Physical Activity in Renal Disease and the Effect on Hypertension: A Randomized Controlled Trial

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Keywords
Chronic kidney disease · Blood-pressure · Hypertension · Physical activity · Randomized controlled trial

Abstract

Introduction: Exercise is an effective strategy for blood pressure (BP) reduction in the general population, but its efficacy for the management of hypertension in chronic kidney disease (CKD) is not known. We evaluated the difference in 24-h ambulatory systolic BP (SBP) with exercise training in people with moderate to severe CKD. Methods: Participants with an estimated glomerular filtration rate (eGFR) of 15–44 mL/min per 1.73 m\textsuperscript{2} and SBP >120 mm Hg were randomized to receive thrice-weekly moderate-intensity aerobic-based exercise over 24 weeks, or usual care. Phase 1 included supervised in-center and home-based sessions for 8 weeks. Phase 2 was 16 weeks of home-based sessions. BP, arterial stiffness, cardiorespiratory fitness, and markers of cardiovascular (CV) risk were analyzed using mixed linear regression. Results: We randomized 44 people; 36% were female, the median age was 69 years, 55% had diabetes, and the median eGFR was 28 mL/min per 1.73 m\textsuperscript{2}. Compared with usual care, there was no significant change in 24-ambulatory SBP at 8 weeks (2.96 mm Hg; 95% confidence interval (CI): −2.56, 8.49) or 24 weeks. Peak oxygen uptake improved by 1.9 mL/kg/min in the exercise group (95% CI: 0.03, 3.79) at 8 weeks with a trend toward higher body mass index 1.84 kg/m\textsuperscript{2} (95% CI: −0.10, 3.78) and fat free mass, but this was not sustained at 24 weeks. Markers of CV risk were unchanged. Conclusions: Despite an improvement in peak aerobic capacity and body composition, we did not detect a change in 24-h ambulatory SBP in people with moderate-to-severe CKD.

Introduction

In people with chronic kidney disease (CKD), hypertension is an important modifiable risk factor for both cardiovascular (CV) events and progressive renal dysfunction [1–5]. Although blood pressure (BP) reduction is a cornerstone of CKD management, the prevalence of uncontrolled hypertension remains high among those with known CKD, ranging from 48 to 69% [6–8]. Antihypertensive medications are the mainstay of BP treatment.
but are often only partially effective [9], frequently confer side effects [10], and are often stopped due to side effects [11], suggesting that additional approaches are needed.

Regular exercise is effective in reducing BP in people without CKD and, based on high quality trials, is strongly recommended as management (Class 1A) [12]. From systematic reviews of randomized controlled trials, the magnitude of BP reduction with exercise was 3.5 to 6.1/2.5 to 3.0 mm Hg, and greater effects have been reported in people with hypertension [13–15]. Due to low quality evidence, exercise for the management of BP is a weak recommendation for hypertensive CKD populations [16]. Whether exercise is an effective means of treating hypertension in people with CKD remains an important question. Both the prevalence of uncontrolled hypertension and the use of multiple antihypertensives are higher among people with CKD than those with normal kidney function [17, 18], raising the question of whether the pathological mechanisms that drive hypertension as CKD advances (i.e., increased sympathetic tone, advanced vascular stiffness due to calcification, and the retention of salt and water) may reduce the response to therapeutic interventions such as exercise.

The primary aim of this study was to determine the efficacy of an aerobic-based exercise intervention on systolic BP (SBP) in people with moderate-to-severe CKD. We hypothesized that compared to control, participants allocated to the exercise intervention will achieve a significant reduction in SBP as measured by 24-h ambulatory BP (ABPM). To improve our understanding of the effect of exercise training in this population on CV risk factors as well as the potential vascular adaptations that may explain a favorable BP response, we included measures of arterial stiffness and CV risk as secondary outcomes.

**Methods**

**Design, Setting, and Participants**

The protocol for this trial has been reported previously [19]. This was a parallel-arm, single-center randomized controlled trial (NCT03551119). Participants were randomized (1:1) to an exercise intervention or enhanced usual care (measurement of physical activity levels) using permuted blocks of four and six and stratified by baseline estimated glomerular filtration rate (eGFR) (15–29 mL/min/1.73 m² and 30–44 mL/min/1.73 m²) generated using Stata 15.1 (www.stata.com). Allocation was concealed by web-based central randomization using The Research Electronic Data Capture System (RedCap; projectredcap.org). Due to the nature of the intervention, participants and study staff could not be blinded to group assignment. Upon trial completion, all participants were offered a consultation with an exercise specialist to develop a post-study exercise plan and received an activity tracker. All participants received standard care according to the Canadian Guidelines for the Management of Chronic Kidney Disease [20]. Written and informed consent was obtained and the University of Alberta Research Ethics Board approved the study (Pro00078564).

Participants were recruited from both the academic and community-based clinics within Alberta Kidney Care (AKC) North in Edmonton, AB, Canada (from November 21, 2018 to March 12, 2020). Recruitment was suspended due to COVID-19 with early termination of the trial due to the pandemic. Adults (≥18 years) with hypertension and two measures of eGFR between 15 and 44 mL/min per 1.73 m² in the previous year were eligible. Hypertension was defined as a mean resting SBP >130 mm Hg measured using a validated electronic sphygmomanometer (Omron HEM-907XL; Omron Healthcare, Kyoto, Japan), after discarding the first of three readings and at least one previous SBP measurement above 130 mm Hg on a separate occasion from any setting within the past 6 months (home or clinic measurement). Post hoc patients who had SBPs >120 mm Hg were included [21]. To minimize contamination from changes to antihypertensive therapy, these medications had to be unchanged over the past 8 weeks. Exclusion criteria included a resting SBP >160 mm Hg or DBP >110 mm Hg, reported inability to mobilize without an assistive device for at least three consecutive minutes, and any absolute contraindication to exercise [22]. Complete eligibility criteria can be found in online supplemental Table S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000524518).

**Trial Conduct and Data Collection**

Data were collected via participant interviews, physical examination, chart reviews, and clinical databases at baseline, 8 weeks, and 24 weeks. Medication use was reviewed by phone at baseline, every 2 weeks until week 8, and every 4 weeks thereafter until study end. Clinical encounters were also audited with respect to antihypertensive changes. Demographics and medical history were ascertained at baseline. Adverse event reviews were also completed 30 days following the discontinuation of the trial intervention. All adverse events were reviewed by the site investigators within 24 h.

**Primary Outcome**

The primary outcome for the trial was the difference in 24-h ABPM at 8 weeks compared to control. ABPM was measured using a validated device (OnTrak Ambulatory Blood Pressure Monitor 90,227–1; Spacelabs Healthcare, Mississauga, ON, Canada) [23] worn on the nondominant arm for a 24-h period. Readings were obtained at 20-min intervals from 6:00 a.m. to 10:00 p.m. and at 30-min intervals from 10:00 p.m. to 6:00 a.m [24]. Participants were advised to perform their regular daily routine (but not to exercise) during the 24-h ABPM period.

**Secondary Outcomes**

**Blood Pressure**

Clinic BPs were measured at each timepoint using the mean of three readings (after discarding the first reading), each 1 min apart with a validated electronic sphygmomanometer (Omron HEM-907XL; Omron Healthcare, Kyoto, Japan). Participants sat quietly for 5 min prior to measurement, using the same arm at each visit. Participants were advised not to exercise within 24-h of the study visit.
Arterial Stiffness
Arterial stiffness was estimated using tonometry (Complior; Alam Medical, Saint Quentin Fallavier, France). The distance between measuring sites: carotid and femoral and the carotid and radial arteries was divided by the time difference between the upslope of the pulse-waves at each measuring site, and arterial stiffness was expressed as the pulse wave velocity (PWV) in meters/second [25]. Mean PWV was calculated as the average of at least 10 consecutive beats in order to cover a full respiratory cycle.

Cardiorespiratory Fitness
To accurately measure exercise-training adaptations and to determine the adequacy of the dose of exercise that was performed, cardiopulmonary exercise testing was performed on an upright cycle ergometer (Ergoselect II 1200 Ergoline) using a calibrated cardiorespiratory metabolic measurement system (Encore229 V max; SensorMedics). After 5 min of rest, participants started cycling at 20 W with an increasing stepped workload of 20 W every 2 min with the aim of achieving a respiratory exchange ratio >1.10 and a Borg Rating of Perceived Exertion (RPE) greater than 8 on a 0–10 scale until volitional fatigue. Peak aerobic capacity (VO2 peak) was derived from breath-by-breath indirect calorimetry and recorded as the peak 20-s average VO2 during the final minute of exercise.

CV Risk and Clinical Measures
To measure fat-free mass, whole-body bioimpedance measurements were performed using the Body Composition Monitor (Fresenius Medical Care, Wendel, Germany). Markers of CV risk included body mass index (BMI) and laboratory parameters collected according to routine laboratory protocol on a nonexercise day after an overnight fast.

Changes in Antihypertensive Drugs
Antihypertensive quantity was determined by defined daily dose (DDD) calculated as per World Health Organization standard to enable comparison across drug classes (e.g., 1 × DDD = 150 mg irbesartan or 5 mg amlopidine) [26] and was reported as standardized dosing per day.

Physical Activity and Adherence
Adherence to the exercise prescription and overall differences in physical activity levels between groups was measured by self-report (audit of participant logbooks and phone follow up) and accelerometer (Actigraph® GT3X+ Actigraph; LLC, Pensacola, FL, USA) worn around the waist for at least 10 waking hours for 7 consecutive days. In Phase 1, adherence to the exercise prescription was defined as >70% of people completing the eight in-center supervised sessions within 12 weeks. Adherence to the home exercise prescription of Phase 1 and Phase 2 was defined as >70% of the home component completed at the prescribed frequency, time, and intensity for the aerobic and isometric components. Time spent in moderate-to-very vigorous physical activity (MVPA) was combined for the purposes of analysis.

Questionnaires
Quality of life was measured using the Kidney Disease and Quality of Life Instrument (KDQOL-12) tool [27], scored using the Veterans RAND 12-item method [28] and the EuroQol Health Questionnaire (EQ-5D) [29].

Interventions
Exercise Intervention
The 24-week exercise program was delivered in two phases and aimed to increase overall physical activity to 150 min/week at a moderate intensity, 40–59% of heart rate reserve (HRR), equivalent to a RPE of 3–4 on the modified Borg 1–10 scale. Phase 1 involved 8 weeks of once-weekly in-center supervised sessions with a certified exercise physiologist and twice-weekly home-based sessions. Supervised sessions included a dynamic warm-up (5 min); isometric resistance training with body weight and resistance bands (10–20 min); continuous aerobic exercise on a treadmill, cycle ergometer, or elliptical trainer, targeting 30 min; and a cooldown with flexibility exercises (5 min). The aerobic exercise prescription was individualized using %HRR, beginning conservatively with light intensity (30–39% HRR) in weeks one to three, and progressing to moderate (40–59%) in weeks 4–8 [30, 31]. Heart rate and RPE were monitored in-session to ensure participants exercised at the prescribed intensity. Phase 2 involved 16 weeks of home-based exercise training with progression tailored individually based on Phase 1 of the program. Contact with participants was maintained (every 1–2 weeks) via telephone and email. Participants were encouraged to attend in-center refresher visits if they experienced difficulty or required further instruction. Throughout the trial, the exercise physiologist used motivational interviewing techniques to identify and reinforce participants’ goals. Participants were provided with an exercise journal to assist with goal setting and monitoring, which also contained exercise education and practical tips. The intervention group received written, formalized comparative feedback on their progress at each timepoint [32].

Control Group (Enhanced Usual Care)
Participants in the control group received usual care. Usual care does not routinely include access to exercise resources. Seven-day accelerometry is not routinely performed in participating CKD clinics.

Statistical Analyses
A sample size of 160 participants (approximately 80 participants per group) was targeted to provide 80% power (with a 5% type 1 error rate and a 20% loss to follow-up) to detect a difference in mean SBP of 5 mm Hg between the exercise and the control groups, assuming a common standard deviation of 10 mm Hg [33]. A 5 mm Hg reduction in BP in high risk patients is associated with a reduction in CV events by 15% [34]. No interim analyses were planned due to the short duration of the trial. The dataset was locked on September 24, 2020. All analyses were completed in Stata/MP 15.1 (www.stata.com) and followed the intent-to-treat principle. The difference in mean 24-h ambulatory SBP between groups at 8 weeks (primary outcome) was analyzed using a mixed linear regression model including fixed effects terms for time point (8 weeks, 24 weeks), intervention, baseline eGFR, baseline 24-h systolic ABPM, and a random effects term for each participant. In the primary analysis, missing values were multiplied and imputed (100 iterations) using predictive mean matching and chained equations [35]. Complete-case results are presented as sensitivity analyses. Estimates and corresponding 95% confidence intervals (CIs) are reported for the overall difference at week 8 (and 24 weeks). All outcomes were analyzed similarly. p values <0.05 were considered statistically significant.
Fig. 1. Participant flow diagram.

BP blood pressure, eGFR estimated glomerular filtration rate
*Patients could be ineligible for multiple reasons
Exercise in Hypertension and CKD

Results

This trial is reported according to the CONSORT guidelines [36].

Participants

We screened 689 people for inclusion; 550 did not give consent and 95 were ineligible. A lack of interest in research participation was the most common reason for nonparticipation, followed by a transportation barrier (Fig. 1). Thirty-five patients were in the process of being screened when the enrollment was stopped early due to the COVID-19 pandemic, leaving 44 patients that were enrolled and randomized. Two participants did not complete the intervention. With the exception of one participant, all participants in the intervention group had completed follow-up.

Overall, the demographic and clinical characteristics of the trial groups were comparable at baseline (Table 1).

Table 1. Demographics and clinical characteristics

| Characteristic                              | All       | Exercise | Usual care |
|---------------------------------------------|-----------|----------|------------|
| N                                           | 44        | 21       | 23         |
| Age                                         | 69 [56, 73] | 70 [60, 73] | 68 [52, 75] |
| Female                                      | 16 (36.4) | 8 (38.1) | 8 (34.8)   |
| Non-Caucasian                               | 7 (15.9)  | 2 (9.5)  | 5 (21.7)   |
| Postsecondary education                     | 32 (72.7) | 16 (76.2) | 16 (69.6)  |
| eGFR, mL/min/1.73 m²                        | 28 [21, 37] | 28 [20, 37] | 28 [22, 37] |

CKD cause

| Cause                        | All     | Exercise | Usual care |
|------------------------------|---------|----------|------------|
| Diabetic nephropathy         | 14 (31.8) | 6 (28.6) | 8 (34.8)   |
| Hypertension                 | 18 (40.9) | 9 (42.9) | 9 (39.1)   |
| Glomerulonephritis           | 6 (13.6)  | 3 (14.3) | 3 (13.0)   |
| PCKD                         | 5 (11.4)  | 1 (4.8)  | 4 (17.4)   |
| Unknown                      | 5 (11.4)  | 3 (14.3) | 2 (8.7)    |
| Other                        | 9 (20.5)  | 4 (19.0) | 5 (21.7)   |

Comorbidity

| Comorbidity | All       | Exercise | Usual care |
|-------------|-----------|----------|------------|
| CHF          | 1 (2.3)   | 0 (0.0)  | 1 (4.3)    |
| PVD          | 2 (4.5)   | 1 (4.8)  | 1 (4.3)    |
| Stroke       | 5 (11.4)  | 4 (19.0) | 1 (4.3)    |
| Diabetes     | 24 (54.5) | 12 (57.1) | 12 (52.2)  |
| Cancer       | 9 (20.5)  | 4 (19.0) | 5 (21.7)   |
| Depression/anxiety | 8 (18.2) | 5 (23.8) | 3 (13.0)   |
| Smoking      | 3 (6.8)   | 1 (4.8)  | 2 (8.7)    |
| BMI, kg/m²    | 32 [27, 35] | 30 [27, 34] | 32 [25, 35] |
| Peak VO₂, mL/min/kg | 16.82 [14.44, 18.42] | 17.01 [13.27, 18.36] | 16.21 [14.71, 18.76] |
| Steps, daily mean | 3,356 [2003, 4,345] | 3,262 [2016, 4,228] | 3,443 [1989, 4,462] |
| Standardized antihypertensive drug utilization, DDD | 2.00 [1.00, 3.54] | 2.50 [1.00, 3.58] | 2.00 [1.00, 3.00] |

N (%) or median [IQR] are reported BMI, body mass index; CHF, chronic heart failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PCKD, polycystic kidney disease; PVD, peripheral vascular disease; DDD, Defined Daily Dose.

The DDD of antihypertensives was modestly higher in the exercise group, 2.50 (interquartile range [IQR] 1.00, 3.58) versus 2.00 (1.00, 3.00). The median age of participants was 69 years [IQR 56, 73]; 36% were female and most were Caucasian (84%). The median eGFR was 28 [IQR 21, 37] mL/min/1.73 m² and the main causes of CKD were diabetes and hypertension; 55% of the cohort had diabetes, and the median BMI was 32 [IQR 27, 35] kg/m². Peak VO₂ (mL/kg/min) and number of daily mean steps were comparable at baseline 16.8 [IQR 14.4, 18.4] and 3,356 [IQR 2003, 4,345], respectively.

Blood Pressure

The primary outcome of the mean difference (MD) in overall 24-h systolic ABPM at 8 weeks between the exercise and the usual care groups was not significant (MD 2.96 mm Hg, 95% CI: −2.56, 8.49; p = 0.29; (Table 2); (Fig. 2). Other measures of BP including clinic BP do not differ between groups.
Secondary Outcomes

The MD in cardiorespiratory fitness at 8 weeks was significant and favored the exercise group: peak metabolic equivalents 0.56 (95% CI: 0.05, 1.07; \( p = 0.03 \)) and peak VO\(_2\) 1.91 mL/kg/min (95% CI: 0.03, 3.79; \( p = 0.05 \)) but not at 24 weeks: peak metabolic equivalents 0.55 (95% CI: −0.08, 1.18; \( p = 0.09 \)) and 1.77 mL/kg/min (−0.49, 4.04; \( p = 0.12 \)), respectively. The MD in BMI in the exercise group tended to be greater at 8 weeks (MD 1.84 kg/m\(^2\), −0.10, 3.78; \( p = 0.06 \)), with a trend toward greater fat free mass (MD 2.34 kg, 95% CI: −1.25, 5.93) and dissipated at 24 weeks (Fig. 2). There were no differences in carotid to femoral PWV between groups at 8 or 16 weeks 0.11 m/s (95% CI: −2.06, 2.28; \( p = 0.92 \)) and −0.53 m/s (95% CI: −3.18, 2.13; \( p = 0.70 \)), respectively, or in carotid to radial measurements at either timepoint. Most markers of CV risk did not differ at either timepoint, except for C-reactive protein, which was higher at 24 weeks in the exercise group. There were no changes in either physical or mental health-related quality of life scores. Results for the complete-case analysis were consistent with these findings and are shown in online supplementary Table S2.

Adherence

In Phase 1, 90% of exercise participants completed the eight in-center sessions. For the home exercises in Phase

| Outcomes | Baseline Mean (95% CI) | 8 weeks MD (95% CI) | 8 weeks p value | 24 weeks MD (95% CI) | 24 weeks p value |
|----------|------------------------|---------------------|-----------------|-----------------------|-----------------|
| Systolic BP, mm Hg | | | | | |
| 24-h – overall | 128.43 (124.84, 132.02) | 2.96 (−2.56, 8.49) | 0.29 | 4.04 (−2.76, 10.85) | 0.24 |
| 24-h – daytime | 132.68 (128.93, 136.44) | 3.23 (−2.46, 8.92) | 0.27 | 4.60 (−2.77, 11.98) | 0.22 |
| 24-h – nighttime | 119.59 (115.32, 123.86) | 4.13 (−3.18, 11.45) | 0.27 | 4.12 (−4.27, 12.52) | 0.34 |
| Clinic | 138.48 (133.91, 143.05) | 4.72 (−3.08, 12.53) | 0.24 | 5.57 (−4.60, 15.74) | 0.28 |
| Diastolic BP, mm Hg | | | | | |
| 24-h – overall | 69.70 (67.22, 72.19) | 0.50 (−2.37, 3.37) | 0.73 | 1.09 (−2.64, 4.81) | 0.57 |
| 24-h – daytime | 72.39 (69.63, 75.14) | −0.19 (−3.20, 2.82) | 0.90 | 0.35 (−3.35, 4.28) | 0.86 |
| 24-h – nighttime | 64.05 (61.60, 66.49) | 1.90 (−2.17, 5.98) | 0.36 | 1.96 (−2.96, 6.87) | 0.44 |
| Clinic | 72.18 (69.06, 75.31) | −2.25 (−7.23, 2.74) | 0.38 | −1.58 (−7.95, 4.80) | 0.63 |
| PWV, m/s | | | | | |
| Carotid to femoral | 6.93 (5.66, 8.21) | 0.11 (−0.26, 2.28) | 0.92 | −0.53 (−3.18, 2.13) | 0.70 |
| Carotid to radial arteries | 8.71 (7.89, 9.53) | 0.51 (−0.66, 1.69) | 0.39 | 0.44 (−1.13, 2.00) | 0.58 |
| Antihypertensive dose, DDD | 2.44 (1.83, 3.04) | −0.19 (−1.21, 0.84) | 0.72 | 0.23 (−1.12, 1.59) | 0.74 |
| CV risk | | | | | |
| BMI, kg/m\(^2\) | 31.18 (29.39, 32.97) | 1.84 (−0.10, 3.78) | 0.06 | 1.11 (−1.16, 3.37) | 0.34 |
| FFM, kg | 55.18 (51.32, 59.03) | 2.34 (−1.25, 5.93) | 0.20 | 1.89 (−2.67, 6.45) | 0.42 |
| C-reactive protein, mg/L | 6.88 (2.67, 11.10) | 3.28 (−1.26, 7.83) | 0.16 | 6.98 (0.37, 13.60) | 0.04 |
| Total cholesterol, mmol/L | 4.05 (3.68, 4.41) | 0.05 (−0.48, 0.59) | 0.84 | 0.10 (−0.58, 0.77) | 0.78 |
| LDL cholesterol, mmol/L | 2.08 (1.79, 2.36) | 0.16 (−0.18, 0.50) | 0.36 | 0.19 (−0.26, 0.65) | 0.40 |
| HDL cholesterol, mmol/L | 1.15 (1.03, 1.27) | 0.03 (−0.12, 0.19) | 0.69 | 0.05 (−0.17, 0.26) | 0.67 |
| Triglycerides, mmol/L | 1.88 (1.45, 2.31) | 0.09 (−0.85, 1.03) | 0.85 | −0.02 (−1.01, 0.98) | 0.98 |
| Sodium, mmol/L | 77.38 (66.76, 88.01) | −3.62 (−35.33, 28.10) | 0.82 | −13.39 (−50.98, 24.21) | 0.49 |
| ACR, mg/mmol/L | 64.50 (37.29, 91.70) | −9.72 (−26.19, 6.75) | 0.25 | −6.12 (−28.17, 15.94) | 0.59 |
| eGFR, mL/min*1.73 m\(^2\) | 28.80 (26.10, 31.49) | −1.23 (−5.41, 2.96) | 0.57 | −2.86 (−7.76, 2.04) | 0.25 |
| Cardiorespiratory fitness | | | | | |
| Peak VO\(_2\), mL/min | 1,601 (1,415, 1,787) | 210.06 (−7.95, 448.07) | 0.08 | 196.02 (−74.77, 466.81) | 0.16 |
| Peak VO\(_2\), mL/min/kg | 17.38 (15.85, 18.90) | 1.91 (0.03, 3.79) | 0.05 | 1.77 (−0.49, 4.04) | 0.12 |
| Peak METS | 4.98 (4.55, 5.42) | 0.56 (0.05, 1.07) | 0.03 | 0.55 (−0.08, 1.18) | 0.09 |
| Veterans RAND-12 | | | | | |
| Physical health composite | 39.31 (37.26, 41.36) | 0.45 (−2.38, 3.29) | 0.75 | 2.78 (−1.00, 6.56) | 0.15 |
| Mental health composite | 36.65 (34.28, 39.02) | 3.57 (−0.00, 7.15) | 0.05 | 2.43 (−2.41, 7.27) | 0.33 |

Primary outcome – systolic BP at 8 weeks. ACR, albumin/creatinine ratio; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FFM, fat-free mass; HR, heart rate; METS, metabolic equivalents; RAND, Research and Development Corporation.

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Kidney Blood Press Res 2022;47:475–485
DOI: 10.1159/000524518
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1, a median of 75% of isometric sessions [IQR 33, 100] were completed, and 69% of aerobic sessions [IQR 44, 94] were completed. In Phase 2, a median of 10% of isometric sessions [IQR 0, 81] were completed and a median of 27% of aerobic sessions were completed [IQR 0, 73]. Detailed accelerometry data is shown in online supplementary Table S3. At baseline, 14% and 22% of participants in the exercise and usual care groups attained 150 min of moderate-to-vigorous activity per week. There was no difference in the percentage of time spent in MVPA between groups at 8 weeks, 0.43% (95% CI: −0.13, 0.98; *p* = 0.14) or 24 weeks, 0.45% (95% CI: −0.25, 1.15; *p* = 0.21).

**Adverse Events**

There were no deaths during this study. Serious adverse events and adverse events are shown in online supplementary Table 4. There were three serious adverse events overall, which occurred in two usual care participants (one myocardial infarction, one cholecystectomy, and one hospital visit for an acute exacerbation of chronic obstructive lung disease). There were 19 nonserious adverse events in seven exercise participants and six usual care participants. Of these events, there were two musculoskeletal injuries in both groups and one symptomatic hypoglycemic event in the exercise group.

**Discussion**

The aim of this trial was to determine the efficacy of an aerobic-based exercise intervention on SBP in people with hypertension and moderate-to-advanced CKD. We also examined the effect of exercise training on a range of clinically relevant CV outcomes. We found an improvement in cardiorespiratory fitness and a nonsignificant trend toward optimized body composition in people at 8 weeks. Despite this improvement, we were unable to demonstrate the BP-lowering effect of exercise in this population. Corresponding with the drop-in adherence in Phase 2, these favorable exercise training adaptations were not detected at 24 weeks. From our group’s previous meta-analysis, we found a nonsignificant trend toward improved BP with exercise training [37]. In that review, exercise training was associated with significant reduction in clinic BP at 24–26 weeks but not at 52 weeks, suggesting that, similar to our study, low adherence to exercise training contributed to the equivocal association.

In people with CKD, measured cardiorespiratory fitness is an independent predictor of mortality [38, 39]. It is notable that we were able to show an improvement in fitness after only 8 weeks of exercise training. From other trials in this population, comparable improvements of 2.39 mL/kg/min (95% CI: 0.99–3.79) were reported after a mean length...
of 35 weeks of aerobic training [40]. In our study, this improvement in fitness was not detected at 24 weeks and may be explained by low adherence, despite incorporating evidence-based strategies to support adherence (e.g., initial supervision and individualizing the prescription to the patient [41], education on expectations and knowledge about risks and benefits [42]). As adherence to the home phase was adequate in Phase 1, it is unclear whether the decline in Phase 2 was due to the lack of a supervised component or simply an effect of time, which is known to be inversely related to exercise adherence [43]. In both phases of the trial, adherence to home exercise followed a bimodal pattern, indicating that individual-level factors also likely influenced exercise participation. It is also important to acknowledge that containment measures of the first wave of the COVID-19 pandemic posed unique challenges for study participants in the home phase, and it is unclear as to what degree this influenced adherence.

There are few trials examining the effect of exercise training on body composition in people with moderate-to-severe CKD. Ikizler et al. [44] performed a pilot, randomized 2 x 2 factorial trial comparing a 4-month intervention of caloric restriction and aerobic exercise with each intervention alone. The combined intervention had modest effects on BMI and fat mass, though this association was primarily driven by calorie restriction. In that study, VO2 peak did not change, suggesting that the received dose of exercise may have been too low. We found a trend toward increased BMI in the exercise group, which is important to consider in the context of the trend toward higher fat free mass and favorable changes in cardiorespiratory fitness. As higher BMI and specifically, higher lean tissue, have been associated with a survival advantage in people with non-dialysis dependent CKD [45, 46], this finding has potential clinical importance and should be evaluated in future trials in this population.

Reduced arterial stiffness as measured by PWV in response to aerobic-based exercise training has been demonstrated in the general population [47, 48] and may precede clinically detectable changes in BP [49]. More pronounced improvements in PWV with exercise training have been reported in studies enrolling participants with higher baseline PWV values (>9.3 m/s) and those not receiving antihypertensive medication [47]. Consistent with previous trials in CKD [50–52], we did not detect a change in arterial stiffness as measured by PWV. However, as in these previous studies, the baseline PWV of participants in our trial was normal or high normal when compared with age- and sex-matched values in the general population [53], and participants were also receiving antihypertensives. In addition, though we also reported peripheral artery stiffness, most exercise studies in CKD have examined central PWV, and larger reductions in PWV after exercise training have been demonstrated in peripheral arteries [48], suggesting exercise may have differential effects depending on the structural properties of the arterial wall.

Despite the established benefit of exercise training on BP control in the general population, data in people with moderate to severe CKD remain limited [37, 40]. To our knowledge, this is only one of two randomized trials in this population to use 24-h ABPM to measure BP changes in response to exercise training [54, 55]. As BP reduction after exercise training is reported to occur as early as 4 to 8 weeks in the general population [13], to minimize contamination from medication adjustment, we selected 8 weeks as the primary outcome. Adding to the strength of this study, we reported antihypertensive use at baseline as well as changes over follow-up using standardized dosing protocols. Our study also has limitations. Most notably, our study was underpowered to detect a change in SBP due to exercise training. It is important to note that despite offering the weekly supervised sessions in a community facility at no cost, transportation remained the main modifiable barrier to participation. This finding, along with the containment measures imposed as a result of the COVID-19 pandemic, demonstrates the need for home exercise prescriptions that are effective and that participants will engage with.

Our findings offer an important insight into the design of future exercise trials in this population. Although fitness improved in the in-center portion of the trial, there were no changes in step-count or MVPA as measured by accelerometry. This suggests that more emphasis on how participants can integrate physical activity into their daily lives is needed. From other exercise trial data in the CKD population, adherence to the exercise prescription is known to be highly variable [56], particularly when transitioning to the home [43], and remains a major challenge to understanding the therapeutic role of exercise in CKD management. The bimodal pattern to adherence described here suggests that evaluating adherence throughout the trial at specific timepoints could help identify specific groups of participants that would benefit from different strategies. Pragmatic approaches to trial design that accommodate more personalized interventions would therefore offer distinct advantages over traditional trials. Finally, given the multiple pathophysiological mechanisms potentially contributing to hypertension in CKD, novel approaches, such as enrolling patients with
characteristics that predict a favorable response; for example, those with a significant postexercise hypotensive response [57], is one approach.

In conclusion, we demonstrated an improvement in exercise capacity at 8 weeks that was not sustained. Though the study was underpowered to detect the main outcome, changes in BMI and fat free mass were favorable training adaptations that warrant further evaluation. The challenges to exercise trial delivery described here are not unique but do inform potential solutions in terms of the rationale for employing novel approaches for trial design in this population.

Acknowledgments

The authors of this report are grateful to the study coordinators Lalantha Coonghe and Sue Szügyi, as well as Ghenette Houston for administrative support and Sophanny Ti for Figure(s). The authors also thank the patients who participated in this research.

Statement of Ethics

All participants gave their written informed consent to participate at baseline. The study was carried out in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved at baseline. The study was carried out in accordance with the authors and all have been involved in reviewing it for important intellectual content and approved the final version.

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