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Physical Activity Alters Superoxide Dismutase Activity and Intercellular Adhesion Molecule 1 Levels in Diabetes Mellitus Type 2 Patients

Anderson Martins Tavares[1#], Leonardo Matta[2#], Jaslana Hainfellner da Silva[3], Christiane de Oliveira Bensusan[1], Carla do Nascimento[2], Giselle Fernandes Taboada[4], Rodrigo Soares Fortunato[2], Luciene de Carvalho Cardoso-Weide[5,6*]

[1]Postgraduate Program in Medical Sciences, School of Medicine, UFF-Universidade Federal Fluminense, Rio de Janeiro, Brazil
[2]Carlos Chagas Filho Institute of Biophysics, UFRJ-Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
[3]School of Biology, University Salgado de Oliveira, Rio de Janeiro, Brazil
[4]Endocrinology Unit, Department of Internal Medicine, School of Medicine, UFF-Universidade Federal Fluminense, Rio de Janeiro, Brazil
[5]Medical School, Department of Pathology, UFF-Universidade Federal Fluminense, Rio de Janeiro, Brazil
[6]Luciene de Carvalho Cardoso Weide, Medical School, Department of Pathology, UFF-Universidade Federal Fluminense, Rio de Janeiro, Brazil
Email: anderson.mtavares@gmail.com, rsfortunato@yahoo.com.br, leonardo.matta@hotmail.com, carla.nascimento66@gmail.com, lana.hain@hotmail.com, giselleftaboada@gmail.com, *lucienecardoso@id.uff.br, *lucienecardoso@gmail.com

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Abstract

Background: Oxidative stress and inflammation are related to the pathophysiology of diabetes mellitus (DM), being involved in the development of micro-and macrovascular complications. Physical activity is beneficial for DM patients, but little is known about the relationship between redox and inflammation biomarkers and the level of physical activity in these patients. Based on this, this research aims to evaluate the effects of physical activity level on redox stress parameters and inflammatory markers in T2DM patients. **Methods:** Eighty-four patients with T2DM were divided according to their physical activity level: group A (n = 48), sedentary; group B (n = 11) active (3 times a week, 150 min) and group C (n = 25), highly active (5 times a week, 150 - 300 mins, at least). Anthropometric and biochemical parameters, superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities, as well as GSH, sRAGE and ICAM-1 levels were assessed. **Results:** Glycated haemoglobin, total cholesterol, and LDL-cholesterol levels were lower in the highly active group in comparison to other groups. Plasma SOD activity was higher in

*Corresponding author.
#These authors contributed equally.

group C compared to Group A, while ICAM-1 levels were significantly higher in group B when compared to other groups. **Conclusion:** Our results suggest that the practice of physical activity is beneficial to T2DM patients, especially at high volume and frequency.

Keywords

Cardiovascular Risk, Exercise, Health, Inflammation, Oxidative Stress

1. Introduction

Diabetes mellitus (DM) is considered a public health issue with increasing incidence and prevalence worldwide. DM is a group of metabolic diseases characterised by chronic hyperglycemia, and has two major forms: type 1 DM (T1DM) and type 2 DM (T2DM). TDM1, which corresponds to 5% - 10% of the cases, is a result of β-pancreatic cell destruction with a consequent deficiency in the synthesis and secretion of insulin [1]. T2DM is the most common form of DM, being related to defects in the action of insulin in its target tissues [2]. In both types of DM, hyperglycemia can affect the structure of small nerves and large vessels, resulting in the development of diabetic micro- and macrovascular complications, respectively. Indeed, the toxic effects of hyperglycemia are highly associated with the development of retinopathy, nephropathy, neuropathy, and cardiovascular disease [3].

Oxidative stress and inflammation are involved in the development of micro and macrovascular complications of DM due to an increased reactive oxygen species (ROS) availability and increased formation of advanced glycation end products (AGEs) [4]. AGEs are formed by the nonenzymatic glycation of plasma proteins or lipids, and glucose autoxidation. Moreover, AGEs can affect cellular function, acting through its plasma membrane-localized receptor (RAGE—Receptor for advanced glycation end products). AGE-bound RAGE mediates nuclear factor-κB (NF-κB) pathway activation that promotes the expression of proinflammatory cytokines and ROS production, leading to inflammation and endothelial dysfunction, related to increase of Intercellular Adhesion Molecule 1 (ICAM-1) [5] [6] [7] [8].

Physical activity is defined as any bodily movement produced by skeletal muscle that results in energy expenditure. It is well known that physical activity is beneficial to DM patients due to its effects on the maintenance of blood glucose levels and prevention of several complications of DM [9]. The practice of moderate intensity physical activity for at least 150 min/week improves insulin sensitivity and ameliorates the lipid profile, decreasing the risk of developing T2DM [10] [11]. According to the United States Department of Health and Human Services, individuals can be classified as sedentary, low, or highly physically active. The physical activity levels can be estimated using physical activity behaviour questionnaires, being possible to access the volume of

physical activity per week. Thus, individuals that have less than 150 minutes of physical activity per week are considered sedentary, while those who perform between 150 - 300 minutes per week are considered active. Finally, individuals that practice physical activity more than 300 minutes per week are classified as highly active [12].

Thus, the purpose of the present study was to evaluate the influence of physical activity on oxidative stress and inflammation biomarkers in the serum of T2DM subjects.

2. Methods

2.1. Patients

Eighty-four T2DM patients (25 men and 64 women) were enrolled in this study. Exclusion criteria were smoking, alcohol abuse, chronic viral diseases (hepatitis B and C or HIV), severe infectious disease in the last 6 months, glomerular filtration rate below 60 mL/min (calculated by the CKD-EPI formula) [13]. Patient's medical records were reviewed to obtain additional data for the study, such as the presence of microvascular complications and comorbidities such as systemic arterial hypertension and dyslipidemia, history of macrovascular disease and/or events (cardio or cerebrovascular events and/or non-traumatic limb amputation; previous diagnosis of coronary, carotid or peripheral arterial disease through a relevant complementary method), current medications used as well as anthropometric data. The study was approved by the Ethics Committee of the Hospital Universitário Antônio Pedro of Universidade Federal Fluminense, Niterói, Rio de Janeiro, Brasil (CEP-CMM/HUAP 252/11) and all participants gave written informed consent.

2.2. Physical Activity Levels

DM patients were asked about their routine of physical activity practices at the time of the medical consultation. Participants who were unable to respond were excluded from the study. This approach was validated by Kurtze *et al.* (2007), presenting acceptable repeatability and being a valid measure for physical activity [12]. After that, the participants were divided into three groups according to their physical activity level: Group A (n = 48) composed by sedentary patients; group B (n = 11) composed by active patients (150 min, 3 times a week), and group C (n = 25) composed by highly active patients (150 - 300 min at least, 5 times a week).

2.3. Collection and Storage of Samples

Blood samples were collected from fasting patients into tubes with or without anticoagulant (EDTA), to obtain serum or plasma, respectively. The tubes were centrifuged at 3.000×g for 15 minutes to obtain serum, and 1.000×g for 20 minutes to obtain plasma. After processing, serum and plasma were aliquoted in cryotubes and stored at −80˚C until further utilization.

2.4. sRAGE Serum Levels

Serum levels of RAGE (sRAGE) (pg/mL) were measured using Enzyme Linked Immuno Sorbent Assay (ELISA) commercial kit (BioVendor, Brno, CZE), following the manufacturer's instructions. The detection limit of the assay was 19.2 pg/mL. Intra and inter-assay coefficients of variation were 4% and 7.2%, respectively.

2.5. Plasma SOD and GPX Activities

Plasma SOD and GPx activities were measured using commercial kits (Cayman Chemical, Michigan, USA), following the manufacturer's instructions. SOD reduces tetrazolium salt, leading to the formation of red formazan, which was read at 440 nm in a spectrophotometer (SpectraMax M3 Multi-Mode Microplate Reader (Molecular Devices, California, USA). GPx activity was indirectly measured by the coupled reaction with glutathione reductase (GR), which oxidizes NADPH. NADPH oxidation was measured at 340 nm in a spectrophotometer (SpectraMax M3 Multi-Mode Microplate Reader (Molecular Devices, California, USA).

The detection limit of the SOD activity assay was 0.025 - 0.25 units (U)/mL SOD. Intra and inter-assay coefficients of variation were 3.2% and 3.7%, respectively. The detection limit of the GPx activity assay was 50 - 344 nmol/min/mL. Intra and inter-assay coefficients of variation were 5.7% and 7.2%, respectively. For both assays, samples were analysed at least in duplicate.

2.6. Total Reduced Thiol Levels

Total reduced thiol groups were determined in a spectrophotometer (Hitachi U-3300) using 5,5-dithionitrobenzoic acid (DTNB). Thiols react with DTNB, cleaving the disulfide bond to give 2-nitro-5-thiobenzoate (NTB^{-}), which ionizes to the NTB^{2-} di-anion in water at neutral and alkaline pH. The NTB^{2-} was quantified in a spectrophotometer at 412 nm [14].

2.7. Plasma ICAM-1 Levels

Plasma ICAM-1 levels (ng/mL) were assessed using ELISA commercial kit (Sigma-Aldrich, Missouri, USA), following the manufacturer's instructions. The detection limit of the ICAM-1 assay was 150 pg/mL. Intra and inter-assay coefficients of variation were <12% and <10%, respectively.

2.8. Statistical Analysis

Data were analysed through the statistical software SPSS 23.0 for Windows. Numerical variables were expressed as median (p25-p75). Kolmogorov-Smirnov test was performed to evaluate for normality of numerical variables. One-Way ANOVA or Kruskal-Wallis tests were used to compare numeric variables between multiple groups. Student's t-test and Mann-Whitney test were used to compare numeric variables between the two groups. Correlations between numerical variables were evaluated using the Pearson or Spearman correlation co-

efficient. p values < 0.05 were considered statistically significant.

3. Results

3.1. Clinical and Laboratory Characteristics

Demographic, anthropometric, and laboratory characteristics of the groups are shown in Table 1 and Table 2. No differences were found among the groups in relation to age, DM duration, body mass index, waist-to-hip ratio, blood pressure, triglycerides (TG), HDL-c, and creatinine clearance (Table 1 and Table 2). HbA1c, total cholesterol (TC), and LDL-c were lower in group C when compared to groups A and B ($p < 0.01$; 0.031 and 0.04, respectively) (Table 1).

3.2. sRAGE, Oxidative Stress and Inflammatory Profile

No differences between groups were found in relation to sRAGE levels (Table 3). Plasma SOD activity was higher in group C when compared to group A. No significant differences were found among the groups for plasma GPx activity and total thiol levels. ICAM-1 levels were significantly higher in group B, compared to groups A and C (Table 3).

4. Discussion

In the present study, diabetic subjects were categorized according to their level of physical activity. No differences between groups were found in relation to age, fasting glucose levels, and DM duration that excludes the influence of these variables in our results. Glycemic control is important to avoid DM complications,

Table 1. Demographic and anthropometric characteristics.

	Group A Median (p25 - p75) n = 48	Group B Median (p25 - p75) n = 11	Group C Median (p25 - p75) n = 25
Gender (M/F)	9/39	3/8	13/12
Age (years)	59 (53 - 66)	59 (54.5 - 61)	57 (51 - 64)
DM duration (months)	132 (54 - 222)	132 (90 - 156)	120 (57 - 177)
Body mass index (Kg/m^2)	30.3 (27.6 - 34.5)	31.2 (29.7 - 32.7)	28.7 (26.6 - 30.8)
Waist hip ratio	0.9 (0.9 - 1.0)	0.9 (0.8– 1.0)	0.9 (0.9 - 1.0)
Systolic blood pressure (mmHg)	131 (116.5 - 143)	135 (124.5 - 140)	120 (110 - 140.7)
Diastolic blood pressure (mmHg)	72 (65 - 84)	75 (70 - 81.5)	69.5 (62 - 73.7)

Physical activity levels: Group A: sedentary; Group B: up to 150 min/week; Group C: more than 150 min/week. Results are represented as median (p25-p75). M: male; F: female; DM: diabetes mellitus.

Table 2. Laboratory parameters.

	Group A Median (p25 - p75) n = 48	Group B Median (p25 - p75) n = 11	Group C Median (p25 - p75) n = 25	P
HbA1c (%)	8.6 (7.2 - 10.7)	9.3 (8.9 - 11.5)	6.8[a,b] (6.5 - 7.8)	a < 0.003 b < 0.001
Total Cholesterol (mg/dL)	180 (144.7 - 206.5)	183 (155 - 224)	150[c,d] (135 - 170)	c < 0.01 d < 0.05
Triglycerides (mg/dL)	100 (70 - 158)	142 (66 - 151.5)	111 (71 - 127)	Ns
HDL-c (mg/dL)	45 (37.7 - 54.2)	53 (42 - 60.5)	42 (38 - 53)	Ns
LDL-c (mg/dL)	110 (80 - 128.5)	104 (79.5 - 156.5)	83.5[c] (77.7 - 100.2)	<0.01
Creatinine clearance (mg/dL)	0.8 (0.7 - 0.9)	0.8 (0.6 - 0.8)	0.8 (0.7 - 1.0)	Ns

Physical activity levels: Group A: sedentary; Group B: up to 150 min/week; Group C: more than 150 min/week. Results are represented as median (p25 - p75). [a]<0.003 versus group A; [b]<0.001 versus group B; [c]<0.01 versus group A; [d]<0.05 versus group B. ns: not significant; HbA1c: glycated hemoglobin; HDL-c: high density lipoprotein; LDL-c: low density lipoprotein.

Table 3. sRAGE, Oxidative stress evaluation and inflammatory profile.

	Group A Median (p25 - p75) n = 48	Group B Median (p25 - p75) n = 11	Group C Median (p25 - p75) n = 25	p
sRAGE (pg/mL)	300 (263 - 501)	306 (284 - 373)	297 (288 - 386)	Ns
SOD (U/mL)	2.1 (1.9 - 3.0)	2.6 (2.10 - 3.8)	3.1[a] (2.3 - 3.7)	[a]p < 0.01
GPx (nmol/min/mL)	73.8 (65.4 - 86.7)	75.9 (64.6 - 81.6)	74.6 (62.1 - 92.7)	Ns
ICAM-1 (ng/mL)	201.0 (167.8 - 226.0)	223.5[b] (198.5 - 255.4)	196.1[c] (162.3 - 221.1)	[b]p < 0.04 [c]p < 0.02
Total Thiol (mmol/mL)	1.11 (0.93 - 1.38)	1.39 (1.17 - 1.71)	1.16 (1.02 - 1.31)	Ns

Physical activity levels: Group A: sedentary; Group B: up to 150 min/week; Group C: more than 150 min/week. Results are represented as median (p25-p75). [a]<0.01 versus group A; [b]<0.04 versus group A; [c]<0.02 versus group B. ns: not significant. sRAGE: soluble receptor for advanced glycation end products, SOD: superoxide dismutase; GPx: glutathione peroxidase; ICAM-1: intercellular adhesion molecule 1.

and HbA1c levels higher than 7% are often associated with the development of micro and macrovascular complications [15]. In the present study, HbA1c levels in the highly physical active group were 6.8 %, being significantly lower than the

other groups. Similar results have already been described in a meta-analysis, in which the practice of aerobic exercise in combination with resistance training was able to reduce HbA1c levels in T2DM patients when compared to their sedentary counterparts [16]. Moreover, Pai *et al.* (2016) also showed that a higher frequency of regular physical activitiy was related to a reduction of HbA1c levels in T2DM patients [17]. Thus, our data reinforce the idea that an increased level of physical activity is related to lower HbA1c levels in T2DM patients. Moreover, TG levels were lower in the group of highly active T2DM subjects when compared to other groups. Besides, LDL-c levels were also lower in this group in relation to the sedentary group. Our results are in line with the literature, in which higher levels of physical activity are related to beneficial effects on the lipid profile of T2DM subjects [18].

In hyperglycemic conditions, there is an increase in ROS and AGEs production, which is involved in the development of DM micro-and macrovascular complications, such as CVD [19]. On the other hand, antioxidant defence overcomes the free radicals accumulation to avoid oxidative stress [20] [21]. High levels of physical activity are related to higher antioxidant capacity in several tissues [22]. In our study, plasma SOD activity was higher in group C compared to group A, but it was not different from group B. It is well established that physical activity levels are related with increases in SOD gene and protein levels, as well with its activity, thus decreasing ROS availability [23] [24]. Moreover, antioxidant enzymes can be selectively activated by physical demand according to the intensity and duration of the physical activity, depending on the amount of ROS produced by tissues and the antioxidant defence capacity of the tissue [23] [24].

ICAM-1, which is induced by NF-κB activation, has a significant role in the pathogenesis of DM vascular complications, due to its stimulatory effects on the migration and adhesion of monocytes to the endothelium [25] [26]. We found higher levels of serum ICAM-1 in T2DM subjects who performed low levels of physical activity when compared to sedentary and highly active T2DM individuals. ICAM-1 is a well-characterized biomarker of vascular inflammation [8]. Physical activity has beneficial effects linked to the prevention of systemic low-grade inflammation [27], and its practice is strongly recommended as a tool to prevent inflammation and CVD [28]. The maximal oxygen capacity seems to be inversely correlated with sICAM-1 in patients with chronic heart failure, suggesting that improved physical fitness may positively influence endothelial health [29]. Moreover, it was demonstrated that serum ICAM-1 levels were higher in healthy sedentary subjects in comparison to their counterparts with optimal physical activity [30]. Thus, more studies are necessary to explain the mechanisms related to the increase of ICAM-1 in T2DM patients that are minimally active.

The interaction of AGEs with RAGE triggers the inflammatory response and ROS generation, which are implicated in the development and progression of DM [31]. However, sRAGE may be protective against T2DM-associated inflammation. High levels of circulating sRAGE can avoid AGE-RAGE interaction,

attenuating this response. sRAGE is reduced in individuals with impaired glucose tolerance and T2DM. On the other hand, physical exercise is able to increase circulating levels of sRAGE and reduce cardiometabolic risk factors in T2DM patients [32]. However, BMI and body fat percentage seem to be highly correlated with sRAGE [31]. In obese individuals, sRAGE is 35% lower when compared to lean subjects. In our study, sRAGE levels of T2DM patients were not affected by their physical activity level. It is important to note that BMI was not different among groups, suggesting that changes in body composition are required for the beneficial effect of physical activity on sRAGE levels, at least in individuals with T2DM.

We showed that physical activity could improve the quality of life of individuals with T2D significantly. The effect of physical activity on social relations needs more time. We suggest evaluating the effect of physical activity on social relations with a longer time follow-up in future studies. In conclusion, the volume and frequency of physical activity play an important role in the control of metabolic parameters, as well as redox and inflammatory biomarkers in T2DM patients. Low levels of physical activity were not efficient to decrease oxidative stress response and proinflammatory markers. Moreover, our data suggest that changes in body composition are important to observe the beneficial effects of physical activity on sRAGE levels in T2DM individuals.

Author Contributions

A.M.T., J.H.S and C.O.B wrote the manuscript and researched data.

L.M.P and C.N contributed to the discussion, R.S.F contributed to the discussion and reviewed the manuscript.

G.F.T. and L.C.C.W. researched the data and reviewed/edited the manuscript.

A.M.T is the guarantor of this work and, as such, has full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

Diabetes mellitus (DM);
Diabetes mellitus type 2 (T2DM);
Superoxide dismutase (SOD);
Glutathione Peroxidase (GPx);
Glutathione (GSH);
Soluble receptor of advanced glycation end product (sRAGE);
Intercellular adhesion molecule 1 (ICAM-1).