Telmisartan Improves Insulin Resistance in Patients With Low Cytokine Levels

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Metabolic syndrome (MS) is a disease with an inflammatory component. Telmisartan improves insulin resistance in MS, but its relationship with the inflammatory state is unknown. We investigated the effect of 3-month telmisartan therapy on homeostatic model assessment-insulin resistance (HOMA-IR) in hypertensive subjects with MS with regard to the levels of circulating plasma cytokines.

Methods: A total of 42 patients were included in this study; 30 were men (71%), aged 50 ± 8.2 years (mean ± SD). Cytokines and metabolic parameters were analyzed before and after treatment with telmisartan.

Results: Twenty-eight patients showed low plasma levels of cytokines (group 1) similar to control subjects, and 14 showed high levels (group 2). Treatment with telmisartan diminished by 35% HOMA-IR in group 1 (4.5 ± 3.1 vs 2.9 ± 2.1), without improvement in group 2. In the multivariate analysis, the predictors of improvement of HOMA-IR in response to telmisartan treatment were low levels of cytokines, whereas systolic and diastolic blood pressure and the elevation of high-sensitivity C-reactive protein had a negative effect.

Conclusions: Our study provides evidence of a more favorable effect of telmisartan on glucose homeostasis in patients with MS and low levels of serum cytokines.

Key Words: telmisartan, metabolic syndrome, cytokines

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Prevention of diabetes represents an important therapeutic goal in current cardiovascular risk reduction strategies. Meta-analysis of studies has shown that blockade of the renin-angiotensin system could reduce the incidence of new-onset diabetes in different patient populations,[1,2] although other studies have yielded inconsistent results.[3,4]

Metabolic syndrome (MS) is characterized by a low-grade chronic inflammatory state associated with insulin resistance (IR) that can predict the development of diabetes mellitus (DM).[5,6] The subclinical inflammatory state peculiar of the MS modulates the atherosclerotic process at different stages, resulting in endothelial dysfunction and increased expression of endothelial adhesion molecules and in enhanced recruitment of monocytes within the arterial wall, in the early stages of the atherosclerotic process. To fully elucidate its complex pathogenetic mechanisms, further inquiry into the inflammatory components of the MS is warranted. Unraveling the role of emerging proinflammatory markers has the promising potential to shed light into the underlying pathophysiology of the epidemic of obesity and the MS and thus help devise effective therapies.[5]

Recent investigations indicate that pathophysiological mechanisms leading to beta-cell damage, IR, and the vascular complications of diabetes include an activation of the inflammation cascade.[7] Therefore, circulating biomarkers may be useful for early diagnosis and guide for treatments.

Telmisartan is an angiotensin receptor blocker drug that, unlike others from their family, improves IR.[2,8–12] Moreover, it seems to have an anti-inflammatory effect,[13–15] although the relation of the vascular actions of telmisartan on IR has not yet been assessed.

The aim of our study was to investigate whether the cytokine profile of patients with MS correlated with a better response to insulin sensitization after treatment with telmisartan.

METHODS

Subject Selection and Inclusion

We selected 56 consecutive patients attending the clinic, until the sample size was achieved. Seven patients were excluded because blood pressure was not controlled, 5 needed new drugs, and 2 were missing. Finally, 42 patients were analyzed. All patients were newly diagnosed as having hypertension, defined as blood pressure numbers by standardized office reading greater than 140/90 mm Hg, and with criteria of MS according to the 2005 NCEP ATP3 criteria (Three or more of the following criteria: a) abdominal obesity (waist circumference > 102 cm in men and >88 cm in women); b) TG ≥150 mg/dL; c) HDL-C values <40 mg/dL in men and <50 mg/dL in women; d) blood pressure ≥130/85 mm Hg or taking antihypertensive treatment; and e) plasma glucose levels ≥110 mg/dL fasting).[16] No patient received or had received any drug treatment. All patients were provided with a series of hygienic dietary recommendations for blood pressure control in the 3 months before inclusion in the study. Age had to be 35 to 60 years, serum creatinine had to be less than 176.6 mmol/L, with normal liver enzymes and smoking behavior, and physical activity had to be stable until the end of the study. Exclusion criteria were known hypersensitivity toward telmisartan and any cardiovascular or chronic disease. Patients in whom blood pressure could not be reduced to the target level will need medication to control their blood glucose levels, and those who did not tolerate the final dose of the drug prescribed during the study period were excluded. After an initial assessment, all patients were prescribed treatment with telmisartan 40 mg daily for 1 week and then 80 mg daily until completion of the study.

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Blood samples were drawn after fasting, and laboratory measurements were done at baseline and after 3 months. As for the control group, we selected 21 normotensive subjects without MS criteria. Patients were divided into 2 groups according to their circulating interleukin (IL) levels. Low IL levels were considered when they were similar to those of healthy controls. High IL levels were considered in those patients with statistically significant higher levels of cytokine than healthy controls. The study was approved by the local ethics committee; all participants gave written informed consent.

Laboratory Measurements

Cytokines were determined using the SearchLight Human Inflammatory Cytokine Array for IL-6, and the SearchLight Human Cytokine Array 2 for the rest of cytokines from Thermo Scientific (Rockford, IL), following the manufacturer's instructions. Insulin resistance (IR) was assessed by homeostatic model assessment-IR (HOMA-IR): (fasting blood glucose [mmol/L] × fasting serum insulin [mU/mL]/22.5).

Statistics

The number of patients was chosen to detect a 20% improvement in HOMA-IR, with $P < 0.05$, and a power of 0.85. Sample size was estimated using a Web-based statistical application (http://home.clara.net/sisa). All the data were expressed as mean ± SD or percentage. The between-group comparison was performed using the Fisher exact test or the Wilcoxon rank sum test. A stepwise multivariate linear regression analysis was used to identify the significant predictors at the start of the treatment for the improvement in HOMA-IR. $P < 0.05$ was considered to indicate a statistically significant difference. Data analysis was performed using the SPSS software package (SPSS, Inc, Chicago, IL).

RESULTS

Table 1 shows the baseline characteristics of patients before starting treatment with telmisartan. All patients had the characteristics of MS when compared with controls. In studying the plasma levels of ILs and comparing them with the control group, patients with MS were differentiated into 2 groups: group 1 (n = 28), those with normal or slightly elevated IL, all certain in the control group, except IL-5 (group 1 vs group 2, 1.1 ± 2.1 versus 0 pg/mL, $P < 0.05$); and group 2 (n = 14), those with significantly higher IL than the control group. All plasma IL levels were significantly different from those from the control group, except for IL-6 (group 1 versus control group, 6.2 ± 3.5 vs 3.9 ± 3.8 pg/mL, P = not significant). Likewise, group 2 showed

TABLE 1. Baseline Characteristic of the Patients

	Control	MS	MS With Low IL	MS With High IL	*P*
	n = 21	n = 42	n = 28	n = 14	Between MS
Sex, male (%)	15 (71)	30 (71)	20 (71)	10 (71)	NS
Age, yr	45 ± 8	50 ± 9*	51 ± 8*	48 ± 8	NS
FamHxCVD	4 (20)	13 (31)	9 (33)	4 (30)	NS
Current smokers	3 (15)	8 (19)	5 (18)	3 (20)	NS
Waist circumference, cm	87 ± 5	109 ± 15†	105 ± 13‡	117 ± 17‡	<0.05
BMI, kg/m^2	24 ± 19	34 ± 12*	33 ± 7*	35 ± 14	NS
Systolic blood pressure, mm Hg	123 ± 12	150 ± 16‡	149 ± 15‡	152 ± 17‡	NS
Diastolic blood pressure, mm Hg	81 ± 6	89 ± 9‡	88 ± 10†	91 ± 8‡	NS
HDL-cholesterol, mmol/L	1.19 ± 0.16	1.0 ± 0.19‡	1.01 ± 0.16‡	0.98 ± 0.23†	NS
LDL-cholesterol, mmol/L	3.13 ± 0.49	3.35 ± 1.1	3.29 ± 1.01	3.42 ± 1.17	NS
Triglycerides, mmol/L	1.11 ± 0.23	2.02 ± 1.0‡	1.99 ± 1.11‡	2.06 ± 0.98‡	NS
C-reactive protein, mg/L	0.3 ± 0.9	3.1 ± 3.2‡	2.4 ± 1.6‡	5.1 ± 4.7‡	<0.01
Fasting glucose, mmol/L	4.94 ± 0.44	5.43 ± 0.95*	5.72 ± 1.05†	5.38 ± 0.72*	NS
Fasting insulin, pmol/L	55.6 ± 41.7	110 ± 49‡	118 ± 62.5‡	97.2 ± 14†	NS
Hb_{A1}, %	4.8 ± 0.4	4.9 ± 0.7	5.0 ± 0.6	4.8 ± 0.8	NS
Interleukins, pg/mL					
IL-2	0.7 ± 2.0	97 ± 17‡	1.6 ± 3.4	320.3 ± 20.6†	<0.001
IL-4	0	3.5 ± 8.1	0.09 ± 0.3	7.7 ± 10.8&	<0.001
IL-5	0	23 ± 54	1.1 ± 2.1*	50 ± 73&	<0.01
IL-8	3.2 ± 8.6	4.7 ± 9	2.4 ± 4.3	9.3 ± 11*	<0.006
IL-10	0.2 ± 0.8	8.0 ± 16*	0.08 ± 0.3	18 ± 20†	<0.001
IL-12P70	0.4 ± 1.7	9.4 ± 15†	0.2 ± 0.8	21 ± 17†	<0.001
IL-13	0	71 ± 150*	2.7 ± 9.9	163 ± 189†	<0.001
IL-6	3.9 ± 3.8	5.8 ± 3.5	5.5 ± 3.4	6.2 ± 3.5	NS
HOMA-IR	1.71 ± 0.82	4.6 ± 2.5‡	4.5 ± 2.9‡	4.8 ± 1.6‡	NS

Values are means ± SD.

BMI indicates body mass index; FamHxCVD, family history of cardiovascular disease; Hb_{A1}, glycated hemoglobin.

*$P < 0.05$, with regard to the control group.

†$P < 0.01$, with regard to the control group.

‡$P < 0.001$, with regard to the control group.

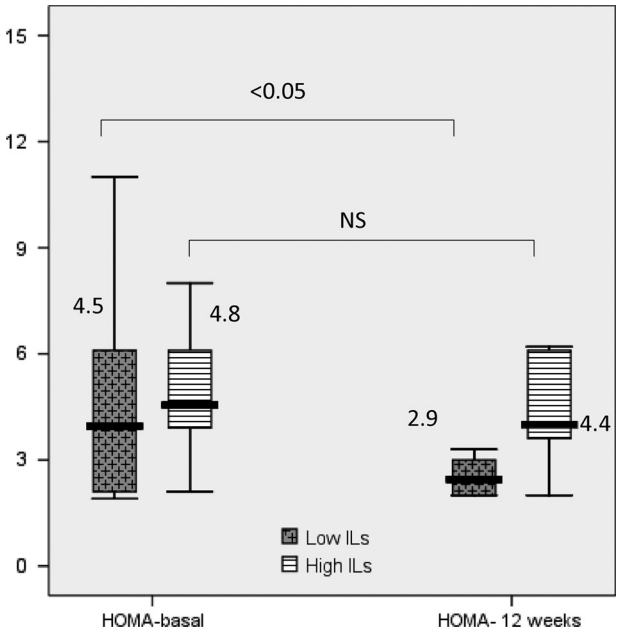

FIGURE 1. HOMA-IR at baseline and after 12 weeks of telmisartan treatment.

significantly elevated levels of plasma IL with respect to those of group 1, except for IL-6 (group 2 vs group 1, 6.2 ± 3.5 vs 5.5 ± 3.4 pg/mL, P = not significant). Their blood pressure decreased at the end of treatment, with respect to baseline levels (systolic pressure of 17 mm Hg and diastolic pressure of 7 mm Hg, without differences between subgroups according to IL levels). HOMA-IR was lower in the control group (1.71 ± 0.82) than in patients with MS (4.6 ± 2.5, $P < 0.001$) and in the subgroups with low (4.5 ± 2.9, $P < 0.001$) and high IL levels (4.8 ± 1.6, $P < 0.001$). There were no significant differences between the different subgroups.

Regarding changes in the HOMA-IR after treatment with telmisartan, Figure 1 reflects the changes in HOMA-IR, comparing study entry and after treatment; the HOMA-IR drops only in the group with low levels of IL (basal vs 12 weeks of treatment: 4.5 ± 3.1 versus 2.9 ± 2.1, $P < 0.05$; absolute difference, −1.7 ± 1.8; $P < 0.05$, 35% decrease).

The multivariable linear regression analysis used to identify the predictors in the improvement of HOMA-IR to study entry showed that elevated systolic blood pressure ($t = -4.03$, $P = 0.001$), elevated diastolic blood pressure ($t = -3.4$, $P = 0.01$), and elevated high-sensitivity C-reactive protein ($t = -2.73$, $P = 0.01$) had negative effects, whereas low levels of IL ($t = 2.9$, $P = 0.007$) predict that the decline of HOMA-IR was independent of that of the abdominal waist, current smoking, vascular reactivity and basal insulin.

DISCUSION

The main finding of this study was that 3 months of treatment with telmisartan decreased the IR in patients with MS. This response was mainly observed in patients who before initiation of treatment showed no elevation of serum cytokines, but not in those with elevated cytokines.

The detailed mechanisms responsible for the effects of telmisartan on the improvement in insulin sensitization are not yet clarified.[2,17] Some of these actions have been related to the stimulation of peroxisome proliferator-activated receptor γ receptors observed with high doses of telmisartan exceeding 40 mg/d.[18,19] Moreover, it seems that patients with more elevated HOMA-IR at baseline show a better response in the IR.[20] Telmisartan dose used in our study was 80 mg/d, considered enough to build a complete response as a peroxisome proliferator-activated receptor γ agonist, but our results suggest that the improvement in HOMA-IR did not depend on its level before beginning treatment. Other actions of telmisartan independent of AT1 blockade, such as changes in adiponectin levels[21] or its effects on vascular reactivity,[20] seem to be unrelated to the improvement in IR. The mechanisms by which ILs or tumor necrosis factor α or angiotensin II crosstalk with insulin signaling are complex and remain a matter of active investigation.[22–25] Overall, in our study, the percentage of improvement in HOMA-IR after 3 months of treatment with telmisartan was 24%, similar to 26% reported in a study in patients with MS.[25] The improvement in the group with low levels of serum cytokines was significantly higher than 35%; therefore, the levels of cytokines in patients with MS could help to identify the group of subjects in whom short-term treatment with telmisartan may significantly improve IR.

The MS is characterized by a chronic inflammatory state of low-grade elevation of tumor necrosis factor α, IL-6, and C-reactive protein associated with IR that predict the development of DM.[5,6] How these ILs have a negative effect on insulin action is unknown.[23–25] The observed response to telmisartan only in patients with lower levels of cytokines may suggest the presence of a minimal inflammatory activity that can be affected by telmisartan. In contrast, telmisartan may not have an effect when the inflammation is too high as in patients with high levels of cytokines.

Whether the anti-inflammatory effects of telmisartan can influence the improvement of IR in patients with MS is unknown. Our results suggest that early treatment of patients with MS with telmisartan, before the development of an inflammatory response, may improve insulin sensitization. It is still unknown whether a more prolonged treatment or whether higher doses of telmisartan may have similar effects. The elevation of high-sensitivity C-reactive protein has been associated with inflammatory changes in the vascular wall.[26] In this regard, we found more elevated high-sensitivity C-reactive protein levels in the group of patients with higher cytokine levels; however, only the group of patients with a low expression of cytokines experienced improvement in IR after telmisartan treatment. It may be possible that high levels of cytokines may be associated with an abnormal inflammatory response in these patients, which may impede their metabolic control.

Among the limitations of our work is the small number of patients studied. Although there are safer methods of measuring the RI, we used the HOMA-IR, representing only the sensitivity to insulin in fasting, but we do not think that this weakens the findings of our study because the HOMA-IR is described as a method that reliably predicts the development of DM.[27]

In conclusion, our study provides evidence of a more favorable effect of telmisartan on glucose homeostasis in patients with MS and low levels of serum cytokines. These promising findings should be confirmed in studies involving larger numbers of patients to appraise their clinical utility.

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