Statins have proven clinical benefits through a reduction in low-density lipoprotein (LDL) cholesterol levels and cardiovascular events in hypercholesterolemic and normolipidemic patients (1,2). Some of the clinical benefits of statin therapy seem to occur even at normolipidemic conditions and before significant cholesterol reduction (3). This has led many to postulate the existence of lipid-dependent and lipid-independent (pleiotropic) mechanisms for the observed clinical benefits of statin therapy. Statins may reduce the plaque lipid content, decrease the inflammation burden, and strengthen the fibrous cap, resulting in stabilization of vulnerable coronary lesions (4,5). Recent human studies have shown regression and stabilization of lipid-rich plaques by statins (6–9).

Despite the significant clinical benefits of statins (up to 35% reduction in cardiac events), investigators are seeking more effective agents and combinations that may improve current standard therapy.

Peroxisomal proliferator-activated receptors (PPARs) are nuclear receptors that act as ligand-activated transcription factors. The PPARs control the expression of specific target genes and regulate a variety of cellular functions. The subfamily member PPAR-gamma plays a central role in adipogenesis and lipid metabolism and is highly expressed in endothelial cells, vascular smooth muscle cells (SMCs),...
lymphocytes, and macrophages (10). In early human atheromatous lesions, PPAR-gamma is present in intimal macrophages (foam cells) and SMCs (11,12).

The PPAR-gamma activators reduce plaque inflammation (13,14) by inhibiting the activation of several pro-inflammatory genes responsible for plaque development and growth, decreasing expression of adhesion molecules (15) and synthesis of cytokines (14), and reducing production of matrix metalloproteinases (MMPs) (11). The PPAR-gamma activators reduce plasminogen activator inhibitor-1 levels (16) and fibrinogen concentrations and enhance fibrinolysis (17). They also reduce endothelin-1 production (18), a potent vasoconstrictor and important atherogenic stimulus. Activation of PPAR-gamma upregulates the expression of the scavenger receptor class B type I human homologue (CLA-1/SR-BI) (19), adenosine triphosphate–binding cassette transporter-1, and apolipoprotein A-I. Therefore, PPAR-gamma agonists may facilitate reverse cholesterol transport from the plaque to the liver. These data suggest that PPAR-gamma agonists may have anti-atherogenic effects such as plaque stabilization and regression (20). Two structurally different synthetic PPAR-gamma ligands have been shown to inhibit the development of lesions in LDL-receptor knockout (KO) mice (21). At the clinical level, oral hypoglycemic insulin sensitizers (glitazones), which act as PPAR-gamma ligands, were shown to decrease intimal thickening in human carotid arteries (22).

High-resolution magnetic resonance imaging (MRI) is a novel, noninvasive, and safe technique that allows serial monitoring of atherosclerotic plaques in vivo, over time, and constitutes a powerful research tool to study progression and regression of atherosclerosis in vivo (9,23–27).

The aim of this study was to evaluate the effects of simvastatin and a direct and selective PPAR-gamma agonist (L-805645), as well as their combination, in atherosclerotic rabbits using serial MRI and histology. To test the hypothesis that statin and PPAR-gamma agonist therapy have lipid-independent (pleiotropic) effects, we normalized plasma lipid levels in rabbits with established atherosclerosis by administering the different drug regimens with standard chow.

**METHODS**

**Experimental model of atherosclerosis.** Aortic atherosclerosis was induced in male New Zealand white rabbits (n = 37, age 3 months, weight 3.5 ± 0.2 kg; provided by Covance, Princeton, New Jersey) by a combination of a nine-month high-cholesterol (HC) diet, a 0.2% cholesterol-enriched rabbit diet (Research Diets Inc., New Brunswick, New Jersey), and aortic double-balloon denudation injury. This approach generates aortic lesions with fibrous- and lipid-rich components similar to those observed in humans. Aortic injury was performed after one month and again at three months of starting the HC diet from the top of the aortic arch to the iliac bifurcation using a 4F Fogarty embolectomy catheter introduced through the iliac artery, as previously described (26,28). All procedures were performed under general anesthesia by an intramuscular ketamine injection (20 mg/kg, Fort Dodge Animal Health, Fort Dodge, Iowa) and xylazine (10 mg/kg, Bayer Corp., Shawnee Mission, Kansas). Complete plasma lipid profiles were analyzed at the time of MR imaging. The study protocol was approved by the Internal Review Board of the Mount Sinai School of Medicine.

**Experimental design (Fig. 1).** During induction of atherosclerotic lesions, the rabbits were maintained on an HC diet and underwent aortic balloon denudation injuries at one and three months. The induction period lasted for nine months, after which all animals underwent a baseline MRI scan of the aorta. Six rabbits were euthanized and processed for histopathology, serving as the atherosclerosis control group. The remaining 31 animals were randomized into five groups followed for an additional six months. The HC diet group (n = 6) continued on the atherogenic HC diet without active drug therapy to determine atherosclerosis progression. The normal chow (NC) diet group (n = 6) received normal rabbit chow without active drug therapy. The NC plus simvastatin group (n = 6) received normal rabbit chow supplemented with simvastatin (5 mg/kg per day). The dose of simvastatin selected in this study is the most commonly used in studies of experimental atherosclerosis in the rabbit model. The NC plus PPAR-gamma agonist group (n = 7) received normal rabbit chow supplemented with the selective PPAR-gamma agonist L-805645 (2–2–4-phenoxy-2-propylphenoxyethyl indole-5-acetic acid; 5 mg/kg per day). The NC plus simvastatin plus PPAR-gamma agonist group (n = 6) received normal rabbit chow supplemented with both simvastatin (5 mg/kg per day) and selective PPAR-gamma agonist (5 mg/kg per day). The treatment continued for six months in each group. Simvastatin and the selective PPAR-gamma agonist L-805645 were provided by Merck & Company (Rathway, New Jersey), and all diets were supplied by Dyets Inc. (Bethlehem, Pennsylvania).

**Magnetic resonance imaging.** The rabbits underwent serial MRI of the aorta on two occasions: immediately before randomization (atherosclerosis baseline, 9 months after atherosclerosis induction by HC diet and balloon injury) to

<table>
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<th>Abbreviations and Acronyms</th>
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<tr>
<td>COX-2 = cyclooxygenase-2</td>
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<tr>
<td>HC = high-cholesterol</td>
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<tr>
<td>KO = knockout</td>
</tr>
<tr>
<td>LDL = low-density lipoprotein</td>
</tr>
<tr>
<td>MMP = matrix metalloproteinase</td>
</tr>
<tr>
<td>MRI = magnetic resonance imaging</td>
</tr>
<tr>
<td>NC = normal chow</td>
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<tr>
<td>PBS = phosphate-buffered saline</td>
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<tr>
<td>PPAR = peroxisomal proliferator-activated receptor</td>
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<tr>
<td>SMC = smooth muscle cell</td>
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<td>VWA = vessel wall area</td>
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assess the degree of atherosclerotic burden and at the end of the six-month treatment. Each animal served as its own control, and true serial data on progression/regression of atherosclerosis in rabbit aortas were obtained. A 1.5-tesla (T) MRI system (Signa CV/i, GE Medical Systems, Milwaukee, Wisconsin) with enhanced gradients (40 mT/m), slow rates (150 mT/m per ms), and a custom-designed “birdcage” volume coil (designed and assembled by Gabor Mizsei, Mount Sinai School of Medicine) was used. The MRI protocol used was validated in previously published work (24,25). Sequential axial images (3-mm thickness) of the aorta from the celiac trunk to the iliac bifurcation were obtained using a fast spin-echo sequence with in-plane resolution of $352 \times 352$ μm$^2$ (protein-density weighted: repetition time/echo time [TR/TE] 2,300/17 ms; T2-weighted: TR/TE 2,300/60 ms, field-of-view 9 × 9 cm, matrix 256 × 256, echo train length = 8, signal averages = 4). Fat suppression and flow saturation pulses were used as previously reported (24,25).

Analysis of MRIs. The MRIs were transferred to a Macintosh computer system for further analysis. The MRIs from the same animal at the two time-frame points were matched using distances from the renal arteries and the iliac bifurcation for registration, as previously validated (24,25). Sequential axial images (3-mm thickness) of the aorta from the celiac trunk to the iliac bifurcation were obtained using a fast spin-echo sequence with in-plane resolution of $352 \times 352$ μm$^2$ (protein-density weighted: repetition time/echo time [TR/TE] 2,300/17 ms; T2-weighted: TR/TE 2,300/60 ms, field-of-view 9 × 9 cm, matrix 256 × 256, echo train length = 8, signal averages = 4). Fat suppression and flow saturation pulses were used as previously reported (24,25).

Histopathology and immunohistochemistry. The rabbits were euthanized by a 5-ml intravenous injection of “Sleep-away” (Fort Dodge Animal Health) within 24 h of the follow-up MRI. Heparin (100 U/kg) was injected intravenously 5 min before euthanasia to prevent postmortem thrombosis. The aortic root was cannulated, and the aorta was immediately flushed with 250 ml physiologic buffer (0.1 mol/l phosphate-buffered saline [PBS], pH 7.4). The ascending aorta, arch, and thoracic aorta were excised, and samples were snap-frozen in liquid nitrogen or embedded in medium for frozen-tissue specimen to ensure an optimal cutting temperature (Tissue-Tek Sakura Finetek USA Inc., Torrance, California) for immunohistologic assays.

The abdominal aorta was further flushed with 250 ml PBS (pH 7.4), followed by perfusion fixation with 250 ml of cold (4°C) 4% paraformaldehyde in PBS at 100 mm Hg. After perfusion fixation, the abdominal aorta was immersed in fresh fixative and stored at 4°C. Serial sections of the aorta immediately following the origin of the left renal artery were cut at 3-mm intervals to match the MRIs. Specimens were paraffin-embedded, serial 5-μm-thick sec-
tions were cut, and one section stained with combined Masson’s trichrome elastin stain. Additional sections were stained immunohistochemically with anti-α–actin antibodies for vascular SMCs (Dako, Copenhagen, Denmark) and monoclonal mouse anti-RAM-11 antibodies for macrophages (Dako, Carpinteria, California).

**Histopathologic analysis.** An observer blinded to the treatment of the various rabbit groups performed the immunohistochemical analysis using a computer-based quantitative color image analysis system (Image Pro-Plus, Media Cybernetics). The percentage of the stained area for each section was measured.

**Activity of MMP by gel zymography.** The MMP activity was assessed by gelatin zymography of aortic arch tissue using a 7.5% acrylamide gel containing 0.2% gelatin, as previously described (29). In brief, the aortic samples were homogenized. After electrophoresis, the substrate gels were soaked twice with Triton-X-100 solution (2.5%) for 30 min at room temperature to remove sodium dodecyl sulfate. The gels were then incubated in 50 mmol/l Tris-HCl (pH 7.4, 0.15 mol/l NaCl, 5 mmol/l CaCl2, 0.02% NaN3) and then 0.01% bromophenol blue for 24 h at 37°C. The lysis of the gelatin substrate in the gels was visualized by staining with 2.5% Coomasie blue (Sigma Chemical Co., St. Louis, Missouri). Gels were digitalized to the computer, and a computer-based quantitative image analysis of the bands was performed using a standard application of the National Institutes of Health (Bethesda, Maryland) Image 1.6. The observer was blinded to the treatment of the rabbits.

**Statistical analysis.** The average of the measurements for each rabbit (MRI was used for VWA and immunohistologic staining for plaque composition) was computed, and the analyses were performed for each animal. The paired Student *t* test was used to compare the value within the group (end of follow-up vs. atherosclerosis baseline). A comparison between the follow-up groups was performed using an overall model error and a Bonferroni adjustment for multiple comparisons (matrix of pairwise mean differences; adjusted for 10 comparisons to assess the difference between the 5 study groups and for 6 comparisons to assess the difference between the 4 groups that resumed a normal diet). When comparing the individual group mean values, we used the mean squared error and the associated degrees of freedom from the overall analysis of variance on the group mean values. We did this to take advantage of the greater statistical power afforded by estimating error from all the subjects rather than just those in the two groups involved in a comparison. All values are expressed as the mean value ± SEM or percent changes from atherosclerosis baseline (corresponding to the time of randomization). A p value <0.05 was considered as statistically significant.

**RESULTS**

**Effects on plasma cholesterol levels.** The administration of the cholesterol-enriched diet during the atherosclerosis induction period was associated with a significant increase in plasma cholesterol levels. At randomization, after nine months of HC diet, the mean plasma cholesterol level of all rabbits was 645 ± 57 mg/dl and did not differ significantly among groups. Plasma cholesterol levels remained elevated in the HC diet group throughout the study duration. In the remaining groups receiving the NC diet, plasma cholesterol levels significantly dropped, reaching the normal range for this animal model, independent of the treatment group (Table 1).

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Atherosclerosis Baseline (mg/dl)</th>
<th>End of Treatment (mg/dl)</th>
<th>p Value</th>
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<tr>
<td>Atherosclerosis control</td>
<td>712 ± 69</td>
<td>—</td>
<td>NS</td>
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<tr>
<td>HC diet</td>
<td>630 ± 125</td>
<td>526 ± 108</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NC diet</td>
<td>861 ± 143</td>
<td>27 ± 10</td>
<td>&lt;0.001</td>
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<tr>
<td>NC diet plus simvastatin</td>
<td>499 ± 85</td>
<td>11 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NC diet plus PPAR-gamma agonist</td>
<td>707 ± 82</td>
<td>37 ± 15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NC diet plus simvastatin plus PPAR-gamma agonist</td>
<td>712 ± 81</td>
<td>15 ± 2</td>
<td>&lt;0.001</td>
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</table>

Data are presented as the mean value ± SEM.

HC = high-cholesterol; NC = normal chow; NS = not significant; PPAR = peroxisomal proliferator-activated receptor.
served as its own control, allowing evaluation of the atherosclerosis evolution course (progression/regression) over six months (Fig. 2).

VESSEL WALL AREA. At the time of randomization (atherosclerosis baseline), all groups had a similar VWA (8.45 ± 0.65 mm²) (Fig. 3A). An overall difference in VWA change induced by the treatments was seen (F ratio 7.40, p < 0.004 with HC diet; F ratio 4.43, p = 0.015 without HC diet).

The HC diet group, which received an additional six months of 0.2% cholesterol-enriched diet, had significant progression of the aortic atherosclerotic lesions (Fig. 3A), with an increase of 15 ± 5% in VWA compared with baseline (p < 0.001) (Fig. 3D).

The NC group, which resumed normal chow, had no significant changes in VWA (−2.5 ± 3%, p = NS). Normalization of plasma lipids level halted the progression of atherosclerosis but did not induce regression. Similarly, the group receiving the NC diet supplemented with PPAR-gamma agonist had a nonsignificant reduction in VWA (±4.5 ± 5%, p = NS), whereas in the groups receiving simvastatin, a significant reduction in VWA of the established atherosclerotic lesions was observed. In fact, the NC plus simvastatin group showed significant regression of the induced atherosclerotic lesions (VWA = −13 ± 4%, p < 0.05). Importantly, the combination of simvastatin and PPAR-gamma agonist (along with the NC diet) was associated with a more accentuated regression of the atherosclerotic lesions (VWA = −22 ± 4%, p < 0.01) (Fig. 3D), despite having cholesterol levels similar to those of the simvastatin group.

A comparison of the treatment groups (using Bonferroni adjustment for 6 comparisons) that received the NC diet after randomization showed that the addition of simvastatin (p = 0.049) or simvastatin plus PPAR-gamma agonist (p = 0.035) to the normal diet had a more significant antiatherogenic effect than normal diet alone. When used together, simvastatin and PPAR-gamma agonist treatment resulted in an additive effect on the regression of atherosclerotic lesions. The groups receiving simvastatin (alone or in combination with the PPAR-gamma agonist) showed a significant reduction in VWA, as compared with the NC diet group, even though the plasma cholesterol levels were similar for all groups.

MAXIMAL VESSEL WALL THICKNESS. The maximal vessel wall thickness at atherosclerosis baseline (1.1 ± 0.2 mm) did not differ between the groups (Fig. 3C). A significant increase (12.9 ± 3.5%, p = 0.018) was seen at the end of treatment in the HC diet group, which was maintained on an atherogenic 0.2% cholesterol-enriched diet in the treatment period, whereas no significant changes were seen in the NC diet group (−4.6 ± 2.2%, p = 0.1). Rabbits receiving a diet supplemented with PPAR-gamma agonist

![Figure 2](image-url)
(NC plus PPAR-gamma agonist) showed a nonsignificant trend toward lesion regression (−8.4 ± 4.7%) (Fig. 3E). The NC plus simvastatin group also showed a significant decrease in maximal vessel wall thickness (−9.9 ± 1.5%, p < 0.05), confirming atherosclerotic lesion regression. The combination treatment (NC plus simvastatin plus PPAR-gamma agonist) induced a more pronounced reduction in maximal vessel wall thickness (−19.5 ± 4.1%, p = 0.01) than either therapy alone (Figs. 3C and 3E).

**LUMEN AREA.** The lumen area at atherosclerosis baseline (8.1 ± 0.4 mm²) did not differ among the groups (Fig. 3B). Even after the six-month treatment period, no difference in lumen area was observed among the various groups (F ratio 0.27, p = 0.85), despite changes in VWA.

**Plaque composition.** The atherosclerosis control group, sacrificed at the end of the induction period, showed atherosclerotic lesions characterized by accumulation of foam cells and extracellular lipid (partially in form of cholesterol crystals), SMC-rich areas, and only sporadic collagen intimal accumulation. Macrophages clustered mainly at the borders (shoulders) of lipid-rich areas, and microcalcifications were rare. Similar lesions have been described in previous reports from our laboratory and other investigators (25,30). At the end of the treatment period, the HC diet group showed 30% average macrophage staining in plaque areas. In contrast, normalization of plasma lipid levels by dietary intervention (NC groups) caused a significant reduction in the percentage of macrophage-positive area. Supplementation of the NC diet with PPAR-gamma agonist or simvastatin, or their combination, did not produce any additional reduction in the macrophage content, compared with the normal rabbit chow (ND) diet group.

Aortic lesions from the HC diet group showed an increase in intimal collagen content with time. All of the NC groups, however, had a more accentuated increase in collagen and SMC content (Fig. 5C). Quantitative analysis substantiated significant changes in combined intimal col-
lagen and SMC content in all lipid-lowering groups. However, the SMC content (defined as the alpha-actin-positive area), when analyzed separately, was significantly increased only in the simvastatin alone and the combination simvastatin plus PPAR-gamma agonist groups (Fig. 5B).

Aortic MMP activity. Activity of MMP, as assessed by gelatin zymography, was significantly reduced in the active treatment group with PPAR-gamma agonist and/or simvastatin (Fig. 6), suggesting that therapy with the PPAR-gamma agonist (similar to statin treatment) increases lesion stability by reducing inflammation and MMP activity.

Figure 4. Representative histologic sections of the different treatment groups. CME is combined Masson's elastin (trichrome) staining; alpha-actin indicates the staining for smooth muscle cells; and RAM-11 represents the staining for macrophages. HC = high-cholesterol; NC = normal chow; PPAR = peroxisomal proliferator-activated receptor.

Figure 5. Quantitative analysis of macrophages (A), smooth muscle cells (B), and combined smooth muscle cell/collagen (C) plaque content. Data are expressed as the mean value ± SEM percent area. *p < 0.05 versus high-cholesterol (HC) diet group. #p < 0.05 versus normal chow diet (ND) group. AT = atherosclerosis; PPAR = peroxisomal proliferator-activated receptor.
DISCUSSION

Our study demonstrates that normalization of plasma lipid levels abolishes atherosclerosis progression. Administration of simvastatin alone or in combination with a selective PPAR-gamma agonist not only halted atherosclerosis progression in rabbits but also induced regression. These changes in atherosclerotic lesion size were accompanied by important cellular and biochemical changes in plaque composition, described to be associated with increased plaque stability. Our observations suggest an additive anti-atherogenic effect of the combination of a hydroxymethylglutaryl coenzyme A reductase inhibitor and a PPAR-gamma agonist. These experimental findings, if confirmed in humans, may translate into an incremental reduction in coronary events beyond the benefits seen with current standard therapy.

Lipid-lowering through dietary manipulation has been previously shown to have salutary effects on plaque progression (26,31), inflammation, and plaque composition (30). Simvastatin, in agreement with previous human studies (9), reduced atherosclerotic plaque size without affecting the lumen area, showing features of vessel wall remodeling. In our study, simvastatin not only reduced atherosclerotic plaque size but also significantly increased the plaque content of SMCs and collagen and reduced inflammation and proteolytic activity, contributing to atherosclerotic plaque stabilization. Despite a similar hypolipidemic effect in our study, simvastatin alone and in combination with the selective PPAR-gamma agonist demonstrated a more pronounced reduction in plaque size, compared with dietary manipulation alone. Sukhova et al. (5) reported a similar observation in the adult monkey model of atherosclerosis: despite a similar reduction in plasma lipid levels among treatment groups, statin treatment resulted in a significantly lower macrophage content, adhesion molecules, cytokines, and tissue factor expression in the lesions, as compared with dietary intervention alone.

The increase in SMCs and collagen content induced by the selective PPAR-gamma agonist was also associated with a decrease in MMP activity, suggesting its potential anti-atherogenic and plaque-stabilizing effects. Compelling evidence for the importance of plaque composition and inflammation in atherosclerosis has been accumulated over the last 10 to 20 years. Plaque composition, rather than severity of stenosis, appears to be the most important predictor of acute coronary events. In fact, about two-thirds of the acute coronary syndromes relate to the disruption and thrombosis of nonseverely stenotic lipid-rich plaques, leading to the concept of vulnerability of coronary lesions (32). Accumulating data indicate that insights gained from the link
between inflammation and atherosclerosis can yield predictive and prognostic information. Experimental and clinical studies indicate that lipid-lowering therapy stabilizes plaque and reduces events by limiting inflammation (33). Clinical observations with a nonspecific PPAR-gamma agonist indicated potential anti-atherogenetic effects in humans through a reduction of intimal thickness in carotid arteries (22,34). The potential mechanism of action for the observed effects of the PPAR-gamma agonist may also include interference with monocyte recruitment, SMC proliferation, cholesterol efflux from macrophages, and blood cholesterol transport to the liver, all of which are crucial to the development and progression of atherosclerosis. A potential mechanism of action of the selective PPAR-gamma agonist may also be mediated through a cholesterol reverse-transport pathway (19,21). The pivotal anti-atherogenetical role of cholesterol reverse transport and high-density lipoprotein cholesterol has been clearly demonstrated in preclinical and clinical studies (35,36).

The effect of PPAR-gamma activation on foam-cell formation has been controversial in the past. Although many studies have shown a pro-atherogenic increase in oxidized LDL uptake by macrophages (using 15-D prostacyclin, a nonspecific prostaglandin metabolite for PPAR-gamma), recent data show no significant cholesterol accumulation in macrophages when using a more selective PPAR-gamma activator (37).

Recently, the PPAR-gamma agonist was shown to prevent restenosis after coronary stenting (38), in agreement with its potential antiproliferative effect (39). Bishop-Bailey et al. (40) showed in vitro that developmental/intimal SMCs contain a functionally higher level of PPAR-gamma and cyclooxygenase-2 (COX-2) than corresponding adult/mural SMC lines, providing a possible mechanistic explanation for the anti-atherogenic and antiinflammatory effects of selective PPAR-gamma ligands. They also demonstrated that COX-2 mediates PPAR-gamma activation in intimal SMCs; therefore, intimal COX-2 could serve as a source of potential endogenous PPAR-gamma ligand. Constitutive activation of PPAR-gamma suppresses the expression of vascular adhesion molecules in endothelial cells (essential for the homing of macrophages), with simultaneous regression of activator protein-1 and nuclear factor-kappa B activity, suggesting that PPAR-gamma may reduce pro-inflammatory phenotypes (41). Interestingly, activator protein-1 and nuclear factor-kappa B are involved in the CD40 ligand-dependent induction of tissue factor gene expression in endothelial cells. These observations highlight the pivotal modulator role of PPAR-gamma in atherogenesis, confirming the active link between inflammation, atherosclerosis, and thrombosis.

Conclusions. Restoring normal plasma lipid levels through dietary changes in our rabbit model of experimental atherosclerosis abolished atherosclerosis progression. The addition of simvastatin to dietary intervention induced regression of established atherosclerotic lesions, decreased inflammation (as reflected by the macrophage content and MMP activity), and increased SMCs and the collagen plaque content. These effects were independent of dietary intervention and lipid lowering and confirm the presence of the pleiotropic effects of statins. These anti-atherogenic pleiotropic effects of simvastatin were accentuated when a selective PPAR-gamma agonist was added to simvastatin therapy, demonstrating the additive effects of combination therapy on plaque regression and composition. We anticipate the combination of a statin and PPAR-gamma agonist will have significant clinical implications in the treatment and/or prevention of atherosclerosis and its clinical sequelae via regression and stabilization of high-risk atherosclerotic plaques.

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