

The Blood Glucose Lowering Effects of Exercise and Glibenclamide in Patients with Type 2 Diabetes Mellitus

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Physical exercise is associated with a fall in serum insulin levels, whereas sulphonylurea administration increases insulin release. To date, the opposing effects of exercise and sulphonylurea administration have not been systematically studied in Type 2 diabetic patients, who are not infrequently treated with sulphonylureas. In this study nine patients with Type 2 diabetes mellitus were subjected to four treatments in random order on separate days: (A) endurance exercise after the administration of 3.5 mg glibenclamide; (B) as A but given only 1.75 mg glibenclamide; (C) as A but with placebo; (D) rest and administration of 1.75 mg glibenclamide. Exercise and placebo resulted in only a small decrease in glycaemia. Rest and administration of 1.75 mg glibenclamide led to a moderate but steady fall in blood glucose concentrations. If glibenclamide administration and exercise were combined, blood glucose concentrations declined more markedly. Serum insulin concentrations showed a physiological decrease during exercise and placebo administration. If patients rested after administration of glibenclamide serum insulin levels rose and remained elevated. When exercise and glibenclamide were combined the rise in serum insulin levels was blunted and insulin levels fell once exercise was begun. Thus, exercise attenuates the glibenclamide induced increase in serum insulin in moderately hyperglycaemic Type 2 diabetic patients. Nevertheless, exercise has a substantial hypoglycaemic effect in glibenclamide treated Type 2 diabetic patients. © 1998 by John Wiley & Sons, Ltd.

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Introduction

In healthy subjects exercise leads to a reduction in insulin secretion, enabling hepatic glucose output to accommodate the increased peripheral glucose uptake of working muscle.¹ If healthy individuals are subjected to exercise following glibenclamide administration, they do not demonstrate this adaptive response in insulin release.² However, the adaptation was observed in healthy subjects with the novel sulphonylurea glimepiride.³ It is not known whether Type 2 diabetic patients treated with sulphonylureas show a physiological insulin response to exercise or not. We hypothesized that if exercise and glibenclamide administration are combined in Type 2 diabetic patients insulin release will not be decreased, leading to a marked fall in blood glucose levels. The present study was designed to evaluate the individual effects of exercise and glibenclamide alone and in combination on glycaemia and serum insulin concentrations in Type 2 diabetic patients.

Research Design and Methods

Nine Type 2 diabetic patients (age 53 ± 9 years (mean \pm SD), body mass index 33.2 ± 5.5 kg m⁻², duration of diabetes 5 ± 6 years, HbA_{1c} 7.8 ± 1.3 % (normal <6.1 %)) took part in the study. All patients were asked to keep a weight maintaining diet during the study period. Three patients had previously used oral hypoglycaemic agents, however, at the time of the study these drugs had not been administered for over 3 months. Patients with self-reported angina, evidence of coronary heart disease, an ischaemic exercise ECG, uncontrolled arterial hypertension, evidence of acute intercurrent illness or diabetic late complications (proliferative retinopathy, symptomatic neuropathy, clinical nephropathy) were excluded. Written informed consent was obtained prior to participation for each subject. The study protocol was approved by the local ethical committee and performed in accordance with the Declaration of Helsinki.

Patients were subjected to four different experimental situations. On the study days they either rested after oral consumption of 1.75 mg glibenclamide (A); exercised after placebo administration (B); or exercised after taking 1.75 mg (C) or 3.5 mg (D) of glibenclamide in a

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micronised formulation (Euglucon 3.5, Hoechst AG, Frankfurt, Germany). Each patient performed all four studies. Assignment to the treatment sequences was random. The minimum interval between each of the four studies was 7 days. Patients were requested to avoid alcohol on the evening before testing and were asked not to smoke or drink coffee or tea on the morning of the study. No medication was given in the 12 h prior to the test period.

Patients reported to the exercise laboratory at 8:00 am after a 12 h fast. Upon arrival, an indwelling intravenous cannula was inserted into a forearm vein and kept patent by slow infusion of physiological saline. Drug or placebo was administered with 100 ml of tap water at $t=0$ min; patients then rested for 60 min in a reclining armchair. Exercise was begun at $t=60$ min and performed for 60 min on an upright bicycle ergometer (Conditronic 30, Keiper Dynavit, Rockenhausen, Germany). The work load was intermittently adjusted to achieve a heart rate of 120 beats min^{-1} . A 60 min recovery period followed.

Blood samples were drawn in 20 min intervals before and after exercise, and at 10 min intervals while exercising. Plasma glucose concentrations were measured immediately by a glucose oxidase method (Glucose-Analyser II, Beckman Industries, Fullerton, USA). Aliquots of blood for all other estimations were stored on ice prior to further analysis. Free-flowing venous blood for the estimation of plasma lactate was collected into fluoride-EDTA. Plasma lactate concentrations were measured amperometrically (YSI Model 27 Lactate-Analyzer, Yellow Springs, USA). Aliquots for the measurement of serum insulin, serum C-peptide and plasma glucagon were stored at -20°C pending measurement by standard radio immunoassays.

Statistical Analyses

All results are presented as mean \pm SD in the tables or as mean \pm SE in the figures. The area under the curve was calculated by trapezoidal rule. Statistical analysis was performed using Student's paired t -test for paired data and analysis of variance for repeated measurements.

Results

Basal blood glucose values were comparable on all four study days (A: 10.0 ± 3.3 mmol l^{-1} ; B: 9.5 ± 3.0 mmol l^{-1} ; C: 9.5 ± 2.6 mmol l^{-1} ; D: 9.3 ± 3.2 mmol l^{-1}). Thirty minutes after administration of 1.75 mg glibenclamide and rest, blood glucose began to fall, and continued to fall to the end of the observation period (Figure 1). Exercise alone resulted in a marginal decrease in blood glucose when placebo was given. The combined effects of glibenclamide and exercise induced a pronounced fall in blood glucose concentrations from the moderately hyperglycaemic basal values to euglycaemic values, with no significant differences between the two glibenclamide doses (glycaemia after exercise with 1.75 mg glibenclamide

ide 6.2 ± 0.9 vs 3.5 mg glibenclamide 6.3 ± 0.7 mmol l^{-1} ; $P=0.652$). The AUC of the blood glucose profiles ($\text{AUC}_{\text{blood glucose}}$) were comparable during the initial rest period ($F=0.84$; NS), but differed significantly during the exercise period ($F=4.35$; $P<0.02$) (Figure 3(a)). Blood glucose was higher with exercise and placebo than after exercise and either doses of glibenclamide. The blood glucose was also lower on both days with glibenclamide and exercise compared to glibenclamide and rest. In the post-exercise period the AUC for blood glucose was greater with placebo and exercise than with glibenclamide and exercise ($F=5.84$; $P<0.005$). AUC for blood glucose was comparable following glibenclamide administration during the post-exercise period on the days with and without exercise.

Baseline serum insulin concentrations (A: 69 ± 33 pmol l^{-1} ; B: 81 ± 50 pmol l^{-1} ; C: 71 ± 29 pmol l^{-1} ; D: 73 ± 36 pmol l^{-1}) were comparable on all four study days. Following administration of glibenclamide, insulin levels rose (Figure 2). If patients continued to rest serum insulin levels remained elevated. If patients exercised insulin levels decreased, then rose abruptly again once exercise stopped. This was observed with either dose of glibenclamide. During the exercise and placebo study, initial serum insulin levels remained unchanged prior to exercise, fell once exercise was begun, and also rose sharply at the end of exercise.

The AUC under the serum insulin profiles were comparable during the initial rest period ($F=2.43$; NS), but differed significantly during the exercise period ($F=10.5$; $P<0.0001$) (Figure 3(b)). During rest and 1.75 mg glibenclamide, the AUC for insulin was significantly greater than during exercise and either doses of glibenclamide. In the post-exercise period the AUC for insulin was greater following glibenclamide than after placebo ($F=4.90$; $P<0.009$). There was no difference in AUC for insulin following glibenclamide administration for the post-exercise period on the days with and without exercise.

Serum C-peptide concentrations paralleled serum insulin levels, i.e. after exercise lower levels were seen with placebo (0.30 ± 0.08 nmol l^{-1}) than with glibenclamide (1.75 mg: 0.41 ± 0.12 nmol l^{-1} ; 3.5 mg: 0.43 ± 0.13 nmol l^{-1} ; $p<0.05$). Plasma glucagon levels showed no systematic changes. The observed increments in heart rate (mean values of all days with exercise: from 76 ± 7 to 116 ± 12 beats min^{-1}), systolic and diastolic blood pressure (from 127 ± 14 to 167 ± 25 mmHg; from 79 ± 10 to 82 ± 9 mmHg), plasma lactate (from 1.6 ± 0.6 to 2.8 ± 1.6 mmol l^{-1}) confirm that the patients exercised at a comparable work load on all study days.

Discussion

The purpose of this study was to determine whether the physiological insulin response to exercise, namely a fall in serum insulin levels, is also seen in patients with Type 2 diabetes mellitus following the administration of

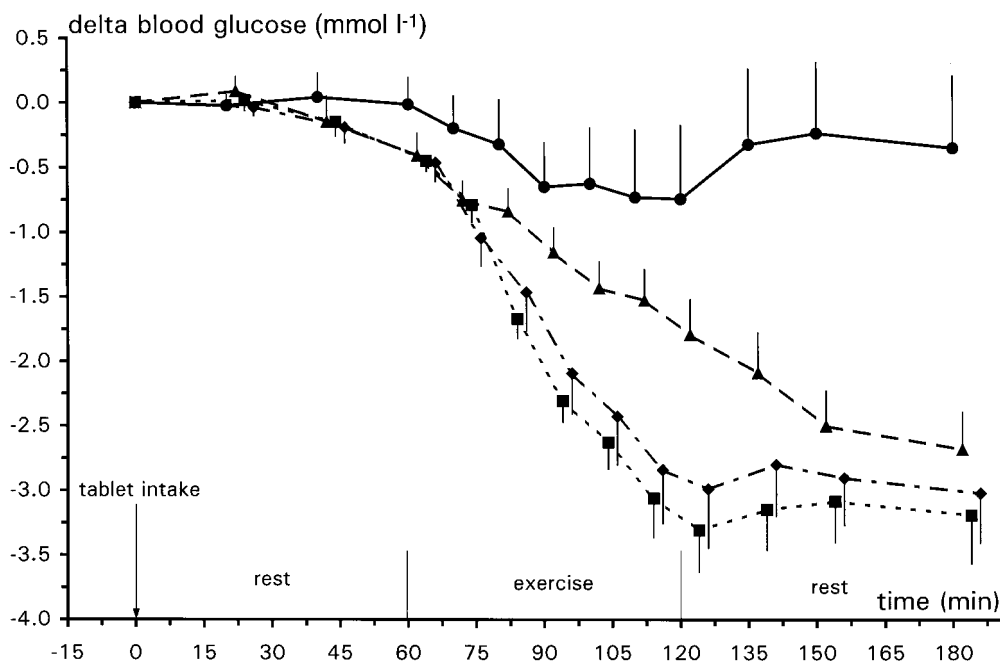


Figure 1. Blood glucose levels of nine Type 2 diabetic patients after 1.75 mg glibenclamide and rest (broken line), placebo and exercise (solid line), 1.75 mg glibenclamide and exercise (dotted line), 3.5 mg glibenclamide (dots and dashes)

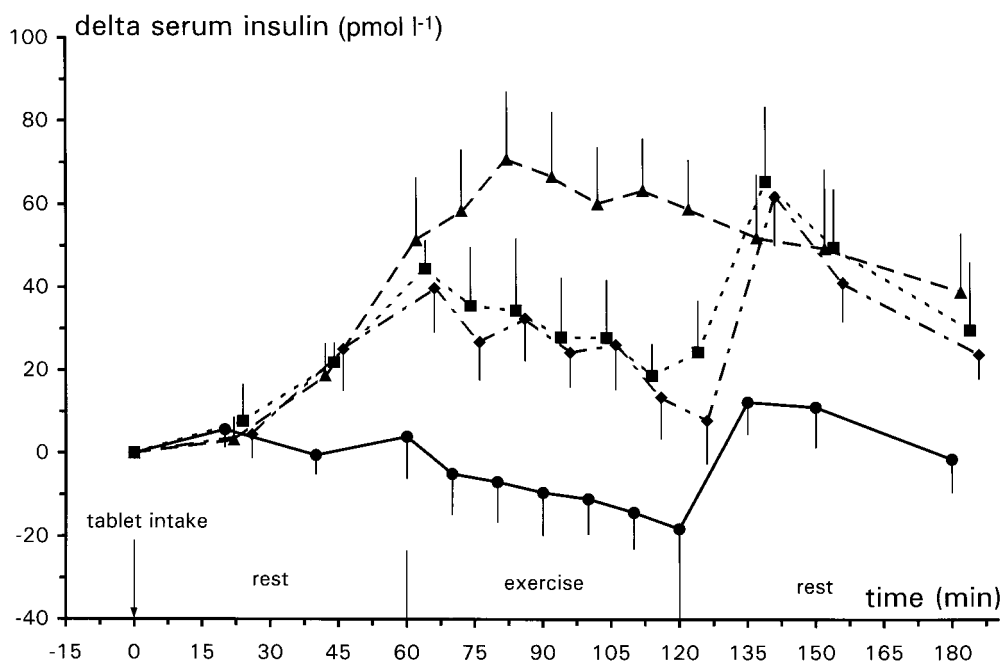


Figure 2. Serum insulin concentrations of nine Type 2 diabetic patients after glibenclamide and rest (broken line), placebo and exercise (solid line), 1.75 mg glibenclamide and exercise (dotted line), 3.5 mg glibenclamide (dots and dashes)

glibenclamide. Contradictory to our working hypothesis, we found that during exercise serum insulin levels fell and rose rapidly once exercise ended when glibenclamide was administered 1 h before exercise. This suggests that the physiological inhibitory effect of exercise on insulin secretion is preserved in Type 2 diabetic patients following administration of glibenclamide.

Previous research in this area has been controversial. A non-significant trend towards a fall in plasma insulin concentrations during exercise was seen in a study of

obese hyperglycaemic Type 2 diabetic patients treated with various sulphonylureas or diet.⁴ No fall in serum insulin concentrations was seen during exercise in healthy subjects following glibenclamide administration.² More recently a significant reduction in insulin secretion during exercise has been reported with the novel sulphonylurea glimepiride in fasting healthy volunteers³ and in Type 2 diabetic patients.⁸ In the latter study, exercise did not lead to a similar reduction in the AUC for insulin following administration of glibenclamide and breakfast

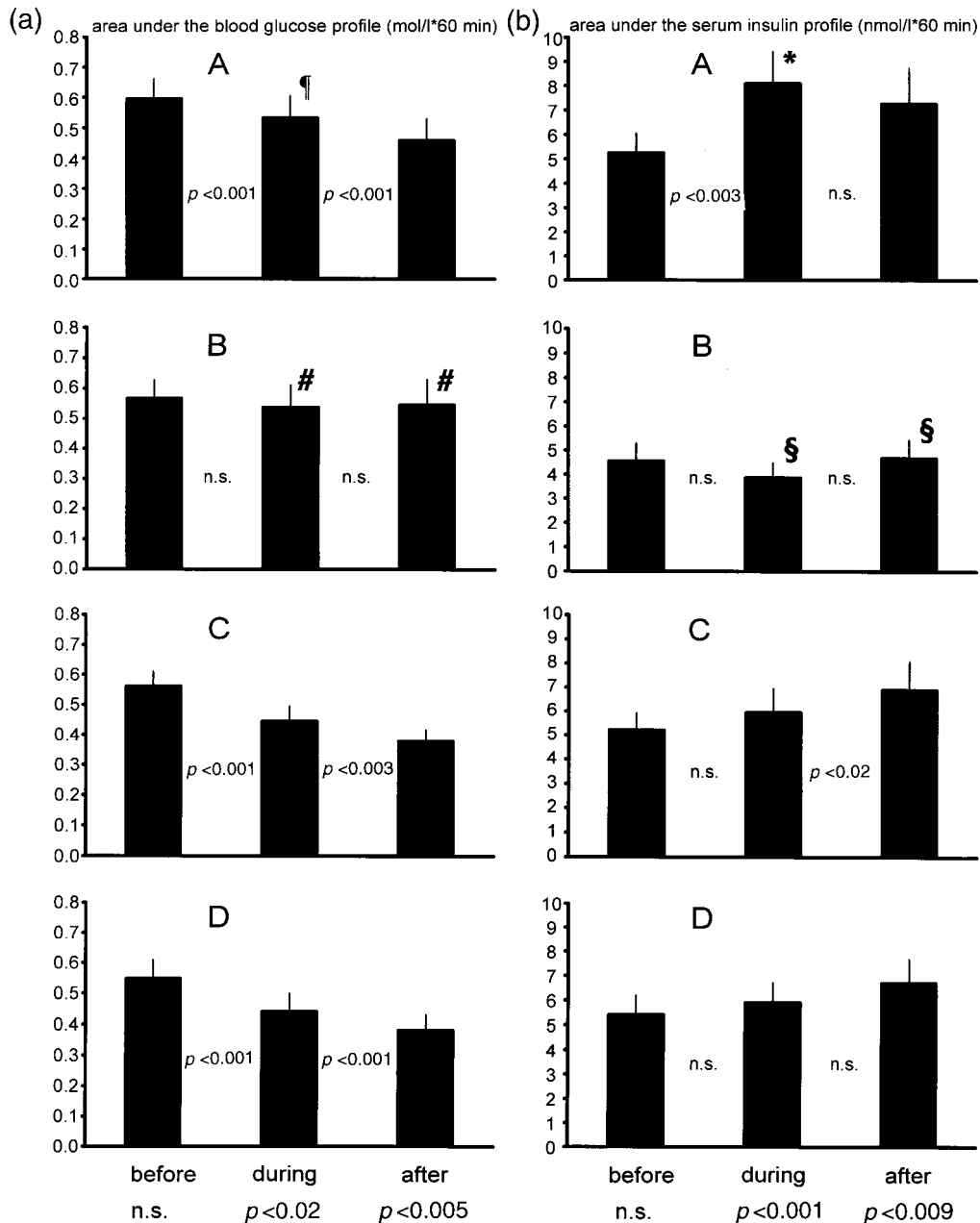


Figure 3. Areas under (a) the blood glucose profiles (b) the serum insulin profiles (mean + SE) for the periods before, during and after the four exercise treatments: A: 1.75 mg glibenclamide and rest; B: placebo and exercise; C: 1.75 mg glibenclamide and exercise; D: 3.5 mg glibenclamide and exercise. Significance of the differences in the AUC within the respective study periods (before, during and after exercise) are shown below the column. Differences between the study periods on a single study day with one treatment are given between the columns. Treatment differences are denoted as follows: ¶ greater AUC on study day A compared to C and D; # greater AUC on study day B compared to C and D; § smaller AUC on study day B compared to A and C; * greater AUC on study day A compared to C and D

as after glimepiride and breakfast.⁸ One possible explanation for this observation may be the differences in baseline plasma insulin concentrations between the two groups of patients studied.

Exercise induced hypoglycaemia in Type 2 diabetic patients treated with sulphonylureas is a practical concern. Although no hypoglycaemic episode was observed during our study, the decline in blood glucose did not stop while exercise continued. The most pronounced fall in blood glucose was observed upon the combined

administration of glibenclamide and exercise, indicating an additive effect of both. If exercise had continued or if the patients had been euglycaemic initially, hypoglycaemia may have occurred. The possibility of a marked fall in blood glucose levels must be taken into consideration by all exercising Type 2 diabetic patients treated with glibenclamide.

Contrary to our expectations the decline in serum insulin concentrations did not differ between the lower and higher glibenclamide dose. Plasma glibenclamide

concentrations, which may have helped to explain this observation, were not determined. Interestingly, others have also failed to find a significant dose–response relationship for single-dose administration of glibenclamide.⁵ Possibly the maximum acute effect of glibenclamide may be achieved at doses well below those commonly recommended.^{6,7}

In conclusion, in moderately hyperglycaemic Type 2 diabetic patients exercise suppress glibenclamide-stimulated endogenous insulin secretion. Nonetheless, the additive effects of exercise and glibenclamide resulted in a pronounced decline of blood glucose levels. This fall in glycaemia seen in our experimental study emphasizes that in daily life exercising Type 2 diabetic patients on glibenclamide therapy must be made aware of their particular risk of hypoglycaemic episodes.

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