Original Article

Effects of Telmisartan and Losartan on Insulin Resistance in Hypertensive Patients with Metabolic Syndrome

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Partial peroxisome proliferator–activated receptor-γ (PPAR-γ) agonists are known to decrease insulin resistance. Experimental studies have shown that the angiotensin type 1 receptor blocker (ARB) telmisartan has a PPAR-γ–activating property, but there does not appear to be a class effect. To test telmisartan's clinical importance, we here investigated its effect on insulin resistance in hypertensive patients with metabolic syndrome (MetS) in comparison with another ARB, losartan. A total of 42 hypertensive MetS patients (29 female, 13 male) were included (mean age: 50±9, range: 20–70 years). NCEP-ATP III criteria were used for the diagnosis of MetS. Patients were randomized to receive either telmisartan 80 mg/day (*n*=21) or losartan 50 mg/day (*n*=21) for 8 weeks. Biochemical assessments were made at baseline and at the end of the 8 weeks. Insulin resistance was evaluated by using homeostasis model assessment of insulin resistance (HOMA-IR). Both groups had similar reductions in systolic and diastolic pressures ($p>0.05$). HOMA-IR did not change significantly in either group throughout the study. In the telmisartan group, the mean HOMA-IR at baseline and at the end of the study were 1.9±07 and 1.9±0.5, respectively. The figures for the losartan group were 1.8±0.6 and 1.8±0.6, corresponding. In conclusion, in contrast with the reports that telmisartan may decrease insulin resistance by an effect associated with its molecular structure, 8 weeks of telmisartan treatment in the present study had a neutral effect on insulin resistance in hypertensive MetS patients, and similar results were obtained for losartan. (*Hypertens Res* 2007; 30: 49–53)

***Key Words*: metabolic syndrome, insulin resistance, telmisartan, losartan**

Introduction

Metabolic syndrome (MetS) has been defined as a cluster of certain clinical conditions including visceral obesity, hyperglycemia, dyslipidemia, and elevated blood pressure, and it represents a significant risk factor for the development of cardiovascular disease and type 2 diabetes mellitus (*1–3*). Insulin resistance has been suggested as an underlying pathogenic factor for MetS (*4*). MetS also represents a disorder of partial genetic background as mutations of the peroxisome proliferator–activated receptor-γ (PPAR-γ) (*5*). PPAR-γ is an intracellular hormone receptor playing a significant role in carbohydrate and lipid metabolism (*6*). PPAR-γ agonists are used in the treatment of type 2 diabetes for their reducing effect on insulin resistance (*7*, *8*).

Hypertension is the most common component of metabolic syndrome and the greatest contributor to carotid arteriosclerosis in apparently healthy individuals (*9*). Antihypertensive medications have varying effects on insulin resistance. β-Blockers and diuretics have unfavorable effects, whereas calcium canal blockers have a neutral effect; however, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) have neutral or favorable effects (*10–12*). A structural similarity has been found between telmisartan—an ARB—and pioglitazone, a PPAR-γ agonist used for the treatment of type 2 diabetes (*13*). Besides its effect in controlling blood pressure, telmisartan has also been reported to have a

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partial agonistic effect on PPAR-γ (*14*). One study has suggested that, by virtue of its dual effect, telmisartan may serve in the treatment of hemodynamic and biochemical aspects of MetS and thus it may be more effective than other conventional antihypertensive agents in preventing atherosclerotic cardiovascular diseases (*15*). The present study investigated the effect of telmisartan on insulin resistance in hypertensive patients with MetS in comparison with another ARB, losartan.

Methods

Included in the study were patients (age range: 20–70 years) attending outpatient clinics at the Internal Medicine Department of Goztepe Training and Research Hospital and fulfilling the criteria given below. The study protocol was approved by the local ethics committee (approval date and number: 04-11-2004/18). All patients gave written informed consent prior to their participation in the study. The study was conducted in accordance with the Declaration of Helsinki.

Inclusion Criteria

The presence of MetS and a systolic blood pressure between 140–169 mmHg or a diastolic blood pressure between 90–109 mmHg (*16*).

A diagnosis of MetS was made if at least two of the diagnostic criteria—other than hypertension—proposed by the National Cholesterol Education Program Adult III Treatment Panel (NCEP-ATP III) were met (fasting plasma glucose ≥110 mg/dl; fasting triglycerides ≥150 mg/dl; high-density lipoprotein (HDL) cholesterol <40 mg/dl [men] or <50 mg/dl [women]; and waist circumference >102 cm [men] or >88 cm [women]) (*17*).

Exclusion Criteria

Use of antihypertensives, insulin or oral antidiabetics, uncontrolled diabetes (HbA1c ≥7%), hepatic or renal functional impairment, drug or substance abuse, congestive heart failure, a history of stroke or acute coronary syndrome within the past 3 months, pharmacological treatment indication for dyslipidemia, any contraindication for telmisartan or losartan treatment.

Study Design

Patients who met the inclusion criteria and gave informed consent were randomized to either the telmisartan or losartan treatment group. Treatment with telmisartan (80 mg/day, p.o) or losartan (50 mg/day, p.o.) was started after demographic data collection, detailed physical examination, 12-lead electrocardiography, and fasting blood sampling for biochemical tests were conducted. An 8-week treatment was planned. Patients were advised to continue their previously adopted diet and exercise programs.

Table 1. Clinical Characteristics of Patients

	Losartan group (n=21)	Telmisartan group (n=21)	p
Age (years)	47.7±9.4	52.3±8.2	0.094
Gender (n (%))			
Male	7 (33.3)	6 (28.6)	0.739
Female	14 (66.7)	15 (71.4)	
BMI (kg/m^2)	32.8±4	31.5±4.6	0.33
Height (cm)	162.2±8.7	159.8±6.3	0.315

Data are expressed as mean±SD or number and percentage. BMI, body mass index.

Anthropometric Assessments

Sitting blood pressure was measured in both arms after at least 10 min of rest with an appropriate mercury sphygmomanometer using the Phase I and Phase IV Korotkoff sounds. A second measurement was made after at least 3 min in the arm with the higher measurement. The mean of two measurements was used for systolic and diastolic blood pressures. Body mass index (BMI) was calculated by using the Quetelet index (weight/height^2 [kg/m^2]) (*18*). The waist circumference was measured at the plane between anterior superior iliac spines and lower costal margins at the narrowest part of the waistline while the patient was standing and during slight expiration.

Biochemical Assessments

Blood samples obtained at baseline and at the end of the treatment following 12 h of fasting were immediately centrifuged (2,500 rpm), and the sera were separated. Glucose, total cholesterol, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels were determined by enzymatic methods. The HbA1c level was measured by an immunoturbidimetric method, and an electrochemiluminescence immunoassay was used to determine insulin levels. Homeostasis model assessment of insulin resistance (HOMA-IR) was used to assess insulin resistance (*19*).

Statistical analyses were made using the GraphPad Prisma V.3 software package. Data are presented as means and standard deviation. The independent t-test was used for the comparison of groups, and the paired t-test was used for the comparison of baseline and end-of-treatment data. Qualitative data were compared by the χ^2 test. Two groups were made for HOMA values (>2 or <2). Inter-group comparisons were made by the Mann-Whitney U-test, and intra-group comparisons (end-of-treatment *vs*. baseline) were made by the Wilcoxon test. A p level <0.05 was considered significant.

Table 2. Anthropometric and Biochemical Features of the Groups

	Losartan group (n=21)			Telmisartan group (n=21)			p
	At baseline	After treatment	% change	At baseline	After treatment	% change	
SBP (mmHg)	144.3±6.0	127.6±5.4	11.5±4.2	149.1±7.7	126.2±9.2	15.3±5.0	0.073
DBP (mmHg)	94.8±5.1	81.4±6.6	14.0±5.8	94.8±7.5	80.0±7.1	15.2±8.6	0.907
WC (cm)	102.9±10.1	102.6±10.4	0.3±2.1	101.8±7.7	101.8±7.7	0.0±2.1	0.725
Weight (kg)	85.6±13.1	84.9±11.2	0.8±1.45	79.5±9.8	79.9±8.6	0.5±1.22	0.876
FPG (mg/dl)	102.5±16.3	104.5±14.2	1.8±8.4	123.8±18.2	106.0±11.4	−16.9±11.2	0.0001
Total-C (mg/dl)	212.8±38.3	207.4±43.4	2.5±10.3	212.2±42.7	207.0±47.7	2.3±12.6	0.86
Triglycerides (mg/dl)	217.3±75.1	197.5±70.7	2.7±52.9	179.9±79.1	188.8±87.6	−16.0±48.3	0.105
LDL-C (mg/dl)	134.8±32.8	129.1±37.7	3.3±18.3	134.9±37.5	126.1±45.9	7.1±20.1	0.505
HDL-C (mg/dl)	34.9±5.8	38.7±7.5	8.8±10.1	41.7±11.2	41.7±13.0	−4.8±29.0	0.097
Insulin (μU/ml)	13.6±5.0	13.2±4.3	0.9±22.9	13.5±5.3	14.1±4.0	12.2±35.1	0.428
HOMA-IR	1.8±0.6	1.8±0.6	−4.8±32.7	1.9±0.7	1.9±0.5	−0.7±29.1	0.91
HbA1c (%)	5.7±0.6	5.8±0.7	0.6±6.7	6.0±0.5	6.1±0.5	0.7±5.5	0.32

Data are expressed as mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; FPG, fasting plasma glucose; C, cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance.

Results

A total of 42 patients were included in this study. Following randomization, 21 patients were assigned to the losartan group (14 female, 7 male, mean age: 47.7±9.4 years) and 21 patients were assigned to the telmisartan group (15 female, 6 male, mean age: 52.3±8.2 years). Demographic data of the patients are given in Table 1, anthropometric and biochemical characteristics are shown in Table 2.

Anthropometric Parameters

Both groups had significant reductions in systolic and diastolic blood pressures at the end of the treatment (p<0.0001, *vs*. baseline for both groups). Neither waist circumference nor BMI changed significantly in either group (p>0.05).

Biochemical Parameters

In the telmisartan group, baseline and end-of-treatment HOMA-IR were 1.9±07 and 1.9±0.5, respectively. In the losartan group, the figures were 1.8±0.6 and 1.8±0.6, respectively. HOMA-IR did not change significantly throughout the study in either group (Fig. 1). In the losartan group, HDL cholesterol increased significantly (from 34.9±5.8 mg/dl to 38.7±7.5 mg/dl, p=0.003). In the telmisartan group, fasting plasma glucose decreased significantly (from 123.8±18.2 mg/dl to 106.0±11.4 mg/dl, p=0.0001). The other biochemical parameters did not change significantly in either group (p>0.05).

Inter-Group Comparison

Groups were compared in terms of percent change from baseline to the end of treatment. No difference was found between groups with regard to anthropometric or biochemical parameters (p>0.05).

Treatment Characteristics

All cases completed the predefined study treatment period. No severe side effects interfering with the treatments were observed throughout the study period.

Discussion

The present study did not provide evidence that telmisartan has an insulin-sensitizing effect. Also, telmisartan and losartan had similar effects on insulin resistance in hypertensive MetS patients.

A partial PPAR-γ agonist effect has been reported for the ARB telmisartan (*20*). Benson *et al*. (*13*) observed reductions in glucose, insulin, and triglyceride levels in telmisartan-administered mice fed a diet rich in fat and carbohydrates. In a study using mouse preadipocyte cell cultures, Schupp *et al*. (*21*) found significant increases in PPAR-γ activity after equal doses of telmisartan, irbesartan, and pioglitazone, although they found no change with losartan or eprosartan. These results were attributed to the high lipophilicity of telmisartan and irbesartan. Takai *et al*. (*22*) compared the protective effects of a highly lipophilic ARB, telmisartan, and an ARB with low lipophilicity, losartan, on vascular function and oxidative stress in stroke-prone spontaneously hypertensive rats. In that study, they concluded that telmisartan might be useful for preventing NAD(P)H oxidase activity and

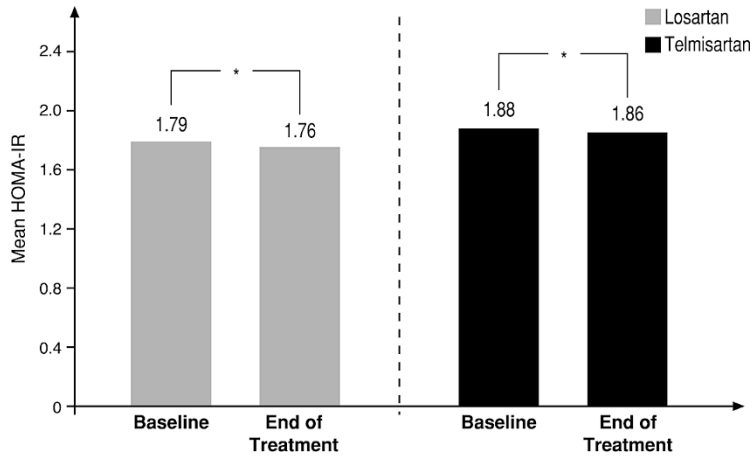

Fig. 1. *Change from baseline in HOMA-IR among groups.* *p *<0.05,* vs. *baseline.*

thereby for conferring vascular protection.

The hyperinsulinemic euglycemic glucose clamp method is the gold standard for the measurement of insulin resistance (*23*). However, epidemiological studies have demonstrated that HOMA-IR provides a useful model for assessing β-cell function and insulin resistance (*24*, *25*). Several studies have shown that the HOMA-IR method has a significant correlation with the hyperglycemic clamp technique (*26*, *27*). However, HOMA-IR's validity is limited in subjects with high fasting glucose levels (*28*). In our study, fasting plasma glucose levels were not very high in either group at baseline (Table 2).

Telmisartan has been reported (*5*) to have some beneficial effects on the hemodynamic and metabolic impairment of MetS, including insulin resistance, glucose intolerance. Vitale *et al*. (*29*) investigated the metabolic effects of 80 mg/day telmisartan or 50 mg/day losartan treatment (for 3 months) in hypertensive MetS patients and found significant decreases in insulin, HOMA-IR, and HbA1c levels with telmisartan. However, losartan did not produce any significant change. That study demonstrated a significant decrease in 24-h mean blood pressure with either treatment; however, telmisartan provided greater reductions in systolic and diastolic blood pressure compared to losartan. These findings were attributed to telmisartan's PPAR-γ activity. In the present study, blood pressure, insulin, HOMA-IR, and HbA1c levels were similar between the telmisartan and losartan groups at the end of the study.

Since Vitale *et al*. used WHO criteria for the diagnosis of MetS, patients with high insulin resistance may have been included. This may explain the difference between our findings and theirs. WHO suggests insulin resistance is the major underlying risk factor in MetS and recommends the demonstration of insulin resistance findings for MetS diagnosis (*30*). In that study, baseline HOMA-IR values were 5.78±3.53 and 5.74±3.35 in losartan and telmisartan groups, respectively, with all cases having a HOMA-IR value greater than 3.5. NCEP-ATP III criteria do not require the demonstration of insulin resistance (*17*). In the present study, NCEP-ATP III criteria were used to establish a MetS diagnosis, and patients with uncontrolled diabetes or those receiving antidiabetic treatment were excluded. Therefore, the baseline mean HOMA-IR values were 1.79±0.64 and 1.86±0.73 in the losartan and telmisartan groups, respectively. Among 42 patients, only 2 had HOMA-IR greater than 3.5 at baseline. These findings suggest that the partial PPAR-γ agonist effect of telmisartan may be prominent at a high level of insulin resistance.

Derosa *et al*. (*31*) observed decreases in total cholesterol, LDL cholesterol, and triglyceride levels after 12 months of telmisartan treatment compared to eprosartan and placebo in their study of 119 hypertensive type 2 diabetes patients. However, the present study demonstrated a neutral effect of telmisartan on plasma lipid levels.

The absence of a placebo group and relatively low baseline HOMA-IR levels may be potential limitations of the present study. Certainly, a longer follow-up with a larger patient group would yield more conclusive results.

In conclusion, in the present study 8 weeks of telmisartan had a neutral effect on insulin resistance in hypertensive MetS patients.

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