Pleiotropic Effects of Statins: Moving Beyond Cholesterol Control

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Current Atherosclerosis Reports 2005, **7:**34–39
Current Science Inc. ISSN 1523-3804

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or "statin" medications are the most commonly prescribed therapy for lowering cholesterol. In use for over a decade, they have demonstrated both safety and tolerability across a broad range of patients. The ability to inhibit the biosynthesis of cholesterol and reduce low-density lipoprotein cholesterol levels is known to play a major part in reducing cardiovascular risk. Multiple clinical trials have cemented their role in both primary and secondary prevention of atherosclerotic disease. Clinical evidence also supports the principle that reductions in cardiovascular risk are interdependent on mechanisms beyond cholesterol reduction alone. These pleiotropic effects of statins have underscored a widening focus and understanding into the mechanisms of vascular dysfunction, inflammation, and injury. They have also brought a new perspective to a broad spectrum of clinical uses that has implications for specialties as varied as infectious disease, rheumatology, and oncology.

Introduction

Statins were designed to lower cholesterol by competitively inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase. The original compound was first isolated from fungi in 1976. It effectively blocked the conversion of HMG CoA to mevalonic acid and bore the name mevastatin [1]. The ensuing years have seen marked proliferation of this drug class. Large-scale clinical trials showed reductions in morbidity and mortality in patients with and without evidence of vascular disease [2–6]. In addition to lipid lowering, it has been well recognized for some time that the beneficial impact of statins may be more directly related to their effects on the vascular wall [7]. An original understanding of that potential stemmed directly from the elucidation of the mevalonate pathway. Goldstein and Brown [8] postulated the benefits that regulation of this system could have on malignancy and cardiovascular disease well before clinical evidence lent its broad support. It is now evident that inhibition of mevalonate synthesis reduces cholesterol production, but it also inhibits production of a diverse group of proteins that play an intimate role in cellular function. The so-called pleiotropic effects of statins are thought to be primarily derived through the regulation of the mevalonate system [9•]. More recent evidence suggests that statins also function independently of this system in a complex interplay of direct cellular signaling [10]. This review seeks to summarize these pleiotropic effects and to describe their impact on vascular and nonvascular processes.

Mediator of Endothelium Dysfunction

It is well appreciated that vascular wall injury and inflammation ultimately result in atherosclerosis [11]. The vascular endothelium is essentially an endocrine organ that modulates these changes, principally through the regulation of nitric oxide (NO). Dysfunction of this system through decreased synthesis, release, or function of endothelial-derived NO plays a critical role in acute and long-term progression of atherosclerosis [12,13]. Availability of NO is negatively influenced by a variety of cardiovascular risk factors, including hypertension, dyslipidemia, diabetes, and smoking. It is known that modification of these factors helps to play a role in the overall improvement of endothelial function [14–17]. NO itself plays a critical role in vascular dilation, platelet response, and smooth muscle cell proliferation [18–20]. The dysfunctional endothelium also expresses a multiplicity of different adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin, components that are essential for the rolling and adhesion of circulating monocytes [21].

These events are all important in the development of atherosclerosis and promotion of cellular injury and inflammation, which can lead to symptomatic disease. Lack of NO creates an optimal setting for ischemic events in which vasoconstriction, in conjunction with platelet activation and thrombus formation, acutely limit blood flow.

Nitric oxide production is directly impacted by the composition of endothelial cell plasma membranes. The concept of "microdomains" or "lipid rafts" within the membrane lipid bilayer has enhanced understanding of cellular signal transduction, particularly as it applies to endothelial cells [22]. Caveolae are a component of the lipid raft subtype

found to play a key role in the metabolism of NO. Their expression is known to markedly increase in the presence of hyperlipidemia. Caveolin, the protein component of caveolae, is known to be an inhibitor of endothelial nitric oxide synthase (eNOS). Under conditions of endothelial cell dysfunction, the high levels of caveolin result in decreased levels of NO [23].

Statin medications have been traditionally thought to have their dominant impact through their cholesterol-lowering properties. It has previously been demonstrated that acute plasma low-density lipoprotein (LDL) apheresis improves vasodilation, supporting the idea that endothelial dysfunction is a mechanism of high cholesterol alone [24]. It is now known that statins play an intimate role in the metabolism of NO by mechanisms involving both direct and indirect pathways. The ultimate effect is an increased production of NO and favorable modification of the endothelial surface. The upregulation of this process was originally thought to play out over the course of hours, if not days. In fact, regulation of the NO system by way of statins can occur on the order of seconds to minutes, a time-frame not previously considered given the presumed dependency on the pathway of HMG CoA reductase inhibition. Harris *et al*. [25] recently reported on the acute activation and phosphorylation of eNOS by lovastatin and pravastatin. This study demonstrated that statins acutely activated eNOS independent of HMG CoA reductase inhibition. The immediate effect upon the NO pathway would seem to support clinical evidence that statin medications have efficacy in acute coronary syndrome. It also helps to support earlier observations that statin medications were having beneficial effects that predated atheroma regression.

A more traditional view of statin pleiotropy, as it applies to endothelial dysfunction, revolves around inhibition of the mevalonate pathway [26••]. The overall impact on NO metabolism occurs through multiple mechanisms. The reduction of plasma membrane cholesterol levels by statins effectively reduces the amount of caveolin present in endothelial cell membranes. The net effect is an increase in eNOS activation and NO production [27]. The reduction of cholesterol in endothelial cell membranes also improves the uptake of L-arginine, an important substrate for eNOS metabolism [28]. It could be debated that these two mechanisms are not actually pleiotropic in nature because they rely on the reduction of membrane cholesterol levels. Their overall impact heavily influences NO metabolism though, a mechanism commonly recognized as having a pleiotropic role.

Statins also increase the bioavailability of NO by reducing oxidative stress, particularly by interfering with the metabolism of oxidized LDL. It was previously thought that the facilitation of LDL oxidation was a direct result of the removal of older LDL particles through upregulation of the LDL receptor, a nonpleiotropic pathway.

Radical scavenging activities and direct antioxidative effects have been reported with statin medications, and these effects were observed at drug levels that did not produce a reduction in plasma lipid levels [29]. These are particularly important properties because oxidized LDL is known to facilitate endothelial dysfunction through expression of chemoattractant molecules. These molecules promote migration of inflammatory monocytes and ultimately the formation of foam cells. Oxidized LDL also promotes the production of growth factors, particularly platelet-derived growth factor. This substance is known to stimulate the migration and proliferation of smooth muscle cells (SMC), a crucial event in the pathogenesis of vascular lesions [30].

It is evident that HMG CoA reductase inhibitors play a crucial role in NO metabolism. Endothelial cell dysfunction plays a basic role in the development of vascular disease and creates a setting in which the influx of inflammatory and promoter cells remodel endothelial surfaces. The model of lipid rafts helps to illustrate some of the dynamic pleiotropic effects that statins have at the level of the endothelial membrane and serves to better elucidate the role of caveolin in the regulation of NO.

Mediator of the Immune Response

Modulation of the immune response also plays an important role in the development of vascular disease. Hyperlipidemia itself increases the production of multiple inflammatory components, and much of the anti-inflammatory benefit of statins may be directly related to lower cholesterol levels. It has been previously shown in animal models that reducing lipid levels by dietary modification alone decreased the expression of the proinflammatory receptor CD40 [31]. A clinical marker of systemic inflammation that is now in routine use is high-sensitivity C-reactive protein (hs-CRP). This is an acute-phase reactant produced by the liver under the influence of the proinflammatory cytokine interleukin-6 (IL-6). High levels of hs-CRP are known to be predictive of an increased risk for coronary artery disease [32]. Statins are known to lower the level of hs-CRP in patients that have hyperlipidemia, indicating that these medications help play a role in the reduction of systemic and vascular inflammation [33]. How statins achieve this effect continues to be an area of intense interest and is multifactorial in nature.

Statin-mediated regulation of the mevalonate pathway seems to play a dominant role in moderating the immune response that leads to endothelial cell injury. Mevalonate functions as a precursor of cholesterol but also of many compounds important in cell biology [8]. Its metabolism yields a series of intermediate compounds called isoprenoids. Two of these compounds, farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP), play a key role in the post-translational modification of crucial protein subunits. These proteins must be “prenylated” to allow effective anchoring and activation within cell membranes. Prenylation describes the process by which

FFP or GGPP is attached to these protein subunits. Isoprenoids prenylate a wide range of signal transducers, including Ras and Rho. Members of this protein family are involved in multiple cell processes, including cellular signaling, differentiation, proliferation, myelination, cytoskeleton function, and the transport processes endocytosis and exocytosis [9•]. Statins diminish the production of isoprenylated proteins, a process that in vitro has been shown to have effects on leukocyte adhesion, cell proliferation and apoptosis, and fibrinolytic activity, all of which are key events in the inflammatory cascade.

One of the earliest events of atherogenesis is the adhesion and migration of inflammatory cells. Statins interfere with this event by reducing the expression of the integrin dimer CD 11b, a key component to the function of ICAM-1. This process interrupts expression of the molecule on the surface of monocytes and prevents adhesion of the leukocytes to endothelial cells [34]. Multiple other molecules, including e-selectin and VCAM, also play a role in leukocyte adhesion, and their expression is thought to be inhibited through interruption of prenylation [34]. One alternate pathway of leukocyte adhesion that is mediated by a nonprenylation pathway is the direct action that statins have on leukocyte-function antigen-1. Statins have been shown to effectively bind this molecule and prevent lymphocyte adhesion during an inflammatory cascade [35].

Once leukocytes have attained adhesion to the vascular wall, they migrate to specific areas of inflammation in the subendothelium. This process is regulated by chemokines, and statins are known to interfere with the expression and function of chemokine monocyte chemoattractant protein-1 and IL-8. Inhibiting these mediators has been shown to reduce macrophage accumulation [36].

Statins also play a role in cellular apoptosis, although the exact mechanism is unclear. At high in vitro concentrations, they promote cellular death by interfering with Rho prenylation. Exposure of SMCs to statins reduced the prenylation of p21-RhoB, a key regulator of apoptosis [37]. Apoptosis itself probably plays a role in facilitating vascular remodeling and preventing atherosclerotic plaque rupture. It is evident that increased levels of apoptosis occur in atherosclerotic plaques when compared with normal vessels because mitotic and apoptic indices of normal adult arteries are relatively low [38]. One mechanism in which statins may have a positive effect on cellular viability is by reducing inflammation within lesions that are potentially apoptic. This effect may have more to do with inducing higher levels of eNOS, which promotes an antioxidant effect that has been shown to reduce endothelial cell apoptosis [27]. The actual influence of statins at in vivo concentrations has been shown to be distinctly different than its in vitro effect. Weis *et al.* [39] demonstrated that statins have a biphasic effect that is proangiogenic at low- to mid-range statin doses and angiostatic at high-dose human concentrations. These effects were reversed in the presence of GGPP, supporting the role of the HMG CoA reductase pathway in cellular apoptosis [39]. If statins can promote both angiogenic and angiostatic effects, this has potential implications for ischemic diseases as well as for tumor growth and diabetic proliferative diseases.

In regards to vascular disease, it is now evident that apoptosis of SMCs plays a direct role in plaque rupture and thrombosis. Using an animal model of plaque rupture in mice, it has been shown that induction of SMC apoptosis in the fibrous cap of plaques resulted in rupture and thrombosis of the plaque. [40]. The role of macrophages in this process is understood less well. The thrombogenic core of an atherosclerotic lesion is separated from the blood stream by a fibrous cap. Collagen is the main component of fibrous caps; however, this undergoes degradation by macrophages, rendering it vulnerable to instability and potential rupture. Macrophages secrete proteolytic enzymes known as metalloproteinases (MMPs), which not only weaken the fibrous cap but also promote the migration of other macrophages. The enzymatic activity of these proteases is also dependent on its interaction with tissue inhibitors of MMP (TIMPs). Statins have been shown to lower the production of a broad range of MMPs and also increase the production of TIMP-1, probably via inhibition of Rho protein prenylation. In actuality, both mechanisms may underlie stabilization of fibrous caps [41]. In theory, a reduction in macrophages should improve plaque stability due to decreased local inflammation and decreased MMP activity. However, a decrease in macrophage numbers prevents active scavenging of apoptic SMCs, an event already known to play a role in plaque rupture [42•]. Current understanding supports the idea that regulation of MMP/TIMP activity and reduction of lipids and macrophages contribute to stabilization of cholesterol plaques.

Should destabilization and rupture of a plaque occur, the lipid core will come into direct contact with blood. In this setting, the lipid core becomes a procoagulant and sets into motion the coagulation cascade that ultimately results in thrombus formation. Statins have been shown to interfere with this process on multiple levels. Several statins have been shown to inhibit production of a procoagulant tissue factor by macrophages and endothelial cells [43]. Statins have also been found to have activity in promoting clot fibrinolysis by reducing the expression of plasminogen activator inhibitor-1 and increasing that of tissue-plasminogen activator [44,45]. Platelet function may also be modulated by statins. Hyperlipidemia itself promotes increases in platelet reactivity, and patients undergoing statin therapy have lower levels of cholesterol content in their membranes [46]. Reduced expression of cyclooxygenase-2 and thromboxane also decrease platelet reactivity [47]. These mechanisms probably translate into an overall decreased thrombogenic potential of platelets.

It is evident that statins have a multiplicity of roles in their effect upon immune and inflammatory responses. A majority of these effects occur as a direct result of inhibi-

tion of GGPP and FPP pathways. The numerous proteins that these compounds prenylate help to play vital roles in all phases of plaque development, as well as the final rupture and procoagulant setting that ultimately results in ischemia.

Clinical Roles

A clearer understanding of cellular pathways continues to create interest in discovering the multiple benefits of statin medications. The information already presented gives several roles in which statins can reduce vascular risk. More recent evidence suggests that these medications may have importance in other areas of medicine. In fact, the anti-inflammatory benefit of statins was recently utilized in a study to test the theory that they might have a protective benefit against severe sepsis. Utilizing statins with empiric antibiotic therapy showed that these medications may be associated with reduced rates of severe sepsis and intensive care unit admission of patients with acute bacterial infections [48].

Statin therapy may also have an emerging role in the treatment of both heart failure and transplant. The proposed benefits of improved NO expression and function, and ultimately their anti-inflammatory effect, resulted in improved cardiac function in a group of patients receiving 14 weeks of statins. Statins decreased levels of tumor necrosis factor and IL-6 while improving functional status of the patients [49]. Statin treatment after heart transplant increased first year survival and reduced evidence of coronary vasculopathy [50]. The rapid rate of arteriosclerosis after transplant is thought to be primarily immunologic in origin. SMCs have been shown to play a central role, and transplant-associated arteriosclerosis is an event marked by the rapid proliferation of these cells. Statins ultimately arrest SMC production by arresting cell cycle development between G phase and S phase transition [51].

Statin-induced apoptosis highlights another area of clinical investigation that has implications for cancer risk reduction and/or treatment. Reports from recent years have actually raised clinical concerns that statins may promote tumor progression by stimulating angiogenesis [52]. As stated previously, there does appear to be some biphasic effect of statins in that at high in vitro doses cellular apoptosis is induced. Sata *et al*. [53•] make a further distinction by advancing the concept that the proangiogenic or antiangiogenic effects of statins might be more dependent on local tissue factors (*ie*, statins increase collateral vessel growth under conditions of ischemia, yet inhibit angiogenesis in the presence of atherosclerosis, tumor, and diabetic proliferative diseases). This view would seem to be more consistent with prior meta-analysis that did not demonstrate an increased cancer risk in long-term statin users [54]. To date, the clinical trials utilizing statins for their antitumor effect have been relatively disappointing, although they have demonstrated some synergism with chemotherapy [55]. What may be more immediately promising is their role in actually achieving risk reduction. A report at the American Society of Clinical Oncology meeting of 2004 cited a rather dramatic 51% reduction in the risk of colorectal cancer, an effect that was specifically tied to statin use [56].

Other specialties also indicate a benefit in some specific disease states. Oral simvastatin was recently shown to decrease the number of gadolinium-enhancing lesions in patients with relapsing-remitting multiple sclerosis [57]. Rheumatology literature is also reporting benefits ranging from decreased levels of proteinuria in systemic lupus erythematosus to reduction of CRP levels associated with clinical benefit in rheumatoid arthritis patients [58]. Both of these studies give credence to the anti-inflammatory effects of statins.

It should be noted that initial in vitro and animal studies that support specific clinical effects of statins do not always reach significance in the general population. This is particularly true in the case of bone mineral density and Alzheimer's disease, neither of which showed significant benefit during statin treatment [59].

Conclusions

The data presented here show a wide range of effects for statin medications. Of course, the actual clinical benefit of their pleiotropic effects is sometimes hard to quantify. In terms of vascular disease, separating the lipid-lowering effect from the pleiotropic effect is difficult because there is some overlap in their mechanisms. Clinical evidence does support the idea of a pleiotropic benefit that functions independent of cholesterol reduction; however, it is difficult to determine which pleiotropic effect is actually clinically relevant. The inhibition of mevalonate synthesis has impact on a plethora of cell signaling pathways important for endothelial and inflammatory cell regulation. It is evident that these medications will continue to have a relevant role in primary and secondary atherosclerotic disease prevention. What is less clear is how wide a scope of influence they will have on medicine in general.

Acknowledgment

I wish to dedicate this paper to Dr. Michael Clearfield, for his support and oversight.

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