High-Density Lipoprotein Deficiency and Dyslipoproteinemia Associated With Venous Thrombosis in Men

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Background—Although dyslipoproteinemia is associated with arterial atherothrombosis, little is known about plasma lipoproteins in venous thrombosis patients.

Methods and Results—We determined plasma lipoprotein subclass concentrations using nuclear magnetic resonance spectroscopy and antigenic levels of apolipoproteins AI and B in blood samples from 49 male venous thrombosis patients and matched controls aged <55 years. Venous thrombosis patients had significantly lower levels of HDL particles, large HDL particles, HDL cholesterol, and apolipoprotein AI and significantly higher levels of LDL particles and small LDL particles. The quartile-based odds ratios for decreased HDL particle and apolipoprotein AI levels in patients compared with controls were 6.5 and 6.0 (95% CI, 2.3 to 19 and 2.1 to 17), respectively. Odds ratios for apolipoprotein B/apolipoprotein AI ratio and LDL cholesterol/HDL cholesterol ratio were 6.3 and 2.7 (95% CI, 1.9 to 21 and 1.1 to 6.5), respectively. When polymorphisms in genes for hepatic lipase, endothelial lipase, and cholesteryl ester transfer protein were analyzed, patients differed significantly from controls in the allelic frequency for the TaqI B1/B2 polymorphism in cholesteryl ester transfer protein, consistent with the observed pattern of lower HDL and higher LDL.

Conclusions—Venous thrombosis in men aged <55 years old is associated with dyslipoproteinemia involving lower levels of HDL particles, elevated levels of small LDL particles, and an elevated ratio of apolipoprotein B/apolipoprotein AI. This dyslipoproteinemia seems associated with a related cholesteryl ester transfer protein genotype difference. (Circulation. 2005;112:893-899.)

Key Words: lipoproteins ■ men ■ risk factors ■ thrombosis

Venous thromboembolic disease (VTE) is a polygenic disease with pathogenic contributions from both genetic and environmental risk factors.1-2 Various molecular dysfunctions in the protein C pathway, including factor V Leiden,3,4 are among the currently most common identifiable genetic risk factors for VTE.5 Although dyslipoproteinemia6-9 is associated with arterial thrombosis, especially in men, little is known about the relationships between VTE and plasma lipids or lipoprotein subclasses. Several observations suggest a relationship between VTE and dyslipidemia. Spontaneous VTE is associated with clinically silent atherosclerotic vascular disease.10 The use of lipid-lowering statins reduces VTE.11,12 Subnormal plasma levels of glucosylceramide, a glycosphingolipid that circulates in lipoproteins, are found in VTE patients.13 Because glucosylceramide and HDL enhance the anticoagulant activity of activated protein C,13-15 we have speculated that glucosylceramide and HDL may help protect against VTE.16

To assess the hypothesis that dyslipoproteinemia in men may cause or at least be associated with VTE, we used proton nuclear magnetic resonance (NMR) spectroscopy to determine each lipoprotein subclass concentration17-19 and also measured serum lipids and antigenic levels of apolipoprotein (apo) AI and B. Initially we studied young adult male subjects because VTE is more prevalent in males than females26 and because male gender itself is associated with higher rates of VTE recurrence.21,22 Because we found a particular pattern of dyslipoproteinemia associated with VTE, we also analyzed single nucleotide polymorphisms (SNPs) in 3 key genes, hepatic lipase, endothelial lipase, and cholesteryl ester transfer protein ( CETP), that influence lipoprotein metabolism and lipoprotein particle subpopulation levels.23-26 The results suggest that dyslipoproteinemia in male VTE patients is associated with a difference in CETP genotype.

Methods

Study Group

The Scripps Venous Thrombosis Registry is an ongoing case-control study of risk factors for VTE. Patients with objectively documented deep venous thrombosis with or without pulmonary embolism were recruited from the Scripps Anticoagulation Service and the commu-
Identification of novel genetic risk factors for VTE is a major goal for the Registry, and genetic factors are more likely to contribute to VTE in younger subjects aged <55 years. Inclusion criteria for this study included age at thrombosis <55 years, >3 months since diagnosis of acute thrombosis, a life expectancy of ≥3 years, and no lipid-lowering medications or cancer. Age matched (±2 years) healthy male controls were recruited through the blood donation program of the General Clinical Research Center (GCRC). Participants in the blood donation program had normal complete blood count and negative HIV and hepatitis B and C testing. Some were from the community, but most were employees or former employees of Scripps. Clinical data collection included detailed medical history and the presence of risk factors for venous thrombosis. The protocol was approved by the institutional review board of Scripps Clinic, and subjects provided written informed consent.

In this study, male VTE patients (n=49) and age-matched controls were analyzed for lipid and lipoprotein characterization. Clinical characteristics, the frequency of identified risk factors, and serum lipid data are shown in Table 1. Forty of 49 VTE patients (82%) presented with idiopathic VTE, defined as events that did not occur within 90 days after surgery, trauma, or major immobilization. Clinical conditions that are associated with changes in lipid metabolism were recorded for VTE patients and controls. Diabetes was present in 1 VTE patient. Hypertension was present in 3 VTE patients and was not present in any controls. Prior smoking history in male VTE patients was similar to that in controls (8 versus 6; P=0.79). Current smoking in male VTE patients was similar to that in male controls (3 versus 4; P=1.0). Of the VTE patients, 18 (37%) had experienced >1 episode of thrombosis, and 17 (35%) had documented pulmonary embolism. Eighty-four percent of patients were taking warfarin when blood was donated. Cancer was not known to be present in VTE patients and controls.

### Results

#### Analysis of Lipoprotein Parameters

Male VTE cases had a significantly lower mean HDL particle concentration than controls (P=0.001) (Figure 1A, Table 2). Among HDL subclasses, large HDL particle concentrations were lower in patients than controls (P=0.047), whereas medium and small HDL particles were not significantly different (Figure 1B to 1D, Table 2). The HDL mean particle size was also smaller in VTE cases than controls (P=0.04) (Table 2).

LDL particle concentrations in VTE patients were significantly higher than in controls (Figure 2A, Table 2; P=0.02). Among LDL subclasses, small LDL particle concentrations were higher in cases (P=0.02), whereas LDL and large LDL particle levels showed no statistical difference (Figure 2B to 2D, Table 2). The 2 subgroups of small LDL particles, namely, medium small particles and very small LDL particles, were elevated in VTE cases (P=0.02 and 0.03, respectively; data not shown). The LDL mean particle size was smaller in cases than in controls (P=0.04) (Table 2). No statistically significant differences between cases and controls were observed for VLDL.
particle total concentration or for VLDL subclasses (large, medium, and small VLDL particles) or for VLDL particle size (data not shown).

Immunoassay data for apoAI and apoB were consistent with NMR-based lipoprotein subclass data. ApoAI levels were lower \((P<0.01)\) (Figure 1E, Table 2), although there was no difference in apoB levels (Figure 2E, Table 2) in VTE patients compared with controls. The apoB/apoAI ratios for VTE patients were significantly higher than for controls \((P<0.001)\) (Figure 2G, Table 2), and the apoB/apoAI mean ratio difference was statistically stronger than the difference in mean values for either apoAI or apoB alone (Table 2).

For VTE patients compared with controls, HDL cholesterol (HDL-C) was lower \((P=0.03)\), whereas there was no difference in LDL cholesterol (LDL-C) \((P=0.11)\) (Figures 1F and 2F, Table 2). Remarkably, however, the LDL-C/HDL-C mean ratio was significantly higher for VTE patients than for controls \((P=0.002)\) (Figure 2H, Table 2).

### Association of VTE With HDL and LDL Parameters

Quartile-based ORs for association with VTE with lipoprotein variables were calculated by comparing quartile 1 (lowest HDL) with quartiles 2 to 4 or quartile 4 (highest LDL) with quartiles 1 to 3 for reduced HDL parameters or elevated LDL parameters, respectively (Table 3). Low levels of total HDL particle concentration and of large HDL particle concentration were associated with increased VTE risk with ORs of 6.5 (95% CI, 2.3 to 19) and 2.8 (95% CI, 1.2 to 6.2), respectively. Smaller HDL mean particle size had a significant OR of 3.2 (95% CI, 1.3 to 7.9). High levels (>75% of controls) of total LDL particle concentration and of 2 subfractions, IDL and small LDL particle concentrations, were significantly associated with the risk of VTE with ORs of 2.2 (95% CI, 1.0 to 4.9), 2.7 (95% CI, 1.0 to 6.8), and 3.1 (95% CI, 1.3 to 7.4), respectively. Two subpopulations of the small LDL particle subclass, ie, medium small and very small LDL particles, gave ORs of 3.0 and 3.1 (95% CI, 1.3 to 7.0 and 1.3 to 7.4), respectively, a value similar to the OR of 3.1 for small LDL particle concentration (Table 3). After adjustment for the known VTE risk factors, factor V Leiden, prothrombin 20210A, and BMI, all statistically significant quartile-based OR values retained statistical significance, with the exception of the concentration of large HDL particles \((P=0.056)\) (Table 3). The reduction in LDL mean particle size had a significant OR of 7.6 (95% CI, 1.5 to 39) after adjustment for factor V Leiden, prothrombin 20210A, and BMI.

Plasma levels of apoAI and apoB were determined by immunoassay. For VTE, based on quartile analyses, low levels of apoAI gave significant OR values (OR=6.0; 95% CI, 2.1 to 17), as did the ratio of apoB/apoAI (OR=6.3; 95% CI, 1.9 to 21). After adjustment for factor V Leiden, prothrombin 20210A, and BMI, the significance remained for these ORs (Table 3). On the basis of clinical laboratory serum cholesterol data, the OR for low HDL-C was statistically significant.
significant (OR = 3.0; 95% CI, 1.3 to 7.1), whereas that for elevated LDL-C did not quite achieve statistical significance (OR = 1.9; 95% CI, 0.84 to 4.2). After adjustment for factor V Leiden, prothrombin 20210A, and BMI, the OR for elevated LDL-C achieved statistical significance (OR = 3.9; 95% CI, 1.1 to 14), and the OR for low HDL-C was not quite statistically significant (OR = 2.6; 95% CI, 0.78 to 8.9).

For the OR for VTE, a ratio of LDL-C/HDL-C in the upper quartile was statistically significant for increased VTE risk (OR = 2.7; 95% CI, 1.1 to 6.5) without adjustment, and the OR was 5.0 (95% CI, 1.3 to 20) after adjustment (Table 3). For LDL-C levels >160 mg/dL, the OR for VTE was 3.5 (95% CI, 1.2 to 11), whereas for HDL-C <40 mg/dL, the OR for VTE was 2.8 (95% CI, 1.1 to 7.2) (data not shown). To evaluate the linear association of VTE risk with lipid parameter levels, matched-pair analysis of quartiles was made, and the probability values for a trend were calculated (Table 4). Lower levels of total HDL particle concentration, large HDL particle concentration, and higher levels of total LDL, IDL, and small LDL particle concentrations were associated with increased VTE risk (P = 0.004, P = 0.009, P = 0.03, P = 0.03, and P = 0.03, respectively). Smaller HDL size and smaller LDL size were also associated with increased VTE risk (P = 0.02 and P = 0.01, respectively).

**SNPs in Hepatic Lipase, Endothelial Lipase, and CETP Genes Associated With Venous Thrombosis**

To identify genetic influences contributing to dyslipoproteinemia in VTE patients, we determined well-known SNPs in 3 key genes, hepatic lipase (LIPC-514CT), endothelial lipase (LIPG T111D), and CETP (Taql B and I405V), that influence the spectrum of lipoprotein subpopulations and HDL-C levels. With the use of χ² analysis for difference in allele frequency between VTE cases and controls, the CETP Taql B2 allele was significantly less common in VTE cases than controls (P = 0.04) (Table 5). No difference in allele frequency was found for the studied SNPs of hepatic lipase or endothelial lipase. To evaluate the association of genotype with VTE, conditional logistic regression was also performed. The CETP Taql B genotype was significantly associated with VTE (P = 0.017), whereas no association was observed for CETP I405V, LIPC, or LIPG polymorphisms (P = 0.15, P = 0.60, and P = 0.48, respectively) (data not shown).

**Discussion**

Although arterial thrombosis and cardiovascular disease are clearly associated with dyslipidemia and dyslipoproteinemia,6–9,31–36 no studies have assessed dyslipoproteinemia in VTE. Here we used NMR technology to analyze lipoprotein subclasses9,17–19,24,26,27 in male VTE patients and controls and showed that VTE patients have markedly lower total HDL particle concentrations and higher LDL particle levels than controls. Lipoprotein subclass analyses show that these differences reflect lower levels of large HDL particles and higher levels of small LDL particles. Confirming the NMR-based demonstration of dyslipoproteinemia in VTE patients, antigenic assay data for the major apolipoprotein of HDL showed lower apoAI levels. The difference in the apoB/apoAI ratio between VTE patients and controls was statistically stronger than differences in either apolipoprotein alone.

On the basis of quartile analyses (Tables 3 and 4), VTE was associated with low levels of HDL particle concentration and appeared to be associated specifically with reduced plasma levels of large HDL particles and not with differences in medium and small HDL particles. Statistically significant OR values were found for VTE associated with elevated LDL particle concentrations due to elevations of small LDL particles and IDL particles but not large LDL particles (Tables 3 and 4).

On the basis of clinical laboratory serum cholesterol data, HDL-C was lower in VTE cases than controls, and the ratio of LDL-C/HDL-C was higher in VTE patients than controls. Although LDL-C data were not particularly striking, the OR for VTE in subjects with LDL-C level >160 mg/dL was 3.5 (95% CI, 1.2 to 11), suggesting that elevated LDL-C is associated with VTE. When the quartile-based OR for VTE associated with elevated LDL-C was calculated, the OR was 1.9 (95% CI, 0.84 to 4.2; P = 0.07).

To identify genetic factors contributing to the observed dyslipoproteinemia, we assessed genetic variation in 3 genes regulating HDL metabolism.23,24,26,30,37,38 Compared with con-
controls, the B2 allele of the CETP TaqI polymorphism was less frequent in male VTE cases. CETP plays a pivotal role in cholesteryl ester transfer from HDL to apoB-containing lipoproteins, and CETP deficiency or CETP inhibitors increase HDL levels. The TaqI B2 allele is linked to decreased CETP plasma levels of antigen and activity that results in larger HDL and LDL particle size and in higher HDL-C levels. Thus, the lower B2 allelic frequency observed in VTE patients is predicted to cause lower HDL and higher LDL levels. Of note, the CETP TaqI locus is in strong linkage disequilibrium with other polymorphisms in the CETP gene that may directly affect CETP activity and concentration. The allele frequencies of hepatic lipase and endothelial lipase polymorphisms that were studied did not differ, thus reducing the likelihood that these genes contribute to dyslipoproteinemia in VTE.

Relevant to this analysis is the comparability between the VTE and control groups for clinical conditions that are associated with changes in lipid metabolism. Such conditions include BMI, smoking, diabetes, hypertension, and atherosclerotic coronary artery disease. BMI was different for VTE patients compared with controls. However, after adjustments for known venous thrombosis risk factors including BMI, statistically significant OR values and trend for VTE were maintained, with few exceptions. The overall finding of dyslipoproteinemia involving both lower HDL levels and elevated LDL levels associated with VTE was strongly supported by the statistical analysis after adjustments. The prior and current smoking rates, diabetes, hypertension, and atherosclerotic coronary artery disease in VTE patients were similar to those in controls and thus cannot explain the observed dyslipoproteinemia.

As reviewed elsewhere, elevated LDL or oxidized LDL can promote thrombin formation, whereas HDL can enhance the protein C anticoagulant pathway and reduce thrombin generation. An increased ratio of LDL to HDL, reflected in apoB/apoAI or LDL-C/HDL-C values, could be prothrombotic by contributing to an imbalance in thrombin generation, resulting in hypercoagulability. Thus, there is substantial biological plausibility for mechanisms by which the observed dyslipoproteinemia might be prothrombotic for VTE. Additional protective effects of HDL and/or harmful effects associated with elevated LDL might also be relevant for understanding mechanisms whereby dyslipoproteinemia might help cause venous thrombosis.

Dyslipidemia and dyslipoproteinemia are distinct but related entities. Although this is the first report to assess dyslipoproteinemia in VTE, a few limited studies of VTE and dyslipidemia based purely on lipid measurements have appeared. Among those studies, the association of dyslipidemia with VTE was not as strong as observed for cardiovascular diseases, and this association was controversial. Gonzalez-Ordonez et al reported an association of dyslipidemia with VTE that was stronger in men than women. In our study, we also found a modest association of VTE with dyslipidemia in men, ie, with low HDL-C or with elevated LDL-C. However, our data show stronger correlations between VTE and dyslipoproteinemia than
between VTE and dyslipidemia, emphasizing the importance of apolipoproteins and lipoprotein particles compared with bulk plasma lipid levels, consistent with the concept that certain HDL particles may be protective for VTE and/or that certain LDL particles directly contribute to increase VTE risk.

More research on dyslipoproteinemia and VTE is clearly needed. Although less convenient than serum lipid assays, ELISA assays to determine apoB and apoAI levels and apoB/apoAI ratios might prove useful. Lipoprotein subclass analysis by NMR technology might not be a practical laboratory test for routine clinical care. However, further clinical research studies using NMR spectroscopy to quantify lipoprotein subclass levels in VTE patients are well warranted, as are studies of SNPs in genes that regulate HDL and LDL metabolism, notably the CETP TaqI B1/B2 polymorphism. Other genetic factors that influence lipoprotein metabolism might also contribute to dyslipoproteinemia in VTE. The role of gender in risk analysis for venous thrombosis is very important because hormone use increases risk for female subjects, whereas male gender per se increases risk.20–22 Studies should address the relationship between dyslipoproteinemia and hormone-associated or recurrent VTE.

VTE environmental risk factors (eg, trauma, immobilization, surgery) may influence analysis. However, when data for patients with idiopathic VTE were analyzed, significant ORs were observed for lower HDL particle concentrations, HDL-C, and apoAI; higher levels of small LDL particles; and higher values for the LDL-C/HDL-C and apoB/apoAI ratios (data not shown). This suggests that dyslipoproteinemia is associated with independent risk factors for VTE.

If it is assumed that our findings that dyslipoproteinemia is associated with VTE in men can be independently confirmed and that they apply to male patients aged >55 years, there are implications for further studies related to therapeutic and diagnostic applications of the concept that dyslipoproteinemia is associated with and may causally contribute to VTE.

This study has several limitations. The number of VTE patients in our study may limit our findings as preliminary, and, as always, true validation of novel clinical findings requires replication in multiple studies, preferably in both prospective studies and retrospective case-control studies. However, the statistical significance of our data is compelling because a number of independently measured parameters, namely, the NMR data for lipoprotein particles, the antigenic data for apolipoproteins AI and B, and the clinical serum cholesterol data, were completely coincident in defining a particular pattern of dyslipoproteinemia characterized by lower levels of large HDL particles and elevated levels of small LDL and IDL particles. We are unaware of any selection bias in recruitment of VTE patients and controls, and the groups show comparability for conditions that are associated with changes in lipid metabolism such as smoking, diabetes, hypertension, and atherosclerotic coronary artery disease. Stratifications that are not apparent might contribute to confound the data. Many of the VTE patients but none of the subjects were taking warfarin; however, warfarin has no significant effects on serum lipid profiles to our knowledge. As noted above, BMI may confound analyses of lipid profiles, and BMI was different for VTE patients compared with controls. Nonetheless, given the pleiotropic effects of obesity, there may be confounding variables that have not been recognized in this study.

In summary, VTE in men aged <55 years is associated with decreased levels of protective large HDL particles and elevated levels of harmful small LDL particles and IDL particles. Genetic studies show that the VTE patients disproportionately carry a CETP allele that conveys elevated CETP activity that likely contributes to the dyslipoproteinemia observed in VTE patients.

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