Metformin and Exercise in Type 2 Diabetes

Examining treatment modality interactions

Normand G. Boule, PhD1
Cheri Robert, MSC2
Gordon J. Bell, PhD1
Steven T. Johnson, PhD2
Rhonda C. Bell, PhD3
Richard Z. Lewanczuk, MD, PhD4
Raniah Q. Gabr, MSC5
Dion R. Brocks, PhD6

OBJECTIVE—To determine the effect of metformin on the acute metabolic response to submaximal exercise, the effect of exercise on plasma metformin concentrations, and the interaction between metformin and exercise on the subsequent response to a standardized meal.

RESEARCH DESIGN AND 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 condition for 28 days. On the last 2 days of each condition, participants were assessed during a nonexercise and a subsequent exercise day. Exercise took place in the morning and involved a total of 35 min performed at 3 different submaximal intensities.

RESULTS—Metformin increased HR and plasma lactate during exercise (both P < 0.01) but lowered respiratory exchange ratio (P = 0.03) without affecting total energy expenditure, which suggests increased fat oxidation. Metformin plasma concentrations were greater at several, but not all, time points on the exercise day compared with the nonexercise day. The glycemic response to a standardized meal was reduced by metformin, but the reduction was attenuated when exercise was added (metformin × exercise interaction, P = 0.05). Glucagon levels were highest in the combined exercise and metformin condition.

CONCLUSIONS—This study reveals several ways by which metformin and exercise therapies can affect each other. By increasing HR, metformin could lead to the prescription of lower exercise workloads. Furthermore, under the tested conditions, exercise interfered with the glucose lowering effect of metformin.

It is estimated that there were over 42 million prescriptions for metformin in the U.S. in 2009 (top 10 for generic drugs) (1). Along with these prescriptions, exercise had likely been recommended to most of these patients since metformin therapy and lifestyle modifications are considered the first step for the management of type 2 diabetes (2).

Despite the vast literature examining the effects of metformin or exercise separately, surprisingly few studies have examined how they affect each other, or if their combination offers additive benefits.

There is some evidence suggesting that the benefits of exercise and metformin are not additive. For example, in the Indian Diabetes Prevention Program, reductions in the risk of diabetes were similar in the combined metformin and lifestyle modification group (−28.2%) compared with the metformin (−26.4%) or lifestyle alone (−28.5%) groups (3). In addition, metformin has been recently suggested to attenuate the insulin sensitizing effect of exercise (4).

Muscle contraction is known to result in the metabolic conditions that lead to activation of 5′-AMP-activated protein kinase (AMPK), and there is growing evidence that metformin also increases AMPK activity in liver, muscle, and other tissues (5). Recently, there has been much attention given to AMPK activators as exercise mimetics (6) and metformin has been shown to improve exercise tolerance in nondiabetic women with clinically defined angina (7).

The objectives of the current exploratory study were threefold: 1) to examine the effect of metformin on the acute metabolic and hormonal responses to exercise, 2) to examine the effect of exercise on plasma metformin concentrations, and 3) to examine the interaction between metformin and acute exercise on the subsequent response to a standardized meal.

RESEARCH DESIGN AND 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 Health Research Ethics Board. Participants met the following eligibility criteria: 1) between 30 and 65 years of age; 2) not taking glucose lowering medication or insulin; 3) no changes in physical activity over the last 3 months and not planning on changing medication, physical activity, or diet over the course of the study, and 4) HbA1c ≤8%, resting blood pressure ≤140/90 mmHg, LDL cholesterol ≤3.5 mmol/L, and total: HDL cholesterol ≤5.0.

Study design

The study used a factorial design and 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 versus placebo conditions was randomized 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...
Metformin and exercise

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 Exercise Physiology Laboratory for a nonexercise and exercise session, respectively. The order of these sessions was not randomly determined. Exercise was always performed on day 28 since the acute glucose lowering effect of exercise may persist for at least 24 h (8).

Study protocol

During the baseline, an exercise stress test with a 12-lead electrocardiogram was performed using a modified Balke-Ware treadmill protocol. Each participant walked at a self-selected speed, determined as comfortable but fast, while the grade was increased by 2% each minute. The test was ended when the participant could no longer continue. This protocol was used to determine the peak oxygen uptake ($V_{O2peak}$) and ventilatory threshold using the V-slope method.

After the baseline visit, 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 1,000 mg were consumed with breakfast and supper during week 4 (total: 2,000 mg/day).

On days 27 and 28 of the metformin and placebo conditions, participants arrived in the laboratory at 8:00 A.M. after a 12-h fast. Fasting glucose was measured with a handheld glucose meter (One Touch Ultra; LifeScan, Milpitas, CA), with measurements of peak torque, mean torque, and a fatigue index were calculated. After a 5-min rest period, the first of three aerobic exercise bouts began. Each bout was separated by a 5-min rest period during which blood samples were drawn from the catheter. During the first exercise bout, all participants walked at 3.5 km/h and 0% grade for 15 min. This corresponded to the estimated average walking speed for individuals with type 2 diabetes in free-living conditions (10). The second bout also lasted 15 min and was completed at a speed and grade equivalent to an intensity below each participant’s measured ventilatory threshold. The third bout was completed at an intensity above their ventilatory threshold and lasted 5 min.

Metabolic outcomes such as the volume of oxygen consumed ($V_{O2}$) and the volume of carbon dioxide produced ($V_{CO2}$) during exercise were measured with a TrueMax metabolic measurement system (Parvo Medics, Salt Lake City, UTab). Heart rate (HR) was measured using a Polar heart rate monitor (Polar Electric, Finland), and rate of perceived exertion was estimated with the Borg Scale.

About 20 min after exercise (at 11:59 A.M.), another blood sample was taken immediately before the standardized meal (556 kcal; 59% carbohydrate, 22% fat, 19% protein). Participants remained in the laboratory, and blood samples were taken every 30 min for 2 h. Each blood sample was first transferred into a 10-mL EDTA vacuum tube. Subsequently, 0.25 mL of whole blood was transferred into 1.0 mL of ice cold 8% perchloric acid, and 2.0 mL was transferred into a tube with 67 μL of proprin. Perchloric acid was added for deproteinization as required for the lactate analysis. Aprotinin was added to eliminate proteases known to interfere with the determination of glucagon. Tubes were centrifuged and cooled before being moved to a −20°C freezer until assays were completed. Serum lactate, glucose, and nonesterified fatty acids (NEFAs) were determined enzymatically with spectrophotometric assays. Glucagon and insulin were measured using commercially available radioimmunoassay (RIA kits (Millipore, St. Charles, MO and Inter Medico, Markham, Ontario, Canada, respectively). All assays were run in duplicate.

Plasma metformin concentrations were assessed in all plasma samples by a high performance liquid chromatographic. The concentration of phosphate solution used in the mobile phase was 20 mmol/L. The assay was validated to a lower limit of quantitation of 7.8 ng/mL of metformin based on 0.1 mL of human plasma (11).

Potential confounding variables

Participants completed a 24-h food recall for the day preceding each testing session. These were analyzed for calorie and macronutrient content using Food Processor SQL (Version 8.3.0; ESHA Research, Salem, OR). Habitual physical activity during each 4-week intervention was assessed using the Godin Leisure Time questionnaire (12). Finally, participants were asked to indicate their perception of which treatment (metformin or placebo) they had just completed on a 150-mm visual analog scales as well as symptoms such as nausea, headache, flatulence, abdominal discomfort, and indigestion.

Statistical analyses

Analyses were conducted using repeated-measures ANOVA with treatment order added as a between-subject factor. To simplify the interpretation, the testing days were broken down into four periods: pre-exercise, exercise, postexercise, and postlunch. The number of within-factors and levels varied among these periods (e.g., postlunch was a 2 × 2 × 4 factorial ANOVA to examine the effect of exercise, metformin, and time, respectively). Insulin, glucagon, glucose, lactate, and NEFAs were log transformed before the statistical analyses to favor normality of residuals and homogeneity of variance. The non-transformed mean ± standard deviations data are presented. Statistical tests were two-tailed, and P values of ≤0.05 were considered significant. Statistical analyses were performed with SPSS 18 (SPSS Inc., Chicago, IL).

RESULTS—Baseline characteristics are presented in Table 1. Some reported mild to moderate gastrointestinal side effects during the metformin intervention; but all participants except one (final metformin dosage, 1,500 mg/day) were able to
affected by metformin (P = 0.60). However, mean RER was lower in the metformin condition (0.96 ± 0.02 vs. 0.98 ± 0.02; P = 0.03). Mean HR was significantly higher in the metformin condition (124 ± 9 vs. 118 ± 8 beats per minute [bpm]; P = 0.009). The mean subjective ratings of perceived exertion during exercise were similar in the metformin and placebo conditions. However, participants reported a higher perceived exertion on their first exercise day regardless of whether they were on metformin or placebo. As well, when considering treatment order in the analyses, RPE was higher in the metformin condition (P = 0.03).

Plasma metformin concentrations
Plasma metformin concentrations were higher on the exercise day compared with the nonexercise day 25 min before exercise (1.897 ± 352 vs. 1.594 ± 363 ng/mL; P = 0.02) and 20 min after exercise (2.230 ± 333 vs. 1.893 ± 323 ng/mL; P = 0.01). Plasma metformin concentrations showed a significant time by exercise interaction (P = 0.05) during the 2-h postmeal period, with metformin concentration becoming similar near the end of the 2-h period.

Potentially confounding variables
There were no significant differences in total calorie intake (1,906 ± 253 vs. 1,978 ± 518 kcal; P = 0.51) or distribution of macronutrients in the 24 h preceding the testing sessions (all P > 0.52). There was no difference in the amount of physical activity completed during the metformin versus placebo conditions (Godin Leisure Time Questionnaire score 36 ± 21 vs. 52 ± 36; P = 0.13). Participants did not report experiencing any difference in symptoms such as abdominal discomfort between conditions. Participants rated a higher likelihood of taking metformin while they were in the metformin condition compared with placebo (89 ± 40 mm vs. 62 ± 47 mm on the 150-mm visual analog scale).

Table 1—Participant characteristics

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>Fasting glucose (mmol/L)</th>
<th>A1C (%)</th>
<th>Weight (kg)</th>
<th>Mean torque</th>
<th>Fatigue index</th>
<th>Peak torque</th>
<th>Mean torque</th>
<th>Fatigue index</th>
</tr>
</thead>
<tbody>
<tr>
<td>women</td>
<td>58 ± 6</td>
<td>28.6 ± 5.3</td>
<td>7.3 ± 0.6</td>
<td>6.5 ± 0.6</td>
<td>86.9 ± 18.7</td>
<td>58 ± 21</td>
<td>33 ± 10</td>
<td>70 ± 25</td>
<td>58 ± 21</td>
<td>33 ± 10</td>
</tr>
<tr>
<td>men</td>
<td>58 ± 6</td>
<td>28.6 ± 5.3</td>
<td>7.3 ± 0.6</td>
<td>6.5 ± 0.6</td>
<td>86.9 ± 18.7</td>
<td>58 ± 21</td>
<td>33 ± 10</td>
<td>70 ± 25</td>
<td>58 ± 21</td>
<td>33 ± 10</td>
</tr>
</tbody>
</table>

Data are reported as mean ± SD.

Table 2—Effect of metformin on exercise-related outcomes

<table>
<thead>
<tr>
<th>Treadmill exercise</th>
<th>Metformin vs. placebo conditions</th>
<th>Low vs. moderate vs. vigorous intensity</th>
<th>Interaction (condition × intensity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V̇O₂ (mL · min⁻¹ · kg⁻¹)</td>
<td>P = 0.60</td>
<td>P &lt; 0.01</td>
<td>P = 0.18</td>
</tr>
<tr>
<td>Low intensity</td>
<td>10.09 ± 1.01</td>
<td>10.01 ± 1.62</td>
<td></td>
</tr>
<tr>
<td>Moderate intensity</td>
<td>20.45 ± 3.69</td>
<td>20.02 ± 3.74</td>
<td></td>
</tr>
<tr>
<td>Vigorous intensity</td>
<td>23.95 ± 4.01</td>
<td>23.81 ± 4.37</td>
<td></td>
</tr>
<tr>
<td>RER</td>
<td>P = 0.03</td>
<td>P &lt; 0.01</td>
<td>P = 0.38</td>
</tr>
<tr>
<td>Low intensity</td>
<td>0.92 ± 0.06</td>
<td>0.95 ± 0.08</td>
<td></td>
</tr>
<tr>
<td>Moderate intensity</td>
<td>0.96 ± 0.03</td>
<td>0.97 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>Vigorous intensity</td>
<td>0.99 ± 0.08</td>
<td>1.02 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>P = 0.01</td>
<td>P &lt; 0.01</td>
<td>P = 0.23</td>
</tr>
<tr>
<td>Low intensity</td>
<td>97 ± 12</td>
<td>91 ± 13</td>
<td></td>
</tr>
<tr>
<td>Moderate intensity</td>
<td>132 ± 21</td>
<td>126 ± 19</td>
<td></td>
</tr>
<tr>
<td>Vigorous intensity</td>
<td>142 ± 24</td>
<td>138 ± 21</td>
<td></td>
</tr>
<tr>
<td>RPE (Borg)</td>
<td>P = 0.03</td>
<td>P &lt; 0.01</td>
<td>P = 0.62</td>
</tr>
<tr>
<td>Low intensity</td>
<td>8 ± 1</td>
<td>8 ± 1</td>
<td></td>
</tr>
<tr>
<td>Moderate intensity</td>
<td>13 ± 1</td>
<td>13 ± 1</td>
<td></td>
</tr>
<tr>
<td>Vigorous intensity</td>
<td>14 ± 1</td>
<td>13 ± 1</td>
<td></td>
</tr>
</tbody>
</table>

Data are reported as mean ± SD. RER is in V̇O₂peak/V̇O₂, RPE is on a scale of 0–20. Analyses were adjusted for treatment order (i.e., metformin first vs. placebo first).

Plasma glucose, lactate, NEFAs, insulin, and glucagon
Fasting glucose was lower in the metformin condition compared with the placebo condition (6.4 ± 0.6 vs. 7.2 ± 0.6 mmol/L; P = 0.02). As shown in Fig. 1, the mean glucose concentration continued to be lower throughout the day in the metformin conditions compared with placebo, with the difference becoming statistically significant after exercise. According to the sample taken immediately before lunch, exercise lowered plasma glucose concentration in the placebo condition but not in the metformin condition (−1.1 ± 2.0 vs. 0.1 ± 1.1 mmol/L, respectively); however, the metformin × exercise interaction was not significant (P = 0.17). The metformin × exercise interaction reached statistical significance during the 2-h postlunch period (P = 0.05), suggesting that exercise caused an increased glycemic response in the metformin condition but not in the placebo condition.

Throughout the entire sessions, lactate concentrations were higher in the metformin condition compared with placebo (all P ≤ 0.05). Lactate concentrations increased with increasing exercise intensity and remained elevated for 20 min after exercise (both P < 0.01). NEFA concentrations were also increased after exercise (P < 0.01).

Insulin concentrations were lowered by exercise but were similar in the metformin versus placebo conditions throughout the day with the exception of higher insulin concentrations after lunch in the placebo condition (P < 0.01). Glucagon concentrations were increased in the metformin conditions (all P < 0.01).
analog scale), but the difference did not reach statistical significance ($P = 0.20$). Body mass was similar after the 28-day placebo condition versus after the 28-day metformin condition (86.7 ± 19.0 vs. 86.7 ± 18.9 kg; $P = 0.93$).

**CONCLUSIONS**—In the 1960s and 1970s several studies had investigated the effect of metformin on exercise performance because of concerns over lactic acidosis (see reference 13 for a detailed review). Although the combination of metformin and exercise was perceived as safe, interest in this area has re-emerged in recent years (4,7,14,15). The current study is unique in that it focused on continuous exercise at several submaximal intensities that are relevant to activity patterns of people with type 2 diabetes and that we examined the interaction between exercise and metformin on the glycemic and hormonal responses to a subsequent meal.

We found that metformin increased lipid oxidation as evidenced by a lower RER during all three submaximal intensities of exercise. According to nonprotein RER tables, this would correspond to an increased lipid oxidation from 16 to 26% of total energy expenditure when walking at 3.5 km/h. Increased lipid oxidation is considered a normal adaption to exercise training. However, metformin increased submaximal HR and lactate concentrations, which are opposite to the direction of changes expected with regular exercise training. In the current study, HR was increased by a mean of 6 bpm. Interestingly, Sharoff et al. (4) also found an increased HR of about 8 and 5 bpm during exercise at 65 and 85% of $V_{\text{O}_2peak}$, respectively; however, in their study the increase in HR did not reach statistical significance. In our study, a higher rating of perceived exertion in the metformin condition was also observed, although participants were all able to complete the exercise bouts. Taken together, this suggests that metformin has the potential to lower some patients’ selected exercise intensity since perceived exertion and HR are common feedback modalities and are frequently used to prescribe exercise intensities.

Although statistical significance was not reached, peak and mean torque for knee extension were lower in the metformin condition. Lower mean torque may have been expected based on the reduced muscle ATP concentrations observed by week 4 of metformin treatment in the study by Musi et al. (16).

Maximal metformin concentrations are typically reached 120–240 min after a dose. In the current study, we observed greater plasma metformin concentrations 25 min before exercise and 20 min after exercise compared with samples taken at the same times on the rest day (150 and 225 min postdose). The reasons for these higher concentrations are unknown but may have been caused by the anticipatory and stress responses to exercise, which are known to increase HR and blood pressure while redistributing blood flow to tissues such as skeletal muscle (17). Hence, the alteration in blood flow may have caused a transient decrease in the distribution of drug to certain tissues, including the liver. Indeed, this may have contributed to the reduced hypoglycemic effect of metformin after exercise even though plasma concentrations were higher at some time points. A reduced renal blood flow could increase plasma concentrations of drugs such as metformin, which are primarily eliminated by the kidneys (18). This may have also contributed to some of the higher concentrations measured in the exercise group, although only a more complete assessment of plasma metformin concentrations and urinary recovery could answer this question. A limitation of the current study is that the three blood
samples taken immediately after each aerobic exercise bout were not taken at the corresponding times on the nonexercise days.

Although some previous studies had suggested that the effects of exercise and metformin on insulin sensitivity (4) or on the risk of diabetes (3) are not additive, our results suggest that in some conditions the combination may in fact be less effective at lowering the glycemic response to a meal than metformin alone. The reasons for this are not clear, but may be related to the strong counterregulatory response when the two were combined. In our study, the glucagon concentrations peaked immediately before lunch and were highest in the combined metformin and exercise condition. In support of the notion that glucose production may have been increased by the higher glucagon concentrations, Sharoff et al. (4) showed that hepatic glucose production was increased 2 h after exercise with metformin, unchanged by metformin alone, and decreased by exercise alone (4). Important differences between our study and Sharoff et al. (4) are that in the latter study participants were nondiabetic and 2 to 3 weeks of metformin use did not appear to alter insulin sensitivity or resting glucose concentration. Nonetheless, taken together these studies provide interesting insight on glucose homeostasis after metformin and exercise.

The lack of improvement in postmeal (lunch) plasma glucose concentrations on the exercise days should not discourage the use of exercise as a treatment modality. Rather, this study emphasizes that it may be important to further consider the timing of exercise and meals to obtain optimal glycemic benefits. For example, others have shown that exercising in the fasting state (a condition that also leads to pronounced counterregulatory responses) was much less effective at lowering plasma glucose than was exercising after a meal (19,20).

Furthermore, it is important to remember that the exercise protocol in the current study ended with 5 min of exercise at an intensity above ventilatory threshold. Similarly, in the study by Sharoff et al. (4), the exercise protocol ended with 10 min at 85% of $V_{O_2peak}$. High intensity exercise (i.e., above ventilatory threshold) in the postabsorptive state is known to cause an increase in counterregulatory hormones and glucose in type 2 diabetes (21). However, high intensity exercise performed 45 min after the beginning of breakfast led to a decreased glycemic response to a meal that was provided 2.5 h after exercise (22). It would be of interest to examine if interactions between metformin and exercise on glucose homeostasis would be as pronounced after lower intensity exercise.

Type 2 diabetes is characterized not only by insulin deficiency but also by hyperglycagonomia (23). We are aware of nonexercise studies that have suggested that metformin may increase glucagon concentrations, but the increases were not statistically significant (24,25). In the nonrandomized exercise studies by Cunha et al. (14,15), glucagon concentrations were significantly higher in the participants with type 2 diabetes taking metformin compared with those taking glibenclamide or those with normal glucose tolerance. Although speculative, the glucose lowering benefits of metformin could be further enhanced by strategies that could help minimize the exercise-induced increased glucagon levels such as exercising after a meal.

In conclusion, our study reports several novel findings regarding the concomitant use of metformin and exercise, specifically: 1) increased HR during exercise with metformin, 2) higher plasma metformin concentrations with exercise, and 3) nonadditive effects of metformin and exercise on the glycemic response to feeding. In our opinion, the magnitudes of these effects were small but have the potential to reduce the effectiveness of this therapeutic combination in diabetes treatment. Additional research could help optimize the concurrent use of these important and widely prescribed treatment modalities for diabetes.

Acknowledgments—Funding for this study was provided by the Alberta Diabetes Institute and the University of Alberta EFF-SAS. The metformin and placebo were graciously provided by Apotex Inc. Canada. R.Q.G. was supported by a studentship from the government of Egypt.

No potential conflicts of interest relevant to this article were reported.

N.G.B. contributed to the design of the study and collected data. C.R. and G.J.B. contributed to the design of the study, collected data, and analyzed the blood samples. S.T.J. contributed to the design of the study and collected data. R.C.B. contributed to the data analysis. All authors, including R.Z.L., R.Q.G., and D.R.R., contributed to discussion and reviewed and edited the manuscript.

The authors would like to thank the study participants for their time and efforts, and to thank Dr. Jeffrey A. Johnson and Dr. Dean Eurch for their input, Jason Howard and Lindsay Hubenig for their assistance with data collection, and Scott Forbes, Ian MacLean, and Shirley Shostak for their assistance with the assays (all at the University of Alberta).

References
chromatography using small sample volume and conventional octadecyl silane column.


