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Original article

Open-label, Randomized Crossover Study Between Telmisartan and Valsartan on Improving Insulin Resistance and Adipocytokines in Nondiabetic Patients with Mild Hypertension

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Abstract

Objective: The comparative effect of telmisartan and valsartan upon insulin resistance and adipocytokines in nondiabetic patients with mild hypertension is unclear.

Methods: Fifty nondiabetic patients with untreated mild hypertension were randomly assigned to telmisartan (40 mg/day) and valsartan (80 mg/day) groups and were switched in a crossover manner at 3-month intervals. Serum leptin, adiponectin, hsCRP and the HOMA-R were measured before and at 3 months during each treatment period.

Results: The HOMA-R significantly improved over the 3 months in the high insulin resistance group (HOMA-R>/=2.5) during the telmisartan treatment period (p=0.042), but not during the valsartan period. Both telmisartan and valsartan significantly decreased serum leptin levels in each female group during each treatment period (p<0.001 and p<0.001, respectively), but not in the male groups. Serum adiponectin did not increase in either treatment group. Serum hsCRP levels also significantly decreased in the high hsCRP subjects (>/=0.1) of both treatment groups (p=0.044 and p=0.015, respectively).

Conclusions: Telmisartan significantly improved insulin resistance, possibly through the effect on PPAR-gamma, while both telmisartan and valsartan significantly decreased serum leptin levels in female groups and hsCRP in both genders, suggesting no significantly different effects on adipocytokines by either drug in nondiabetic patients with mild hypertension.

Key words: telmisartan, valsartan, leptin, insulin resistance, adiponectin

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Introduction

Peroxisome proliferator-activated receptor gamma (PPAR-gamma) plays a pivotal role in progressing insulin resistance and cardiovascular diseases including hypertension[1, 2]. Activation of PPAR-gamma may become a new therapeutic target to prevent hypertensive vascular, renal and perhaps brain changes in hypertension [3]. A recent study by Bensen *et al.* demonstrated that telmisartan, a structurally unique angiotensin II type 1 receptor blocker (ARB), can function as a partial agonist of PPARgamma, while no other commercially available ARBs appeared to activate PPARgamma[4]. In that study, telmisartan activated the expression of the PPARgamma gene involved in carbohydrate and lipid metabolism and reduced glucose, insulin and triglyceride levels in rats fed a high-fat and high-carbohydrate diet. In humans, Pershadsingh *et al.* first reported that 80 mg/day of telmisartan improved insulin resistance and reduced plasma triglycerides in a male patient with hypertension, visceral obesity (BMI 34.4 kg/m^2) and impaired glucose tolerance (prediabetes)[5]. When the patient was switched to valsartan, the improvement of metabolic changes reversed. Then, switching back to telmisartan improved insulin sensitivity again[5]. This suggested that telmisartan predominantly improved insulin resistance compared with valsartan.

In addition to the effects of telmisartan on insulin resistance, it has recently been reported that telmisartan also affected adipocytokines such as leptin and adiponectin. Leptin is a 167-amino-acid-containing peptide that is specifically produced and secreted by mature adipocyte[6]. This adipocyte-derived protein acts in the hypothalamus to con-

trol appetite, energy expenditure and sympathetic nervous system outflow. Previous studies showed the close relationship of leptin with obesity and insulin resistance[7]. A very recent study by Usui *et al.* demonstrated that 20–40 mg of telmisartan for 3 or 6 months significantly reduced the fasting insulin level and the insulin resistance index estimated using homeostasis model assessment (HOMA-R) and that serum leptin significantly increased within 3 months in outpatients with both hypertension and type 2 diabetes mellitus for 6 months[8]. However, whether telmisartan affects the leptin level in the common nondiabetic patient with hypertension is unclear.

Adiponectin is a 30-kDa protein that is also specifically produced and secreted by mature adipocytes. Telmisartan treatment is considered to beneficially increase serum adiponectin. A recent study by Clasen *et al.* indicated that telmisartan induced adiponectin in adipocytes, which was associated with an improvement of parameters of insulin sensitivity and was likely mediated via PPARgamma activation involving a post-transcriptional mechanism[9]. Telmisartan treatment also decreased the weight of visceral adipose tissue and improved hyperglycemia, hyperinsulinemia, and hypertriglyceridemia in diet-induced obese mice while also increasing the serum adiponectin and uncoupling protein 1 levels and reducing the serum resistin level[10]. However, the effect of telmisartan on increasing the serum adiponectin level was not sufficiently investigated in the common nondiabetic patient with hypertension.

The aim of this randomized crossover study was to evaluate the effects of telmisartan on improving insulin resistance and adipocytokines compared with valsartan, another major commercialized ARB available worldwide, in common nondiabetic outpatients with mild hypertension.

Methods

Subjects of the study

The study was approved by the ethics committees of Gifu University and Tohno-Kousei Hospital, and all patients gave written informed consent. The clinical significance and purpose of the study and the possible disadvantages of participation associated with switching medications in a crossover manner were explained in detail to each patient. Before enrollment in the study, we excluded patients who met the following exclusion criteria: 1) previous usage of the ARBs, 2) taking any medication considered to affect the PPAR and insulin resistance such as pioglitazone and fibrates, 3) taking medication for chronic heart diseases, 4) severe hepatic, respiratory or renal disease, failure, hematologic diseases or other grave complications, 5) oral steroid use and 6) history of poor drug compliance.

The subjects enrolled in the study were 50 nondiabetic outpatients with untreated mild hypertension. According to the guideline of the Japanese Society of Hypertension, values for systolic blood pressure of 140–159 mmHg or diastolic blood pressure of 90–99 mmHg are diagnosed as mild hypertension. After obtaining full informed consent from each participant, the participants were randomly divided into two groups, the initial telmisartan group and the initial valsartan group. The study subjects in the initial telmisartan group were treated with 40 mg/day of telmisartan for the first 3 months and were switched to a therapeutically equivalent dose of valsartan (80 mg/day) for the next 3 months. In contrast, those in the initial valsartan group were treated with 80 mg/day of valsartan for the first 3 months and then 40 mg/day of telmisartan for the next 3 months. Other kinds of medications used before the study, were allowed as concurrently taken drugs during the study, with the doses of these drugs being kept constant throughout the study periods. This study was carried out in accordance with the principles embodied in the Helsinki Declaration of 1995 (as revised in Edinburgh 2000).

Study protocol (Figure 1A)

The protocol of the study is shown in Figure 1A. Blood pressure was measured twice after resting for more than 15 minutes, and the lesser value was chosen. Each subject was examined for serum leptin, adiponectin and high sensitive C reactive protein (hsCRP), together with ordinary blood laboratory examinations including hepatic function and cholesterols, before, at one and three months after the start of the study and at three months after switching to the other ARB. The HOMA-R was used as the index of insulin resistance (a value of more than 2.5 is considered to indicate existence of insulin resistance). A fasting venous blood sample was obtained to measure blood laboratory data such as the plasma levels of cholesterols and glucose. These assays were performed using an automated analyzer (TBA-120FR, Toshiba, Tokyo, Japan). Each patient's serum was immediately frozen at –70ºC, and serum adipocytokines were measured within 24 hours. Serum levels of leptin, adiponectin and hsCRP were measured using a leptin RIA kit (Linco Research, Inc., St. Charles, MO, USA), adiponectin ELISA kit (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) and N-latex CRP II kit (Dade Behring, Deerfield, IL, USA), respectively. The heights (measured to the nearest 0.1 cm), weights (measured to the nearest 0.1 kg) and waist circumferences (measured to the nearest 0.1 cm) of the subjects were measured by the same trained staff. Waist circumference was measured horizontally at the level of the umbilicus.

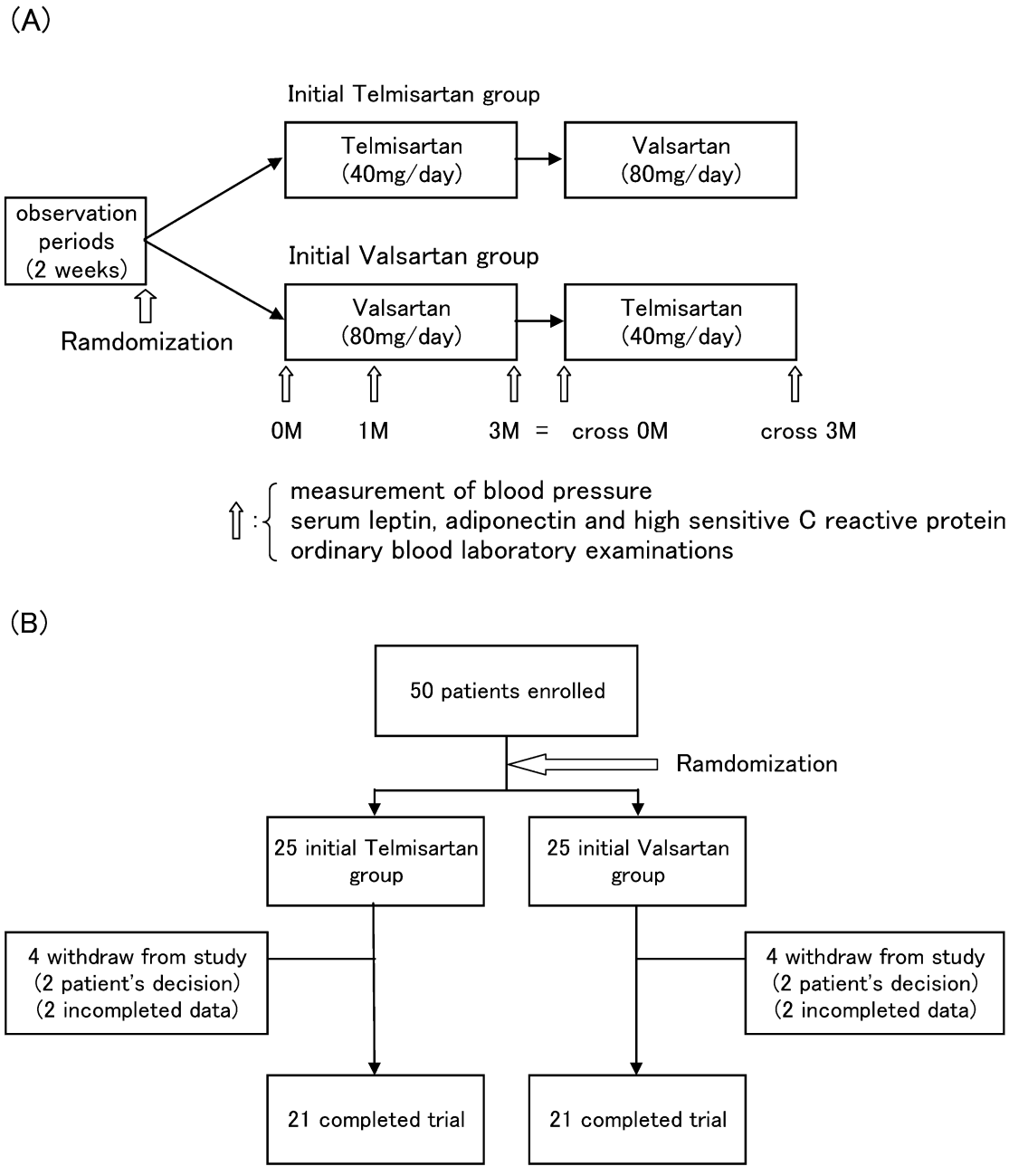


Figure 1. (A) Study protocol and (B) Flow chart of study participants.

Statistical analyses

The significance level was set at 5%. Values of blood pressure, major blood laboratory data, BMI and waist circumference are presented as means ± SD. Comparisons between the initial telmisartan and initial valsartan groups in Table 1 were analyzed using Fisher's exact test or the Mann-Whitney U test. Values of serum leptin, adiponectin, hsCRP and the HOMA-R index are presented as median and 25–75 percentiles. Statistical differences of blood pressure were analyzed by repeated measures one-way ANOVA and the Scheffe method as a post hoc test. Time-course changes in leptin, adiponectin, hsCRP, HOMA-R index and major blood laboratory tests were analyzed by the Friedman test and Wilcoxon signed-rank test with Bonferroni's correction. Correlation between changes in Δleptin levels and ΔHOMA-R indexes for 3 months was examined with Spearman rank

Table 1 Patient characteristics

	Initial Telmisartan group	Initial Valsartan group	Statistical significance (p value)
N	21	21	–
Gender (male/female)	7 / 14	11 / 10	0.22
Mean age (yr)	70.3 ± 9.4	70.3 ± 10.9	0.807
BMI	24.3 ± 3.5	24.1 ± 2.6	0.685
Waist circumstance (cm)	88.7 ± 7.9	89.9 ± 7.0	0.714
Smoker/ ex-smoker/ non-smoker	0 / 6 / 19	0 / 8 / 17	0.563
SBP (mmHg)	150.6 ± 6.5	150.1 ± 6.2	0.942
DBP (mmHg)	81.0 ± 7.3	78.6 ± 5.2	0.338
AST (IU/L)	22.8 ± 13.6	26.7 ± 9.3	0.409
ALT (IU/L)	34.5 ± 22.0	24.1 ± 13.3	0.507
γ-GTP (IU/L)	34.5 ± 22.0	32.4 ± 24.1	0.957
LDH (IU/L)	213.2 ± 39.0	210.9 ± 34.6	0.725
CK (IU/L)	117.8 ± 75.8	128.5 ± 84.7	0.877
UA (IU/L)	5.54 ± 1.51	5.41 ± 1.17	0.432
FBS (mg/dL)	104.8 ± 9.8	108.8 ± 18.4	0.745
IRI (IU/L)	7.0 ± 9.8	5.1 ± 3.0	0.107
HOMA-R (whole group)	1.82 ± 0.92	1.38 ± 0.91	0.133
HOMA-R (male)	1.58 ± 0.37 — 0.709	1.41 ± 1.10 — 0.818	0.497
HOMA-R (female)	1.94 ± 1.10	1.36 ± 0.72	0.106
HbA1c (%)	5.53 ± 0.45	5.49±0.55	0.549
Total cholesterol (mg/dL)	220.3 ± 34.3	202.3 ± 23.4	0.194
HDL-C (mg/dL)	58.2 ± 12.4	59.8 ± 18.5	0.999
LDL-C (mg/dL)	130.1 ± 41.2	110.6 ± 21.9	0.223
TG (mg/dL)	134.6 ± 67.7	120.4 ± 69.1	0.665
adiponectin (ng/dL)	9.7 ± 6.0	11.2 ± 6.1	0.351
leptin (ng/dL) female	11.7 ± 5.4 — 0.003	11.7 ± 5.5 — 0.005	0.764
male	4.6 ± 2.2	5.3 ± 3.5	0.845
hsCRP (mg/dL)	0.126 ± 0.121	0.074 ± 0.083	0.256

Abbereviations: N; numbers, BMI; Body Mass Index, SBP; systolic blood pressure, DBP; diastolic blood pressure, FBS; Fasting blood sugar, HOMA-R; homeostasis model assessment -R, TG; Triglyceride, HDL-C; HDL-cholesterol, hs-CRP; high-sensitivity C-reactive protein.

correlation. Statistical analyses were carried out using JMP, version 5.1.2 (SAS Institute Inc., Cary, NC, USA).

Results

Subjects

Ultimately, 42 nondiabetic patients with mild hypertension completed the study (Figure 1B). Patient characteristics are shown in Table 1. There was no statistical significance concerning the major indexes between the initial telmisartan and initial valsartan groups at enrollment in the study. During the study, the 42 subjects did not complain of any side effects.

Comparison of blood pressure between the two groups (Figure 2)

Time-course changes in systolic and diastolic blood pressure in both groups are shown in Figure 2. In the initial telmisartan group, both the systolic and diastolic blood pressures were significantly improved one month after administration. This significant improvement in both blood pressures remained at three months after switching to valsartan. On the other hand, the changes in the systolic blood pressure were significantly decreased beginning one month after administration of valsartan in the initial valsartan group, while the diastolic blood pressure was not improved during the study period. As shown in Table 2, there were significant decreases in systolic blood pressure during each 3-month treatment period for telmisartan and valsartan. However, there was no statistical difference in the ΔSBP (3 months changes in systolic blood pressure) between both ARBs in males and females (p=0.122 and p=0.874, respectively). On the other hand, there were also significant improvements in

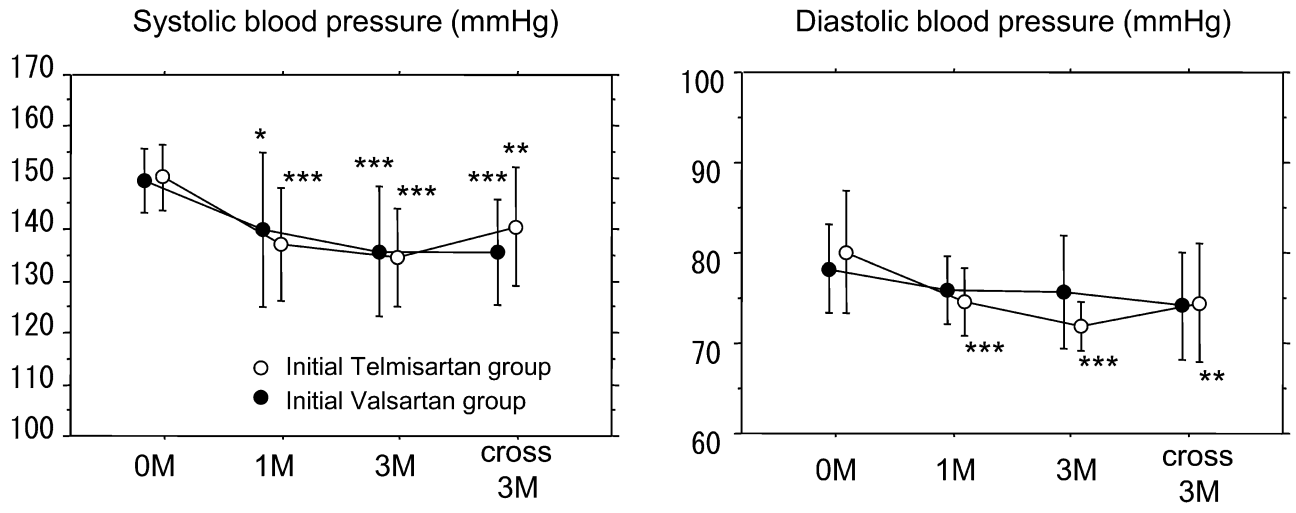
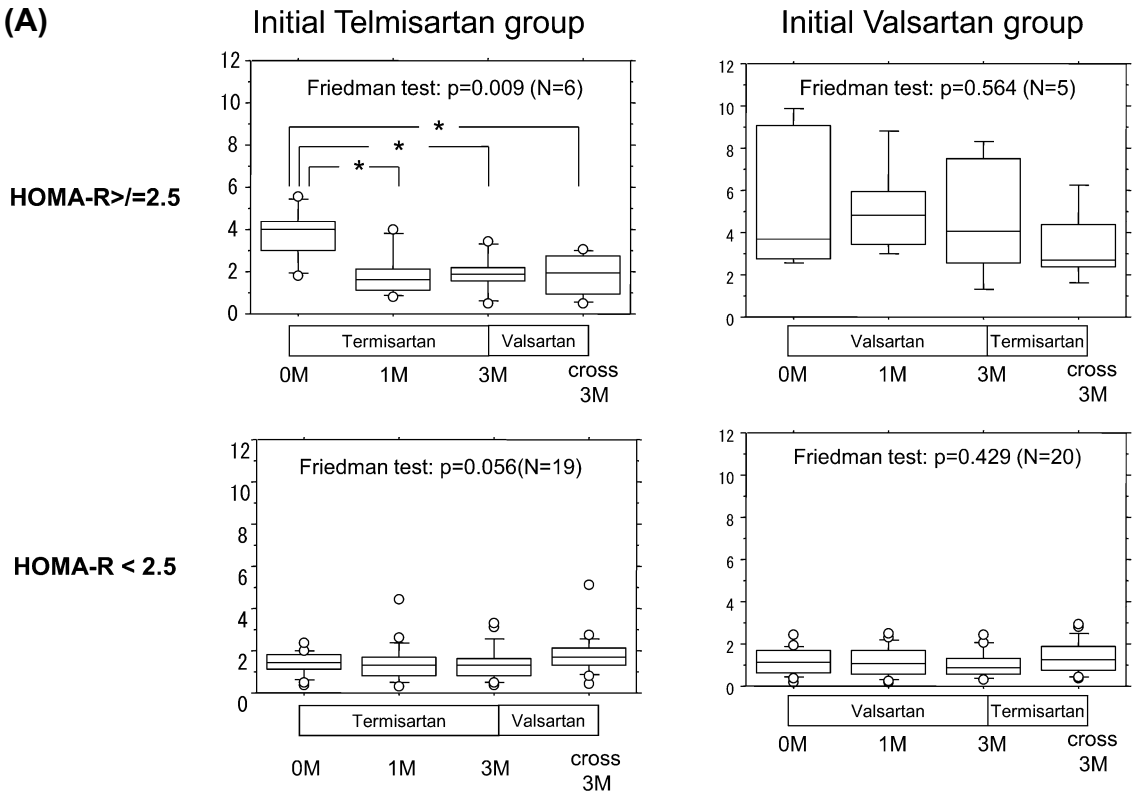


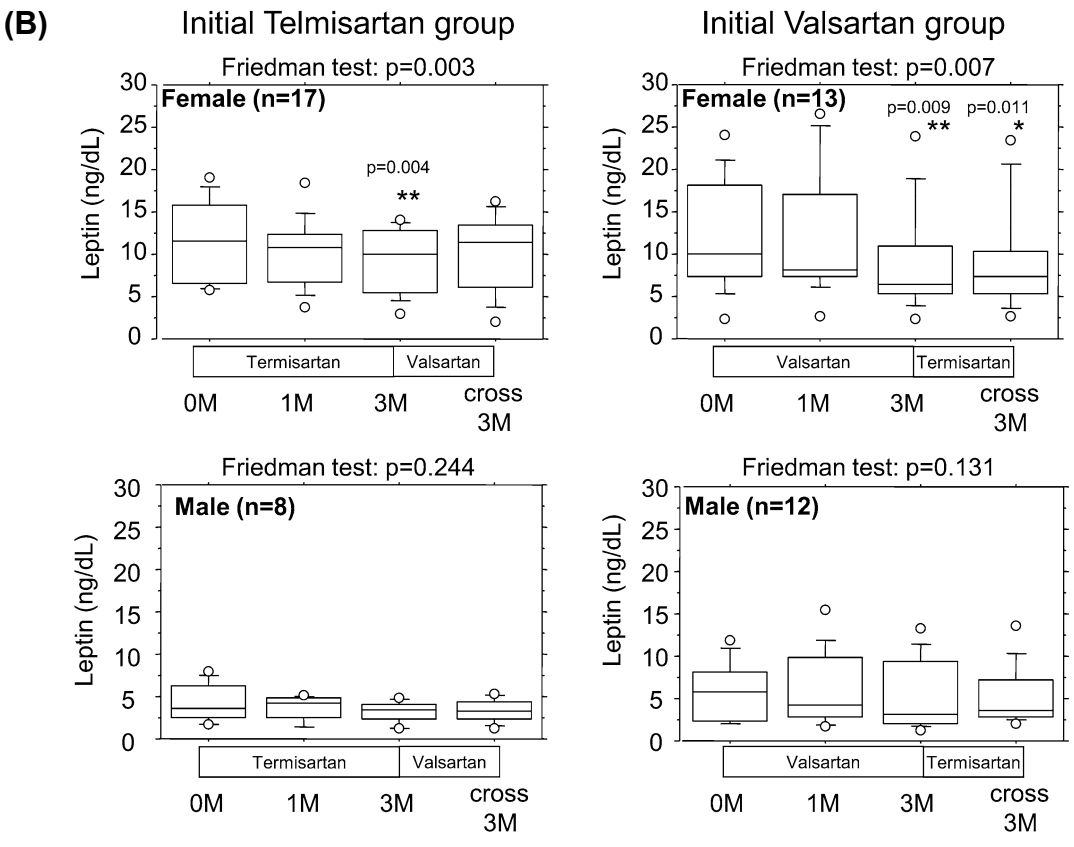
Figure 2. Time-course changes in systolic and diastolic blood pressures over the study period. Statistical significance: *p<0.05, **p<0.01 and ***p<0.001 compared with the values at the start of the study.

Table 2 Comparative effects of telmisartan and valsartan during each 3 months treatment period

	duration of telmisartan treatment		duration of valsartan treatment		p value (statistical significance between both groups)
	Δ	p value (statistical significance compared with 0 M)	Δ	p value (statistical significance compared with 0 M)	
Δ SBP (mmHg)					
female	–15.5 ± 9.7	<0.001 (***)	–9.7 ± 15.3	0.005 (**)	0.122
male	–17.5 ± 10.1	<0.001 (***)	–18.1 ± 10.8	<0.001 (***)	0.874
Δ DBP (mmHg)					
female	–7.5 ± 6.5	<0.001 (***)	–2.1 ± 8.6	0.232	0.018 (*)
male	–6.5 ± 8.3	0.004 (**)	–8.1 ± 6.2	<0.001 (***)	0.529
Δ HOMA-R					
female	–0.4 (–0.5, 0.3)	0.391	–0.2 (–0.4, 0.4)	0.346	0.853
male	0.0 (–0.1, 0.3)	0.632	–0.0 (–0.4, 0.3)	0.795	0.704
Δ HOMA-R (initaial value >/=2.5)	–0.3 (–0.7, –0.1)	0.042 (*)	–0.8 (–1.4, –0.0)	0.050	0.529
Δ leptin (ng/dL)					
female	–2.7 (–4.0, –0.7)	<0.001 (***)	–2.5 (–4.5, –0.5)	<0.001 (***)	0.853
male	–0.6 (–2.4, –0.5)	0.106	–0.8 (–1.6, –0.0)	0.356	0.558
Δ adiponectin (ng/dL)					
female	–1.1 (–1.8, –0.69)	0.004 (**)	–0.9 (–2.6, 0.5)	0.004 (**)	0.948
male	–0.18 (–1.1, –0.75)	0.632	–0.1 (–0.7, 0.7)	0.948	0.987
Δ hsCRP (mg/dL)					
female	–0.002 (–0.018, 0.010)	0.346	0.002 (–0.036, 0.011)	0.438	0.869
male	–0.004 (–0.123, 0.032)	0.317	0.002 (–0.116, 0.040)	0.557	0.728
Δ hsCRP (mg/dL) (initial value >/= 0.1)	–0.100 (–0.150, 0.042)	0.044 (*)	–0.107 (–0.153, –0.036)	0.015 (*)	0.763

the ΔDBP in both males and females in the telmisartan treatment group (p=0.004 and p<0.001, respectively), but there was no significant improvement in the ΔDBP in the female valsartan group (p=0.232). Accordingly, there was a significant difference in the ΔDBP between the female telmisartan and valsartan treatment groups (p=0.018).


(A)
Initial Telmisartan group
Initial Valsartan group
HOMA-R>/=2.5
HOMA-R < 2.5
Friedman test: p=0.009 (N=6)
Friedman test: p=0.564 (N=5)
Friedman test: p=0.056(N=19)
Friedman test: p=0.429 (N=20)
Termisartan
Valsartan
0M
1M
3M
cross 3M


(B)
Initial Telmisartan group
Initial Valsartan group
Leptin (ng/dL)
Female (n=17)
Female (n=13)
Male (n=8)
Male (n=12)
Friedman test: p=0.003
Friedman test: p=0.007
Friedman test: p=0.244
Friedman test: p=0.131
p=0.004
p=0.009
p=0.011
Termisartan
Valsartan
0M
1M
3M
cross 3M

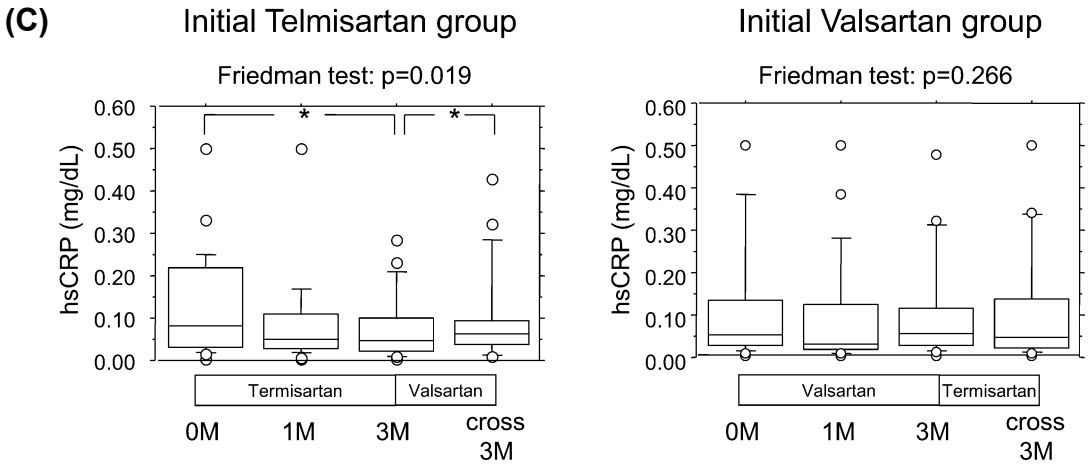


Figure 3. Time-course changes in (A) the HOMA-R indexes, (B) serum leptin levels, (C) serum adiponectin levels and (D) serum hsCRP levels over the study period. Statistical significance: *p/3<0.05 and **p/3<0.01 compared with the values at the start of the study.

Changes in insulin resistance

During the treatment period with telmisartan, although the changes were not significant, the values of IRI decreased from 9.4 ± 8.6 to 8.1 ± 13.4 (IU/L). The changes in the IRI tended to be remarkable in the high insulin resistance group (HOMA-R >/= 2.5), from 17.2 ± 10.9 to 13.1 ± 12.6 (IU/L; p=0.412). On the other hand, we found no change in the IRI during valsartan treatment period, from 8.5 ± 3.9 to 8.6 ± 4.7 (IU/L). We found no significant changes in the FBS values in both the telmisartan and valsartan treatment periods. As shown in Figure 3 (A), telmisartan significantly improved the levels of HOMA-R in the high insulin resistance group (the HOMA-R >/= 2.5) at one month after administration, while valsartan did not. In the high insulin resistance group of the initial valsartan group, the HOMA-R tended to decrease 3 months after changing from valsartan to telmisartan. In contrast, there were no statistically significant differences in either lower insulin resistance group (HOMA-R < 2.5). Furthermore, when evaluating the changes in the HOMA-R together with the male and female groups in each ARB treatment group, telmisartan significantly improved the ΔHOMA-R during the 3-month treatment periods, but valsartan did not (Table 2).

Changes in serum adipocytokines and hsCRP levels

As shown in Figure 3 (B), the serum leptin levels significantly improved at 3 months of the treatment in both female ARB groups (p=0.004 and p=0.009 compared with those at the start of the study, respectively). The significant improvement of serum leptin was lost three months after switching to valsartan in the female initial telmisartan group. In contrast, the significant improvement of the serum leptin levels at three months in the female initial valsartan group remained three months after changing to telmisartan (p=0.011). On the other hand, there were no significant changes in both male groups. Table 2 shows that the Δleptin over 3 months significantly decreased in both female ARB treatment groups, while it did not in the male groups. There was no significant difference in the value of Δleptin between the telmisartan and valsartan treatments for each 3-months period (Table 2). Serum adiponectin did not increase in both treatment groups.

The changes in hsCRP levels significantly decreased over the study period in the initial telmisartan group (p=0.019), while they did not in the initial valsartan group (p=0.266; Figure 3 (C)). Serum hsCRP was significantly improved after three months of treatment with telmisartan and significantly worsened at 3 months after the switch to valsartan. When selecting the subjects according to an initial hsCRP level of at least 0.1 mg/dL, we found a significant decrease in the value of ΔhsCRP over 3 months in both ARB treatment groups (Table 2).

Correlation to each index

The initial leptin levels at the start of the study were significantly correlated to the initial values of HOMA-R in both the male (p=0.001, R^2=0.490, n=18 in total for both ARB groups) and female groups (p=0.002, R^2=0.355, n=24 in total for both ARBs groups), respectively. As shown in Figure 4, the ΔHOMA-R (3M-0M) was significantly correlated to the ΔLeptin (3 M-0 M) in the female initial telmisartan group (p=0.021, R^2=0.308), while it was not in the male ini-

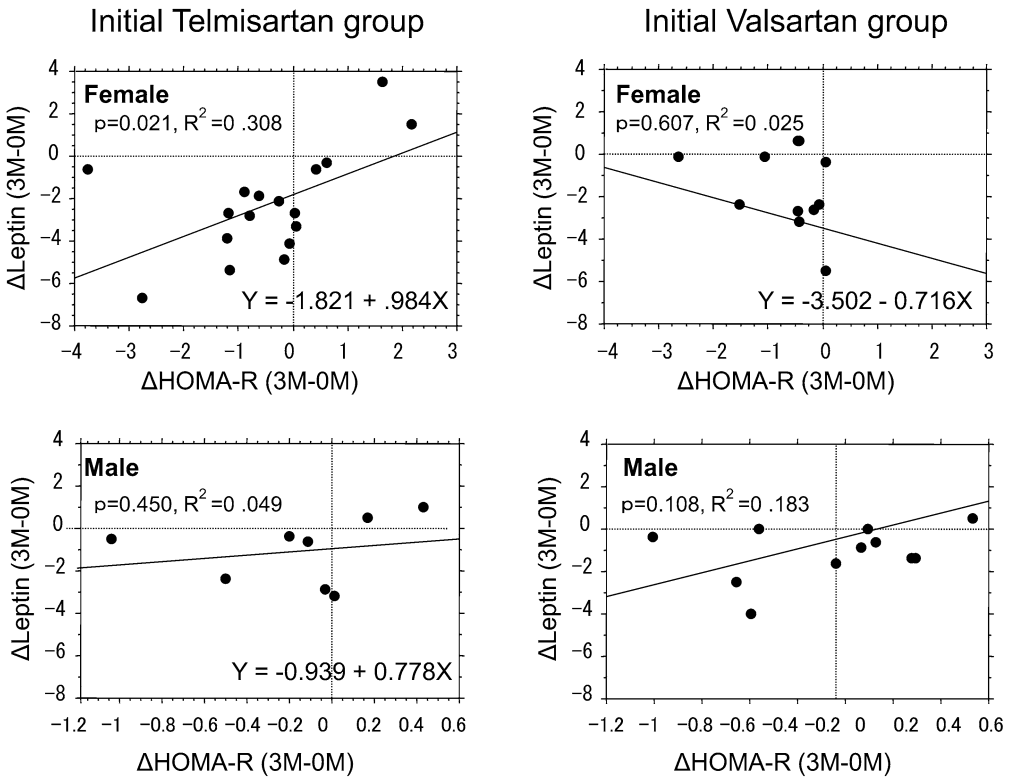


Figure 4. Correlation between change in leptin levels and the HOMA-R indexes for 3 months.

Table 3 Time-course changes in major blood laboratory indexes over the study

	Initial Telmisartan group					Initial Valsartan group					Statistical significance between two groups (0 M-3 M) (p value)
	0 M	1 M	3 M	cross 3 M	Statistical significance (p value)	0 M	1 M	3 M	cross 3 M	Statistical significance (p value)	
UA (IU/L)	5.36 ± 1.51	5.42 ± 1.37	5.55 ± 1.43	5.32 ± 1.40	0.134	5.41 ± 1.17	5.38 ± 1.32	5.55 ± 1.20	5.39 ± 1.19	0.580	0.923
AST (IU/L)	25.4 ± 12.3	23.6 ± 9.8 (†)	23.1 ± 7.5	25.8 ± 9.1 (*)	0.004	26.3 ± 8.6	25.1 ± 6.6	26.9 ± 9.3	29.3 ± 18.5	0.671	0.301
ALT (IU/L)	22.7 ± 13.4	20.2 ± 10.6	21.0 ± 10.2	24.4 ± 14.2	0.185	24.6 ± 12.4	24.2 ± 12.2	26.4 ± 13.7	29.2 ± 25.6	0.367	0.321
γ-GTP (IU/L)	32.2 ± 21.0	31.8 ± 21.6	31.4 ± 20.6	34.7 ± 34.0	0.956	30.8 ± 22.3	29.0 ± 19.9	30.8 ± 24.5	31.8 ± 21.3	0.767	0.728
LDH (IU/L)	213.8 ± 37.7	221.6 ± 42.2	211.4 ± 39.9	213.2 ± 39.1	0.215	210.8 ± 32.7	210.2 ± 34.3	207.4 ± 34.9	209.9 ± 31.7	0.441	0.313
CK (IU/L)	117.5 ± 69.7	124.5 ± 70.0	113.2 ± 84.3	112.8 ± 53.3	0.091	124.2 ± 78.6	127.5 ± 61.0	113.0 ± 62.3	123.0 ± 84.9	0.802	0.747
HbA1c (%)	5.87 ± 0.95	5.88 ± 0.95	5.86 ± 1.00	5.89 ± 0.99	0.870	5.90 ± 1.16	6.07 ± 1.51	5.98 ± 1.46	6.08 ± 1.63	0.330	0.593
Total Cho (mg/dL)	219.4 ± 35.7	222.3 ± 41.6	216.6 ± 35.2	223.6 ± 41.6	0.257	207.6 ± 27.5	208.6 ± 30.4	203.6 ± 27.5	209.7 ± 30.7	0.600	0.958
HDL-C (mg/dL)	58.8 ± 12.2	57.1 ± 15.4 (†)	54.7 ± 13.8 (††)	55.4 ± 13.6 (††)	0.003	57.8 ± 17.2	55.8 ± 15.2	52.1 ± 15.7 (††)	53.9. ± 14.7 (†)	< 0.001	0.700
LDL-C (mg/dL)	126.6 ± 39.5	129.7 ± 43.5	123.6 ± 38.8	129.0 ± 43.2	0.528	117.7 ± 25.5	118.2 ± 26.7	113.2 ± 28.0	114.4 ± 31.4	0.692	0.693
TG (mg/dL)	143.4 ± 95.3	152.3 ± 119.0	155.9 ± 116.8	143.3 ± 91.3	0.303	127.5 ± 72.0	151.7 ± 93.0	160.0 ± 111.7	164.8 ± 132.7	0.377	0.921

*p/3<0.05 compared with the value at the three months after the start (the Wilcoxon signed-rank test with Bonferroni's correction). †p/3<0.05 and ††p/3<0.01 compared with the value at the start of the study (the Wilcoxon signed-rank test with Bonferroni's correction).

tial telmisartan group and both initial valsartan groups. Furthermore, in this study, although we investigated the correlation among HOMA-R, leptin, adiponectin, hsCRP and blood pressure, we found no significant relationship in either ARB group (data not shown).

Changes in blood laboratory examinations (Table 3)

Table 3 shows time-course changes in major blood laboratory indexes over the study period. The serum levels of AST significantly decreased in the initial telmisartan treatment group. The levels of HDL-C also decreased in the both ARB groups.

Discussion

In this study, we evaluated the differences in the effects of telmisartan and valsartan upon the insulin resistance, adipocytokines and inflammation in common nondiabetic patients with mild hypertension. First, we showed that telmisartan significantly improved insulin resistance in the HOMA-R >/= 2.5 group at one month after administration in nondiabetic patients with mild hypertension, while valsartan did not (Figure 3 (A)). Furthermore, HOMA-R tended to worsen after switching to treatment with valsartan in this HOMA-R >/= 2.5 initial telmisartan group. These results are not inconsistent with the report by Pershadsingh *et al.*[5]. In addition, telmisartan beneficially had no influence on insulin resistance in the normal range group (the HOMA-R<2.5). These findings suggest that telmisartan can significantly and beneficially improve insulin resistance in common nondiabetic patients with mild hypertension. A recent study by Benndorf *et al.* showed that telmisartan improved insulin sensitivity in nondiabetic patients with essential hypertension[11]. Another very recent study by Ichikawa also showed that HOMA-R was significantly reduced by telmisartan compared with the baseline value, but not by valsartan, in hypertensive patients with metabolic syndrome[12]. Our findings are consistent with those of the above studies. Although there was no significant difference between the initial ARB groups in the present study, there may have been a tendency for subjects who had high insulin resistance to be chosen in the initial valsartan group through the first process of randomization. However, if valsartan has a sufficient effect upon the improvement of insulin resistance, the drug should improve the HOMA-R in a prominent situation compared with telmisartan.

As it is well-known that leptin is linked to insulin resistance[7], we confirmed that the leptin levels were significantly correlated with the initial values of HOMA-R in both the male and female groups at the start of the study (p=0.001 and p=0.002, respectively). Furthermore, we found a significant gender difference in leptin levels between the initial male and female groups; those of the women were higher than those of the men in both the initial telmisartan and valsartan groups (p=0.003 and p=0.005, respectively; Table 1), which is consistent with the results of Takizawa *et al.*[13]. In the present study, we showed that both telmisartan and valsartan significantly decreased the serum leptin levels in both female groups, not but in the male groups (Table 2 and Figure 3 (B)). We also demonstrated that the changes in HOMA-R over 3 months (ΔHOMA-R) were significantly correlated with those of leptin over 3 months (Δleptin) in the female initial telmisartan group, but not in the male telmisartan group or either gender valsartan groups (Figure 4). The above results suggest that the reductive effect of both ARBs on leptin appeared to occur through a different mechanism from the improvement of insulin resistance in common nondiabetic patients with mild hypertension.

According to the results of *in vivo* and animal model experiments[9, 10], we initially began the study with the anticipation that telmisartan would significantly increase the serum adiponectin levels during the treatment period. However, the results in this study showed that serum adiponectin did not increase in both ARB treatment groups (Table 2). This may be partly caused by the dose-dependent effects of telmisartan. Although previous studies used 80 mg of telmisartan[5], we used only 40 mg/day of telmisartan for the common nondiabetic patients with hypertension in this study. However, we also showed the possibility that telmisartan may directly activate the PPAR-gamma receptor and improve insulin resistance with an independent mechanism through adiponectin elevation. A recent study by Usui *et al.* also demonstrated that 20–40 mg of telmisartan significantly reduced the HOMA-R for 3 or 6 months and significantly increased serum leptin within 3 months in outpatients with both hypertension and type 2 diabetes mellitus, and the authors reported that total and high molecular adiponectin, fasting plasma glucose, HbA1c, total and HDLcholesterol, triglyceride, body weight, BMI and waist length were unchanged[14]. Another study by Benndor *et al.* also showed that telmisartan did not affect serum adiponectin levels in nondiabetic patients with essential hypertension, in spite of improving insulin sensitivity[11]. In addition, they demonstrated that telmisartan significantly enhanced PPAR-gamma receptor activity in vitro using a PPAR-gamma reporter gene assay, suggesting that telmisartan improved insulin sensitivity by mechanisms apparently not involving adiponectin induction[11]. A randomized, placebo-controlled, double-blind and crossover study by Nagel *et al.* also showed that 40 mg of telmisartan did not significantly increase the adiponectin level in nondiabetic insulin-resistant subjects over 12 weeks compared with a placebo, instead of the reduction of the HOMA-R[15]. A very recent in vitro study by Moriuchi *et al.* indicated that the transcription of the human adiponectin gene by telmisartan may be regulated by the independent mechanism of PPAR-gamma[16]. Considering all the above studies, the result in this study that telmisartan significantly improved insulin resistance with no elevation of adiponectin may be consistent.

Both telmisartan and valsartan also significantly reduced the serum hsCRP levels in the hsCRP level >/= 0.1 groups (Table 2), but telmisartan decreased the levels more effectively compared with valsartan (Figure 3 (C)). Previous studies have shown the anti-inflammatory effect of telmisartan. A previous study by Koulouris *et al.* showed the same reductive effect of telmisartan on hsCRP in patients with type 2 diabetes mellitus[17]. Pathophysiological crosstalk

between advanced glycation endproducts (AGEs) and their receptor (RAGE) plays a pivotal role in the pathogenesis of accelerated atherosclerosis in diabetes[18]. Telmisartan downregulated RAGE mRNA and inhibited superoxide generation in mesangial cells via PPAR-gamma activation, while Candesartan did not[19]. Another study demonstrated that telmisartan decreased the serum levels of RAGE in patients with essential hypertension[20]. A recent study by Yoshida *et al.* showed that telmisartan dose-dependently inhibited AGE-induced CRP expression in a human hepatoma cell line, which indicated that telmisartan may play an anti-inflammatory role via PPAR-gamma activation[21]. Although the exact reason for the reductive effect on hsCRP in this study is unclear, this reduction may be partly mediated by the inhibition of AGE via PPAR-gamma activation.

In conclusion, this open-label, randomized crossover study showed that telmisartan significantly and beneficially improved the high status of insulin resistance in common nondiabetic patients with hypertension compared with valsartan. Telmisartan and valsartan significantly decreased the serum leptin levels in the female group, but not in the male group. However, we found no increase in the serum adiponectin levels during both ARB treatment periods. Both telmisartan and valsartan also significantly reduced the high status of serum hsCRP levels. These results may possibly be reflected by the difference in potency of PPAR-gamma activation between telmisartan and valsartan.

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