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Objective—Lipids, through effects on the coagulation and fibrinolytic systems, may contribute to the development of venous thrombosis. This association has been investigated in a few studies, with conflicting results.

Methods and Results—We conducted a population-based, case-control study at a health maintenance organization in Washington State, to assess the association of serum lipid levels with the risk of venous thrombosis. Cases were 477 postmenopausal women with a first venous thrombosis during January 1995 through December 2001. Control subjects (1986) were a random sample of postmenopausal women. Medical records, computerized pharmacy databases, and a cancer registry served to collect data on lipid levels and risk factors for thrombosis. Total cholesterol levels were not associated with venous thrombosis. Only high HDL cholesterol levels were associated with a decreased risk of venous thrombosis after adjustment for hospitalization, malignancy, height and weight, postmenopausal hormone therapy, and vascular disease (for high-density lipoprotein [HDL] cholesterol levels >1.79 mmol/L versus those <1.79 mmol/L; odds ratio [OR], 0.71; 95% confidence interval [CI], 0.52 to 0.97). In contrast, elevated triglyceride levels were associated with an increased risk (OR, 2.13; 95% CI, 1.34 to 3.37) for women with triglyceride levels >1.05 mmol/L compared with women with lower levels.

Conclusion—Elevated triglyceride levels were associated with a doubling of risk of venous thrombosis in postmenopausal women, whereas elevated HDL cholesterol levels were associated with a decreased risk. (*Arterioscler Thromb Vasc Biol.* 2004;24:1970-1975.)

Key Words: total cholesterol ■ high-density lipoprotein cholesterol ■ triglycerides ■ venous thrombosis ■ risk

Venous thrombosis, including deep vein thrombosis and pulmonary embolism, is a serious and potentially fatal event.¹ The average annual incidence is ≈ 1 to 3 per 1000 and affects young and old, regardless of gender.^{2,3} Risk factors for venous thrombosis may be genetic or acquired. Several abnormalities of the coagulation system increase the risk of thrombosis, such as factor V Leiden, the prothrombin 20210 G \rightarrow A mutation, and high levels of procoagulant factors, for example, factor II, factor VIII, factor IX, and factor XI. Acquired risk factors classically are those associated with immobilization, such as surgery, trauma, malignancy, and pregnancy.⁴ However, there are still many patients with venous thrombosis in whom no risk factor can be identified.

Elevated total serum cholesterol, elevated low-density-lipoprotein (LDL) cholesterol, and low high-density-lipoprotein (HDL) cholesterol are all well-established risk factors for atherothrombotic disorders.⁵ Besides their strong effects on atherogenesis, lipids and lipoproteins could influence hemostasis by modulating the expression and function of procoagulant, fibrinolytic, and rheological factors.⁶ Triglycerides, for example, seem to increase factor VII levels, plasminogen activator inhibitor (PAI-1) levels, and blood

viscosity. LDL promotes platelet activation and tissue factor expression. HDL has anti-atherothrombotic properties that may result from inhibition of platelet aggregation, reduction of viscosity, suppression of tissue factor activity, and PAI-1 activity levels, and enhancement of inactivation of factor Va by activated protein C.⁷ Because of these possible biological effects on the hemostatic system, lipids may also contribute to the development of venous thrombosis.

The associations of venous thrombosis incidence with total serum cholesterol, LDL and HDL cholesterol, as well as triglyceride levels have been investigated in only a few studies, and the results are inconsistent.⁸ We investigated the association of total cholesterol, HDL cholesterol, and triglyceride levels with the risk of incident venous thrombosis among postmenopausal women in a population-based, case-control study.

Methods

Design and Setting

The setting for this population-based, case-control study was Group Health Cooperative (GHC), a large health maintenance organization based in western Washington State, serving $>400\,000$ members. The

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study was reviewed and approved by the human subjects review committee at GHC.

Study Subjects, Eligibility, and Index Dates

Case subjects were all postmenopausal women aged 30 to 89 years who had a first fatal or nonfatal venous thrombosis between January 1, 1995 and December 31, 2001. Potential cases were identified from 5 sources: (1) computerized Group Health hospital discharge records; (2) Washington State death registry files; (3) billing records for GHC members who received medical care or services from non-GHC providers; (4) computerized GHC outpatient pharmacy files indicating use of low-molecular-weight heparin; and (5) anticoagulation treatment programs for GHC members treated for venous thrombosis as outpatients. Control subjects were a random sample of postmenopausal female GHC members sampled from the GHC computerized enrollment files. Control subjects were identified from a parallel ongoing case-control study of risk factors for myocardial infarction, and were frequency matched on age, calendar year of identification, and treated hypertension status to myocardial infarction cases.⁹ From this stratified sample of control subjects, those who met the same eligibility criteria as the venous thrombosis cases and did not have a venous thrombosis before their index dates were included. We excluded women with chronic liver disease (n=19), those without a total cholesterol measurement before their index date (n=189), women with extreme lipid values (n=2), women using lipid-lowering drugs (n=220), and women without a measurement of weight and height (n=11).

We identified 477 postmenopausal women with a venous thrombosis. Deep vein thrombosis in the leg and pulmonary embolism were objectively verified with a venogram, Doppler or duplex study, a pulmonary angiogram, lung scan with a high probability, or a computer tomography scan in 94% of all cases. Of the remaining 28 women, 15 died before any diagnostic test or treatment could be started, and 12 women were treated with coumarin derivatives or had a vena cava filter after the diagnosis of venous thrombosis was clinically made. Women who had a thrombosis in the arm because of an indwelling vascular catheter or shunt were excluded.

All subjects had an index date. The index date for cases was the date of their first venous thrombosis, and the index date for control subjects was a computer-generated random date during the year for which they were selected as control subjects.

Data Collection

Ambulatory medical records were used to determine eligibility and to ascertain demographic and behavioral risk factors, medical conditions, and lipid levels before the index date. This approach ensured comparability between case and control subjects in the assessment of eligibility criteria and risk factors. Abstraction of the information from the medical records was performed by trained research assistants who were not blinded to case-control status, but were unaware of the research question. The GHC computerized pharmacy database was used to assess current use of lipid-lowering drugs and postmenopausal hormone therapy before the index date as described in previous publications.^{10,11} The GHC cancer registry, which is derived from the Surveillance, Epidemiology, and End Results (SEER) registry, was used to retrieve information on malignancies.¹² Previous hospitalization and fracture data were collected from GHC inpatient and outpatient files using International Classification of Diseases, 9th revision, Clinical Modification codes and were limited to events that occurred within 90 days before the index date.

We collected information from the medical record before the index date on postmenopausal status, weight and height, vascular procedures, medical conditions such as chronic liver disease, hypertension, and vascular disease, and lipid levels. Women were considered to be postmenopausal if ovarian function ceased because of either natural menopause >6 months before the index date or bilateral oophorectomy before natural menopause. Women aged 55 years or older for whom menopausal status at the index date was unclear were assumed to be postmenopausal. Body mass index was obtained by dividing weight in kilograms by the square of height in meters. Vascular procedures included coronary artery bypass grafts,

coronary angioplasty, carotid endarterectomy, bypass grafting, and angioplasty of the peripheral vessels. We considered women to be hypertensive if they were pharmacologically treated for hypertension. Vascular disease was defined as a history of myocardial infarction, angina pectoris, stroke, transient ischemic attack, or claudication. Women with malignancies included those with a history of cancer and those with cancer diagnosed within 3 months after the index date. The most recent levels of total cholesterol, HDL cholesterol, and triglycerides as recorded in the medical records before index date were used in the analyses. The GHC primary prevention guidelines for hyperlipidemia use the ratio of total cholesterol to HDL cholesterol as the preferred method of assessing risk. As a result of this policy, fasting lipid tests that include triglycerides, which may be ordered at the discretion of the physician, are available for only a subset of those with total and HDL cholesterol measurements.

Statistical Analyses

χ^2 Tests for categorical variables and Student *t* test or analyses of variance for continuous variables were used to assess differences between cases and control subjects. All probability values represent 2-sided tests. Mean values are presented with their range or standard deviation (SD). Because triglyceride levels were skewed, ln-transformed values were used to test differences by using the *t* test. Quartiles were defined on the basis of the distribution of lipid levels among control subjects. The lowest quartiles were used as reference categories for calculating odds ratios (OR). Unconditional logistic regression analysis was used to adjust for age, index year, and hypertension, as well as for potential confounders. The 95% confidence intervals (CI) for the adjusted ORs were calculated using the standard errors of the coefficients estimated by maximum likelihood methods. In models that used continuous measures of lipid levels, each measure was divided by its SD in control subjects to facilitate comparison among total cholesterol, HDL cholesterol, and triglyceride levels. Statistical analyses were performed using STATA 8.0 (Stata Corp).

Results

Eligible postmenopausal women (477) had a first fatal (n=26) or nonfatal (n=451) venous thrombosis diagnosed; 340 (71%) had deep vein thrombosis, 53 (11%) had pulmonary embolism, and 84 (18%) had both. We identified 1986 eligible control subjects among postmenopausal female GHC members. Characteristics of women with a first venous thrombosis and control subjects are shown in Table 1. Mean ages of cases and control subjects were, respectively, 70.9 (range, 42.0 to 89.8) and 69.0 (range, 40.2 to 89.9) years. A larger proportion of cases than control subjects had a hospitalization and fracture within 3 months before the index date, as well as a history of malignancy and vascular disease.

In Table 2, the association between total cholesterol, HDL cholesterol levels, and the risk of venous thrombosis is presented for continuous measures and for quartiles. No differences in mean total cholesterol level were identified between cases and control subjects ($P=0.77$). After adjustment for the matching factors of age, index year, and treated hypertension, SD change of 1.02 mmol/L in total cholesterol level was not associated with the risk of venous thrombosis (OR, 1.02; 95% CI, 0.92 to 1.13), which is supported by the analysis using quartiles. The OR estimate per SD increased slightly after further adjustment for hospitalization, malignancy, weight, height, postmenopausal hormone therapy, and vascular disease (OR, 1.06; 95% CI, 0.95 to 1.19). Further adjustment for fractures, vascular procedures, race, and recency of measurement did not affect the estimate.

TABLE 1. Characteristics of Postmenopausal Women with a First Venous Thrombosis and Control Subjects

Characteristic	477 Cases	1986 Control Subjects	P
Age, mean (SD)* years	70.9 (11.2)	69.0 (9.6)	
Non-white, %	6.1	12.5	<0.001
Time enrolled in GHC,† mean (SD) years	22.4 (12.7)	23.1 (11.6)	0.3
Postmenopausal hormone therapy, %	37.1	36.5	0.8
Body mass index, mean (SD) kg/m ²	28.7 (7.9)	27.8 (6.3)	0.01
Hospitalization in prior 3 months, %	31.2	2.2	<0.001
Major fracture in prior 3 months, %	5.2	0.9	<0.001
Malignancy, %	35.6	12.2	<0.001
Vascular disease,‡ %	31.5	19.8	<0.001
Vascular procedures,§ %	1.0	0.1	<0.001

*Standard deviation.

†Group Health Cooperative

‡History of myocardial infarction, angina pectoris, stroke, transient ischemic attack, or claudication.

§Coronary artery bypass grafts, coronary angioplasty, carotid endarterectomy, bypass grafting, or angioplasty of the peripheral vessels.

For women for whom HDL cholesterol levels were available, HDL cholesterol levels were lower among 450 cases compared with 1913 control subjects, respectively: 1.48 (SD 0.44) mmol/L and 1.53 (SD 0.42) mmol/L ($P=0.02$). Elevated HDL cholesterol was associated with a decreased risk of venous thrombosis after adjustment for age, index year, and treated hypertension (OR per SD change in HDL [0.42 mmol/L] 0.81; 95% CI, 0.73 to 0.91). The estimated decrease in risk was attenuated after further adjustments were made for hospitalization, malignancy, weight, height, postmenopausal hormone therapy, and vascular disease (OR, 0.88 per SD change; 95% CI, 0.78 to 1.00). Further

adjustments did not change the OR. The analysis by quartiles suggested only a decreased risk for persons with relatively high HDL levels, which again was less pronounced after adjustments were made (ORs corresponding to quartiles of increasing HDL: 1, 1.03, 0.98, 0.71). The risk of venous thrombosis associated with HDL cholesterol levels >1.79 mmol/L was estimated to be decreased by 29% relative to HDL cholesterol levels <1.79 mmol/L (adjusted OR, 0.71; 95% CI, 0.52 to 0.97).

Values of all 3 lipid levels, total cholesterol, HDL cholesterol, and triglyceride levels, were available for 1357 women: 248 cases and 1109 control subjects (Table 3). In this group,

TABLE 2. Total Cholesterol and HDL Cholesterol Levels and the Risk of Venous Thrombosis in Postmenopausal Women

			OR (95% CI)*	OR (95% CI)†
Total cholesterol, mmol/l	477 cases	1986 control subjects		
Mean (SD)	6.03 (1.11)	6.02 (1.02)		
Per SD increase			1.02 (0.92–1.13)	1.06 (0.95–1.19)
≤5.30	123	489	1	1
5.31–5.95	114	528	0.84 (0.63–1.12)	0.85 (0.61–1.18)
5.96–6.65	114	471	0.95 (0.71–1.27)	0.94 (0.68–1.32)
≥6.66	126	498	1.02 (0.77–1.36)	1.17 (0.84–1.62)
HDL cholesterol, mmol/l	450 Cases	1913 Control Subjects		
Mean (SD)	1.48 (0.44)	1.53 (0.42)‡		
Per SD increase			0.81 (0.73–0.91)	0.88 (0.78–1.00)
≤1.21	119	450	1	1
1.22–1.47	128	480	0.91 (0.69–1.22)	1.03 (0.74–1.44)
1.48–1.78	119	520	0.76 (0.57–1.02)	0.98 (0.69–1.37)
≥1.79	84	463	0.54 (0.40–0.75)	0.71 (0.49–1.03)

*Odds ratio adjusted for matching factors of age, index year, and treated hypertension.

†Odds ratio adjusted for matching factors, hospitalization, malignancy, weight, height, postmenopausal hormone therapy, and vascular disease.

‡ $P<0.05$

To convert from mmol/l to mg/dl divide total and HDL cholesterol levels by 0.0259.

TABLE 3. Total Cholesterol, HDL Cholesterol and Triglyceride Levels and the Risk of Venous Thrombosis in Postmenopausal Women who had a Triglyceride Level Measured

			OR (95% CI)*	OR (95% CI)†
Total cholesterol, mmol/l	248 cases	1109 control subjects		
Mean (SD)	6.16 (1.17)	6.08 (1.05)		
Per SD increase			1.10 (0.96–1.26)	1.17 (1.01–1.37)
≤5.30	53	260	1	1
5.31–5.95	63	296	1.07 (0.71–1.61)	1.21 (0.75–1.95)
5.96–6.65	57	244	1.15 (0.76–1.76)	1.18 (0.72–1.93)
≥6.66	75	309	1.27 (0.86–1.89)	1.59 (1.00–2.52)
HDL cholesterol, mmol/l				
Mean (SD)	1.46 (0.44)	1.52 (0.42)		
Per SD increase			0.83 (0.71–0.96)	0.86 (0.73–1.03)
≤1.21	70	282	1	1
1.22–1.47	63	275	0.86 (0.58–1.26)	0.96 (0.61–1.50)
1.48–1.78	71	291	0.90 (0.62–1.31)	1.09 (0.70–1.70)
≥1.79	44	261	0.57 (0.37–0.87)	0.68 (0.41–1.12)
Triglycerides, mmol/l				
Mean (SD)	1.97 (1.01)	1.85 (1.24)‡		
Per SD increase			1.14 (1.00–1.30)	1.10 (0.94–1.30)
≤1.05	35	284	1	1
1.06–1.58	61	271	1.85 (1.17–2.92)	1.79 (1.05–3.04)
1.59–2.28	85	280	2.62 (1.69–4.06)	2.66 (1.60–4.43)
≥2.29	67	274	2.25 (1.42–3.55)	1.94 (1.13–3.34)

*Odds ratio adjusted for matching factors of age, index year, and treated hypertension.

†Odds ratio adjusted for matching factors, hospitalization, malignancy, weight, height, postmenopausal hormone therapy, and vascular disease.

‡ $P < 0.01$.

To convert from mmol/l to mg/dl divide total and HDL cholesterol levels by 0.0259, and triglyceride levels by 0.0113.

total cholesterol levels were associated with an increased risk of venous thrombosis (after adjustment for matching factors, hospitalization, malignancy, weight, height, postmenopausal hormone therapy, and vascular disease [OR, 1.17 per SD change; 95% CI, 1.01 to 1.37]), in contrast to those in the overall group. High HDL cholesterol levels were associated with a decreased risk (adjusted OR, 0.86 per SD change; 95% CI, 0.73 to 1.03) and limited to those with relatively high HDL levels, findings similar to those in the overall group. Mean triglyceride levels were higher among cases compared with control subjects, respectively: 1.97 (SD 1.01) mmol/L and 1.85 (SD 1.24 mmol/L; $P < 0.01$). The risk of venous thrombosis was increased in women with elevated triglyceride levels after adjustment for the matching factors (OR, 1.14 per SD change [1.24 mmol/L]; 95% CI, 1.00 to 1.30). The ORs corresponding to quartiles of increasing triglycerides were 1, 1.85, 2.62, and 2.25. Further adjustments changed risks slightly. The risk of venous thrombosis associated with triglyceride levels >1.05 mmol/L was estimated to be increased by 2-fold relative to triglyceride levels <1.05 mmol/L (OR, 2.13; 95% CI, 1.34 to 3.37) after adjustment for matching factors, hospitalization, malignancy, weight, height, postmenopausal hormone therapy, and vascular disease. Adjustments for other factors had little effect on the point estimate of the risk.

Similar results were found when only considering women not receiving postmenopausal hormone therapy. Again, elevated HDL cholesterol levels were associated with a decreased risk, especially high levels (OR, 0.87 per SD change; 95% CI, 0.74 to 1.02), ORs corresponding to quartiles of increasing HDL (1, 1.16, 0.96, 0.70) adjusted for matching factors, hospitalization, malignancy, weight, height, postmenopausal hormone therapy, and vascular disease. Elevated triglyceride levels were associated with an increased risk (OR 1.20 per SD change (95% CI 0.97 to 1.47), adjusted ORs corresponding quartiles of increasing triglyceride levels 1, 2.69, 6.16 and 3.19).

Discussion

In this population-based case-control study, total cholesterol levels overall were not associated with the risk of venous thrombosis among postmenopausal women. High HDL cholesterol levels were associated with a decrease in risk of venous thrombosis. In contrast, elevated triglyceride levels >1.05 mmol/L were associated with a 2-fold increased risk of venous thrombosis compared with women with lower levels. Adjustment for potential confounders could only partly explain the associations.

Our findings of no association between total cholesterol and the risk of venous thrombosis among postmenopausal

women overall are similar to the results of 2 prospective follow-up studies^{13,14} and a small case-control study.¹⁵ However, findings of the prospective Framingham Heart Study indicated that total cholesterol levels ascertained at entry were significantly higher in women but not in men with subsequent autopsy-confirmed major pulmonary embolism compared with all participants, even after adjustment for other risk factors.¹⁶ A Japanese case-control study reported that hypercholesterolemia was associated with a higher risk of deep vein thrombosis.¹⁷ Results of the prospective follow-up "Study of Men born in 1913" indicated a reverse association, with a lower total cholesterol level among those developing a venous thromboembolic event,¹⁸ as did a small case-control study.¹⁹

High HDL cholesterol levels were associated with a decreased risk of venous thrombosis in our study among postmenopausal women. Only 3 previous studies investigated HDL cholesterol as a potential risk factor. One of these also found lower HDL cholesterol levels among women with venous thrombosis compared with control subjects,¹⁹ whereas the other 2 studies did not find any association.^{14,15}

Our results indicated an increased risk of venous thrombosis with elevated triglyceride levels. Several previous studies have reported a similar association,^{17,19,20} whereas other studies found no association between triglyceride levels and risk.^{14,15,18} Triglyceride levels showed an inverse correlation with activated protein C ratio in women.²¹ Because a low activated protein C ratio is known to increase the risk of venous thrombosis,²² this might explain the association with triglyceride levels as found in our study. Another possible mechanism by which increased triglyceride levels may act is elevation of factor VIIc levels,²³ a possible risk factor for venous thrombosis.²⁴ Triglyceride levels are also associated with increases in factor VIII, factor IX, and fibrinogen levels in women,²⁵ all of which are independent risk factors for venous thrombosis.^{26,27} Unfortunately, we were unable to measure (anti)coagulation factors in our study to clarify the relationships.

Postmenopausal hormone therapy is known to increase HDL cholesterol and triglyceride levels,^{28,29} and >35% of all postmenopausal women in this study were using hormones. However, the association between HDL cholesterol, triglycerides, and venous thrombosis remained unchanged in the subgroup of women not using postmenopausal hormones.

Several possible explanations for the different results between studies exist. In a few studies measurements were made on admission,¹⁵ after the event,¹⁹ or the timing of the lipid measurement was not reported at all.¹⁷ Lipid measurements need to be performed before the initial venous thrombosis, because lipid levels are known to decline in the presence of acute vascular events.³⁰ Second, persons using lipid-lowering drugs should be excluded, because treatment would influence the lipid levels. Several studies failed to exclude these persons.¹³⁻¹⁸ Third, to avoid misclassification, the diagnosis of venous thrombosis should be made objectively by standardized methods instead of self-report. Other possible explanations for the inconsistency of the findings include the various ethnic origins of the populations and sex or age differences.

The strengths of our study include the population-based study design and the measurement of lipid levels before the index date for cases with venous thrombosis and control subjects. Although cases were identified after their event, the assessment of lipid exposure and other risk factors before the index date was based on information accrued in medical records, in a cancer registry, and in a computerized pharmacy database, thereby avoiding the possibility of information bias. Almost all diagnoses of venous thrombosis were objectively verified by standard diagnostic tests for deep vein thrombosis and pulmonary embolism. Only 6% of all venous thromboses were based solely on clinical grounds (including several rapidly fatal events), hence minimizing misclassification.

Our study has a few limitations. Triglyceride levels were not measured on 47% of our study population. Those women who did have a triglyceride level measured had higher total cholesterol levels, as might be expected. Another limitation of our study is that several measurements were performed years before the index date. If lipids have an immediate effect on the risk of venous thrombosis, then we may have missed such an association.

In conclusion, our findings suggest that elevated triglyceride levels may be of importance in the development of venous thrombosis in postmenopausal women, perhaps through their effect on coagulation factors. Total cholesterol levels do not appear to play a role, and elevated HDL cholesterol levels were associated with a decreased risk of venous thrombosis. Additional studies should be performed to confirm these findings.

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