Effects of short-term resistance training on oxidative stress, lipid panel, liver and kidney function in patients with and without type 2 diabetes

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Abstract

Background: Resistance training is considered a non-pharmacological treatment for several comorbidities, including type 2 diabetes mellitus (T2D) and other non-communicable diseases that accompany it. Objectives: Investigate the effects of short-term resistance training (RT) in patients with T2D on markers of fasting glycaemia, oxidative stress, liver function parameters, lipid profile and renal function in individuals with and without T2D. Methods: 29 participants were included for final analysis, 16 T2D and 13 non-diabetic (ND). Participants were randomized into an intervention group (T2DEX and NDEX) or control group (T2DCTL or NDCTL). Subjects completed questionnaires about their medical history and were assessed for body composition and blood samples were collected for oxidative stress using Thiobarbituric acid reactive substances (TBARS), fasting blood glucose, lipid panel, liver function and renal function, baseline, 4 weeks and 8 weeks of intervention. This comprised circuit training of approximately 20 minutes (2 sets of 6 resistance training exercises) to be performed 3 times a week. Results: T2DEX showed lower TBARS levels after 8 weeks of training (10.0 ±2.0 vs. 6.8 ±4.2 mmol·L⁻¹; p<0.05). High-density lipoprotein (HDL) was significantly reduced in T2DEX (37.5 ±7.9 vs. 24.8 ±6.0 mg·dL⁻¹) and T2DCTL (34.9 ±6.1 vs. 32.0); 3 ±7.6 mg·dL⁻¹) in week 4. Low-density lipoprotein (LDL) (219.2 ±40.5 vs. 130.4 ±49.6 mg·dL⁻¹; p<0.05) and total cholesterol (247.6 ±33.4 vs. 205.8 ± 57.2 mg·dL⁻¹) decreased significantly (p<0.05), on T2DEX after training. Both groups that did not exercise had elevated total cholesterol levels after 8 weeks. Conclusion: Short-term circuit training is effective in promoting benefits in oxidative stress and lipid panel in overweight individuals with DM.

Keywords: Strength training; circuit training; antioxidant; diabetes mellitus.

BACKGROUND

Type 2 Diabetes Mellitus (T2D), overweight and obesity are metabolic non-communicable diseases that together affects more than 30% of the world population[1-3]. Furthermore, these diseases are commonly related to several other comorbidities and diseases such as hypertension, dyslipidemia, cardiovascular diseases, psychological disorders and even cancer[1,3]. Consequently, oxidative stress, which is an imbalance between pro- and antioxidants, has been postulated as a cause and consequence of T2D and several other metabolic disorders[4].
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Reactive oxygen species (ROS) can impair the insulin signaling in a cell, thus decreasing its ability to absorb glucose from the blood stream, decreasing insulin sensitivity and in turn resulting in chronic hyperglycemia\(^{(5,6)}\). Furthermore, this metabolic disease affects all systems in the body, including the liver. Hyperglycemia affects the metabolism of lipids, carbohydrates and proteins leading to increased oxidative stress, which may lead to liver tissue injury\(^{(7,10)}\).

Among the metabolic abnormalities that commonly follow T2D, there is a malfunction in the production and clearance of plasma lipoproteins\(^{(11)}\). Diabetic dyslipidemia, consists of decreased high-density lipoprotein (HDL), increased triglycerides, and postprandial lipemia\(^{(11)}\). This dysregulation in metabolic systems such as hyperglycemia, hyperlipidemia, and insulin resistance are a strong trigger for chronic kidney disease\(^{(12)}\), which is a major risk factor for T2D that decreases life span by up to 10 years\(^{(1-3)}\).

On the other hand, exercise has been suggested as a great non-pharmacological therapy to reduce overweight\(^{(13)}\), oxidative stress\(^{(14)}\) and as treatment for T2D\(^{(15)}\). Evidence shows that exercise can also improve liver function\(^{(16)}\), lipid panel\(^{(17)}\) and renal function\(^{(18)}\). However, to the best of our knowledge, there are no studies investigating the effects of resistance training (RT) on fasting blood glucose, oxidative stress markers, liver function parameters, lipid profile, and renal function jointly in T2D individuals.

It is noteworthy that a great body of evidence has been suggesting RT as an alternative to aerobic training, reporting similar health outcomes\(^{(15,19-21)}\), with benefits such as muscle mass maintenance and increased strength and functionality \(^{(21)}\). However, RT is a method that also has a poor adherence in people with T2D and/or who are overweight\(^{(22)}\), possibly due to long and tedious training sessions of the traditional protocols. Thus, variations of the traditional RT, such as circuit training, have been suggested to increase adherence\(^{(22)}\), this includes reducing idle minutes between sets, decreasing the peripheral intensity and increasing the central physiological demands that could elevate the dynamic of the session. There are a few studies that investigated the effect of circuit training on clinical and physiological variables in those who are overweight, reporting improvement in body composition metabolic syndrome parameters\(^{(23-25)}\). Therefore, the aim of this manuscript was to investigate the effects of a short-term RT intervention on fasting blood glucose, oxidative stress markers, liver function parameters, lipid profile and renal function in individuals with and without T2D.

**METHODS**

The study was approved by the Ethics Committee of the Catholic University of Brasilia (protocol number 005/2014) and followed the items proposed in the guidelines of CONSORT for reporting parallel group randomized trials. All procedures were performed in accordance with the Declaration of Helsinki (466/2012). Eligible assigned to a resistance training group (T2DEX and NDEX) or control group (T2DCTL or NDCTL).

**Sample**

Eligibility criteria included a negative history of myocardial infarction or any other condition that could risk the subject health during RT. All subjects had to fulfill an anamnesis form with their record of personal and family history of coronary artery
disease, eating habits, recent history of smoking alcohol use, and physical activity habits. All subjects included had no history of cardiovascular complications, were non-smokers and have not engaged in any physical activity programs for at least 1 year. T2D individuals were under medical treatment using oral hypoglycemic agents (Metformin, Metformin + Glibenclamide). Thirty-six (36 women) initially eligible community-local subjects older than 50 years (near the university campus) were contacted and agreed to participate in this study and 29 were included for final analysis, being 16 T2D and 13 non-diabetic (ND). Screening procedures included confirmation of the diagnosis of diabetes by glycated hemoglobin ≥ 6.5% or use of pharmacological treatment for T2D. Throughout the intervention, three T2D subjects and four ND subjects dropped out or were excluded for not attending the minimum of 80% of training sessions or not returning for blood sample collection. A priori statistical power was applied considering the statistical model used (ANOVA 4X3), an effect size (ES) of 0.30, four groups and three moments (baseline, 4th-wk, 8th-wk), and α = 0.05. The statistical power conferred to the final sample size (n = 29) was 82%. For the aforementioned analysis we used the software (G*Power® version 3.1.9.7).

**Screening**

Screening procedures included confirmation of the diagnosis of diabetes based on glycated hemoglobin ≥6.5% or on the use of diabetes medications; the screening also included a physical examination, blood pressure measurement and an at-rest electrocardiogram. In addition, an anamnesis was performed, and the form included personal and family history of coronary artery disease, risk factors associated with medication and treatment, eating habits and diet, history of personal and family smoking, and current patterns of physical activity. The T2D patients were given medical treatment using oral hypoglycemic agents (Metformin alone or combined with Glibenclamide).

**Randomization**

Eligible subjects gave written informed consent, and after initial screening, were randomly into four groups, resistance training group: type 2 diabetes exercise (T2DEX; n=9), nondiabetes exercise (NDEX; n=7) and control group T2D control (T2DCTL; n = 7), and ND control (NDCTL; n = 6). The randomization sequence was computer generated (randomizer.org) and created by a third party not involved in the day to day running of the trial. A simple randomization was applied. The randomization process was made by lot from a paper stored in sealed opaque envelopes. The allocation of participants was concealed from the blinded assessor. Envelopes were opened with the participant after the baseline assessment. Participants were reminded not to disclose their group allocation during follow-up assessment.

**General Procedures**

Details on the initial screening and anthropometric measures were previously described at Sales, et al. In general, the participants arrived in the laboratory in the morning (8:00–10:00 AM) for a RT or control session. In the first day and at end of the 4th and 8th weeks, blood samples were obtained. The RT consisted of a 25-minute session performed three times per week in inconsecutive days. Participants performed six
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exercises in a structured and fixed order (leg press, seated pulley, let curl, bench press, leg extension and rowing machine). The training was conducted in a circuit design, which the participants had to perform one set, and go to next exercise with a ~20” interval until the end of six exercises, and then repeat the full circuit two more times. The exercise intensity was progressive in each week: 50%-1RM at 1st wk (12 reps); 60%-1RM at 2nd wk (10 reps); 70%-1RM at 3rd and 4th wk (8 reps), then reassessed for 1-RM and underwent four more weeks with the same format. The 1-RM tests were conducted as previously described(29).

Subjects assigned to the control group received phone calls every week and came to the university for blood sample collection. All participants were strongly advised to continue their usual care, diet and physical activity habits. All changes in the initial medication (new drug or new dosage) were reported, and those participants' results excluded from analysis.

Blood samples were taken as soon as the participants arrived on collection day, using a cannula, which was inserted into an antecubital vein prior to collection. Blood was collected in tubes suitable for storage of 10mL (Vacutainer) with EDTA K polymer material blasted on the inner wall, centrifuged at 3,800rcf (4º C) to separate the plasma and stored at -80º C until analysis.

Biochemical Analyses

To estimate total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides (TG), creatinine, urea, glutamic-pyruvic transaminase (GPT) and e glutamic-oxalacetic transaminase (GOT), an automated chemistry analyzer (COBAS c111 system, Roche Diagnostics, Switzerland) was used. Assessment of TBARS is one of the most used methods to determine lipid peroxidation and oxidative damage in cells and tissues. The protocol used in the present study was adapted from Ohkawa et al.(30). Serum samples were diluted in 320μL MiliQ H2O (1:5), and then 1mL of 5 trichloroacetic acid (TCA) 17.5%, pH 2.0 and 1mL of thiobarbituric acid (TBA) 0.6%, pH 2.0 were added, respectively. After homogenization, the samples were kept in a water bath for 30 minutes at 95ºC. The reaction was interrupted with the immersion of the microtubes in ice and the addition of 1mL of TCA 70%, pH 2.0 and another incubation for 20 minutes at room temperature. After centrifugation (3,000rpm for 15 minutes), the supernatant was removed and put in new microtubes and read by spectrophotometry at 540nm. The concentration of lipid peroxidation products was calculated using the molar extinction coefficient equivalent for malondialdehyde (MDA-equivalent = 1.56x105 M-1cm-1).

Statistical Procedures

All statistical procedures were carried out using Statistical Package for the Social Sciences for Windows SPSS 20.0 for Windows® software (Chicago, USA) and GraphPad Prism 8.0.1 software for Windows. The Shapiro-Wilk and Levene tests were applied for normality and homogeneity, respectively. A split-plot ANOVA was applied with interaction time×disease×training. When interactions were found (p<0.05), pairwise comparisons were applied to identify the differences more accurately. The hypothesis of sphericity was verified by Mauchly test, and when violated, the degrees of freedom are corrected by the Greenhouse–Geisser estimates. A priori statistical power was used,
Resistance training promotes benefits in oxidative stress and lipid panel in T2D considering the statistical model used (ANOVA 4X3), and small EF (0.30), four groups and three moments (baseline, 4th-wk, 8th-wk), and α=0.05. Effect size was based in a 12-week clinical trial41, in which resistance training was the exercise model of intervention on metabolic syndrome and inflammatory markers. The statistical power conferred to the final sample size (n = 29) was 82% (G*Power® version 3.1.9.7). The level of significance utilized was p \leq 0.05.

RESULTS

Regarding their characteristics in Table 1, the groups only differed in glycated hemoglobin, which was higher for T2D subjects. Age and body composition measures presented no statistical differences between the groups. Flowchart 1 shows the sequence of events in the experimental line. Age and body composition measures presented no statistical differences between the groups.

Flowchart 1. Sequence of events in the experimental line

Table 1. Age, glycated hemoglobin and body composition of type 2 diabetic and non-diabetic individuals at baseline.

<table>
<thead>
<tr>
<th></th>
<th>T2D (n = 16)</th>
<th>ND (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EX</td>
<td>CTL</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.1 (54.9 – 69.4)</td>
<td>62.9 (58.8 – 66.9)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.9 (6.0 – 7.8)</td>
<td>6.9 (6.2 – 7.5)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.0 (64.2 – 83.7)</td>
<td>76.2 (69.2 – 83.2)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163 (157 – 169)</td>
<td>160 (154 – 167)</td>
</tr>
<tr>
<td>BMI (kg·m⁻²)</td>
<td>27.7 (25.4 – 30.1)</td>
<td>29.8 (26.8 – 32.9)</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>26.2 (23.0 – 29.5)</td>
<td>32.7 (26.5 – 39.0)</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>35.8 (31.7 – 39.9)</td>
<td>42.5 (35.8 – 49.3)</td>
</tr>
</tbody>
</table>

Notes*: HbA1c – glycated hemoglobin; BMI – body mass index. Data presented as mean (CI 95%)
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Blood glucose presented a single statistical difference, in which the T2DCTL groups presented higher values than the NDEX in the 4th week (Figure 1-A). The T2DEX reduced their TBARS levels after 8 weeks of training (Figure 1-B). No differences were identified in GPT, OGT, creatinine or urea.

HDL significantly reduced in both T2D groups in the 4th week, but at 8th week was similar to baseline values (Figure 2-A). LDL was significantly higher in the T2DEX group at baseline and significantly decreased after 8 weeks of training (Figure 2-B). Total cholesterol was higher for T2DEX at baseline, but significantly reduced in the 4th wk and remained until the 8th-wk (Figure 1-C). Both non-exercise groups had elevated total cholesterol levels after 8 weeks. No differences were identified for triglycerides levels (Figure 1-D).

**Figure 1.** Responses at baseline and after 4 and 8 weeks of resistance training in individuals with and without T2D

**Notes:** TBARS: thiobarbituric acid-reactive substances; GPT: glutamic-pyruvate transaminase; OGT: oxalacetate-glutamic transaminase; *: between-group statistical difference (p < 0.05); a: intra-group statistical difference from baseline (p < 0.05); b: intra-group statistical difference from 4th week (p < 0.05).
DISCUSSION

The main findings of the present investigation were that short-term circuit training was effective in reducing oxidative stress in T2D individuals, but not in ND. Furthermore, although no improvements in blood glucose or kidney function were observed, a reduction in total cholesterol and LDL-c levels was observed in T2D individuals. Regardless of the type of training, chronic exercise seems to reduce oxidative stress, mainly through an increase in an antioxidant capacity. Perhaps with circuit training there is no notable difference in blood glucose or kidney function markers. Additionally, the study only identified a lipid peroxidation reduction in overweight individuals with T2D, whereas ND subjects presented no change. This could be partially explained by elevated TBARS levels of T2D already at baseline, as suggested by the law of initial values. This may make the T2D group more responsive to training in a pro-antioxidant scope. Individuals with T2D have been reported to have increased oxidative stress.

Chronically, exercise would induce greater activity of the antioxidant superoxide dismutase (SOD), reducing O2- to hydrogen peroxide (H2O2), which then reacts with catalase to form carbon dioxide and water. The increase in the activity of SOD and CAT can lead to a reduction in lipid peroxidation (TBARS). Furthermore, greater activity of SOD and CAT may also indicate a greater bioavailability of NO- since it reacts with O2- when there is insufficient antioxidant activity. This mechanism may be critical for T2D.
increased as a limitation. Nevertheless, pre
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There is a lack of consensus related to exercise mode, intensity and volume to induce optimal benefits in metabolic parameters\(^{37-40}\). Oliveira et al.\(^{40}\) submitted individuals with T2D to 12 weeks of either aerobic, RT or combined (aerobic+RT) and reported metabolic changes only in the RT group, which was also the group that did not present any changes in oxidative stress parameters. Improvements in oxidative stress levels in response to exercise training are mainly due to non-exhaustive sessions lead to an increase in pro-oxidant substances, which in turn lead to an antioxidant adaptive response\(^{14}\). However, exhaustive and very-low intensity exercise may not lead to an antioxidant response capable of reflecting metabolic and clinical measures. Since all participants had no previous experience with RT, we believe that the fear of getting hurt may preclude some individuals from performing at their maximum ability in assessment tests, as well as during training.

Individuals from each group (T2D and ND) were randomized into an exercise or control group, independent of their baseline characteristics. Although the difference between the groups was not statistically significant, one may argue that the difference between the populations could be suggested as a limitation. Nevertheless, pre-post comparisons are the main focus of the data interpretation. Furthermore, we did not measure any antioxidant parameter, which could also be pointed as a limitation since it does not allow us to mechanistically discuss oxidative stress without being too speculative. Nevertheless, a meta-analysis of the effects of exercise on oxidative stress (pro- and antioxidants) previously reported after an exercise intervention, an antioxidant increase is much more sensible than a pro-oxidant activity/damage\(^{14}\). Therefore, the non-change in TBARS levels for the ND exercise group after intervention should be interpreted with some caution.

**CONCLUSION**

In conclusion, short-term circuit training is effective in promoting benefits in oxidative stress parameters and lipid profiles in overweight individuals with T2D. For ND overweight subjects, this protocol should be tested with increased intervention time and antioxidant parameters could be measured in order to identify more sensitive changes in oxidative stress.

Acknowledgment: The authors would like to thank the Universidade Estadual de Goiás - UEG, for providing resources for the development of this research, as well as for covering publication fees (Recursos Pró-Programas UEG/2022). Moreover, the authors would like to thank CAPES for providing master’s level scholarships to students.

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**Financial Support:** The present study did not receive funding.

**Conflict of interest:** The present study does not present conflicts of interest.

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