Acta Diabetol (2005) 42:S9–S16
DOI 10.1007/s00592-005-0176-0

T.W. Kurtz

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 (PPARγ) 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. PPARγ 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 PPARγ and achieved 25–30% of maximal receptor activation attained with conventional PPARγ ligands. Preclinical and clinical studies indicate that administration of telmisartan can improve carbohydrate and lipid metabolism without causing the side effects that accompany full PPARγ 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

T.W. Kurtz (✉)
Laboratory of Medicine
185 Berry Street, Suite 290
San Francisco, CA 94107, USA
E-mail: KurtzT@Labmed2.ucsf.edu

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, β-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	*fos, myc, myb, jun, jun-B, egr-1*
Growth factor genes	Transforming growth factor-β1, 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-α1, collagen type III-α1, laminin-β1, laminin-β2
Hypertrophic marker genes	Atrial natriuretic peptide, brain natriuretic peptide, skeletal muscle actin-α1
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 (PPARγ), a well-known target for insulin-sensitising antidiabetic drugs [23].

PPARγ and metabolic syndrome

PPARγ 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 PPARγ receptor gene produce severe hyperinsulinaemia and the metabolic syndrome, reinforcing the central role of PPARγ in maintaining normal glucose and lipid metabolism [41].

PPARγ 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 PPARγ 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 PPARγ 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 PPARγ 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 PPARγ ligand pioglitazone and have the capacity to activate PPARγ [42, 46]. In cellular PPARγ transactivation assays, telmisartan was found to produce significant activation of PPARγ 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 PPARγ 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 PPARγ 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 PPARγ receptor (EC_{50}) was approximately 4.5 μM, which is of a similar order of magnitude to that of pioglitazone (EC_{50}=1.5 μM). Furthermore, the effect was specific for PPARγ, with telmisartan exhibiting no activation of PPARα or PPARδ when tested at concentrations achieved in plasma with usual oral dosing for hypertension.

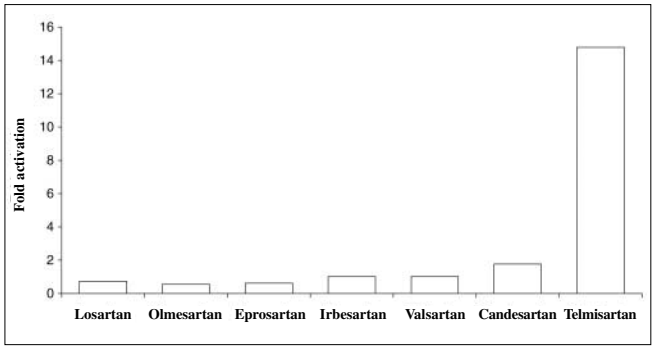

Fig. 1 Comparison of PPARγ activation by different angiotensin II receptor blockers in a cell-based transactivation assay. Cells were treated with 5 μmol/l losartan, olmesartan, eprosartan, irbesartan, valsartan, candesartan or telmisartan. With permission from [23]

Table 2 Clinical properties of conventional and selective PPARγ activators

	Conventional PPARγ activators (e.g., rosiglitazone, pioglitazone)	Selective PPARγ 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 PPARγ activators induce full activation of the receptor, selective PPARγ 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 PPARγ modulators have even shown the potential to attenuate weight gain, whereas conventional PPARγ agonists are known to promote weight gain [42].

Telmisartan has also been shown to modulate selectively the expression of key PPARγ 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 PPARγ 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 PPARγ-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 PPARγ activator. Clinical evidence

The clinical evidence for telmisartan being a therapeutically important PPARγ 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).

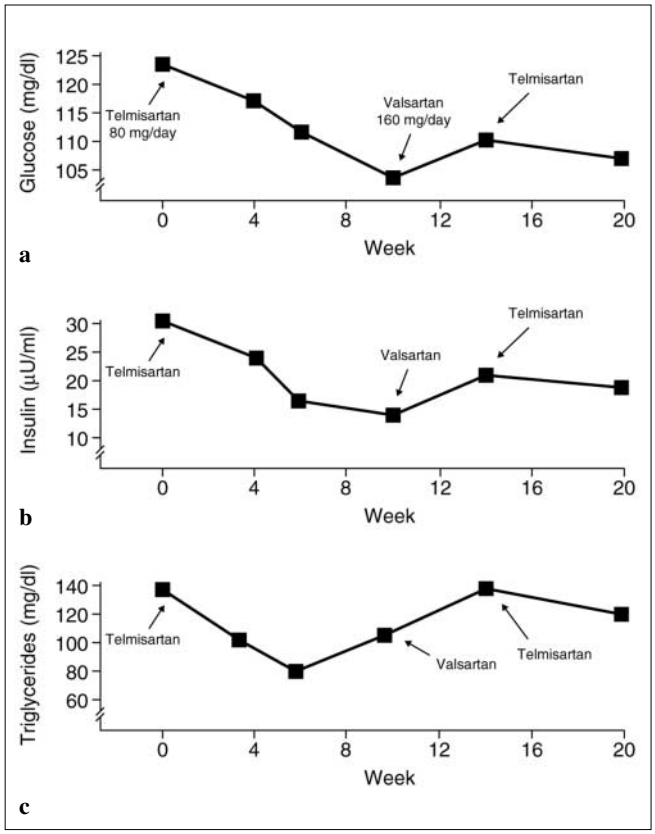

Fig. 2 Clinical case observations in a 52-year-old male with metabolic syndrome. Effects of telmisartan and valsartan on (**a**) plasma glucose, (**b**) serum insulin and (**c**) serum triglyceride concentrations. With permission from [49]

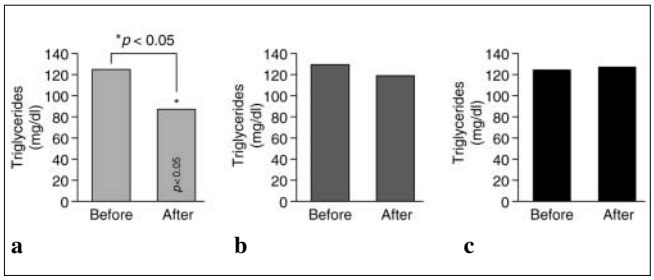

Fig. 3 Effect of (**a**) telmisartan 40 mg, (**b**) eprosartan 600 mg or (**c**) placebo on triglyceride levels after 12 months' treatment in patients with mild hypertension and type 2 diabetes [51]

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±26.9 mg/dl) and serum triglyceride (–22.7±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 PPARγ 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 PPARγ ligand-binding domain and thereby induce receptor activation in a manner similar to that of other partial agonists of PPARγ [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 PPARγ–RXR complex within the cell nucleus than the other ARBs [53].

A potential role in atherogenesis

The PPARγ-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 PPARγ activators can interfere with the pathogenesis of atherosclerosis [54–59]. PPARγ 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 PPARγ, may not only inhibit angiotensin II-mediated pathways of atherosclerosis, but also stimulate PPARγ 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 PPARγ-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 PPARγ 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 PPARγ-induced changes in lipid and glucose metabolism are well established. Initial clinical studies show that telmisartan retains these properties but unlike conventional PPARγ activators, which are often accompanied by fluid retention, weight gain and oedema, telmisartan acts as a selective PPARγ 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.

References

1. Kurtz TW, Gardner DG (1998) Transcription-modulating drugs: a new frontier in the treatment of essential hypertension. Hypertension 32:380–386
2. National Cholesterol Education Program (2002) Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 106:3143–3421
3. Alberti KGMM, Zimmet PZ, for the WHO Consultation (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabet Med 15:539–553
4. Balkau B, Vernay M, Mhamdi L, Novak M, Arondel D, Vol S, Tichet J, Eschwege E (2003) The incidence and persistence of the NCEP (National Cholesterol Education Program) metabolic syndrome. The French D.E.S.I.R. study. Diabetes Metab 29:526–532
5. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L (2001) Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 24:683–689
6. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT (2002) The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 288:2709–2716
7. Meigs JB, Wilson PW, Nathan DM, D'Agostino RB, Sr., Williams K, Haffner SM (2003) Prevalence and characteristics of the metabolic syndrome in the San Antonio Heart and Framingham Offspring Studies. Diabetes 52:2160–2167
8. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB (2003) The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988–1994. Arch Intern Med 163:427–436
9. Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA (2002) Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. Am J Epidemiol 156:1070–1077
10. Dostal DE, Hunt RA, Kule CE, Bhat GJ, Karoor V, McWhinney CD, Baker KM (1997) Molecular mechanisms of angiotensin II in modulating cardiac function: intracardiac effects and signal transduction pathways. J Mol Cell Cardiol 29:2893–2902
11. Feener EP, Northrup JM, Aiello LP, King GL (1995) Angiotensin II induces plasminogen activator inhibitor-1 and -2 expression in vascular endothelial and smooth muscle cells. J Clin Invest 95:1353–1362
12. Hsueh WA, Do YS, Anderson PW, Law RE (1995) Angiotensin II in cell growth and matrix production. Adv Exp Med Biol 377:217–223
13. Ju H, Dixon IM (1996) Effect of angiotensin II on myocardial collagen gene expression. Mol Cell Biochem 163–164:231–237
14. Kagami S, Border WA, Miller DE, Noble NA (1994) Angiotensin II stimulates extracellular matrix protein synthesis through induction of transforming growth factor-beta expression in rat glomerular mesangial cells. J Clin Invest 93:2431–2437
15. Kakiki M, Morohashi K, Nomura M, Omura T, Horie T (1997) Expression of aldosterone synthase cytochrome P450 (P450aldo) mRNA in rat adrenal glomerulosa cells by angiotensin II type 1 receptor. Endocr Res 23:277–295
16. Regenass S, Resink TJ, Kern F, Buhler FR, Hahn AW (1994) Angiotensin-II-induced expression of laminin complex and laminin A-chain-related transcripts in vascular smooth muscle cells. J Vasc Res 31:163–172
17. Chan P, Wong KL, Liu IM, Tzeng TF, Yang TL, Cheng JT (2003) Antihyperglycemic action of angiotensin II receptor antagonist, valsartan, in streptozotocin-induced diabetic rats. J Hypertens 21:761–769
18. Yusuf S, Gerstein H, Hoogwerf B, Pogue J, Bosch J, Wolffenbuttel BH, Zinman B, for the HOPE Study Investigators (2001) Ramipril and the development of diabetes. JAMA 286:1882–1885
19. Niklason A, Hedner T, Niskanen L, Lanke J (2004) Development of diabetes is retarded by ACE inhibition in hypertensive patients – a subanalysis of the Captopril Prevention Project (CAPPP). J Hypertens 22:645–652
20. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group (2002) Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 288:2981–2997
21. Henriksen EJ, Jacob S (2003) Modulation of metabolic control by angiotensin converting enzyme (ACE) inhibition. J Cell Physiol 196:171–179

22. Rumble JR, Komers R, Cooper ME (1996) Kinins or nitric oxide, or both, are involved in the antitrophic effects of angiotensin converting enzyme inhibitors on diabetes-associated mesenteric vascular hypertrophy in the rat. J Hypertens 14:601–607
23. Kurtz TW, Pravenec M (2004) Antidiabetic mechanisms of ACE inhibitors and AII receptor antagonists: beyond the renin–angiotensin system. J Hypertens 22:2253–2261
24. Lindholm LH, Persson M, Alaupovic P, Carlberg B, Svensson A, Samuelsson O (2003) Metabolic outcome during 1 year in newly detected hypertensives: results of the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE study). J Hypertens 21:1563–1574
25. Lindholm LH, Ibsen H, Borch-Johnsen K, Olsen MH, Wachtell K, Dahlöf B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristianson K, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wedel H, Aurup P, Edelman JM, Snapinn S (2002) Risk of new-onset diabetes in the Losartan Intervention For Endpoint reduction in hypertension study. J Hypertens 20:1879–1886
26. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh JH, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A (2004) Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomized trial. Lancet 363:2022–2031
27. Bengtsson C, Blohme G, Lapidus L, Lissner L, Lundgren H (1992) Diabetes incidence in users and non-users of antihypertensive drugs in relation to serum insulin, glucose tolerance and degree of adiposity: a 12-year prospective population study of women in Gothenburg, Sweden. J Intern Med 231:583–588
28. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL (2000) Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. N Engl J Med 342:905–912
29. Mykkanen L, Kuusisto J, Pyorala K, Laakso M, Haffner SM (1994) Increased risk of non-insulin-dependent diabetes mellitus in elderly hypertensive subjects. J Hypertens 12:1425–1432
30. Samuelsson O, Hedner T, Berglund G, Persson B, Andersson OK, Wilhelmsen L (1994) Diabetes mellitus in treated hypertension: incidence, predictive factors and the impact of non-selective beta-blockers and thiazide diuretics during 15 years treatment of middle-aged hypertensive men in the Primary Prevention Trial Goteborg, Sweden. J Hum Hypertens 8:257–263
31. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, CHARM Investigators and Committees (2003) Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM - Preserved Trial. Lancet 362:777–781
32. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K, CHARM Investigators and Committees (2003) Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 362:772–776
33. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA, CHARM Investigators and Committees (2003) Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM – Added trial. Lancet 362:767–771
34. Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Zanchetti A, SCOPE Study Group (2003) The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens 21:875–886
35. Epstein M, Brunner H (2001) Angiotensin II receptor antagonists. Hanley and Belfus, Philadelphia
36. Picard F, Auwerx J (2002) PPAR(gamma) and glucose homeostasis. Annu Rev Nutr 22:167–197
37. Hsueh WA, Law R (2003) The central role of fat and effect of peroxisome proliferator-activated receptor-gamma on progression of insulin resistance and cardiovascular disease. Am J Cardiol 92:3J–9J
38. Schiffrin EL, Amiri F, Benkirane K, Iglarz M, Diep QN (2003) Peroxisome proliferator-activated receptors: vascular and cardiac effects in hypertension. Hypertension 42:664–668
39. Wakino S, Law RE, Hsueh WA (2002) Vascular protective effects by activation of nuclear receptor PPARgamma. J Diabetes Complications 16:46–49
40. Walczak R, Tontonoz P (2002) PPARadigms and PPARadoxes: expanding roles for PPARgamma in the control of lipid metabolism. J Lipid Res 43:177–186
41. Savage DB, Tan GD, Acerini CL, Jebb SA, Agostini M, Gurnell M, Williams RL, Umpleby AM, Thomas EL, Bell JD, Dixon AK, Dunne F, Boiani R, Cinti S, Vidal-Puig A, Karpe F, Chatterjee VK, O'Rahilly S (2003) Human metabolic syndrome resulting from dominant-negative mutations in the nuclear receptor peroxisome proliferator-activated receptor-gamma. Diabetes 52:910–917
42. Benson SC, Pershadsingh HA, Ho CI, Chittiboyina A, Desai P, Pravenec M, Qi N, Wang J, Avery MA, Kurtz TW (2004) Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARγ-modulating activity. Hypertension 43:993–1002
43. Delea TE, Edelsberg JS, Hagiwara M, Oster G, Phillips LS (2003) Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes: a retrospective cohort study. Diabetes Care 26:2983–2989
44. Mudaliar S, Chang AR, Henry RR (2003) Thiazolidinediones, peripheral edema, and type 2 diabetes: incidence, pathophysiology, and clinical implications. Endocr Pract 9:406–416
45. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, Le Winter M, Porte D, Semenkovich CF, Smith S, Young LH, Kahn R (2004) Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Diabetes Care 27:256–263
46. Schupp M, Janke J, Clasen R, Unger T, Kintscher U (2004) Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-gamma activity. Circulation 109:2054–2057
47. Tordjman J, Chauvet G, Quette J, Beale EG, Forest C, Antoine B (2003) Thiazolidinediones block fatty acid release by inducing glyceroneogenesis in fat cells. J Biol Chem 278:18785–18790

48. Fujimoto M, Masuzaki H, Tanaka T, Yasue S, Tomita T, Okazawa K, Fujikura J, Chusho H, Ebihara K, Hayashi T, Hosoda K, Nakao K (2004) An angiotensin II AT1 receptor antagonist, telmisartan augments glucose uptake and GLUT4 protein expression in 3T3-L1 adipocytes. FEBS Lett 576:492–497
49. Pershadsingh HA, Kurtz TW (2004) Insulin-sensitizing effects of telmisartan: implications for treating insulin resistant hypertension and cardiovascular disease. Diabetes Care 27:1015
50. Michel MC, Bohner H, Koster J, Schafers R, Heemann U (2004) Safety of telmisartan in patients with arterial hypertension. An open-label observational study. Drug Saf 27:335–344
51. Derosa G, Ragonesi PD, Mugellini A, Ciccarelli L, Fogari R (2004) Effects of telmisartan compared with eprosartan on blood pressure control, glucose metabolism and lipid profile in hypertensive, type 2 diabetic patients: a randomized, double-blind, placebo-controlled 12-month study. Hypertens Res 27:457–464
52. Rosano G, Vitale C, Castiglioni C, Cornoldi A, Fini M, Mercuro G (2004) Comparative effects of telmisartan and losartan on glucose metabolism in hypertensive patients with the metabolic syndrome. Scientific Session American Heart Association, New Orleans
53. Burnier M, Maillard M (2001) The comparative pharmacology of angiotensin II receptor antagonists. Blood Press 10[Suppl 1]:6–11
54. Corti R, Osende JI, Fallon JT, Fuster V, Mizsei G, Jneid H, Wright SD, Chaplin WF, Badimon JJ (2004) The selective peroxisomal proliferator-activated receptor-gamma agonist has an additive effect on plaque regression in combination with simvastatin in experimental atherosclerosis: in vivo study by high-resolution magnetic resonance imaging. J Am Coll Cardiol 43:464–473
55. Inoue I, Katayama S (2004) The possible therapeutic actions of peroxisome proliferator-activated receptor alpha (PPAR alpha) agonists, PPAR gamma agonists, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, angiotensin converting enzyme (ACE) inhibitors and calcium (Ca)-antagonists on vascular endothelial cells. Curr Drug Targets Cardiovasc Haematol Disord 4:35–52
56. Levi Z, Shaish A, Yacov N, Levkovitz H, Trestman S, Gerber Y, Cohen H, Dvir A, Rhachmani R, Ravid M, Harats D (2003) Rosiglitazone (PPARgamma-agonist) attenuates atherogenesis with no effect on hyperglycaemia in a combined diabetes-atherosclerosis mouse model. Diabetes Obes Metab 5:45–50
57. Sidhu JS, Cowan D, Kaski JC (2003) The effects of rosiglitazone, a peroxisome proliferator-activated receptor-gamma agonist, on markers of endothelial cell activation, C-reactive protein, and fibrinogen levels in non-diabetic coronary artery disease patients. J Am Coll Cardiol 42:1757–1763
58. Wang TD, Chen WJ, Lin JW, Chen MF, Lee YT (2004) Effects of rosiglitazone on endothelial function, C-reactive protein, and components of the metabolic syndrome in non-diabetic patients with the metabolic syndrome. Am J Cardiol 93:362–365
59. Sidhu JS, Kaposzta Z, Markus HS, Kaski JC (2004) Effect of rosiglitazone on common carotid intima-media thickness progression in coronary artery disease patients without diabetes mellitus. Arterioscler Thromb Vasc Biol 24:930–934
60. Teo KK, Yusuf S, Anderson C, Mookadam F, Ramos B, Hilbrich L, Pogue J, Schumacher H; ONTARGET/TRANSCEND Investigators (2004) Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials. Am Heart J 148:52–61