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Perspectives in Practice

The Effect of Exercise with or Without Metformin on Glucose Profiles in Type 2 Diabetes: A Pilot Study

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ABSTRACT

The study's goals were 1) to confirm the previously observed increase in postprandial glucose levels immediately after exercise in people with type 2 diabetes who are being treated with metformin; 2) to determine how long the increased glucose persists; 3) to examine the effect of skipping a dose of metformin before or after exercise. We recruited 10 participants with type 2 diabetes who were taking metformin. They completed 4 experimental conditions in random order: 1) morning and evening metformin doses, without exercise (M-M); 2) morning and evening metformin doses, with exercise (M-Ex-M); 3) exercise with evening metformin dose only (Ex-M); and 4) morning metformin dose only, with exercise (M-Ex). Exercise consisted of walking for 50 minutes at a moderate intensity at 11 AM on the first day of each condition. Glucose was measured for 72 hours using continuous glucose monitoring systems. Standardized breakfasts were provided for 3 days in each condition, and standardized lunches and dinners were provided on the first day. Compared to M-M, M-Ex-M increased the average 2-hour incremental postprandial area under the curve following the 5 standardized meals ($p<0.01$) but did not affect daily mean glucose or fasting glucose concentrations. M-Ex ($p<0.05$), but not Ex-M ($p=0.08$) increased mean glucose concentrations compared to M-Ex-M on day 1. There were no differences among the 3 exercise conditions for fasting or postprandial glucose concentrations. The addition of a bout of exercise to metformin led to an increase in postprandial glucose levels without affecting mean glucose concentrations. Removing a metformin dose before or after exercise did not attenuate this negative effect.

Mots clés :
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glucose post-prandiale

RÉSUMÉ

Les objectifs de l'étude étaient les suivants: 1) confirmer l'augmentation de la glycémie postprandiale précédemment observée immédiatement après l'exercice chez les personnes souffrant du diabète de type 2 qui sont traitées par la metformine; 2) déterminer la durée de l'augmentation de la glycémie; 3) examiner l'effet de l'omission d'une dose de metformine avant ou après l'exercice. Nous avons recruté 10 participants souffrant du diabète de type 2 qui prenaient de la metformine. Ils se soumettaient aux 4 conditions expérimentales selon un ordre aléatoire: 1) doses de metformine le matin et le soir, sans exercice (M-M); 2) doses de metformine le matin et le soir, avec exercice (M-Ex-M); 3) exercice avec une dose de metformine le soir seulement (Ex-M); 4) dose de metformine le matin seulement, avec exercice (M-Ex). L'exercice consistait en une marche de 50 minutes à intensité modérée à 11 h le premier jour de chacune des conditions. La glycémie était mesurée durant 72 heures à l'aide de systèmes de surveillance de la glycémie en continu. Des déjeuners standards étaient fournis durant 3 jours pour chacune des conditions, puis des dîners et des soupers standards étaient fournis le premier jour. Comparativement à la condition expérimentale M-M, la M-Ex-M augmentait l'aire incrémentale moyenne sous la courbe de la glycémie postprandiale 2 heures après les 5 repas standards ($p<0.01$), mais n'affectait pas la glycémie moyenne quotidienne ou la glycémie à jeun. La condition expérimentale M-Ex ($p<0.05$), mais non la Ex-M ($p=0.08$), augmentait la glycémie moyenne comparativement à la M-Ex-M le jour 1. Aucune différence dans la glycémie à jeun et la glycémie postprandiale n'était observée entre les 3 conditions ayant recours à l'exercice. L'ajout

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d'une période d'exercice à la prise de metformine menait à une augmentation de la glycémie postprandiale sans affecter la glycémie moyenne. La suppression d'une dose de metformine avant ou après l'exercice n'atténuait pas cet effet négatif.

Introduction

The glucose-lowering effects of exercise are one of the most well-documented findings in diabetes research. The average effect on glycemic control is clinically meaningful, but it is important to consider that there can be variability in the responses to exercise (1). Practitioners and patients alike may be surprised by the suggestion that 2 of the first-line treatments for managing type 2 diabetes, metformin and exercise, may interfere with each other's effects. Exploring approaches to combining them in better ways has become particularly relevant in light of recent studies demonstrating that their combination led to no better or even to poorer improvements in glycemic control or insulin sensitivity than either treatment alone (2–4).

The lower-than-expected improvement in glycemic control, or insulin sensitivity, when exercise and metformin are combined is unlikely to prevent these therapies from being recommended together because the benefits of exercise, and perhaps metformin, are not limited to lowering glucose concentrations. Consequently, novel strategies to combine metformin and exercise more optimally are needed.

After oral consumption, peak plasma metformin concentration is reached after approximately 2 to 4 hours, and 90% of the absorbed metformin is eliminated in the urine, unchanged, after about 20 hours (5).

It may therefore be possible to improve the concomitant use of these therapies by exercising at a time of reduced plasma metformin concentrations or by reducing metformin consumption during the postexercise period. Similar approaches have been successfully translated into practical recommendations. For example, leading authorities, including the Canadian Diabetes Association, regularly emphasize the importance of modifying insulin doses in response to changes in physical activity (6,7).

The objectives of the present study are threefold: 1) to confirm the previously observed increase in postprandial glucose immediately after exercise; 2) to determine whether this increase persists beyond 1 meal; 3) to examine the novel hypothesis that skipping a single dose of metformin before or after exercise could help to improve glycemic control more efficiently when exercising.

Methods

Participants

For this study, we recruited 10 volunteers with type 2 diabetes (5 men, 4 postmenopausal women and 1 premenopausal woman) who were taking metformin. The study was approved by the University Health Research Ethics Board. The premenopausal participant was tested in the follicular phase in all experimental conditions. Participants met the following eligibility criteria: 1) being between 40 and 70 years of age; 2) taking metformin for at least 3 months without any other glucose-lowering medication; 3) absence of diabetes-related complications or limitations to regular exercise; and 4) glycated hemoglobin (A1C) levels <9% and resting blood pressure <140/90 mm Hg.

Baseline assessment

During the first meeting, the eligibility of the participants was confirmed, and A1C levels were assessed (DCA 2000; Siemens Healthcare Diagnostics, Tarrytown, New York, United States). Participants reported a second time to the laboratory to perform a submaximal graded exercise test on a treadmill so as to determine ventilatory thresholds (VTs) using a TrueMax (Parvo Medics, Sandy, Utah, United States) metabolic measurement system.

Study design

The study followed a randomized crossover design. Each participant completed 4 conditions: 1) metformin with breakfast and dinner, without exercise (M-M); 2) metformin with breakfast and dinner, with exercise (M-Ex-M); 3) metformin with dinner only, with exercise (Ex-M); and 4) metformin with breakfast only, with exercise (M-Ex). A single exercise session was performed 3 hours after breakfast on the first day of each exercise conditions.

Study protocol

Eligible participants took part in a treadmill habituation phase consisting of 3 exercise sessions lasting 30, 40 and 50 minutes, respectively. Participants were then invited to the laboratory on the evening preceding the first condition day to insert a continuous glucose monitor system (CGMS) (iPro2; Medtronic, Brampton, Ontario, Canada). The CGMS was used and calibrated as in our previous reliability study (8).

On day 1 of each condition, participants arrived at the laboratory at 7:45 AM after an overnight fast. Between 8:00 and 8:15 AM they received a standardized breakfast, and in all conditions except Ex-M, they consumed their regular metformin doses. Following breakfast, participants remained sedentary until 11:00 AM, at which time the exercise session, or the rest period for the M-M condition, began. The exercise protocol consisted of 50 minutes of walking at 85% of VT and a 5-minute cool down. Participants then rested for 15 minutes and had their standardized lunch at 12:10 PM. Before leaving the laboratory, 3 standardized meals were provided (day 1 dinner and days 2 and 3 breakfasts). In all conditions except M-Ex, participants consumed their regular metformin doses with day 1 dinners. Participants were asked to refrain from structured exercise for the remainder of the 72-hour periods and to eat their breakfasts immediately after waking up. On days 2 and 3, participants were asked to consume the same standardized breakfasts as on day 1, after which they were advised to consume their regular diets.

Dietary intake and pills adherence

On the first day of the first condition, participants were allowed to eat ad libitum from a selection of items (breakfast, lunch and dinner), knowing they would have to consume the exact same meals in subsequent conditions. Adherence was assessed by self-reported journals, which were then discussed with the study coordinator at each meeting. Mean (SD) macronutrient proportions and total kilocalories were as follows: breakfasts (69±3% carbohydrate, 20±3% fat, and 11±1% protein; 566±140 kcal); lunch (56±13% carbohydrate, 24±10% fat, and 20±5% protein; 614±241 kcal); and dinner (61±7% carbohydrate, 16±5% fat, and 23±2% protein; 796±236 kcal).

Continuous glucose monitoring system measures

Participants consumed their breakfasts at 8:00 AM on day 1, but at times of their convenience on days 2 and 3, so not all had 24-hour data from breakfast to breakfast. Thus, the CGMS data from a