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Effects of telmisartan on adiponectin levels and body weight in hypertensive patients with glucose intolerance

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Abstract

Few studies have analyzed intraclass differences in angiotensin II receptor blockers (ARBs) with respect to antidiabetic or metabolic effects. We designed a prospective randomized study to compare a peroxisome proliferator–activated receptor–γ (PPARγ)–activating ARB with a nonactivating ARB to delineate the effects on metabolic factors associated with cardiovascular disease. Subjects initially comprised 153 hypertensive patients (72 men, 81 women; mean age, 67.9 ± 7.8 years) with diagnosed glucose intolerance on the glucose loading test. Patients were randomly assigned to receive 6-month administration of telmisartan 47.0 mg/d (TEL) or candesartan 8.4 mg/d (CAN), or to have no change in drug regimen (control group, CTL). Fasting plasma glucose level was significantly reduced in TEL (n = 46) compared with CTL (n = 47) (percentage of change from baseline, −1.7% vs +2.2%; $P = .045$). Percentage of increase in adiponectin was significantly larger in TEL than in CTL (+10.5% vs +2.2%, $P = .025$), but not significantly larger in CAN (n = 44) than in CTL (+4.9% vs +2.2%; $P = .13$). Percentage of decrease in body weight from baseline was significantly enhanced in TEL compared with CTL (−2.2% vs −0.8%, $P = .023$) and CAN (−2.2% vs −0.3%, $P = .007$). Telmisartan decreased body weight while increasing serum adiponectin levels in hypertensive patients with glucose intolerance. Candesartan did not achieve similar improvements in these patients. Among ARBs, telmisartan may have a larger impact on obesity-related diseases that can lead to cardiovascular disorders.

1. Introduction

Adipose tissue is now recognized as an endocrine organ that secretes various proteins, many of which affect the processes of fat accumulation and metabolism. Adiponectin is one of the adipocyte-derived hormones that has profound anti-inflammatory and antiatherogenic properties [1]. Adiponectin has also been postulated to play an important role in the modulation of glucose and lipid metabolism in insulin-sensitive tissues. Circulating adiponectin concentrations are decreased in obesity [2], type 2 diabetes mellitus (DM) [3,4], and coronary heart disease [5]. This reduction is believed to have a role in the pathogenesis of cardiovascular diseases associated with metabolic syndrome [6].

Inhibition of the renin-angiotensin system (RAS) by antihypertensive agents such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARBs) has been known to reduce the incidence of new-onset DM [7-10]. Among RAS inhibitors, telmisartan has been shown to activate peroxisome proliferator–activated receptor–γ (PPARγ) and increase the expression of PPARγ target genes [11,12]. A recent clinical trial showed that telmisartan reduces visceral fat accumulation in patients with metabolic syndrome compared with calcium channel blocker [13]. In animal models, several reports have shown that telmisartan protects against weight gain [12,14,15]. However, whether such protective effects against weight gain are also found in humans has remained unclear. Moreover, few clinical studies have analyzed intraclass ARB differences with respect to metabolic effects.

We designed a prospective randomized study to compare the PPARγ-activating ARB telmisartan with a nonactivating ARB, candesartan, to delineate the effects on metabolic factors including adiponectin level and body weight in hypertensive patients with glucose intolerance.

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2. Materials and methods

2.1. Study population

Hypertensive outpatients treated with antihypertensive drugs at the Iwate Medical University hospital and Saiki Hospital receive a 75-g oral glucose tolerance test (OGTT). Of these, consecutive patients between December 2004 and September 2006 who displayed glucose intolerance including DM pattern or impaired glucose tolerance (IGT) and provided informed consent to the study protocol were enrolled (n = 153; 72 men, 81 women; mean age, 67.9 ± 7.8 years; range, 40-80 years). Impaired fasting glucose was included as IGT. Based on the results of the OGTT, *IGT* was defined as a 2-hour glucose value ≥140 mg/dL but <200 mg/dL; and *impaired fasting glucose* was defined as a fasting glucose level ≥110 mg/dL without IGT or DM. *Diabetes mellitus* was diagnosed as a fasting blood glucose level ≥126 mg/dL or a 2-hour glucose value ≥200 mg/dL. These diagnoses were made according to World Health Organization criteria. Patients were included in the study if antihypertensive or lipid-lowering drug regimens had not changed in the past 3 months. Patients whose blood pressure (BP) and glycemic status at the baseline were poorly controlled were not included in the study subjects. Patients who had previously been diagnosed with DM or IGT or who had clinically evident atherosclerotic disease of the coronary or peripheral arteries or cerebrovascular disease were excluded. Patients who were receiving candesartan or telmisartan at baseline were also excluded.

2.2. Study protocol

Subjects were randomly assigned to receive 6-month administration of candesartan (CAN, n = 50) or telmisartan (TEL, n = 51), or to have no change in their drug regimen (CTL, n = 52). Candesartan (8 or 12 mg/d) or telmisartan (40 or 80 mg/d) was added or changed from other current antihypertensive drugs in CAN and TEL, respectively. The change of a current antihypertensive drug to telmisartan or candesartan was principally performed using the following order of priority: other ARB; ACE inhibitor; calcium antagonist; and *β*-blocker. All patients were equally instructed in nonpharmacologic hypertension management such as diet counseling (low salt intake) and regular light exercise. However, intensive instruction in losing weight was not performed. Antihypertensive agents and lipid-lowering drugs were not changed during the 6-month study period. The goal of BP control was to achieve at-home values of less than 135 mm Hg for systolic BP and less than 85 mm Hg for diastolic BP. Systolic and diastolic BPs at home were measured in the morning within 1 hour of arising and then again at around 8:00 PM (automatic sphygmomanometer, HEM-705IT; Omron, Kyoto, Japan). The mean of these 2 measures was used for assessment. At 3 months after randomization, if systolic BP at home was consistently greater than 140 mm Hg despite increased doses of each randomized agent, the subject was discontinued from the study; and other antihypertensive agents were added (n = 5 in CTL, n = 3 in CAN, and n = 3 in TEL). Blood samples were unable to be obtained from 3 patients at 6 months. Ultimately, 47 patients in CTL, 44 patients in CAN, and 46 patients in TEL completed the follow-up. Clinical parameters were analyzed for these 137 patients. This study protocol was blinded to examiners who evaluate the metabolic factors and physical findings.

2.3. Measurement of clinical variables

Systolic and diastolic BPs were measured by trained physicians using an automatic digital sphygmomanometer after the subject had rested in a sitting position with the upper arm at the height of the heart for 10 minutes in a calm environment. Blood samples were collected from an antecubital vein after overnight fasting. Samples were collected into vacuum tubes containing a serum separator gel and were centrifuged at 1500*g* for 10 minutes. Routine hematology and biochemistry data were immediately measured. Aliquots of serum were stored at −80°C for measurement of C-reactive protein (CRP), insulin, and total adiponectin levels. Serum adiponectin level was measured by enzyme-linked immunosorbent assay (Otsuka Pharmaceutical, Tokushima, Japan), and insulin level was measured by chemiluminescent immunoassay. The CRP level was determined using a high-sensitivity method (N Latex II; Dade Behring, Deerfield, IL). The intraassay and interassay coefficients of variation for the biomarkers were as follows: CRP, 5.4% and 8.0%; adiponectin, 2.9% and 3.4%; insulin, 2.8% and 5.4%; respectively. The collected samples were measured by the same assay before and after the randomization. Waist circumference was measured midway between the lower rib margin and iliac crest with the subject standing, and insulin resistance was measured using the homeostasis model assessment of insulin resistance (HOMA-IR).

All study protocols were approved by our institutional ethics committee, and all participants provided written informed consent to participate.

2.4. Statistical analysis

Paired *t* tests were used to compare clinical data between baseline and after 6 months. Analysis of variance with the Bonferroni post hoc test was used to compare crude values or percentage of changes from baseline in the 3 groups. The χ^2 test was used to compare the prevalence of DM or IGT between groups. To determine associations between body weight and other metabolic factors, including adiponectin level, simple linear regression analysis was performed. Logarithm-transformed CRP level was used for comparisons. All analyses were performed using the SPSS (Chicago, IL) statistical package, version 11.0. Data are expressed as mean ± standard deviation, and error bars in

Table 1
Status of drug replacement or addition in groups assigned to ARBs

	CAN group (n = 44)	TEL group (n = 46)	*P*
Additional administration	14 (31.8%)	12 (26.1%)	NS
Change from other agents			
Other ARBs	14 (31.8%)	12 (26.1%)	NS
ACE inhibitors	11 (25.0%)	14 (30.4%)	NS
Ca antagonists	3 (6.8%)	5 (10.9%)	NS
β-Blockers	2 (4.5%)	3 (6.5%)	NS

NS indicates not significant.

figures for percentage of change from baseline show standard error of the mean.

3. Results

Status of drug replacement or additional administration in the groups assigned to ARBs is shown in Table 1. No significant differences were seen in status of drug change between CAN and TEL. Mean dose of each ARB was 8.4 mg/d in CAN and 47.0 mg/d in TEL at the end of the study.

No significant differences were seen in baseline clinical characteristics between the 3 groups (Table 2). Only high-density lipoprotein tended to be low in CTL compared with the other 2 groups ($P = .07$).

Comparisons of clinical variables in the 3 randomized groups between baseline and after 6 months are shown in Table 2. No significant change in systolic or diastolic BP was found in CTL at baseline and after 6 months. In CAN and TEL, although no significant differences in systolic BP at office or at home were identified, diastolic BPs were significantly reduced during follow-up except in TEL at home. Body weight and body mass index (BMI) were unchanged in CAN, but were significantly decreased in TEL during follow-up. Serum adiponectin levels were significantly increased in both CAN and TEL. Serum creatinine level was significantly increased in CAN, but not in TEL. No significant differences in high-sensitivity CRP were found for CAN or TEL.

In the comparison of percentage of change from baseline between groups, fasting plasma glucose was reduced in TEL (−1.7%, $P = .045$ vs CTL), but not in CAN (+1.3%, $P = .36$ vs CTL), compared with CTL (+2.2%). Although no significant difference in percentage of change of serum adiponectin from baseline level was found in CAN compared with CTL (+4.9% vs +2.2%, $P = .11$), percentage of increase of adiponectin was significantly larger in TEL than in CTL (+10.5% vs +2.2%, $P = .025$). The percentage of decrease in body weight from baseline was significantly enhanced in TEL compared with CTL (−2.2% vs −0.8%, $P = .023$) and CAN (−2.2% vs −0.3%, $P = .007$) (Fig. 1).

In TEL, percentage of change in body weight correlated inversely with percentage of change in adiponectin level ($r = −0.313$, $P = .042$) (data not shown).

There were no patients who required glucose-lowering medications during the study protocol. No severe adverse effects including gastrointestinal disturbance

Table 2
Baseline clinical characteristics in the 3 groups and comparison of clinical variables between baseline and after 6 months

	CTL group (n = 47)			CAN group (n = 44)			TEL group (n = 46)			Trend *P* for baseline of the 3 groups
	Baseline	6 mo	*P*	Baseline	6 mo	*P*	Baseline	6 mo	*P*	
Age, y	67.9 ± 7.0	–	–	66.8 ± 8.9	–	–	68.6 ± 7.9	–	–	.33
Male/female	24/23	–	–	21/23	–	–	21/25	–	–	.67
IGT/DM pattern, n	33/14	–	–	33/11	–	–	32/14	–	–	.58
sBP (office), mm Hg	143 ± 15	146 ± 15	.21	145 ± 17	143 ± 18	.26	143 ± 15	142 ± 15	.44	.80
dBP (office), mm Hg	82 ± 9	79 ± 9	.33	85 ± 12	79 ± 11	.027	81 ± 11	76 ± 12	.042	.20
sBP (home), mm Hg	129 ± 12	127 ± 13	.28	127 ± 14	123 ± 15	.09	127 ± 13	125 ± 12	.14	.29
dBP (home), mm Hg	74 ± 10	72 ± 11	.35	76 ± 10	71 ± 8	.031	74 ± 10	71 ± 11	.08	.61
Body weight, kg	63.0 ± 8.7	62.3 ± 9.2	.43	60.2 ± 9.7	59.6 ± 9.8	.38	60.0 ± 10.0	57.9 ± 9.3	.016	.34
BMI	25.6 ± 2.2	25.3 ± 2.1	.51	24.7 ± 2.7	24.4 ± 2.5	.43	25.2 ± 3.0	24.6 ± 3.0	.050	.43
Waist circumference, cm	88.8 ± 5.3	90.6 ± 5.5	.15	87.2 ± 7.3	89.1 ± 5.6	.29	90.2 ± 8.3	89.4 ± 7.9	.51	.18
FPG, mg/dL	104 ± 12	105 ± 12	.47	104 ± 15	103 ± 13	.58	105 ± 13	103 ± 11	.17	.61
Hemoglobin A_{1c}, %	5.41 ± 0.49	5.49 ± 0.46	.21	5.30 ± 0.51	5.36 ± 0.40	.53	5.40 ± 0.43	5.42 ± 0.40	.46	.50
Fasting insulin, μU/mL	8.64 ± 7.62	7.42 ± 4.46	.28	6.88 ± 5.03	5.67 ± 5.51	.09	8.71 ± 6.80	7.37 ± 5.62	.16	.51
HOMA-IR	2.20 ± 1.82	1.97 ± 1.35	.38	1.92 ± 0.96	1.46 ± 0.71	.08	2.35 ± 2.14	1.98 ± 1.75	.11	.51
Total cholesterol, mg/dL	186 ± 28	190 ± 28	.51	203 ± 35	199 ± 30	.44	195 ± 21	192 ± 26	.70	.10
Triglyceride, mg/dL	136 ± 59	136 ± 64	.92	132 ± 40	128 ± 62	.41	131 ± 66	123 ± 56	.21	.98
HDL, mg/dL	47 ± 10	50 ± 12	.14	55 ± 20	54 ± 16	.74	55 ± 16	52 ± 14	.16	.07
Creatinine, mg/dL	0.77 ± 0.17	0.79 ± 0.18	.52	0.71 ± 0.15	0.77 ± 0.22	.039	0.73 ± 0.19	0.76 ± 0.27	.25	.35
Adiponectin, μg/mL	8.8 ± 3.1	9.2 ± 3.4	.34	9.3 ± 4.1	10.3 ± 4.6	.042	9.7 ± 3.9	11.3 ± 5.3	.031	.66
hs-CRP, mg/L	1.10 ± 1.72	1.01 ± 1.25	.67	0.94 ± 1.35	0.82 ± 1.87	.68	1.18 ± 2.09	1.04 ± 1.99	.38	.94

Data are expressed as mean ± SD. sBP indicates systolic BP; dBP, diastolic BP; FPG, fasting plasma glucose; HDL, high-density lipoprotein; hs-CRP, high-sensitivity CRP.

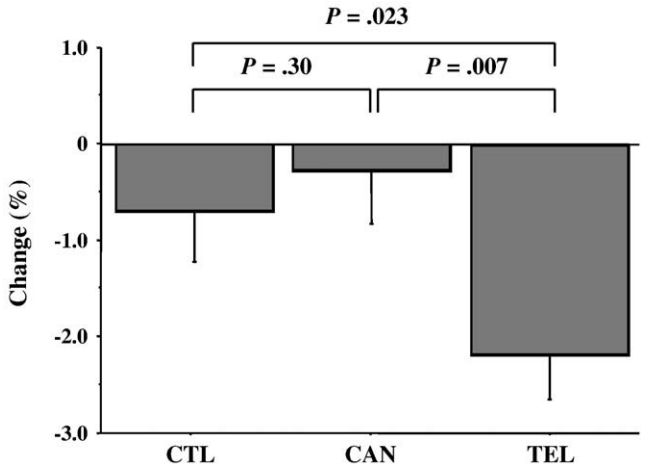

Fig. 1. Percentage of change in body weight from baseline. Graphs and error bars are expressed as mean ± SE.

were found throughout the study among patients who completed the study.

4. Discussion

This prospective randomized study demonstrated that, in hypertensive patients with glucose intolerance, telmisartan had an inhibitory effect on fasting plasma glucose levels when evaluated by the percentage of change compared with that in the control group. Furthermore, in patients receiving telmisartan, the serum adiponectin level was increased and body weight decrease was enhanced compared with control patients under similar conditions of diet and exercise counseling. However, these effects were obscured in patients receiving candesartan.

The ARBs have been recognized as regulators of glucose and lipid metabolism in adipocytes. Several large-scale clinical studies have shown prevention of new-onset DM in patients treated with ARBs [7-9]. Recent studies have implicated angiotensin II in the growth and development of adipose tissue [16]. Increased expression of both angiotensin II and ACE has been shown in the subcutaneous and abdominal adipose tissue of overweight and obese individuals [17]. Blunting the actions of angiotensin II with ARBs could facilitate differentiation of preadipocytes into mature adipocytes, which would subsequently increase lipid storage capacity in adipose tissue.

Serum adiponectin levels increase with the administration of a PPARγ agonist, the insulin-sensitizing thiazolidinedione [18]. Telmisartan has likewise been shown to have an agonist effect on the PPARγ [11,12], and this effect may play an additional role in reducing glucose levels and risk of DM [19]. Some previous clinical studies have shown that telmisartan increases serum adiponectin levels [20,21]. Conversely, other ARBs such as losartan, valsartan, and candesartan also reportedly increase adiponectin concentrations in various grades in human and animal models [22-24]. The effects of antihypertensive drugs on adiponectin levels are speculated to relate to effects on BP reductions or RAS inhibition per se. However, the present results show that telmisartan has a larger effect on serum adiponectin levels than candesartan, independent of the magnitude of BP-lowering effects. These data were in agreement with our previous cross-sectional reports that only the use of telmisartan was found to have a significant positive correlation with the serum adiponectin level when adjusted by age, sex, waist circumference, and statin use [25]. Clasen et al [20] demonstrated that PPARγ-activating ARBs induce adiponectin protein expression at a posttranscriptional level, independent of angiotensin II type 1 receptor–blocking properties, whereas the non–PPARγ-activating ARB eprosartan had no effect. Adiponectin levels can apparently be altered by many metabolic factors, although the effect may be weaker than that from PPARγ activation.

Mori et al [26] showed that telmisartan downsized adipocytes in diabetic rats with visceral obesity, and this effect was greater than valsartan. Furthermore, Benson et al [12] and Sugimoto et al [14] reported that telmisartan reduced visceral fat accumulation and attenuated weight gain by increasing caloric energy expenditure in rats fed a high-fat, high-carbohydrate diet. They also found that telmisartan, but not valsartan, increases the expression of genes for a nuclear-encoded transcription factor that regulates mitochondrial function [14]. Araki et al [15] showed that the suppressed weight gain induced by telmisartan is associated with messenger RNA expression of uncoupling protein–1, a crucial factor in energy expenditure. In the present study, enhancement of body weight decreases in patients receiving telmisartan was found under the condition of nonpharmacologic hypertension management such as diet and light exercise counseling. Although no published reports have described this finding in human subjects, Shimabukuro et al [13] performed a clinical study of subjects with metabolic syndrome and found that body weight, BMI, and waist circumference tended to be decreased in the telmisartan-treated group over the course of 24 weeks.

Great improvements in adiponectin levels are known to be obtained by exercise or decreases in body weight among individuals with glucose intolerance or obesity [27,28]. Although a significant correlation was seen between percentage of change in adiponectin level and percentage of change in body weight in the present study, which of the decrease in body weight and activation of PPARγ contributed most to increases in adiponectin level was unclear. However, increased adiponectin level may not simply be caused by body weight decrease, as no correlations between percentage of change in these 2 parameters were found in CTL or CAN.

Although serum adiponectin levels were significantly increased by telmisartan, other clinical indices related to lipid metabolism or insulin resistance were not significantly affected in the present study. Peroxisome proliferator–activated receptor–γ activation is known to

improve lipid metabolism and insulin resistance [21,29,30]. The following reasons for this discordance were considered. First, previous clinical trials examined diabetic human subjects receiving antidiabetic therapy, patients with metabolic syndrome, or obese animal models. In the present study, although patients who showed IGT or DM pattern in the OGTT were enrolled, insulin resistance was less severe at baseline. Telmisartan treatment for 8 weeks reportedly had a neutral effect on insulin resistance in hypertensive patients with a HOMA-IR level of 1.9 [31]. The PPARγ agonist effects of telmisartan may be prominent at high levels of insulin resistance. Second, more than half of our study patients were assigned to receive ARBs (telmisartan or candesartan) as a replacement for other RAS inhibitors. Class effects of RAS inhibitors may have masked any specific effect of the randomized ARBs. Third, a relatively low dose (47.0 mg/d) of telmisartan was used in this study; and because telmisartan acts as a partial PPARγ agonist, this may have been insufficient for full manifestation of the efficacy on insulin sensitivity or lipid metabolism. Alternatively, it is possible that clinical dose of telmisartan does not express the PPARγ agonist effect in vivo [32]. This assumption does not conflict with our result of body weight decrease found in the telmisartan group because the PPARγ activation usually induces body weight increase.

One study limitation should be noted. Appetite conditions, food intake in terms of total calories, and physical activity in each patient were not precisely monitored. These factors can all directly affect body weight. However, no drug adverse events such as gastrointestinal disturbance or effects likely to reduce daily activity were observed in the final analyzed groups.

In conclusion, telmisartan decreased body weight while increasing serum adiponectin levels in hypertensive patients with glucose intolerance. Candesartan did not achieve similar improvements in these patients. Among ARBs, telmisartan may have a larger impact on the pathogenesis of obesity-related diseases that can lead to cardiovascular disorders.

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