# A Case-control Study of Exercise and Kidney Disease: Hemodialysis and Transplantation

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## ABSTRACT

We aimed to analyze the effect of an exercise training program in autonomic modulation, and exercise tolerance of hemodialysis and kidney-transplanted patients. 4 groups of exercised and non-exercised patients undergoing hemodialysis and kidney-transplanted subjects had their biochemical tests, and heart rate variability evaluations analyzed. Also, sleep quality, anxiety and depression questionnaires were evaluated. Both exercised groups showed improvements in cardiovascular autonomic modulation, biochemical markers, and exercise tolerance after the exercise training program. The exercised kidney-transplanted patients group showed better improvements in cardiovascular autonomic modulation, biochemical markers, and exercise tolerance when compared to the exercised hemodialysis patients group. Both groups showed improvements in sleep quality, anxiety, and depression. The group of kidney-transplanted patients show better results in the cardiovascular autonomic modulation than subjects undergoing hemodialysis. However, the patients undergoing hemodialysis showed improvements in blood pressure, HDL, hemoglobin and phosphorus, changes not observed in the kidney-transplanted group. Exercise is beneficial for both hemodialysis and kidney-transplanted patients groups. However, exercise programs should be focused mainly in improving cardiovascular risk factors in the HD patients.

# Introduction

Chronic kidney disease (CKD) is a multifactorial disease with a prevalence of 11–13 % in the general population around the world [14]. The leading causes of CKD development are hypertension, diabetes, obesity and other kidney-related diseases like glomerulonephritis and other upper urinary tract infections [14]. CKD has a strong relationship with other cardiovascular diseases such as hypertension and autonomic imbalance, a substantial risk factor for sudden death and short survival [28, 29]. The decreased kidney function is associated with increased levels of hospitalization, cognitive dysfunction and poor quality of life [11, 14].

Beyond the filtration problems, CKD patients undergoing hemodialysis (HD) have been shown to present higher levels of stress, anxiety, and depression, also leading to poor sleep quality [3, 7].

The golden standard solution for CKD is kidney transplantation (KTx) [15, 16, 21]. This procedure has shown kidney, cardiovascular, social and cognitive benefits when compared to CKD patients in HD and it is currently the final gold standard procedure for HD patients [15, 16].

In both HD and KTx cases, exercise training has been used as a non-pharmacological tool for reducing risks of cardiovascular events in CKD during HD and after the KTx surgery, mainly improving the cardiac autonomic modulation and kidney function, all of which had been investigated in our research group [1, 8, 23].

However, to this date, no study has ever described the benefits of exercise training among HD and KTx patients. Furthermore, the investigation of this topic is of utmost importance, seeing that before and after the KTx surgery, sedentary individuals with CKD present a higher risk for cardiovascular events and present worse mood state and poor sleep quality [1].

With this in mind, we aimed to analyze the effect of an exercise training program in both HD and KTx patients, regarding cardiovascular autonomic modulation and, exercise tolerance.

# Materials and Methods

## Sample

The sample was constituted of CKD patients from a reference hospital in São Luís, Brazil. The control groups (HD and KTx) was composed of routine patients at the same reference hospital. The exercised groups (HD + Ex and KTx + Ex) were already enrolled in an institutional exercise program inside the hospital at the beginning of the study and were evaluated for later comparison with the control groups.

For the KTx + Ex group, after a public call, 13 patients were eligible according to the inclusion criteria, but 3 subjects left the study for changes in the treatment (n = 2) and graft rejection (n = 1). For the HD + Ex group, 30 patients were eligible for the study according to our inclusion criteria (see above), but only 7 remained in the study. The other 23 left the study for transplantation (n = 2), changes in the pharmacological treatment (n = 2), cardiac catheterism (n = 1), zika virus infection (n = 4), atrial fibrillation (n = 1), anemia (n = 3) and abandon (n = 10).

For the transplanted groups (KTx and KTx + Ex), all patients older than 18 years of age, who underwent kidney transplantation at least 6 months before the start of the study joined the study. Also, for the inclusion in the KTx group, stable blood pressure and diabetes mellitus variables were required for eligibility. Participants were included in a physical evaluation routine, consisting of anamnesis, laboratory tests, anthropometric evaluation, and an electrocardiogram.

For the hemodialysis group (HD and HD + Ex), subjects were regularly undergoing hemodialysis in a reference hospital in São Luís, Brazil joined the study. All subjects must have met the following criteria: over 18 years-of-age, at least 3 months of continuous hemodialysis, stable pharmacological treatment for at least 3 months, and declared ability for exercise execution.

Patients who smoked or with myopathies, heart disease, cardiac arrhythmias, pacemaker, atrial fibrillation, or any other symptom or illnesses which could jeopardize the analysis of heart rate variability (HRV) were excluded from the study.

## Study design

Initially, a public call for the participants was made in the hospital. All patients who were eligible for the study underwent a series of anamnesis and evaluations, as can be seen in the results session (▶ **Table 1**, **2**).

All subjects were submitted to a physical examination protocol which included an anamnesis, a resting electrocardiogram (4-lead ECG), to blood tests (▶ **Table 2**), and an anthropometric evaluation (weight and height were measured using a digital scale with a stadiometer [Balmak, São Paulo, Brazil]), body composition was evaluated using a tetrapolar bioimpedance device (BF 906; Maltron, Rayleigh, UK).

## Estimated glomerular filtration rate

Glomerular filtration rate (eGFR) was calculated using Levey et al. [20] formula for adult black males and females. This an alteration from the original formula, adding Creatinine and a 1.73 $m^2$ body surface, used in Modification of Diet in Kidney Disease (MDRD) study.

## The 6-Min Walk Test (6 MWT) and Peak of oxygen consumption

All subjects underwent a 6 MWT, conducted following the established guidelines from the American Thoracic Society [10]. The test was performed at screening and habituation visit considering a possible learning effect, (14).

## Heart rate variability

RR interval was continuously recorded for 10 min in individuals sitting, using an electrocardiogram device (Micromed Wincardio 600 hz, Brasilia, DF, Brazil) to power spectral analyses of HRV. The spectrum resulting from the Fast Fourier Transforms modeling is derived from all the data present in a minimum 5-min window from the recorded signal; it includes the entire signal variance, regardless of whether its frequency components appear as specific spectral peaks or as nonpeak broadband powers. The frequency bands used for the spectral analysis are low-frequency (LF, 0.04–0.15 Hz), and high-frequency (0.15–0.4 Hz).

The symbolic analysis was calculated to provide a quantification of the complexity of the pattern distribution. All possible patterns (i. e., 216) were grouped without any loss into 3 families referred

▶ **Table 1** General characteristics between groups.

| | HD (n = 7) | HD + Ex (n = 7) | KTx (n = 10) | KTx + EX (n = 10) |
|---|---|---|---|---|
| Sex (Male/Female) | 4/3 | 4/3 | 8/2 | 8/2 |
| Age (years) | 43 ± 7 | 38 ± 13 | 37 ± 9 | 43 ± 13 |
| Hemodialysis time (months) | 41 ± 87 | 44 ± 66 | 31 ± 28 | 35 ± 31 |
| Chronic kidney disease time (months) | 103 ± 29 | 97 ± 36 | 127 ± 54 | 132 ± 60 |
| Transplant time (months) | - | - | 69 ± 42 | 72 ± 39 |
| Height (cm) | 159 ± 10 | 164 ± 5 | 159 ± 8 | 165 ± 8 |
| Weight (kg) | 58 ± 6 | 52 ± 4 | 64 ± 11 | 69 ± 14# |
| Hospitalizations | | | | |
| 0 | 2 | 4 | 4 | 4 |
| 1–2 | 3 | 2 | 3 | 3 |
| 2–4 | 1 | 0 | 0 | 1 |
| 4 or more | 1 | 1 | 3 | 2 |
| Mycophenolate sodium | - | - | 7 | 8 |
| Tacrolimus | - | - | 10 | 10 |
| Azathioprine | - | - | - | 1 |
| Prednisone | 2 | 2 | 6 | 7 |
| ACE inhibitors | 1 | 1 | 7 | 6 |
| Beta-blockers | 2 | 3 | 8 | 6 |
| Calcium channel blockers | 1 | 1 | 4 | 5 |
| Furosemide | 1 | 2 | - | - |
| Erythropoietin | 4 | 4 | - | - |
| Sevelamer | 1 | 3 | - | - |
| Calcitriol | 2 | 1 | 1 | 1 |

# p < 0.05 same condition (control or exercise) vs. Hemodialysis group (mean ± standard deviation)

▶ **Table 2** Mean and standard deviations of biochemical tests between groups.

| | Reference values | HD (n = 7) | HD + Ex (n = 7) | KTx (n = 10) | KTx + Ex (n = 10) |
|---|---|---|---|---|---|
| Systolic arterial pressure (mm/Hg) | < 130 | 136.50 ± 3.87 | 121.20 ± 14.27 | 114.22 ± 10.99 | 118.5 ± 9.23 |
| Diastolic arterial pressure (mm/Hg) | < 90 | 83 ± 5.13 | 75 ± 8.69 | 69.89 ± 8.52 | 75 ± 6.51 |
| Glycemia (mg/dL) | 60–99 | 84.5 ± 7.14 | 82.25 ± 10.01 | 103 ± 8.23# | 94.2 ± 5.9† |
| HDL cholesterol (mg/dL) | > 60; Low < 40 | 40.33 ± 3.21 | 58 ± 24.70 | 46 ± 9.88 | 45.7 ± 10.1 |
| LDL cholesterol (mg/dL) | < 100; High > 160 | 124 ± 45.08 | 105.3 ± 22.69 | 85 ± 10# | 91 ± 8.48 |
| Phosphorus (mg/dL) | 2.5–4.5 | 4.42 ± 0.66 | 4.94 ± 0.49 | 3.12 ± 0.40# | 3.17 ± 0.48# |
| Potassium (mg/dL) | 3.5–5.1 | 4.88 ± 0.74 | 4.6 ± 0.48 | 4.15 ± 0.33# | 4.17 ± 0.44 |
| Urea (mg/dL) | 2.5–7.8 | 112 ± 30 | 96.4 ± 42 | 51.3 ± 15# | 30.20 ± 11.76 |
| Calcium (mg/dL) | 8.6–10.2 | 8.76 ± 0.53 | 9.34 ± 0.69 | 9.57 ± 0.40# | 10.06 ± 1† |
| Hemoglobin (g/dL) | 13–18 | 10.8 ± 2.27 | 12.78 ± 0.83* | 13.09 ± 1.93 | 14.15 ± 1.33# |
| Serum creatinine (mg/dL) | 0.4–1.40 | 9.98 ± 1.39 | 7.66 ± 2.35* | 1.32 ± 0.22 | 1.01 ± 0.15# |
| Glomerular filtration rate (mL/min) | > 90 | 5.3 ± 0.6 | 7.4 ± 0.8* | 59 ± 2# | 82 ± 7* †# |
| Kt/V | > 1.3 | 1.29 ± 0.33 | 1.51 ± 1.51 | - | - |
| 6 MWT distance (meters) | - | 450 ± 62 | 612 ± 77* | 433 ± 55 | 607 ± 69* |
| 6 MWT ( % of predicted) | - | 78 ± 6 | 108 ± 10* | 69 ± 8 | 103 ± 12* # |

* p < 0.05 vs. same condition without exercise; #p < 0.05 vs. Hemodialysis group; † vs. HD + Ex group (mean ± standard deviation)

to as (1) patterns with no variation. The sequences are spread across 6 levels, and all possible patterns are divided into 4 groups, consisting of patterns with:

1) no variations (0 V, 3 symbols equal, associated with sympathetic modulation); 2) one variation (1 V, 2 symbols equal and one different associated with sympathetic and parasympathetic modulation); 3) 2 like variations (2 LV and associated with parasympathetic modulation); and 4) 2 unlike variations (2 UV and associated with parasympathetic modulation).

## Exercise program

The sequence of exercises was: 1, unilateral knee flexion in standing position; 2, shoulder abduction in standing position; 3, leg abduction in the lateral position; 4, scapular retraction in sitting position; 5, elbow flexion in standing position; 6, unilateral knee extension in sitting position; 7, leg adduction in the lateral position; 8, elbow extension in the supine position.

The Borg scale was used to determine exercise intensity, with the range proposed of 12–13 (slightly tiring). Anklets and dumbbells calibrated in 0.5 kg were used to add resistance during movement and with intervals of 60 s between sets.

All participants were already enrolled in a 3-times-per-week exercise program, supervised by the hospital's exercise professionals. All groups performed a combined exercise training protocol, where aerobic exercise was divided into 3 stages: warm-up, conditioning, and cool-down. Strength training was composed of a total of 8 exercises.

The aerobic exercise protocol was performed in a horizontal cycle ergometer (Athletic, Active, 50 BH), where exercise intensity was controlled by the participant's rate of perceived exertion, through Borg scale (moderate levels, slightly tiring). The conditioning session included local muscular endurance exercises, with 3 sets of fifteen repetitions with isotonic contractions, with 2-s duration for each type of contraction (concentric and eccentric) using the alternating segment method.

## Anxiety, depression and sleep quality assessments

The quality of sleep and the presence of sleep disturbances were evaluated using the Pittsburgh Sleep Quality Index as initially described by de Buysse [5]. To evaluate the quality of sleep of the subjects, the SQ was used. It is a questionnaire that evaluates the SQ and sleep disorders. The SQ used 7 components: (1) quality subjective sleep, (2) sleep latency, (3) duration of sleep, (4) habitual sleep efficiency, (5) sleep disorders, (6) use of medication to sleep, and (7) daytime sleepiness and disorders during the day.

The score of each component was added to give an overall score ranging from 0 to 21 points. Each component was individually determined. The higher the value obtained, the worse the quality of sleep (global score is between 6 and 21). For good sleep quality, the sum of the scores is only 5. The Beck Anxiety Inventory and the Beck Depression Inventory were used to evaluate anxiety and depression levels as initially described by Beck [2].

## Statistical analysis

Initially, a Shapiro-Wilk normality test was used to determine the normality of the sample data. A 2-way ANOVA was conducted to evaluate the difference between groups. A $p < 0.05$ was considered significant. Also, the Student's t-test was made for comparisons between the time of treatment (▶ **Table 1**). The clinical significance (effect size) was computed using Cohen's d formula, as described elsewhere [6]. Briefly, Cohen's d value of 0.8 or higher was considered with very strong clinical significance; values between 0.6 to 0.8 were considered with strong clinical significance; values ranging from 0.4–0.8 were considered to have moderate clinical significance, and values lower than 0.4 were considered to have weak clinical significance [6].

## Ethical considerations

This study was approved by the Institutional Ethical Board Committee and follows all national and international ethical standards, such as the Helsinki declaration. All subjects signed the Informed Consent before the study beginning. This study followed the STROBE recommendations for reporting observational (case-control) studies [31]. Also, the study followed the Standards for Ethics in Sport and Exercise Science Research [13] as well as those of this journal.

# Results

## Biochemical tests

▶ **Table 1** shows the general characteristics of the sample. No statistical difference was found in the Glycemia in the HD groups (Tukey's $p > 0.05$; $d = -0.26$), and KTx groups, but, a clinical significance was achieved (Tukey's $p > 0.05$; $d = -1.22$). When comparing the control groups, a significant and clinical significance was found (Tukey's $p < 0.05$; $d = 2.40$), with the same pattern present in the KTx + Ex vs. HD groups, with no difference, but with clinical significance (▶ **Table 3**; Tukey's $p > 0.05$; $d = 1.53$).

The HDL showed no significant difference but presented clinical significance in the HD groups (Tukey's $p < 0.05$; $d = 1.00$). However, no clinical or statistical significance was found in the KTx groups (Tukey's $p > 0.05$; $d = -0.03$). Also, a clinical significance was achieved in the comparison of the control groups (Tukey's $p > 0.05$; $d = 2.40$), and, as well as in the KTx + Ex vs. HD comparison, but with lower values (Tukey's $p > 0.05$; $d = 0.71$).

LDL showed no significant difference but presented clinical significance in the HD (Tukey's $p > 0.05$; $d = -0.52$) and the KTx groups (Tukey's $p > 0.05$; $d = 0.64$). Also, a clinical significance was achieved in the comparison of the control groups (Tukey's $p < 0.05$; $d = -1.19$). Also, a clinical significance was found in the KTx + Ex vs. HD comparison (Tukey's $p > 0.05$; $d = -1.01$).

Phosphorus showed no significant difference in the HD groups but achieved a clinical significance (Tukey's $p > 0.05$; $d = 0.89$). In the KTx groups, neither statistical difference nor clinical significance was achieved (Tukey's $p > 0.05$; $d = 0.11$). When comparing the control groups, a significant difference and a clinical significance were found (Tukey's $p < 0.05$; $d = -2.38$). In KTx + Ex vs. HD comparison, a statistical difference was found, and clinically relevant effect size was found (Tukey's $p < 0.05$; $d = -2.16$).

Potassium showed neither statistical nor clinical significance in the HD groups comparison, as well as in the KTx groups comparison (Tukey's $p > 0.05$; $d = 0.05$). However, in the control groups comparison, both statistical and clinical significance were found (Tukey's $p < 0.05$; $d = -1.28$), as well as in the KTx + Ex vs. HD comparison (Tukey's $p < 0.05$; $d = -1.16$).

Calcium showed no statistical difference, but a strong clinical significance in the HD groups comparison was achieved (Tukey's $p > 0.05$; $d = 0.94$), as well as in the KTx groups comparison (Tukey's $p > 0.05$; $d = 0.64$). However, in the control groups comparison, both statistical and clinical significance were found (Tukey's $p < 0.05$; $d = 1.72$).

Urea showed no statistical difference and, no clinical significance in the HD groups comparison was achieved (Tukey's $p > 0.05$; $d = 0.42$). Despite no statistical difference, a strong clinical signifi-

▶ **Table 3** Mean difference and effect size between groups.

| | (KTx control – HD control) | | HD (exercise – control) | | KTx (exercise – control) | |
|---|---|---|---|---|---|---|
| | Δ (CI) | d | Δ (CI) | d | Δ (CI) | d |
| Systolic arterial pressure (mm/Hg) | − 22.28 ( − 36.04/ − 8.51) | − 2.70 | − 15.30 ( − 30.22/ − 0.37) | − 1.47 | 4.28 ( − 8.21/16.77) | 0.42 |
| Diastolic arterial pressure (mm/Hg) | − 13.11 ( − 22.79/ − 3.42) | − 1.87 | − 8.00 ( − 18.50/2.50) | − 1.12 | − 5.11 ( − 3.68/13.90) | − 0.67 |
| Glycemia (mg/dL) | 18.5 (8.03/28.94) | 2.40 | − 2.25 ( − 9.10/13.6) | − 0.26 | − 8.80 ( − 18.3/0.69) | − 1.22 |
| HDL cholesterol (mg/dL) | 5.67 ( − 12.50/23.84) | 0.77 | 17.67 ( − 37.38/2.04) | 1.00 | − 0.30 ( − 16.79/16.19) | − 0.03 |
| LDL cholesterol (mg/dL) | − 39 ( − 71.12/ − 6.89) | − 1.19 | − 18.70 ( − 53.53/16.12) | − 0.52 | 6.00 ( − 23.13/35.13) | 0.64 |
| Phosphorus (mg/dL) | − 1.3 ( − 1.97/ − 0.62) | − 2.38 | 0.52 ( − 0.20/1.25) | 0.89 | 0.05 ( − 0.56/0.66) | 0.11 |
| Potassium (mg/dL) | − 0.73 ( − 1.39/ − 0.06) | − 1.28 | − 0.28 ( − 1.00/0.44) | − 0.44 | 0.02 ( − 0.58/0.62) | 0.05 |
| Calcium (mg/dL) | 0.81 (0.22/1.39) | 1.72 | 0.58 ( − 0.05/1.21) | 0.94 | 0.49 ( − 0.04/1.02) | 0.64 |
| Urea (mg/dL) | − 60.7 ( − 94.64/ − 26.75) | − 2.55 | − 15.6 ( − 52.41/21.21) | − 0.42 | − 21.10 ( − 51.9/9.70) | − 1.56 |
| Hemoglobin (g/dL) | 2.29 (0.04/4.53) | 1.08 | 1.98 ( − 0.45/4.41) | 1.15 | 1.06 ( − 0.98/3.10) | 0.63 |
| Serum creatinine (mg/dL) | − 8.66 ( − 10.30/7.01) | − 8.70 | − 2.32 ( − 4.10/ − 0.53) | − 1.20 | − 0.31 ( − 1.80/1.18) | − 1.64 |
| Glomerular filtration rate (mL/min) | 53.7 (48.32/59.07) | 36.37 | 2.10 ( − 3.73/7.93) | 2.96 | 23.00 (18.12/27.88) | 4.46 |
| Kt/V | - | - | 0.22 ( − 1.49/1.05) | 0.20 | - | - |
| 6 MWT distance (meters) | − 17.00 ( − 104/70.76) | − 0.29 | 162 (66.80/257) | 2.31 | 174 (94.35/254) | 2.78 |
| 6 MWT ( % of predicted) | − 9.00 ( − 21.68/3.68) | − 1.27 | 30.00 (16.24/43.75) | 3.88 | 34.00 (22.49/45.50) | 3.33 |

Negative numbers indicate higher values in the Control group; Positive numbers indicate higher values in the Experimental group; Δ (CI), mean difference and 95 % confidence interval; d, Cohen's d for effect size (negative numbers favours control group; positive numbers favour experimental group); Kt/V, indicator of hemodialysis adequacy (K, urea clearance by the dialyzer; t, treatment time; V, urea distribution volume)

cance was found in the KTx groups comparison (Tukey's $p > 0.05$; $d = -1.56$). Also, in the control groups comparison, both statistical and strong clinical significance were found (Tukey's $p < 0.05$; $d = -2.55$).

Hemoglobin showed no statistical difference, but a strong clinical significance in the HD groups comparison was achieved (Tukey's $p > 0.05$; $d = 1.15$). Despite no statistical difference, a moderate clinical significance was found in the KTx groups comparison (Tukey's $p > 0.05$; $d = 0.63$). However, in the control groups comparison, both statistical and strong clinical significance were found (Tukey's $p < 0.05$; $d = 1.08$).

Creatinine showed a statistical difference and, a strong clinical significance in the HD groups comparison was achieved (Tukey's $p < 0.05$; $d = -1.20$). Despite no statistical difference, a strong clinical significance was found in the KTx groups comparison (Tukey's $p > 0.05$; $d = -1.64$). However, in the control groups comparison, both statistical and strong clinical significance were found (Tukey's $p < 0.05$; $d = -8.70$).

The Glomerular filtration rate showed no statistical difference, but a clinical significance in the HD groups comparison was achieved (Tukey's $p > 0.05$; $d = 2.96$). Both statistical difference and a strong clinical significance were found in the KTx groups comparison (Tukey's $p < 0.05$; $d = 4.46$). Also, in the control groups comparison, both statistical and a very strong clinical significance were found (Tukey's $p < 0.05$; $d = 36.37$).

## Exercise tolerance

The 6 MWT distance showed a statistical difference, and a clinical significance in the HD groups comparison was achieved (Tukey's $p < 0.05$; $d = 1.78$). Also, significant statistical difference and a strong clinical significance were found in the KTx groups comparison (Tukey's $p > 0.05$; $d = 1.13$). However, in the control groups comparison, both statistical and clinical significance were not achieved (Tukey's $p > 0.05$; $d = -0.29$).

The expected distance achieved in the 6 MWT distance showed a statistical difference, and a clinical significance in the HD groups comparison (Tukey's $p < 0.05$; $d = 3.88$). Also, significant statistical difference and a strong clinical significance were found in the KTx groups comparison (Tukey's $p < 0.05$; $d = 3.33$). Also, in the control groups comparison, both statistical and clinical significance were achieved (Tukey's $p < 0.05$; $d = -1.27$).

## Autonomic modulation

Concerning autonomic modulation, results can be seen in ▶ **Table 4**, **5**. The total variability showed no statistical difference, but a clinical significance in the HD groups comparison was achieved (Tukey's $p > 0.05$; $d = 1.13$). However, a statistically higher value in the exercised group and, a strong clinical significance was found in the KTx groups comparison (Tukey's $p < 0.05$; $d = 4.63$). Also, in the control groups comparison, both statistically higher values in the exercised group and, a strong clinical significance were found (Tukey's $p < 0.05$; $d = 3.16$).

RR showed no statistical difference, and, no clinical significance in the HD groups comparison was achieved (Tukey's $p > 0.05$; $d = 0.30$). Also, no statistical difference was found in the KTx groups, but, a strong clinical significance was found (Tukey's $p > 0.05$; $d = 1.15$).

SDNN showed neither statistical difference nor clinical significance in the HD groups comparison (Tukey's $p > 0.05$; $d = -0.43$). Also, no statistical were found in the KTx group but, a strong clini-

▶ **Table 4** Mean and standard deviations of heart rate variability indexes between groups.

| | HD (n = 7) | HD + Ex (n = 7) | KTx (n = 10) | KTx + Ex (n = 10) |
|---|---|---|---|---|
| Time domain | | | | |
| Total variability (ms²) | 231 ± 76 | 312 ± 66* | 488 ± 86# | 923 ± 101* # |
| RR (ms) | 777 ± 108 | 810 ± 105 | 750 ± 40 | 794 ± 36 |
| SDNN (ms) | 14 ± 9 | 18 ± 8* | 22 ± 3.5 | 30 ± 6# |
| Frequency domain | | | | |
| LF (ms²) | 51 ± 53 | 33 ± 26 | 170 ± 30# | 307 ± 143* # |
| HF (ms²) | 39 ± 34 | 108 ± 143 | 77 ± 16# | 237 ± 86* |
| LF (nu) | 56 ± 21 | 30 ± 19* | 72 ± 9 | 54 ± 4* # |
| HF (nu) | 44 ± 21 | 69 ± 19* | 28 ± 9 | 46 ± 4* # |
| LF/HF | 1.3 ± 1 | 0.45 ± 0.3 | 2.7 ± 0.4# | 1.16 ± 1* # |
| Symbolic analysis | | | | |
| 0 V (%) | 25 ± 19 | 16 ± 13 | 35 ± 5 | 21 ± 3* |
| 1 V (%) | 45 ± 12 | 41 ± 17 | 43 ± 5 | 46 ± 4 |
| 2 LV (%) | 11 ± 10 | 17 ± 7 | 5 ± 0.8 | 8 ± 0.6# |
| 2 UV (%) | 19 ± 6 | 26 ± 5* | 17 ± 2.5 | 23 ± 1.5* |

*p < 0.05 vs. Control; # p < 0.05 same condition (control or exercise) vs. Hemodialysis group (mean ± standard deviation);

▶ **Table 5** Difference between groups and moments for heart rate variability.

| | (KTx control – HD control) | | HD (exercise – control) | | KTx (exercise – control) | |
|---|---|---|---|---|---|---|
| | Δ (CI) | d | Δ (CI) | d | Δ (CI) | d |
| Total variability (ms²) | 257 (142/371) | 3.16 | 81 (−43/205) | 1.13 | 435 (331/538) | 4.63 |
| RR (ms) | −27 (−125/71.51) | −0.33 | 33 (−79/139) | 0.30 | 44 (−45.4/133) | 1.15 |
| SDNN (ms) | 8 (−0.83/16.83) | 1.17 | 4 (−5.58/13.58) | 0.46 | 8 (−0.02/16.01) | 1.62 |
| LF (ms²) | 119 (6.08/231) | 2.76 | −18 (−140/104) | −0.43 | 137 (34.53/239) | 1.32 |
| HF (ms²) | 38 (70/7147) | 1.43 | 69 (−49.21/187) | 0.66 | 160 (61.09/259) | 2.58 |
| LF (nu) | 16 (−2.44/34.44) | −0.99 | −26 (−46.00/−5.99) | −1.29 | −18 (−1.26/−34.73) | −2.58 |
| HF (nu) | −16 (−34.44/2.44) | 0.99 | 25 (4.99/45.06) | 1.25 | 18 (1.26/34.73) | 2.58 |
| LF/HF | 1.4 (0.39/2.40) | 1.83 | −0.85 (−1.94/0.24) | −1.15 | −1.54 (−2.45/−0.62) | −2.02 |
| 0 V (%) | 10 (−4.44/24.44) | 0.71 | −9 (−24.66/6.66) | −0.55 | −14 (−27.10/−0.89) | −3.39 |
| 1 V (%) | −2 (−15.32/11.32) | −0.21 | −4 (−18.45/10.45) | −0.27 | 3 (−9.09/15.1) | 0.66 |
| 2 LV (%) | −6 (−13.35/1.35) | −0.84 | 6 (−1.97/13.97) | 0.69 | 3 (−3.67/9.67) | 4.24 |
| 2 UV (%) | −2 (−7.14/3.14) | −0.43 | 7 (1.41/12.58) | 1.26 | 6 (1.33/10.67) | 2.91 |

Negative numbers indicate higher values in the Control group; Positive numbers indicate higher values in the Experimental group; Δ (CI), mean difference and 95 % confidence interval; d, Cohen's d for effect size (negative numbers favour control group; positive numbers favours experimental group);

cal significance was found in the KTx groups comparison (Tukey's $p > 0.05$; d = 1.62). Also, in the control groups comparison, no statistical difference was found, but, a strong clinical significance was found (Tukey's $p > 0.05$; d = 1.17).

The absolute values of LF and HF showed no statistical difference, but a moderate clinical significance in the HD groups comparison was achieved (Tukey's $p > 0.05$; d = −0.43 and 0.66, respectively). However, statistically significant higher values and, strong clinical significance were found in the KTx groups comparison (Tukey's $p < 0.05$; d = 1.32 and 2.58, respectively). Also, in the control groups comparison, both statistically significant higher values in the KTx + Ex group and, strong clinical significance were found (Tukey's $p < 0.05$; d = 2.37 and 3.02, respectively).

The normalized values of LF and HF showed a statistical difference with a strong clinical significance in the HD groups comparison (Tukey's $p < 0.05$; d = −1.29 and 1.25, respectively). Also, statistically significant difference and strong clinical significance were found in the KTx groups comparison (Tukey's $p < 0.05$; d = −2.58 and 2.58, respectively). Although, in the control groups comparison, no significant values were found, but a strong clinical significance were found (Tukey's $p > 0.05$; d = −0.99 and 0.99, respectively).

The LF/HF showed no statistical difference, but a strong clinical significance in the HD groups comparison was achieved (Tukey's $p > 0.05$; d = −1.15). However, statistically significant difference and strong clinical significance were found in the KTx groups comparison (Tukey's $p < 0.05$; d = −2.02). Although, in the control groups comparison, no significant values were found, but, a strong clinical significance was found (Tukey's $p > 0.05$; d = 1.83).

The 0 V showed no statistical difference, and a moderate clinical significance in the HD groups comparison was achieved (Tukey's p > 0.05; d = − 0.55). However, statistically significant difference and strong clinical significance were found in the KTx groups comparison (Tukey's p < 0.05; d = − 3.39). Although, in the control groups comparison, no significant values were found, but, a moderate clinical significance was found (Tukey's p > 0.05; d = 0.71).

The 1 V showed no statistical difference and no clinically relevant in none of the case, except for the KTx groups comparison, which showed a moderate effect size (d = 0.66). In the 2 LV, no significant difference was found in none of the comparisons. Although, a moderate effect size was found in the HD comparison (d = 0.69). However, a strong clinical relevance in the KTx groups comparison was achieved (d = 4.24), as well as in the control groups comparison (d = − 0.84).

In the 2 UV, significant differences were found in HD and KTx groups comparison (Tukey's p < 0.05), with strong effect sizes (d = 1.26 and 2.91, respectively). However, no statistical differences were found in the control and KTx + Ex vs. HD comparisons (p < 0.05), but, a moderate effect size was found in the control groups comparison (d = − 0.43).

### Sleep, anxiety and depression inventories

The sleep, anxiety and depression inventories results are described in ▶ **Table 6**, **7**.

## Discussion

This study aimed to analyze the effect of an exercise training program on cardiovascular autonomic modulation and, exercise capacity of HD and KTx patients. Our data display improvements in cardiovascular autonomic modulation and exercise tolerance in both groups. Also, our data shows the HD + Ex group demonstrated lower values in important cardiovascular risk markers such as systolic blood pressure, diastolic blood pressure, LDL cholesterol, urea, and, increases in HDL cholesterol, hemoglobin, 6 MWT distance and % of predicted. These changes are clinically relevant, seeing that the HD + Ex was able to enter normal reference values for blood pressure, LDL, HDL and, Hemoglobin (▶ **Table 2**).

To the best of our knowledge, this is the first study to describe the effect of exercise training on autonomic modulation and kidney function of HD and KTx patients comparatively. Our group has been investigating the effects of exercise in CKD patients and had observed its positive effects on autonomic modulation, kidney function, anxiety, depression and sleep quality [1, 23].

CKD it has been recognized as an independent risk factor for cardiovascular diseases [14], with a marked cardiovascular autonomic imbalance [23, 28]. Exercise has been used as an intervention for promoting a better quality of life and increased cardiac function [1, 24, 26]. Our results show improvements in essential markers of kidney function in both groups after training, such as phosphorus and creatinine (▶ **Table 2**). As expected, the KTx + Ex group showed higher improvements in those biochemical markers than the HD + Ex group. The management of the biochemical markers are essential, seeing that usually, CKD patients under hemodialysis suffer from parathyroid problems, that can cause hypercalcemia and, hyperphosphatemia [12], complications that can further lead to vascular problems like artery calcification and even graft failure [9, 12, 22]. Exercise can also be impaired by alterations in sodium and potassium availability in the skeletal muscle [25], an activity that is profoundly impaired in patients with CKD. Other studies from our group had demonstrated that exercised CKD patients tend to have lower values of creatinine, phosphorus, and potassium [1, 23].

Also, the KTx + Ex group showed improved cardiac autonomic modulation, but with far more benefits and improvements than the HD + Ex group (▶ **Table 4**, **5**). This improvement in the KTx group is remarkable because our data show decreased overall heart rate variability in the HD + Ex group. The KTx + Ex group also shows a reduction in sympathetic modulation, as expressed by the LF (n.u. and $ms^2$), and increases in vagal modulation, as expressed by HF (n.u. and $ms^2$).

Other studies have shown the beneficial effect of exercise in the autonomic modulation of CKD patients. Kouidi et al. had shown not only benefits in cardiovascular autonomic modulation (similar to those we found), but also baroreflex sensitivity improvements in patients with end-stage kidney disease, with a significant correlation between baroreflex sensitivity indexes and $VO_2$max, an important index of exercise capacity [19]. From the same group, Konstantinidou et al. as well showed the benefits of exercise in patients with CKD undergoing hemodialysis, with the same baroreflex and $VO_2$max benefits cited before [18]. Our data corroborate with these 2 studies, taking into account that we analyzed trained patients undergoing hemodialysis and after kidney transplantation.

Nonetheless, the autonomic imbalance is correlated with increased risk for cardiovascular diseases and re-hospitalization in subjects with CKD [4]. These data highlight the importance of

▶ **Table 6** Sleep, anxiety and depression scores in both groups.

| | HD (n = 7) | HD + Ex (n = 7) | KTx (n = 10) | KTx + Ex (n = 10) |
|---|---|---|---|---|
| Pittsburgh Sleep Quality Index | 6.5 ± 2 | 4.5 ± 2 | 7 ± 2 | 5 ± 1.5 |
| Beck Depression Index | 9 ± 5 | 5 ± 4 | 5 ± 3 | 9 ± 5 |
| Beck Anxiety Index | 10 ± 7 | 5.5 ± 3 | 7 ± 4 | 6 ± 4 |

▶ **Table 7** Difference and effect sizes of the sleep quality, anxiety and depression inventories.

| | (KTx control – HD control) | | HD (exercise – control) | | KTx (exercise – control) | |
|---|---|---|---|---|---|---|
| | Δ (CI) | d | Δ (CI) | d | Δ (CI) | d |
| Pittsburgh Sleep Quality Index | 0.5 ( − 1.99/2.99) | 0.25 | − 2.00 ( − 4.70/0.70) | − 1.00 | − 2.00 ( − 4.26/0.26) | − 1.13 |
| Beck Depression Index | − 4.00 ( − 9.74/1.74) | − 0.97 | − 4.00 ( − 10.23/2.23) | − 0.88 | 4.00 ( − 1.21/9.21) | 0.97 |
| Beck Anxiety Index | − 3.00 ( − 9.16/3.16) | − 0.52 | − 4.50 ( − 11.19/2.19) | − 0.83 | − 1.00 ( − 6.59/4.59) | − 0.25 |

Δ (CI), mean difference and 95 % confidence interval; d, Cohen's d for effect size effective interventions (such as exercise) to reduce the autonomic imbalance in these patients, thus reducing the risk of cardiovascular diseases and re-hospitalization among CKD and kidney transplanted patients.

We did not assess the baroreflex sensitivity, but, we may suggest based on the increase of overall variability and changes the sympathovagal balance that these positive changes may have also occurred. Furthermore, we assessed baroreflex sensitivity after an acute session of exercise in CKD patients undergoing hemodialysis and found significant differences in response to exercise stimuli [8].

Both HD + Ex and KTx + Ex groups showed improved exercise capacity, as can be seen by the significant elevations of the 6 MWT distance (▶ **Table 2**). The increases in exercise capacity have been correlated with increased life expectancy and better kidney function in patients with CKD [17, 30]. Also, increased exercise capacity is correlated with increased overall autonomic modulation and reduced risk for cardiovascular diseases [27, 30].

The most important finding of this study shows that HD + Ex patients show significant clinical improvements in important markers of cardiovascular disease such as blood pressure, lipid profile, hemoglobin and 6 MWT distance. Other studies had been shown the benefits of exercise for HD patients, with reductions in blood pressure and increases in exercise capacity [19, 24, 26]. This finding in comparison with the KTx patients highlights the increased risk for cardiovascular disease of the HD patients and gives a pathway leading to the use of exercise as a tool inside the hospital, focusing primarily in the HD patients instead of KTx patients.

In conclusion, our data show that an exercise program combined with the kidney transplantation procedure is capable of increasing autonomic modulation and, exercise tolerance of CKD patients. However, the patients undergoing hemodialysis that were also submitted to an exercise program showed better prognosis in important cardiovascular risk factors, and as well, increased autonomic modulation.

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### Conflict of Interest

The authors declare no conflict of interest.

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