Exercise Prevents Cardiometabolic Alterations Induced by Chronic Use of Glucocorticoids

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Summary
Background: Chronically, glucocorticoids induce adverse cardiometabolic alterations including insulin resistance, diabetes, dyslipidemia, liver steatosis and arterial hypertension.

Objectives: To evaluate the effect of regular practice of aerobic exercise on cardiometabolic alterations induced by chronic administration of dexamethasone (Dex – 0.5 mg/kg/day ip) in rats.

Methods: Male Wistar rats (n = 24) were divided in four groups: Control group; Trained group; Treated with Dex group and Treated with Dex and trained group. The exercise training (initiated 72 hours after the first dose of Dex) was carried out three times a week until the end of the treatment. At the end of this period, the following biochemical assessments were performed: fasting glycemia, oral glucose tolerance test and analysis of the blood lipid profile that included total cholesterol (TC), LDL-c, HDL-c, VLDL-c and triglycerides (TG). The weight of the gastrocnemius muscle, the histopathological analysis of the liver and cardiometabolic indices (TC/HDL-c, LDL-c/HDL-c and TG/HDL-c) were also performed.

Results: Hyperglycemia, lower glucose tolerance, increased TC, LDL-c, VLDL-c, TG, CT/HDL-c, LDL-c/HDL-c and TG/HDL-c, decreased HDL-c, presence of liver steatosis and muscular hypotrophy were observed in the animals treated with Dex. The exercise training reduced hyperglycemia, improved glucose tolerance, decreased dyslipidemia and prevented liver steatosis, muscular hypotrophy and reduced CT/HDL-c, LDL-c/HDL-c and TG/HDL-c ratios. However, there was no significant effect on HDL-c.

Conclusion: The aerobic exercise training have a protective effect against the cardiometabolic alterations induced by the chronic use of glucocorticoids. (Arq Bras Cardiol 2009; 93(3) : 372-380)

Key words: Exercise, glucocorticoid, insulin resistance, cholesterol, dyslipidemia, dexamethasone.

Introduction

Glucocorticoids (GCs) are corticosteroids, substances derived from cholesterol, synthesized and secreted by the adrenal glands. The GCs are hormones that act on the transcriptional control of genes involved in the regulation of metabolic, cardiovascular and immunological functions. This effect is processed through the nuclear glucocorticoid receptor (GR), which is activated, transiently, only after the exposition of the cells to the GCs.

The term “glucocorticoid” is due to the action of these substances on the carbohydrate metabolism. In the skeletal muscle, the GCs cause insulin resistance resulting in a lower uptake of blood glucose and reduced glycogen synthesis. In this tissue, protein synthesis inhibition and increased protein catabolism are also observed, which result in muscular hypotrophy. The amino acids mobilized from the muscular tissue are used in liver gluconeogenesis. Together, the insulin resistance and increased gluconeogenesis result in hyperglycemia.

In the 1950s, the discovery of the potent anti-inflammatory effect of the GCs led to their prescription in the treatment of chronic rheumatic diseases. Currently, the synthetic GCs are broadly used in the treatment of autoimmune diseases and in the prevention of allograft rejection. However, the chronic use of GCs is associated to several adverse cardiometabolic effects. As in Cushing’s syndrome, caused by elevated levels of blood cortisol, the chronic use of GCs causes insulin resistance, diabetes, dyslipidemia and arterial hypertension. If left untreated, Cushing’s syndrome may result in death by cardiovascular disease.

The GCs would have a role in the physiopathology of the metabolic or plurimetabolic syndrome. Recently, it was demonstrated that the elevated gene expression of GR in the skeletal muscle is associated to lower insulin sensitivity. Additionally, the 11-beta-hydroxysteroid dehydrogenase, which converts cortisone (inactive GC) into cortisol (biologically active GC), has also been implicated...
in the development of obesity, insulin resistance and type 2 diabetes\textsuperscript{10}. Rats chronically treated with dexamethasone (a synthetic GC) have been used in the experimental study of the metabolic syndrome. These animals present insulin resistance, hypercholesterolemia, hypertriglyceridemia, non-alcoholic fatty liver disease (liver steatosis), endothelial dysfunction and arterial hypertension\textsuperscript{7}. Clinical directives on the treatment and prevention of atherosclerosis\textsuperscript{11} acknowledge the cardiometabolic risk caused by the chronic use of GCs and stimulate lifestyle changes as a strategy to promote cardiovascular health.

The regular physical activity is an important non-pharmacological resource in the management of the cardiometabolic risk\textsuperscript{11}. Exercise increases uptake and oxidation of glucose and fatty acids from the blood\textsuperscript{12-13}, improve insulin signaling\textsuperscript{14,15}, increase the activity and expression of transporters and enzymes that regulate the glucose and fatty acid metabolism\textsuperscript{14,15}, promotes mitochondrial biogenesis\textsuperscript{12} and improves endothelium-dependent vasodilation in skeletal muscle\textsuperscript{16}.

However, scientific evidence on the effect of exercise training on cardiometabolic alterations caused by the chronic use of GCs is scarce in the literature. In the present study, the impact of aerobic exercise training upon cardiometabolic parameters in long-term glucocorticoid-treated rats was investigated.

Methods

Ethical aspects

The present study was approved by the Committee of Ethics in Animal Research of Medicine School of Federal University of Ceará. All animals received humane care in compliance with the Ethical Principles of the Brazilian College of Animal Experimentation (COBEA) and according to the rules established by the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, National Academy of Sciences, Washington, D. C. 1996).

Animals

Male albino Wistar rats (\textit{Rattus norvegicus alvinus}, Rodentia, Mammalia), aged 5 months and weighing between 230 and 250 g were studied. The animals were fed a standard rodent chow (Purina\textsuperscript{®}, Cargill Incorporated, Monsanto do Brasil Ltda) and received water \textit{ad libitum}. They were housed in groups of three per cage, maintained on a 12-hour light-dark cycle and ambient temperature of $23 \pm 2$ °C.

Experimental design

The animals ($n = 24$) were randomly distributed in four groups: Control group (comprising sedentary rats that were not treated with GC; $n = 6$); Trained group (comprising rats submitted to physical training only; $n = 6$); Treated group (comprising sedentary rats treated with GC; $n = 6$); Treated and trained group (comprising rats treated with GC and submitted to the physical training; $n = 6$).

At the end of the study, the following biochemical analyses were performed in blood: fasting glycemia, oral glucose tolerance test (OGTT), serum levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), very-low density lipoprotein cholesterol (VLDL-c) and triglycerides (TG). The body weight was monitored weekly throughout the study. At the end of the study, the gastrocnemius muscle weight was determined and the liver was used for slide preparation and posterior histopathological analysis.

The following cardiometabolic parameters were also assessed: Castelli’s atherogenic ratios (CT/HDL-c I and II (LDL-c/ HDL-c), and the TG/HDL-c ratio. Castelli’s ratios are used for the analysis of coronary risk in the presence of cardiovascular risk factors\textsuperscript{17}. The TG/HDL-c ratio is associated to the cardiovascular risk conferred by the insulin resistance\textsuperscript{18}.

Glucocorticoid therapy experimental protocol

The animals were treated with dexamethasone (Dex - 0.5 mg/kg/day ip) (Decadron\textsuperscript{®}, Prodome, Brazil), for one month, always at the same time of the day. This dose results in insulin resistance after seven days\textsuperscript{19}.

Progressive exercise stress test

Previously, a progressive stress test was carried out in the animals submitted to the physical training. The test was carried out in a Rota Rod Treadmill (model 7700, Ugo Basile\textsuperscript{®}, Milan, Italy). After the period of adaptation to the equipment, suggested by the manufacturer, a personalized protocol was applied, with an initial velocity of 3 rotations per minute (rpm) and 3 rpm increments every 3 minutes (Table 1). This protocol presents good reproducibility ($R$ Square = 0.96). The test was carried out until exhaustion set in and the fatigue criterion used was that of three falls during a 100-second interval\textsuperscript{20}. The maximum velocity attained by the animals during the test was recorded and expressed as an arithmetic mean. The characteristics of the equipment and of the animals’ responses to the progressive stress test are shown in Figure 1.

Exercise training protocol

The aerobic exercise training was carried out 3 times a week, always at the same time of the day (7:00 p.m) until the end of the glucocorticoid treatment. The intensity of the exercise was 60% of the maximum velocity attained by the animals during the exercise stress test, being the exercise training protocol considered as moderate intensity. Before reaching the training velocity, the animals were submitted to low-velocity warming-up (2 rpm), for 6 minutes. The exercise duration was 60 minutes and the first session was carried out 72 hours after the first Dex dose.

Body weight monitoring

The body weight was monitored through weekly measurements and the first one was carried out before the first Dex dose.

Measurement of blood glycemia and oral glucose tolerance test (OGTT)

Seventy-two hours after the last exercise session, the animals were submitted to a 12-hour fasting period and then
were anesthetized with sodium pentobarbital (40 mg/kg i.p.; Nembutal®, Abbot Laboratories, Abbot Park, Illinois, USA). A surgical incision was made on the posterior paw and the femoral vein was located. A blood specimen (300 µl) was collected for blood glycemia measurement, which was performed with a digital glucosimeter (Accu-Check Active®, Roche Diagnostic System, Branchburg, NJ, USA). The OGTT was carried out after the oral administration of glucose (1 g/kg of body weight) by gavage. New blood specimens were collected after 30, 60 and 120 minutes.

**Blood lipid profile assessment**

The serum lipid levels were measured by spectrophotometry according to the instructions and recommendations of the National Cholesterol Education Program (NCEP)\textsuperscript{21}. The fasting animals were euthanized by cervical displacement and immediately after it, a heart puncture was performed to collect blood samples, which were stored in ice. The serum was obtained by centrifuging at 2500 rpm, for 20 minutes, at 4°C. The biochemical analyses were carried out by spectrophotometry. A wavelength of 500 nm was used to measure the TC levels, according to the manufacturer’s instructions (Kit Colesterol Liquiform, Labtest Diagnóstica, Lagoa Santa, MG, Brazil). The TG measurement was carried out using the kit Triglicerides Liquiform (Labtest Diagnóstica, Lagoa Santa, MG, Brazil) and a wavelength of 510 nm. The measurement of the HDL-c was carried out with the kit HDL LE (Labtest Diagnóstica, Lagoa Santa, MG, Brazil) and a wavelength of 600 nm. The levels of LDL-c and VLDL-c were calculated using Friedewald equation\textsuperscript{22}.

\[
\text{Friedewald equation} = [\text{LDL-c} = \text{CT} - (\text{HDL-c} + \text{TG}/5)]
\]

**Skeletal muscle weight determination**

After euthanization, the gastrocnemius muscle was surgically removed and the proximal and distal insertions were preserved.

**Table 1 – Protocol used for the progressive exercise stress test.**

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rpm - rotations per minute; min (minutes).

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**Fig. 1 – Characterization of fatigue during the exercise stress test carried out at the Rota Rod Treadmill.** The animal that is positioned at the rotation axis, on the right, is experiencing fatigue. Panels A, B and C show the posterior positioning of the animal at the rotation axis of the equipment, which indicates difficulty to overcome gravitational force. Panel D shows the subsequent fall.
The weight of the skeletal muscle was measured with a precision scale (model 750 SW - OHAUS Corp., Pine Brook, NJ, USA). The gastrocnemius muscle was chosen for the study of the effect of Dex on protein metabolism as it presents a large number of fast contraction fibers, considering that these fibers are more susceptible to the catabolic action of GCs. As the animals had similar weights and were of similar ages, we chose the non-normalization of the skeletal muscle weight variable.

**Histopathological analysis**

The liver was removed before the heart puncture and was immediately fixed in a 10% formaldehyde solution. After the material was paraffin-embedded, histological slides were prepared using hematoxylin and eosin (HE) stain. The histopathological analysis was performed by optical microscopy (Nikon E800, Nikon USA, Melville, NY, USA).

**Statistical analysis**

The data were expressed as means ± standard error (SEM) and the comparison between the groups was carried out by one-way Analysis of Variance (ANOVA) statistical test combined with Tukey-Kramer post-test. The level of significance was set at $p < 0.05$.

**Results**

**Exercise training decrease hyperglycemia and improve glucose tolerance in rats treated with glucocorticoid**

After 4 weeks, the animals treated with a daily dose of Dex presented hyperglycemia when compared to the control group (181.25 ± 12 mg/dl vs. 85 ± 10 mg/dl; $p < 0.05$). The exercise training reduced this increase in glycemia by approximately 47%. Among the animals that received GC, the glycemia was lower in the trained animals, when compared to the sedentary ones (140.67 ± 10 mg/dl vs. 181.25 ± 12 mg/dl; $p < 0.05$). However, the training protocol used in the study was not effective in preventing the glycemia increase in relation to controls (140.67 ± 10 mg/dl vs. 85 ± 10 mg/dl; $p < 0.05$). There was no effect of the exercise training on the glycemia levels of the animals that did not received Dex. The fasting blood glycemia of the study groups is shown in Figure 2A.

The treatment with Dex altered the glycemic response to the OGTT. The sedentary animals presented higher glycemic levels at 30, 60 and 120 minutes when compared to the control group, which represents lower glucose tolerance. The animals submitted to exercise training concomitantly with Dex treatment presented a glycemic response similar to that of the control group. The exercise training had no effect on the glucose tolerance in the animals that were not treated with Dex. The OGTT data are shown in Figure 2B.

**Effect of exercise training on body weight and lipid profile of the rats treated with glucocorticoid**

The chronic administration of Dex induced dyslipidemia characterized by hypercholesterolemia, hypertriglyceridemia and decreased serum levels of HDL-c, when compared to the control group. We also observed an increase in the LDL-c and VLDL-c levels in sedentary animals treated with GC.

The exercise training was effective in preventing hypercholesterolemia (TC, LDL-c and VLDL-c) and hypertriglyceridemia induced by the chronic administration of Dex. However, the exercise had no significant effect on serum levels of HDL-c ($p > 0.05$). The exercise training also reduced the TG and VLDL-c levels in the animals that were not treated with GC.

In parallel to the improvement in the dyslipidemia condition, the animals treated with Dex and trained presented higher weight loss when compared to the control group and the sedentary animals. The exercise training also reduced the body weight in the untreated animals. The treated sedentary animals showed weight gain after 7 days of treatment and subsequently, they presented a progressive decrease of this variable. The blood TC and lipoprotein levels are shown in Figure 3. The behavior of body weight and blood TG levels are shown in Figure 4.

**Effect of exercise training on skeletal muscle hypotrophy induced by glucocorticoid**

The animals treated with Dex presented lower gastrocnemius muscle weight when compared to the control group (0.8 ± 0.07 g vs. 1.23 ± 0.03 g; $p < 0.05$). The exercise training prevented the muscular hypotrophy in the animals chronically treated with GC. Among the treated animals, those submitted to the exercise training did not present a significant difference in gastrocnemius weight when compared to the control group (1.25 ± 0.03 g vs. 1.23 ± 0.03 g; $p > 0.05$). When compared to the control group, the weight of the gastrocnemius muscle was also higher in the trained animals that were not treated with Dex (1.53 ± 0.06 g vs. 1.23 ± 0.03 g; $p < 0.05$).
Chronic effect of the glucocorticoid and physical exercise on the liver

The histopathological analysis of the liver in the animals treated with GC showed the presence of lipid vacuolization in the hepatocytes, which morphologically characterizes the non-alcoholic fatty liver disease (liver steatosis). The exercise training prevented this liver alteration. The liver histopathological analysis is shown in Figure 5.
Chronic effect of the glucocorticoid and physical exercise on the cardiometabolic parameters

The sedentary animals submitted to the chronic treatment with Dex presented higher cardiometabolic risk in comparison to controls. An increase in Castelli’s ratio I and II and the TG/HDL-c was verified. Regarding the treated and trained animals, they presented lower values of all these ratios, when compared to sedentary animals. The data regarding the effect of the GC and exercise training on the cardiometabolic risk are shown in Figure 6.

Discussion

Dexamethasone (Dex) has been broadly used as an experimental model for the study of the metabolic syndrome, because one of its main adverse effects is insulin resistance. According to some authors, rats treated with Dex present decreased glucose uptake stimulated by insulin in the skeletal muscle and fat tissue, whereas in the liver, there was a reversion of gluconeogenesis suppression. A permissive effect to the action of lipolytic hormones (adrenaline, noradrenaline and growth hormone) was observed in the fat tissue, resulting in the increased hydrolysis of triglycerides, release of fatty acids into the blood (substances that induce oxidative stress and endothelial dysfunction) and glycerol for liver gluconeogenesis. The peripheral insulin resistance and the increased gluconeogenesis mediated by GCs cause persistent hyperglycemia, diabetes, dyslipidemia and arterial hypertension due to endothelial dysfunction.

In the present study, the chronic administration of Dex to rats resulted in hyperglycemia, decreased glucose tolerance, hypercholesterolemia, hypertriglyceridemia and decreased serum HDL-c levels, and induced liver steatosis and muscular hypotrophy. The cardiometabolic risk indices were also higher in these animals, when compared to the control group.

The data of the present study are in accordance with those described by Severino et al. The main contribution of the present study was to demonstrate that the cardiometabolic alterations induced by the chronic use of GCs can be reduced and/or prevented by the regular practice of aerobic exercise. In the present study, the aerobic exercise training decreased hyperglycemia, prevented hypercholesterolemia, hypertriglyceridemia, the increase in cardiometabolic indices, the liver steatosis and muscular hypotrophy in rats chronically treated with Dex. However, exercise training had no effect on the serum HDL-c levels.

In the skeletal muscle tissue, the GCs inhibit the glucose uptake stimulated by insulin. In the skeletal muscle of rats treated with Dex, there is inhibition of phosphatidylinositol-3-kinase (PI3K). The PI3K is involved in the activation mechanism of the translocation of the Glucose Transporter Isoform 4 (GLUT4) to the sarcolemma after the insulin stimulus, mainly, in the postprandial period. The treatment with GCs also decreases the synthesis of glycogen in this tissue.

The contraction is a powerful stimulus capable of increasing the blood glucose uptake in the skeletal muscle. The muscle contraction activates the translocation of GLUT4 to the sarcolemma through a signaling pathway independent from the activation of PI3K, that is, through a cascade of signal transduction events independent from insulin signaling. Ruzzin and Jensen demonstrated that the increase in the glucose uptake mediated by the muscle contraction is preserved in rats chronically treated with Dex, whereas the insulin-induced uptake is impaired. Some authors demonstrated that insulin sensitivity in the skeletal muscle also increases after the physical exercise. According to Howlett et al., the muscle contraction increases the phosphorylation of insulin receptor substrate-2 (IRS-2), an alternative pathway in insulin signaling. There is also a higher phosphorylation in protein-kinase B (PKB or AKT), important for the activation of the GLUT4 translocation to the sarcolemma.

In addition to increasing the translocation of GLUT4 to the sarcolemma, the contraction also increases the gene expression of GLUT4 in the skeletal muscle. Thus, the trained skeletal muscle uptakes more glucose due to a higher gene expression and larger amount of GLUT4 in the sarcolemma and through the increase in insulin sensitivity.
Exercise training is an effective non-pharmacological resource in the treatment of insulin resistance and promotes glycemic control in animals with insulin resistance induced by obesity. The evidence generated by the present study reinforces the indication of aerobic exercise as a treatment for insulin resistance induced by GCs. To date, no study had demonstrated this effect, which has a very significant clinical relevance.

In addition to insulin resistance in peripheral tissues, the increased liver gluconeogenesis and the augmented blood mobilization of muscle amino acids have an important role in hyperglycemia caused by the chronic use of GCs. The stimulation of the muscular protein synthesis can favor the glycemic control through the decreased release of amino acids for the liver gluconeogenesis. According to Lapier, the practice of endurance exercise is an effective resource in the prevention of muscular hypotrophy induced by GCs. The protocol of exercise training used in the present study is characterized by strength and aerobic resistance exercise, as the animals were exercised during 60 minutes at a constant velocity and needed to overcome the force of gravity to keep them on the equipment. It was also demonstrated that the physical training prevented the muscular hypotrophy and improved the glycemic control in the animals chronically treated with Dex.

In the present study, the aerobic exercise also decreased the secondary dyslipidemia induced by the chronic use of GC. The increase in the oxidation of fatty acids during the aerobic exercise has been well demonstrated. During contractions in the skeletal muscle, the increase in the concentrations of adenosine monophosphate (AMP) and the decrease in the concentrations of creatine phosphate lead to the activation of the AMP-activated protein kinase (AMPK). The AMPK phosphorylates and inhibits the acetyl-CoA-carboxylase and, consequently, reduces the concentrations of malonyl-CoA, an allosteric inhibitor of carnitine palmitoyltransferase 1 (CPT1). That increases the long-chain fatty acids oxidation within the mitochondria. The exercise training also promotes the mitochondrial biogenesis and increases the expression of transporters and enzymes that regulate fatty acid oxidation in the skeletal muscle. In our experimental model, the exercise training decreased dyslipidemia and lipid accumulation in the liver. Similar results were observed by Severino et al. in response to the treatment with metformin (a potential AMPK activating drug) in rats chronically treated with Dex.

Alterations in the lipid metabolism are accompanied by changes in body weight. Clinically, weight gain is observed in patients with Cushing’s syndrome and in those submitted to chronic treatment with GCs. This is due to the stimulating effect of GCs in the hypothalamic appetite regulation center. Differently from what is observed in humans, there is a decrease in body weight in animal models. As in the present study, Severino et al. also demonstrated a weight decrease in rats treated with Dex. That is probably due to the intense lipolysis caused by the insulin resistance in the fat tissue and the permissive effect of GCs on the lipolytic action of adrenaline and noradrenaline. The lower uptake of glucose caused by the insulin resistance in the skeletal muscle leads to a preference of oxidation of fatty acids in this tissue. Venkatesan et al.

![Fig. 6](image-url) - Effect of corticotherapy and physical exercise on the cardiometabolic parameters. In Panel C, data from the control group were considered as 100%. LDL-c: Low-density lipoprotein cholesterol; HDL-c: High-density lipoprotein cholesterol.
demonstrated that the administration of etomoxir, an inhibitor of CPT1, inhibits the oxidation of fatty acids in the skeletal muscle, with a consequent increase in the concentrations of free fatty acids in the blood, decreasing hyperglycemia and hyperinsulinemia in rats treated with Dex. Therefore, the increase in the bioavailability of fatty acids in the blood caused by the increase in lipolysis stimulates the oxidation of these energetic substrates in the skeletal muscle. 

The improvement in the lipid metabolism in response to the exercise training is accompanied by a decrease in body weight. The animals treated with Dex and trained presented the highest weight loss when compared to the sedentary animals. Such fact can be attributed to the increased oxidation potential of fatty acids in the muscles of trained animals and also to the permissive effect of GCs on the lipolytic action of adrenaline and noradrenaline, of which plasma concentrations are elevated during the exercise. The oxidation of fatty acids during the exercise depends on the bioavailability of these substrates in blood, activation of AMPK and the content of transporters and enzymes involved in the oxidation of these lipids in the skeletal muscle.

Finally, the exercise training could have a beneficial effect on the control of GC-induced arterial hypertension. Although this parameter was not evaluated in the present study, it is believed that the exercise training might have positively influenced the blood pressure control in animals treated with Dex. Dex does not have a significant mineralocorticoid action, but it has a hypertensive effect. It is believed that Dex decreases the expression of nitric oxide synthase (NOS) and impairs the endothelium-dependent vasodilation. This would be caused by the increase in the concentration of free fatty acids in blood, the oxidative stress induction and insulin resistance. Severino et al. demonstrated that rats treated with low Dex doses developed arterial hypertension and that the latter is preceded by insulin resistance and dyslipidemia. Such fact suggests that insulin resistance is an event that precedes the development of hypertension in animals treated with Dex. Therefore, aerobic exercise training improves the insulin sensitivity and could have an effect on the blood pressure control decreasing oxidative stress and improving endothelial dysfunction.

Conclusion
The present study demonstrated that the regular practice of aerobic exercises decreases hyperglycemia, improves glucose tolerance, reduces secondary dyslipidemia and prevents non-alcoholic fatty liver disease and muscular hypotrophy in rats chronically treated with glucocorticoid. Although no effect of exercise training was observed on blood levels of HDL-C, it is believed that other protocols can demonstrate, in this experimental model, the already known effect of physical activity on the metabolism of this lipoprotein. The data presented herein suggest the use of aerobic exercise training in the prevention and treatment of cardiometabolic alterations induced by the chronic use of glucocorticoids.

Potential Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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Study Association
This study is not associated with any post-graduation program.

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