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Peroxisome Proliferator-activated Receptor Gamma Concentrations in Newly Diagnosed Hypertension Patients and the Metabolic Effects of Olmesartan

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Background and Aims. We undertook this study to investigate the effects of olmesartan treatment on PPAR-gamma (PPAR-γ) concentrations and metabolic syndrome (MetS) components in hypertensive (HT) patients.

Methods. The study included 46 newly diagnosed hypertensive patients and 30 healthy controls. All hypertensive patients were given 40 mg of olmesartan, and they were evaluated weekly in the first month and then twice weekly during follow-up visits. At the end of 3 months, MetS components were assessed and serum PPAR-γ transcription factor concentrations were again measured.

Results. MetS was noted in 80.4% of HT patients. Serum PPAR-γ transcription factor concentration were significantly lower in those with HT compared with the controls ($p = 0.005$). PPAR-γ concentrations of controls were 1.14-fold higher than hypertensive patients. HDL levels were significantly increased after treatment ($p = 0.004$), triglyceride, total cholesterol, fasting blood glucose (FBG), and LDL levels were significantly reduced ($p < 0.05$). There was a tendency toward increased PPAR-γ concentrations after treatment, but these were not statistically significant ($p = 0.154$).

Conclusions. Olmesartan treatment was found to generate beneficial effects on MetS parameters in HT patients but did not produce any significant increases in serum PPAR-γ transcription factor concentration.

Key Words: Peroxisome proliferator-activated receptor, Olmesartan.

Introduction

Hypertension (HT) is one of the components of metabolic syndrome (MetS), another public health problem that is increasingly becoming more prevalent worldwide (1). Among several components of MetS, insulin resistance plays a crucial role in its pathophysiology. MetS is characterized by abdominal obesity, high blood pressure, dyslipidemia, and impairment of glucose tolerance or hyperglycemia (2,3). Furthermore, cardiovascular morbidity and mortality is significantly increased in patients with MetS (4,5). As a whole, it also increases the risk of coronary artery disease (CAD), whereas each of its components also contributes to this increased risk (6). Antihypertensive drugs have diverse effects on metabolic factors and insulin resistance. In addition, plasma insulin levels are considerably higher with insulin resistance, which escalates angiotensin I receptor gene expression and the effects of angiotensin II. On the other hand, the effects of insulin on vascular endothelium are inhibited via several mechanisms by the increased angiotensin II levels. This can lead to a vicious cyle by further raising the insulin levels, resulting in an upsurge in HT, atherosclerosis, and insulin resistance (7).

Partial peroxisome proliferator-activated receptors (PPARs) belong to the nuclear receptor family (8). Similar to transcription factors, PPARs regulate the expression and production of many genes and influence glucose and

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lipid metabolism, vascular tonus, and inflammation (9). In particular, it has been hypothesized that PPAR-gamma (PPAR-γ) activation generates positive effects on glycemic control, insulin resistance, lipid metabolism, vascular tonus, and inflammation. Among several ARBs used in the treatment of HT, telmisartan, losartan, and high-dose irbesartan have been reported to increase PPAR-γ activity. However, the question whether this effect is a specific feature of only these molecules or whether it is all of the ARBs contain this dynamic has not been answered. Due to this dual effect, it has been suggested that ARBs can be used for the treatment of hemodynamic and biochemical features of MetS (10).

The aim of this study was to investigate the prevalence of MetS in newly diagnosed hypertensive patients as well as the effects of olmesartan on MetS parameters and PPAR-γ activity in these patients.

Patients and Methods

Patient Selection

Fifty newly and previously diagnosed treatment-naive hypertensive (HT) patients who were admitted to the Outpatient Internal Medicine Clinic of Ankara Diskapi Yildirim Beyazit Training and Research Hospital were initially included in this study. However, one dropped out due to noncompliance, and three did not attend for follow-up visits. Therefore, 46 patients were included in the final analysis. Diagnosis of HT was based on the criteria in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) (11). The patients were evaluated for the presence of MetS according to the ATP III diagnostic criteria (4), and those found to have any contraindications for the use of olmesartan on physical examination and routine biochemical tests were excluded from the study. Additionally, patients with renal, hepatic, or cardiac failure, those known to have had a previous allergic reaction to olmesartan, those receiving immunosuppressive treatment, those who may be pregnant, and those who were lactating were also not included. The control group was formed from otherwise healthy individuals. The study was approved by the ethics board, and written informed consent was obtained from all study participants.

Weight and height were measured in light clothing without shoes. Body mass index (BMI) was calculated, dividing weight by height squared (kg/m^2). Waist circumference was measured at the narrowest level between the costal margin and iliac crest. Blood pressure measurements were obtained from each patient (using the right arm) in the seated position, using a standard mercury sphygmomanometer. Korotkoff I was accepted systolic blood pressure (SBP) and Korotkoff V was accepted diastolic blood pressure (DBP). Blood pressure was measured by the same investigator at each visit, in the morning after the patient had rested for at least 10 min in a quiet room. Three successive blood pressure readings were obtained at 1-min intervals, and the mean of the three readings was calculated.

Following a 12-h nighttime fast, venous blood samples were obtained from the antecubital vein to measure serum glucose, total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides and PPAR-γ transcription factor concentration. Blood samples were placed in biochemistry tubes that did not contain any material. Samples were centrifuged for 5 min at 3500 rpm and stored at −20°C. The samples were placed at room temperature on the same day for measurements and studied at the same time. Plasma glucose was determined with glucose oxidase/peroxidase method (Gordion Diagnostic, Ankara, Turkey). Levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) were determined with enzymatic colorimetric assays by spectrophotometry. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula.

PPAR-γ transcription factor concentrations were determined using Cayman's enzyme-linked immunosorbent assay (ELISA) method. After adding 90 µl of Complete Transcription Factor Binding Buffer (CTFB), 10 µl of competitive dsDNA, 10 µl of positive control or 10 µl of sample were dispensed into a 96-well plate. This was incubated overnight without agitation at 4°C. Each well was then washed five times with 200 µl of washing buffer; 100 µl of diluted antibody was added (except for blank wells) and after being incubated at room temperature for 1 h without agitation, all wells were washed five times with 200 µl of washing buffer. After adding 100 µl of developing solution, the samples were incubated with mild shaking. After adding 100 µl of stop solution, the results were read at 450 nm wavelength (12).

The patients started on the last molecule or ARB 40 mg olmesartan treatment were assessed weekly in the first month and then twice weekly during follow-up visits. At the end of 3 months, the MetS components were assessed, and PPAR-γ concentrations were again measured. The patients were also questioned about adverse effects at 1 and 3 months.

Statistical Analyses

Statistical analyses were performed using the SPSS for Windows v.15.0 software program (SPSS Inc., Chicago, IL). Between-group comparisons of qualitative variables were performed using a χ^2 test, and the Kolmogorov-Smirnov test and variance test were used to determine whether the variables were parametric or nonparametric. Comparisons between the patient and control groups were performed via an independent sample t-test when the parametric test hypotheses were satisfied and by the Mann-Whitney U test when they were not. Comparisons of treatment-induced changes were performed by a dependent