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The effect of telmisartan on glucose and lipid metabolism in nondiabetic, insulin-resistant subjects

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Abstract

Intervention studies have shown that angiotensin receptor blocker therapy may reduce the incidence of type 2 diabetes mellitus. It is unknown whether short-term angiotensin receptor blocker therapy can improve glucose and lipid metabolism in insulin-resistant subjects. We evaluated the effect of telmisartan (40 mg/d, 12 weeks) in 20 subjects with insulin resistance (body mass index, 31.8 ± 3.31 kg/m^2; triglycerides, 179 ± 98 mg/dL; glucose, 104 ± 9 mg/dL; homeostasis model assessment index, 3.78 ± 1.52) in a randomized, placebo-controlled, double-blind, cross-over study. At the end of each treatment phase, oral and intravenous glucose tolerance tests including C-peptide and insulin measurements were performed, and fasting and postprandial lipids were determined. Compared to placebo, telmisartan resulted in a reduction in homeostasis model assessment index (−11%, P = .06) and glucose area under the curve during intravenous glucose tolerance (−11%, P = .04). We observed an increase (+32%, P = .05) in the insulinogenic index indicating an improved beta-cell function. Fasting and postprandial lipid parameters did not change. We observed an increase in adiponectin (6%, P = .09), whereas IL-6, high-sensitivity C-reactive protein, fibrinogen, and free fatty acid concentrations did not change. This indicates that the improvement in glucose metabolism is rather mediated by direct effects, such as activation of PPARγ. Our data indicate that in insulin-resistant persons 12 weeks of telmisartan result in a significant improvement in glucose metabolism with a predominant improvement in beta-cell function.

1. Introduction

The metabolic syndrome describes the presence of visceral obesity, insulin resistance or glucose intolerance, atherogenic dyslipidemia, hyperuricemia, and hypertension in a patient. All entities are common cardiovascular risk factors, with a calculated risk increase of 2- to 4-fold for cardiovascular disease and death [1]. The risk of developing diabetes mellitus type 2 for subjects with metabolic syndrome is increased 5- to 9-fold [2,3].

Large clinical trials evaluated the effect of angiotensin receptor blockers (ARBs) on cardiovascular endpoints. An analysis of comorbidity showed that such therapy also substantially lowers the risk for type 2 diabetes compared with other antihypertensive drugs and placebo [4-6]. Furthermore, it lowers cardiovascular mortality independent of its antihypertensive effects. A large angiotensin-converting enzyme blocker trial showed that the incidence of diabetes was lower in the active treatment group than in the placebo group [7]. This reduction in incidence was associated with lowering of blood pressure, but independent of other predictors for the development of diabetes. Moreover, an anti-inflammatory effect by treatment was observed, as well as an influence on the metabolism of free fatty acids. Because inflammatory processes and an altered metabolism of free fatty acids play a central role in the pathogenesis of insulin resistance and thus of diabetes, the lower incidence of diabetes could be attributed to the modifying effects of ARB therapy on inflammation and free fatty acid metabolism. However, angiotensin can promote insulin resistance; thus, any approach leading to a decreased concentration (angiotensin-converting enzyme inhibitors) or effect (ARB) of angiotensin may result in improved insulin sensitivity. Furthermore, it has been proposed that some ARBs act as partial activators of peroxisome proliferator–activated receptor γ (PPARγ) at concentrations that are achieved with the recommended oral doses for antihypertensive treatment [8].

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As disturbances of glucose and lipid metabolism are intimately linked to each other in the metabolic syndrome, it could be hypothesized that changes in glucose metabolism will also be reflected in changes in lipid metabolism. Indeed, several small clinical studies evaluated the effect of ARB therapy on lipid metabolism and found an improvement in triglyceride concentration, high-density lipoprotein (HDL) cholesterol concentration, and susceptibility of low-density lipoprotein (LDL) to oxidation [9-11]. The exact mechanisms that link the beneficial effects of ARBs on glucose metabolism with those on lipid metabolism are presently unknown.

Although some of the observed effects on glucose and lipid metabolism may relate to a class effect, there might be substantial differences between individual compounds. In an in vitro study, it was shown that telmisartan has particularly strong agonistic effects on PPARγ and may thus be particularly potent in improving glucose metabolism [12].

The aim of the present study was to determine whether telmisartan can affect the parameters of glucose and lipid metabolism, and whether it can modify the inflammatory processes in subjects with insulin resistance. Moreover, we aimed to determine whether short-term ARB therapy at oral doses recommended for antihypertensive therapy is sufficient to achieve the proposed effects. To address these issues, we designed a randomized, placebo-controlled, double-blind, cross-over study to evaluate the effects of telmisartan (40 mg/d for 3 months) in subjects with insulin resistance.

2. Methods

The study population included 20 volunteers with insulin resistance and abdominal overweight. Insulin resistance was defined as HOMA index of 2.3 or higher. Subjects with manifest diabetes mellitus or secondary reasons for insulin resistance (eg, steroid therapy) were excluded. Abdominal overweight was defined as body mass index of 25 mg/m^2 or higher and waist circumference of 95 cm or higher in men or 80 cm or higher in women, respectively. Only subjects with a minimum blood pressure of 120/80 mm Hg were included. Subjects with a known history of atherosclerosis (cerebrovascular, peripheral arterial, or coronary) were excluded, as well as subjects with severe hyperlipoproteinemia (defined as triglycerides >800 mg/dL or LDL cholesterol >190 mg/dL).

Other exclusion criteria were a blood pressure of greater than 160/95 mm Hg, habitual alcohol consumption of more than 30 g/d, antihypertensive medication, statin or lipid-lowering therapy, consuming illness, or a contraindication against the use of angiotensin II receptor blockers.

2.1. Study design

The study was performed as a randomized, placebo controlled, double-blind, cross- over study. The Ethics Committee of the Ludwig Maximilians University Munich approved the study protocol and all subjects gave written informed consent. Subjects were randomized to first receive placebo or telmisartan (40 mg/d) for 12 weeks, after which they received the other medication (telmisartan or placebo). At screening and at the end of each treatment phase, primary and secondary parameters were determined. Participating subjects were asked not to change their dietary habits and physical activity throughout the study.

2.2. Glucose metabolism

Glucose metabolism was evaluated by fasting plasma glucose (FPG), an oral glucose tolerance test (OGTT), and an intravenous glucose tolerance test (GTT). Fasting values included glucose, insulin, and C-peptide concentrations. Insulin resistance was measured using the homeostasis model assessment (HOMA), defined as: HOMA = FPG (mmol/L) × fasting plasma insulin (mU/L)/22.5 [13].

The oral glucose tolerance test was performed using 75 g glucose after a 12-hour fast and was evaluated concerning the area under the curve (AUC) defined by glucose concentrations determined at 0, 30, 60, 90, and 120 minutes. In addition, insulin concentration was measured at 0 and 30 minutes to calculate the insulinogenic index [14]. This is defined as: Insulinogenic Index = $\Delta\text{insulin}_{(30\text{-}0)}/\Delta\text{glucose}_{(30\text{-}0)}$.

To calculate the area under the insulin curve during OGTT, insulin was also determined at 60, 90, and 120 minutes.

The intravenous glucose tolerance test was performed using 25 g glucose. Both plasma glucose and insulin were measured at 0, 2, 4, 6, 8, and 10 minutes after glucose bolus application. The AUC for plasma glucose and insulin was determined.

2.3. Lipid metabolism

Triglyceride and cholesterol concentrations were measured using a commercial kit (Boehringer Mannheim, Mannheim, Germany). Preparative ultracentrifugation was performed to isolate very low density lipoprotein (VLDL), and VLDL-cholesterol and VLDL-triglyceride concentrations were determined. In the infranatant, LDL- and HDL cholesterol were determined. In addition, postprandial

Table 1
Parameters of study participants at baseline

Parameter	Mean ± SD
Age (y)	36.8 ± 11.2
Body mass index (kg/m^2)	31.8 ± 3.31
Waist/hip ratio	0.87 ± 0.08
$RR_{systolic}$ (mm Hg)	139 ± 12
$RR_{diastolic}$ (mm Hg)	82 ± 10
Fasting plasma glucose (mg/dL)	104 ± 9
Fasting insulin (μU/mL)	14.8 ± 6.1
HOMA index	3.78 ± 1.52
Total cholesterol (mg/dL)	201 ± 39
LDL cholesterol (mg/dL)	113 ± 43
HDL cholesterol (mg/dL)	52.5 ± 10.5
Triglycerides (mg/dL)	179 ± 98

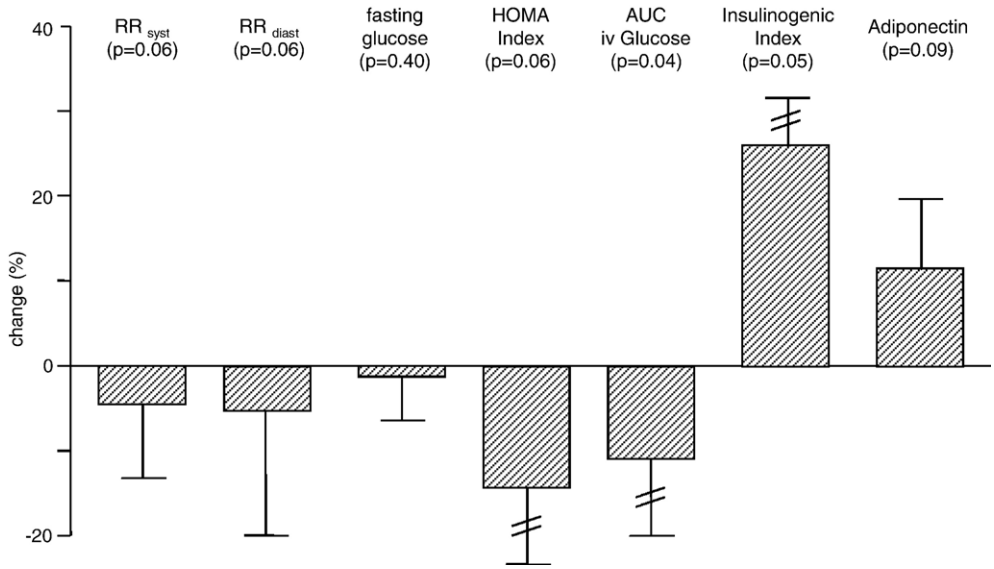

Fig. 1. Changes induced by telmisartan compared to placebo. Indicated is the mean percent reduction with standard deviation. RR_{syst} indicates systolic blood pressure; RR_{diast}, diastolic blood pressure.

lipoprotein metabolism was evaluated using a standardized oral fat tolerance test as described previously [15]. Shortly, after fasting for 12 hours all subjects ingested a fatty meal, consisting of 100 mL milk (3.5% fat), 150 mL cream (30% fat), 70 mL corn oil, 90 g egg, 10 g sugar, and 3.5 g coffee flavor. This standard meal yields 5460.12 kJ, 87% from fat, 7% from carbohydrates, and 6% from protein. After the fat load, samples were taken every 2 hours for 10 hours. Total triglycerides and triglycerides in the *d* of less than 1.006 g/mL fraction, containing chylomicrons, chylomicron remnants, and VLDL, were determined.

2.4. Additional parameters

To elucidate the possible effects on inflammatory processes, high-sensitivity C-reactive protein (CRP), interleukin-6 (IL-6), fibrinogen, adiponectin, and free fatty acid concentrations were determined. The albumin/creatinine ratio was determined in the morning spot urine. At 6-week intervals, liver function tests and electrolytes were determined as safety parameters.

2.5. Statistical analysis

The primary endpoint was a change in HOMA. Based on a 10% change for the primary endpoint (HOMA), a sample size of 20 is necessary to detect a 10% improvement in HOMA with a *P* value of less than .05 and a power of greater than 0.8. A paired analysis of the different parameters was performed, comparing the parameters determined during telmisartan therapy with those determined during placebo. Differences between parameters obtained during telmisartan and placebo therapy were analyzed by Wilcoxon testing. All statistical tests were performed using the SPSS software (SPSS, Chicago, IL).

3. Results

A total of 20 patients were enrolled and randomized to either placebo or telmisartan therapy first. Baseline clinical characteristics of study patients are shown in Table 1. All study subjects tolerated telmisartan and placebo without side

Table 2
Parameters of glucose metabolism during placebo and telmisartan treatment

Parameter	Placebo treatment (mean ± SD)	Telmisartan treatment (mean ± SD)	ΔTelmisartan (*P*)
Fasting plasma glucose (mg/dL)	101.8 ± 9.7	100.3 ± 10.7	.40
Fasting insulin (μU/mL)[a]	16.69 ± 11.60	12.50 ± 5.44	.13
Fasting C-peptide (ng/mL)	2.80 ± 0.87	2.51 ± 0.60	.22
Glucose AUC intravenous GTT (mg · min/dL)[a]	2895 ± 794	2587 ± 396	.04
Glucose AUC oral GTT (mg · h/dL)[a]	267 ± 27	260 ± 43	.35
Insulin AUC intravenous GTT (μU · min/mL)[b]	746 ± 509	780 ± 544	.46
Insulin AUC oral GTT (μU · h/mL)[b]	152 ± 81	161 ± 100	.94
HOMA index	4.32 ± 3.00	3.15 ± 1.53	.06
Insulinogenic index (μU/mL)[c]	0.0115 ± 0.008	0.0139 ± 0.0098	.05
HbA_{1c} (%)	5.46 ± 0.29	5.45 ± 0.30	.37

[a] Refers to OGTT.
[b] Refers to intravenous GTT.
[c] $\Delta insulin_{(30\text{-}0)}/\Delta glucose_{(30\text{-}0)}$.

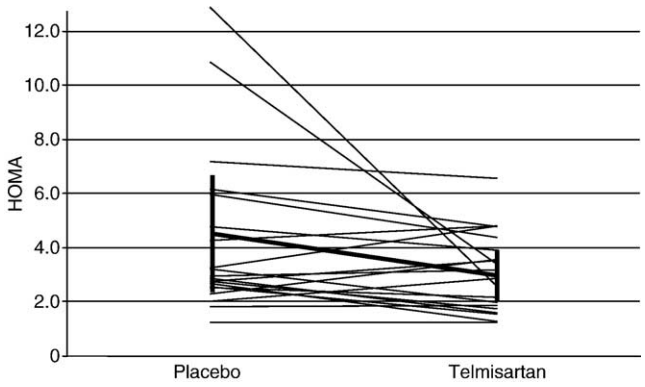

Fig. 2. Individual changes in HOMA (placebo compared with telmisartan).

effects. At screening, all subjects were mildly to moderately hypertensive. During treatment with 40 mg telmisartan daily, blood pressure was effectively reduced yet without reaching statistical significance (P = .06, for both systolic and diastolic blood pressure) (Fig. 1).

Treatment with telmisartan resulted in an improvement in glucose metabolism compared with placebo (Table 2, Figs. 1 and 2). Although FPG concentration and HbA_{1c} were unchanged during active treatment, we observed a lower area under the glucose curve during intravenous glucose tolerance test and a borderline significant reduction in the HOMA-index (−11%, P = .06), indicating improved insulin sensitivity (Fig. 1). We also observed an increase (+32%, P = .05) in the insulinogenic index ($\Delta insulin_{(30\text{-}0)}/\Delta glucose_{(30\text{-}0)}$) during the oral glucose tolerance test, indicating an improved first-phase insulin secretion and thus improved beta-cell function. There was no change in the AUC of insulin or C-peptide during the OGTT.

Compared to placebo, there was no change in lipid metabolism (Table 3). Fasting and postprandial lipid parameters did not change.

To evaluate a possible mechanism for the effects of telmisartan treatment, we determined the concentrations of adiponectin and free fatty acids, hs-CRP, IL-6, and fibrinogen (Table 4). We observed a trend toward an increase in adiponectin (6%, P = .09), whereas all other parameters were unchanged during telmisartan treatment compared toplacebo.

Table 4
Blood pressure and parameters of inflammation during placebo and telmisartan treatment

Parameter	Placebo treatment (mean ± SD)	Telmisartan treatment (mean ± SD)	ΔTelmisartan (P)
$RR_{systolic}$ (mm Hg)	142.3 ± 12.5	134.8 ± 11.3	.06
$RR_{diastolic}$ (mm Hg)	86.5 ± 11.4	79.3 ± 10.9	.06
Albumin/creatinine ratio in urine (mg/g)[a]	9.9 ± 7.0	6.8 ± 4.8	.27
Adiponectin (ng/mL)	2623 ± 1455	2791 ± 1603	.09
Free fatty acids (mmol/L)	0.63 ± 0.38	0.59 ± 0.19	.94
High-sensitivity CRP (mg/L)	4.87 ± 3.39	5.26 ± 3.77	.17
IL-6 (pg/mL)	1.66 ± 0.92	1.80 ± 1.02	.96
Fibrinogen (mg/dL)	418 ± 70	421 ± 65	.32

[a] Refers to morning spot urine.

The observed changes in HOMA index, insulinogenic index, and adiponectin did not correlate with each other. However, the observed changes in HOMA index and in insulinogenic index correlated with baseline HOMA index and baseline insulin concentration. Thus, the higher the baseline HOMA the more the HOMA index and the insulinogenic index improved with telmisartan treatment (r^2 = 0.28, P = .02; r^2 = 0.27, P = .02, respectively) (Fig. 2). Indeed, the 2 subjects in whom the drop in HOMA was particularly strong were the most insulin resistant at baseline. These 2 subjects did not differ in age, weight, lipids, or other parameters from the other subjects. Furthermore, we observed a correlation between the telmisartan-induced change in adiponectin and body weight (r^2 = 0.19, P = .05).

We also evaluated whether the sequence (first telmisartan or first placebo) affected the observed parameters. The subgroup who first received placebo (HOMA placebo, 4.2 5 ± 3.42; HOMA telmisartan, 2.79 ± 1.70; P = .05) had a somewhat stronger response than the group who first received telmisartan (HOMA placebo, 4.39 ± 2.70; HOMA telmisartan, 3.52 ± 1.34; not significant), although there was no significant difference between these groups.

Table 3
Parameters of fasting and postprandial lipid metabolism during placebo and telmisartan treatment

Parameter	Placebo treatment (mean ± SD)	Telmisartan treatment (mean ± SD)	ΔTelmisartan (P)
Fasting total cholesterol (mg/dL)	189 ± 41	183 ± 39	.25
Fasting HDL cholesterol (mg/dL)	48.3 ± 11.0	48.0 ± 11.3	.94
Fasting LDL cholesterol (mg/dL)	106 ± 34	100 ± 40	.13
Fasting triglycerides (mg/dL)	192 ± 111	195 ± 118	.74
Fasting VLDL triglycerides (mg/dL)	111 ± 80	122 ± 87	.28
Fasting VLDL cholesterol (mg/dL)	26 ± 17	28 ± 20	.94
Triglycerides AUC fat tolerance (mg · h/dL)[a]	2895 ± 2037	2870 ± 1754	.90
Triglycerides incremental AUC fat tolerance (mg · h/dL)[a]	1015 ± 941	1000 ± 760	.97
VLDL triglycerides AUC fat tolerance (mg · h/dL)[a]	461 ± 477	357 ± 204	.97
Chylomicron triglycerides AUC fat tolerance (mg · h/dL)[a]	977 ± 780	1055 ± 829	.90

[a] Refers to oral fat tolerance test.

4. Discussion

This study found that 12 weeks of telmisartan 40 mg resulted in an improvement in glucose metabolism compared with placebo. We observed a significant reduction in the glucose AUC during intravenous glucose tolerance test and a reduction in the HOMA-index and a borderline significant increase in the insulinogenic index. This suggests that insulin sensitivity and beta-cell function improved [14]. This was associated with a trend toward an increase in adiponectin. Other parameters of glucose metabolism and all parameters of lipid metabolism remained unchanged. Furthermore, we did not observe a change in free fatty acid concentration or inflammatory parameters.

Our observations are consistent with previous studies. Large clinical trials showed that ARB therapy substantially lowers the risk for type 2 diabetes mellitus compared to other antihypertensive therapies or placebo [4-6]. A number of small clinical trials have therefore evaluated the effect of ARB therapy, and particularly telmisartan, on glucose metabolism. Most studies were performed in diabetic patients and gave ambiguous results. Some studies showed an improved glucose metabolism, whereas others showed an improvement in lipid metabolism [9,10] or a reduction in oxidized LDL and inflammatory parameters [11], but no effect on glucose.

To further elucidate the topic, we evaluated the effect of telmisartan in insulin-resistant subjects using a detailed analysis of glucose and lipid metabolism, and also determined possible mediators. In our study, some parameters of beta-cell function and of insulin resistance improved, whereas others remained unchanged. These results suggest that parameters of glucose metabolism do not change uniformly. However, these inconsistencies also point to some limitations of the study (small number of patients, the short duration, and the high selectivity of the population to be studied). Furthermore, some of the effects may be dose dependent because in a study comparing the effects of 20 vs 40 mg telmisartan, HbA_{1c} was significantly reduced after 3 months of telmisartan 40 mg, whereas there was no significant change in the 20-mg group [11]. In another study comparing 80 mg telmisartan with 50 mg losartan, a significant reduction in HOMA and HbA_{1c} as well as a reduction in both fasting and OGTT plasma glucose and plasma insulin was observed [16]. Unlike the studies cited above, we evaluated insulin resistant, nonhypertensive, nondiabetic subjects who received 40 mg telmisartan only. Thus, the metabolic disturbances were not as pronounced as in patients with manifest type 2 diabetes, which could explain some of the observed differences with previous studies. This is supported by the finding that the worse the insulin resistance, the more improved the glucose metabolism with telmisartan treatment. Longer and more intense treatment may be necessary to achieve more pronounced changes. This is supported by an observation from our study. When we compared patients who first received placebo with those first receiving telmisartan, the effect was stronger in the former. This could indicate that there was a carryover effect from the initially given telmisartan in the latter group, which indicates that the effect of telmisartan on glucose metabolism is not immediate and may be long lasting.

Several mechanisms could link ARB therapy with an improvement in glucose metabolism. Angiotensin receptor blockers may affect inflammatory processes and alter free fatty acid concentration and/or metabolism. Although inflammation is a major cause of insulin resistance and although ARBs have anti-inflammatory activities, we observed no changes in inflammatory parameters or free fatty acids, indicating that these mediators are not the primary link for the observed improvement. More sensitive measurements may help reveal more subtle changes. Thus, although the role of inflammatory mediators and free fatty acids cannot be ultimately evaluated, other processes may play a role in mediating the improvement in glucose metabolism.

Angiotensin receptor blockers have been identified as transcriptional upregulators of PPARγ, a central regulator of insulin sensitivity [12]. Among the ARBs, telmisartan was found to be unique because it selectively activates PPARγ and acts as a partial agonist [8]. Moreover, telmisartan was shown to induce adiponectin via PPARγ activation [17]. Because we did not conduct a head-to-head comparison of telmisartan with other ARBs in this study, we cannot ultimately discern whether the metabolic effects are mediated by blocking of the angiotensin II receptor or activation of PPARγ.

Although we observed an improvement in insulin sensitivity and beta-cell function, we did not observe any changes in lipid metabolism. This is somewhat surprising, because antidiabetic therapies that improve insulin sensitivity can improve lipid metabolism independent of their glucose-lowering effect [18]. However, our patients were not selected because of dyslipidemia and presented with a wide range of lipid concentrations. Stronger effects on glucose metabolism and severely altered baseline lipid parameters may be necessary to see an improvement in lipid metabolism due to an improvement in glucose metabolism.

In summary, our results show that 12 weeks of telmisartan resulted in an improvement in glucose metabolism in insulin-resistant subjects. Although we did not observe significant changes in all parameters, the changes all point to 1 direction. This indicates that telmisartan induces a mild but consistent improvement in insulin resistance. Therefore, short-term therapy with telmisartan 40 mg may be effective in reducing the progression of the metabolic syndrome in insulin-resistant nondiabetic patients with mild hypertension.

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