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Acute effects of concentric and eccentric exercise on glucose metabolism and interleukin-6 concentration in healthy males

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ABSTRACT: Acute muscle-damaging eccentric exercise (EE) negatively affects glucose metabolism. On the other hand, long-term eccentric endurance exercise seems to result in equal or superior positive effects on glucose metabolism compared to concentric endurance exercise. However, it is not known if acute non-muscle-damaging EE will have the same positive effects on glucose metabolism as acute concentric exercise (CE). Interleukin-6 (IL-6) released from the exercising muscles may be involved in the acute adaptations of glucose metabolism after CE and non-muscle-damaging EE. The aim of this study was to assess acute effects of uphill walking (CE) and non-muscle-damaging downhill walking (EE) on glucose metabolism and IL-6 secretion. Seven sedentary non-smoking, healthy males participated in a crossover trial consisting of a 1 h uphill (CE) and a 1 h downhill (EE) walking block on a treadmill. Venous blood samples were drawn before (pre), directly after (acute) and 24 h after (post) exercise. An oral glucose tolerance test (OGTT) was performed before and 24 h after exercise. Glucose tolerance after 1 and 2 hours significantly improved 24 hours after CE (-10.12±3.22%: P=0.039; -13.40±8.24%: P=0.028). After EE only the 1-hour value was improved (-5.03±5.48%: P=0.043). Acute IL-6 concentration rose significantly after CE but not after EE. We conclude that both a single bout of CE and a single bout of non-muscle-damaging EE elicit positive changes in glucose tolerance even in young, healthy subjects. Our experiment indicates that the overall metabolic cost is a major trigger for acute adaptations of glucose tolerance after exercise, but only the IL-6 production during EE was closely related to changes in glycaemic control.

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INTRODUCTION

Recently it has been shown that concentric (muscle shortening contractions; CE) and eccentric (muscle lengthening contractions; EE) endurance exercises (e.g. uphill and downhill walking, respectively) are similarly effective in improving glucose and lipid metabolism in sedentary healthy subjects [1,2]. Although using different training protocols, Paschalis et al. [3] and Drexel et al. [1] demonstrated that EE positively modified insulin resistance and glucose tolerance in males and females. When considering energy expenditure, these adaptations to glucose tolerance seem even to be superior compared to those elicited by CE [2]. Nevertheless, the results remain controversial as other studies failed to show equal or superior effects after EE on glucose metabolism compared to CE [4] and physiological explanations are up to now missing.

While a single bout of concentric endurance exercise is generally associated with improved insulin action and glucose transport [5], several studies have shown that muscle damage induced by unaccustomed EE may negatively affect glucose metabolism [6]. For example, Kirwan et al. [7] suggested a 37% decrease in insulin-mediated glucose disposal 48 h after EE compared to CE without alterations in glucose disposal. Reduced glucose transporter type 4 (GLUT4) levels after muscle damaging EE seem to be the major reason for the transient insulin resistance [8,9,10]. Reduced GLUT4 content in muscles after damaging EE was explained by a decreased GLUT4 transcription rate [11].

However, a recent study found no alteration and no significant differences in glucose tolerance and insulin response to an OGTT (oral glucose tolerance test) 12 h after acute CE and EE when exercise intensity was matched (60% VO_2max), but no objective or subjective signs of delayed onset muscle soreness (DOMS) were measured [12]. These findings may indicate that when exercise is matched for energy expenditure, CE and EE without concomitant muscle damage may evoke comparable effects on glucose metabolism.

Interleukin-6 (IL-6), released by muscle contraction [13], supports the maintenance of metabolic homeostasis during exercise [14]. IL-6 can induce insulin-independent GLUT4 translocation to the cell membrane and enhance insulin-stimulated glucose disposal [15]. The

improved insulin stimulated glucose transport after exercise may be regulated by the activation of AMPK [16] through the release of IL-6 [17,18,19]. IL-6 concentrations after non-muscle-damaging exercise could be a direct indicator for GLUT4 translocation and may explain improved glucose tolerance after a short delay following exercise. The main contributor to changes in IL-6 serum concentration seems not to be the type of exercise (EE vs. CE) but rather exercise intensity, time and muscle mass involved in exercise [20].

In addition, this muscle-derived IL-6 inhibits the production of the pro-inflammatory cytokine tumour necrosis factor alpha (TNFα) [21,22].

The aim of this study was to assess acute effects of uphill walking (CE) and non-muscle-damaging downhill walking (EE) on fasting glucose, glucose tolerance and insulin resistance and their link to acute IL-6 secretion in healthy males. We hypothesized that single bouts of CE and non-muscle-damaging EE should increase IL-6 and glucose tolerance and reduce TNFα in an intensity-dependent manner (%VO_2max). In addition, we expected positive correlations between the post-exercise IL-6 concentrations and glucose tolerance and negative correlations between IL-6 concentrations and TNFα.

The results from this study may provide a better and deeper understanding of physiological adaptations following acute CE and EE.

MATERIALS AND METHODS

Study participants. Based on the results reported by Mikines et al. [23], a total sample size of N = 5 for >80% power has been calculated for changes in glucose tolerance due to CE (G*Power, Version 3.1.5). Seven young, healthy males volunteered to participate in the study. Each participant underwent medical routine examination including medical history. The subjects had to meet the following criteria: male sex, being sedentary (less than 1.5 h of physical exercise per week), non-smoker, no acute or chronic diseases that would hamper the safe performance of exercise tests, and must not be accustomed to eccentric training. The participants were advised not to perform strenuous exercise or unaccustomed activities during the study period. Characteristics of the study participants are shown in Table 1. Written informed consent was provided by every participant. The study was approved by the institutional review board of the Department of Sport Science of the University of Innsbruck.

Study protocol

The study was designed as a non-randomized cross-over trial. The study was separated into 2 blocks: block 1 was the concentric block (CE: uphill walking) and block 2 the eccentric block (EE: downhill walking) (see Figure 1). On test days, subjects presented to the laboratory in a fasting state (minimum 10 hours without food intake and water as the only fluid).

All tests (exercise test to exhaustion, CE as well as EE) were performed on the same treadmill (described in detail below). For the CE trial the treadmill slope was set at +16% and the walking speed was adapted to match an exercise intensity corresponding to 55% of the VO_2max. To avoid muscle damage that could influence potential beneficial effects of EE [7,24], the walking speed for the EE trial was the same as during the CE trial with a slope of -16%. The average walking speed for CE and EE was 1.1 ± 0.12 m · s^{-1}. Before (pre test), immediately after (acute) and 24 hours after (post test) CE and EE blood samples were drawn from the antecubital vein.

TABLE I. Characteristics of study participants (N = 7)

	Mean ± SD
Age [years]	27.43 ± 5.13
Height [m]	1.82 ± 0.07
Body mass [kg]	74.54 ± 11.04
BMI [kg · m^{-2}]	22.45 ± 1.66
Hear rate peak [beats · min^{-1}]	194.14 ± 6.77
VO_2peak [ml · kg^{-1} · min^{-1}]	49.29 ± 4.21

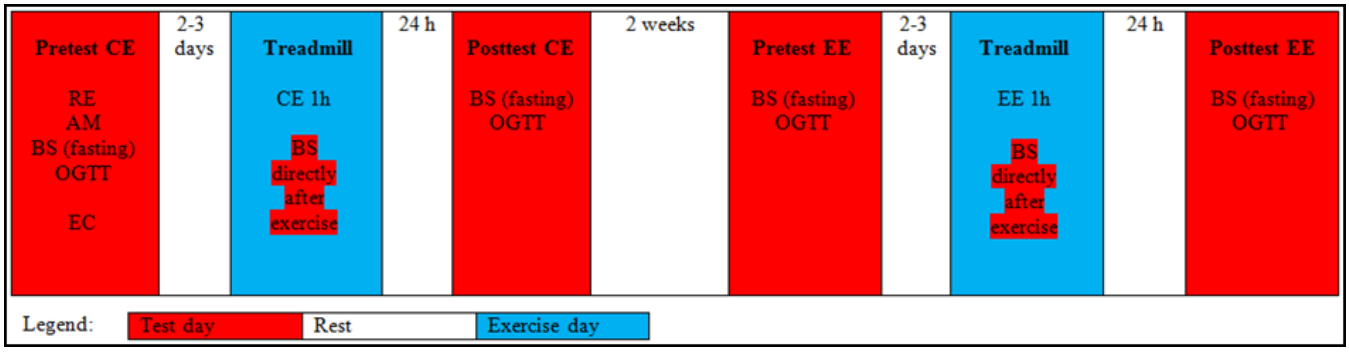

FIG. 1. Study protocol.
Note: RE: routine examination; AM: anthropometric measurements; BS: blood sampling; OGTT: oral glucose tolerance test; EC: exercise capacity testing; CE 1h: walking uphill at 16% elevation for 1 hour at a velocity corresponding 55% VO_2max; EE 1h: walking downhill at 16% elevation for 1 hour at the same velocity as when walking uphill.

Measurements of glucose metabolism, IL-6, TNFα

Venous blood samples were used to assess insulin sensitivity pre- and post test (24 hours after exercise) by using the homeostasis model assessment (HOMA = fasting insulin ($\mu U \cdot ml^{-1}$) · fasting glucose ($mg \cdot dl^{-1}$) / 405). Additionally, IL-6 and TNFα were determined pre- and post test and directly after exercise. All parameters were assessed using standard, state-of-the-art techniques at the laboratory of the Medical University of Innsbruck. Plasma glucose was quantified using a commercially available enzymatic kit (Roche Diagnostic Systems, Basel, Switzerland) on a Hitachi 902 autoanalyzer (Roche Diagnostic Systems, Basel, Switzerland). Insulin was determined using automated analyzers within the central clinical laboratory at the University Hospital Innsbruck. IL-6 and TNFα were both determined using ELISA kits commercially available (R&D systems, Minneapolis, Minnesota, USA) following the manufacturer's instructions. Glucose tolerance was assessed via an oral glucose tolerance test (OGTT). Participants had to drink 75 g glucose dissolved in 300 ml of water. Capillary blood samples were drawn and analyzed before (OGTT fasting) and 1 hour (1-hour OGTT) and 2 hours (2-hour OGTT) after ingestion (Reflotron Sprint, Boehringer Mannheim, Mannheim, Germany).

Measurement of muscle damage and delayed onset muscle soreness (DOMS)

Creatine kinase (CK) as an indicator of muscle damage was assessed from capillary blood at the time points pre test CE, post test CE and post test EE (Reflotron Sprint, Boehringer Mannheim, Mannheim, Germany).

24 h after CE and EE DOMS was assessed via a graded scale for muscle pain and muscle soreness respectively, ranging from 1 to 10 (1 meaning no pain/soreness and 10 meaning maximal pain/soreness).

Exercise capacity

Exercise capacity was assessed on a treadmill (Pulsar, h/p/cosmos, Nussdorf-Traunstein, Germany) by using respiratory gas analysis (Oxycon Pro, Viasys Healthcare, Hoechberg, Germany). The test began at a velocity of 3 $km \cdot h^{-1}$ and an elevation of 5% for 2 minutes followed by 2 minutes at the same speed at 10% elevation. After that, elevation rose by 2% each minute without a change in velocity until 16% elevation was reached. Then, velocity rose by 0.5 $km \cdot h^{-1}$ each minute without a change in elevation until exhaustion or limitation by symptoms.

Statistical analysis

Data are presented as means (SD) or frequencies (%). One-way repeated measures ANOVA was used to compare differences between the 2 experimental conditions (CE vs. EE) over the 3 time points (pre test, acute, post test). Post-hoc t-test was performed to calculate within- and between-group changes. Within- and between-group effects for pre test vs. post test were analyzed by the Wilcoxon test. Multivariate linear regression analysis was calculated to determine independent predictors of changes in glucose tolerance. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Pre test CE/EE to post test CE/EE

Changes of all baseline metabolic and inflammatory parameters compared to 24 hours post-exercise are presented in Table 2. One-hour OGTT and 2-hour OGTT improved significantly 24 hours after CE (-10.12 ± 3.22 %: P = 0.039; -13.40 ± 8.24 %: P = 0.028), whereas after EE only 1-hour OGTT improved (-5.03 ± 5.48 %: P = 0.043). No other metabolic or inflammatory parameters were significantly modified 24 hours after CE or EE. There was no significant difference between CE and EE post-exercise for any parameter.

Assessment of muscle damage and delayed onset muscle soreness (DOMS)

There was no significant change in CK (baseline: 58.1 ± 38.3 $U \cdot l^{-1}$; 24 h after CE: 68.6 ± 61.2 $U \cdot l^{-1}$; 24 h after EE: 84.6 ± 39.0 $U \cdot l^{-1}$)

TABLE 2. Percent change of metabolic and inflammatory parameters 24 hours after concentric exercise (CE) and eccentric exercise (EE).

	CE		EE		
	Mean (%) ± SD (%)	Within P-values	Mean (%) ± SD (%)	Within P-values	Between P-values
OGTT fasting	-2.96 ± 7.11	n.s.	-0.98 ± 8.55	n.s.	n.s.
1-hour OGTT	-10.12 ± 3.22	0.039	-5.03 ± 5.48	0.043	n.s.
2-hour OGTT	-13.40 ± 8.24	0.028	-0.13 ± 16.99	n.s.	n.s.
IL-6	0.25 ± 1.11	n.s.	0.01 ± 0.36	n.s.	n.s.
TNFα	0.11 ± 0.17	n.s.	0.16 ± 0.38	n.s.	n.s.
Fasting insulin	1.63 ± 2.18	n.s.	-0.02 ± 0.58	n.s.	n.s.
HOMA insulin resistance	140.91 ± 188.16	n.s.	11.59 ± 57.75	n.s.	n.s.

Note: CE: concentric exercise; EE: eccentric exercise; OGTT: oral glucose tolerance test; OGTT fasting: fasting glucose concentration in capillary blood; 1-hour OGTT: glucose concentration in capillary blood 1 hour after drinking 75 g of glucose dissolved in 300 ml of water; 2-hour OGTT: glucose concentration in capillary blood 2 hours after drinking 75 g of glucose dissolved in 300 ml of water; IL-6: interleukin-6; TNF : tumour necrosis factor alpha; HOMA: homeostasis model assessment; n.s.: not significant.

from the baseline value to the post-exercise values of CE and EE (P = 0.499; P = 0.128) and there was no significant difference between the post-exercise values of CE and EE (P = 0.310). The perceived muscle soreness and muscle pain were not significantly different between CE and EE 24 h after exercise (CE: muscle soreness: 1.57 ± 0.79; muscle pain: 1.00 ± 0.00; EE: muscle soreness: 1.29 ± 0.49; muscle pain: 1.71 ± 0.95; P = 0.414; P = 0.102).

Acute effects of CE and EE

Repeated measures ANOVA revealed a significant time effect for IL-6 concentration (P = 0.010). Moreover, there was a significant interaction between (time · condition) CE and EE (P = 0.031). Post-hoc analysis revealed that within CE there were significant differences of IL-6 concentrations between pre test and acute (P = 0.029) and between acute and post test (P = 0.013). There was no significant IL-6 concentration change within EE. Post test values were not significantly different from pre test values within CE and within EE. The acute IL-6 concentration was significantly higher after CE than after EE (P = 0.029), but post test and pre test values were not significantly different between CE and EE (Figure 2).

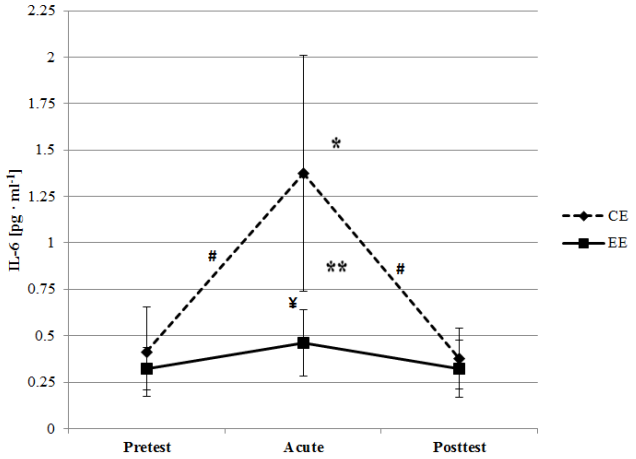

FIG. 2. Changes in human IL-6
Note: *: significant time effect; **: significant interaction between CE and EE; #: significant change within CE; ɪ: significant change within EE; ¥: significant difference between CE and EE.

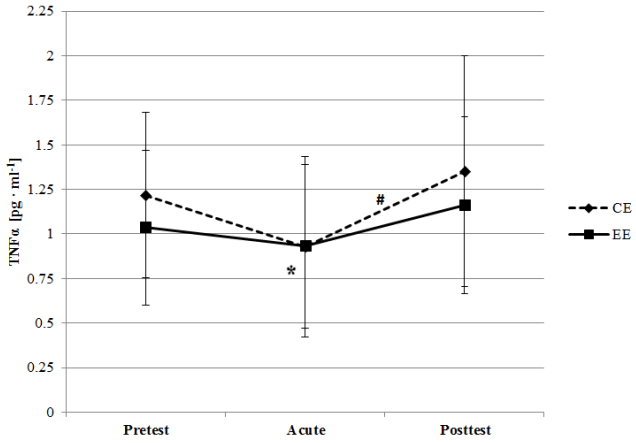

FIG. 3. Changes in TNFα
Note: *: significant time effect; **: significant interaction between CE and EE; #: significant change within CE; ɪ: significant change within EE; ¥: significant difference between CE and EE.

Repeated measures ANOVA revealed a significant time effect for TNFα concentration (P = 0.026). There was no interaction (time x condition) between CE and EE. Post-hoc analysis revealed that within CE there was a significant difference of TNFα concentration between acute and post test (P = 0.027). There was no further significant difference within CE or EE and between CE and EE for the 3 time points (Figure 3).

Correlation analysis

Linear regression revealed a significant inverse relationship between %changes of 2-hour OGTT pre test to post test and %changes of IL-6 pre test to acute for EE (R^2 = 0.972, B = -0.189, P = 0.025, 95% confidence interval [CI] [-0.32, -0.058]).

DISCUSSION

The main results of this study are: (1) that both a single bout of CE and a single bout of non-muscle-damaging EE improved glucose tolerance 24 h after exercise (improved 1-hour and 2-hour OGTT after CE and 1-hour OGTT after EE), (2) that only acute changes of IL-6 blood levels from pre- to post-EE explained changes in the OGTT 24 hours after exercise.

The present study shows that a single bout of CE and even a single bout of EE induce positive adaptations to glucose tolerance. This is in contrast to the common findings in the literature reporting acute negative effects of EE on glucose metabolism, especially transient insulin resistance, non-insulin dependent glucose uptake and muscle glycogen replenishment [7,25,26,27,28,29,30]. Our findings are in contrast to those where subjects performed unaccustomed EE causing DOMS. In the present investigation no muscle damage, as indicated by unaltered CK values, muscle pain and muscle soreness scores, was induced. Therefore, it is of clinical importance to choose EE not provoking any muscle damage. Accordingly, Green et al. [26] were able to demonstrate that a single bout of EE resulting in reduced glucose tolerance when performed for the first time led to no adverse changes of glucose tolerance when performed 14 days later.

Our results are not in line with the long-term results of Drexel et al. [1], who reported an equal or even slightly higher effectiveness of EE in improving glucose tolerance compared to CE despite the lower metabolic cost of EE. In our experiment CE improved glucose metabolism more effectively than EE despite lower metabolic cost of downhill walking. Johnson et al. [31] concluded that VO_2 of downhill walking at the same velocity and opposite slope (in our experiment +16% and -16%) is approximately 0.5*VO_2 of uphill walking. The myokine IL-6 is considered as an energy sensor of the muscle [19,32] and the acute rise of IL-6 was significantly higher directly after CE compared to EE. Thus, the overall metabolic cost is assumed to be

the major trigger for IL-6 release and the related metabolic adaptations to exercise.

The significant rise in IL-6 directly after CE may have provoked enhanced translocation of GLUT4 to the cell membrane and may explain the improved glucose tolerance 24 h later [15]. However, a highly significant relationship between acute IL-6 rise and improved glucose disposal 24 h afterwards was only found for EE. This would favour a rather non-energy dependent pathway for glucose uptake by the muscle during EE that was recently proposed by Sylow et al. [33,34,35]. The GTPase Rac1 seems to be a key regulator of insulin- and AMPK-independent glucose transport in muscle induced by muscle stretching, i.e. mechanical stress [33,34,35]. However, up to now there is little evidence about how long after exercise Rac1 may have positive effects on glucose transport.

Despite the fact that IL-6 secretion during exercise seems to be predominantly energy cost dependent, our findings also indicate that IL-6 production during exercise types inducing strong mechanical and low metabolic stress, i.e. EE, is closely related to changes in glycaemic control.

Our findings do not confirm the assumption of negative correlations between IL-6 concentrations and TNFα. Nevertheless, we found a significant time effect for TNFα, which resulted from a significant difference between TNFα acute and post test within CE. This significant difference resulted from a slight but not significant decrease of TNFα concentration directly after CE and a slight increase of TNFα concentration 24 h after CE. The slight decrease of TNFα concentration directly after exercise may be an indicator for anti-inflammatory action likely induced by muscle-derived IL-6. This supports the findings of Starkie et al. [22], who reported that exercise-induced IL-6 production inhibited endotoxin-induced TNFα production in humans, thereby inducing anti-inflammatory activity.

Limitations

First of all, the small sample size may be considered to be a weakness of our study, which we tried to overcome by the use of a cross-over design. Secondly, CE and EE were not performed in a randomized order. This combined with a wash-out phase of only 2 weeks may have led to a carry-over effect. In fact, OGTT values of pre test EE were similar to those seen at post test CE and significantly different from pre test CE. However, due to the second pre test before EE and by comparing post test OGTT values with values that were collected shortly before CE and EE respectively, we may have eliminated an inaccuracy that could have occur when comparing OGTT values collected after the first and the second exercise block with one baseline OGTT.

CONCLUSIONS

In conclusion, both a single bout of CE and a single bout of non-muscle-damaging EE improved glucose tolerance 24 h after exercise even in young, healthy subjects. Our data suggest that the overall metabolic cost is a major trigger for IL-6 production and acute improvements of glucose tolerance after exercise. However, only the IL-6 production during EE (predominantly mechanical stress) was closely related to changes in glycaemic control. These findings may have important clinical implications.

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