Review

The role of dyslipidemia and statins in venous thromboembolism

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Abstract

Recent studies have proposed an association between hyperlipidemia and venous thromboembolism (VTE). We review the epidemiological evidence linking dyslipidemia with VTE and examine several possible underlying mechanisms. We discuss the possible role of HMG CoA reductase inhibitors (statins) in the prevention and treatment of VTE and suggest future directions for research.

Keywords deep vein thrombosis, HMG CoA reductase inhibitors, hyperlipidemia, lipids, statins, venous thromboembolism

Any textbook of cardiovascular medicine published within the past 20 years is sure to contain a lengthy discussion of the role of dyslipidemia in the development of both atherosclerosis and acute arterial thrombosis [1]. Elevated total serum cholesterol, elevated low-density-lipoprotein cholesterol (LDL-C), and decreased high-density-lipoprotein cholesterol (HDL-C) are all well-established risk factors for coronary heart disease [1], while there is still debate about the contribution of hypertriglyceridemia to this process [2].

Perhaps it is not surprising that major textbooks of hematology [3] and thrombosis medicine [4] do not mention any role for dyslipidemia in the pathogenesis of venous thromboembolism (VTE). One reason may be the absence of pathological evidence of lipid deposition within either the venous system or the so-called 'red thrombus' that may develop therein [5]. Accordingly, there has been little hypothesis-generating research exploring the interplay between lipid dysfunction and VTE. In the following paper, we discuss the evidence linking hyperlipidemia to the formation of VTE and the possible role of HMG CoA reductase inhibitors (statins) in its prevention and treatment.

What is the epidemiological evidence linking dyslipidemia to VTE?

Two cohort [6,7] and six case–control studies [8–13] have examined the relation between dyslipidemia or serum lipoprotein (a) [Lp(a)] and VTE. Goldhaber *et al* retrospectively evaluated several risk factors among 46 adults diagnosed with pulmonary embolism at autopsy and 3424 individuals enrolled at baseline in the Framingham Study [6]. Total serum cholesterol was observed to be a significant risk factor for pulmonary embolism in women ($P = 0.049$), but not men ($P > 0.05$). In the Nurses' Health Study, 280 middle-aged women with a self-reported history of pulmonary embolism were compared with a cohort of 112,542 women without a history of pulmonary embolism [7] (Table 1). They found that those with a self-reported diagnosis of hypercholesterolemia were at no increased risk for pulmonary embolism (multivariate relative risk 1.1, 95% confidence interval [CI] 0.7–1.5).

Kawasaki *et al* were the first to demonstrate an association between hypercholesterolemia and objectively verified deep vein thrombosis (DVT) of the leg among middle-aged

ASA = acetylsalicylic acid; CABG = coronary artery bypass graft; CI = confidence interval; DVT = deep vein thrombosis; FVII:C = factor VII coagulant; HDL-C = high-density-lipoprotein cholesterol; HERS = Heart Estrogen Replacement Study; HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; HR = hazard ratio; LDL-C = low-density-lipoprotein cholesterol; Lp(a) = lipoprotein (a); OR = odds ratio; VTE = venous thromboembolism.

Table 1

Epidemiological studies of the associated risk between dyslipidemia and venous thromboembolism (VTE)

Study [reference]	No. cases/ controls	Mean age of cases (years)	VTE type	% cases with situational risk factors*	Serum lipid risk factor(s)	Prevalence of lipid risk factor among cases (%)	Odds ratio (95% CI) for VTE
Goldhaber *et al* [7]	280/112542	30–55	PE	55	Self-reported elevated TC	18	1.1 (0.7–1.5)
Kawasaki *et al* [8]	109/109	50	Leg DVT	34	TC > 5.7 mmol/L and TG > 1.7 mmol/L	23	5.1 (2.0–13.0)
					TC > 5.7 mmol/L and TG ≤ 1.7 mmol/L	26	2.6 (1.2–5.3)
Nowak-Gottl *et al* [10]	186/186	5	Any VTE	60	Lp(a) > 30 mg/dL	42	7.2 (3.7–14.5)
von Depka *et al* [11]	685/266	34	Any VTE	21	Lp(a) > 10 mg/dL	40	1.6 (1.2–2.2)
					Lp(a) > 20 mg/dL	25	2.2 (1.5–3.3)
					Lp(a) > 30 mg/dL	20	3.2 (1.9–5.3)

*Defined as either immobilization (i.e. trauma, surgery, or bedridden) or presence of an indwelling venous catheter at the site of thrombosis. DVT = deep vein thrombosis; Lp(a) = lipoprotein (a); PE = pulmonary embolism; TC = total cholesterol; TG = triglycerides; VTE = venous thromboembolism.

men and women [8]. In comparison with matched controls, the risk for DVT was greatest in the presence of elevated fasting total serum cholesterol, either with or without concomitant hypertriglyceridemia (Table 1). Among individuals whose total serum cholesterol was below 5.8 mmol/L, isolated hypertriglyceridemia was not a risk factor for DVT (odds ratio [OR] 0.9, 95% CI 0.4–2.1).

McColl and colleagues compared 62 women with objectively confirmed VTE before age 50 years with 98 healthy, age-matched controls and observed a lower mean fasting total serum cholesterol among cases versus controls (4.74 versus 5.13 mmol/L, respectively; $P < 0.02$) [9]. Although the mean LDL-C was also lower among the cases (2.76 versus 3.18 mmol/L, respectively; $P = 0.01$), serum triglycerides were slightly higher (1.29 versus 1.09 mmol/L, respectively; $P = 0.02$), and there was no difference seen for serum Lp(a) ($P = 0.47$).

Two subsequent studies, both of similar design, evaluated the risk for VTE in the presence of elevated serum Lp(a) in children [10] and adults [11] (Table 1). In the pediatric study, an Lp(a) concentration at or above the upper-quartile value of 30 mg/dL was significantly associated with VTE, in comparison with the lowest-quartile value. This effect persisted among a subgroup of children without an underlying illness (adjusted OR 7.1, 95% CI 2.7–18.6) [10]. In the study among adults, an Lp(a) concentration greater than 30 mg/dL was also associated with VTE [11], even after adjustment for the presence of other common thrombophilia risk factors (adjusted OR 2.8, 95% CI 1.6–4.9) [11]. Furthermore, the risk for VTE in that study rose linearly with increasing Lp(a) concentrations (Table 1).

In a seventh study, Lp(a) concentrations were measured in 64 patients with previous VTE and 64 matched controls with either atrial fibrillation or valvular heart disease [12]. The median Lp(a) concentrations were not significantly different between cases and controls (69 versus 83 mg/L, respectively; $P = 0.34$). An eighth group of investigators compared plasma Lp(a) concentrations in 40 patients with chronic thromboembolic pulmonary hypertension, 50 patients with primary pulmonary hypertension, and 50 matched disease-free controls [13]. In that study, median Lp(a) concentrations were higher in subjects with chronic thromboembolism (26.7 mg/dL) than in those with either primary pulmonary hypertension (9.7 mg/dL) or no disease (7.0 mg/dL) [13].

Although some studies suggest an association between hyperlipidemia and VTE, their results conflict somewhat. The degree of precision and moderately high effect size seen in the three positive studies (Table 1), considered in conjunction with a 20% or greater prevalence of dyslipidemia among the cases, suggests that elevated concentrations of total serum cholesterol and Lp(a) may be important risk factors for VTE in adults and children. While some studies used fasting samples, only two described collecting specimens at least 3 months after the initial thrombotic event [10,11]. Specimen collection remote from the initial VTE event may be important, since lipids are known to decline in the presence of acute vascular events, such as VTE or myocardial infarction [14,15], potentially introducing a negative confounding effect between dyslipidemia and VTE. In the two negative cohort studies, their methods for lipid measurement were not reported [6,7], while in the Nurses' Health Study, recognition of pulmonary embolism and hypercholesterolemia depended on a self-reported diagnosis of both diseases [7], thereby casting some doubt on the validity of their findings. Future studies could help to clarify whether dyslipidemia is a causal risk factor for VTE and, if so, which lipid molecule is most thrombogenic.

Why might lipids induce venous thrombosis?

Before the routine use of acetylsalicylic acid (ASA) and heparin, patients with acute myocardial infarction previously experienced high rates of VTE, often independent of their degree of immobilization during the recovery period [16–18]. Since then, systemic factors such as homocysteine [19–21] and antiphospholipid antibodies [22,23] have been shown to activate the coagulation cascade or impair the process of fibrinolysis, resulting in both arterial and venous thrombosis [21,22]. Similarly, if dyslipidemia is a risk factor for VTE, just as for arterial thrombosis, then the underlying mechanism is also probably best conceptualized as a systemic, rather than merely a depositional or 'venosclerotic' [24], disorder within the vessel wall.

Circulating lipids appear to have both prothrombotic [25] and endothelium-altering properties [26]. For example, studies in rats suggest about a 2.3-fold greater generation of thrombi in hyperlipidemic than normolipidemic controls, associated with an 8-fold higher rate of platelet activation [27]. The thrombogenic potential of Lp(a) may be explained at several levels. First, the apolipoprotein B-100 molecule that forms Lp(a) is commonly associated with circulating LDL-C and postprandial triglyceride-rich particles [28]. Ingestion of a fatty meal appears to cause venous endothelial dysfunction in healthy adults [29], while postprandial lipemia has been associated with transient changes in factor VII coagulant (FVII:C) activity in humans [30], suggesting a temporary and reversible hypercoagulable state [25]. Furthermore, among individuals with venographically proven DVT, FVII:C activity was significantly correlated with triglyceride concentrations ($r = 0.36$, $P = 0.021$) [31]. Since neither FVII concentrations, nor the *Msp*I polymorphism in the *FVII* gene, are themselves demonstrable risk factors for VTE [32], perhaps FVII:C requires specific lipid activation to be thrombogenic, as after the ingestion of a fatty meal [30].

Lp(a) is also structurally and functionally homologous to plasminogen, leading to potential competitive binding to fibrin and hence to impaired fibrinolysis [33]. Of 136 individuals with ischemic stroke, those with a suspected cardioembolic mechanism (i.e. atrial fibrillation or left ventricular thrombus) had significantly higher concentrations of Lp(a) than those with a noncardioembolic source, implying a greater association between Lp(a) and acute arterial thrombosis than between Lp(a) and progressive atherosclerosis [34]. Thus, it is conceivable that Lp(a) and associated lipid-rich molecules play a role in the initiation or progression of VTE. VTE formation occurs through systemic activation of platelets and specific coagulation factors, in addition to either direct or indirect impairment of the venous endothelium.

Why might statins reduce the risk of venous thrombosis?

There now exists a compelling body of evidence for both early and late benefits of statin therapy in the secondary prevention of coronary heart disease and stroke [35–38]. Because these agents are also effective in individuals with 'normal' baseline lipid measurements [37,38], it has been suggested that they may also possess antithrombotic [39] and anti-inflammatory [40] properties.

Recent studies suggest that statins may alter elements within the vascular endothelium and coagulation cascade in a manner consistent with an antithrombotic effect. For example, indirect markers of thrombin generation, such as prothrombin fragment 1+2, appear to be significantly reduced after 6 months of pravastatin therapy in women [41], with a similar effect observed with simvastatin use in men [42]. One hypothesis to explain these effects is that these agents inhibit platelet-derived protease-activated receptor-1 (PAR-1) and tissue factor upregulation, leading to thrombin generation [43]. Others have demonstrated a reduction in concentrations of both FVII:C [44] and soluble thrombomodulin [45] with statin use. There may also be a rapid biological effect of statins on endothelial barrier permeability and nitric oxide production. For example, exposure *in vitro* of human umbilical vein or aortic endothelial cell monolayers to simvastatin for 24 hours attenuates thrombin-induced endothelial barrier dysfunction by 55%. This effect is related to both the dose and the duration of drug exposure [46]. Exposure *in vitro* of isolated human endothelial cells from the saphenous vein to cervistatin has also led to a twofold rise in production of both endothelial nitric oxide synthase and nitric oxide [47].

Once a saphenous vein coronary artery bypass graft (CABG) is transplanted into the aortocoronary circulation, it typically takes on certain morphological features akin to those of native arteries [48]. However, the vessel also retains some of its original venous properties, and some venous grafts thrombose within days or weeks of transplantation [48], well in advance of the more common scenario of occlusive 'venosclerosis' [24]. This may serve as an indirect human model for the interplay between dyslipidemia, statin use, and venous thrombosis.

For example, in a retrospective series of 212 consecutive undergoing percutaneous angioplasty of occluded saphenous vein grafts, the most significant risk factor for the development of restenosis unstable angina was dyslipidemia (adjusted OR 3.55, 95% CI 1.64–8.39) [49]. Of the 118 individuals with dyslipidemia, use of lipid-lowering therapy, principally statins, was associated with a lower risk of restenosis and unstable angina (crude OR 0.41, 95% CI 0.17–0.97).

Dyslipidemia was also found to be a major prognostic risk factor for saphenous vein graft disease in the Post-

coronary Artery Bypass Graft (Post-CABG) trial [50]. Among patients randomized to receive high-dose lovastatin (40 mg daily), there was a significant reduction in both the rate of progression of saphenous vein graft occlusion and the need for coronary revascularization, in comparison with patients given low-dose lovastatin (2.5 mg daily) [51]. Interestingly, lovastatin had no effect on Lp(a) concentrations, but lipoprotein B concentrations were significantly reduced in the high-dose group [52]. In a more recent clinical trial, patients with preoperative hypercholesterolemia (total serum cholesterol greater than 6.2 mmol/L) were randomized to receive either no therapy (Group 1, $n = 37$) or 4 weeks of preoperative simvastatin, 20 mg daily (Group 2, $n = 40$). Those assigned simvastatin continued their therapy for 1 year postoperatively. Ninety-eight percent of participants underwent routine follow-up angiography at 1 year. The rate of detectable graft disease at 1 year, the primary study endpoint, was 46% in Group 1 and 10% in Group 2, indicating a benefit with statin therapy (relative risk 0.30, 95% CI 0.13–0.66). The rate of myocardial infarction was also significantly higher in Group 1 (5%) than in Group 2 (0%) ($P = 0.036$). The greatest relative benefit with statin therapy was observed among those with saphenous vein grafts [53].

Perhaps the most compelling direct evidence that statins may reduce the risk for VTE comes from two recent studies [54,55]. In the Heart Estrogen Replacement Study (HERS), 1380 women were randomized to hormone replacement therapy and 1383 women to placebo [54]. During 10,985 woman-years of follow-up, 47 women developed VTE. In a post-trial analysis, it was found that statins, but not other lipid-lowering agents, reduced the risk for VTE by 50% (adjusted hazard ratio [HR] 0.5, 95% CI 0.2–0.9). The association between statin use and DVT was also evaluated, in a retrospective Canadian cohort study comprising 125,862 men and women aged 65 years and older [55]. After 190,601 person-years of observed drug use, there was an associated decreased risk of DVT among statin users compared with controls prescribed thyroid replacement hormones, even after controlling for the presence of cancer, recent hospitalizations, and ASA or warfarin use (adjusted HR 0.78, 95% CI 0.69–0.87). Just as in the HERS study, nonstatin lipid-lowering agents did not appear protective against DVT (adjusted HR 0.97, 95% CI 0.79–1.18). In both studies, however, the apparent protective effect of statins against VTE might also be explained by the possibility that statin users were healthier (i.e. healthy-user bias) or had fewer VTE risk factors that were not measured.

What further evidence is needed for clinicians?

Dyslipidemia and VTE

We argue that, at present, dyslipidemia should not be included as part of any thrombophilia work-up in persons with idiopathic VTE. Consistent epidemiological evidence is needed to demonstrate that commonly assayed lipids (e.g. total serum cholesterol, LDL-C, triglycerides), as well as other lipoproteins [e.g. Lp(a), lipoprotein B], are risk factors for VTE. In such studies, investigators should consider collecting fasting specimens remote from the time of the VTE event. Investigators in previous and future epidemiological studies and clinical trials designed to evaluate the effect of lipid reduction on cardiovascular disease might also consider evaluating data on VTE events among their study participants.

Statins and VTE

Statins cannot be recommended for use in either the prevention or the treatment of VTE. Research studies should attempt to quantify the risk reduction for VTE with statin use. A clinical trial aimed at secondary prevention of recurrent VTE may be one starting point. For example, patients who have had a first idiopathic VTE and who have completed 3 or 6 months of anticoagulant therapy could be randomized to either continue warfarin for another 12 to 18 months [56] or discontinue their warfarin and begin on statin therapy. The primary, composite endpoint of such a trial might be the development of recurrent VTE or major hemorrhage. Before such a trial can be justified, more epidemiological evidence is needed linking statin use to reduced VTE.

A greater understanding is also needed about whether there is a difference in the antithrombotic properties of the various statin agents, either in conjunction with, or independent of, their lipid-lowering properties. For example, in an audit of 126 individuals with atheroslcerosis who switched from simvastatin (mean daily dose 22 mg) to fluvastatin (mean daily dose 37 mg), there was a significant rise in total serum cholesterol, LDL-C, and triglycerides, as well as an increase in the subsequent number of arterial thrombotic events after a mean of 17 weeks [57]. In addition, researchers should focus on whether statins, in conjunction with drugs such as ASA [58], may offer an alternative and safe approach to VTE prevention among individuals at high risk for anticoagulant-related hemorrhage.

Conclusion

In summary, there is a new and growing body of epidemiological evidence supporting a possible link between dyslipidemia and the development of VTE, as well as the potential for statins to reduce the risk of VTE. The association between both elevated total serum cholesterol and Lp(a) and VTE is not consistent, although studies have shown that dyslipidemia is a significant risk factor for CABG vein graft occlusion, and that statins reduce that risk. Finally, preliminary research suggests that statins may lower the risk for VTE through several mechanisms.

Competing interests

None declared.

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