The effects of home-based progressive resistance training in chronic kidney disease patients

Thaís B. de Araújo a,1, Hugo de Luca Corrêa a,1, Lysleine A. de Deus a, Rodrigo V.P. Neves a, Andrea L. Reis a, Fernando S. Honorato a, Jessica M. da S. Barbosa a, Thalyta R.C. Palmeira a, Samuel S. Aguiar b, Caio V. Sousa c, Cláudio A.R. Santos d, Luiz S.S. Neto e, Carlos E.N. Amorim e, Herbert G. Simões a, Jonato Prestes a, Thiago S. Rosa a,∗

a Graduate Program in Physical Education, Catholic University of Brasília, Brasília, DF, Brazil
b Graduate Program in Physical Education, Federal University of Mato Grosso, Cuiabá, Brazil
c Health Technology Lab, College of Arts, Media and Design, Bouve College of Health Sciences, Northeastern University, Boston 02115, MA, USA
d Federal University of Tocantins, Medicine Department, Tocantins, Brazil
e Federal University of Maranhão, Physical Education Department, Maranhão, Brazil

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ABSTRACT

Introduction: Faced with lockdowns, it was mandatory the development of supervised home-based RT protocols to keep patients with chronic kidney disease engaged in programs. Nonetheless, there is a lack of scientific literature regarding its effects on patients.

Purpose: To investigate the effects of a supervised home-based progressive resistance training program on functional performance, bone mineral density, renal function, endothelial health, inflammation, glycemic homeostasis, metabolism, and redox balance.

Methods: Patients (n = 31) were randomized and allocated into the control group (CTL; n = 15; 56.07 ± 5.22 yrs) or resistance training group (RT; n = 16; 57.94 ± 2.74 yrs). RT group performed 22 weeks of supervised progressive home-based resistance exercises. Bone mineral density, anthropometric measurements, and functional performance were assessed. Venous blood samples were collected at baseline and after the intervention for the analysis of markers of renal function, endothelial health, inflammation, glycemic homeostasis, metabolism, and redox balance.

Results: Twenty-two weeks of home-based RT were effective in improving (P < 0.05) functional performance, bone mineral density, uremic profile, ADMA, inflammatory markers, the Klotho-FGF23 axis, glycemic homeostasis markers, and exerkines. These improvements were accompanied by higher concentrations of exerkines and anti-inflammatory cytokines. RT group displayed a decrease in cases of osteopenia after the intervention (RT: 50 % vs. CTL: 86.7 %; X2 = 4.763; P = 0.029).

Conclusion: Results provide new evidence that supervised home-based progressive RT may be a relevant intervention to attenuate the progression of CKD and improve functional capacity, bone mineral density, and the immunometabolic profile. These improvements are associated with positive modulation of several exerkines.

1. Introduction

An age-related decline in renal function is an inevitable phenomenon that can worsen secondary non-communicable diseases including obesity, hypertension, and diabetes (Cockwell and Fisher, 2020; Kovesdy et al., 2017; O’Sullivan et al., 2017; Shahwan et al., 2021). Notably, these comorbidities are consistently increasing worldwide and acting as key hallmarks of the chronic kidney disease (CKD) global burden (Cockwell and Fisher, 2020). CKD has been characterized as the progressive and irreversible loss of renal function (Kalantar-Zadeh et al., 2008).
The progression of CKD could lead to renal failure, requiring kidney function substitutive therapies for patient survival (Kalantar-Zadeh et al., 2021; Ma and Zhao, 2017). Once developed, CKD is a striking feature for the reduction in life quality and expectancy (Kraus et al., 2016; Ma and Zhao, 2017). Therefore, clinicians and researchers are joining forces to search for pharmacological and non-pharmacological therapies to blunt the progression of CKD to renal failure (Barellós et al., 2018; Corrêa et al., 2021a; Corrêa et al., 2021b; de Deus et al., 2021; Deus et al., 2022; Toyama et al., 2019).

The importance of resistance training (RT) in the treatment of patients with CKD is recognized due to its beneficial effects. RT-induced benefits include improvements in body composition, bone mineral density (BMD), blood pressure, glucose homeostasis, cardiac autonomic function, depressive symptoms, and quality of life, as well as helping to attenuate the decline in renal function (Corrêa et al., 2020; Corrêa et al., 2021a; Corrêa et al., 2021b; de Deus et al., 2021; Deus et al., 2021a; Deus et al., 2022; Deus et al., 2021b; Deus et al., 2021c; Neves et al., 2021). These improvements are accompanied by up-regulation of exerkines, that is, humoral factors secreted into circulation by tissues in response to exercise (Magliulo et al., 2022). Well-known exerkines include irisin, adiponectin, sirtuin-1, and Klotho which are involved in several biological processes essential to RT-induced benefits in the inflammatory profile, redox balance, skeletal muscle, and bone, and that lead to a protective effect on multiple physiological systems (Corrêa et al., 2021a; Corrêa et al., 2021b; Corrêa et al., 2021b; Deus et al., 2021a; Deus et al., 2022; Deus et al., 2021c; Magliulo et al., 2020; Safdar and Tarnopolsky, 2018; Sato et al., 2022).

Despite the potential positive health-related RT outcomes, there are still many issues to be considered for the implementation of exercise training programs for patients with CKD. For example, the above-mentioned studies were performed in clinics and/or in specialized exercise centers. The maintenance of these structures requires high-cost investments, which could affect adherence and adherence to the training programs. In addition, owing to the Coronavirus pandemic in the year 2020/2021, additional caution and awareness became necessary in relation to exercise practices for frail populations.

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Randomization was stratified according to baseline variables, including sex, body mass (kg), body mass index (BMI), and medication. The patients were randomized into the Control group (CTR, n = 15) and the Resistance Training group (RT, n = 16). All patients underwent physical testing to determine initial muscle strength to prescribe RT.

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Patients were weighed on a mechanical scale (Filizola®, São Paulo, Brazil), and height was measured with a stadiometer built into the scale (precision: 0.5 cm). Waist circumference was assessed at the level of the umbilicus using an anthropometric tape (Sanny®, São Paulo, Brazil). Body composition and bone mineral density were measured using Prodigy Advance Plus (LUNAR, Corp./General Electric; Madison, Wisconsin, USA) dual-energy X-ray absorptiometry (DXA) according to previously specified procedures (Gadelha et al., 2021b; Neves et al., 2021). Patients were asked to remove all objects from the shirt and pant pockets (wallet, cell phones, tablets, and any metallic pieces). The procedure was standardized for pre- and post-training analyses to avoid artifacts. The patients were placed in the supine position to scan the total BMD, although the subjects’ bodies were aligned with the apparatus base’s central line, and straps were used to secure the legs and feet.

Handgrip strength was measured with a hydraulic hand dynamometer (Jamar® - Sammons Preston, Bolingbrook, USA), according to procedures detailed elsewhere (Corrêa et al., 2021a). Briefly, it was determined with the average of three attempts and was analyzed in the contralateral arm of the arteriovenous fistula. Timed up and go and 6-minute walking tests were carried out according to Balke (1963). For TUG, subjects were individually seated in a standard chair, 45 cm high, with their back against the chair, both arms resting along the body, and both feet completely resting on the floor. Participants were instructed to get up and walk three meters forward as fast as possible, turn around an obstacle, return to the chair, and sit down again. Three attempts were timed, with 60 s of rest between them. The best performance was recorded and used for the present analyses. The 6MWT measures the distance an individual can walk in a total of 6 min on a hard, flat surface. The goal is for the individual to walk as far as possible in 6 min. The individual was allowed to self-pace and rest as needed as they traversed back and forth along a marked walkway.

Systolic and diastolic blood pressure were measured according to the recommendations of the American Heart Association (Kurtz et al., 2005) as already performed elsewhere (Corrêa et al., 2021a). Heart rate variability (HRV) parameters were assessed during 5 min of rest as stated by de Deus et al.
All subjects remained comfortably seated in a quiet room, with open eyes, and were asked to breathe normally. It was performed following 8 h of fasting.

2.4. Blood samples

Venous blood samples were collected at baseline and after 22 weeks of intervention to analyze markers of renal function, endothelial health, inflammation, glycemic homeostasis, metabolism, and redox balance. Samples were collected in a dry and EDTA tube (both 4 mL) and was obtained in the morning after 8-h fasting (the average time was 8:00 AM). Blood was centrifuged at 1500 g for 15 min. After processing, the specimens were aliquoted into cryovials and stored at -80 °C until subsequent biochemical analysis.

2.5. Uremic profile

The uremic profile was assessed by the levels of creatinine, cystatin C, albumin, urea, calcium, phosphorus, proteinuria, and eGFR. These molecules 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. (2004).

2.6. Biochemical analysis

Endothelial health was assessed by nitric oxide bioavailability and asymmetric-dimethyl-L-arginine (ADMA). Nitric oxide was analyzed through the Griess reaction, assessing serum nitrite and nitrate, as described by Rosa et al. (2020). Serum ADMA concentration was determined by ELISA, the intra- and inter-assay coefficients of variation (CV) were ≤ 12 %, respectively (Human ADMA ELISA Kit, MyBioSource, San Diego, USA). Tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-10, IL-15, IL-17, IL-18, monocyte chemoattractant protein 1 (MCP-1), transforming growth factor beta (TGF-β), and growth differentiation factor 15 (GDF-15), were analyzed in triplicate by ELISA kits from R&D systems (Minneapolis, MN, USA) according to the manufacturers’ instructions. Overall inter-assay CVs were < 10 %. Adiponectin (Novus Biologicals, CO, USA), insulin, albumin, sirtuin 1 (SIRT-1) (Abcam, São Paulo, Brazil), C reactive protein (Thermo Fisher Scientific, Vienna, Austria), and Irisin (Phoenix Pharmaceuticals, Burlingame, CA, USA) were also determined by ELISA kits with CVs < 14 %. All ELISA assays were performed in triplicate.

Glycosylated hemoglobin (HbA1c) and lipid profile,
characterized by total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDLc), and low-density lipoprotein cholesterol (LDLc), were determined using an automated chemistry analysis (COBAS c111 system; Roche Diagnostics, Rotkreuz, Switzerland). The intra- and inter-assay CV values were determined automatically by COBAS.

Paraoxonase 1 (PON-1) was measured in triplicate using a human PON1/Paraoxonase 1 Picokine ELISA kit (Glory Science Co., Ltd. TX, the USA); inter- and intra-assay coefficients of variation were between 3 and 4.9%. Myeloperoxidase (MPO) was analyzed in the plasma and in triplicate using an enzyme immunoassay kit 10 (MPO ELISA; Immunodagnostik Bensheim, Germany); inter- and intra-assay coefficients of variation were between 3.4 and 5.0.

2.7. Supervised home-based progressive resistance training

Table 1 provides a detailed description of supervised home-based progressive resistance training that can be used or adapted as a model of RT prescription to patients with CKD in stage 2.

In summary, the exercise group completed a 22-week program consisting of five cycles, with 3–6 weeks each cycle. Elastic-based and bodyweight exercises were included, and the training load was assessed by the OMNI-RES scale (Lagally and Robertson, 2006). The 1st and 2nd cycles were carried out on 3 days/wk, and exercises were performed alternately for upper and lower limbs during the session. In the 3rd cycle, patients trained 4 days/wk, and exercises were performed as follows: Monday/Thursday upper body, and Tuesday/Friday lower body. Exercises were performed with a low cadence (2 s) for both concentric and eccentric contractions. All patients exercised under the individualized supervision of strength and conditioning professionals in their homes. Illustrative pictures of the technical execution of the exercises are provided in the Supplementary Material. The sum of the load and the set × rep × kg for each week of home-based RT is described in Fig. 2.

2.8. Statistical analysis

By calculating the post hoc achieved power for all 31 subjects included in the study given an alpha of 5% and effect size of 0.4 was obtained a power of 99% for within – between interaction analysis. Data are presented as mean and standard deviation unless otherwise stated. The Shapiro-Wilk and Levene tests were used to verify data distribution and homogeneity, respectively. X2 tests were performed to compare categorical variables. Continuous variables with normal distribution were tested for significance by performing a two-way mixed ANOVA (2 × 2 groups [CTL and RT] × time [pre and post]) with Tukey post-hoc, whereas Kruskal-Wallis followed by Dunn’s multiple comparison test were used for non-parametric variables. From the 54 continuous variables investigated in the present study, 26 were parametric: Total femur, L3-L4, T-score, femoral neck, handgrip strength, 6-minute walking test, systolic blood pressure, diastolic blood pressure, SDNN, LF, HF, creatinine, albumin, proteinuria, NO3, ADMA, TNF, IL6, IL15, GDF-15, CRP, Klotho, GGF23, insulin, fasting blood glucose, HbA1C, triglycerides, and cholesterol. Delta post – pre were performed for the variables that presented statistical significance. A Spearman test was applied to verify the correlation among these variables with pooled data from the CTL and RT groups. Correlations were presented as a heat map. Results were considered significant at $P < 0.05$. The P-values from the tables
Fig. 2. Load progression through the 22 wks of resistance training.
represents group * time interaction for the parametric variables and the main effect of Kruskal-Wallis for non-parametric variables. All statistical analyses were performed using IBM Corp. Released 2013, IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY: IBM Corp. and GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com.

3. Results

There were no adverse effects reported by the 31 subjects that completed the RT protocol. All patients performed at least 54 days of the training program, representing 66.67 % of the sessions attended. Three subjects dropped-out of the RT (15.8 %). From the total sample, 38.7 % were post-menopausal women without any hormone replacement therapy. Baseline characteristics presented in Table 2 demonstrates that there are no differences in age, body mass index, waist circumference, and body mass. Noteworthy, 83.9 % of the patients presented osteopenia; 86.7 % from the CTL, and 81.3 % from the RT group, respectively. After the protocol, RT group decreased by 30 % from the cases of osteopenia (from 81.3 % to 50 %).

Table 3 presents the effects of 22 weeks of RT on bone mineral density, anthropometry, and hemodynamic variables in CKD patients. The RT group demonstrated improvement in total bone mineral density, handgrip strength, 6MWT, and TUG compared to baseline and to the CTL group (P < 0.01). A two-way ANOVA revealed that there was a statistically significant group * time interaction for handgrip strength (P = 0.01; F[1, 58] = 5.99), 6MWT (P = 0.01; F[1, 58] = 6.54), ADMA (P < 0.001; F[1, 58] = 7.99), Irisin (P < 0.001; F[1, 58] = 17.17), fasting blood glucose (P < 0.001; F[1, 58] = 13.37), HbA1C (P < 0.001; F[1, 58] = 15.85), TNFα (P = 0.005; F[1, 58] = 8.38), IL6 (P = 0.042; F[1, 58] = 4.31), IL15 (P = 0.017; F[1, 58] = 6.053), and CRP (P < 0.001; F[1, 58] = 14.2).

No changes were found for blood pressure and heart rate variability. Table 4 demonstrates that RT improved the uremic profile, ADMA, inflammatory markers, Klotho-FGF23 axis, and glycemic homeostasis markers. RT group significantly increased Irisin and SIRT-1, while leptin, blood glucose, and HbA1C appears to decrease following RT We performed a heat map with the Spearman Correlation Coefficients based on the delta of all variables and found that, in general, they were associated with each other. See Fig. 3.

4. Discussion

After 22 weeks of home-based RT, significant improvements were observed in physiological variables, including functional performance, bone mineral density, uremic profile, ADMA, inflammatory markers, Klotho-FGF23 axis, glycemic homeostasis markers, and exerines. These improvements were accompanied by higher concentrations of exerines and anti-inflammatory cytokines. This response might explain, in part, RT blunting the decline in glomerular filtration rate and, consequently, avoiding renal failure. Taken together, these data reinforce the protective effect of RT on renal physiology.

All exercises included in our protocol were chosen to focus on increasing bone mineral density (Benedetti et al., 2018). Significant improvements were found for total BMD, but not for total femur, femoral neck, and L3-L4. This finding is clinically important, as the current protocol included a cautious progression of training load and volume. It is known that the effectiveness of strength exercise to improve total BMD is related to training intensity, frequency, and volume, with loads between 70 and 90 % of 1RM, 2–3 sets of 8–10 reps, 3 times a week (Zehnacker and Bemis-Dougherty, 2007). In the present study, the RT load was manipulated according to the OMNI-RES scale. It is argued that between perceived exertion scales and 1-RM there are plenty of differences, nevertheless perceived exertion might present higher safety and practicality than 1-RM since it is based on each subject's perception. In the first seven weeks of training, the OMNI scale ranging from 3 to 5 (easy) and 1 series for each exercise were adopted with the intention of facilitating the patient's engagement with the protocol, as it allowed more time for familiarization and possible impacts on adherence and adhesion to the program. In the present study, we observed a drop-out rate of 15.8 % and a minimum frequency of 54 sessions.

| Table 2 | Baseline characteristics. |
|---|---|---|---|
| Variables | Total (n = 31)/ Control (n = 15) | RT (n = 16) | P value |
| Age (years) | 58 ± 4.06 | 58.07 ± 5.22 | 57.94 ± 2.74 | 0.931 |
| Body mass index (kg/ m²) | 26.74 ± 2.79 | 26.84 ± 1.95 | 26.64 ± 3.47 | 0.848 |
| Waist circumference (cm) | 96.19 ± 11.55 | 95.46 ± 11.43 | 96.87 ± 11.99 | 0.410 |
| Body mass (kg) | 72.66 ± 12.79 | 72.16 ± 9.98 | 73.13 ± 15.28 | 0.835 |

The independent t-test was performed to compare groups: RT: resistance training.

| Table 3 | Bone mineral density, anthropometric, and hemodynamic responses to RT. |
|---|---|---|---|---|
| Variables | CTL Pre | RT Pre | Post | P value |
| Fat free mass (kg) | 42.65 ± 4.27 | 42.37 ± 3.43 | 45.83 ± 3.20 | 0.5492 |
| Fat mass (kg) | 29.51 ± 29.76 | 29.94 ± 28.88 | 0.9752 |
| Total bone mineral density (cm²) | 0.05 ± 0.05 | 0.06 ± 0.06 | 0.0889 |
| Total femur (cm²) | 0.82 ± 0.81 | 0.81 ± 0.88 | 0.1340 |
| L3-L4 (cm²) | 1.05 ± 1.05 | 1.05 ± 1.11 | 0.1222 |
| T score | −1.35 ± −1.38 | −1.24 ± −0.84 | 0.0984 |
| Femoral neck | 0.85 ± 0.84 | 0.86 ± 0.91 | 0.0992 |
| Handgrip strength (kgf) | 18.3 ± 18.2 | 20.5 ± 22.75 | 0.0174 |
| Timed up and go test (s) | 3.75 ± 3.22 | 3.65 ± 3.11 | 0.0061 |
| 6MWT (m) | 446.8 ± 451.2 | 455.19 ± 581.13 | 0.0132 |
| CRP (mg/L) | 0.30 ± 0.30 | 0.30 ± 0.30 | 0.9752 |
| ADMA (μmol/L) | 1.6 ± 1.6 | 1.6 ± 1.6 | 0.8010 |
| IL15 (pg/mL) | 370.69 ± 370.69 | 370.69 ± 370.69 | 0.8073 |
| VLF (m²) | 356.33 ± 356.33 | 356.33 ± 356.33 | 0.7603 |
| LF (m²) | 356.33 ± 356.33 | 356.33 ± 356.33 | 0.7603 |
| HF (m²) | 356.33 ± 356.33 | 356.33 ± 356.33 | 0.7603 |

Data expressed as means and standard deviation. Two-way mixed ANOVA followed by Tukey post-hoc or Kruskal-Wallis test followed by Dunns' post-hoc was performed to compare groups. 6MWT: 6-minutes walking test. a P < 0.05 vs CTL pre; b P < 0.05 vs. CTL post; c P < 0.05 vs. RT pre; d P < 0.05 vs. RT post.
Table 4
RT improved circulating biomarkers related to cardio-renal homeostasis.

| Variables                           | CTL Pre | RT Pre | RT Post | P value |
|-------------------------------------|---------|--------|---------|---------|
|                                    |         |        |         |         |
| Uremic profile                      |         |        |         |         |
| Creatinine (mg/dL)                  | 1.58 ±  | 1.89 ± | 1.67 ±  | 1.78 ±  | 0.1306  |
| Cystatin C (mg/L)                   | 0.24    | 0.34   | 0.22    | 0.23    |         |
| Albumin (g/dL)                      | 2.65 ±  | 2.25 ± | 2.53 ±  | 2.91 ±  | 0.0836  |
| Urea (mg/dL)                        | 7.2     | 582.4 ±| 549.2 ± | 59.34 ± | <0.0001 |
| Calcium (mg/dL)                     | 8.85 ±  | 8.95 ± | 9.12 ±  | 9.49 ±  | 0.0841  |
| Phosphorus (mg/dL)                  | 0.94    | 0.53   | 0.53    | 0.74    |         |
| Proteinuria (g/24h/1.73 m2)         | 1.03 ±  | 1.21 ± | 1.12 ±  | 1.02 ±  | 0.3040  |
| eGFR (mL/kg/1.73 m2)                | 64.99 ± | 57.73 ±| 66.14 ± | 63 ± 6.09| <0.0001 |
| Markers of endothelial health       |         |        |         |         |
| Nitric oxide (μM)                   | 32.2 ±  | 31.07 ±| 26.78 ± | 35.47 ± | 0.0601  |
| ADMA (μM)                           | 11.27 ± | 12.13 | 8.52 ±  | 8.02    |         |
| Markers of inflammation             |         |        |         |         |
| TNF-α (ng/mL)                       | 22.69 ± | 23.99 ±| 24.6 ±  | 19.3 ±  | 0.0054  |
| IL6 (ng/mL)                         | 15.3 ±  | 15.99 ±| 16.09 ± | 13.14 ± | 0.0424  |
| IL15 (ng/mL)                        | 5.18 ±  | 4.95 ± | 5.59 ±  | 7.6 ±   | 0.0169  |
| IL10 (ng/mL)                        | 5.67 ±  | 5.36 ± | 5.26 ±  | 8.76 ±  | <0.0001 |
| MCP1 (pg/mL)                        | 90.93 ± | 88.37 ±| 86.72 ± | 58.2 ±  | 0.2071  |
| IL17 (pg/mL)                        | 22.9 ±  | 21.5 ± | 1.5 ±   | 1.54 ±  | 0.0094  |
| IL18 (pg/mL)                        | 1127.93 ±| 1069 ± | 1066.65 | 855 ±  | 0.0878  |
| TGF-β (μg/L)                        | ± 344.48| 406.13 ±| 422.19 ±| 367.81 ±| 0.0005  |
| Markers of osteo-renal axis         |         |        |         |         |
| Klotho (pg/mL)                      | 499 ±   | 407.53 ±| 483.25 ±| 585.94 ±| <0.0001 |
| FGF23 (RU/mL)                       | 259.73 ±| 341.53 ±| 258.31 ±| 256.38 ±| <0.0001 |

Data expressed as means and standard deviation. Two-way mixed ANOVA followed by Tukey post-hoc or Kruskal-Wallis test followed by Dunns’ post-hoc was performed to compare groups. eGFR: estimated glomerular filtration rate by the modified 41-kg/m2 formula; ADMA: asymmetric dimethylarginine; TGF: tumor necrosis factor; IL: interleukin; MCP: monocyte chemotactic protein; TGF: transforming growth factor; GDF: growth differentiation factor; CRP: C-reactive protein; FGF: fibroblast growth factor; SIRT-1: sirtuin 1; HBA1C: glycated hemoglobin; LDL: low density lipoprotein; HDL: high density lipoprotein; MPO: myeloperoxidase; PON: paraoxonase. a P < 0.05 vs CTL pre; b P < 0.05 vs RT pre; c P < 0.05 vs RT post. From 16 patients in the RT group, 13 presented osteopenia at baseline. After the training program, only 8 maintained the same classification. 

From 16 patients in the RT group, 13 presented osteopenia at baseline. After the training program, only 8 maintained the same classification, demonstrating that although we did not observe improvements for the indices related to the spine and femur, we observed some degree of improvement in total BMD in <1 year of training, the time needed to improve BMD of the femur and spine (Benedetti et al., 2018; Zehnacker and Beimis-Dougherty, 2007). The results suggest that continuity of the progressive overload protocol could bring benefits with greater magnitude over time. This statement is reinforced by the improvement in the serum concentration of osteo-renal axis markers, such as Klotho and FGF-23. This indicates that a supervised home-based progressive RT protocol is also able to modulate humoral factors related to bone remodeling in patients with CKD in stage 2, and not only in hemodialysis patients (Aguilar et al., 2020; Neves et al., 2021). Point out that the progression of overload is an important factor for bone remodeling, while Rosa et al. (2021), indicate an association between work overload and molecular factors capable of modulating metabolism and hemodynamics, such as nitric oxide. These statements show an important role of strength assessment as a connection between molecular factors linked to general health and physical-functional fitness in CKD.

Significant improvements were observed in all tests assessing physical-functional fitness, regardless of fat-free mass, suggesting that the current 22-week supervised home-based progressive RT protocol can induce improvement in muscle strength and function, but is not able to increase muscle mass. More weeks of training at higher intensities of around 60 to 80 % of 1RM of 2 to 3 sets of 10 to 15 reps may be required to improve muscle mass and may be able to reverse or avoid sarcopenia (Csapo and Alegre, 2016; Gadelha et al., 2021a). In the current study, however, an intensity of 7 to 8 on the OMNI scale was used in the final 6 weeks of the protocol. Therefore, the present protocol intervention appears to promote improvements in muscle function through the increase in isometric strength, strength resistance, and gait speed. Age-induced dynapenia indicates a worse prognosis for patients with CKD regardless of muscle mass, as it is closely associated with frailty, the risk of falls, and inflammatory status (Correa et al., 2021c).

Our findings showed that supervised home-based progressive RT decreased the concentrations of TNF-α CRP, TGF-β, IL-6, and IL-17, pro-inflammatory cytokines that are associated with increased renal fibrosis and diabetic nephropathy (Wada and Makino, 2013). Furthermore, a
The key finding of this study was the increase in IL-10 and IL-15, given their capacity to induce important signaling pathways related to an anti-inflammatory action and leading to mitochondrial biogenesis. Taken together, this condition may be related to an improved muscle function (Huh, 2018; Patidar et al., 2016). This evidence reinforces the importance of maintaining physical and functional fitness to avoid inflammatory conditions related to CKD.

Differently from the results found by Corrêa et al. (2021b), we did not find changes in IL-18 concentrations after RT, suggesting that the protocol used in that study may be more effective in modulating this cytokine. Noteworthy, IL-18 plays a key role in atherosclerotic plaque formation, being an important indicator of cardiovascular death in CKD patients. Therefore, we suggest more attention in the exercise protocols aiming to reduce IL-18 concentrations, leading to a cardioprotective effect of exercise training (Formanowicz et al., 2015). In addition, we did not find improvement in hemodynamic variables, such as blood pressure.

![Correlation matrix of the delta (post–pre) change of each variable that presented a significant difference in Tables 1 and 2. A) Heatmap of the Spearman correlation coefficient among variables. Blue to violet represents a moderate to strong negative correlation. Yellow to red represents a moderate to strong positive correlation.](image)

![P value of the correlation matrix](image)

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**Fig. 3.** Correlation matrix of the delta (post–pre) change of each variable that presented a significant difference in Tables 1 and 2. A) Heatmap of the Spearman correlation coefficient among variables. Blue to violet represents a moderate to strong negative correlation. Yellow to red represents a moderate to strong positive correlation. B) P value of the correlation matrix. BMD: bone mineral density; HGS: handgrip strength; TUG: timed up and go test; 6MWT: 6-minute walking test; eGFR: estimated glomerular filtration rate by Larsson equation; ADMA: asymmetric-dimethyl-L-arginine; TNF: tumor necrosis factor; IL: interleukin; FGF: fibroblast growth factor; SIRT: sirtuin; TGF: transforming growth factor; FBG: fasting blood glucose; HbA1C: glycated hemoglobin; CRP: c-reactive protein. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
pressure, heart rate variability, nitric oxide, oxidative stress (MPO and PON-1), and lipid profile (Corrêa et al., 2021a; Corrêa et al., 2021b; de Deus et al., 2021; Deus et al., 2022).

We observed improvement in a smaller number of variables than other studies, including fasting glucose and glycated hemoglobin concomitantly with irisin, SIRT-1, and leptin levels (Deus et al., 2022). Herein, we draw attention to the protocol differences between the present 22-week home-based progressive RT model and other previously tested protocols. The protocol performed by Corrêa et al., consisted of a linear periodization (i.e, increase in load and decrease in volume), using machines and free weights, with a volume of 3 sets of 8–12 repetitions and load adjustment based on 1RM tests. In contrast, we used a non-periodized progressive overload with adjustments based on the OMNI scale, and exercises were performed with elastic bands or body weight (calisthenics). The choice to use elastic bands and body weight aimed to induce different biomechanical conditions that can influence the physiological and molecular responses following RT. Furthermore, elastic bands are low-cost, portable implements, and load quantification can be performed using a portable dynamometer or by predictive equations based on centimeters of elastic elongation (Reis et al., 2021).

In addition, we highlight that the possibility of managing training variables is important for prescribing RT for patients with CKD, similarly, to prescribing training in athletes. Corrêa et al. (2021a) pointed to improvements in blood pressure, the renin-angiotensin-aldosterone system, and nitric oxide bioavailability in patients with CKD in stage 2, while Rosa et al. (2021) suggested that training overload is an important variable to modulate nitric oxide levels and glycemic homeostasis in end-stage CKD. Of note, Deus et al. (2022) and Deus et al. (2021c) raised the need for hypoxic stress to induce changes in metabolic and hormonal responses, which may not have been promoted due to the low intensity of training at the beginning of the protocol. Furthermore, we noticed great dispersion and variability in these data when compared to data from protocols developed in training centers. Despite the limitations of the present protocol, it still contributed to attenuation of the progression of CKD, verified by the smaller decline in the glomerular filtration rate.

The results of the present study should be interpreted with caution since the training intensity/volume was too conservative in the first 16 weeks, and only in the final 6 weeks the intensity and volume followed current recommendations for hypertrophy (Schoenfeld et al., 2017). This approach was given to avoid any adverse events during training sessions. Furthermore, the lack of nutritional assessment limits our inference power, and we suggest further investigations to control these variables.

The practical application of a 22-week home-based progressive RT protocol is its differential. Performing exercises without leaving home has become extremely relevant during the coronavirus pandemic period. Patients with CKD are considered a risk group for severe Covid-19 (Gao et al., 2019), so being able to receive benefits from exercise training without leaving home could be an important strategy to reduce the risk of infection, as well as keeping these individuals engaged in their treatment.

In the present study, significant associations were observed between the exercises/proteins studied and the physiological benefits promoted by RT. In this context, we suggest that the molecules studied can, at least in part, aid understanding of the RT-induced benefits in CKD. However, studies are still needed to investigate the extent to which this relationship may be causal or only associated.

Finally, we conclude that supervised home-based progressive RT delayed the progression of CKD, and improved functional capacity, total bone mineral density, and the immunometabolic profile in patients with CKD in stage 2. Moreover, these improvements are associated with the positive modulation of several exerkines.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Thais Branquinho de Araújo; Hugo Luca Corrêa; Thiago dos Santos Rosa: Conceptualization; Rodrigo Vanerson Passos Neves; Cláudio Avellino Rodrigues Santos; Luiz Sinesio Silva Neto; Thiago dos Santos Rosa: Data curation; Hugo Luca Correia; Caio Victor Sousa; Jessica Mycaelle da Silva Barbosa; Lysleine Alves Deus; Andreia Lucena Reis; Thiago dos Santos Rosa: Formal analysis Thaís Branquinho de Araújo; Herbert Gustavo Simoes; Thalyta Raeline Cesar Palmeira: Funding acquisition; Hugo Luca Correa; Thiago dos Santos Rosa: Investigation; Samuel da Silva Aguiar; Fernando Sousa Honorato; Jonato Prestes; Carlos Eduardo Neves Amorim, Thiago dos Santos Rosa: Methodology; Thaís Branquinho de Araújo; Hugo Luca Correia; Thiago Santos Rosa: Project administration; Thaís Branquinho de Araújo; Hugo Luca Correia; Thiago Santos Rosa: Roles/Writing - original draft; Thaís Branquinho de Araújo; Hugo Luca Correia; Jonato Prestes; Thiago dos Santos Rosa: Writing - review & editing.

Declaration of competing interest

The authors declare no conflict of interest.

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The authors declare that the results of the study were presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation, and statement that results of the present study do not constitute endorsement by ACSM.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2022.112030.

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