Effects of Exercise and Lifestyle Intervention on Cardiovascular Function in CKD

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Summary

Background and objectives CKD is associated with poor cardiorespiratory fitness (CRF). This predefined substudy determined the effect of exercise training and lifestyle intervention on CRF and explored the effect on cardiovascular risk factors and cardiac and vascular function.

Design, setting, participants, & measurements Between February 2008 and March 2010, 90 patients with stage 3–4 CKD were screened with an exercise stress echocardiogram before enrollment. Patients (n=83) were randomized to standard care (control) or lifestyle intervention. The lifestyle intervention included multidisciplinary care (CKD clinic), a lifestyle program, and aerobic and resistance exercise training for 12 months. CRF (peak $\dot{V}O_2$), left ventricular function, arterial stiffness, anthropometric, and biochemical data were collected at baseline and 12 months.

Results Ten percent of randomized patients had subclinical myocardial ischemia at screening and completed the study without incident. There was no baseline difference among 72 patients who completed follow-up (36 in the lifestyle intervention group and 36 in the control group). The intervention increased peak $\dot{V}O_2$ (2.8±0.7 ml/kg per minute versus −0.3±0.9 ml/kg per minute; P=0.004). There was small weight loss (−1.8±4.2 kg versus 0.7±3.7 kg; P=0.02) but no change in BP or lipids. Diastolic function improved (increased e′ of 0.75±1.16 cm/s versus −0.47±1.0 cm/s; P=0.001) but systolic function was well preserved and did not change. The change in arterial elastance was attenuated (0.11±0.76 mmHg/ml versus 0.76±0.96 mmHg/ml; P=0.01). Δ peak $\dot{V}O_2$ was associated with group allocation and improved body composition.

Conclusions Exercise training and lifestyle intervention in patients with CKD produces improvements in CRF, body composition, and diastolic function.

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Introduction

Patients with CKD have increased prevalence of cardiovascular disease (CVD), which is the leading cause of mortality and morbidity in this population (1). Obesity, type 2 diabetes, and hypertension are common, and contribute to the progression of kidney dysfunction and cardiovascular risk. Conventional treatment strategies are only partially effective in improving outcomes and are frequently underutilized (2). Alternate strategies to address these risks are required. CKD patients have reduced cardiorespiratory fitness (CRF) compared with the general population (3), and those CKD patients who are inactive (4) have an increased risk of mortality. Exercise can be effective in management of cardiovascular risk factors (5,6); however, there are few long-term exercise studies in the CKD population (7).

Abnormal left ventricular (LV) structure (LV hypertrophy and dilation) and impaired diastolic and systolic function are strongly associated with morbidity and mortality in ESRD (8). Patients with early CKD have relatively preserved systolic function but demonstrate increased risk of diastolic dysfunction (9). Newer echocardiographic techniques such as tissue Doppler imaging provide information about myocardial tissue velocities associated with relaxation (e′) and contraction (s′) of the LV. Two-dimensional speckle tracking imaging allows the determination of myocardial deformation or change in length of the myocardial fiber over time, referred to as global strain and strain rate. Global strain has been shown to be a powerful independent predictor of mortality in patients with preserved systolic function (10), and is reduced in patients with CKD.

There is increasing recognition of the importance of the bidirectional interaction between the arterial system and the heart ("ventricular-vascular coupling"). This matching ensures that cardiac performance is optimized during physiologic stress. Effective arterial elastance (E_A) measures the net arterial load imposed on the LV. LV end systolic elastance (E_{LV}) is a load-independent measure of LV performance. At rest, E_A/E_{LV} is maintained within a narrow range in healthy individuals, allowing the optimal transfer of blood from the LV to the periphery. Patients with CKD are at risk of increased vascular stiffness *via*

multiple mechanisms (hypertension, diabetes, vascular calcification). Therefore, resting LV filling pressure is increased and LV contractility is enhanced in CKD in order to maintain E_A/E_{LV} and cardiac performance (11). Unfit individuals have less favorable cardiac filling profiles at rest than active participants (12), and exercise training can elicit positive changes in diastolic (13) and vascular function (14) in patients with existing CVD.

The aim of this study was to investigate the effect of exercise training and lifestyle intervention on CRF (change in peak $\dot{V}O_2$ at 12 months), secondary aims were to assess the effect on cardiovascular risk factors, cardiac function, arterial stiffness, and ventricular-vascular interaction in CKD.

Materials and Methods

Patient Selection

Detailed methods are available in the Supplemental Material. This study was a prespecified substudy of an ongoing open-label randomized controlled trial (LANDMARK III), which is a 3-year study comparing the effect of a nurse practitioner–led model of care with standard nephrologic care on cardiovascular risk factors. The study received approval from the Princess Alexandra Human Research Ethics Committee (HREC 2007/190) and University of Queensland Medical Research Ethics Committee (MREC 2008000184), and was registered at www.anzctr.org.au (Registration Number ANZCTR 12608000337370). Patients were eligible for inclusion if they were aged 18–75 years, had moderate CKD (estimated GFR [eGFR] 25–60 ml/min per 1.73 m^2), and had one or more uncontrolled cardiovascular risk factors such as BP exceeding target, overweight (body mass index [BMI] >25 kg/m^2), poor diabetic control (hemoglobin A1c >7%), or lipids exceeding target. Exclusion criteria were as follows: intervention for or symptomatic coronary artery disease (within 3 months), current heart failure (New York Heart Association class III and IV) or significant valvular heart disease, pregnant or planning to become pregnant, and life expectancy or anticipated time to dialysis or transplant <6 months. Participants provided written informed consent and the study complied with the Declaration of Helsinki.

Outcomes

The primary outcome of this substudy was change in CRF (as measured by peak $\dot{V}O_2$) at 12 months. Secondary outcomes were change in cardiovascular risk factors (weight, BP, lipids), cardiac function (measured by systolic [s′] and diastolic [e′] tissue velocity), arterial stiffness (augmentation index and aortic pulse wave velocity), and ventricular-vascular coupling (arterial and ventricular elastance).

Baseline Assessment and Random Assignment

Patients were screened for inducible myocardial ischemia by exercise stress echocardiography (ESE). Patients with an abnormal ESE were reviewed by a cardiologist and randomized if deemed safe to participate in a supervised exercise program. Patients were assigned to either the lifestyle intervention group or to the usual care control group in a 1:1 ratio using a computer random assignment program. Groups were stratified by renal function (eGFR high [>44] or low [≤44] ml/min per 1.73 m^2), sex, and diabetes status.

Control Group

The control group received standard nephrologic care, which included review by a nephrologist, recommended lifestyle modification but no specific information or education, and referral to an allied health professional on an *ad hoc* basis.

Exercise Training and Lifestyle Intervention

In addition to usual care, cardiovascular risk factor management was provided by a multidisciplinary clinic (including a CKD nurse practitioner, dietitian, exercise physiologist, diabetic educator, psychologist, and social worker) and targeted risk factors to national guidelines (15,16).

The exercise training component involved 150 minutes of moderate intensity exercise per week , with 8 weeks of training supervised by an accredited clinical exercise physiologist. Patients attended gym sessions two to three times per week. The sessions included a warm-up, 20–30 minutes of aerobic activity using a treadmill, stationary bike, or rowing ergometer, and whole-body resistance training with machines and free weights. On completion of the gym-based training, patients began a home-based program and were provided a booklet depicting resistance exercise using Thera-Bands and a Swiss ball. Regular contact was maintained *via* telephone and Email. Participants were questioned on their ability to maintain the prescribed exercise; if they identified difficulty, they were encouraged to attend gym-based refresher visits. Patients performed exercise at a moderate intensity, with perceived exertion of 11–13 on the 20-point Borg scale (17), and progression was tailored individually.

Lifestyle intervention involved 4 weeks of group behavior and lifestyle modification facilitated by a dietitian and psychologist. The program focused on sustainable diet and behavior change to assist with weight loss. The dietitian therapy complied with the Evidence-Based Practice Guidelines for Nutritional Management of CKD for patients with eGFR between 25 and 60 ml/min per 1.73 m^2 (18).

Outcome Measures

All measures were obtained before randomization and after 12 months of intervention.

Biochemical Analyses. After an overnight fast, patients provided blood samples for biochemical analysis. Kidney function was determined as the eGFR using the Modified Diet in Renal Disease formula based on the isotope dilution mass spectrometry standardized creatinine assay ($MDRD_{175}$) (19).

Maximal Exercise Capacity. CRF was assessed as peak $\dot{V}O_2$. Testing was performed according to American College of Sports Medicine guidelines for exercise testing (20). CRF was derived from breath-by-breath indirect calorimetry (Vmax29c; SensorMedics, Yorba Linda, CA) and recorded as the peak 20-second average $\dot{V}O_2$ during the final minute of exercise.

Echocardiography. Conventional two-dimensional echocardiography and pulse wave tissue Doppler imaging was performed at rest using standard equipment (Vivid 7;

General Electric Medical Systems, Milwaukee, WI). All echocardiographic parameters were measured offline in batches by an observer blinded to treatment allocation and previous results.

Evaluation of Diastolic and Systolic Function. Systolic dysfunction was identified on the basis of an ejection fraction <50%. Diastolic dysfunction was categorized as normal diastolic function, delayed relaxation (21), pseudo normal (22,23), or restrictive diastolic filling (24).

Arterial Compliance. Arterial waveforms were acquired as previously published (25) using commercial software (SphygmoCor 8.1; AtCor Medical, Sydney, Australia). Central arterial stiffness was estimated in duplicate by aortic pulse wave velocity (PWV). PWV was acquired with electrocardiography-gated sequential tonometry at the carotid and femoral sites.

Ventricular-Vascular Interaction. Measures were derived noninvasively using a combination of echocardiography for end systolic volume (ESV) and tonometry for end systolic pressure (ESP). Arterial elastance (E_A) was calculated as the ratio of ESP and stroke volume (SV) E_A= (ESP/SV), and end systolic elastance (E_{LV}) was calculated E_{LV} = (ESP/ESV – V_0), where V_0 is the *x*-axis intercept of the pressure-volume relationship (26). The value of V_0 is considered to be negligible compared with ESV and is therefore approximated as zero (26). These methods have been validated against invasive measures of ventricular pressure-volume loops (27,28).

Dietary Assessment. Dietary assessment was conducted using three-day diet records of a subset of participants. Dietary intake data were analyzed using FoodWorks version 7 using NUTTAB 2010 database (Xyris Software, Australia) for total energy (kcal), macronutrient, and dietary fiber intake.

Power Analyses

Baseline peak $\dot{V}O_2$ was assumed to be 22.0±6.0 ml/kg per minute, and a 20% increase (effect size of 0.73) in the intervention group compared with the control participants would be clinically significant. Therefore, we required 41 participants in each group to have 90% power to detect a difference between groups (α=0.05); however, to account for drop out, we planned to recruit 90 patients.

Statistical Analyses

Analysis was performed on available data. Data were checked for normality using the Kolmogorov–Smirnov test. Results are expressed as mean ± SD, median (interquartile range), or *n* (%) for categorical data. Baseline characteristics and change scores were compared between groups using independent *t* tests and chi-squared tests for

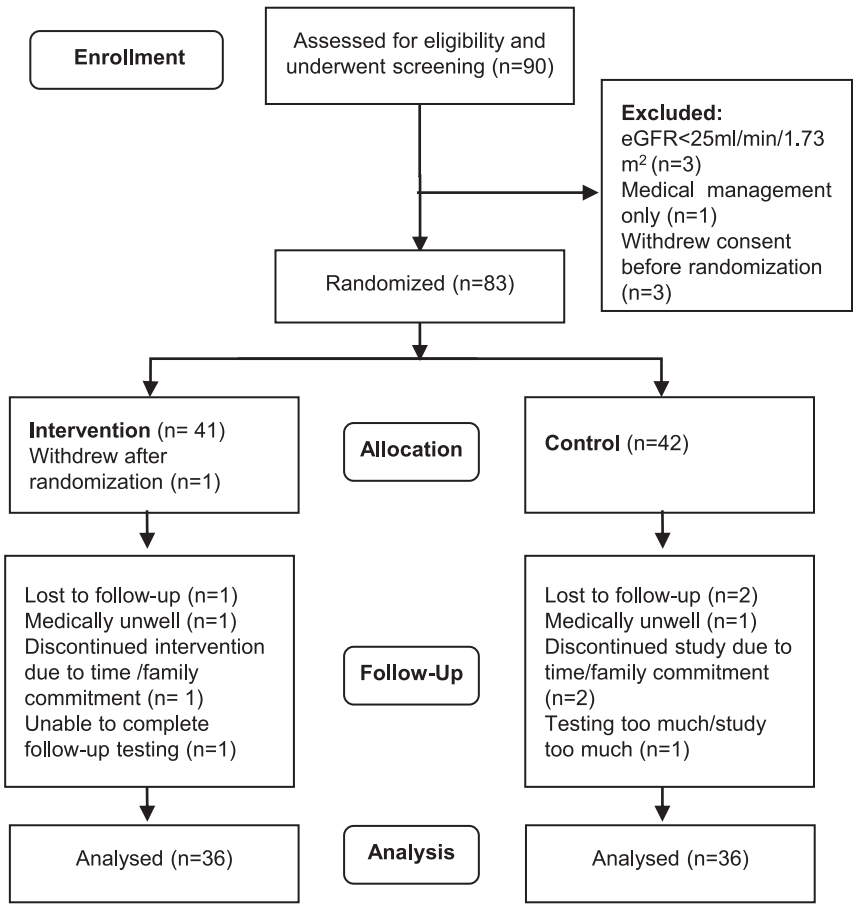

Figure 1. | **Consolidated Standards of Reporting Trials diagram**.

categorical variables. Pearson and Spearman correlations were performed between change in main outcome measure and other secondary measures. Data were analyzed using standard commercially available statistical software (SPSS version 18; PASW, Chicago, IL). Statistical significance was $P \leq 0.05$.

Results

Patient Characteristics

Ninety patients were screened between February 2008 and March 2010. Twelve percent (n=11) of patients were identified as having abnormal wall motion suggestive of subclinical ischemia on ESE and were reviewed by a cardiologist before randomization. Nine patients were cleared, enrolled in the study, and completed the study without incident. In total, seven screened patients were not randomized, three did not meet inclusion criteria due to kidney function outside of range, one had significant inducible ischemia on baseline testing (suitable for medical management only and the patient's cardiologist declined the patient's participation), and three patients withdrew consent before randomization (including one patient requiring bypass surgery who no longer wished to participate), meaning that 83 patients were randomized. Of the 83 patients randomized, follow-up testing was completed in 72 patients (Figure 1).

The baseline characteristics of this patient group are summarized in Table 1 and there were no significant group differences at baseline. Men comprised the majority of the patient group and the prevalence of type 2 diabetes was 42%. Diastolic dysfunction was evident in 61% of patients, whereas 8% of patients had evidence of systolic heart failure (Table 1). The lifestyle intervention group attended 70% of the supervised gym-based training and five additional visits (range, 0–10) during the home-based maintenance phase.

Responses to Intervention

Exercise Capacity. At baseline, peak $\dot{V}O_2$ (24.7±8.4 ml/kg per minute in the lifestyle intervention group versus 23.6±6.2 ml/kg per minute in the control group) was similar between groups. Compared with normative values, 47% of the control group met their age-predicted exercise capacity and 41% in the lifestyle intervention group (Figure 2). The intervention was effective in improving peak $\dot{V}O_2$ as evident by an 11% increase in the lifestyle intervention group and 1% decrease in the control (Figure 2). Furthermore, at 12 months, an additional 10 patients in the lifestyle intervention group met their age-predicted exercise capacity, which was significantly greater than controls (P=0.01). The hemodynamic response to exercise was similar between groups at baseline. Maximal systolic BP decreased in both groups at 12 months; however, the change was significantly greater in the control group (Table 2).

Cardiovascular Risk Factors. Table 3 outlines changes in body habitus (weight, BMI, waist circumference) in

Table 1. Baseline demographics, causes of kidney disease, myocardial status, and medication usage of patients randomized to lifestyle intervention or control groups that completed a 12-month follow-up visit

	Lifestyle Intervention Group (n=36)	Control Group (n=36)	Lost to Follow-Up (n=11)
Women	12 (33)	15 (42)	6 (45)
Age (yr)	60.2±9.7	62.0±8.4	54.4±10.1
eGFR (ml/min per 1.73 m^2)	38.4±8.8	39.4±8.9	42.0±8.7
Cause of CKD			
Diabetes	9 (25)	11 (30)	4 (36)
Renovascular	6 (17)	5 (14)	—
GN	10 (28)	11 (30)	3 (27)
APKD	—	3 (8)	1 (9)
Other	11 (30)	6 (17)	3 (27)
Risk factors			
Type 2 diabetes	15 (42)	15 (42)	3 (27)
Current smoker	5 (14)	3 (8)	3 (27)
Previous myocardial infarction	5 (14)	7 (24)	—
Systolic dysfunction	4 (11)	2 (5)	—
Diastolic dysfunction	19 (56)	25 (78)	3 (27)
Medications			
ACEi	17 (47)	19 (54)	6 (55)
ARB	22 (61)	20 (56)	5 (45)
β blocker	14 (39)	15 (42)	—
Calcium blocker	10 (28)	17 (47)	3 (27)
Platelet inhibitor	19 (53)	14 (39)	1 (9)
Statin	23 (64)	24 (67)	5 (45)
Insulin	9 (25)	10 (28)	1 (9)

Values are mean ± SD for normally distributed values, or n (%) for categorical variables. There were no significant differences (P>0.05 for all) between groups at baseline. eGFR, estimated GFR; APKD, autosomal dominant polycystic kidney disease; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

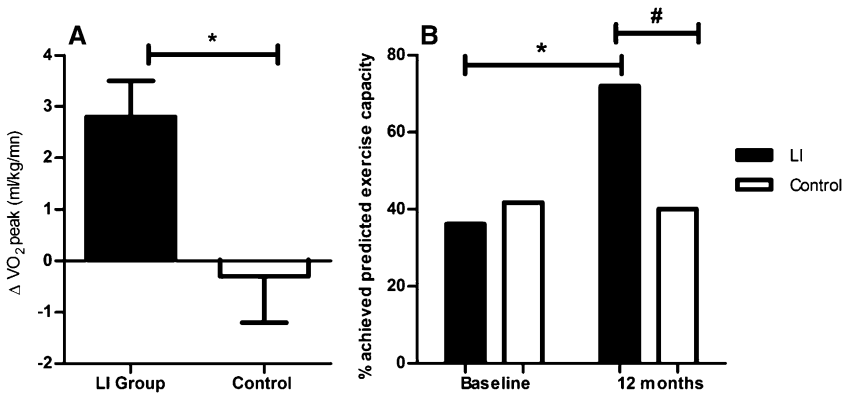

Figure 2. | Lifestyle intervention was associated with improved cardiorespiratory fitness. (A) Change in cardiorespiratory fitness after 12 months of intervention. Values are Δ mean ± SD and a significant difference between the lifestyle intervention and control groups. *P=0.01. (B) Percentage of patients to achieve age-predicted exercise capacity at baseline and 12 months. Values are the percentage of participants to achieve individual age-predicted exercise capacity. There was no statistical difference at baseline between the lifestyle intervention group and controls. Significantly more participants in the lifestyle intervention group at 12 months compared to baseline achieved age-predicted exercise capacity. *P=0.002. Significantly more participants in the lifestyle intervention group achieved age-predicted exercise capacity compared with the control group. #P=0.01 at 12 months. LI, lifestyle intervention.

response to the intervention, but not BP, lipids, or indicators of kidney function. Other electrolytes and indicators of kidney function, including phosphate and urine albumin/creatinine ratio, were unchanged by the intervention (data not included).

Echocardiography. Table 3 shows that there were no significant differences between echocardiographic characteristics at baseline. The intervention had a significant effect on diastolic tissue velocity (e') (Table 3), which increased by 20% in the lifestyle intervention group and decreased by 6% in the control group (P=0.001).

Arterial Compliance. There were no significant baseline differences between any peripheral or central BP parameters, and arterial stiffness parameters and the intervention had no statistically significant effect on these parameters (Table 3).

Ventricular-Vascular Interaction. At baseline, the ventricular-vascular interaction parameters were similar between groups (Table 3). E_A was significantly lower in the lifestyle intervention group at 12 months (Table 3).

Dietary Analyses

Thirty-six participants completed diet records at baseline and follow-up (19 in the lifestyle intervention group and 17 in the control group). At baseline, total energy intake was similar between groups (7422±2872 kJ in the lifestyle intervention group versus 8002±2553 kJ in the control group). Macronutrient intake was not significantly different (% of total energy intake: protein lifestyle intervention, 20%±4% versus control, 19%±5%; carbohydrate lifestyle intervention, 41%±7% versus control, 43%±7%; fat lifestyle intervention, 32%±6% versus control 31%±6%;) and fiber (20.6±8.4 g versus control, 22.4±9.6 g) at baseline. There were no statistically significant differences between intervention and standard care groups for change in total energy intake or contribution of energy from macronutrients or fiber at 12 months.

Correlates of Functional Change

Change in peak $\dot{V}O_2$ was not correlated with age, sex, history of diabetes, subclinical ischemia, or history of myocardial infarction. Δ peak $\dot{V}O_2$ was associated with group allocation (r=0.31, P=0.01) and baseline peak $\dot{V}O_2$ (r=−0.28, P=0.03), Δ BMI (r=−0.36, P=0.003), Δ waist circumference (r=−0.26, P=0.04), and Δ body weight (r=−0.26, P=0.003).

Discussion

This study is the largest exercise training study in CKD patients to date and was a predefined substudy of the

Table 2. Results from the maximal exercise test

	Lifestyle Intervention Group		Control Group		P Value
	Baseline	Δ 12 mo	Baseline	Δ 12 mo	
$\dot{v}O_2$ (ml/kg per minute)	24.0±8.27	2.8±4.3	23.0±6.3	−0.4±4.9	0.01
Respiratory exchange quotient	1.06±0.1	0.02±0.1	1.04±0.1	−0.0±0.1	0.22
Max heart rate (bpm)	149.4±27.1	1.5±20.9	144.9±19.3	−3.7±16.4	0.27
Max systolic BP (mmHg)	178.4±20.4	−4.0±27.7	191.9±22.2	12.2±27.2	0.02
Max diastolic BP (mmHg)	81.6±11.3	−2.0±13.0	86.3±11.8	−7.4±11.3	0.08

Values are mean ± SD for normally distributed values. P value indicates significant difference in Δ between groups.

Table 3. Baseline and changes in secondary outcome measures

	Lifestyle Intervention Group		Control Group		*P* Value
	Baseline	Δ 12 mo	Baseline	Δ 12 mo	
Cardiovascular risk factors					
Weight (kg)	92.6±22.5	−1.8±4.2	92.7±24.1	0.7±3.7	0.01
Height (cm)	168.6±9.9	−0.0±0.8	167.3±9.0	−0.2±1.0	0.51
BMI (kg/m^2)	32.5±6.8	−0.6±1.4	33.0±8.0	0.3±1.4	0.01
Waist (cm)	106.9±18.5	−1.4±5.5	107.6±17.9	1.6±5.0	0.01
Serum creatinine (μmol/L)	157.7±37.5	4.6±30.0	150.1±33.3	3.4±26.6	0.85
eGFR (ml/min per 1.73 m^2)	38.4±8.8	−1.4±7.5	39.4±8.9	0.5±6.9	0.26
Serum albumin (g/L)	36.7±3.6	0.7±3.8	37.8±3.4	1.0±2.4	0.70
Fasting glucose (mmol/L)	7.2±3.9	−1.0±3.2	6.5±2.6	0.3±2.8	0.07
HbA1c (DM only, *n*=30) (%)	7.3±1.2	0.1±1.3	7.3±1.2	0.8±1.6	0.18
Triglycerides (mmol/L)	1.7±1.1	−0.0±0.7	1.8±1.0	0.2±1.3	0.42
Total cholesterol (mmol/L)	4.5±1.0	−0.2±1.0	4.4±1.1	0.0±1.0	0.48
HDL cholesterol (mmol/L)	1.2±0.5	0.0±0.2	1.1±0.3	0.0±0.2	0.55
LDL cholesterol (mmol/L)	2.5±0.8	−0.2±0.9	2.5±1.0	0.0±0.8	0.29
Echocardiography					
Mitral E wave (cm/s)	67.7±17.2	0.03±0.03	75.0±18.7	−0.07±0.03	0.03
Mitral A wave (cm/s)	70.1±29.5	−0.02±0.02	76.4±23.5	0.04±0.02	0.07
E/A	1.01±0.29	0.11±0.07	1.05±0.36	−0.17±0.04	0.002
Deceleration time (m/s)	240.6±52.2	−14.5±7.8	240.0±39.7	16.2±7.5	0.01
LA Vol index (cm^3/m^2)	37.3±13.4	−1.0±7.4	40.2±11.5	−3.0±9.3	0.65
EDV index (ml/m^2)	45.0±14.9	−1.8±7.5	45.4±12.8	11.3±10.5	<0.001
ESV index (ml/m^2)	16.4±8.9	−0.7±3.9	14.9±5.9	−3.0±4.4	0.03
Ejection fraction (%)	64±1	3.1±1.3	68±1	1.2±1.5	0.19
LV mass index (g/m$^{2.7}$)	55.2±15.8	−3.9±2.1	54.6±12.9	−3.0±2.9	0.98
S′ (cm/s)	6.13±1.2	0.01±0.01	6.28±1.17	0.0±0.0	0.50
e′ (cm/s)	5.59±1.5	0.75±1.16	5.88±1.4	−0.47±1.0	0.001
E/e′	13.6±9.4	−1.8±1.1	13.6±4.9	−0.26±3.7	0.30
Global longitudinal strain (%)	−18.4±3.9	−0.4±0.7	−19.5±2.8	1.3±0.5	0.05
Average global strain rate (s^{-1})	−1.09±0.2	0.1±0.0	−1.12±0.19	0.0±0.0	0.45
Hemodynamic					
Peripheral SBP (mmHg)	128.8±16.1	−2.4±16.2	132.3±12.4	−0.5±17.5	0.65
Peripheral DBP (mmHg)	74.9±8.1	0.6±10.6	71.1±9.4	3.2±8.2	0.78
Central SBP (mmHg)	117.8±14.3	−1.9±14.6	119.5±12.8	−0.4±17.0	0.71
Central DBP (mmHg)	75.9±8.2	0.9±10.4	73.0±10.2	3.2±8.4	0.65
AIx (%)	25.7±10.4	−0.2±8.5	24.5±8.1	−1.0.±8.5	0.73
Heart rate (bpm)	68.5±13.6	−2.4±9.9	66.0±9.3	1.1±8.5	0.18
Pulse wave velocity					
Aortic (m/s)	9.2±2.1	0.4±1.4	9.8±2.3	0.1±2.0	0.85
Ventricular-arterial interaction					
E_A (mmHg/ml)	2.3±0.7	0.1±0.8	2.2±0.6	0.8±1.0	0.01
E_{LV} (mmHg/ml)	4.8±2.8	0.2±1.7	4.7±1.6	1.0±2.0	0.11
E_A/E_{LV}	0.57±0.2	−0.0±0.1	0.49±0.1	0.03±0.2	0.46

Values are mean ± SD for normally distributed values, or median (IQR) for non-normally distributed data. *P* value indicates significant difference in Δ between groups. BMI, body mass index; eGFR, estimated GFR; HbA1c, hemoglobin A1c; DM, diabetes mellitus; E/A, mitral E wave to mitral A wave ratio; LA, left atrial; EDV, end diastolic volume; ESV, end systolic volume; LV, left ventricular; S′, systolic tissue velocity; e′, diastolic tissue velocity; E/e′, estimated left ventricle filling pressures; SBP, systolic BP; DBP, diastolic BP; Aix, augmentation index; E_A; arterial elastance, E_{LV}; LV end systolic elastance. VLDL, very low density lipoproteins.

ongoing LANDMARK III randomized controlled trial. The findings demonstrated that patients with moderate CKD randomized to receive an exercise and lifestyle intervention improved CRF, body composition, diastolic function, and preserved ventriculovascular coupling.

Our results are in agreement with previous reported findings from small studies (29–35) showing that exercise training is effective in improving CRF in patients with CKD. Uremic cardiomyopathy, comprising LV dilation, hypertrophy, and impaired diastolic and systolic function, is common in late stage CKD and a strong predictor of adverse cardiovascular prognosis (8). Similar, but less severe abnormalities of LV function, as well as decreased arterial and ventricular elastance, exist in early CKD (11). The disturbances in myocardial function in CKD are likely multifactorial, with contributions from abnormal relaxation (due to myocardial disease and arterial disturbances leading to augmented wave reflection and increased

afterload) as well as fibrosis. The role of aerobic exercise training on cardiac function is controversial (12,36). A previous training study in patients with coronary heart disease and preserved systolic function reported that exercise lessened the severity of diastolic dysfunction (37). In this study, we have shown that exercise may be effective through improvement in e′.

This intervention ameliorated disturbances in the ventricular-arterial relationship. Disturbances in ventricular-arterial interaction, which are common in early stages of CKD (11), may be estimated indirectly by echocardiography (26,38). The matching between the LV and the arterial system at rest results in optimal transfer of blood from the LV to the periphery without excessive changes in pressure. The changes in arterial elastance were interesting. This finding suggests that better cardiac compensation with the maintenance of ventricular coupling ratio allows preservation of cardiac performance and may contribute to improved CRF in moderate CKD. It was of interest to note that there was deterioration in end systolic and end diastolic volumes in the control group that was abrogated in the lifestyle intervention group. Further work in this area is required.

We were unable to show any effect on arterial stiffness as measured by both aortic PWV and AIx. Improvement in arterial stiffness is associated with increased fitness (39,40) in the general population; however, the pathophysiology of vascular disease in CKD may be different and more resistant to change (41). Mustata *et al*. (35) demonstrated an improvement in arterial stiffness with exercise training in a small study of CKD patients. In contrast to our study, they did not use the standard measure of arterial stiffness (PWV) and included patients with more advanced CKD.

The findings from this study suggest that CKD patients, independent of preexisting comorbidities have the potential to improve CRF with exercise training. Improvement in CRF was associated with a small but significant improvement in body composition. The effect on clinical outcomes such as cardiovascular events needs to be tested in larger studies.

This study had a few limitations. We are unable to separate the individual components of the lifestyle intervention; however, the various components are likely to be complementary and integral to promoting successful lifestyle change. Changes in doses of medication were not recorded and it cannot be determined whether the lack of change in variables such as BP relates to modification of dose. However, the medication profile (number of patients taking different types of medication) did not significantly change in either group. We are unable to accurately quantify the amount of exercise performed by each participant in the lifestyle intervention group; however, the improvement in peak $\dot{V}O_2$ suggests that the participants in the lifestyle intervention group were regularly exercising.

We observed unexpected changes in the end diastolic volume and ESV in the control group. The analysis of pro-brain natriuretic peptide may help explain these interesting results; however, it was beyond the scope of this analysis. Our assessment of ventricular-arterial interaction was based on noninvasive techniques. These techniques have been validated (26), but are less accurate than invasive methods. Furthermore, our study was not powered to assess changes in arterial compliance although smaller studies have reported improvement with exercise training (35). No corrections for multiple comparisons of secondary outcomes have been made and the risk of a type I error may be increased. As such, results are exploratory and further studies are required.

In this study of patients with moderate CKD and well managed cardiovascular risk factors, randomization to the intervention led to significant improvements in CRF, body composition, and cardiovascular parameters at 12 months. Interestingly, improvement of CRF appeared to be more responsive to lifestyle intervention than dietary or weight change, despite the high prevalence of obesity in this group.

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Disclosures

None.

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Effects of Exercise and Lifestyle Intervention on Cardiovascular Function in CKD

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Detailed Methods

Patient selection. This study was a pre-specified sub-study of an ongoing open-label randomized controlled trial investigating the effect of cardiovascular risk factor modification in patients with CKD (LANDMARK 3).The study has received approval by the Princess Alexandra Human Research Ethics Committee (HREC 2007/190) and University of Queensland Medical Research Ethics Committee (MREC 2008000184)and was registered at www.anzctr.org.au (Registration Number ANZCTR 12608000337370). Patients were eligible for inclusion if they were between 18 and 75 years of age, had moderate CKD (MDRD eGFR 25-60mL/min/1.73m^2) and had one or more uncontrolled cardiovascular risk factors (blood pressure [BP]exceeding target; overweight [BMI>25]; poor diabetic control [HbA1c >7]; or lipids exceeding target). Exclusion criteria for the study were: Intervention for or symptomatic coronary artery disease (within 3 months), current heart failure (NYHA class III and IV) or significant valvular heart disease, pregnant or planning to become pregnant, life expectancy or anticipated time to dialysis or transplant <6 months. All participants provided written informed consent and the study complied with the Declaration of Helsinki.

Outcomes. The primary outcome of this sub-study was change in CRF (as measured by peak VO_2) at 12 months, secondary outcomes were change in cardiovascular risk factors (weight, BP, lipids), cardiac function (as measured by systolic [s'] and diastolic [e'] tissue velocity), arterial stiffness (augmentation index and aortic pulse wave velocity) and ventricular-vascular coupling (arterial and ventricular elastance).

Baseline Assessment and Random assignment. Patients were initially assessed for inducible myocardial ischemia by stress echocardiography. Patients with an abnormal stress echo were reviewed by a Cardiologist and subsequently randomized if deemed safe to participate in a supervised exercise program. Patients were assigned to: Lifestyle intervention (LI) group or usual care controls in a ratio of 1:1 using a computer random assignment program. Groups were stratified by renal function (eGFR high [>44] or low [≤44]ml/min/1.73m^2), gender and diabetes status.

Control Group. The control group received standard nephrological care. At our site this includes being seen by a nephrologist and lifestyle modification recommended, but no specific information or education, and referred on an ad-hoc basis to allied health.

Exercise Training and Lifestyle Intervention. In addition to usual care provided by a nephrologist, assistance in managing cardiovascular risk was provided by a nurse-led multi-disciplinary clinic. The multidisciplinary team (including a nurse practitioner specialized in CKD, dietitian, exercise physiologist, diabetic educator, psychologist and social worker) managed risk factors to national targeted levels.[12, 13] The CKD nurse practitioner and diabetes educator worked closely with participants to ensure cardiovascular risk factors were at target, be this through increasing statin dosage or improving diabetes awareness.

Exercise Training. Patients randomised to LI received eight weeks of supervised individualised exercise training. The goal of training was for patients to achieve the American College of Sports Medicine target of performing at least 150 minutes of moderate intensity aerobic exercise and two sessions of resistance training per week.[4] Patients underwent a detailed initial assessment

with an accredited exercise physiologist to determine previous exercise experience, identify potential barriers to exercise including previous history of osteoarthritis, soft tissue injuries, gout, diabetes status and cardiovascular disease history, and finally develop personal short and long term goals specific to exercise training.

Following this, patients attended supervised gym sessions two to three times per week. Each supervised session included an aerobic warm-up, followed by 20-30 minutes of aerobic exercise performed on a treadmill, stationary bike or rower ergometer at a moderate to vigorous intensity (RPE 12-15). Resistance training included exercises that targeted the whole body. Patients performed a combination of exercises each session including: four upper body exercises either chest press, latissimus pull down, seated row, fly, shoulder press, tricep extension, bicep curl, three lower body exercise: squats, lunges, calf raise, knee extension and flexion, and two core exercises. The intensity of the resistance training was gauged by the patient's ability to complete each set with the patient reporting substantial fatigue by the final set, the patient performed three sets of 12-15 repetitions of each exercise, or as required to meet specific goals of the individual. Patients who identified a concern about balance and falls were provided with specific exercises to promote improvement in these areas. The sessions concluded with 5-10 minutes of stretching and cool down. Prior to commencing exercise, during and following the session, as required, blood pressure and blood glucose levels were monitored.

The eight week gym based program was designed to progress exercise prescription for the patient on an individual basis. In general, the focus during the initial four weeks of training was to develop confidence in performing exercise and improve fitness, the following two weeks

focused on teaching the patient exercises that could be performed safely at home or in the community, and the final two weeks involved the patient leading the sessions.

On completion of the gym based training, patients were given a swiss ball, therabands, and an exercise handbook to assist with exercising independently at home. The exercise handbook included detailed descriptions and photographs of how to perform resistance exercises and instructions for performing aerobic activity. Regular contact was maintained with participants via telephone and email (e.g. weekly for the first month, then monthly thereafter); participants were questioned on their ability to maintain the prescribed exercise and if they identified difficulty were encouraged to attend gym-based refresher visits. The LI group attended additional gym visits as required, this was not a pre-determined number as the intervention was delivered as what would be delivered in clinical practice, i.e. some patients required more support than others to be active. During the maintenance period patients were encouraged to perform exercise at a moderate intensity or the highest intensity tolerable, and were provided with education on how to independently measure intensity. All patients were assessed and trained by the same EP.

Dietary Intervention. Patients allocated to the LI attended the CKD clinic for a four-week behavior and lifestyle modification program. The program was conducted in groups of up to five patients, and was facilitated by a Clinical Psychologist, and a Dietician. The program focused on sustainable diet and behavior change to assist with weight loss and included the following weekly topics; Week 1 – Goal Setting, Guide to Healthy Eating, Self- Monitoring; Week 2 – Mediterranean-style diet (education on Cholesterol, Fats, Sugars, Sodium) and developing a Healthy Meal Plan; Week 3 – Motivating Change; Week 4 – Sustaining change, which included

label reading and recipe modification. Patients were provided with a workbook that included information on the discussed topics, self-monitoring exercises, homework and evaluation. Following the four week program patients were reviewed and counseled by a dietitian every three months in person or via telephone, for the remainder of the trial. The dietitian therapy complied with the Evidence Based Practice Guidelines for Nutritional Management of CKD for patients with eGFR of between 25-60ml/min.[15]

Outcome Measures. All measures were obtained prior to randomization and following 12 months of intervention.

Biochemical analyses. After an overnight fast, patients provided blood samples for the measurement of serum/plasma concentrations of creatinine, glucose, HbA1c and lipids (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides), calcium, phosphate and hemoglobin were analyzed using standard techniques. Kidney function was determined as eGFR using the Modification of Diet in Renal Disease formula based on the isotope dilution mass spectrometry standardized creatinine assay ($MDRD_{175}$).[16]

Maximal exercise capacity. CRF was assessed as peakVO_2. Participants completed a Duke Activity Status Index to determine predicted peak VO_2 and based on these results, a suitable graded treadmill exercise test protocol was selected (Bruce, Naughton, Balke or modified Balke). Testing was performed according to American College of Sports Medicine guidelines for exercise testing.[17] Cardiorespiratory fitness was derived from breath-by-breath indirect calorimetry (Vmax29c, SensorMedics, CA, USA) and was recorded as the peak 20 second average VO_2 during the final minute of exercise with continuous 12-lead ECG monitoring (GE

CASE, GE Healthcare, Waukesha, WI). Exercise blood pressure was measured in the last minute of each exercise stage using a mercury sphygmomanometer.

Echocardiography. Conventional two-dimensional echocardiography was performed at rest using standard equipment (Vivid 7, General Electric Medical Systems, Milwaukee, WI). Evaluation of LV volumes and ejection fraction (EF) was performed using the Simpson's biplane method. LV mass index (LVMI) was assessed according to the method of Devereux.[20] Transmitral flow was interrogated by pulsed wave Doppler. The application of this method to measurement of LV filling permits measurement of peak mitral inflow velocity in passive (E wave) and active filling (A wave) and the mitral deceleration time (DT). The primary diastolic variable was early diastolic relaxation velocity (e') measured by pulsed wave tissue Doppler at the septal mitral annulus.[21] The same method was used to measure systolic (s') velocity. The E/e' ratio was used to estimate LV filling pressures.[22] Left atrial (LA) volume was measured using the area-length method and indexed to body surface area (LA volume index, LAVI).

Two-dimensional speckle tracking imaging was measured off-line using specialized software (Echopac, GE Medical Systems, Horten, Norway) for determination of peak longitudinal strain and strain-rate and reported as the average of 6 basal segments from three standard apical views. All echocardiographic parameters were measured offline in batches by an observer blinded to treatment allocation and previous results.

Evaluation of Diastolic and Systolic Function. Systolic dysfunction was identified on the basis of ejection fraction <50%. Diastolic dysfunction was categorized as normal diastolic function, delayed relaxation, pseudonormal or restrictive diastolic filling. Delayed relaxation was defined

as a mitral E wave deceleration time greater than published age-specific normal values (mean+2SD).[20] For those with normal deceleration times, patients were classified as having pseudonormal filling if they had evidence of elevated filling pressure on the basis of E/e' >15 or E/e' 8-15 with LAVI ≥34ml/m^2.[21, 22] Restrictive filling was defined by deceleration time <140msec with at least one other criterion suggesting elevated filling pressures as outlined above.[23]

Arterial Compliance. Arterial waveforms were acquired in duplicate at the radial artery using hand-held applanation tonometry, calibrated with brachial BP measured in duplicate immediately prior to waveform acquisition. The central pressure waveform was derived from the radial pulse using a generalized transfer function and commercial software (SphygmoCor 8.1, AtCor Medical, Sydney, Australia). The augmentation index (AIx) represents the augmented pressure as a percentage of total central pulse pressure. End-systolic pressure was calculated as the pressure at the nadir of dicrotic notch on the central pressure waveform. Central arterial stiffness was estimated in duplicate by aortic pulse wave velocity (PWV). PWV was acquired with ECG-gated sequential tonometry at the carotid and femoral arterial sites.

Ventricular-Vascular Interaction. Measures to assess the interaction between the LV and vasculature were derived by non-invasive means using a combination of echocardiography (for end systolic volume [ESV]) and tonometry (for end systolic pressure [ESP]). Arterial elastance (E_A) was derived from the ratio of end systolic pressure and stroke volume (ESP/SV), end-systolic elastance (E_{LV}) was derived by the following equation (end-systolic pressure/end-systolic volume – V_0), where V_0 is the x-axis intercept of the pressure-volume relationship.[28]

The value of V_0 is considered to be negligible compared with ESV and is therefore approximated as zero.[28] The ratio of E_A/E_{LV} provides insight on the interaction between the LV pump function and the arterial system. These methods have been validated against invasive measures of ventricular pressure-volume loops.

*Dietary Assessment***.** Dietary assessment was conducted using three-day diet records on a sub-set of participants. Dietary intake data was analyzed using FoodWorks version 7 using NUTTAB 2010 database (Xyris Software (Australia)) for total energy (kcal), macronutrient and dietary fibre intake.

Power Analysis. Baseline VO_2 peak was assumed to be 22.0±6 mL/kg/min, and a 20% increase (effect size 0.73) in the intervention group compared to the control participants would be clinically significant. Therefore we would require 41 participants in each group to have 90% power to detect a difference between groups (alpha 0.05), however to account for drop out we aimed to recruit 90 patients.

Statistics. Analysis was performed by available data. Data were checked for normality using the Kolmogorov-Smirnov Test. Results are expressed as mean ± SD, median [interquartile range] or n (%) for categorical data. Baseline characteristics and change scores were compared between groups using independent Student t-tests and chi square tests for categorical variables. Pearson and Spearman correlations were performed between the change in the main outcome measure and other secondary measures. Data were analyzed using standard commercially available statistical software (SPSS version 18, PASW. Chicago, IL). Statistical significance for the primary outcome measure was $p \leq 0.05$.