Effect of Antidiabetic Medications on Microalbuminuria in Patients With Type 2 Diabetes

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The progression of diabetes and hypertension complications is associated with microalbuminuria. Intensive glycemic control prevents or retards microalbuminuria in patients with type 2 diabetes, but little is known about the respective benefits of different antidiabetic drugs. We studied the effect of gliclazide and pioglitazone on microalbuminuria in patients with type 2 diabetes. We excluded patients with very poor glycemic control (glycated hemoglobin [HbA_{1c}] >10%), impaired liver function, nondiabetic renal diseases, and those whose urine contained red blood cells, hemoglobin, or casts. Each patient received the designated drug for 12 weeks and their body weight, blood pressure (BP), fasting plasma glucose (FPG), HbA_{1c}, lipids (triglycerides [TG], total, and high-density lipoprotein-cholesterol [HDL-C]), 1,5 anhidroglucitol (1,5-AG), immunoreactive insulin (IRI), and urinary albumin to creatinine ratio (UACR) were measured every month. The effects of the drugs were analyzed using 2-way repeated measures analysis of variance (ANOVA). The 2 groups of patients were well matched for age, duration of diabetes, retinal status, blood pressure, body mass index (BMI), IRI, FPG, HBA_{1c}, 1,5-AG, lipids, and UACR, as well as the use of antihypertensive drugs. After treatment, no significant differences were seen in drug efficacy between the 2 groups. Gliclazide and pioglitazone significantly reduced FPG ($F = 26.0$, $P < .0001$), HBA_{1c} ($F = 48.1$, $P < .0001$), and total cholesterol (TC) levels ($F = 3.5$, $P < .05$). Decrements in these metabolic parameters were comparable between the groups. 1,5-AG increased in both groups ($F = 27.5$, $P < .0001$), and the increment was comparable in both groups. Gliclazide and pioglitazone significantly reduced UACR ($F = 15.7$, $P < .0001$) with a comparable decrement in both groups. No other variables changed significantly throughout the 12-week treatment. These results suggest that 12 weeks of treatment with gliclazide or pioglitazone are equally effective in reducing microalbuminuria with similar improvements in blood glucose and cholesterol levels, independent of their mechanisms of actions.

Microalbuminuria, a slight elevation in urinary albumin excretion, is a strong predictive factor for the development of proteinuria. The prevalence of microalbuminuria is increased in patients with hypertension and diabetes.[1,2] Recent studies also suggest that in patients with diabetes mellitus, microalbuminuria is associated with cardiovascular disease and higher mortality.[3]

During the development of nephropathy, microalbuminuria appears early and is often reversible if proper therapeutic measures are taken. In patients with type 2 diabetes, microalbuminuria is retarded or prevented by intensive blood pressure (BP) and glycemic control.[1,4] Although several studies have demonstrated that specific antihypertensive agents are more effective than others in preventing or retarding microalbuminuria,[5,6] there are few similar studies concerning the antidiabetic drugs.

Patients with type 2 diabetes suffer from insulin secretion and insulin action anomalies, and the antidiabetic drugs reduce hyperglycemia by a variety of mechanisms. For example, sulfonylureas increase insulin secretion, whereas thiazolinedione compounds increase insulin sensitivity without stimulating endogenous insulin secretion. Previous studies have shown that among the sulfonylureas, gliclazide has a protective effect against diabetic complications,[7-10] whereas among thiazolidinediones, pioglitazone hydrochloride may have a beneficial effect on vascular risk factors in patients with type 2 diabetes[11,12]; the vascular improvements are independent of the improvements in hyperglycemia.[13,14]

Because these 2 drugs are commonly used for the treatment of type 2 diabetes and have been reported to prevent some complications of diabetes, we studied their effects on the urinary albumin to creatinine ratio (UACR) in patients with microalbuminuria.

PATIENTS AND METHODS

Study Design and Subjects

Patients recruited for this study were between 40 and 80 years of age, with type 2 diabetes and microalbuminuria. Microalbuminuria was defined as a UACR between 30 and 300 mg/g creatinine in the first morning urine sample when measured on at least 2 occasions before study entry.

At first, patients were underwent diet therapy alone for at least a month. In addition, dietary sodium intake was restricted to 7 to 10 g/d. We excluded patients who responded well to diet therapy (glycated hemoglobin [HbA_{1c}] $< 7\%$) or poorly ($HbA_{1c} > 10\%$), with impaired liver function, with a known history of nondiabetic renal disease, or those whose urine contained red blood cells, hemoglobin, or casts.

After obtaining informed consent, patients whose blood glucose was not well controlled by diet alone ($7\% \leq HbA_{1c} \leq 10\%$) were randomized to 1 of 2 treatment groups: gliclazide ($n = 21$) or pioglitazone ($n = 19$). Each patient received the designated drug for 12 weeks, and every month their body weight, blood pressure (BP), fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), HBA_{1c}, 1,5-anhidroglucitol (1,5-AG), immunoreactive insulin (IRI), and UACR were measured. Retinal status of each patient was checked before drug treatments.

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Table 1. Baseline Characteristics

Characteristic	Glicazide (n = 21)	Pioglitazone (n = 19)
Retinopathy (n)	3	2
Antihypertensive drug use (n)		
ACE inhibitors	3	3
D-CCBs	4	3
Age (yr)	54.0 ± 11.1	54.0 ± 10.3
BMI (kg/m^2)	24.0 ± 3.5	24.6 ± 2.0
Duration of diabetes (yr)	6.0 ± 4.8	6.7 ± 5.2
Blood pressure (mm Hg)		
Systolic	134.0 ± 17.0	130.0 ± 12.0
Diastolic	81.0 ± 10.0	80.0 ± 7.0
FPG (mg/dL)	167.0 ± 31.0	186.0 ± 30.0
HbA_{1c}	8.3 ± 0.9	8.3 ± 0.7
1,5-AG (μg/mL)	3.9 ± 3.4	3.0 ± 1.8
TC (mg/dL)	215 ± 31	221 ± 28
TG (mg/dL)	164.0 ± 134.0	140.0 ± 72.0
HDL-C (mg/dL)	50.0 ± 14.0	57.0 ± 13.0
IRI (U/L)	9.9 ± 6.2	9.9 ± 6.0
UACR (mg/g creatine)*	85.3 ± 45.8	67.1 ± 69.1
Median (range)	70.8 (45–122)	60.2 (38–83)

NOTE. Data are mean ± SD.

Abbreviations: ACE, angiotensin converting enzyme; D-CCB, dyhydropyridine calcium channel blockers; FPG, fasting plasma glucose; HbA_{1c}, gycated hemoglobin; 1,5-AG, 1,5 anhidroglucitol; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; IRI, immunoreactive insulin; UACR, urinary albumin to creatinine ratio.

*UACR values were not normally distributed and were subjected to logarithmic transformation before statistical analysis. Medians with 25 to 75 percentile are shown.

Laboratory Methods

HBA_{1c} was estimated using enzyme immunoassay kits (Abbott Diagnostics, Abbott Park, IL). Serum concentration of 1,5-AG was evaluated by a modified column enzymatic test with an autoanalyzer system.[15] A glucose analyzer (glucose oxidase method) was used for glucose estimation. The biochemical analyzer TBA-80FR (Toshiba, Tokyo, Japan) with an enzymatic method was used for TC, TG, HDL-C, and creatinine determinations. A commercially available enzyme immunoassay kit (Roche Diagnostics, Tokyo, Japan) was used for the urinary albumin concentration measurements.

Statistical Analysis

Statistical analysis was performed with Stat-View 5.0 software (SAS, Cary, NC). Because the UACR values were not normally distributed in the population under study, they were subjected to logarithmic transformation before statistical analysis. Body mass index (BMI) was calculated as follows: weight (in kilograms) divided by height (in meters) squared. The different parameters between the groups were compared using the student's *t* test for unpaired data. Data are presented as means ± SD or ± SEM. Differences in the effect of the drugs were analyzed with 2-way repeated measure analysis of variance (ANOVA). *P* values less than .05 were considered significant.

RESULTS

Patient Characteristics

Table 1 summarizes the clinical characteristics and metabolic parameters of patients before treatment. Twenty-one patients (15 men and 6 women) received gliclazide and 19 patients (13 men and 6 women) received pioglitazone. The 2 groups were well matched for age, BMI, duration of diabetes, retinal status, BP, FPG, HBA_{1c}, 1,5-AG, lipids, UACR, and IRI values. The usage of angiotensin-converting-enzyme inhibitors or dihydropyridine calcium channel blockers was similarly distributed between the 2 groups.

Effect of Drugs on Metabolic and Physiologic Parameters

Table 2 shows the changes in metabolic and physiologic parameters during treatment. The F values of "Course" indicate the changes in each parameter in the whole population of patients who were treated with 1 of the 2 drugs, and those of "Course*Drug" indicate whether the changes of the specific parameter were different between the 2 drugs.

Changes in FPG, HBA_{1c}, 1,5-AG, and TC levels are shown in Fig 1. Gliclazide and pioglitazone significantly reduced the FPG ($F = 26.0$, $P < .0001$, 3 *df*), HBA_{1c} ($F = 48.1$, $P < .0001$, 3 *df*), and TC levels ($F = 3.5$, $P < .05$, 3 *df*). Decrements in these metabolic parameters were comparable between the groups (FPG: $F = 1.1$, not significant [NS], 3 *df*; HBA_{1c}: $F = 0.8$, NS, 3 *df*; TC: $F = 1.4$, NS, 3 *df*). On the other hand, 1,5-AG increased in both groups ($F = 27.5$, $P < .0001$, 3 *df*), and the increment was comparable in both groups ($F = 0.1$, NS, 3 *df*).

BP (systolic: $F = 1.5$, NS, 3 *df*) (diastolic: $F = 2.6$, NS, 3 *df*), BMI ($F = 0.6$, NS, 3 *df*), IRI ($F = 0.3$, NS, 3 *df*), TG ($F = 0.4$, NS, 3 *df*), and HDL-C ($F = 0.1$, NS, 3 *df*) did not change throughout the 12-week treatment with either gliclazide or pioglitazone (Table 2).

Table 2. Effect of Drugs on Metabolic or Physiologic Parameters

	Course		Course*Drug	
	F Value	*P* Value	F Value	*P* Value
FPG	26.0	<.0001	1.1	NS
HbA_{1c}	48.1	<.0001	0.8	NS
1,5-AG	27.5	<.0001	0.1	NS
TC	3.5	<.05	1.4	NS
BMI	0.6	NS	0.7	NS
IRI	0.3	NS	0.1	NS
SBP	1.5	NS	2.1	NS
DBP	2.6	NS	1.9	NS
TG	0.4	NS	1.4	NS
HDL-C	0.1	NS	1.6	NS
UACR	15.7	<.0001	0.8	NS

NOTE. Changes during treatment are shown. The F values of "Course" indicate the changes of each parameter in the whole population of patients who were treated with 1 of the 2 drugs, and those of "Course*Drug" indicate whether the changes of the specific parameter were different between the 2 drug treatments. Data were analyzed by 2-way repeated measures ANOVA.

Abbreviations: FPG, fasting plasma glucose; NS, not significant; HbA_{1c}, gycated hemoglobin; 1,5-AG, 1,5 anhidroglucitol; TC, total cholesterol; BMI, body mass index; IRI, immunoreactive insulin; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; UACR, urinary albumin to creatinine ratio.

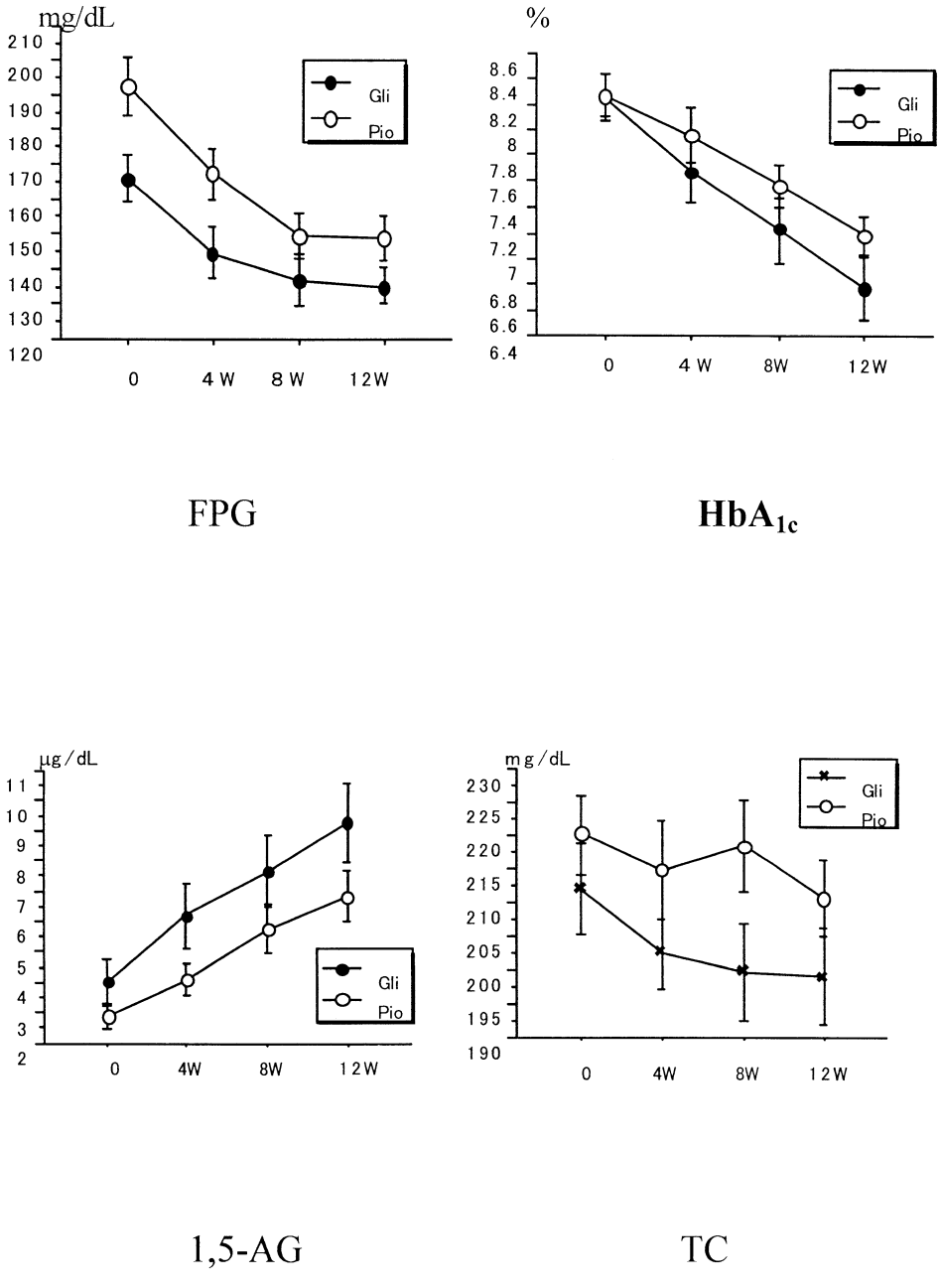

Fig 1. Changes in glycemic and cholesterol parameters in patients treated with gliclazide (Gli) or pioglitazone (Pio). Values are mean ± SEM. FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; 1,5-AG, 1,5 anhidroglucitol; TC, total cholesterol.

Effect of the Drugs on UACR

Gliclazide and pioglitazone significantly reduced UACR ($F = 15.7$, $P < .0001$, 3 *df*) with a decrement comparable in both treatment groups ($F = 0.8$, NS, 3 *df*) (Fig 2, Table 2).

The reduction in microalbuminuria was similar in patients with higher or lower systolic BP (cutoff, 130 mm Hg), or higher or lower HbA_{1c} levels (cutoff, 8%) (data not shown). The results were unchanged when the groups were subdivided with respect to the use of antihypertensive medications (data not shown).

DISCUSSION

Increased urinary albumin excretion has been associated with the development of complications associated with diabetes and hypertension.[1-3] The pathophysiologic mechanisms leading to the development of microalbuminuria are not completely understood, although they may represent early renal impairment with altered intrarenal hemodynamics.[16-19] The conventional method to determine albuminuria levels requires a 24-hour urine collection; however, several reports have suggested that the measurement of UACR in the first morning urine

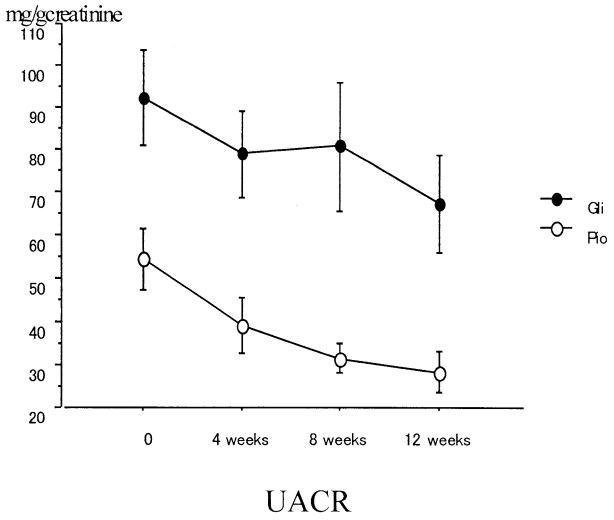

Fig 2. Effect of glicozide (Gli) or pioglitazone (Pio) on UACR values. Values are mean ± SEM. The statistical analysis was performed after the values were subjected to logarithmic transformation because they were not normally distributed.

provides an adequate estimate of 24-hour urinary albumin excretion.[19,20] Thus, we used this method because it is the recommended screening method for microalbuminuria.[21]

Treatment of patients with type 2 diabetes and hyperglycemia aims to minimize chronic micro- or macrovascular complications: glycemic control close to normal values significantly retards or prevents chronic complications. In addition, recent studies have shown that macrovascular complications are also increased in patients with isolated incidences of hyperglycemia.[22,23] It is better to detect glycemic variations in patients with near normoglycemic ranges, and postprandial glucose increases in subjects with impaired glucose tolerance, using 1,5-AG estimations rather than HbA_{1c} values.[15] For this reason, we chose to measure 1,5-AG to assess the relationship between postprandial hyperglycemia and the risk of microvascular complications.

The main purpose of this study was to compare the effect of gliclazide and pioglitazone treatment on microalbuminuria. After treatment, FPG, HBA_{1c}, 1,5-AG, TC, and UACR levels similarly improved in both groups; the other evaluated parameters did not change throughout treatment. These results indicate that both medications are equally effective in reducing microalbuminuria with similar improvements in glucose and cholesterol metabolism. In addition, our results suggest that these agents have a greater effect on glucose metabolism than cholesterol metabolism because of the larger corresponding F values (Table 2). It is not known how improved glycemic control results in reduced microalbuminuria. Possible explanations include the following: (1) high glucose causes glomerular mesangial cell growth, production of transforming growth factor, and increased synthesis of matrix proteins, such as fibronectin[24]; (2) glycated albumin and angiotensin II contribute to nephrin downregulation[25]; and (3) concentrations of oxidized low-density lipoprotein immune complexes may be involved.[26]

It has been reported that microalbuminuria is reduced by intensive glycemic control and effective BP treatment.[1,4] In addition, among the antihypertensive drugs, angiotensin-converting enzyme inhibitors may specifically protect renal function, because they lead to arteriolar vasoconstriction and a reduction in intraglomerular hypertension.[5] Because dietary sodium intake may confound the results, we restricted it to 7 to 10 g/d in this study.

Recently, antidiabetic drugs with various modes of actions have become available; for example, sulfonylureas increase endogenous insulin secretion, whereas thiazolinedione derivatives improve insulin sensitivity without stimulating insulin secretion. These medications are widely used, and it is important to know whether a specific antidiabetic drug prevents complications more efficiently than another drug. Among sulfonylureas, gliclazide has been reported to prevent diabetic macrovascular complications more effectively than other sulfonylureas because of its antiplatelet activity,[7] prostaglandin-I2 synthesis stimulation inside the vascular wall,[8] antithrombotic activity,[9] and fibrinolysis enhancement.[27] On the other hand, pioglitazone has been reported to inhibit vascular smooth muscle cell proliferation[13] and to have a protective effect against diabetic microvascular complications.[14] Our data suggest that both drugs are equally effective against microalbuminuria. One must note that little is known about the respective effects on microalbuminuria of other sulfonylureas, α-glucosidase inhibitors, or metformin. A recent report indicates that whenever similar reductions of plasma glucose and HbA_{1c} are obtained, troglitazone is more beneficial than metformin in treating microalbuminuria[28]; this result suggests that the various antidiabetic drugs affect renal function differently, irrespective of their actions on blood glucose levels.

Additional long-term studies are necessary to compare the effect of different classes of antidiabetic drugs (not only sulfonylureas and thiazolidinedione derivatives, but also α-glucosidase inhibitors and metformin), on microalbuminuria observed in patients with diabetes.

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