Decreased Androgen Levels and Improved Menstrual Pattern after Angiotensin II Receptor Antagonist Telmisartan Treatment in Four Hypertensive Patients with Polycystic Ovary Syndrome: Case Series

We describe 4 consecutive hypertensive women with polycystic ovary syndrome, classified according to the National Institute of Child Health and Human Development (NICHD) criteria, treated with telmisartan 40 mg/d for six months. Blood pressure, menstrual pattern, body mass index (BMI), homeostasis model assessment of insulin resistance, testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione were recorded and measured before and after telmisartan treatment. Obese hypertensive polycystic ovary syndrome patients had a decrease in systolic blood pressure. Marked drop-off in serum androgen concentrations was observed in all four patients. Three patients improved their menstrual cyclicity. The improvements were independent of changes in weight. The reduction of androgen concentrations and improvement in menstrual pattern was achieved despite a non-significant change of fasting insulin levels in patients, who were not considered severely insulin resistant at baseline. These findings may provide a new basis for a proper choice of the antihypertensive drug in hypertensive women with polycystic ovary syndrome.

Correspondence to:
Mojca Jensterle
Department of Endocrinology, Diabetes, and Metabolic Diseases
University Medical Centre Ljubljana
Zaloška 7
1525 Ljubljana, Slovenia
mojcajensterle@yahoo.com

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Over the last twenty years it has been widely recognized that most women with polycystic ovary syndrome, in addition to endocrine and reproductive abnormalities, demonstrate metabolic disturbances, which put them at a substantial risk for the development of cardiovascular diseases (1). This is not a surprising finding, since insulin resistance, followed by compensatory hyperinsulinemia, has been recognized as the central pathogenetic feature of the syndrome, causing arterial hypertension, dyslipidemia, proatherogenic, and prothrombotic environment (2). Women with polycystic ovary syndrome often have an adverse cardiovascular risk profile characteristic of the metabolic syndrome (3). Compared with age and weight matched control, they have higher rate and degree of central obesity, impaired glucose tolerance, type 2 diabetes (4), atherogenic dyslipidemia (5), arterial hypertension, and even subclinical signs of atherosclerosis (6). These insights into the association between insulin resistance and polycystic ovary syndrome have recently been incorporated into the framework of polycystic ovary syndrome treatment. There is increasing evidence that insulin-sensitizing drugs, metformin, and peroxisome proliferator-activated receptors (PPAR) gamma agonists thiazolidinediones have favorable endocrine, reproductive, and metabolic effects in polycystic ovary syndrome (7-13).

Telmisartan is a structurally unique angiotensin II receptor antagonist used for the treatment of hypertension. Some recent reports have shown that this antihypertensive drug may have insulin-sensitizing effects related to its ability to activate PPAR gamma. Telmisartan has been shown to influence the expression of PPAR gamma target genes involved in carbohydrate and lipid metabolism and to reduce glucose, insulin, and triglyceride levels (14-18). However, its potential, beneficial endocrine, reproductive, and metabolic effects in hypertensive women with polycystic ovary syndrome have not been studied yet. We evaluated the effects of telmisartan on endocrine, reproductive, and metabolic features of 4 hypertensive women with polycystic ovary syndrome.

Methods

The study was performed at the University Medical Center Ljubljana in 2005 and 2006. We followed 4 consecutive hypertensive women with polycystic ovary syndrome, classified according to the National Institute of Child Health and Human Development (NICHD) criteria (19), treated with telmisartan 40 mg/d for 6 months. Increased blood pressure was defined as systolic blood pressure of at least 130 mm Hg and/or diastolic blood pressure of at least 80 mm Hg (20). Clinical hyperandrogenism was defined as the presence of hirsutism, represented by a modified Ferriman-Gallwey score (21) of 7 or more, persistence of acne during the third decade of life or later, or the presence of androgenetic alopecia. Hyperandrogenemia was defined as a total or free testosterone, androstenedione, and/or dehydroepiandrosterone sulfate (DHEAS) level above the 95th percentile of normal values. Menstrual dysfunction was defined as more than six cycles longer than 35 days per year or as absence of menstrual bleeding for 3 consecutive months during the previous year. All patients fulfilled the ultrasonographic criteria of polycystic ovary syndrome and had normal serum prolactin concentrations and thyroid function tests. Cushing syndrome, early menopause, or congenital (non-classical) adrenal hyperplasia were excluded (19). Patients were not taking any insulin-sensitizing drugs before the study or any other drugs throughout the study. All subjects gave their written informed consent and the study was conducted in accordance with the Declaration of Helsinki and approved by the National Ethical Committee.
On the first day of the study, the women were admitted to the clinical research center after 12-hour overnight fast. We recorded their menstrual history and performed the clinical examination. In each patient, body mass index (BMI) was calculated. Blood pressure was measured three times consecutively using cuff sphygmomanometry, and a fasting blood draw was taken for determination of hormones. Homeostasis model assessment of insulin resistance as a measure of insulin resistance was calculated using the following formula: fasting serum insulin (mU/L) × fasting plasma glucose (mmol/L)/22.5 (22). Patients were prescribed telmisartan 40 mg/d. The following conditions were considered as possible adverse drug reactions: worsening of renal function in patients dependent on renin-angiotensin-aldosterone system, chest pain, peripheral edema, headache, dizziness, pain, fatigue, diarrhea, dyspepsia, nausea, abdominal pain, urinary tract infection, back pain, myalgia, upper respiratory infection, sinusitis, pharyngitis, cough, and flu-like syndrome. After 6 months of treatment, patients were readmitted to the clinical research center and re-evaluated.

All blood samples were centrifuged and the separated serum was kept frozen at -40°C until the time of the assay. Glucose levels were determined using glucose oxidase method (Roche Hitachi 917, Roche Diagnostic, Mannheim, Germany). Androstenedione and DHEAS were measured by specific double antibody RIA using 125 I-labeled hormones (Diagnostic Systems Laboratories, Webster, TX, USA). Free testosterone levels were measured by coated tube RIA (Diagnostic Products Corporation, Los Angeles, CA, USA). Insulin was determined by immunoradiometric assay (Biosource Europe S.A., Nivelles, Belgium). Intraassay variation ranged from 1.6 to 6.3% and interassay variation ranged from 5.8 to 9.6%. Pre- and post-treatment samples from all patients were assayed in the same bath.

Case reports

Patient 1 was an obese 31-year-old woman with oligomenorrhea and the length of menstrual cycle of maximum 45 days. During the previous 6 months, she had had 4 menstrual bleedings. She had signs of clinical hyperandrogenism represented by the presence of hirsutism (modified Ferriman-Gallwey score of 9) and persistence of acne during the third and fourth decade of her life. Her blood pressure was 135/90 mm Hg. Her weight remained practically unchanged during the course of the study. Administration of telmisartan 40 mg/d was associated with a significant decrease in serum concentrations of all androgens. The frequency of menstrual bleeding increased and the cycles became regular.

Patient 2 was an obese 21-year-old woman with deteriorating hirsutism, moderate acne, and oligomenorrhea with the length of the cycle of maximum 60 days. Her blood pressure was 145/80 mm Hg. Her father had hypertension and diabetes mellitus and her older sister had hirsutism. During the study, she unintentionally lost 8 kg. With treatment, there was a decrease in systolic blood pressure. Diastolic blood pressure remained stable. The reduction of all androgen levels was noted. Menstrual cycles were completely restored.

Patient 3 was a 24-year-old woman with severely expressed clinical hyperandrogenism (hirsutism and acne) and secondary amenorrhea. Mean frequency of her menstrual bleedings was 1 to 2 per year. For the previous two months, her systolic blood pressure had been between 140 and 160 mm Hg. Ninety days before entering the study, she stopped using contraceptive pills that she had been taking for 3 months. Her weight remained stable during the study. Her blood pressure...
and androgen levels were markedly reduced. However, she did not have spontaneous menstruation during the time of telmisartan treatment.

**Patient 4** was an obese 32-year-old woman with oligomenorrhea and mild hypertension (140/90 mm Hg). Mild androgenetic alopecia was her only clinical manifestation of androgen excess. She had conceived two times in the past after treatment with clomiphene citrate and has two children. She got pregnant without our knowledge after being on telmisartan for about four months and immediately decided to have an abortion without interrupting her therapy. She lost about 10 kg after the abortion. Her androgen levels decreased and she had two menstrual bleedings during the study period.

**Summary of the results**

The patients’ characteristics and treatment results are reported in Table 1.

As expected, obese hypertensive patients with polycystic ovary syndrome described in this report had a decrease in systolic blood pressure. In addition, a marked drop-off in serum androgen concentrations was observed in all 4 patients. Three patients improved their menstrual cyclicity, one of them even got pregnant. The clinical and hormonal improvements in two patients were completely independent of changes in weight. The other 2 patients had lost some of their baseline weight (less than 10%) during the course of the observation and it is possible that telmisartan administration and weight loss had synergistic beneficial effects in the improvement of the symptoms of polycystic ovary syndrome. A reduction in androgen concentrations and improvement in menstrual pattern was achieved despite a non-significant change of fasting insulin levels in patients, who were not considered severely insulin resistant at baseline (homeostasis model assessment of insulin resistance between 1.5 and 2.6).

The drug was well tolerated and a few clinically minor adverse events did not lead to discontinuation of the treatment in any of the patients. One subject complained about mild transient headaches and one subject had temporary mild dizziness.

**Discussion**

According to our knowledge, these are the first case reports demonstrating that the angiotensin II receptor antagonist telmisartan, besides being an effective antihypertensive drug, may have beneficial effects in polycystic ovary syn-

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*Abbreviations: BMI – body mass index; DHEAS – dehydroepiandrosterone sulfate; HOMAIR – homeostasis model assessment of insulin resistance.*
drome patients. The case reports provide interesting new information about unexpected effect and possible new indication of telmisartan in patients with polycystic ovary syndrome.

Since insulin resistance plays a major role in the pathogenesis of polycystic ovary syndrome, several trials have confirmed that insulin-sensitizing drugs, metformin (7-9), and thiazolidinediones (11-13,23,24) have favorable endocrine, reproductive, and metabolic effects in polycystic ovary syndrome. Considering that telmisartan may have insulin-sensitizing effects related to its ability to activate PPAR gamma (14-18), we hypothesized that the administration of telmisartan would also improve menstrual dysfunction, hyperandrogenemia, and hyperinsulinemia of patients with polycystic ovary syndrome.

As we assumed, after 6 months of treatment with telmisartan, we observed significant reduction in free testosterone (around 35% on average), DHEAS (around 40% on average), and androstenedione concentration (around 20% on average) in all 4 patients. Three out of four women improved their menstrual cyclicity. One additional menstruation in one woman and two additional menstruations in the other two women were attained in 6 months of telmisartan treatment. The intensity of telmisartan effects appeared to be in the usual range for insulin-sensitizing drugs, metformin, or thiazolidinediones in patients with polycystic ovary syndrome.

Metformin’s efficiency in increasing ovulation rates, when used alone, and in increasing ovulation and pregnancy rates, when combined with clomiphene citrate, has been demonstrated in observational, randomized controlled trials and meta-analyses (7-9). It is usually suggested that metformin doubles ovulation rates from basal levels. In comparison with our observation, two studies concluded that on average one additional ovulation is attained every five months with metformin treatment (7,8). Reduction of androgen levels is generally reported to be around 20% with metformin, as opposed to placebo (7).

Troglitazone, which is now unavailable due to reports of hepatic toxicity, is the most researched TZD agent in the context of polycystic ovary syndrome, and it demonstrated significant benefits in endocrine, metabolic, and ovulatory performance. This was extensively studied by the polycystic ovary syndrome/troglitazone study group (10). In this multicenter study troglitazone given for 44 weeks improved ovulatory function, hyperandrogenemia, and insulin resistance of polycystic ovary syndrome in a dose-related fashion. Fifty seven per cent of polycystic ovary syndrome patients treated with 600 mg of troglitazone had ovulatory cycles more than 50% of the time, compared with 12% of placebo-treated patients. The improvement in ovulation was also reflected in the improvement of menstrual cycle regularity. Studies on the effect of rosiglitazone, a newer PPAR gamma activator, in women with polycystic ovary syndrome are more limited. Rosiglitazone has been shown to increase ovulation rates alone or in combination with clomiphene citrate, reduce hyperandrogenism, and improve insulin resistance and glucose tolerance (11-13,23,24). Dareli et al (24) demonstrated 36.5% and 31.9% reduction in free testosterone level after 8-month-treatment with 4 mg and 2 mg rosiglitazone, respectively.

We reported about a suppressive effect of telmisartan on androgen secretion and an improvement in menstrual pattern in 4 polycystic ovary syndrome patients. It needs to be pointed out that the response to telmisartan was observed in patients who were not considered severely insulin-resistant at baseline. Similarly, response to treatment with metformin (25,26) or rosiglitazone (26) was even shown in lean women with seemingly normal indices of insulin action, and no clear predictors of a positive response to metformin or thiazolidin-
ediones have been identified. In addition, the reduction in androgens in our patients seemed to be independent of changes in BMI, fasting serum insulin levels, and homeostasis model assessment of insulin resistance score, implying that the effects of telmisartan reported in our study may involve mechanisms beyond the effect on insulin resistance. In fact, several lines of evidence support the notion that thiazolidinediones may have a direct effect on ovarian steroidogenesis apart from improved insulin sensitivity (27-34). There are similar mechanisms possible for the telmisartan-induced androgen suppression in our patients, but these should be proven with further research on the cellular and molecular level.

The limitation of the current study is some degree of clinical variability in the cases presented. Also, because of the design of our study we cannot draw any conclusions on causality, since the improvement in symptoms in 2 patients could have been caused by the loss of weight. Clearly, to draw more reliable conclusions, randomized controlled trials of long-term treatment remain to be conducted. We think, however, that the data presented here might serve as a good starting point to evaluate this interesting approach in a carefully designed clinical trial in which telmisartan would be compared with another antihypertensive drug lacking the PPAR gamma agonist effect. Our observation may provide a new basis for a potential new drug indication for telmisartan in hypertensive women with polycystic ovary syndrome.

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