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Telmisartan improves insulin sensitivity in nondiabetic patients with essential hypertension

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Abstract

Hypertension is a cardiovascular risk factor commonly associated with insulin resistance, the metabolic syndrome, and type 2 diabetes mellitus. Recent in vitro data indicate that certain angiotensin receptor antagonists, for example, telmisartan, activate peroxisome proliferator–activated receptor γ (PPAR-γ) and increase adiponectin protein content in adipocytes. By this means, they may improve insulin sensitivity in vivo. To investigate the effect of antihypertensive treatment on insulin sensitivity and fasting adiponectin serum levels, 37 nondiabetic patients with essential hypertension were randomized to receive telmisartan, the calcium channel blocker nisoldipine, or their combination for 6 weeks in a prospective, parallel group study. Fasting serum glucose, insulin, and adiponectin were evaluated before, 3 weeks (low dose), and 6 weeks (high dose) after initiation of treatment. Furthermore, the effect of telmisartan on PPAR-γ receptor activity was investigated in vitro using a PPAR-γ reporter gene assay. As reported previously, telmisartan significantly enhanced PPAR-γ receptor activity in vitro. At baseline, a positive correlation between insulin serum levels and body mass index of investigated subjects was observed, whereas body mass index and serum adiponectin levels were negatively associated. High-dose treatment with telmisartan but not with nisoldipine reduced serum insulin levels as well as the homeostasis model assessment of insulin resistance, but did not affect serum adiponectin levels. In conclusion, in our study cohort of nondiabetic patients with essential hypertension, telmisartan improved insulin sensitivity by mechanisms apparently not involving adiponectin induction. Future studies will demonstrate whether these telmisartan-induced effects may contribute to a blood pressure–independent reduction in cardiovascular morbidity.

1. Introduction

The important role of angiotensin II in the pathogenesis of essential hypertension has been widely acknowledged in recent years [1]. Consecutively, the use of angiotensin-converting enzyme inhibitors and, because of their better tolerability, angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]) has largely increased. This was supported by the results of controlled clinical trials in which the benefits of these classes of drugs beyond their mere blood pressure–lowering effects have been documented [2].

Hypertension and insulin resistance are 2 symptoms of a metabolic disorder which has been called the metabolic syndrome and also comprises adiposity and dyslipidemia [3,4]. As the prevalence of the metabolic syndrome is one of the most rapidly increasing disease entities in the Western world, much attention has been focused on optimization of both antihypertensive treatment and glycemic control in an attempt to lower the burden of major adverse cardiovascular events in the Western world [4]. Therefore, 2 recent studies showing that the ARB telmisartan activates peroxisome proliferator–activated receptor γ (PPAR-γ) in vitro have received great interest [5,6]. Peroxisome proliferator–activated receptor γ is a transcription factor that controls the gene expression of several key enzymes of glucose metabolism and thereby increases insulin sensitivity (for a comprehensive review on PPAR-γ receptors and their function, see Refs. [7,8]). In vitro, telmisartan-induced PPAR-γ activation was AT1 receptor independent and occurred at therapeutically relevant concentrations of 1 to 5 μmol/L, whereas the potency of other ARBs to activate PPAR-γ receptors tested in this setting was considerably lower [6]. In addition, telmisartan was just recently shown

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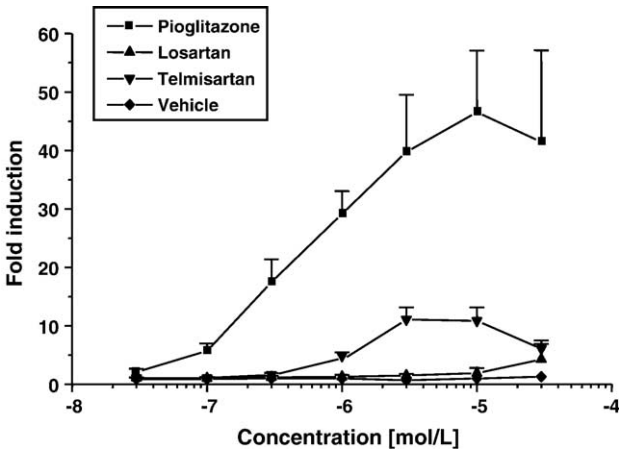

Fig. 1. Telmisartan acts as a partial agonist of PPAR-γ receptors transiently transfected in HEK293 cells. Activation of PPAR-γ receptors is shown as fold induction of luciferase activity after stimulation with increasing concentrations of telmisartan (reversed triangles), losartan (triangles), pioglitazone (squares), or vehicle (rhombuses). Concentrations of telmisartan higher than 10^{-6} mol/L significantly induced PPAR-γ activity ($P < .001$ vs baseline). Data are given as mean ± SD.

to induce adiponectin protein content in cultured adipocytes by a posttranscriptional mechanism involving a reduction of 26S proteasome activity [9]. We performed a clinical study to investigate the effects of telmisartan compared with nisoldipine on 24-hour blood pressure control when these experimental data were published, and, therefore, we decided to investigate the potential metabolic effects (eg, adiponectin, insulin serum levels) of telmisartan in vivo in our study. To assess insulin sensitivity in fasting human subjects from single blood samples, we used the homeostatis model assessment (HOMA) index, which has been shown to reliably mirror insulin sensitivity in vivo [10-12].

2. Materials and methods

2.1. Patients and study protocol

Thirty-seven patients with essential hypertension took part in this study, which was performed as a single-center, randomized, blinded study. The local ethics committee approved the study design; the study was conducted according to the Principles of Good Clinical Practice and the Declaration of Helsinki.

Patients were eligible for the study if they had been diagnosed with essential hypertension, were between 20 and 80 years old, and had signed the informed consent form. Patients were excluded if they had liver or renal dysfunction, severe heart failure, diabetes mellitus, acute or unstable coronary artery disease, or had previously experienced hyperreactivity against AT1 receptor antagonists or calcium channel blockers. Patients who were on stable antihypertensive treatment underwent a washout phase of all antihypertensive and vasoactive medication during 2 weeks before the beginning of the study. During this period, clonidine and hydrochlorothiazide were available as rescue medication if blood pressure rose to levels of 180/110 mm Hg or above.

The patients came to the clinic on the morning of day 1 for blood sampling, physical examination, and to have 24-hour blood pressure monitors mounted. After 24 hours, the patients returned the blood pressure recorders and received study medication. Medication was either telmisartan 40 mg qd, nisoldipine 10 mg qd, or a combination of telmisartan 40 mg plus nisoldipine 10 mg qd for 3 weeks. On day 21, the patients returned to the clinic for another blood sample and 24-hour blood pressure recording. Thereafter, study medication was provided for the second medication period, during which telmisartan treatment was increased to 80 mg qd, nisoldipine was increased to 20 mg qd, and combination treatment was increased to telmisartan/nisoldipin 80/10 mg qd for another 3 weeks. On day 42, the patients returned to the clinic to have their last blood sampling and 24-hour blood pressure recording done. After the end of the study, the previous blood pressure–lowering regimen was started again, and patients were supervised until their blood pressure was on the same level like before the study.

2.2. Measures of adiponectin plasma levels and insulin sensitivity

Serum adiponectin levels were determined using a commercially available ELISA kit according to the instructions of the manufacturer (B-Bridge International, Sunnyvale, CA).

Table 1
Patient characteristics

	Telmisartan (n = 12)	Nisoldipine (n = 13)	Combination (n = 12)	P
Sex (male/female)	7/5	6/7	7/5	NS
Age (y)	59.0 ± 7	56.9 ± 8	59.6 ± 8	NS
Mean blood pressure (mm Hg)	103.6 ± 8.7	108.6 ± 12.5	99.8 ± 7.5	NS
BMI (kg/m^2)	23.0 ± 3.0*	27.1 ± 4.1*	24.5 ± 4.2	*<.05
Cholesterol (mg/dL)	244 ± 32	236 ± 48	254 ± 46	NS
HDL (mg/dL)	63 ± 13	56 ± 11	58 ± 16	NS
LDL (mg/dL)	158 ± 25	150 ± 41	164 ± 28	NS
C-reactive protein (mg/L)	0.95 (0.7-1.925)	2.1 (1.25-3.7)	1.9 (1.125-3.15)	NS
Creatinine (mg/dL)	0.95 ± 0.17	0.95 ± 0.15	0.93 ± 0.18	NS
Fasting glucose (mmol/dL)	5.1 ± 0.6	5.4 ± 0.4	5.4 ± 0.7	NS
Fasting insulin (μU/mL)	10.1 ± 7.0	10.2 ± 6.1	9.6 ± 6.8	NS
Fasting adiponectin (μg/mL)	5.2 (3.9-10.5)	4.2 (3.6-4.7)	4.4 (3.5-6.1)	NS
Current smokers	0	1	1	NS
Washout medication				
Hydrochlorothiazide	6	8	7	NS
Clonidine	2	2	1	NS

Data are given as mean ± SD (parametric data) or median with IQR (nonparametric data). NS indicates not significant.

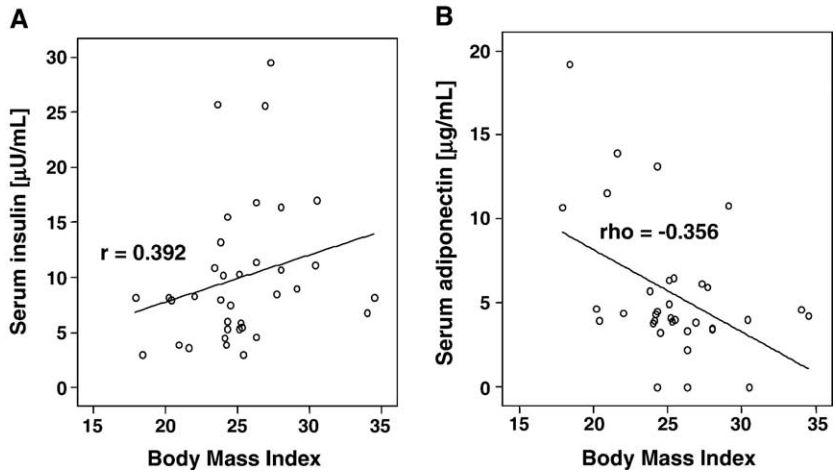

Fig. 2. Fasting serum insulin as well as adiponectin levels significantly correlates with the BMI of enrolled hypertensive patients. A, Positive association of serum insulin and BMI ($P < .05$). B, Negative correlation of serum adiponectin and BMI ($P < .05$).

Plasma glucose was measured by validated standard clinical chemical methods using the photometric glucose dehydrogenase method in the local clinical laboratory. Serum insulin concentrations were measured by using a commercially available highly specific enzyme immunoassay for human insulin (Mercodia, Uppsala, Sweden). The HOMA index was calculated according to Matthews et al [12] with the formula: fasting serum insulin (mU/L) × fasting plasma glucose (mmol/L)/22.5. The HOMA index has been validated in several studies as an index of insulin sensitivity [11,13]. A high HOMA score denotes low insulin sensitivity (= insulin resistance).

2.3. Other biochemical assays

Serum total cholesterol, LDL and HDL cholesterol, and triglyceride levels, as well as serum creatinine concentrations, were determined in the local clinical chemical laboratory by standard laboratory methods using certified assays.

2.4. Activation of PPAR-γ receptors in cell culture experiments

HEK 293 cells were grown to subconfluence in 96-well multiplates with Dulbecco's Modified Eagle's Medium (Biochrom, Berlin, Germany) plus 10% fetal calf serum (FCS), 1% glutamine, 1% penicillin, and 1% streptomycin. The cells were transiently transfected with the use of Polyfect with pPPAR-γ/GAL4 (120 ng); pRL-CMV (12 ng), a renilla luciferase control vector; and pCMV-Var-Gal (60 ng), a firefly luciferase reporter vector. During transfection, the medium contained only 1% FCS. After 24 hours, the transfection medium was replaced by new medium also containing 1% FCS plus different concentrations of telmisartan, losartan, pioglitazone (each 30 nmol/L to 10 µmol/L), or vehicle. Luciferase activity was measured after 24 hours of incubation with the drugs using Promega (Mannheim, Germany) reagents with a multi-detection reader (GENios, Tecan, Maennedorf, Switzerland). Luciferase activity was expressed as a ratio of PPAR-γ/GAL4 firefly luciferase to TK-renilla luciferase to correct for transfection efficiency.

2.5. Statistical analyses

Distribution of data was tested with the Kolmogorov-Smirnov test. Continues variables were expressed as arithmetic mean ± SD if normally distributed or otherwise as median with 25% and 75% percentiles (interquartile range [IQR]). Differences in baseline characteristics among groups were tested with 1-way analysis of variance if normally distributed, whereas baseline differences of variables with skewed distribution were tested with Kruskal-Wallis H or Mann-Whitney U test. Changes during treatment within different treatment groups were tested either with repeated-measure analysis of variance followed by Dunnett's test, the nonparametric test of repeated measures on ranks (Friedman test) followed by Wilcoxon's

Table 2
Effect of antihypertensive treatment on blood pressure and serum adiponectin levels

	Telmisartan			Nisoldipine			Combination			P
	Baseline	Day 21	Day 42	Baseline	Day 21	Day 42	Baseline	Day 21	Day 42	
Mean blood pressure (mm Hg)	103.6 ± 8.7	99.9 ± 9.4	96.6 ± 12.5$^{\#}$	108.6 ± 12.5	103.5 ± 10.7†	104.7 ± 9.7‡	99.8 ± 7.5	94.9 ± 6.6$^{\#}$	91.6 ± 5.3$^{\#}$	$^{\#}$<.05 vs baseline, $^{\dagger}P = .082$, $^{\ddagger}P = .090$
Adiponectin (µmol/mL)	5.2 (3.9-10.5)	6.0 (3.9-8.5)	5.1 (3.9-9.2)	4.2 (3.6-4.7)	5.0 (3.8-6.1)	4.3 (3.7-6.8)	4.4 (3.5-6.1)	4.8 (4.2-6.6)	4.8 (3.5-6.9)	NS

Data are given as mean ± SD (parametric data) or as median (IQR) (nonparametric data).

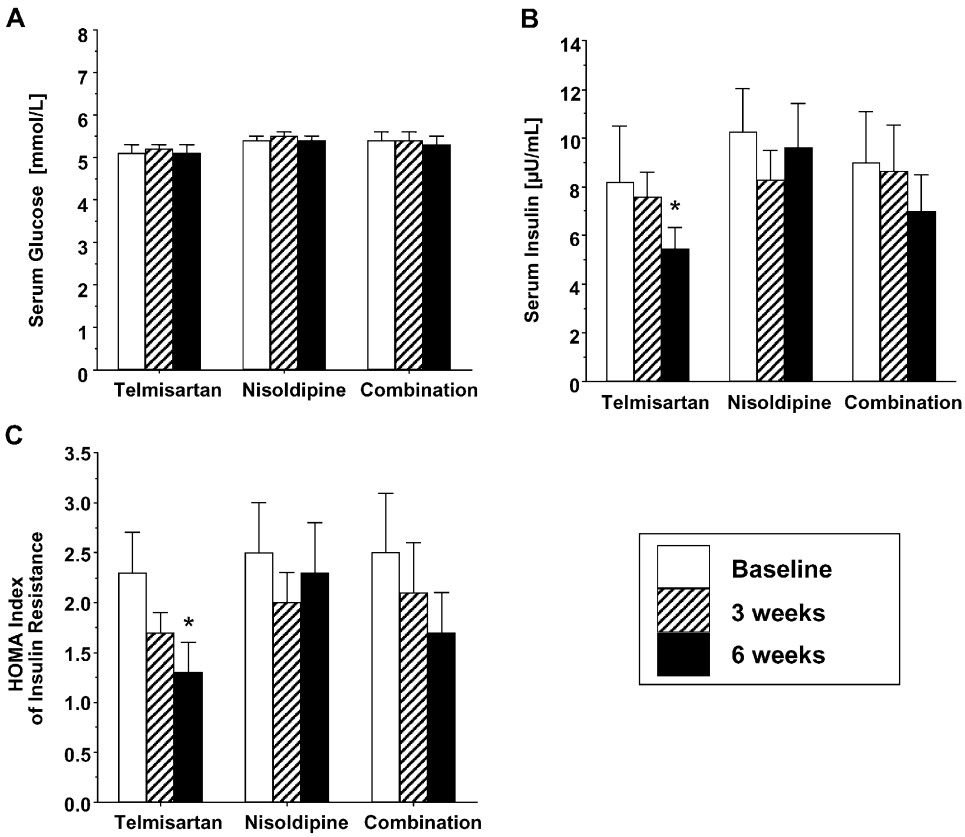

Fig. 3. Treatment with telmisartan reduces serum insulin levels and improves the HOMA of insulin resistance in patients with essential hypertension. Development of fasting serum glucose (A), serum insulin levels (B), and insulin resistance (C) as expressed by HOMA during study period. Data are given as mean ± SD. *$P < .05$ vs baseline.

test, or with Wilcoxon's test alone. Bivariate correlations were analyzed using either Spearman's ρ or Pearson's r. Probability values less than .05 were considered significant. For all statistical analyses, SPSS version 12.0 (SPSS, Chicago, IL) was used.

3. Results

3.1. Effects of telmisartan on PPAR-γ activation in vitro

Telmisartan significantly induced luciferase activity at concentrations of 1×10^{-6} mol/L (6.1 ± 1.4-fold induction) or higher as compared to vehicle alone ($P < .001$; Fig. 1). At a concentration of 3×10^{-6} mol/L, telmisartan reached its maximum effect (11.1 ± 2.0-fold induction). In contrast, another AT1 blocker, losartan, did not show any significant induction even at higher concentrations (3×10^{-5} mol/L). Pioglitazone, a known effective PPAR-γ agonist, caused a maximal induction of luciferase activity at a concentration of 1×10^{-5} mol/L (46.5 ± 10.6-fold; $P < .001$; Fig. 1).

3.2. Patients' characteristics and blood pressure–lowering effect of antihypertensive treatment

Baseline characteristics of studied patients are shown in Table 1. In the study population, patients randomized to receive nisoldipine had a significantly higher body mass index (BMI) than patients randomized to receive telmisartan (27.1 ± 4.1 vs 23.0 ± 3.0; $P < .05$). Except for this observation, baseline characteristics showed no clinically relevant differences among treatment groups. At baseline, BMI positively correlated with serum fasting insulin ($r = 0.392$, $P < .05$; Fig. 2A) and C-reactive protein levels (0.354; $P < .05$); it was positively associated with mean arterial blood pressure ($r = 0.346$; $P < .05$) and showed a negative correlation with fasting serum adiponectin levels ($\rho = -0.356$, $P < .05$; Fig 2B). Moreover, there was a trend toward negative association of baseline HOMA values and adiponectin serum levels ($\rho = -0.332$; $P = .055$). As shown in Table 2, mean blood pressure was reduced in patients after 6 weeks of antihypertensive treatment with telmisartan (−7.0 mm Hg; $P < .05$) and the combination of both substances (−8.2 mm Hg; $P < .05$). In patients treated with nisoldipine alone, a trend toward lower blood pressure values was observed, but values failed to reach statistical significance during the study period (−3.9 mm Hg; $P = .090$).

3.3. Effects of telmisartan and nisoldipine on insulin sensitivity and serum adiponectin levels

Fasting serum glucose concentration was within the normal range and unchanged during the study period in all

experimental groups (Fig. 3A). However, fasting serum insulin concentration declined in the telmisartan-treated groups, reaching statistically significantly lower levels at 6 weeks in the telmisartan group ($P < .05$; Fig. 3B). However, this trend missed formal statistical significance in the telmisartan-plus-nisoldipine group ($P = .091$). No such trend was seen in the nisoldipine group. The HOMA index of insulin resistance was also significantly lower after 6 weeks of treatment with telmisartan alone ($P < .05$; Fig. 3C), whereas the trend toward reduced HOMA index failed to reach statistical significance in the combination group ($P = .092$; Fig. 3C). Again, no trend whatsoever was observed in the nisoldipine group.

In contrast to insulin serum levels, adiponectin serum levels were not significantly affected by telmisartan treatment (neither mono- nor combination therapy) nor by nisoldipine treatment (Table 2).

4. Discussion

The main findings of the present study are that (1)—as recently described—the angiotensin receptor antagonist telmisartan induced PPAR-γ activity in vitro at therapeutically relevant concentrations of 1 μmol/L; (2) treatment with telmisartan significantly improved insulin sensitivity in nondiabetic patients with essential hypertension (as measured by its surrogate, fasting glucose, and insulin levels); and (3) treatment with telmisartan did not significantly affect adiponectin serum levels in studied individuals.

Multiple associations have been demonstrated in the past between insulin actions and blood pressure regulation. Essential hypertension has been shown to be an insulin-resistant state in its own right [14]. Neurohumoral mechanisms involved in blood pressure regulation may contribute to this relationship, for example, angiotensin II infusion has been shown to induce insulin resistance in rats and might directly interfere with insulin signaling to induce insulin resistance, an effect that appears to be mediated at least partly through AT1 receptor activation [15-17].

Telmisartan has recently been identified experimentally as an exceptional AT1 receptor blocker in that it activates PPAR-γ receptors [5,6]. These data were generated in a cellular transient transfection model and were shown to be independent of AT1 receptor activation [5]. However, it remained unclear from that study whether therapeutic plasma levels of telmisartan are high enough to induce similar effects in human patients in vivo.

We investigated PPAR-γ activity using a dual luciferase activity assay which yields valid results in a variety of cell types, for example, HEK 293 cells [5,6,18]. As HEK 293 cells are known for their high transfection efficiency, we chose this model to investigate PPAR-γ activity. The data generated in this in vitro system suggest that PPAR-γ–modulating activity can be seen at telmisartan concentrations that are reached therapeutically, using doses of 80 mg/d, as observed in pharmacokinetical approaches in our laboratory (unpublished data). Moreover, we found that another ARB, losartan, had no effect on PPAR-γ activity at similar or higher concentrations.

One of the mechanisms underlying the effect of telmisartan on glucose homeostasis may be antagonism of angiotensin II's effects on insulin resistance mediated via the AT1 receptor [19]. However, a recent study by Vitale et al [20] provided data from another small clinical trial in which telmisartan was compared to losartan in 40 patients with metabolic syndrome. Telmisartan, but not losartan, significantly reduced plasma glucose and insulin levels during an oral glucose tolerance test after 3 months of treatment. Telmisartan also lowered systolic and diastolic blood pressure significantly more than losartan in that study. Another recent study comparing the angiotensin-converting enzyme inhibitor lisinopril with the AT1 blocker losartan also showed that the latter had no significant effect on insulin sensitivity [21].

Our data add to the available evidence on the favorable effects of telmisartan on glucose metabolism. They extend previous findings in that we included patients without clinical evidence of diabetes mellitus or metabolic syndrome, but still found a reduction of fasting insulin concentration after 6 weeks of treatment.

In a recently published study, Clasen et al [9] demonstrated that telmisartan reduces cellular adiponectin protein depletion in cultured adipocytes by protein-stabilizing mechanisms presumably involving PPAR-γ receptors and the 26S proteasome. To further determine the role of adiponectin in telmisartan-induced insulin sensitivity, we therefore investigated adiponectin serum concentrations during treatment in our study cohort. In contrast to the above-described in vitro findings, adiponectin serum levels did not significantly change within the studied individuals (Table 2). In this context, we cannot exclude that the negative result is due to the small number of studied patients and/or short duration of therapy. However, the study design allowed for determination of increases in insulin sensitivity, indicating that it was appropriate to detect clinically relevant changes in parameters affecting glucose homeostasis. Furthermore, adiponectin serum levels measured within the study cohort displayed previously described associations with BMI and insulin sensitivity (Fig. 2, Table 2) and were consistent with those observed in other clinical studies involving hypertensive patients [22]. It is therefore tempting to speculate that telmisartan-induced adiponectin content/secretion of adipocytes might only affect insulin sensitivity in clinical conditions accompanied with adiponectin depletion, for example, metabolic syndrome, whereas telmisartan-mediated induction of insulin sensitivity in nonobese and nondiabetic, hypertensive patients might not primarily depend on adiponectin regulation.

Our study has limitations: Firstly, the number of patients included was small, eliciting a relatively high level of variability in our data. Secondly, parameters of glucose

metabolism were not defined as the primary endpoint of our study, which therefore was not primarily designed to prove with adequate statistical power a difference in insulin sensitivity during treatment. Furthermore, the patients were not preselected for the presence of a disturbance in glucose metabolism. Despite these limitations, we were able to detect a stable trend toward reduction of serum insulin levels in all patients receiving telmisartan. Moreover, telmisartan significantly lowered blood pressure in our study, whereas nisoldipine-treated patients only showed a statistically nonsignificant trend toward lower blood pressure, a problem also likely to be prominent in placebo-treated controls, which, for ethical concerns, were not included in this study. Although we cannot exclude that the different blood pressure–lowering effects of telmisartan and nisoldipine account for different effects on insulin sensitivity, neither insulin serum levels nor HOMA values were associated with blood pressure or blood pressure reduction during treatment (data not shown). Therefore, it is rather unlikely that blood pressure reduction is considerably involved in telmisartan-mediated induction of insulin sensitivity. Nonetheless, it is crucial to perform larger studies in patients whose baseline glucose metabolism is better characterized and with metabolic markers as primary endpoint. In this context, the ongoing ONTARGET trial will provide data from a large patient cohort to show whether telmisartan elicits beneficial effects in this regard [23].

In summary, our study provides clinical evidence for a favorable effect of telmisartan on glucose homeostasis, supporting and confirming previous experimental evidence for a specific PPAR-γ–activating effect of this ARB. Further controlled clinical trials will now be necessary to assess whether telmisartan has a beneficial long-term effect on glucose metabolism in larger cohorts of hypertensive patients with or without the metabolic syndrome.

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