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Aerobic exercise training promotes additional cardiac benefits better than resistance exercise training in postmenopausal rats with diabetes

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Abstract

Objective: The aim of this study was to evaluate the effects of aerobic exercise training or resistance exercise training on cardiac morphometric, functional, and oxidative stress parameters in rats with ovarian hormone deprivation and diabetes.

Methods: Female Wistar rats (200-220 g) were divided into a sham-operated group (euglycemic sham-operated sedentary [ES]; n = 8) and three ovariectomized (bilateral removal of ovaries) and diabetic (streptozotocin 50 mg/kg IV) groups as follows: diabetic ovariectomized sedentary (DOS; n = 8), diabetic ovariectomized undergoing aerobic exercise training (DOTA; n = 8), and diabetic ovariectomized undergoing resistance exercise training (DOTR; n = 8). After 8 weeks of resistance (ladder) or aerobic (treadmill) exercise training, left ventricle function and morphometry were evaluated by echocardiography, whereas oxidative stress was evaluated at the left ventricle.

Results: The DOS group presented with increased left ventricle cavity in diastole and relative wall thickness (RWT), and these changes were attenuated in both DOTA and DOTR groups. Systolic and diastolic function was impaired in the DOS group compared with the ES group, and only the DOTA group was able to reverse this dysfunction. Lipoperoxidation and glutathione redox balance were improved in both trained groups compared with the DOS group. Glutathione peroxidase and superoxide dismutase were higher in the DOTA group than in the other studied groups. Correlations were observed between lipoperoxidation and left ventricle cavity in diastole ($r = 0.55$), between redox balance and RWT ($r = 0.62$), and between lipoperoxidation and RWT ($r = -0.60$).

Conclusions: Aerobic exercise training and resistance exercise training promote attenuation of cardiac morphometric dysfunction associated with a reduction in oxidative stress in an experimental model of diabetes and menopause. However, only dynamic aerobic exercise training is able to attenuate systolic and diastolic dysfunction under this condition.

Key Words: Resistance exercise – Aerobic exercise – Menopause – Diabetes – Cardiac function – Oxidative stress.

Cardiovascular diseases (CVDs) are the main cause of mortality among women in many countries,[1-3] and CVD incidence significantly increases in women after menopause.[4-6] Although the mechanisms through which the prevalence of cardiac diseases increases during the climacteric stage are not well established, estrogen has been suggested to play a cardioprotective role in women before menopause, thus reducing the incidence of these diseases in relation to men.[7]

Indeed, individuals with diabetes are more prone to congestive cardiac insufficiency, regardless of the presence of coronary disease or hypertension, and CVD is the leading cause of mortality among individuals with diabetes. Diabetic cardiomyopathy is now well documented in experimental, clinical, and epidemiological studies. Around 60% of normotensive individuals with diabetes have left ventricle systolic and diastolic dysfunction, together with a reduction in maximal oxygen consumption (VO_{2max}).[8,9] Abnormalities in cardiac function, decrease in peak left ventricle pressure, and reduction in contraction and relaxation derivatives of the left ventricle are all present in animals with streptozotocin (STZ)–induced diabetes.[10,11] Left ventricle dysfunction was observed in individuals with diabetes, with or without manifestation of cardiac disease.[12,13]

Functional abnormalities of cardiac muscles in diabetes have been related to hyperglycemia,[14,15] but others believe them to be independent of glycemic control.[16] Moreover, studies have reported that insulin resistance and hyperinsulinemia increase

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lipoperoxidation (LPO) and reduce antioxidants in plasma, suggesting that both are interconnected.[17,18] The increase in oxidative stress was related to both hyperinsulinemia and reduced concentrations of catalase (CAT) in animals.[18] These findings, among others, have led many researchers to suggest that an excessive increase in reactive oxygen species characterizes the mechanism involved in the development of insulin resistance, diabetes, and CVD. However, the role of the association of hyperglycemia with ovarian hormone deprivation in cardiac dysfunction and the role of oxidative stress in this process remain unclear.

On the other hand, the benefits of aerobic exercise training or resistance exercise training for metabolic control in individuals with diabetes are well documented. However, few studies have evaluated the effects of these types of training on cardiac dysfunction associated with either diabetes or ovarian hormone deprivation. In an experimental model of female rats in menopause, we have shown that dynamic aerobic physical training induced body weight loss, resting bradycardia, normalization of arterial pressure values, and improvement in baroreflex associated with decreased oxidative stress.[19] We also reported hemodynamic and autonomic improvement in ovariectomized rats with diabetes.[20] Furthermore, a meta-analysis has concluded that resistance exercise training plays an important role in the control of risk factors such as obesity, glycated hemoglobin, and systolic arterial pressure, and should be indicated in the management of diabetes.[21] It is worth stressing that, after menopause, exercise capacity, physical strength, and bone mass decline, whereas body weight increases, together with a higher prevalence of diabetes mellitus, osteoporosis, and CVDs.[5]

Therefore, the present study aims to test the hypothesis that aerobic exercise training or resistance exercise training promotes cardiac benefits associated with a reduction in oxidative stress parameters in ovariectomized rats with STZ-induced diabetes.

METHODS

Experiments were performed using 32 female Wistar rats (aged 10 wk) obtained from the Animal Shelter of University of São Paulo (São Paulo, Brazil). The rats received standard laboratory chow (Nuvital, Colombo, Brazil) and water ad libitum. The animals were housed in individual cages in a temperature-controlled room (22°C) with a 12-hour dark-light cycle. Four experimental groups were used in this study: euglycemic sham-operated sedentary (ES; n = 8), diabetic ovariectomized sedentary (DOS; n = 8), diabetic ovariectomized undergoing aerobic exercise training (DOTA; n = 8), or diabetic ovariectomized undergoing resistance exercise training (DOTR; n = 8). All rats were treated similarly for daily manipulation. All surgical procedures and protocols were in accordance with the International Animal Care and Use Committee and were approved by Nove de Julho University (protocol number AN001/08).

Ovariectomy

At 10 to 12 weeks, animals from the DOS, DOTA, and DOTR groups were anesthesized (ketamine 80 mg/kg IP and xylazine 12 mg/kg IP), the oviduct was sectioned, and the ovary was removed, as described in detail elsewhere.[19-22] At the same age, rats from the ES group underwent a sham surgical operation. Data from our laboratory demonstrated that the mean (SEM) estrogen concentration, measured by immunoassay, was 39 (7) pg/mL in healthy female rats. However, in the present study, estrogen concentration was nondetectable in the studied ovariectomized groups (TKE21, Coat-A-Count Estradiol; Siemens Medical Solutions Diagnostics), thus confirming ovarian hormone deprivation.[20]

Diabetes

Five days after ovariectomy, diabetes induction was performed on animals in the DOS, DOTA, and DOTR groups, using a single injection of STZ (50 mg/kg IV; Sigma Chemical Co) dissolved in citrate buffer (pH 4.5), after 6 hours of fasting.[20,23]

Glycemia

Blood samples (50 μL) were collected, using Gluco test (Advantage; Roche Laboratories), to measure glycemia 72 hours after STZ injection and at the end of the protocol.[20,23]

Aerobic exercise training

One week after diabetes induction, all animals (ES, DOS, DOTA, and DOTR groups) were adapted to a motor treadmill (TK-01; Imbramed, Brazil) for 1 week (10 min/d; 0.3 km/h) before the beginning of the exercise training protocol. Sedentary and trained rats underwent a maximal running test, as described in detail in a previous study.[24] Tests were performed at the beginning of the experiment and on the fourth and eighth weeks of the training protocol. The purpose of the test was to determine physical capacity and exercise training intensity on a treadmill. After adaptation, the sedentary group underwent exercise training only during the maximal running test. However, the animals were placed on the stationary treadmill at least three times a week to provide a similar environment. Aerobic exercise training was performed on a motor treadmill (TK-01; Imbramed) at low to moderate intensity (40%-60% of maximal running speed) for 1 hour/day, 5 days/week for 8 weeks, with a gradual increase in speed from 0.3 to 1.0 km/hour (first week, 0.3-0.6 km/h; second week to fourth week, 0.3-0.8 km/h; fifth week to eighth week, 0.6-1.0 km/h).[20,22]

Resistance exercise training

This protocol was performed in a ladder adapted for rats, as previously described in detail.[23] One week after diabetes induction, the animals were adapted to the act of climbing for five consecutive days, before the maximal load test. The test consisted of an initial load of 75% of body weight. After completion of the first climb, a 2-minute resting period preceded the following climb. For this next climb, the load was increased by another 15 %, 25%, or 40% of body weight in the test performed on the first, fourth, and eighth weeks of the protocol, respectively. This increment was repeated successively until the animal could not complete the climb while bearing the load (maximum of six climbs). The protocol of

resistance exercise training was performed using the normalized value of maximal load for each rat and was adjusted weekly according to the body weight of the animal. The resistance exercise training protocol was performed for 8 weeks, 5 days/week, at moderate intensity (40%-60% of the maximal load), as recommended for individuals with diabetes or other diseases,[25,26] with 15 climbs per session and a 1-minute time interval between climbs.

Echocardiographic measurements

Echocardiography was performed by a double-blind observer, under the guidelines of the American Society of Echocardiography, at the end of the protocol. Rats were anesthesized (ketamine 80 mg/kg IP and xylazine 12 mg/kg IP), and images were obtained with a 10- to 14-mHz linear transducer in a SEQUOIA 512 (ACUSON Corp, Mountain View, CA) for measurement of morphometric parameters left ventricle mass (LVM; corrected for body weight), left ventricle cavity in diastole (LVDIA), and relative wall thickness (RWT); systolic function parameters velocity of circumferential fiber shortening (VCF) and fractional shortening (FS); and diastolic function parameters left ventricle isovolumetric relaxation time (IVRT) and E-wave deceleration time (Desac E), as described in detail elsewhere.[10,12]

Oxidative stress evaluation

After cardiac evaluation, the animals were euthanized; the left ventricle was rapidly removed, washed in phosphate-buffered saline, weighed, and frozen at −70°C until analysis for oxidative stress. The remainder of the left ventricle was placed in an ice-cold solution containing 140 mM KCl and 20 mM HEPES (pH 7.4). The left ventricle was homogenized using an Ultra Turrax blender and 1 g of tissue per 5 mL of a solution of 1.15% (wt/vol) KCl and 20 mM phenylmethylsulfonyl fluoride. Homogenates were centrifuged at 600*g* for 10 minutes at 2°C to remove nuclei and cell debris, as described elsewhere. Protein concentration was determined by the method of Lowry et al[27] using bovine serum albumin as standard.

Protein carbonylation was measured using a reaction of protein carbonyl groups with 2,4-dinitrofenylhydrazyne to form 2,4-dinitrophenylhydrazone, which can be measured spectrophotometrically as previously described by Reznick and Packer.[28] The product of the reaction was measured at 360 nm. Results were expressed as nanomolars of 2,4-dinitrofenylhydrazyne per milligram of protein.

LPO was assessed by chemiluminescence assay performed with an LKB Rack Beta liquid scintillation spectrometer 1215 (LKB Producer AB) in out-of-coincidence mode at room temperature (25°C-27°C). Supernatants were diluted in 140 mmol/L KCl and 20 mmol/L phosphate buffer (pH 7.4) and added to glass tubes, which were placed in scintillation vials; 3 mmol/L *tert*-butylhydroperoxide was added, and chemiluminescence was determined up to the maximal level of emission.[29]

Antioxidant enzyme activities

Quantification of superoxide dismutase (SOD) activity (U/mg protein) was based on inhibition of the reaction between $O_2^{-\cdot}$ and pyrogallol.[30] CAT activity was determined by measuring the decrease in H_2O_2 absorbance at 240 nm. CAT concentration was expressed as micromoles of H_2O_2 reduced per minute per milligram of protein.[31] Glutathione peroxidase (GPx) activity was expressed as nanomoles of peroxide per hydroperoxide reduced per minute per milligram of protein based on consumption of reduced nicotinamide-adenine dinucleotide phosphate at 480 nm.[32]

For determination of reduced glutathione (GSH) and oxidized glutathione (GSSG) concentrations, tissue was deproteinized with 2 mol/L perchloric acid and centrifuged for 10 minutes at 1,000*g*, and the supernatant was neutralized with 2 mol/L potassium hydroxide. The reaction medium contained 100 mmol/L phosphate buffer (pH 7.2), 2 mmol/L nicotinamide dinucleotide phosphate acid, 0.2 U/mL glutathione reductase, and 70 mmol/L 5,50 dithiobis (2-nitrobenzoic acid). For determination of GSH concentration, the supernatant was neutralized with 2 mol/L potassium hydroxide for reaction with 70 mmol/L 5,50 dithiobis (2-nitrobenzoic acid), and absorbance values were measured at 420 nm.[33]

Statistical analysis

Data are presented as mean (SEM). One-way analysis of variance, followed by Student-Newman-Keuls post hoc test, was used to compare groups. Paired Student's *t* test and intraclass correlation coefficient (ICC) were used to analyze the reproducibility of intrareader and interreader measurements with 95% CI. ICC was characterized as follows: high reliability, 0.80 to 0.99; moderate reliability, 0.60 to 0.79; low reliability, less than 0.60. Pearson correlation was used to study the association between variables in the diabetic groups. Differences were considered significant at $P \leq 0.05$ for all tests.

RESULTS

Metabolic parameters

At the beginning of the protocol, when the animals were divided into their respective groups for subsequent ovariectomy and diabetes induction, body weight was similar between groups. However, at the end of the protocol, animals with diabetes (DOS, DOTA, and DOTR) presented with reduced body weight compared with the ES group (Table 1). For fasting glucose levels measured at the end of the protocol, the diabetic groups (DOS, DOTA, and DOTR) had, as expected, higher blood glucose levels than ES animals (Table 1). No statistical differences in body weight or glycemia were observed among the DOS, DOTA, and DOTR groups (Table 1).

Exercise capacity

For running time in the maximal treadmill exercise test, animals that underwent aerobic exercise training (DOTA) showed an increase in running time after 8 weeks of aerobic exercise training compared with all other studied groups (ES, DOS, and DOTR), indicating the effectiveness of the aerobic exercise training protocols used. In addition, we observed a reduction in this parameter in the DOS group compared with the ES group. The DOTR group presented with a similar running time as the ES group (Table 1).

TABLE 1. *Body weight, glycemia, maximal running test, and maximal load test in the studied groups at the end of the protocol*

Parameters	Groups			
	ES (n = 8)	DOS (n = 8)	DOTA (n = 8)	DOTR (n = 8)
Body weight, g	260 (10)	213 (6)[a]	215 (11)[a]	206 (17)[a]
Glycemia, mg/dL	102 (5)	475 (17)[a]	486 (41)[a]	486 (21)[a]
Maximal running test, s	701 (55)	548 (33)[a]	953 (20)[a,b]	646 (63)[c]
Maximal load test, % of body weight	204 (11)	183 (9)	167 (10)	259 (9)[a,b,c]

Data are presented as mean (SEM).
ES, euglycemic sham-operated sedentary; DOS, diabetic ovariectomized sedentary; DOTA, diabetic ovariectomized undergoing aerobic exercise training; DOTR, diabetic ovariectomized undergoing resistance exercise training.
[a]$P < 0.05$ versus ES.
[b]$P < 005$ versus DOS.
[c]$P < 0.05$ versus DOTA.

Animals that underwent resistance exercise training (DOTR) also showed increased maximal load compared with the other studied groups (ES, DOS, and DOTA) at the end of the resistance exercise training protocol (Table 1).

Cardiac morphometry and function

LVM and RWT were lower whereas LVDIA was increased in the DOS group compared with ES animals; however, both types of exercise training were able to normalize these variables. No differences in morphometric parameters were observed between the DOTA group and the DOTR group (Table 2).

The DOS group showed reduced VCF and FS compared with the ES group, and aerobic exercise training was able to attenuate these systolic dysfunctions. In this sense, the DOTA group had higher systolic function than both the DOS group and the DOTR group, but the values were still lower compared with the ES group (Table 2). IVRT and Desac E were increased in DOS and DOTR animals compared with ES animals. The DOTA group presented with improved diastolic function compared with the DOS and DOTR groups (Table 2).

There were no significant differences between intrareader measurements ($P > 0.05$) and interreader measurements ($P > 0.05$) when morphometric parameters, systolic functions, and diastolic functions were compared by paired t test. The intrareader and interreader ICCs were, respectively, 0.99 and 0.89 (LVM), 0.98 and 0.98 (LVDIA), 0.96 and 0.92 (RWT), 0.94 and 0.93 (FS), 0.92 and 0.97 (VCF), 0.97 and 0.96 (IVRT), and 0.99 and 0.85 (Desac E), thus showing the high reliability of echocardiographic evaluation, with $P < 0.05$ for all variables.

Cardiac oxidative stress

Diabetes associated with ovariectomy (DOS) induced an increase in LPO compared with the ES group. Aerobic exercise training and resistance exercise training showed lower values compared with the ES and DOS groups. The DOTA and DOTR groups showed similar LPO values. Protein carbonyls were increased in all diabetic groups (DOS, DOTA, and DOTR) compared with the ES group (Table 3).

CAT was increased in the ovariectomized (DOS) and trained (DOTA and DOTR) groups compared with the ES group. GPx was higher in the diabetic groups (DOS, DOTA, and DOTR) compared with the ES group. The trained groups (DOTA and DOTR) showed an additional increase in cardiac GPx compared with the diabetic ovariectomized (DOS) group. The group that underwent aerobic exercise training (DOTA) showed a further increase in GPx compared with the resistance group (DOTR), but CAT was similar between these groups. SOD was also increased in all diabetic ovariectomized groups compared with the ES group. However, only aerobic

TABLE 2. *Cardiac morphometry and function in the studied groups as assessed by echocardiography*

Parameters	Groups			
	ES (n = 8)	DOS (n = 8)	DOTA (n = 8)	DOTR (n = 8)
Morphometric parameters				
LVM, g	1.07 (0.01)	0.98 (0.02)[a]	1.06 (0.02)[b]	1.05 (0.02)[b]
LVDIA, cm	0.65 (0.01)	0.71 (0.01)[a]	0.67 (0.01)[b]	0.66 (0.02)[b]
RWT	0.45 (0.01)	0.38 (0.01)[a]	0.43 (0.02)[b]	0.46 (0.01)[b]
Systolic function				
FS, %	44 (1)	38 (2)[a]	45 (1)[b]	39 (1)[a,c]
VCF $\times 10^{-4}$, circ/s	54 (1)	36 (2)[a]	45 (3)[a,b]	34 (1)[a,c]
Diastolic function				
IVRT, ms	24 (0.7)	33 (1.3)[a]	27 (0.5)[a,b]	32 (1.0)[a,c]
Desac E, ms	41 (0.6)	50 (1.9)[a]	43 (0.7)[b]	55 (3.0)[a,c]

Data are presented as mean (SEM).
ES, euglycemic sham-operated sedentary; DOS, diabetic ovariectomized sedentary; DOTA, diabetic ovariectomized undergoing aerobic exercise training; DOTR, diabetic ovariectomized undergoing resistance exercise training; LVM, left ventricle mass; LVDIA, left ventricle cavity in diastole; RWT, relative wall thickness; FS, fractional shortening; VCF, velocity of circumferential fiber shortening; IVRT, isovolumetric relaxation time; Desac E, E-wave deceleration time.
[a]$P < 0.05$ versus ES.
[b]$P < 005$ versus DOS.
[c]$P < 0.05$ versus DOTA.

TABLE 3. *Cardiac oxidative stress in the studied groups*

Parameters	Groups			
	ES (n = 8)	DOS (n = 8)	DOTA (n = 8)	DOTR (n = 8)
LPO, cps/mg protein	2,661 (358)	2,987 (318)	889 (310)[a,b]	714 (54)[a,b]
CARB, nmol/mg protein	3.00 (0.23)	13.27 (2.72)[a]	14.14 (0.98)[a]	12.75 (1.85)[a]
CAT, nmol/mg protein	0.80 (0.04)	1.31 (0.13)[a]	1.47 (0.35)[a]	1.34 (0.23)[a]
GPx, nmol/min/mg protein	32.00 (3.55)	56.00 (9.30)[a]	112.0 (15.00)[a,b]	84.00 (15.00)[a,b,c]
SOD, U/mg protein	16.00 (0.58)	31.53 (2.27)[a]	50.35 (5.66)[a,b]	33.86 (1.77)[a,c]
Total glutathione, mmol/g	0.28 (0.01)	0.26 (0.02)	0.22 (0.01)	0.25 (0.01)
GSH, mmol/g	0.25 (0.01)	0.22 (0.02)	0.19 (0.01)[a]	0.23 (0.01)
GSSG, mmol/g	0.024 (0.002)	0.038 (0.002)[a]	0.028 (0.001)[b]	0.033 (0.002)[a]

Data are presented as mean (SEM).
ES, euglycemic sham-operated sedentary; DOS, diabetic ovariectomized sedentary; DOTA, diabetic ovariectomized undergoing aerobic exercise training; DOTR, diabetic ovariectomized undergoing resistance exercise training; LPO, lipoperoxidation; CARB, protein carbonylation; CAT, catalase; GPx, glutathione peroxidase; SOD, superoxide dismutase; GSH, reduced glutathione; GSSG, oxidized glutathione.
[a] $P < 0.05$ versus ES.
[b] $P < 0.05$ versus DOS.
[c] $P < 0.05$ versus DOTA.

exercise training (DOTA) induced an additional increase in this variable compared with the DOTR and DOS groups (Table 3).

The concentration of total glutathione did not differ between groups. GSH concentration was lower in the DOTA group compared with the other groups (ES, DOS, and DOTR). However, GSSG concentration was higher in the DOS and DOTR groups compared with the ES group, but this change was not observed in the DOTA group (Table 3). Glutathione redox balance (GSH/GSSG) was lower in the diabetic groups (DOS, DOTA, and DOTR) compared with the ES group. However, the trained groups (DOTA and DOTR) had an attenuation of this impairment, as they presented with higher redox ratios compared with the DOS group. GSH/GSSG was similar between the DOTA group and the DOTR group (Fig.).

Table 4 presents a correlation analysis of variables in the diabetic groups (DOS, DOTA, and DOTR; n = 5-7 animals per group). We observed a positive correlation between LPO and protein carbonylation (CARB). In addition, we found a positive correlation between LPO and LVDIA and a negative correlation between LPO and RWT. We observed a negative correlation between redox balance and CARB ($r = -0.58$, $P < 0.05$). Glutathione redox ratio was inversely correlated with LPO and carbonyls, and positively correlated with RWT. Moreover, we observed a negative correlation between VCF and Desac E ($r = -0.65$).

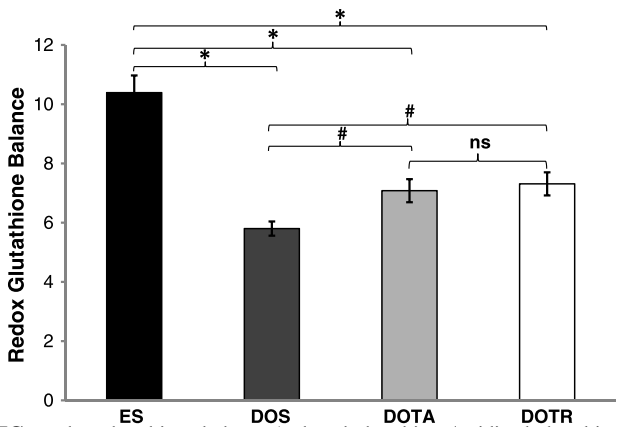

FIG. Redox glutathione balance (reduced glutathione/oxidized glutathione) in the studied groups showing impaired redox balance in the diabetic group (DOS [n = 8] vs ES [n = 8], $P < 0.05$), which was attenuated by training protocols (DOS vs DOTA [n = 8], $P < 0.05$; DOS vs DOTR [n = 8], $P < 0.05$). ES, euglycemic sham-operated sedentary; DOS, diabetic ovariectomized sedentary; DOTA, diabetic ovariectomized undergoing aerobic exercise training; DOTR, diabetic ovariectomized undergoing resistance exercise training. *$P < 0.05$ versus ES. #$P < 0.05$ versus DOS. ns, $P > 0.05$.

DISCUSSION

In the present study, we associated ovarian hormone deprivation with an experimental model of STZ-induced diabetes. STZ destroys pancreatic β cells, resulting in deficient insulin secretion. This model of diabetes has been widely used in the literature on the relationship between diabetes and autonomic cardiovascular dysfunction.[34] Rats with STZ-induced diabetes showed many of the alterations derived from noncontrolled diabetes in humans with type I diabetes, such as hyperglycemia, hypoinsulinemia, glycosuria, and weight loss.[35-37] Indeed, in the present study, we observed hyperglycemia and weight loss in animals with STZ-induced diabetes compared with the ES group.

Given that menopause has been associated with reduced exercise capacity, reduced muscle strength (sarcopenia), reduced mineral bone density, osteoporosis, increased body weight, hyperglycemia, and CVDs,[4,5] we chose an experimental model of menopause induced by ovariectomy to study

TABLE 4. *Pearson correlations between variables*

	LPO
CARB	0.63[a]
LVDIA	0.55[a]
RWT	−0.60[a]
	Glutathione redox balance
LPO	−0.45[a]
CARB	−0.58[a]
RWT	0.62[a]

LPO, lipoperoxidation; CARB, protein carbonylation; LVDIA, left ventricle cavity in diastole; RWT, relative wall thickness.
[a] $P < 0.05$ (Pearson correlation involving diabetic groups).

alterations derived from ovarian hormone suppression, thus mimicking the conditions of menopause.[19,22,38,39] Furthermore, the benefits of aerobic exercise training have been widely investigated in many physiological (aging and menopause) and pathological (diabetes and hypertension) situations; however, the scientific community has, in recent years, turned its attention to the effects of resistance exercise training owing to its accessibility and large acceptance by the population, particularly in gyms and through physical activity incentive programs. Unlike aerobic exercise training, prescription of resistance exercise training allows the modulation of many parameters, such as the number of repetitions, series, exercise load intensity, and duration of intervals between one series and the next.[40] The possible combinations of these variables change the short-term and long-term physiological effects of resistance exercise training, making the use of this type of exercise challenging for at-risk populations. Indeed, international guidelines increasingly suggest resistance exercise training in association with aerobic exercise training as an important nonpharmacological strategy for preventing and/or attenuating many of the risk factors associated with metabolic diseases and CVDs.[41-43] In the present study, we showed improvement in specific physical capacity (aerobic or resistance) according to training type.

The results that we obtained for female ovariectomized rats were very similar to findings from the literature on cardiac dysfunction in STZ-induced diabetes in male rats, which are related to alterations in left ventricle morphometry and impairment in left ventricle systolic and diastolic functions.[44,45] In fact, in the evaluation of male rats with STZ-induced diabetes, Wichi et al[46] showed that the systolic and diastolic cardiac dysfunction and alterations reported for cardiac morphometry were similar to those observed in the present study. The ovariectomized diabetic group (DOS) presented with a reduction in RWT and LVM and an increase in LVDIA, both of which are evidence for diabetic cardiomyopathy.

For morphometric parameters, the animals that underwent exercise training (DOTA or DOTR) presented with increased RWT and reduced LVDIA, resulting in LVM increase, compared with the DOS group. This may be interpreted as normalization in relation to the ES group, suggesting attenuation of diabetic cardiomyopathy.

Oxidative stress evaluation showed increased parameters of damage, such as LPO and CARB, in left ventricle tissue in the presence of an association between ovarian hormone deprivation and diabetes (DOS vs ES). We have previously reported increased heart LPO in ovariectomized rats[19] and in skeletal muscle of male rats with diabetes.[11] Interestingly, the activity of the main antioxidant enzymes (CAT, SOD, and GPx) was increased in the DOS group compared with the ES group. These changes probably represent an attempt to counterbalance the increase in reactive oxygen species under this pathophysiological condition. In fact, analysis of glutathione redox balance (an excellent index of oxidative stress) showed a marked decrease in the DOS group compared with the ES group, confirming increased oxidative stress in the DOS group that was probably related to unfavorable changes in cardiac morphometry. In addition, redox balance was also correlated with reduced LPO and damage to proteins (CARB), suggesting that animals with impairment in redox balance presented with increased LPO and protein carbonylation.

Importantly, the applied protocols of aerobic exercise training or resistance exercise training induced attenuation of oxidative stress conditions through adaptive response to both types of training (ie, increased antioxidant enzyme defense, reduced LPO, and normalization of glutathione redox balance). We have also previously reported that reduced LPO and increased SOD were associated with improvement in autonomic control of circulation in aerobically trained ovariectomized rats.[19] Indeed, we found a positive correlation between LPO and RWT, which shows that diabetic ovariectomized rats with lower LPO in heart tissue had the highest wall thickness. In addition, LPO was correlated with LVDIA, indicating that LPO reduction was associated with lower left ventricle dilation. These findings show that this reduction in oxidative stress parameters in the trained groups was associated with improvements in cardiac morphometry.

Moreover, the results of the present study showed that aerobic exercise training induces attenuation of left ventricle systolic and diastolic dysfunctions in an experimental model of diabetes and menopause. However, resistance exercise training did not induce such benefits, in line with a previous study that showed improved contraction and relaxation in the isolated heart of male rats with diabetes that underwent aerobic exercise training.[44]

Potential clinical value

Given that individuals with diabetes and postmenopausal women are often older and sedentary, with reduced muscular strength and endurance,[4,47] resistance exercise training can promote improvement in muscular strength and aerobic exercise training can promote increase in endurance. These benefits improve overall functional capacity, thus contributing to general health and quality of life.[4,25,41,42,48] Furthermore, aerobic exercise training and resistance exercise training also seem to be able to reduce the risk factors involved in the development of CVDs.[4,41,42] In fact, our results showed that resistance exercise training in an experimental model improved load capacity, left ventricle morphometric parameters, and oxidative stress, and did not cause any adverse effects on diabetic cardiomyopathy when prescribed in moderate intensity and using dynamic movements. All of these benefits, along with additional improvement in left ventricle systolic and diastolic functions, were observed in animals that underwent aerobic exercise training. Together, these data suggest that both types of training, when well prescribed, could be safe and can play important roles in the management of diabetic cardiomyopathy after ovarian hormone deprivation. Future studies needs to clarify the role of the association of aerobic exercise training with resistance exercise training in this population.

CONCLUSIONS

Aerobic exercise training or resistance exercise training induces attenuation of cardiac morphometric dysfunction associated with oxidative stress reduction in an experimental model of diabetes and menopause. However, only dynamic exercise training is able to attenuate systolic and diastolic dysfunction under this condition.

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