Effect of Acarbose on Insulin Sensitivity in Elderly Patients With Diabetes

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OBJECTIVE — To study the effect of acarbose, an α-glucosidase inhibitor, on insulin release and insulin sensitivity in elderly patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Elderly patients with type 2 diabetes were randomly treated in a double-blind fashion with placebo (n = 23) or acarbose (n = 22) for 12 months. Before and after randomization, subjects underwent a meal tolerance test and a hyperglycemic glucose clamp study designed to measure insulin release and sensitivity.

RESULTS — After 12 months of therapy, there was a significant difference in the change in fasting plasma glucose levels (0.2 ± 0.3 vs. −0.5 ± 0.2 mmol/l, placebo vs. acarbose group, respectively; P < 0.05) and in incremental postprandial glucose values (−0.4 ± 0.6 vs. −3.5 ± 0.6 mmol/l, placebo vs. acarbose group, P < 0.001) between groups. There was a significant difference in the change in HbA1c, values in response to treatment (0.4 ± 0.2 vs. −0.4 ± 0.1%, placebo vs. acarbose group, P < 0.01). The change in fasting insulin in response to treatment (−2 ± 2 vs. −13 ± 4 pmol/l, placebo vs. acarbose group, P < 0.05) and incremental postprandial insulin responses (−89 ± 26 vs. −271 ± 59 pmol/l, placebo vs. acarbose group, P < 0.01) was also significantly different between groups. During the hyperglycemic clamps, glucose and insulin values were similar in both groups before and after therapy. However, there was a significant difference in the change in insulin sensitivity in response to treatment between the placebo and the acarbose groups (0.001 ± 0.001 vs. 0.004 ± 0.001 mg/kg · min⁻¹ · [pmol/l]⁻¹, respectively; P < 0.05).

CONCLUSIONS — Acarbose increases insulin sensitivity but not insulin release in elderly patients with diabetes.

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Abbreviations: HOMA, homeostasis model assessment.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Emerging Treatments and Technologies

ORIGINAL ARTICLE

Effect of Acarbose on Insulin Sensitivity in Elderly Patients With Diabetes

By the age of 75 years, ~20% of the older population is afflicted with type 2 diabetes (1). Recent studies have characterized the metabolic abnormalities that occur in this patient population (2,3). In lean older patients, there is a profound impairment in glucose-induced insulin secretion. In obese older people with type 2 diabetes, the principal metabolic defect is resistance to insulin-mediated glucose disposal. When diet and exercise fail, oral hypoglycemic agents or insulin are often used. Unfortunately, the risk of severe or fatal hypoglycemia associated with the use of sulfonylureas increases exponentially with age (4). Biguanides can be effective therapy in older patients with diabetes, but these medications can be contraindicated because of renal insufficiency, liver disease, or congestive heart failure, or they may not be tolerated because of gastrointestinal side effects. For this reason, there has been increasing interest in the use of alternative therapeutic agents for the treatment of diabetes in the elderly.

α-Glucosidase inhibitors have recently been released for use in Canada and the U.S. These drugs are thought to act by competitively inhibiting enzymes at the brush border of the small intestine (5), thereby retarding glucose absorption. However, other potential mechanisms of action for α-glucosidase inhibitors have not been explored in the elderly population. We undertook this study to determine if the α-glucosidase inhibitor acarbose modifies the principal metabolic defects, namely impaired insulin secretion and insulin resistance, in elderly patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Experimental subjects

These studies were conducted in older people with type 2 diabetes (Table 1). These subjects were enrolled in a larger study assessing the effectiveness of acarbose in elderly patients with type 2 diabetes, the results of which will be published separately. Subjects at 5 centers were randomly assigned to undergo the studies described below. Patients with diabetes were excluded if they were being treated with insulin or...
Table 1—Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Acarbose</th>
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<tr>
<td>n</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70 ± 1</td>
<td>68 ± 1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29 ± 1</td>
<td>28 ± 1</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>8.3 ± 0.4</td>
<td>8.1 ± 0.3</td>
</tr>
<tr>
<td>Fasting Insulin (pmol/l)</td>
<td>87 ± 9</td>
<td>104 ± 10</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.0 ± 0.2</td>
<td>7.3 ± 0.1</td>
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Data are n or means ± SEM.

oral agents, if they suffered from a major debilitating disease, if they had evidence of documented gastrointestinal diseases or were taking drugs that could impair intestinal motility or alter absorption of nutrients, if they had a recent major cardiovascular event, or if they had abnormal renal or liver function. Patients were also excluded if they had an HbA1c value <10% or >50% above the upper limit of normal for the reference laboratory at the time of enrollment (<6.4%). These studies were approved by each participating center’s Committee on Human Investigations. All subjects gave written informed consent before participation.

At baseline, 26 weeks, and 52 weeks, subjects were asked to record a 3-day food recall and were interviewed by a research diettian. Based on these data, at each visit, subjects were advised to adjust their dietary intake in an attempt to ensure that total caloric intake and nutrient composition was similar throughout the study. After a 6-week pretreatment period, each patient underwent a meal tolerance test and a hyperglycemic glucose clamp study as detailed below. Patients were then randomly assigned to receive acarbose or placebo for a period of 12 months. Patients were asked to take study medication with the first bite of each meal 3 times a day. The initial dose was 50 mg 3 times a day. If necessary, the dose was titrated upward on subsequent visits to 100 mg 3 times a day, based on postprandial plasma glucose levels in response to a meal tolerance test. Patients were seen every 6 weeks during the study. Drug compliance was verified by pill counts. At the end of 1 year, the subjects underwent a second meal tolerance test and hyperglycemic glucose clamp study.

The meal tolerance tests and the glucose clamp studies were conducted after an overnight fast and were separated by at least 1 week. Subjects did not take their pills on the mornings of the clamp or the meal tolerance test. In the meal tolerance test, blood samples were taken at baseline to measure glucose and insulin values. Each subject was given 400 ml Ensure with fiber (450 kcal, 55% carbohydrate, 30% fat, and 15% protein). Blood samples were taken at 60, 90, and 120 min to measure glucose and insulin values. Hyperglycemic glucose clamp studies were conducted by the method of Andres and colleagues (6,7). In each study, 3 blood samples were taken at 10-min intervals from −20 to 0 min to measure basal glucose and insulin values. In the initial study, at time 0, glucose was infused to increase the plasma glucose to 5.4 mmol/l above basal, and glucose was kept at that level for 120 min. In the second study, the glucose level during the hyperglycemic clamp was maintained at the same level as the initial study. During the studies, insulin and glucose values were measured every 2 min for the first 10 min. Glucose was then measured every 5 min, and insulin was measured every 10 min for the duration of the study.

Plasma glucose was measured immediately at the bedside by the glucose oxidase method using a glucose analyzer. The remaining blood was placed in prechilled test tubes containing heparin and centrifuged at 4°C. Samples were stored at −70°C until assay. Radioimmunoassay measurements were performed in duplicate, as previously described, using a highly specific and sensitive insulin assay, which cross-reacts <1% with proinsulin (8). All samples from each individual were analyzed in the same assay. HbA1c values in all subjects were measured by high-performance liquid chromatography at our reference laboratory, as previously described (9).

Results are presented as means ± SEM. First-phase insulin secretion was calculated as the mean of all insulin values from 0–10 min of the clamp. Steady-state (90–120 min) insulin values during the clamp were used as a measure of second-phase insulin secretion. Insulin sensitivity was determined from the clamp data as previously described (10). Briefly, the average glucose infusion rate from the last 30 min of the clamp was divided by the average insulin value over the same time period. Insulin sensitivity was also calculated from fasting insulin and glucose values by the homeostasis model assessment (HOMA) method, as previously described (11). Correlation coefficients were calculated by the method of least squares. The trapezoidal rule was used to calculate the incremental area under the curve for postprandial insulin and glucose values. Paired and unpaired Student’s t tests were used to analyze the data as appropriate. P < 0.05 was considered significant in all analyses.

RESULTS—Subject characteristics are shown in Table 1. Before treatment, subjects were similar in age, BMI, and fasting glucose, insulin, and HbA1c levels. The change in weight in response to 12 months of treatment was not different between groups (placebo −1.9 ± 0.8 kg, acarbose −1.9 ± 0.6 kg, NS). There was no significant change in total caloric intake in response to therapy (placebo −1 ± 55 kcal, acarbose 90 ± 50 kcal, NS). There was also no significant change in the proportion of calories as carbohydrate (placebo −0.7 ± 0.8%, acarbose −0.7 ± 0.8%, NS), fat (placebo 1.4 ± 0.9%, acarbose 0.9 ± 0.8%, NS), or protein (placebo −0.3 ± 0.5%, acarbose −0.5 ± 0.5%, NS). However, there was a significant difference in the change in fasting plasma glucose levels in response to treatment between groups (placebo 0.2 ± 0.3 mmol/l, acarbose −0.5 ± 0.2 mmol/l, P < 0.05) and in incremental postprandial glucose values.

Table 2—Changes in glucose, insulin, HbA1c, and insulin sensitivity and resistance in response to therapy

<table>
<thead>
<tr>
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<th>Placebo</th>
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<tbody>
<tr>
<td>n</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>0.2 ± 0.3</td>
<td>−0.5 ± 0.2*</td>
</tr>
<tr>
<td>Postprandial glucose (mmol/l)</td>
<td>−0.4 ± 0.6</td>
<td>−3.5 ± 0.6†</td>
</tr>
<tr>
<td>Fasting insulin (pmol/l)</td>
<td>−2 ± 2</td>
<td>−13 ± 4*</td>
</tr>
<tr>
<td>Postprandial insulin (pmol/l)</td>
<td>−89 ± 26</td>
<td>−271 ± 159†</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.4 ± 0.2</td>
<td>−0.4 ± 0.1†</td>
</tr>
<tr>
<td>Insulin sensitivity (clamp) (mg/kg · min⁻¹ · [pmol/l]⁻¹)</td>
<td>0.001 ± 0.001</td>
<td>0.004 ± 0.001*</td>
</tr>
<tr>
<td>Insulin resistance (HOMA)</td>
<td>−0.2 ± 0.2</td>
<td>1.1 ± 0.3†</td>
</tr>
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</table>

Data are n or means ± SEM. *P < 0.05 vs. placebo; †P < 0.01 vs. placebo.
Acarbose and the elderly

Figure 1—Glucose and insulin values during the hyperglycemic clamp in the placebo and acarbose groups at baseline and after 12 months of therapy. A: Glucose values in the placebo group. B: Glucose values in the acarbose group. C: Insulin values in the placebo group. D: Insulin values in the acarbose group. Results are presented as means ± SEM.

(Placebo — 0.4 ± 0.6 mmol/l, acarbose — 3.5 ± 0.6 mmol/l, P < 0.001) (Table 2). There was also a significant difference in the change in HbA1c concentrations in response to treatment (placebo 0.4 ± 0.2%, acarbose — 0.4 ± 0.1%, P < 0.01) (Table 2). The change in fasting insulin in response to treatment (placebo — 2 ± 2 pmol/l, acarbose — 13 ± 4 pmol/l, P < 0.05) and incremental post-prandial insulin responses (placebo — 89 ± 26 pmol/l, acarbose — 271 ± 59 pmol/l, P < 0.01) was significantly different between groups (Table 2).

Plasma glucose and insulin values and glucose infusion rates during the hyperglycemic clamps are shown in Fig. 1. Glucose values were similar in both groups before and after therapy. There was no measurable first-phase insulin secretion in either the placebo or the acarbose groups before or after therapy. Steady-state insulin values during the clamp were similar in the placebo (168 ± 19 vs. 174 ± 21 pmol/l, NS) and acarbose (191 ± 19 vs. 198 ± 19 pmol/l, NS) groups before and after therapy, respectively. Glucose infusion rates between 100 and 120 min did not change in the placebo group before and after treatment (2.29 ± 0.21 vs. 2.11 ± 0.27 mg · kg⁻¹ · min⁻¹, respectively, NS), but they increased in the acarbose group (1.68 ± 0.19 vs. 2.69 ± 0.19 mg · kg⁻¹ · min⁻¹, P < 0.001) (Fig. 2). There was no change in insulin sensitivity as measured by the metabolic rate of glucose divided by the steady state insulin level (M/I ratio) in the placebo versus the acarbose group (0.012 ± 0.002 vs. 0.016 ± 0.003 mg/kg · min⁻¹ · [pmol/l]⁻¹, respectively, NS). However, there was an ~30% increase in insulin sensitivity in the acarbose group in response to therapy (0.011 ± 0.001 vs. 0.015 ± 0.001 mg/kg · min⁻¹ · [pmol/l]⁻¹, before vs. after therapy, P < 0.01). In addition, there was a significant difference in the change in insulin sensitivity in response to treatment between groups (0.003 ± 0.001 vs. 0.004 ± 0.001 mg/kg · min⁻¹ · [pmol/l]⁻¹, placebo vs. acarbose, P < 0.05) (Fig. 3 and Table 2). There was no correlation between change in weight during the study and change in M/I ratio in the placebo (r = 0.27, NS) and the acarbose (r = 0.31, NS) groups.

To confirm that there was a change in insulin sensitivity in response to acarbose, we analyzed fasting glucose and insulin values using the HOMA method. There was no change in relative insulin resistance in the placebo group in response to therapy (5.5 ± 0.6 vs. 5.7 ± 0.7, before vs. after therapy, NS). However, there was a significant improvement in relative insulin resistance in the acarbose group (6.1 ± 0.5 vs. 5.0 ± 0.5, before vs. after therapy, P < 0.01). There was also a significant difference in the change in relative insulin resistance in
CONCLUSIONS — \(\alpha\)-Glucosidase inhibitors have been demonstrated to be safe and efficacious agents for the treatment of type 2 diabetes in the elderly (12). In this study, we evaluated the effect of acarbose on insulin sensitivity and insulin release in older people with type 2 diabetes.

Insulin responses to oral glucose in patients with type 2 diabetes on acarbose have shown a decrease, no change, or an increase in insulin secretion (9,13–15). In this study, the insulin responses to a mixed nutrient stimulus were reduced in the acarbose group. During the hyperglycemic clamp, we found no effect of acarbose on first- or second-phase insulin release. It is possible that acarbose altered insulin clearance. This is unlikely, because treatment with \(\alpha\)-glucosidase inhibitors does not alter insulin clearance in younger patients with type 2 diabetes (16,17).

Chiasson et al. (18) measured insulin sensitivity using the insulin suppression test and found that insulin sensitivity increased in response to acarbose in obese patients with impaired glucose tolerance. Using the minimal model technique, Calle-Pascual et al. (19) found that 16 weeks of acarbose increased insulin sensitivity in obese middle-aged patients with type 2 diabetes. In contrast, several studies that evaluated the effects of acarbose on insulin-mediated glucose disposal using the euglycemic glucose clamp technique in middle-aged patients with poorly con-
Acarbose and the elderly

progresses and insulin resistance gives way to
insulinopenia as the mechanism for hyper-
glycemia. Both the placebo and acarbose
groups lost weight despite being on a
weight-maintaining diet. This is unlikely to
have altered the results because there was
no correlation between change in weight
and change in the M/I ratio in either the
placebo or the acarbose group. It is possible
that the hyperglycemic glucose did not
provide an accurate assessment of insulin
sensitivity. We have recently shown that
the hyperglycemic clamp provides a mea-
sure of insulin sensitivity that correlates
closely with that obtained from a eugly-
cemic glucose clamp study in older people
with type 2 diabetes (r = 0.71) (10). How-
ever, because the subjects on acarbose had
lower fasting glucose levels at the end of the
study, greater amounts of glucose were
needed to achieve the glycemic target,
which could have caused an overestimation
of insulin sensitivity. Finally, our reported
changes in insulin sensitivity could be due
to increased insulin-mediated glucose dis-
posal, increased suppression of hepatic glu-
cose output, or both. Our experimental
design did not allow us to evaluate these
parameters simultaneously.

In summary, acarbose appears to
increase insulin sensitivity but not insulin
release in elderly patients with diabetes.

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Figure 3 — Insulin sensitivity measured during the hyperglycemic clamp in the placebo (A) and acar-
bose (B) groups in response to 12 months of therapy. Results are presented as means ± SEM.