Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Heart rate variability and plasma biomarkers in patients with type 1 diabetes mellitus: Effect of a bout of aerobic exercise

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ARTICLE INFO

Article history:
Received 27 July 2015
Received in revised form
24 September 2015
Accepted 20 October 2015
Available online 26 November 2015

Keywords:
Type 1 diabetes mellitus
Blood glucose
NO_x^-
Thiobarbituric acid reactive substances (TBARS)
Acute aerobic exercise
Heart rate variability

ABSTRACT

Objective: The aim of this study was to evaluate: (1) the cardiovascular parameters and plasma biomarkers in people with type 1 diabetes mellitus (T1DM) at baseline; and (2) the heart rate variability (HRV) and blood glucose in response to a session of aerobic exercise (AE) and during recovery period.

Research design and methods: Adults (18–35 years) were divided into two groups: control (CT, $n = 10$) and T1DM ($n = 9$). Anthropometric, cardiovascular, and biochemical parameters, and aerobic capacity (indirect peak oxygen uptake, VO_{2peak}) were evaluated at baseline. Thirty minutes of AE (40–60% intensity) was performed on a treadmill. Blood glucose and HRV were determined at rest, during AE, and during the recovery period.

Results: Anthropometric measurements, cardiovascular parameters, aerobic capacity, and biochemical parameters were similar between the groups at baseline. In the T1DM group, blood glucose, glycated hemoglobin, and thiobarbituric acid reactive substances concentrations were increased while nitrite/nitrate (NO_x^-) levels were reduced. During AE, the magnitude of the reduction of blood glucose was greater than that during the recovery period in the T1DM group. The RR intervals and SDNN were reduced at rest as well as in the recovery period in T1DM subjects, whereas the RMSSD and pNN50 were only reduced during the recovery period. No changes were observed in low frequency (LF), high frequency (HF), and LF/HF ratio.

Conclusion: Our study shows that T1DM patients on insulin therapy have poor blood glucose control with greater lipid peroxidation and lower NO_x^- levels, accompanied by an imbalance in autonomic function detected by the challenge of AE.

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http://dx.doi.org/10.1016/j.diabres.2015.10.025
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1. Introduction

Diabetes mellitus (DM) is a chronic disease clinically characterized by hyperglycemia which, in turn, can activate several signaling pathways such as protein kinase C, advanced glycation end-products (AGEs) and polyol leading to significant reactive species oxygen (ROS) production [1–4]. Furthermore, a number of studies have systematically shown that ROS overproduction and a decrease in nitric oxide (NO) bioavailability are the primary causes of most complications in patients with type 1 (T1DM) and type 2 DM (T2DM) [5]. Cardiovascular autonomic neuropathy (CAN) is considered a common complication in people with diabetes, causing abnormalities in heart rate control and vascular dysfunction and is considered the most important cause of mortality in T1DM [6,7]. However, the diagnosis of CAN is only detected when complications are already established and the burden and outcomes are, in general, irreversible. Thus, it is critical to identify any signs of CAN in the early stage of T1DM in an attempt to prevent its complications.

Heart rate variability (HRV) analysis has been largely used as an indirect indicator of autonomic nervous system function [8,9]. Increased sympathetic and/or decreased parasympathetic activities have been associated with high risk of sudden death. Indeed, several studies have shown that patients with T1DM and T2DM showed autonomic dysfunction [10–12]. Interestingly, most studies have focused on patients with T2DM and only a few studies have investigated T1DM and autonomic dysfunction.

In T1DM, hyperglycemia occurs as a consequence of impaired insulin production caused by pancreatic β-cell destruction; this occurs as a consequence of a complex process where genetic and environmental factors lead to an autoimmune response. At present, T1DM is not preventable and daily insulin administration is required as treatment; however, poor blood glucose control remains a challenge [13]. Thus, proper care and preventive actions to avoid CAN complications in these patients should be the highest priority in the healthcare system.

A healthy lifestyle is fundamental to the management of DM and the inclusion of aerobic exercise is advised to prevent the deleterious effects of the disease. Several studies have shown that regular physical exercise, of mild to moderate intensity, has cardiovascular benefits, and physically active patients have increased longevity associated with reduction in morbidity and mortality [14]. Therefore, this study had two objectives: (1) to examine cardiovascular parameters, redox state (concentration of thiobarbituric acid reactive substances (TBARS) and superoxide dismutase (SOD) activity), and concentrations of N^{ε}-(carboxymethyl) lysine (CML) and nitrite/nitrate (NO_x^-) that reflect AGEs and nitric oxide formation, respectively, in patients with T1DM at baseline; and (2) to evaluate the HRV and concentrations of blood glucose and lactate in response to a challenge of aerobic exercise session as well as during the recovery period. The objective of this study was to detect early autonomic dysfunction in patients with diabetes without cardiovascular diseases that could be associated with plasma biomarkers, with a view to preventing complications of T1DM and encourage patients to improve metabolic control of blood glucose, as well as providing a feasible test for the physician to detect early autonomic dysfunction in this population.

2. Methodology

2.1. Study participants

The study was approved by the Ethical Committee of Institute of Bioscience at the Sao Paulo State University (protocol: 5128). All the volunteers were recruited through advertisements in Rio Claro-SP, BRA. Data collection was carried out from May 2012 to November 2013. A total of 19 male volunteers were eligible to participate in the present study. They were divided into two groups: control (CT, $n = 10$) and people with T1DM ($n = 9$). T1DM was determined according to previous medical diagnosis and in agreement with the International Diabetes Federation [15]. The inclusion criteria of this study were: males with T1DM (diagnosis of disease <15 years); age 18–35 years; body mass index <30 kg/m^2; sedentary (<150 min of moderate physical activity per week or <60 min of vigorous physical activity per week); and serum creatinine <2.0 mg/dl. The exclusion criteria were: insulin resistance; arterial hypertension; congenital heart disease; use of β-adrenergic blocking agents and digoxin; renal dysfunction; respiratory, thyroid, and hematologic diseases; orthopedic disorders; smoking; alcohol abuse; and other conditions that preclude the practice of physical exercise. The inclusion criteria for the control group was similar, but without T1DM.

2.2. Study protocol

First appointment: The volunteers were informed about the procedures and risks of the study and signed a consent form in accordance with Ethical Committee of UNESP. The medical records, medication inventory, anthropometric parameters, resting heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and glycemia were measured. Volunteers were familiarized with the treadmill (Movement RT 250 PRO) while HR, blood glucose, and β-ketones were monitored.

Second appointment: Volunteers were familiarized with the treadmill while HR, blood glucose, and β-ketones were monitored.

Third appointment: To indirectly determine the peak oxygen uptake (VO_{2peak}) the volunteers performed a 1 mile walk test as previously described [16] while HR, blood glucose, and β-ketone were monitored.

Fourth appointment: Baseline blood collection for biochemical analysis.

Fifth appointment: Acute aerobic exercise performance.

The experimental design of this cross-sectional study is illustrated in Fig. 1A.

2.3. Acute exercise session

All volunteers performed an exercise session in the afternoon, after 4:00 p.m. to avoid the interference of insulin administration (eight volunteers used insulin glargine and one volunteer

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