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Metabolic and Additional Vascular Effects of Thiazolidinediones

Fabrice M.A.C Martens,[1] *Frank L.J. Visseren*,[1] *Jacinthe Lemay*,[2] *Eelco J.P. de Koning*[1] and *Ton J. Rabelink*[1]

1 Department of Internal Medicine, Section of Vascular Medicine and Diabetology, University Medical Center Utrecht, Utrecht, The Netherlands
2 Department of Pharmacology, Faculty of Medicine, Université de Montréal, Montréal, Canada

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Abstract

Several cardiovascular risk factors (dyslipidaemia, hypertension, glucose intolerance, hypercoagulability, obesity, hyperinsulinaemia and low-grade inflammation) cluster in the insulin resistance syndrome. Treatment of these individual risk factors reduces cardiovascular complications. However, targeting the underlying pathophysiological mechanisms of the insulin resistance syndrome is a more rational treatment strategy to further improve cardiovascular outcome.

Our understanding of the so-called cardiovascular dysmetabolic syndrome has been improved by the discovery of nuclear peroxisome proliferator-activated receptors (PPARs). PPARs are ligand-activated transcription factors belonging to the nuclear receptor superfamily. As transcription factors, PPARs regulate the expression of numerous genes and affect glycaemic control, lipid metabolism, vascular tone and inflammation. Activation of the subtype PPAR-γ improves insulin sensitivity. Expression of PPAR-γ is present in several cell types involved in the process of atherosclerosis. Thus, modulation of PPAR-γ activity is an interesting therapeutic approach to reduce cardiovascular events.

Thiazolidinediones are PPAR-γ agonists and constitute a new class of pharmacological agents for the treatment of type 2 (non-insulin–dependent) diabetes mellitus. Two such compounds are currently available for clinical use: rosiglitazone and pioglitazone. Thiazolidinediones improve insulin sensitivity and glycaemic control in patients with type 2 diabetes. In addition, improvement in endothelial function, a decrease in inflammatory conditions, a decrease in plasma levels of free fatty acids and lower blood pressure have been observed, which may have important beneficial effects on the vasculature.

Several questions remain to be answered about PPAR-γ agonists, particularly with respect to the role of PPAR-γ in vascular pathophysiology. More needs to be known about the adverse effects of thiazolidinediones, such as hepatotoxicity, increased low-density lipoprotein cholesterol levels and increased oedema. The paradox of adipocyte differentiation with weight gain concurring with the insulin-sensitising effect of thiazolidinediones is not completely understood. The decrease in blood pressure induced by thiazolidinedione treatment seems incompatible with an increase in the plasma volume, and the discrepancy between the stimulation of the expression of CD36 and the antiatherogenic effects of the thiazolidinediones also needs further explanation. Long-term clinical trials of thiazolidinediones with cardiovascular endpoints are currently in progress.

In conclusion, studying the effects of thiazolidinediones may shed more light on the mechanisms involved in the insulin resistance syndrome. Furthermore, thiazolidinediones could have specific, direct effects on processes involved in the development of vascular abnormalities.

Cardiovascular disease is the number one cause of morbidity and mortality in the Western world. Several risk factors for the development of cardiovascular disease have been identified. Some of these risk factors (dyslipidaemia, hypertension, glucose intolerance, hyperinsulinaemia, obesity, low-grade inflammation, endothelial dysfunction and hypercoagulability) have been found to cluster and often precede clinically manifest type 2 (non-insulin–dependent) diabetes mellitus. Insulin resistance is generally regarded as an important feature of this cluster of risk factors and therefore the term 'insulin resistance syndrome' has been coined.[1] 'Cardiovascular dysmetabolic syndrome',[2] or 'syndrome X'[3] are other terms which have been used to describe this metabolic state.

The prevalence of type 2 diabetes has soared in the past decades because of changing lifestyles and eating habits. Obesity associated with insulin resistance is one of the main determinants of the increase in occurrence of type 2 diabetes. Not surprisingly, the major long-term complications of type 2 diabetes are an increased risk of myocardial infarction, stroke and peripheral vascular disease. Although microvascular complications cause considerable morbidity in patients with type 2 diabetes, up to 80% of patients die from macrovascular pathology.[4]

Treatment of individual risk factors has been shown to reduce cardiovascular events in type 2 diabetes. Dysglycaemia does not appear to be the major determinant of cardiovascular disease in type 2 diabetes, a concept supported by observations in the UK Prospective Diabetes Study.[5] Therefore, targeting the underlying pathophysiological mechanisms of the insulin resistance syndrome may be a more logical and beneficial strategy for reduction of cardiovascular morbidity and mortality. Pharmacological modulation of the insulin resistance syndrome will not only improve glycaemic control, but may also have beneficial effects on inflammation, dyslipidaemia and possibly other components of the syndrome independently from improvements in glucose metabolism.

The discovery of nuclear peroxisome proliferator-activated receptors (PPARs) and subsequent insight into their role in several metabolic pathways was a major breakthrough in our understanding of pathophysiological mechanisms underlying the insulin resistance syndrome.[6]

Thiazolidinediones are clinically available agonists of the PPAR-γ subtype and constitute a new class of antihyperglycaemic agents. Activation of PPAR-γ not only improves insulin sensitivity but may also have additional beneficial vascular effects.

The aim of this review is to focus on the potential role of thiazolidinediones in the pathophysiological mechanisms involved in vascular disease.

1. Peroxisome Proliferator-Activated Receptors (PPARs)

PPARs are ligand-activated transcription factors belonging to the nuclear receptor superfamily, which include receptors for steroids, retinoid and thyroid hormones.[7-9] Once PPARs are activated by ligand binding, they form heterodimers with the ligand-activated retinoic acid receptor (RXR). Through its DNA binding domain, this heterodimer binds to specific DNA sequences, called PPAR-responsive elements (PPREs), and induces transcriptional activation of specific genes (figure 1).[10] PPARs function as regulators of glucose, lipid and protein metabolism, and influence cellular proliferation, differentiation and apoptosis. They also play a role in neoplastic proliferation and inflammatory diseases.[11]

Three subtypes of PPARs are known: PPAR-α, PPAR-γ and PPAR-δ. The tissue distribution of these subtypes varies considerably.[10,12] Whereas PPAR-δ is ubiquitously distributed, its function remains to be elucidated. PPAR-α is found in liver, intestine, kidney, heart, adipose tissue, skeletal muscle and recently in vascular cells.[13] PPAR-α has an important role in lipid metabolism. Its molecular targets include genes for enzymes that are important for the β-oxidation of fatty acids.[14] Synthetic ligands for this receptor subtype are fib-

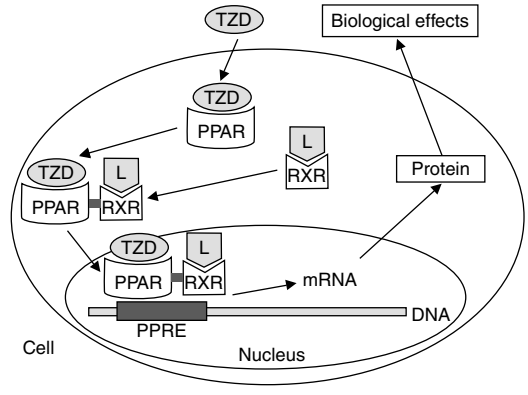

Fig. 1. Mechanism of action of the peroxisome proliferator-activated receptors (PPARs). **L** = ligand; **PPRE** = PPAR-responsive elements; **RXR** = retinoic acid receptor; **TZD** = thiazolidinediones.

ric acid derivatives, which are used in clinical practice as lipid-lowering agents. PPAR-γ is found in adipose tissue, pancreas, skeletal muscle and vasculature.[10,12,13,15] High levels of expression are found in adipocytes. In addition, PPAR-γ is also expressed in macrophages, T cells, neutrophils, epithelial cells and smooth muscle cells.[16] The most potent natural ligands are 13-hydroxyoctadecadienoic acid (HODE) and 15-deoxyΔ-prostaglandin J2 (15d-PGJ_2).[17] Thiazolidinediones are potent synthetic ligands for PPAR-γ activation.

2. Thiazolidinediones

Thiazolidinediones are a new class of drugs that act primarily by improving insulin sensitivity in different target tissues such as liver, skeletal muscle and adipose tissue. They have been shown to improve glycaemic control in patients with type 2 diabetes and appear to have favourable direct effects on other components of the insulin resistance syndrome because of the role of PPAR-γ in vascular physiology (figure 2).[18,19] Thiazolidinediones are chemically and functionally unrelated to other classes of oral antihyperglycaemic agents. Two compounds in this class are currently available for clinical use, namely, rosiglitazone, which was approved by the US Food and Drug Administration (FDA) in May 1999, and pioglitazone, which was approved in July 1999. Troglitazone, the first drug

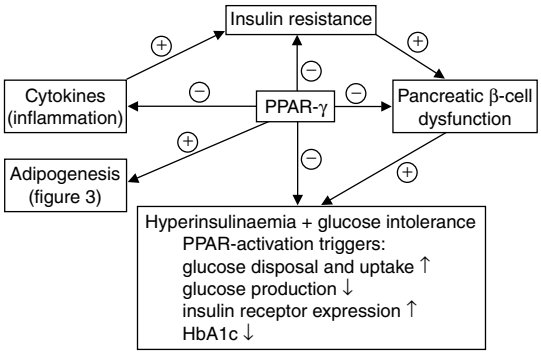

Fig. 2. The central role of peroxisome proliferator-activated receptor (PPAR)-γ in vascular physiology. **HbA1c** = glycosylated haemoglobin.

of this class, was marketed in the US from March 1997 until it was withdrawn in March 2000, when the FDA decided that the risk of hepatotoxicity associated with troglitazone therapy outweighed its potential benefits. The mode of action and magnitude of effects of different thiazolidinediones show some variation.[20-22] Pioglitazone may perhaps also have PPAR-α agonistic effects, which is of interest with regard to lipid-lowering effects similar to fibric acid derivatives.

3. Thiazolidinediones and Glycaemic Control

Several thiazolidinediones have been shown to improve insulin sensitivity by increasing glucose disposal in skeletal muscle and decreasing hepatic glucose production. Thiazolidinediones increase glycogen synthase activity and glucose metabolism in skeletal muscle but also in adipocytes. They also decrease gluconeogenesis in cultured hepatocytes.[23-25] Stimulation of PPAR-γ normalises glucose uptake associated with glucose transporter 4 (GLUT4) expression and stimulates insulin receptor expression and activation.[26-32]

Improvement of glycaemic control by thiazolidinediones has been shown in different animal models of diabetes[33-36] and in patients with type 2 diabetes. Although troglitazone has been withdrawn from the market, it was very effective in lowering plasma glucose, insulin and glycosylated haemoglobin (HbA1c) levels in patients with type 2 diabetes.[37-40] Rosiglitazone resulted in significant reductions in fasting plasma glucose, HbA1c and insulin levels, and was more effective than troglitazone in maintaining low fasting plasma glucose levels in the long term.[41] Rosiglitazone also improved glycaemic control in patients with type 2 diabetes when administered in combination with metformin, sulphonylurea derivatives or insulin.[42,43] Similar significant decreases in fasting plasma glucose and HbA1c levels are achieved with pioglitazone in monotherapy;[44,45] furthermore, combination therapy with metformin, sulphonylurea derivatives or insulin, improves glycaemic control more than pioglitazone monotherapy

does.[44] Unfortunately, studies comparing the individual effects of thiazolidinediones with metformin in glycaemic control have not been published yet. In addition, thiazolidinediones improve insulin sensitivity in nondiabetic insulin-resistant states, such as obese individuals and individuals with impaired glucose tolerance.[46,47]

What mechanisms could be involved in the beneficial effects of thiazolidinediones on glycaemic control and insulin resistance? Since obesity, causing insulin resistance, is a main determinant for the development of type 2 diabetes, mechanisms related to adipocyte function are likely to be involved.

3.1 Differentiation of Adipocytes

PPAR-γ is expressed mainly in adipose tissue and is a key factor in the differentiation of adipocytes and adipogenesis (figure 3).[48,49] PPAR stimulation alters adipocyte metabolism by increasing the expression of specific adipocyte genes involved in glucose regulation (e.g. GLUT4, lipoprotein lipase [LPL], fatty acid transporter protein, Acyl CoA synthase and malic enzymes).[50] Recent observations in PPAR-γ knockout mice show that homozygous PPAR-γ-null mice are completely devoid of adipose tissue and that mice heterozygous for the mutation (PPAR-γ +/- mice) are characterised by a decreased adipose tissue mass.[51] These *in vivo* results are further supported by *in vitro* data showing that embryonic stem cells lacking both copies of PPAR-γ fail to differentiate into adipocytes after appropriate treatment, whereas embryonic stem cells expressing PPAR-γ readily differentiate into adipocytes.[52] Moreover, forced expression of PPAR-γ in fibroblasts makes them differentiate into adipocytes.[53] Pioglitazone affects the early stage of adipocyte differentiation and enhances growth arrest, protein synthesis and hypertrophy of 3T3-L1 adipocytes.[54] Exposure of 3T3-L1 adipocytes to tumour necrosis factor (TNF)-α, a potent inhibitor of adipocyte differentiation, results in lipid depletion and a complete reversal of adipocyte differentiation.[55] Consistent with the opposing effects of PPAR-γ and

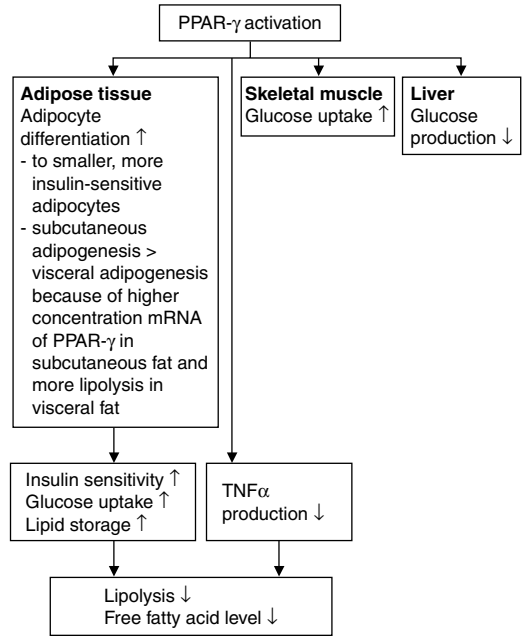

Fig. 3. The peroxisome proliferator-activated receptor (PPAR)-γ paradox of increased adipogenesis and beneficial diabetic treatment. **TNF**α = tumour necrosis factor α.

TNFα in adipose tissue, treatment of obese animals with PPAR-γ agonists reduces the adipose tissue expression of TNFα, which contributes to the weight gain.[56]

An interesting concept is the 'lipid-steal hypothesis'.[53,57] This hypothesis states that stimulation of adipose differentiation leads to increased numbers of small adipocytes, which are thought to be more sensitive to insulin than large adipocytes. These smaller adipocytes take up free fatty acids more easily and thus reduce free fatty acid flux to the muscles or liver. Pioglitazone strongly induces adipocyte differentiation and increases adipocyte glucose utilisation at post-absorptive insulin levels *in vivo*.[27] However, thiazolidinediones also exert beneficial effects on glucose and lipid metabolism in the absence of adipose tissue,[28] suggesting that an alteration in adipocyte differentiation cannot be a sole explanation for the improvement in insulin sensitivity.

How can the paradox of beneficial effects of PPAR-γ activation with improvement of insulin resistance on one hand and stimulation of adipogenesis on the other hand be explained?

Thiazolidinedione-induced adipogenesis occurs mainly in subcutaneous fat and not in visceral fat. An increase in visceral fat is associated with a higher cardiovascular risk. In line with this, levels of mRNA for PPAR-γ and leptin are higher in subcutaneous fat than in visceral fat.[58] Furthermore, 3T3-L1 pre-adipocytes in subcutaneous fat become resistant to apoptosis after differentiation into mature adipocytes, a process stimulated by PPAR-γ activation and resulting in decreased apoptosis in subcutaneous fat.[59] Finally, the recently identified protein, resistin, a protein that causes insulin resistance in mice and which is inhibited by PPAR-γ activation, may also be involved.[60] Unfortunately, these results are controversial because resistin is not found in humans, once again showing the discrepancy between experimental animal studies and human physiology.

3.2 Modulation of Tissue Triglyceride Content

Improvement in insulin resistance is associated with a decrease in the triglyceride content of liver and skeletal muscle. Treatment with thiazolidinediones reduces the triglyceride content in liver and skeletal muscle, which may be an important factor in the observed improvement in peripheral glucose disposal and decreased hepatic glucose output.[61] In addition, thiazolidinediones also lower the triglyceride content of β cells, which is associated with an improvement of β cell function.[62] Supporting these data is the clinical observation that the high ratio of proinsulin to insulin typically found in patients with type 2 diabetes mellitus is normalised upon thiazolidinedione treatment, suggesting an effect of these drugs on β cell function.[37,63]

3.3 Effect on Adipocyte-Derived Factors

Other mechanisms of the thiazolidinediones include regulation of storage and release of adipocyte-derived signaling factors that affect insulin sensitivity of muscle. These factors include free fatty acids, adiponectin, TNFα and leptin.

3.3.1 Free Fatty Acids

Fatty acids are key mediators of the storage or release of adipocyte-derived signaling factors affecting insulin sensitivity. High levels of free fatty acids have been linked to the induction of insulin resistance, because increased free fatty acid metabolism in the liver leads to increased gluconeogenesis.[64] There is evidence for a direct regulatory effect of fatty acids on the production of macrophage lipoprotein lipase (involved in the pathogenesis of atherosclerosis) in the vascular wall.[65] It is well established that increased fatty acid levels decrease glucose metabolism in muscle. Because fatty acids are ligands for PPAR-γ, activation of PPARs by thiazolidinediones increases fatty acid clearance in adipose tissue with a concomitant decrease in the uptake of fatty acids in muscle, which potentially improves insulin sensitivity.[66,67]

The mechanism underlying these effects may be related to the regulation by PPAR-γ of the expression of the fatty acid transporter CD36, which is also implicated in the control of insulin sensitivity.[68-70] There is also a correlation between PPAR-γ transactivation and intracellular levels of liver fatty acid-binding protein, which could explain the decrease in plasma levels of free fatty acids.[71] Furthermore, PPAR-γ is required for the expression of adipocyte phosphoenolpyruvate carboxykinase (PEPCK). PEPCK is the key enzyme in glyceroneogenesis, an important metabolic pathway that limits the release of non-esterified fatty acids from adipocytes.[72] Therefore, PEPCK could be a major target gene for the antidiabetic actions of thiazolidinediones. Thus, lowering the elevated plasma levels of non-esterified fatty acids is likely to be an important mechanism to explain the beneficial metabolic effects induced by thiazolidinediones.

3.3.2 Adiponectin

Adiponectin is an adipocyte-derived hormone that decreases insulin resistance by lowering the triglyceride content of muscle and liver in obese mice. This effect results from increased expression

of molecules involved in fatty-acid combustion in muscle. Moreover, insulin resistance in lipoatrophic mice can be completely reversed by physiological doses of adiponectin and leptin.[73] In addition, adiponectin suppresses adhesion molecule expression in vascular endothelial cells and inhibits cytokine production by macrophages. Recent publications show that thiazolidinediones can markedly enhance the expression and secretion of adiponectin *in vitro* and *in vivo*, possibly (partly) mediated by antagonising the suppressive effect of TNFα on the production of adiponectin.[74] However, the exact role of adiponectin in insulin resistance in humans has not been elucidated.

3.3.3 Tumour Necrosis Factor-α

The expression of TNFα by adipose tissue is upregulated in obesity and TNFα levels are increased in patients with features of the insulin resistance syndrome. This cytokine decreases PPAR-γ expression, insulin receptor synthesis and activation, and glucose uptake in adipose tissue, skeletal muscle and liver by attenuating the expression of the glucose transporter GLUT4.[30,75-77] Chronic hyperglycaemia is associated with increased TNFα production, which may be derived from adipose tissue.[78] Thiazolidinediones restore sensitivity to insulin by down-regulating adipose cytokines such as TNFα.[6,79,80] Furthermore, it has been shown that pioglitazone improves TNFα-induced insulin resistance by improving insulin-stimulated tyrosine phosphorylation of the insulin receptor and insulin receptor substrate.[81]

3.3.4 Leptin

Thiazolidinediones have also been implicated in the regulation of leptin expression. Administration of thiazolidinediones reduces the expression of leptin mRNA and protein in adipocytes *in vivo* and *in vitro*.[82] The role of leptin in insulin resistance is controversial, but some reports indicate that leptin might interfere with insulin signalling in certain cell types.

In conclusion, glycaemic control and insulin-sensitising properties of thiazolidinediones may involve a wide range of inter-related mechanisms in different target tissues involved in insulin activity and glucose production and uptake.

4. Thiazolidinediones and Additional Vascular Effects

4.1 Improvement of Endothelial (Dys-)Function

Atherosclerotic disease is characterised by endothelial dysfunction. Endothelial dysfunction is characterised by decreased availability of endothelium-derived nitric oxide (NO) and can be assessed clinically by impaired vasoreactivity of the brachial artery after an ischaemic or other stimulus. Impaired endothelial function has prognostic significance for future development of cardiovascular events. All known cardiovascular risk factors are associated with endothelial dysfunction.[83,84] Endothelial dysfunction appears to be an important feature of the insulin resistance syndrome. Upon binding to the endothelial insulin receptor, insulin activates endothelial NO synthase (eNOS), thereby stimulating NO production, resulting in vasodilation. This vasodilation is impaired in insulin-resistant states, which has been termed vascular insulin resistance. Patients with insulin-resistant states such as obesity, hypertension and type 2 diabetes exhibit blunted insulin-mediated vasodilation and impaired endothelium-dependent vasodilation.[85] Quenching of NO by decreased NO or an increased inactivation of NO by reactive oxygen species (ROS) might be a major driving force for instability of atherosclerotic plaques in patients with diabetes.[86]

In both obese people and healthy volunteers, it was shown that a single oral dose of troglitazone improved the ischaemia-induced flow-mediated vasodilatation in the forearm.[87,88] Normalisation of impaired brachial artery vasoreactivity also occurred during troglitazone therapy in individuals with peripheral vascular disease and impaired glucose tolerance.[89]

How can thiazolidinediones improve endothelial function? Improved metabolic control will most likely contribute to the effects observed.

High levels of glucose and free fatty acids stimulate ROS production, for example through protein kinase C-dependent activation of nicotinamide adenine dinucleotide (phosphate) [NAD(P)H] oxidase.[90] Reduction of the glucose and free fatty acid concentrations by thiazolidinediones will therefore have beneficial effects. A reduction in formation of ROS by both polymorphonuclear leukocytes and mononuclear cells after administration of troglitazone may also contribute to improvement in endothelial function.[88] Incubation with insulin plus pioglitazone improves vasodilation induced by acetylcholine, suggesting that pioglitazone augments the endothelium-dependent vasodilation mediated by insulin.[91]

Direct effects of thiazolidinediones on vascular smooth muscle cells have also been observed. Thiazolidinediones attenuate vasoconstriction as well as inhibit L-type Ca^{2+} currents in vascular smooth muscle cells (VSMC) *in vitro*.[92] The vasodilative action of pioglitazone after removal of the endothelium[93] is not yet completely understood. Pioglitazone appears to act mainly on VSMC rather than the vascular endothelium. However, expression of PPAR-γ mRNA is very low in VSMC.[94]

In patient groups with a high incidence of cardiovascular diseases and endothelial dysfunction (congestive heart failure, diabetes, atherosclerosis) TNFα levels are increased. There may be an interesting link between TNFα and endothelial function because of the direct association between TNFα and NO bioavailability. TNFα downregulates mRNA for eNOS by shortening its half-life in human umbilical vein endothelial cells.[95] In a rat model, recombinant TNFα infusion *in vivo* depresses endothelium-dependent relaxation without decreasing mean arterial pressure.[96] In addition, brief exposure of the human forearm resistance artery to TNFα may increase the basal bioavailability of the vasoconstrictor prostaglandin and reduce the basal bioavailability of NO. However, in acetylcholine-stimulated endothelium-dependent vasodilatation, TNFα did not impair the vascular function, maybe because of an overwhelming NO bioavailability in healthy humans.[97] It is noteworthy to mention that interpretation of these results are difficult in the light of the effects of TNFα on the inducible form of NOS (iNOS).

4.2 Decreased Inflammatory Conditions

Low-grade inflammation plays an important role in the initiation and progression of cardiovascular diseases.[98] Accumulation of monocyte-derived lipid-loaded macrophages or foam cells, smooth muscle cell proliferation and *de novo* formation of extracellular matrix results in the formation of the atherosclerotic plaque.[99] Markers of inflammation, such as the acute-phase protein C-reactive protein (CRP), TNFα and interleukin (IL)-6, are increased in patients with the insulin resistance syndrome.[100,101] Elevated serum levels of CRP, which is indicative of a low-grade inflammatory state, are associated with a diminished systemic endothelial vasodilator function.[102]

PPARs are mainly expressed in adipocytes and could have an important role in downregulation of the inflammatory cytokine TNFα as discussed in sections 3.6 and 4.1. Expression of PPARs in macrophages, T cells and neutrophils suggests that they may have an important role in modulating the function of inflammatory cells.[16]

4.2.1 Modulation of PPAR Activity in Inflammatory Cells

Several studies have reported that PPAR agonists dampen inflammatory responses in macrophages. PPAR-α agonists inhibit tissue factor expression in human monocytes and macrophages,[103,104] and PPAR-γ agonists reduce macrophage homing to atherosclerotic plaques.[105] PPAR-γ is a negative regulator of macrophage activation and may limit chronic inflammation by inhibiting the induced expression of circulating vascular cell adhesion molecule-1 (VCAM-1) and monocytes without affecting the acute inflammation mediated by endothelial-leucocyte adhesion molecule–1 (E-selectin).[106,107] *In vitro*, PPAR-γ agonists suppress the release of inflammatory cytokines, such as TNFα, IL-1 and IL-6, from monocytes at agonist concentrations similar to those effective in promoting adipogenesis.[108] An increased expression of PPAR-

γ during the differentiation of monocytes and macrophages initially suggested that PPAR-γ may regulate macrophage differentiation.[68,109] However, there are also studies, performed with PPAR-γ–deficient stem cells, suggesting that PPAR-γ is not essential for either myeloid development, or for certain functions of mature macrophages such as phagocytosis and inflammatory cytokine production.[16,110] Several reports indicate that PPAR-γ agonists dampen macrophage inflammatory responses by reducing the expression of matrix-degrading metalloproteinases, cytokines, NO and modified lipoprotein receptors,[106,108,110,111] whereas others do not.[16,112] Part of this contradiction can be explained by the widely varying doses of PPAR-γ agonists used. At high concentrations these agents appear to have PPAR-γ–independent actions, which are as yet poorly understood.[113]

4.2.2 CD36 Expression in Mononuclear Cells

PPAR-γ stimulation induces CD36 gene expression.[68,110,114] CD36 is a transporter of long-chain fatty acids and is a high-affinity receptor for oxidised low-density lipoproteins (oxLDL).[115] CD36-deficient mice have a 6-fold reduction in atheroma compared with controls,[116] probably because of a reduced uptake of oxLDL, which results in diminished foam cell formation.[109] Since PPAR-γ increases the expression of CD36, there is concern about the overall antiatherogenic effect of thiazolidinediones. Some investigators have reported that PPAR activation leads to an induction of foam cell formation from macrophages,[68,109,110] whereas others have reported suppression of inflammatory cytokines and induction of cholesterol efflux from macrophages as antiatherogenic effects of PPAR activation.[114,117] However, overall results indicate that foam cell development can occur in the absence of PPAR-γ and that PPAR-γ agonists decrease atherosclerosis in animal models of LDL receptor and apolipoprotein E deficiency.[118] The induction by PPAR of cholesterol efflux through the adenosine triphosphate (ATP)-binding cassette transporter 1 (ABCA1) may be a counterbalancing mechanism. The liver X receptor-α (LXRα) and the scavenger receptor A (SR-A) may have a central role in this concept of cholesterol efflux induced by PPAR activation.[16,110,117]

Recently, CD36-deficient humans were found to have an increased insulin resistance, including higher plasma triglyceride and glucose levels, lower plasma high-density lipoprotein (HDL) cholesterol levels and much higher blood pressure than controls.[70] So far, most studies show a net antiatherogenic effect of thiazolidinediones, but the major mechanisms for this still have to be clarified.[80,119] Agonists of PPAR-α and PPAR-γ inhibit the cardiac expression of TNFα, in part by antagonising nuclear factor-κB activity.[120]

Taken together, these complex observations suggest that thiazolidinediones may have beneficial effects in modulating the inflammatory state and thus atherogenesis.

4.3 Effects on the Lipid Profile

Dyslipidaemia is a well-established risk factor for the formation of atherosclerotic plaques. Insulin resistance and type 2 diabetes are associated with a characteristic pattern of lipid abnormalities, including an increased number of small dense LDL particles, elevated plasma triglyceride levels, and low plasma HDL cholesterol levels.[121] The disturbance of lipid metabolism may not be the result of insulin resistance alone, but may also be directly involved in the metabolic abnormalities observed. Evidence obtained from obese animal models (eg. rats fed high-fat diets) shows excess accumulation of muscle triglyceride together with the development of insulin resistance.[122] Several studies demonstrate an increased muscle triglyceride content in insulin-resistant states in humans as well.[123-125] The factors leading to this accumulation are not clear yet, but it could well be a result of elevated circulating free fatty acids associated with impaired triglyceride clearance, or reduced muscle free fatty acid oxidation.

4.3.1 Reduction of Plasma Triglycerides

In humans, troglitazone[4,20] and pioglitazone[126,127] lower triglyceride levels by approximately 9 to 20%. In contrast, mean triglyceride levels were increased after rosiglitazone treatment

by 38.4%.[128] The exact mechanism by which thiazolidinediones affect triglyceride levels is currently not known. Pioglitazone has been reported to increase the expression of lipoprotein lipase and to decrease the expression of apolipoprotein C-III (key players in plasma triglyceride metabolism), indicating that pioglitazone has PPAR-α agonistic activity.[129] The triglyceride-lowering action of PPAR-γ activation may be the result of a reduction in fatty acid and triglyceride synthesis, and consequently a decrease in the production of very-low-density lipoprotein (VLDL).

4.3.2 Effects on Lipoprotein Metabolism

Several trials have been conducted to study the effects of thiazolidinediones on plasma lipoproteins. In general there appears to be an increase in HDL (up to ≈20%).[130] The increase in HDL levels is likely to be explained by the decrease in triglyceride levels.

LDL levels tend to increase (≈10%),[130] are unaffected or are lowered (≈15%) by thiazolidinedione treatment.[128,131,132] However, the concomitant changes in plasma HDL and LDL levels resulted in unaltered LDL to HDL ratios.[4,130] The increase in total cholesterol and LDL cholesterol levels observed in several studies is cause for concern. This increase may be predominantly caused by larger, buoyant LDL particles. Larger LDL particles are less prone to oxidative modification and are therefore thought to be less atherogenic.[133,134] Support for this hypothesis comes from a study showing that troglitazone increases the resistance of LDL cholesterol to oxidation.[135,136] Recent studies reported a decrease in LDL levels after pioglitazone treatment.[128,131,132]

There appears to be a differential effect of thiazolidinediones: LDL levels apparently increase more during rosiglitazone than pioglitazone treatment.[126,137] In a head to head comparison, treatment with pioglitazone was associated with overall greater beneficial effects on blood lipid levels (total cholesterol, HDL, LDL and triglycerides) than treatment with rosiglitazone, while similar effects were demonstrated in respect to weight gain and glycaemic control.[131,132] A possible reason is that pioglitazone may perhaps also have PPAR-α agonistic effects, which is in line with lipid-lowering effects of fibric acid derivatives. The different effects of the various thiazolidinediones on lipid metabolism need further investigation, but considering its central role in lipid metabolism, pharmacological modulation of PPAR-γ activity by thiazolidinediones may result in an overall improvement of the dyslipidaemic phenotype.[126,138,139]

4.4 Lowering Blood Pressure

Troglitazone and rosiglitazone decrease blood pressure by ≈10%. This effect has been observed in patients with hypertension and type 2 diabetes,[140,141] individuals with normal blood pressure and type 2 diabetes,[141,142] and obese individuals without diabetes.[46,143] Pioglitazone therapy decreased arterial pressure in rat models of hypertension [92,93] and prevented the development of hypertension.[144] Other animal and human studies have shown that thiazolidinediones decrease blood pressure associated with decreased insulin levels and improvement of endothelial function.[91,145,146] However, the exact role of decreased insulin levels on the thiazolidinedione-mediated regulation of blood pressure is debated because some reports show insulin- and glucose-independent blood pressure–lowering mechanisms.[87,147] It has also been suggested that thiazolidinediones may lower blood pressure by a direct vascular effect involving decreased calcium uptake into vascular cells.[93,148,149] Alternatively, a thiazolidinedione-induced decrease in the activity of the renin-angiotensin system and of the sympathetic system may also play an important role in the modulation of blood pressure.[91]

In conclusion, thiazolidinediones lower blood pressure by multiple mechanisms, including a decrease in plasma insulin levels.

4.5 Additional Antiatherogenic Effects

4.5.1 Intimal Hyperplasia

The proliferation and migration of vascular smooth muscle cells play a role in the pathogenesis and progression of atherosclerosis. Troglitazone

has been shown to inhibit VSMC growth and intimal hyperplasia.[150] In clinical trials, troglitazone reduced intimal hyperplasia in patients with type 2 diabetes, with and without coronary stent implants.[151,152] Pioglitazone shows similar effects; a significant decrease in the intima-media thickness of the carotid arteries was observed as early as 3 and 6 months after its administration in patients with type 2 diabetes.[153] Pioglitazone also reduced the VSMC density of rat carotid arterial intima induced by balloon catheterisation and had vasculo-protective effects against neointimal thickening and hypertensive vascular hypertrophy.[154,155] New insights show that pioglitazone is a potent inducer of apoptosis in vascular lesions. Furthermore, thiazolidinediones inhibit VSMC migration mediated by multiple chemoattractants and attenuate the development of intimal hyperplasia in animal models of balloon catheter vascular injury.[156] The underlying mechanism of a reduction in intimal hyperplasia by thiazolidinediones is not known but improved insulin sensitivity may play an important role.[157]

4.5.2 Effects on the Prothrombotic State

Increased levels of the inhibitor of fibrinolysis, plasminogen activator inhibitor-1 (PAI-1), create a prothrombotic state. Levels of PAI-1 are increased in patients with type 2 diabetes and are strongly correlated with body mass index, insulin resistance and fasting levels of insulin, triglycerides and HDL cholesterol. So far, only troglitazone has been shown to reduce PAI-1 to near-normal levels in patients with diabetes.[158] Pioglitazone decreases PAI-1 production in cultured human umbilical vein endothelial cells *in vitro*.[159]

Thus, thiazolidinediones may have favourable effects on cardiovascular events by improvement of the prothrombotic state.

5. Special Considerations

Thiazolidinedione treatment is associated with some undesirable effects. Some of these adverse effects need further consideration.

5.1 Increase in Bodyweight

Gain of bodyweight is a dose-dependent adverse effect of thiazolidinediones, whether administered alone or in combination with other antihyperglycaemic agents, especially sulphonylureas.[160] The weight gain, 4kg on average, plateaus after 6 months. Despite the weight gain, thiazolidinediones clearly decrease insulin resistance as discussed in section 3. An increased fat mass consisting of small adipocytes and increased plasma volume have been proposed to explain these observations.

5.1.1 Increased Fat Mass

It is believed that the thiazolidinedione-induced differentiation of adipocytes and adipogenesis, as discussed in section 3.1, may be partly responsible for the increase in bodyweight seen in humans and animals.[161,162]

In humans, long-term troglitazone treatment results in increased accumulation of subcutaneous fat without a change in the total amount of visceral fat, probably because of the activation of PPAR-γ subcutaneously.[163] Thus, troglitazone appears to promote fat accumulation in subcutaneous adipose tissue rather than in visceral adipose tissue, which may have little impact on atherogenesis.[164] One study even shows that troglitazone treatment of patients with type 2 diabetes decreases the intra-abdominal fat mass but does not affect the total body fat mass or bodyweight.[165]

Thus, increased adipocyte differentiation associated with increased bodyweight may not be as harmful as first thought, but the clinical significance of this modest weight change will require further evaluation in long-term studies.

5.1.2 Increase in Plasma Volume

The weight gain caused by thiazolidinedione treatment is also associated with an increase in the plasma volume, which occurs whether thiazolidinediones are administered alone or in combination with metformin or sulphonylureas. Again, there is a paradox because thiazolidinediones cause a substantial decrease in blood pressure while increasing plasma volume. An explanation

could be the effects of thiazolidinediones on down-regulation of endothelin-1, a potent vasoconstrictor.[166] As a consequence of an increased plasma volume, haemoglobin and haematocrit levels are decreased. These haematological alterations are observed during the first weeks of therapy but do not change further thereafter.

Because of this plasma volume expansion, thiazolidinediones are not recommended for patients with heart failure (New York Heart Association class III or IV).

5.2 Hepatotoxicity

As mentioned in section 2, troglitazone was withdrawn from the market because of an increased risk of idiosyncratic hepatic toxicity. Three cases of severe hepatotoxicity have recently been reported with rosiglitazone.[167,168] It is uncertain whether the drug directly induces these hepatic disturbances. All patients recovered fully after discontinuing treatment. Currently, no cases of pioglitazone-induced severe hepatotoxicity have been reported but it must be realised that there is considerably less clinical experience with rosiglitazone and pioglitazone than with troglitazone. The largest study conducted so far shows no evidence of hepatotoxic effects observed in studies that involved 5006 patients taking rosiglitazone as monotherapy or combination therapy for 5508 person-years.[169] These findings suggest that the idiosyncratic liver toxicity observed with troglitazone is unlikely to be a thiazolidinedione class effect.

Patients with poorly controlled type 2 diabetes may have moderate elevations of serum alanine transferase (ALT) that will decrease with improved glycaemic control during treatment with rosiglitazone or other antihyperglycaemic agents. Thiazolidinediones should not be given to patients with signs of serious hepatic dysfunction. However, in patients with non-alcoholic steatohepatitis and small increases in plasma transaminases, thiazolidinediones may be particularly useful because of their beneficial effects on visceral fat accumulation; regular monitoring of plasma transaminases is recommended in these patients.

5.3 Effects on Gonadal Function in Women

Since the increased insulin sensitivity induced by thiazolidinediones is associated with an improvement of ovulation and fertility in woman with polycystic ovary syndrome (PCOS) and with an increased estrogen clearance in pre- and postmenopausal women, caution should be taken in women receiving oral contraceptives or hormone replacement therapy. Medications with a higher estrogen content may be beneficial to avoid the possibility of reduced effectiveness. Thiazolidinediones should not be administered to women during pregnancy and breast-feeding since it is not known whether these drugs have teratogenic effects or are secreted in human breast milk.

5.4 Drug Interactions

Pioglitazone induces the cytochrome P450 (CYP) isoenzyme CYP3A4, and thus physicians should be cautious when prescribing pioglitazone to patients receiving other drugs metabolised by this isoenzyme. In contrast, rosiglitazone does not induce CYP hepatic enzymes, and thus no CYP-related drug interactions have been reported.

6. Conclusion

The co-occurrence of metabolic disorders such as type 2 diabetes, dyslipidaemia, hypertension, hypercoagulability, vasculopathy, obesity and atherosclerotic disease, and the central role of insulin resistance in this cluster, provide a target to potentially reduce vascular incidents. Until now these vascular risk factors have been treated separately and thus patients often need polypharmacy. Obviously, insulin resistance plays a key role and pharmacological intervention aimed at the insulin resistance syndrome may therefore have beneficial effects on several cardiovascular risk factors, resulting in a decreased risk of future cardiovascular disease.

Thiazolidinediones are uniquely able to exert direct beneficial effects on insulin resistance by binding to PPAR-γ and probably to PPAR-α. As transcription factors, PPARs regulate the expres-

sion of numerous genes with key roles in glucose and lipid metabolism. In addition, activation of PPARs could improve vascular function and inflammatory processes resulting in additional vascular effects.

Several issues are yet to be resolved. The apparent paradox of adipocyte differentiation with weight gain concurring with the insulin-sensitising effects of thiazolidinediones is not completely understood. The thiazolidinedione-induced decrease in blood pressure accompanied by an increase in the plasma volume has not been fully explained. The discrepancy of the stimulation of expression of CD36 and the antiatherogenic effect of the thiazolidinediones also needs to be further explained. It would be interesting to know whether thiazolidinediones act directly by activating PPAR-γ or stimulate PPAR-α activity at the same time, which could also explain the broad metabolic and additional vascular effects of thiazolidinediones. An important issue that needs to be resolved is the importance of raised cholesterol levels, in particular raised LDL levels, caused by some thiazolidinediones. Future research may provide answers to these questions, particularly with respect to the role of PPAR-γ in vascular pathophysiology. Although the concept of thiazolidinediones is very promising, long-term clinical trials concerning cardiovascular end points are needed.

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Correspondence and offprints: Dr *Fabrice M.A.C Martens*, Department of Internal and Vascular Medicine, University Medical Center Utrecht, Room F.02.126, Heidelberglaan 100, PO Box 85500, Utrecht, 3508 GA, The Netherlands.
E-mail: F.M.A.C.Martens@azu.nl