PROCEEDINGS REPORT

Impact of β -blocker treatment and nutritional status on glycemic response during exercise in patients with type 2 diabetes

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Abstract

Purpose: Most individuals with type 2 diabetes are affected by hypertension and thus have higher risk of cardiac complications. In addition to behavioural modifications, such as healthy food choices and regular physical activity, β -blocker treatment may be considered to reduce morbidity and mortality, especially after a cardiovascular event. However, this medication is generally associated with a deleterious impact on glucose metabolism. The objective of the study was to assess the impact of β -blocker treatment on glucose response during exercise in patients with type 2 diabetes, free of cardiovascular complications.

Methods: Ten sedentary men, treated with diet and/or hypoglycemic agents have performed four exercise sessions at 60% of their $\dot{V}O_{2peak}$, in the fasted state or 2 hours following a standardized breakfast, with and without β -blockers (atenolol 100 mg id for five consecutive days).

Blood samples were drawn during the resting period, at 15-min intervals during the exercise session and during the recovery period.

Results: A reduction of blood glucose levels was observed following the exercise session in the postprandial state (48% and 44% reduction with and without β -blockers respectively; $P < 0.001$). One hour of exercise performed in the fasted state had a minimal impact on glucose and insulin levels, whether with or without β -blockers. β -blocker treatment was not associated with increased baseline blood glucose or insulin levels in the fasted or the postprandial situation.

Conclusion: Dietary status has a more important impact on plasma glucose and insulin modulation than short-term use of β -blockers.

The risk of coronary heart disease is increased 2 to 4-fold in the presence of type 2 diabetes, and has been reported to cause 50% to 80% of the mortality in these patients.^{1,2} Sustained lifestyle and pharmacological interventions are needed to reduce body weight, con-

trol blood pressure, serum cholesterol concentration and achieve optimal glycemic control. Various medications have been shown to improve morbidity and mortality among patients with diabetes. For example, large controlled trials have shown β -blockers to be highly effective in reducing the risk of cardiovascular events and death in post myocardial infarction patients with diabetes.^{3,4} However, β -blocking agents interfere with glucose metabolism either by a direct effect on insulin secretion or on peripheral insulin uptake. The consequence is reduced sensitivity to hypoglycemic events, and inhibited glycogenolysis.⁵

Nutritional status influences plasma glucose levels (PGL) during a submaximal aerobic exercise in subjects with type 2 diabetes.⁶ Pre-exercise hyperglycemia and hyperinsulinemia result in minimal changes in PGL (± 1.0 mmol/L) when subjects exercise while fasted, whereas an important decrease in PGL occurs when exercise is performed in a postprandial state.⁶⁻⁹ Based on data reporting that β -blocking agents induce elevations in PGL via inhibition of insulin secretion in patients with type 2 diabetes, we hypothesized that using a β -blocker treatment would increase preexercise PGL and influence glucose and insulin modulation during exercise. The aim of the study was to evaluate the impact of acute β -blocker usage on glucose and insulin response during exercise performed with different dietary states in patients with type 2 diabetes. Four different situations were evaluated in random order: 1) exercise in the fasted state without β -blocker (FS), 2) exercise in the fasted state with β -blocker (FS β_b), 3) exercise in the postprandial state without β -blocker (PC) and, 4) exercise in the postprandial state with β -blocker (PC β_b).

Materials and methods

Study population

The protocol was approved by the Ethics Committee of Laval Hospital. Ten sedentary men with type 2 diabetes but free of cardiovascular complications were studied after having given informed consent. Patients

were recruited to assess the impact of acute β -blockade on glucose and insulin response during submaximal exercise performed at 60% of their respective $\dot{V}O_{2peak}$ with and without the use of β -blockers. Each subject served as their own control, and the fasting state situation served as reference (we have previously shown that the changes in insulin and glucose levels in that situation are minimal in patients with type 2 diabetes).^{6,9} Subjects were treated by diet and/or oral hypoglycemic agents which were not taken the day of the experimentation. No subject was receiving insulin therapy or was engaged in a regular exercise program for up to 3 months before entering the study. All subjects were instructed to maintain their usual dietary habits, to prevent fluctuations in their weight, until the protocol was completed. Standard clinical and preliminary laboratory examinations showed no evidence of diabetic complications. Atenolol, 100 mg daily, was then randomly prescribed for 5 days and then crossed over for the situation without medication. We used a pharmacological non-cardioselective dose of atenolol in order to influence both β_1 and β_2 -receptors. In the situations with β -blocker, atenolol was taken the 4 previous days and the morning of the experimental procedures.

Measurement of maximal oxygen uptake

At the time of the $\dot{V}O_{2peak}$ tests, blood was taken for determination of glycated hemoglobin (HbA_{1c}) and fasting glucose. Peak oxygen uptake was evaluated with and without β -blocker on an electromagnetically braked cycle ergometer (Corival, Lode, Netherlands) with an incremental protocol of 15 watts/min to the point of exhaustion, as previously described.¹⁰ Subjects were asked to avoid physical activity and alcohol for 48 hr and to abstain from caffeine for 24 hr before each exercise session.

Exercise protocol

On each of the four experiment days, subjects reported to the laboratory after a 12 hr overnight fast. An 18-gauge polyethylene catheter was inserted into a forearm vein for blood sampling while the subject was in a supine position. The catheter was kept patent with a continuous infusion of 0.9% saline before exercise and between sampling, in order to replace the volume of fluid taken during the experiment. Subjects were then randomly assigned to exercise either in the fasted state or 2 hr after a 452-kcal standardized breakfast (60% carbohydrate, 30% fat, 17% protein), with or without atenolol usage. A 60-min submaximal exercise was performed on a cycle ergometer (Corival, Lode, Netherlands) at 60% of $\dot{V}O_{2\text{peak}}$ established from the data obtained from the $\dot{V}O_{2\text{peak}}$ test with and without β -blocker. Basal blood samples were obtained and gas exchange (indirect calorimetry) was recorded 2 hr post meal, corresponding to 15 min before the onset of the exercise. In addition to the basal blood sample, further samples were obtained at the following times; 0, 15, 30, 45, 60 min during the exercise period, and at 75 and 90 min while recovering. Glucose and insulin were assayed using hexokinase-glucose-6-phosphate dehydrogenase method (Roche Diagnosis, Indianapolis, IN)¹¹ and polyethylene glycol precipitation (Roche Diagnosis, Indianapolis, IN) respectively.¹²

Statistical analysis

Analysis of variance was used for comparison between treatment (with and without β -blocker). Student's paired t-test was used for comparisons between each group. The comparisons of interest were baseline vs. time 60 min. Two-way analysis of variance was used for comparison between nutritional states and β -blocker usage. The Holm-Sidak test was used for data not normally distributed. A P value <0.05 was considered statistically significant. Results are expressed as mean $\pm$ SE unless otherwise designated.

Results

Subjects were between 36 and 64 yr (mean 53 ± 8). The patients' body weight remained unchanged throughout the protocol (95.4 ± 16.7 kg vs. 97.0 ± 17.2 kg; $P=0.1$) with and without β -blockers. PGL (7.5 ± 2.2 vs. 6.7 ± 1.2 mmol/L; $P=0.6$) and HbA_{1c} (7.2 ± 1.0 vs. $6.1 \pm 0.6\%$; $P=0.2$) did not differ from the situations with or without β -blockers respectively. However, atenolol reduced $\dot{V}O_{2\text{peak}}$ by 12.5% (29.5 ± 3.9 vs. 25.8 ± 3.4 mL $\cdot$ kg⁻¹ $\cdot$ min⁻¹; $P<0.001$), resting heart rate by 27% (54 ± 4 vs. 74 ± 12 bpm; $P<0.001$), resting systolic blood pressure by 6% (123 ± 11 vs. 131 ± 14 mmHg; $P=0.1$), peak heart rate by 35% (110 ± 9 vs. 169 ± 14 bpm; $P<0.001$), and peak systolic blood pressure by 21% (167 ± 24 vs. 211 ± 20 mmHg; $P<0.001$) compared with that without β -blockers.

β -blocker utilization had no effect on baseline PGL (Figure 1) or insulin levels (Figure 2) when exercise was performed in the same dietary status, i.e. during fasting ($P=0.2$; FS vs. FS $_{\beta\text{b}}$) and 2 hr after a standardized breakfast ($P=0.3$; PC vs. PC $_{\beta\text{b}}$). PGL and insulin were higher in the postprandial states compared to the fasting situations ($P \leq 0.01$). The hyperglycemic state was associated with the postprandial situations, inducing an important decrease in PGL (-4.9 mmol/L for the PC and -5.7 mmol/L for the PC $_{\beta\text{b}}$) ($P<0.001$) in response to exercise compared with the fasting, whereas no changes were observed. A reduction of insulin levels was also observed after the exercise session performed in the postprandial states, with and without β -blocker ($P<0.001$). PGL decreased within a normal range of PGL at the end of the two exercise sessions performed in the postprandial states (6.3 and 6.0 mmol/L for the PC and the PC $_{\beta\text{b}}$ respectively). One hour of exercise performed in the fasted state had minimal impact on glucose and insulin levels, whether with or without β -blockers.

FIGURE 1. Plasma glucose concentrations in 10 subjects with type 2 diabetes in the fasted state without β -blockers ($\bullet$), the fed state without β -blockers ($\circ$), the fasted state with β -blockers ($\blacktriangle$) and the fed state with β -blockers ($\triangle$) measured at 15-min intervals. * $P = 0.05$ fasted vs. fed state; † $P < 0.001$ baseline vs after a 60-min exercise period performed in the fed state, with and without a β -blocker treatment.

FIGURE 2. Plasma insulin concentration in 10 subjects with type 2 diabetes in the fasted state without β -blockers ($\bullet$), the fed state without β -blockers ($\circ$), the fasted state with β -blockers ($\blacktriangle$) and the fed state with β -blockers ($\triangle$) measured at 15-min intervals. * $P = 0.05$ fasted vs. fed state; † $P < 0.001$ baseline vs after a 60-min exercise period performed in the fed state, with and without a β -blocker treatment.

Discussion

Our results demonstrated that a 5 day course of atenolol is sufficient to produce β -blockade, as shown by decreases in resting heart rate, peak heart rate, peak systolic blood pressure and $\dot{V}O_{2\text{peak}}$. These haemodynamic changes during rest and peak exercise conditions were similar to those observed in subjects without diabetes under chronic β -blocking.¹³ However, this short term β -blockade is not sufficient to increase fasting and postprandial PGL, nor to decrease fasting and postprandial insulin concentrations. Thus, short term β -blockade did not influence either glucose or insulin responses during exercise performed under different nutritional status.

Although exercise began with mild to elevated PGL in both nutritional states, the PGL changes were small ($\sim 3\%$) when subjects exercised while fasted, whereas a similar decrease ($\sim 46\%$) occurred when exercise was performed 2 hr. after breakfast, with and without β -blockers. Hyperinsulinemia induced by the

postprandial state inhibits hepatic glycogenolysis.^{6,9} A decrease in PGL following exercise performed in the postprandial state in subjects with type 2 diabetes is likely attributed to a mismatch between hepatic glucose production and glucose utilization by peripheral tissues compared with the fasted state.⁶ Contrary to our hypothesis, β -blockers did not seem to have both affected either insulin secretion or hepatic glycogenolysis during exercise, which was reflected by a similar decrease in PGL levels in response to submaximal exercise. We speculate that short term non-cardioselective β -blockade itself does not have a deleterious impact on glucose metabolism. The typical weight gain observed with chronic β -blockade may be the mechanism underlying the alteration of carbohydrate metabolism in patients with type 2 via a decrease in insulin secretion and an increase in insulin resistance.¹⁴

Conclusion

Acute treatment with the β -blocking agent atenolol had no effect on glucose and insulin response during exercise in patients with type 2 diabetes. The negative impact of β -blockers on glucose metabolism may be related to the weight gain associated with the chronic treatment with these agents. Thus, dietary status has a more important impact on plasma glucose and insulin modulation than short-term use of β -blockers.

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References

- Herlitz J, Malmberg K. How to Improve the Cardiac Prognosis for Diabetes. *Diabetes Care*. 1999;22 Suppl 2:B89-B96.
- Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other Risk Factors, and 12-yr Cardiovascular Mortality for Men Screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993;16:434-44.
- UK Prospective Diabetes Study (UKPDS) Group. Tight Blood Pressure Control and Risk of Macrovascular and Microvascular Complications in Type 2 Diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ*. 1998;317:703-13.
- Kjekshus J, Gilpin E, Cali G, Blackey AR, Henning H, Ross J, Jr. Diabetic Patients and Beta-Blockers After Acute Myocardial Infarction. *Eur Heart J*. 1990;11:43-50.
- Mills GA, Horn JR. Beta-Blockers and Glucose Control. *Drug Intell Clin Pharm*. 1985;19:246-51.
- Poirier P, Mawhinney S, Grondin L, et al. Prior Meal Enhances the Plasma Glucose Lowering Effect of Exercise in Type 2 Diabetes. *Med Sci Sports Exerc*. 2001;33:1259-64.
- Gaudet-Savard T, Ferland A, Broderick TL, et al. P. Safety and Magnitude of Changes of Blood Glucose Levels Following Exercise Performed in the Fasted and the Postprandial State in Type 2 Diabetes Men. *Eur J Cardiovasc Prev Rehab*. 2007 (in press).
- Ferland A, Brassard P, Poirier P. Is Aspartame Really Safer on Risk to Induce Hypoglycemia During Exercise in Type 2 Diabetic Patients? *Diabetes Care*. 2007;30:59.
- Poirier P, Tremblay A, Catellier C, Tancredi G, Garneau C, Nadeau A. Impact of Time Interval from the Last Meal on Glucose Response to Exercise in Subjects with Type 2 Diabetes. *J Clin Endocrinol Metab*. 2000;85:2860-4.
- Brassard P, Ferland A, Bogaty P, Desmeules M, Jobin J, Poirier P. Influence of Glycemic Control on Pulmonary Function and Heart Rate in Response to Exercise in Subjects with Type 2 Diabetes Mellitus. *Metabolism*. 2006;55:1532-7.
- Schmidt FH. Enzymatic Determination of Glucose and Fructose Simultaneously. *Klin Wochenschr*. 1961;39:1244-7.
- Arnqvist H, Olsson PO, Von Schenck H. Free and Total Insulin as Determined after Precipitation with Polyethylene Glycol: Analytical Characteristics and Effects of Sample Handling and Storage. *Clin Chem*. 1987;33:93-6.
- Vyssoulis GP, Kouremetis MT, Valioli MA, Michaelides AP, Toutouzas PK. Effect of Beta-Blockade on Exercise Capacity in Hypertensive Subjects: A One-Year Double-Blind Study of Celiprolol and Metoprolol. *Cardiovasc Drugs Ther*. 1995;9:133-9.
- Kendall MJ. Impact of Beta 1 Selectivity and Intrinsic Sympathomimetic Activity on Potential Unwanted Noncardiovascular Effects of Beta Blockers. *Am J Cardiol*. 1987;59:44F-7F.

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