Glycaemic control is improved by 7 days of aerobic exercise training in patients with type 2 diabetes

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Abstract

Aims/hypothesis—Cardiovascular events and death are better predicted by postprandial glucose (PPG) than by fasting blood glucose or HbA_{1c}. While chronic exercise reduces HbA_{1c} in patients with type 2 diabetes, short-term exercise improves measures of insulin sensitivity but does not consistently alter responses to the OGTT. The purpose of this study was to determine whether short-term exercise training improves PPG and glycaemic control in free-living patients with type 2 diabetes, independently of the changes in fitness, adiposity and energy balance often associated with chronic exercise training.

Methods—Using continuous glucose monitors, PPG was quantified in previously sedentary patients with type 2 diabetes not using exogenous insulin (n=13, age 53±2 years, HbA_{1c} 6.6±0.2% (49.1±1.9 mmol/mol)) during 3 days of habitual activity and during the final 3 days of a 7 day

aerobic exercise training programme (7D-EX) which does not elicit measurable changes in cardiorespiratory fitness or body composition. Diet was standardised across monitoring periods, with modifications during 7D-EX to offset increases in energy expenditure. OGTTs were performed on the morning following each monitoring period.

Results—7D-EX attenuated PPG ($p<0.05$) as well as the frequency, magnitude and duration of glycaemic excursions ($p<0.05$). Conversely, average 24 h blood glucose did not change, nor did glucose, insulin or C-peptide responses to the OGTT.

Conclusions/interpretation—7D-EX attenuated glycaemic variability and PPG in free-living patients with type 2 diabetes but did not significantly alter responses to the laboratory-based OGTT. These effects appeared to be independent of changes in fitness, body composition or energy balance.

Introduction

Glycaemic control is the primary focus of diabetes management. There is a strong, inverse association between HbA_{1c} and the risk of diabetes-related complications, including micro- and macrovascular diseases and mortality [1]. Evidence from epidemiological analyses indicates that the largest reductions in risk occur when patients with poor glycaemic control achieve fair or good glycaemic control ($HbA_{1c} <7\%$), but that additional reductions in risk, albeit smaller, may be achieved by further lowering HbA_{1c} (<6.0–6.5% [42.1–48.6 mmol/mol]) [1, 2]. Randomised controlled trials have demonstrated significant reductions in cardiovascular complications and death when HbA_{1c} is lowered to 7% or below, but have failed to provide sufficient evidence to support amending the current guidelines to include a universal HbA_{1c} target of 6.0–6.5% (42.1–48.6 mmol/mol) [3].

Three important trials, Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and the Veterans' Affairs Diabetes Trial (VADT), established that intensive pharmaceutical interventions to lower HbA_{1c} below 6.0% or 6.5% (42.1–48.6 mmol/mol) were no more effective than standard therapy in reducing adverse cardiovascular outcomes [4–6]. On the contrary, the intensive glycaemic control arm of the ACCORD trial was terminated prematurely due to significantly higher rates of mortality [4]. Although it has been difficult to pinpoint the cause of the higher mortality rate associated with intensive glycaemic control, higher rates of severe hypoglycaemia might have contributed [7]. Intensive glycaemic control is associated with a twofold increase in severe hypoglycaemia over standard therapy [8], and recent severe hypoglycaemia was a significant predictor of cardiovascular events and death in VADT [6]. Thus, there remains a need to identify safe, effective interventions to improve glycaemic control while simultaneously reducing glycaemic variability and minimising hypoglycaemic events.

While HbA_{1c} is strongly predictive of diabetes-related complications and events, it is an index of long-term glycaemic control and does not provide insight into changes in glycaemic variability or hypoglycaemia [9]. Thus, even as HbA_{1c} is lowered together with decreases in average blood glucose, increases in the magnitude, frequency or duration of hypoglycaemia or glycaemic variability may go undetected. Furthermore, HbA_{1c} does not distinguish pre- and postprandial conditions. These are considerable limitations given that hypoglycaemia initiates many of the same complications as hyperglycaemia (reviewed in [10]), and, because large fluctuations in blood glucose trigger physiological events thought to drive the micro- and macrovascular complications associated with type 2 diabetes [11], elevated glycaemic variability may be more damaging or additive to the complications caused by chronic hyperglycaemia [12, 13]. Correspondingly, mounting evidence points to postprandial glucose (PPG) as a better predictor of cardiovascular disease and death than fasting blood glucose or HbA_{1c} [12–16], indicating that direct measures of PPG are warranted.

As part of a healthy lifestyle, exercise has been shown to be more effective than some pharmacological agents in preventing the progression of prediabetes to overt type 2 diabetes [17]. Chronic exercise training reduces HbA_{1c} and is recognised by national and international health organisations as a key component of diabetes prevention and management [18–20]. The beneficial effects of exercise are commonly attributed to adaptations to exercise training, such as improvements in fitness, muscle oxidative capacity or body composition [21, 22]. However, 7 day aerobic exercise training programmes that do not measurably alter these factors [23, 24] consistently improve insulin sensitivity but not responses to the OGTT in patients with type 2 diabetes [23, 25, 26]. Because traditional measures of glycaemic control do not directly assess blood glucose in free-living persons consuming mixed meals, the specific effects of exercise on PPG and glycaemic variability, independently of changes in fitness or body weight and/or composition in patients with type 2 diabetes, are not clear.

In the current study we measured the effect of 7 days of aerobic exercise on PPG and glycaemic variability in free-living individuals with type 2 diabetes using a continuous glucose monitoring system (CGMS) and laboratory-based measures of glucose tolerance determined by OGTT. Additional snacks were provided during the 7-day exercise programme in order to offset increases in energy expenditure. This enabled us to examine the specific effects of short-term exercise on glycaemic control in free-living patients with type 2 diabetes, independently of changes in fitness, muscle oxidative capacity, body composition or energy balance.

Methods

Subjects and design

The investigation was carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000. Protocols were approved by the University of Missouri Health Sciences Institutional Review Board, and written informed consent was obtained from all volunteers.

Overweight and obese (BMI 25–43 kg/m^2), sedentary (<60 min structured exercise/week) volunteers aged 30–65 years with type 2 diabetes not requiring exogenous insulin were recruited. Participants were screened via detailed medical history questionnaire, physical examination, graded exercise test, and blood and urine analysis. Exclusion criteria included: HbA$_{1c}$ 10% (85.8 mmol/mol), evidence of advanced cardiovascular, renal or hepatic diseases, contraindications to exercise training, body weight change 3% within 6 months, medication change within 3 months, and smoking. Of the 67 participants screened, 13 were eligible for participation.

Experimental design

Glycaemic control was assessed by continuous glucose monitoring (*i*Pro CGM; Medtronic, Minneapolis, MN, USA) during 3 days of habitual, sedentary activity (baseline) and during the final 3 days of a 7 day aerobic exercise training programme (7D-EX). Fasting-state OGTTs were performed on the morning immediately following each monitoring period.

Exercise intervention

The exercise programme consisted of 60 min of supervised exercise (alternating 20 min of treadmill walking and stationary cycling) for 7 consecutive days at 60–75% heart rate reserve, as previously described [27]. Resting heart rate (HR$_{rest}$) and peak heart rate (HR$_{peak}$) values obtained from the cardiorespiratory fitness test were used to calculate the target heart rate (THR) by the Karvonen method: THR = [(HR$_{peak}$ – HR$_{rest}$) × %intensity] + HR$_{rest}$ [28].

Fitness and anthropometrics

Cardiorespiratory fitness (peak oxygen consumption [$\dot{V}O_{2peak}$]) was determined by indirect calorimetry (TrueOne 2400; Parvo Medics, Salt Lake City, UT, USA) during a graded exercise test on a Monarch bicycle ergometer (Monarch, Varberg, Sweden) as previously described [27]. Height, weight and body composition (dual-energy X-ray absorptiometry: Hologic QDR 4500A; Hologic, Waltham, MA, USA) were measured at baseline.

Continuous glucose monitoring

During the evening prior to each 3 day monitoring period, a glucose sensor was inserted subcutaneously in the periumbilical region and connected to the CGMS. Participants were allotted 3 h between meals and snacks and recorded the exact timing and composition of each meal. Diet was strictly standardised across both monitoring periods, and additional snacks were provided during 7D-EX to offset increases in energy expenditure and minimise changes in energy balance. Energy expenditure during the exercise bout was estimated using American College of Sports Medicine calculations [29]. Diet records were analysed for macronutrient content using Food Processor SQL (ESHA Research, Salem, OR, USA). Participants recorded the results of four or more fingerstick glucose readings (Accu-Chek Compact Plus; Roche Diagnostics, Indianapolis, IN, USA) each day for CGMS calibration. CGMS data were processed using Solutions Software for *i*Pro CGM. PPG and PPG excursions (PPG; postmeal minus premeal blood glucose) were determined at 30 min postmeal intervals, as previously described [30]. According to guidelines from the ADA, the

threshold for high glucose excursions was set at >10 mmol/l, and the threshold for low excursions was set at <4 mmol/l [3].

OGTT

OGTTs (75 g glucose) were performed after an overnight (10–12 h) fast at the same time of day across phases. Participants refrained from exercise and medication use on the morning of testing. Post-intervention OGTTs were performed within 12–24 h of the final bout of exercise, as previously described [26, 27, 31]. Blood samples were collected at 30 min intervals for measurement of glucose by the glucose oxidase method (Sigma-Aldrich, St Louis, MO, USA), and insulin and C-peptide by chemiluminescent enzyme immunoassay (Immulite 1000 Analyzer; Siemens Healthcare Diagnostics, Deerfield, IL, USA). The AUC for glucose, insulin and C-peptide responses to the OGTT was calculated using the trapezoidal method.

The homeostasis model assessment of insulin resistance was calculated from fasting glucose and insulin concentrations [32], and the Matsuda insulin sensitivity index was calculated from the glucose and insulin values at different time points during the OGTT [33].

Statistical analysis

There was no effect of meal or day on PPG or PPG (i.e. within each phase, PPG and PPG were not different between meals or across days and did not interact with the change in PPG or PPG during 7D-EX). Therefore, PPG and PPG were pooled across all meals and all days within each 3 day phase to calculate individual means (i.e. mean PPG and PPG for each patient averaged for every meal during each 3 day phase) for analysis, as previously described [30]. Differences in pre- and postintervention PPG and PPG were detected using two-way repeated measures ANOVA (time × treatment), as previously described [30]. Tukey post hoc testing was applied to identify specific between-phase differences. Paired t tests were performed to detect phase differences in paired observations. Statistical significance was set at $p<0.05$; all data are expressed as means±SEM. Statistical analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC, USA).

Results

All 13 (eight men, five women) sedentary, obese individuals with type 2 diabetes (HbA$_{1c}$ 6.64±0.16% (49.1±1.8 mmol/mol)) completed the study (Table 1).

Physical activity and energy balance

Sedentary individuals with type 2 diabetes acquired 5,801±770 steps/day at baseline and 6,049±806 steps/day, excluding steps taken during the exercise sessions, during 7D-EX (Table 1), suggesting habitual activity was not altered by the exercise intervention. Compliance with 7D-EX was 100%. Participants expended an estimated 112±8 kJ per exercise session and consumed an additional 89±20 kJ/day during 7D-EX.

Glycaemic control

Average 24 h blood glucose concentrations did not change significantly during 7D-EX. However, maximum daily blood glucose was lowered ($p<0.05$), the difference between minimum and maximum daily blood glucose was reduced ($p<0.05$), the number of high ($p<0.07$) and low ($p<0.05$) glucose excursions per day was reduced, and the amount of time spent both above ($p<0.07$) and below ($p<0.05$) the high and low glucose limits was also reduced (Table 2). Likewise, PPG, peak PPG, and PPG were reduced during 7D-EX ($p<0.05$; Fig. 1). Premeal blood glucose concentrations did not change.

Glucose tolerance

Fasting glucose, insulin and C-peptide, as well as glucose, insulin and C-peptide responses to the OGTT, were largely unaltered by the exercise intervention (Table 3).

Discussion

These data demonstrate that 7 days of aerobic exercise training reduces PPG and glycaemic variability in free-living individuals with type 2 diabetes but does not influence responses to the laboratory-based OGTT.

The health benefits of exercise training, including improvements in insulin sensitivity and glycaemic control, are commonly attributed to the adaptations associated with chronic exercise, including increases in cardiorespiratory fitness, changes in energy balance, or reductions in total or regional adiposity [21, 22]. In the present study we implemented a 7 day aerobic exercise programme that does not significantly change fitness or adiposity [23], and we provided supplemental food to offset increases in energy expenditure due to the exercise training programme, allowing us to ascertain the specific effects of exercise on glycaemic control. Therefore, the data presented here provide new evidence that daily exercise directly improves glycaemic control in patients with type 2 diabetes, prior to changes in fitness or adiposity and independently of changes in energy balance.

In agreement with previous studies, we did not observe significant changes in fasting glucose, insulin or C-peptide after 7D-EX in patients with type 2 diabetes, nor did we observe changes in the glucose, insulin or C-peptide responses to the OGTT. By contrast, we did observe significant changes in the postprandial response to meal ingestion as well as in glycaemic variability using CGMS, indicating that CGMS may be a more sensitive tool to detect changes in glucose control in patients with type 2 diabetes.

It is not yet clear why changes in PPG were captured by CGMS under free-living conditions but not by the laboratory-based OGTT. However, the differences in the macronutrient content of the glucose drink consumed during the OGTT (100% of energy from carbohydrate) and the mixed meals consumed during CGMS monitoring (60% of energy from carbohydrate, 24% from fat and 14% from protein) would differentially influence rates of absorption, gastric emptying and insulin secretion and might have been a contributing factor. Furthermore, these data agree with findings from others and suggest that responses to the OGTT may not be indicative of day-to-day glycaemic control [30, 34]. Similarly, whereas 7 days of exercise training typically improves insulin sensitivity measured via the

hyperinsulinaemic–euglycaemic clamp in patients with type 2 diabetes [26], responses to the OGTT are generally unaffected [27]. Prior investigations using the clamp and OGTT have provided important experimental insight into the effects of exercise on insulin sensitivity and glucose tolerance. However, as evidenced here, traditional measures of glycaemic control do not adequately reflect PPG responses to mixed-meal ingestion under free-living conditions [35–37], and therefore may not provide the most accurate insight into the effect of short-term exercise training on PPG in individuals with type 2 diabetes. Here we present new evidence that daily exercise improves day-to-day glycaemic control, reducing the frequency, magnitude and duration of glycaemic excursions in previously sedentary patients with type 2 diabetes under free-living conditions. Moreover, these favourable changes occurred without increasing the prevalence of hypoglycaemia, which is thought to cause many of the same complications as elevated blood glucose (reviewed by Dandona et al. [10]).

Although these data provide evidence that exercise directly modulates PPG, the precise time course for these changes is unclear. We did not observe significant differences in PPG across treatment days (within days 5–7 of 7DEX), indicating that the improvement in glycaemic control occurred quickly. Nonetheless, we speculate that glycaemic control would improve further with chronic exercise in patients with type 2 diabetes, as longer training regimens commonly produce structural and functional adaptations that influence insulin sensitivity, including increases in skeletal muscle mitochondrial content, oxidative capacity and capillary density.

While these data are promising, the volume of exercise used in this study is above the amount currently recommended for patients with type 2 diabetes [18]. Additional studies are warranted to determine the precise mode, frequency, amount and intensity of exercise necessary to optimise glycaemic control in this population and to determine whether similar results may be obtained in more diverse populations in those treated with insulin therapies or with uncontrolled type 2 diabetes.

Finally, the advantages and limitations associated with the CGMS technology should be considered. There is a well-documented lag time between the equilibrium of glucose in the capillary blood measured by traditional glucometers and the interstitial fluid measured by the CGMS [38, 39]. At times when blood glucose concentrations are changing at very high rates (>27 mmol/l per min), the delay may result in an underestimation of the rate of change in blood glucose concentrations [40] or failure to detect rapid, transitory excursions [41]. However, CGMS has been validated against measures of venous and capillary blood as a tool to measure glycaemic responses to meal ingestion [42], and exercise does not appear to influence the duration of the lag time between changes in capillary and interstitial glucose [38], the relative difference (~15%) in CGMS and glucometer recordings [41], or the rate of accurately identifying hypoglycaemic excursions in patients with type 1 diabetes [41]. Thus, it is unlikely that exercise appreciably influenced the accuracy or reliability of the CGMS measures in the present study. Furthermore, unlike laboratory-based measures of insulin sensitivity (hyperinsulinaemic–euglycaemic clamp), glucose tolerance (OGTT) or long-term glycaemic control (HbA$_{1c}$), the CGMS records minute-to-minute measures of blood glucose

over multiple days, allowing direct quantification of the magnitude and duration of PPG in free-living individuals consuming mixed meals [43].

In summary, we demonstrate that short-term daily exercise reduces PPG and glycaemic variability in patients with type 2 diabetes and does not produce the increases in the incidence of hypoglycaemia sometimes associated with some intensive pharmacological interventions. These data also show that the effects of exercise to improve glycaemic control take place quickly, are not reliant on adaptations to chronic exercise and are not reflected by changes in the response to the laboratory-based OGTT. Overall, our findings reinforce the utility of daily exercise to reduce glycaemic variability quickly and safely in patients with well-controlled type 2 diabetes.

Acknowledgments

Abbreviations

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7D-EX	7 Day aerobic exercise training programme
CGMS	Continuous glucose monitoring system
PPG	Postprandial glucose
PPG	Postprandial glucose excursions
$\dot{V}O_{2peak}$	Peak oxygen consumption

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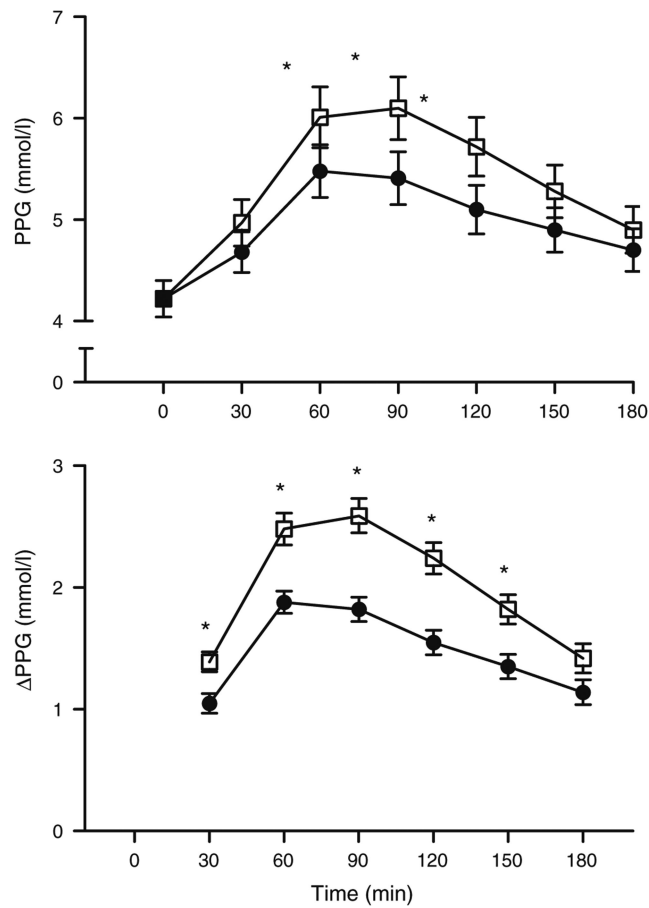
Fig. 1.
Mean PPG (a) and PPG (b) in patients with type 2 diabetes during 3 days of habitual physical activity (baseline; white squares) and during the final 3 days of a 7 day aerobic exercise training programme (7D-EX; black circles). *$p<0.05$ (significantly different from corresponding baseline time point)

Table 1

Baseline characteristics of sedentary patients with type 2 diabetes ($N = 13$)

Age (years)	53±2
Sex	8 male, 5 female
Weight (kg)	98.4±5.8
BMI (kg/m²)	34.1±1.3
Body fat (%)	33.6±2.0
$V\dot{O}_{2peak}$ (ml kg^{-1} min^{-1})	22.9±1.5
Energy intake (kJ/day)	462±40
Macronutrients	
Energy from carbohydrate (%)	60±2
Energy from fat (%)	26±2
Energy from protein (%)	14±1

All data are expressed as means±SE

Table 2

Glycaemic control in 13 previously sedentary patients with type 2 diabetes during 3 days of habitual physical activity (baseline) and the final 3 days of 7D-EX

Variable	Baseline	7D-EX	*p* value
Average blood glucose (mmol/l)	7.0±0.4	6.7±0.3	0.26
Minimum blood glucose (mmol/l)	3.6±0.3	4.0±0.2	0.17
Maximum blood glucose (mmol/l)	13.6±1.2	10.9±0.8	<0.01
Min-max blood glucose (mmol/l)	10.0±1.1	6.9±0.7	<0.01
High excursions (no. per day)	1.4±0.4	1.0±0.4	0.07
Low excursions (no. per day)	0.8±0.2	0.2±0.1	0.02
Duration above high limit (min/day)	140.4±48.3	66.5±33.4	0.06
Duration below low limit (min/day)	35.5±14.3	7.7±4.0	0.04

All data are expressed as means±SE

The minimum and maximum blood glucose values were the lowest and highest measured during each 3 day monitoring period

According to ADA guidelines [3], the thresholds for high and low glucose excursions were >10 mmol/l and <4 mmol/l, respectively; thus, the number and duration of excursions correspond to the average number of times and duration for which blood glucose concentrations were above or below the defined thresholds each day

Min-max blood glucose, difference between minimum and maximum daily blood glucose

Table 3

Blood chemistry, glucose tolerance and insulin sensitivity in 13 previously sedentary patients with type 2 diabetes during 3 days of habitual physical activity (baseline) and the final 3 days of a 7 day aerobic exercise training programme (7D-EX)

Variable	Baseline	7D-EX	*p* value
Fasting glucose (mmol/l)	6.99±0.39	6.76±0.36	0.66
Fasting insulin (pmol/l)	66.8±8.5	65.9±7.1	0.93
Fasting C-peptide (nmol/l)	1.06±0.08	1.03±0.09	0.76
Glucose AUC_{0-120}	1530.4±93.1	1506.1±76.8	0.50
Insulin AUC_{0-120}	34,986±5,502	29,304±4,188	0.68
C-peptide AUC_{0-120}	327.7±35.7	319.7±33.4	0.69
Matsuda insulin sensitivity index	2.96±0.34	3.57±0.55	0.03
HOMA- IR	3.49±0.46	3.37±0.44	0.85
Total cholesterol (mmol/l)	4.09±0.20	3.66±0.17	0.12
LDL-cholesterol (mmol/l)	2.39±0.18	2.14±0.15	0.30
HDL-cholesterol (mmol/l)	0.93±0.06	0.91±0.05	0.80
Triacylglycerol (mmol/l)	1.67±0.20	1.39±0.07	0.30

HOMA-IR, HOMA of insulin resistance