Effect of exercise on glucose variability in healthy subjects: randomized crossover trial

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ABSTRACT: The aim of this study was to evaluate the acute effect of aerobic (AER) and eccentric (ECC) exercise on glucose variability, correlating it with circulating markers of inflammation and oxidative stress in healthy subjects. Sixteen healthy subjects (32 ± 12 years old) wore a continuous glucose monitoring system for three days. Participants randomly performed single AER and ECC exercise sessions. Glucose variability was evaluated by glucose variance (VAR), glucose coefficient of variation (CV%) and glucose standard deviation (SD). Blood samples were collected to evaluate inflammatory and oxidative stress markers. When compared with the pre-exercise period of 0-6 h, all the indices of glucose variability presented comparable reductions 12-18 h after both exercises (∆VAR = 151.5, ∆CV% = 0.55 and ∆SD = 3.1 and ECC: ∆VAR = 221.2, ∆CV% = 3.7 and ∆SD = 6.5). Increased interleukin-6 (IL-6) levels after AER (68.5%) and ECC (30.8%) (P<0.001) were observed, with no differences between sessions (P = 0.459). Uric acid levels were increased after exercise sessions (3% in AER and 4% in ECC, P = 0.001). In conclusion, both AER and ECC exercise sessions reduced glucose variability in healthy individuals. Inflammatory cytokines, such as IL-6, and stress oxidative markers might play a role in underlying mechanisms modulating the glucose variability responses to exercise (clinicalTrials.gov NCT02262208).

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INTRODUCTION

The treatment of hyperglycaemia in diabetes mellitus aiming at glycated haemoglobin (HbA1c) lower than 7% is recommended, reducing rates of acute and chronic complications of the disease [1]. While hyperglycaemia indicates sustained high levels of glucose, it is relevant to discuss glucose fluctuations, which may also be related to the pathogenesis of diabetic complications [2]. In addition, several consequences of excess glucose variability support this relationship ultimately due to excessive oxidative stress. Indeed, compared with the constant high glucose, the 24-h urinary excretion rates of free 8-iso prostaglandin F2a (8-iso PGF2), a stress oxidative marker, are increased when glucose oscillation is high, [3]. Furthermore, urinary excretion rates of 8-iso PGF2 are not correlated with insulin levels, HbA1c and plasma glucose, but are positively correlated with one of the glucose variability indices, MAGE [4]. However, not all studies have shown a relationship between glucose variability and 8-iso PGF2 [5-6]. Glucose variability, moreover, is a complex phenomenon that includes intraday and interday variability and also a combination of minor and major glucose fluctuations.

Although primarily studied in patients with diabetes, glucose variability has been explored in other settings, such as obesity, metabolic syndrome [7], cystic fibrosis [8] and also in healthy subjects [9]. Individuals with diabetes present higher indices of glucose variability when compared to controls without the disease, whereas in the population without diabetes age-related increases in glucose variability have been shown [10]. Therefore, the development of diabetes may be affected by a progressive loss of complexity in glucose variability.

Key words: Glucose variability Oxidative stress Inflammation Acute exercise aerobic Acute exercise eccentric
profile, probably reflecting insulin resistance and a progressive failing of glucoregulation. Importantly, the loss of complexity may anticipate the hyperglycaemic states [7]. Insulin resistance and inflammation were suggested to be involved in the generation of these fluctuations, reflecting a possible relationship between specific physiological mechanisms and mathematical characteristics of glucose variation [11].

On the other hand, exercise is an efficacious non-pharmacological intervention for type 2 diabetes [12]. Even in non-diabetic subjects, physical activity interventions are associated with reduced HbA1c [13]. We have recently shown that acute bouts of aerobic or combined (aerobic and resistance) exercise can reduce glucose variability in patients with type 2 diabetes [14-15]. However, possible mechanisms involved in glucose variability changes induced by different types of exercises are still unknown.

In healthy subjects, increased glucose variability is observed during inactivity after a meal [16], reinforcing the role of exercise in changing glucose patterns irrespective of the absence of hyperglycaemia. Also, circulating markers of oxidative stress and inflammation, which can be influenced by different exercise protocols in healthy subjects [17], have been previously related to changes in glucose variability in type 2 diabetes [18,19]. We therefore hypothesized that different types of exercise modalities could have a distinct impact on glucose variability, and that changes in oxidative stress and inflammation could be involved in these responses.

In this way, we aimed to assess glucose variability in healthy subjects through glucose variance (VAR), the glucose coefficient of variation (CV%) and glucose standard deviation (SD), and correlated them with circulating markers of oxidative stress and inflammation at rest and after aerobic (AER) and eccentric (ECC) exercise sessions.

MATERIALS AND METHODS

Research Design and Participants

Sixteen healthy subjects participated in the experiments in a randomized crossover trial design. Exclusion criteria were regular practice of exercise (more than three exercise sessions per week), or having any chronic disease, mainly diabetes mellitus, hypertension, heart failure and cancer. At the entry of the study, clinical characteristics, self-reported usual physical activity (International Physical Activity Questionnaire – IPAQ; long-form) [20], anthropometric evaluation, and a 12-h fasting blood sample (glucose, HbA1c) were obtained for each subject. One week prior to the first experimental exercise session, subjects underwent maximal cardiopulmonary exercise testing and maximal strength testing.

Ethics

The protocol was approved by the Institutional Review Board at Hospital de Clínicas de Porto Alegre (Number: 120148) and all patients provided their written informed consent before participation.

Maximal Cardiopulmonary Exercise Testing

The maximal incremental exercise test was performed on an electrically braked cycle ergometer (ER-900, Jaeger, Würzburg, Germany) with increments of 20 W/minute, as previously described [21]. During the test, gas exchange variables were measured by a previously validated system (Oxycon Delta, VIASYS, Healthcare GmbH, Jaeger, Germany). Heart rate was continuously monitored by a 12-lead electrocardiogram (Nihon Kohden Corporation, Japan) and blood pressure was measured with an automatic oscillometric device every 2 min.

Strength Testing

Strength was measured by one-repetition maximum test (1-RM), which was preceded by exercises at mild intensity for movement familiarization and warm-up. Proper technique was demonstrated and practised for the leg press exercise (Sculptor, Porto Alegre, Brazil), When new attempts were needed, a 5-min resting period was allowed between successive attempts [22].

Randomization

Subjects were randomly assigned to two experimental sessions according to a computer-generated sequence, which was handled by a researcher who was not involved in interventions. Such a process occurred once before subjects were recruited to the study, indicating the order of both 40-min sessions of AER (n = 16) and ECC (n = 16) exercise sessions, which were performed at least seven days apart.

Exercise Protocols

Two exercise sessions, consisting of either AER or ECC protocols, were executed by all participants. Exercise intensity was recorded for each individual by a heart rate monitor (Polar F1 TM, Polar Electro Oy, Helsinki, Finland), and a Borg 0-10 scale was used to register individuals’ perceived exertion every five minutes throughout the experimental sessions. In the AER session, subjects exercised on a cycle ergometer (Embreek 360, Brusque, Brazil). Each session included a 5-min warm-up at 20 W, followed by 40 min at 70% of the VO2peak (peak oxygen uptake per kilogram, ml·kg⁻¹·min⁻¹), as determined in the incremental exercise test, and 5 min of stretching exercise as cool down. In the ECC session, subjects initially performed a specific warm-up of 15 repetitions on the leg press. Thereafter, the main part of this session was conducted during 40 min, in which subjects completed six eccentric sets of 10 repetitions at 120% of 1-RM for each leg (the exercise was one-sided), with a completely unloaded concentric phase (lasting approximately two seconds), and 2-second eccentric phase. Resting between sets and exercises lasted 2 min.

Continuous Glucose Monitoring System (CGMS) Measurements

Subjects were admitted to the laboratory in the morning at approximately 9:00 a.m., 24 h before the exercise session, when a glucose sensor (Sof-Sensor, Guardian REAL-Time System/Medtronic,
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Northridge, USA) was inserted subcutaneously. This procedure is fully described elsewhere [15]. For each experimental session, glucose profiles were collected sequentially during three days: (i) previous to the allocated exercise session, (ii) on the exercise day, and (iii) the day following the exercise bout. Each sensor was not used longer than 72 h and subjects were oriented to avoid exercise workouts except for the protocol.

**Glucose Variability Evaluation**: Glucose variability was assessed from series of absolute values of glucose, obtained by CGMS, sampled every 5 minutes. The first set period for analysis was obtained 6 h before each exercise onset and was compared with a set periods in a 6-hour timeframe obtained until 18 h after each of the allocated exercise sessions. Glucose variability was evaluated using conventional analysis, constructed from the statistical properties of the series, obtaining the indices VAR, CV%, and SD in each period [23-24].

**Blood Collection**: Venous blood was drawn 10 min before and immediately after each exercise bout. Approximately 9 mL of blood was collected from an antecubital vein using a disposable needle and vacutainer containing sodium heparin or ethylene diamine tetraacetic acid (EDTA). The blood was centrifuged for 10 min at 1000g to separate plasma and evaluate total protein sulfhydryl and protein carbonyl; for interleukin-6 it was centrifuged for 15 min at 1500g and then stored at -80°C for further analysis.

**Total Protein Sulfhydryl**: Briefly, 45 µL of plasma was mixed with 120 µL of PBS and 35 µL of 30 mM Tris/3 mM EDTA (pH 8) in a microplate well. After reading baseline absorbances (412 nm), samples were reacted with 10 µL of 5,5'-dithiobis-(2-nitrobenzoic acid) (10 mM in ethanol) for one hour. Samples were read again (412 nm) and baseline absorbances were discounted. The obtained values were compared with those obtained with a cysteine standard curve and results were expressed as nmol –SH/mg protein [25].

**Protein carbonyl**: Briefly, protein content in samples was determined with the Bradford method, using a commercial kit (Bio-Rad, cod. 500-0001). A sample containing 1 mg of protein was reacted with 10 mM 2,4-dinitrophenylhydrazine for 30 min and subjected to protein precipitation with 10% TCA followed by centrifugation (11,000 xg, 3 min, 4°C) three times. After, pellets were suspended in 6 M guanidine hydrochloride (in 20 mM KH2PO4, pH 2.4) and read in a spectrophotometer (380 nm). Blank samples reacted with 2 M HCl instead of 10 mM 2,4-dinitrophenylhydrazine and were run in parallel. Results were expressed as nmol carbonyl/mg protein [26].

**Interleukin-6 (IL-6)**: The commercially available Human Ultrasensitive IL-6 Magnetic Bead Kit was used according to the manufacturer’s instructions (Life Technologies, catalogue number: LHC0063M, Carlsbad, United States), and data were collected using the Luminex (Carlsbad, United States).

**Uric Acid**: The enzymatic colorimetric method in plasma was used in analyses (Roche/Hitachi Cobas c 311, Cobas c 501/502, Mannheim, Germany).

**FRAP (Ferric Reducing Ability of Plasma)**: The FRAP assay is able to detect non-enzymatic antioxidants present in plasma, based on the plasma mediated ferric reduction. Briefly, 7 µL of plasma was mixed with 18 µL of distilled water and reacted with 175 µL of FRAP reagent for 10 min. FRAP reagent was prepared as required by mixing 10 mL acetate buffer (300 mM, pH 3.6), 1 mL 2,4,6-Tris(2-pyridyl)-s-triazine (10 mM in 40 mM HCl), and 1 mL 20 mM FeCl3. A standard curve was built out of Fe(II) and run in parallel and absorbances were read at 593 nm. Results are expressed as mmol/L of plasma [27].

**Statistical Analysis**

Descriptive data are presented as mean and SD or SE, or median and interquartile range (P25-P75). Whenever we use delta values in results descriptions, such numbers were derived by the post values subtracted from pre values in each exercise session. Given that most variables presented skewed data distributions, responses to the interventions were compared by generalized estimating equations (GEE), and multiple comparisons were performed with the Bonferroni correction.

**TABLE 1. Baseline characteristics of the healthy volunteers studied.**

| No. of men/women | 6/9 |
|------------------|-----|
| Age (yr)         | 32 ± 12 |

**Anthropometrics**

| Body weight (kg)       | 69 ± 9 |
| Body mass index (kg/m²) | 23.8 ± 2.8 |
| Waist circumference (cm) | 85 ± 11 |

**Blood pressure (mmHg)**

| Systolic           | 113 ± 15 |
| Diastolic          | 68 ± 10  |
| Heart rate (bpm)   | 75 ± 12  |
| HbA1c (%)          | 5.0 ± 0.3 |
| Fasting blood glucose (mg/dl) | 84 ± 8 |

**Physical activity level (IPAQ), n (%)**

| Insufficiently active | 8 (53) |
| Sufficiently active   | 4 (27) |
| Very active           | 3 (20) |
| VO2 peak (ml/kg/min)  | 29.7 ± 5.6 |
| Heart rate peak (bpm) | 175 ± 13 |
| RERpeak               | 1.2 ± 0.1 |

**Maximal strength testing (1-RM), kg**

| Leg extension (right) | 60 ± 15 |
| Leg extension (left)  | 59 ± 14 |

HbA1c: glycated hemoglobin; VO2peak: peak oxygen uptake per kilogram of body weight/fat-free mass; RERpeak: peak respiratory exchange ratio. **Data are expressed as mean ± SD. Categorical variables are presented as numbers (%).**
TABLE 2. Biochemical analyses before and after aerobic (AER) or eccentric (ECC) exercise sessions.

|                          | AER exercise |          |          | ECC exercise |          |          |          |          |                          |          |          |                          |          |          |
|--------------------------|--------------|----------|----------|--------------|----------|----------|----------|----------|--------------------------|----------|----------|--------------------------|----------|----------|
|                          | Pre          | Post     | Pre      | Post         |          |          |          |          | Group                    |          |          | Time                     |          |          |
| IL-6 (pg/mL)             | 0.89 ± 0.13  | 1.50 ± 0.21 | 1.30 ± 0.37 | 1.70 ± 0.70 | 0.459     | 0.016    | 0.551    |          |                          |          |          |                          |          |          |
| Sulfhydryl (nmol/mg protein) | 7.22 ± 0.38  | 6.98 ± 0.31 | 6.91 ± 0.38 | 6.98 ± 0.30 | 0.690     | 0.749    | 0.503    |          |                          |          |          |                          |          |          |
| Carbonyl (nmol/mg protein) | 0.56 ± 0.06  | 0.46 ± 0.07 | 0.42 ± 0.57 | 0.43 ± 0.06 | 0.077     | 0.413    | 0.335    |          |                          |          |          |                          |          |          |
| Uric Acid (mg/dL)        | 4.50 ± 0.27  | 4.65 ± 0.28 | 4.13 ± 0.28 | 4.29 ± 0.30 | 0.001     | <0.001   | 0.639    |          |                          |          |          |                          |          |          |
| FRAP (mmol/L)            | 864 ± 54     | 881 ± 46  | 832 ± 36  | 818 ± 49    | 0.056     | 0.951    | 0.357    |          |                          |          |          |                          |          |          |

Note: IL-6, Interleukin-6; FRAP, Ferric Reducing Ability of Plasma. Data are reported as estimated marginal mean ± SE. Repeated measures generalized estimating equations (GEE), *P < 0.001 vs. pre-exercise values (AER and ECC).
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correction. In our exploratory analyses, we used Spearman correlation, testing the association between either inflammatory (IL-6) or oxidative (sulfhydryl; carbonyl; uric acid; FRAP) biomarkers with deltas of glucose variability indices. Statistical significance was accepted when P<0.05. Version 20.0 of SPSS software was used for statistical analysis.

RESULTS

Twenty healthy subjects were screened for participation. One subject was excluded because pre-diabetes was diagnosed and three others withdrew for personal reasons including engagement in a physical activity programme and time constraints. Then, 16 subjects were included to participate in protocols and one was excluded from the analysis because of insufficient CGMS data. Demographic and clinical characteristics of participants are shown in Table 1. Patients were 32 ± 12 years old, predominantly women. Eight subjects were classified as insufficiently active, four were sufficiently active, while three were classified as very active. A flow diagram of the sample selection and study conduction is shown in Fig. 1.

Both AER and ECC sessions elicited increases in heart rate and systolic blood pressure (P < 0.001), but no changes were observed in glucose levels (CGMS, average of 30 min before vs. 30 min after the exercise session, P= 0.859).

Fig. 2 presents absolute glucose levels evaluated by CGMS before and after both sessions. There were no changes in glucose levels in the first 5 h (Fig. 2) and also until the 18th hour after both exercise sessions (data not shown).

Fig. 3 shows the results of glucose variability, as evaluated by VAR, CV% and SD. When compared with the pre-exercise period of 0-6 h, all the indices of glucose variability presented comparable reductions 12-18 h after both exercise sessions (AER: ∆VAR= 151.52, ∆CV%= 0.55 and ∆SD= 3.12 and ECC: ∆VAR= 221.22 , ∆CV%= 3.67 and SD= 6.54 ). However, compared with the pre-exercise period of 0-6 h, none of the indices of glucose variability presented differences 0-6 and 6-12 h after both exercise sessions.

Table 2 shows the plasma biochemical analysis results obtained before and after exercise sessions. Interleukin-6 levels increased by 68.5% and 30.8% after the AER and ECC sessions, respectively. Among stress oxidative markers, only uric acid levels showed changes immediately after the experimental sessions (+3% and +4% for AER and ECC, respectively).

No correlations were found between changes in inflammatory or oxidative biomarkers with changes in glucose variability indices following AER sessions. However, in the ECC session there was an inverse correlation between delta of total protein sulfhydryl and delta of VAR (r = -0.59 P = 0.02) and between delta of total protein sulfhydryl and delta of SD (r = -0.56 P = 0.03). There were no significant correlations between other biomarkers and other indices of glucose variability.
In this trial, we showed that acute sessions of AER and ECC promote comparable reductions in glucose variability evaluated by VAR, CV% and SD in non-trained healthy individuals. Increased IL-6 levels and uric acid were observed after both exercise sessions and an oxidative stress marker (total protein sulfhydryl) inversely correlated with VAR and SD specifically in ECC exercise.

The reduction in glucose variability after AER or ECC exercise sessions is in accordance with our previous study, although performed in patients with type 2 diabetes [15]. This evidence indicates a specific effect of exercise in reducing glucose variability, not related to glucose homeostasis derangements. Changes in glucose variability irrespective of mean glucose were previously observed in subjects with or without metabolic syndrome and diabetes [11]. Interestingly, we did not find differences between the exercise modalities tested either in diabetic [15] or non-diabetic subjects (present data).

Comparable to our findings, previous studies showed that AER and ECC exercises are associated with increases in IL-6 [28-30], a cytokine that has both pro- and anti-inflammatory actions. In response to exercise, the increase in IL-6 without concomitant increases in tumour necrosis factor-α (TNF-α) and IL-1β determines production of interleukin 1 receptor antagonist (IL-1ra), IL-10 and soluble TNF-α receptors, all anti-inflammatory molecules that suppress inflammation [31]. Data from a systematic review [28] indicate that a single bout of AER exercise of moderate to high intensity (55% VO₂max, 60% VO₂max and 90% VO₂max) is associated with an increase in IL-6 (145%). We used an intensity of AER exercise of 70% of the VO₂peak (peak oxygen uptake per kilogram, ml·kg⁻¹·min⁻¹) with a single IL-6 evaluation after exercise, which can account for non-different IL-6 changes between protocols. We also point out that the correlation between IL-6 and glucose variability was tested based on single evaluations that limit us in a definitive conclusion.

The use of large muscle groups during the ECC exercise sessions could lead to increases in IL-6 levels, because the amount of muscle mass involved in exercise is important in the stimulation of a systemic response [30]. Although there is equivocal evidence whether eccentric protocols acutely induce an exacerbated increase in IL-6, varied intensities of resistance exercise (50%, 75%, 90%, and 110% 1-RM) with concentric-eccentric contractions seem to increase IL-6 in a healthy population [32]. Therefore, plasma IL-6 during recovery may present a delayed peak and slower decrease, as observed when ECC was performed with intensity of 150% of the isotonic 1-RM of the dominant knee extensors [33] or 300 eccentric repetitions on an isokinetic dynamometer [34].

Based on reports evaluating diabetic subjects [35-36], we hypothesized that inflammation would be related to glucose variability. Here we observed that the relationship between IL-6 responses after exercise, expressed by delta indices, did not correlate with glucose variability indices. Despite this observation, exercise elicited increases in IL-6 immediately after both sessions and decreases in glucose variability 12-18 h after the sessions. This variation may still provide insight for a linked response between inflammation and glucose variability, as IL-6 might initiate the secretion of anti-inflammatory cytokines, promoting a range of downstream benefits for glucose metabolism [28]. However, these effects could be perceived later and would require analyses of downstream molecules in the inflammatory cascade and insulin signalling.

Oxidative stress markers were not substantially altered after the exercises. However, uric acid increased significantly after the exercise sessions, as observed previously in healthy adults [37]. This compound is generated through the catabolism of ATP and has antioxidant potential as a side effect [38]. At least in part, acid uric increase is likely induced by inhibition of the renal clearance of uric acid by lactate, which is accumulated in plasma during exercise [39]. Additionally, exercise stimulates purine catabolism, which accumulates hypoxanthine, xanthine and uric acid. The latter is released from the cells into the plasma and could act as a free radical scavenger and chelator of transitional metal ions in skeletal muscle. It would result in a sustained antioxidant effect after an oxidative challenge [40-41]. Besides that, plasma volume change is another possible cause of uric acid increase. Bloomer et al. found that plasma volume decreased significantly immediately after aerobic exercise performed for 60 minutes at 70% heart rate reserve. Unfortunately, we did not evaluate plasma volume in the present study [42].

Total protein sulfhydryl inversely correlated with glucose variability (VAR and SD) in ECC exercises. High levels of serum protein sulfhydryl groups reflect favourable redox status, indicating less oxidative stress [43]. The inverse correlation thus suggests that increasing protein sulfhydryl is related to less glucose variability. Inadequate antioxidant defence with oscillating glucose levels may induce more damage in protein structure than a constantly high glucose level [18, 44], which is a condition that could favour the development of diabetic complications [18, 45]. Some studies have reported a positive correlation of oxidative stress with glucose variability [36, 46]. In patients with type 2 diabetes, the serum levels of oxidative stress markers (evaluated by 8-iso PGF2) are positively correlated with mean amplitude of glycaemic excursion (MAGE) and standard deviation of HbA1c [36]. Likewise, the endogenous anti-oxidant molecule serum bilirubin is associated (r= 0.588, P < 0.001) with glucose variability (MAGE) in women with type 2 diabetes [46]. Because monitoring oxidative stress markers depends on the sampling timing, we cannot rule out potential changes in oxidative stress parameters with later measurements after exercise sessions.

**Limitations**

The small sample size may have influenced the analyses of glucose variability. In addition, we carried out measurements of blood only once before and immediately after both exercise sessions, which limits inferences about markers of inflammation and oxidative stress in the present study. Clinical insights offered by a study that uses only one bout of exercise are limited.
CONCLUSIONS

In conclusion, both AER and ECC exercise sessions were associated with reductions in glucose variability in healthy individuals. Inflammatory cytokines, such as IL-6, and oxidative stress might be part of the glucose variability controlling mechanism.

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