Improved insulin sensitivity after a single bout of exercise is curvilinearly related to exercise energy expenditure

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ABSTRACT

A single bout of moderate-intensity exercise increases whole-body insulin sensitivity for 12–48 h post-exercise; however, the relationship between exercise energy expenditure and the improvement in insulin sensitivity is not known. We hypothesized that the exercise-induced increase in whole-body insulin sensitivity, assessed with HOMAIR (homoeostasis model assessment of insulin resistance), is directly related to the energy expended during exercise. We studied 30 recreationally active non-obese men (age, 27 ± 5 years; body mass index, 24 ± 2 kg/m²) in the post-absorptive state on two separate occasions: once after exercising at 60 % of \( \dot{V}_{O_2} \text{peak} \) (peak oxygen consumption) for 30–120 min on the preceding afternoon (expending a total of 1.28–5.76 MJ) and once after an equivalent period of rest. Blood samples were obtained the following morning. Exercise-induced changes in HOMAIR were curvilinearly related to exercise energy expenditure \((r = -0.666, P = 0.001)\) with a threshold of approx. 3.77 MJ (900 kcal) for improvements in HOMAIR to be manifested. In particular, HOMAIR was reduced by 32 ± 24 % \((P = 0.003)\) in subjects who expended more than 3.77 MJ during exercise, but did not change for those who expended fewer than 3.77 MJ \((-2 \pm 21 \%; P = 0.301)\). Furthermore, the magnitude of change in HOMAIR after exercise was directly associated with baseline (i.e. resting) HOMAIR \((r = -0.508, P = 0.004)\); this relationship persisted in multivariate analysis. We conclude that improved whole-body insulin resistance after a single bout of exercise is curvilinearly related to exercise energy expenditure, and requires unfeasible amounts of exercise for most sedentary individuals.

INTRODUCTION

Regular, moderate-intensity, endurance-type physical activity is associated with significantly reduced risk for Type 2 diabetes and cardiovascular disease, in part due to enhanced insulin action [1]. Whole-body insulin sensitivity is higher in trained athletes than in untrained subjects, and improves considerably with exercise training in previously sedentary individuals [2]. Most of the enhancement in insulin action associated with exercise training is attributed to the last bout of exercise, and is lost after 3–6 days of inactivity [2–5]. In fact, insulin-mediated whole-body glucose uptake is increased 12–48 h after a single exercise session in both healthy [6–9] and insulin-resistant subjects [8,10,11], but returns to baseline values thereafter [2–5].

The amount of exercise required to elicit an enhancement in insulin sensitivity remains uncertain. Furthermore, there is considerable inter-individual variability

Key words: energy expenditure, exercise, glucose disposal, homoeostasis model assessment of insulin resistance (HOMAIR), insulin sensitivity, oxygen consumption \((\dot{V}_{O_2})\).

Abbreviations: HOMAIR, homoeostasis model assessment of insulin resistance; mU, milli-international unit; \( \dot{V}_{O_2} \), oxygen consumption; \( \dot{V}_{O_2}\text{peak} \), peak \( \dot{V}_{O_2} \).

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Table 1  Subject characteristics
Values are means ± S.D. *P < 0.001 compared with the corresponding value in subjects who expended < 3.77 MJ (900 kcal) during exercise. †Values in parentheses are expressed as a percentage of the \( \dot{V}O_2\text{peak} \); ‡values in parentheses are in kcal.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All subjects</th>
<th>Exercise energy expenditure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt; 3.77 MJ (900 kcal)</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>30</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27 ± 5</td>
<td>27 ± 5</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24 ± 2</td>
<td>24 ± 2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79 ± 11</td>
<td>77 ± 7</td>
</tr>
<tr>
<td>Body fat (% of body weight)</td>
<td>17 ± 4</td>
<td>17 ± 4</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>61 ± 8</td>
<td>61 ± 6</td>
</tr>
<tr>
<td>( \dot{V}O_2\text{peak} ) (l/min)</td>
<td>3.3 ± 0.7</td>
<td>3.2 ± 0.7</td>
</tr>
<tr>
<td>( \dot{V}O_2 ) during exercise (l/min)‡</td>
<td>2.0 ± 0.3 (62 ± 2)</td>
<td>1.9 ± 0.3 (61 ± 2)</td>
</tr>
<tr>
<td>Total energy expenditure during exercise (MJ)‡</td>
<td>3.23 ± 1.40 (771 ± 336)</td>
<td>2.25 ± 0.80 (537 ± 190)</td>
</tr>
</tbody>
</table>

in the metabolic response to acute exercise and the concomitant changes in glucose and insulin dynamics [12], some of which may be related to baseline insulin resistance [10,11,13]. Understanding the dose–response nature of these relationships will have important physiological and public health implications. Current public guidelines advocate 30–60 min of moderate-intensity exercise on most days of the week [1]; however, approx. 70 % of the adult population fails to meet the recommended 30-min goal of regular exercise and approx. 40 % does not engage in any kind of physical activity [14]. It was therefore our objective to examine the relationship between the energy expended during exercise and basal whole-body insulin sensitivity, assessed by using the HOMA IR (homeostasis model assessment of insulin resistance), in healthy untrained men.

MATERIALS AND METHODS

Subjects and preliminary testing
A total of 30 non-obese recreationally active but untrained men participated in the study (Table 1). All subjects engaged in moderate-intensity physical activities ≤ twice/week, and were considered to be in good health after completing a medical evaluation, which included a history and physical examination and standard blood tests. None were smokers or taking medication. Body composition (fat mass and fat-free mass) was determined by dual-energy X-ray absorptiometry [Delphi-W (Hologic) and DPX-MD+ (Lunar)], and \( \dot{V}O_2\text{peak} \) (peak \( \dot{V}O_2 \) (oxygen consumption)) was measured with an incremental exercise test on a treadmill (Vmax229; SensorMedics) or a cycloergometer (TrueOne 2400; ParvoMedics), depending on whether subjects were assigned to perform running or cycling exercise (see below). Written informed consent was obtained from all subjects before participation in the study, which was approved by the Human Studies Committee and the General Clinical Research Center Advisory Committee at Washington University School of Medicine in St. Louis, MO, U.S.A. and the Bioethics Committee of Harokopio University, Athens, Greece.

Experimental protocol
Each subject completed two studies within 3 weeks in a randomized order: once after resting and once after exercising on the preceding afternoon. Subjects were instructed to adhere to their regular diet and to refrain from exercise for a minimum of 3 days before the start of each study (rest and exercise). For the exercise study, they came to the laboratory and cycled on a semi-recumbent cycloergometer (Cateye Fitness) or ran on a motor-driven treadmill (Technogym Runrace) at 60 % of their \( \dot{V}O_2\text{peak} \) for 30–120 min between 17.30 and 19.30 hours (seven subjects exercised for 30 min; seven for 60 min; nine for 90 min, and seven for 120 min). There were no significant differences in \( \dot{V}O_2\text{peak} \) between individuals who exercised for different amounts of time (3.3 ± 0.8, 3.2 ± 0.6, 3.3 ± 0.7 and 3.2 ± 0.5 l/min, respectively; \( P = 0.883 \) as determined by one-way ANOVA). \( \dot{V}O_2 \) was measured at regular intervals during exercise (every 5, 15 or 30 min, depending on the duration of exercise) to calculate total energy expenditure of the bout (range, 1.28–5.76 MJ; i.e. 306–1376 kcal) [15] and adjust the workload, if necessary, to maintain the desired \( \dot{V}O_2 \) within ± 5 %. The different modes and durations of exercise were chosen in order to cover the range from the minimum recommended amount of exercise (i.e. 30 min of moderate-intensity) [1] to an exercise session that most untrained individuals would find it difficult to complete (i.e. 2 h in duration) [16], and ensured that the experimental conditions would closely reflect a realistic situation, in which unacclimated individuals engage in various activities for variable amounts of time. Subjects were not allowed access to any kind of food or beverage during exercise,
other than water. For the resting study, subjects lay in bed or sat in a chair. After completion of the exercise or the equivalent period of rest, they consumed the same standardized meal [50 kJ (12 kcal)/kg of body weight; 50–55 % carbohydrate, 30–35 % fat and 15–20 % protein] at approx. 20.00 hours, in order to eliminate between-trial differences in energy balance other than the energy deficit incurred by exercise, and then fasted (except for water) until completion of the study the next day.

At 08.00 hours the following morning, an arterialized blood sample was obtained from a heated forearm vein for the determination of basal plasma glucose and insulin concentrations. Blood was collected in chilled tubes containing heparin (for glucose) or EDTA plus aprotinin (for insulin) and placed immediately on ice. Plasma was separated by centrifugation within 30 min of collection, and samples were stored at −80 °C until analysis. Plasma glucose concentration was determined by the glucose oxidase method on an automated glucose analyser (YSI 2300 STAT+; Yellow Spring Instruments). Plasma insulin concentration was measured by RIA (Linco Research). The HOMA<sub>IR</sub> score, which reflects whole-body insulin resistance, was calculated as the product of fasting plasma insulin [in mU/l (milli-international units/l)] and glucose (in mmol/l) concentrations divided by 22.5 [17].

**Statistical analysis**

Data were analysed with SPSS 13 for Windows (SPSS Inc). All datasets were normally distributed according to the Kolmogorov–Smirnov procedure. Results are presented as means ± S.D. Results after rest and exercise were compared with a two-tailed paired Student’s t test. Relationships between variables of interest were examined with correlation and regression analyses. P < 0.05 was considered statistically significant.

**RESULTS**

Fasting plasma glucose and insulin concentrations, and therefore the HOMA<sub>IR</sub> score, were significantly lower in the morning after exercise than at rest (Table 2). These responses varied considerably between individuals (Table 2), but were not affected by the mode of exercise (running or cycling) in any consistent manner (results not shown).

Total energy expenditure during exercise correlated negatively with exercise-induced changes in fasting plasma glucose (r = −0.482, P = 0.007) and insulin (r = −0.521, P = 0.003) concentrations.

There was a negative curvilinear relationship between total energy expenditure during exercise and changes in HOMA<sub>IR</sub> score, with no apparent effect of exercise below a caloric expenditure of approx. 3.77 MJ (i.e. 900 kcal) (r = −0.666, P = 0.001; Figure 1). Hence HOMA<sub>IR</sub> was reduced by approx. 30 % in subjects who expended more than 3.77 MJ during exercise (n = 12; P = 0.003), but did not change for those who expended fewer than 3.77 MJ (n = 18; P = 0.301; Figure 1). There were no significant differences in subject characteristics between these two groups (Table 1).
Exercise-induced changes in HOMA

The relationship between changes in HOMA(IR) score and exercise energy expenditure was linear when the latter was expressed relative to body weight (\( r = -0.577, P = 0.001 \)). However, the percentage variance explained by this linear relationship (\( R^2 = 33.3\% \)) was less than that explained by the curvilinear relationship with total energy expenditure of exercise (\( R^2 = 44.4\% \)).

The magnitude of change in HOMA(IR) after exercise was inversely correlated with the baseline (i.e. resting) HOMA(IR) score (\( r = -0.508, P = 0.004 \); Figure 2).

In multivariate linear regression analysis, including exercise energy expenditure, age, body mass index, body weight, fat mass and fat-free mass, \( \dot{V}O_{2\text{peak}} \), and baseline (i.e. resting) plasma glucose and insulin concentrations and HOMA(IR) score, total energy expenditure during exercise (standardized \( \beta = -0.494, P = 0.001 \)) and baseline HOMA(IR) score (\( \beta = -0.420, P = 0.005 \)) were the only significant independent predictors of the exercise-induced change in HOMA(IR), accounting for 49.4% of the total variance (\( F = 13.2, P < 0.001 \)).

**DISCUSSION**

In the present study, we investigated the relationship between the energy expended during a single bout of moderate-intensity endurance exercise, performed in the evening, and fasting plasma glucose and insulin concentrations and insulin resistance (HOMA(IR)) the following morning in healthy, non-obese, untrained men. Our findings suggest that improvements in whole-body insulin sensitivity, reflected by a decreased HOMA(IR) score, are curvilinearly related to exercise energy expenditure with a threshold of approx. 3.77 MJ (900 kcal) for a beneficial effect to be manifested. However, exercise-mediated changes in whole-body insulin resistance are inversely related to baseline HOMA(IR) score, even within this group of normoglycaemic and normoinsulinemic subjects with normal HOMA(IR) [18], implying that insulin-resistant individuals may benefit more from exercise than insulin-sensitive ones. Nonetheless, single sessions of typical recreational activities are unlikely to have a significant impact on whole-body insulin sensitivity in healthy sedentary individuals.

It is well established that a single session of strenuous exercise leads to increased insulin-mediated whole-body glucose uptake for some 12–48 h post-exercise in healthy and insulin-resistant subjects [6–8,10,11]. In our present study, whole-body insulin sensitivity improved proportionally with the energy expended during exercise when this exceeded approx. 3.77 MJ, whereas no changes in HOMA(IR) score occurred after a total energy cost of exercise less than 3.77 MJ (900 kcal). This energy expenditure threshold is equivalent to \( \geq 60–90 \) min of exercise at 60% of \( \dot{V}O_{2\text{peak}} \) in our recreationally active men, which by far exceeds current public recommendations for physical activity [1]. In fact, most sedentary individuals will probably not be able to exercise for more than 1 h at this intensity [16]. The existence of an energy expenditure threshold in the insulin-sensitizing effect of exercise is in line with findings on other physiological outcomes of acute exercise, for example the lowering of plasma triacylglycerol (triglyceride) concentrations [19,20]. Our present findings also help to explain the lack of a consistent effect of exercise on insulin sensitivity in some previous studies because too little exercise was performed (corresponding to total caloric expenditures \( \leq 2.1 \) MJ or 500 kcal) [13,21]. These results collectively suggest that improvements in basal whole-body insulin sensitivity after a single bout of exercise require unfeasible amounts of exercise for most untrained individuals.

It is possible that regular exercise training lowers the threshold of exercise required to improve whole-body insulin sensitivity; the effects of acute exercise on insulin action appear to be more pronounced in the trained state [2] and everyday leisure-time physical activity is associated with dose-dependent reductions in diabetes risk in epidemiological surveys [22–25]. However, whether exercise training or the intensity of exercise modify the dose–response relationship between energy expenditure and insulin sensitivity in any way remains to be determined. Furthermore, the inverse association between exercise-induced changes in HOMA(IR) and baseline HOMA(IR) implies that less exercise may be required to improve insulin sensitivity in insulin-resistant subjects than those with good insulin sensitivity at baseline, i.e. before engaging in exercise. For instance, some of our subjects with higher baseline HOMA(IR) scores, albeit within the normal range [18], exhibited large improvements in insulin resistance (i.e. approx. 20–40% reduction) after expending only 1.26–2.51 MJ (i.e. 300–600 kcal) during exercise. Likewise, insulin-mediated whole-body glucose disposal increased to a greater extent in insulin-resistant obese subjects compared with insulin-sensitive lean subjects approx. 12 h after a strenuous session of

**Figure 2** Exercise-induced changes in HOMA(IR) as a function of baseline (resting) HOMA(IR) score

The relationship between changes in HOMA(IR) score and exercise energy expenditure was linear when the latter was expressed relative to body weight (\( r = -0.577, P = 0.001 \)). However, the percentage variance explained by this linear relationship (\( R^2 = 33.3\% \)) was less than that explained by the curvilinear relationship with total energy expenditure of exercise (\( R^2 = 44.4\% \)).

The magnitude of change in HOMA(IR) after exercise was inversely correlated with the baseline (i.e. resting) plasma glucose and insulin concentrations and insulin resistance (HOMA(IR)) as a function of baseline (resting) HOMA(IR) score. The regression equation was given by

\[
\Delta \text{HOMA}_{\text{IR}} = \beta_0 + \beta_1 \times \text{HOMA}_{\text{IR}} + \beta_2 \times \text{Energy} + \beta_3 \times \text{Age} + \beta_4 \times \text{BMI} + \beta_5 \times \text{Body Weight} + \beta_6 \times \text{Fat Mass} + \beta_7 \times \text{Fat-Free Mass} + \beta_8 \times \text{Resting glucose} + \beta_9 \times \text{Resting Insulin}
\]

where \( \Delta \text{HOMA}_{\text{IR}} \) is the change in HOMA(IR) score, \( \text{HOMA}_{\text{IR}} \) is the baseline HOMA(IR) score, \( \text{Energy} \) is the total energy expenditure during exercise, \( \text{Age} \) is the age of the subject, \( \text{BMI} \) is the body mass index, \( \text{Body Weight} \) is the body weight, \( \text{Fat Mass} \) is the fat mass, \( \text{Fat-Free Mass} \) is the fat-free mass, \( \text{Resting glucose} \) is the baseline fasting glucose concentration, and \( \text{Resting Insulin} \) is the baseline fasting insulin concentration. The coefficients \( \beta_0, \beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6, \beta_7, \beta_8, \) and \( \beta_9 \) were estimated using multiple linear regression analysis.

The percentage variance explained by the curvilinear relationship with total energy expenditure of exercise (\( R^2 = 44.4\% \)). However, the percentage variance explained by this linear relationship (\( R^2 = 33.3\% \)) was less than that explained by the curvilinear relationship with total energy expenditure of exercise (\( R^2 = 44.4\% \)).

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exercise [10], and HOMA_{IR} decreased in the morning after a single 90-min exercise bout at 60% of \( V_{O_{peak}} \) in men, but not in women, whose baseline HOMA_{IR} was half that of men [26]. Regular exercise, even of low energy cost, should therefore not be rejected as a means of improving insulin sensitivity in insulin-resistant subjects.

The exact cellular mechanisms responsible for the increase in insulin sensitivity late into recovery from a single bout of exercise are not well understood. Exercise-induced changes in insulin sensitivity have been linked to the depletion of skeletal muscle glycogen and/or triacylglycerol stores [27]. Depletion of muscle glycogen [6–8,10,11] leads to enhanced post-exercise uptake of glucose to facilitate glycogen replenishment [2,3,28].

The major cellular event underlying this phenomenon is increased translocation of the GLUT4 isoform of the glucose transporter from its intracellular storage sites to the cell surface [29]; however, the mechanism(s) responsible for mediating this event, the signals involved and the amount of exercise required to elicit these signals remain poorly defined [28]. Glycogen repletion in the recovery from exercise occurs in two distinct phases: an early insulin-independent period of rapid glycogen resynthesis (lasting approx. 1 h after cessation of exercise) and a subsequent period (up to 1–2 days post-exercise) of slow glycogen resynthesis which is insulin-dependent [30]. This mechanism fits well with the results from our present study, in which muscle glycogen stores were probably not depleted to any significant extent, except for those subjects who exercised for \( \geq 60–90 \) min and expended more than approx. 3.77 MJ (900 kcal), as skeletal muscle glycogen is reduced dose-dependently with the total energy cost and, hence, the duration of exercise [30,31]. We are not aware of any studies examining the possible dose-dependency of exercise-induced changes in relevant signalling pathways. Furthermore, glycogen resynthesis rates are substantially slower in insulin-resistant subjects compared with insulin-sensitive subjects in the late post-exercise period [32], which could help explain our present observation that relatively insulin-resistant subjects (as indicated by higher baseline HOMA_{IR} scores) enjoyed greater decreases in HOMA_{IR} after exercise than relatively insulin-sensitive ones, because persistence of low glycogen stores augments the exercise-induced enhancement in muscle insulin action [28]. Intramuscular triacylglycerol content is also closely associated with insulin sensitivity [33]. Diminution of skeletal muscle lipid stores and/or enhanced lipid oxidation after exercise could therefore also facilitate muscle insulin action [34]. The relative contribution of changes in skeletal muscle glycogen and triacylglycerol metabolism to the exercise-induced improvements in insulin sensitivity and the role, if any, of the energy expenditure of exercise are currently not known.

In summary, in the present study, we investigated the relationship between the total energy expended during a single bout of moderate-intensity evening exercise and changes in fasting plasma glucose and insulin concentrations and HOMA_{IR} in healthy, non-obese, untrained men. Our results indicate that more than 1 h of moderate-intensity exercise is required to improve basal whole-body insulin sensitivity, assessed with the HOMA_{IR} score. Whether the same applies for repeated exercise sessions (i.e. training) remains to be studied. Although the interpretation of our findings is limited by the use of HOMA_{IR} as a surrogate index of whole-body insulin resistance, there is a good correlation (\( r = 0.7–0.9 \)) between HOMA_{IR} and estimates of insulin sensitivity derived from hyperinsulinaemic–euglycaemic clamp and minimal model analysis [35]. These findings may therefore be useful for the development of appropriate exercise protocols targeted at ameliorating insulin resistance.

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REFERENCES