Original Article

Thiazolidinedione Effects on Blood Pressure in Diabetic Patients with Metabolic Syndrome Treated with Glimepiride

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The aim of our study was to compare the long-term effect of pioglitazone and rosiglitazone on blood pressure control of diabetic patients with metabolic syndrome treated with glimepiride. We evaluated 91 type 2 diabetic patients with metabolic syndrome. All were required to have been diagnosed as diabetic for at least 6 months, and to have failed to achieve glycemic control by dietary changes and the maximum tolerated dose of the oral hypoglycemic agents sulfonylureas or metformin. All patients took a fixed dose of 4 mg/day glimepiride. We administered pioglitazone (15 mg/day) or rosiglitazone (4 mg/day) for 12 months in a randomized, double-blind fashion, and evaluated body mass index (BMI), glycemic control, blood pressure and heart rate (HR) throughout the treatment period. A total of 87 patients completed the study and were randomized to receive double-blind treatment with pioglitazone or rosiglitazone. An increase in BMI was observed after 12 months ($p < 0.05$) in both groups. After 9 and 12 months, there were significant decreases in glycated hemoglobin (HbA_{1c}), mean fasting plasma glucose (FPG), postprandial plasma glucose (PPG), fasting plasma insulin (FPI), and postprandial plasma insulin (PPI) in both treatment groups ($p < 0.05$ at 9 months and $p < 0.01$ at 12 months for all parameters). Furthermore, homeostasis model assessment index (HOMA index) improvement was obtained at 9 and 12 months ($p < 0.05$ and $p < 0.01$, respectively) in both groups. Significant systolic blood pressure (SBP) and diastolic blood pressure (DBP) improvement ($p < 0.05$, respectively) was observed in both groups after 12 months. There were no significant changes in transaminases at any point during the study. We can conclude that the association of a thiazolidinedione to the glimepiride treatment of type 2 diabetic subjects with metabolic syndrome is associated to a significant improvement in the long-term blood pressure control, related to a reduction in insulin-resistance. (*Hypertens Res* 2005; 28: 917–924)

Key Words: thiazolidinediones, pioglitazone, rosiglitazone, glimepiride, metabolic syndrome

Introduction

Type 2 diabetes mellitus is a progressive disorder, and

although oral monotherapy is often initially successful, it is associated with a high secondary failure rate, which contributes to the development of long-term diabetes complications resulting from persistent hyperglycemia (1). For patients not

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taking insulin, accumulating evidence suggests that combination therapy using oral antidiabetic agents with different mechanisms of action may be highly effective in achieving and maintaining target blood glucose levels (2). In the course of the disease, the use of combinations of oral agents may delay the need for insulin while maintaining glycemic control, thus making aggressive oral treatment more acceptable for many patients (3).

Glimepiride, the latest second-generation sulfonylurea for treatment of type 2 diabetes mellitus, is a direct insulin secretagogue; indirectly, it also increases insulin secretion in response to fuels such as glucose. Its convenient once daily dosing may enhance compliance for diabetic patients. Glimepiride is approved for monotherapy, as well as for combination therapy with metformin and with insulin, while its possible use in association with other antihyperglycemic drug classes is still under investigation (4). Thiazolidinediones are a new class of oral hypoglycemic agents. The hypoglycemic effect of the thiazolidinediones is related to their ability to increase insulin sensitivity and, consequently, increase peripheral glucose utilization. Although the exact mechanism of action is not completely understood, the most widely accepted hypothesis is that their effect on insulin sensitivity is related to their well-known ability to bind and activate the nuclear peroxisomal proliferator-activated receptor- γ (PPAR- γ) (5).

In some previous studies, it was observed that the association of sulphonylureas (rarely including glimepiride) to rosiglitazone improve the glycemic control in type 2 diabetic patients (6–8), while the effect of pioglitazone has been tested more often in monotherapy (9).

While the metabolic effect of thiazolidinediones has already been adequately studied, there are only limited data in regard to their differential effects on blood pressure.

Thus, the aim of our study was to compare the long-term effect of pioglitazone and rosiglitazone on blood pressure control of diabetic patients treated with glimepiride.

Methods

Study Design

This multicenter, double-blind randomized trial was conducted at the Department of Internal Medicine and Therapeutics of the University of Pavia, in the G. Descovich Atherosclerosis Study Center of the Clinical Medicine and Applied Biotechnology Department of the University of Bologna, and in the Diabetes Care Unit of the S. Carlo Hospital of Milano. For this study we enrolled Caucasian patients affected by type 2 diabetes and arterial hypertension, all complying with the diagnostic criteria of metabolic syndrome as defined by the National Cholesterol Education Program (NCEP) (ATP III) (10).

The primary objective of the study was to directly compare

the effects of pioglitazone and rosiglitazone on a large set of biochemical parameters related to the metabolic control and the hemorheology of these patients, as already reported in Derosa *et al.* (11). The aim of this report was to show data relative to a secondary endpoint of our study, *i.e.*, the effects of different thiazolidinediones on blood pressure control in these patients.

Subjects began a controlled-energy diet (near 600 kcal daily deficit) based on American Diabetes Association (ADA) recommendations (12) and containing 50% as carbohydrates, 20% as proteins, and 30% as lipids (6% saturated), with a maximum cholesterol content of 300 mg/day, and 35 g fiber. Each center's standard diet advice was given by a dietitian and/or specialist doctor. Dietitians and/or specialist doctors periodically provided instruction on dietary intake recording procedures as part of a behavior modification program and then later used the subject's food diaries for counseling. During the study, there was one behavior modification session on weight-loss strategies (at baseline), one at 6 months, and four seminars with all patients at 3, 6, 9, and 12 months. Individuals were also encouraged to increase their physical activity by walking briskly for 20 to 30 min, 3 to 5 times per week, or by using a stationary bicycle. The recommended changes in physical activity throughout the study were not assessed. All patients took a fixed dose of 4 mg/day glimepiride (in two doses per day).

Subjects were randomized for 1 year of study to also receive pioglitazone 15 mg/day (in a single dose) or rosiglitazone 4 mg/day (in a single dose). They took three capsules, a glimepiride capsule in the morning before breakfast and before dinner, and a pioglitazone or rosiglitazone capsule during lunch. Randomization was done using a drawing of envelopes containing randomization codes prepared by a statistician. A copy of the code was provided only to the responsible person performing the statistical analysis. The code was only broken after database lock, but could have been broken for individual subjects in the case of an emergency. Medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits. Pioglitazone and rosiglitazone were supplied as matching opaque white capsules in coded bottles to ensure the double-blind status of the study. At baseline, we weighed participants and gave them a bottle containing a supply of study medication for at least 100 days. Throughout the study, we instructed patients to take their first dose of new medication on the day after they were given the study medication. A bottle containing the new study medication for the next treatment period was given to participants on the first day of the new quarter. At the same time, all unused medication was retrieved for inventory. All medications were provided free of charge.

The study protocol was approved at each site by institutional review boards and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Table 1. Data at Baseline in Pioglitazone and Rosiglitazone Group

	Glimepiride + pioglitazone baseline	Glimepiride + rosiglitazone baseline
N	45	42
Sex (M/F)	21/24	22/20
Age (years)	53±6	54±5
Duration of diabetes (years)	5±2	6±3
Height (m)	1.68±0.04	1.67±0.05
Weight (kg)	68.9±3.5	67.8±3.1
BMI (kg/m ²)	24.4±0.8	24.3±0.7

Data are means±SD; all group differences are nonsignificant. M, male; F, female; BMI, body mass index.

Patients

Diabetic patients of either sex were eligible for inclusion in the study if they had type 2 diabetes mellitus according to the ADA criteria (13). All were required to have been diagnosed as diabetic for at least 6 months, and to have failed to achieve glycemic control by dietary changes and the maximum tolerated dose of the oral hypoglycemic agents sulfonylureas or metformin. No patients were taking glimepiride. All patients had a fasting C-peptide level >1.0 ng/ml. Furthermore, they were all hypertensive according to the World Health Organization (WHO) criteria (systolic blood pressure [SBP]≥130 mmHg and diastolic blood pressure [DBP]≥85 mmHg) (14) and were all affected by metabolic syndrome (10). Suitable subjects, identified from review of case notes and/or computerized clinic registers, were contacted personally or by telephone.

Patients with a history of ketoacidosis or with unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy were excluded, as were patients with impaired liver function, impaired kidney function, or anemia. Patients with unstable cardiovascular conditions (e.g., New York Heart Association class III or IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months of study enrolment were excluded. Women who were pregnant or lactating, or who were of child-bearing potential but not taking adequate contraceptive precautions were also excluded.

Participants comprised 43 men (49.4%) and 44 women (50.5%) aged 47–59 years. There were no significant differences between centers in sex distribution, age, diabetes duration, or diabetes treatment.

At entry, 35 subjects (40.2%) were taking antihypertensive drugs (13 subjects, angiotensin-converting enzyme [ACE]-inhibitors [37.1%]: ramipril [6 subjects], lisinopril [4 subjects], and enalapril [3 subjects]; 10 subjects, calcium-antagonists [28.5%]: amlodipine [7 subjects], and lercanidipine [3 subjects]; 8 subjects, angiotensin II [AT II] antagonists

[22.8%]: losartan [3 subjects], candesartan [3 subjects], and valsartan [2 subjects]; and 4 subjects, α_1 -antagonists [11.4%]: doxazosin [4 subjects]).

During the study, 45 subjects (51.7%) required antihypertensive treatment (18 subjects, ACE-inhibitors [40.0%]: ramipril [9 subjects], lisinopril [5 subjects], enalapril [3 subjects], and perindopril [1 subject]; 12 subjects, calcium-antagonists [26.6%]: amlodipine [6 subjects], and lercanidipine [6 subjects]; 10 subjects, AT II antagonists [22.2%]: losartan [4 subjects], and candesartan [6 subjects]; and 5 subjects, α_1 -antagonists [11.1%]: doxazosin [5 subjects]).

Ten patients (11.4%) required addition of hydrochlorothiazide; 7 patients did not require antihypertensive drugs, because blood pressure control was sufficient with diet regimen only.

All diabetic patients were allocated to receive a fixed dose of glimepiride and a randomized dose of pioglitazone or rosiglitazone because they had poor glycemic control; in particular, 46 subjects (52.8%) had an insufficient glycemic control (HbA_{1c} >7.5%) with metformin, 27 subjects (31.0%) had an insufficient glycemic control with sulfonylureas, and exactly 13 subjects (14.9%) with gliclazide and 14 subjects (16.0%) with glyburide; 11 subjects (12.6%) resulted intolerant to the metformin; and 3 subjects (3.4%) resulted intolerant to the sulfonylureas and exactly 1 subject (1.1%) to gliclazide and 2 subjects (2.2%) to glyburide. No patients were taking lipid-lowering or antiaggregation drugs.

Assessments

Before starting the study, all patients underwent an initial screening assessment that included a medical history, physical examination, vital signs, a 12-lead electrocardiogram, measurements of height, weight, body mass index (BMI), glycated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), postprandial plasma glucose (PPG), fasting plasma insulin (FPI), postprandial plasma insulin (PPI), blood pressure, and heart rate (HR). Changes in BMI, HbA_{1c} , and blood pressure were the primary efficacy variables. Fasting plasma glucose, PPG, and homeostasis model assessment index (HOMA index) were also used to assess efficacy. Other parameters have been evaluated in regard to metabolic pattern and hemorheology, and they have been already reported elsewhere (11).

All plasmatic parameters were determined after a 12-h overnight fast, except PPG and PPI, which were determined 2 h after lunch. Venous blood samples were taken for all patients between 8:00 and 9:00 AM. We used plasma obtained by addition of 1 mg/ml Na_2 -EDTA, and centrifuged at $3,000 \times g$ for 15 min at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at –80°C for no more than 3 months. All measurements were performed in a central laboratory.

BMI was calculated as weight in kg divided by the square of the height in m. The estimate of insulin resistance was cal-

Table 2. Parameter Changes at 3, 6, 9, and 12 Months of the Study in Pioglitazone Group

	Glimepiride + pioglitazone				
	Baseline	3 months	6 months	9 months	12 months
BMI (kg/m ²)	24.4±0.8	24.8±0.8	25.0±0.9	25.1±0.7	25.6±0.9*
HbA _{1c} (%)	8.2±0.7	7.9±0.8	7.6±0.7	7.2±0.6*	6.8±0.8**
FPG (mg/dl)	163±31	152±29	144±27	140±36*	132±25**
PPG (mg/dl)	195±25	188±24	179±23	170±23*	160±22**
FPI (μU/ml)	24.7±3.2	21.8±3.0	18.6±2.8	16.2±2.7*	14.8±2.6**
PPI (μU/ml)	59.6±7.4	54.5±7.2	52.3±6.8	48.3±6.5*	46.1±6.3**
HOMA index	10.0±3.4	8.6±3.2	7.4±3.0	6.5±2.7*	4.9±1.9**
Tg (mg/dl)	156±35	150±33	144±27	130±29	121±28* [§]
SBP (mmHg)	138.2±4.4	136.5±4.6	136.1±5.0	135.3±4.5	134.4±4.2*
DBP (mmHg)	87.4±4.2	86.8±4.0	85.9±3.7	85.4±3.6	84.2±3.4*
HR (beats/min)	72±7	74±8	73±7	75±8	74±6

Data are means±SD; * $p<0.05$ vs. baseline; ** $p<0.01$ vs. baseline; [§] $p<0.05$ vs. glimepiride + rosiglitazone. BMI, body mass index; HbA_{1c}, glycated hemoglobin; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; FPI, fasting plasma insulin; PPI, postprandial plasma insulin; Tg, triglycerides; HOMA index, homeostasis model assessment index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Table 3. Parameter Changes at 3, 6, 9, and 12 Months of the Study in Rosiglitazone Group

	Glimepiride + rosiglitazone				
	Baseline	3 months	6 months	9 months	12 months
BMI (kg/m ²)	24.3±0.7	24.9±0.6	25.2±0.8	25.5±0.7	25.8±0.9*
HbA _{1c} (%)	8.0±0.8	7.8±0.9	7.3±0.8	7.0±0.6*	6.7±0.9**
FPG (mg/dl)	158±33	150±30	142±29	136±29*	127±28**
PPG (mg/dl)	193±28	186±26	180±25	171±24*	164±25**
FPI (μU/ml)	24.1±2.8	22.4±2.7	17.9±2.6	15.1±2.5*	13.3±2.1**
PPI (μU/ml)	57.4±6.8	53.6±6.9	50.5±6.6	49.1±6.5*	44.7±6.5**
HOMA index	9.5±3.1	8.5±3.0	7.6±2.6	5.3±2.2*	4.2±1.7**
Tg (mg/dl)	162±29	176±30	183±31	185±30	191±32*
SBP (mmHg)	137.6±3.4	136.2±3.3	135.6±3.5	135.1±4.1	133.2±3.1*
DBP (mmHg)	88.8±4.6	87.6±4.5	86.9±4.2	85.4±4.0	84.0±3.8*
HR (beats/min)	70±6	74±6	73±8	75±7	72±8

Data are means±SD; * $p<0.05$ vs. baseline; ** $p<0.01$ vs. baseline. BMI, body mass index; HbA_{1c}, glycated hemoglobin; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; FPI, fasting plasma insulin; PPI, postprandial plasma insulin; Tg, triglycerides; HOMA index, homeostasis model assessment index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

culated by HOMA index using the formula $\text{FPI } (\mu\text{U/ml}) \times \text{FPG } (\text{mmol/l}) / 22.5$, as described by Matthews and coworkers (15).

The HbA_{1c} level was measured by an HPLC method (DIAMAT, Bio-Rad, USA; normal values 4.2–6.2%), with intra- and interassay coefficients of variation (CsV) of <2% (16). Plasma glucose was assayed by the glucose-oxidase method (GOD/PAP, Roche Diagnostics, Mannheim, Germany) with intra- and interassay CsV of <2% (17). Plasma insulin was assayed with Phadiaseph Insulin RIA (Pharmacia, Uppsala, Sweden) by using a second antibody to separate the free and antibody-bound ¹²⁵I-insulin (intra- and interassay CsV: 4.6 and 7.3%, respectively) (18). Blood pressure measurements were obtained from each patient (right arm) in the

seated position, by using a standard mercury sphygmomanometer (Korotkoff I and V) (Erkameter 3000, ERKA, Bad Tolz, Germany) with a cuff of appropriate size. Measurements were always taken by the same investigator in the morning before daily drug intake (*i.e.* ~24 h after dosing) and after the subject had rested 10 min in a quiet room. Three successive blood pressure readings were obtained at 1 min intervals and averaged. BMI, HbA_{1c}, FPG, PPG, FPI, PPI, HOMA index, SBP, DBP, and HR were evaluated at baseline and after 3, 6, 9, and 12 months.

In order to evaluate the tolerability assessments, all adverse events were recorded. Blood pressure values were measured by physicians not belonging to the study to preserve study blindness by experimenters.

Fig. 1. Change in SBP and DBP from baseline to 12 months in patients receiving pioglitazone or rosiglitazone. Values are the mean $\pm$ SD. * $p < 0.05$, change from baseline. SBP, systolic blood pressure; DBP, diastolic blood pressure.

Statistical Analysis

An intention-to-treat analysis was conducted in patients who had received at least one dose of study medication and had a subsequent efficacy observation. Patients were included in the safety analysis if they had received one dose of trial medication after randomization and had a subsequent safety observation. The null hypothesis that the expected mean SBP and DBP change from baseline to the end of 12 months of double-blind treatment did not differ significantly between pioglitazone and rosiglitazone treatments was tested using analysis of variance (ANOVA) and analysis of covariance (ANCOVA) models (19). Similar analyses were applied to the other parameters. The statistical significance of the independent effects of treatments on the other parameters was determined by ANCOVA. A one-sample t test was used to compare values obtained before and after treatments administration; and two-sample t tests were used for between-group comparison. Statistical analysis of data was performed by means of the SPSS statistical software package for Windows (version 11.0; Chicago, USA); data are presented as the mean $\pm$ SD. For all statistical analysis, $p < 0.05$ was considered statistically significant.

Results

Study Sample

A total of 91 patients were enrolled in the trial. Of these, 87 completed the study: 45 of the 87 (51.7%) were randomized to receive pioglitazone and 42 (48.2%) to receive rosiglitazone in a double-blind fashion. There were 4 patients (2 males and 2 females) who did not complete the study and the reasons for premature withdrawal included protocol violation, loss to follow-up, and non-compliance. The characteristics of

Fig. 2. Correlation between FPI decrease and DBP decrease in pioglitazone and rosiglitazone group. Pioglitazone: $DBP\ delta = 0.124x + 0.299$; $p = 0.005$. Rosiglitazone: $DBP\ delta = -0.789x - 0.266$; $p = 0.013$. DBP, diastolic blood pressure; FPI, fasting plasma insulin.

the patient population at study entry, shown in Table 1, were similar in the two treatment groups.

Body Mass Index Value

No BMI change was observed after 3, 6, or 9 months in both groups, while a significant BMI increase was present after 12 months compared to the baseline ($p < 0.05$) in both groups. There was no difference in BMI value between the pioglitazone and rosiglitazone group. The results are reported in detail in Tables 2 and 3.

Glycemic Control

No HbA_{1c} change was observed after 3 and 6 months in both groups, while a significant HbA_{1c} decrease was obtained after 9 ($p < 0.05$) and 12 ($p < 0.01$) months in both groups. No significant FPG and PPG variation was present at 3 and 6 month in both groups. After 9 and 12 months, the mean FPG and PPG levels were significantly decreased in both groups ($p < 0.05$ and $p < 0.01$, respectively) (Tables 2 and 3). Fasting plasma insulin and PPI did not show any significant change after 3 or 6 months, while a significant decrease was observed at 9 and 12 months ($p < 0.05$ and $p < 0.01$, respectively) compared to the baseline value in both groups. Furthermore, HOMA index improvement was obtained only at 9 and 12 months ($p < 0.05$ and $p < 0.01$, respectively) compared to the baseline value in both groups.

Blood Pressure Effects

No SBP or DBP change was observed in either group after 3, 6, or 9 months. Significant SBP and DBP improvement ($p < 0.05$, respectively) was present in both groups after 12 months compared to the baseline values (Figs. 1 and 2). No significant HR variation was obtained during the study in either group (Tables 2 and 3).

Safety

Of the 87 patients who completed the study, 6.6% (3/45) of patients in the pioglitazone group and 11.9% (5/42) of patients in the rosiglitazone group had side effects (not significant). In the pioglitazone group, 1 patient had aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values that increased to 1.5 times the upper limit of normal (< 40 U/l), but these values regressed after 15 days and returned to within the limit of normal; 1 patient reported transient headache (only for 5 days from the start of therapy); and 1 patient reported transient flatulence (only for 3 days from the start of therapy). In the rosiglitazone group, 2 patients had AST and ALT values that increased to 2.0 times the upper limit of normal (< 40 U/l), but these values regressed after 15 days and returned to within the limit of normal; 2 patients reported transient flatulence (only for 2 days and only for 1 day from the start of therapy, respectively); and 1 patient reported transient headache (only for 2 days from the start of therapy).

Altogether, we did not have statistically significant changes in transaminases. In particular, in pioglitazone group, AST and ALT values were 24 ± 8 and 23 ± 9 U/l at baseline, respectively, and 26 ± 9 and 24 ± 10 U/l at 12 months, respectively. In rosiglitazone group, AST and ALT values were 25 ± 9 and 22 ± 8 U/l at baseline, respectively, and 27 ± 10 and 24 ± 9 U/l at 12 months, respectively.

Discussion

Coronary artery disease (CAD) causes much of the serious morbidity and mortality in patients with diabetes who have a 2- to 4-fold in the risk of CAD (20). Hypertension, hypercholesterolemia and low high-density lipoprotein cholesterol (HDL-C) values exponentially increase the cardiovascular risk profile of type 2 diabetic patients, among whom these risk factors are highly prevalent. On the other hand, an intensive treatment of all modifiable risk factors significantly improves the prognosis of these patients (1). In particular, an adequate antihypertensive treatment has clearly been shown to prevent or to slow the diabetes-related renal damage (21). However, beyond that evidence, the control rate of blood pressure in these patients remains very low (22).

Therefore, it is not sufficient to simply treat each risk factor, but rather the treatment must be very intensive in order to obtain both blood pressure and cholesterolemia at levels suf-

ficiently low to be considered safe for the diabetic patient: in fact, it is important to remember that the third report of the NCEP Expert Panel on the Detection, Evaluation and Treatment of High Blood Cholesterol in Adults has defined the diabetic disease as a coronary heart disease risk equivalent (10). Because insulin-resistance syndrome is also considered a primary cause of hypertension (23–25) and cardiovascular disease (26), a specific treatment to improve this syndrome is also required.

Indeed, hypertension control represents the most important intervention, since it limits cardiovascular events far more effectively than tight glycemic control (20), but not all antihypertensive treatments have the same impact on the metabolic control of diabetic patients (27). To the best of our knowledge, this is the first study to compare the long-term effects of glycemic control by thiazolidinediones on the blood pressure control of type 2 diabetic subjects.

It has already been established that thiazolidinediones have an optimal effect on glycemic control in diabetic subjects (28), and this was further confirmed in the present study: both combination treatment with glimepiride and pioglitazone and that with glimepiride and rosiglitazone significantly improved the glycemic control in the studied subjects. We observed a 1.3% improvement in HbA_{1c} plasma level ($p < 0.01$), a 19.3% in FPG ($p < 0.01$), a 16.3% in PPG ($p < 0.01$), a 42.4% in FPI ($p < 0.05$) and a 23.3% in PPI ($p < 0.05$), without significant differences between treatment groups. Furthermore, we found a slight, but statistically significant reduction in both SBP and DBP in both the pioglitazone- and rosiglitazone-treated groups, while no significant change in HR was observed. In contrast to what has already been observed for some metabolic parameters (more specifically, the different effect of the two available thiazolidinediones on plasma lipid pattern), a nonsignificant difference has been noted in regard to blood pressure improvement under thiazolidinediones treatment (11). Of course, we recognize that in this case the lack of a control group renders our results slightly weaker. The observed result was confirmed even repeating statistical analysis by classes of antihypertensive drug assumed by the patients. These data could suggest an independent effect of concomitant blood pressure lowering drug eventually co-assumed. A similar antihypertensive effect has been seen even with other drugs affecting the lipid metabolism, such as statins and fibrates (29, 30). The antihypertensive effect of thiazolidinediones appears to be mainly related to the decrease in insulin-resistance and the consequent improvement of endothelial function (31, 32). In our study, we observed a correlation between FPI decrease and DBP decrease in both groups (Fig. 2). The observed antihypertensive effect of thiazolidinediones was probably attenuated by the concomitant treatment with glimepiride, which is already known to have a long-term improving effect on blood pressure control (33).

On the basis of our results, we can conclude that the association of a thiazolidinedione to the glimepiride treatment of

type 2 diabetic subjects is associated to a significant improvement in the long-term blood pressure control related to a reduction in insulin-resistance. The choice of the best molecule to prescribe has to be driven by the drug effects on other parameters such as body weight, plasma lipid levels and prothrombotic risk factors.

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