Sulfonylurea Treatment of Type 2 Diabetic Patients Does Not Reduce the Vasodilator Response to Ischemia

**OBJECTIVE** — Sulfonylureas block the activation of vascular potassium-dependent ATP channels and impair the vasodilating response to ischemia in nondiabetic individuals, but it is not known whether this occurs in type 2 diabetic patients under chronic treatment with these drugs. Glimepiride, a new sulfonylurea, apparently has no cardiovascular interactions. The aim of our study was to compare the effect of the widely used compound glibenclamide, the pancreas-specific glimepiride, and diet treatment alone on brachial artery response to acute forearm ischemia.

**RESEARCH DESIGN AND METHODS** — Brachial artery examination was performed by a high-resolution ultrasound technique on 20 type 2 diabetic patients aged (mean ± SD) 67 ± 2 years and on 18 nondiabetic patients matched for age, hypertension, and dislipidemia. Diabetic subjects underwent three separate evaluations at the end of each 8-week treatment period, during which they received glibenclamide, glimepiride, or diet alone according to crossover design. Scans were obtained before and after 4.5 min of forearm ischemia. Postischemic vasodilatation and hyperemia were expressed as percent variations in vessel diameter and blood flow.

**RESULTS** — Postischemic vasodilatation and hyperemia were, respectively, 5.42 ± 0.64 and 357 ± 64% during glibenclamide, 5.46 ± 0.69 and 326 ± 28% during glimepiride, and 5.17 ± 0.64 and 357 ± 39% during diet treatment (NS). These results were similar to those found in the nondiabetic patients (6.44 ± 0.68 and 406 ± 42%, NS).

**CONCLUSIONS** — In type 2 diabetic patients, the vasodilating response to forearm ischemia was the same whether patients were treated with diet treatment alone or with glibenclamide or glimepiride at blood glucose-lowering equipotent doses.

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Sulfonylureas represent the most commonly prescribed pharmacological treatment for type 2 diabetic patients, despite early observations suggesting a possible deleterious effect of these drugs (1–3). However, the question is still open. In fact, in the early 1970s, the University Group Diabetes Program (UGPDP) suggested that the use of sulfonylureas might increase cardiovascular mortality, but the more recent U.K. Prospective Diabetes Study (UKPDS) showed no evidence that intensive treatment with sulfonylureas had any specific adverse effect on cardiovascular disease in type 2 diabetic patients (3,4). A physiological basis explaining the potentially detrimental effects of sulfonylureas has been provided by the discovery that sulfonylurea drugs stimulate insulin secretion by blocking β-cell ATP-sensitive K⁺ (K_{ATP}) channels (5). K_{ATP} channels are also abundantly present in the cardiac muscle and in vascular smooth muscle cells in coronary and peripheral arteries, where they play a key role in the protective mechanisms that are triggered during ischemia (6,7). Soon after the onset of ischemia, the activation of K_{ATP} channels decreases vascular resistance and increases blood flow (ischemic vasodilation) and renders myocardial cells more resistant to a subsequent bout of ischemia (the so-called ischemic preconditioning) (8,9). A great deal of experimental evidence shows that glibenclamide and the other sulfonylurea compounds, which are not β-cell–specific, block cardiovascular K_{ATP} channels and prevent both protective phenomena (8–11). Glimepiride is a new sulfonylurea compound that interacts more selectively with the β-cell K_{ATP} channels (12). In agreement with experimental evidence, studies in humans have shown that acute administration of glibenclamide, but not of the pancreas-specific glimepiride, induces potentially harmful cardiovascular effects in both nondiabetic patients with coronary artery disease and healthy volunteers (13–17).

Less is known about the clinical situation of type 2 diabetic patients who are chronically treated with sulfonylureas. The evidence of poor outcome in diabetic patients undergoing percutaneous coronary angioplasty for acute myocardial infarction while taking sulfonylureas is consistent with the hypothesis that long-term inhibition of K_{ATP} channels may impair myocardial tolerance to severe ischemia (18). This hypothesis contrasts with the early observations by Paasikivi and with a recent retrospective analysis showing that treatment with glibenclamide does not affect infarct size and in-hospital mortality in type 2 diabetic patients with acute myocardial infarction (19,20). However, to our knowledge, no studies have ever examined whether ther-
and the mean level of HbA1c was 7.59

diabetes (means

duration of di-

METHODS

RESEARCH DESIGN AND

METHODS

Twenty type 2 diabetic subjects aged 57–80 years were recruited from the dia-

revascularization response to a brief episode of arterial occlusion in type 2 diabetic

patients may compromise vascular blood flow regulation in response to ischemia.

The aim of this work was to investigate the effects of chronic administration of the

lyluric agents were then discontinued, and efforts were made to control hyperglycemia

for at least 4 weeks by adjusting their diet. Hypoglycemic drugs could not be discont-

ined in four patients, and three patients dropped out because they found the re-

strictive diet too demanding. At the end of each treatment period with glibenclamide

and glimepiride, all diabetic patients underwent noninvasive assessment of bra-

chial artery response to acute ischemia. Of the diabetic patients, 13 on diet therapy

alone were also evaluated a third time. Nondiabetic patients were only evaluated

once. A total of 11 diabetic subjects and 9 nondiabetic control subjects were on car-

diovascular drug therapy, and this treatment was not discontinued. However, every

effort was made to maintain a constant drug regimen throughout the study in all diabetic

patients undergoing repeated examinations.

Table 1—General characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Diabetic patients</th>
<th>Nondiabetic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.4 ± 1.9</td>
<td>67.5 ± 1.8</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>14/6</td>
<td>13/5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.8 ± 0.7*</td>
<td>26.9 ± 0.5</td>
</tr>
<tr>
<td>Hypertension (yes/no)</td>
<td>14/6</td>
<td>13/5</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.17 ± 0.17</td>
<td>5.24 ± 1.17</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.0 ± 0.3</td>
<td>1.02 ± 0.3</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.27 ± 0.16</td>
<td>3.03 ± 0.12</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>130 ± 14</td>
<td>119 ± 13</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>7.55 ± 0.2†</td>
<td>5.22 ± 0.14</td>
</tr>
<tr>
<td>Ace inhibitors (yes/no)</td>
<td>7/13</td>
<td>5/13</td>
</tr>
<tr>
<td>β-blockers (yes/no)</td>
<td>5/15</td>
<td>5/13</td>
</tr>
<tr>
<td>Calcium antagonists (yes/no)</td>
<td>2/18</td>
<td>2/16</td>
</tr>
<tr>
<td>Lipid-lowering drugs (yes/no)</td>
<td>7/13</td>
<td>5/13</td>
</tr>
<tr>
<td>History of cardiovascular disease (yes/no)</td>
<td>5/15</td>
<td>4/14</td>
</tr>
</tbody>
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Data are means ± SE or n. *P < 0.05 compared to nondiabetic patients; †P < 0.001 compared to nondiabetic patients.

Protocol

All subjects were examined in the afternoon, 120–180 min after the main meal of the day and intake of the study drug. High-resolution ultrasound (Acuson Sequoia C256) with an 8-MHz linear array transducer was used to measure the brachial artery diameter. Machine operating parameters were kept constant during each study. The subject was required to recline on an examination bed for 10 min in a quiet setting. The brachial artery was longitudinally imaged ~5 cm above the antecubital crease. Once an optimal position was obtained, the transducer was no longer moved. A baseline scan was obtained and pulsed Doppler blood flow velocity was determined with the signal at a 70° angle to the vessel and with the range gate adjusted to 1.5 mm and positioned in the center of the artery. A cuff placed on the forearm was then inflated to 300 mmHg for 4.5 min. A second scan was carried out continuously for 30 s before and 90 s after cuff deflation. Measurements were calculated on the basis of S-VHS video recordings by two observers who were blinded to clinical data and the type of therapy being administered. Diameter measurements were made at end-diastole, incident with the R wave on a continuously recorded electrocardiogram, 45–60 s after cuff deflation. Doppler flow signals were recorded during the first 15 s after cuff release. Volume flow was calculated by multiplying the velocity time integral of the Doppler signal (corrected for angle) by the heart rate and the artery cross-sectional area. Changes in vessel diameter and blood flow after cuff deflation are expressed as the percentage relative to the baseline scan.

Statistical analysis

Comparisons between subject groups were performed by using paired or un-
paired t tests for continuous variables and a χ² test for categorical variables. Post-
ischemic vasodilation and hyperemia were examined by nonparametric statis-
tics (Wilcoxon’s test for paired data and Mann-Whitney U test, as appropriate).

Data are given as means ± SEM. A value of P < 0.05 was considered statistically significant.

RESULTS — Baseline characteristics of the study patients are provided in Table 1. The characteristics of diabetic and nondiabetic patients were comparable. The two
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Table 2—Baseline brachial artery diameter and flow, blood pressure, and metabolic determinations during brachial artery examination

<table>
<thead>
<tr>
<th></th>
<th>Diabetic subjects (n = 20)</th>
<th>Non-diabetic patients (n = 18)</th>
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<tr>
<td></td>
<td>Glibenclamide</td>
<td>Glimepiride</td>
</tr>
<tr>
<td>Baseline diameter (mm)</td>
<td>4.12 ± 0.19</td>
<td>4.12 ± 0.14</td>
</tr>
<tr>
<td>Baseline flow (ml/min)</td>
<td>164 ± 27</td>
<td>131 ± 12</td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>233 ± 24*</td>
<td>229 ± 21*</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>11.60 ± 0.47†</td>
<td>11.42 ± 0.40†</td>
</tr>
<tr>
<td>HbA1c (%)†</td>
<td>7.23 ± 0.25†</td>
<td>7.29 ± 0.28†</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>142 ± 4</td>
<td>141 ± 5</td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
<td>144 ± 5</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>84 ± 2</td>
<td>83 ± 3</td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
<td>83 ± 2</td>
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<tr>
<td></td>
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<td>85 ± 2</td>
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</tbody>
</table>

Data are means ± SEM. Note that only 13 diabetic patients were treated with diet therapy alone. *P < 0.05 compared with nondiabetic patients. †P < 0.01 compared with nondiabetic patients. ‡Nondiabetic range = 4–5.7%.

groups that were matched for age, sex, and hypertension did not differ with regard to total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride levels, and cardiovascular therapy. They did, however, differ significantly with respect to BMI and fasting blood glucose. Three diabetic patients and two nondiabetic patients had prior myocardial infarctions, and two patients in each of the groups had stable effort angina.

All brachial artery examinations were performed in the afternoon, 136 ± 14 min after the main meal of the day. In diabetic subjects, the mean dose of glibenclamide was 7.2 ± 0.9 mg/day, whereas the dose of glimepiride was 2.35 ± 0.19 mg/day. Both sulfonylureas were equally effective in achieving glycemic control (Table 2).

Baseline brachial artery diameter and blood flow values in diabetic patients were similar to those in nondiabetic patients (Table 2), and in the diabetic subjects, there was no difference between those values recorded during treatment with glibenclamide or glimepiride and those recorded during diet treatment alone. There was no difference in mean arterial blood pressure between diabetic and nondiabetic patients. Assays performed on blood drawn immediately before brachial artery examination showed that glucose, insulin, and HbA1c levels were higher in diabetic patients than in nondiabetic subjects. However, diabetic subjects showed no changes in these values during any of the three study treatments (Table 2).

Brachial artery responses after cuff deflation are shown in Fig. 1. Among diabetic subjects, postischemic vasodilation and hyperemia were, respectively, 5.42 ± 0.90% (95% CI 3.53–7.30) and 331 ± 38% (252–410) during glibenclamide, 5.46 ± 0.69% (4.01–6.91) and 326 ± 28% (266–384) during glimepiride, and 5.17 ± 0.64% (3.79–6.56) and 357 ± 35% (280–434) during diet treatment (NS). No differences were observed between diabetic patients with and without microvascular complications. These results were similar to the ones observed in nondiabetic patients (6.44 ± 0.68% [5–7.88], NS, and 406 ± 42% [280–434], NS).

CONCLUSIONS — K_{ATP} channels play a key role in the regulation of insulin secretion and in the modulation of vascular tone (5,8). In the resting pancreatic β-cells, K_{ATP} channels are normally open, but when plasma glucose rises, the enhanced glucose metabolism brings about their closure. The decrease of potassium permeability leads to an increase of cytosolic calcium that triggers the release of insulin. On the other hand, K_{ATP} channels in the vascular smooth muscle cells are normally closed or inactive. When ischemia occurs, the decline in the intracellular concentration of ATP activates these channels. The subsequent hyperpolarization of the cells decreases the inward flow of calcium, resulting in vasodilation that, in turn, combats the effects of hypoxia (8).

Sulfonylureas, as a class, interact specifically with K_{ATP} channels of cell membranes. Evidence shows that though glibenclamide and other sulfonylureas promote insulin secretion by the blockade of pancreatic K_{ATP} channels, they also neutralize the vascular protective mechanism that is triggered during ischemia (8, 13,14). By contrast, the new-generation sulfonylurea, glimepiride, is more pancreas-specific and does not interfere with vascular K_{ATP} channel activation (12,16). However, it must be stressed that this data was derived from studies in which sulfonylureas were acutely administered in animals and in nondiabetic humans. It is not known what would happen in the clinical setting if ischemia occurred in diabetic patients chronically treated with sulfonylureas (2). The salient information derived from the present study is that the vascular response to ischemia in the forearm skeletal muscle vascular bed was the same whether diabetic patients were being treated with glibenclamide or glimepiride at blood glucose–lowering equipotent doses or with diet treatment alone. Several reasons may explain the discrepancies among the findings of previous studies and our results. First, the doses used in animal models produced blood concentrations that were, in general, much higher than the clinical range. Second, in humans, sulfonylureas are largely (90–99%) bound to plasma proteins (2); thus, the actual free drug concentrations in the steady state are probably lower than those reached during acute administration. A third possible reason is the presence of confounding variables in a clinical study. There is evidence that hypertension, obesity, and hypercholesterolemia (21) affect endothelium-mediated vasodilation and impair vascular response to ischemia through a mechanism that differs from K_{ATP} channel blockade. We decided a priori not to exclude subjects with coronary risk factors, because these variables often cluster with hyperglycemia and may be considered components of the syndrome. Excluding diabetic patients with coronary risk factors in an attempt to eliminate confounders might have made it easier to document differences between the two sulfonylurea drugs; however, it would have encompassed only a subset of the type 2 diabetic patients who were not representative of the type 2 diabetic population. This reason, together with evidence that strongly supports the chronic use of ACE inhibitors or antihypertensive or lipid-lowering drugs in most patients with type 2 diabetes, is why we did not stop the administration of these drugs for the study (22–24). By the second week of the study, small increments in the doses of a
calcium antagonist were necessary in one patient receiving glibenclamide and in one patient receiving glimepiride. No other changes occurred throughout the study.

The fourth possible reason for the discrepancies among previous findings and our results is that previous studies were performed on healthy volunteers with high vascular response to ischemia. Interestingly, the effects of glibenclamide on healthy subjects was slight, although statistically significant (14). The present study involves an elderly population with impaired vascular response to ischemia. It may be that, in this context, the contribution of a vascular K\textsubscript{ATP} channel-blocking agent that further impairs post-ischemic dilation is too small to be detected in a similar sample-size of patients.

Diabetic patients are often exposed to myocardial ischemia, and investigation of the coronary vasodilating response to ischemia is clinically relevant. However, an invasive technique is necessary to explore coronary circulation, because a noninvasive method is not currently available. Even though noninvasive assessment of vascular response in the forearm arterial bed can be considered a convenient indicator of the responsiveness of coronary arteries to myocardial ischemia (13,14,21,25), caution is needed before concluding that the lack of detectable effects of hypoglycemic therapy with glibenclamide can be extrapolated to the cardiac level. Because the coronary vasculature has a higher density of sulfonylurea-sensitive receptors than the peripheral vascular bed, we cannot rule out a difference between glibenclamide and glimepiride with regard to their influence on coronary reactivity (26). It must also be taken into account that besides vascular smooth muscle cells, sulfonylureas target the myocardium and prevent preconditioning, the endogenous protective mechanism by which a brief episode of ischemia can protect the myocardium from subsequent ischemic insults. Indeed, the acute administration of glibenclamide in nondiabetic patients during coronary angioplasty attenuates preconditioning, whereas glimepiride has no effect (17). However, despite these results, it is not known whether chronic administration of sulfonylureas in diabetic individuals has similar effects on preconditioning. To our knowledge, the only study that investigated the effects of prolonged sulfonylurea treatment demonstrated that chronic glicazide treatment improves, rather than worsens, basal and postischemic cardiac function in diabetic rats (27).

In conclusion, we found that 8 weeks of treatment with glibenclamide does not determine effects on the vascular response to ischemia in diabetic patients. Although this result may be considered quite reassuring as far as the use of sulfonylureas is concerned, we would like to emphasize that the study refers to the phenomenon of postischemic vasodilation. Further clinical studies are needed to clarify whether treatment with the new compound glimepiride is superior to less pancreas-specific sulfonylureas in terms of enhanced myocardial tolerance to ischemia.

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References