Telmisartan Improves Cardiometabolic Profile in Obese Patients with Arterial Hypertension

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Abstract

Objective: There are several lines of evidence that telmisartan may improve cardiometabolic profile. The aim of the study was to estimate changes of insulin resistance and plasma concentrations of adipokines after long-term antihypertensive treatment with telmisartan in obese hypertensive patients.

Methods: 34 previously untreated obese adults with arterial hypertension were enrolled. Glucose cellular uptake (M value) and the M to insulin ratio (M/I value) were measured by euglycemic-hyperinsulinemic clamp technique, body fat content (by dual-energy X-ray absorptiometry method), as well as plasma concentrations of selected adipokines and cytokines were estimated before and after 6-month telmisartan therapy in 25 patients who completed the study.

Results: Telmisartan therapy was followed by 14.2% decrease of systolic and by 19.6% decrease of diastolic blood pressure. Body fat mass did not change significantly. Both M and M/I values (by 24.4 and by 38.6%, respectively) as well as plasma levels of total and high-molecular-weight adiponectin (by 10.8 and by 23.5%, respectively) increased significantly. Plasma concentrations of high-sensitivity C-reactive protein and interleukin-8 decreased significantly, while those of interleukin-6 and tumor necrosis factor-α tended to decline.

Conclusions: Telmisartan monotherapy improves cardiometabolic profile in obese hypertensive patients by improving insulin sensitivity and increasing of plasma adiponectin concentration, including its high-molecular-weight fraction, and by suppressing of microinflammation.

Introduction

In view of the current pandemic of obesity and diabetes mellitus type 2 in both developed and developing countries [1, 2], the usage of antihypertensive drugs with beneficial metabolic properties in the treatment of arterial hypertension becomes of great clinical challenge. β-Blockers and diuretics were proved to have a detrimental influence on insulin sensitivity and glucose metabolism, calcium channel blockers seem to be metabolically neutral, while angiotensin-converting enzyme inhibitors and angiotensin receptors blockers (ARBs) may improve metabolic profile [3].

The results from studies estimating the influence of ARBs on insulin sensitivity are not consistent. In the
LIFE study a significant reduction of new-onset diabetes mellitus was found after losartan therapy in comparison with patients receiving atenolol [4]. However, the favorable effect of losartan could result only from β-blockers’ diabetogenic properties. Additionally, a significantly lower rate of diabetes was found in patients treated with valsartan in comparison to amlodipine in the VALUE study [5]. However, in the SCOPE study such differences between candesartan and placebo did not reach the statistical significance [6].

Telmisartan – one of the ARBs – has some structural similarities to antidiabetic agent pioglitazone (a peroxisome proliferator activated receptor-γ (PPARγ) agonist) [7]. Activation of PPARγ regulates carbohydrate and lipid metabolism and influences the inflammatory processes [8]. Therefore, it was hypothesized that telmisartan might have a beneficial influence on insulin sensitivity. Insulin resistance is often associated with the excess of white adipose tissue which is not only an energy storage, but also an important source of biologically active substances named adipokines. Adipokines have endocrine and paracrine properties and may influence whole body metabolism. One of them is adiponectin that is supposed to have anti-diabetic, anti-inflammatory and anti-atherogenic properties. Plasma adiponectin concentration is reduced in patients with obesity [9], diabetes mellitus type 2 [10], hypertension [11] and coronary heart disease [12]. In the circulation, adiponectin molecules form several types of multimers: trimers, hexamers to 12-mers (high molecular weight, HMW) [13]. There are several lines of evidence suggesting that the anti-diabetic and anti-atherogenic properties of this hormone are related mainly to HMW fraction of adiponectin [14–16]. In contrast to adiponectin, serum concentration of leptin increases along with the mass of adipose tissue [17]. In obese subjects, elevated leptin concentration is involved in the pathogenesis of arterial hypertension and obesity-related glomerulopathy [18]. It was shown that stimulation of PPARγ receptors by thiazolidinediones increases plasma adiponectin concentration (and especially its HMW fraction) [19] and diminishes plasma leptin concentration [20].

Adipose tissue is also an important source of proinflammatory cytokines including tumor necrosis factor-α (TNFα), interleukin (IL)-6 and IL-8. It is believed that these proinflammatory cytokines participate in the pathogenesis of atherosclerosis and insulin resistance. It was shown that TNFα increases insulin resistance directly (by altering of insulin signaling) and indirectly by reducing adiponectin secretion [21] and increasing the oxidative stress [22]. The secretion of IL-6 is increased in obese and insulin-resistant subjects [23, 24]. It was shown that IL-6 exerts detrimental effects on carbohydrates and lipid metabolism [25, 26], and reduces adiponectin secretion [27]. IL-8 plays a role in the pathogenesis of atherosclerosis and insulin resistance [28, 29]. Its concentration is also increased in obese subjects [30].

The euglycemic-hyperinsulinemic clamp originally described by DeFronzo et al. [31] in 1979 remains a ‘gold standard’ for insulin sensitivity estimation. Until now the euglycemic-hyperinsulinemic clamp technique as a modified version has been applied only in a single published study estimating the influence of telmisartan on insulin resistance [32]. However, the duration of telmisartan treatment was shorter (8 weeks) than in our study (6 months).

There are also only few studies examining the influence of telmisartan on circulating adipokines and proinflammatory cytokine concentration. Therefore, the aim of the study was to estimate changes of insulin resistance by the euglycemic-hyperinsulinemic clamp technique, plasma levels of total adiponectin and its HMW fraction, and several proinflammatory cytokines after long-term antihypertensive treatment with telmisartan in obese patients with arterial hypertension.

**Methods**

**Study Protocol**

Thirty-four obese (BMI between 30 and 40 kg/m²) adult patients with mild or moderate hypertension without diabetes mellitus were enrolled in this study. These patients were recruited from previously untreated hypertensive patients referred to the outpatient clinic. None of the patients were taking any antihypertensive drugs or drugs affecting insulin sensitivity for at least 4 weeks before entering the study. The study protocol was approved by local ethics committee and informed consent was obtained from each patient. Patients received telmisartan (Micardis; Boehringer Ingelheim) in monotherapy at the initial dose of 40 mg once per day. Blood pressure was estimated at the beginning, at the end of the study and every month during control visits. Blood pressure was measured on the left arm according to the Korotkoff method using a standard mercury sphygmomanometer with a cuff of appropriate size. Measurements were always taken three times by the same, single investigator in the morning after resting for 5 min in the sitting position. The mean from the measured values was then calculated. A daily dose of telmisartan (40 or 80 mg/day) was adjusted to achieve blood pressure values <130/85 mm Hg. Patients who did not obtain such a blood pressure after 1-month treatment with the maximum dose of telmisartan were excluded from the study. 25 patients completed the study (table 1). The mean dose of telmisartan after 6 months was 56 ± 20 mg/day.
Body weight and waist circumference were measured at every visit. Before and after 6 months of treatment with telmisartan the following parameters were estimated: insulin sensitivity by an euglycemic-hyperinsulinemic clamp technique (and additionally homeostasis model assessment of insulin resistance (HOMA-IR) and QUICKI indexes were calculated before initiation of telmisartan treatment based on the fasting insulin and glucose concentrations [33, 34]), serum concentration of high-sensitivity C-reactive protein (hsCRP), creatinine, sodium, potassium, plasma concentration of total adiponectin and its HMW fraction, leptin, IL-6, IL-8 and TNFα, and body fat content by dual energy X-ray absorptiometry (DEXA) using a Lunar DPX-L scanner (Lunar Radiation Co., Madison, Wisc., USA). Additionally, blood count and lipid profiles were tested every month. Serum creatinine and plasma sodium and potassium concentrations as well as the activity of aminotransferases were also measured 2 weeks after initiation of treatment with telmisartan due to safety reasons.

### Table 1. Characteristics of patients with arterial hypertension and obesity who completed the study (data are given as mean ± SE or median with interquartile range and range of values)

| Characteristic                        | Male/female | Age, years | Body mass, kg | BMI | Waist circumference, cm | Systolic blood pressure, mm Hg | Diastolic blood pressure, mm Hg | Hemoglobin, g/dl | Leukocytes, 10^3/μl | Neutrophils, 10^3/μl | Platelets, 10^3/μl | hsCRP, mg/l | Total cholesterol, mmol/l | LDL cholesterol, mmol/l | HDL cholesterol, mmol/l | Triglycerides, mmol/l | Sodium, mmol/l | Potassium, mmol/l | Creatinine, μmol/l | eGFR, ml/min/1.73 m² | Glucose, mmol/l | Total adiponectin, μg/ml | Fraction HMW of adiponectin, μg/ml | Fraction non-HMW of adiponectin, μg/ml | Leptin, ng/ml | TNFα, pg/ml | IL-6, pg/ml | IL-8, ng/ml | Insulin, μU/ml | M, mg/kg/min | M/I, mg/kg/min/μU/ml | HOMA-IR | QUICKI |
|--------------------------------------|-------------|------------|---------------|-----|------------------------|-------------------------------|-------------------------------|-------------------|---------------------|---------------------|-----------------------|------------|----------------------------|--------------------------|--------------------------|------------------------|---------------|-------------|-------------|------------|----------------|-------------|------------------------|----------|--------|
| Male/female                          | 11/14       | 50.7 ± 8.9 | 101.5 ± 14.4  | 35.2 ± 3.8 | 111.7 ± 7.9            | 148.0 ± 8.0                  | 97.0 ± 8.0                  | 14.2 ± 1.3        | 7.2 ± 1.8           | 4.0 ± 1.3            | 228.0 ± 50.0         | 4.2 ± 3 (1.3–5.2) | 5.5 ± 1.1                   | 3.3 ± 0.9                 | 1.2 ± 0.3                 | 1.8 ± 1.5             | 141.8 ± 2.8   | 4.1 ± 0.3    | 83.1 ± 14.3 | 79.6 ± 19.5 | 4.9 ± 0.4 | 7.6 ± 4.4 | 1.7 ± 1.0 | 5.9 ± 3.7 | 25.2 ± 16.5 | 4.4 ± 2.0 | 3.5 ± 2.4 | 3.8 ± 2.1 | 20.6 ± 12.2 | 4.1 ± 2.0 | 4.4 ± 3.3 | 4.6 ± 2.8 | 0.23 ± 0.03 | 0.09–0.8 |

M value = Glucose cellular uptake; I = insulin plasma concentration; M/I ratio = a marker of tissues sensitivity to insulin; HMW = high-molecular-weight fraction of adiponectin.

**Euglycemic-Hyperinsulinemic Glucose Clamp**

A euglycemic-hyperinsulinemic glucose clamp technique is regarded as a ‘gold standard’ for insulin sensitivity estimation. It was performed according to the method described by DeFronzo et al. [31]. Two veins on both forearms were cannulized. To the right cannula insulin dissolved in 20% glucose solution were infused. During the first 8 min the rate of insulin infusion was gradually decreased from 100 to 60 mU/m²/min. Afterwards, insulin was infused at a stable speed of 50 mU/m²/min throughout the clamp study, which achieves a mean plasma insulin concentration of about 100–120 mU/l (physiologic insulin concentration after an average meal). Glucose infusion rate was adjusted to the current blood glucose level to maintain the patients in a stable euglycemic state. Glucose concentration was estimated every 5 min during the first 2 h and every 10 min during the third hour from the left cannula. Glucose concentration was estimated with the use of glucometer Medisense Optium (precision of glucose measurement: ± 15%).
Plasma insulin concentration was estimated at the beginning of the clamp study and then every 60 min. The glucose cellular uptake (M value; milligrams per kilogram per minute) was calculated as a mean of three glucose infusion rates achieved in last three 20-min periods of the clamp study. Glucose cellular uptake to plasma insulin concentration ratio (M/I value, mg/kg/min/μU/ml) was considered as a marker of tissue sensitivity to insulin.

Laboratory Investigations
Plasma insulin was measured using enzyme-linked immunosorbent assay (ELISA) kits for Elecsys from Roche Diagnostics GmbH (Mannheim, Germany). Plasma total adiponectin concentration and its HMW fraction concentration was measured using ELISA kits from Lincor Research Laboratories (St. Louis, MO, USA). A radioimmunoassay method was applied for estimation of plasma leptin (Linco Research Laboratories) and TNFα (Biostep Europe SA, Nivelles, Belgium). Plasma IL-6 and IL-8 concentrations were measured using high-sensitivity ELISA kits from R&D Systems (Minneapolis, Minn., USA). Serum CRP concentration was measured by nephelometric method using ‘Car-dioPhase hsCRP’ kits from Siemens Healthcare Diagnostics (Deerfield, Ill., USA).

Serum cholesterol (total and HDL fraction), triglyceride, and creatinine concentrations were measured by an automated method (Synchron Cx-9; Beckman Coulter Inc., Fullerton, Calif., USA).

Statistics
Statistical analysis was performed using Statistica version 7.0. All quantitative variables are expressed as mean ± SD or in median with interquartile range. Wilcoxon test was used to determine the differences between dependent variables. p < 0.05 was considered as statistically significant.

Results
All study participants had abdominal obesity (according to IDF definition from 2005), and 22 of 25 patients fulfilled the population criteria of insulin resistance (HOMA-IR ≥ 2.29 for the European population [35]). The average value of HOMA-IR was 4.6. Detailed characteristics of the study group before and after treatment of telmisartan are given in tables 1 and 2.

The 6-month therapy with telmisartan was followed by a significant decrease of systolic (by 14.2%, p < 0.001) and diastolic (by 19.6%, p < 0.001) blood pressure (table 2). Transient hypotension was observed in 2 patients. No changes in total body mass, BMI, waist circumference and total fat content estimated by DEXA were observed.
The only significant change in lipid profile after the 6-month telmisartan treatment was the increase in the concentration of HDL cholesterol ($p < 0.001$) (table 2).

After the 6-month telmisartan therapy an increase of insulin sensitivity parameters was demonstrated: the $M$ value by 24.4% ($p = 0.02$) (table 2; fig. 1a) and the $M/I$ value by 38.6% ($p = 0.02$) (table 2; fig. 1b). There was no change in fasting glucose and insulin concentration.

A significant increase in plasma adiponectin concentration (by 10.8%, $p = 0.02$) (table 2; fig. 2a) and its HMW fraction (by 23.5%, $p = 0.03$) (table 2; fig. 2b) was observed. There was no significant change in plasma leptin concentration (table 2).

Moreover, after the 6-month telmisartan therapy a significant reduction of inflammatory parameters was observed: hsCRP by 19.2% ($p = 0.02$) and IL-8 by 28.9% ($p = 0.03$) (table 2). The concentrations of IL-6 and TNFα also tended to decrease, but the observed changes did not reach statistical significance (table 2).

**Side Effects**

No side effects were observed during the 6-month therapy with telmisartan. The average serum potassium concentration rose significantly (by 0.3 mmol/l, $p = 0.003$) (table 2), but in all patients serum potassium concentrations remained within the normal range.

**Discussion**

The study revealed that 6-month treatment with telmisartan improves insulin sensitivity, increases the concentration of serum adiponectin and its HMW fraction and decreases concentrations of the inflammatory markers in obese patients with arterial hypertension.

The main goal of the present study was the estimation of changes of insulin resistance after 6 months of antihypertensive treatment with telmisartan, based on the euglycemic-hyperinsulinemic glucose clamp technique, which is a 'gold standard' for insulin sensitivity studies. We have found a significant increase of the $M$ parameter without a concomitant reduction of glucose and insulin serum concentration. Our group failed to demonstrate such an increase in the $M$ parameter in a group of hypertensive patients after 8 weeks of therapy with losartan [36]. Perhaps the beneficial influence of telmisartan on...
insulin sensitivity might be partially explained by the activation of PPARγ receptor. However, the beneficial effect of PPARγ stimulation by sartans has not been incontestably proven. Sharma et al. [37] did not observe any difference in fasting glucose concentration in head-to-head comparison between telmisartan with valsartan (that lacks PPARγ activity).

The improvement of insulin sensitivity during telmisartan treatment has also been observed in other studies in hypertensive patients with obesity and/or diabetes/impaired glucose tolerance, however based on other than glucose clamp methods [38–41]. Only in a few of those studies was a significant reduction of serum insulin and glucose concentration found. Vitale et al. [42] investigated 40 patients randomly allocated to two groups receiving telmisartan or losartan. After 3 months, patients in the telmisartan group were characterized by a significant reduction of glycemia, insulinemia, HbA1c and HOMA-IR index. In the other study no beneficial effect of telmisartan treatment on insulin sensitivity was observed in 42 patients with metabolic syndrome treated alternatively with telmisartan or losartan [43]. A similar result was obtained by Derosa et al. [44] in a group of 119 diabetic patients treated with telmisartan, eprosartan or placebo. The results of the above-mentioned studies should not be directly compared with the current study because insulin sensitivity indexes such as HOMA-IR and QUICKI calculated from fasting insulinemia and glyemia reflect mainly hepatic insulin sensitivity. In the current study the M parameter measured with the euglycemic-hyperinsulinemic glucose clamp technique reflects the peripheral tissue glucose uptake. The M/I ratio is considered as a marker of insulin resistance. The euglycemic-hyperinsulinemic clamp originally described by DeFronzo et al. [31] in 1979 still remains a ‘gold standard’ for estimating insulin sensitivity. Until now the euglycemic-hyperinsulinemic clamp technique for the estimation of the influence of telmisartan on insulin resistance has been applied only in a single, recently published study [32]. The results of that study are in line with the ones achieved in the current study.

What is the clinical meaning of the improvement of insulin sensitivity related to telmisartan therapy found in the current study? Recently published results of the ON-

Fig. 2. a Plasma adiponectin concentrations in 25 patients before and after 6 months of telmisartan treatment (p = 0.02). b Plasma HMW fraction of adiponectin concentrations in 25 patients before and after 6 months of telmisartan treatment (p = 0.03).
TARGET study could undermine the results of the present study. In the ONTARGET study no predomination of telmisartan over ramipril was found as far as the number of new cases of diabetes is concerned [45]. A similar effect, suggesting the lack of telmisartan influence on insulin sensitivity, was obtained in the TRANSCEND study, which compared telmisartan with placebo [46]. Nevertheless, it must be noted that in the ONTARGET and TRANSCEND studies, insulin resistance was not the inclusion criterion. In the present study, 22 out of 25 participants were insulin-resistant according to the definition of insulin resistance regarded for European population. Thus the demonstration of improvement of insulin sensitivity was probably easier in these insulin-resistant patients. Therefore, a clinical study including patients especially predisposed to diabetes may be required to prove clinical relevance of beneficial effect of telmisartan on carbohydrate metabolism. Moreover, one can speculate that the observation time in the ONTARGET and TRANSCEND studies was too short to find a significant difference in such a hard metabolic endpoint as the new onset of diabetes mellitus.

Insulin sensitivity improvement observed in the current study was independent of body weight and fat mass changes. Moreover, we did not observe changes in fat distribution by the DEXA method. However, we applied the DEXA method which allows to estimate the fat localized in specified body regions but cannot differentiate between visceral and subcutaneous fat. In two other studies a significant reduction in visceral fat measured by computed tomography was observed after a 6-month telmisartan treatment in patients with arterial hypertension [47] or metabolic syndrome [48]. Such changes observed in these studies may interfere with the estimation of insulin sensitivity changes.

HMW is the main metabolically active fraction of adiponectin – an adipokine which is supposed to have anti-diabetic properties. A HMW fraction appears as a result of posttranslational modifications inside the adipocytes. The serum concentration of the HMW fraction is decreased in patients with diabetes mellitus and coronary artery disease. In the current study we found the increase in total adiponectin and its HMW fraction plasma concentration after a 6-month telmisartan therapy. Therefore, we confirmed the beneficial influence of telmisartan on total adiponectin serum concentration found in other studies [40, 49–51]. Until now the influence of telmisartan on the HMW fraction of adiponectin has been studied only in a single recently published study [52]. Similarly, as in the current study an increase of plasma concentration of the HWM adiponectin fraction after telmisartan therapy was found. Therefore, it seems that telmisartan increases the production of HMW multimers inside the adipocytes. The results obtained suggest that the increase in adiponectin and its HMW fraction concentration may contribute to the improvement in insulin sensitivity. The excretion of adiponectin and its HMW fraction may be induced via receptor PPARγ activation.

These results of clinical studies are in line with the recently published adipocyte culture study. Brody et al. [53] found that telmisartan and, to a lesser extent, losartan, has increased production and secretion of adiponectin from 3T3-L1 adipocytes.

Obesity is accompanied by an increased concentration of inflammatory markers (‘microinflammation’), which contributes to metabolic disturbances and accelerates development of atherosclerosis. We have observed a significant reduction of serum concentrations of hsCRP and IL-8. The levels of TNFα and IL-6 only tended to decline. The completely original aspect of the study was the estimation of IL-8 plasma concentration that seems to have an important role in the pathogenesis of atherosclerosis. The present study is the first to measure the influence of one of the angiotensin II receptor type 1 antagonists on plasma IL-8 concentration. Adipose tissue is the main source of IL-8 in obesity [30]. Perhaps the increase in total adiponectin and its HMW fraction concentration observed in our study could also be the result of the reduction of microinflammation.

Conclusion

Telmisartan monotherapy improves insulin sensitivity by increasing the plasma adiponectin concentration, including its HMW fraction, and by suppressing microinflammation. Both the improvement of insulin sensitivity and suppression of inflammation are of potential clinical significance.

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Disclosure Statement

The authors have no conflicts of interest to disclose.


