*Original Article*

# Comparison of the Effects of Valsartan and Felodipine on Plasma Leptin and Insulin Sensitivity in Hypertensive Obese Patients

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**Aim of this study was to compare the effect of valsartan and felodipine on blood pressure (BP), plasma leptin (L), insulin sensitivity and plasma norepinephrine (NE) in obese hypertensive patients. Ninty-six obese patients (body mass index [BMI] ≥30 kg/m²) with mild to moderate essential hypertension (diastolic blood pressure [DBP] >90 and <110 mmHg, as evaluated with an appropriately sized cuff) aged 31–60 years, were randomized to a valsartan (80 mg/day for 16 weeks; *n*=48) or felodipine (5 mg/day for 16 weeks; *n*=48) treatment group after a 2-week wash-out period. After the first 4 weeks of treatment there was a titration with dose-doubling in non responder patients (DBP > 90 mmHg). At the end of the placebo period and of active treatment period, BP and BMI were evaluated and a venous sample was drawn at the same hour in the morning to evaluate plasma L and NE. Insulin resistance index (HOMA-IR) was calculated. No dietary advice was prescribed. Both valsartan and felodipine significantly decreased BP values (−19.3/15 mmHg and −18.9/13.6 mmHg, respectively *p*<0.001 *vs.* placebo), with no difference between treatments. However, felodipine increased plasma NE (+124 pg/ml, +38.2%, *p*<0.05 *vs.* placebo and <0.01 *vs.* valsartan) and had no effect on L, body weight and HOMA-IR index, while valsartan did not modify NE and produced a significant reduction in L (−3.7 ng/ml, −10.1%, *p*<0.05 *vs.* placebo), BMI (−1.7 kg/m², −4.7%, *p*<0.01 *vs.* placebo) and HOMA-IR index (−1.6, −20%, *p*<0.05 *vs.* placebo). These results suggest that in hypertensive obese subjects, treatment with valsartan might offer an advantage over treatment with felodipine, since valsartan may help to improve obesity-related disorders in addition to lowering BP. (*Hypertens Res* 2005; 28: 209–214)**

***Key Words*: valsartan, leptin, insulin sensitivity, hypertension, obesity**

## Introduction

Obesity, defined as abnormal body weight with a body mass index (BMI) greater than 30 kg/m², has become a major health concern since it currently affects several hundred million people worldwide and is associated with increases in all-cause mortality, including death from cardiovascular disease (CVD) and heart failure (*1*–*4*). The relationship between obesity, especially the central or visceral type, and CVD is complex: some investigators have reported that the connection is indirect and dependent on increased prevalence of hypertension, diabetes and dyslipidemia, which together with insulin resistance are constituents of the so-called metabolic syndrome, whereas others have found that obesity is an independent risk factor for CVD (*5*–*7*). While previously adipose tissue was considered an inert organ for storing excess calories, more recently adipocytes have been demonstrated to synthesize and secrete biologically active molecules that interact with each other and may affect CVD risk factors (*7*, *8*). Of particular importance is the putative role of leptin (L), an adipocyte derived hormone that acts in the central nervous system to promote weight loss by decreasing food intake and increasing metabolic rate (*9*). Leptin is involved in the patho-

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Received October 6, 2004; Accepted in revised form December 7, 2004.

**Table 1. Demographic and Clinical Characteristics of the Patients in the Two Treatment Groups at Baseline**

| | Valsartan | Felodipine |
|---|---|---|
| Number | 48 | 48 |
| Sex (M/F) | 25/23 | 26/22 |
| Age (years) | 55.1±7.9 | 56.2±8.2 |
| SBP (mmHg) | 159.5±13 | 160.1±14 |
| DBP (mmHg) | 101.4±5 | 100.4±5 |
| HR (beats/min) | 75.1±9.1 | 74.9±10.0 |
| BMI (kg/m$^2$) | 35.9±3.9 | 35.4±4.0 |
| Plasma L (ng/ml) | 36.7±18.5 | 36.2±18.4 |
| Plasma NE (pg/ml) | 332±113 | 324±122 |
| HOMA-IR | 7.7±2.4 | 7.8±2.5 |

M, male; F, female; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BMI, body mass index; L, leptin; NE, norepinephrine; HOMA-IR, homeostasis model assessment of insulin resistance.

genesis of obesity-hypertension, since it causes a significant increase in overall sympathetic nervous activity, exerts a direct effect on the kidneys resulting in increased sodium reabsorption and regulates vasomotion involving nitric oxide-dependent and -independent mechanisms (*10–16*). On the other hand, obesity increases vasoconstriction and may have structural effects on the kidneys that may perpetuate hypertension (*17*). Insulin resistance and hyperinsulinemia, associated with obesity, are considered to increase blood pressure (BP) through sympathetic nervous system activation, renin-angiotensin system stimulation and vascular muscle cell proliferation (*18–20*).

Optimal pharmacological management of obesity-hypertension needs antihypertensive agents that at least do not exacerbate and possibly improve obesity-associated metabolic and neuro-hormonal disorders, beyond lowering BP values. Both dihydropyridine calcium channel blockers (CCBs) and angiotensin (Ang) II type 1 (AT1)-receptor antagonists are suitable for the treatment of obesity-hypertension, since they are devoid of adverse metabolic effects (*21*). However, contrasting findings have been reported in the literature with regard to their influence on sympathetic activity (*22*) and few studies have evaluated their effects on plasma L (*23*, *24*). With this background, the present study aimed to evaluate the effects of the AT1-receptor antagonist valsartan (*25*) as compared to the CCB felodipine (*26*) on plasma L, plasma norepinephrine (NE) and insulin sensitivity in the treatment of hypertensive obese patients.

## Methods

This was an open-label, randomized, parallel-group study of 16-week duration. Ninety-six outpatients of both sexes, with obesity (BMI ≥ 30 kg/m$^2$) and mild to moderate essential hypertension (diastolic blood pressure [DBP] >90 and <110 mmHg after a 2-week wash-out period) were considered eligible for the study. Subjects with diabetes, liver or kidney diseases, angina, myocardial infarction or stroke within 6 months, congestive heart failure, neurologic or psychiatric illness, secondary hypertension, known hypersensitivity to the drugs used in the study were excluded, as were those with conditions that may have caused metabolic alterations within the past year (pregnancy, abdominal surgery, weight gain or loss of more than 3 kg).

The study protocol was approved the local Ethical Committee and informed written consent was obtained from each participant at the time of enrolment.

After an initial 2-week wash-out period, during which previous antihypertensive medications, if any, were discontinued and placebo was administered, patients fulfilling the inclusion criteria were randomly assigned to receive valsartan 80 mg once daily (o.d.) or felodipine 5 mg o.d. for 16 weeks. After 4 weeks of treatment, if the BP was still not controlled (DBP > 90 mmHg) 160 mg of valsartan or 10 mg of felodipine were administered for the next 12 weeks. No dietary advice was prescribed for the duration of the study.

At the end of the wash-out and of active treatment period, office BP, BMI, plasma levels of L and NE and insulin resistance were evaluated. All BP measurements were made with calibrated mercury manometers (Korotkoff I and V). Arm circumferences were measured to determine the appropriate cuff size. BP was measured in the morning, before daily drug intake (*i.e.* 24 h after dosing) and after the patient had been sitting comfortably for 10 min in a quiet room. Three separate measurements were taken at least 2 min apart and the average of these values was calculated.

Body weight was measured in the fasting state with the subjects wearing only light clothes and without shoes and BMI was calculated as weight in kg/m$^2$.

For evaluation of L, NE and insulin resistance blood samples were always drawn in the morning, between 08:00 and 09:00 hours, after an overnight fast and at least 20 min after we had positioned an intravenous line in the antecubital vein. The blood samples were vortexed and centrifuged immediately at 4°C for 20 min at 300 rpm and plasma samples were stored at −80°C until assayed.

Plasma L concentrations were assessed in duplicate using commercial available ELISA kits (TiterZyme EIA kit Assay Designs, Inc., Ann Arbor, USA) according to the manufacturer's instructions. The intra-assay correlation variance was 4.5% and the interassay-correlation variance was 6.5%.

Plasma NE levels were determined by high-performance liquid chromatography (HPLC) using a modification of the method of Remie and Zaagsma (*27*) described by Hjemdahl (*28*). The detection limit was 10 pg/ml, the recovery in plasma was 98% and the coefficient of variation for both the intra- and inter-assay was 4%.

Insulin resistance was evaluated using the homeostasis model assessment of insulin resistance index (HOMA-IR), defined as fasting glucose (mmol/l) × fasting insulin (μU/ml)

**Table 2. Mean Values of Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Body Mass Index (BMI), Plasma Levels of Leptin (L), and Norepinephrine (NE) and Insulin Resistance (HOMA-IR) at Baseline and after Treatment with Valsartan and Felodipine**

| | Valsartan | | Felodipine | |
|---|---|---|---|---|
| | Baseline | After | Baseline | After |
| SBP (mmHg) | 159.5±13 | 140.2±12*** | 160.1±14 | 141.2±12*** |
| DBP (mmHg) | 101.4±5 | 86.4±4*** | 100.4±5 | 86.8±4*** |
| BMI (kg/m$^2$) | 35.9±3.9 | 34.2±2.5** | 35.4±4.0 | 35.5±4.1 |
| Plasma L (ng/ml) | 36.7±18.5 | 33.0±17.1* | 36.2±18.4 | 36.8±19.1 |
| Plasma NE (pg/ml) | 332±113 | 286±99 | 324±112 | 448±122*,† |
| HOMA-IR | 7.7±2.4 | 6.1±2.1* | 7.8±2.5 | 7.5±2.4 |

*$p<0.05$, **$p<0.01$, ***$p<0.001$ *vs.* baseline; †$p<0.01$ *vs.* valsartan.

divided by 22.5 (*29*), which has been shown to correlate well with insulin resistance evaluated using clamp technique (*30*). Blood glucose was measured by the glucose oxidase method and plasma insulin levels were determined by radioimmunoassay.

Data are expressed as means±SD. The statistical analysis of the results was performed by analysis of variance (ANOVA). Values of $p<0.05$ were considered to indicate statistical significance.

## Results

Of the 96 patients initially randomized to valsartan ($n=48$) or felodipine ($n=48$), 5 subsequently dropped out: three in the felodipine group (two for side effects and one for insufficient compliance) and two in the valsartan group (one for insufficient compliance and one for lack of cooperation). The two treatment groups were well matched in terms of their demographic and clinical characteristics at baseline (Table 1). Of the patients, 61 needed to be titrated to the higher dose after 4 weeks of therapy because their DBP was >90 mmHg (33 in the valsartan group and 28 in the felodipine group).

The main results of the study are shown in Table 2.

Administration of valsartan and felodipine similarly reduced BP values. The mean decrease in SBP/DBP obtained after 16 weeks of treatment were 17.3/14 mmHg with valsartan (−10.8/13.8%, $p<0.001$ *vs.* placebo) and 17.9/12.6 mmHg with felodipine (−11.2/12.5%, $p<0.001$ *vs.* placebo), with no significant difference between the two drugs.

BMI was slightly but significantly reduced by valsartan (from 35.9±3.9 to 34.2±2.5 kg/m$^2$, −4.7%, $p<0.01$ *vs.* placebo), while felodipine did not significantly modify it (from 35.4±4.0 to 35.5±4.1 kg/m$^2$, +0.1%).

Valsartan produced a significant reduction in plasma L levels (from 36.7±18.5 to 33.0±17.1 ng/ml, −10.1%, $p<0.05$ *vs.* placebo), while felodipine did not significantly affect them (from 36.2±18.4 to 36.8±19.1 ng/ml, +0.6%).

A significant increase in plasma NE levels was observed with felodipine (from 324±112 to 448±122 pg/ml) but not with valsartan (from 332±113 to 286± 99 pg/ml, −13.8%); the difference between the two treatments was statistically significant ($p<0.01$).

HOMA-IR index was significantly reduced by valsartan treatment (from 7.7±2.4 to 6.1±2.1, −20%, $p<0.05$ *vs.* placebo), while felodipine did not influence it (from 7.8±2.5 to 7.5±2.4, −3.8%).

## Discussion

The results of this study show that in obese patients with mild to moderate essential hypertension monotherapy with valsartan and felodipine is effective in significantly lowering SBP and DBP values, with no statistical difference between the two treatments.

Despite equivalent BP reduction, felodipine did not influence plasma L levels, insulin resistance and BMI, while valsartan significantly reduced them. Furthermore, unlike valsartan, felodipine increased plasma NE levels.

The most original findings were those regarding the effects on plasma L. This hormone, whose levels have been found consistently elevated in obese hypertensive subjects, has multiple actions that may be important not only in the control of body fat and energy metabolism but also in physiologic and pathophysiologic cardio-renal regulation (*9–15*). Furthermore, L may directly contribute to atherogenesis through multiple mechanisms, such as oxidative stress, inhibition of apoptotic cell death, stimulation of vascular smooth muscle cell proliferation and migration, vascular calcification and impaired arterial distensibility (*31–33*). To our knowledge, few studies have evaluated the influence of antihypertensive drugs on plasma L levels. In sucrose-fed spontaneously hypertensive rats, Ang II receptor antagonists have been shown to reduce plasma L and L mRNA in adipose tissue (*23*, *34*), but data are lacking about the effects of these drugs in humans. In patients with essential hypertension, Ficek *et al*. observed that therapy with the Ang II converting enzyme inhibitor perindopril or the CCB felodipine did not influence leptinemia, whereas the β-blocker pindolol significantly decreased it (*24*). In the present study, unlike felodipine, valsartan produced a significant reduction in plasma L levels.

Mechanisms and clinical significance of such an effect remain unclear. Current evidence indicates that obesity activates the renin-Ang system (RAS) in adipose tissue as well in cardiovascular organs (*35*). Adipocytes contain a fully functional local RAS and Ang II activates the expression of adipocyte genes, including those that regulate L (*35–37*). Thus, inhibition of Ang II by Ang II receptor antagonists might result in reduced L production. However, further studies are needed to confirm this action. It should be studied whether pharmacological treatments that interfere with L levels can affect obesity-associated cardiovascular morbidity and mortality.

With the caution due to the fact that HOMA-IR, although acceptable, is not the most valid measure of insulin resistance, it is still noteworthy that valsartan improved insulin resistance in the present study, while felodipine had a neutral effect. Contrasting results have been reported in the literature about the effects of Ang II receptor antagonists on insulin sensitivity, with some studies showing no influence (*38–40*) and others an improvement (*41*, *42*). Such a discrepancy might depend on several factors that make the various studies poorly comparable (different baseline characteristics of both patients and animal models studied, different dosages of drugs used, different measures of insulin resistance *etc.*). Particular relevance has been attributed to baseline insulin sensitivity of hypertensive patients, in that Ang II antagonists seem to have neutral effect in subjects with normal insulin sensitivity, but improve it in insulin resistant subjects. Indeed, in the present study the reduction of insulin resistance by valsartan occurred in patients with enhanced insulin resistance at baseline.

As regards the effects on plasma NE levels, in agreement with most previous observations in the literature (*43–45*) treatment with felodipine produced a significant increase in NE values, while valsartan did not significantly affect them, although a decreasing trend was observed. With the limitation that plasma NE determinations, although widely used in clinical studies to assess sympathetic activity, provide only an indirect measure (*46*), our findings suggest that reflex sympathetic activation occurred during antihypertensive treatment with felodipine but not with valsartan, as a consequence of their different mechanism of hypotensive action. Although the exact contribution remains to be clarified, the use of drugs that do not activate the sympathetic nervous system should theoretically be beneficial, given the role of sympathetic activation in both the progression of hypertensive disease and the reduction of survival in cardiac patients (*47*, *48*).

It has already been reported that both the suppression of norepinephrine and improved insulin resistance in hypertension accompany weight loss in moderately obese people (*49*). The plasma L in humans has been reported to be closely correlated with both the fat mass and the subcutaneous fat (*50–52*). Segal *et al*. reported that insulin resistance was associated with elevated plasma L independent of body fat mass (*53*). On the other hand, Mohamed-Ali *et al*. found that plasma L correlated with insulin concentration, but not with insulin resistance (*54*). The possible relation of plasma L to insulin resistance remains controversial. A study suggested that mean BP and plasma L showed a significant positive correlation (*55*), but the relationship between changes in the plasma L and changes in BP after weight loss have yet to be elucidated. Itoh *et al*. found that obese hypertensive patients showed not only insulin resistance, evaluated by HOMA-IR index, but also high plasma L concentration, and the changes in plasma L correlated to the changes in BP after weight loss only in the obese hypertensive patients (*56*).

In our study we did not find any significant relationship among BMI, plasma L and HOMA-IR index, or any significant relationship when we divided patients into two subgroups according to each of these parameters (reduced-BMI group *vs.* a non-reduced-BMI group).

Interestingly, in the present study patients treated with valsartan experienced a reduction in BMI, despite no diet modification. Whether such an effect was a cause or a consequence of the observed modification in L levels and insulin resistance remains to be clarified. Correlation analysis, however, showed no relationship between BMI and plasma L changes.

In conclusion, the results of the present study suggest that in the treatment of obese hypertensive subjects, although the Ang II receptor antagonist valsartan and the CCB felodipine have equivalent BP-lowering effects, valsartan may offer an advantage due to its improvement of some obesity-related metabolic disorders, such as hyperleptinemia and insulin resistance, and its lack of sympathetic activation.

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