PPAR-γ Agonists: Shifting Attention from the Belly to the Heart?

Jeroen P.H. van Wijk, Ton J. Rabelink

Second generation thiazolidinediones (TZDs), synthetic ligands for the peroxisome proliferator activated receptor-γ (PPAR-γ), have recently been introduced in clinical medicine to improve insulin resistance in type 2 diabetes. The two isoforms of PPAR-γ are preferentially expressed in adipose tissue, and the improvement of insulin resistance in skeletal muscle and liver tissue is probably secondary to enhanced lipid storage in subcutaneous adipocytes and improved adipocyte function, as reflected by the altered secretion of adipocytokines. These effects are mediated by receptor-dependent activation of the PPAR-γ-retinoid X receptor (RXR) complex and subsequent transcriptional activation of target genes. The PPAR-γ-1 isoform is also expressed in endothelial cells, vascular smooth muscle cells (VSMCs), and monocytes/macrophages in the vasculature. PPAR-γ agonists have been shown to have interesting effects on these cells, which appear to be partially independent of the PPAR-γ-RXR-mediated transcriptional effects. For example, in endothelial cells, TZDs have been shown to enhance endothelial nitric oxide synthase (eNOS) activity by phosphorylation and to inhibit leukocyte–endothelial cell interaction. TZDs inhibit growth factor–induced proliferation and migration of VSMCs. Also in vivo, in a model of angiotensin II induced hypertension, TZDs could normalize endothelial function and correct structural vascular abnormalities. In monocytes/macrophages, TZDs upregulate the scavenger receptor CD36 and induce the cholesterol efflux pump ATP-binding cassette, subfamily A, member 1 (ABCA1), suggesting altered lipid handling by macrophages whereby proatherogenic lipoproteins are taken up and antiatherogenic lipoproteins are generated. Finally, and perhaps most importantly, TZDs are very potent inhibitors of inflammation. There appears to be a generalized repression of NF-κB, CCAAT/enhancer-binding protein, and activator protein-1–mediated transcription of inflammatory genes. The exact mechanism is still unknown, but probably involves increased levels of corepressor molecules or transcriptional superregulation, for example by chromatin remodeling, as has been described for other nuclear hormone receptors. As a result, a broad spectrum of proinflammatory cytokines (eg, IL-6, TNF-α, G-CSF, CD40, MCP-1, MMP) as well as adhesion molecules (eg, ICAM-1, VCAM-1), inducible NOS (iNOS), and C-reactive protein are suppressed. The potent antiinflammatory actions of TZDs are also illustrated by the fact that TZDs have been used to treat primary inflammatory conditions, such as colitis. These modes of action suggest that TZDs may have important antiatherosclerotic actions. These effects can be indirect by improving insulin resistance–related metabolic risk factors. However, TZDs may also have important direct antiatherosclerotic effects, caused by repression of inflammatory transcription and resulting in restoration of endothelial function and reduced vascular (micro)inflammation.

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In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Sidhu et al describe that the TZD rosiglitazone reduces common carotid intima media thickness (IMT) progression, a well established intermediate endpoint of atherosclerotic disease progression, after 48 weeks of treatment compared with placebo in nondiabetic patients with coronary artery disease. Previous studies have demonstrated that TZDs have beneficial effects on intermediate endpoints of atherosclerosis, such as endothelial function and IMT, in type 2 diabetes. The interesting point of the study by Sidhu et al is that these effects are not confined to diabetic patients, but can be extrapolated to patients with documented coronary artery disease without manifest diabetes. Another important point of the current study is that in these high-risk patients, rosiglitazone retarded carotid IMT progression on top of statins and antihypertensive agents. These observations could be interpreted as a strong argument in favor of direct vascular effects of TZDs on atherosclerosis.

It should be noted that in patients with clinical cardiovascular disease the prevalence of the metabolic syndrome is very high, despite the absence of diabetes. We have recently reported that in such a cohort, almost half of the patients fulfilled the criteria of the metabolic syndrome (defined as 3 or more of the following: low high-density lipoprotein (HDL)-cholesterol, increased triglycerides, high blood pressure, glucose intolerance, and high waist circumference). Regrettably, there was no information about the prevalence of the metabolic syndrome in the Sidhu study, although a similar percentage would not be unlikely. For example, almost a quarter of the patients had impaired fasting glucose. This would indicate that the study group indeed could have had benfited from improved metabolic control by TZD treatment. However, only minor effects on metabolic parameters were observed. First, during rosiglitazone treatment, there...
was a small but significant reduction in homeostasis model assessment (HOMA), as a marker of insulin sensitivity, compared with placebo. HOMA is an independent predictor of cardiovascular events in both diabetic and nondiabetic patients, particularly in the case of high HOMA values. The study group in the Sidhu study had relatively low HOMA values, and rosiglitazone caused quantitatively only a minimal reduction in HOMA, which makes an important role on retarded IMT progression less likely. Second, rosiglitazone-treated patients showed a small transient increase in low-density lipoprotein (LDL)-cholesterol and triglycerides. This phenomenon is frequently observed during TZD treatment, as TZDs generally cause a shift toward larger, more buoyant LDL particles, which are less prone to oxidative modification and are therefore thought to be less atherogenic. Unfortunately, LDL density cannot be estimated in the current study, as there is no information available on apolipoprotein B. Nevertheless, in conjunction with statin treatment, there were no sustained effects overall on lipid parameters by rosiglitazone treatment, which makes a lipid-based explanation for the observed effect on atherosclerotic disease progression also less likely.

The fact that TZDs modulate atherosclerosis progression, potentially independent of metabolic changes, offers additional opportunities to improve cardiovascular risk in a broader group of high-risk patients. However, one also has to consider potential side-effects. Edema formation and expansion of the extracellular volume is found in 3% to 5% of the patients for each of the TZDs, and the incidence increases in combination with insulin. Obviously, this increased risk may give rise to concern when considering treatment with TZDs in patients with cardiovascular disease accompanied by heart failure. So far, TZDs have not been studied in patients with New York Heart Association (NYHA) class III or IV congestive heart failure (CHF) and therefore are not recommended for use in these patients. In the study by Sidhu et al, patients with CHF (NYHA class I to IV) were also excluded.

As we begin to better understand the vascular pathobiology of atherosclerosis, drugs that interfere with key processes in atherosclerosis biology, such as endothelial function and vascular (micro)inflammation, become important as they potentially allow cardiovascular risk reduction beyond treatment of a risk factor. The study by Sidhu et al provides us with clues that TZDs, drugs that were introduced primarily to treat such a risk factor (ie, insulin resistance), may have relevant clinical effects on the pathobiology of atherosclerosis.

Acknowledgments
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References
8. Diep QN, El Mabrouk M, Cohn JS, Endemann D, Amiri F, Virdis A, Neves MF, Schiffrin EL. Structure, endothelial function, cell growth, and inflammation in blood vessels of angiotensin II-infused rats: role of Putative mechanisms by which TZDs reduce atherosclerosis. TZDs can improve free fatty acid (FFA) trapping in adipocytes by altering the transcription of PPAR-γ-FXR complex-activated genes involved in FFA storage and lipolysis (e.g., aP2-adipocyte fatty acid binding protein [FABP], fatty acid transport protein 1 [FATP-1], fatty acid synthase [FAS], insulin receptor substrate-2 [IRS-2] FAS, and Acyl-coenzyme A [CoA] synthase).

Together with increased secretion of a fat-specific secreted protein (adipocyte complement-related factor 30 [Acrp30]), this leads to enhanced insulin sensitivity. There also appears to be a generalized repression of NF-κB, CCAAT/enhancer-binding protein, and activator protein-1–mediated transcription of inflammatory genes, which may result in restoration of endothelial function and reduced vascular (micro)inflammation.
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