Effects of Telmisartan Therapy on Metabolic Profiles and Serum High Molecular Weight (HMW)-Adiponectin Level in Japanese Male Hypertensive Subjects with Abdominal Obesity

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Aim: Telmisartan, an angiotensin II receptor blocker (ARB), was reported to have partial peroxisome proliferator-activated receptor gamma (PPARγ) activity in vitro. Also, adipocyte-derived protein adiponectin, especially its high molecular weight (HMW) form, has been reported to have beneficial effects on insulin resistance and atherosclerosis. We investigated the effects of 3-month telmisartan therapy on various metabolic parameters, including serum HMW adiponectin and high-sensitivity C-reactive protein (hs-CRP) levels in male hypertensive subjects with abdominal obesity.

Methods: This study included 19 Japanese male hypertensive subjects, aged 51.2 ± 7.6 (mean ± SD) years, and body mass index 27.7 ± 4.1 kg/m². In these subjects, 14 were naive to telmisartan treatment (40.0 ± 15.7 mg daily), and 5 were changed from other ARBs to telmisartan. Serum HMW adiponectin concentration was assayed using HMW-selective ELISA kit.

Results: In all 19 subjects, systolic/diastolic blood pressure (BP) decreased from 153/98 to 134/85 mmHg (p < 0.001 for both). Serum HMW-adiponectin level increased from 2.06 ± 0.81 to 2.40 ± 0.96 μg/mL (+16.4%, p = 0.017). Body weight, glucose, insulin, lipids and hs-CRP did not change during the study period, and there were no adverse effects in any subject. In the newly administered group (n = 14), the results were almost the same: BP decreased from 155/98 to 134/84 mmHg (p = 0.0015 for both), and serum HMW-adiponectin level increased from 2.07 ± 0.68 to 2.39 ± 0.99 μg/mL (+15.5%, p = 0.089).

Conclusion: These data suggest that telmisartan therapy is efficient for controlling BP, and may exert beneficial effects on HMW adiponectin in male hypertensive subjects with abdominal obesity.


Key words: Obesity, Insulin resistance, High-sensitivity C-reactive protein, PPAR gamma

Introduction

Obesity is the most common cause of type 2 diabetes mellitus, hypertension, dyslipidemia, and atherosclerotic vascular diseases (ischemic heart disease, cerebro-vascular disease and peripheral artery disease). In recent years, the prevalence of obesity has increased markedly and become a major health priority world-wide, including Japan. In the treatment of hypertension, it is very important to use anti-hypertensive agents which ameliorate, rather than worsen, insulin resistance. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are such candidates, because these drugs have been reported to have favorable effects on insulin sensitivity¹,²) and to reduce the incidence of new-onset diabetes mellitus in clinical trials³,⁴). Telmisartan, an ARB, is widely used as an anti-hypertensive agent and reported to have partial activity of peroxisome proliferator-activated receptor gamma (PPARγ) in vitro⁵,⁶).

Accumulating evidence has revealed that adipose tissue is not only an energy storage organ, but also a highly active endocrine organ⁷). Moreover, it is well
established that adipokines, a variety of biologically active peptides secreted from adipose tissue, play crucial roles in the pathophysiology of obesity-related complications. Among the many known adipokines, adiponectin has attracted considerable attention and has been shown to be an anti-diabetic, anti-inflammatory and anti-atherogenic cytokine. We and other groups have reported that serum adiponectin levels correlate negatively with adiposity variables and insulin resistance. Genetic variation of the adiponectin gene, especially the single nucleotide polymorphism (SNP) 276G>T, has been reported to relate to type 2 diabetes mellitus and carotid atherosclerosis in Japanese subjects.

Furthermore, prospective studies have shown that low adiponectin levels predict the development of type 2 diabetes and cardiovascular diseases. In addition, adiponectin exists in a variety of multimer complexes in circulating blood, i.e., low-molecular weight trimers, middle-molecular weight hexamers and high molecular weight (HMW) 12- to 18-mer. Recent studies have revealed that the HMW form is the active form of adiponectin and a useful biomarker for insulin resistance. We have previously reported that a thiazolidinedione, pioglitazone, increases the serum adiponectin level up to 3-fold in male type 2 diabetic patients, using the monoclone antibody IH7, which is reported to react specifically with the HMW form of adiponectin.

In the present study, we investigated the effects of 3-month treatment with 20–60 mg/day telmisartan in male hypertensive subjects with abdominal obesity on various metabolic parameters, including body weight, blood pressure, plasma glucose, serum insulin, lipids, HMW adiponectin and high-sensitivity C-reactive protein (hs-CRP).

**Subjects**

This study included 19 Japanese male hypertensive subjects, aged 51.2 ± 7.6 (mean ± SD) years, and body mass index (BMI) 27.7 ± 4.1 kg/m², with waist circumference at the umbilical level ≥85.0 cm (Table 1). In these subjects, 14 were naive to telmisartan treatment (40.0 ± 15.7 mg daily). In the other five subjects, anti-hypertensive agents were changed from another ARB to telmisartan (40 mg daily): changed from losartan (50 mg/day) in three patients, and from candesartan (8 mg/day) in two patients. None of the subjects had been treated with other anti-hypertensive agents, and two subjects had been treated with oral anti-diabetic medicine (glibenclamide and glimepiride, respectively).

**Table 1. Baseline patient profile in 19 male hypertensive subjects with abdominal obesity**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.2 ± 7.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.5 ± 5.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.8 ± 15.0</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.7 ± 4.1</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>94.6 ± 9.5</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>153 ± 15</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>98 ± 9</td>
</tr>
<tr>
<td>Dosage at 3 months (mg)</td>
<td>40.0 ± 13.3</td>
</tr>
</tbody>
</table>

BP, blood pressure. Data are n or the mean ± SD.

The present study was conducted according to the principles expressed in the Declaration of Helsinki 1975, as revised in 1983. Informed consent was obtained from each subject after a full explanation of the purpose, nature, and risk of all procedures used. The protocol was approved by the ethics review committee of the Health Center and the Department of Internal Medicine, School of Medicine, Keio University, Tokyo.

**Methods**

**Clinical Variables**

Height was measured to the nearest 0.1 cm. Weight was measured in light indoor clothing with shoes removed. BMI was calculated as weight in kilograms divided by height in meters squared.

**Biochemical Measurements**

Plasma glucose and serum lipids were assayed by routine automated laboratory methods, as described previously. Serum insulin concentration was measured by an enzyme immunoassay, using a commercially available kit (Tosoh, Tokyo), with intra- and inter-assay coefficients of variation (CVs) of 2.9–4.6% and 4.5–7.0%, respectively. The insulin resistance index was calculated based on homeostasis model assessment (HOMA-IR).

HMW adiponectin was measured using a commercially available kit (High molecular weight Adiponectin ELISA Kit; Fujirebio Inc., Tokyo). This ELISA system does not need a denaturing step, and the monoclonal antibody, IH7, is reported to react specifically with the HMW form of adiponectin. The dilution curve was parallel to the standard curve. Intra- and inter-assay CVs were 2.4–3.0% and 4.2–5.1%, respectively. Serum hs-CRP concentration was measured by...
nephelometry, a latex particle-enhanced immunoassay (N Latex CRP II; Dade Behring, Tokyo) with both intra- and inter-assay CVs of <5.0%. The assay could detect 0.005 mg/L CRP.

**Statistical Analysis**

Statistical analyses were performed using the SPSS® program for Windows (version 15.0-J; SPSS Japan Inc., Tokyo). *P* values <0.05 were considered to denote statistical significance. The Wilcoxon signed-rank test was used to compare parameters from before to 3 months after starting telmisartan therapy. Because serum insulin, HOMA-IR, triglycerides, HMW adiponectin, and hs-CRP levels were normally distributed after logarithmic transformation, we used logarithms of these data for the analyses.

**Results**

In all 19 subjects (Table 2), systolic blood pressure (SBP)/diastolic blood pressure (DBP) decreased from 153/98 mmHg to 134/85 mmHg (*p* <0.001 for both SBP and DBP). The serum HMW-adiponectin level increased from 2.06 ± 0.81 μg/mL to 2.40 ± 0.96 μg/mL (Fig. 1) (+16.4%, *p* =0.017). BMI, waist circumference, glucose, insulin, HOMA-IR, lipids and hs-CRP did not change from baseline to completion of the therapy. The change in the HMW-adiponectin level did not correlate with the change in SBP, that in DBP, or the dosage of telmisartan used in this study. There were no adverse effects, such as skin eruption or liver dysfunction, in any subject.

In the newly administered telmisartan group (*n* = 14), the results were almost the same: blood pressure decreased from 155/98 mmHg to 134/84 mmHg (*p* = 0.0015 for both SBP and DBP). The heart rate also decreased from 81 ± 12 beat/min to 74 ± 13 beat/min (*p* = 0.041), and the HMW-adiponectin level increased from 2.07 ± 0.68 μg/mL to 2.39 ± 0.99 μg/mL (+15.5%, *p* = 0.089), despite the increased tendency of the BMI. Also in the changed group (*n* = 5), blood pressure tended to decrease from 148/100 to 136/87 mmHg (*p* =0.138 and *p* =0.068, respectively). The serum HMW-adiponectin level increased from 2.02 ± 1.19 μg/mL to 2.40 ± 0.99 μg/mL (+18.8%, *p* =0.068).

**Discussion**

Adiponectin, also independently found as a gelatin-binding protein of 28 kDa (GBP28), is an adipocyte-specific secretory protein, and its HMW form has especially been reported to have beneficial effects on insulin resistance and atherosclerosis. The serum adiponectin level correlates well with insulin sensitivity and lipid metabolism. There have been many reports that adiponectin is related to the metabolic syndrome, type 2 diabetes, obesity, and coronary artery disease, and weight reduction.

**Table 2.** Effects of 3-month treatment with telmisartan (20–60 mg/day) on various metabolic parameters in 19 male hypertensive subjects with abdominal obesity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Baseline</th>
<th>3 Months</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>19</td>
<td>81.8 ± 15.0</td>
<td>82.3 ± 14.6</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>19</td>
<td>27.7 ± 4.1</td>
<td>27.9 ± 4.0</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>19</td>
<td>153 ± 15</td>
<td>134 ± 12</td>
<td>0.0003</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>19</td>
<td>98 ± 9</td>
<td>85 ± 7</td>
<td>0.0003</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td>19</td>
<td>81 ± 11</td>
<td>77 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>19</td>
<td>117 ± 36</td>
<td>119 ± 41</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin (μU/mL)</td>
<td>9</td>
<td>8.5 ± 3.5</td>
<td>10.1 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>9</td>
<td>2.50 ± 0.84</td>
<td>2.78 ± 1.42</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>19</td>
<td>225 ± 32</td>
<td>215 ± 33</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>19</td>
<td>215 ± 170</td>
<td>196 ± 112</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>19</td>
<td>134 ± 36</td>
<td>127 ± 27</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>19</td>
<td>48.2 ± 8.4</td>
<td>49.2 ± 8.9</td>
<td>NS</td>
</tr>
<tr>
<td>HMW adiponectin (μg/mL)</td>
<td>19</td>
<td>2.06 ± 0.81</td>
<td>2.40 ± 0.96</td>
<td>0.0173</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>7</td>
<td>0.407 ± 0.231</td>
<td>0.270 ± 0.167</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>19</td>
<td>0.82 ± 0.13</td>
<td>0.81 ± 0.12</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are the mean ± SD. *By Wilcoxon signed-rank test. NS, not significant (*p* >0.2); BP, blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; HDL, high-density lipoprotein; HMW, high molecular weight; hs-CRP, high-sensitivity C-reactive protein.
increases the adiponectin level in obese patients. Recent studies have demonstrated that the HMW multimer form of adiponectin is the active form of this protein; for example, the HMW form was the most active form in suppressing hepatic glucose production, and Kobayashi et al. reported that only HMW adiponectin selectively suppressed endothelial cell apoptosis.

Although telmisartan was reported to have partial PPARγ activity in vitro, its effects on metabolic parameters and serum adiponectin levels in clinical use are controversial. Furthermore, the HMW type of adiponectin levels in circulation have been measured in only a few reports so far: in one report, the HMW-adiponectin level was unchanged but, in another report, its level was increased after telmisartan treatment. In the present study, 3-month therapy with telmisartan (20–60 mg/day) induced good blood pressure control, and increased the serum HMW-adiponectin level even with a tendency toward increased body weight in male subjects with hypertension, although the glucose and lipid profiles, and serum hs-CRP level were not changed.

While the lack of a control group and a small sample size are major limitations of this study, there is a possibility that telmisartan therapy exerts beneficial effects, especially on HMW adiponectin in subjects with abdominal obesity. It is not clear whether these effects were mediated through partial PPARγ activity of telmisartan, because other metabolic parameters were unchanged in this study; however, the serum HMW-adiponectin level tended to increase even in the changed group in this study, and some reports suggest that telmisartan may be superior to valsartan or candesartan for the increase in adiponectin levels. Further studies with different ARB, age, sex and ethnicity, with a larger sample size and a prospective study design would clarify this important issue.

In conclusion, it is suggested that treatment with telmisartan is efficient for controlling blood pressure, and may exert beneficial effects by increasing the HMW-adiponectin level in male hypertensive subjects with abdominal obesity.

**Acknowledgments**

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We would like to disclose a possible conflict of interest as follows: Fujirebio Co., Tokyo (formerly Chugai Diagnostic Science Co., Tokyo) and Dr. Hirose have a partial patent concerning an HMW-adiponectin measurement kit. Dr. Saito has received a research grant from Astellas Pharma Inc., Tokyo.

**References**


7) Yamagishi S, Takeuchi M: Telmisartan is a promising cardiometabolic sartan due to its unique PPAR-gamma-inducing property. Med Hypotheses, 2005; 64:476-478


9) Erin EK, Jeffrey SF: Adipose tissue as an endocrine organ. J Clin Endocrinol Metab, 2004; 89:2548-2566


31) Miwa R, Nakamura T, Kihara S, Kumada M, Shibazaki S,