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Effects of olmesartan vs irbesartan on metabolic parameters and visfatin in hypertensive obese women

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Abstract. – *Background:* **Angiotensin II regulates the production of adipokines. The objective was to study the effect of treatment with irbesartan versus olmesartan in obese hypertensive women.**

Subjects: **A sample of 34 obese hypertensive women was analyzed in a prospective way with a randomized trial. Patients were randomized to irbesartan (300 mg/day) or olmesartan (40 mg/day) for 3 months. Weight, body mass index, blood pressure, basal glucose, insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, HOMA and visfatin were determined at basal time and after 3 months of treatment.**

Results: **Thirty four patients gave informed consent and were enrolled in the study. A significative decrease in systolic and diastolic blood pressures was reached without changes in weight. Patients treated with olmesartan had a significative decrease of total cholesterol, LDL cholesterol, insulin, HOMA and visfatin levels. Decrease in total cholesterol and LDL cholesterol was similar with both angiotensin receptor blockers. Decrease in insulin (2.28±2.77 vs 0.66±4.4 mUI/L: $p<0.05$), HOMA (0.69±1.1 vs 0.48±1.6 units: $p<0.05$) and visfatin (5.16±13 vs 1.85±9.1 ng/ml: $p<0.05$)levels was higher in olmesartan than irbesartan group.**

Conclusion: **The administration of olmesartan improved blood pressure, insulin, HOMA, visfatin and lipid profile in hypertensive obese women. Irbesartan improved blood pressure and lipid levels.**

Key Words:

Angiotensin blockers, Hypertension, Insulin resistance, Obese, Visfatin, Women.

Introduction

Obesity and insulin resistance are associated with cardiovascular risk factors, including altered levels of adipocytokines[1]. Epidemiologic evidence of this rising tide of obesity and associated pathologies has led, in the last years, to a dramatic increase of researches on the role of adipose tissue as an active participant in controlling the body's physiology[2].

Visfatin was recently identified as a protein preferentially expressed in visceral adipose tissue, compared with subcutaneous adipose tissue[3]. It can be found in skeletal muscle, liver, bone marrow and lymphocytes, where it was initially identified as pre-B-cell colony-enhancing factor (PBEF). Fukuhara et al[4] clearly suggested an endocrine role for visfatin. It can not be excluded that visfatin might also have a paracrine effect on the visceral adipose tissue through its pro-adipogenic and lipogenic actions. In fact, the over expression of visfatin in a preadipocyte cell line facilities its differentiation to mature adipocytes and promotes the accumulation of fat through the activation of glucose transport. Contrary to the most intuitive hypothesis, visfatin treatment did not promote insulin resistance, but actually exhibited insulin mimetic properties resulting in a stimulating muscle and adipocyte glucose transport and inhibiting hepatocyte glucose production. Therefore, the mechanism of action of visfatin results in a glucose lowering effect.

Circulating angiotensin II, the active product of the renin-angiotensin system, is a hormonal regulator of cardiovascular function and electrolyte metabolism. Angiotensin II is also produced by local renin-angiotensin system in many organs including adipose tissue, which is, in turn, an important source of the angiotensin II precursor angiotensinogen. Moreover, formation and release of adipocytokines are apartly regulated via PPAR-dependent pathways. This has been demonstrated in rosiglitazone-treated rats em-

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ploying analysis of mRNA expression of visfatin in visceral fat[5] and was corroborated in isolated human adipocytes[6], which release visfatin upon incubation with rosiglitazone. Recently, one study[7] has demonstrated an activation of PPARgamma and release of visfatin with telmisartan and valsartan in isolated human adipocytes and skeletal muscle. The discovery of this curious new adipokine has great potential to significantly enhance our understanding of hypertension and its treatment[8].

To investigate this potential effect of angiotensin II system blockade on visfatin, we studied the effect of treatment with olmesartan versus irbesartan in a randomized clinical trial in obese hypertensive women.

Subjects and Methods

Subjects

A sample of 34 obese hypertensive women with mild to moderate hypertension was analyzed in a prospective way with an open-randomized trial. We used WHO[9] definitions for hypertension defined as systolic and diastolic blood pressure >140 or >90 mm Hg, respectively. The study has been approved by the local Ethic Committee and written informed consent was obtained.

Procedure and Calculations

Patients were randomized (computed generated list) to olmesartan (40 mg/day) or irbesartan (300 mg/day) for 3 months. Weight, body mass index, blood pressure, basal glucose, insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, HOMA and visfatin levels were measured at basal time and after 3 months of treatment.

Body weight was measured to an accuracy of 0.1 kg and body mass index (BMI) was calculated as follows: BMI= body weight (kg)/(body height $(m)^2$.

Blood pressure was measured twice after a 10 minutes rest with a random zero mercury sphygmomanometer, and averaged.

Assays

Serum total cholesterol and triglyceride concentrations were determined by enzymatic colorimetric assay (Technicon Instruments, Ltd., New York, N.Y., USA), while HDL cholesterol was determined enzymatically in the supernatant after precipitation of other lipoproteins with dextran sulphate-magnesium. LDL cholesterol was calculated using Friedewald formula. Glycated haemoglobin was measured as HbA_{1c} by HPLC (Menarini, Florence, Italy). Plasma glucose levels were determined by using an automated glucose oxidase method (Hitachi 917, Roche Diagnostics, Mannheim, Germany). Insulin was measured by enzymatic colorimetry (Insulin, WAKO Pure-Chemical Industries, Osaka, Japan). The homeostasis model assessment for insulin sensitivity (HOMA) was calculated as follows: HOMA = (glucose × insulin)/22.5[10].

Visfatin was analyzed using a commercially available ELISA kit (Phoenix Peptides, Belmont, CA, USA). Assay sensitivity was 2 ng/ml and interassay and intraassay coefficients of variation were less than 10% and less than 5%, respectively.

Statistical Analysis

A power calculation based on visfatin improvement was performed. Twelve patients in each group were necessary to detect a change of 4 ng/dl in visfatin levels, with an error type I <0.05 and a statistical power of 80%. The results were expressed as average ± standard deviation.

Table I. Clinical and epidemiological characteristics of study population.

Characteristics	Olmesartan n = 17	Irbesartan n = 17	p
Age(yrs)	58.4 ± 8.6	58.6 ± 10	ns
BMI(kg/m^2)	31.9 ± 5.9	32.0 ± 3.9	ns
Weight (kg)	85.8 ± 10	86.6 ± 14	ns
Systolic BP (mmHg)	150.9 ± 17.3	154.3 ± 16.4	ns
Diastolic BP (mmHg)	85.1 ± 9.4	84.2 ± 9.1	ns

BP: Blood pressure. ns: no significative.

Table II. Changes in anthropometric variables and blood pressure.

Parameters	Olmesartan (n = 17)		Irbesartan (n = 17)	
	Baseline	3 months	Baseline	3 months
BMI(kg/m^2)	31.9 ± 5.9	31.7 ± 5.3	32.0 ± 3.9	31.8 ± 6.1
Weight (kg)	85.8 ± 10	85.3 ± 9.9	86.6 ± 9.1	86.1 ± 6.9
Systolic BP (mmHg)	150.9 ± 17	134.9 ± 8.9*	154.3 ± 16.4	125.6 ± 14.9*
Diastolic BP (mmHg)	85.1 ± 9.4	78.2 ± 7.9*	84.2 ± 9.1	76.8 ± 8.1*

BP: Blood pressure. t-Student test and Wilcoxon test were used as statistical methods. (*) $p<0.05$, in each group with basal values.

The distribution of variables was analyzed with Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with a two-tailed, paired Student's-t test. Non-parametric variables were analyzed with the Wilcoxon tests. Qualitative variables were analyzed with the chi-square test, with Yates correction as necessary, and Fisher's test. A p-value under 0.05 was considered statistically significant.

Results

Thirty four patients gave informed consent and were enrolled in the study. Baseline characteristics of patients were presented in Table I, without statistical differences.

Table II shows a significative decrease in systolic and diastolic blood pressures without changes in weight. The decrease of systolic and diastolic blood pressure was similar with both drugs.

Table III shows the differences in classic cardiovascular risk factors and visfatin levels. Patients treated with olmesartan had a significative decrease of total cholesterol, LDL cholesterol, insulin, HOMA and visfatin levels. Decrease in total cholesterol and LDL cholesterol was similar with both angiotensin receptor blockers. Decrease in insulin (2.28±2.77 vs 0.66±4.4 mUI/L: $p<0.05$), HOMA(0.69±1.1 vs 0.48±1.6 units: $p<0.05$) and visfatin (5.16±13 vs 1.85±9.1 ng/ml: $p<0.05$) levels was higher in olmesartan than irbesartan group.

Discussion

The major finding of this study was that olmesartan significantly improved lipid, HOMA, in-

Table III. Classical cardiovascular risk factors and visfatin.

Parameters	Olmesartan (n = 17)		Irbesartan (n = 17)	
	Baseline	3 months	Baseline	3 months
Glucose (mg/dl)	143.1 ± 41	139.5 ± 28	145.2 ± 36	135.7 ± 45
Total ch. (mg/dl)	218 ± 47	198 ± 45*	208 ± 35	187.1 ± 22*
LDL-ch. (mg/dl)	134 ± 47	111.7 ± 28*	133.9 ± 47	112.4 ± 35*
HDL-ch. (mg/dl)	55.4 ± 10	56.3 ± 12.6	48.5 ± 10	48.1 ± 12
TG (mg/dl)	146 ± 55	145 ± 67	153.5± 96	139.3± 57
Insulin (mUI/L)	12.9 ± 4.5	9.7 ± 3.5*	16.2 ± 10	15.6 ± 9.1
HOMA (units)	3.1 ± 1.2	2.3 ± 0.9*	4.7 ± 1.7	4.3 ± 2.1
Visfatin (ng/ml)	17.7 ± 13.1	12.5 ± 4.5*	15.1 ± 9.8	13.2 ± 6.1

BP: Blood pressure. t-Student test and Wilcoxon test were used as statistical methods. (*) $p<0.05$, in each group with basal values.

sulin and visfatin levels. However, irbesartan improved only lipid levels. Both drugs had the same beneficial effect on blood pressure levels.

Furuhashi et al[11] showed that blockade of the renin-angiotensin system by angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin II receptor blocker (ARB)decreased adipocyte size with improvement in insulin sensitivity. Other study[12] suggests that the candesartan-induced decrease in plasma insulin level might be induced an increase in plasma adiponectin in patients with renal dysfunction. In agreement with these results, the blockades of renin-angiotensin system are reported to decrease plasma insulin level and to increase plasma adiponectin level in patients without renal dysfunction, too[13,14]. Our study did not measure adiponectin levels, but olmesartan decrease visfatin levels. This significant decrease could explain the metabolic effects of olmesartan. There is a general consensus that angiotensin II has a trophic role in adipose tissue[11,12]. However the effects of angiotensin II on adipocyte metabolism and differentiation are not conclusive[13,14], while others show that angiotensin II promotes it[11]. In animal models, angiotensin II AT1 receptor blockers enhanced insulin sensitivity and improved the serum lipid profile in obese[15].

The physiological role of visfatin is still poorly understood. Animal data have described a synergism between visfatin and insulin to enhance cellular glucose uptake[16]. Elevated plasma visfatin concentrations have been described in obese subjects and diabetics patients[17]. Moreover, weight reduction after a hypocaloric diet has been associated with a significant decrease in circulating concentrations of visfatin in midly obese subjects[18]. Recently, one in vitro study[7] has demonstrated an activation of PPARgamma and release of visfatin with telmisartan and valsartan in isolated human adipocytes and skeletal muscle.

With our results and previous published data it is unclear if an acute visfatin release "in vitro studies" may serve a feed back mechanism for sudden changes in glucose concentrations or a chronic visfatin decrease "hypocaloric diet studies or other interventiosn such as angiotensin receptor blockers" could improve metabolic parameters in obese patients.

In summary, the administration of olmesartan improved blood pressure, insulin, HOMA, visfatin and lipid profile in hypertensive obese women. Irbesartan improved blood pressure and lipid levels. These results suggest that olmesartan could have pleiotropic effects on adipose tissue and might be more useful in preventing atherosclerosis in hypertensive obese women[19].

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