Effects of acute exercise on insulin sensitivity, glucose effectiveness and disposition index in type 2 diabetic patients

S. Bordenave, F. Brandou, J. Manetta, C. Fédou, J. Mercier, J.-F. Brun

Original article

Abstract

Aim. – The aim of this work was to quantify the magnitude of changes in insulin sensitivity (SI) and glucose effectiveness (SG) in response to acute exercise in type 2 diabetic (T2D) patients, as previously studied in non-diabetic subjects.

Methods. – Seven T2D patients and seven non-diabetic controls participated in the study. Two intravenous glucose tolerance tests (0.5 g/kg) with frequent blood sampling over 180 minutes and mathematical modelling were carried out in a randomized fashion, one at rest and the other immediately following 15 minutes of exercise at 50% of the maximum theoretical heart rate (HRmax) followed by five minutes at 85% of HRmax. SI and SG were calculated using Bergman’s minimal model.

Results. – After exercise, SI was increased by 773% (from 0.62 ± 0.16 to 5.41 ± 1.59 min−1 × 10−4/(U/mL) and even reached the zone of control values at rest (5.52 ± 2.28), whereas SG remained unchanged. The disposition index acute insulin response (AIRG) × SI and the product of fasting insulin (IB) × SI also increased after exercise.

Conclusion. – A single bout of exercise at moderate intensity in type 2 diabetics did not improve SG, but markedly improved the low SI values found in these patients, indicating that the acute effects of exercise on SI are quantitatively important in the interpretation of training-related SI changes and may even be therapeutically useful on their own. Surrogates such as homoeostasis model assessment (HOMA) and quantitative insulin-sensitivity check index (QUICKI) were not sensitive enough to detect this increase in SI and should probably be used with caution in the follow-up of exercise protocols in diabetic patients.

Résumé

Effets aigus d’un exercice isolé sur la sensibilité à l’insuline, l’efficience du glucose et l’index AIRG × SI mesurés par le minimal model chez des sujets diabétiques de type 2.

Objectif. – Le but de ce travail était de mesurer l’amplitude des modifications de la sensibilité à l’insuline (SI) et de l’efficience du glucose (SG) dans les suites immédiates d’un exercice chez des diabétiques de type 2 (T2D), comme précédemment étudié chez des sujets non diabétiques.

Méthodes. – Quatorze sujets (sept témoins non diabétiques: C et sept T2D) ont participé à l’étude. Deux hyperglycémies intraveineuses avec prélèvements rapprochés (frequently sampled intravenous glucose tolerance test [FSIVGTTs], 0.5 g/kg) sur 180 minutes et analyse par modélisation mathématique ont été effectuées d’une manière randomisée, l’une au repos et l’autre juste après un exercice de 15 minutes à 50 % de la fréquence cardiaque maximale (FCmax) suivi de cinq minutes à 85 % de FCmax. SI et SG sont calculées avec le minimal model de Bergman.

Résultats. – Après l’exercice, SI a augmenté de 773 %, passant de 0.62 ± 0.16 à 5.41 ± 1.59 min−1 × 10−4/(U/mL), se rapprochant de SI au repos chez les témoins (5.52 ± 2.28), alors que SG est resté inchangé. L’index réponse aiguë de l’insuline (AIRG) × SI et le produit de la concentration de l’insuline basale (IB) × SI effondrés avant l’exercice augmentaient (P < 0.05) sans atteindre les valeurs normales.
1. Introduction

The physiological effects of exercise on glucose homeostasis include both long- and short-term effects. The importance of the long-term effects of regular exercise is evidenced by its diabetes-preventing effects [1,2]. However, glucose disposal is markedly increased by a single bout of exercise [3,4], which can, in diabetics, exert glucose-lowering effects [5–7]. A considerable body of knowledge has been collected over the past few years on the molecular mechanisms behind the effects of both regular training and acute exercise on glucose handling in muscles. As reviewed by Zierath [8], exercise potentiates most of the insulin-mediated postreceptor events that lead to GLUT-4 translocation from intracellular stores to membrane. In addition, it improves blood supply to muscles [9,10], counteracts the ability of lipids to induce insulin resistance [11] and modifies the hormonal regulation of hepatic glucose output. These exercise-induced alterations in muscle glucose handling are likely to explain most of the insulin-sensitizing and diabetes-preventing effects of exercise and many (but not all) defects of insulin action observed in type 2 diabetes and insulin resistance are reversed by the effects of exercise [8].

In terms of whole-body glucose disposal, the effects of exercise can be measured by the minimal model analysis of intravenous glucose load. This approach has the advantage of measuring the dose–response relationship between insulin and glucose handling by tissues (insulin sensitivity \( S_I \)) together with glucose disposal that is independent of any change in insulin (glucose effectiveness \( S_G \)). In non-diabetic controls, both regular training [12] and acute exercise [3] are known to markedly enhance both parameters.

However, there is less information concerning the acute effects of exercise on these two parameters in type 2 diabetic subjects, a population for whom exercise has become a well-recognized therapeutic tool. Indeed, it would be useful to determine the extent of the short-term effects of exercise in this patient population. Therefore, the aim of this study was to measure the effects of a single bout of exercise on minimal model parameters in type 2 diabetes using the same protocol as in a previous study of the acute effects of exercise in non-diabetic subjects [3].

2. Subjects and methods

The present study involved seven type 2 diabetics (T2D; five men and two women) and seven non-diabetic individuals (controls [C]) who were matched for age, body mass index (BMI) and physical activity. The characteristics of both these groups are presented in Table 1. As a comparison, we also give the values for glucose disposal parameters \( S_I \) and \( S_G \) as previously measured, using the same technique, in two previous studies by our unit [3,13]. Manetta et al. [13] studied four well-defined groups of non-diabetic individuals: 16 male cyclists [eight young (24.7 ± 1.4 years; 21.7 ± 0.6 kg m\(^{-2}\)) and eight middle-aged (51.6 ± 1.2 years; 23.9 ± 0.3 kg m\(^{-2}\))] and 16 sedentary men [eight young (23.9 ± 0.8 years; 22.1 ± 0.4 kg m\(^{-2}\)) and eight middle-aged (52.3 ± 1.1 years; 25.1 ± 0.6 kg m\(^{-2}\))]. The characteristics of these four groups of men have been reported elsewhere [13]. Brun et al. [3] studied a non-diabetic sedentary group (29.6 ± 2.0 years; 22.8 ± 1.1 kg m\(^{-2}\)) before (ND bef) and after (ND aft) the same type of acute exercise as used in the present trial.

The T2D in the present study were all being treated with metformin and glibenclamide, but no oral treatments were taken on the morning of the exercise test. Informed consent was obtained from all study participants after an explanation of the nature of and risks involved in participation in the experiment. The study was also approved by the local ethics committee.

2.1. Protocol

The diabetic patients came twice, in random order, to the laboratory. On the first occasion, after overnight fasting, they underwent a frequently sampled intravenous glucose tolerance test (FSIVGTT); three days later, they underwent an FSIVGTT immediately after having done a standardized exercise protocol. Only the diabetics did the exercise test, which was performed on a cycloergometer (Ergoline). Heart rate was monitored by ECG. The patients were asked to exercise for 15 minutes at 50% of their theoretical maximum heart rate for age (using tables from the American Heart Association), followed by five minutes at 85% of this same heart rate. The controls visited the hospital at 9.00 am after an overnight fast and underwent a FSIVGTT.

### Table 1

Clinical characteristics of the study population (means ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Type 2 diabetics</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>55.6 ± 1.9</td>
<td>57.7 ± 2.6</td>
</tr>
<tr>
<td>BMI (kg m(^{-2}))</td>
<td>25.9 ± 0.9</td>
<td>27.1 ± 0.7</td>
</tr>
<tr>
<td>HbA(_{1c}) (%)</td>
<td>5.8 ± 0.1</td>
<td>9.5 ± 1.4</td>
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<tr>
<td>Duration of diabetes (years)</td>
<td>–</td>
<td>10.6 ± 5.1</td>
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</tbody>
</table>

Although no alimentary restrictions were imposed, all participants were asked to fast for 12 h before being tested. At 9.00 AM, a cannula was placed in the cephalic vein at the level of the cubital fossa for taking the blood samples, while glucose was injected into the contralateral cephalic vein. Glucose (0.5 g/kg body weight, 30% solution) was slowly injected over three minutes. Insulin (0.02 U/kg body weight) was injected intravenously after 19 minutes.

Two blood samples were drawn before the glucose bolus and also at one, three, four, eight, 10, 15, 19, 20, 22, 30, 41, 70, 90 and 180 minutes after glucose injection. All of these samples were necessary for the minimal model calculations.

### 2.2. Laboratory measurements

All samples were analyzed for plasma insulin by radioimmunoassay (Bi-insulin IRMA kit; CIS Bio International, Gif-sur-Yvette, France) and, for plasma glucose, with an Olympus 2700 automated analyzer.

### 2.3. Measurement of $S_I$ and $S_G$

The minimal model analysis from the FSIVGTT was performed according to the method reported by Bergman [14], using the TISPAG software, based on a non-linear least-squares estimation, that is usually used by our laboratory [3]. This programme produced the values for $S_I$ and $S_G$. In the minimal model, $S_I$ represents the dose–response effect on glucose disposal when insulin is increased above baseline, while $S_G$ is the rate of glucose disposal observed with no changes in insulin levels [14,15]. These calculations have been previously described [3].

$S_G$ is divided into two components: the contribution of hyperglycaemia per se to tissue glucose uptake [$GEZI = S_G - (I_B \times S_I)$]; and the effect of basal insulin on glucose uptake [BIE = $I_B \times S_I$]. $G_B$ and $I_B$ represent basal values of glucose and insulin.

In addition to the minimal model method, surrogates of insulin resistance or $S_I$ were used — namely, the homoeostasis model assessment insulin-resistance index [HOMA-IR; $I_B (\mu U/mL) \times G_B (\text{mmol/L}/22.5)$] [16] and the quantitative insulin-sensitivity check index (QUICKI; $1/\log (I_B) + \log (G_B)$) [17]. For a better evaluation of insulin resistance from fasting values, we also calculated HOMA%S with the software HOMA2, kindly provided by Dr Jonathan Levy.

### 2.4. Assessment of $\beta$-cell function

First-phase insulin secretion ($I_{1+3}$) was calculated as the sum of insulin concentrations at one and three minutes after glucose injection. The incremental insulin value over baseline (difference between $I_B$ and the maximum insulin value during the first phase) was also calculated. The acute insulin response (AIRG), reflecting insulin secretion, was also calculated as the mean serum insulin measured at multiple times after glucose injection compared with the mean value above baseline at two to 10 minutes. The products of AIRG $\times S_I$ and $I_B \times S_I$ were calculated as previously detailed by Bergman [14,15].

### 2.5. Statistics

Results are presented as means ± SEM. Comparisons between the controls and diabetics were investigated using the non-parametric Mann–Whitney test. Modifications of parameters of glucose assimilation induced by exercise in the diabetic group were investigated using the non-parametric Wilcoxon test. The level of significance for both these tests was defined as $P<0.05$.

### 3. Results

#### 3.1. Comparison of T2D and C before exercise

Diabetics and controls were not significantly different in age and BMI. However, $S_I$ was markedly lower in T2D than in C: 0.62 ± 0.16 versus 5.52 ± 2.28 minute$^{-1} \times 10^{-4}/(\mu U/mL)$, respectively ($P<0.01$) (Fig. 1). Also, BIE was significantly lower in T2D compared with C: 0.06 ± 0.02 versus 0.55 ± 0.23 minute$^{-1} \times 10^{-2}$, respectively ($P<0.01$) (Fig. 2). In addition, AIRG, AIRG $\times S_I$, and $I_B \times S_I$ were significantly lower in T2D compared with the controls (Table 2).

#### 3.2. Effects of exercise

The bout of exercise did not significantly change the $I_{1+3}$ in the diabetic group, but it did increase (non-significantly) from 22 ± 4.6 to 38 ± 6.5 $\mu U/mL$ ($P=0.06$), as did AIRG (from 8.97 ± 1.85 to 15.29 ± 2.61; $P=0.06$). However, AIRG $\times S_I$ and $I_B \times S_I$ significantly increased in T2D after exercise (Table 2). Moreover, $S_I$ dramatically increased by about 773%, from 0.62 ± 0.16 minute$^{-1} \times 10^{-4}/(\mu U/mL)$ at rest to 5.41 ± 1.59 minute$^{-1} \times 10^{-4}/(\mu U/mL)$ after exercise ($P<0.05$), reaching the range of control values (5.52 ± 2.28 minute$^{-1} \times 10^{-4}/(\mu U/mL)$) (Fig. 1). On studying the patients individually, all except one increased their $S_I$ (range: −67% to 2688%; (Fig. 3).

Furthermore, $S_G$ and GEZI did not significantly change with exercise (Fig. 2), whereas BIE was significantly increased ($P<0.05$). As for HOMA-IR and QUICKI, they were significantly higher and lower, respectively, in the diabetics and controls, respectively. Nevertheless, neither group showed any modification of insulin sensitivity after exercise (Table 2). We also calculated HOMA%S with the HOMA2 software, considered a better method for calculating insulin sensitivity from baseline values. However, as shown in Table 2, this also detected no improvement of $S_I$, although there was a non-significant trend to do so.

### 4. Discussion

The main finding of this study was that a single bout of sub-maximum exercise in type 2 diabetics induced a major increase in $S_I$ and in the disposition indices measuring the homoeo-
Static loop between $S_I$ and insulin release, while $S_G$ remained unchanged. This modification of $S_I$ was clearly evident on the minimal model analysis of an FSIVGTT, while simple surrogates of $S_I$, such as QUICKI or HOMA, even when calculated with specifically designed software, failed to detect it.

This study used a protocol similar to that of a previous study by our group involving non-diabetic subjects [3] to allow comparison of the effects of the same type of acute exercise in type 2 diabetics (see Figs. 1 and 2).

It is well known [18] that, after a few hours, these acute effects of exercise gradually disappear. However, in the short term, $S_I$ achieved values similar to those seen in controls at rest (although it was still lower than those measured after exercise in controls [3]). Nevertheless, there was wide interindividual variability in the magnitude of the increase (as shown in Fig. 3).

Glucose effectiveness, which represents the body’s ability to lower blood glucose independently of any change in insulin levels, did not significantly increase after acute exercise, in contrast to what has been repeatedly observed after both acute exercise [17,19,20] and training in non-diabetic subjects [17,19,20]. Moreover, the part of the $S_G$ called GEZI, representing the specifically insulin-independent effects, did not change. The reason for this lack of increase in $S_G$ and GEZI in T2D patients may be related to methodology or to a specific aspect of glucose metabolism in diabetics. Calculation of $S_G$ in the classical form of the minimal model, as in the present study, has been the subject of a number of methodological studies [17,19,20]. Compared with the more sophisticated approaches using isotope tracers, minimal model $S_G$ has been found to somewhat overestimate glucose effectiveness [21,22]. Much of this overestimation...
is probably related to the overly simplistic model used for the calculation, which assumes a monocompartmental distribution of glucose. The simplicity of the model, however, does not render it invalid and, despite the overestimation, the classical minimal model procedure is widely used to assess $S_G$ and has always led to results in accordance with more sophisticated methods. As for the effects of exercise on glucose disposal, the minimal model has been widely used to assess changes in $S_G$ [3,4,12,13,23–28,29,30] and is, therefore, a common and well-recognized method for this purpose. Nevertheless, given the present findings, we cannot conclude that exercise has no effect on $S_G$ in diabetics. Perhaps more modest effects, not evidenced

### Table 2

<table>
<thead>
<tr>
<th>Insulin-sensitivity parameters in the present study and in previously studied non-diabetic controls [3]</th>
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<tr>
<td>-------------------------------------------------</td>
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<tr>
<td>Fasting insulin ($I_B$; µU mL$^{-1}$)</td>
</tr>
<tr>
<td>Fasting glycaemia (mmol L$^{-1}$)</td>
</tr>
<tr>
<td>$S_I$ [min$^{-1}$ × 10$^{-4}$/µU/mL]]</td>
</tr>
<tr>
<td>$S_G$ (min$^{-1}$ × 10$^{-2}$)</td>
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<tr>
<td>AIRG$_G$ (µU mL$^{-1}$)</td>
</tr>
<tr>
<td>$p2$</td>
</tr>
<tr>
<td>$p3$</td>
</tr>
<tr>
<td>AIRG$_G$ × $S_I$</td>
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<tr>
<td>$I_B$ × $S_I$</td>
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<td>$K_g$</td>
</tr>
</tbody>
</table>

Surrogates of insulin sensitivity

- HOMA-IR
- HOMA%S
- HOMA%B
- QUICKI
- $S_I = 40/I_B$

Data are expressed as means ± SEM.

* $P<0.05$ versus controls.
** $P<0.01$ versus controls.
*** $P<0.001$ versus controls.

† $P<0.05$ versus type 2 diabetics before exercise.
with the minimal model, might be detectable by more sensitive methods, as revealed by the slightly higher values of $S_G$ and GEZI in obese adolescents that were detectable only by isotope labelling [31].

What can be reasonably concluded from our findings is that a marked effect on $S_G$, as found in the controls [3], is no longer seen in diabetics using this sophisticated method, indicating that the $S_G$-enhancing effect of exercise is at least markedly reduced, if not totally blunted, in such patients. However, Kennedy et al. [32] showed that the effects of a single bout of exercise on GLUT-4 translocation to the plasma membrane (explaining $S_G$) are similar in both T2D and controls. In fact, they employed an exercise protocol that was somewhat different from ours (45–60 minutes at 60–70% $V_{O_{2max}}$ Versus 20 minutes). Presumably, the lack of $S_G$ response to exercise in our study can be explained by T2D-related metabolic defects and perhaps also by the short duration of the exercise [32].

In contrast, the response in $S_I$ was impressive and achieved the level of control values at rest. This is fully in accordance with the daily clinical observation of the marked acute effects of exercise on glucose disposal in T2D. All of our diabetic patients had low or very low $S_I$ values. Therefore, the recently discovered subgroup of insulin-sensitive type 2 diabetics [33] was not represented here. In fact, some of our patients had $S_I$ values in the range of the so-called ‘$S_I$-zero values’ — almost indistinguishable from zero. These $S_I$-zero values are often observed in diabetics or in severe insulin-resistance syndromes and have been the subject of in-depth methodological studies [34]. Such values, which are less frequently found when a minimal model is applied to oral glucose tolerance tests [35,36], are due to a ten-
capacity of insulin to increase when rise in S during exercise as a result of the increase in S. Because BIE is the product of S1 × SB, the marked increase in S1 (with no change in SB) will lead to an increase in BIE, which means that insulin at baseline is more effective. However, this is only a mechanical effect of the rise in S1 and will occur regardless of what happens to the SG. To better evaluate the overall effect of this rise in S1 on glucose tolerance, other FSIVGTT-derived parameters can be used. For example, as seen in Table 2, the exponential decrease in blood glucose after IV glucose loading, called KG, is not improved. In contrast, both the product of AIRG × S1, which quantifies the homeostatic feedback between insulin sensitivity and insulin secretory response, and of S1 × SB, which quantifies the feedback under baseline conditions, are increased. These improvements in glucose disposal fail to normalize these products, as only insulin sensitivity is increased, with no significant change in insulin release. The most widely employed methods for evaluating insulin resistance are clearly not able to detect this important increase in S1, and neither QUICKI nor HOMA was significantly changed in our patients after exercise.

This inability of the usual surrogates of insulin sensitivity to detect a change that is obvious with the minimal model is not surprising if we scrutinize the literature on this topic. These surrogates, based on fasting values of glucose and insulin, provide a good evaluation of insulin sensitivity in non-diabetic subjects, but are no longer valid in subjects whose glycaemia is greater than 7 mmol [38] (as confirmed by our findings [39]), and they cannot detect the insulin-sensitizing effect of training in healthy subjects [13,39]. This is because their validity relies on the capacity of insulin to increase when S1 decreases, a function that is perturbed in overt diabetes, but is also irrelevant in situations such as training, when S1 is very high and insulin can no longer decrease. Besides the simplistic calculation of HOMA-IR as the crude product of Gb × I0/22.5, we also calculated the HOMA%S using the software HOMA2, which is generally considered to be the better approach. Even with this procedure, however, the rise of S1 as revealed by the minimal model was not significant, but showed only a tendency to increase.

It may be argued that neither minimal model parameters (S1 or SG) nor surrogates of insulin sensitivity (HOMA or QUICKI) were designed for assessing postexercise glucoregulation. Surrogates require fasting basal conditions, and minimal model equations assume that the model parameters p1, p2 and p3 are constant over the 180 minutes of the IVGTT. In the immediate postexercise period, metabolic changes such as rebound in blood glucose or in FFA might theoretically interfere with the determination of S1, but both would yield an underestimation of S1 rather than an overestimation and, thus, do not explain the rise in S1. On the other hand, the physiological postexercise rise in blood glucose and insulin might interfere with the calculation of surrogates and explain why they fail to detect the rise in S1.

Nevertheless, our finding that QUICKI and HOMA are not appropriate markers of the acute insulin-sensitizing effects of exercise in diabetes are logical and consistent with the currently available literature. This suggests that these indices (albeit useful in other situations) should not be used in the follow-up of exercise protocols in diabetics to detect changes in S1.

Clearly, the present data do not allow any conclusions to be drawn regarding the possible metabolic effects of moderate acute exercise under other experimental conditions, such as a more prolonged period of moderate exercise without the heavier five-minutes bout at the end. Similarly, in diabetics, there is a paucity of information on the effects on minimal model parameters observed much later following a similar bout of exercise (for instance, the next day after an overnight fast), or after a training period using similar or more moderate exercise, but of longer duration.

In general, the new information provided by our study is that S1 as measured by the minimal model is dramatically improved in type 2 diabetic patients and, in the short term, can even achieve the zone of control values at rest. This resulted in a marked, albeit incomplete, improvement in the disposition index. In contrast, the exercise-induced increase in SG observed in control subjects using the same protocol was not seen in diabetics, suggesting little or no effect of short bouts of acute exercise on SG in type 2 diabetics. This finding is important for interpreting minimal model measures of S1 and SG during exercise-training protocols, as the acute effects of exercise are quantitatively important and need to be separated from chronic effects. Also, the magnitude of the short-term rise in S1 suggests that repeated acute exercise may be, on its own, a powerful insulin-sensitizer independent of the additional and well-demonstrated long-term effects of regular exercise training.

References
