Blood Flow Restriction Training Blunts Chronic Kidney Disease Progression in Humans

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ABSTRACT

CORRÊA, H. L., R. V. P. NEVES, L. A. DEUS, M. K. SOUZA, A. S. HARO, F. COSTA, V. L. SILVA, C. A. R. SANTOS, M. R. MORAES, H. G. SIMÕES, J. W. NAVALTA, J. PRESTES, and T. S. ROSA. Blood Flow Restriction Training Blunts Chronic Kidney Disease Progression in Humans. *Med. Sci. Sports Exerc.*, Vol. 53, No. 2, pp. 249–257, 2021. **Purpose:** This study aimed to verify the effect of 6 months of periodized resistance training (RT) with and without blood flow restriction (BFR) in patients with stage 2 chronic kidney disease (CKD) on glomerular filtration rate (GFR), uremic parameters, cytokines, and klotho–fibroblast growth factor 23 (FGF23) axis. **Methods:** A total of 105 subjects were randomized in three groups of 35 each: control (CTL), RT, and RT + BFR. A first visit was required for an anamnesis to evaluate the number of medications and anthropometric measurements (body weight, height, and body mass index). Muscle strength (one-repetition maximum) was assessed. Venous blood samples were collected at baseline and after 6 months of training in all patients for the analysis of markers of renal function and integrity, as well as for the determination of the inflammatory profile. Statistical significances were adopted with $P < 0.05$. **Results:** Both training therapies attenuated the decline of GFR ($P < 0.05$). The majority of CTL patients declined to stage 3 CKD (88.5%), whereas fewer incidents were noted with RT (25.7%) and RT + BFR (17.1%). Improved uremic parameters as well as inflammation (IL-6, IL-10, IL-15, IL-17a, IL-18, and TNF-α) and klotho–FGF23 axis in RT and RT + BFR ($P < 0.05$) were observed. Monocyte chemoattractant protein 1 was not changed ($P > 0.05$) but presented a large effect size (Cohen's d), demonstrating a propensity for improvement. **Conclusion:** Six months of periodized RT with and without BFR in patients with stage 2 CKD attenuated the progression of the disease by maintaining GFR, improving uremic parameters, cytokine profile regulation, and klotho–FGF23 axis. **Key Words:** INFLAMMATION, KLOTHO–FGF23 AXIS, RENAL FUNCTION, NEPHROLOGY, UREMIC PROFILE, STRENGTH TRAINING

Normal kidney function is essential in the modulation of systemic and molecular pathways related to the role of other cells, tissues, and organs (1). On the other hand, kidney function is also affected by intrinsic and extrinsic components that may promote several changes in renal integrity (i.e., immune-related injuries) (2). There is a close relation between the renal function and the immune system, with chronic inflammation mediating renal damage and the progression of chronic kidney disease (CKD) (3).

CKD is recognized as a public health problem, affecting 10% to 15% of the population (4,5). This disease is characterized by the progressive decline in glomerular filtration rate (GFR) and stratified into five stages, although the last stage is considered the end stage of the disease, in which approximately 90% of the nephrons are deteriorated (5). The final stage requires dialysis and is associated with increased comorbidities such as frailty, cardiovascular diseases, and mortality (6). Another condition associated with CKD is the accumulation of fibroblast growth factor 23 (FGF23, which is a marker of renal deterioration) and the decrease of klotho (antiaging protein), which directly impairs bone metabolism and cardiovascular protection, respectively (7). Indeed, because the klotho–FGF23 axis follows the GFR decline, both have

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pharmacological applications with respect to the prevention and treatment of CKD (8). However, the effect of exercise training on the klotho–FGF23 axis is still poorly explored.

Considering the "silent revelation," CKD is rarely diagnosed in its early stages, and its progression is irreversible (4). Moreover, patients with stage 3 and four CKD have a higher probability of death due to cardiovascular outcomes before reaching the end stage (9). In this regard, identifying patients in stage 2 and proposing treatment to attenuate the progression of CKD can be an essential tool for the prevention of the outcomes inherent to this chronic condition. Thus, pharmacological and nonpharmacological strategies are being investigated to blunt the progression of CKD (10–14).

Recent scientific investigations in humans (10,11) and rats (13,14) with CKD provide evidence that physical exercise is a nonpharmacological therapy that contributes to the prevention and treatment of the disease. Resistance training (RT) seems to improve renal function and decrease blood pressure (BP) and macrophage infiltration, along with increasing the anti-inflammatory defense in the kidney, muscle mass, and strength in an animal model of CKD—5/6Nx (13,14). Hence, exercise is considered as medicine for patients with CKD (15).

There is a high rate of abandonment of this population in training programs due to side effects from pharmacological treatment and conditions such as anemia, frailty, and depression that decrease the likelihood of participation in exercise sessions (5). In this regard, blood flow restriction (BFR) training has been used as a method that promises similar effects as conventional training, enabling the prescription of lower exercise intensities in both healthy (16) and pathological (10,11,17) subjects. Therefore, the possibility of applying this training model as a novel exercise therapy against the progression of CKD is of importance.

This research aimed to verify the effect of 6 months of periodized RT with and without BFR in patients with stage 2 CKD on GFR, uremic parameters, inflammation, and FGF23–klotho axis. We hypothesize that both training models attenuate the progression of CKD with a similar impact on GFR and uremic parameters, with a decrease in inflammatory markers, and improved FGF23–klotho axis.

METHODS

Study population. Two hundred and twenty-nine male and female patients diagnosed and classified with stage 2 CKD based on estimated GFR (eGFR) according to the equation of Larsson et al. (18) were enrolled to participate in this clinical trial. Participants were informed about the procedures and possible risks of participation in the study. Before participation in the research project, each participant completed a medical history questionnaire and signed a written informed consent form. The study was conducted according to the Declaration of Helsinki (1975). All methods and procedures were approved by the Local Human Research Ethics Committee, Brazil (no. 08856012.6.0000.5505). Obese patients with stable renal function and proper adherence to medication were recruited by their higher levels of inflammation once it hastened the progression of CKD (19). Although people with stage 2 CKD who are not obese do not have the same levels of inflammation, FGF, and klotho, they present a constant decrease of renal function and other comorbidities associated to CKD progression, such as hypertension and diabetes that also increase inflammation, and tissue damage. Exclusion criteria were as follows: decompensated patients, CKD of stage 3 or higher, neurodegenerative diseases, osteoarticular diseases, autoimmune diseases, lupus erythematosus, congenital renal diseases, and other possible comorbidities that could limit the individual to perform the physical tests and exercise training. Thus, 88 participants were excluded: 63 because they did not meet the inclusion criteria, and 25 who declined to participate. Therefore, 141 patients were allocated and randomized into the experimental groups.

Randomization and intervention. Randomization was stratified according to baseline variables, including sex, body weight, body mass index, and medication. The 141 patients were randomized into three groups: control group (CTL; n = 47), RT group (n = 50), and RT with BFR group (RT + BFR; n = 44). All patients underwent physical testing to determine initial muscle strength to prescribe RT. Following this, there were 12 exclusions in CTL, 7 due to physical complications, 3 sleep problems, and 2 withdrawals. In the RT group, 15 subjects were excluded, 8 due to physical complications and 7 withdrawals. In the RT + BFR group, 9 subjects were excluded, 5 with physical complications and 4 due to family problems. In the follow-up of these analyses, each group consisted of n = 35. The subject enrollment and randomization flowchart is shown in Figure 1.

Physical assessment. A first visit was required for an anamnesis to evaluate the number of medications and anthropometric measurements (body weight, height, and body mass index). Muscle strength (one-repetition maximum [1-RM]) was assessed according to Fleck and Kraemer (20), using Technogym® equipment (Cesena, Italy). Before 1-RM testing, a warm-up for the first exercise of both upper and lower limbs was performed. The warm-up consisted of 8 repetitions at 50% of the estimated 1-RM, plus 3 repetitions of the estimated 1-RM with 1 min of rest between the sets. In the case of concentric failure, an opportunity for the patient to try again with a lower resistance (5%–10% of the load) was provided. 1-RM tests were performed for eight exercises: bench press, seated row, shoulder press, triceps pulley, barbell curls, leg press 45°, leg extension, and leg curl. Tests alternated between upper and lower limbs and were performed at least 5 min apart. 1-RM was tested after 2 wk of familiarization, after 3 min of rest, and subjects completed three to five 1-RM attempts with progressive charges (~5%). In addition, 1-RM was evaluated every 2 months throughout the intervention.

RT prescription. Patients in the CTL group completed the initial physical tests but did not participate in any physical training program. Both treatment groups that performed physical training had 6 months of programming with intensity adjusted every 2 months, according to the applied model: RT, first 2 months, 1–3 sets of 12 repetitions at 50% 1-RM, 3 $d \cdot wk^{-1}$; next 2 months, 2–3 sets of 10 repetitions at 60%

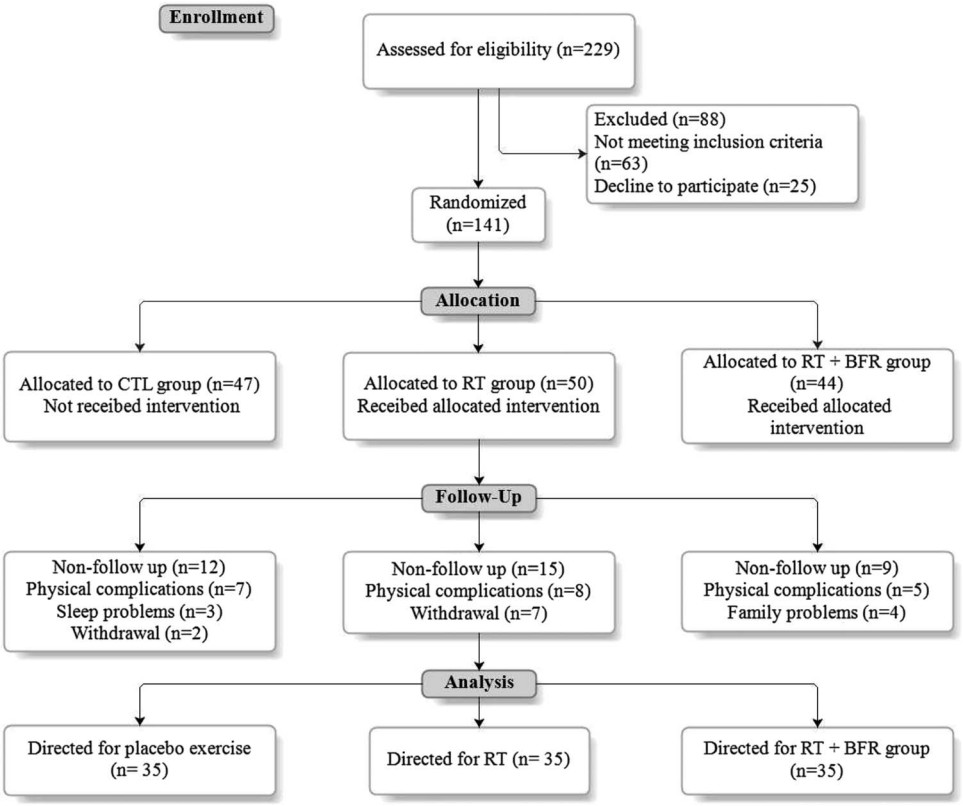

FIGURE 1—Participant flowchart. CTL, control group; RT, resistance training group; RT + BFR, resistance training with BFR group.

of 1-RM, 3 d·wk^{-1}; last 2 months, three sets of 8 repetitions at 70% 1-RM, 3 d·wk^{-1}; RT + BFR, first 2 months, 1–3 sets of 12 repetitions at 30% of 1-RM, 3 d·wk^{-1}; middle 2 months, 2–3 sets of 10 repetitions at 40% 1-RM, 3 d·wk^{-1}; last 2 months, three sets of 8 repetitions at 50% 1-RM, 3 d·wk^{-1}. Systolic BP (SBP) was evaluated, and for the patients from the RT + BFR group, 50% of SBP restriction was used to prescribe RT (21,22). All training sessions were performed with fixed repetitions, alternating between superior and inferior limbs with a low cadence. All patients exercised under the individualized supervision of a strength and conditioning professional. Training programs are described in Figure 2.

Determination of BFR. To prescribe RT + BFR training, SBP was measured using an automated oscillometric BP device (Microlife®, 3A-BP 1PC, 5 Switzerland). The patient was kept in a calm environment, seated for 10 min, while BP was measured according to the recommendations of the American Heart Association (23), in both arms. Restriction of 50% of the measured SBP was applied to each arm for the application of RT + BFR of the upper limbs (21) using equipment from CardioMed Scientific (Curitiba, Brazil). To prescribe RT + BFR for the lower limbs, an 18-cm-wide cuff (CardioMed Scientific) was placed in the proximal portion of the thigh (inguinal fold region) and inflated until the absence

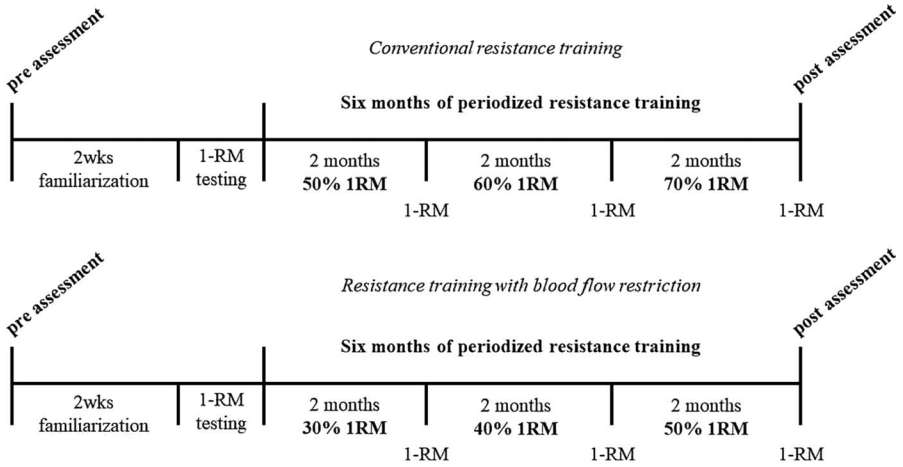

FIGURE 2—Experimental design.

of the tibial artery blood pulse. Thus, a 50% restriction of SBP was applied in both legs during lower body exercises (22). SBP was evaluated once a week to adjust the training pressure when necessary. The mean cuff pressure during the training period was 73 ± 11 mm Hg. The cuff was kept inflated during all exercise training sessions. The occlusion pressure for upper (brachial artery) and lower (tibial artery) limbs was checked regularly by a strength and conditioning professional and adjusted as necessary during the sessions. The oscillometric and aneroid devices for BFR were sent to a company for calibration before the study started, but we did not perform calibrations throughout the protocol. However, the research team checked whether the cuff used for restriction blocked the radial pulse and oxygen saturation when inflated until reaching values of 100% of the SBP measured by the oscillometric device throughout the protocol.

Blood collection. Venous blood samples were collected at baseline and after 6 months of training for the analysis of markers of renal function and integrity, as well as for the determination of the inflammatory profile. Samples were obtained in the morning after an 8-h fast (median time was 8:00 AM) and centrifuged at 1500*g* for 15 min. After processing, the specimens were aliquoted into cryovials and stored at −80°C until subsequent biochemical analysis.

Biomarkers of renal integrity and function. Serum levels of klotho and fibroblast growth factor 23 (FGF23) were determined using the specific human enzyme-linked immunosorbent assay (ELISA) methods (IBL Co., Ltd., Gunma, Japan, and Immutopics Inc., San Clemente, CA), as previously described by Pedersen et al. (18). Serum creatinine, cystatin C, urea, and urinary protein excretion were determined using an automated chemistry analyzer (COBAS c111 system; Roche Diagnostics, Switzerland). GFR was estimated from the analysis of cystatin C serum levels according to the recommendations from Larsson et al. (24).

Inflammatory profile. The systemic levels of tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), IL-10, IL-15, IL-18, and monocyte chemoattractant protein 1 (MCP-1) were measured in triplicate by ELISA kits from R&D Systems (Minneapolis, MN) according to manufacturer instructions. Serum IL-17a concentration was determined by ELISA method (Mini ELISA Development Kit, 900-M21; PeproTech Inc., Rocky Hill, NJ). The detectable limit for TNF-α, IL-6, IL-10, IL-15, IL-18, IL-17a, and MCP-1 were 10, 18, 0.2, 12.5, <1, and 10 $pg \cdot mL^{-1}$, respectively. The overall intra- and interassay coefficient of variation values for inflammatory markers were in a range of 4% to 10%.

Statistical analysis. The primary end point was the effect of RT on eGFR, klotho, FGF23, and urinary parameters. The secondary end point was the effect of RT on anti- and proinflammatory cytokines. The power of the sample was calculated with G*power version 3.1.9.4 with a large effect size, an alpha of 5%, presenting a power of 0.999. Initially, the power of the sample was calculated with G*power version 3.1.9.4 with a large effect size, an alpha of 5%, presenting a power of 0.999. The normality and homogeneity of data were verified by the Shapiro–Wilk and the Levene tests, respectively. All normally distributed variables are presented as mean ± SD. Chi-square test was used to analyze the baseline characteristics of the individuals. Nonnormality data are presented as box plot and dispersion (with median and interquartile ranges). A one-way ANOVA was used to compare basal characteristics of patients. Groups were compared at pre- and posttraining by Kruskal–Wallis tests, followed by Dunn's tests (multiple comparisons test). Spearman's correlation coefficient (r) was used to test for the association between klotho and IL-18.

Furthermore, the effect size method (Cohen's d) was also used for comparisons. Statistical significance was accepted at $P < 0.05$. All procedures were carried out using GraphPad Prism (version 6.0).

RESULTS

Baseline characteristics are described in Table 1, and groups displayed no differences in age, sex, body weight, body mass index, and medications. All women were at the postmenopausal stage without any hormonal therapy. Therefore, they were grouped together with men for statistical analysis. All patients were diagnosed with stage 2 CKD using the analysis of serum cystatin C levels according to the recommendations from Larsson et al. (18). One hundred percent of the patients presented levels of cystatin C higher than the cutoff point of 0.91 $mg \cdot L^{-1}$. Nearly all patients (95.2%) presented values higher than the cutoff point of 0.15 $g \cdot 24\ h^{-1}$ per 1.73 m^2 of proteinuria. Also, 86.7% of the patients presented values higher than the cutoff point for creatinine of 0.3 $mg \cdot dL^{-1}$. Supplemental Digital Content 1 provides the coefficient of variation and reference range of all variables of the present study (see Table, Supplemental Digital Content 1, Coefficient of variation of the primary endpoint, http://links.lww.com/MSS/C69).

Both models of RT attenuated the decrease in GFR to a greater extent compared with CTL ($P < 0.05$) in which ~70% of individuals progressed to stage 3 CKD. Moreover, the RT and the RT + BFR groups displayed a decrease in GFR when compared with the pretraining period (Figs. 3A and 3B). The klotho–FGF23 axis was improved in both RT

TABLE 1. Basal characteristics of patients.

Variables	CTL (n = 35)	RT (n = 35)	RT + BFR (n = 35)	P
Age (yr)	58 ± 5	58 ± 6	58 ± 7	0.9268
Sex, men/women	24/11	23/12	25/10	0.8758
Body weight (kg)	99 ± 10	101 ± 9	100 ± 11	0.8486
BMI ($kg \cdot m^{-2}$)	33.2 ± 1.6	33.6 ± 2.0	33.3 ± 1.9	0.6320
Creatinine ($mg \cdot dL^{-1}$)	1.63 ± 0.24	1.64 ± 0.24	1.65 ± 0.29	0.9666
Cystatin C ($mg \cdot dL^{-1}$)	1.13 ± 0.05	1.14 ± 0.05	1.14 ± 0.04	0.4301
eGFR ($mL \cdot min^{-1}$ per 1.73 m^2)	65.82 ± 4.04	65.46 ± 3.48	65.00 ± 2.48	0.2143
Proteinuria ($g \cdot 24\ h^{-1}$ per 1.73 m^2)	0.99 ± 0.46	1.11 ± 0.50	0.99 ± 0.54	0.8583
Hypertension, n (%)	35 (100%)	35 (100%)	35 (100%)	1.0000
Diabetes, n (%)	35 (100%)	35 (100%)	35 (100%)	1.0000
Medications (n)				
Antihypertensive	4 to 6	3 to 5	5 to 6	0.9358
Antihyperglycemic	2 to 3	1 to 3	2 to 3	0.8694
Statins	0 to 1	0 to 1	0 to 1	1.0000

Data are shown as mean ± SD. Chi-square test was used to analyze the baseline characteristics of individuals. One-way ANOVA was used to analyze differences between groups. CTL, control group; RT, resistance training group; RT + BFR, resistance training with BFR group; BMI, body mass index.

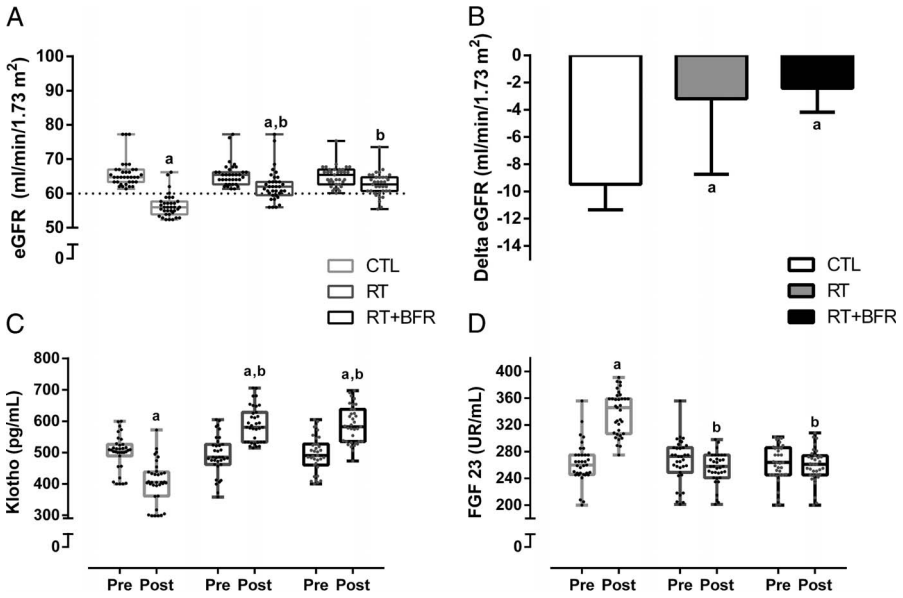

FIGURE 3—Estimated GFR and FGF23–klotho axis. A, Box plot and dispersion of estimated GFR. B, Delta of estimated GFR. C, Box plot and dispersion of klotho. D, Box plot and dispersion of FGF23. CTL, control group; RT, conventional resistance training group; RT + BFR, resistance training with BFR; FGF23, fibroblast growth factor. Groups were compared at pre- and posttraining by Kruskal–Wallis tests, followed by Dunn's tests (multiple comparisons test). $^{a}P < 0.05$ with baseline; $^{b}P < 0.05$ with CTL group.

groups as observed by the maintenance of reduced FGF23 and increased klotho ($P < 0.05$). The CTL group presented the opposite response, with increased FGF23 and decreased klotho ($P < 0.05$) (Figs. 3C and 3D).

RT and RT + BFR maintained creatinine concentrations in the urine, whereas CTL presented an increase after 6 months ($P < 0.05$) (Fig. 4A). Cystatin C increased in all groups; however, both RT and RT + BFR were lower than CTL ($P < 0.05$) (Fig. 4B). There was no difference in urinary protein excretion in all groups after 6 months of intervention (Fig. 4C). Figure 4D shows increased urea in the CTL group compared with the preintervention period ($P < 0.05$). This response was not observed in both training groups ($P < 0.05$).

Inflammation was reduced after 6 months of RT with and without BFR (Fig. 5). TNF-α was decreased in RT and RT + BFR compared with baseline and when compared with the CTL group ($P < 0.05$) (Fig. 5A). There was no change in MCP-1 (Fig. 5B). IL-6 decreased in the RT group compared with baseline and compared with CTL ($P < 0.05$), and there was no modification in the RT + BFR group (Fig. 5C). Both RT and RT + BFR groups displayed increased IL-10 and IL-15 compared with baseline measurements and compared

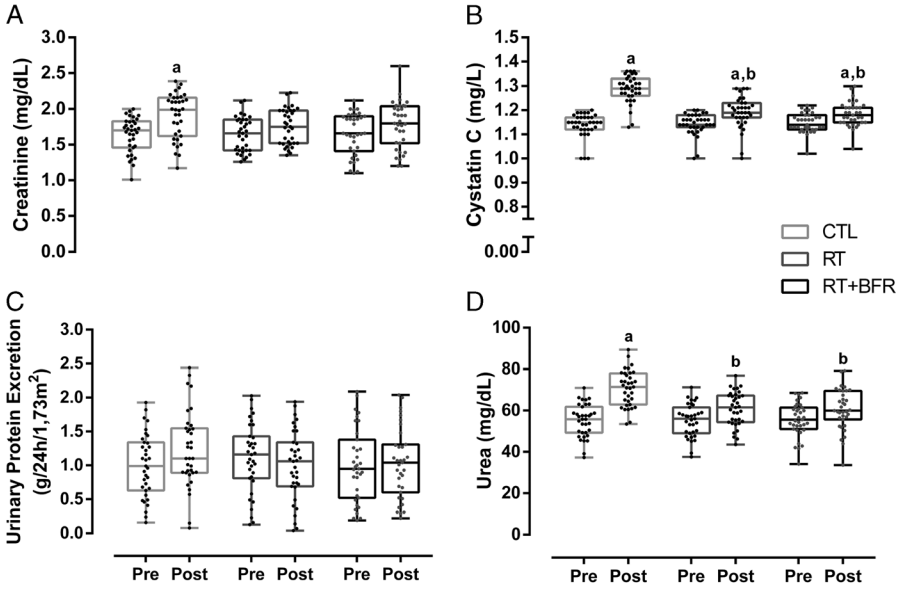

FIGURE 4—Uremic parameters. Box plot and dispersion of creatinine (A), cystatin C (B), urinary protein excretion (C), and urea (D). CTL, control group; RT, conventional resistance training group; RT + BFR, resistance training with BFR. Groups were compared at pre- and posttraining by Kruskal–Wallis tests, followed by Dunn's tests (multiple comparisons test). $^{a}P < 0.05$ with baseline; $^{b}P < 0.05$ with CTL group.

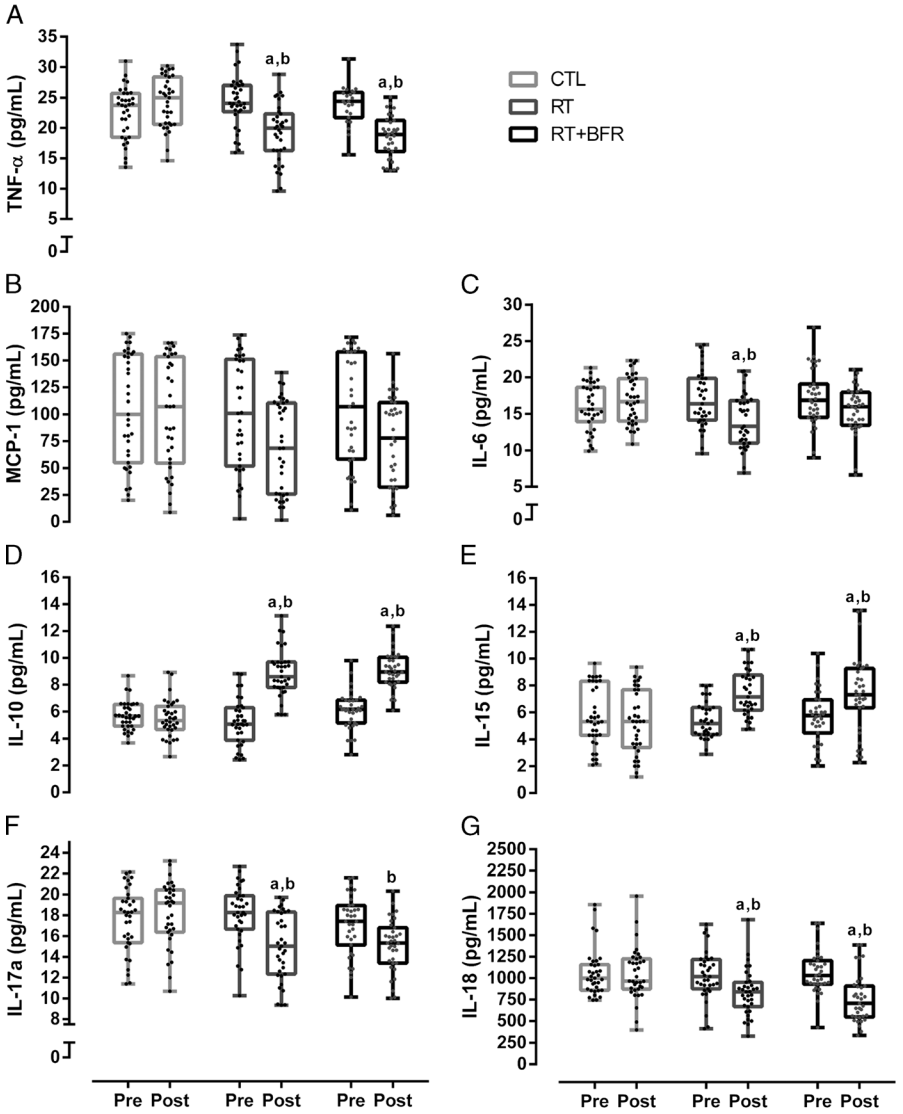

FIGURE 5—Inflammatory profile. Box plot and dispersion of TNF-α (A), MCP-1 (B), IL-6 (C), IL-10 (D), IL-15 (E), IL-17a (F), and IL-18 (G). CTL, control group; RT, conventional resistance training group; RT + BFR, resistance training with BFR. Groups were compared at pre- and posttraining by Kruskal–Wallis tests followed by Dunn's tests (multiple comparisons test). $^{a}P < 0.05$ with baseline; $^{b}P < 0.05$ with CTL group.

with CTL ($P < 0.05$) (Figs. 5D and 5E). RT decreased IL-17a as compared with baseline, and CTL. RT + BFR presented lower IL-17a compared with CTL ($P < 0.05$) (Fig. 5F). IL-18 was decreased in both training groups as compared with baseline and CTL group ($P < 0.05$) (Fig. 5G).

There were similar strength gains for both training protocols. In addition, RT + BFR presented 93% of sessions attended and RT presented 89% ($P < 0.05$; see Figures, Supplemental Digital Content 2, 1-RM sum of the sum of upper and lower limbs exercises and the number of sessions attended for each group, http://links.lww.com/MSS/C70; Supplemental Digital Content 3, 1-RM for all exercises, http://links.lww.com/MSS/C71).

DISCUSSION

After 6 months of RT therapy with and without BFR in patients with stage 2 CKD, we observed that (i) both training therapies attenuated the decline in GFR and improved uremic parameters, (ii) patients of control group displayed a significant progression from stage 2 CKD to stage 3, (iii) inflammation was regulated in both training groups by the decrease of proinflammatory cytokines and the increase of anti-inflammatory cytokines, and (iv) the FGF23–klotho axis was improved in patients that participated in both RT models, with increased klotho concentration and decreased FGF23. These novel findings confirm our initial hypothesis.

For the past decades, it was believed that the positive effects of RT were intensity dependent, whereas BFR may question this theory, presenting similar systemic and molecular adaptations induced with lower intensities (25). BFR seems to limit venous return and reduce the inflow of blood to the skeletal muscle generating a hypoxic environment (25,26). Therefore, hypoxia signaling generated by this training method resembles the mechanisms of remote ischemic preconditioning that

intensify the exercise response by promoting a transient increase of reactive oxygen species leading to inflammation, which precede the expression and concentrations of higher anti-inflammatory proteins (25).

Inflammation is a natural and required reaction to antigens and pathogens to activate the production of cytokines that are necessary to recruit other defense factors that will contribute to tissue repair (2). The end product of these mechanisms is a reduction of inflammation. On the other hand, under some circumstances, inflammation is extended, resulting in cell damage and death in response to proinflammatory cytokines, intermediating the relation between health and disease (27). We draw attention to IL-17a, produced by T_H17 cells, a specific class of CD^{4+} T helper, and essential cytokine for the immune response against a series of microorganisms. However, this protein also causes inflammatory tissue damage and increases proinflammatory IL-6 that induces a considerable number of adverse effects in CKD (27,28).

On the other hand, anti-inflammatory proteins seem to repair or inhibit immune-related side effects (2). This response was identified in the present study by the increase of IL-10 and IL-15 concomitant with the decline of TNF-α, IL-6, IL-17, and IL-18. Although MCP-1 reductions in the trained groups were not statically significant, the observed changes represented a large effect size of 1.00 and 2.06, respectively, for the conventional RT and RT with BFR as calculated by Cohen's *d*. These results indicate a trend of MCP-1 to decrease in both training groups. It is possible that with a larger sample size and more protracted intervention, a statically significant reduction in MCP-1 could be observed. In previous studies, our research group identified such a response in experimental models (13), demonstrating that RT downregulates macrophage infiltration in the kidney. In this sense, Tecklenborg et al. (3) provided evidence that renal dysfunction is associated with an immune system decline, which can affect renal integrity or involve multiple organs. Thus, one clinically relevant application of the present study is the possibility of downregulating inflammation through RT (Fig. 5) because the effects of immunosenescence are more widespread in CKD (2).

Another cytokine of interest in the current investigation is IL-18. Recent studies (29,30) presented this protein as a proinflammatory cytokine that belongs to the large family of IL-1. In the CKD population, IL-18 seems to predict cardiovascular mortality (29) and promotes fibroblast senescence in pulmonary fibrosis through a decrease in klotho concentration (30). To investigate this inverse relationship between IL-18 and klotho, a linear regression between the two variables was performed (see Figure, Supplemental Digital Content 4, Linear regression between IL-18 and klotho, http://links.lww.com/MSS/C72). It was determined that higher levels of IL-18 are associated with lower levels of klotho.

Klotho is an antiaging protein present in the kidney that regulates renal function and also presents anti-inflammatory properties (31). This protein acts as a coreceptor of FGF23 (32), a bone-derived protein that increases urinary phosphate excretion and reduces the levels of calcitriol (i.e., active form of vitamin D). However, as the GFR decreases in the kidney, there is an increasing phosphate accumulation in the blood, which in turn leads to a reduction in calcitriol production and also stimulates the increase in parathyroid hormone secretion leading to hyperparathyroidism (32). Therefore, another key finding of the present study is the renoprotective effect of both RT models by downregulating FGF23 and increasing klotho concentrations. This highlights that BFR training performed at lower intensities may be equally effective when compared with conventional RT.

Despite downregulated inflammation-related markers, and an increased level of klotho induced by both RT models, the progression of CKD was irreversible. However, exercise training appears to decelerate the decline of GFR and improve uremic parameters in patients with stage 2 CKD. Those findings are remarkable for this population, as the deterioration from stage 3 to the end stage is more accentuated than the initial stages (5). As verified in the present study, ~70% of the control group progressed from stage 2 to stage 3 CKD concomitant with the increase of urinary creatinine, cystatin C, and urea, which demonstrates a faster progression of CKD when compared with the training groups. In this sense, RT with and without BFR seems to be an essential tool for the decline of mortality inherent in the progression of CKD, as patients with advanced stages of CKD have a higher probability of death compared with those in the initial stages (6).

There are some limitations in the present study to point out. The absence of a group that performed BFR only, without RT, would enable the identification of the isolated effects of BFR. However, we identified this method of training as another tool to promote the benefits of RT with lower intensities in this population. Socioeconomic status might limit some people to access a supervised RT + BFR training, as the costs of strength and conditioning specialists, gyms, RT equipment, BP devices, and cuffs for BFR are expensive. Furthermore, there are some other factors to consider despite socioeconomic limitation, such as the availability of a strength and conditioning specialist who is trained in the application of BFR, especially in this population, as well as the acceptance of this professional in hospitals, clinics, and ambulatory to work with chronic diseases patients. By contrast, the Brazilian government funds resource to hospital, clinics, ambulatories, and universities to improve a multidisciplinary health approach; however, this fund may not be universal for using a strength and conditioning specialist applying BFR. In this regard, future studies might consider this approach to explore how clinics and health centers can apply the RT + BFR in patients with CKD. Thus, maybe indirectly, our study could contemplate needy patients by the insertion of more health professionals in these institutions. Another limitation of the present study is that just 35 subjects per group is a limited sample. All participants completed 6 months of exercise training therapy using two different models of RT, which addresses some gaps in regard to the application of BFR on the inflammatory profile and renal function of patients with CKD. Also, the results of the present study can be generalized to other stages

of CKD, once our patients presented more severe kidney decline due to obesity, diabetes, and hypertension (33–35). Thus, if exercise has managed to mitigate the condition of these patients, it will probably also be able to mitigate the condition of people in a less severe state.

In the present study, we revealed some possible inflammatory mechanisms related to CKD. Indeed, the application of RT + BFR to the public has limitations because it requests professional supervision, movement corrections, load control, and BFR adjustments. Thus, there are guidelines to the prescription of training for chronic disease that recommend the measuring of hemodynamic parameters before, during, and after training sections, load control, and attention to signs and symptoms of possible complications that can occur with high risk patients. Therefore, supervision by a strength and conditioning specialist seems to be essential to the orientation of both training models applied in our study, especially to the early stages of CKD, in which there are no consolidated guidelines for exercise prescription. This study presents a practical orientation approach to strength and conditioning specialist in clinics, ambulatory, and gyms that intend to meet the chronic disease patients, which are an increasing population.

In conclusion, 6 months of periodized RT with and without BFR in patients with stage 2 CKD attenuated the progression of the eGFR, improving uremic parameters, downregulating inflammation-related markers, and decreasing the FGF23–klotho axis. RT with BFR and lower exercise loads could be an additional tool for this population, as the results that were similar to those observed through conventional training. Indeed, our data demonstrated that the application of those models of training brings perspectives to the adhesion and adherence of both RT models due to lower intensities, reinforced by the higher number of sessions attended by the RT + BFR group as compared with the RT group (see Figure, Supplemental Digital Content 2, 1-RM sum of the sum of upper and lower limbs exercises and the number of sessions attended for each group, http://links.lww.com/MSS/C70). Nonetheless, further studies are needed to verify the subjective perceived exertion and adherence to these models of training.

Perspectives. As verified in the present study, chronic exercise appears to change the concentration of different circulating proteins in patients with CKD. These proteins with potential benefits to the organism are defined by "exerkines," which are the sum of all humoral exercise factors produced and excreted by all tissues and organs influenced by exercise (36). Our results reinforce IL-10 as an exerkine for patients with CKD. Although klotho is not considered to be an exerkine, findings from a plethora of studies (37–41), and based in the current investigation, we must consider klotho as an exerkine with a perspective for therapeutic target for patients with CKD.

In this regard, it is important to map the benefits of exerkines in patients with CKD and to compare the protein-release profile with healthy subjects. This may enable the creation of databases that expose all exerkines that are released by healthy people versus patients with CKD to be developed. These will facilitate the design of further studies with the aim of identifying exercise mimetics, contributing to those that have physical impairments that preclude the practice of physical exercise.

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The authors declare no conflict of interest.

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