Can J Diabetes 37 (2013) 375–380

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Original Research

Effects of Aerobic Exercise with or without Metformin on Plasma Incretins in Type 2 Diabetes

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ARTICLE INFO

Article history:
Received 10 June 2013
Received in revised form
18 July 2013
Accepted 18 July 2013

Keywords:
glucagon-like peptide-1
glucose-dependent insulinotropic polypeptide
metformin
physical activity

ABSTRACT

Objective: Despite positive effects of incretins on insulin secretion, little is known about the effect of exercise on these hormones. Metformin can affect incretin concentrations and is prescribed to a large proportion of people with diabetes. We, therefore, examined the effects of aerobic exercise and/or metformin on incretin hormones.
Methods: Ten participants with type 2 diabetes were recruited for this randomized crossover study. Metformin or placebo was given for 28 days, followed by the alternate treatment for 28 days. On the last 2 days of each condition, participants were assessed during a non-exercise day and a subsequent exercise day. Aerobic exercise took place in the morning and blood samples were taken in the subsequent hours (before and after lunch).
Results: Aerobic exercise did not increase total plasma glucagon-like peptide-1 (GLP-1) or glucose-dependent insulinotropic polypeptide (GIP) in the pre- or post-lunch periods (all $p>0.1$). GLP-1 was higher in the pre-lunch ($p=0.016$) and post-lunch ($p=0.018$) periods of the metformin conditions compared with the placebo. Total plasma GIP was higher in the pre-lunch period ($p=0.05$), but not in the post-lunch period ($p=0.95$), with metformin compared with placebo.
Conclusions: In contrast to our hypothesis, aerobic exercise did not acutely increase total GLP-1 and GIP levels in patients with type 2 diabetes. Metformin, independent of exercise, significantly increased total plasma GLP-1 and GIP concentrations in these patients.

Mots clés :
le glucagon-like peptide-1
polypeptide insulinotrope glucose-dépendante
metformine
l'activité physique

RÉSUMÉ

Objectif : En dépit des effets positifs des incrétines sur la sécrétion d'insuline, on en connaît peu sur l'effet de l'exercice sur ces hormones. La metformine, qui est prescrite à une grande proportion de personnes ayant le diabète, peut influer sur les concentrations d'incrétine. Nous avons donc examiné les effets de l'exercice aérobique ou de la metformine, ou des deux, sur les hormones incrétines.
Méthodes : Dix (10) participants ayant le diabète de type 2 ont été recrutés pour participer à cette étude croisée à répartition aléatoire. La metformine ou le placébo a été donné pendant 28 jours, et a été suivi de l'autre traitement pendant 28 jours. Les 2 derniers jours de chaque traitement, les participants ont été évalués durant une journée sans exercice et durant une journée comportant de l'exercice. L'exercice aérobique a eu lieu en matinée et les échantillons de sang ont été recueillis au cours des heures subséquentes (avant et après le dîner).
Résultats : L'exercice aérobique n'a pas fait augmenter les concentrations plasmatiques totales du GLP-1 (*glucagon-like peptide -1*) ou du GIP (*glucose-dependent insulinotropic polypeptide*) durant les périodes précédant et suivant le dîner (tous $p > 0,1$). Le GLP-1 a été plus élevé durant les périodes précédant le dîner ($p = 0,016$) et suivant le dîner ($p = 0,018$) pour ce qui est du traitement à la metformine comparativement à celui du placébo. La concentration plasmatique totale du GIP a été plus élevée durant la période précédant le repas ($p = 0,05$), mais non durant la période suivant le repas ($p = 0,95$) pour ce qui est de la metformine comparativement au placébo.
Conclusions : Contrairement à notre hypothèse, l'exercice aérobique ne faisait pas augmenter de manière considérable les concentrations totales du GLP-1 et du GIP chez les patients ayant le diabète de type 2. La

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1499-2671/$ – see front matter © 2013 Canadian Diabetes Association
http://dx.doi.org/10.1016/j.jcjd.2013.07.030

metformine, indépendamment de l'exercice, augmentait significativement les concentrations plasmatiques totales du GLP-1 et du GIP chez ces patients.

Introduction

Type 2 diabetes is a metabolic disorder characterized by hyperglycemia caused by a combination of insulin resistance and impaired insulin secretion. It has been known for more than 40 years that insulin secretion is greater in response to oral glucose compared with an intravenous glucose load that leads to a similar plasma glucose profile (1). This is known as the incretin effect, and the 2 main incretin hormones are considered to be glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP; also called gastric inhibitory polypeptide) (2,3). Incretin hormones have been shown to be responsible for about 60% of postprandial insulin secretion in healthy subjects (4,5). The secretion of these incretins, especially GLP-1, is impaired in patients with type 2 diabetes (6–8). Pharmacologic interventions targeting these hormones recently were approved in Canada (9). Some of these drugs are classified as GLP-1-receptor agonists (e.g. exenatide and liraglutide) or dipeptidyl peptidase-4 inhibitors (e.g. sitagliptin, saxagliptin and linagliptin) that exert their effects through a dipeptidyl peptidase-4 (DPP-4)-resistant analogue to GLP-1 (10) or by increasing GLP-1 half-life, respectively (11).

Compared with the knowledge accumulated on these pharmacologic interventions, very little is known about the effects of exercise on GLP-1 or GIP. This is important because exercise is considered to be a first-line intervention for the prevention and management of type 2 diabetes (12–14). Previous research consistently has shown that exercise can increase incretins in healthy subjects (15,16). However, to our knowledge, only the study of Solomon et al (17) has examined the effect of exercise on incretins. They showed that increased GIP concentrations after 3 months of diet and exercise was significantly related to increased insulin secretion (17).

In addition to exercise, metformin also is considered a first-line therapy for type 2 diabetes (18) and this is notable because a large proportion of individuals with diabetes are treated with metformin. Although Canadian data are scarce, the estimated number of metformin prescriptions in the United States has increased from about 38 million in 2006 to more than 48 million in 2010 (top 10 for generic drugs) (19). Yasuda et al (20) showed that a single dose of metformin can significantly increase total GLP-1 in subjects without diabetes (20). Metformin also has been shown to increase plasma concentrations of GLP-1 in rats (20). It is unknown if the combination of metformin and exercise leads to greater incretin responses than after metformin alone. Interestingly, we recently observed that the combination of metformin and aerobic exercise acutely increased glucagon concentrations (21). This increased glucagon could be expected to occur if incretin hormone concentrations were lowered by the combination of metformin and exercise (22–24).

Therefore, the objectives of the current study were to examine the effects of aerobic exercise, metformin and their combination on preprandial and postprandial plasma concentrations of GLP-1 and GIP. It was hypothesized that both aerobic exercise and metformin would increase GLP-1 and GIP in people with type 2 diabetes.

Methods

Participants

Ten volunteers (8 men and 2 postmenopausal women) with type 2 diabetes were recruited for this study, which was approved by the University of Alberta Health Research Ethics Board. The present study was part of a larger research project for which details have been published previously (21). The GLP-1 and GIP data reported here were not published previously but were measured in the plasma samples taken during the previous study. Briefly, participants met the following eligibility criteria, as previously reported (21): (1) between 30 and 65 years of age; (2) not taking glucose-lowering medication or insulin; (3) no changes in physical activity of more than 1 hour per week over the past 3 months and not planning on changing medication, physical activity or diet over the course of the study; and (4) glycated hemoglobin level of 8% or less, resting blood pressure of 140/90 mm Hg or less, LDL cholesterol level of 3.5 mmol/L or less and total:HDL cholesterol ratio of 5.0 or less.

The inclusion criteria and study information provided to participants did not specifically proscribe dietary supplements. Although not specifically required by our inclusion criteria, the women were not on hormone replacement therapy.

Study design

The study used a 2×2 factorial design during which each participant was exposed to 4 conditions: (1) metformin and no exercise, (2) metformin and exercise, (3) placebo and no exercise and (4) placebo and exercise. The order of the metformin vs. placebo conditions was assigned randomly by personnel not involved with the study, and allocation was concealed in sealed envelopes until participants completed the study. Participants, study personnel and investigators were blinded to the order of the placebo/metformin conditions. Metformin or placebo was given for 28 days, immediately followed by the alternate condition for 28 days. On the last 2 days of each condition (days 27 and 28), participants returned to the laboratory for a non-exercise and exercise session, respectively. The order of these sessions was not determined randomly and exercise always was performed on day 28 because the acute glucose-lowering effect of exercise may persist for at least 24 hours (25). The experimental design of this study and a portion of the methods have been published previously, but there was no duplication in any of the dependent variables reported in this article (21).

Study protocol

As previously described (21), a baseline exercise stress test was performed to determine the participants' peak oxygen uptake ($V_{O_{2peak}}$) and ventilatory threshold. Participants were given either metformin or placebo pills and were asked to maintain their routine physical activity and dietary habits. Each participant consumed 500 mg of metformin with breakfast during the first week of the intervention followed by a 500 mg increase in each of the subsequent weeks until 1000 mg were consumed with breakfast and supper during week 4 (total, 2000 mg/day).

On days 27 and 28 of the metformin and placebo conditions, participants arrived in the laboratory at 8:00 AM after a 12-hour fast. Participants ate a standardized breakfast (549 kcal; 56% carbohydrate, 30% fat and 14% protein) and took their assigned pills. At 10:00 AM, an intravenous catheter was inserted into an antecubital vein kept patent with 0.9% sterile saline. On day 27 of the metformin and placebo conditions, the participants remained at rest for the duration of the testing period. At 10:45 AM on day 28 during both conditions, participants performed a series of exercises that were selected to represent different intensities, modes and energy systems. They began with 20 consecutive maximal leg extensions