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ORIGINAL ARTICLE

Different actions of losartan and ramipril on adipose tissue activity and vascular remodeling biomarkers in hypertensive patients

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We planned a randomized, double blind clinical trial to evaluate whether an antihypertensive intervention at the proximal or distal level of the renin–angiotensin–aldosterone system could have different effects on a broad range of innovative cardiovascular risk biomarkers. A total of 288 hypertensive Caucasian patients (115 men and 113 women), aged ⩾18 years, were enrolled in this study. They were randomized to take losartan 50 mg per day or ramipril 5 mg per day for 1 month and titrated up to 100 mg per day and 10 mg per day for 13 months, respectively. At baseline, 1, 2 and 14 months after therapy initiation, we evaluated the following parameters: body weight, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), *M*-value, adiponectin (ADN), resistin (r), retinol binding protein-4 (RBP-4), visfatin, vaspin, high-sensitivity C-reactive protein (Hs-CRP), matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9). No variation of body weight, BMI, FPG or vaspin was obtained with either treatment. We recorded a similar improvement in SBP, DBP and Hs-CRP with both treatments; however, losartan also increased *M*-value, ADN and visfatin, whereas ramipril did not. Furthermore, losartan decreased r, RBP-4, MMP-2 and MMP-9, whereas ramipril did not have any effect on these parameters. In conclusion, we observed that short-term treatment with losartan improved several metabolic parameters (*M*-value, ADN, RBP-4, r and visfatin) and decreased vascular remodeling biomarkers (MMP-2 and MMP-9) in hypertensive subjects, whereas ramipril did not.
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INTRODUCTION

The increased risk of cardiovascular events appears to be related to a large number of factors, including hyperactivation of the renin–angiotensin–aldosterone system (RAAS),[1] direct vascular damage caused by hyperglycemia in diabetics,[2] systemic subclinical inflammation,[3] aberrant modulation of adipokine synthesis[4] and a pathological increase in the vascular remodeling rate.[5] Angiotensin II (Ang II), the major actor of the RAAS, acts through two receptor subtypes: Ang II type 1 (AT1R) and type 2 (AT2R). Activation of AT1R leads to elevated blood pressure (BP) through vasoconstriction increased cardiac output, aldosterone release and sodium reabsorption. In addition to these peripheral effects, AT1R also mediates the central effects of Ang II, including vasopressin release, water and salt intake and increased sympathetic drive, all of which contribute to the development of high BP. However, Ang II binding to the AT2R is thought to counteract AT1R-mediated effects.[6–7] Thus, international guidelines for BP management suggest that a blocker of the RAAS should be either the preferred monotherapy or a regular component of combination treatment to reach target BP.[8]

From a metabolic point of view, drugs interacting with the RAAS are usually defined as neutral in the sense that, contrary to β-blockers and thiazides, these drugs do not negatively interact with lipid and glucose metabolism.[9] However, some AT1R blockers could have positive metabolic effects because of a mild activating action on nuclear peroxisome proliferator-activated receptors.[10–12]

On the other hand, it is not yet clear whether angiotensin-converting enzyme inhibition or AT1R blockade have some action on adipokine metabolism. In particular, it is not clear whether these different therapeutic approaches could have a direct positive or negative modulating effect on insulin resistance similar to those seen with resistin (r) and visfatin.[13] Therefore, it is not known if RAAS blockade could significantly reduce the serum levels of vascular remodeling biomarkers, which are typically increased in patients at increased risk for cardiovascular disease;[14–15] such markers include

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matrix metalloproteinases (MMPs). In this context, we planned a randomized, double blind clinical trial to evaluate whether an antihypertensive intervention at the proximal or distal levels of the RAAS could have different effects on a broad range of innovative cardiovascular risk biomarkers.

METHODS

Study design and patients

This multicenter, randomized, double blind clinical trial was conducted in the Internal Medicine and Therapeutics Department at the University of Pavia and in the G Descovich Atherosclerosis Study Center, Internal Medicine, Aging and Kidney Disease Department at the University of Bologna. The study protocol was approved at each site by institutional review boards and was conducted in accordance with the Declaration of Helsinki and its amendments.

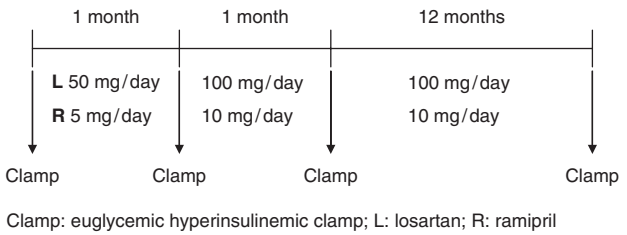
Patients

We enrolled 288 hypertensive Caucasian patients (115 men and 113 women), aged $\geqslant$18 years. Hypertension was defined as diastolic BP (DBP) $\geqslant$80 mm Hg and systolic BP (SBP) $\geqslant$130 mm Hg. Patients with secondary hypertension were excluded, as were patients with impaired liver function (defined as higher than normal plasma aspartate aminotransferase (normal values: 11–39 mU ml^{-1}) and alanine aminotransferase (normal values: 11–34 mU/ml^{-1}) and/or gamma-glutamyltransferase (normal values: 11–53 mU/ml^{-1})), impaired kidney function (defined as higher than normal serum creatinine level (normal values: 0.6–1.3 mg per 100 ml)) or anemia. Patients with unstable cardiovascular conditions (for example, New York Heart Association class I–IV congestive heart failure or a history of myocardial infarction or stroke) or past incidences of cerebrovascular conditions within 6 months of study enrollment were also excluded. Women who were pregnant, breastfeeding or who might become pregnant (because of inadequate contraceptive precautions) were also excluded. Patients with known contraindications or intolerance to sartans or angiotensin-converting enzyme inhibitors were also not included in the study.

Suitable subjects, identified from review of case notes and/or computerized clinic registers were contacted personally or by telephone. All patients provided written informed consent.

Treatments

Patients were randomized to take losartan 50 mg per day or ramipril 5 mg per day for 1 month and titrated to 100 mg per day and 10 mg per day for 13 months, respectively; the total treatment period was 14 months (Figure 1). Both losartan and ramipril were supplied as identical, opaque, white capsules in coded bottles to ensure the blind status of the study. Randomization was done using a drawing of envelopes containing randomization codes prepared by a statistician. A copy of the code was provided only to the person responsible for performing the statistical analysis. The code was only broken after database lock, but could have been broken for individual subjects in cases of an emergency. Medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits. At baseline, we weighed participants and gave them a bottle containing a supply of study medication for at least 100 days. Throughout the study, we instructed patients to take their first dose of new medication on the day after they were given the study medication. At the same time, all unused medication was retrieved for inventory. All medications were provided free of charge.



Clamp: euglycemic hyperinsulinemic clamp; L: losartan; R: ramipril

Figure 1 Study design. Clamp: euglycemic hyperinsulinemic clamp; L, losartan; R, ramipril.

Assessments

Before starting the study all patients underwent an initial screening assessment that included a medical history, physical examination, vital signs, a 12-lead electrocardiogram, measurements of body weight, body mass index (BMI), SBP, DBP, fasting plasma glucose, *M*-value, adiponectin (ADN), r, retinol binding protein-4 (RBP-4), visfatin, vaspin, high-sensitivity C-reactive protein (Hs-CRP) and matrix metalloproteinase-2 (MMP-2) and -9 (MMP-9).

To evaluate the tolerability assessments, all adverse events were recorded. All plasmatic parameters were determined after a 12-h overnight fast. Venous blood samples were taken for all patients between 0800 and 0900 h. We used plasma obtained by addition of Na_2-EDTA, 1 mg ml^{-1} and centrifuged the samples at 3000 *g* for 15 min at 4 °C. Immediately after centrifugation, the plasma samples were frozen and stored at −80 °C for no more than 3 months. All measurements were performed in a central laboratory.

Body mass index was calculated by the investigators as weight in kilograms divided by the square of height in meters. BP measurements were obtained from each patient (using the right arm) in the seated position, using a standard mercury sphygmomanometer (Erkameter 3000, ERKA, Bad Tolz, Germany) (Korotkoff I and V) with a cuff of appropriate size. BP was measured by the same investigator at each visit, in the morning, after the patient had rested for $\geqslant$10 min in a quiet room. Three successive BP readings were obtained at 1-min intervals, and the mean of the three readings was calculated.

Plasma glucose was assayed by the glucose-oxidase method (GOD/PAP, Roche Diagnostics, Mannheim, Germany) with intra- and interassays coefficients of variation (CsV) $<$2%.[16]

Adiponectin levels were determined using enzyme-linked immunosorbent assay (ELISA) kits (B-bridge International, Sunnyvale, CA, USA). Intraassay CsV were 3.6% for low-control and 3.3% for high-control samples, whereas interassay CsV were 3.2% for low-control and 7.3% for high-control samples.[17]

Resistin value was measured by a commercially available ELISA kit (BioVendor Laboratory Medicine, Brno, Czech Republic). Intraassay CsV was 3.4% and interassay CsV was 6.9%.[18]

Retinol binding protein-4 was measured using a RBP-4 (Human) enzyme immunoassay (EIA) kit (Phoenix Pharmaceuticals, Inc., Burlingame, CA, USA). The intra- and interassay CsV were less than 5.0% and less than 14.0%, respectively.[19]

Visfatin levels were measured by EIA kit obtained from Phoenix Pharmaceuticals. The intra- and interassays CsV were 10% and less than 14%, respectively.[20]

Vaspin was measured by a two-site ELISA method using commercially available ELISA kits (Adipogen, Seoul, Korea); the intra- and interassays CsV were 1.74% and 8.32%, respectively.[21]

High-sensitivity C-reactive protein was measured using a latex-enhanced immunonephelometric assays on a BN II analyzer (Dade Behring, Newark, DE, USA). The intra- and interassays CsV were 5.7% and 1.3%, respectively.[22]

MMP-2 and MMP-9 levels were determined by a two-site ELISA method using commercial reagents (Amersham Biosciences, Uppsala, Sweden). The intra- and interassays CsV for measuring MMP-2 levels were 5.4% and 8.3%, respectively.[23] The intra- and interassay CsV to evaluate MMP-9 levels were 4.9% and 8.6%, respectively.[24]

Glucose clamp technique

Insulin sensitivity (*M*-value) was assessed with the use of the euglycemic, hyperinsulinemic clamp, according to the technique described by De Fronzo *et al.*[25] At 0900 h, after the subjects had fasted for 12 h overnight, an intravenous catheter (18 g polyethylene cannula; Venflon, Viggo, Helsingborg, Sweden) was placed in an antecubital vein for infusion of insulin and 20% glucose. A second catheter was inserted in a retrograde fashion into a wrist vein. The hand was heated to about 70 °C in a thermoregulated box with the aim of arterializing venous blood within 20 to 40 min.[26] Plasma glucose was assessed at five 10-min intervals during the clamping. A 10-min priming infusion of insulin (Humulin R; Lilly Corporate, Indianapolis, IN, USA) was administered at a rate of 1 mU min^{-1} per kilogram for 2 h, during which time the plasma glucose concentration was held constant at the basal state (95 mg per 100 ml) by a variable infusion of exogenous glucose. The amount of glucose

required maintaining isoglycemia equals whole-body disposal of glucose, provided that endogenous glucose production is essentially absent. During insulin infusion, normal fasting blood glucose levels were maintained by adjustment of an infusion of a 20% glucose solution. The *M*-value (amount of glucose infused, that is, whole-body glucose disposal, expressed as μmol per minute per kilogram of body weight (μmol min^{-1} per kg)) was calculated as the mean value for each 20-min interval during the last 60 min of the clamp.

Statistical analysis

An intention-to-treat analysis was conducted in patients who had received more than one dose of study medication and had a subsequent observed efficacy. Patients were included in the tolerability analysis if they had received more than one dose of trial medication and had been observed to tolerate the medication. Considering a clinically significant difference to be ±10% compared with the baseline and an α error of 0.05, the actual sample size was adequate to obtain a power higher than 0.80 for all measured variables. Continuous variables were tested using repeated measurements of the analysis of variance. Intervention effects were adjusted for additional potential confounders using analysis of covariance. Analysis of variance was also used to assess the significance within and between groups. The statistical significance of the independent effects of treatments on the other variables was determined using analysis of covariance. Paired tests were also used: a one sample *t*-test was used to compare values obtained before and after treatment administration, and two sample *t*-tests were used for between-group comparisons.[27] Statistical analysis of data was performed using the Statistical Package for Social Sciences software, version 14.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± s.d. For all statistical analyses, $P<0.05$ was considered statistically significant.

RESULTS

Study sample

A total of 228 patients were enrolled in the study. Of these, 215 completed the study. Overall, 108 (50.2%) were allocated to the losartan group and 107 (49.8%) to the ramipril group. There were 13 patients (7 men and 6 women) who did not complete the study, and the reasons for premature withdrawal were side effects, such as nausea (one man in the losartan group after 1 month and one woman in the ramipril group after 1 month), headache (one man in the losartan group after 2 months and one woman in the ramipril group after 14 months) and dizziness (one woman in the losartan group after 1 month and one man in the ramipril group after 2 months), lost to follow-up (two men in the ramipril group after 1 and 2 months), protocol violation (one woman in the losartan group after 1 month), non-compliance (one man in the losartan group after 2 months and one man in the ramipril group after 14 months) and administrative errors (two women in the losartan group after 2 and 14 months). The characteristics of the patient population at study enrollment are shown in Table 1.

Body weight and BMI

We did not observe any significant variation of body weight or BMI with either treatment (Tables 2 and 3).

Fasting plasma glucose

Fasting plasma glucose did not change during the study in either group (Tables 2 and 3).

Blood pressure

We recorded a significant decrease in DBP and SBP in both groups compared with baseline after 2 and 14 months ($P<0.05$ and $P<0.01$, respectively) without significant differences between the two treatments (Tables 2 and 3).

Table 1 General and anthropometric patients characteristics at baseline in the study

	Patients characteristics
N	228
Gender (M/F)	115/113
Age (years)	54.5 ± 7.5
Sm st (M/F)	32/28
Hypert dur (months)	3.1 ± 1.2
Height (m)	1.68 ± 0.05
Weight (kg)	80.3 ± 4.9
BMI ($kg\,m^{-2}$)	28.3 ± 1.5
FPG (mg per 100 ml)	88 ± 10
SBP (mm Hg)	152 ± 10
DBP (mm Hg)	97 ± 8
TC (mg per 100 ml)	196 ± 13
LDL-C (mg per 100 ml)	131 ± 11
HDL-C (mg per 100 ml)	46 ± 6
Tg (mg per 100 ml)	97 ± 41

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; F, female; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; Hypert dur, hypertension duration; LDL-C, low-density lipoprotein cholesterol; M, male; SBP, systolic blood pressure; Sm st, smoking status; TC, total cholesterol; Tg, triglycerides.
Data shown are values expressed as means ± s.d. or *n*.

Lipid profile

We did not observe any significant variation in lipid profile with either losartan or ramipril.

Insulin resistance parameters

Increases in *M*-value and ADN were observed after 14 months compared with baseline with losartan, but not with ramipril; furthermore, the values obtained with losartan were significantly better than the values obtained with ramipril after 14 months ($P<0.05$) (Tables 2 and 3, Figure 2a).

Resistin and RBP-4 were lowered by losartan, but not by ramipril after 14 months ($P<0.05$) compared with baseline, and the values reached with losartan were significantly lower than the values reached with ramipril after 14 months ($P<0.05$) (Tables 2 and 3; Figures 2b and c).

Losartan significantly increased visfatin after 14 months compared with baseline ($P<0.05$); ramipril ($P<0.05$) had no effect on this parameter (Tables 2 and 3; Figure 2d).

Neither of the treatment reduced vaspin (Tables 2 and 3; Figure 2e).

Inflammatory parameters

An improvement of Hs-CRP was registered in both the groups after 14 months compared with baseline ($P<0.01$ for losartan and $P<0.05$ for ramipril), without any significant difference between the two groups (Tables 2 and 3, Figure 2f).

Matrix metalloproteinases

Losartan, but not ramipril, gave a reduction of both MMP-2 and MMP-9 after 14 months compared with baseline ($P<0.05$); furthermore, the values reached with losartan were significantly lower than the values reached with ramipril after 14 months of treatment ($P<0.05$) (Tables 2 and 3; Figures 3a and b).

Correlations

A stepwise multilinear regression analysis was undertaken to establish which metabolic factors could best predict insulin resistance

Table 2 Patients data during the study in losartan group

	Losartan			
	Baseline	*1 month*	*2 months*	*14 months*
N	115	112	109	108
Age (years)	55 ± 8	–	–	–
Gender (M/F)	58/57	57/55	55/54	55/53
Sm st (M/F)	17/12	16/11	15/11	15/11
Weight (kg)	80.5 ± 5.2	80.0 ± 4.9	79.7 ± 4.6	80.3 ± 4.8
BMI (kg m^{-2})	28.2 ± 1.5	28.0 ± 1.3	27.9 ± 1.2	28.1 ± 1.4
FPG (mg per 100 ml)	88 ± 10	87 ± 9	87 ± 9	88 ± 10
M (μmol min^{-1} per kg)	4.2 ± 2.1	4.5 ± 2.5	4.7 ± 2.6	5.9 ± 3.3*^
SBP (mm Hg)	151 ± 9	148 ± 8	139 ± 7*	126 ± 5**
DBP (mm Hg)	97 ± 8	94 ± 6	90 ± 5*	80 ± 4**
TC (mg per 100 ml)	197 ± 14	195 ± 12	196 ± 13	192 ± 10
LDL-C (mg per 100 ml)	132 ± 12	130 ± 9	131 ± 10	127 ± 7
HDL-C (mg per 100 ml)	45 ± 5	44 ± 4	46 ± 6	47 ± 7
Tg (mg per 100 ml)	101 ± 46	104 ± 47	99 ± 44	90 ± 36
ADN (μg ml^{-1})	6.1 ± 3.9	6.3 ± 4.0	6.5 ± 4.1	7.4 ± 4.5*^
Resistin (ng ml^{-1})	4.2 ± 1.2	4.0 ± 1.0	3.7 ± 0.8	3.1 ± 0.6*^
RBP-4 (μg ml^{-1})	23.7 ± 5.5	21.4 ± 5.1	17.5 ± 4.7	11.6 ± 2.9*^
Visfatin (ng ml^{-1})	14.2 ± 4.5	15.9 ± 5.2	17.1 ± 7.2	22.8 ± 9.9*^
Vaspin (ng ml^{-1})	0.7 ± 0.3	0.7 ± 0.3	0.6 ± 0.2	0.6 ± 0.2
Hs-CRP (mg l^{-1})	1.9 ± 0.8	1.8 ± 0.7	1.5 ± 0.5	1.1 ± 0.3°
MMP-2 (ng ml^{-1})	1491.6 ± 198.6	1364.2 ± 172.4	1144.8 ± 141.7	522.7 ± 96.9*^
MMP-9 (ng ml^{-1})	674.2 ± 72.8	602.8 ± 65.2	558.2 ± 54.7	251.7 ± 36.4*^

Abbreviations: ADN, adiponectin; BMI, body mass index; DBP, diastolic blood pressure; F, female; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; M, male; MMP-2, metalloproteinases-2; MMP-9, metalloproteinases-9; RBP-4, retinol binding protein-4; SBP, systolic blood pressure; Sm st, smoking status; TC, total cholesterol; Tg, triglycerides.
Data shown are values expressed as means ± s.d.
*$P<0.05$ *vs.* baseline; °$P<0.01$ *vs.* baseline; **$P<0.001$ *vs.* baseline; ^$P<0.05$ *vs.* ramipril.

Table 3 Patients data during the study in ramipril group

	Ramipril			
	Baseline	*1 month*	*2 month*	*14 month*
N	113	111	109	107
Age (years)	54 ± 7	–	–	–
Gender (M/F)	57/56	56/55	54/55	53/54
Sm st (M/F)	15/16	14/16	14/16	14/15
Weight (kg)	80.2 ± 4.7	80.0 ± 4.9	79.3 ± 4.4	78.7 ± 4.1
BMI (kg m^{-2})	28.4 ± 1.6	28.2 ± 1.5	28.1 ± 1.4	27.9 ± 1.2
FPG (mg per 100 ml)	87 ± 9	88 ± 10	86 ± 8	87 ± 9
M (μmol min^{-1} per kg)	4.1 ± 2.0	4.2 ± 2.1	4.3 ± 2.2	4.4 ± 2.4
SBP (mm Hg)	152 ± 10	149 ± 9	141 ± 8*	127 ± 6**
DBP (mm Hg)	96 ± 7	93 ± 5	89 ± 4*	79 ± 3**
TC (mg per 100 ml)	195 ± 12	196 ± 13	193 ± 11	190 ± 9
LDL-C (mg per 100 ml)	129 ± 8	133 ± 14	127 ± 7	126 ± 5
HDL-C (mg per 100 ml)	47 ± 7	45 ± 5	47 ± 7	46 ± 6
Tg (mg per 100 ml)	94 ± 38	91 ± 35	95 ± 39	88 ± 33
ADN (μg ml^{-1})	6.0 ± 3.7	6.1 ± 3.8	6.3 ± 4.0	6.5 ± 4.1
Resistin (ng ml^{-1})	4.4 ± 1.3	4.2 ± 1.2	4.2 ± 1.2	4.1 ± 1.1
RBP-4 (μg ml^{-1})	23.1 ± 5.3	22.8 ± 5.2	22.1 ± 5.0	21.6 ± 4.9
Visfatin (ng ml^{-1})	14.5 ± 4.6	14.6 ± 4.7	14.8 ± 4.8	14.9 ± 4.9
Vaspin (ng ml^{-1})	0.8 ± 0.4	0.7 ± 0.3	0.6 ± 0.2	0.7 ± 0.3
Hs-CRP (mg l^{-1})	1.8 ± 0.7	1.7 ± 0.6	1.7 ± 0.6	1.4 ± 0.4*
MMP-2 (ng ml^{-1})	1405.8 ± 171.2	1399.2 ± 163.4	1391.6 ± 154.1	1388.3 ± 148.6
MMP-9 (ng ml^{-1})	681.4 ± 79.5	637.6 ± 77.2	591.5 ± 73.8	567.4 ± 70.1

Abbreviations: ADN, adiponectin; BMI, body mass index; DBP, diastolic blood pressure; F, female; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high-sensitivityC-reactive protein; LDL-C, low-density lipoprotein cholesterol; M, male; MMP-2, metalloproteinases-2; MMP-9, metalloproteinases-9; RBP-4, retinol binding protein-4; SBP, systolic blood pressure; Sm st, smoking status; TC, total cholesterol; Tg, triglycerides.
Data shown are values expressed as means ± s.d.
*$P<0.05$ *vs.* baseline; **$P<0.001$ *vs.* baseline.

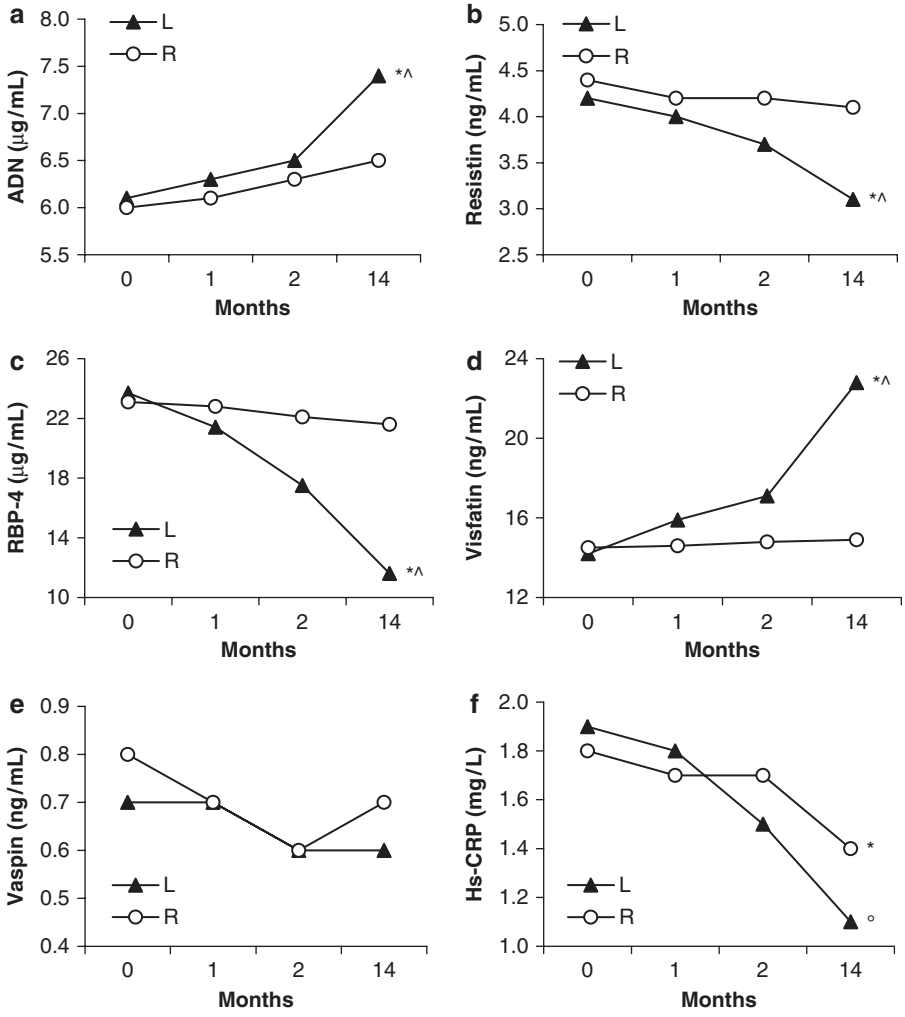


Figure 2 Variation of insulin resistance and inflammatory parameters in losartan and ramipril group. *$P<0.05$ *vs.* baseline; °$P<0.01$ *vs.* baseline; ^$P<0.05$ *vs.* ramipril **a**: ADN, adiponectin; **b**: resistin; **c**: RBP-4, retinol binding protein-4; **d**: visfatin; **e**: vaspin; **f**: Hs-CRP, high-sensitivity C-reactive protein.

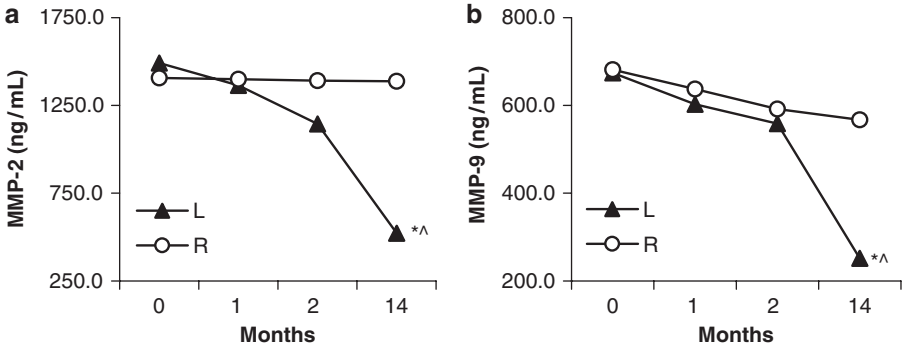


Figure 3 Variation of metalloproteinases-2 and -9 in losartan and ramipril group. *$P<0.05$ *vs.* baseline; ^$P<0.05$ *vs.* ramipril **a**: MMP-2, metalloproteinases-2; **b**: MMP-9, metalloproteinases-9.

(*M*-value) improvement. The significant predictors of change in insulin resistance (*M*-value) were RBP-4 ($r = -0.59$, $P<0.01$), r ($r = -0.63$, $P<0.01$), ADN ($r = 0.61$, $P<0.01$), MMP-2 ($r = -0.54$, $P<0.05$) and MMP-9 ($r = -0.55$, $P<0.05$) concentrations in the losartan group. Other correlation analysis did not indicate patterns of association.

DISCUSSION

In our double blind, randomized clinical trial carried out on hypertensive patients, we observed that, beyond a similar BP reduction and Hs-CRP decrease, only losartan-treated patients, not ramipril-treated patients, experienced a significant improvement in insulin sensitivity (+40.5%), ADN (+21.3%), r (−26.2%), RBP-4

(−51.1%), visfatin (+60.6%), MMP-2 (−64.9%) and MMP-9 (−62.6%).

Contrasting findings support a weaker insulin-sensitizing effect of losartan in hypertensive patients. In fact, some authors observed an improvement in insulin resistance associated with a reduction in ADN,[28] others observed improvements of both[29] and still others found no improvement at all.[30] Adiponectin is a protein exclusively synthesized by adipocytes; it is decreased in obesity and inversely related to glucose and insulin.[31] Ablation of the ADN gene in mice results in insulin resistance, glucose intolerance, dyslipidemia and increased susceptibility to vascular injury and atherosclerosis.[32–34] Adiponectin reverses these abnormalities by stimulating oxidation of fatty acids, suppressing gluconeogenesis, inhibiting monocyte adhesion and inhibiting macrophage transformation, as well as proliferation and migration of smooth muscle cells in blood vessels.[17,32,35] In our study, we observed an improvement in both insulin resistance and adiponectinemia in losartan-treated patients. In contrast to other studies,[36] we did not observe any significant change in adiponectinemia in ramipril-treated patients. With regard to the other adipokines, RBP-4 concentration has been reported to be increased in obese subjects and insulin-resistant subjects compared with lean subjects.[37] Still, the mechanisms by which RBP-4 induces insulin resistance are not well understood. On the other hand, r is produced by mononuclear cells and activated macrophages; it has been demonstrated that overexpression of r decreases the ability of insulin to suppress hepatic glucose output and increase glucose uptake by muscle.[38] Available data also support a role of r in determining an increase of inflammation and atherosclerosis.[39] The positive effect of losartan in reducing r had already been observed in an experimental model of acute hyperinsulinemia in healthy humans.[40] However, to the best of our knowledge, no other study, except ours, has evaluated the effects of either losartan or ramipril on such a large spectrum of adipokines.

Insulin-sensitizing action of losartan appears not to be related to adipokines or inflammatory markers.[41] Even if previous literature considered losartan inert with regards to its effect on peroxisome proliferator-activated receptor gamma, recent data support the possibility that its active metabolite, EXP3174, stimulates peroxisome proliferator-activated receptor gamma at conventional losartan dosages.[42] This finding could explain part of the positive losartan metabolic effects together with the fact that the AT2R is left unoccupied. Furthermore, given the selective AT1R blockade of losartan, its activation by Ang II can help reinforce these positive effects.

In vitro experiments show that Ang II induces MMP-9 expression.[43] This observation is in agreement with the observations of our trial, in which we first observed the ability of losartan to decrease the serum levels of MMP-2 and MMP-9. However, this result is in contrast with a previous clinical trial that did not demonstrate an ability of losartan to decrease MMP-9 in hypertensive, non-diabetic subjects by leveraging AT1 inhibition.[44] The reason for this disagreement may be because of the shorter period of administration of antihypertensive drugs in the study by Li-Saw-Hee[44] (2 months) compared with our study in which losartan or ramipril was administered for 14 months.

Angiotensin II also induces CRP generation.[45] Treatment with losartan was already known to reduce CRP level in type-2 diabetics,[45] but no data are available about this effect in non-diabetic hypertensive subjects. On the other hand, CRP reduction has also been observed with ramipril.[46] In this context, our results obtained in non-diabetic hypertensive subjects are in agreement with these previous observations.

Our study has some limitations. The main one is that we considered a single marker of insulin resistance (M) and a single marker of subclinical inflammation (Hs-CRP) and we did not evaluate the effect of both treatments on MMP activity. However, we evaluated a large number of parameters (most of them innovative) regarding a wide range of metabolic aspects, particularly those related to adipose tissue activity. Another problem is the relatively short duration of our observation. We were only able to clearly observe the differing metabolic effects of losartan and ramipril in this observation window. It is possible that ramipril could have some similar metabolic effects to losartan that are only observed during a longer follow-up period.

In conclusion, we observed that in a randomized clinical trial, short-term treatment with losartan improved several metabolic parameters (M, ADN, RBP-4, r and visfatin) and reduced vascular remodeling biomarkers (MMP-2 and MMP-9) in hypertensive subjects, whereas ramipril did not. These results increase the interest in AT1 blockade effects on cardiovascular risk factor modulation and should encourage the use of losartan over ramipril in clinical practice, especially in diabetic subjects where the cardiovascular risk is higher compared with non-diabetic subjects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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