Original Article

Telmisartan Treatment Decreases Visceral Fat Accumulation and Improves Serum Levels of Adiponectin and Vascular Inflammation Markers in Japanese Hypertensive Patients

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Hypertension contributes to the occurrence and progression of cardiovascular diseases. The angiotensin II type 1 receptor blocker telmisartan is reported to activate the peroxisome proliferator–activated receptor γ and improve insulin sensitivity. We investigated the effects of telmisartan treatment on visceral fat, serum adiponectin and vascular inflammation markers in Japanese hypertensive patients. This was an open-label, non-controlled study. Twenty-eight essential hypertensive patients (22 men and 6 women; age 60.6±1.9 years; body mass index [BMI] 25.5±0.6 kg/m^2) participated. Fat area was assessed with computerized tomography. All the subjects were started on telmisartan 40 mg/day, which was increased to 80 mg/day to achieve the blood pressure target of less than 130/80 mmHg. We assessed the visceral and subcutaneous fat areas, serum adiponectin levels, and vascular inflammation markers at baseline and 24 weeks of telmisartan treatment. There were significant reductions in visceral fat area (from 103.1±7.9 to 93.3±8.4 cm^2, $p<0.01$) and pulse wave velocity (from 1,706±52 to 1,587±51 cm/s, $p<0.01$) at 24 weeks. In contrast, significant increases in serum high-density lipoprotein cholesterol (from 5.06±0.15 to 5.32±0.13 mmol/L, $p<0.05$) and adiponectin levels (from 8.27±0.76 to 9.13±0.81 μg/mL, $p<0.05$) were observed. Also, there were reductions in the interleukin-6 level (from 2.26±0.27 to 1.60±0.14 pg/mL, $p<0.01$). We also conducted these investigations in male subjects alone and similar findings were obtained for all of these parameters. In conclusion, telmisartan treatment was associated with an improvement of vascular inflammation, reductions in visceral fat and increases in serum adiponectin. (*Hypertens Res* 2007; 30: 1205–1210)

***Key Words*: telmisartan, visceral fat, insulin resistance**

Introduction

Insulin resistance and hyperinsulinemia are characteristic findings of metabolic syndrome (MetS) and are very common in patients with essential hypertension (*1–3*). Compensatory insulin resistance is considered to ameliorate systemic vascular damages, resulting in cardiovascular events (*4*, *5*). Most of metabolic and vascular abnormality of MetS are derived from visceral adipose tissue accumulation accompanying depleted adiponectin secretion.

Telmisartan, the angiotensin II type 1 receptor blocker, has been reported to activate the peroxisome proliferator–activated receptor γ (PPAR-γ) and thereby improve insulin sensi-

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Table 1. Baseline Metabolic Parameters and Their Changes after 24-Week Telmisartan Treatment in the Whole Subjects

	Baseline (mean±SEM)	24 week (mean±SEM)	% change	*p*
Body mass index (kg/m^2)	25.5±0.6	25.7±0.7	+0.78	n.s.
Waist circumference (cm)	89.7±1.7	88.6±1.9	−1.27	<0.05
Visceral fat area (cm^2)	103.1±7.9	93.3±8.4	−9.5	<0.01
Subcutanoues fat area (cm^2)	159.9±14.0	156.3±14.8	−2.2	n.s.
Systolic BP (mmHg)	147.0±1.1	129.0±2.0	−11.8	<0.001
Diastolic BP (mmHg)	87.3±1.1	76.8±0.9	−12.0	<0.001
Total cholesterol (mmol/L)	5.06±0.15	5.32±0.13	+5.06	<0.01
Triglycerides* (mmol/L)	1.48±0.19	1.42±0.18	−4.07	n.s.
HDL-C (mmol/L)	1.42±0.06	1.49±0.07	+5.40	<0.05
Fasting plasma glucose (mmol/L)	6.31±0.13	6.38±0.15	+1.26	n.s.
Uric acid (mg/dL)	5.51±0.21	5.44±0.20	−1.46	n.s.
Pulse wave velocity (m/s)	1,706±52	1,587±51	−7.01	<0.01
HOMA-IR	1.73±0.19	1.67±0.19	−3.41	n.s.
Adiponectin (μg/mL)	8.27±0.76	9.13±0.81	+10.4	<0.05
Leptin (ng/mL)	7.01±1.16	8.58±1.49	+22.3	<0.01
Interleukin-6 (pg/mL)	2.27±0.27	1.60±0.14	−30.0	<0.01
TNF-α (pg/mL)	15.8±0.7	15.3±0.7	−3.27	n.s.
Hs-CRP (mg/dL)	0.09±0.02	0.06±0.01	−26.7	n.s.

BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; TNF-α, tumor necrosis factor-α; Hs-CRP, high-sensitivity C-reactive protein. *Triglycerides were logarithmically transformed before conducting *t*-test.

tivity (*6*, *7*). *In vivo* experiments have shown that telmisartan increased the mRNA expression of adiponectin in a cultured adipocyte cell line, 3T3-L1 (*8*). In another report, telmisartan improved insulin sensitivity in diet-induced obese mice without weight gain (*9*). In a study in rats, both the accumulation of visceral fat and the hepatic triglyceride levels decreased to a much greater extent in telmisartan-treated animals than in valsartan-treated animals (*10*). In addition, a recent report has shown that telmisartan treatment might prevent the development of obesity and related metabolic disorders by altering the levels of adiponectin, resistin, and uncoupling protein 1 in diet-induced obese mice (*11*). Because telmisartan directly regulates insulin sensitivity *via* the PPAR-γ pathway, it is expected to improve insulin sensitivity more drastically than some other antihypertensive drugs (*12*, *13*), including other angiotensin II receptor blockers (ARBs), which are reported to improve insulin resistance through various mechanisms, including quenching of intracellular oxidative stress (*14–17*). Therefore, telmisartan improves insulin resistance (*18*) and reduces free plasma glucose, free plasma insulin, homeostasis model assessment of insulin resistance (HOMA-IR) values, and HbA1c (*16*). However, to the best of our knowledge, there has been only one, very recent clinical report (*19*) on the effect of telmisartan treatment on body fat distribution and inflammatory markers.

The aim of this study, therefore, was to clarify the effects of telmisartan as a partial agonist of PPAR-γ on body fat distribution, insulin resistance as represented by HOMA-IR, serum adiponectin levels, and vascular inflammation markers in Japanese hypertensive patients.

Methods

Subjects

Twenty-eight essential hypertensive patients (22 men and 6 women; age 60.6±1.9 years; body mass index [BMI] 25.5±0.6 kg/m^2) participated in this study. Fifteen of these patients had diabetes with HbA1c levels of less than 7.0%; none of the fifteen were receiving oral hypoglycemic agents. Patients with endocrinological disorders, systemic inflammatory diseases, or malignant neoplasms and patients receiving glucocorticoids were excluded.

Methods

This was an open-label, non-controlled study. All subjects were started on a treatment regimen of telmisartan 40 mg/day. The dosage was increased to 80 mg/day to achieve a target blood pressure level of less than 130/80 mmHg. During this study period, subjects were instructed not to change their lifestyles, including their diet and exercise. The study protocol was approved by the local ethical committee and conducted in accordance with the principles of the Declaration of Helsinki as revised in 2000, and all participants gave informed consent. We assessed the visceral and subcutaneous fat areas,

Table 2. Baseline Metabolic Parameters and Their Changes after 24-Week Telmisartan Treatment in Men

	Baseline (mean±SEM)	24 week (mean±SEM)	% change	*p*
Body mass index (kg/m^2)	25.1±0.6	25.3±0.6	+0.48	n.s.
Waist circumference (cm)	89.0±1.8	88.0±1.8	−1.1	<0.05
Visceral fat area (cm^2)	108.4±9.1	95.3±9.7	−12.1	<0.001
Subcutanoues fat area (cm^2)	137.1±12.6	132.7±12.0	−3.2	n.s.
Systolic BP (mmHg)	146.0±1.0	127.0±1.9	−13.4	<0.001
Diastolic BP (mmHg)	87.7±1.1	76.6±1.0	−12.7	<0.001
Total cholesterol (mmol/L)	4.92±0.13	5.25±0.14	+6.82	<0.01
Triglycerides* (mmol/L)	1.56±0.23	1.45±0.22	−6.77	n.s.
HDL-C (mmol/L)	1.41±0.07	1.52±0.09	+8.18	<0.05
Fasting plasma glucose (mmol/L)	6.42±0.16	6.46±0.16	+0.60	n.s.
Uric acid (mg/dL)	5.65±0.25	5.59±0.24	−0.97	n.s.
Pulse wave velocity (m/s)	1,677±54	1,568±61	−6.5	<0.01
HOMA-IR	1.73±0.20	1.58±0.18	−8.99	n.s.
Adiponectin (μg/mL)	7.37±0.84	8.47±0.97	+15.0	<0.05
Leptin (ng/mL)	5.29±0.62	6.21±0.73	+17.4	<0.05
Interleukin-6 (pg/mL)	2.39±0.34	1.66±0.20	−30.6	<0.05
TNF-α (pg/mL)	15.8±0.7	15.6±0.7	−1.1	n.s.
Hs-CRP (mg/dL)	0.09±0.02	0.07±0.01	−24.1	n.s.

BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; TNF-α, tumor necrosis factor-α; Hs-CRP, high-sensitivity C-reactive protein. *Triglycerides were logarithmically transformed before conducting *t*-test. Age was 59.0±2.2 years.

insulin resistance represented by HOMA-IR, serum adiponectin levels, and vascular inflammation markers at baseline and 24 weeks of telmisartan treatment. The clinical backgrounds of the subjects are shown in Table 1.

Laboratory Measurements

BMI was calculated as weight (in kg) divided by height (in m) squared. Waist circumference at the umbilical level was measured in the exhalation phase of respiration while standing. Venous blood samples were obtained after a 12-h overnight fast. Serum total cholesterol (TC) and triglyceride (TG) levels were determined by enzymatic methods, and high-density lipoprotein cholesterol (HDL-C) levels were measured by a polyanion-polymer/detergent method. Serum immunoreactive insulin (IRI) was measured by enzyme-linked immunosorbent assay, blood glucose with the glucose oxidase method, and HbA1c by high-pressure liquid chromatography. The insulin resistance index was calculated based on HOMA-IR [fasting glucose (mmol/L) × fasting insulin (mU/mL)/22.5] (*20*). Plasma adiponectin levels were measured with an enzyme-linked immunosorbent assay kit (Otsuka Pharmaceutical Co., Tokushima, Japan), and leptin was measured by radioimmunoassay. Tumor necrosis factor-α (TNF-α) was measured by an ultrasensitive, solid-phase sandwich enzyme-linked immunosorbent assay using a monoclonal antibody specific for TNF-α (R&D Systems, Minneapolis, USA). High sensitivity C-reactive protein (Hs-CRP) was measured by nephelometry (SRL, Tokyo, Japan). Interleukin-6 (IL-6) was measured using an enzyme-linked immunosorbent assay based on purified protein and polyclonal anti–IL-6 antibodies (Calbiochem, San Diego, USA).

Measurements of Blood Pressure and Pulse Wave Velocity

Systolic and diastolic blood pressures (SBP and DBP) were measured twice with an automatic electronic sphygmomanometer (BP-103i II; Nippon Colin, Komaki, Japan) with the patient in the sitting position after an at least 5-min rest. A newly developed device that allows an automated multiple pulse wave measurement, ABI-form (model BP-203RPE, Nippon Colin), was used to measure pulse wave velocity (PWV). This noninvasively produced PWVs in four different part of the body. PWV was measured before and 3 months after the telmisartan treatment. In this study, PWV was calculated as the mean of the left brachial-ankle PWV and the right brachial-ankle PWV.

Body Fat Distribution

All subjects underwent CT at the umbilical level to measure cross-sectional abdominal subcutaneous fat area (SFA) and visceral fat area (VFA) using Fat Scan software (N2 System Corp, Osaka, Japan) (*21*). The VFA/SFA ratio was calculated as the visceral fat area divided by the subcutaneous fat area.

Table 3. Correlations of % Changes in Systolic or Diastolic Blood Pressure with Those in Several Metabolic Parameters in the Whole Subjects

	% changes in			
	Systolic blood pressure		Diastolic blood pressure	
	r	*p*	*r*	*p*
% changes in				
Pulse wave velocity	0.462	<0.05	0.462	<0.05
Visceral fat area	0.151	n.s.	0.097	n.s.
Subcutaneous fat area	0.100	n.s.	−0.167	n.s.
Adiponectin	−0.245	n.s.	0.058	n.s.
Leptin	0.310	n.s.	0.303	n.s.
HOMA-IR	0.095	n.s.	−0.042	n.s.

HOMA-IR, homeostasis model assessment of insulin resistance.

Table 4. Correlations of % Changes in Systolic or Diastolic Blood Pressure with Those in Several Metabolic Parameters in the Male Subjects

	% changes in			
	Systolic blood pressure		Diastolic blood pressure	
	r	*p*	*r*	*p*
% changes in				
Pulse wave velocity	0.507	<0.05	0.495	<0.05
Visceral fat area	0.015	n.s.	0.007	n.s.
Subcutaneous fat area	0.027	n.s.	−0.195	n.s.
Adiponectin	−0.015	n.s.	0.179	n.s.
Leptin	0.172	n.s.	0.206	n.s.
HOMA-IR	−0.041	n.s.	−0.029	n.s.

HOMA-IR, homeostasis model assessment of insulin resistance.

Statistical Analysis

All data are shown as the means±SEM unless otherwise noted. Differences between paired variables were analyzed by Student's *t*-test. A χ^2 test was used to confirm that the genotype frequency was in Hardy-Weinberg equilibrium and to compare differences. Continuous variables were compared by ANOVA after being adjusted for age, BMI, and sex. All statistical analyses were conducted with the program StatView 5.0 for Macintosh (Abacus Concepts, Berkeley, USA). A *p* value of less than 0.05 was considered statistically significant.

Results

Baseline metabolic parameters and their changes after 24 weeks of telmisartan treatment in the study subjects are shown in Table 1. Telmisartan treatment was associated with significant reductions in waist circumferences, visceral fat area, SBP and DBP, and PWV at 24 weeks. In contrast, significant increases in serum HDL-C levels and adiponectin levels were observed. Also, there were reductions in the IL-6 level and there was a tendency toward a decrease in high sensitivity C-reactive protein ($p=0.055$). HOMA-IR did not significantly decrease, but did so (from 2.03±0.20 to 1.83±0.19, $p<0.05$) when subjects were limited to the 14 patients with MetS. Since the majority of the study subjects were men (22 out of 28 subjects), we conducted the same analysis in male subjects alone, and similar changes after 24-week telmisartan treatment were observed in all of the metabolic parameters (Table 2).

Next we investigated whether or not the changes in blood pressure during telmisartan treatment were associated with changes in several metabolic parameters (Table 3). Changes in PWV showed significant associations with those in both SBP and DBP. In contrast, changes in visceral and subcutaneous fat areas, adiponectin, leptin and HOMA-IR did not show significant association with either SBP or DBP. The same analysis was then conducted for male subjects alone. Again, none of the investigated metabolic parameters except for PWV had any correlations with changes in blood pressure (Table 4).

Discussion

This was a 24-week follow-up study on 28 Japanese mildly overweight subjects with essential hypertension, including 14

MetS subjects. Various MetS parameters, inflammatory markers and PWV as an atherosclerosis marker were significantly improved in the overall subject group, as well as in the subgroup of male subjects alone. These results suggested that oral administration of telmisartan improved systemic insulin resistance, resulting in decreased visceral fat accumulation as well as decreased inflammatory markers and increased serum adiponectin concentration.

Telmisartan is an ARB; however, it also has the rather unique characteristics of a partial PPAR-γ agonist. This pharmacokinetic feature prompted us to perform this study. Our results clearly showed the clinical efficacy of this compound. To our knowledge, there has been only one previous clinical report investigating the effect of telmisartan treatment on VFA (*19*). In rats, however, it has already been shown that visceral fat accumulation is suppressed by telmisartan treatment (*10*). Telmisartan also modulates adipocyte size and fat accumulation, resulting in protection against diet-induced visceral obesity. We consider that the increased expression of mitochondrial energy expenditure genes in skeletal muscle is the mechanism by which telmisartan decreases the visceral fat accumulation, as previously shown in rat models (*9*).

It is known that the plasma adiponectin level is inversely associated with visceral fat accumulation (*22–24*). Thus, we conjectured that adiponectin concentration was increased by telmisartan mainly through visceral fat mass reduction. Also, the present finding that plasma leptin levels significantly increased during telmisartan treatment is consistent with the very recent study by Usui *et al*. (*25*), although their study period was 3 months.

We found that telmisartan treatment caused considerable reductions in hs-CRP, which is in line with the previous report (*17*). It should be noted that a very recent report has shown that down-regulation of advanced glycation end products (AGE) receptor by telmisartan results in a decrease in the AGE-induced CRP production (*26*). Interestingly, as shown in Tables 3 and 4, changes in blood pressure were significantly correlated with those in PWV, but not with those in visceral and subcutaneous fat area, adiponectin, leptin or HOMA-IR. This finding indicated that changes in PWV are at least in part due to changes in blood pressure, whereas changes in the other metabolic parameters mentioned above may be independent of blood pressure lowering by telmisartan treatment. We speculate that various pathways are regulated by telmisartan administration.

During the preparation of our manuscript, Shimabukuro *et al*. (*19*) reported that a 24-week treatment with telmisartan produced considerable reductions in VFA, which is quite similar to our current finding. However, clinical parameters such as age, BMI, VFA at baseline and daily dose of telmisartan were considerably different between their study and ours (age, 49 *vs*. 61 years, respectively; BMI, 29.2 *vs*. 25.5 kg/m^2; VFA, about 200 *vs*. 103 cm^2; daily dose, 20–40 *vs*. 40–80 mg/day).

The main limitations of this study were the small number of subjects and the fact that we did not compare the effect of telmisartan treatment to that of a placebo or other antihypertensive compounds. However, we consider that our study subjects were reasonably representative of moderately overweight, Japanese hypertensive patients. Even with insulin resistance, Asian subjects tend to be less obese than European subjects due to the lower secretion potency of insulin. Therefore, it could be possible to extrapolate our findings into morbid obesity in Western countries in which morbid obesity is widespread. Also, it is essential to rule out other accidental changes in metabolic parameters during this study period. We previously reported that walking with a pedometer 8,200 steps per day produced an approximately 5 mmHg reduction in SBP in about 2 months (*27*). Given that our subjects did not change their dietary, exercise, or other lifestyle habits during the study period, and still the average reduction in SBP was as high as 18 mmHg (Table 1), it is highly likely that the considerable reductions in BP in the current study were caused by telmisartan.

In conclusion, the results of this study showed that telmisartan was quite effective at modifying body fat distribution in a clinical setting. Telmisartan treatment may prevent the development of atherosclerosis through reductions in visceral fat accumulation and vascular inflammation, and increases in serum adiponectin concentrations, especially in patients with MetS.

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