Effects of Exercise and Lifestyle Intervention on Cardiovascular Function in CKD

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Short title: Exercise and Lifestyle Intervention in CKD

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 $p \leq 0.05$.