Rosiglitazone Attenuates Atherosclerosis in a Model of Insulin Insufficiency Independent of Its Metabolic Effects

Anna C. Calkin, Josephine M. Forbes, Craig M. Smith, Markus Lassila, Mark E. Cooper, Karin A. Jandeleit-Dahm, Terri J. Allen

Objectives—Recent studies have demonstrated a role for thiazolidinediones in attenuating atherosclerosis. However, these studies were performed in insulin-resistant animal models in association with reductions in insulin and glucose levels. To assess the vascular effects of thiazolidinediones, independent of their metabolic effects, we observed the effect of rosiglitazone on diabetes-associated atherosclerosis in a model of insulin insufficiency.

Methods and Results—Control and diabetic apolipoprotein E–deficient mice received rosiglitazone or placebo. Diabetic mice demonstrated a 3-fold increase in plaque area, which was attenuated by rosiglitazone. There was no significant difference in glucose, insulin, or cholesterol levels between treated and untreated diabetic animals. Rosiglitazone attenuated the increase in superoxide production observed in diabetic mice. A 4-fold increase in the reverse cholesterol transport marker ABCA1 was observed in treated diabetic mice. Rosiglitazone reduced angiotensin II receptor gene expression in control and diabetic mice, and macrophage accumulation was increased in diabetic mice compared with controls and was attenuated by rosiglitazone.

Conclusions—These findings suggest peroxisome proliferator-activated receptor-γ ligands such as rosiglitazone confer vascular protection independent of their effects on metabolic control. These antiatherosclerotic effects may have important clinical ramifications not only in insulin resistance/type 2 diabetes and also in type 1 diabetes. (Arterioscler Thromb Vasc Biol. 2005;25:1903-1909.)

Key Words: ABCA1 ■ atherosclerosis ■ diabetes ■ macrophages ■ oxidative stress
Thus the aims of this study were firstly to determine whether the PPARγ agonist, rosiglitazone, exerts antiatherogenic properties in vivo, independent of its effects on insulin sensitivity and glycemic control. This study used an animal model of insulin deficiency, streptozotocin–diabetes, in which PPARγ agonism has no significant impact on insulin and glucose levels. The second aim was to explore the potential molecular and cellular mechanisms responsible for the antiatherosclerotic effect observed with rosiglitazone.

Methods

Animals

Six-week-old male apo E−/− mice (backcrossed 20 times to a C57BL/6 background; Animal Resource Centre, Canning Vale, Western Australia) were housed at the Precinct Animal Centre, Baker Heart Research Institute, and studied according to National Health and Medical Research Council (NHMRC) guidelines. Mice were rendered diabetic via 5 daily intraperitoneal injections of streptozotocin (MP Biomedicals, Eschwege, Germany) 55 mg/kg per day, resulting in a model of insulin deficiency. Control animals received vehicle (citrate buffer) alone. Control and diabetic mice were randomized to rosiglitazone (20 mg/kg per day) by gavage or no treatment for 20 weeks (n=30/group). Animals received standard mouse chow and water ad libitum. Mice were bled by euthanasia using intraperitoneal injection of Euthal (10 mg/kg) (Delvet Limited, Seven Hills, Australia), followed by exsanguination by cardiac puncture. Excised aortas were placed in 10% neutral buffered formalin and quantitated for lesion area before being processed for immunohistochemical analysis. In a subset of animals, aortas were used fresh for measurement of oxidative stress markers or snap-frozen in liquid nitrogen (LN2) and stored at −70°C for subsequent RNA extraction.

Metabolic Parameters

Red blood cells were collected for measurement of glycohemoglobin by high-performance liquid chromatography.19 Plasma glucose, high-density lipoprotein (HDL) cholesterol, total cholesterol, and triglycerides were measured using an automated system (Abbott Architect ci8200; Abbott Laboratories, Abbott Park, Ill), and low-density lipoprotein (LDL) cholesterol was calculated according to Friedewald formula.20 Fasting plasma insulin was determined by a radioimmunoassay (Linco Research, St Charles, Minn).

Plaque Area Quantitation

Plaque area was quantitated as described previously.21 Aortas removed from mice were cleaned of excess fat under a dissecting microscope and subsequently stained with Sudan IV-Herxheimer’s solution (0.5% wt/vol) (Gurr; BDH Limited, Poole, UK). Aortas were dissected longitudinally, divided into arch, thoracic, and abdominal segments, and pinned flat onto wax. Images were acquired with a dissecting microscope equipped with an AxioCam camera (Zeiss, Heidelberg, Germany). Total and segmental plaque area was quantitated as a percentage area of aorta stained (Adobe Photoshop version 7.0). Tissue was subsequently embedded in paraffin and sections cut for immunohistochemical analysis.

Vascular Superoxide Production

Vascular superoxide was quantitated by lucigenin-enhanced chemiluminescence as established by Omar et al.22 Freshly excised aortas were cleaned of peripheral fat in chilled Krebs buffer, cut into 2-mm sections, and placed in a 96-well plate such that aortic origin (arch, thoracic, or abdominal) was randomized. NADH (125 μmol/L) or NADPH (125 μmol/L) was added to wells with either diphenylene iodinium (30 μmol/L), an inhibitor of NAD(P)H oxidase, or rotenone (100 μmol/L), a mitochondrial complex I inhibitor, respectively (Sigma-Aldrich, St Louis, Mo). Lucigenin (Sigma-Aldrich) was added to a final concentration of 3.75 μmol/L. Luminescence measurements were taken at 6-minute intervals for a period of 60 minutes and results were averaged per well and expressed as relative light units (RLU) per 10 mg.

Real-Time Reverse-Transcription Polymerase Chain Reaction

Total RNA was extracted from whole aorta by homogenizing (Polytron PT-MR2100; Kinematica AG) in Trizol (Life Technologies, Rockville, Md). Total RNA was then DNase-treated (DNA removal kit; Ambion, Austin, Tex) and cDNA was synthesized by reverse transcription (Pierce, Rockford, Ill). Quantitative real-time reverse-transcription polymerase chain reaction was performed using the Taqman System as described previously on an ABI Prism 7700 Sequence Detector (Applied Biosystems, Foster City, Calif) and analyzed using software detection systems (SDS version 1.9) software. Gene expression was normalized to 18S rRNA (Applied Biosystems). For detailed information on probes, please see http://atvb.ahajournals.org.

Immunohistochemistry

Serial sections were stained for gp91phox, CuZnSOD, and p47phox using a standard immunohistochemical procedure as previously described.3 Sections were incubated with primary antibody at dilutions of 1:100 for gp91phox (Santa Cruz Biotechnology, Santa Cruz, Calif), 1:50 for CuZnSOD (Sigma-Aldrich) or 1:500 for p47phox (Upstate Biotechnology, Charlottesville, Va) overnight at 4°C. Secondary antibody (Vector Laboratories, Burlingame, Calif), anti-goat immunoglobulin (1:500), anti-mouse immunoglobulin (1:250), or anti-rabbit immunoglobulin (1:500), respectively, was applied for 10 minutes at room temperature. The TSA mouse amplification kit (Dako Corporation, Carpinteria, Calif) was used to stain for macrophage marker F4/8023 (Serotec Ltd, Oxford, UK). Primary antibody was added at a dilution of 1:50 and left overnight at 4°C. Secondary antibody, anti-rat immunoglobulin (Vector Laboratories) was added at a dilution of 1:200 to sections for 15 minutes at room temperature. Images were quantitated on an Olympus BX50 microscope using Optimis (version 6.2) and digitized using a color video camera (3-charge coupled device; JVC, Wayne, NJ). Results were quantitated as percent of positively stained tissue.3

Statistical Analysis

Data were analyzed by ANOVA using Statview (version 5.0). Post-hoc comparisons were made among the various groups using Fishers least significant difference method. Data are expressed as mean±SEM unless otherwise specified. P<0.05 was considered to be statistically significant.

Results

Metabolic Parameters

At the end of the study period, diabetic mice had lower body weights than control animals (P<0.0001), and increased plasma glucose, total cholesterol, LDL cholesterol, triglyceride, and glycohemoglobin levels (Table 1). Rosiglitazone had no significant effect on body weight, glycemic control, or lipids in diabetic mice. Insulin levels were markedly reduced in diabetic compared with control mice (P<0.0001). Rosiglitazone reduced plasma insulin levels in control mice (P<0.005) but had no significant effect on insulin levels in diabetic mice.

Plaque Area

Diabetic mice had a 3-fold increase in total plaque area as compared with control mice (Figure 1A). Rosiglitazone attenuated total plaque area in both control (P<0.005) and diabetic (P<0.0001) mice when compared with their untreated counterparts. Quantitation of plaque area revealed that...
plagues were predominantly seen in the aortic arch (Figure 1B) and rosiglitazone was most effective at reducing plaque accumulation at this site.

**Inflammation**

Using F4/80 as a marker of macrophage accumulation, we investigated F4/80 staining across all groups within the present study. We demonstrated a significant increase in F4/80 staining in diabetic animals (14.6±1.8%) compared with controls (9.1±1.9%), which was attenuated by rosiglitazone treatment (6.1±1.6%; \( P<0.002 \)) (Figure 2). Furthermore, we demonstrated an increase in gene expression of the NF-κB subunit p65 in diabetic mice, which was attenuated by rosiglitazone (Table 2).

**Lipid Regulation**

Gene expression of the ATP-binding cassette transporter A1, ABCA1, was significantly increased in rosiglitazone-treated diabetic animals compared with all other groups (\( P<0.02 \)) (Table 2). Using real-time reverse-transcription polymerase chain reaction, we demonstrated in our model that rosiglitazone had no effect on the regulation of the scavenger receptor, CD36, at the mRNA level (Table 2).

**Oxidative Stress**

We demonstrated that aortic tissue from diabetic mice exhibited an increase in NADPH-dependent superoxide production compared with control mice in the presence of rotenone (Figure 3). Rosiglitazone significantly attenuated NADPH-dependent superoxide production in both control and diabetic mice (\( P<0.0005 \)). There was no difference in NADH-dependent superoxide production between control and diabetic mice (data not shown). To further elucidate the regulation of NADPH-dependent superoxide production by rosiglitazone, subunit expression was analyzed. No change in gp91phox gene (Table 2) or protein expression was observed across all groups (see http://atvb.ahajournals.org). Analysis of p47phox gene expression revealed a 2.6-fold upregulation in diabetic mice compared with control mice (\( P<0.001 \)), and this was attenuated by rosiglitazone treatment (\( P<0.05 \)) (Table 2). Furthermore, immunohistochemistry revealed a diabetes-related increase in p47phox protein expression, which was attenuated by rosiglitazone treatment (Figure 4).

In addition, superoxide production can increase via activation of the receptor for advanced glycation end products (RAGE)\(^{\text{24}}\) or the angiotensin II type 1 receptor (AT1).\(^{\text{25}}\) In our study, although diabetes was associated with >2.5-fold increase in RAGE gene expression, rosiglitazone had no effect on this parameter (Table 2). In contrast, AT1 gene expression was not altered in diabetic mice compared with control; however, rosiglitazone attenuated AT1 expression in both control and diabetic mice (Table 2).

**Discussion**

The current study has demonstrated that rosiglitazone, a PPARγ agonist, attenuates diabetes-associated atherosclerosis. This was observed in the absence of changes in glycemic

![Figure 1](http://atvb.ahajournals.org)
control and, most importantly, in the absence of an effect on insulin levels in diabetic apo E<sup>−/−</sup> mice. Further examination of potential mechanisms of action of rosiglitazone suggests that this attenuation in plaque area by the PPARγ agonist may be mediated through pathways involving inflammation as well as modulation of pathways linked to the generation of oxidative stress.

The apo E<sup>−/−</sup> mouse model is a well-characterized animal model of atherosclerosis, exhibiting advanced lesions when fed a high-fat diet, with a morphology similar to that seen in humans. The induction of diabetes by streptozotocin in this model has been previously established, and studies have demonstrated attenuation of atherosclerotic plaques via the inhibition of the renin-angiotensin system<sup>3,21</sup> or reduction in AGE-mediated phenomena<sup>27,28</sup> in this model. Furthermore, the changes seen in this model appear to be directly related to the increase in glucose and are not a toxic effect of streptozotocin because a recent study using a different approach to induce type 1 diabetes, viral-induced pancreatic destruction with a MCP-1 agonist may explain the reduction in macrophage homing to atherosclerotic plaques. Further examination of potential mechanisms of action of rosiglitazone acting as insulin sensitizers. Rosiglitazone had no effect on fasting insulin levels in diabetic mice because streptozotocin had induced insulin insufficiency. This lack of effect on insulin in the diabetic mice by rosiglitazone has allowed us to assess the direct vascular effects of this agent. Therefore, it is tempting to suggest that the antiatherosclerotic effects of rosiglitazone observed in the diabetic mice are essentially independent of its effects on both insulin and glucose levels. Another group has recently demonstrated that short-term treatment with rosiglitazone reduces plaque area in diabetic apo E<sup>−/−</sup> mice but did not determine whether the effects seen were linked to insulin sensitization.<sup>30</sup>

PPARγ agonists have been shown previously to reduce MCP-1, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1, and thus monocyte–macrophage homing to atherosclerotic plaques. We demonstrated in the present study that diabetes was associated with an increase in macrophage staining in the aorta. The anti-inflammatory effect of PPARγ agonists may explain the reduction in macrophage

![Figure 2](image2.png)

**Figure 2.** Representative histological sections demonstrating F4/80 staining of macrophages in aorta of (A) control (9.1 ± 1.9%), (B) diabetic (14.6 ± 1.8%), and (C) rosiglitazone-treated diabetic mice (6.1 ± 1.6%). Original magnification ×430. *P < 0.05 vs control group; † P < 0.05 vs diabetic group.

![Figure 3](image3.png)

**Figure 3.** NADPH-dependent superoxide production is shown for all groups. Data are expressed as mean ± SEM. *P < 0.05 vs control group; † P < 0.05 vs diabetic group.

![Figure 4](image4.png)

**Figure 4.** Representative histological sections demonstrating p47phox staining in the vessel of (A) control (4.9 ± 0.8%), (B) diabetic (8.4 ± 1.2%), and (C) rosiglitazone-treated diabetic mice (4.7 ± 0.6%). Original magnification ×430. *P < 0.05 vs control group; † P < 0.05 vs diabetic group.

This study has specifically investigated the direct antiatherosclerotic effects of a PPARγ agonist after long-term treatment in a model of insulin deficiency. In our study, rosiglitazone did not affect glucose levels in either control or diabetic mice. However, as anticipated, this agent significantly reduced plasma insulin levels in control mice consistent with PPARγ agonists acting as insulin sensitizers. Rosiglitazone had no effect on fasting insulin levels in diabetic mice because streptozotocin had induced insulin insufficiency. This lack of effect on insulin in the diabetic mice by rosiglitazone has allowed us to assess the direct vascular effects of this agent. Therefore, it is tempting to suggest that the antiatherosclerotic effects of rosiglitazone observed in the diabetic mice are essentially independent of its effects on both insulin and glucose levels. Another group has recently demonstrated that short-term treatment with rosiglitazone reduces plaque area in diabetic apo E<sup>−/−</sup> mice but did not determine whether the effects seen were linked to insulin sensitization.<sup>30</sup>

<table>
<thead>
<tr>
<th>TABLE 2. Gene Expression of Parameters Linked to Vascular Injury at the Conclusion of the Study</th>
<th>Parameters</th>
<th>C</th>
<th>C + R</th>
<th>D</th>
<th>D + R</th>
</tr>
</thead>
<tbody>
<tr>
<td>rac-1</td>
<td>1.2 ± 0.3</td>
<td>1.8 ± 0.6</td>
<td>4.9 ± 2.3*</td>
<td>0.6 ± 0.1†</td>
<td></td>
</tr>
<tr>
<td>p47phox</td>
<td>1.1 ± 0.2</td>
<td>1.4 ± 0.3</td>
<td>2.7 ± 0.7*</td>
<td>1.2 ± 0.2†</td>
<td></td>
</tr>
<tr>
<td>gp91phox</td>
<td>1.2 ± 0.2</td>
<td>2.9 ± 1.6</td>
<td>3.6 ± 0.5</td>
<td>4.5 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>CuZnSOD</td>
<td>1.0 ± 0.1</td>
<td>1.8 ± 1.0</td>
<td>0.9 ± 0.2</td>
<td>0.7 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>AT1</td>
<td>1.1 ± 0.2</td>
<td>0.5 ± 0.1*</td>
<td>1.4 ± 0.2</td>
<td>0.8 ± 0.1†</td>
<td></td>
</tr>
<tr>
<td>RAGE</td>
<td>1.1 ± 0.2</td>
<td>1.3 ± 0.5</td>
<td>2.6 ± 0.6*</td>
<td>2.5 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>ABCA1</td>
<td>1.0 ± 0.1</td>
<td>1.6 ± 0.6</td>
<td>2.1 ± 0.4</td>
<td>4.3 ± 1.1†</td>
<td></td>
</tr>
<tr>
<td>CD36</td>
<td>1.1 ± 0.2</td>
<td>1.0 ± 0.3</td>
<td>1.8 ± 0.4</td>
<td>2.2 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>p65</td>
<td>1.2 ± 0.2</td>
<td>1.6 ± 0.7</td>
<td>3.4 ± 1.1*</td>
<td>1.0 ± 0.3†</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SEM.

*P < 0.05 vs control group; † P < 0.05 vs diabetic group.

Arbitrary units representing gene expression as assessed by real-time reverse-transcription polymerase chain reaction (n=10 per group).
accumulation observed in the vessel wall of the diabetic mice treated with rosiglitazone.

Whereas PPARs are recognized to work through DNA-dependent mechanisms, more recent studies have shown that they may exert some of their antiinflammatory effects through the transrepression pathway, interfering with the activation of nuclear transcription factors such as nuclear factor-κB (NF-κB), STAT, and activator protein-1 (AP-1). This effect was confirmed in our study as demonstrated by a reduction in gene expression of the NF-κB subunit p65 with rosiglitazone treatment in diabetic mice.

Our study demonstrated an increase in ATP-binding cassette transporter A1 (ABCA1) gene expression in diabetic mice in association with rosiglitazone treatment. ABCA1, a mediator of reverse cholesterol transport, is involved in apolipoprotein A1–mediated cholesterol efflux from macrophages, which can lead to an increase in HDL cholesterol. PPARγ agonists have been previously shown to increase cholesterol efflux from macrophages via the ABCA1 pathway in vitro. In the current study, an increase in ABCA1 gene expression did not lead to changes in HDL levels. Thus, changes in lipoproteins do not appear to be a major mechanism, whereby rosiglitazone is mediating its antiatherogenic actions. This interpretation is consistent with previous studies exploring links between PPARγ agonists and ABCA1 expression in vivo. Although in vitro studies had suggested that PPARγ agonism promotes ABCA1 expression, such an effect was not observed in vivo in that study.

PPARγ agonists have also been demonstrated to influence macrophage biology by regulation of the scavenger receptor CD36. CD36 is responsible for the uptake of oxidized LDL, which is itself a ligand for PPARγ. This leads to increased expression of CD36, a target gene for PPARγ. However, in vivo studies have demonstrated that despite an increase in CD36 expression, troglitazone, another TZD, caused attenuation of fatty streak formation in high-fat–fed apo E−/− mice. Thus, controversy has surrounded the role of PPARγ in macrophages biology. In the current study, we demonstrated no change in CD36 expression in response to PPARγ activation by rosiglitazone in the setting of a clearly documented antiatherosclerotic effect of this agent.

Oxidative stress leads to an upregulation of adhesion molecules, acceleration of foam cell formation, reduced plaque stability, and endothelial dysfunction. In the current study, we observed an increase in exogenous NADPH-stimulated superoxide production, (inhibitable by apocynin and DPI) in aortas from diabetic mice. This effect was attenuated by rosiglitazone, consistent with previous literature demonstrating a role for PPARγ agonists in reducing oxidative stress in such settings as human endothelial cells, hypercholesterolemic rabbits, and obese subjects.

Hyperglycemia per se has been associated with an increase in oxidative stress. Rosiglitazone had no significant effect on plasma glucose levels in this study, suggesting that the rosiglitazone effect did not occur via direct effects on glucose-induced upregulation of oxidative stress. RAGE expression was investigated because of previous findings that, first, RAGE activation increases oxidative stress and, second, that rosiglitazone, albeit in a cell culture medium, modulates RAGE expression. However, in the current study, RAGE gene expression was unaltered by rosiglitazone treatment.

Previous studies have shown that PPARγ agonists can modulate expression of NAD(P)H oxidase subunits as well as antioxidant expression. In the current study, we demonstrated that rosiglitazone attenuated the increase in expression of p47phox observed in diabetic mice, an effect previously shown in vitro in endothelial cells. Similarly, diabetes was associated in a marked increase in rac-1, which was also abrogated by rosiglitazone. Rac is a GTPase involved in NAD(P)H oxidase activation, and its inhibition has been associated with reductions in angiotensin II–mediated oxidative stress. This may further contribute to the reduction in superoxide production observed in rosiglitazone-treated diabetic mice.

Angiotensin II has been shown to increase reactive oxygen species through modulating NAD(P)H-dependent pathways, and inhibition of angiotensin II via AT1 blockade results in a reduction in superoxide production. Interestingly, angiotensin II has been shown to regulate p47phox expression. Thus, inhibition of angiotensin II–mediated superoxide production via downregulation of the angiotensin II receptor, as seen in response to rosiglitazone in this study, may be a major mechanism responsible for the reduction in superoxide production seen with rosiglitazone treatment. Whereas no change in gp91phox expression was observed in the current study, there may have an alteration in other isoforms shown to be expressed in the vasculature, including nox1 or nox4.

Previous studies have demonstrated an upregulation of the RAS in the vessel wall in diabetic apo E−/− mice and blockade of the RAS either via AT1 blockade or via angiotensin-converting enzyme inhibition has been demonstrated to attenuate plaque formation in apoE−/− mice. Angiotensin II has been reported to increase plaque area 6-fold in apo E−/− mice fed an atherogenic diet. Angiotensin II has also been demonstrated to mediate effects on monocyte recruitment, foam cell formation, and inflammation. Furthermore, angiotensin II has been demonstrated to mediate proinflammatory effects via the activation of NF-κB. In the current study, the finding that rosiglitazone attenuated AT1 gene expression further emphasizes the potential role of the vascular renin-angiotensin system in atherogenesis, including in the context of diabetes. The antiinflammatory effects mediated by rosiglitazone as observed by F4/80 staining may be mediated via downregulation of AT1 expression. This effect in vivo on expression of this receptor subtype is consistent with previous studies demonstrating that PPARγ agonists reduce AT1 receptor promoter activity. It remains to be determined if this indirect effect via interruption of the RAS, specifically the angiotensin II receptor 1 subtype, or a direct effect of the PPARγ agonist on NF-κB/κB regulation plays the dominant role in mediating the antiatherogenic effects of rosiglitazone. Ultimately, it would be of interest to assess if these effects seen with rosiglitazone treatment lead to improvements in endothelial function. This issue warrants further investigation to determine whether the molecular and cellular events observed in this study ultimately translate to improved vascular function.
Rosiglitazone also attenuated atherosclerosis in control mice. Treatment in these animals was associated with reductions in AT1 receptor and superoxide production and an increase in the antioxidant CuZnSOD. The beneficial effects seen in control mice may partly be caused by insulin-sensitizing effects of this agent, as has been previously reported with PPARγ agonists in high-fat-fed LDLR−/− mice.16,17 and apo E−/− mice.18

There are now a small number of clinical studies investigating the effect of PPARγ agonists in patients with and without diabetes on cardiovascular risk factors and, in particular, on endothelial function, a well-recognized marker of atherosclerosis.45–47 However, although PPARγ agonism was associated with improvement in cardiovascular risk, even in those patients without diabetes, concomitant changes in insulin sensitivity and/or glycemic control as measured by fasting insulin levels, HbA1c, or the HOMA-R index were observed. Whereas those studies support our experimental findings, they still were unable to differentiate whether the effects of these PPARγ agonists on cardiovascular risk are independent of alterations in insulin sensitivity. We consider that the in vivo animal studies described have led to further characterization of the mechanisms of action of these drugs, which are now so widely administered as part of the treatment regimen for type 2 diabetes.

Further studies are required to fully elucidate the effect of PPARγ agonists on atherosclerosis. Currently, we await the outcome of a large number of long-term clinical trials, including ADAPT,48 PROACTIVE,49 and DREAM.50 These studies will greatly assist clinicians in determining the future role of PPARγ agonists in the treatment of cardiovascular disease. Nevertheless, if PPARγ agonists can be shown to have vascular benefits independent of their effects on glucose homeostasis, it is predicted that these agents may also be useful in other clinical settings such as in type 1 diabetes or even in the absence of insulin resistance.

Acknowledgments

A.C.C. is a recipient of a postgraduate scholarship from the National Heart Foundation. J.M.F. is a recipient of a JDRF Career Development Award. M.L. is supported by grants from the Finnish Academy, Einar, and Karin Stroom’s Foundation, the Helsingin Samomat Centennial Foundation, and the Puuvo Nuomi Foundation. K.A.J.D. is a recipient of a National Heart Foundation Fellowship. T.J.A is an RD Wright Fellow of the National Health & Medical Research Council. Reproduction of color figures was sponsored by GlaxoSmithKline (Australia). We thank Josefa Pete, Chris Tikellis, Vicki SmithKline, and Gavin Langmaid for their expertise in caring for the animals. We thank Paula Aldersea, Sandra Miljavec, and Gavin Langmaid for their expertise in caring for the animals for the duration of the study.

References

1. International Diabetes Federation http://www.idf.org/home/index.cfm?


4. Spiegelman BM. PPAR-gamma: adipogenic regulator and thiazo-


14. Tao L, Liu HR, Gao E, Tong ZP, Lopez BL, Christopher TA, Ma XL, Batincic-Haberle I, Willette RN, Ohiestein EH, Yue TL. Antiadhesive, antinflammatory, and vasculoprotective effects of a peroxisome proliferator-


20. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentra-

21. Candido R, Allen TJ, Lassila M, Cao Z, Thallas V, Cooper ME, Jandelet-Dahn KA. Irbesartan but not amlodipine suppresses diabetes-

22. Omar HA, Cherry PD, Mortelliti MP, Burke-Wolin T, Wolin MS. Inhi-

23. Kazriel WA, Dawson TC, Quinones M, Garavito E, Chenaux G, Ahuja SS, Reddick RL, Maeda N. CCR5 deficiency is not protective in the early


Rosiglitazone Attenuates Atherosclerosis in a Model of Insulin Insufficiency Independent of Its Metabolic Effects
Anna C. Calkin, Josephine M. Forbes, Craig M. Smith, Markus Lassila, Mark E. Cooper, Karin A. Jandeleit-Dahm and Terri J. Allen

Arterioscler Thromb Vasc Biol. 2005;25:1903-1909; originally published online July 14, 2005; doi: 10.1161/01.ATV.0000177813.99577.6b
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/25/9/1903

Data Supplement (unedited) at:
http://atvb.ahajournals.org/content/suppl/2005/07/14/01.ATV.0000177813.99577.6b.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/