Effects of telmisartan on insulin resistance and visceral fat distribution in Chinese hypertensive patients with obesity

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ABSTRACT

الأهداف: التحقق من تأثير التيلميسارتان (telmisartan) على توزيع الدهون في الجسم، وحساسية الأنسولين لدى المرضى المصابين بارتفاع ضغط الدم والسمنة.

الطريقة: أُجريت هذه الدراسة الاستطلاعية العشوائية في قسم العيادات الخارجية بمستشفى الشعب السادس التابع لجامعة شانغهاي جيوتونغ، شانغهاي، الصين. لقد قمنا بتقسيم المشاركين في الدراسة إلى مجموعتين: مجموعة المرضى التي أُعطيت التيلميسارتان (العدد: 23)، والمجموعة التي أُعطيت اللوزارتان (العدد:22) وكلاهما تناول العلاج لمدة 16 أسبوع من ديسمبر 2009م إلى يناير 2011م. لقد قمنا بتحليل المقاييس التالية قبل وبعد العلاج وهي كالتالي: محيط الخصر والفخذين، ومؤشر كتلة الجسم، ومستويات غلوكوز الدم أثناء الصيام، ومستويات الدهون، والأديبونكتين في مصل الدم، ومعامل ألفا لتنخر الأورام. فيما تم التحقق من مقاييس منطقة الدهون الحشوية البطنية ومنطقة الدهون تحت الجلد باستخدام صور الرنين المغناطيسي. وتم تقييم حساسية الأنسولين باستخدام اختبار مقاومة الأنسولين بنموذج الاستتباب.

النتائج: أشارت نتائج الدراسة إلى الانخفاض الكبير في ضغط الدم الانقباضي والانبساطي في كلتي المجموعتين وذلك بالمقارنة مع معدلات الضغط الأولية. وبالمقابل فقد انخفضت مستويات مقاومة الأنسولين بنموذج الاستتباب، والأديبونكتين في مصل الدم، ومعامل ألفا لتنخر الأورام في مجموعة التيلميسارتان فحسب، كما تقلصت مقاييس منطقة الدهون الحشوية البطنية في هذه المجموعة في حين لم تتغير مقاييس منطقة الدهون تحت الجلد في كلتي المجموعتين.

خاتمة: أظهرت هذه الدراسة فعالية التيلميسارتان في تحسين ديناميكية الدم وعملية الأيض لدى المرضى المصابين بارتفاع ضغط الدم والسمنة، وقد يعود ذلك جزئياً إلى دوره في إعادة تشكيل الدهون الحشوية.

Objectives: To investigate the effects of telmisartan on body fat distribution and insulin sensitivity in patients with hypertension and obesity.

Methods: In this prospective, randomized study, outpatients from the Sixth People's Hospital affiliated to Shanghai Jiaotong University, Shanghai, China were treated with telmisartan (n=23), or losartan (n=22) for 16 weeks between December 2009 to January 2011. Parameters such as waist and hip circumference, body mass index, fasting blood glucose, insulin, lipids, serum adiponectin, and tumor necrosis factor-alpha (TNF-alpha) were measured before and after treatment. The abdominal visceral fat area (VFA) and subcutaneous fat area (SFA) were determined by magnetic resonance imaging. Insulin sensitivity was estimated by homeostasis model assessment (HOMA-IR).

Results: Compared with baseline, the systolic and diastolic blood pressure decreased significantly in both groups. However, the levels of HOMA-IR, serum adiponectin, and TNF-alpha only improved in the telmisartan group. Similarly, the VFA was reduced in the telmisartan group, while the SFA did not change in either group.

Conclusion: Telmisartan improves both hemodynamic and metabolic abnormalities found in hypertensive patients with obesity. The additional benefits may be partly due to visceral fat remodeling.

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Metabolic disorders of blood glucose and lipids are very common in patients with essential hypertension, especially in those with obesity, and frequently accompanied with decreased insulin sensitivity. Insulin resistance (IR) is considered to be the main pathophysiologic basis of metabolic dysfunction and the key point in the development of type 2 diabetes mellitus (DM), which ameliorates atherosclerosis regardless of diabetes. Therefore, it is important to improve insulin sensitivity and prevent diabetes during the treatment of essential hypertension. Peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonists are well known to decrease IR.[1] Experimental studies have shown that telmisartan, an antihypertensive agent which belongs to the angiotensin type 1 receptor blocker (ARB), and widely used throughout the world, has a partial PPAR-γ activating property.[1,2] The aim of this study was to test its metabolic effects on IR, serum levels of cytokines, and body fat distribution in Chinese hypertensive patients with obesity.

Methods. ***Participants.*** Forty-five outpatients from the Sixth People's Hospital affiliated to Shanghai Jiaotong University, Shanghai, China, aged between 40 and 75 years of both genders were included in the study from December 2009 to January 2011. The enrollment of essential hypertension is based on the diagnostic criteria of China (Guideline for the Prevention and Treatment of Hypertension, 2005)[3] office systolic blood pressure (SBP) 140-180 mmHg, diastolic blood pressure (DBP) 90-110 mmHg. All patients were overweight or obese (body mass index [BMI] >23 kg/m^2) accompanied with IR (the homeostasis model assessment of insulin resistance [HOMA-IR], 4.31 for males, or 4.51 for females).[4] Patients were excluded if they had the following conditions: independent of drugs that may affect glucose tolerance, such as diuretics, alpha/beta blocker, angiotensin converting enzyme inhibitors (ACEI), glucocorticoids; prescribed lipid-lowering drugs or increasing the doses within the last 2 months; taking ARB within the last half a year, or having contraindications to ARB; DM, severe diseases of the heart (unstable angina, myocardial infarction, heart failure), brain (stroke), liver (serum glutamate pyruvate transaminase [SGPT], alanine amino transferase [ALT], serum glutamic oxaloacetic transaminase [SGOT], aspartate amino transferase [AST] >2x upper limits of normal), kidney (serum creatinine ≥150 umol/l); and other situations considered to be not suitable for the trial.

This study was approved by the Ethics Committee of Shanghai Sixth People's Hospital according to the principles of the Helsinki Declaration. Informed consent was obtained from all subjects.

Study protocol and drugs. All concomitant medications mentioned above in the exclusion criteria were withdrawn 2 weeks before the study. After evaluation of all inclusion and exclusion criteria, the eligible patients entered into a randomized, paralleled-group study. Patients were assigned into the different groups according to the random digits table, and received either telmisartan 80 mg or losartan 100 mg, once daily for 16 weeks. Blood pressure was measured for each patient using a cuff sphygmomanometer every 2 weeks. Nifedipine controlled-release tablets (30-60 mg/d) or amlodipine (5-10 mg/d) was offered if blood pressure could not be well controlled (>140/90 mmHg). Patients were asked to adhere to their standard diet and physical activity habits throughout the study.

Measurements. Patients were evaluated at baseline and after treatment for 16 weeks. Fasting blood samples were obtained to determine the clinical biochemistry parameters, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides (TG), glucose (FBG), insulin (FBI, chemiluminescence method), adiponectin (Adipo, ELISA) and tumor necrosis factor-α (TNF-α, ELISA). Blood pressure, heart rate, body height and weight, waist, and hip circumference were recorded. The BMI was calculated by weight (kg) divided by height square (m^2). Waist circumference (W) was measured with a tape placed horizontally around the abdomen at the level of the iliac ridge at the end of a normal expiration, keeping the tape well tense, adhered to the skin, and parallel to the floor. Hip circumference (H) was measured at the level where the size is maximal. Waist-to-hip ratio (W/H) was then calculated. Any adverse events were recorded. The abdominal visceral fat area (VFA) and subcutaneous fat area (SFA) were measured by magnetic resonance imaging (Sigma 1.5T; General Electric Co.) at the level of L4-L5. Each fat area was calculated as previously described.[5]

Statistical analysis. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) program for windows version 3.11. Data were presented as mean ± standard deviation. Each variable was examined for normal distribution. Data were analyzed by paired or unpaired Student's t-test to detect significant differences among groups before and after treatment, or among the groups before treatment only. The effects of losartan and telmisartan on blood pressure, biochemical parameters,

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and serum levels of adipocytokines were analyzed by one way repeated measures analysis of variance (ANOVA, data before treatment as covariate). All reported *p*-values were two-tailed, and a value of $p<0.05$ was considered to be statistically significant.

Results. ***Basic data.*** A total of 45 patients were enrolled. They were randomly divided into the telmisartan (n=23, 16 male/7 female, 59.9±11.7 years old), or losartan (n=22, 17 male/5 female, 59.2±10.2 years old) group. There was no difference in gender and age ($p=0.835$) between these 2 groups. The ratios of the patients taking calcium antagonist because of poor blood pressure control were 11/23 in the telmisartan group, and 10/22 in the losartan group. The other baseline characteristics of the patients in the 2 treatment groups were also comparable (**Tables 1 & 2**).

Blood pressure and body lipid parameters. After treatment for 16-weeks, notable reductions from baseline in seated SBP/DBP were found in either telmisartan or losartan group (both $p<0.01$) (**Table 1**). There were no significant changes in BMI, W, and WHR after treatment in both groups.

Glucose and lipid metabolism. There was no significant change compared with baseline in FPG, FPI, TC, LDL-C, HDL-C, and TG after therapy with telmisartan or losartan, except for HOMA-IR, which was improved by telmisartan (**Table 2**, $p=0.037$).

Adipocytokines. Telmisartan, while not losartan, significantly reduced serum levels of TNF-α ($p=0.023$), and raised serum levels of adiponectin (**Table 2**, $p=0.027$).

Abdominal fat distribution. Subcutaneous and visceral fat areas at L4 level were measured at baseline and endpoint by MRI scanning. The results showed that the VFA decreased in the telmisartan group ($p=0.009$), the SFA increased, but insignificantly. Compared with telmisartan, losartan did not have a meaningful effect on either of the fat distribution markers ($p>0.05$).

Discussion. Patients with essential hypertension, especially those accompanied with obesity, are

Table 1 - Changes of blood pressure and body lipid parameters in the 2 groups.

Variables	Telmisartan (n=23)				Losartan (n=22)			
	Baseline	At 16 weeks	Pre- versus post-treatment (95% CI)	*P*-value	Baseline	At 16 weeks	Pre- versus post-treatment (95% CI)	*P*-value
BMI (kg/m^2))	27.3 ± 2.4	27.1 ± 2.2	0.22 (-0.15, 0.59)	0.229	27.4 ± 2.1	27.3 ± 1.8	0.10 (-0.24, 0.44)	0.553
Waist (cm)	95.9 ± 4.7	95.4 ± 4.5	0.43 (-0.08, 0.95)	0.096	95.2 ± 4.6	95.2 ± 3.9	0.04 (-0.47, 0.56)	0.862
WHR	0.95 ± 0.04	0.94 ± 0.05	0.01 (-0.01, 0.03)	0.065	0.95 ± 0.06	0.95 ± 0.03	0.00 (-0.18, 1.73)	0.948
SBP (mm Hg)	153.6 ± 9.6	133.1 ± 8.1*	20.5 (14.6, 26.4)	0.000	154.1 ± 6.3	135.8 ± 4.4*	18.3 (15.3, 21.3)	0.000
DBP (mm Hg)	98.3 ± 4.7	83.5 ± 6.0*	14.9 (12.7, 17.0)	0.000	98.1 ± 3.8	83.9 ± 6.5	14.1 (12.2, 16.1)	0.000

*Compared with baseline - blood pressure, $p=0.000$, BMI - body mass index, WHR - waist-to-hip ratio, SBP - systolic blood pressure, DBP - diastolic blood pressure

Table 2 - Effects on glucose/lipid metabolism and cytokines.

Variables	Telmisartan (n=23)				Losartan (n=22)			
	Baseline	At 16 weeks	Pre- versus post-treatment (95% CI)	*P*-value	Baseline	At 16 weeks	Pre- versus post-treatment (95% CI)	*P*-value
FBG (mmol/L)	6.12 ± 0.51	5.86 ± 0.61	0.25 (-0.09, 0.60)	0.143	5.92 ± 0.58	5.75 ± 0.55	0.19 (0.44, 1.51)	0.145
FBI (mU/L)	26.7 ± 6.88	22.8 ± 7.23	4.61 (-0.25, 9.48)	0.062	27.0 ± 7.41	25.1 ± 7.30	2.22 (-1.28, 5.71)	0.202
HOMA-IR	7.24 ± 1.82	6.02 ± 2.16*	1.33 (0.09, 2.57)	0.037	7.18 ± 2.04	6.47 ± 2.16	0.77 (-0.18, 1.73)	0.11
TC (mmol/L)	5.06 ± 0.88	4.85 ± 0.65	0.21 (-0.10, 0.52)	0.173	5.18 ± 0.7	4.93 ± 0.54	0.25 (-0.02, 0.52)	0.073
LDL-C (mmol/L)	3.52 ± 0.84	3.27 ± 0.79	0.26 (-0.05, 0.56)	0.100	3.58 ± 0.62	3.39 ± 0.50	0.19 (-0.02, 0.39)	0.070
HDL-C (mmol/L)	1.17 ± 0.27	1.20 ± 0.24	-0.04 (-0.10, 0.03)	0.255	1.15 ± 0.30	1.21 ± 0.20	-0.06 (-0.15, 0.03)	0.162
TG (mmol/L)	1.98 ± 0.87	1.84 ± 0.50	0.14 (-0.17, 0.44)	0.360	2.29 ± 0.77	2.09 ± 0.68	0.20 (-0.06, 0.46)	0.131
Adipo (μg/ml)	8.98 ± 3.95	11.2 ± 3.17*	-2.20 (-41.4 -2.74)	0.027	9.07 ± 0.28	9.67 ± 2.4	-0.60 (-1.88, 0.69)	0.343
TNF-α (pg/ml)	86.5 ± 28.0	71.6 ± 23.1†	14.9 (2.23, 27.6)	0.023	87.4 ± 24.6	80.3 ± 23.5	7.09 (-4.3, 18.5)	0.210

*Compared with baseline - Adipo, $p=0.027$, †compared with baseline - tumor necrosis factor-alpha (TNF-α), $p= 0.023$. FBG - fasting blood glucose, FBI - fasting blood insulin, TC - total cholesterol, LDL - low-density lipoprotein cholesterol, HDL - high-density lipoprotein cholesterol, TG - triglycerides, Adipo - adiponectin, HOMA-IR - homeostasis model assessment of insulin resistance

Table 3 - Changes of fat distribution in the 2 groups.

Variables	Telmisartan (n=23)				Losartan (n=22)			
	Baseline	At 16 weeks	Pre- versus post-treatment (95% CI)	*P*-value	Baseline	At 16 weeks	Pre- versus post-treatment (95% CI)	*P*-value
SFA (cm^2)	180.1 ± 42.1	187.1 ± 38.8	-7.0 (-18.0, 4.0)	0.193	185.3 ± 28.5	176.7 ± 27.4	8.58 (-5.58, 22.7)	0.213
VFA (cm^2)	164.5 ± 33.4	146.5 ± 20.1*	18.0 (5.26, 30.7)	0.009	162.2 ± 33.6	156.0 ± 24.7	6.26 (-6.26, 18.8)	0.300

*Compared with baseline - visceral fat area (VFA) ($p<0.01$), SFA - subcutaneous fat area

more prone to develop diabetes than those who are normotensive. Therefore, it is important to improve IR in the treatment of hypertension. The effects on insulin sensitivity are very different among the 5 classes of commonly used antihypertensive agents. It is now widely recognized that dihydropyridine calcium antagonists had no apparent effects on glucose metabolism and IR, large doses of thiazide diuretics and β-blockers may lead to new onset of diabetes, while ACEI and ARB can enhance insulin sensitivity.[6] However, some research groups reported that the effects of ACEI and ARB on insulin resistance are limited when administered in conventional doses to treat hypertension. For example, the CROSS study[7] and the ALPINE study[8] did not confirm that candesartan improved insulin resistance. In the LIFE study,[9] there were less new onset diabetes cases in the losartan group. However, β-blocker therapy is a risk factor for the development of diabetes, so the results may be induced by the hyperglycemic effect of atenolol.[9]

The thiazolidinediones (TZDs) are a new class of agent that act as PPAR-γ agonists, which have been developed to treat type 2 diabetics. These drugs not only improve glycemic control but also decrease IR, thereby improve many of the abnormalities that are part of the IR syndrome.[10] Telmisartan recently identified as a unique angiotensin II receptor antagonist with selective PPARγ-modulating activity in normal therapy dose, can improve insulin sensitivity. Some scholars[2] even called it "metabolic sartan". None of the other commercially available ARB appeared to activate PPAR-γ at conventional oral dosing. For instance, Vitale[11] reported that compared with losartan, telmisartan treatment on hypertension for 3 months improved fasting and 2-hour postprandial blood glucose and insulin. Another study[12] showed that telmisartan treatment for 3 months improved serum levels of glucose and adiponectin better than candesartan in hypertensive diabetic patients. Recently, Ichikawa and colleagues[13] showed that a lower dose of telmisartan (20 mg) is sufficient to significantly improve glucose metabolism, whereas an effect was not observed in valsartan-treated subjects.

In contrast to the above reports, Bahadir et al[14] found that either telmisartan or losartan treatment had a neutral effect on insulin resistance in hypertensive and metabolism syndrome patients. However, the course of treatment was shorter, for only 8 weeks. In the present study, blood pressure decreased significantly after treatment, and there was no significant difference in descending amplitude between the 2 groups. Although there was no obvious change in fasting blood glucose and insulin levels after treatment in both groups, our study found that, compared with losartan, telmisartan reduced the values of HOMA-IR, which suggested that telmisartan, but not losartan, improved the sensitivity of insulin and support that the PPAR-γ agonism exhibited by telmisartan has clinical values. These results are consistent with most reports derived from reports mentioned above.[11,12]

In our study, losartan 100 mg/d was applied, because this dose corresponds to the commonly used telmisartan dose of 80 mg/d in China. The long-acting calcium antagonist, amlodipine, or nifedipine GITS was added when ARB alone could not control the blood pressure well. These antihypertensive agents have no novel effects on blood sugar and insulin metabolism.[15] Shimabukuro[16] reported that patients with metabolic syndrome were treated either with amlodipine (n=26) or with telmisartan (n=27) for 24 weeks, the VFA, determined by abdominal CT scan was reduced in the telmisartan group, but the subcutaneous fat area did not change in either group. They did not use another ARB as control, and thus cannot eliminate the possibility of ARB class effects. We have achieved this by using losartan as a control.

Adiponectin is a well-known anti-inflammatory adipocytokine. It is increased by insulin sensitizers and PPAR-γ agonists in mice and humans.[17] Hypoadiponectinemia is a key factor in metabolic syndrome, and may be improved by telmisartan.[18,19] Our study showed that, telmisartan, but not losartan, significantly reduced serum levels of TNF-α, and increased the serum level of adiponectin. The severity of obesity-related diseases such as DM, lipid disorders, and

cardiovascular disease correlate to body fat distribution more than to the extent of body fat accumulation. The negative relationship between adiponectin and adipose tissue is stronger with visceral fat rather than subcutaneous fat. Recently, it is reported that telmisartan treatment was associated with improvement of vascular inflammation, reductions in visceral fat, and increases in serum adiponectin.[20,21] This study showed that the VAT was decreased by telmisartan. The SAT increased slightly but this was insignificant. This may be due to the effects of PPAR-γ agonism, which leads to fat redistribution from visceral fat to subcutaneous fat.[22] Compared with telmisartan, losartan did not have a meaningful effect on either of the fat distribution markers.

This study has the limitation of a relatively small number of patients and short period of observation. It cannot be concluded that losartan does not have an insulin-sensitizing effect, but we believe that telmisartan has stronger effects on insulin sensitivity compared with losartan.

In conclusion, treatment with telmisartan for 16 weeks, instead of losartan, improved metabolic parameters and visceral fat distribution in patients with obesity hypertension. The additional benefits of this antihypertensive drug should be helpful in the treatment of patients with hypertension, especially when accompanied by multiple cardiovascular risk factors related to insulin resistance, such as obesity, glucose intolerance, and dyslipidemia. It is necessary to conduct large-scale clinical trials to observe its effects on the long-term prognosis.

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