Antiatherogenic Effects of Thiazolidinediones?

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Treatment of type 2 diabetes mellitus (DM) is directed at relieving symptoms of hyperglycemia and reducing the incidence of diabetes-associated pathologies. Complications of atherosclerosis, including myocardial infarction and stroke, are the most common causes of death in diabetic patients. Thiazolidinediones (TZDs) represent a relatively recent addition to the arsenal of pharmaceutical options for diabetes treatment. These agents are potent insulin sensitizers and significantly improve glycemic control in the majority of diabetic patients. Troglitazone, the first TZD to be marketed, has been replaced in clinical practice by the more potent TZDs, rosiglitazone and pioglitazone. There are now upwards of a million diabetic patients taking these agents in the United States, and the rising incidence of obesity and type 2 DM predicts an ever-growing patient population of patients who will be candidates for treatment with insulin sensitizers.

Given their antidiabetic actions, TZDs would be expected to reduce atherosclerotic complications. Although there are a few hints from small clinical studies that this may be the case, TZDs have not been in clinical use for sufficient time to establish their long-term effects on the development and clinical consequences of atherosclerosis in diabetic patients. In 1995, troglitazone was found to be a high-affinity ligand for the peroxisome proliferator–activated receptor-γ (PPAR-γ). There is now extensive evidence that the TZD class of molecules exerts its insulin-sensitizing effects through this receptor. PPAR-γ is a ligand-activated transcription factor that is related to receptors for steroid and thyroid hormones. In addition to regulating glucose homeostasis, it has been shown to play important roles in the development of adipose tissue. PPAR-γ exerts its biological effects by activating or repressing gene transcription, although the specific target genes that are responsible for the insulin-sensitizing effects of TZDs remain to be established.

A potential connection of PPARs to the development of atherosclerosis was first suggested by studies demonstrating that TZDs could inhibit vascular smooth muscle cell growth and intimal hyperplasia in a balloon injury model in rats. Smooth muscle cell migration and proliferation are important during the progression of atherosclerosis from early to intermediate lesions. However, the initiation of atherosclerosis is believed to involve the adhesion of monocytes to activated endothelial cells at lesion-prone sites in the artery wall. These cells subsequently migrate into the subendothelial space in response to chemotactic signals, such as macrophage chemotactic protein-1 (MCP-1), and differentiate into macrophages. This program of differentiation includes the up-regulation of scavenger receptors, including CD36 and scavenger receptor-A, that are capable of mediating the uptake of oxidized forms of LDL (oxLDL). In the presence of sufficient oxLDL, this pathway leads to formation of macrophage foam cells that are the major cellular elements of fatty streaks, the earliest recognizable atherosclerotic lesions.

Evidence that PPAR-γ might influence macrophage-dependent events in the development of atherosclerosis was initially suggested by a series of articles that appeared in 1998. PPAR-γ was demonstrated to be expressed not only in normal human monocytes and murine macrophages but also in macrophage foam cells of human and murine atherosclerotic lesions. Natural and synthetic PPAR-γ ligands were demonstrated to inhibit expression of inflammatory response genes in cultured macrophages, suggesting that PPAR-γ might play a physiological role as a negative regulator of macrophage activation. Because atherosclerosis can be considered to be a form of chronic inflammation, these observations also raised the possibility that TZDs might exert antiatherogenic effects within the vessel wall. An opposing view emerged from the discovery that the CD36 gene is a direct target of PPAR-γ and that oxidized lipids present in oxLDL can serve as activating ligands of PPAR-γ. These observations formed the basis of a hypothetical “PPAR-γ cycle,” in which stimulation of PPAR-γ would lead to upregulation of CD36, mediating increased uptake of oxLDL. OxLDL lipids brought into the cell via CD36 would complete the cycle by further stimulation of PPAR-γ activity and CD36 expression. Such a cycle was predicted to promote foam cell formation and the development of atherosclerosis.

Recent studies in which apolipoprotein E–deficient mice were crossed with CD36-deficient mice demonstrated that mice lacking CD36 developed significantly less atherosclerosis, consistent with this possibility.

The article by Law and colleagues provides a significant contribution to our understanding of atherosclerosis. Their work demonstrates that PPAR-γ ligands can influence the development of atherosclerosis in the vessel wall and that this influence can be mediated through the actions of CD36.

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Editorial
that led to marked hypercholesterolemia and mild insulin resistance. In the second dietary condition, mice were fed a high-cholesterol, high-fructose diet that led to marked hypercholesterolemia but did not induce insulin resistance. Troglita-
zone inhibited the development of atherosclerosis by 30% in the high-fat group and by 42% in the high-fructose group. Although metabolic effects cannot be excluded, morphometric analysis of the macrophage content of lesions suggested that antiatherogenic effects of troglitazone were related, in part, to decreased monocyte recruitment. Consistent with this, in vitro studies demonstrated that troglitazone inhibited trans-
endothelial migration of THP-1 monocytes in response to MCP-1. This effect may reflect the recent observation that TZDs can downregulate expression of chemokine receptor 2 (CCR2), the receptor for MCP-1, in murine and human monocytes. A potential caveat to the studies of Law and colleagues is that troglitazone contains a vitamin E moiety and could in theory inhibit the development of atherosclerosis by preventing oxidation of LDL directly. This is unlikely, however, as the equivalent dose of vitamin E received by these animals is much lower than that reported to affect atherosclerosis.

The recent article by Li et al \(^{13}\) examined the effects of rosiglitazone and the tyrosine-based PPAR-\(\gamma\) ligand GW7845 on the development of atherosclerosis in male and female LDLR\(^{-}\) mice. These mice were fed a high-fat, high-choles-
terol diet that induced marked hypercholesterolemia and mild insulin resistance, similar to the high-fat, high-cholesterol treatment group studied by Law et al. Treatment of these mice with rosiglitazone or GW7845 markedly reduced the extent of atherosclerosis in male mice. Intriguingly, these drugs had no significant effect on the development of atherosclerosis in female mice. Metabolic studies demonstrated that rosigli-
tazone and GW7845 improved insulin resistance in male mice but not in female mice. This lack of an effect is likely to reflect a species-specific difference between humans and mice, as TZDs exert insulin-sensitizing effects in women. Rosiglitazone and GW7845 also reduced HDL cholesterol levels and increased IDL and VLDL cholesterol in female mice, which may have prevented protective effects of these agents on the vessel wall. Studies of gene expression in the artery wall also indicated that rosiglitazone and GW7845 induced expression of CD36 and decreased expression of gelatinase-B and tumor necrosis factor-\(\alpha\).

In contrast, these 2 studies demonstrate that PPAR-\(\gamma\) agonists have the potential to exert potent antiatherogenic effects in animal models. It is also clear, however, that these agents exert complex effects on metabolism and the biology of the artery wall. In the case of male mice, the net effect was a significant reduction in atherosclerosis, but this was not the case in the female mice studied by Li et al. \(^{14}\) It thus cannot yet be ruled out that in some genetic or environmental back-
grounds, TZDs could actually exacerbate atherosclerosis. It will therefore be of importance to evaluate the influence of rosiglitazone and pioglitazone on the development of athero-
sclerosis in human patients who are currently taking these drugs. These observations also suggest that opportunities exist for the development of new classes of PPAR-\(\gamma\) ligands that are selected for both insulin-sensitizing and antiathero-
genic activities. There is good reason to think that this may be possible, based on the development of selective estrogen receptor modulators that exert proestrogenic effects on some genes and antiestrogenic effects on others.\(^{15,16}\) PPAR-\(\gamma\) li-
gands with potent antiatherogenic activities might ultimately be considered for use not only in patients with type 2 DM but also in nondiabetic patients who are at high risk for develop-
ment of atherosclerosis due to other constellations of risk factors.

References

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