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# Renal effects of isolated resistance training in rats fed with high-fat diet.

## Efeitos renais do exercício resistido isolado em ratos alimentados com dieta hiperlipídica.

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## RESUMO

Objetivo: A atividade física regular é uma das principais ações para o tratamento e prevenção da obesidade. Nosso objetivo é avaliar os efeitos do treinamento resistido no perfil inflamatório e dano renal produzido por dieta hiperlipídica em ratos. Métodos: ratos Wistar machos foram randomizados em quatro grupos: 12 semanas de dieta padrão sem (C) ou com treinamento resistido (RT) e dieta hiperlipídica sem (HF) e com treinamento resistido (HF-RT). Adiponectina, interleucina-6, leptina, MCP-1 e insulina foram avaliadas no plasma ou soro. O tamanho glomerular foi analisado por histologia e o conteúdo renal mTOR, p-mTOR, PAI-1, STAT3 e p-STAT3 foi quantificado por western blot. Resultados: a dieta hiperlipídica aumentou os níveis leptina, MCP-1 e TNF-α e o treinamento resistido foi capaz de normalizar estes níveis. A hipertrofia do tufo glomerular e o aumento na expressão renal de STAT, p-STAT3, mTOR e p-mTOR expression foram observados nos animais HF e normalizados com o treinamento. Conclusões: nosso protocolo de treinamento resistido teve efeitos benéficos no estado próinflamatório e nas alterações glomerulares em ratos alimentados com dieta hiperlipídica.



**Palavras-chave:** Doença renal crônica; Obesidade; Inflamação.


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## ABSTRACT

Objective: Regular physical activity is one of the most critical actions for treatment and prevention of obesity. Our aim is to evaluate the effects of resistance training in the inflammatory profile and renal damage promoted by high-fat diet in rats. Methods: Male Wistar rats were randomized into four groups: 12 weeks of a standard diet without (C) or with association with a 12 weeks resistance training program (RT), and high-fat diet without (HF) or with association with resistance training (HF-RT). Adiponectin, interleukin-6, leptin, MCP-1 and insulin were evaluated in plasma or serum. Glomerular size was analyzed by histology and total kidney content of mTOR, p-mTOR, PAI-1, STAT3 and p-STAT3 were quantified by western blot. Results: High-fat diet increased leptin, MCP-1 and TNF-α levels and resistance training normalized these levels in these animals. Glomerular tuff hypertrophy and renal increase in STAT, p-STAT3, mTOR and p-mTOR expression were observed in HF animals and normalized with RT. Conclusions: Our resistance training protocol had beneficial effects on proinflammatory state ang glomerular alterations in rats fed high-fat diet.



**Keywords:** Chronic kidney disease; Obesity; Inflammation.


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## INTRODUCTION

Obesity is a disease characterized by an abnormal or excessive accumulation of adipose tissue with several deleterious consequences for health. Many of them are prevalent and include insulin resistance (IR) and metabolic syndrome (MS), glucose intolerance or type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD), hypertension, dyslipidemia, and some types of cancers (STEMMER et al., 2012; DIAS et al., 2013)(1, 2).

Like obesity, chronic kidney disease (CKD) is considered a worldwide public health problem with high costs and poor outcome. Not surprisingly, similar pathologic pathways involved in obesity-related morbidity are associated with kidney damage. In fact, there is an increased risk for development of kidney diseases in obesity, ranging from kidney stones to renal cell cancer (ALICIC; PATAKOTI; TUTTLE, 2013)(3). Among other reasons, obesity affects kidneys due to its low-grade chronic inflammation due to increased secretion of adipocytokines by the adipose tissue (TANG; YAN; ZHUANG, 2012)(4).

Since the origin of obesity is multifactorial, so should be the strategies to combat this disease. Regular physical activity is one of the most critical actions for its treatment and prevention, reducing risk factors associated with CVD, CKD and adipokine mediated chronic inflammation (PANVELOSKI-COSTA et al., 2011; TALEBI-GARAKANI; SAFARZADE, 2013)(5, 6). Strength training improves the inflammatory profile in eutrophic (CHUPEL et al., 2017)(7) and individuals with obesity (STRASSER; ARVANDI; SIEBERT, 2012)(8), putting physical activity in the central role for non-pharmacological interventions spectra not only for obesity but also for its co-morbidities.

Discussions about which modality of exercise is the most efficient for health gains are still contradictory. However, resistance training has many associated benefits, such as improvement of endothelial function, hemodynamic and metabolic profiles, body composition, and physical fitness in nondiabetic adolescents with obesity regardless of changes in body mass, fat reduction gain in muscle strength and cardiovascular fitness (DIAS et al., 2015)(9), besides changing adipocytokines levels and improving low-grade inflammatory profile (STRASSER; ARVANDI; SIEBERT, 2012)(8).

Only few studies tested isolated resistance training as a mean for improving the inflammatory profile promoted by states of excessive adiposity and evidence of this impact on the kidneys are even scarcer. Therefore, we aimed to study the effects of an

isolated resistance training protocol in the inflammatory profile of rats fed a high-fat diet, evaluating systemic adipocytokines levels, renal biomarkers expression and renal histology.

## METHODS

### ANIMALS AND EXPERIMENTAL GROUPS

Thirty-five male Wistar rats weighing 421.9±7.3g were used in this study. They were housed in collective cages (four or five animals per cage) in a 12:12 h light/dark facility at controlled temperature (22±2ºC) with food and water provided ad libitum. All experiments were conducted according to the Guide for Care and Use of Laboratory Animals (National Research Council, 1998) and approved by the State University of Rio de Janeiro (UERJ) Committee on Experimental Animals (CEUA/060/2012).

At 21 days-old, the animals were weaned and randomized into four different experimental groups: sedentary associated with a standard diet (C, n= 10), resistance training associated with a standard diet (RT, n=9), sedentary associated with high-fat diet (HF, n=8) and resistance training associated with high-fat diet (HF-RT, n=8). All groups were maintained with their respective diets but without any type of exercise during the following 12 weeks. After this period, animals received their specific diet, and those from trained groups (RT and HF-RT) performed 12 weeks of an isolated resistance training program while sedentary groups (C and HF) were kept without any training program during the same period.

### DIET

C and RT groups received the standard chow diet (Nuvilab CR-1, Quimtia S.A, Nuvilab®, Colombo, PR, Brazil) in pellets, composed of 71% of carbohydrate, 23% of protein, 6% of fat and 5% of fiber. HF and HF-RT received a diet composed of 55% of carbohydrate, 30% of fat and 15% of protein (PINHEIRO et al., 2007)(10). Caloric densities of high-fat diet and standard chow were respectively, 5.50 and 4.28 kcal·g-1. All procedures were in agreement with the America Institute of Nutrition for quality control of animal chow (11).

## RESISTANCE TRAINING PROTOCOL

To perform the resistance training we used a vertical ladder (1.1 m x 0.18 m, 2 cm between steps, 80º incline) according to a previously published protocol (LEITE et al., 2009)(12). The rats were adapted to the protocol by climbing the ladder with the load apparatus (empty) for two non-consecutive days, with 48 h of rest interval (Monday and Wednesday). The apparatus was fixed on rats' tail (proximal portion) with an adhesive tape. After attachment, each rat was placed at the bottom of the ladder and familiarized with the climbing procedure, composed of 8-12 climbings per trial. In case of stopping, a grip was applied in the tail to restart the movement. When the animals arrived at the top of the ladder (house chamber; 20 cm x 20 cm x 20 cm), they were allowed to rest for 2 min. All procedures were repeated until the rats voluntarily climb the ladder for three consecutive turns without any external stimulus.

After two days of familiarization with the procedure, the rats had the maximum carrying load established by 4 to 9 ladder climbs with progressively heavier loads. The maximal carrying capacity for the training session was considered as the highest load that the animal successfully carried the entire length of the ladder. Relative training load was obtained with the relation between maximal carrying capacity (g) and body weight (g).

## TRAINING PERIOD

After the above-mentioned procedures, the resistance training period was started and performed on Mondays, Wednesdays, and Fridays for 12 weeks. Each session was constituted of four ladder climbs with 50%, 75%, 90% and 100% of the previously established maximal carrying load. After the last climb, an additional load (30g) was added until a new maximal carrying load was established. These procedures were repeated until failure.

## PLASMA COLLECTION AND ADIPOCYTOKINES ASSAYS

Forty-eight hours after the last training session, animals were sacrificed by decapitation. Troncular blood was collected in two different vacutainers (plasma and serum), centrifuged and the supernatant fraction isolated and stored at -80ºC.

All systemic adipocytokines assays were performed by ELISA method in accordance with manufactures' protocols.

## RENAL SAMPLING FOR PROTEIN EXTRACTION AND HISTOLOGY

After blood collection, the animals underwent kidney perfusion with sterile saline (0.9% NaCl) via the renal veins. Their right kidney pediculum was clamped, the kidney was excised, and total protein extracted. After excision of the right kidney, the left kidney was perfused with paraformaldehyde 4% and then excised and processed for histological analysis. Both kidneys were decapsulated by hand.

## PROTEIN EXTRACTION AND WESTERN BLOTTING

The right kidney tissue was homogenized in RIPA lysis buffer using a glass Potter homogenizer with Teflon piston. After homogenization, the tissue homogenate was centrifuged at 600×g for 5 min. 100 µg of each sample was subjected to standard SDS-PAGE using a 10% polyacrylamide running gel. After SDS-PAGE, the proteins were electrophoretically transferred to a polyvinylidene fluoride membrane (Bio-Rad, California, USA).

Specific primary antibodies were used for mTOR (Cell Signaling Technology®, Danvers, MA, USA), Phospho-mTOR (Cell Signaling Technology®, Danvers, MA, USA), PAI-1 (Cell Signaling Technology®, Danvers, MA, USA), Stat3 (Cell Signaling Technology®, Danvers, MA, USA), Phospho-Stat3 (Cell Signaling Technology®, Danvers, MA, USA) and β-actin (Sigma-Aldrich, St. Louis, MO, USA) detection.

The membranes were incubated with their respective secondary antibodies conjugated to peroxidase enzyme. Immunodetection of the blots was performed using Clarity Western ECL Substrate and the chemiluminescence signal was directly captured by a Bio-Rad Molecular Imager ChemiDoc XRS+Imaging system.

The densitometry of the bands was analyzed using the ImageJ program for Windows. Relative protein expression was determined from the ratio of arbitrary densitometric values for each target to their respective β-actin.

## HISTOLOGY AND HISTOMORPHOMETRY

For histomorphometry, paraffin embedded PAS-stained sections were used to capture 15–20 photomicrographs of glomerulus, chosen randomly, in an Axio Scope.A1 (Carl Zeiss, Göttingen, Germany) microscope with ZEN blue software version 3.5.093.00003. Glomerular area and glomerular tuff area were measured in each image using Image-Pro® Plus, V 4.0 (Media Cybernetics, Rockville, MD, USA).

## STATISTICAL ANALYSIS

Data normality was certified by Shapiro-Wilk normality test for all variables. Variables with Gaussian distributions were analyzed with one-way analysis of variance (ANOVA) followed by Tukey's post hoc test and represented as mean±standard error of the mean (SEM).

Relative and training loads were analyzed using Student t-test.

All analyses were performed using GraphPad Prism®, version 8.4.2 (San Diego, CA, EUA) and results were considered statistically significant when $p<0.05$.

# RESULTS

## BODY WEIGHT, CHOW INTAKE AND TRAINING LOAD

Table 1 describes the changes after the experimental period regarding body weight, chow intake and training load. All animals fed with high-fat diet presented higher body weight compared to groups of standard chow. No significant differences ($p>0.05$) were observed between C and RT animals, as well as between HF and HF-RT animals.

Standard chow fed animals had higher intake compared to groups of high-fat diet. No significant differences were observed between groups fed with the same chow ($p>0.05$).

Regarding the training loads, RT group presented higher maximal carrying load and relative load than HF.

Table 1. Body weight, chow intake and training load.

| Parameters | C | RT | HF | HF-RT |
|---|---|---|---|---|
| Body weight (g) | 422 ± 4.39 | 419 ± 3.58 | 509 ± 9.51 $^{***}$ - $^{###}$ | 494 ± 8.70 $^{***}$ - $^{###}$ |
| Chow intake (g) | 25.3 [23.4 - 27.9] | 23.3 [22.3 - 28.9] | 18.9 [18.2 - 19.4] $^{**}$ - $^{#}$ | 18.8 [17.9 - 19.3] $^{***}$ - $^{##}$ |
| Carrying load (g) | - | 630 ± 32.5 | - | 470 ± 41.9 $^{###}$ |
| Relative load (g / g of bw.) | - | 1.50 ± 0.0670 | - | 0.956 ± 0.0731 $^{###}$ |

All values are presented as mean±SEM. $^{*}$differs from C (** $p<0.01$; *** $p<0.001$) and $^{\#}$differs from RT ($^{\#}$ $p<0.05$; $^{\#\#}$ $p<0.01$; $^{\#\#\#}$ $p<0.001$). (Source: Authors, 2023).

## SYSTEMIC ADIPOCYTOKINES LEVELS

Our animal model was able to promote an increase in systemic leptin, MCP-1 and TNF-α levels in HF animals, compared to C animals. Resistance training was able to reduce these cytokines to control levels (Table 2).

Resistance training was not able to modulate any of the cytokines in rats fed a standard chow.

Although we performed ultra-sensitive kits to analyze these cytokines, we did not detect plasmatic IL-6 in any of the tested animals, as well as TNF- α in the plasma in C and RT rats.

Table 2. Systemic adipocytokines levels.

| Parameters | C | RT | HF | HF-RT |
|---|---|---|---|---|
| Insulin (ng/ml) | 2.27 ± 0.200 | 2.52 ± 0.521 | 3.87 ± 0.401 | 3.95 ± 0.825 |
| Leptin (pg/ml) | 5080 ± 428 | 5935 ± 579 | 13303 ± 1840 **** - ### | 8654 ± 1227 $ |
| Adiponectin (µg/ml) | 16.4 ± 1.78 | 12.1 ± 0.540 | 16.0 ± 0.863 | 16.6 ± 0.860 |
| MCP-1 (pg/ml) | 145 ± 4.61 | 158 ± 6.60 | 223 ± 8.94 **** - #### | 162 ± 13.3 $$$ |
| TNF-α (pg/ml) | - | - | 3.41 ± 0.803 **** - #### | 1.27 ± 0.466 $ |

All values are presented as mean±SEM. *differs from C (**** p<0.0001), #differs from RT (### p<0.001) and $differs from HF ($ p<0.05). (Source: Authors, 2023).

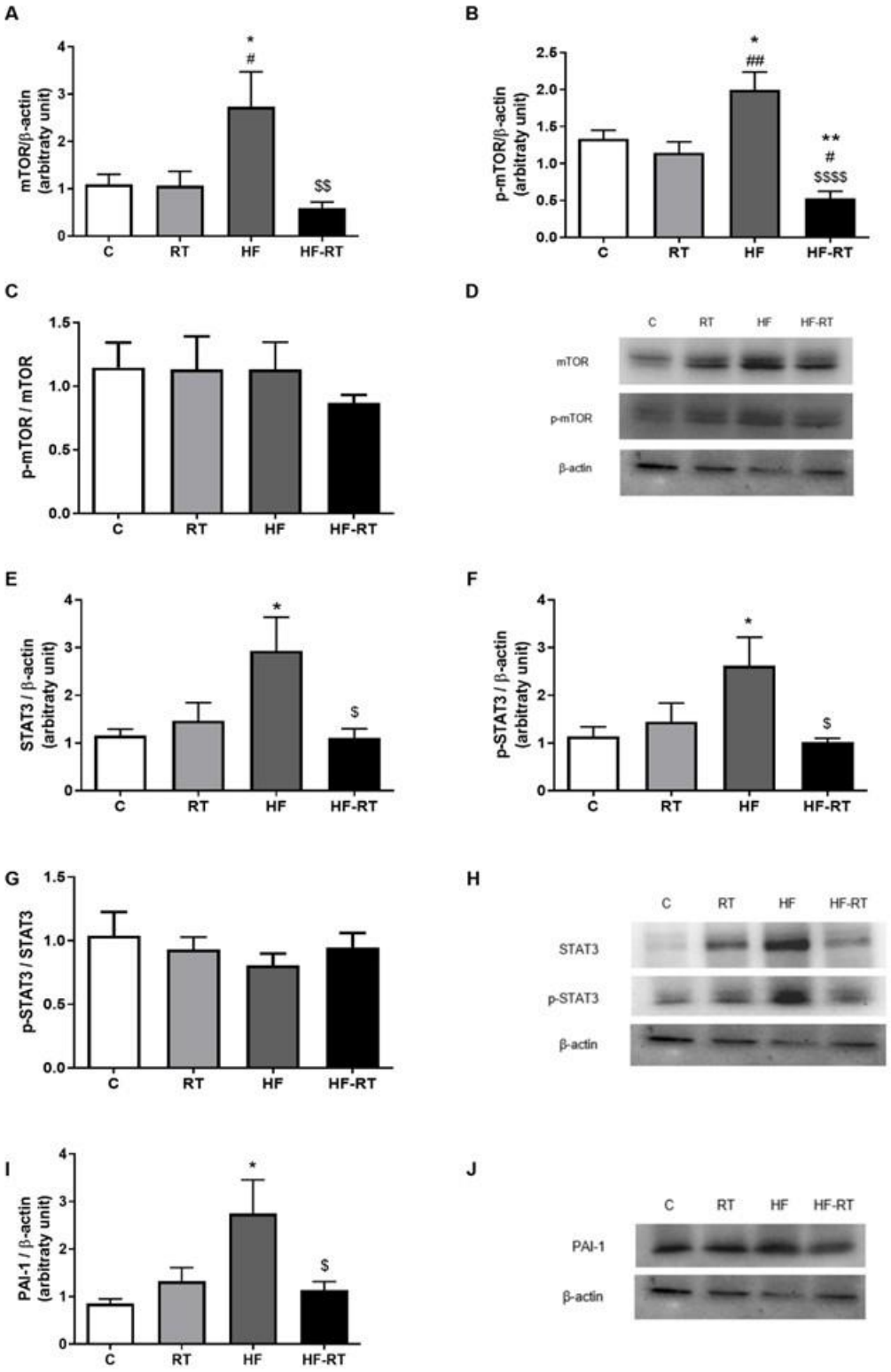
## RENAL BIOMARKERS

The HF group presented higher renal expression of mTOR and p-mTOR compared to C. The HF-RT group had lower renal expression of mTOR and p-mTOR compared to HF animals. No significant differences were observed between C and RT animals. The ratio of p-mTOR/mTOR expression in the kidneys presented no statistical differences between the groups (Figure 1).

Similarly, the HF group had higher renal expression of STAT3 and p-STAT3 compared to C. The HF-RT group had lower renal expression of STAT3 and p-STAT3 compared HF animals. No significant differences were observed between C and RT animals. No significant differences were observed in the ratio of p-STAT3/STAT3 expression in the kidneys between the groups (Figure 1).

Renal expression of PAI-1 was higher in HF compared to C and returned to control levels in HF-RT group (Figure 1).

Figure 1. Protein expression of renal injury biomarkers.

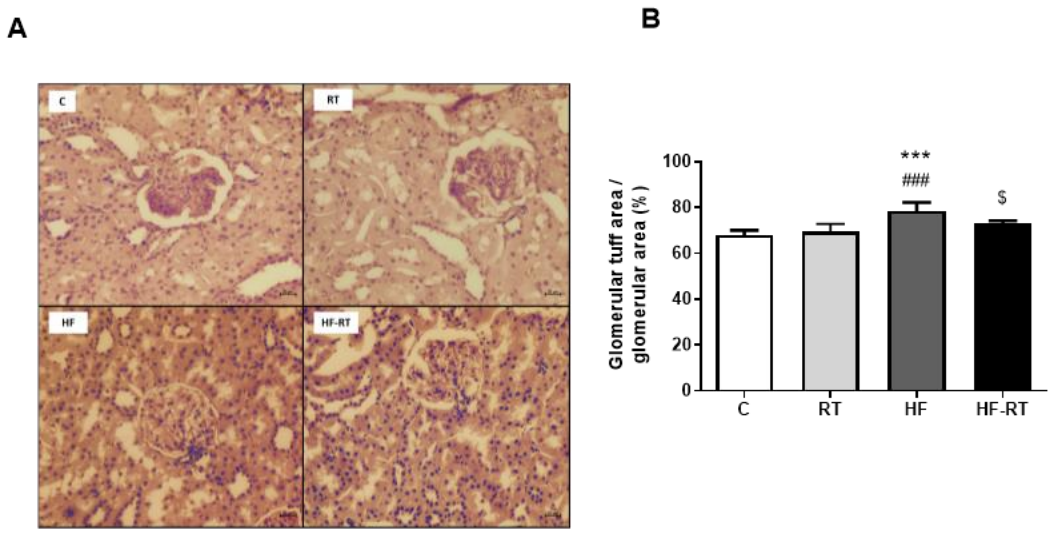


In A: mTOR relative expression. In B: p-mTOR relative expression. In C: p-mTOR/mTOR expression ratio. In D: representative blots for mTOR, p-mTOR and β-actin. In E: STAT3 expression. In F: p-STAT3 expression. In F: p-STAT3/STAT3 expression ratio. In G: representative blots for STAT3, p-STAT3 and β-actin. In H: PAI-1 expression. In J: representative blots for PAI-1 and β-actin. All values are presented as mean±SEM. *differs from C (* p<0.05; ** p<0.01), #differs from RT (# p<0.05; ## p<0.01) and $differs from HF ($ p<0.05; $$ p<0.01; $$$$ p<0.0001). (Source: Authors, 2023).

## RENAL HISTOMORPHOMETRY

In Figure 2, it is shown that HF animals presented higher ratio between glomerular tuff area and glomerular area when compared to C and RT groups and it reached control levels in HF-RT animals.

Figure 2. Renal histomorphometry.




In A: Representative photomicrograph of kidney sections stained with PAS emphasizing the glomeruli of C, RT, HF, and HF-RT animals. (B) Graphic representation of the relation between glomerular tuff area and total glomerular area. All values are presented as mean±SEM. *differs from C (*** p<0.001), #differs from RT (### p<0.001) and $differs from HF ($ p<0.05). (Source: Authors, 2023).

## DISCUSSION

The high-fat diet used in our study induced weight gain in the animals, mimicking the effects found in humans exposed to hypercaloric diets. We also observed a reduction in food intake in this group, possibly due to the caloric density of high-fat diet. Fattening promoted by hyperlipidic diets is already described in the literature (PINHEIRO et al.,

2007; ROPELLE et al., 2010; PANVELOSKI-COSTA et al., 2011)(5, 10, 13), as well as the observed reduced food behavior (SENE-FIORESE et al., 2008)(14).

The resistance training applied was efficient to promote muscle strength gains, evidenced by progressive and continuous increase of loads throughout the experimental period. This evolution of physical performance is a protective factor for several diseases, such as metabolic syndrome (GUTTIERRES; MARINS, 2008; FRAGALA et al., 2019)(15, 16). RT group have higher strength than HF-RT, even with lower body weight, meaning that the highest absolute load was borne by animals fed standard chow and lower body weight than animals fed a high fat diet.

Although higher insulin levels are commonly observed in animals fed with high-fat diet (ROPELLE et al., 2010)(13), we did not find any alterations in insulinemia among the groups. However, hyperleptinemia was observed in HF animals and resistance training was able to reduce these levels.

Adiponectin levels in HF-RT animals were higher than in RT group. In the literature, there is a controversial role of resistance training in adiponectin levels (FATOUROS et al., 2005; ASAD et al., 2012)(17, 18). Our data indicate that our training protocol may not be able to induce an adiponectin increase in animals fed a standard chow. Although it successfully increased adiponectin levels in animals fed a high-fat diet.

On the other hand, we observed an increase in leptin levels in HF animals and normalization of its levels after resistance training in HF-RT group. An increase in leptin levels is termed hyperleptinemia and it is correlated with the development of type 2 diabetes mellitus in individuals with obesity (PRETZ et al., 2021)(19) due to an increase in hypothalamic inflammation associated with disruption of energy homeostasis.

Leptin also shows strong association with circulating TNF-α levels (LEON-CABRERA et al., 2013)(20) that, along with increased levels of plasma IL-1, IL-6, and MCP-1 suggests the occurrence of moderate degree of inflammation in high-fat-fed rats (CANO et al., 2009)(21). An increase in MCP-1 levels may also contribute to development of insulin resistance (SARTIPY; LOSKUTOFF, 2003)(22).

MCP-1 and TNF-α have also been related to kidney lesion (MATOBA et al., 2010; MUNSHI et al., 2011)(23, 24). In our animal model, the high-fat diet in sedentary animals seems to promote an inflammatory process that can trigger renal and metabolic disorders. Also, we were able to show that resistance training in animals fed with high-fat chow

normalized MCP-1 and TNF-α increased levels, indicating a decreased risk for diseases, such as insulin resistance (PANVELOSKI-COSTA et al., 2011)(5).

One of the main alterations on the kidney of animals fed a high-fat diet is glomerular hypertrophy (WEI et al., 2004)(25). Our data corroborates with this finding, and we could also show that resistance training was able to normalize glomerular tuff hypertrophy. One of the mechanisms that leads to renal and glomerular hypertrophy is the activation of STAT3-mTOR pathway (CHEN et al., 2005; LEE; INOKI; GUAN, 2007)(26, 27). This pathway plays an important role in inflammation, cell growth, and proliferation (ZHENG et al., 2020)(28). Other correlations of STAT3 with kidneys reinforce evidence that this factor is potentially related to the severity of renal diseases (STEMMER et al., 2012)(2).

We could observe not only an increase in renal expression of mTOR and STAT3 but also an increase in the amount of activated mTOR (p-mTOR) and STAT3 (p-STAT3). These findings may indicate that resistance training acts as a potential protector for renal disorders, since the stimulation of this pathway is a strong indicator of cell proliferation, pre-neoplastic lesions, renal fibrosis, and other alterations found in renal pathologies, such as diabetic nephropathy (CHEN et al., 2012)(29).

Interestingly, the same group of higher leptinemia (early processes of T2DM) have a greater presence of renal mTOR. This protein is a modulator of various renal diseases (LIEBERTHAL; LEVINE, 2009)(30) and our findings show that resistance training decreased mTOR and p-mTOR expressions in the kidneys of animals fed a high-fat diet. Interestingly, HF-RT also presented lower phosphor-mTOR compared to C.

Also, increased PAI-1 expression in the HF group evidences the high-fat diet as a possible risk factor for kidney disease, especially if a sedentary lifestyle is maintained. PAI-1 is increased in inflammatory processes in renal tissue and is directly associated with the severity of CKD, diabetic nephropathy and glomerulosclerosis, being one of the most aggressive markers in kidney diseases (HUANG; NOBLE, 2005; EDDY; FOGO, 2006)(31, 32). The resistance training protocol herein employed did not seem to have any effect on PAI-1 renal expression.

Taken together, our results suggest a protective role of resistance training protocol on renal injury of animals fed a high-fat diet probably due to a beneficial effect on systemic proinflammatory state, which reduces renal activation of STAT3-mTOR pathway and the development of glomerular hypertrophy.

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