body mass all no change
Moros-Garcia[33]	34 (23)	HD	AT	4 Months, Cycling ND	↑Peak VO_2
Oliveros[52]	15 (9)	HD	CT	4 Months ND	↑Strength, ↑QOL, Cytokines
Painter[34]	24 (10)	HD	AT	5 Months, Cycling, ID	↑Peak VO_2
Parsons[53]	13 (6)	HD	AT	2 Months Cycling, ID	↑SF-36
Reboredo[38]	22 (11)	HD	AT	3 Months, ID	↑HRV and ↑LVEF
Van Vilsteren[35]	96 (53)	HD	CT	3 Months, Cycling/Strength ID	↑Peak VO_2, ↑SF-36
Wilund[54]	17 (8)	HD	AT	4 Months, ID CYCLING	↓Oxidative stress and body fat

Abbreviations: AT, aerobic training; RT, resistance training; CT, combined training; ID, intra-dialytic training; ND, non-dialysis training; HD, haemodialysis; HRV, heart rate variability; LVEF, left ventricular ejection fraction.
† Some patients also received nandralone.
‡ Compared home versus outpatient exercise training.

nutrition. Several resistance training studies[21–25] have produced improvements in muscle strength, although concomitant reductions in pro-inflammatory cytokine expression are ambiguous.[24,25] Elevated cytokine expression and poor nutrition are associated with catabolism and CKD disease progression. Two studies[26,27] employed dietary recall to estimate daily energy intake, which increased in exercising CKD participants by approximately 5% from baseline. However, recent work has failed to show additional benefit of exercise training over oral nutritional supplementation in CKD patients.[23]

Published aggregate data exists on approximately 1000 study participants where, generally, exercise and control groups are extremely well matched at baseline for age, gender, erythropoietin use and peak VO_2, time receiving haemodialysis and co-morbid disease prevalence. A recent meta-analysis reported study designs were generally poor with median Jadad score of 2.[20,28] Only about a third of published studies provide complete CONSORT statements, and in many data on eligibility, withdrawal and completion were deficient. Most studies failed to conduct intention to treat analyses, which could quantify impact of study withdrawals. Available data suggests about 25% of patients approached are ineligible due to various medical exclusion criteria, a further 28% refused to participate, so exercise may be underutilised in CKD. Exercise training appears safe with no deaths reported directly due to exercise training in over 30,000 patients-hours.[20] Published studies show no evidence of publication bias, with low to moderate heterogeneity.

Nine studies[27,29–36] measured peak VO_2 in a total of nearly 400 patients. Mean baseline ± standard deviation of peak VO_2 for both exercise and control participants was $21.0 \pm 5.0\,\mathrm{ml\,kg^{-1}\,min^{-1}}$. Mean age was 51 years and the age-predicted peak VO_2 for a 51 year old, sedentary, non-obese adult is $28.8\,\mathrm{ml\,kg^{-1}\,min^{-1}}$ indicating CKD patients have a peak VO_2 about 70% of age-predicted value.[20] Exercise training may be beneficial as low peak VO_2 is associated with increased mortality risk.[11] Data from studies of combined aerobic and strength training convey a weighted mean 29 ± 11% improvement in peak VO_2, similar to the 23 ± 10% from isolated aerobic studies. Peak VO_2 data from resistance training studies is unavailable. Intra-dialytic training (ID) produced weighted mean change in peak VO_2 of 18 ± 8% while training on non-dialysis days showed 34 ± 6% improvement in peak VO_2 ($p = 0.03$).[20]

Improvements in physical fitness are related to improved quality of life and decreased depression in CKD patients.[17] Assessments using the short-form-36 (SF-36) general health questionnaire[37] and the Beck Depression Inventory[31] have been conducted in CKD patients before and after exercise training interventions, although limited existing data cannot demonstrate any significant change in either measure.

Two studies showed significant improvements in heart rate variability[30,32] with 6 months exercise training, although a shorter 3 month study reported no change.[38] The former studies suggest long-term (6 months) exercise training has a favourable sympatho-adrenal effect in CKD patients. Cardiovascular disease is a common cause of death in CKD patients[3,39] therefore exercise-induced improvements in sympatho-adrenal function may reduce cardiovascular mortality risk.

3. Exercise prescription-recommendations

Before prescribing exercise each CKD patient should undergo a thorough medical review. One should first take a full medical history and clinical examination including cardiovascular assessment including blood pressure. In addition, a detailed medication usage history and review of recent biochemistry and haematology will inform prescription to potentially reduce adverse clinical, biochemical, haematological and medication-exercise interactions. Subsequently baseline cardiopulmonary exercise testing with 12-lead ECG is recommended to; (i) establish those unsuitable for exercise or those who first require medical stabilization, and (ii) provide data for an individually tailored exercise prescription.

In line with the 2011 Cochrane review on exercise in adults with CKD,[13] current scientific evidence supports exercising regularly for >30 min/session three times/week to improve physical fitness, cardiovascular dimensions and health related quality of life.[13] Similarly the recent Kidney Disease Improving Global Outcomes document recommends that people with CKD be encouraged to

Table 2
Guidelines for aerobic and resistance exercise prescriptions in ESKD patients undertaking (non-nocturnal) haemodialysis.

	ESKD inter-dialysis	ESKD intra-dialysis	Non-dialysis
Aerobic			
Session duration	Build up to 30–45 min	Build up to 30–45 min	Build up to 30–45 min
Session timing	Non-dialysis days	During first 2 h of dialysis	According to patient needs
Intensity (% max. HR) or RPE (6–20 point scale)	55–70% max HR, RPE 11–13 Moderate (preferably >60% max HR)	55–70% max HR, RPE 11–13 moderate (preferably >60% max HR)	55–90% max HR, RPE 11–16 moderate to vigorous (60–90% max HR)
Weekly duration	Up to 180 min	Up to 180 min	Up to 180 min
Modality	Walking/cycling/other	Cycling while seated using arm or leg ergometer	Walking/jogging/cycling/other
Resistance*			
Initial frequency per week	Two non-consecutive days	Two non-consecutive days	Two non-consecutive days
Different muscle groups/exercises	8–12 exercises prioritizing major muscle groups	Up to 12, as many as practical in dialysis session	8–12 exercises (major muscles)
Initial volume	1 set to fatigue, 12–15 reps or 60–70% Repetition Maximum	1 set to fatigue, 12–15 reps or 60–70% Repetition Maximum	1 set to fatigue, 10–15 reps or 60–70% repetition maximum
Timing	Non-dialysis days	Before or during dialysis	As comfortable
Modality	Weight-bearing activity, thera-bands, weight cuffs, light dumbbells, weight machines	Weight-bearing activity, thera-bands, weight cuffs, light dumbbells – as practical in dialysis	Weight-bearing activity, thera-bands, machine and free weights.
Indications	Cachexia, poor bone density, low BMI or lean body mass	Cachexia, poor bone density, low BMI or lean body mass	Cachexia, poor bone density, low BMI or lean body mass
Flexibility	5–7 days per week for a duration of about 10 min per session. Where possible combine with aerobic or resistance exercise session and include balance exercises for those at risk of falls.		

*Both resistance and aerobic activity should be completed (although not necessarily in the same session); recommendations assume no contraindications to exercise.
Abbreviations: Reps, repetitions; BMI, body mass index; RPE, rate of perceived exertion; HR, heart rate.

undertake physical activity compatible with cardiovascular health and tolerance (aiming for at least 30 min 5 times per week).[2] It is suggested that exercise training include aerobic, resistance and flexibility activities and that clinical judgement should determine the relative contributions of each. Individual recommendations by stage and/or treatment modality of kidney disease do not presently exist, however, the following suggestions may guide exercise prescription for the CKD/ESKD patient.

Patients with peak VO_2 values (<17.5 ml kg^{-1} min^{-1}) may derive the largest survival benefit from exercise training.[11] Training should be performed in the presence of qualified clinical staff. Cachectic patients exhibiting poor bone density or low body mass index (<20 kg m^{-2}) should commence resistance exercise as soon as possible. Resistance training during dialysis is limited by sitting, we have therefore taken a practical, evidence based approach to aerobic and resistance exercise prescription, see Table 2. Based upon a meta-analysis,[18] 5 studies with statistically significant improvements in peak VO_2 had the following attributes; all were >6 months duration, all but one used >240 min weekly (90 min or more exercise session durations) and exercise intensities were 60–70% of predicted heart rate maximum. Based partially on previous work[40] we also recommend resistance exercise on twice weekly on non-consecutive days, details of sets and repetitions can be seen in a Table 2.

4. Special considerations

While studies reporting exercise benefits have not reported any safety issues arising from exercise interventions,[13] identification and appropriate management of any co-morbidities is essential for safe exercise delivery. In their excellent review, Johansen and Painter state that exercise appears to be safe in the CKD patient population if begun at moderate intensity and increased gradually.[41] Moreover, the evidence suggests that the risk of remaining inactive is higher.[41] Exercise should be tailored to accommodate additional co-morbidities as well as CKD. Recommendations for several common co-morbidities including hypertension, type II diabetes and cardio-myopathies have already been published.[42,43] Those with diabetic nephropathy[36] and cardio-renal syndrome[44] require closest supervision.

In ESKD patients several additional considerations must be taken into account. CKD patients often exhibit significant physical deconditioning and co-morbidities. Larger adaptations may occur when exercise is completed on non-dialysis days, although intradialytic exercise training may produce better adherence rates, but exercise should be within the first 2 h of dialysis initiation.[18] Peritoneal dialysis patients perform exercise more comfortably with abdominal cavities emptied of dialysis fluid, reducing diaphragmatic pressure, breathlessness and, in some types of peritoneal dialysis, chest discomfort. Haemodialysis patients should avoid upper limb activity with temporary or healing arterio-venous fistulas. Fistula arms should not be used for functional assessment, thus avoiding false blood pressure testing and using the fistula arm for blood pressure measurement is contraindicated. A role exists for both intra and interdialytic exercise with exercise adherence tending to be greater in the former, due to increased supervision. Interdialytic exercise also results in improved outcomes when adherence is maintained.[45] We recommend patients perform exercise during the first 2 h of haemodialysis, when blood pressure control is best.

Regular blood pressure and electrocardiogram (ECG) monitoring during exercise training is recommended, especially when ECG is affected by electrolyte abnormalities (e.g. hypo/hyperkalaemia). If this occurs a nephrologist consultation is recommended.

5. Contraindications to exercise

In addition to the American College of Cardiology Foundation/American Heart Association contraindications to exercise[46] the following are specific to CKD patients:

- Electrolyte abnormalities – especially hypo/hyperkalaemia
- Recent changes to the ECG, especially symptomatic tachyarrhythmias or brady-arrhythmias
- Excess inter-dialytic weight gain >4 kg since last dialysis or exercise session
- Unstable on dialysis treatment and changing (titrating) medication regime
- Pulmonary congestion
- Peripheral oedema

6. Gaps in the literature

There exists the need for large, well-designed randomized, controlled trials with reliable outcome measures that will provide exercise dose (intensity, frequency, duration and modality) for people with CKD, including ESKD. It is also important to understand whether aerobic or resistance exercise or a combination of both will provide optimal benefits to ESKD patients with cachexia. Only four resistance training studies in CKD have been conducted and there exists obvious need for further trials examining the possible anti-catabolic/inflammatory effects of this intervention as this has implications for other co-morbid diseases.

7. Summary

Exercise training appears safe and proffers a range of benefits to CKD patients, including improvements in cardio-respiratory fitness, sympathy-adrenal activity, heart rate variability, quality of life and energy intake. It remains unclear whether some outcomes such as pro-inflammatory cytokine expression are improved.[13,24] The optimal exercise prescription also remains unclear.

8. Practical implications

Regular exercise training should be a component of the management of patients with CKD to reduce the risk of cardiovascular complications.

Exercise programs for patients with CKD should be designed and delivered by appropriately trained and qualified personnel and take into account individual patient needs.

Further research is required to determine the optimal dose and modality of exercise for CKD patients in general and pre-dialysis patients.

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