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Telmisartan Improves Lipid Metabolism and Adiponectin Production But Does Not Affect Glycemic Control in Hypertensive Patients With Type 2 Diabetes

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ABSTRACT

Angiotensin II receptor blockers as a class are reported to act as insulin sensitizers. Of these, telmisartan has been shown to have additional unique peroxisome proliferator–activated receptor-gamma–mediated, insulin-sensitizing properties. In this study, investigators explored the effects of telmisartan on glycemic control and lipid metabolism in hypertensive patients with type 2 diabetes who had switched to telmisartan from another angiotensin II receptor blocker. The study subjects were 42 hypertensive outpatients with type 2 diabetes who were being treated with candesartan 8 mg/d and who agreed to switch to treatment with telmisartan 40 mg/d. Relevant laboratory variables were measured 6 mo before treatment switching, at the time of switching, and 6 mo after switching. No significant differences were noted in blood pressure, body mass index, or glycosylated hemoglobin among subjects before and after therapy was switched. No adverse reactions such as edema or hepatic toxicity were noted. No significant changes in fasting plasma glucose, fasting insulin, HOMA-R (insulin resistance as measured by the homeostasis model), preheparin lipoprotein lipase mass, high-density lipoprotein cholesterol, and free fatty acids were noted. Triglyceride levels

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were significantly decreased, however, and adiponectin levels were significantly increased (8.1±3.1 μg/mL at switching; 8.6±3.0 μg/mL 6 mo after switching; $P<.01$) after the switch to telmisartan therapy. Study results show that telmisartan did not affect glycemic control, but it improved lipid metabolism and adiponectin production in patients with type 2 diabetes, suggesting that AT_1-receptor antagonism and selective peroxisome proliferator–activated receptor-gamma activation by telmisartan combine to account for observed effects on lipid metabolism and adiponectin production.

Keywords: telmisartan; adipocyte; adiponectin; insulin resistance; hypertriglyceridemia

INTRODUCTION

Recent reports suggest that angiotensin II receptor blockers (ARBs) can suppress the onset of diabetes mellitus,[1-3] and that the renin-angiotensin system (RAS) is implicated in the onset of type 2 diabetes mellitus in patients with hypertension. It is assumed that angiotensin II inhibits the intracellular insulin–signaling pathway at the levels of insulin receptor substrate-1 and phosphatidylinositol-3 kinase in vascular smooth muscle cells. In addition, angiotensin II–induced increases in oxidative stress are assumed to act antagonistically on the intracellular insulin–signaling pathway. In this context, ARBs are thought to eliminate the effects of angiotensin II by blocking the AT_1 receptors, thereby improving insulin resistance.[4,5] It is also assumed that angiotensin II suppresses the differentiation of adipocytes and increases the number of enlarged adipocytes,[6,7] and ARBs promote the differentiation and recruitment of pre-adipocytes and increase the number of small, insulin-sensitive adipocytes.[8] Suppression of the AT_1 receptor–mediated action of angiotensin II that induces insulin resistance by directly blocking these receptors is considered a class effect of ARBs. In this regard, it is suggested that, unlike other ARBs, telmisartan may have peroxisome proliferator–activated, receptor-gamma (PPAR-γ)–mediated, insulin-sensitizing properties.[9,10] In this study, investigators studied the effects of telmisartan on glycemic control and lipid metabolism in hypertensive patients with type 2 diabetes who switched to telmisartan from another ARB.

PATIENTS AND METHODS

Patients

The study subjects were 42 hypertensive patients with type 2 diabetes who were being treated with candesartan 8 mg/d who agreed to switch to treatment with telmisartan 40 mg/d. Clinical characteristics of study patients are shown in Table 1. Treatments these patients received for diabetes included diet therapy alone in 18, oral hypoglycemic agents in 20, and insulin therapy in 4 patients. All patients had received nutritional counseling and had been encouraged to exercise 6 mo before switching therapy to telmisartan. Calcium channel blockers were given to 22 of 42 patients 6 mo before the switch to telmisartan therapy. Patients receiving oral thiazolidinedione derivatives or fibrates, those with a history of ischemic heart disease

or stroke, patients whose glycemic status or blood pressure was poorly controlled, and those whose medication for diabetes mellitus, hyperlipidemia, or hypertension had been changed, other than the switch to telmisartan, were excluded from the study. The present study was conducted with the approval of the ethics committee of the National Hospital Organization at Utsunomiya National Hospital, and all subjects provided informed consent to the study protocol.

Table 1. Clinical Characteristics of Patients

Patients, N	42
Sex, male/female	15/27
Age, y	51.8±27.2
BMI, kg/m^2	26.9±4.9
Duration of diabetes, y	10.7±6.9
Treatment of diabetes mellitus, n	
Diet alone	18
OHA	20
α-GI	4
SU	16
Insulin	4
Treatment of hypertension	
ARB before switching to telmisartan	
Candesartan	42
Combination with CCB	22
Treatment of hyperlipidemia	
Statins	17

OHA=oral hypoglycemic agents; α-GI=α-glucosidase inhibitors; CCB=calcium channel blocker.

Protocol

Blood pressure, body weight, fasting plasma glucose, and glycosylated hemoglobin (HbA_{1c}) were measured every month. Fasting plasma insulin, lipid (total cholesterol [TC], triglyceride [TG], high-density lipoprotein cholesterol [HDL-C], free fatty acid [FFA]), preheparin lipoprotein lipase (LPL) mass, adiponectin, and high-sensitive C-reactive protein (hs-CRP) levels were measured at appropriate times. The estimation of insulin resistance was based on a homeostasis model assessment (HOMA-R), as described by Matthews et al.[11] Low-density lipoprotein cholesterol (LDL-C) concentration was estimated through application of the Friedewald formula to TC, TG, and HDL-C measurements when TG levels were below 400 mg/dL. Blood pressure was measured with subjects in a seated position after at least 5 min of

rest. Body mass index (BMI, kg/m^2) was calculated on the basis of current weight and height. Relevant laboratory variables were used for the statistical analyses performed 6 mo before switching, at the time of switching, and 6 mo after switching to telmisartan therapy. As for fasting insulin levels and HOMA-R, patients who were receiving insulin therapy were excluded from the analyses.

Plasma glucose levels were determined through glucose dehydrogenase methods. HbA_{1c} was measured by cation-exchange high-performance liquid chromatography (Bio-Rad Laboratories, Hercules, Calif, USA). Serum lipids (TG, FFA, TC, and HDL-C) were measured enzymatically with the use of enzyme reagents (L-Type TG H, Wako Pure Chemicals, Osaka, Japan; NEFA-SS, Eiken Chemical, Tokyo, Japan; L-Type CHO H, Wako Pure Chemicals, Osaka, Japan; Cholestest N HDL, Daiichi Pure Chemicals, Tokyo, Japan). Preheparin LPL mass was measured by sandwich enzyme-linked immunosorbent assay (ELISA) with the use of a specific monoclonal antibody against bovine milk LPL, as described by Kobayashi et al.[12] For the assay, a kit from Daiichi Pure Chemicals (Tokyo, Japan) was used. Insulin and adiponectin levels were determined with the use of commercial enzyme immunoassay kits (LS Eiken Insulin Kit, Eiken Chemical, Tokyo, Japan; Adiponectin ELISA Kit, Otsuka, Tokushima, Japan). hs-CRP was measured through latex nephelometry assay (N High Sensitivity CRP, Dade Behring, Marburg GmbH, Marburg, Germany).

Statistical Analysis

For statistical analysis, all numeric values were represented as means±SD (standard deviation). The paired *t* test was used to test for significance of differences in values obtained at the time of switching therapy and 6 mo after switching therapy to telmisartan ($P<.05$).

RESULTS

No patients dropped out during the follow-up period. No remarkable changes in blood pressure, body weight, fasting plasma glucose (FPG), and HbA_{1c} levels were noted during the observation period. No significant differences were reported in all relevant laboratory variables 6 mo before switching and at the time of switching (Table 2). Moreover, no significant differences in BMI, HbA_{1c}, FPG, fasting immunoreactive insulin (FIRI), or HOMA-R values were noted at the time of switching and 6 mo after switching to telmisartan (Table 2). No adverse reactions such as edema, cardiac failure, or hepatic toxicity were described. No significant changes were observed in preheparin LPL mass, TC, HDL-C, and FFA at the time of switching and 6 mo after switching to telmisartan (Table 2). TG levels (mg/dL) were significantly decreased (147±48 at switching; 127±46 6 mo after switching; $P<.01$), however, and adiponectin levels were significantly increased (8.1±3.1 µg/mL at switching; 8.6±3.0 µg/mL 6 mo after switching; $P<.05$) after therapy was switched.

Table 2. Laboratory Test Findings 6 Mo Before Switching, at the Time of Switching, and 6 Mo After Switching Therapy to Telmisartan

	6 Mo Before Switching	At the Time of Switching	6 Mo After Switching to Telmisartan
Blood pressure, mm Hg	132±9/ 80±7	133±14/ 82±8	129±10/ 81±6
BMI, kg/m^2	27.0±5.0	26.9±4.9	27.0±4.6
HbA_{1c}, %	6.9±1.1	6.9±1.3	6.9±1.3
FPG, mg/dL	136±31	134±30	137±31
FIRI, μU/mL	10.3±5.4	10.8±6.4	11.2±6.0
LPL, mg/dL	52.6±19.3	51.1±18.6	52.1±16.9
HOMA-R	3.5±1.9	3.8±2.7	3.9±2.6
TC, mg/dL	209±37	202±39	197±32
LDL-C, mg/dL	123±30	118±37	113±33
HDL-C, mg/dL	56±14	55±14	58±17
TG, mg/dL	149±55	147±48	127±46*
FFA, mEq/mL	0.64±0.30	0.59±0.23	0.64±0.27
Adiponectin, μg/mL	8.2±3.8	8.1±3.1	8.6±3.0†
hs-CRP, ng/mL	3868±5408	4266±6388	5210±9588

*P<.01, †P<.05, vs values at the time of switching.

DISCUSSION

Study results show that telmisartan did not affect glycemic control, but it did improve lipid metabolism and adiponectin production in hypertensive patients with type 2 diabetes. The beneficial effects of telmisartan on insulin resistance and lipid metabolism as compared with other non–PPAR-γ–activating ARBs have been reported in an animal experiment[9] and in a number of clinical studies.[13-15] Data show no significant changes in the insulin resistance indicator of HOMA-R or in glycemic control associated with switching therapy to telmisartan. The reason for this is unclear, but it is assumed that in subjects with type 2 diabetes mellitus with fasting blood glucose levels of about 135 mg/dL before switching to telmisartan, HOMA-R may be too high to be an accurate indicator of insulin resistance. This could be due at least in part to the fact that most subjects who were taking oral hypoglycemic agents were sulfonylurea (SU) users.

With regard to the effects of ARBs on lipid metabolism, olmesartan has been reported to improve insulin resistance and decrease TG and FFA in fructose-fed rats.[16] When

no significant changes are observed in LPL, olmesartan likely suppresses the overproduction of TG in the liver. Although angiotensin II is known to suppress the differentiation of adipocytes and to increase the number of large adipocytes,[6,7] olmesartan has also been reported to downsize adipocytes in fructose-fed rats,[8] suggesting that the downsizing of adipocytes by olmesartan leads to a decrease in the quantity of FFAs released from adipocytes on lipolysis; thus, entry of FFA into the liver is reduced, and TG synthesis in the liver is decreased, thereby accounting for the predominant decrease in very-low-density lipoproteins. The investigators believe that this adipocyte downsizing leads to increased production of adiponectin within adipocytes.

On the other hand, of all the ARBs, telmisartan has been suggested to have not only AT_1-receptor antagonism but also PPAR-γ–mediated ability to improve insulin resistance. This PPAR-γ–mediated effect, which is unique to telmisartan, can be explained by its chemical structure–related properties and its lipid solubility.[9] PPAR-γ is a transcription factor that is expressed in adipocytes,[17] and it has been suggested that, as PPAR-γ activity is increased, adipocytes become better differentiated and more highly activated, the ability of adipose tissue to accumulate fat is increased, the secretion of TNF-α and resistin is suppressed, and the production of adiponectin is promoted,[18,19] all of which leads to improvement in insulin resistance.

In support of these observations, the present study demonstrated significant decreases in TG levels and significant increases in adiponectin levels after the switch to telmisartan, as compared with those associated with the use of the non–PPAR-γ–activating ARB candesartan. It has been reported that in an experimental system in which 3T3-L1 adipocytes were used, the PPAR-γ–activating ARB telmisartan increased adiponectin protein expression in adipocytes, but the non–PPAR-γ–activating ARB eprosartan showed no such effect.[20] In agreement with these experimental results, the findings of the present study appear to suggest that telmisartan can induce adiponectin protein expression independently of its effects on the RAS of adipocytes or its AT_1-receptor antagonism.

It has also been suggested that activation of adipocytes, while improving insulin resistance, can facilitate enlargement of adipocytes when the energy supply is excessive. It was previously reported that the administration of troglitazone, a thiazolidinedione derivative, as a full PPAR-γ agonist led to improved insulin resistance and glycemic control and to marked increases in body weight and subcutaneous fat mass in patients with type 2 diabetes mellitus.[21] In contrast, telmisartan, which is known to have the same PPAR-γ–mediated effect, did not cause weight gain even after the switch was made from the non–PPAR-γ–activating ARB candesartan. Although the reason for this is unclear, it has been suggested that activation by telmisartan of PPAR-γ is selective but less potent, and thus is less likely to cause weight gain than are thiazolidinediones.[22] Moreover, telmisartan was recently reported to increase energy expenditure and to protect against diet-induced weight gain in high-fat, high-carbohydrate–fed rats[23] and to increase the expression of uncoupling protein 1 in the brown adipose tissue of diet-induced obese mice.[24]

It was thus concluded that telmisartan improved lipid metabolism through AT_1-receptor antagonism and via selective PPAR-γ activation, thereby increasing adiponectin production without causing weight gain.

The results reported here suggest that AT_1-receptor antagonism and selective PPAR-γ activation by telmisartan combine to account for observed effects on lipid metabolism and adiponectin production.

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