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## Treating the metabolic syndrome: telmisartan as a peroxisome proliferator-activated receptor-gamma activator

**Abstract** Hypertension commonly occurs as part of a genetically complex disorder of carbohydrate and lipid metabolism known as the metabolic syndrome. Most current antihypertensive drugs appear ineffective against the metabolic syndrome, which is a strong predictor of cardiovascular disease and death in affected patients. Angiotensin II can influence the activity of certain genes and cellular and biochemical pathways that may contribute to the pathogenesis of the metabolic syndrome. However, as a class, angiotensin II receptor blockers (ARBs) have proven only minimally to modestly effective in ameliorating the disturbances in carbohydrate and lipid metabolism that characterise the metabolic syndrome. Recent preclinical studies indicate that the ARB telmisartan acts as a selective peroxisome proliferator-

activated receptor-gamma (PPAR $\gamma$ ) modulator when tested at concentrations that might be achievable with oral doses recommended for treatment of hypertension; this property does not appear to be shared by other ARBs. PPAR $\gamma$  is a nuclear receptor that influences the expression of multiple genes involved in carbohydrate and lipid metabolism and is an attractive therapeutic target for the prevention and control of insulin resistance, type 2 diabetes and atherosclerosis. In cellular transactivation assays, telmisartan functioned as a partial agonist of PPAR $\gamma$  and achieved 25–30% of maximal receptor activation attained with conventional PPAR $\gamma$  ligands. Preclinical and clinical studies indicate that administration of telmisartan can improve carbohydrate and lipid metabolism without causing the side effects that accompany full PPAR $\gamma$  activators. If the preliminary data are supported by the results of ongoing large-scale clinical studies, telmisartan could have a central role in the prevention and treatment of metabolic syndrome, diabetes and atherosclerosis.

**Key words** Metabolic syndrome • Telmisartan • Type 2 diabetes mellitus • Peroxisome proliferator-activated receptor • Carbohydrate metabolism • Lipid metabolism • Insulin resistance • Hypertension

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### Introduction

Hypertension is often associated with an array of other risk factors for cardiovascular disease including visceral obesity, insulin resistance, disordered glucose metabolism and dyslipidaemia, collectively termed ‘the metabolic syndrome’ [1–3]. This clustering of risk factors is present in about 15–25% of individuals in industrialised countries [4–8] and carries a greatly increased risk of cardiovascular morbidity and mortality. The metabolic syndrome

increases the likelihood of developing type 2 diabetes by five- to nine-fold [9] and of cardiovascular disease and death by two- to four-fold [5, 6].

For the most part, the drugs currently used to lower blood pressure are not considered to be effective against the metabolic syndrome [1]. This is not surprising given that the antihypertensive agents in use today were developed before the connection between hypertension and the metabolic syndrome was well recognised. Thus, current antihypertensive drugs were designed exclusively to lower blood pressure rather than to treat the complex metabolic disorder of which hypertension is only a part.

Angiotensin-converting enzyme (ACE) inhibitors, which block angiotensin II formation, and angiotensin II receptor blockers (ARBs), which prevent the binding of angiotensin II to the type 1 receptor, are both widely used for the treatment of high blood pressure and prevention of cardiovascular disease. In addition to causing vasoconstriction, angiotensin II affects the transcription of multiple genes concerned with cell growth and proliferation, atherogenesis and thrombus formation (Table 1) [1]. Pharmacological blockade of the renin–angiotensin system has been shown to inhibit angiotensin II-induced changes in the expression of a variety of genes [10–16]. Recent observations suggest that angiotensin II receptor blockade may also affect the expression of genes involved in glucose metabolism [17]. Thus far, however, neither ACE inhibitors nor ARBs have been considered in conventional treatment programmes for managing insulin resistance and dyslipidaemia in patients with diabetes or the metabolic syndrome.

Large-scale prospective studies in patients with hypertension have recently begun to explore the ability of ACE inhibitors to decrease the risk for type 2 diabetes. In the Heart Outcomes Prevention Evaluation (HOPE) study, for example, a significantly lower incidence of new-onset diabetes was observed among the patients treated with the ACE inhibitor ramipril (3.6%) compared with those receiving placebo (5.4%; relative risk 0.66; 95% confidence interval 0.51, 0.85;  $p < 0.001$ ) [18]. In addition, in the CAPtopril Prevention Project (CAPPP) [19] and in the

Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT) study [20], the rate of new-onset diabetes was lower in patients treated with an ACE inhibitor than in those treated with diuretics,  $\beta$ -blockers or calcium channel blockers. Although further mechanistic studies are required, experiments investigating the influence of ACE inhibitors on glucose metabolism have suggested that the antidiabetic effects of these compounds may involve more than just reductions in angiotensin II levels and could involve alterations in kinin–nitric oxide pathways [21–23].

The effects of ARBs on insulin resistance and dyslipidaemia have been investigated in several well-conducted randomised, controlled studies. For example, in the Antihypertensive treatment and Lipid Profile In a North Sweden efficacy Evaluation (ALPINE) study, the metabolic effects of the ARB candesartan and the diuretic hydrochlorothiazide (HCTZ) were compared over a 1-year period in 392 hypertensive patients, 370 of whom had not previously been treated with antihypertensive agents [24]. At baseline, both treatment groups had nearly identical fasting plasma glucose, serum insulin and serum triglyceride concentrations. After 12 months' candesartan therapy, there were no significant changes in glucose, insulin or triglyceride levels, whereas those patients treated with HCTZ for 12 months displayed significant ( $p < 0.001$ ) increases. There was also a greater decrease in serum high-density lipoprotein cholesterol in the HCTZ-treated patients compared with those treated with candesartan. Over the duration of the study, eight patients in the HCTZ group developed diabetes and 18 were diagnosed as having metabolic syndrome as opposed to only one ( $p = 0.030$ ) and five ( $p = 0.007$ ) patients, respectively, in the candesartan group. The authors concluded that candesartan was 'metabolically neutral' in terms of glucose and lipid metabolism, but that HCTZ aggravated the metabolic profile in these newly diagnosed hypertensive patients.

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study evaluated the incidence of new-onset type 2 diabetes as a secondary endpoint in 7998

**Table 1** Examples of genes that are regulated by angiotensin II. With permission from [1]

Type of gene	Examples
Early genes/proto-oncogenes	<i>fos, myc, myb, jun, jun-B, egr-1</i>
Growth factor genes	Transforming growth factor- $\beta$ 1, platelet-derived growth factor-A chain, fibroblast growth factor-2, insulin-like growth factor-1, insulin-like growth factor-1 receptor
Cell matrix factor genes	Fibronectin, collagen type 1- $\alpha$ 1, collagen type III- $\alpha$ 1, laminin- $\beta$ 1, laminin- $\beta$ 2
Hypertrophic marker genes	Atrial natriuretic peptide, brain natriuretic peptide, skeletal muscle actin- $\alpha$ 1
Fibrinolytic system genes	Plasminogen activator inhibitor, types 1 and 2
Miscellaneous genes	Aldosterone synthase (CYP11B2), endothelial nitric oxide synthase

at-risk hypertensive patients [25]. In losartan-treated patients, the incidence was 13.0 per 1000 patient-years, which was significantly lower ( $p < 0.001$ ) than the 17.5 per 1000 patient-years recorded among the atenolol-treated patients. In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study, the rate of new-onset diabetes was found to be lower in hypertensive patients treated with valsartan than in those treated with amlodipine [26]. However, neither the LIFE study nor the VALUE study involved a placebo control group, and it is unclear whether the lower incidence of new-onset diabetes in the patients treated with ARBs represented an antidiabetic effect of the ARB or a prodiabetic effect of the comparator agent. Although calcium channel blockers are not generally suspected as causing diabetes, previously published studies have shown that beta-blockers can promote the development of type 2 diabetes in patients with hypertension [27–30]. It should also be noted that in several placebo-controlled trials, significant antidiabetic effects of the ARB candesartan have not been consistently observed [31–34].

Although some clinical trials have suggested that ARBs may be associated with a reduced incidence of new-onset diabetes, the lack of consistently positive metabolic benefits in other studies may have encouraged the belief that all ARBs are ‘metabolically neutral’ [35]. New experimental evidence, however, suggests that all ARBs are not the same and that the ARB telmisartan may positively influence metabolic function at a molecular level by its ability to activate the peroxisome proliferator-activated receptor-gamma (PPAR $\gamma$ ), a well-known target for insulin-sensitising antidiabetic drugs [23].

### PPAR $\gamma$ and metabolic syndrome

PPAR $\gamma$  is a nuclear receptor that plays an important role in carbohydrate and lipid metabolism and is a proven therapeutic target in the treatment of insulin resistance, diabetes and metabolic syndrome [36–40]. Human genetic linkage studies have revealed that mutations in the PPAR $\gamma$  receptor gene produce severe hyperinsulinaemia and the metabolic syndrome, reinforcing the central role of PPAR $\gamma$  in maintaining normal glucose and lipid metabolism [41].

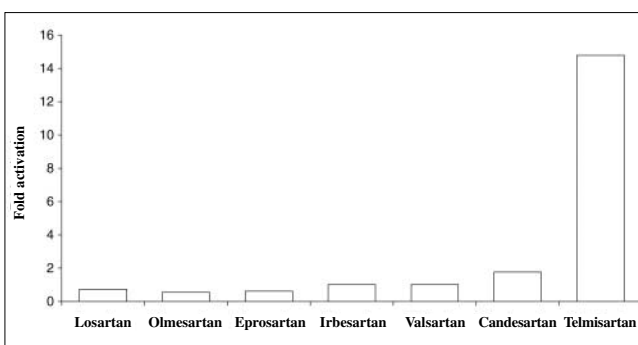
PPAR $\gamma$  exists as a complex with the retinoid X receptor (RXR) within the cell nucleus. Once activated, the complex influences the expression of key target genes that mediate a variety of effects on fatty acid metabolism, insulin sensitivity and adipocyte differentiation [1, 36, 42].

Two PPAR $\gamma$  activators – pioglitazone and rosiglitazone – have been shown to increase insulin sensitivity, decrease serum fatty acid and triglyceride concentrations and, in some cases, increase levels of the beneficial high-

density lipoprotein cholesterol; these agents are already licensed for the treatment of type 2 diabetes. However, these thiazolidinedione ligands of PPAR $\gamma$  have limited effects on blood pressure and, furthermore, are associated with side effects, such as fluid retention, weight gain, oedema and heart failure, that limit their value in the treatment of prediabetic and diabetic individuals with hypertension [43–45].

### Telmisartan as a PPAR $\gamma$ activator. Preclinical evidence

Recently, it was reported that telmisartan, a clinically approved ARB with well-documented efficacy in blood pressure reduction, may share some structural homology with the PPAR $\gamma$  ligand pioglitazone and have the capacity to activate PPAR $\gamma$  [42, 46]. In cellular PPAR $\gamma$  transactivation assays, telmisartan was found to produce significant activation of PPAR $\gamma$  when tested at concentrations that may be achieved in plasma following administration of doses used for the treatment of essential hypertension (Fig. 1). By contrast, the other commercially available ARBs – losartan, eprosartan, candesartan, valsartan, olmesartan and irbesartan – had little ability to activate PPAR $\gamma$  when tested at the same concentrations, although higher concentrations of irbesartan were able to cause some activation of the receptor [42, 46]. In these assays, telmisartan was a moderately potent selective PPAR $\gamma$  agonist, activating the receptor to 25–30% of the maximum level achieved by conventional full agonists, such as pioglitazone and rosiglitazone. The concentration of telmisartan that yielded half-maximal activation of the PPAR $\gamma$  receptor ( $EC_{50}$ ) was approximately 4.5  $\mu$ M, which is of a similar order of magnitude to that of pioglitazone ( $EC_{50}$ =1.5  $\mu$ M). Furthermore, the effect was specific for PPAR $\gamma$ , with telmisartan exhibiting no activation of PPAR $\alpha$  or PPAR $\delta$  when tested at concentrations achieved in plasma with usual oral dosing for hypertension.



**Fig. 1** Comparison of PPAR $\gamma$  activation by different angiotensin II receptor blockers in a cell-based transactivation assay. Cells were treated with 5  $\mu$ mol/l losartan, olmesartan, eprosartan, irbesartan, valsartan, candesartan or telmisartan. With permission from [23]

**Table 2** Clinical properties of conventional and selective PPAR $\gamma$  activators

	Conventional PPAR $\gamma$ activators (e.g., rosiglitazone, pioglitazone)	Selective PPAR $\gamma$ activators (e.g., telmisartan, nTZDpa)
Receptor activation	Full	Partial
Improved glucose and lipid metabolism	Yes	Yes
Marked adipogenesis	Yes	No
Weight gain	Yes	No
Fluid retention	Yes	No

The partial agonist behaviour displayed by telmisartan has potentially important consequences for treatment (Table 2). Whereas conventional PPAR $\gamma$  activators induce full activation of the receptor, selective PPAR $\gamma$  modulators, such as telmisartan and the experimental agent nTZDpa, only induce partial activation. This may result in improvements in glucose and lipid metabolism while causing less potential for undesirable side effects, such as fat accumulation and weight gain. In animal studies, selective PPAR $\gamma$  modulators have even shown the potential to attenuate weight gain, whereas conventional PPAR $\gamma$  agonists are known to promote weight gain [42].

Telmisartan has also been shown to modulate selectively the expression of key PPAR $\gamma$  target genes when tested at concentrations achievable with therapeutic oral doses. For example, in human visceral adipocytes, telmisartan potently enhanced expression of the *PCK1* target gene that encodes phosphoenolpyruvate carboxykinase (PEPCK-C) [42]. PEPCK-C is the enzyme responsible for the increased glyceroneogenesis and fatty acid re-esterification that largely accounts for the ability of PPAR $\gamma$  activators to reduce fatty acid levels [42, 47]. In addition, recent studies by Fujimoto and colleagues have shown that in 3T3L1 preadipocytes, telmisartan, but not valsartan, can induce increases in glucose uptake and expression of the GLUT4 glucose transporter [48].

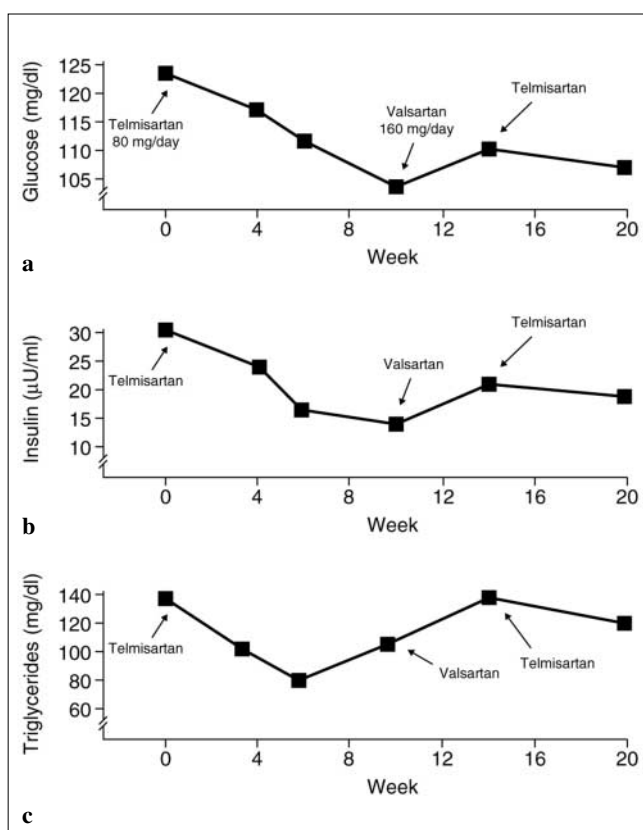
The antidiabetic actions of telmisartan associated with its PPAR $\gamma$ -modulating activity have been tested in rats fed a high-fat, high-carbohydrate diet. After 50 days, telmisartan 5 mg/kg reduced serum insulin concentrations and caused a significant reduction in plasma glucose ( $p < 0.01$ ) and serum triglyceride concentrations ( $p < 0.05$ ) compared with losartan 5 mg/kg, and significantly attenuated weight gain compared with either losartan 5 mg/kg or controls (~10% less;  $p < 0.01$ ) [42].

### Telmisartan as a PPAR $\gamma$ activator. Clinical evidence

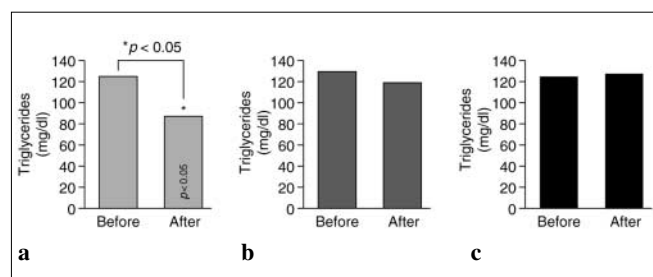
The clinical evidence for telmisartan being a therapeutically important PPAR $\gamma$  activator is still accruing. The data

gathered so far – one case study, a post-marketing surveillance study and two small-scale clinical trials – strongly suggest that telmisartan treatment can be associated with improvements in glucose and lipid metabolism.

In a case study, a 52-year-old male with metabolic syndrome was started with once-daily telmisartan 80 mg treatment [49]. After only 8 weeks of treatment, glucose and insulin levels fell to within normal limits. The patient was then switched to once-daily valsartan 160 mg. After 6 weeks of valsartan, his fasting glucose and insulin levels had risen, but returning the patient to telmisartan restored his glucose and insulin levels back towards normal (Fig. 2).



**Fig. 2** Clinical case observations in a 52-year-old male with metabolic syndrome. Effects of telmisartan and valsartan on (a) plasma glucose, (b) serum insulin and (c) serum triglyceride concentrations. With permission from [49]



**Fig. 3** Effect of (a) telmisartan 40 mg, (b) eprosartan 600 mg or (c) placebo on triglyceride levels after 12 months' treatment in patients with mild hypertension and type 2 diabetes [51]

This isolated case shows how telmisartan improved the insulin and glucose profile in a high-risk patient with metabolic syndrome and highlights the absence of a similar effect with valsartan.

A large-scale clinical study has also shown beneficial metabolic effects of telmisartan. Specifically, in a post-marketing surveillance study of hypertensive patients receiving once-daily telmisartan 40–80 mg and attending general-practice clinics in Germany, 3643 patients with overt type 2 diabetes had reduced plasma glucose ( $-13.0 \pm 26.9$  mg/dl) and serum triglyceride ( $-22.7 \pm 62.2$  mg/dl) concentrations after 6 months' treatment compared with baseline values [50].

The metabolic effects of telmisartan have been further explored in two prospective, double-blind, placebo-controlled studies. In the first study, 119 patients with mild hypertension and type 2 diabetes were randomised to telmisartan 40 mg/day, eprosartan 600 mg/day or placebo [51]. After 12 months of once-daily treatment, this relatively low dose of telmisartan produced a significant 25–30% ( $p < 0.05$ ) reduction in triglyceride concentrations compared with baseline; in contrast, neither eprosartan nor placebo had any detectable effect on triglyceride levels (Fig. 3) [51]. In the second study, which was a 3-month randomised, parallel-group trial comparing telmisartan 80 mg/day with losartan 50 mg/day in 40 patients with metabolic syndrome, telmisartan produced significant reductions from baseline in fasting glucose ( $p < 0.05$ ), insulin resistance ( $p < 0.05$ ) and insulin levels ( $p < 0.06$ ), whereas losartan did not [52].

### Possible mechanism of action

The mechanism by which telmisartan is able to activate PPAR $\gamma$  remains to be precisely defined. However, at least part of the answer is likely to lie in its chemical structure, which is quite different from that of the other clinically approved ARBs. Molecular modelling reveals that telmisartan is able to interact with specific amino acid residues in the PPAR $\gamma$  ligand-binding domain and

thereby induce receptor activation in a manner similar to that of other partial agonists of PPAR $\gamma$  [42]. Moreover, given telmisartan's very high volume of distribution, which is much greater than that of the other ARBs, it may have a superior capacity to gain access to the PPAR $\gamma$ -RXR complex within the cell nucleus than the other ARBs [53].

### A potential role in atherogenesis

The PPAR $\gamma$ -modulating properties of telmisartan may also have therapeutic implications for the prevention and management of atherosclerosis. Atherosclerosis is a multifactorial disease caused by a combination of insulin resistance, dyslipidaemia, cell inflammation, cell proliferation, hypertension and oxidative stress. There is a considerable body of evidence accumulating to show that PPAR $\gamma$  activators can interfere with the pathogenesis of atherosclerosis [54–59]. PPAR $\gamma$  activators, such as rosiglitazone, have been shown to induce plaque regression in animal models of atherosclerosis [54, 56], reduce progression of common carotid intima-media thickness in patients with coronary artery disease [59] and reduce markers of endothelial cell activation and levels of acute-phase reactants in patients with coronary artery disease and/or metabolic syndrome [57, 58]. Telmisartan, by virtue of its ability to block angiotensin II type 1 receptors and to activate PPAR $\gamma$ , may not only inhibit angiotensin II-mediated pathways of atherosclerosis, but also stimulate PPAR $\gamma$  pathways that help prevent atherosclerosis. Thus, further studies are warranted to explore this potential clinical benefit.

### Large-scale clinical trials

The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE-intolerant subjects with cardiovascular Disease (TRANSCEND) are large-scale studies that have been designed to evaluate the potential cardiovascular and metabolic benefits of telmisartan. These trials are investigating the effects of telmisartan, alone and in combination with the ACE inhibitor ramipril, vs. ramipril or placebo on cardiovascular and metabolic endpoints in high-risk patients with major vascular disease and/or diabetes with end-organ damage [60]. On the basis of its angiotensin II-inhibiting and PPAR $\gamma$ -activating properties, it is quite possible that telmisartan will show benefits in terms of reducing both the incidence of new-onset diabetes and the risk of cardiovascular events.

## Conclusions

Hypertension is just one aspect of the complex matrix of haemodynamic and metabolic risk factors for cardiovascular disease. The ARBs as a class have been generally considered to be metabolically neutral. An exception to this appears to be telmisartan. Data from experimental studies, as well as accumulating clinical evidence, suggest that telmisartan is unique among the ARBs. Telmisartan acts not only as an angiotensin II type 1 receptor antagonist, but also as a selective PPAR $\gamma$  modulator when tested at concentrations that may be achievable in plasma with oral doses used for the treatment of high blood pressure.

The therapeutic benefits of PPAR $\gamma$ -induced changes in lipid and glucose metabolism are well established. Initial clinical studies show that telmisartan retains these properties but unlike conventional PPAR $\gamma$  activators, which are often accompanied by fluid retention, weight gain and oedema, telmisartan acts as a selective PPAR $\gamma$  modulator without these undesirable side effects. If the preliminary clinical trial findings are supported by the results of ongoing large-scale studies, telmisartan could have an important role to play in the prevention and treatment of the metabolic syndrome, diabetes and atherosclerosis.

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