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Effects of resistance training on hepcidin levels and iron bioavailability in older individuals with end-stage renal disease: a randomized controlled trial

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Abstract

Anemia is an inherent complication of older individuals with end-stage renal disease (ESRD) that is associated with inflammation which in turn is an important factor in the activation of hepcidin that contributes to the decrease in serum iron. Athough resistance training (RT) seems to reduce inflammation in ESRD, its influence on hepcidin and iron availability in hemodialysis patients is unclear. Therefore, the aim of this study was to exemine the effects of RT in on inflammatory profile, hepcidin, and iron status in older individuals with ESRD. End-stage renal disease patients (N: 157, age: 66.8±3.6; body mass: 73±15 body mass index:27±3), were assigned to control (CTL n: 76) and exercise groups (RT n: 81). RT consisted of 24 weeks/3 days per week of a moderate intensity. There was an increase in the bioavailability of iron (ΔRT: 22.2; ΔCTL: -1 µg/dL, $p < 0.0001$), a decrease in hepcidin levels (ΔRT: -7.9; ΔCTL: 0.2 ng/mL, $p < 0.0001$),and an improvement of the inflammatory profile. These novel findings show that RT is a potential coadjuvant to reduce iron deficiency by decreasing the levels of hepcidin and pro-inflammatory markers in older patients undergoing hemodialysis.

Keywords: Resistance training, nephrology, hepcidin, hematology, cytokines, hemodialysis.

1. Introduction

Anemia is a common complication characterized by low levels of circulating hemoglobin and has been linked to older people with end-stage renal disease (ESRD) (Bennett and others 2019; Collister and others 2017; Drakesmith and Prentice 2012; Moranne and others 2009; Ueda and Takasawa 2017). The mechanism can be explained by a decreased glomerular filtration rate leading to an inadequate production of erythropoietin for erythropoiesis and, consequently, iron deficiency (Bilar and others 2020; Wong and others 2019). It is already known that older people with ESRD present low iron availability and high accumulation of substances with toxicity that inhibit erythropoiesis (McClellan and others 2004). Thus, not treating anemia will likely damage other tissues, such as the heart and brain, increasing cardiac risk, and decreasing physical functionality in aged people with ESRD (Kopple 2001; McClellan and others 2004).

Another factor that affects and is affected by anemia is acute and chronic inflammatory status, which is one of the most common complications in chronic kidney disease (CKD) patients (Bennett and others 2019). Pro-inflammatory cytokines inhibit steady-state erythropoiesis, and stimulate an increased expression and concentration of hepcidin, responsible for decreasing iron fissionability and, thus, aggravating anemia status (Bennett and others 2019; Collister and others 2017; Drakesmith and Prentice 2012; Ueda and Takasawa 2017). Moreover, the overexpression of hepcidin and pro-inflammatory proteins negatively affects the cardio-renal axis in CKD (Ganz and Nemeth 2016).

Hepcidin, a hypoferremia-inducing hormone, binds to ferroportin, allowing this transmembrane protein to undergo endocytosis and intracellular proteolysis (Drakesmith and Prentice 2012; Nemeth and others 2004). This decreases the delivery of cellular iron to blood plasma (Camaschella and others 2020; Ganz and Nemeth 2016), lowering iron concentration. This iron deffficiency is more common in aged people with ESRD, and in most cases caused by inflammation, leading to elevated iron concentration in liver, intestines, macrophages, and spleen (Van der Weerd and others 2015). Even if patients with ESRD are treated with iron supplementation, anemia can still be found (Ganz and Nemeth 2016). This phenomenon can be a consequence of high levels of hepcidin, which impairs the release of iron from storage cells, such as asenterocytes, macrophages,and hepatocytes (Ganz and Nemeth 2016). Therefore, based on early insights (Pelusi and others 2013; Van der Weerd and others 2015; Wish 2006), hepcidin measurement has been suggested to assess anemia status in CKD patients.

According to the aforementioned scenario, research has been carried out in order to determine interventions to decrease inflammation and, consequently, antagonize the expression, and high concentration of hepcidin (Domínguez and others 2018; Ganz and Nemeth 2016; Wish 2006). This may be an important finding with clinical utility for older people with ESRD by improving their anemia status and iron balance (Drakesmith and Prentice 2012). Among the treatments known to improve health in aged people with ESRD, resistance training (RT) has shown both chronic anti-inflammatory and anti-oxidant effects (Petersen and Pedersen 2005b).

Chronic exercise-training can improve inflammatory profile, which can regulate the production of hepcidin; however, it is still unknown if chronic exercise can antagonize the expression of hepcidin and iron bioavailability. Aerobic and resistance exercise can also stimulate hypoxia inducible factor alpha (Holloway and others 2018; Lindholm and Rundqvist 2016), which is an important antagonist of hepcidin (Kaplan and others 2018), increasing the possibility for exercise-training to become a relevant treatment for anemia in older people with ESRD. Therefore, the aim of the present study was to examine the effects of RT on inflammatory profile, hepcidin, and iron status in oder people with ESRD. We hypothesize that RT should decrease hepcidin and increase iron levels due to the improvement of the inflammatory profile.

2. Methods

2.2. Subjects

One hundred and fifty-seven patients of both sexes undergoing maintenance phase hemodialysis completed this research investigation which lasted from January 2019 until November of 2019 (age: 66.8±3.6 years; body mass: 73±15kg : 27±3kg/m^2) (**Figure 1**). This study was registered with the Brazilian clinical trials registration: URL: http://www.ensaiosclinicos.gov.br/rg/RBR-3gpg5w/, nºRBR-3gpg5w (30/06/2019) and also registered in the World Health Organization international clinical trial resistry platform: URL: http://apps.who.int/trialsearch/utn.aspx, nº U1111-1237-8231 (30/06/2019).Written informed consent was obtained from all participants involved in the study. All experimental protocols were approved by the Local Ethics Committee, under the number: 23007319.0.0000.0029. The study conforms that all procedures were carried out to conform to the principles outlined in the declaration of Helsinki (1975). Inclusion criteria for participants were as follows: i) age ≥ 60 years old; ii) hemodialysis treatment for at least three months; iii) dialysis at least three times per week; and iv) no significant medical complications in the last three months, with the exception of vascular access correction. The exclusion criteria were: i) recent acute myocardial infarction within the last three months or unstable angina; ii) systemic lupus erythematosus; iii) congenital kidney malformation or some autoimmune disease that affected the kidneys; iv) osteoarticular complications that could compromise physical exercise; v) decompensated heart failure that could limit participation in training; vi) severe decompensated diabetes; and vii) severe neuropathy, retinopathy, or diabetic nephropathy. Only patients who read, agreed and signed the written informed consent participated in this study. The participants were then randomized into two groups by simple randomization by just one resercher using a random number generator (Suresh 2011): control group (CTL, n= 76) and resistance training group (RT, n= 81). All patients underwent nutritional follow-up by a clinical nutritionist, however, CTL group did not receive any exercise intervention. **Figure 1** presents the participant flow-chart.

****Figure 1****

2.3. Resistance-training protocol

The RT group completed 24 weeks of training, with sessions held three times per week on alternate days. The volume of 3 sets of 8 to 12 repetitions was used to facilitate the prescription for more than 1 patient at the same time. The rest interval between sets and between exercises was 120 seconds. We initially indicated a pre-established OMNI Scale rating of perceived exertion (RPE) load, encouraging the number of 8 repetitions. If the individual started to find it easy, we encouraged an increase in repetitions and, if the patient exceeded 12 repetitions, there was a load adjustment. In the initial 12 weeks the load was based on the previously validated OMNI scale (Lagally and Robertson 2006; Robertson and others 2003) from 5 to 6 and, over the remaining 12 weeks, from 7 to 8. The patients performed pre-dialysis exercise, that is about one hour before the start of the hemodialysis session. Each training session consisted of 12 exercises that included: chest press, squat (they used only body weight, and were encouraged to complete only a few repetitions [4 repetitions] at the beginning of the program), unilateral row, unilateral knee extension, unilateral knee flexion, unilateral shoulder press, hip thrust, unilateral biceps curl, unilateral hip adduction, unilateral hip abduction, unilateral elbow extension with dumbells and seated calf raise. For the chest press, unilateral row, unilateral hip adduction and unilateral hip abduction exercises, and dynamometer, App and elastics (e-Lastic®, Brasília, Brazil) cable was used for training. The e-Lastic load was recorded as the peak [maximum] load achieved in each movement to count the repetitions). Dumbbells were used for unilateral shoulder press, unilateral biceps curl and unilateral elbow extension. For unilateral knee extension, unilateral knee flexion, hip thrust, and seated calf raise were realized with ankle weight. For the upper limbs, we prioritized unilateral exercises in a conservative measure in order to preserve arteriovenous fistula and programmed three sets of 8 to 12 repetitions with two minutes of rest between sets with two seconds of candence in both the concentric and eccentric phases.

2.4. Biochemical analysis

Venous blood samples were collected at baseline and after 24 weeks of training to measure hemoglobin, ferritin, iron, hepcidin, tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and interleukin 10 (IL-10). Samples were obtained in the morning (8 to 12 hours of fasting) and all patients were instructed not to practice any physical activity 48 hours before. Samples were centrifuged at 1500 x g for 15 min; after processing, the specimens were aliquoted into cryovials and stored at -80º C. Serum hemoglobin, ferritin and hepcidin were determined using an automated chemistry analyzer (COBAS c111 system, Roche Diagnostcs, Switzerland). The intra- and inter-assays from all markers analized by COBAS were 10%. The systemic levels of TNF-α, IL-6 and IL-10 were measured in triplicate by enzyme-linked immunosorbent assay (ELISA) kits from R&D Systems (Minneapolis, MN, USA) according to the manufacturer's instructions. The detectable limit for TNF-α, IL-6 and IL-10 were 10, 18 and 0.2 pg/mL, respectively. The overall intra- and inter-assays CVs for inflammatory markers and hepcidin were in a range of 2.3 to 10 % .

2.5. Statistical Analysis

Due to the lack of previous data about iron, ferritin, hemoglobin and hepcidin, we based the sample size calculation on the following protocol: 157 participants provided a statistical power of 95% (1-β = 0.95), considering an alpha of 5% (α = 0.05) with a moderate effect size (f = 0.40) calculated a priori by G*power (version 3.1.9.4). The evaluators were blinded to group assigments when collecting and analyzing the data. Initially, normality and homogeneity of data was verified using the Shapiro-Wilk and Levenes test, respectively. For categorical variables, the chi-square test was used. The unpaired T-test was applied to compare age, body mass and body mass index between groups before training. In order to analyze the pre *vs.* post-training, the Kruskal-Wallis test was used followed by Dunn's multiple comparisons. All analyses were evaluated using the software GraphPad Prism 6.0 (GraphPad Software, Inc., CA, United States).

3. Results

There were no adverse effects throughout the 81 subjects that completed RT protocol. The baseline characteristics are described in **Table 1.** There were no significant differences between groups for age, body mass, body mass index, number of hypertensive, diabetic, smokers and number of medications used.

****Table 1****

There was a significant increase in iron and a decrease in hepcidin in the RT group as compared with the pre-training, CTL post and CTL pre ($p < 0.0001$), as described in **Figure 2**. There were no significant differences for hemoglobin and ferritin.

****Figure 2****

There was a significant decrease in TNF-α and IL-6 after the intervention in RT post as compared with pre-training, CTL post and CTL pre ($p < 0.0001$). IL-10 displayed a significant increase after six months of RT as compared with pre-training, CTL post and CTL pre ($p < 0.0001$). **Figure 3**.

****Figure 3****

There was a significant incresase in IL-10/TNF-α ratio and IL-10/IL-6 after the intervention in RT post as compared with pre-training, CTL post and CTL pre ($p < 0.0001$). Also, iron/hepcidin ratio presented a significant increase after six months of RT as compared with pre-training, CTL post and CTL pre ($p < 0.0001$). (**Figure 4**)

****Figure 4****

4. Discussion

The present RCT aimed to investigate the effects of RT on inflammatory profile, hepcidin, and iron status in older people with ESRD. The main findings revealed that RT promoted an increase of both iron and IL-10 levels, while hepcidin, TNF-α, and IL-6 concentrations in blood decreased. These results suggest that this model of exercise-training may be a relevant therapy for anemia related to CKD.

The vast majority of renal patients under hemodialysis treatment cannot rely on their own iron storage among other factors, due to high levels of hepcidin and low production of erythropoietin, thus, requiring iron supplementation (Gafter-Gvili and others 2019; Mikhail and others 2017). CKD patients with anemia have increased risk of mortality and morbidity (Gafter-Gvili and others 2019), as this state is associated with the production of pro-inflammatory cytokines which can stimulate hepcidin expression and, consequently, lower iron bioavailability (Bennett and others 2019; Ganz and Nemeth 2016). Considering that exercise training has a potential anti-inflammatory effect (Negaresh and others 2018; Petersen and Pedersen 2005a), it could be an important mediator to improve iron balance in the body.

An important finding of the present study was improved iron availability after six months of RT, demonstrating that it can be applied both as a preventive measure, and treatment of anemia in aged people with ESRD. This improvement of iron level is justified by the decrease of hepcidin, which regulates cellular iron efflux by binding to ferroportin, and inducing its internalization (Nemeth and others 2004). Moreover, cell cultures (Nemeth and others 2004) showed that when hepcidin binds to ferroportin, it becomes internalized and degraded, decreasing the export of cellular iron. In addition to iron status, hepcidin is also stimulated by pro-inflammatory cytokines via Janus kinase/signal transducers and activators of transcription 3 signaling (Ueda and Takasawa 2018), specially by IL-6.

Therefore, the significant decrease of TNF-α and IL-6 (**Figure 2**) may explain the decrease of hepcidin, since its expression is strongly related to the inflammatory process (Ueda and Takasawa 2018). There is a dose-response of exercise-released cytokines (Petersen and Pedersen 2005a), while the acute-phase response to exercise implies the release of pro-inflammatory proteins, chronically, exercise-training enhances the expression and activity of anti-inflammatory substances, which generally improves the inflammatory profile (Petersen and Pedersen 2005a). These conditions were already investigated in patients undergoing hemodialysis by Zhi-Juan et al. (Dong and others 2019), which demonstrated that intradialytic RT reduced inflammatory reactions. However, rather than being intradialytic, the present study employed an interdialytic training design in CKD patients (*i.e.* one hour before the hemodialysis). Therefore, exercise training seems to down-regulate TNF-αand IL-6, which are inducers of hepcidin released from liver, leading to the improvement of iron availability.

Song and others (2010) identified, *in vitro,* the minimal concentration of IL-6 which can induce relative hepcidin expression. They demonstrated that IL-6 at 0.1 to

10ng/dL promotes an increase of hepcidin levels in a dose-dependent manner, confirming that IL-6 is involved in hepcidin expression. In the same study, they verified that the suppression of hepcidin by tocilizumab treatment, a humanized monoclonal antibody that acts by blocking IL-6 receptors is accompanied by the improvement of iron bioavailability (Song and others 2010). In our study, although we did not apply tocilizumab treatment, RT seems to act as a suppressor of IL-6, which decreases hepcidin concentration, and improves iron metabolism.

This study presents some limitations, we did not have tissue biopsy analysis to investigate iron balance before or after RT. Moreover, the analysis of redox balance and hypoxia inducible factor alpha could strengthen the mechanisms associated with decreased hepcidin after exercise training. In spite of this, all patients were individually supervised by a strength and conditioning professional together with nurses and clinicians. Therefore, this study improves our understanding regarding the effects of interdialytic RT on hematological patterns and inflammation in CKD patients. Moreover, 81 patients completed the intervention and this data brings mechanistic insights of how exercise-training could act in the improvement of iron metabolism. This also reinforces that this type of RT is well-tolerated by patients under these conditions.

5. Conclusions

The present study opens perspectives for the clinical application of RT as a convenient tool for future guidelines of the treatment of anemia in older subjects with ESRD due to the potential effect in decreasing hepcidin, which could maximize the effect of the supplementation of erythropoietin and ferrous sulfate and, consequently, increase iron availability in this population. In conclusion, six months of RT improved the inflammatory profile, which may suppress hepcidin concentration and increase iron availability in older people with ESRD. Thus, these findings provide support for the concept that RT should be recommended as an important tool to improve the clinical status of this population.

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Table 1. Baseline characteristics of the subjects.

Variables	CTL (*n* = 76)	RT (*n* = 81)	*p* Value
Age, yr	66.3 ± 3.9	67.3 ± 3.2	0.0997
Sex, men/women	40/36	46/35	0.6328
Body Mass	72.8 ± 14.6	73.9 ± 16.6	0.6438
BMI	26.8 ± 2.9	27.3 ± 3.7	0.3807
Diabetes, *n* (%)	52 (68.42%)	43 (53.0%)	0.0525
Hypertension, *n* (%)	76 (100%)	81 (100%)	10.000
Smokers, *n* (%)	21 (27.63%)	22 (27.16%)	10.000
Medications, *n* (%)			
Erythropoietin	53 (69.73%)	61 (75.30%)	0.4768
Ferrous Sulfate	42 (55.26%)	43 (53.08%)	0.8729
ARBs	68 (89.47%)	70 (86.41%)	0.6294
ACEi	68 (89.47%)	69 (85.18%)	0.4786
Statins	17 (22.36%)	17 (20.98%)	0.8488

Data expressed as mean ± SD. CTL: control group; RT: resistance training group; ACEi: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; BMI: body mass index. Chi-square and T - Test were used to analyze the baseline characteristics of individuals.

Figure legends

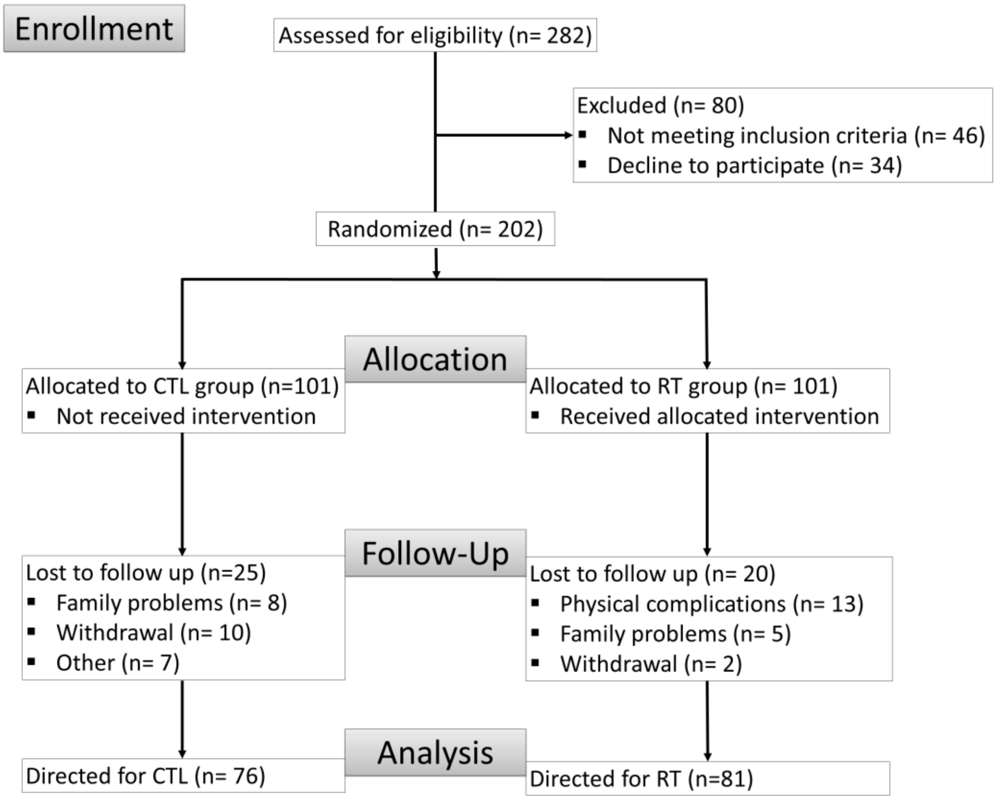
Figure 1- Participant flow-chart. CTL: control; RT: resistance training.

Figure 2. Data expressed by mean ± SD. Hemoglobin, ferritin, iron and hepcidin response pre- and post-training in maintenance hemodialysis patients. CTL, control group; RT, resistance training group. Kruskal-Wallis test followed by the Dunn's multiple comparisons between groups pre- vs. post-training.[a]p < 0.0001 *vs.* CTL Pre; [b]p < 0.0001 *vs.* CTL Post; [c]p < 0.0001 *vs.* ST Pre.

Figure 3. Data expressed by mean ± SD. Pro- and anti-inflammatory marker response pre- and post-training in maintenance hemodialysis patients. CTL, control group; RT, resistance training group. Kruskal-Wallis test followed by the Dunn's multiple comparisons between groups pre- vs. post-training.[a]p < 0.0001 *vs.* CTL Pre; [b]p < 0.0001 *vs.* CTL Post; [c]p < 0.0001 *vs.* ST Pre.

Figure 4. Data expressed by mean ± SD. IL-10/TNF-α ratio, IL-10/IL-6 and iron/hepcidin ratio response pre- and post-training in maintenance hemodialysis patients. CTL, control group; RT, resistance training group. Kruskal-Wallis test followed by the Dunn's multiple comparisons between groups pre- vs. post-training. [a]p < 0.0001 *vs.* CTL Pre; [b]p < 0.0001 *vs.* CTL Post; [c]p < 0.0001 *vs.* ST Pre.

Fig. 1


Enrollment
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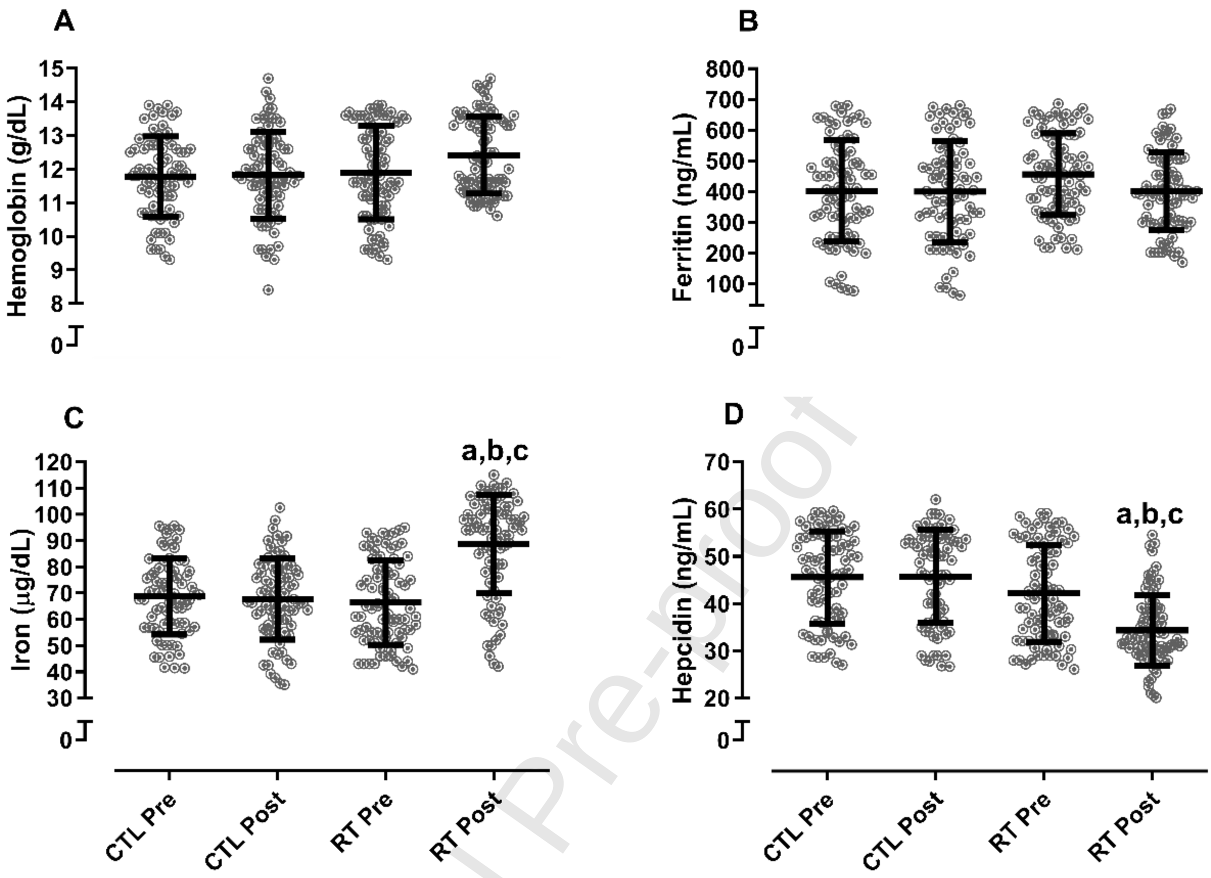
Excluded (n= 80)
Not meeting inclusion criteria (n= 46)
Decline to participate (n= 34)
Randomized (n= 202)
Allocation
Allocated to CTL group (n=101)
Not received intervention
Allocated to RT group (n= 101)
Received allocated intervention
Follow-Up
Lost to follow up (n=25)
Family problems (n= 8)
Withdrawal (n= 10)
Other (n= 7)
Lost to follow up (n= 20)
Physical complications (n= 13)
Family problems (n= 5)
Withdrawal (n= 2)
Analysis
Directed for CTL (n= 76)
Directed for RT (n=81)

Fig. 2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14
13
12
11
10
9
8
0
B
Ferritin (ng/mL)
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700
600
500
400
300
200
100
0
C
Iron (μg/dL)
120
110
100
90
80
70
60
50
40
30
0
a,b,c
D
Hepcidin (ng/mL)
70
60
50
40
30
20
0
a,b,c
CTL Pre
CTL Post
RT Pre
RT Post

Fig. 3

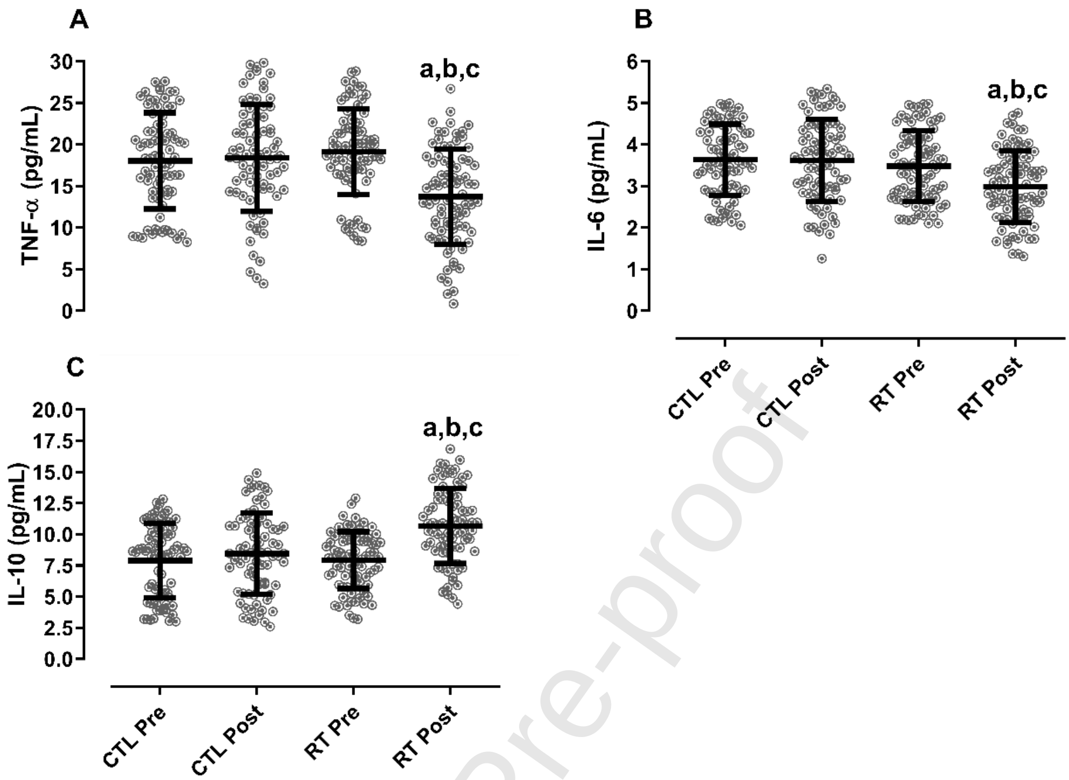
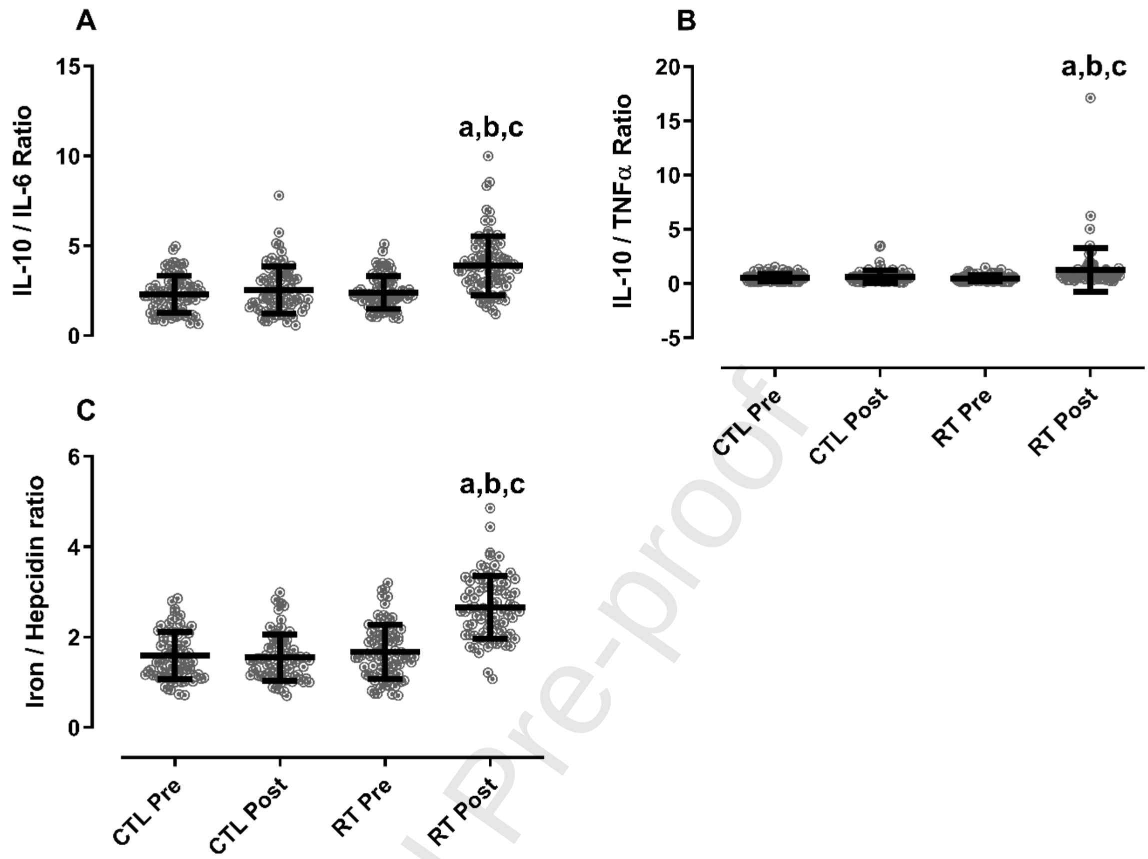

A
TNF-α (pg/mL)
30
25
20
15
10
5
0
a,b,c
B
IL-6 (pg/mL)
6
5
4
3
2
1
0
a,b,c
CTL Pre
CTL Post
RT Pre
RT Post
C
IL-10 (pg/mL)
20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0.0
a,b,c
CTL Pre
CTL Post
RT Pre
RT Post

Fig. 4


A
IL-10 / IL-6 Ratio
15
10
5
0
a,b,c
B
IL-10 / TNFα Ratio
20
15
10
5
0
-5
a,b,c
CTL Pre
CTL Post
RT Pre
RT Post
C
Iron / Hepcidin ratio
6
4
2
0
a,b,c
CTL Pre
CTL Post
RT Pre
RT Post

Author Statment

Sting Ray Gouveia Moura; Hugo Luca Corrêa; Thiago dos Santos Rosa: Conceptualization; **Sting Ray Gouveia Moura; Rodrigo Vanerson Passos Neves; Cláudio Avelino Rodrigues Santos; Luiz Sinésio Silva Neto; Thiago dos Santos Rosa:** Data curation; **Sting Ray Gouveia Moura; Hugo Luca Corrêa; Victor Lopes Silva; Michel Kendy Souza; Lysleine Alves Deus; Andrea Lucena Reis; Thiago dos Santos Rosa:** Formal analysis **Sting Ray Gouveia Moura; Herbert Gustavo Simões; Fabiani Lage Rodrigues Beal; Milton Rocha Moraes:** Funding acquisition; **Sting Ray Gouveia Moura; Hugo Luca Corrêa; Thiago dos Santos Rosa:** Investigation; **Sting Ray Gouveia Moura; Jonato Prestes; André Bonadias Gadelha, Thiago dos Santos Rosa:** Methodology; **Sting Ray Gouveia Mora; Hugo Luca Corrêa; Thiago Santos Rosa:** Project administration; **Sting Ray Gouveia Mora; Hugo Luca Corrêa; Thiago Santos Rosa**: Roles/Writing - original draft; **Sting Ray Gouveia Moura; Hugo Luca Corrêa; Jonato Prestes; James W. Navalta; Thiago dos Santos Rosa**: Writing - review & editing

Highlights

- Resistance training increase iron bioavailability and decrease hepcidin levels in older individual with end-stage renal disease;
- Inflammatory profile was improved after six months of resistance training in maintenance hemodialysis patients;
- Resistance training should be recommended as an important tool to improve the clinical status of this population.

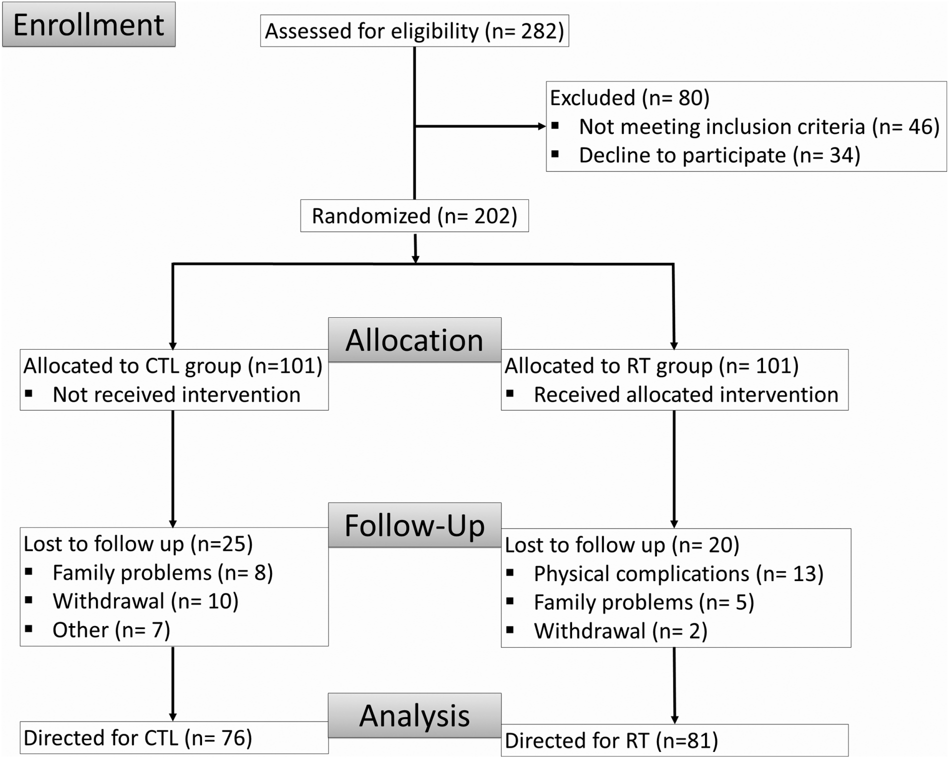
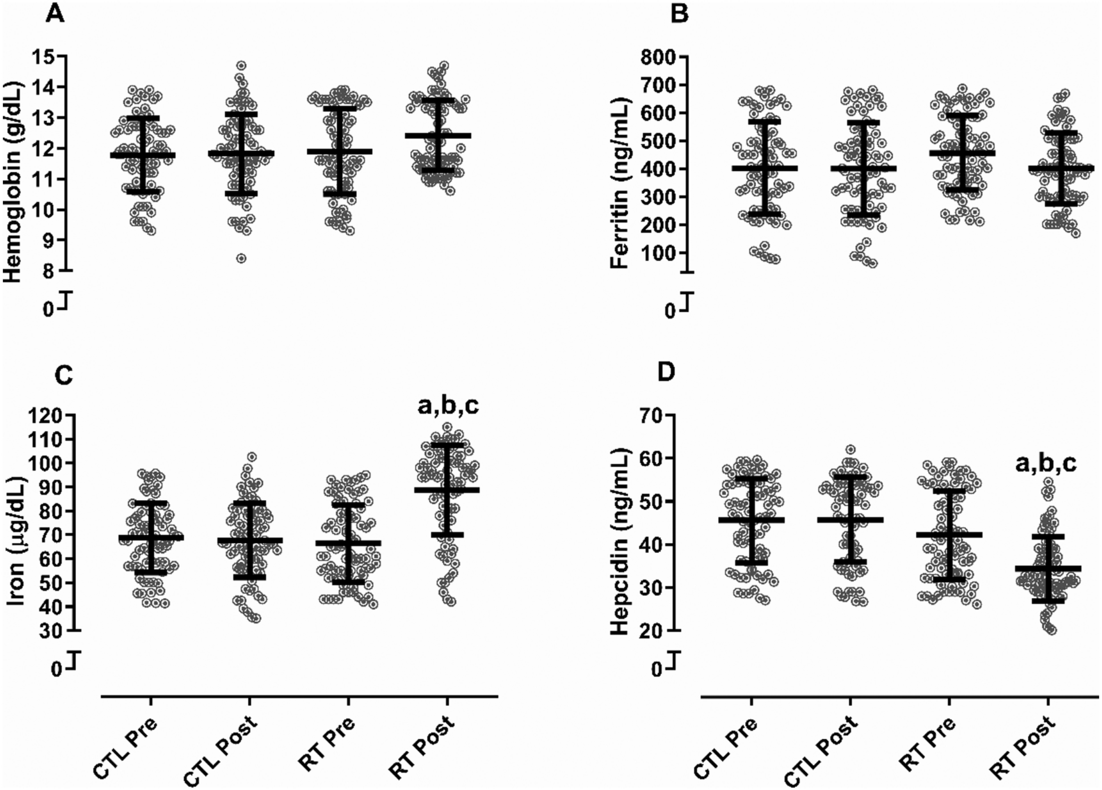

Enrollment
Assessed for eligibility (n= 282)
Excluded (n= 80)
Not meeting inclusion criteria (n= 46)
Decline to participate (n= 34)
Randomized (n= 202)
Allocation
Allocated to CTL group (n=101)
Not received intervention
Allocated to RT group (n= 101)
Received allocated intervention
Follow-Up
Lost to follow up (n=25)
Family problems (n= 8)
Withdrawal (n= 10)
Other (n= 7)
Lost to follow up (n= 20)
Physical complications (n= 13)
Family problems (n= 5)
Withdrawal (n= 2)
Analysis
Directed for CTL (n= 76)
Directed for RT (n=81)

Figure 1



A
Hemoglobin (g/dL)
15
14
13
12
11
10
9
8
0
B
Ferritin (ng/mL)
800
700
600
500
400
300
200
100
0
C
Iron (µg/dL)
120
110
100
90
80
70
60
50
40
30
0
a,b,c
D
Hepcidin (ng/mL)
70
60
50
40
30
20
0
a,b,c
CTL Pre
CTL Post
RT Pre
RT Post
CTL Pre
CTL Post
RT Pre
RT Post

Figure 2

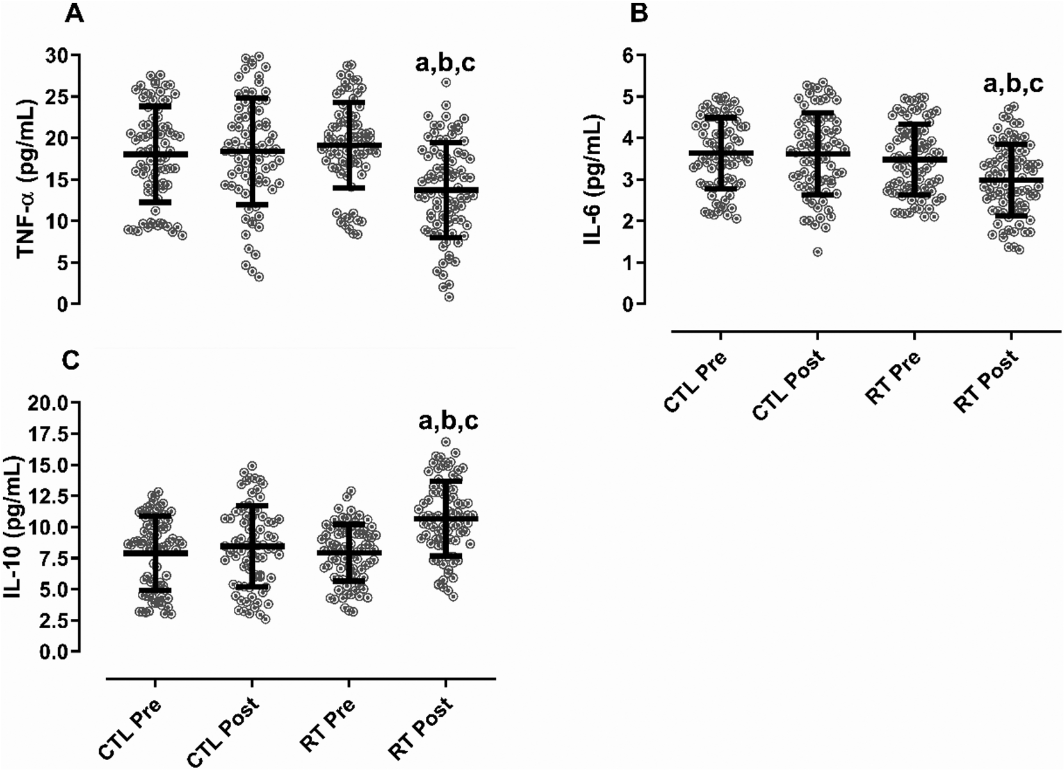
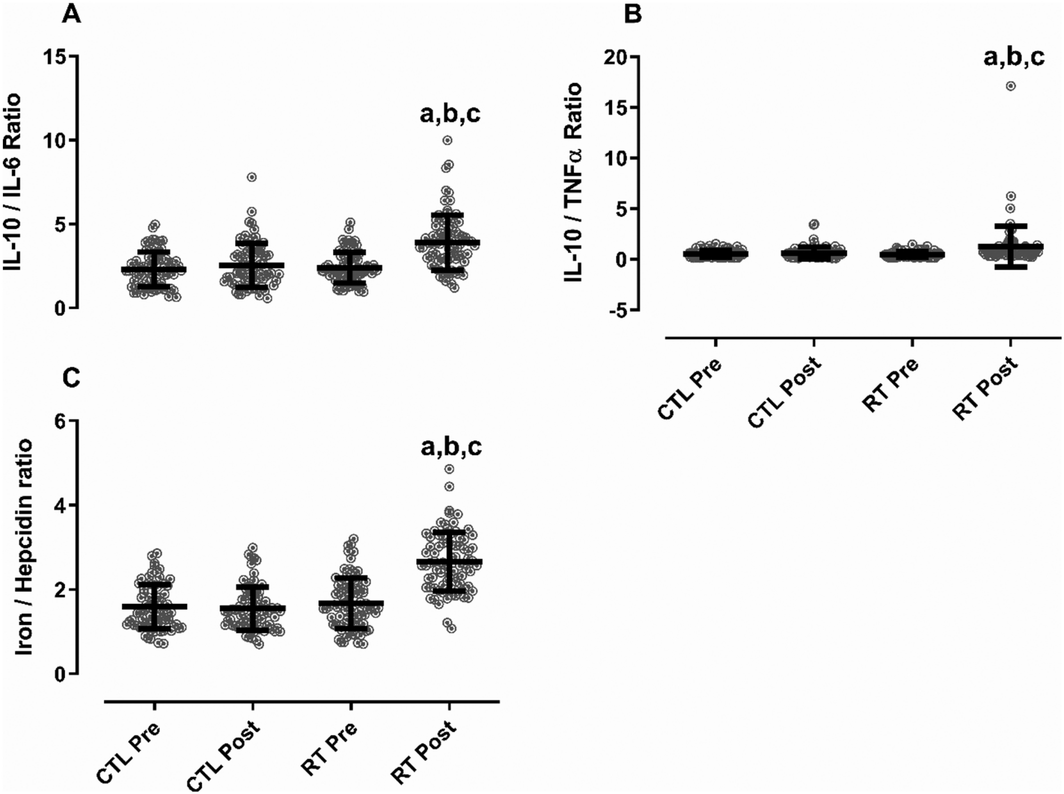

A
TNF-α (pg/mL)
a,b,c
B
IL-6 (pg/mL)
a,b,c
C
IL-10 (pg/mL)
a,b,c
CTL Pre
CTL Post
RT Pre
RT Post

Figure 3



A
15
10
5
0
IL-10 / IL-6 Ratio
a,b,c
B
20
15
10
5
0
-5
IL-10 / TNFα Ratio
a,b,c
CTL Pre
CTL Post
RT Pre
RT Post
C
6
4
2
0
Iron / Hepcidin ratio
a,b,c
CTL Pre
CTL Post
RT Pre
RT Post

Figure 4