Telmisartan improves insulin resistance in high renin nonmodulating salt-sensitive hypertensives
Ramiro A. Sanchez, Lucas D. Masnattá, Carolina Pesiney, Patricia Fischer and Agustín José Ramirez

**Background** Nonmodulating (NMHT) is a high-renin subtype of salt sensitive hypertension, which additionally develops insulin resistance and oxidative stress. Conversely, modulating hypertensives (MHT) normally regulates renal hemodynamics after high sodium intake without metabolic impairment. We postulate that telmisartan, an angiotensin receptor blocker with partial peroxisome proliferators-activated receptor partial agonist, may improve insulin resistance compared with ramipril, an angiotensin-converting enzyme inhibitor (ACEI) in NMHT.

**Methods** We studied 18 NMHT (32 ± 5 kg/m²) and 16 MHT (34 ± 4, 10 men, BMI 28 ± 5 kg/m²) before and after the crossover administration of ramipril 10 mg (3 months) or telmisartan 80 mg (3 months). In each patient studied we measured, before and after each treatment period, office blood pressure, glycemia and insulinemia. In NMHT, telmisartan, after 3 months treatment, significantly reduced fasting and 120 min glycemia and insulinemia. In NMHT, telmisartan, after 3 months treatment with either ramipril or telmisartan no changes were found in fasting and 120 min glycemia and insulinemia. In MHT, after 3 months treatment with either ramipril or telmisartan no changes were found in fasting and 120 min glycemia and insulinemia. In NMHT, telmisartan improved the HOMA-IR index in both MHT (2.76 ± 0.16 to 2.24 ± 0.18, P<0.05) and NMHT (from: 4.4 ± 1 to 2.3 ± 0.7) and triglyceride plasma levels (MHT: from 139 ± 1.85 to 122 ± 2.4 mg%, P<0.05; NMHT: from: 223 ± 12 to 146 ± 10 mg%, P<0.01). Finally, highly sensitive C-protein-reactive protein values were higher in NMHT (0.33 ± 0.07 mg.dl) than in MHT (0.14 ± 0.06 mg.dl; P<0.01). Both treatments reduced highly sensitive C-protein-reactive protein in NMHT. (ramipril from 0.32 ± 0.05 mg.ml to 0.26 ± 0.06 mg.ml (P<0.05) and telmisartan from 0.34 ± 0.05 to 0.20 ± 0.05 mg.ml (P<0.01).

**Conclusion** Our data suggest that the improvement of the insulin sensitivity by telmisartan, instead of a similar effect on blood pressure shown by both drugs, could be ascribed to the PPAR agonistic action of telmisartan. This opens an interesting therapeutic approach for patients with hypertension and altered glycemic metabolism. *J Hypertens* 26:2393–2398 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

**Abbreviations:** A II, Angiotensin II; ACEI, Angiotensin Converting Enzyme Inhibitor; ERPF, Effective Renal Plasma Flow; GFR, Glomerular Filtration Rate; HOMA-IR, Homeostasis Model Assessment; hsCRP, High sensitive C Reactive Protein; NA+, Sodium; NMHT, Non-Modulating Hypertension; PPAR γ, Peroxisome Proliferator-Activated Receptor gamma; RAS, Renin Angiotensin System

*Hypertension Section and Metabolic Unit. Fundación Favaloro and Universidad Dr RG Favaloro, Buenos Aires, Argentina

Correspondence to Dr Agustín José Ramirez, MD, PhD, Hypertension Section and Metabolic Unit,ICYCC, Fundación Favaloro, Belgrano 1782 P: 4 (C1093AA), Buenos Aires, Argentina

Tel: +54 11 4378 1337; e-mail: sanchez@ffavaloro.org

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**Introduction**
Nonmodulating hypertension (NMHT) is a subset of salt sensitive essential hypertensive individuals, who fail to adequately excrete Na⁺ in response to high Na⁺ intake [1]. This subgroup of hypertensives can be identified because they fail to increase effective renal plasma flow and decrease filtration fraction when submitted to a Na⁺ load, as previously described [2]. This altered renal
hemodynamic response has been linked to either an over activity of the renin-angiotensin system (RAS), an altered angiotensin II (A II) receptor sensitivity [2], a decreased activity of the kallikrein–kinin system [3] or a combination of some or all of them. Recently, we provided evidences in NMHT and in nonmodulating offspring of hypertensive parents [4] showing that blocking the RAS restores both the renal hemodynamic and the peripheral endothelial dysfunction. In addition, we also reported that insulin resistance or an impaired glucose metabolism is a frequent finding in nonmodulation [5] and is associated with an increased oxidative stress [5]. This is further supported by the fact that inhibition of the renin–angiotensin system (RAS) may improve insulin sensitivity by different actions beyond angiotensin-receptor blockade [6,7].

In-vitro studies showed that the A II receptor blocker (ARB) telmisartan, by activating peroxisome proliferator-activated receptor gamma (PPAR γ), increases the expression of PPAR γ target genes in preadipocytes [8,9]. Additionally, administration of telmisartan to individuals with metabolic syndrome, but not amlodipine, was able to induce a reduction in abdominal fat volume associated with an improvement in insulin sensitivity [10]. Furthermore, similar to pioglitazone, telmisartan also induced a decrease in C-reactive proteins and an increase in adiponectin, related to an abdominal fat remodeling [11].

On the contrary, different studies with angiotensin-converting enzyme inhibitors (ACEI) showed contradictory results in reducing the risk of diabetes. For instance, the Heart Outcomes Prevention Evaluation (HOPE) trial [12] showed, in patients with high cardiovascular risk, a beneficial effect of ramipril compared with placebo on the outcome of new cases of diabetes, whereas in the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) [13] study, the same ACEI, ramipril, failed to prevent diabetes in predisposed individuals.

Thus, the main objective of this study was to evaluate, in NMHT compared with MHT, if blocking the actions of the RAS by two different compounds: an ACEI, ramipril, or an ARB with partial PPAR γ activity, telmisartan, may show differential responses in glucose metabolism and high sensitive C reactive protein (hsCRP), as inflammation marker.

**Methods**

**Subject selection and inclusion**

In 42 preselected essential hypertensive patients from the outpatients’ clinic, after 2 weeks antihypertensive treatment withdrawal, renal hemodynamic studies were initially performed to identify modulators and nonmodulators, as previously described [4,5]. In this way, 18 NMHT (32 ± 5 years, nine men) and 16 MHT (34 ± 4 years, 10 men) were identified and submitted to a 2-week placebo period to ratify their hypertensive condition. Afterwards, individuals in each group were randomized in a crossover fashion to receive either ramipril 10 mg daily or telmisartan 80 mg daily for 3 months. In this way, as shown in Fig. 1, each one of the individuals studied, either being MHT or NMHT were allocated for 3 months under ramipril and, after a second placebo period of 2 weeks, to telmisartan for 3 months.

The remaining eight patients were excluded as they failed to complete the 10-day periods of salt intake or to fail in compliance to the daily sodium intake (assessed by 24-h urinary sodium excretion measurement, vide infra). Secondary forms of hypertension were excluded by history and physical examination, screening biochemical testing, renal echography and nuclear resonance or renal arteriography. Renal function was normal in all patients (serum creatinine: 0.8 to 1.2 mg/dl). Antihypertensive treatment was withdrawn at least 4 weeks before the beginning of the study.

**Renal hemodynamic characterization**

Nonmodulation and modulation were characterized by renal hemodynamic evaluation performed, after 10 days of low-sodium intake (20 mmol Na +) followed by 10 days of high Na + intake (250 mmol Na +). Briefly, glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were both calculated by the insulin and paraaminohippuric acid clearances [4], as the steady-state infusion rate divided by the plasma concentration of the respective substances. After that, filtration fraction was calculated as: ERPF/GFR. Finally, those individuals who, after a high Na + diet, had reached a minimum increase of 30% in ERPF and a minimum decrease of 30% in filtration fraction were characterized as modulating hypertensives [4,5]. Those who failed to reach this change were classified as nonmodulating hypertensive. From this, 16 out of 34 patients (34 ± 4 years; ten men) were found to be modulating and the remaining 18 (32 ± 5 years; nine men) to be nonmodulating essential hypertensives.
Blood pressure measurement

Blood pressure values were registered after 10 days of low and 10 days of high Na\textsuperscript{+} intake, using a Dinamap 8100 (Critikon, Tampa, Florida, USA). Blood pressure values, herein reported, are the mean value of three consecutive measurements, elapsed by 1 min, performed in each patient at the end of each one of the above mentioned conditions.

Laboratory determinations

Oral glucose tolerance test

After a fasting blood sample had been taken, 75 g of glucose was orally administered and blood sampling were performed at 60 and 120 min. Both plasma glucose and insulin were measured in all individuals. Insulin resistance was characterized by the Homeostasis Model Assessment (HOMA-IR) and calculated as previously reported [14]: HOMA = fasting glucose (mmol) × fasting insulin (μU/ml)/22.5. A HOMA below 3.0 was considered normal (range: 1.5–3.0). Plasma renin activity (PRA) was measured by radioimmunoassay before and after 10 days of low and high Na\textsuperscript{+} intakes [3]. After that, PRA was normalized in each individual relating to the corresponding 24-h urinary sodium excretion, as previously suggested by Laragh et al. [15]. hsCRP was measured by immunoturbidimetric assay (Tina-quant; Roche), with a limit detection of 0.03 mg/l, variation coefficient less than 10% and functional sensitivity of 0.11 mg/l. This protocol was approved by the Institutional Review Board and an informed consent was signed by all participants.

Statistical analysis

Data was expressed as mean ± SD. For a comparison of all ramipril therapy measurements and all telmisartan measurements in NMHT and MHT, two-way repeated measures ANOVA were used. If variance ratios reached statistical significance, differences between the means were analyzed with the Student-Newman-Keuls test. A P < 0.05 was considered as statistical significant.

Results

As shown in Table 1 at baseline, NMHT had, compared with MHT, a higher waist circumference, microalbuminuria and PRA with lower high-density lipoprotein cholesterol and higher triglycerides plasma levels (P < 0.05).

Table 1 Tabular comparison of nonmodulating hypertensives to modulating hypertensives

<table>
<thead>
<tr>
<th></th>
<th>MHT</th>
<th>NMHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (men/women)</td>
<td>10/6</td>
<td>9/9</td>
</tr>
<tr>
<td>BMI (kg/m\textsuperscript{2})</td>
<td>28 ± 5</td>
<td>29 ± 3</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>93 ± 10</td>
<td>115 ± 8*</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>221 ± 12</td>
<td>214 ± 13</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>54 ± 6</td>
<td>37 ± 8*</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>6.8 ± 0.6</td>
<td>6.2 ± 0.8</td>
</tr>
<tr>
<td>PRA (ng/ml·h)</td>
<td>2.6 ± 0.9</td>
<td>4.4 ± 0.5*</td>
</tr>
</tbody>
</table>

HDLC, high-density lipoprotein; MHT, modulating hypertensives; NMHT, nonmodulating hypertensives; PRA, plasma renin activity. *P < 0.05

In MHT (Fig. 2, upper panel) or NMHT (Fig. 2, lower panel), systolic and diastolic blood pressures were similarly reduced either by ramipril or telmisartan.

As shown in Figure 3, fasting and 120-min glycemia and insulinemia were higher in NMHT than in MHT. When HOMA-IR was evaluated three out of the 16 (18.75%) MHT and 14 out of 18 (77.78%) NMHT patients were insulin resistant.

In MHT, after 3 months treatment with either ramipril or telmisartan no changes were found in fasting and 120-min glycemia and insulinemia. In NMHT, telmisartan, after 3 months treatment, significantly reduced fasting and 120-min glycemia and insulinemia compared either to basal values or ramipril treatment.

Telmisartan improved the HOMA-IR index (Fig. 4, upper panel) in both MHT and NMHT compared with
basal values and ramipril treatment that failed to show any significant change.

Triglycerides (Fig. 4, lower panel), were significantly decreased by telmisartan both MHT and NMHT, compared with the respective basal value and after ramipril treatment. The final triglyceride plasma levels reached were similar in MHT and NMHT. On the contrary, ramipril induced a significant increase in both MHT and NMHT.

Finally, hsCRP values were higher in NMHT (0.33 ± 0.07 mg.dl) than in MHT (0.14 ± 0.06 mg.dl; \( P < 0.01 \)). Both treatments reduced hsCRP in NMHT, (ramipril from 0.32 ± 0.05 to 0.26 ± 0.06 mg.dl \( P < 0.05 \)) and telmisartan from 0.34 ± 0.05 to 0.20 ± 0.05 mg.dl \( P < 0.01 \)).

**Discussion**

The main finding of this study was that telmisartan but not ramipril improved different parameters related to insulin sensitivity and reduced triglycerides in nonmodulating essential hypertensives. Moreover, telmisartan also was able to reduce in greater extent than ramipril, CRPs in this group of nonmodulating hypertensives. It is known that NMHT individuals but not MHT develop insulin resistance and endothelial dysfunction even in an early stage of hypertension. This metabolic alteration seems to be related at least in part with an over-activity of the RAS [4,5]. The presence of microalbuminuria and endothelial dysfunction in NMHT [4], gives support to the idea that this metabolic cluster could accelerate organ damage in these individuals and increase their cardiovascular risk. Both, telmisartan and ramipril are able to blunt the RAS effects in different ways and might improve, by this mechanism, insulin sensitivity in patients affected by this metabolic disarray [16,17]. However, in our study only telmisartan has shown a positive metabolic effect in NMHT and MHT. Angiotensin II may adversely affect glucose metabolism by increasing reactive oxygen species, inducing inflammation, decreasing blood flow, in many tissue beds and impair insulin-signaling pathways and pancreatic function [18–24]. In addition, A II is able to inhibit the adipocyte differentiation and, by this way, may affect adiponectin release. Another putative mechanism by which telmisartan may reduce insulin resistance is through the activation of PPAR \( \gamma \) receptors [8,9], which is inhibited by angiotensin.
In our study only telmisartan was able to reduce lipid metabolism, thereby ameliorating type 2 diabetes metabolic abnormalities, not only to normalize high blood pressure values but also to improve insulin resistance. The metabolic effects seems to be related to a PPAR γ receptor activation rather than to the inhibition of the A II actions as in individuals treated with ramipril this effect was not observed. Furthermore, the DREAM study [13] showed that in a longer period of time (3 years) and a larger population (n = 5269), ramipril failed to reduce diabetes susceptibility.

**Limitations of the study**

We did not evaluate insulin sensitivity by a glucose clamp which is known to represent the gold standard for insulin sensitivity evaluation but hardly applicable to clinical studies. On the contrary, this study included a limited number of patients and a larger study should be necessary to confirm our results. Our study was conducted during a short period (3 months) and a longer period study may be necessary to confirm these results. In support of our data are the above-mentioned results related to the DREAM study [13] where it was shown that ramipril failed to reduce diabetes susceptibility in a larger population of individuals and a longer period of time.

**References**


