Statins Therapy: Effects on Plasma Fibrinogen Levels and Fibrinolysis

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Abstract
Elevated plasma fibrinogen levels have been identified as an independent and strong risk factor for cardiovascular disease. At present, there are no selective oral agents that lower fibrinogen; however different drugs can influence its levels as ticlopidine (inhibitor of platelet aggregation) and fibrates (lipid lowering drugs). Statins lower cholesterol by inhibiting HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase, which catalyzes the conversion of HMG-CoA to mevalonate, the rate limiting step in cholesterol biosynthesis. In addition to lowering cholesterol, several non-lipids related benefits of statins have been reported. Briefly, statins improve endothelial function, modulate the inflammatory response, may stabilize atherosclerotic plaques, restrain thrombus formation, and others. Many of these are mediated by their ability to block the synthesis of important isoprenoid intermediates, which serve as lipid attachments for a variety of intracellular signaling molecules (Rho, Ras, and Rac). The beneficial effect of statin on plasma fibrinogen concentration still controversial. Although several studies have shown a mild decrease in plasma fibrinogen (mostly when the Clauss method is used), many others fail to find an effect of statins on plasma fibrinogen concentration. In vitro studies using different cell types have shown that statins increase tPA and decrease PAI-1 levels; however, clinical results are ambiguous. Statins modify fibrin structure leading to increased clot lysis rate and clot permeability, by decreasing tissue factor expression that alters thrombin formation.

Statins
Statins are drugs widely prescribed in cholesterol-lowering therapy. HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase (HMGR) catalyzes the conversion of HMG-CoA to mevalonate, the rate limiting step in cholesterol biosynthesis in the liver and other tissues [1-3]. This step is the four-electron reductive deacetylation of HMG-CoA to CoA and mevalonate by HMGR, a reaction that proceeds as follow:

\[
(S) - \text{HMG-CoA} + 2\text{NADPH} + 2\text{H}^+ \rightarrow (R) - \text{mevalonate} + 2\text{NADP}^+ + \text{CoASH}
\]

Statins are competitive inhibitors of HMGR suppressing the biosynthesis of isoprenoids and sterols (Figure 1). The reduction in intracellular cholesterol concentration stimulates the expression of LDL-receptors on the hepatocyte cell surface which enhances removal of LDL cholesterol (LDL-C) from the circulation [1,3]. Compstatin is the first statin discovered from fungi [4]. All statins share an HMG-like moiety; lovastatin, pravastatin and simvastatin are fungal-derived inhibitors of HMGR, while atorvastatin, cerivastatin, fluvastatin, pravastatin, pitavastatin, and rosuvastatin, are fully synthetic inhibitors of HMGR suppressing the biosynthesis of isoprenoids and sterols (Figure 1). The reduction in intracellular cholesterol concentration stimulates the expression of LDL-receptors on the hepatocyte cell surface which enhances removal of LDL cholesterol (LDL-C) from the circulation [1,3]. Compstatin is the first statin discovered from fungi [4]. All statins share an HMG-like moiety; lovastatin, pravastatin and simvastatin are fungal-derived inhibitors of HMGR, while atorvastatin, cerivastatin, fluvastatin, pravastatin, pitavastatin, and rosuvastatin, are fully synthetic compounds [3]. Cerivastatin was withdrawal in 2001 from the market due to potentially serious side efects [1].

The chemical structures of the different statins are shown in figure 2. These structures contain an analogue of the target enzyme substrate, HMG-CoA: a complex hydrophobic ring structure that is covalently linked to the substrate analogue and is involved in binding of the statin to the reductase enzyme; side groups on the rings that define the solubility properties of the drugs.

All statins are competitive inhibitors of HMGR with respect to the binding of the substrate HMG-CoA but not for that of the co-enzyme NADPH, suggesting that their HMG-CoA-like moieties bind to the HMG-CoA-binding portion of the enzyme active site.

In addition to lowering cholesterol, statins appear to have a number of pleiotropic effects, nonlipid related [5-7], due to the inhibition of mevalonate synthesis. Statins improve endothelial function, modulate the inflammatory response, have plaque stabilization effects, and restrain thrombus formation, among others. Many of these pleiotropic effects of statins are mediated by their ability to block the synthesis of important isoprenoid intermediates of the cholesterol biosynthesis pathway, such as farnesyl-pyrophosphate and geranylgeranyl-pyrophosphate, which serve as important lipid attachments for the post translational modification of a variety of proteins such as heterodimeric G proteins, heme-a, nuclear lamins, and small guanosine triphosphate (GTP)-binding proteins (Rho, Ras, and Rac) [8]. In this way, protein isoprenylation allows the covalent attachment, subcellular localization, soluble, and non-lipid related benefits of statins have been reported. Briefly, statins improve endothelial function, modulate the inflammatory response, may stabilize atherosclerotic plaques, restrain thrombus formation, and others. Many of these are mediated by their ability to block the synthesis of important isoprenoid intermediates, which serve as lipid attachments for a variety of intracellular signaling molecules (Rho, Ras, and Rac). The beneficial effect of statin on plasma fibrinogen concentration still controversial. Although several studies have shown a mild decrease in plasma fibrinogen (mostly when the Clauss method is used), many others fail to find an effect of statins on plasma fibrinogen concentration. In vitro studies using different cell types have shown that statins increase tPA and decrease PAI-1 levels; however, clinical results are ambiguous. Statins modify fibrin structure leading to increased clot lysis rate and clot permeability, by decreasing tissue factor expression that alters thrombin formation.

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Figure 1: Mevalonate pathway in mammalian cells. PP: pyrophosphate. Adapted from Corsini et al.[106].

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- The chemical structures of the different statins are shown in figure 2.
- These structures contain an analogue of the target enzyme substrate, HMG-CoA: a complex hydrophobic ring structure that is covalently linked to the substrate analogue and is involved in binding of the statin to the reductase enzyme; side groups on the rings that define the solubility properties of the drugs.

- All statins are competitive inhibitors of HMGR with respect to the binding of the substrate HMG-CoA but not for that of the co-enzyme NADPH, suggesting that their HMG-CoA-like moieties bind to the HMG-CoA-binding portion of the enzyme active site.

- In addition to lowering cholesterol, statins appear to have a number of pleiotropic effects, nonlipid related [5-7], due to the inhibition of mevalonate synthesis. Statins improve endothelial function, modulate the inflammatory response, have plaque stabilization effects, and restrain thrombus formation, among others. Many of these pleiotropic effects of statins are mediated by their ability to block the synthesis of important isoprenoid intermediates of the cholesterol biosynthesis pathway, such as farnesyl-pyrophosphate and geranylgeranyl-pyrophosphate, which serve as important lipid attachments for the post translational modification of a variety of proteins such as heterodimeric G proteins, heme-a, nuclear lamins, and small guanosine triphosphate (GTP)-binding proteins (Rho, Ras, and Rac) [8]. In this way, protein isoprenylation allows the covalent attachment, subcellular localization, and biological function.
patients with primary hypercholesterolemia [34]. and by 9% in patients with thrombotic vascular disease [41]. Fenofibrate fibrinogen levels by 26% in patients with peripheral arterial disease [40] in non-insulin-dependent diabetic patients [39]. Clofibrate reduced levels by 10 to 40% in patients with atherosclerosis [37,38] and 25% the incidence of CHD [35,36].

No all fibrates reduce fibrinogen levels, gemfibrozil has shown to reduce approximately by 10 to 25% plasma fibrinogen levels (fibric acid analogs, lipid lowering drugs). Ticlopidine has repeatedly influence its levels as an additional effect [22,24-28]. The most studied agents for lowering fibrinogen [20-23]; however, different drugs can and pro-coagulants effects [7]. At present, there are no selective oral macrophages, blood viscosity, and by producing pro-inflammatory the activity of specific receptors located on platelets and monocytes/ by affecting the functioning and permeability of vascular endothelium, stimulating both proliferation and migration of smooth muscle cells, the reaction that consequently increases fibrinogen levels [14].

Fibrinogen exerts its complex pro-atherogenic action by stimulating both proliferation and migration of smooth muscle cells, by affecting the functioning and permeability of vascular endothelium, the activity of specific receptors located on platelets and monocytes/macrophages, blood viscosity, and by producing pro-inflammatory and pro-coagulants effects [7]. At present, there are no selective oral agents for lowering fibrinogen [20-23]; however, different drugs can influence its levels as an additional effect [22,24-28]. The most studied drugs are ticlopidine that inhibit platelet aggregation, and fibrates (fibrin acid analogs, lipid lowering drugs). Ticlopidine has repeatedly shown to reduce approximately by 10 to 25% plasma fibrinogen levels [24,29-32]. No all fibrates reduce fibrinogen levels, gemfibrozil has been reported to increase circulating fibrinogen [33,34] and reduces the incidence of CHD [35,36].

Different studies have found that bezafibrate reduced fibrinogen levels by 10 to 40% in patients with atherosclerosis [37,38] and 25% in non-insulin-dependent diabetic patients [39]. Clofibrate reduced fibrinogen levels by 26% in patients with peripheral arterial disease [40] and by 9% in patients with thrombotic vascular disease [41]. Fenofibrate and bezafibrate reduced fibrinogen by 9 and 15%, respectively, in patients with primary hypercholesterolemia [34].

The mechanisms by which fibrates lower fibrinogen levels have not fully elucidated; however, several mechanisms can explain its action [23]: 1) activation of peroxisome proliferation-activated receptor-alpha (PPARα) [42] that inhibits C/EBPβ (transcription factor for FGA and FGB), 2) inhibition of the increase in cAMP induced by adrenaline leading to a decrease in IL-6 production, 3) inhibition of lipolysis by reduction of free fatty acids, 4) inhibition of acetyl-CoA carboxylase (the rate-limiting enzyme in fatty acid synthesis) affecting the hepatic secretion efficiency.

The beneficial effect of statins on fibrinogen plasma concentration is not clear, varying between and within the different statins [7,23,43,44]. For example, it has been reported that atorvastatin [45-47], fluvastatin [48], simvastatin [47], and lovastatin [49] increase fibrinogen levels. Other studies have found that atorvastatin [50,51], fluvastatin [52], rosuvastatin [53], pravastatin [54,55], simvastatin [47,56] decrease fibrinogen levels, and others that atorvastatin [57-62], pravastatin [57,60-63], rosuvastatin [64], simvastatin [34,57,62], fluvastatin [62], and lovastatin [57,62] did not change fibrinogen levels.

The discrepancy among the results found on the effects of statin in fibrinogen levels have been attributed to different inclusion criteria in clinical trials, different methods of measuring plasma fibrinogen levels, where the nephelometric and turbidimetric method showed the greatest values. The seasonal variation [7] and the genetic predisposition of fibrinogen concentration [65] were not considered. Also, it has to be remarked that, in general, the number of patients included in the clinical trials are low.

Nevertheless, most of the studies found that pravastatin decreases fibrinogen levels and simvastatin has no effect on fibrinogen [43,47,55]. Regarding pitavastatin, no information was found in the literature revised, and in a recent publication the effect on fibrinogen was not included among its pleiotropic effects [66].

Different studies have shown that statins can decrease IL-6 mRNA expression and secretion, thus is reasonable to expect that statins can diminish plasma fibrinogen. Inoue et al. [67] have studied the effect of several statins (pravastatin, simvastatin, fluvastatin, and cerivastatin) on the production and expression of inflammatory cytokines in cultured human umbilical vein endothelial cells (HUVECs) and found that all HMG-CoA reductase inhibitors significantly reduced IL-6 protein levels.

Using cultured human pulmonary artery smooth muscle cells (PASMCs) Li et al. [68] found that stimulation of these cells with C-reactive protein (CRP) resulted in elevated IL-6 secretion and mRNA expression that were dose- and time-dependent. Preincubation of PASMCs with atorvastatin significantly decreased the secretions of IL-6 induced by CRP. Also, experiments performed using human vascular smooth muscle cells (VSMCs) in the presence of fluvastatin decreases IL-6 synthesis through the inhibition of the Rho pathway [69]. Kagami et al. [70] using bone marrow-derived mast cells (BMMCs) found that simvastatin inhibited IL-6 production from LPS-stimulated BMMCs. Other approaches to study the effect of statins on IL-6 consisted to cultivate fibroblast-like synovioocytes (FLS) from rheumatoid arthritis patients. The secretion of IL-6 by FLS was reduced by the presence of simvastatin in a time- and dose-dependent manner [71]. Interestingly, the determination of IL-6 from carotid atherosclerotic plaques extracted from 378 patients undergoing carotid endarterectomy revealed that IL-6 levels were diminished on the plaques of patients treated with pravastatin, simvastatin, and atorvastatin [72]. In animal models have also been found that treatment with statins decreased IL-6 expression [73,74]. For example, Wistar rats infused with angiotensin II and
receiving atorvastatin had decreased expression of IL-6 compared to those without statin treatment [73].

**Statins and Fibrinolysis**

In mammalian blood the fibrinolytic system has the function of dissolving the formed fibrin clots in order to maintain the patency of the vascular system [75]. The enzyme that degrades fibrin circulates in the bloodstream as an inactive proenzyme, plasminogen, which is converted to plasmin by the presence of two plasminogen activators: the tissue-type plasminogen activator (tPA) and the urokinase-type plasminogen activator (uPA) [76]. The activity of the fibrinolytic system is regulated by the plasminogen activator inhibitor (PAI-1), by the thrombin-activable fibrinolysis inhibitor (TAFI), and by α2-antiplasmin, a direct inhibitor of plasmin.

The contribution of endothelial cells (ECs) to fibrinolysis varies with their metabolic status, i.e., quiescent vs. activated, their site in the vasculature, and the concentration of other hemostatically active molecules in the local plasma milieu [77]. Only a distinct subpopulation of ECs in the microvasculature is likely associate in vivo to tPA production [78]. The endothelium also can produce large amounts of PAI-1 [79]. Quiescent ECs express little or no PAI-1; however, the endothelium over-expresses PAI-1 in virtually all tissues after exposure to inflammatory stimuli [80].

The dissolution of the fibrin clots is achieved by the formation of a ternary complex between tPA-plasminogen and fibrin (cofactor of the reaction) [81], resulting in the formation of plasmin on the fibrin surface; whereas uPA binds to its receptor (u-PAR) resulting in enhanced activation of cell-bound plasminogen [75]. Plasmin cleaves fibrin at specific lysine residues, generating free C-terminal lysine residues that are removed by TAFI, down regulating the fibrin lysis process [82].

It has been found that statins have a pro-fibrinolytic effect by increasing tPA activity, as the result of increasing tPA expression and by diminishing PAI-1 expression [7]. Experiments performed in vitro with different ECs type, as rat aorta, human umbilical vein, human peritoneal mesothelial cells, and human aortic smooth muscle cells, incubation with lovastatin, simvastatin, fluvastatin and pitavastatin increased the level and activity of tPA, and the level of tPA mRNA [83-86]; and incubation with lovastatin, simvastatin, fluvastatin, atorvastatin and pitavastatin decreased the level, activity and synthesis of PAI-1 [83-89]. These effects can be reversed in the presence of mevalonate [83,85].

It has been recently elucidated the mechanism by which fluvastatin alters the balance of the endothelial cell plasminogen activation system [85]. The statin effect can be partially reproduced by inhibition of several Rho family GTPases, and completely by inhibition of actin depolymerization. Furthermore, the mechanism involved in the changes of tPA and PAI-1 expression are distinct, where tPA elevation requires p38 MAP kinase activity.

While in vitro studies are coherent about the beneficial role of statins on promoting fibrinolysis, clinical trials have shown discrepancies. In a study, 20 patients with type 1 diabetes and dyslipidemia were treated with atorvastatin (80 mg/day) during 6 months, resulting in no change of tPA and PAI-1 antigen after treatment [59]. In another study, 71 patients with primary hypercholesterolemia were assigned randomly to treatment with either pitavastatin (2 mg/day) or atorvastatin (10 mg/day) during 3 months, and the level of PAI-1 (as fibrinolytic parameter tested) did not change during this period [90]. In a meta-analysis study of patients with high cholesterol or stable coronary disease, only one of 14 studies reported a change with statin therapy [91]. In the DALY study, which studied stable subjects with type 2 diabetes mellitus, reported significant lower PAI-1 levels in subjects randomized to atorvastatin 10 mg or 80 mg [92].

The factors that may contribute to the study-dependent effects of statins on the level and activity of tPA and PAI-1 are: different inclusion criteria, drug- and dose-related differences, the duration of treatment, diurnal variations in fibrinolytic system activity, and/or methodological differences [7]. Furthermore, adipose tissue can produce PAI-1 [93], tPA antigen increases with age [94,95] and body mass index [94,96]. In randomized trials, weight loss reduces tPA/PAI-1 concentrations [96,97], and exercise training improves tPA release from endothelium in vivo [95]. Other important aspects to be considered is that tPA antigen assays do not distinguish active free tPA from inactive tPA bound in a tPA/PAI-1 complex; measurement of PAI-1 requires special blood collection and sample preparation techniques, as degranulation of platelets during routine phlebotomy and sample preparation spuriously elevates PAI-1 levels [98].

Furthermore, statins affect fibrin structure leading to faster fibrin clot lysis rate and clot permeability. A study performed in 30 subjects with cholesterol below 3.4 nM found that the administration of simvastatin (40 mg/day) during 3 months increases significantly clot permeability by 4.4% and shortened the clot lysis rate by 11.2% [99]. In another study, 56 patients with chronic obstructive pulmonary disease received simvastatin (40 mg/day) during 3 months, and a significant shortening of clot lysis rate and increased fibrin permeability were found [100]. Also patients with history of myocardial infarction that were randomly allocated with atorvastatin (40 mg/day; n=12), and simvastatin (40 mg/day; n=13) during 28 ± 2 days, showed shorter fibrinolysis time and increased permeability post-treatment [101]. Tehrani et al. [59] have studied the effect of atorvastatin (80 mg/day, during two months) in clot permeability in a group of 20 patients with type 1 diabetes and dyslipidemia that resulted in a significant increase in fibrin clot permeability. The increase in fibrin porosity, reflected in higher permeation values after statin treatment, was attributed to the formation of thicker fibers [101]. Fibrin structure directly affects the rate of fibrinolysis [102]. In general, clots made up of thicker fibers are digested more rapidly than those made up of thinner fibers [102-104]. These findings can be related to that statins down regulate tissue factor expression, and as consequence thrombin formation is diminished [7,44]. Fibrin formed in the presence of lower thrombin concentration is composed by thicker fibers, big pores, and less branch points compared to that formed in the presence of higher thrombin concentration [105].

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