

RESEARCH ARTICLE

# Effects of the inspiratory muscle training and aerobic training on respiratory and functional parameters, inflammatory biomarkers, redox status and quality of life in hemodialysis patients: A randomized clinical trial

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## Abstract

### Objective

Evaluate and compare the isolated and combined effects of Inspiratory Muscle Training (IMT) and Aerobic Training (AT) on respiratory and functional parameters, inflammatory biomarkers, redox status and health-related quality of life (HRQoL) in hemodialysis patients.

### Methods

A randomised controlled trial with factorial allocation and intention-to-treat analysis was performed in hemodialysis patients. Volunteers were randomly assigned to perform 8-weeks of IMT at 50% of maximal inspiratory pressure (MIP), low intensity AT or combined training (CT). Before the interventions, all the volunteers went 8-weeks through a control period (without training). Measures are taken at baseline, 8-week (after control period) and 16-week (after the interventions). Primary outcomes were functional capacity (incremental shuttle walk test), MIP and lower limbs strength (Sit-to-Stand test of 30 seconds). Plasma levels of interleukin-6 (IL-6), soluble tumor necrosis factor receptor 1 (sTNFR1) and 2 (sTNFR2), adiponectin, resistin and leptin, redox status parameters and HRQoL (KDQOL-

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SF questionnaire) were the secondary outcomes. Data analyses were performed by *two-way repeated measurements ANOVA*.

## Results

37 hemodialysis patients aged 48.2 years old (IC95% 43.2–54.7) were randomized. Increase of MIP, functional capacity, lower limbs strength and resistin levels, and reduction of sTNFR2 levels in 16-week, compared to baseline and 8-week, were observed in all the groups ( $p < 0.001$ ). IMT improved functional capacity, MIP and lower limbs strength in 96.7m (IC95% 5.6–189.9), 34.5cmH<sub>2</sub>O (IC95% 22.4–46.7) and 2.2repetitions (IC95% 1.1–3.2) respectively. Increase in resistin levels and reduction in sTNFR2 levels after IMT was 0.8ng/dL (IC95% 0.5–1.1) and 0.8ng/dL (IC95% 0.3–1.3), respectively, without between-group differences. Compared to baseline and 8-week, adiponectin levels ( $p < 0.001$ ) and fatigue domain of the HRQoL ( $p < 0.05$ ) increased in 16-week only in CT.

## Conclusion

IMT, AT and CT improved functional parameters and modulated inflammatory biomarkers, in addition, IMT provoked a similar response to low intensity AT in hemodialysis patients.

## Trial registration

Registro Brasileiro de Ensaio s clínicos RBR-4hv9rs.

## Introduction

Abnormalities in muscle structure and function, such as a decrease in strength and endurance, [1] are common clinical findings in patients with End-stage Renal Disease (ESRD). These changes are determined by factors associated with the ESRD progression and hemodialysis treatment and a contribution to protein-energy wasting and uremic myopathy.[2] Among these factors, chronic inflammation and changes in the redox state are cited as determining factors for the alterations in energetic function and in the capacity of muscular contraction in ESRD, associated with the sedentary lifestyle.[2] Associations between inflammatory markers and redox state parameters with peripheral muscle weakness have been demonstrated in chronic kidney disease [3–6], as well as being predictors of death.[7, 8]

As happens in the muscles of the locomotor system, the function of the inspiratory muscles can also be impaired in patients with ESRD. In a recent study, the reduction in the inspiratory muscle strength, evaluated by maximum inspiratory pressure (MIP), was demonstrated in a sample from hemodialysis patients. In addition, the inspiratory muscle weakness was an independent predictor of functional capacity impairment in this population.[9] Thus, inspiratory muscle training (IMT) could improve functional capacity in hemodialysis patients.[10]

The efficacy of IMT in the functional capacity improvement has already been described in other health conditions.[11] In ESRD, evidence for this therapeutic modality in increasing MIP and functional capacity is based on the results of a few studies.[12–15] Furthermore, the magnitude of IMT, compared to a conventional aerobic training (AT) modality, are not known. Thus, the objectives of the present study were to evaluate and compare the isolated and combined effects of the IMT and low intensity AT on nutritional, respiratory and functional parameters, inflammatory biomarkers and redox status, as well as on the health-related

quality of life (HRQoL) domains of hemodialysis patients. The alternative hypothesis this study was that the improvements induced by IMT are lower than that induced by low intensity AT and that the combined IMT and AT induce greater improvements than the isolated approaches.

## Materials and methods

### Study design

In this randomised controlled trial with factorial allocation and intention-to-treat analysis, participants were randomly allocated into three experimental conditions: IMT, AT or combined training (CT). After selection of participants, the volunteers were stratified by hemodialysis schedule (7:00h, 12:30h e 16:30h). Randomisation was performed using individual allocation codes placed within opaque, sealed envelopes by a person having no contact with the participants. Potential participants were screened to verify eligibility before baseline assessment and randomisation. The research was carried out in accordance with the declaration of Helsinki and was approved by the ethics committee of the Centro Universitário UNA-BH (protocol 37412314.5.0000.5098). All the patients gave their written, informed consent before participating in the study.

### Participants

Between January 2015 and December 2015, ESRD patients receiving hemodialysis treatment in the Santa Casa de Caridade de Diamantina Hospital were selected. To be included in the study, patients had to be more than 18 years old. They should not be receiving anti-inflammatory or antiallergic medication, under hemodialysis treatment three times a week for at least three months, and with arteriovenous fistula for hemodialysis access. Exclusion criteria were any contraindication to physical exercise or inability to perform the functional tests. The sample size was calculated a priori, according to the procedure proposed by Jakel et al (2005) for repeated measures [16]. Considering functional capacity variations of 47% between IMT and lower limb training, standard deviation of 30%, [13] power of 80% and alpha of 5% (two-tailed). The sample size was estimated in 10 volunteers per group.

### Interventions

All interventions (IMT, AT and CT) were intradialytic, and they were performed during the first two hours of dialysis, three times a week for eight weeks or 24 sessions. The sessions lost by the volunteers were not restored. Thus, adherence was recorded by the number of sessions held in the 24 offered.

IMT was performed using Threshold IMT® (Respironics, Murrysville PA, USA) or Power-Breathe light or median Resistance (Powerbreathe, HaB International Ltd, Southam, UK), according to the previously evaluated MIP. Participants performed three sets of 15 deep inspirations at the equipment mouthpiece and rested for 60 seconds with the linear load adjusted to 50% of MIP. [13] MIP was reevaluated every six sessions for load adjustment.

The AT was performed by cycle ergometer (Mini Bike E5, ACTE Sports, São Paulo, Brasil) positioned in the front of patients' chairs. The cycling session consisted of a 5-minute warm-up, 30 minutes of cycling at target workload, and a 5-minute cooling-down period. During exercise, patients were asked every 5 minutes about the fatigue score, and the cycle ergometer load was adjusted to achieve a fatigue score between three and five points in the modified Borg Scale. The speed remained  $\geq 50$  rpm. [17]

In the CT sessions, IMT was performed immediately before AT and, in the AT group, the participants performed sets of inspirations with IMT devices, but without resistance to inspiration (Sham-IMT). The eight weeks prior to initiating the interventions were considered to represent the control period. During eight weeks prior to initiating the interventions the volunteers did not receive any type of training to represent the control period. The dialysis prescription and medication therapy remained unchanged during the study.

After medical and dental evaluation, the volunteers were evaluated in the baseline, 8-week follow-up (after control period) and 16-week follow-up (after intervention period), on dialytic days, immediately before the hemodialysis sessions, except for the evaluation of body composition.

## Outcome measures

**Primary outcomes. Maximum inspiratory pressure.** With the volunteers seated, MIP were evaluated with a calibrated aneroid manovacuumeter (MV-150/300, Ger-Ar, São Paulo, Brazil), equipped with a 2-mm-diameter hole in the nozzle, from residual volume. The highest value of three valid measurements was considered.[18] Maximum predicted values were estimated.[19]

**Functional capacity.** The functional capacity was evaluated by the Incremental Shuttle Walk Test (ISWT).[20, 21] Volunteers were instructed to walk or run in a 10 m corridor and the minimum speed was determined by an audio signal. The ISWT has 12 progressive intensity levels, and the test was terminated when the volunteer failed to reach the minimum speed required on a level surface two consecutive times.[22, 23] The distance walked was recorded, and the predicted values were estimated.[24]

**Lower limbs strength.** The lower limbs strength was assessed by the Sit-to-Stand test of 30 seconds (SST).[25] Volunteers were instructed to stand up completely from a 45 cm chair and sit down as quickly as possible until the volunteer touched the back on the backrest, with no support from the upper limbs. The best performance (number of full movements in 30 seconds) of two tests with a minimum interval of 5 minutes between them was considered. No verbal encouragement was provided.

**Secondary outcomes. Inflammatory biomarkers.** Ethylenediaminetetraacetic acid vacutainers (BD vacutainers, Franklin Lakes, NJ, USA) were used to collect 8-ml venous blood samples immediately before the second weekly hemodialysis session (midweek), without fasting. The tubes were centrifuged at 2500 rpm for 10 min at 4°C and were stored as plasma and erythrocyte aliquots at -80°C until use. Plasma soluble tumor necrosis factor receptor 1 and 2 (sTNFR1 and sTNFR2, respectively), leptin, adiponectin and resistin levels were measured using conventional sandwich ELISA kits (DuoSet, R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. The detection limits were 5.0 pg/mL for all the kits. The plasma interleukin 6 (IL-6) level was measured using the cytometric bead arrays kit (BD Bioscience, San Jose, CA, USA) according to the manufacturer's protocol. Samples were acquired in a FACSCanto flow cytometer (BD Biosciences, San Jose, CA, USA) and analyzed using the FCAP Array v1.0.1 software (Soft Flow Inc.).

Measurements of redox status. The redox status was evaluated by the plasmatic level of the thiobarbituric-acid-reactive substances (TBARS) and ferric reducing antioxidant power (FRAP), as well as by use of the antioxidant enzymes dismutase superoxide (SOD) and catalase (CAT) activity in the erythrocyte lysate. The erythrocyte lysate was prepared as described by Glass and Gershon.[26] The protein concentration of samples was determined by the Bradford method[27] using bovine serum albumin (BSA) (1 mg/mL) as the standard. TBARS levels were measured according to the method described by Ohkawa et al.,[28] and the reactions

between thiobarbituric acid and malondialdehyde (MDA) was used to determine the degree of lipid peroxidation. The total antioxidant capacity (FRAP) was determined according to the method of Benzie and Strain.[29] The assay to determine SOD activity was performed according to Srivastava et al.[30] and expressed in U/mg of protein. The CAT activity was measured according to the method of Nelson and Kiesov[31] and expressed as  $\Delta E/\text{min}/\text{mg}$  protein, where  $\Delta E$  represents the variation in enzyme activity during one minute.

**Health-related quality of life (HRQoL).** The HRQoL was evaluated by a specific questionnaire—Kidney Disease Quality of Life (KDQOL-SF).[32]

**Anthropometric/physical Parameters.** The Anthropometric/physical parameters were blind and evaluated immediately after the second weekly hemodialysis session. Weight, body mass index (BMI), waist circumference and body fat percentage were evaluated. Body fat percentage was evaluated by an analogic plicometer (Sanny, American Medical do Brasil, Brasil). Three skinfolds (tricipital, suprailiac and abdominal in women and tricipital, subscapular and middle pectoral in men) were measured on the right side. The percentage of fat mass was obtained by use of the equations of Jackson & Pollock (1985)[33] and Siri (1961).[34] The measurement of inflammatory biomarkers, redox status and Anthropometric/physical parameters were blinded, performed by a person having no contact with the participants.

## Statistical analysis

The Sigma Stat (Version 9.0) statistic program was used for the statistical analysis. The normality of data were verified using the Shapiro-Wilk test. Categorical variables are presented as absolute and relative frequencies, and continuous variables are presented as the mean (IC95%). Categorical variables were compared by the Chi-squared test. The effects of the interventions were compared by Two-Way Repeated Measures ANOVA (within-group, between-group and interactions) with Tukey's post hoc test. For variables with a statistical significance to the within-group differences, the comparisons of the 8-week to 16-week variations (intervention period) was performed by the one-way ANOVA or Kruskal Wallis test, with Tukey's post hoc test. The significance level was set at 0.05. For reasons of cost, secondary outcomes were assessed only in participants who completed all steps of the treatment originally allocated (Per-protocol analysis).

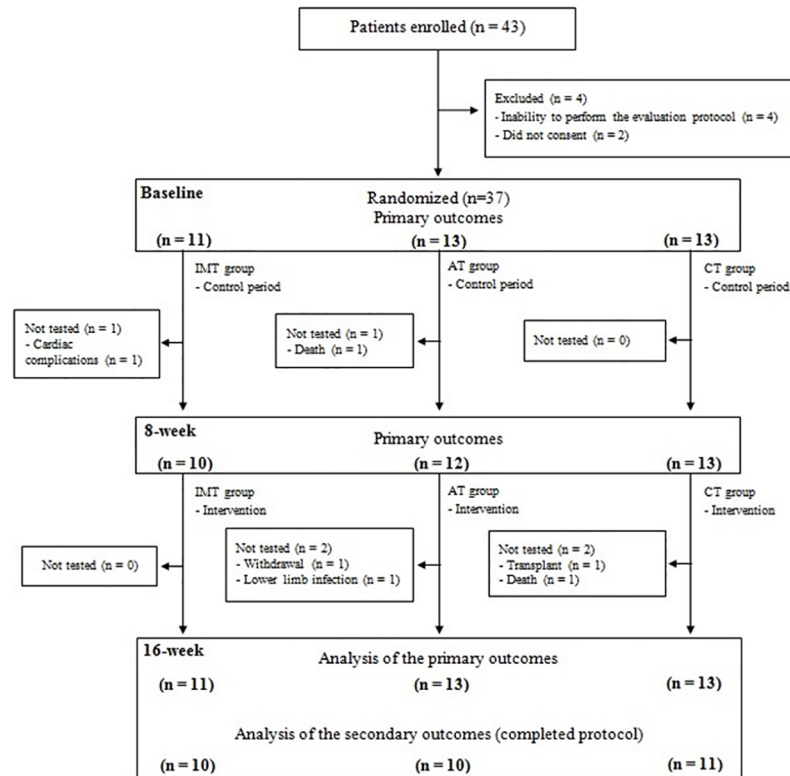
## Results

### Flow of participants through the study

Out of a total of 93 ESRD patients, 43 were selected and 37 were randomized (11 in IMT group, 13 in AT group and 13 in CT group). The flow of the participants through the study is illustrated in Fig 1. The participants' demographics and clinical characteristics are presented in Table 1. The three groups were similar at the baseline. The volunteers were predominantly male (70.3%) and had a mean age of 48.2 years (IC95% 44.5–51.9) and dialysis data, kt/v indexes of 1.5 (IC95% 1.4–1.7) and urea reduction rate of 70.8% (IC95% 67.0–74.7), demonstrated the efficiency of hemodialysis treatment.

### Adherence to the study protocol

The number of the exercise sessions in the IMT, AT and CT groups were 23.1 (22.5–24.0), 23.1 (IC95% 22.5–24.0) and 22.7 (IC95% 21.8–23.6), respectively ( $p = 0.279$ ). This number represents an assiduity of 96.4% (IC95% 93.3–99.6), 96.4% (IC95% 93.0–99.8) and 94.9% (IC95% 91.3–98.5), respectively ( $p = 0.279$ ). Two participants, one of the IMT group and one of the AT group, did not participate in the 8-week and 16-week follow-up assessments. The data of these



**Fig 1. Flow chart.** IMT: inspiratory muscle training; AT: aerobic training; CT: combined training.

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patients were imputed on analysis, repeating the results of baseline assessment in the 8-week and 16-week follow-up. During intervention periods, two participants of the AT group and two volunteers of the CT group were not evaluated in the 16-week follow-up assessment. Data were imputed for these participants using the mean of the baseline and 8-week measurements in 16-week follow-up. The results of the study were similar when these values were not imputed.

The interventions performed in the AT group and the CT group were low intensity physical training programs with fatigue scores at 3.3 (IC95% 2.4–4.1) and 3.0 (IC95% 2.4–3.5), respectively, without any differences between them ( $p = 0.701$ ). However, their fatigue scores were higher than those observed in the IMT group (0.3 (IC95% 0.0–0.5);  $p < 0.001$ ). The whole duration of the IMT sessions did not exceed 10 minutes and no adverse effects associated to the interventions were observed.

### Primary outcomes

The effects of the interventions in primary outcomes are demonstrated in Fig 2. Was shown within-group difference, with an increase of the inspiratory muscle strength (Fig 2A), functional capacity (Fig 2B) and lower limb strength (Fig 2C) in 16-week, compared to baseline and 8-week. There were no between-group differences. The MIP increased 34.5 cmH<sub>2</sub>O (IC95% 22.4–46.7) after IMT (8-week to 16-week). This increase was similar ( $p = 0.06$ ) to AT and CT group (18.5 cmH<sub>2</sub>O (IC95% 9.9–27.0) and 26.9 cmH<sub>2</sub>O (IC95% 17.2–36.7), respectively). The increases in functional capacity after IMT, AT and CT were 96.7 m (IC95% 5.6–187.9), 86.6 m (IC95% 21.8–151.5) and 147.7 m (IC95% 94.1–201.3), respectively ( $p = 0.251$ ), as well the lower lib strength increased in 2.2 repetition (IC95% 1.1–3.2), 3.1 repetition (IC95%



Table 1. Characteristics of the sample according to treatment allocation.

	IMT (N = 11)	AT (N = 13)	CT (N = 13)	p
<b>Sex, n%</b>				
Male	7 (63.6)	10 (76.9)	9 (69.2)	0.77
Female	4 (36.4)	3 (23.1)	4 (30.8)	
<b>Race, n%</b>				
Caucasian	5 (45.5)	6 (46.1)	5 (38.4)	0.64
Black	5 (45.5)	4 (30.8)	4 (30.8)	
Other	1 (9.0)	3 (23.1)	4 (30.8)	
<b>Age, years</b>	52.8 (43.1–62.5)	49.5 (41.6–57.3)	45.2 (34.8–55.5)	0.46
<b>Weight, kg</b>	67.7 (54.9–80.5)	69.1 (57.5–80.8)	64.5 (52.9–76.2)	0.82
<b>BMI, kg/m<sup>2</sup></b>	25.1 (21.1–29.2)	25.2 (21.5–28.8)	24.2 (20.9–27.2)	0.85
<b>Waist, cm</b>	86.2 (73.4–98.9)	87.9 (77.4–98.4)	84.5 (73.9–95.2)	0.89
<b>ESRD etiology, n%</b>				
Hypertensive nephropathy	4 (36.4)	3 (23.1)	6 (46.1)	
Diabetic nephropathy	2 (18.2)	3 (23.1)	3 (23.1)	
Glomerulonephritis	2 (18.2)	1 (7.7)	1(7.7)	
Polycystic kidneys	0	1 (7.7)	0	
Others	3 (27.2)	5 (38.4)	3 (23.1)	
<b>Comorbidity conditions, n%</b>				
Tabagism	2 (18.2)	1 (7.7)	3 (23.1)	0.56
Ethylism	0	0	0	—
Diabetic	2 (18.2)	2 (15.4)	3 (23.1)	0.88
Obesity	2 (18.2)	2 (15.4)	3 (23.1)	0.88
<b>Periodontal disease, n%</b>				
Periodontal health	7 (63.6)	7 (53.9)	8 (61.5)	0.80
Gingivitis	2 (18.2)	5 (38.4)	3 (23.1)	
Mild disease	2 (18.2)	1(7.7)	2 (15.4)	
<b>Duration of dialysis, years</b>	4.4 (1.4–7.5)	3.0 (0.5–6.4)	4.9 (2.7–7.1)	0.30
<b>kt/v</b>	1.7 (1.4–1.7)	1.6 (1.4–1.7)	1.5 (1.3–1.7)	0.74
<b>Urea reduction ratio, %</b>	70.5 (66.6–74.4)	72.4 (68.6–76.2)	71.7 (67.2–76.1)	0.70
<b>Hb, mg/dL</b>	10.9 (9.8–11.8)	10.3 (9.4–11.2)	10.9 (10.3–11.5)	0.52
<b>Hematócrit, %</b>	34.4 (31.2–37.5)	32.1 (29.6–34.6)	33.8 (31.8–35.9)	0.37
<b>Albumin, g/dL</b>	3.7 (3.5–3.9)	3.8 (3.6–4.0)	3.9 (3.7–4.0)	0.43
<b>Beginning of dialysis, n(%)</b>				
7:00h	3(27.2)	2 (15.4)	4 (30.8)	0.81
12:30h	3(27.2)	6 (46.2)	5 (38.4)	
16:30h	5(45.6)	5 (38.4)	4 (30.8)	

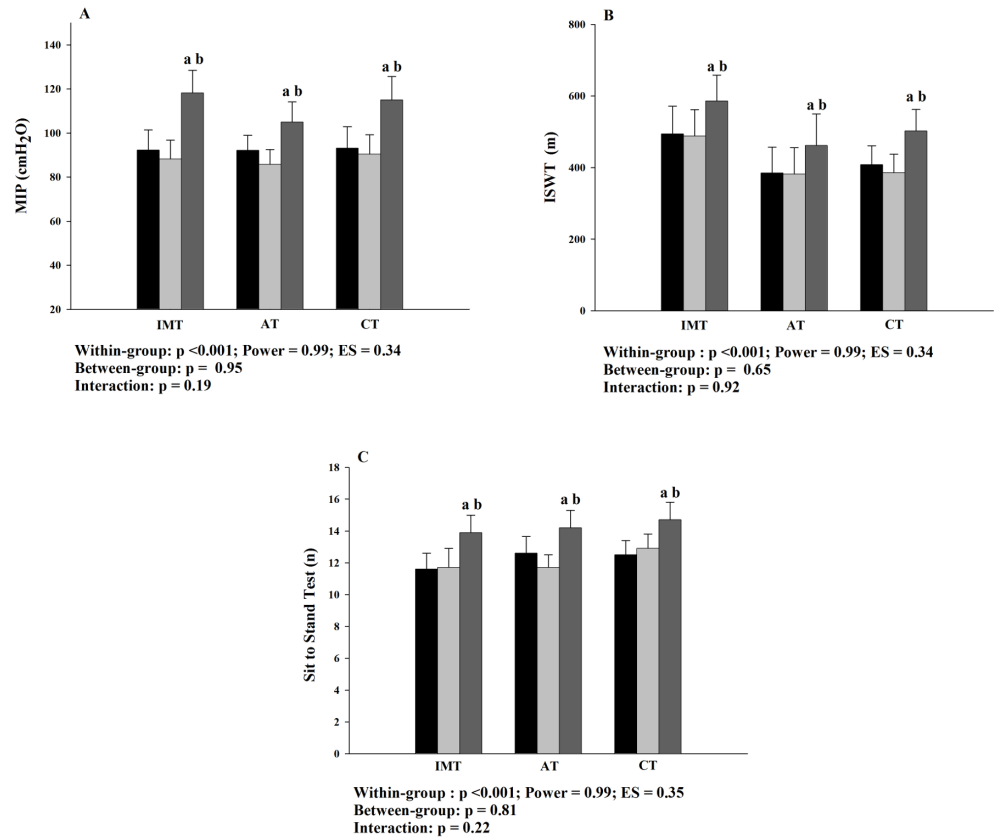
Data represented as mean (IC95%) or n (%). IMT: inspiratory muscle training group; AT: aerobic training group; CT: combined training group; BMI: body mass index; ESRD: End-Stage Kidney Disease; Kt/V:dialysis efficiency; Hb: hemoglobin.

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2.1–4.1) and 2.4 repetition (IC95%1.4–3.5) after IMT, AT and CT, respectively (p = 0.671). No interaction was found and there were no statistical differences during the control period for the variables evaluated.

### Secondary outcomes

The results of the interventions on anthropometric/physical parameters are presented in [Table 2](#). There were no significant differences for the anthropometric/physical variables evaluated. Similar results were found for redox status parameters ([Table 3](#)).



**Fig 2. Effects of the interventions in primary outcomes.** A: inspiratory muscle strength; B: functional capacity; C: lower limb strength; MIP: maximal inspiratory pressure; ISWT: incremental shuttle walk test; IMT: inspiratory muscle training; AT: aerobic training; CT: combined training; ES: effect size; ■ Baseline; ■ 8-week; ■ 16-week. Baseline to 8-week: control period; 8-week to 16-week: intervention period. a:  $p < 0.05$  to baseline; b:  $p < 0.05$  to 8-week.

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The effects of the interventions on inflammatory biomarkers are illustrated in Fig 3 and Fig 4. Reductions in plasma sTNFR2 levels (Fig 3B) were found after interventions in all the groups, when compared to baseline and 8-week ( $p < 0.001$ ). The reductions in plasma sTNFR2 were 0.8 ng/dL (IC95% 0.3–1.3), 0.5 ng/dL (IC95% 0.2–0.8) and 0.7 ng/dL (IC95% 0.5–1.1) after IMT, AT and CT, respectively ( $p = 0.393$ ). There were no between-group differences or interactions for plasma sTNFR2 and there were no significant differences for the sTNFR1 and Il-6 (Fig 3A and Fig 3C, respectively).

There were increase in all groups in adiponectin levels in 16-week, compared to baseline (Fig 4A). However, the intervention-associated effect (8-week to 16-week) was only found after CT. The increase of the adiponectin levels after CT was 3.4 ng/dL (IC95% 1.1–5.7). Similarly, within-group differences was shown for plasma resistin levels (Fig 4B). There were increases of the resistin levels in 16-week, relative to baseline and 8-week in all the interventions. Plasma resistin levels increased in 0.7 ng/dL (IC95% 0.5–1.1), 0.9 ng/dL (IC95% 0.5–1.3) and 0.8 ng/dL (IC95% 0.2–1.4) after IMT, AT and CT, respectively ( $p = 0.875$ ). There were no between-group differences or interactions for plasma adiponectin or resistin levels and no significant differences were found for leptin levels (Fig 4C).

The results of the interventions in HRQoL domains are showed in S1 Table. Was observed within-group differences in the “energy/fatigue” domain, with an increase in the scores 16-week relative to 8-week and baseline. Through post hoc analysis, these effects were only



**Table 2. Effects of the interventions on anthropometric/physical parameter.**

Variables	IMT (n = 10)	AT (n = 10)	CT (n = 11)	Within- group	Between-group	Interaction
				P	P	P
<b>Weight, kg</b>				0.201	0.713	0.451
Baseline	70.0 (53.6–82.3)	71.9 (58.6–85.2)	64.6 (50.6–78.6)			
8-week	68.7 (54.3–83.0)	71.7 (59.0–84.3)	65.2 (51.6–78.8)			
16-week	68.5 (54.1–82.9)	72.2 (59.6–84.8)	64.9 (51.5–78.3)			
<b>BMI, kg/m<sup>2</sup></b>				0.628	0.905	0.451
Baseline	25.2 (20.7–29.6)	25.8 (21.2–30.5)	24.2 (20.6–27.8)			
8-week	25.4 (21.0–29.8)	26.2 (22.2–30.3)	24.4 (20.9–27.9)			
16-week	25.3 (20.9–29.8)	26.4 (22.3–30.4)	24.3 (20.9–27.8)			
<b>Waist, cm</b>				0.090	0.744	0.181
Baseline	85.1 (71.0–99.2)	89.5 (77.2–101.7)	83.4 (71.8–94.9)			
8-week	85.9 (71.3–100.4)	90.3 (77.8–102.8)	83.6 (72.7–94.4)			
16-week	86.1 (71.9–100.3)	87.4 (74.6–100.2)	82.3 (72.1–92.4)			
<b>Body fat, %</b>				0.168	0.501	0.944
Baseline	16.7 (12.8–20.5)	18.6 (13.6–23.3)	15.4 (8.5–22.3)			
8-week	16.8 (12.9–20.6)	18.7 (8.7–22.3)	15.5 (8.7–22.3)			
16-week	16.7 (12.8–20.6)	18.8 (13.9–23.6)	15.5 (8.7–22.4)			

Data represented as mean (IC95%). IMT: inspiratory muscle training group; AT: aerobic training group; CT: combined training group; BMI: body mass index; Baseline to 8-week: control period; 8-week to 16-week: intervention period.

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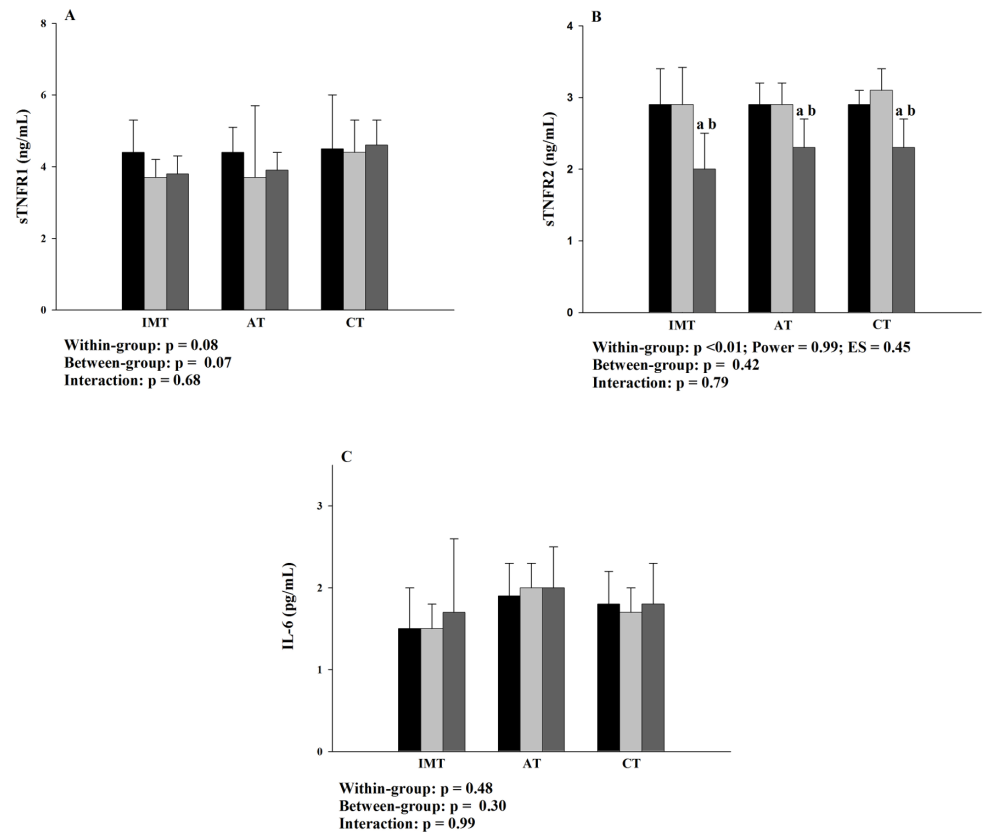
found after CT. Similar results was shown for scores of the “physical functioning” and “role physical” domains. However, the individual effects of interventions were not observed through

**Table 3. Effects of the interventions on redox status parameters.**

Variables	IMT (n = 10)	AT (n = 10)	CT (n = 11)	Within-group	Between-group	Interaction
				P	P	P
<b>SOD, U/mg protein</b>				0.58	0.63	0.75
Baseline	27.3 (13.1–41.6)	16.0 (12.1–19.9)	24.1 (8.1–40.1)			
8-week	22.2 (12.7–31.8)	14.3 (8.06–20.6)	25.1 (15.4–34.9)			
16-week	22.3 (13.8–30.7)	17.3 (13.4–21.2)	24.4 (14.5–34.3)			
<b>Catalase, ΔE/min/mg</b>				0.62	0.37	0.88
Baseline	36.7 (31.2–42.2)	26.5 (19.2–33.8)	34.9 (24.1–48.7)			
8-week	39.7 (29.2–50.2)	29.5 (18.7–40.3)	40.5 (28.9–52.1)			
16-week	42.2 (31.4–52.9)	25.8 (18.4–33.1)	38.2 (29.1–47.2)			
<b>TBARS, nmol MDA/μg protein</b>				0.37	0.45	0.37
Baseline	0.3 (0.1–0.4)	0.2 (0.1–0.2)	0.2 (0.1–0.3)			
8-week	0.2 (0.1–0.4)	0.2 (0.1–0.2)	0.2 (0.1–0.3)			
16-week	0.1 (0.0–0.2)	0.2 (0.1–0.2)	0.2 (0.1–0.4)			
<b>FRAP, mmolFeSO<sub>4</sub>/L/mg protein</b>				0.57	0.18	0.32
Baseline	49.2 (29.7–68.6)	41.5 (34.6–48.3)	36.8 (31.0–42.7)			
8-week	46.8 (29.9–63.6)	44.7 (35.1–54.4)	38.2 (34.3–42.0)			
16-week	35.9 (27.2–44.6)	43.1 (36.0–50.1)	36.6 (24.4–46.8)			

Data represented as mean (IC95%). IMT: inspiratory muscle training group; AT: aerobic training group; CT: combined training group; SOD: superoxide dismutase; TBARS: thiobarbituric-acid-reactive substances; FRAP: ferric reducing antioxidant power; Baseline to 8-week: control period; 8-week to 16-week: intervention period.

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**Fig 3. Effects of the interventions on plasma sTNFR1, sTNFR2 and IL-6 levels.** A: plasma sTNFR1 levels; B: plasma sTNFR2 levels; C: plasma IL-6 levels; sTNFR1 and 2: soluble receptors 1 and 2, respectively, of the tumor necrosis alpha factor; IL-6: interleukin 6; IMT: inspiratory muscle training group; AT: aerobic training group; CT: combined training group; ES: effect size; ■ Baseline; ▒ 8-week; ▓ 16-week. Baseline to 8-week: control period; 8-week to 16-week: intervention period. a:  $p < 0.05$  to baseline; b:  $p < 0.05$  to 8-week.

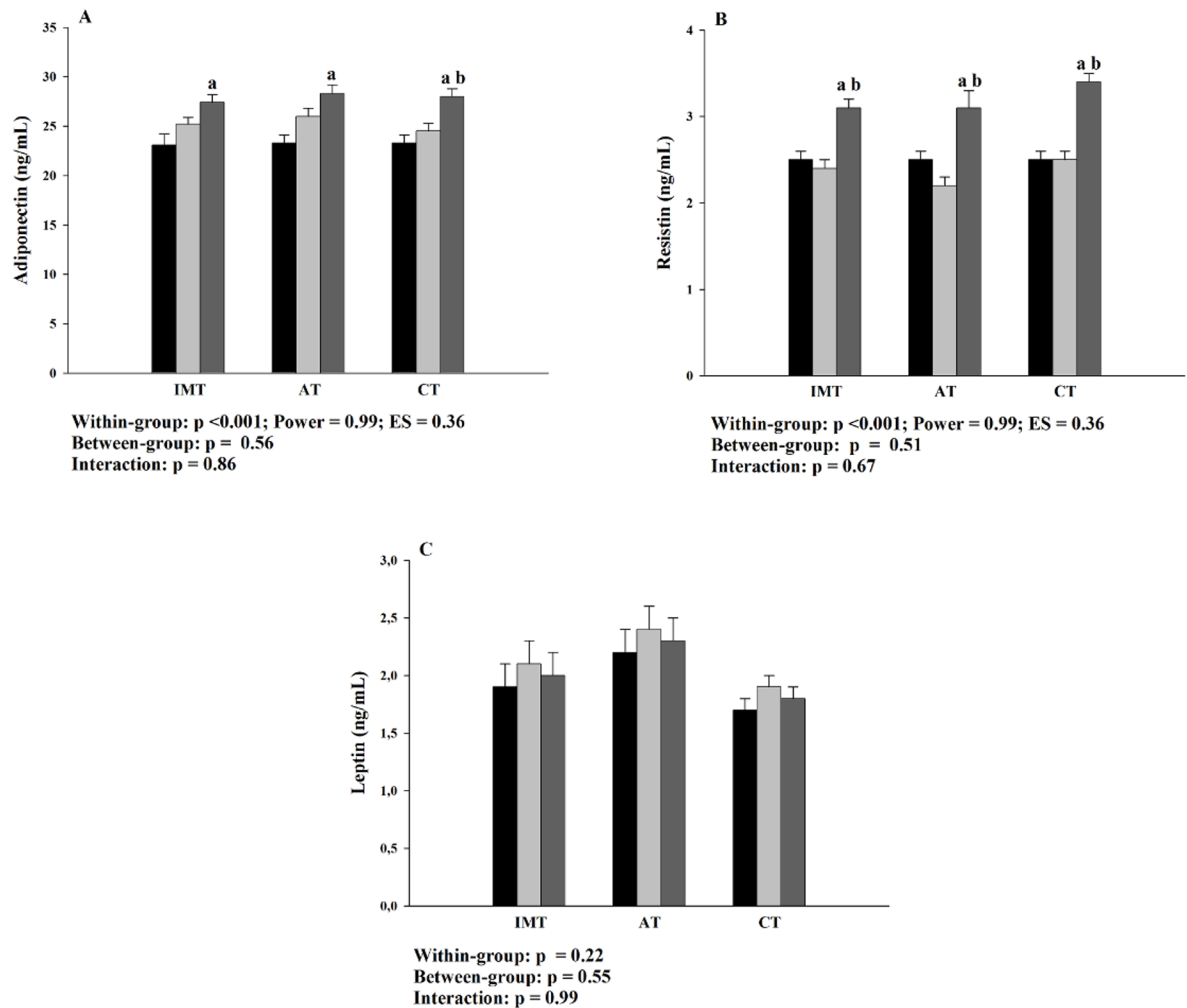
<https://doi.org/10.1371/journal.pone.0200727.g003>

post hoc analysis, as well as for “emotional being health” domains. Finally, the scores of the “pain” domain increased during the control period before IMT. There was no statistical significance for other domains of the KDQOL-SF questionnaire.

## Discussion

To the best of our knowledge, this is the first study that compared the effects of IMT, performed in isolation and combined with aerobic training, on anthropometric/physical, respiratory and functional parameters, inflammatory biomarkers, redox status and HRQoL in people with ESRD undergoing hemodialysis. The main findings of the present study were: (1) the effects of IMT on the evaluated parameters were similar to those of low intensity AT; and (2) the addition of IMT to AT increases adiponectin levels and improves physical domains of HRQoL. The present study suggests that the IMT, a low-cost, easy-to-perform training that does not require physical space, can be a therapeutic model in the hemodialysis units when conventional AT can not be implemented.

The effects of IMT on the MIP were similar to those of previous studies.[12, 13, 15] However, Silva et al.[14] did not find significant changes in MIP after IMT. The intensity of IMT performed by the authors was lower than that of the present study. In the comparison among groups, no differences were demonstrated, suggesting a similar increase in MIP after IMT, AT



**Fig 4. Effects of the interventions on plasma adipokines levels.** A: plasma adiponectin levels; B: plasma resistin levels; C: plasma leptin levels; IMT: inspiratory muscle training group; AT: aerobic training group; CT: combined training group; ES: effect size; ■ Baseline; ▨ 8-week; ▩ 16-week. Baseline to 8-week: control period; 8-week to 16-week: intervention period. a:  $p < 0.05$  to baseline; b:  $p < 0.05$  to 8-week.

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and CT. In addition, the increase in MIP after all interventions was greater than the minimal clinically important difference in individuals with chronic respiratory disease.[35] Considering that the MIP is an independent predictor to functional capacity in hemodialysis patients, [9] increases of the distance covered during ISWT would be expected. In fact, we also demonstrated the increase in functional capacity after all three interventions. The increase in functional capacity after IMT was higher than the minimal clinically important difference proposed for the ISWT (70 m) in cardiovascular rehabilitation [36] and for persons with chronic kidney disease (60 m). [37] The improvement in functional capacity after interventions was similar between-group. This finding has an important clinical meaning, because IMT increased functional capacity in magnitude similar to conventional AT. A similar clinical meaning can be attributed to the strength of the lower limb muscles because the sit-to-stand test is cited as a test for the functional evaluation of people with ESRD.[1] Although the specific values of minimal detectable change for this test for hemodialysis patients are not known, the increase of the SST after IMT was higher than they showed by others studies, after different physical training programs.[38, 39]

To date, the effects of IMT on inflammatory biomarkers in hemodialysis patients have been evaluated in only one study.[13] The authors demonstrated reductions in C-reactive protein after intervention. Regarding sTNFR, this is the first study to evaluate the effects of IMT in this population, and the effects of physical training programs have been little explored. In 2014, Viana et al.[40] demonstrated that the sTNFR1 level decreased after six months of home-based AT, without sTNFR2 changes, a result contrary to that observed in our study. This result may be due to the difference in the volume of training. In addition, the sample studied by the authors was composed of older individuals. It is important to consider that the reduction of the sTNFR2 level might be clinically relevant because it is determinant for manifestation of erythropoietin resistance in ESRD,[41] as well as being an independent predictor for death.[7] In the analysis of the other inflammatory biomarkers, the levels of sTNFR1 and IL-6 were lower than those observed by other authors,[7, 40, 41] probably because of the recruitment of younger, a shorter time of dialysis treatment than in the other studies or both.

In addition to the reduction in sTNFR2, there was an increase in adiponectin level, especially after CT. This result suggests a positive effect of the combination of IMT and AT on the modulation of anti-inflammatory activity, considering the role of adiponectin in the immune system and in cardioprotection.[42] Also, all three interventions increased resistin levels. The effects of exercise training on resistin levels are poorly understood. Although it is traditionally associated with increased insulin resistance and pro-inflammatory activity,[43] increased levels after physical training in healthy men[44] and higher levels in athletes[45] have been demonstrated. This response could be related to the increase in the lipid metabolism in the exercise muscle,[45] to an antioxidant action of resistin induced by the training[43] or to a potential cross-talk between resistin and signaling of an insulin/insulin-like growth factor.[46] In addition, low resistin levels have been associated with poor hospitalization-free survival in hemodialysis patients.[47] Although the mechanisms involved in these associations remain unknown, the effects of interventions on the levels of resistin, sTNFR2, and adiponectin suggest a positive modulating effect on the attenuation of the inflammatory process.

Regarding the leptin level, no significant changes after intervention were observed, possibly because there were no changes in the body composition of the volunteers. The low training volumes might also justify the results of the redox status parameters, considering that the improvement of the antioxidant capacity induced by the exercise training is directly dependent on the training volume and the target population.[48] For example, in the study by Wiuld and colleagues,[49] the moderate aerobic training performed during four months reduced TBARS from eight subjects, mostly obese, in hemodialysis treatment.

The global effects of interventions on inflammatory biomarkers can be considered clinically relevant. This assumption is based on the observed results in the sTNFR2, adiponectin and resistin levels. In the present study, the reduction of sTNFR2 levels, an independent predictor of death in ESRD,[7] occurred concomitantly with increasing of adiponectin and resistin levels. In ESRD, the increased of the adiponectin (especially after CT) and resistin levels, without changes in body composition and redox status, may result in a positive modulatory effect.[50, 51] Although the long-term clinical and functional effects of the observed results are unknown, the clinical influence of the biomarkers evaluated in the ESRD [7, 41, 42, 47] make the results of this work relevant. However, the effects of a long duration physical training programs on these variables need to be studied in this population.

In the setting of the HRQoL, the effects of IMT were previously reported[13], and a greater variation of the domains related to physical aspects after 10 weeks of IMT was demonstrated. The effects of AT are well established.[52] In the present study, at baseline, higher values were observed in most domains of the KDQOL-SF, which can be partially explained by the characteristics of the sample, considering the association between age and HRQoL.[53] Together

with the low training volume, the characteristics of the sample might have contributed to the absence of significant effects. However, the score of the “energy/fatigue” domain increased in CT, which demonstrated an additional effect of the inclusion of IMT in AT. Thus, HRQoL results suggest that the applied interventions positively influence factors related to physical aspects, as reported in a recent meta-analysis.[52]

The present study demonstrated that the IMT can promote positive effects on respiratory, functional, inflammatory and HRQoL aspects in magnitudes similar to that of low intensity AT. Thus, the IMT, a low-cost and easy-to-perform training, can be a therapeutic model in the hemodialysis units when conventional AT can not be implemented. Interestingly the applied protocols presented a high adherence, which can be explained by the low intensity of the exercises. This highlights the applicability of the applied training modalities.

However, some issues need to be elucidated for the routine IMT application in dialysis centers: Which subgroup of patients would most benefit from IMT? What is the clinical meaning of IMT performed in a long-term setting? The elucidation of these questions can help in the elaboration of specific guidelines for IMT performance in hemodialysis patients.

As limitations, the lung volumes and capacities were not evaluated, and it was not possible to determine the degree of respiratory impairment in our sample. Also, our sample was younger and had fewer comorbidities than other studies.

We can conclude that eight weeks of IMT improved functional and inflammatory parameters of patients in hemodialysis treatment similarly to the effect of a low intensity AT. Although the combination of the two therapeutic modalities did not increase the functional capacity more expressively, improvements in the self-perception of HRQoL, especially in physical aspects, would justify the combined use of these therapies in ESRD patients undergoing hemodialysis.

## Supporting information

**S1 Table. Effects of the interventions on health related quality of life.**

(DOCX)

**S1 File. CONSORT checklist.**

(PDF)

**S2 File. Study protocol.**

(PDF)

**S3 File. Committee approval documents.**

(PDF)

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