Effects of Telmisartan on Insulin Resistance in Japanese Type 2 Diabetic Patients

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Abstract

Objective PPARγ agonists are widely used in type 2 diabetic patients to reduce insulin resistance. Recently, telmisartan, an AT1 receptor antagonist, was reported to function as a partial agonist of PPARγ based on in vitro experiments. The aim of the present study was to investigate whether the PPARγ enhancing activity of telmisartan is exerted clinically in diabetic patients.

Methods We compared the effects of telmisartan with those of candesartan, on insulin sensitivity, the serum levels of various adipocytokines and oxidative stress.

Patients In total, 85 Japanese type 2 diabetic patients with hypertension, maintained on 8 mg per day of candesartan, were randomly assigned to the TM group (candesartan switched to 40 mg of telmisartan, n=38) or the CD group (no treatment change, n=47).

Results After 3 months, oxidized lipids were significantly decreased only in the TM group. Although the homeostasis assessment model of insulin resistance (HOMA-R) tended to be improved and serum concentrations of HDL-cholesterol and HMW adiponectin tended to be increased only in the TM group, these alterations were too small to be significant by unpaired t-test. Interestingly, in subgroup analysis, the alterations of HOMA-R, serum concentrations of oxidized lipids, and HMW adiponectin were more apparent in obese TM group subjects and the changes reached statistical significance.

Conclusion Switching from candesartan to telmisartan in obese subjects increases serum adiponectin and improves both insulin resistance and oxidative stress, while these effects were not statistically apparent in the total patient population. These results support the idea that telmisartan exerts its PPARγ enhancing activity clinically in obese type 2 diabetic patients.

Key words: insulin resistance, telmisartan, PPARγ, adiponectin

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Introduction

Metabolic syndrome (MetS) has been defined as a cluster of clinical conditions, including central obesity, insulin resistance, dyslipidemia and hypertension (1). In particular, the association of diabetes with hypertension increases the risk of cardiovascular morbidity and mortality (2). There is widespread agreement that the renin-angiotensin system (RAS) plays an important role in the pathogenesis of insulin resistance and cardiovascular diseases (CVD) in diabetes and large clinical trials have demonstrated substantial benefits of the blockade of this system for end-organ protection (3-5). Thus, interruption of the RAS with angiotensin II type 1 receptor blockers (ARBs) has recently been shown to prevent the onset of diabetes, as well as to reduce CVD in diabetic patients with hypertension (6, 7).

A nuclear hormone receptor, peroxisome proliferator-activated receptor-γ (PPARγ), plays a pivotal role in the regulation of insulin sensitivity (8). PPARγ activated by its ligands, insulin-sensitizing thiazolidinediones (TZD), functions as a transcriptional regulator of multiple genes involved in carbohydrate and lipid metabolism, leading to reduced insulin resistance in type 2 diabetic patients. Notably,
the up-regulation of serum adiponectin by TZD ameliorates type 2 diabetes and inhibits atherosclerosis (9). Thus, enhancing PPARγ activity is one of the promising therapeutic strategies for patients with type 2 diabetes or MetS. Recently, telmisartan, one of the ARBs, was demonstrated to function as a partial agonist of PPARγ in in-vitro experiments (10-12) and a structural similarity has actually been found between telmisartan and pioglitazone (10). In addition, telmisartan was reported to reduce glucose, insulin and triglyceride levels in animal models of MetS (10). Given these dual effects, telmisartan is expected to be useful in the treatment of both hemodynamic and biochemical aspects of type 2 diabetes.

Herein, to investigate whether the PPARγ enhancing activity of telmisartan is exerted clinically in diabetic patients, we compared the effects of telmisartan with those of candesartan, on insulin sensitivity, the serum levels of various adipocytokines and oxidative stress. The aim of the present study was to clarify the actual clinical effects of telmisartan in reducing insulin resistance, given that the apparently unique characteristic of telmisartan is its capacity to enhance PPARγ activity.

Methods

Study design and methods

In total, 85 Japanese type 2 diabetic patients with hypertension, maintained on 8 mg per day of candesartan, were randomly assigned to the TM group (candesartan treatment switched to 40 mg of telmisartan, n=38) or the CD group (no treatment change, n=47). All had been treated with candesartan for at least six months. The patients treated with oral hypoglycemic agents included 40 (TM: 17, CD: 23) on sulfonylureas, 32 (TM: 14, CD: 18) on metformin and 21 (TM: 11, CD: 10) on alpha-glucosidase inhibitors. We excluded patients treated with insulin and TZD. The percentages of patients receiving each of these oral hypoglycemic agents did not differ significantly between the CD and TM groups.

Patients with impaired hepatic function (serum AST/ALT >40) or renal function (serum creatinine >1.5) were excluded from both studies. Treatments with other drugs including hypoglycemic agents remained unchanged throughout the three-month study period. The following were measured by standard laboratory techniques at baseline and at 3 months after the initiation of treatment; serum total cholesterol, HDL-cholesterol, triglycerides, fasting plasma glucose (FPG), fasting insulin (IRI), HbA1C and urinary microalbumin. In addition, indexes that are considered to reflect insulin resistance (HOMA-R = FPG X IRI/405) were calculated. At baseline and at initiation of this study, body weight and blood pressure (SBP/DBP) were measured. We also measured several adipocytokines and, as an oxidative stress marker, the serum concentration of super-oxidized lipids. Serum concentrations of these adipocytokines were measured using commercially available procedures, i.e., serum adiponectin (both total and high molecular weight [HMW]) was measured by enzyme-linked immunosorbent assay (Otsuka Pharmaceutical, Tokyo, Japan), serum leptin by radioimmunoassay (Linco Research, St. Charles, MO), and serum TNFα by enzyme immunoassay (Golden Bridge Internal Inc., Lynnwood, WA). Serum super-oxidized lipids were measured using the hemoglobin-methylene blue (Hb-MB) method. All patients gave written informed consent prior to their participation in these studies.

Statistical analysis

Data are presented as means ± SEs. Log transformation of continuous variables was used when needed to satisfy distributional requirements for parametric tests. Differences in clinical characteristics were assessed using the paired or unpaired Student’s t test and a p value <0.05 was considered statistically significant. The Extended Fisher’s exact test was used to examine the significance of associations between two variables in a 2×2 contingency table. Statistical analyses were performed using Stat View software (Version 5.01; SAS Institute, Cary, NC).

Results

Table 1 shows changes in metabolic parameters and serum concentrations of adipocytokines in each group. Before treatment, there were no significant differences in these parameters between the two groups including the proportion of obese (BMI >25) subjects (20 and 18 obese subjects, respectively, in the CD and TM groups). A significant reduction of HOMA-R (from 3.81 to 3.49, p<0.05) was observed only in the TM group, while the parameters reflecting glycemic control (FPG and HbA1C) were not altered in either group. Regarding lipid profiles, a significant HDL-cholesterol increase (p<0.01) was observed, while triglycerides were decreased, though not significantly, in the TM group. We observed significant increases in serum total and HMW adiponectin concentrations only in the TM group (Table 1). However, these changes were only significant when analyzed using the paired t-test, i.e. not with the unpaired t-test. Thus, the effects of telmisartan as compared with candesartan are likely to be small and restricted. The serum super-oxidized lipid concentration was significantly decreased only in the TM group (p=0.04), according to the unpaired t-test. There were no other major changes in adipocytokines. As shown in Figure 1, which presents individual changes in serum adiponectin concentrations to facilitate understanding, four subjects in the TM group showed remarkable increases in adiponectin after treatment. No other subjects in the TM group showed significant changes in adiponectin concentrations. To investigate whether telmisartan exerts different effects in obese versus non-obese subjects, we analyzed five parameters, which were significantly changed (paired t-test) by telmisartan treatment, by dividing the CD and TM groups into obese and non-obese subjects. As shown in Ta-
Table 1. Changes in Metabolic Parameters and Adipocytokines in Each Group

|                          | CD Group (n=47) | TM Group (n=38) |
|--------------------------|----------------|-----------------|
|                          | At baseline    | After treatment | At baseline    | After treatment |
| Male/Female              | 29/18          |                 | 22/16          |                 |
| Age (years)              | 61.7±1.7       |                 | 62.7±1.6       |                 |
| Duration of candesartan  | 24.3±4.5       |                 | 21.4±6.5       |                 |
| treatment (months)       |                |                 |                |                 |
| BMI (kg/m²)              | 25.9±0.7       | 26.0±0.7        | 25.9±0.7       | 26.2±0.7        |
| Body Weight (kg)         | 66.2±2.0       | 66.5±2.0        | 66.6±2.2       | 67.1±2.2        |
| SBP (mmHg)               | 132.7±3.0      | 131.0±2.9       | 135.1±1.8      | 135.0±2.1       |
| DBP (mmHg)               | 80.9±1.2       | 81.9±1.4        | 82.4±1.0       | 81.8±1.4        |
| Urinary albumin (mg/g Cr) | 35.7±7.5      | 41.1±7.8        | 30.6±6.0       | 38.6±6.7        |
| FPG (mg/dL)              | 140.2±5.1      | 146.4±4.7       | 139.0±4.1      | 135.2±3.7       |
| HbA1C (%)                | 7.23±0.19      | 7.32±0.17       | 7.07±0.13      | 7.20±0.14       |
| Fasting IRI (IU/mL)      | 11.3±0.8       | 12.8±1.5        | 10.4±1.2       | 9.3±0.9         |
| HOMA-R                   | 3.65±0.18      | 3.98±0.15       | 3.81±0.12      | *3.49±0.10      |
| Triglycerides (mg/dL)    | 163.7±24.1     | 163.5±18.0      | 171.5±16.8     | 160.8±17.3      |
| T-Chol (mg/dL)           | 197.4±7.1      | 202.3±6.6       | 193.5±4.9      | 197.1±7.7       |
| HDL-cholesterol (mg/dL)  | 46.1±1.3       | 47.9±1.4        | 44.9±1.6       | *49.3±1.9       |
| Total adiponectin (µg/mL)| 7.50±0.82      | 7.56±0.82       | 8.05±0.72      | *8.96±0.82      |
| HMW adiponectin (µg/mL)  | 1.92±0.21      | 1.94±0.19       | 2.06±0.22      | *2.30±0.21      |
| Leptin (ng/dL)           | 9.8±1.5        | 9.9±1.7         | 10.0±1.0       | 10.3±1.1        |
| TNFα (pg/dL)             | 5.9±0.4        | 5.8±0.4         | 5.7±0.5        | 5.5±0.6         |
| Super-oxidized lipid (nmol/mL) | 0.75±0.08 | 0.79±0.12      | 0.85±0.12      | **0.61±0.04    |

Data are presented as means ± SE. *P value <0.05 by paired t-test **P value <0.05 by unpaired t-test

Table 2, serum concentrations of total and HMW adiponectin, HOMA-R and super-oxidized lipids exhibited far more significant changes in obese TM group subjects than in the TM group as a whole, while no significant alterations were observed in non-obese TM group subjects. These results were obtained with both the paired and the unpaired t-test. In addition, these five parameters were not significantly changed in either the obese or the non-obese CD group subjects. These results indicate that telmisartan has a greater impact on the metabolic profiles of obese subjects than on those of non-obese subjects.

Discussion

In comparison with candesartan, we found telmisartan to enhance insulin sensitivity, increase serum adiponectin concentrations and decrease super-oxidized lipids only in obese subjects. These effects were not apparent in the total subject population. Based on the previously published observations that PPARγ is most abundant in adipose tissue and that its clinical pharmacological actions are more striking and effective in obese subjects (13-15), our results support the idea that telmisartan has a PPARγ stimulating effect under clinical conditions. A number of previous reports clinically demonstrated the HDL-cholesterol increasing effects of the PPARγ agonist, glitazone (16). However, the precise mechanism of action remains unknown. This effect may be a secondary one following improvements in insulin resistance. We observed no marked HDL-cholesterol increasing effect of telmisartan. Oxidized lipids, an oxidative stress marker, selectively reflect the amount of lipid peroxide (LPO) produced in contact with excessive ROS. It was previously reported that pioglitazone reduced LPO, which was increased in diet-induced obesity (17). Thus, these metabolic effects of telmisartan may be at least partially attributable to its PPARγ-enhancing activity (18-20). However, it is probably too early to reach this conclusion. Another possible explanation for these results is that the lipophilicity of telmisartan is so high that it may provide more useful protection against oxidative stress than other ARBs (4, 21). Thus, the increases in adiponectin and insulin sensitivity can also be explained by this effect of telmisartan (22). In addition to these properties of telmisartan, i.e. PPARγ-enhancing activity and high lipophilicity, many other biochemical properties have been demonstrated by in-vitro experiments (23-25). Thus, the present results are likely attributable to various pleiotropic effects of telmisartan, not simply to its PPARγ-enhancing activity.

To date, many clinical studies have focused on the metabolic effects of telmisartan (26-28). However, results obtained to date, including those of the present study, are not consistent. For example, one study demonstrated that switching from valsartan or candesartan to telmisartan improved glycemic control in hypertensive patients with type 2
diabetes (28), while another found the effects of telmisartan and losartan to be neutral (27). This discrepancy may be explained by differences in study population background factors including race, BMI and glycemic control levels. Though earlier studies are limited by relatively small patient numbers and treatment durations, a further large-scale trial or a cross-over study is anticipated to clarify these issues and resolve the discrepancies.

In conclusion, our study revealed that switching from candesartan to telmisartan increased serum adiponectin and reduced both insulin resistance and oxidative stress in obese subjects, but not in the total subject population. These results may support the idea that telmisartan exerts its PPARγ enhancing activity clinically in obese type 2 diabetic patients. These unique effects of telmisartan on metabolic parameters are potentially beneficial, especially in type 2 diabetic patients with obesity or MetS, for preventing atherosclerosis and CVD.

Figure 1. Changes in plasma adiponectin concentrations with 3-month candesartan or telmisartan treatment in individual patients.

Table 2. Changes in Four Parameters in CD and TM Groups with Versus without Obesity

| CD group | Non-obese (n=27) | Obese (n=20) |
|----------|-----------------|--------------|
|          | At baseline     | After treatment | At baseline | After treatment |
| HOMA-R   | 2.30 ± 0.31     | 2.65 ± 0.47   | N.S.        | 4.64 ± 1.11 | 4.95 ± 0.96 | N.S. |
| HDL-chol (mg/dL) | 47.4 ± 3.0    | 49.4 ± 2.8 | N.S.        | 41.9 ± 2.4 | 43.5 ± 2.1 | N.S. |
| Total adiponectin (µg/dL) | 9.4 ± 1.1 | 9.5 ± 0.9 | N.S.        | 7.0 ± 1.2 | 7.2 ± 1.3 | N.S. |
| HMW adiponectin (µg/dL) | 2.4 ± 0.3 | 2.4 ± 0.2 | N.S.        | 1.8 ± 0.3 | 1.9 ± 0.3 | N.S. |
| Super-oxidized lipid (nmol/mL) | 0.49 ± 0.05 | 0.53±0.05 | N.S.        | 0.92 ± 0.13 | 0.96 ± 0.14 | N.S. |

| TM group | Non-obese (n=20) | Obese (n=18) |
|----------|-----------------|--------------|
|          | At baseline     | After treatment | At baseline | After treatment |
| HOMA-R   | 2.42 ± 0.43     | 2.73 ± 0.37   | N.S.        | 4.84 ± 1.09 | 4.27 ± 0.80 | p<0.01 |
| HDL-chol (mg/dL) | 46.2 ± 3.0    | 53.2 ± 3.6 | N.S.        | 40.7 ± 2.4 | 43.6 ± 2.8 | N.S. |
| Total adiponectin (µg/dL) | 9.8 ± 1.2 | 10.1 ± 0.9 | N.S.        | 7.5 ± 1.2 | 8.5±1.3 | p<0.01 |
| HMW adiponectin (µg/dL) | 2.5 ± 0.3 | 2.6 ± 0.2 | N.S.        | 1.9 ± 0.3 | 2.2 ± 0.3 | p<0.01 |
| Super-oxidized lipid (nmol/mL) | 0.59 ± 0.05 | 0.61±0.07 | N.S.        | 1.09 ± 0.27 | 0.67 ± 0.08 | p<0.01 |

Data are presented as means ± SE. *P value <0.01 by paired t-test
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