Review

Effects of statins on vascular wall: vasomotor function, inflammation, and plaque stability

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Abstract

Clinical trials of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statin therapy demonstrate an improvement in cardiovascular end points and coronary stenosis. However, an improvement in cardiovascular end points and coronary stenosis is incompletely explained by the baseline or treated LDL cholesterol level. The beneficial effects of statins on clinical events may involve nonlipid mechanisms that modify endothelial function, smooth muscle cells, and monocyte-macrophage: vasomotor function, inflammatory responses, and plaque stability. Augmented bioactivity of NO by statin therapy either indirectly by its effect on lipoprotein levels and protection of LDL from oxidation, or directly by effects on NO synthesis and release, might account for enhancement of endothelium-dependent vasodilation. Recent experimental and animal studies have demonstrated that statins dose-dependently decrease smooth muscle cells migration and proliferation, independently of their ability to reduce plasma cholesterol. Moreover, statins are able to reduce the in vitro cholesterol accumulation in macrophages and expression of matrix metalloproteinase, resulting in plaque stability. These effects of statins were completely prevented by the addition of mevalonate and partially by all-trans farnesol and all-trans geranylgeraniol, confirming the specific role of isoprenoid metabolites, probably through prenylated proteins, in regulating these cellular events. Statins have been shown to prevent the activation of monocytes into macrophages, inhibit the production of pro-inflammatory cytokines, C-reactive protein, and cellular adhesion molecules. Statins decrease the adhesion of monocyte to endothelial cells. Accordingly, statins exert their cardiovascular benefits through a direct antiatherogenic properties in the arterial wall, beyond their effects on plasma lipids. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

The acute and chronic manifestations of atherosclerosis are increasingly being considered to be a consequence of a chronic inflammatory process [1]. Clinical trials of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statin therapy demonstrate an improvement in cardiovascular end points and coronary stenosis [2–7]. This database of trials, which now consists of more than 30,000 patients from at least three continents and tests three different statins (lovastatin, pravastatin, and simvastatin), is consistent in its positive results. In particular, clinical trials in the 1980s and 1990s have provided compelling evidence of the benefits of cholesterol-lowering. Low-density lipoprotein (LDL) cholesterol levels serve as the focus of cholesterol treatment guidelines [8,9]. However, an improvement in cardiovascular end points and coronary stenosis is incompletely explained by the baseline or treated LDL cholesterol level [2–7]. The relationship between baseline and treated LDL cholesterol levels and cardiovascular end points has been evaluated in several clinical trials [2,4,6]. In the Scandinavian Simvastatin Survival Study, survivors of coronary artery disease mostly with highly elevated LDL-C levels reported that major coronary events were reduced by a similar amount regardless of the baseline LDL cholesterol level [2]. The West of Scotland Coronary Prevention Study (WOSCOPS) included men who were without myocardial infarction but...
at high risk because of their LDL-C levels and other factors [4]. This study evaluated the relationship between on-treatment LDL-C levels or total cholesterol change and coronary heart disease (CHD) risk using the Framingham CHD-risk model. The CHD event rate in pravastatin-treated patients was not related to the magnitude of LDL cholesterol level lowering when the LDL cholesterol level reduction ranged from 19 to 54% [4]. The Framingham model accurately predicted the CHD event risk rate in the placebo group but underestimated the CHD risk reduction in the pravastatin therapy group by 35%.

Indeed, elevated LDL cholesterol levels identify less than one half of individuals who will die from CHD [10]. The LDL cholesterol concentrations had a sensitivity of 47% in predicting 10-year CHD death rates in the Lipid Research Clinics Prevalence Study [11]. The revised National Cholesterol Education Program (NCEPII) guidelines [9] that stratify risk by LDL cholesterol levels and conventional risk factors are no better in predicting risk [11].

Meanwhile, statins can modulate directly the phenotype of vascular cells [12]. Early intermediates of cholesterol synthesis, isoprenylated proteins are necessary for cell proliferation and other important cell function, and their metabolism needs to be increased during cell activation [13,14]. Statins are taken up by the cells and prevent the production of isoprenoid molecules [15], downstream to mevalonate within the cells, independent of their lipid-lowering properties [16,17]. This in vitro inhibition was completely prevented by the addition of mevalonate and partially by all-trans farnesol and all-trans geranylgeraniol [17–19]. These results suggest that statins exert a direct antiatherosclerotic effect in the arterial wall, beyond their effects on plasma lipids.

Therefore, recent studies suggest that the beneficial effects of statins on clinical events may involve nonlipid mechanisms that affect endothelial function, smooth muscle cells, and monocyte-macrophage: vasomotor function, inflammatory responses, and plaque stability [12,20,21]. These nonlipid mechanisms of statins may contribute to the cardiovascular event reduction and explain the early clinical benefit in these clinical trials [4–6].

Patients with CHD or risk factors for CHD including hypercholesterolemia, systemic hypertension, smoking, diabetes, or estrogen deficiency, hyperhomocysteinemia, and the aging process itself, have been associated with impaired functions of the endothelium. The vessel wall in these conditions may promote inflammation, oxidation of lipoproteins, smooth muscle proliferation, extracellular matrix deposition or lysis, accumulation of lipid-rich material, platelet activation, and thrombus formation. All of these consequences of endothelial dysfunction may contribute to development and clinical expression of atherosclerosis. In other words, abnormalities in the function of the endothelium are therefore likely to play an important role in the pathogenesis of CHD. Nitric oxide (NO) plays a pivotal role in maintaining vascular health and protecting from vascular injury under these pathological conditions.

Thus, as the role of endothelium, smooth muscle cell and monocyte-macrophage is important in the pathogenesis of atherosclerosis and CHD, we will review the effects of statins on vascular wall as plausible mechanisms to prevent or regress atherosclerosis and CHD.

2. Endothelial dysfunction, atherosclerosis, and coronary artery disease

Several groups have shown that epicardial coronary arteries in patients with coronary artery disease constRICT both at sites of angiographically obstructive atherosclerotic disease and at sites of plaquing in response to acetylcholine [22,23]. These same doses of acetylcholine cause vasodilation in coronary arteries of patients without evidence of coronary artery disease. In contrast to the different responses of these two patient groups to acetylcholine, the responses to nitroglycerin (a NO donor) are similar, indicating normal smooth muscle responsiveness to NO, at least in mildly atherosclerotic arteries. Even risk factors for atherosclerosis have been associated with constrictor responses of the epicardial coronary arteries to acetylcholine in patients with normal-appearing coronary angiograms [24]. In hypercholesterolemic subjects, \( \text{N}^\text{G}-\text{monomethyl-L-arginine} \) has similar effect on basal forearm flow compared to normals. However, the effect of \( \text{N}^\text{G}-\text{monomethyl-L-arginine} \) on the forearm flow response to acetylcholine was reduced compared with normocholesterolemic subjects, suggesting preserved release of NO in the basal state but reduced NO activity during endothelial stimulation [25].

These observations suggest that endothelial dysfunction of epicardial coronary arteries precedes development of atherosclerotic disease that is either angiographically apparent or of sufficient obstructive severity to cause myocardial ischemia and angina pectoris. In these regards, serial angiographic studies performed prior to and following an acute myocardial infarction indicate that the underlying plaque responsible for unstable angina and myocardial infarction was usually less than 50% narrowed prior to the acute event [26,27]. Indeed, a recent angiographic study suggests that the positive correlation between the number of severely diseased arteries and coronary mortality may not just be related to the number of arteries with 70% or greater stenosis, but may be also tied in with the amount of minor plaque disease in other vessels [28]. It is possible that patients with multivessel disease perhaps have a higher mortality than those with single vessel disease because they have more non-stenotic or mildly stenotic plaques that are sites for future coronary events. These observations and the finding that the progression to an acute infarction is not proportionately related to the
prior severity of the coronary stenosis [26,27] has been driving the search for other mechanisms. An increasing body of evidence is now highlighting a potentially important player in atherosclerosis and CHD, the endothelium.

3. Mechanisms and consequences of endothelial dysfunction in hypercholesterolemia

Endothelial cells in hypercholesterolemic animal models of atherosclerosis may also produce increased quantities of highly reactive molecules such as superoxide anion [29] and oxidative stress product, 8-epi-prostaglandin \( \text{F}_{2\alpha} \) [30]. What is unclear is whether the actual synthesis of NO by the dysfunctional endothelium in hypercholesterolemia is increased or decreased. In support of the possibility of increased NO formation, the release of nitrogen oxides is increased from atherosclerotic rabbit aorta compared with control tissue [31]. LDL added to endothelial cells [32] or macrophages [33] in culture stimulates the release of nitrogen oxides (especially peroxynitrite). On the other hands, oxidized LDL has been shown to stimulate the transcription and synthesis of constitutive NO synthase [34]. In contrary, some studies demonstrated that oxidized LDL inhibited the transcription and synthesis of inducible NO synthase [35,36]. However, increased expression of the inducible form of NO, capable of synthesizing even larger quantities of NO than the constitutive form of this enzyme, has been detected in human atherosclerotic plaques [37]. Thus, endothelial cells in hypercholesterolemia and atherosclerosis may synthesize greater than normal quantities of NO, but increased NO formation may be with rapid oxidative inactivation or conversion to toxic nitrogen oxides due to the excess accumulation of superoxide anions and free radical molecules.

In patients with hypercholesterolemia and in patients with coronary atherosclerosis, coronary and systemic arteries may constrict during exercise [38] or with mental stress [39], likely due to loss of dilator regulation by the coronary endothelium as consequence of diminished release of NO to the visceral smooth muscle, whether by decreased synthesis or excess degradation, and enhanced vascular sensitivity to constrictor stimuli such as norepinephrine [39]. Reduced NO could also stimulate the synthesis and releases of endothelin in resulting in enhanced vasoconstrictor tone, promote the release and activity of growth factors resulting in smooth muscle hyperplasia and migration into the intima, and enhance the synthesis and release of proinflammatory cytokines. Additionally, reduced NO could promote platelet attachment and release of growth factors in the vessel wall. Reducing NO availability through a synthase inhibitor increases the development of atherosclerosis, whereas increasing its availability through the administration of L-arginine decreases its development, at least transiently [40,41]. All of these consequences of endothelial dysfunction and reduced NO bioactivity may be important in the initiation, progression, and clinical expression of atherosclerosis.

4. Infection, inflammation and endothelial dysfunction

There has been also considerable interest in the links between chronic infections and the slow process of atherogenesis [42]. Deaths from cardiovascular disease increase during and after epidemics of influenza [43]. This occurs not only in the frail elderly but also in previously well middle-aged men. Bacterial infections also seem to be associated with increased risk [44]. Together, these observations suggest that infection or acute systemic inflammation might temporarily increase the risk of an acute cardiovascular event. It seems unlikely that this increased risk is due to acute changes in the overall bulk of atheroma, but rather that the pre-existing atheroma becomes more likely to support thrombosis and vasospasm. Consistent with this idea, the transition from stable to unstable angina appears to be associated with a systemic inflammatory response [45], and markers of acute inflammation (including cytokines, C-reactive protein and white cell count) are all related at increased cardiovascular risk [45,46]. Interestingly, instability of atheroma is not always confined to one plaque, but can occur at multiple sites in different vascular beds, again suggesting that the underlying process may be systemic rather than local in origin [47].

How might inflammation or infection alter the risk associated with atheroma? Bacterial endotoxin, or certain pro-inflammatory cytokines, may also inhibit the ability of endothelial cells to generate NO and/or certain vasodilator anti-aggregatory prostanoids [48,49]. These effects have been observed in whole animals [48] and in experimental models in healthy volunteers [49]. In healthy volunteers, even a very brief exposure to endotoxin or certain cytokines impairs endothelium-dependent relaxation for many days, and the degree of the impairment is considerably greater than that produced by chronic risk factors. This effect has been termed endothelial ‘stunning’ [49]. The experimental and epidemiological data together suggest that endothelial dysfunction following acute infection or inflammation may indeed provide a transient risk factor for myocardial infarction and unstable angina, which might promote abnormal vascular behavior and be amenable at pharmacological intervention.

Indeed, several studies now report the potential benefit in treating patients with known ischemic heart disease with antibiotics and report a significant reduction in the incidence of unstable angina and myocardial infarction [50]. In contrast, Ridker et al. investigated the association between Chlamydia pneumoniae [51] or herpes simplex virus or cytomegalovirus [52] IgG seropositivity and risks of future myocardial infarction among apparently healthy middle-
aged men in a prospective cohort study. They found no evidence of association between both. Anderson et al. [53] performed a randomized secondary prevention trial of azithromycin in patients with coronary artery disease and serological evidence for Chlamydia pneumoniae infection. In patients with coronary artery disease positive for Chlamydia pneumoniae antibodies, global tests of four markers of inflammation (C-reactive protein, interleukin-1 and 6, TNF-α) improved at 6 months with azithromycin. However, there were no differences in antibody titers and clinical events.

5. Biological effects of statins

5.1. Effects of statins on vasomotor function

Endothelial-mediated vasodilatation is impaired in hypercholesterolemia and atherosclerosis [54]. In coronary arteries of patients with atherosclerosis, cholesterol lowering with pravastatin and lovastatin improves endothelial function as evidenced by limiting acetylcholine-induced vasoconstriction [54,55]. The LDL cholesterol-lowering therapy with simvastatin improves peripheral NO-mediated vascular relaxation [56]. The improved coronary blood flow and vasodilator response with statin therapy alleviate transient ischemia in patients with stable angina pectoris [57] and improve myocardial perfusion [58]. Statin therapy may contribute to the observed clinical benefits of these agents through ameliorating endothelial dysfunction.

Goode and Heagerty [59] isolated small arteries from subcutaneous biopsies performed in 18 hypercholesterolemic patients and demonstrated impaired dilator responses to acetylcholine. Ten of these patients underwent repeat biopsies about 10 months after lipid-lowering therapy, which reduced LDL levels by 56%. Significant improvement in vasodilator responses to acetylcholine was observed in these patients compared with their baseline values. Recently, we randomly assigned 28 women to conjugated estrogen 0.625 mg, simvastatin 10 mg, and their combination per day, with each treatment period lasting 6 weeks [60]. Brachial artery dilator responsiveness to hyperemia and to nitroglycerin was measured by ultrasonography. Compared with respective baseline values, simvastatin alone significantly reduced LDL cholesterol by 25%. Simvastatin improved flow-mediated dilation from 4.3 to 10.0%, compared with respective baseline values (Fig. 1). Some studies have demonstrated that fluvastatin [61] or LDL apheresis [62] improved endothelium-dependent vasodilatation in hypercholesterolemic patients, respectively.

In our study, we expected either conjugated estrogen or simvastatin therapy would increase serum nitrate/nitrite levels, which reflect in part the luminal release of NO [63]. Despite enhanced NO bioactivity, simvastatin alone or simvastatin combined with conjugated estrogen lowered with marginal significance serum nitrate/nitrite levels by 5±37 and 6±30%, respectively. Conjugated estrogen insignificantly increased serum nitrate/nitrite levels by 5±38% (Fig. 2). Reduction in luminal release of NO after statin therapy may indicate reduced synthesis of NO required for endothelial homeostasis as a consequence of reduced degradation of NO by oxidized lipoproteins and free radical molecules from the endothelium and from inflammatory cells [64]. In our recent studies [65,66], this speculation was confirmed.

Augmented bioactivity of NO by statin therapy either indirectly by its effect on lipoprotein levels and protection of LDL from oxidation, or directly by effects on NO synthesis and release, might account not only for enhance-
ment of endothelium-dependent vasodilation but also for much of the anti-atherogenic effects of statin by inhibition of platelet aggregation, platelet and inflammatory cell attachment to the endothelial surface of the vessel wall, and release of factors that stimulate growth and migration of smooth muscle cells within the vessel wall [67].

Besides lipid-lowering effects of statins, one of the important mechanisms regarding improvement of vaso-motor function may be antioxidant effects of statins, which enhances NO bioactivity by preventing NO degradation from free radical molecules. In this regard, Kleinveld et al. [68] reported that 18 weeks of pravastatin or simvastatin decreased LDL cholesterol levels by 36% and significantly reduced the rate and extent of copper-catalyzed LDL oxidation. LDL particles after therapy were changed in composition to contain less lipid relative to protein, possibly rendering the particle less susceptible to oxidation [69]. Indeed, Giroux et al. [70] reported the simvastatin diminished superoxide anion formation and LDL oxidation by human macrophages in tissue culture and Giroma et al. [71] recently demonstrated that simvastatin decreased aldehyde production derived from lipoprotein oxidation, suggesting simvastatin as an antioxidant in lipoprotein particles. However, Palomaki et al. [72] reported that lovastatin decreased the depletion time of reduced α-tocopherol in metal ion-independent oxidation by 44% and shortened the lag time of conjugated-diene formation in metal ion-dependent oxidation by 7%, suggesting each statin may act differently regarding an antioxidant effect.

Of interest, some studies have shown that LDL induces angiotensin II type 1 receptor upregulation in isolated vascular smooth muscle cells and that hypercholesterolemic rabbits display an enhanced vascular expression of angiotensin II type 1 receptors [73,74]. Angiotensin II type 1 receptor overexpression may account for enhanced release of free radicals and increased vasoconstriction and cell proliferation. Indeed, angiotensin II type 1 receptor expression was significantly enhanced in hypercholes- terolemic individuals [75]. Further, lipid-lowering treatment with statins reversed the elevated blood pressure response to angiotensin II infusion and downregulated angiotensin II type 1 receptor density [75]. In another study, cholesterol level reduction achieved with lovastatin or pravastatin was associated with an additional significant reduction in diastolic blood pressure in patients taking enalapril or lisinopril [76].

5.3. Effects of statins on inflammation

An early step in atherogenesis involves monocyte adhesion to the endothelium and penetration into the subendothelial space. Oxidized LDL binds to the scavenger cell receptor on monocyte-derived macrophages and contributes to foam cell formation. Inflammatory cytokines secreted by macrophages and T lymphocytes can modify endothelial function, smooth muscle cell proliferation, collagen degradation, and thrombosis [80].

Scalia et al. [81] clearly demonstrated the role of P-selectin, intercellular adhesion molecule (ICAM-1), and vascular cell adhesion molecule (VCAM-1) in leukocyte–endothelium interaction during the early stages of hypercholesterolemia in the rabbit model. They observed upregulation of the endothelial cell adhesion molecules immunohistochemically in the intestinal microvascular endothelium of hypercholesterol diet-fed rabbits. Paster-kamp et al. [82] investigated the prevalence and distribution (local versus general) of inflammatory cells in nonruptured atherosclerotic plaques. Inflammation of the cap and shoulder of the plaque is a common feature, locally observed, in atherosclerotic femoral and coronary arteries. Cholesterol level lowering in experimental models was accompanied by a reduction of inflammatory cells within atherosclerotic plaque [83,84].

Subjects with hypercholesterolemia have increased geranylglyceranylation of RhoGTPase [18,19]. In this regard, Raiteri et al. [17] demonstrated that statins (simvastatin, cerivastatin, fluvastatin) dose-dependently decreased smooth muscle cell proliferation, independently of their ability to reduce plasma cholesterol. This effect was prevented by mevalonate, all-trans farnesol and all-trans geranylgeraniol, precursors of protein prenyl groups. Further, Stark and his colleagues [18] showed that geranylglyceranylated proteins were required for growth and protected smooth muscle cell against apoptosis, and Laufs et al. [19] reported that the down-regulation of p27kip1 by Rho GTPase mediated platelet-derived growth factor-indu-ced smooth muscle cell DNA synthesis, and statins attenuated smooth muscle cell proliferation by preventing Rho GTPase-induced down-regulation of p27kip1. These data obtained in vitro have been confirmed in vivo in experimental models of smooth muscle cell activation [16,77]. The inhibitory effect of lipophilic statins on smooth muscle cell proliferation has been recently shown in different models of proliferating cells such as cultured arterial myocytes [77] and rapidly proliferating carotid and femoral intimai lesions in rabbits [16]. Interestingly, the treatment with the various statins did not modify rabbit plasma cholesterol concentrations. Finally, ex vivo studies showed that sera from fluvastatin-treated patients interfered with smooth muscle cell proliferation [78,79]. Thus, statins exert a direct antiatherosclerotic effect in the arterial wall, beyond their effects on plasma lipids.

5.2. Effects of statins on smooth muscle cells

Since mevalonate, the product of the enzyme reaction, is the precursor of numerous metabolites, statins have the potential to result in pleiotropic effects [13,14]. A key event in the atherogenesis is the migration and proliferation of arterial smooth muscle cells in the arterial wall [1,42]. Smooth muscle cell proliferation involves the mevalonate pathway [17] mainly via the prenylation and
adhesiveness of isolated monocytes to fixed endothelial cells in vitro, and this response is diminished with lovastatin and simvastatin [83]. In contrast, this group demonstrated that lovastatin enhanced Mono Mac 6 adhesiveness to human umbilical vein endothelial cells by the increased CD11b and CD14 expression [85]. Hypercholesterolemic rats treated with fluvastatin have significantly attenuated leukocyte-adherence responses to platelet activation factor and leukotriene B4 [84]. Indeed, cellular interaction between monocytes and endothelial cells was inhibited by fluvastatin, mediated via reducing the expression of lymphocyte function associated antigen-1 and ICAM-1, particularly in the side of monocyte [86]. Of interest, the inhibitory effects of fluvastatin on the expression of adhesion molecules were completely reversed by the addition of mevalonate. This effect of statins may be mediated through decreasing the expression of LDL receptor on monocytes [87]. In a rabbit atherosclerosis model, atorvastatin abolished arterial macrophage infiltration and monocyte chemoattractant-protein-1 in the neointima and in the media [88]. Simultaneously, atorvastatin downregulated monocyte chemoattractant-protein-1 expression and NF-kB activity induced by tumor necrosis factor α in cultured vascular smooth muscle cell. This study concluded that atorvastatin diminished the neointimal inflammation and this could contribute to the stabilization of the atherosclerotic plaque.

With regard to a clinical study, Abe et al. [89] observed significantly increased levels of soluble ICAM-1 and VCAM-1 in patients with hypertriglyceridemia and low high-density lipoprotein cholesterol. Rohde et al. [90] recently demonstrated that age-adjusted soluble ICAM-1 and VCAM-1 levels increased in a stepwise fashion across common carotid intima-media thickness tertiles. This study supports the hypothesis that systemic inflammation may have a role in atherosclerotic lesion development. In patients with cardiac transplants, pravastatin may suppress the inflammatory response and inhibit natural killer cell activity in cyclosporin-treated patients [91]. In our current study, simvastatin alone did not significantly change soluble E-selectin, ICAM-1, and VCAM-1 levels [60]. Of interest, simvastatin significantly lowered serum interleukin-6 levels from 2.20 ± 1.30 to 1.88 ± 0.97 ng/ml in our study. Indeed, lovastatin suppressed interleukin-6 or -8, but -1β, by activated monocytes in vitro [92]. The addition of mevalonate prevented the attenuation of interleukin-8 production by lovastatin.

C-reactive protein is a marker of inflammation [93]. Strandberg et al. [94] demonstrated that simvastatin or atorvastatin lowered C-reactive protein in hyperlipidemic coronary patients. Indeed, with respect to the clinical benefits of statins on C-reactive protein, the association between C-reactive protein and subsequent risk of recurrent coronary events was significant among those randomized to placebo, but was attenuated and no longer significant among those assigned to pravastatin in the Cholesterol and Recurrent Events trial [95]. These effects were present even though those with and without elevated levels of C-reactive protein had virtually identical baseline lipid levels. Further, regarding the long-term effects of pravastatin on C-reactive protein, randomization to pravastatin resulted in significant reductions of C-reactive protein that were not related to the magnitude of lipid alterations observed, in contrast to survivors of myocardial infarction on standard therapy plus placebo showing increasing C-reactive protein levels over 5 years of follow-up [96]. These data strongly support the potential for nonlipid effects of statins.

5.4. Effects of statins on plaque stability

Collagen is the main component of fibrous caps responsible for their tensile strength. Macrophages are capable of degrading extracellular matrix by phagocytosis or by secreting proteolytic enzymes, in particular a family of metalloproteinases that may weaken the fibrous cap, predisposing its rupture. Lipids in the atheroma not only create mechanical instability, but also biologically active lipids participate in promoting oxidative stress and inflammatory responses such as monocyte migration. Lipid-lowering may therefore influence the matrix degradation cascade that appears most active in macrophage-rich areas of the atheroma, as well as promote mechanical stability within the plaque.

Statins inhibit cholesterol ester accumulation in monocyte-derived macrophages either by reducing the availability of free cholesterol toward the enzyme acyl–coenzyme A cholesterol acyltransferase by trapping it in phospholipid-containing pools, or by inhibiting LDL endocytosis related to reduced synthesis of mevalonate or mevalonate by-products required for cholesterol esterification [13]. The addition of mevalonate or all-trans geranylgeraniol fully prevented the inhibitory effect of fluvastatin and simvastatin, suggesting that a non-sterol derivatives of mevalonate is involved in the endocytosis and esterification of exogenous cholesterol delivered to macrophages by modified LDL [13]. Interestingly, the efficacy of fluvastatin in inhibiting cholesterol esterification was greater in cholesterol-loaded than in normal cells, suggesting a possible specific and more pronounced effect on the atherogenous arterial wall. Kempen et al. [97] reported a dose-dependent inhibition of cholesterol accumulation in macrophages that was greater with lovastatin and simvastatin than with pravastatin. Lowering blood LDL cholesterol levels may facilitate plaque stability either through a reduction in size [98] or by an alteration of the physicochemical properties of lipid cores [99]. Hydrolysis of liquid cholesterol esters to solid cholesterol crystal can yield firmer plaques.

In this regard, Aikawa et al. [100] demonstrated that lipid lowering favored accumulation of mature smooth muscle cells in the atherosclerotic intima in association with reduced levels of platelet-derived growth factor-B.
expression. They also showed that intimal smooth muscle cells in the low cholesterol group displayed reduced expression of matrix metalloproteinases-3 and -9 compared with control and high cholesterol groups. In another study, Aikawa et al. [101] demonstrated that the lipid-lowering group showed progressive reduction in both macrophage content and matrix metalloproteinase-1 immunoreactivity with time. Aortic content of interstitial collagen increased in the lipid-lowering group compared with the baseline or continued hyperlipemic group, indicating that lipid lowering reinforced the fibrous skeleton of the atheroma.

Indeed, Xu et al. [102] demonstrated that oxidized LDL upregulated matrix metalloproteinase-9 expression while reducing tissue inhibitor of metalloproteinase-1 in monocyte-derived macrophages. Furthermore, HDL abrogated oxidized LDL-induced metalloproteinase-9 expression. Statins have been recently shown to inhibit metalloproteinase-9 production by macrophages in culture, an inhibition reverted by the addition of mevalonate, providing further insights on their direct antiatherosclerotic potentials [103]. Similar data were obtained with simvastatin in this study. Recently, Williams et al. [104] demonstrated that the arteries of pravastatin-treated monkeys had better dilator function and plaque characteristics more consistent with plaque stability than those of monkeys not receiving pravastatin, compared with control monkeys. Of interest, these beneficial arterial effects of pravastatin occurred independently of plasma lipoprotein concentrations and despite similar changes in plaque size between the groups. These observations raise another nonlipid effects of statins.

6. Conclusion

Statins have enhanced endothelium-dependent vasodilation and dose-dependently decreased smooth muscle cells migration and proliferation, independently of their ability to reduce plasma cholesterol. Moreover, statins are able to reduce the in vitro cholesterol accumulation in macrophages and expression of matrix metalloproteinase, resulting in plaque stability. These activities, which affect major processes involved in the formation of atherosclerotic lesions, are linked to the local modulation of the mevalonate pathway. Accordingly, statins exert their cardiovascular benefits through a direct antiatherogenic properties in the arterial wall, beyond their effects on plasma lipids.

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