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ARTICLE

Exercise in patients with hypertension and chronic kidney disease: a randomized controlled trial

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Abstract

Hypertension and chronic kidney disease (CKD) are global public health problems, both associated with higher risk of cardiovascular (CV) and renal events. This trial randomized non-diabetic adult patients with hypertension and CKD stages 2–4 to 16 weeks of aerobic and resistance training or usual care. The primary outcome was the change in estimated glomerular filtration rate (eGFR). Secondary outcomes included changes in systolic and diastolic blood pressure (BP), body weight, fasting blood glucose, lipid profile, high-sensitivity C-reactive protein (hs-CRP), and functional capacity. The analysis was performed by intention-to-treat, using linear mixed-effects models for repeated measures over time. A hundred fifty patients were included in the intervention (76) or control (74) groups. No difference was found in eGFR, BP, body weight, or lipid profile changes between the groups. However, there were significant decreases in hs-CRP [−6.7(−11.7 to −1.8) mg/L] and fasting blood glucose [−11.3(−20.0 to −1.8) mg/dL], and an increase in functional capacity [2′ Step Test 33.9 (17.7–50.0); 30″ Stand Test 2.3 (0.9–3.7)] in exercise group compared with control group. The results of this RCT show that combined aerobic and resistance training could reduce inflammation and insulin resistance in hypertensive patients with earlier stages of CKD, without a significant effect on kidney disease progression. Clinical trials.gov NCT01155128.

Introduction

The benefits of physical activity for the health of the general population are well established, in which large-scale observational studies have found a clear association between exercise and better quality of life, lower risk of adverse events and all-cause mortality [1, 2]. Randomized controlled trials (RCT) have shown similar effects of exercise in chronic diseases, such as heart and respiratory illness, cancer, arthritis, and diabetes. Exercise has been shown to be as effective as any key drugs in reducing the death risk among coronary heart disease patients [3].

Chronic kidney disease (CKD) and hypertension are both worldwide public health problems associated with a substantial increase in the cardiovascular risk. In addition, CKD presents the potential to evolve into end-stage renal disease (ESRD) requiring renal replacement therapy (RRT) [4].

Regardless of all the available evidence on the benefits of exercise, the prevalence of physical inactivity among CKD patients is 50–120% higher than that described in the general population [5]. Only recently this issue has gone to receive proper attention [6]. Although large cohort studies have shown survival benefits for CKD patients who are physically active [7], there are few RCT evaluating the effects of exercise on the health of this population. The available studies are mostly focused on hemodialysis (HD) patients, often showing the benefits of aerobic training on fitness and quality of life [6].

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Despite the ratio of ten patients with earlier stages of CKD to one patient with ESRD [4], there are fewer studies on the effect of exercise in patients with non-dialytic CKD [6]. Exactly this subset of patients that could get the greater benefit from the intervention, not only due to the higher prevalence of earlier CKD, associated with increased cardiovascular risk, as well as due to the possibility of exercise to slow down the decline of kidney function and to delay the need for RRT [8–11]. Given the lack of high-quality evidence on the effects of exercise on the health of patients with CKD in earlier stages, research focusing on this subgroup has been recommended [6].

The present study was designed to evaluate the effects of a 16-week supervised aerobic and resistance training on the rate of estimated glomerular filtration rate (eGFR) decline and changes in cardiovascular risk factors in non-diabetic, hypertensive patients with CKD stages 2–4.

Methods

The methodology of the study was previously reported [12]. It was a parallel design randomized controlled clinical trial. Participants were randomized to one of the following groups: exercise intervention group (IG) or control group (CG). The intervention was applied thrice weekly over 16 weeks.

The institutional review board of the Medical School of the Federal University of Pelotas (number 01/11) approved the protocol. All participants provided written informed consent before entering in the study. The protocol was registered at www.clinicaltrials.gov (Registration Number NCT01155128).

Subjects

The records of the "HiperDia" project at the Primary Health Care Units (PCHU) of the city of Pelotas were reviewed and eligible patients were identified. Hiperdia is a National Health Program of the Ministry of Health to register and monitor patients with hypertension and/or diabetes treated in the Sistema Único de Saúde (SUS), the Brazilian public health system.

Inclusion criteria

Non-diabetic patients 18+ years-old, with high blood pressure diagnosis, and with serum creatinine levels greater than or equal to 1.0 mg/dL and glomerular filtration rate ≤ 60 ml/min/1.73 m^2 estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, or proteinuria ≥ 300 mg/24 h were identified. Since about 80% of patients with earlier stages of CKD are hypertensive [13] we chose the HiperDia program (registration of diabetic and/or hypertensive patients) as a useful way of locating the study sample. The reason for excluding diabetic patients is related to the different course of the disease in these patients, as explained in the study protocol [12]. The diagnosis of hypertension and diabetes was made at the time of inclusion of the patient in the "HiperDia" program, according to the criteria established in the Notebook of Basic Health Care/Diabetes and Hypertension, of the Brazilian Health Ministry [14].

Exclusion criteria

Patients with one or more of the following conditions were excluded: (a) concurrent diagnosis of diabetes mellitus; (b) severe disability, or a lower limb amputation without prosthesis; (c) history of acute myocardial infarction in the past six months; (d) prior renal transplantation; or (e) currently on dialysis.

Primary outcome

Chronic kidney disease progression

eGFR was calculated using the CKD-EPI formula as a measure of kidney function. Serum creatinine measurements were taken at baseline, 8th and 16th week of the study. Serum creatinine was collected on days without exercise and analyzed using the Jaffe Method with distilled water and Roche chemicals.

Secondary outcomes

Blood pressure

Both systolic and diastolic blood pressures (BP) were considered as the means of two separate measurements, 5 min apart. BP measurements were performed in a physician's office, by blinded trained personnel. All measurements were undertaken using an Omron HEM 705-CP digital sphygmomanometer, while the individual was sitting. Each participant was fitted for an appropriately sized arm cuff whose width corresponded to 40%, and length to 80% of the circumference of the individual's arm.

Laboratory measures

At baseline and follow-up PHCU visits, blood was collected and processed after an overnight fasting. Enzymatic colorimetric cholesterol esterase tests were used to measure total cholesterol, as well as high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) levels. High-sensitivity C-reactive protein (hs-CRP) levels were measured by means of a colorimetric competitive ELISA. All biochemical analyses were performed in the same laboratory.

Health-related quality of life (HRQOL)

The Medical Outcomes Study 36—Item Short-Form Health Survey (SF-36) validated to Portuguese language was used to measure participants' quality of life [15]. The domains functional role, physical health, general health, vitality, emotional health, and mental health were included as measures of an individual's quality of life.

Functional capacity was assessed with senior fitness test

(A) 30-s chair stand (sit to stand): Number of full stands that can be completed in 30 s with arms folded across chest [16]. This test involves rising unassisted from a standard height chair (42.6 cm) and sitting back on the chair as fast as possible. Participants were instructed to keep their hands crossed over their chest so they do not use them to push themselves up and their feet should remain in contact with the ground always.

(B) 2-min step test: Number of full knee elevations in front of a wall completed in 2 min, raising each knee to a point midway between the patella (kneecap) and iliac crest (top hip bone). Score is number of times right knee reaches the required height.

(C) 8-foot up-and-go: Number of seconds required to get up from a seated position, walk 8 feet (2.44 m), turn, and return to seated position.

All outcomes assessments were performed by examiners blinded to the subject allocation.

Study procedures

The individuals identified from the PCHU records were visited at home and invited to participate in the study. Eligible participants received a detailed study overview and provided consent. Those who agreed to participate were interviewed by a previously trained professional using a structured questionnaire with information on demographic characteristics (age, race, gender, and marital status); socioeconomic level; and behavioral attributes (tobacco use, alcohol consumption). Use of medications (specifically nonsteroidal anti-inflammatory and antihypertensive drugs) as well as other measures, including height and weight, blood pressure, and physical function, were also obtained at baseline. Body weight was measured using a digital Tanita scale, which is accurate to 100 g. Participants were instructed to stand barefoot while both height and weight were being measured. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Participants were advised to continue their usual clinical appointment schedule.

Randomization

Eligible participants were randomized after baseline assessment. The randomization sequence was obtained using a randomly generated list, in fixed-size blocks of six individuals. There were different intervention and assessment teams, and researchers responsible for randomization were concealed to group assignment.

Exercise protocol

The intervention lasted 16 weeks, with three 60-min physical exercise sessions per week. Each exercise session consisted of 10 min of initial warm-up exercises and joint flexibility, followed by aerobic and muscular endurance exercises. The intensity of each session was personally measured and controlled using the Borg Rating of Perceived Exertion (RPE) scale [17]. The progression of sessions was based on increasing individual's effort: pause ratio, reducing their break times and increasing the time spent on aerobic exercises or muscular endurance sets during each session (Supplemental Table 4). All intervention sessions were led by three physical education professionals.

Participation adherence promotion

To ensure that participation rates remained high for intervention sessions and follow-up examinations, promotion strategies were used. All participants received sportswear, including shoes, pants and t-shirts, suitable for physical exertion, either at the beginning of the study (IG) or at the end of the study (CG). Participants in the IG received transportation vouchers to facilitate their travel to the intervention site. During the baseline analysis, participants were informed of the importance of the intervention sessions and follow-up visits. They were asked to provide contact information, including their full name and address, as well as a telephone number for two close friends of relatives to be used in the event of their absence. Throughout the study, IG participants who skipped a physical activity session were contacted using the previously provided contact information to clarify the reason for their absence. At that time, they were also encouraged to continue participating in the remaining intervention sessions.

CG protocol

The CG continued to receive the usual care at the PCHU, according to the Guidelines of Primary

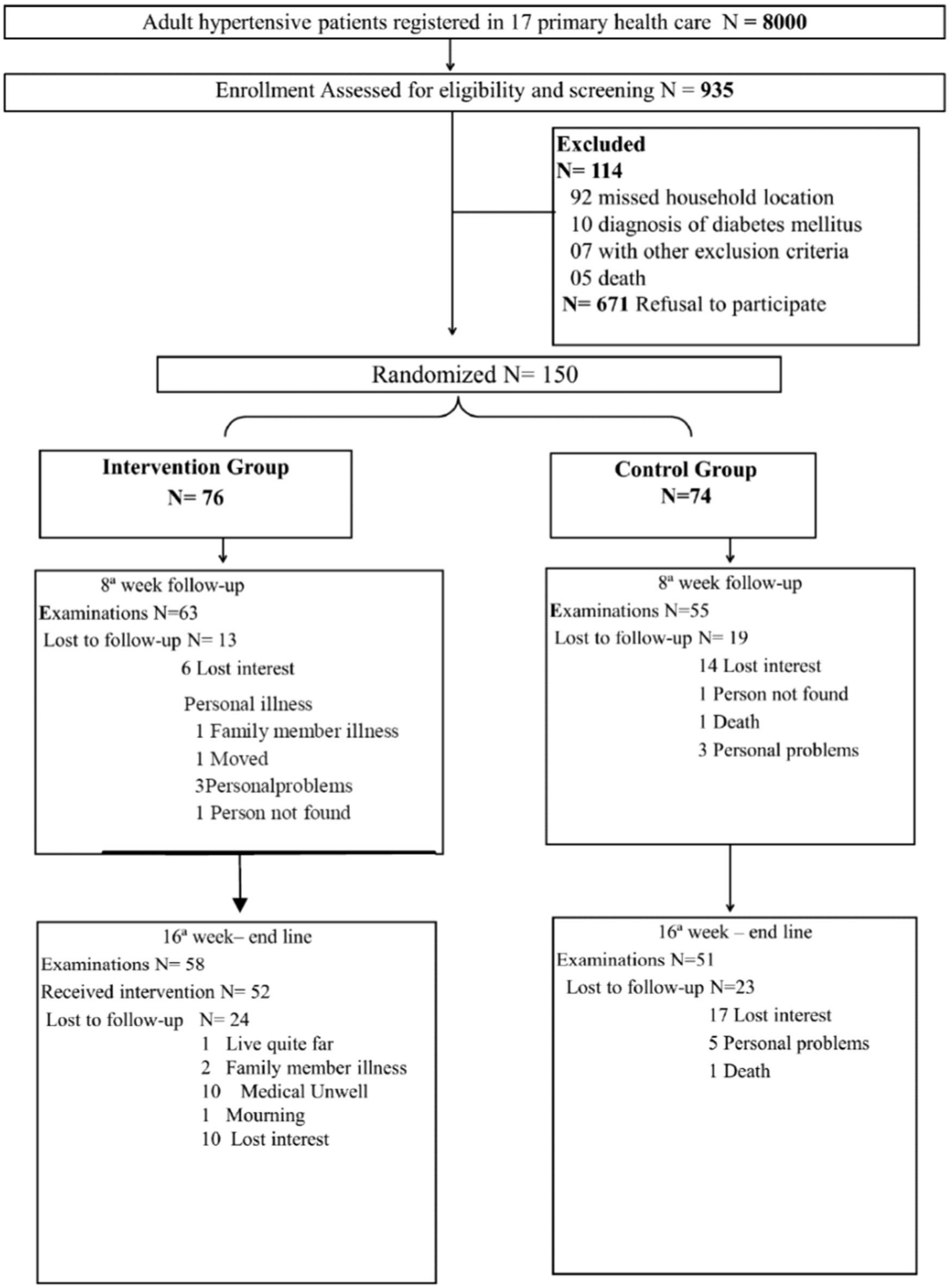

Fig. 1 Flow chart of the intervention model

Health Care from the Ministry of Health for the prevention of cardiovascular diseases [18]. The intervention protocol was offered to all control individuals after the end of the study.

Statistical analyses

A group of 290 non-diabetic patients with hypertension and CKD stages 2–4, followed in one of the Primary Health

Table 1 Baseline characteristics of participants in intervention and CGs

Baseline measures (mean (SE), median (IQR) or *n* (%))	Intervention (*n* 76)[a]	Control (*n* 74)[a]	*p* Value**
Female	49 (64.5%)	46 (62.2%)	0.77
Age (years)	65.0 (1.2)	65.1 (1.3)	0.92
Caucasian	46 (67.7%)	45 (68.2%)	0.61
No litteracy	11 (14.9%)	10 (13.9%)	0.88
Body weight (kg)	73.0 (62.7–85.0)	74.4 (66.7–83.4)	0.70
BMI (kg/m^2)	29.7 (0.7)	30.1 (0.6)	0.66
SBP (mmHg)	161.6 (3.4)	162.0 (3.5)	0.88
DBP (mmHg)	89.8 (1.6)	91.4 (1.6)	0.46
ACE use	37 (56.9%)	38 (62.3%)	0.54
ARB use	13 (22.0%)	5 (10.7%)	0.10
Hemoglobin (g/dL)	14.3 (0.2)	14.1 (0.2)	0.62
hs-CRP (mg/L)	2.0 (0.5–6.6)	1.5 (0.5–4.3)	0.47
Total cholesterol (mg/dL)	204.0 (177.0–228.0)	204.0 (186.0–241.0)	0.42
HDL cholesterol (mg/dL)	57.3 ± 1.4	51.7 ± 1.5	0.01
LDL cholesterol (mg/dL)	121.0 (99.4–135.2)	127.2 (100.0–153.6)	0.26
Blood glucose (mg/dL)	99.0 (87.5–105.5)	94.0 (89.0–109.0)	0.82
eGFR (mL/min/1.73 m^2)	63.4 (2.3)	61.6 (2.4)	0.58
Functional capacity (SF-36)	60.0 (40.0–77.5)	65.0 (45.0–80.0)	0.21
Role physical (SF-36)	25.0 (0–100.0)	50.0 (0–100.0)	0.63
General health (SF-36)	65.0 (52.5–80.0)	67.0 (50.0–75.0)	0.44
Vitality (SF-36)	60.0 (45.0–77.5)	55.0 (40.0–75.0)	0.38
Role emotional (SF-36)	67.0 (0–100.0)	67.0 (0–100.0)	0.82
Mental health (SF-36)	74.0 (56.0–84.0)	72.0 (48.0–84.0)	0.36
Up-and-Go test (s)	6.3 (5.4 to 7.9)	5.9 (4.8 to 6.6)	0.04
Step Test 2′ (*n*)	117.4 ± 6	128.8 ± 5.8	0.21
Chair-Stand 30″ test (*n*)	10.7 ± 0.5	10.5 ± 0.4	0.70

***p* Value for difference between treatment and CGs at baseline analyzed by *t*-test for parametric variables, Mann–Whitney for non-parametric, and χ^2 test for categorical variables

[a] The highest number of missing values was 4 (for BMI)

Units, was used in a pilot analysis to calculate the sample size. The mean eGFR in this sub-sample was 48.47 ± 9.61 mL/min/1.73 m^2. The sample size was calculated to allow the detection of a difference in eGFR between the IG and CG greater than or equal to 10%, significant at the 5% level (two-tailed), and with a power of 80%. To fulfill these requirements, it was estimated the minimal sample size of 63 individuals in each group.

The χ^2 and Student's *t*-tests were used to compare categorical and continuous variables, respectively, between the two groups at baseline. All available data were examined using linear mixed-effects models for repeated measures over time, including data of the baseline, 8th week and 16th week. Covariates included baseline value, age, sex, race/ethnicity, and use of medications. Results are presented as least squares adjusted means with 95% confidence intervals (CI). Main analysis used the intention-to-treat principle and included all participants as randomized. To analyze the efficacy of the exercise program in participants who effectively engaged in the intervention, we conducted a per-protocol analyses limited to a subgroup of control participants who had assessments at baseline, weeks 8 and 16 compared with the participants of the IG who completed at least 70% of the exercise sessions.

All participants were asked to return for follow-up measurements, regardless of their adherence to their assigned group. Differences between the study participants that adhered to the study and those who dropped out after randomization were assessed using the χ^2 test and *t*-test. Additional analyses included multivariate regression and post hoc subgroup analyses. First, multivariate linear regression models were performed to adjust for potential imbalances in baseline characteristics between the two groups. Second, in post hoc analyses, the effect of the

Table 2 Effect of the 16-week exercise intervention on clinical outcomes (intention-to-treat analysis)

Variable	Baseline (mean (95% CI))	Week 16 (mean (95% CI))	Within-group (diff (95% CI))	Between-group (diff (95% CI))
eGFR (mL/min/1.73)				
Control (49)	61.6 (57.1–66.1)	59.0 (54.2–63.8)	−2.6 (−6.1 to 0.9)	–
Exercise (58)	63.4 (59.1–67.8)	61.5 (57.0–66.1)	−1.9 (−5.1 to 1.3)	0.7 (−4.0 to 5.4)
SBP (mmHg)				
Control (49)	162.0 (153.3–170.7)	150.9 (143.3–158.5)	−11.1 (−17.7 to −4.4)	–
Exercise (58)	159.4 (151.8–167.1)	147.0 (141.0–153)	−12.1 (−18.4 to −5.8)	−1.6 (−18.2 to 7.0)
DBP (mmHg)				
Control (49)	84.2 (80.6–87.8)	90.5 (86.6–94.4)	−6.3 (−10.1 to −2.5)	–
Exercise (58)	89.1 (85.7–92.5)	83.3 (80.4–86.2)	−5.8 (−9.4 to −2.1)	0.7 (−4.0 to 5.4)
Weight (kg)				
Control (50)	75.2 (71.0–79.4)	75.0 (71.0–79.2)	−0.2 (−2.9 to 2.6)	–
Exercise (58)	75.9 (71.7–80.2)	75.0 (70.9–79.1)	−0.9 (−1.5 to −0.3)	−0.3 (−0.2 to 1.7)
hs-CRP (mg/L)				
Control (47)	5.5 (0.4–11.5)	12.1 (1.5–22.7)	6.6 (1.1–12.1)	–
Exercise (56)	7.7 (3.6–11.9)	6.1 (3.4–8.9)	−1.6 (−5.1 to 1.9)	−6.7 (−11.7 to −1.8)**
T Chol. (mg/dL)				
Control (49)	212.1 (200.2–224.9)	189.0 (176.3–201.8)	−23.1 (−31.3 to −15.0)	–
Exercise (58)	206.6 (193.5–219.7)	189.4 (177.5–201.2)	−17 (−24.9 to −9.1)	5.6 (−5.8 to 17.1)
HDL (mg/dL)				
Control (49)	52.2 (48.5–55.8)	46.3 (43.2–49.5)	−5.8 (−8.1 to −3.6)	–
Exercise (58)	58.0 (54.5–61.4)	51.9 (48.4–55.4)	−6.0 (−8.14 to −3.9)	0.0 (−2.7 to 2.7)
LDL (mg/dL)				
Control (47)	126.0 (117.0–135.0)	109.0 (99.4–118.6)	−17.0 (−24.8 to −9.3)	–
Exercise (56)	122.4 (111.1–133.7)	110.9 (100.9–120.9)	−11.4 (−18.9 to −4.0)	7.8 (−2.9 to 17.8)
Glucose (mg/dL)				
Control (49)	107.6 (97.8–117.3)	106.5 (93.9–119.0)	−1.1 (−12.0 to 9.9)	–
Exercise (58)	105.2 (97.5–112.9)	94.3 (90.0–98.6)	−10.9 (−17.9 to −3.9)	−11.3 (−20.0 to −1.8)*
Up-and-go				
Control (43)	6.4 (5.8–7.0)	6.0 (5.4–6.5)	−0.4 (−0.9 to 0.1)	–
Exercise (55)	6.7 (6.2–7.3)	5.7 (5.2–6.2)	−1.0 (−1.4 to −0.6)	−0.6 (−1.2 to 0.1)
Step Test 2′				
Control (44)	127.6 (115.2–140.1)	136.3 (123.7–148.9)	8.7 (−3.4 to 20.7)	–
Exercise (55)	125.7 (113.6–137.9)	168.3 (156.5–180.0)	42.6 (31.8–53.3)	33.9 (17.7 to 50.0)***
Stand 30″				
Control (44)	10.2 (9.2–11.2)	11.3 (10.3–12.3)	1.1 (0.1–2.1)	–
Exercise (55)	11.0 (10.1–12.0)	14.4 (13.5–15.4)	3.4 (2.4–4.3)	2.3 (0.9–3.7)**

Values are expressed as fitted mean (mixed linear model analysis), 95% CI for difference between means of exercise and CGs at 16 weeks, *CI* confidence interval; $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$

intervention on the change in glomerular filtration rate was evaluated in subsets of participants defined by sex, age (greater than vs. less than 65 years), baseline glucose (greater or equal vs. <100 mg/dL), and baseline eGFR (greater or equal vs. <60 mL/min/1.73 m^2). $P \leq 0.05$ (two-tailed) was considered as statistical significance. Data analysis was conducted using the statistical program Stata (Version 13.0, StataCorp, College Station, Texas)

Results

After reviewing the medical records of ~8000 adults with high blood pressure registered in 17 PCHU in Pelotas, Brazil, 935 individuals who fulfilled the eligibility criteria were identified.

Of these, 114 patients were excluded from the study because unknown household location (92), concurrent diagnosis of diabetes mellitus or presence of others

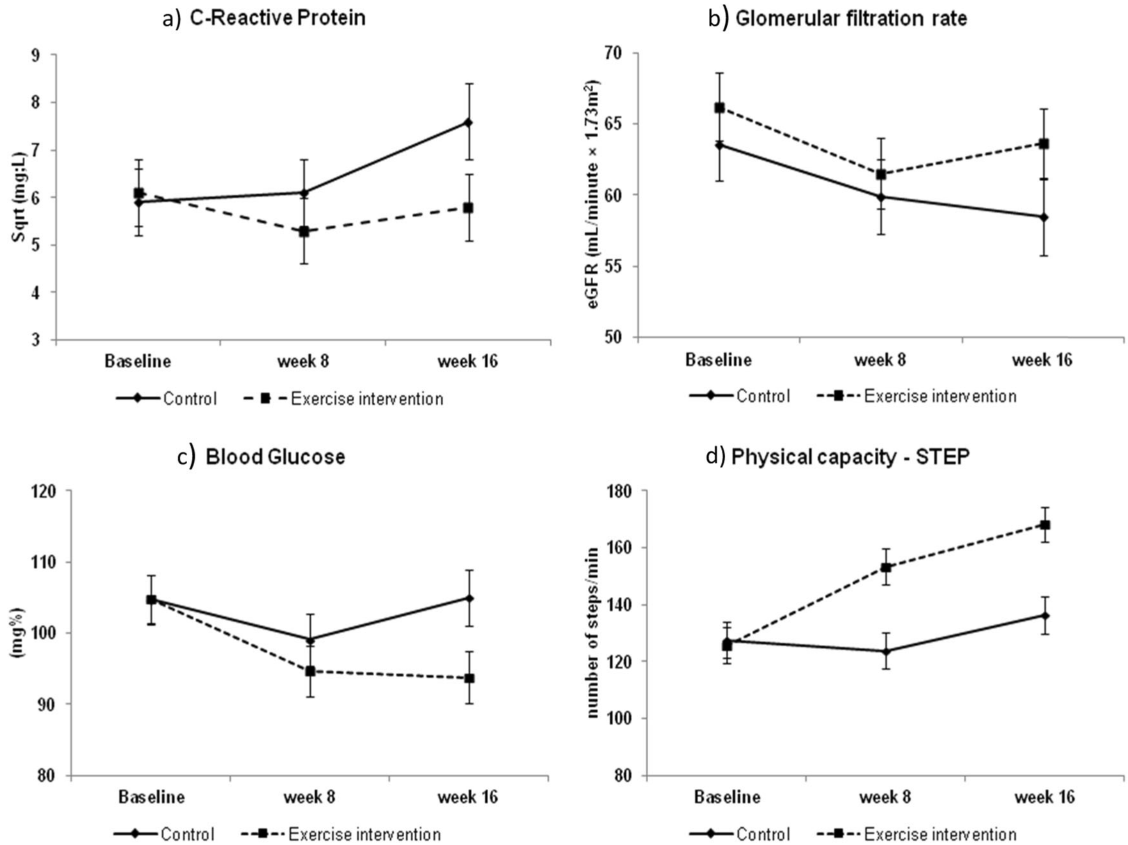

Fig. 2 **a** Mean change in hs-CRP between groups. **b** Mean change in eGFR between groups. **c** Mean change in fasting blood glucose between groups. **d** Mean change in physical capacity (Step 2′) between groups (intention-to-treat analysis)

exclusion criteria (17), or death (5). Of 821 subjects invited to participation, 671 individuals refused to participate in the study. The main reason given for refusal was a perceived difficulty in getting to and from the intervention site (271), although individuals were informed that they would receive travel vouchers to facilitate transportation. The remaining 150 individuals who agreed to participate were included in baseline measurements and randomly allocated to either the IG (76) or the CG (74). After 8 weeks of intervention, 63 individuals from the IG and 55 from the CG were examined. At the final evaluation, 58 individuals from IG and 51 individuals from CG were examined (Fig. 1).

Baseline data

The average age of participants in both groups was 65 years, and about 2/3 of all participants were white females. The mean BMI was 29.9 kg/m^2 (SE 0.7) in the IG and 29.6 kg/m^2 (SE 0.7) in the CG. There was no significant difference between groups at baseline, except for HDL cholesterol, that was slightly higher in the IG. The eGFR was 63.4 mL/min/1.73 m^2 (SE 2.3) in the IG and 61.6 mL/min/1.73 m^2 (SE 2.4) in the CG ($p = 0.58$). The use of drugs that affect the renin-angiotensin system was similar between groups, but only 115 participants could provide information about drugs, and no patient was using non-steroidal anti-inflammatory drugs. The fitness test scores were similar between IG and CG at baseline, except for the Up-and-Go scores, which were worst in the IG (median 6.3, IQR 5.4–7.9 s) than in the CG (median 5.9, IQR 4.8–6.6 s). The Up-and-Go Test and Test Step 2′ scores were within normal range for 50% of the population. Chair-Stand 30′ test was 10.7 (SE 0.5) (the number of times the subject stood up from a chair) in IG and 10.5 (SE 0.4) in CG (values between 11 and 16 are expected to general population) (Table 1).

Intervention monitoring and adherence

A total of 109 individuals completed the study, 58 in the IG (66%) and 51 in the CG (78%), $p = 0.120$. Six participants of the IG dropped-out and 24 were lost at follow-up. Twenty-three participants of the CG were lost at follow-up. There was no documented case of musculoskeletal injury among participants during the intervention. One participant randomized to IG had an increase in BP during exercise, leading to the interruption of that session, and one participant of the CG died during the study. Among IG participants, only 37 individuals adhered to more than 70% of the

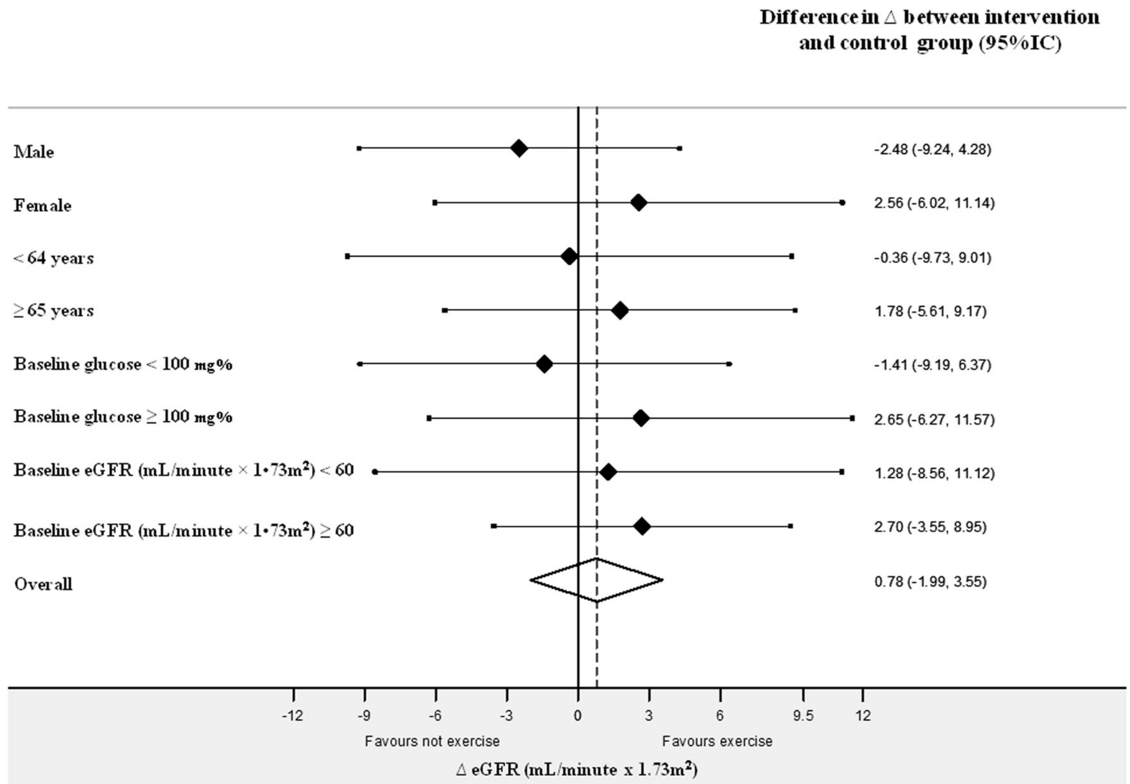

Fig. 3 Subgroup analysis: difference in mean GFR variation between exercise and CGs

training sessions and were included in the per-protocol analysis. At baseline, patients who were lost during follow-up, dropped-out of training, or had low attendance at training sessions were not different in demographic, laboratory or clinical aspects from those who strongly adhered to the intervention. However, participants with low or no compliance had significantly lower physical and mental HRQOL, in addition to a tendency to lower objective measures of functional capacity (Supplemental Table 1).

Outcome measures

Table 2 describes the variation (delta, Δ) that occurred throughout the study among all the variables according to intention-to-treat analyses, derived from a linear mixed model. The decrease in eGFR levels did not significantly differ between the CG and IGs, although the change was in the hypothesized direction. The between-groups difference in eGFR was estimated to be +0.7 (−4.0 to +5.4 mL/min/1.73 m^2) considering time and intervention interaction.

As shown in Fig. 2a, hs-CRP levels were reduced after 16 weeks of exercise, −6.7 (−11.7 to −1.8) mg/L when compared to the CG. The blood glucose decreased in the IG in −11.3 (−20.0 to −1.8) mg/dL compared the CG (Fig. 2c). The functional fitness, as assessed by the Step Test and the Chair Stand, improved by nearly 34 further steps for 2 min, and two full stands in 30 s, respectively, in the IG, when compared with the CG (Fig. 2d). There was no significant difference in other variables between groups after intervention. Considering the analysis within the groups, patients who exercised had a decrease in body weight of −0.9 (−1.5 to −0.3) kg, while the CG showed no change in body weight. However, there was no difference in delta body weights between the groups. The blood pressure (systolic and diastolic), hemoglobin, hematocrit, total cholesterol, HDL cholesterol, and low-density lipoprotein (LDL) cholesterol decreased significantly in exercise and CGs compared with baseline levels, but also had no difference between the groups.

The per-protocol analysis, which included only the 37 participants of the IG with at least a 70% attendance rate at exercise sessions, showed no different results from the intention-to-treat analysis for most outcomes. However, the greater reduction of glycemia in the IG showed by the ITT analysis became non-significant in the per-protocol analysis (−7.6 95% CI −18.2 to 2.9, $p = 0.15$), despite the direction of the effect has remained the same. On the other hand, the functional capacity test Up-and-Go attained significant difference between CG and IG (−1.3 95% CI −2.0 to −0.5, $p = 0.001$) (Supplemental Table 2). The e-GFR decreased from 63.2 (95% CI 57.9–68.5) to 61.4 (95% CI 55.9–66.8) at 8th exercise week, and to 60.3 (95% CI 54.9–65.5) at 16th week, in the low or no-adherent group ($n = 39$). Among the highly adherent group ($n = 37$), the e-GFR was 66.7 (95% CI 60.4–72.9), 65.5 (95% CI 59.2–71.8), and 65.8 (95% CI 59.5–72.1) at the same time points. Although no statistically significant difference was obtained, the direction of the association suggests a possible decline of e-GFR only among the non-adherent group (Supplemental Fig. 1). The results were also not different from the crude analysis when adjusting for gender, age, education level, and HDL cholesterol at baseline (Supplemental Table 3).

In subgroup analyses, no difference in eGFR decline between IG and CG was observed within each pre-defined subgroup (sex, age, glucose, or eGFR at baseline) (Fig. 3).

Discussion

The major finding of this RCT is that a 16-week aerobic and endurance exercise program had no effect on the glomerular filtration rate decline in patients with CKD stages 2–4. To our knowledge, this is currently the largest RCT designed to evaluate the effect of physical training on short-term progression of CKD.

Previous studies in animal models of CKD have found that swimming exercise preserves glomerular filtration [8, 9, 19]. However, if the exercise applied to the animal model was land-based, no beneficial effect on kidney function was observed [20]. Besides animal studies, there are few previous RCT on the issue, all of them with sample sizes below 30 patients [10, 11, 21, 22]. Castaneda et al. study describes slowing of GFR decline with resistance training associated to low-protein diet applied for 12 weeks in 14 CKD patients, compared with 12 control patients [10]. However, data on GFR, a secondary outcome, were available only in 8 patients in the exercise group and 10 in the CG, while protein restriction was applied only to the IG, making it difficult to know if the change in kidney function was due to exercise, diet, or the combination of these interventions. Greenwood et al. applied 12 months of aerobic and resistance training to 10 patients with CKD stages 3 or 4, compared with 10 patients in usual care, and found a slower decline in eGFR among exercisers, despite no significant difference in eGFR at the end of the study [11]. The RCT with the longest follow-up (20 months) applied unsupervised aerobic exercise and reported no effect of physical activity on glomerular filtration decline [21]. Two other studies with sample sizes of 21 and 13 CKD patients also found no effect of aerobic exercise on CKD progression [11, 23].

The divergence of results between clinical trials and studies using animal models could be due to different effects of the exercise on CKD across animal species. Another possibility is that the environment where the exercise was developed could be a determinant of its effects. Water immersion per se is known to improve kidney function due to improved hemodynamic and hormonal balance [24]. The divergence of results could also be due to insufficient power of previous RCT, all with small sample size.

However, despite the larger sample size and the significant improvement of aerobic fitness achieved, the present study also found no effect of exercise on GFR decline in patients with CKD.

We also could not find any effect of exercise on BP control. There was a significant decrease in BP throughout the study period, but this reduction was not different between the groups, being probably caused by regression to the mean or Hawthorne effects. Despite the inverse relationship between physical activity and blood pressure that has been demonstrated in the general population [2], most studies in CKD patients have found no effect of exercise on BP control [6, 23].

However, we found salutary effects of exercise on other secondary outcome measures, such as hs-CRP, and fasting glucose. The effects of exercise on inflammatory biomarkers in CKD patients have been evaluated in some RCT, most of them in HD patients, in general with positive results [6]. Six studies in earlier stages of CKD assessed hs-CRP [23, 25–29], of which only one, that have also applied resistance training, found a positive association between exercise and reduction in this biomarker [25]. Considering that chronic inflammation is always present in CKD and may be a mediator of malnutrition, cardiovascular disease, progression to ESRD and poorer survival [30], the potential control of the inflammatory status through exercise, especially resistance training, is a noteworthy finding.

There was a decrease in body weight throughout the study period among patients who exercised, but this decrease was not significantly different between groups. Therefore, our findings suggest a direct effect of exercise on inflammation and fasting glucose among CKD patients, independent of weight loss. Most studies about effects of exercise on heath in general population have found a correlated decrease in body weight and hs-CRP, with some authors even stating that exercise training without weight loss is not associated with a reduction in hs-CRP [31].

There was also a significant reduction in fasting blood glucose in the IG, while fasting glycemia remained unchanged in the CG. Some studies have found that insulin resistance is the major determinant of higher fasting glucose [32]. Thus, although no validated measure of insulin sensitivity has been employed, our finding suggests that exercise could reduce insulin resistance.

The present study has some limitations. First, there was a low adherence to exercise. However, it is important to note that exercise improved physical performance, even with low levels of compliance among participants, and that low adherence to exercise is a real-life phenomenon. In our per protocol analysis, we found that individuals who attended 70% or more of the exercise sessions could maintain stable eGFR. Those individuals who did not adhere to the intervention sessions, or were placed in the CG, showed decreased kidney function. However, other variables that lead to poor adherence may also have effect on kidney disease progression, such as worse physical and mental quality of life due to clinical conditions. Health-related quality of life was lower in our subgroup of non-adherent patients, which may reflect a poorer general health status. In addition, the generalizability of our findings is limited because diabetic and normotensive patients were excluded. Therefore, caution should be exercised prior to extrapolating any of this study's findings to all patients with CKD.

Another potential shortcoming was the use of creatinine to estimate GFR. The serum levels of this endogenous filtration marker may be affected by variables other than GFR, such as body mass and diet. Some authors have also described significant differences in serum creatinine levels between physically active and sedentary individuals. However, this difference depends on the training modality and is directly related to the increase in BMI and lean mass. The exercise training session, on the other hand, seems to cause minimal and transient changes in the serum level of serum creatinine [33]. Although the gold standard for the measurement of GFR is urinary clearance of an exogenous filtration marker, these measurements are expensive, inconvenient, and may vary throughout the day. The most frequently used end-point of doubling of serum creatinine concentration from baseline, corresponding to a 57% reduction in eGFR, is a late event, requiring longer follow-up. In addition, declines in estimated GFR smaller than a doubling of serum creatinine concentration occurred more commonly and were strongly and consistently associated with the risk of ESRD and mortality, supporting consideration of smaller declines in estimated GFR as an alternative end-point for CKD progression. Finally, the short follow-up could have precluded the identification of potential effects of exercise on kidney function.

Despite no decrease in CKD progression could be identified in subjects who were randomized to the exercise group, the positive changes observed in hs-CRP and blood glucose levels indicate that exercise training could improves the overall health of individuals with hypertension and earlier stages of CKD. All the health parameters modified by physical activity in this study are cardiovascular disease risk factors, the leading cause of death in individuals with CKD. Therefore, although we need RCT measuring long-term outcomes, we consider our current evidence as sufficient to advocate for exercise be encouraged by the health system, with the inclusion of exercise programs in the care of patients with CKD as a major priority.

Summary Table

What is known about topic?

- Physical activity is associated with improved health outcomes in the general population, and in patients with several chronic diseases, including CKD on hemodialysis;
- CKD is associated with high rates of physical inactivity.

What this study adds?

- Exercise applied to patients with earlier stages of CKD did not change the rate of glomerular filtration decline in the short term;
- Exercise reduces fasting glucose and hs-CRP levels among hypertensive and non-diabetic patients, with earlier-stages CKD.

Author contributions FCB, ISS, and PCH conceived the concept for the study and are accountable for its design. FCB, AR, FBDV, and GM conducted the data management process and statistical analyses with help and guidance from drafted the manuscript. MB, DU, GM, ISS, and PCH contributed to the interpretation of the data. All the authors revised the text for important intellectual content, approved the final manuscript, and are accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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