Original Article
The influence of hypoglycemic drugs on exercise-mediated hypoglycemic effects in elderly type 2 diabetic patients

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Abstract: Background: To evaluate the impact of different hypoglycemic drugs on exercise-mediated blood glucose (BG) reduction. Methods: One-hundred and five retirees who were diagnosed with type 2 diabetes mellitus (T2DM) within a two-year period were included in this study. The participants were instructed to walk for 20 to 30 minutes at a moderate-speed (4.0 to 4.5 km/h) after breakfast. Blood pressure and fingertip BG were measured before and after walking. Results: The rate of BG reduction was significantly higher in all exercise groups when compared to that of non-exercised patients. Among all groups, BG declined the most in the un-medicated group, while the lowest BG reduction was observed in the acarbose group. Surprisingly, the BG reduction in acarbose group was significantly lower when compared with non-acarbose groups (P<0.0001). Interestingly, after further correcting for sex, age, BMI, diabetes history, walking time, walking speed and walking distance, only age was found to be an influencing factor (t=-3.304, P=0.001). Pearson correlation of age and BG reduction showed that correlation coefficient of age was only 0.183 and revealed no statistical significance. Conclusions: Walking at a moderate speed for 20 to 30 minutes after breakfast provided a beneficial BG reduction effect in elderly T2DM patients. Among the medicated groups, the smallest BG reduction rate was observed in patients taking acarbose. We suggest that acarbose might influence hypoglycemic effects of exercise. The results of this study will be helpful for determining the best clinical usage of hypoglycemic medications in elderly T2DM patients.

Keywords: Type 2 diabetes mellitus, hypoglycemia, exercise, acarbose

Introduction
T2DM is a metabolic disorder that can lead to serious long term health problems [1]. Studies have indicated that obesity and immobility have a direct relationship with T2DM [1, 2]. Physical inactivity is one of the major risk factors for the development of T2DM and its complications [3]. Therefore, an important goal in T2DM management is to achieve and maintain an appropriately protective level of physical activity [4]. Physical activity has been reported to improve glycemic control [1, 3, 4]. Physical activity is also associated with reduced risks of total and cardiovascular mortality [5, 6]. In 2002, the American Diabetes Association (ADA) recommended an aerobic exercise training program with an intensity level equal to 50 to 80 percent of the patient’s maximum aerobic capacity (approximately three to four times a week for 30 to 60 minutes) [1, 3, 7]. Systematic reviews of physical intervention studies showed that exercise improves not only biomedical but also psychological outcomes in both healthy and person with diabetes [2, 3, 5, 7-9].

Despite the number of studies examining the synergistic hypoglycemic action of hypoglycemic medication and exercise, most of these studies have focused on mid- to long-term glycemic control and only a few have assessed the immediate glycemic changes in blood glucose following exercise. We previously demonstrated that moderate-intensity exercise (walking at four kilometers per hour) after breakfast immediately reduced the postprandial BG. We also found that the BG reduction correlated with the subjects’ body mass indexes (BMI), ages and BG levels before exercise [10]. However, we did not evaluate the impact of hypoglycemic drugs
on excised-mediated BG reduction in our previous study. In the present study, we compared the influence of hypoglycemic drugs including acarbose [11], metformin [12], sulfonylureas [13], insulin and insulin analogues on exercise-mediated hypoglycemic effects in elderly patients with T2DM.

Methods

Subjects

One hundred and five retirees (95 male and 10 female) who had been diagnosed as T2DM within a recent two-year period were included in this study. Participation was voluntary and each participant approved the data collection. The subjects were divided into eleven groups according to the hypoglycemic drugs they had been using for more than two months. The groups were as follows: group A (9 patients, 0 females) taking acarbose alone; group B (10 patients, 3 females) taking metformin alone; group C (16 patients, 0 females) taking sulfonylureas alone; group D (9 patients, 1 female) taking insulin or insulin analogues alone; group E (8 patients, 1 female) taking metformin and sulfonylureas jointly; group F (4 patients, 1 female) taking acarbose and metformin jointly; group G (21 patients, 2 females) taking acarbose and sulfonylureas jointly; group H (8 patients, 0 females) taking acarbose, metformin and sulfonylureas jointly; group I (9 patients, 2 females) taking insulin and hypoglycemic drugs jointly; group J (11 patients, 0 females) taking no drugs; group K (14 patients, 2 females) were willing to stop exercising for one to two days and continuing to take the originally used hypoglycemic drugs. The patients in group K rested instead of exercising for the same period of time, and this group was used as a control for the exercised groups. Because of the obvious beneficial hypoglycemic effect of exercise, most patients were unwilling to stop exercising and, therefore, the number of patients in the control group was fewer than expected. The experimental period was fifteen days, and every patient participated in five to six exercise (or rest control) sessions. Patients made no changes in their usage of hypoglycemic drugs during the study period. All drugs were from the same manufacturer and supplied by the pharmacy of our center; however, the lot number of the drugs varied due to the long time span of the assessment. All patients' diets during the experimental period were similar and were formulated by dietitians to be suitable for T2DM patients.

Exercise and observations

Physical examination and medical history were recorded for each patient. Patients with cardiopulmonary insufficiency, lower limb motor dysfunction, diabetes nephropathy and fundus lesions were excluded from this study. Exercise was not contraindicated for patients with fasting blood glucose (BG) and BG before exercise exceeding 16 mmol/L. The study was performed in the spring, summer and fall of a two-year period. Walking started one hour after breakfast (the patients were requested to rest quietly for one hour before the walk). Fingertip BG was measured with a BG meter (Johnson OneTouch UltraVue) and the resting blood pressure was measured with a mercury sphygmomanometer. Our medical staff accompanied the patients during the four-hundred-meter walk. Patients were asked to keep a uniform speed (about 4.0 to 4.5 km/h) during walking. Since there were great differences between age, physical capacity and exercise tolerance, the walking distance and duration were determined according to each patients' individual conditions and therefore, variations existed within the groups. The walking period was 20 to 30 minutes and the distance was 1.6 km to 2.4 km. Patients with walking distances less than the minimum range were excluded. The walking distance for the patients with better physical capacity was appropriately increased without changing walking speed. The medical staff recorded the duration and distance of walking, observed the degree of fatigue and monitored the patients for any adverse reactions to avoid extreme sports-induced sympathetic excitation. No pre-exercise warm-up activity or post-exercise relaxation activity was performed. During the experimental periods, no hypoglycemia, cardiovascular incident or physical injury occurred. Fingertip BG, blood pressure and heart rate were measured immediately after the walk. The BG reduction rate after walking was calculated as follows: \((\text{BG after the exercise})-(\text{BG before the exercise}))/(\text{BG before the exercise}) \times 100\%\) .

Statistical analysis

Data analysis was performed with SPSS 13.0 software (SPSS Inc. Chicago, IL). Data were pre-
Table 1. Baseline characteristics and clinical measurements of the participants in this study

<table>
<thead>
<tr>
<th>Group A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (Female)</td>
<td>9 (0)</td>
<td>10 (3)</td>
<td>16 (0)</td>
<td>9 (1)</td>
<td>8 (1)</td>
<td>4 (1)</td>
<td>21 (2)</td>
<td>8 (0)</td>
<td>9 (2)</td>
<td>11 (0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>77.8 ± 2.3</td>
<td>67.1 ± 8.4</td>
<td>77.0 ± 4.1</td>
<td>73.6 ± 6.9</td>
<td>70.7 ± 6.6</td>
<td>69.7 ± 9.2</td>
<td>77.6 ± 6.4</td>
<td>72.4 ± 7.3</td>
<td>68.1 ± 9.5</td>
<td>72.5 ± 8.3</td>
</tr>
<tr>
<td>BMI</td>
<td>23.3 ± 3.4</td>
<td>26.8 ± 2.8</td>
<td>25.3 ± 1.7</td>
<td>24.2 ± 4.2</td>
<td>23.6 ± 1.6</td>
<td>23.5 ± 1.9</td>
<td>23.9 ± 3.1</td>
<td>25.7 ± 2.1</td>
<td>24.5 ± 1.8</td>
<td>23.8 ± 3.2</td>
</tr>
<tr>
<td>Years of T2DM</td>
<td>8.2 ± 7.8</td>
<td>3.5 ± 3.1</td>
<td>8.2 ± 5.4</td>
<td>10.8 ± 2.4</td>
<td>10.8 ± 2.4</td>
<td>7.3 ± 4.3</td>
<td>10.8 ± 2.4</td>
<td>10.8 ± 2.4</td>
<td>7.3 ± 4.3</td>
<td>10.8 ± 2.4</td>
</tr>
<tr>
<td>Years of HBP</td>
<td>10.6 ± 9</td>
<td>10.4 ± 9.7</td>
<td>14.4 ± 15.4</td>
<td>10.2 ± 15.7</td>
<td>10 ± 7.6</td>
<td>6.9 ± 9.1</td>
<td>7.7 ± 7.4</td>
<td>8.9 ± 10.97</td>
<td>4.1 ± 6.3</td>
<td>4.1 ± 6.3</td>
</tr>
<tr>
<td>Exercise times</td>
<td>47</td>
<td>59</td>
<td>105</td>
<td>56</td>
<td>54</td>
<td>23</td>
<td>139</td>
<td>49</td>
<td>57</td>
<td>77</td>
</tr>
<tr>
<td>BG before exercise (mmol/L)</td>
<td>9.6 ± 1.9</td>
<td>10.7 ± 3.3</td>
<td>11.7 ± 2.0</td>
<td>12.9 ± 2.9</td>
<td>9.8 ± 1.5</td>
<td>11.3 ± 2.6</td>
<td>11.9 ± 2.2</td>
<td>10.5 ± 2.1</td>
<td>11.3 ± 1.8</td>
<td>10.2 ± 2.2</td>
</tr>
<tr>
<td>BG after exercise (mmol/L)</td>
<td>8.1 ± 1.7</td>
<td>8.1 ± 2.1</td>
<td>8.8 ± 2.1</td>
<td>9.7 ± 2.3</td>
<td>8.7 ± 2.4</td>
<td>9.6 ± 2.8</td>
<td>9.9 ± 2.1</td>
<td>8.2 ± 2.1</td>
<td>8.3 ± 1.8</td>
<td>9.9 ± 2.5</td>
</tr>
<tr>
<td>BG reduction (%)</td>
<td>-14.5 ± 14.9</td>
<td>-23.7 ± 19.7</td>
<td>-24.5 ± 14.9</td>
<td>-22.2 ± 17.6</td>
<td>-11.3 ± 17.4</td>
<td>-14.9 ± 16.1</td>
<td>-16.4 ± 12.5</td>
<td>-20.85 ± 17.1</td>
<td>-26.4 ± 13.8</td>
<td>-10.2 ± 2.2</td>
</tr>
<tr>
<td>Systolic pressure before exercise (mm Hg)</td>
<td>122.3 ± 13.5</td>
<td>126.9 ± 16.4</td>
<td>129.2 ± 13.0</td>
<td>124.6 ± 19.3</td>
<td>130.6 ± 15.4</td>
<td>128.5 ± 15.1</td>
<td>128.3 ± 12.5</td>
<td>130.8 ± 18.1</td>
<td>128.6 ± 12.9</td>
<td>124.1 ± 11.7</td>
</tr>
<tr>
<td>Diastolic pressure before exercise (mm Hg)</td>
<td>73.3 ± 9.1</td>
<td>68.4 ± 7.6</td>
<td>70.4 ± 12.9</td>
<td>73.3 ± 10.9</td>
<td>74.7 ± 14.4</td>
<td>68.1 ± 8.3</td>
<td>74.7 ± 7.2</td>
<td>76.4 ± 10.1</td>
<td>71.5 ± 5.6</td>
<td>69.7 ± 10.1</td>
</tr>
<tr>
<td>Systolic pressure after exercise (mm Hg)</td>
<td>127.5 ± 17.7</td>
<td>128.3 ± 17.2</td>
<td>132.2 ± 15.4</td>
<td>124.2 ± 15.9</td>
<td>127.2 ± 16.3</td>
<td>126.6 ± 16.9</td>
<td>130.8 ± 15.8</td>
<td>126.4 ± 13.1</td>
<td>128.1 ± 16.4</td>
<td>130.4 ± 16.1</td>
</tr>
<tr>
<td>Diastolic pressure after exercise (mm Hg)</td>
<td>73.7 ± 10.2</td>
<td>69.7 ± 6.5</td>
<td>68.8 ± 12.2</td>
<td>73.8 ± 10.2</td>
<td>72.2 ± 13.8</td>
<td>68.2 ± 10.34</td>
<td>73.2 ± 7.2</td>
<td>76.2 ± 8.5</td>
<td>72.3 ± 6.4</td>
<td>68.3 ± 7.8</td>
</tr>
<tr>
<td>Walking distance (m)</td>
<td>1710.6 ± 246.0</td>
<td>1813.9 ± 268.1</td>
<td>1756.5 ± 232.3</td>
<td>1726.6 ± 383.9</td>
<td>2044.4 ± 401.3</td>
<td>2228.6 ± 616.9</td>
<td>1757 ± 335.2</td>
<td>1908.7 ± 421.1</td>
<td>1854.5 ± 493.9</td>
<td>239 ± 4.9</td>
</tr>
<tr>
<td>Walking time (min)</td>
<td>23.9 ± 3.6</td>
<td>24.5 ± 4.0</td>
<td>23.6 ± 3.3</td>
<td>23.6 ± 4.1</td>
<td>279 ± 4.4</td>
<td>23.0 ± 4.8</td>
<td>24.8 ± 6.7</td>
<td>25.2 ± 4.5</td>
<td>24.9 ± 4.9</td>
<td>—</td>
</tr>
</tbody>
</table>

BMI, body mass index; T2DM, type 2 diabetes mellitus; HBP, high blood pressure; BG, blood glucose; group A, acarbose alone; group B, metformin alone; group C, sulfonylureas alone; group D, insulin or insulin analogues alone; group E, metformin and sulfonylureas jointly; group F, acarbose and metformin jointly; group G, acarbose and sulfonylureas jointly; group H, acarbose, metformin and sulfonylureas jointly; group I, insulin and hypoglycemic drugs jointly; group J, no drugs; group K were willing to stop exercising for one to two days and continuing to take the originally used hypoglycemic drugs.

Table 3. BG reduction (%) in acarbose and non-acarbose group

<table>
<thead>
<tr>
<th>Group</th>
<th>n (female)</th>
<th>Age</th>
<th>BMI</th>
<th>Years of T2DM</th>
<th>Exercise times</th>
<th>BG before exercise (mmol/L)</th>
<th>BG after exercise (mmol/L)</th>
<th>Decline (%)</th>
<th>95% CI</th>
<th>Distance (m)</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>42 (3)</td>
<td>75.9 ± 6.7</td>
<td>24.0 ± 2.9</td>
<td>8.9 ± 6.1</td>
<td>258</td>
<td>10.9 ± 2.4</td>
<td>9.3 ± 2.5</td>
<td>-14.8 ± 15.3</td>
<td>-16.7</td>
<td>1780 ± 401</td>
<td>23.9 ± 4.8</td>
</tr>
<tr>
<td>non-acarbose</td>
<td>43 (5)</td>
<td>72.8 ± 7.3</td>
<td>25.1 ± 2.8</td>
<td>9.7 ± 8.3</td>
<td>274</td>
<td>11.6 ± 2.8</td>
<td>8.8 ± 2.6</td>
<td>-23.0 ± 16.3</td>
<td>-25.0</td>
<td>1827 ± 339</td>
<td>24.6 ± 4.1</td>
</tr>
<tr>
<td>t value</td>
<td>—</td>
<td>73.358</td>
<td>52.004</td>
<td>9.421</td>
<td>—</td>
<td>71.643</td>
<td>57.966</td>
<td>-15.507</td>
<td>—</td>
<td>63.814</td>
<td>79.183</td>
</tr>
<tr>
<td>P value</td>
<td>—</td>
<td>&lt;0.00001</td>
<td>&lt;0.00001</td>
<td>&lt;0.00001</td>
<td>—</td>
<td>&lt;0.00001</td>
<td>&lt;0.00001</td>
<td>&lt;0.00001</td>
<td>—</td>
<td>&lt;0.00001</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

BG, blood glucose; CI, confident interval; BMI, body mass index; T2DM, type2 diabetes mellitus.
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Table 2. BG reduction (%) in exercised and non-exercised groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Exercise times</th>
<th>BG reduction (%)</th>
<th>t value</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>666</td>
<td>-20 ± 16.3</td>
<td>-31.766</td>
<td>&lt;0.0001</td>
<td>-21.3 to -18.8</td>
</tr>
<tr>
<td>Non-exercise</td>
<td>16</td>
<td>-2.3 ± 19.1</td>
<td>-0.480</td>
<td>&lt;0.0001</td>
<td>-12.5 to -7.9</td>
</tr>
</tbody>
</table>

BG, blood glucose; CI, confidence interval.

Results

One hundred and five patients (10 female) were included in this study, with an average age of 73.6 ± 7.6 years. Six-hundred and sixty-six walks were performed by all subjects throughout the study. The control group included 14 patients (2 female), with an average age of 76.3 ± 7.7 years. No significant differences were observed in the baseline characteristics of patients in all groups. During the experimental period, BG changes were observed sixteen times and the results are shown in Table 1. The BG reduction in all exercised patients was significantly greater than that of non-exercised patients (-20 ± 16.3 vs. -2.3 ± 19.1; *t*-test for independent samples, *t*=-31.766, *P*<0.0001) (Table 2).

As shown in Table 1, the BG reduction in group J (the non-medicated group) was the greatest among all the groups, possibly because these were the newly diagnosed diabetics and had not take medication yet. Surprisingly, the BG reduction was the least in groups A (acarbose alone), F (combination of acarbose and metformin), G (combined of acarbose and sulfonylureas) and H (combination of acarbose, metformin and sulfonylureas) suggesting that acarbose influenced excised-induced hypoglycemic effects. To prove this hypothesis, patients taking acarbose (alone or combination with other drugs) were re-distributed to form an acarbose group, while the rest patients were merged into a non-acarbose group. The variance between acarbose and non-acarbose group was analyzed with a *t*-test. As shown in Table 3, the BG reduction in the acarbose group was significant less when compared to that of the non-acarbose groups (*P*<0.0001), further confirming that acarbose might offset the hypoglycemic effects of walking.

Since other factors might also influence the hypoglycemic effects of walking, factors such as usage of individual hypoglycemic drugs, multiple combined hypoglycemic drugs and the absence of drug usage were analyzed with multiple linear stepwise regression (stepwise method). The results suggested that the factors affecting BG reduction were acarbose alone and acarbose combined with sulfonylureas, metformin and metformin with sulfonylureas. However, the effect of medication on BG was eliminated after further correction for sex, age, BMI, diabetes history, walking time, walking speed and walking distance. After examination of all factors, only age was confirmed to be an influencing factor (*t*=-3.304, *P*=0.001). Further correlation analysis (Pearson correlation) of age and BG reduction showed that the correlation coefficient was only 0.183 and no statistical significance was observed (*P*=0.061).

Discussion

Diabetes mellitus is a chronic metabolic disorder that, without proper treatment, will result in severe life-threatening complications, such as cardiovascular disease, retinopathy, neuropathy and nephropathy [14]. Many studies have shown that exercise plays a critical role in improving T2DM. Exercise not only improves glycemic control, but also improves insulin sensitivity [7]. In the present study, we compared the impact of different hypoglycemic drugs on exercise-induced BG reduction and found that acarbose partially offset the hypoglycemic effects of exercise.

In the guidelines for diabetes treatment, aerobic exercise is considered an important method to control diabetes mellitus [15, 16]. Generally, aerobic exercise was thought to decrease the levels of glycosylated hemoglobin and ameliorate insulin resistance. However, in recent years, researchers have paid more attention to...
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the influence of exercise on the hypoglycemic effects of hypoglycemic drugs. In subjects with mild T2DM, exercise improved insulin sensitivity but had no effect on glycemic control. The addition of acarbose to exercise, however, was associated with significant improvement of glycemic control and cardiovascular risk factors [17]. Acarbose, especially in combination with a low calorie diet and exercise, seems to encourage effective weight loss in obese and overweight patients in communities that have a high carbohydrate intake (similar to the Persian diet) [18]. Insulin sensitivity was considerably improved after 12 weeks of exercise with or without metformin usage in both prediabetic men and women [19]. Under certain conditions, exercise interfered with the glucose-lowering effect of metformin [20]. It has been suggested recently that metformin attenuates the insulin-sensitizing effect of exercise [21]. However, no report has demonstrated the influences of hypoglycemic drugs on BG reduction immediately after exercise. In the present study, we observed a substantial decrease in BG when elderly T2DM patients walked at a moderate speed (4.0-4.5 km/h) for 20 to 30 minutes after breakfast. The BG reduction in the non-medicated group was the most obvious in comparison with the medicated groups, because patients in non-medicated group usually had a short history of diabetes and may therefore be more sensitive to exercise-mediated BG reduction.

The hypoglycemic effects of metformin enhance tissue insulin sensitivity and BG uptake. Muscle contraction is known to lead to activation of AMP-activated protein kinase (AMPK), and there is growing evidence that metformin also increases AMPK activity in liver, muscle and other tissues [22]. Recently, more attention has been given to AMPK activators as exercise mimetic [23] and metformin has been shown to improve exercise tolerance in non-diabetic women with clinically defined angina [24].

Our results also revealed that acarbose partially offset hypoglycemic effects of postprandial exercise we observed. This study was not designed to examine middle- or long-term changes in BG; however, our results reveal significant beneficial short-term changes in BG with postprandial aerobic exercise.

Conclusions

In this study, we demonstrated that BG was significantly decreased in elderly T2DM patients after walking at a moderate speed (4.0-4.5 km/h) for 20 to 30 minutes after breakfast. The BG reduction in patients taking sulfonylureas was most obvious, while the BG reduction in patients taking acarbose alone or in combination with other drugs was least obvious. We propose that acarbose might decrease the hypoglycemic effects of postprandial exercise. These results may provide useful information when determining the best course of treatment and medication for elderly T2DM patients.

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Disclosure of conflict of interest

None.

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