

Original

Effects of telmisartan vs olmesartan on metabolic parameters, insulin resistance and adipocytokines in hypertensive obese patients

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Abstract

Background: Angiotensin II regulates the production of adipokines. The objective was to study the effect of treatment with telmisartan versus olmesartan in hypertensive obese and overweight patients.

Subjects: A sample of 65 overweight and obese patients with mild to moderate hypertension was analyzed in a prospective way with a randomized trial. Patients were randomized to telmisartan (80 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, QUICKI, leptin and adiponectin were determined at basal time and after 3 months of treatment.

Results: Sixty five patients gave informed consent and were enrolled in the study. Patients treated with telmisartan had a significant decrease of glucose 10.53 mg/dl (CI 95%: 2.6-18.5), insulin 2.51 mUI/L (CI 95%: 2.07-7.17) and HOMA 1.08 (CI 95%: 0.39-2.55). Patients treated with olmesartan had a significant decrease of total cholesterol 20.2 mg/dl (CI 95%: 5.8-34.9) and LDL cholesterol 22.6 mg/dl (CI 95%: 9.7-35.6). Only leptin levels have a significant decrease in telmisartan group 7.39 ng/ml (CI 95%: 1.47-13.31).

Conclusion: Telmisartan improved blood pressure, glucose, insulin, HOMA and leptin in hypertensive diabetic patients. Olmesartan improved blood pressure and lipid levels.

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Key words: *Adiponectin. Hypertension. Insulin resistance. Leptin. Olmesartan. Telmisartan.*

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EFFECTOS DE TELMISARTAN VS OLMESARTAN SOBRE PARÁMETROS ANTROPOMÉTRICOS, RESISTENCIA A LA INSULINA Y ADIPOCITOQUINAS EN PACIENTES HIPERTENSOS OBESOS

Resumen

Introducción: La angiotensina II puede regular la producción de adipocitoquinas. El objetivo de nuestro trabajo fue evaluar el efecto sobre parámetros bioquímicos del tratamiento con telmisartan versus olmesartan en pacientes obesos hipertensos.

Pacientes: Se analizó una muestra de 65 pacientes con hipertensión moderada severa y obesidad, mediante un ensayo clínico randomizado. Los pacientes fueron randomizados en dos ramas; telmisartan (80 mg/día) u olmesartan (40 mg/día) durante 3 meses. Se determinaron en el tiempo basal y tras 3 meses los siguientes parámetros; peso, índice de masa corporal, presión arterial, glucosa, insulina, colesterol total, LDL-colesterol, HDL-colesterol, triglicéridos, HOMA, QUICKI, leptina y adiponectina.

Resultados: Los pacientes que recibieron telmisartan tuvieron una disminución significativa de los niveles de glucosa 10,53 mg/dl (CI 95%: 2,6-18,5), insulina 2,51 mUI/L (CI 95%: 2,07-7,17) y HOMA 1,08 (CI 95%: 0,39-2,55). Los pacientes tratados con olmesartan presentaron una disminución significativa de colesterol 20,2 mg/dl (CI 95%: 5,8-34,9) y LDL colesterol 22,6 mg/dl (CI 95%: 9,7-35,6). Solo, los niveles de leptina disminuyeron de manera significativa con telmisartan 7,39 ng/ml (CI 95%: 1,47-13,31).

Conclusion: Telmisartan mejora los niveles de presión arterial, glucosa, insulina, HOMA y leptina en pacientes hipertensos obesos. Olmesartan mejoró los niveles de presión arterial y el perfil lipídico.

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Palabras clave: *Adiponectina. Hipertensión. Resistencia a la insulina. Leptina. Olmesartan. Telmisartan.*

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 research on the role of adipose tissue as an active participant in controlling pathologic processes.^{2,3}

The current view of adipose tissue is that of an active secretory organ, sending out and responding to signals that modulate appetite, insulin sensitivity, energy expenditure, inflammation and immunity. Adipocytokines are proteins produced mainly by adipocytes.⁴ These molecules have been shown to be involved in the pathogenesis of the metabolic syndrome and cardiovascular disease. Adiponectin is an adipocyte-derived collagen like protein identified through an extensive search of adipose tissue. Hypoadiponectinemia increased risk of coronary artery disease together with the presence of multiple risk factors, indicating that adiponectin is a key factor of the metabolic syndrome.⁵ Leptin is a 16 KDa protein secreted primarily from adipocytes. Recent reports suggest that leptin contributes to atherosclerosis and cardiovascular disease in obese patients.⁶ Insulin resistance and hyperinsulinemia are characteristic findings of this metabolic syndrome (MetS) and are very common in patients with essential hypertension.⁷

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 systems in many organs including adipose tissue.⁸ In addition, angiotensin II regulates the production of adipokines. Angiotensin II increases the expression and the release of pro-inflammatory cytokines,⁹ increases leptin ob gene expression and secretion,¹⁰ and reduces plasma levels and gene expression of adiponectin, and insulin-sensitizing, anti-inflammatory adipokine.¹¹ In turn, blockade of the renin-angiotensin system with inhibitors of angiotensin II formation or angiotensin II AT1 receptor blockers decreases body weight, improves insulin-sensitivity and prevents development of insulin resistance.¹² Telmisartan and olmesartan are two antagonists of angiotensin II receptors used as antihypertensive drugs.

To clarify the effect of angiotensin II system blockade on adipocytokines, we studied the effect of treatment with telmisartan versus olmesartan in a randomized clinical trial in hypertensive obese and overweight patients.

Subjects and methods

Subjects

A sample of 65 obese and overweight patients with mild to moderate hypertension was analyzed in a

prospective way with an open-randomized trial. We used WHO/ISH¹³ definitions for hypertension defined as systolic and diastolic blood pressure > 140 or > 90 mmHg, respectively. These patients were studied in an Endocrinology Unit and written informed consent was obtained. The study has been approved by the local ethics committee. Exclusion criteria included a history of cardiovascular disease or stroke during the previous 36 months, total cholesterol > 300 mg/dl, triglycerides > 400 mg/dl, blood pressure > 140/90 mmHg, the use of sulfonylurea, metformine, acarbose, thiazolidinediones, insulin, glucocorticoids, antineoplastic agents, angiotensin-converting enzyme inhibitors, psychoactive medications, drinking and/or smoking habit.

Procedure and calculations

Patients were randomized to telmisartan (80 mg/day) or olmesartan (40 mg/day) for 2 months. Weight, body mass index, blood pressure, basal glucose, insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, leptin and adiponectin 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: $BMI = \text{body weight (kg)} / (\text{body height (m)})^2$.

The homeostasis model assessment for insulin sensitivity (HOMA) was calculated as follows: $HOMA = (\text{glucose} \times \text{insulin}) / 22.5$.¹⁴ Quantitative Insulin-Sensitivity Check index (QUICKI), a surrogate index of insulin sensitivity, was calculated as follows: $QUICKI = 1 / (\log(\text{insulin}) + \log(\text{glucose}))$.¹⁵

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. 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).

Adipocytokines

Leptin was measured by ELISA (Diagnostic Systems Laboratories, Inc., Texas, USA) with a sensitivity

Table I
Clinical and epidemiological characteristics of study population

Characteristics	Telmisartan n = 34	Olmesartan n = 31	P
Male/female	14/20	12/19	ns
Age(years)	56.2 ± 14.7	59.8 ± 15.7	ns
BMI(kg/m ²)	29.2 ± 5.9	29.9 ± 3.6	ns
Weight (kg)	78.9 ± 11.1	77.8 ± 9.6	ns
Systolic BP (mmHg)	150.7 ± 19.1	145.6 ± 15.1	ns
Diastolic BP (mmHg)	85.7 ± 9.4	85.9 ± 9.1	ns

BP: Blood pressure; ns: no significant.

of 0.05 ng/ml and a normal range of 10-100 ng/ml. Adiponectin was measured by ELISA (R&D systems, Inc., Mineapolis, USA) with a sensitivity of 0.246 ng/ml and a normal range of 865-21424 ng/ml. Ratio adiponectin/leptin levels were calculated.

Statistical analysis

A power calculation based on weight improvement was performed. Thirty patients in each group were necessary to detect a change of 6 ng/dl in leptin levels, with an error type I < 0.05 and a statistical power of 80%.

The results were expressed as average ± standard deviation. 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 and ANOVA test. Non-parametric variables were analyzed with the Friedman and 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

Sixty five patients gave informed consent and were enrolled in the study. Baseline characteristics of patients were presented in table I, without statistical differences.

Table II
Changes in anthropometric variables and blood pressure

Parameters	Telmisartan (n=34)		Olmesartan (n=31)	
	Baseline	3 months	Baseline	3 months
BMI	29.2±5.9	29.6±8.5	29.9±3.6	29.8±5.2
Weight (kg)	78.9±11.1	79.0±10	77.8±9.6	77.7±9.5
Systolic BP (mmHg)	150.7±19.1	126.3±7.7*	145.6±15.1	124.8±9.6*
Diastolic BP (mmHg)	85.7±9.4	76.2±8.3*	85.9±9.1	80.5±6.6*

BP: Blood pressure.

T Student test and Wilcoxon test were used as statistical methods.

* p < 0.05, in each group with basal values.

Table III
Classical cardiovascular risk factors

Characteristics	Telmisartan (n=34)		Olmesartan (n=31)	
	Baseline	3 months	Baseline	3 months
Glucose (mg/dl)	139.6 ± 35	129.1 ± 28*	138.2 ± 36	134.2 ± 41
Total ch. (mg/dl)	198.1 ± 37	200.4 ± 30	214.2 ± 41	193.8 ± 43*
LDL-ch. (mg/dl)	101.1 ± 31	108.4 ± 36	127.4 ± 39	104.7 ± 37*
HDL-ch. (mg/dl)	52.3 ± 9.8	52.4 ± 9.6	51.2 ± 10.7	50.9 ± 12.9
TG (mg/dl)	169 ± 71	181 ± 86	183.5 ± 98	169.9 ± 77
Insulin (mUI/L)	14.1 ± 9.1	11.6 ± 8.2*	15.9 ± 8.9	14.8 ± 8.4
HOMA	4.9 ± 3.7	3.9 ± 3.1*	4.7 ± 4.9	4.5 ± 3.7
QUICKI	0.54 ± 0.11	0.56 ± 0.14	0.51 ± 0.07	0.6 ± 0.07

LDL-ch: low density lipoprotein. HDL: high density lipoprotein. Chol: Cholesterol. TG: Triglycerides.

(HOMA): Homeostasis model assessment, HOMA = (glucose x insulin)/22.5

(QUICKI): Quantitative Insulin-Sensitivity Check index, QUICKI = 1/(log(insulin)+ log(glucose))

T Student test and Wilcoxon test were used as statistical methods.

(*) p < 0.05, in each group with basal values.

Table II shows a significantly decrease in systolic and diastolic blood pressures without changes in weight, with both treatments.

Table III shows the differences in classic cardiovascular risk factors. Patients treated with telmisartan had a significantly decrease of glucose 10.53 mg/dl (CI 95%: 2.6-18.5), insulin 2.51 mUI/L (CI 95%: 2.07-7.17) and HOMA 1.08 (CI 95%: 0.39-2.55). Patients treated with olmesartan had a significantly decrease of total cholesterol 20.2 mg/dl (CI 95%: 5.8-34.9) and LDL cholesterol 22.6 mg/dl (CI 95%: 9.7-35.6).

Table IV shows differences between basal and after treatment levels of adipocytokines. Only leptin levels have a significant decrease in telmisartan group 7.39 ng/ml (CI 95%: 1.47-13.31).

Discussion

The major finding of this study was that telmisartan 80 mg per day significantly improved insulin, HOMA, glucose and leptin levels. However, olmesartan improved lipid levels. Both drugs had the same beneficial effect on blood pressure levels.

Recently, Furuhashi et al.¹⁶ showed that blockade of the renin-angiotensin system by angiotensin-convert-

Table IV
Circulating adipocytokines

Variables	Telmisartan (n=34)		Olmesartan (n=31)	
	Baseline	3 months	Baseline	3 months
Adiponectin (ng/ml)	13.5 ± 8.5	14.4 ± 15.8	20.2 ± 17.3	21.4 ± 19.5
Leptin (ng/ml)	38.8 ± 30.5	31.4 ± 28.3*	35.8 ± 47	34.2 ± 37.1

T Student test and Wilcoxon test were used as statistical methods.

* p < 0.05, in each group with basal values.

ing enzyme inhibitor (ACEI) and/or angiotensin II receptor blocker (ARB) decreased adipocyte size with improvement in insulin sensitivity. This previous data may partially explain our results with telmisartan. Other study¹⁷ suggests that other ARB (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.¹⁸ Our study did not show modification in levels of adiponectin, but telmisartan decrease leptin levels.

Recently, telmisartan displays the ability to act as partial agonist of PPARgamma,¹⁹ this stimulation induces the differentiation of pre-adipocytes to mature adipocytes, increases the subcutaneous fat and reduces the visceral fat related with insulin resistance. Several are the mechanisms through to explain the increased insulin sensitivity induced by blockade this system. They are represented by 1) vasodilatation, which increases the blood flow in skeletal muscle,²⁰ 2) inhibition of the impairment of insulin signaling induced by angiotensin II,²¹ decrease of tumor necrosis factor (TNF-alpha in skeletal muscle,²² increase in the ratio of insulin-sensitive type 1 fiber in muscle fiber composition.²³ In summary, the effect of ARB on adiponectin levels may be mediated by the decrease in insulin levels, which is due to the effect of ARB on enhancing insulin sensitivity²⁴. Moreover, RAS blockade may stimulate phosphatidylinositol-3-kinase activity, which regulates insulin-stimulated adiponectin exocytosis.²⁵

In our study, two characteristics differentiated telmisartan from olmesartan 1) telmisartan showed a reduction of blood pressure and leptin levels while olmesartan did not decrease leptin and 2) a greater impact of telmisartan on the glucose control.

Physiological increase in plasma leptin has been shown to significantly inhibit glucose-stimulated insulin secretion in vivo and to determine insulin resistance.²⁶ Serum leptin concentrations reflects the total amount of fat present in the body, and lower plasma leptin levels have been reported consistently among weight losing patients.²⁷ The results of our study show that significant reduction in leptin levels after telmisartan treatment occur when weight is unchanged. The decrease of leptin levels, which may reflect a drug induced improvement of leptin sensitivity, may play a role, indirectly or directly, in the induction of diabetes control. Telmisartan improved glucose tolerance and it can be due to a possible insulin-independent mechanism, possibly acting through an enhanced uptake and utilization of glucose by tissues mediated by leptin without changes in insulin sensitivity measured as HOMA (homeostasis model assessment).

As above-mentioned, there is a general consensus that angiotensin II has a trophic role in adipose tissue. However the effects of angiotensin II on adipocyte metabolism and differentiation are not conclusive, while others

show that angiotensin II promotes it. Leptin gene expression is under the control of PPARgamma. PPARgamma represses the expression of leptin ob gene.²⁸ In animal models, angiotensin II AT1 receptor blockers enhanced insulin sensitivity and improved the serum lipid profile in obese.²⁹

In summary, the administration of telmisartan improved blood pressure, glucose, insulin, HOMA and leptin in hypertensive obese patients. Olmesartan improved blood pressure and lipid levels. These results suggest that telmisartan could be more useful in preventing atherosclerosis in these patients than olmesartan.

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