Original Article

Telmisartan and Irbesartan Therapy in Type 2 Diabetic Patients Treated with Rosiglitazone: Effects on Insulin-Resistance, Leptin and Tumor Necrosis Factor- α

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The aim of our study was to investigate the metabolic effect of telmisartan and irbesartan in subjects treated with rosiglitazone, a well-known insulin-sensitizing drug, in order to clarify the direct metabolic effects of the two former drugs. Patients were enrolled, evaluated, and followed at 3 Italian centers. We evaluated 188 type 2 diabetic patients with metabolic syndrome (94 males and 94 females in total; 49 males and 46 females, aged 56 ± 5 , treated with telmisartan; and 45 males and 48 females, aged 55 ± 4 , treated with irbesartan). All had been diabetic for at least 6 months, and glycemic control by the maximum tolerated dietary changes and maximum tolerated dose of oral hypoglycemic agents had been attempted and failed in all cases. All patients took a fixed dose of rosiglitazone, 4 mg/day. We administered telmisartan (40 mg/day) or irbesartan (150 mg/day) in a randomized, controlled, double-blind clinical manner. We evaluated body mass index (BMI), glycemic control (HbA_{1c} , fasting plasma glucose and insulin levels [FPG, and FPI, respectively], and homeostasis model assessment [HOMA] index), lipid profile (total cholesterol [TC], low density lipoprotein-cholesterol [LDL-C], high density lipoprotein-cholesterol [HDL-C], and triglycerides [TG]), systolic and diastolic blood pressure (SBP and DBP), tumor necrosis factor- α (TNF- α), and leptin during the 12 months of this treatment. No BMI change was observed after 6 or 12 months in either group. Significant decreases in HbA_{1c} and FPG were observed after 6 months in the telmisartan group, and after 12 months in both groups. The decrease in HbA_{1c} and FPG at 12 months was statistically significant only in the telmisartan group. A significant decrease in FPI was observed at 12 months in both groups, and this decrease was significantly greater in the telmisartan group. Significant decreases in the HOMA index were observed at 6 and 12 months in both groups, and the decrease in the HOMA index after 12 months was significantly greater in the telmisartan group than in the irbesartan group. Significant changes in SBP, DBP, TC, and LDL-C were observed after 6 and 12 months in both groups. Significant decreases in TNF- α and leptin levels were observed after 6 months in the telmisartan group, and after 12 months in both groups. In conclusion, in this study of patients with type 2 diabetes mellitus and metabolic syndrome, telmisartan seemed to result in a greater improvement in glycemic and lipid control and metabolic parameters related to metabolic syndrome compared to irbesartan. These observed metabolic effects of different angiotensin type 1 receptor blockers could be relevant when choosing a therapy to correct metabolic derangement of patients affected by metabolic syndrome and diabetes. (*Hypertens Res* 2006; 29: 849–856)

Key Words: telmisartan, irbesartan, rosiglitazone, type 2 diabetes, metabolic syndrome

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Introduction

Increases in blood pressure (BP), even at modest levels, are associated with an increased risk of cardiovascular complications in patients with diabetes mellitus. Large trials and meta-analyses have shown that treatment with BP-lowering agents in type 2 diabetes significantly lowers the risk of cardiovascular and microvascular complications (1).

Angiotensin II receptor blockers represent a class of effective and well-tolerated orally active antihypertensive drugs, both in the general population and diabetic patients (2). Activation of angiotensin type 1 (AT₁) receptors leads to vasoconstriction, stimulation of the release of catecholamines and antidiuretic hormone, and promotion of the growth of vascular and cardiac muscle. AT₁ receptor blockers thereby relax vascular smooth muscle, increase salt excretion, decrease cellular hypertrophy and induce antihypertensive effects without modifying heart rate or cardiac output (3). Most of the AT₁ receptor blockers in use are able to control BP with a once-daily dose, without evidence of producing tolerance to the antihypertensive effect and with a low incidence of side effects even when used over the long term. In cases of mild-to-moderate hypertension, monotherapy controls BP in 40% to 50% of patients. This level of efficacy is similar to those of angiotensin-converting enzyme (ACE) inhibitors, diuretics, calcium antagonists and β -blocking agents (4). AT₁ receptor blockers are particularly indicated for patients with hypertension who are being treated with ACE inhibitors and have developed side effects, such as cough or angioedema (5). Diabetes is the main cause of renal insufficiency in Western countries, and different studies have shown that some AT₁ receptor blockers act as nephroprotective drugs in diabetic patients (6). Moreover, some AT₁ receptor blockers appear to help prevent diabetes through a direct effect on pancreatic islet cells as well as by improving insulin resistance (7). However, there is a lack of data comparing the effects of long-term treatment with different AT₁ receptor blockers on biochemical markers of insulin resistance and metabolic syndrome in diabetic patients. Recently, Schupp *et al.* demonstrated *in vitro* that telmisartan and irbesartan could be considered partial and selective peroxisome proliferator-activated receptor (PPAR) γ modulators (8). The aim of our study was to investigate the metabolic effect of telmisartan and irbesartan in subjects treated with rosiglitazone, a well-known insulin-sensitizing drug, in order to clarify the direct metabolic effects of the two former drugs.

Methods

Study Design

This 12-month, multicenter, double-blind, randomized con-

trolled trial was conducted at the Department of Internal Medicine and Therapeutics, University of Pavia (Pavia, Italy), at the G. Descovich Atherosclerosis Study Center, D. Campanacci Clinical Medicine and Applied Biotechnology Department, University of Bologna (Bologna, Italy), and at the Diabetes Care Unit at S. Carlo Hospital of Milan (Milan, Italy).

The study protocol was approved at each site by institutional review boards and was conducted in accordance with the Declaration of Helsinki and its amendments.

Patients

Caucasian patients aged ≥ 18 of either sex were eligible for inclusion in the study if they had type 2 diabetes mellitus according to the American Diabetes Association (ADA) criteria (9) (duration, ≥ 6 months), and if they had poor glycemic control (glycosylated hemoglobin [HbA_{1c}] level, $> 7.0\%$) or experienced adverse effects with the maximum tolerated diet modification or the maximum tolerated dose of oral hypoglycemic agents, such as sulfonylureas, meglitinide derivatives, acarbose, or metformin. All patients also were diagnosed with metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III classification (10), and they presented with low high density lipoprotein (HDL)-cholesterol (HDL-C, < 40 mg/dl [men] and < 50 mg/dl [women]) (10), and hypertension according to the World Health Organization criteria (11) (systolic/diastolic BP [SBP/DBP], $\geq 130/\geq 85$ mmHg). All patients had a fasting C-peptide level > 1.0 ng/ml. They were overweight (body mass index [BMI], 26.5 – 28.9 kg/m²) (12) (Table 1). Suitable patients, identified from a review of case notes and/or computerized clinic registers, were contacted by the investigators in person or by telephone.

Patients were excluded if they had a history of ketoacidosis or had unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy; impaired hepatic function (defined as plasma aminotransferase and/or γ -glutamyltransferase level higher than the upper limit of normal [ULN] for age and sex), impaired renal function (defined as serum creatinine level higher than the ULN for age and sex), or severe anemia. Patients with serious cardiovascular disease (CVD) (*e.g.*, New York Heart Association class I–IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrollment also were excluded. Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded. No patients were taking antihypertensive drugs, while 49 patients (26.9%) were taking lipid-lowering therapy (Table 2).

All patients provided written informed consent to participate.

Table 1. Baseline Characteristics and Parameter Changes at 6, and 12 Months of the Study in Both Groups

	Telmisartan + rosiglitazone			Irbesartan + rosiglitazone		
	Baseline	6 months	12 months	Baseline	6 months	12 months
BMI (kg/m ²)	27.6±1.1	27.8±1.2	28.1±1.3	27.7±1.2	27.5±1.0	27.9±1.2
HbA _{1c} (%)	7.6±0.4	6.8±0.3*	6.4±0.2**,#	7.7±0.5	7.3±0.4	6.9±0.3*
FPG (mg/dl)	144±12	130±10*	121±9**,#	141±11	136±10	132±9*
FPI (μU/ml)	20.2±4.3	18.6±4.0	17.1±3.6*,#	19.7±4.0	19.2±3.9	18.0±3.7*
HOMA index	7.2±3.9	6.0±3.2*	5.1±2.7**,#	6.9±3.7	6.2±3.4*	5.7±3.0**
SBP (mmHg)	135±4	130±3*	124±4**	136±4	131±4*	125±3**
DBP (mmHg)	86±4	81±3*	78±2**	84±3	80±3*	77±3**
TC (mg/dl)	193±12	179±10*	168±8**	195±14	181±12*	172±14**
LDL-C (mg/dl)	129±10	118±9*	110±7**	128±10	119±9*	111±8**
HDL-C (mg/dl)	40±4	41±5	39±4	42±5	40±4	41±5
TG (mg/dl)	119±38	101±33	95±30	125±41	109±34	99±32
TNF-α (ng/ml)	3.1±0.7	2.6±0.6*	2.2±0.5**	3.0±0.6	2.8±0.5	2.5±0.4*
Leptin (ng/ml)	28.6±13.1	24.2±11.3*	20.1±10.4**	28.1±12.8	26.5±12.0	23.3±11.1*

Data are means±SD. * $p < 0.05$ vs. baseline; ** $p < 0.01$ vs. baseline; # $p < 0.05$ vs. irbesartan + rosiglitazone. BMI, body mass index; HbA_{1c}, glycated hemoglobin; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HOMA index, homeostasis model assessment index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; TG, triglycerides; TNF-α, tumor necrosis factor-α.

Table 2. Concomitant Lipid-Lowering Therapy during the Study

	Telmisartan + rosiglitazone	Irbesartan + rosiglitazone
Number of patients (M/F)	23 (13/10)	26 (12/14)
Rosuvastatin	3 (2/1)	4 (2/2)
Atorvastatin	6 (3/3)	7 (3/4)
Simvastatin	7 (4/3)	8 (4/4)
Pravastatin	4 (2/2)	4 (2/2)
Fluvastatin	3 (2/1)	3 (1/2)

All group differences are nonsignificant. M, male; F, female.

Treatment

All patients received one of various treatments (sulfonylureas, meglitinide derivatives, acarbose, or metformin) (Table 3) for type 2 diabetes mellitus, self-administered for 12 months. The starting dose was variable, depending on the patient tolerance or glycemic control (Table 4). All patients were also taking rosiglitazone (4 mg once daily).

In addition, patients were randomized (using envelopes containing randomization codes prepared by a statistician) to receive a dose of telmisartan, 40 mg once daily, or irbesartan, 150 mg once daily, self-administered for 12 months each day after breakfast. A copy of the randomization code was provided only to the person responsible for performing the statistical analysis. The code was only broken after database lock, but could have been broken for individual patients in cases of emergency, such as hospitalization or suspicion of a seri-

ous adverse event.

Telmisartan and irbesartan were supplied as identical, opaque white capsules in coded bottles to ensure the double-blind status of the study. At baseline, we gave each patient a bottle containing a 100-day supply of the study medication. 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 study medication for the next treatment period was given to participants at the 3-month visit. At the same time, all unused medication was retrieved for inventory. All medications were provided free of charge.

Diet and Exercise

At baseline, patients began a controlled-energy diet (~600 kcal daily deficit), based on ADA recommendations (13), that contained 50% of calories from carbohydrates, 30% from fat (6% saturated), and 20% from proteins, with a maximum cholesterol content of 300 mg/day, and 35 g/day of fiber. Each center's standard diet advice was given by a dietitian and/or specialist physician. Each 2 weeks, dietitians and/or specialists provided instruction on dietary intake—recording procedures as part of a behavior-modification program, and from month 1 used the patients' food diaries for counseling. During the study, behavior-modification sessions on weight-loss strategies were given to individual patients once at baseline, once at 6 months, and once at 12 months. Individuals were also encouraged to increase their physical activity by walking briskly or riding a stationary bicycle for 20 to 30 min, 3 to 5 times per week. The recommended changes in physical activity throughout the study were not assessed.

Table 3. Doses of Oral Hypoglycemic Agents (OHA) in Telmisartan and Irbesartan Group

OHA	Telmisartan + rosiglitazone	Irbesartan + rosiglitazone
Sulfonylureas		
Gliburide	7.5±2.5	5.0±1.25
Glimepiride	3±1	3±1
Gliclazide	200±40	200±40
Meglitinide derivatives		
Repaglinide	3.0±1.5	4.0±1.5
Nateglinide	240±60	180±60
α-Glucosidase inhibitor		
Acarbose	175±25	200±50
Biguanides		
Metformin	1,750±250	1,750±250

All group differences are nonsignificant.

Efficacy, Tolerability, and Compliance 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 and body weight; calculation of BMI; assessment of glycemic control (HbA_{1c}, fasting plasma glucose [FPG] and insulin [FPI] levels, and homeostasis model assessment [HOMA] index), lipid profile (total cholesterol [TC], low density lipoprotein-cholesterol [LDL-C], HDL-C, and triglycerides [TG]), SBP, DBP, tumor necrosis factor-α (TNF-α), and leptin.

BMI, HbA_{1c}, FPG, FPI, HOMA index, lipid profile, SBP, DBP, TNF-α, and leptin values were also assessed at 6 and 12 months. Changes in the HOMA index, lipid profile, SBP, DBP, TNF-α, and leptin variables were the primary efficacy factors. HbA_{1c}, FPG, and FPI were also used to assess efficacy.

All plasmatic variables were determined after a 12-h overnight fast. All venous blood samples were drawn by a research nurse between 8:00 AM and 9:00 AM. We used plasma obtained by addition of Na₂-EDTA, 1 mg/ml, and centrifuged at 3,000 × *g* for 15 min at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at -80°C for ≤3 months. All measurements were performed in a central laboratory.

BMI was calculated by the investigators as the weight in kg divided by the square of the height in m. The estimate of insulin resistance was calculated using the HOMA index with the formula

$$\text{Insulin resistance} = \text{FPI } (\mu\text{U/ml}) \times \text{FPG (mmol/l)} / 22.5$$

as described by Matthews *et al.* (14) (normal if <2.5, marker of insulin-resistance if ≥2.5).

Table 4. Starting and Final Dose of Oral Hypoglycemic Agents (OHA) in Both Groups

OHA	Starting dose (mg)	Final dose (mg)
Sulfonylureas		
Gliburide (TR)	7.5±2.5	10.0±2.5
Gliburide (IR)	5.0±2.5	7.5±2.5
Glimepiride (TR)	2±1	4±1
Glimepiride (IR)	2±1	5±1
Gliclazide (TR)	160±40	200±40
Gliclazide (IR)	120±40	200±40
Meglitinide derivatives		
Repaglinide (TR)	1.5±0.5	4.0±1
Repaglinide (IR)	1.5±0.5	5.0±1
Nateglinide (TR)	240±60	300±60
Nateglinide (IR)	180±60	240±60
α-Glucosidase inhibitor		
Acarbose (TR)	150±50	200±50
Acarbose (IR)	150±50	250±50
Biguanides		
Metformin (TR)	1,500±500	2,000±500
Metformin (IR)	1,250±250	1,750±250

Data are means±SD; all group differences are nonsignificant. TR, telmisartan + rosiglitazone; IR, irbesartan + rosiglitazone.

BP measurements were obtained from each patient (using the right arm) in the seated position using a standard mercury sphygmomanometer (Erkameter 3000; ERKA, Bad Tolz, Germany) (Korotkoff I and V) with a cuff of appropriate size. BP was measured by the same investigator at each visit, in the morning before daily drug intake and after the patient had rested for ≥10 min in a quiet room. Three successive BP readings were obtained at 1-min intervals, and the mean of the 3 readings was calculated.

BP measurements were performed by physicians not belonging to the study in order to preserve the blindness of the experimenters.

Laboratory technicians drew blood samples and the biologist responsible for the laboratory performed the assays.

The HbA_{1c} level was measured using high-performance liquid chromatography (DIAMAT; Bio-Rad Laboratories, Inc., Hercules, USA; normal value, 4.2–6.2%) (15). Plasma glucose was assayed using a glucose-oxidase method (GOD/PAP; Roche Diagnostics, Mannheim, Germany) (16). Plasma insulin was assayed with a Phadiaseph Insulin Radioimmunoassay (Pharmacia, Uppsala, Sweden) using a second antibody to separate the free and antibody-bound ¹²⁵I-insulin (17).

TC and TG levels were determined using fully enzymatic techniques (18, 19) on a clinical chemistry analyzer (Hitachi 737; Hitachi, Tokyo, Japan). The HDL-C level was measured after precipitation of plasma apo B-containing lipoproteins with phosphotungstic acid (20). The LDL-C level was calculated using the Friedewald formula (21).

Table 5. Treatment with Oral Hypoglycemic Agents (OHA) in Telmisartan and Irbesartan Group

OHA	Number of patients (M/F)	
	Telmisartan + rosiglitazone	Irbesartan + rosiglitazone
Sulfonylureas		
Gliburide	18 (10/8)	16 (8/8)
Glimepiride	11 (5/6)	12 (7/5)
Gliclazide	10 (5/5)	9 (4/5)
Meglitinide derivatives		
Repaglinide	9 (5/4)	10 (4/6)
Nateglinide	13 (7/6)	12 (5/7)
α -Glucosidase inhibitor		
Acarbose	12 (6/6)	10 (5/5)
Biguanides		
Metformin	19 (9/10)	21 (11/10)

All group differences are nonsignificant. M, male; F, female.

The TNF- α level was assessed using a commercially available ELISA kit according to the manufacturer's instructions (TiterZyme EIA kit; Assay Designs, Inc., Ann Arbor, USA) (22).

Leptin concentrations were assessed in duplicate by a commercially available ELISA kit (TiterZyme EIA kit; Assay Designs, Inc.) according to the manufacturer's instructions (23).

Treatment tolerability was assessed at each using an accurate interview of patients by the investigators, and comparisons of clinical and laboratory values with baseline levels. Medication compliance was assessed by the investigators by counting the number of pills returned at the time of specified clinic visits.

Statistical Analysis

An intention-to-treat (ITT) analysis was conducted in patients who had received ≥ 1 dose of study medication and had a subsequent clinic visit where the efficacy of treatment was evaluated. Patients were included in the tolerability analysis if they had received ≥ 1 dose of trial medication after randomization and had undergone a subsequent clinic visit where the tolerability of the treatment was evaluated. The null hypothesis that the expected mean SBP, DBP, HOMA index, lipid profile, TNF- α , and leptin change from baseline to 12 months of double-blind treatment did not differ significantly between telmisartan and irbesartan treatments was tested using analysis of variance and analysis of covariance (ANCOVA) models (24). Similar analyses were applied to the other variables. The statistical significance of the independent effects of treatments on the other variables was determined using ANCOVA. A 1-sample *t*-test was used to compare values obtained before and after treatment administration; 2-sample

t-tests were used for between-group comparisons. The Bonferroni correction for multiple comparisons also was carried out. Statistical analysis of data was performed using the Statistical Package for Social Sciences software version 11.0 (SPSS Inc., Chicago, USA). Data are presented as the mean $\pm$ SD. For all statistical analyses, values of $p < 0.05$ were considered statistically significant.

Results

Study Sample

A total of 188 patients were enrolled in the trial. Of these, 182 completed the study; 92 (50.5%) were randomized to double-blind treatment with telmisartan and 90 (49.5%) to double-blind treatment with irbesartan. There were 6 patients (3 males and 3 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 the patient population at study entry, shown in Table 1, were similar in the two treatment groups. The doses and types of oral hypoglycemic agents used prior to enrollment were also not significantly different between the groups (Table 5).

Efficacy

Body Mass Index

No significant BMI change was observed after 6 or 12 months in either group, and there was no significant difference in the BMI values between the two groups (Table 1).

Glycemic Control

Significant decreases in HbA_{1c} and FPG were observed after 6 months ($p < 0.05$) in the telmisartan group, but not in the irbesartan group and significant decreases in both parameters were observed after 12 months in both groups ($p < 0.01$ and $p < 0.05$, respectively). Furthermore, the decreases in HbA_{1c} and FPG after 12 months were significantly greater ($p < 0.05$) in the telmisartan group than in the irbesartan group (Table 1).

FPI did not show any significant variation after 6 months, while it was showed a significant decrease at 12 months ($p < 0.05$) compared to the baseline value in both groups. The decrease in FPI after 12 months was significantly greater in the telmisartan group than in the irbesartan group ($p < 0.05$) (Table 1).

A significant HOMA index decrease was achieved at 6 and 12 months ($p < 0.05$ and $p < 0.01$, respectively) compared to the baseline value in both groups, and the decrease in the HOMA index after 12 months ($p < 0.05$) was significantly higher in the telmisartan group than in the irbesartan group (Table 1).

Blood Pressure Variables

Significant SBP and DBP changes were observed after 6 (both $p < 0.05$) and 12 months (both $p < 0.01$) vs. baseline in

Fig. 1. Changes in the levels of leptin, and TNF- α between baseline and 12 months in patients receiving telmisartan or irbesartan. * $p < 0.05$ compared to the baseline value; ** $p < 0.01$ compared to the baseline value.

both the telmisartan and irbesartan groups. There were no statistically significant differences in SBP or DBP between the two groups at either time point (Table 1).

Lipid and Lipoprotein Variables

Significant TC and LDL-C decreases were observed after 6 months (both $p < 0.05$) and 12 months (both $p < 0.01$) vs. baseline in both the telmisartan and irbesartan groups. There were no statistically significant differences in TC or LDL-C between the two groups at either time point. There were no significant changes in HDL-C or TG at either 6 or 12 months compared to the baseline values in either the telmisartan or irbesartan group (Table 1).

Adipocytokines Measurements

Significant decreases in TNF- α and leptin levels were observed after 6 months ($p < 0.05$ for both hormones) in the telmisartan group, and after 12 months in both groups ($p < 0.01$ and $p < 0.05$, respectively for telmisartan and irbesartan group), while no significant change was obtained after 6 months compared to the baseline value in the irbesartan group. There were no significant differences in the TNF- α or leptin levels between the two treatment groups at any time point (Table 1, Fig. 1).

Discussion

In patients with type 2 diabetes mellitus, the main aims are to prevent the emergence of insulin resistance, to maintain a favorable lipid profile, and to control hypertension in order to minimize cardiovascular complications and improve the prognosis (25).

Telmisartan has already been demonstrated to have a reno-

protective effect similar to that achieved with enalapril (26), and to have a good metabolic effect in diabetic patients (27). Similar results have also been observed with irbesartan (28, 29).

As expected from previous reports (30–32), both drug regimens had a significant and persistent antihypertensive effect in the present study.

Next, we observed that both drug regimens had a similar positive effect on LDL-C after 6 months of treatment (an approximately 8% reduction), while at 12 months we observed a 22.5% reduction in LDL-C in the telmisartan-treated group vs. a 13.3% reduction in the irbesartan-treated group (difference not statistically significant). This result is particularly impressive considering that usually rosiglitazone treatment has the tendency to slightly but significantly increase LDL-C in diabetic patients (33, 34). At 6 months only the telmisartan-treated patients experienced a significant improvement in glucose homeostasis parameters (HbA_{1c} = -10.5%, FPG = -9.7%, HOMA index = -16.7%) and in overweight-related parameters (TNF- α = -16.1%, leptin = -15.4%). After 12 months of treatment both groups experienced an improvement in glucose parameters, and this improvement was significantly greater in the telmisartan-treated group than in the irbesartan-treated one: HbA_{1c} = -15.8% vs. 10.4%, FPG = -16.0% vs. -6.4%, FPI = 15.3% vs. -8.6%, HOMA index = 29.2% vs. -17.4%, respectively. After 12 months of treatment, adiposity-related parameters also improved in the irbesartan group, even if to a lesser degree.

Some AT₁ receptor blockers induce synthesis of adiponectin, an adipose-specific protein adiponectin that has recently been discovered to improve insulin sensitivity, presumably via PPAR γ activation involving a post-transcrip-

tional mechanism (35).

Of course, our study has the limitation of a relatively small number of patients, but because the antidiabetic agent was the same in all subjects, we were nonetheless able to clarify the relative contribution of the two antihypertensive agents to the metabolic normalization. In fact, rosiglitazone and other PPAR γ activators have already been shown to reduce the TNF- α level (36); in our study this effect was greater by treatment with telmisartan than by treatment with irbesartan.

Another possible limitation of this study involves the hypoglycemic treatment of our subjects: although all patients took various oral hypoglycemic agents and the statistical analysis did not demonstrate any statistically significant difference in both types or doses of hypoglycemic agents between the two groups, the oral hypoglycemic agents dosage was titrated till the end of the study, and this could be a critical point. The levels of the HbA_{1c}, FPG, FPI, and HOMA index in the telmisartan group were significantly lower than those in the irbesartan group. From this, we conclude that only telmisartan improved the glucose metabolism.

Moreover, to the best of our knowledge, this is the first direct comparison of the effects of telmisartan and irbesartan on a wide range of metabolic parameters in patients affected by diabetes and metabolic syndrome. Telmisartan and irbesartan act as selective modulator of PPAR γ and selective gene regulation, which then triggers specific metabolic effects *in vitro* (37–39). Analysis of PPAR γ protein conformation using protease protection has shown that telmisartan and irbesartan directly interact with the receptor, producing a different conformational change than pioglitazone (8). In fact, telmisartan and irbesartan are characterized as PPAR γ -activating and thus are classified as selective PPAR modulators (SPPARMs).

In conclusion, our data appear to agree with the recent data of Schupp *et al.* (8); telmisartan and irbesartan, considered as selective PPAR γ activators, improved insulin sensitivity both in their study and ours. The observed metabolic effect of different AT₁ receptor blockers could be relevant to the choice of therapy for the correct management of patients affected by metabolic syndrome and diabetes.

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