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Risk factors for peripheral venous disease resemble those for venous thrombosis: the San Diego Population Study

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Abstract

Background—Clinically silent deep vein thrombosis (DVT) is common and may cause chronic venous disease that resembles post-thrombotic syndrome.

Objective—We evaluated whether peripheral venous disease in a general population shares risk factors with DVT.

Methods—In an established cohort of 2,404 men and women, the San Diego Population Study, peripheral venous disease was evaluated using physical exam, symptom assessment, and venous ultrasound. We performed a case control study including 308 cases in 4 hierarchical groups by severity, and 346 controls without venous abnormalities, frequency matched to cases by 10-year age group, race and sex. Cases and controls had no prior history of venous thrombosis. Hemostatic risk factors were measured in cases and controls.

Results—Accounting for age, obesity and family history of leg ulcer, ORs for elevated factor VIII, von Willebrand factor, D-dimer, and for factor V Leiden were 1.4 (95% CI 0.9–2.1), 1.5 (CI 1.0–2.3), 1.7 (CI 1.1–2.8), and 1.1 (CI 0.5–2.4), respectively. These associations were larger in the two most severe case groups; ORs 2.0 (CI 1.0–3.8), 1.7 (CI 0.9–3.3), 2.7 (CI 1.2–6.1) and 2.3 (CI 0.8–7.1). Each hemostatic factor was also associated with severity of venous disease, for example elevated D-dimer was associated with a 2.2-fold increased odds of being in one higher severity group. Prothrombin 20210A was not associated with venous disease.

Conclusions—DVT risk factors are associated with presence and severity of peripheral venous disease. Results support a hypothesis that peripheral venous disease may sometimes be post-thrombotic syndrome due to previous unrecognized DVT.

Keywords

deep vein thrombosis; venous insufficiency; risk factors; epidemiology; blood coagulation

Deep vein thrombosis (DVT) and pulmonary embolus (PE) affect 1–3 per 1000 adults annually. Other than PE, major sequelae of DVT are recurrence and post-thrombotic syndrome. The burden of post-thrombotic syndrome is large, affecting 25–50% of patients after a first DVT [1–4]. Post-thrombotic syndrome includes a spectrum of findings ranging

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There are no relationships that might represent a conflict of interest.

from minor skin problems to edema, pain and/or severe trophic skin changes including venous ulcers.

Deep vein thrombosis is often asymptomatic or unrecognized, especially in settings of provoking factors such as surgery, cancer, trauma, or hospitalization [5–8]. Even though many of these asymptomatic DVT are limited to the calf, post-thrombotic syndrome may occur, presenting as peripheral venous disease [9,10].

Under a hypothesis that clinically silent DVT can contribute to peripheral venous disease, we studied the associations of risk factors for clinically overt DVT with presence and severity of peripheral venous disease in a general population sample without previous venous thrombosis. Our focus was on medical and family history and common hemostatic risk factors for venous thrombosis: elevated factor VIII, von Willebrand factor and D-dimer [11], factor V Leiden and prothrombin 20210A.

Methods

Participants

The San Diego Population Study consists of 2,408 men and women randomly selected from employees and retirees of the University of California, San Diego and enrolled between 1994–1998[12,13]. Random selection was made in strata of age, sex and ethnicity. Spouses or significant others of participants were included, and 199 volunteers who asked to participate were enrolled (these being primarily University employees or retirees who learned of the study from other participants). Participants self-defined race/ethnicity from a list. Informed consent was provided according to institutional review boards of participating institutions.

Enrollment Visit

Personal and family health history, anthropomorphic measures and physical examination were collected. Thrombosis history was defined by structured interview as self-reported DVT or PE treated with anticoagulants. Superficial vein thrombosis was defined as a positive response to history of a “blood clot, phlebitis or inflamed vein” in a superficial leg vein. Serious leg injury was defined as fracture, burn, gunshot, stab wound, or crush injury. Surgery was defined as lying for surgery for longer than one hour. Venous surgery was defined as sclerotherapy injection, vein stripping or ligation or other surgery for a “problem with veins in your legs”. Standardized questions determined presence of current or past leg symptoms of aching, heaviness, itching, tired, swelling, or cramping.

Blood was drawn and centrifuged within 3 hours with serum or plasma stored at -70°C . Whole blood was blotted onto DNA blot kits (Life Technologies) and stored in individual cardstock envelopes in Ziploc bags at -70°C .

Duplex ultrasound was used with standardized methods to quantify valvular insufficiency (reflux time), flow velocity and the degree and location of obstruction [13,14]. Acuson128 duplex ultrasonography (Siemens Corporation, Mountain View CA) with a 5-MHz transducer was used as previously published [12]. Valvular insufficiency was defined as reflux or Valsalva reflux ≥ 0.5 seconds. Partial and complete venous obstruction was assessed by degree of compressibility of the venous walls, with normal defined as complete compressibility and complete obstruction by no compressibility. A hierarchical classification of normal, superficial venous functional disease (SFD), and deep venous functional disease (DFD) was used to define venous anatomy by ultrasound [12]. SFD and DFD were defined as reflux or abnormal compression in superficial and deep veins, respectively. We classified 26 legs with history of vein stripping as SFD if ultrasound was normal.

Visible venous disease corresponded to the Clinical Etiologic Anatomic Pathologic (CEAP) classification categories [15]: C0 (none), C1 (telangiectasias or reticular veins), C2 (varicose veins; VV), C3 (edema); C4 (pigmentation, eczema, lipodermatosclerosis or atrophie blanche), C5 (healed venous ulcer); C6 (active venous ulcer). We defined trophic changes of skin (TCS) as C4–6. Edema was considered separately.

Case-control Study

A nested case-control study population was drawn from the 2,404 participants as outlined in figure 1. We selected hierarchical case groups with increasing severity of peripheral venous disease based on a priori definitions using clinical and imaging characteristics likely to represent post-thrombotic syndrome. Each participant was classified based on their worst leg. The lowest severity group was 125 participants with DFD on ultrasound and no TCS, aching or edema. The next group was 137 participants with SFD and TCS or edema (n=113), plus those with TCS and a normal ultrasound (n=24), as DVT often recanalizes without reflux by ultrasound. The following two groups most closely resembled post-thrombotic syndrome, with the first group including 59 participants with DFD and aching or edema but no TCS. The last group included 49 participants with DFD and TCS, regardless of symptoms. Both case and control groups could have a history of venous thrombosis. The total case group included 370 participants. From the remaining participants we identified 1313 potential control participants with no SFD, DFD, edema, leg aching, varicose veins or TCS. There were 725 participants who did not meet criteria for being a case or control and they were excluded from all analyses. Among 1270 potential controls and 352 cases with available blood samples, we randomly selected one control per case, frequency matched to cases by sex, 10-year age group and ethnicity. For this analysis focused on whether clinically silent venous thrombosis might relate to venous insufficiency, we then excluded those with previous thrombosis from further analysis, leaving 308 cases and 346 controls for analysis.

In cases and controls Factor V Leiden and prothrombin 20210A were measured using TaqMan 5' nuclease allelic discrimination assays. Plasma hemostasis markers were measured on the STAR automated coagulation analyzer, (Diagnostics Stago, Parsippany, NJ). D-dimer and von Willebrand factor were measured by immuno-turbidometric assays (Liatest D-DI and Liatest vWF) and Factor VIII as coagulant activity (STA-Deficient VIII). Analytical coefficients of variation were 8%, 4% and 10%, respectively.

Statistical Methods

We used SAS 9.1 (Cary, NC) for analysis. Means or prevalences of risk factors in 352 cases and 352 controls were compared using analysis of variance or chi-squared tests. Associations of participant characteristics with peripheral venous disease combining all case groups compared to controls were first determined using univariable logistic regression models to calculate odds ratios with 95% confidence intervals. Variables with confidence intervals excluding 1.0 were included in a multivariable logistic regression model to determine independent risk factors for peripheral venous disease. The final model excluded risk factors with confidence intervals including 1.0.

We divided hemostasis factors into tertiles (defined based on the control group distributions). For genetic factors heterozygotes plus homozygotes were compared to unaffected. Logistic regression adjusting for the matching factors was used to calculate odds ratios of being a case by tertiles of hemostatic factors and for genetic factors. Body-mass index (BMI) and family history of leg ulcer were added to the models to control for potential confounding. We used ordinal logistic regression to evaluate associations of risk factors with severity of peripheral venous disease across the hierarchical case groups. We also evaluated

the two most severe case groups separately, compared to controls. In sensitivity analyses we assessed whether associations differed by sex and among whites only compared to overall associations.

Results

Table 1 shows participant characteristics in the 346 controls and the case groups ordered by severity of peripheral venous disease. Prevalences of superficial and deep venous disease by ultrasound are shown, with distal deep disease isolated to the calf being very uncommon (not shown). The only variables that differed comparing the combined case groups to controls were BMI, history of leg injury, prior venous surgery and family history of venous ulcer. Other than family history of venous ulcer, these factors (but not other risk factors in the table) also increased across the case groups in analyses adjusted for age, sex and ethnicity ($p < 0.05$).

Table 2 shows the odds ratios of peripheral venous disease for clinical factors, assessed by univariable then multivariable logistic regression. In the multivariable model, only family history of venous ulcer and obesity were associated with risk of venous disease. Results were similar in analyses stratified by sex or in whites only.

In table 3, levels of hemostasis factors are shown by case-control status. Factor VIII, von Willebrand factor and D-dimer were higher in cases than controls, and the gene variants were more common.

Table 4 shows the odds ratios of peripheral venous disease by tertiles of hemostasis factors with the four case groups combined and compared to controls. Factor VIII and von Willebrand factor in the top tertile were similarly associated with risk of venous disease, with age, race and sex-adjusted odds ratios of 1.6 and 1.7, respectively. Additional adjustment for BMI or family history of ulcer had small influences on these odds ratios. Odds ratios were slightly higher in analyses limited to whites, and were lower in men than women (data not shown). The odds ratios adjusting for age, race, sex, BMI and family history of ulcer were higher in analysis of the two most severe case groups: 2.0 (95% CI 1.0–3.8) for factor VIII and 1.7 (95% CI 0.9–3.3) for von Willebrand factor. The association of D-dimer with peripheral venous disease was higher than for factor VIII and von Willebrand factor, with an odds ratio of 2.0 adjusting for age, race and sex. There were also small impacts of adjustment for BMI and family history of leg ulcer. The adjusted odds ratio considering the two most severe case groups was 2.7 (95% CI 1.2–6.1) for D-dimer in the top tertile. Associations were stronger in men than women and did not differ from overall results considering whites only (data not shown).

The age, sex and race-adjusted odds ratio of venous disease for Factor V Leiden was 1.2 (95% CI 0.5–2.6) and for prothrombin 20210A was 0.8 (95% CI 0.2–2.4). Considering the two worst case groups of venous disease these odds ratios were 2.3 (95% CI 0.8–7.1) and 1.4 (95% CI 0.3–7.4), respectively. Results did not differ materially in analyses stratified by sex or in whites only.

Adjusted for age, race and sex, comparing the top to bottom tertiles of factor VIII, the odds ratio of being in one higher severity group of peripheral venous disease was 1.7 (95% CI 1.2–2.5). Corresponding odds ratios for von Willebrand factor and D-dimer were 1.8 (95% CI 1.2–2.7) and 2.2 (95% CI 1.4–3.4), and for factor V Leiden and prothrombin 20210A were 1.3 (95% CI 0.6–2.7) and 1.0 (95% CI 0.4–2.7).

Discussion

The main finding of this study is that elevated factor VIII, von Willebrand factor and D-dimer were associated with peripheral venous disease among those without a history of venous thrombosis. The elevated coagulation factors were also associated with severity of peripheral venous disease. Results for factor V Leiden and prothrombin 20210A were less clear, with factor V Leiden only being associated with more severe venous disease, with an odds ratio of 2.3. Results support a conclusion that there are shared risk factors between peripheral venous disease and venous thrombosis, and a hypothesis that for some patients, peripheral venous disease may be post-thrombotic syndrome due to previous unrecognized DVT.

Our conclusions are supported by other evidence. A systematic review of seven studies reported a 59% increased risk of post-thrombotic syndrome after asymptomatic post-operative DVT [10], highlighting that undetected DVT can cause peripheral venous disease. Other studies suggest that inherited thrombophilic disorders relate to venous insufficiency. In a kindred with type I protein C deficiency and thrombosis, persons with protein C deficiency and no history of venous thrombosis, had a relative risk of 9.0 (95% CI 1.1–74) for deep venous obstruction or reflux on ultrasound [16]. This is higher than we observed for the studied hemostasis disorders here, and similar to the risk of venous thrombosis with protein C deficiency. Factor V Leiden was studied in small referral populations with venous disease. Munkvad reported that ¼ of 46 consecutive patients with venous ulcers had activated protein C resistance [17], the biochemical abnormality caused by factor V Leiden. Only 4 of these had a history of DVT. Maesson-Visch evaluated 92 patients with venous leg ulcers and 53 controls, showing factor V Leiden in 23% of cases compared to 7% of controls [18]. Among 100 consecutive patients with leg ulcers, Gaber reported only a few had history of DVT, yet 53 had ultrasound evidence of previous thrombosis, and 36% of these had factor V Leiden [19]. Hafner reported similar findings in 73 consecutive patients with venous ulcer [20]. Darvall reported a higher prevalence of some thrombophilias in 54 referred patients with venous insufficiency but no analyses of confounding was undertaken [21]. Our findings extend previous studies in important ways. We evaluated a general population sample rather than selected patients, and we evaluated associations of risk factors with severity of peripheral venous disease defined based on clinical, anatomic and symptom criteria.

Our findings agree with some studies of risk factors for post-thrombotic syndrome after clinically recognized DVT and disagree with others. Factor V Leiden and prothrombin 20210A were associated with a lower risk and lower severity of post-thrombotic syndrome following DVT in a clinical trial [22] and factor V Leiden and prothrombin 20201A were not risk factors for post-thrombotic syndrome in an inception cohort of 406 patients with DVT [23], consistent with our findings of weak relationships of these disorders with peripheral venous disease. Prandoni reported no association of thrombophilia with risk of post-thrombotic syndrome [24], however this study had few cases of post-thrombotic syndrome, the prevalence or type of thrombophilia was not reported, nor was the relative risk. Findings might seem surprising for factor V Leiden, given that thrombi with factor Va Leiden are more adherent to the venous wall than thrombi with normal factor Va [25], so might be expected to contribute to post-thrombotic syndrome. This is consistent with our findings that the association of factor V Leiden with venous disease was most apparent among those with more severe venous disease. Our findings agree with a study of children with DVT, where higher levels of D-dimer or factor VIII measured 3–6 months after thrombosis, were associated with subsequent post-thrombotic syndrome [26], and with the report by Stain, who also observed that higher D-dimer was a risk factor for post-thrombotic

syndrome, although elevated factor VIII was not a risk factor in that population, as seen here [23].

Strengths of our study include the general population sample and careful ascertainment of risk factors. Limitations require discussion. First, the study used prevalent cases, so reverse-causality for associations might play a role such that peripheral venous disease caused increases in coagulation factors. We argue that this is unlikely, given that results were similar for analyses of these same risk factors in both cross-sectional and prospective studies of DVT risk [11,27–29]. However, confirmation of our findings in prospective studies is desirable. Second, we relied on self-report of previous venous thrombosis to classify participants. It is possible that some individuals experienced previous thrombosis and did not report it, although given that thrombosis is relatively uncommon, the impact on our findings should be small. Third, recall of participants for risk factors like family history of venous ulcers might be better in symptomatic patients, yielding over-estimation of the risk of venous disease associated with these factors. Fourth, we do not know the sensitivity or specificity of our case classification for selecting patients with previous DVT. Fifth, as with any study of coagulation factors, assay imprecision always leads to underestimation of associations. Finally due to the number of venous disease cases, power for analyses of factor V Leiden and prothrombin 20210A was not optimal.

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The findings of this study support a hypothesis that some portion of chronic venous disease in the general population is due to previous unrecognized DVT.

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Figure 1. Participant Flow Diagram. Numbers in parentheses are those without available blood samples. DFD=deep functional disease; TCS=trophic skin changes; SFD=superficial functional disease; US=ultrasound; VV=varicose veins

Table 1

Characteristics of Cases* of Peripheral Venous Disease and Controls.

Characteristic	Controls [Group 1] N = 346	All Cases [Groups 2-5] N = 308	Case Group 2 N = 108	Case Group 3 N = 122	Case Group 4 N = 46	Case Group 5 N = 32
Imaging Findings						
Superficial reflux or obstruction	0%	65%	44%	82%	52%	91%
Deep reflux or obstruction	0%	60%	100%	0%	100%	100%
Participant factors						
Age, years (SD) [‡]	62.2 (11.2)	62.7 (11.6)	60.5 (12.4)	65.3 (10.5)	59.1 (12.3)	65.3 (9.0)
Sex, male [‡]	41%	41%	46%	41%	26%	41%
Ethnicity [‡] , white	68%	65%	62%	66%	70%	59%
African-American	10%	11%	8%	10%	11%	22%
Hispanic	11%	12%	11%	14%	13%	9%
Asian	11%	12%	19%	10%	7%	9%
BMI, kg/m2 (SD)	26.3 (4.6)	27.8 (5.2) [‡]	26.4 (4.8)	28.1 (4.5)	29.1 (5.8)	30.2 (6.3)
Ever Smoking	55%	48%	48%	45%	52%	53%
Hypertension	29%	33%	26%	38%	35%	38%
Diabetes	6%	6%	4%	8%	7%	9%
Past Cancer	11%	8%	6%	9%	7%	13%
Current Cancer	3%	2%	0%	5%	0%	0%
Serious leg injury	19%	26% [‡]	27%	19%	39%	28%
Any venous surgery	1%	13% [‡]	10%	13%	15%	22%
Family history venous thrombosis	4%	7%	6%	10%	9%	3%
Family history venous ulcer	1%	4% [‡]	2%	6%	4%	0%

VT-venous thrombosis; FH = family history

Controls: No SFD or DFD on ultrasound; no edema, varicose veins, TCS, or leg aching.

* Case Definitions:

Group 1: deep functional disease (DFD) on ultrasound and no trophic skin changes (TCS), aching or edema.

Group 2: superficial functional disease (SFD) on ultrasound plus TCS or edema, or TCS and a normal ultrasound.

Group 3: DFD on ultrasound and aching or edema but no TCS.

Group 4: DFD on ultrasound and TCS, regardless of symptoms.

[†] matching factors

[‡] p value comparing combined case group to controls <0.05; p not shown for imaging characteristics, which defined case groups.

Table 2

Odds ratios (95% confidence interval) of peripheral venous disease in 308 cases and 346 controls.

Risk Factor	Univariable Model	Multivariable Model*
BMI 25–30 kg/m ² vs <25 kg/m ²	1.3 (0.9–1.9)	1.3 (0.9–1.9)
BMI ≥30 kg/m ² vs <25 kg/m ²	2.2 (1.5–3.4)	2.4 (1.5–3.6)
Ever Smoking	0.8 (0.6–1.0)	-
Hypertension	1.2 (0.9–1.7)	-
Diabetes	1.1 (0.6–2.1)	-
Past Cancer	0.7 (0.4–1.2)	-
Current Cancer	0.7 (0.3–2.1)	-
Serious leg injury	1.5 (1.0–2.1)	-
FH venous thrombosis	1.9 (1.0–3.8)	-
FH venous ulcer	4.2 (1.2–15.3)	5.0 (1.4–18.6)

* Multivariable model includes those variables which retained statistical significance and is adjusted for the matching factors of age, sex and ethnicity. Variables without odds ratios shown were not retained in the multivariable model.

Table 3

Hemostasis factors in the case-control groups*

	Control Group (n=346)	Case Group 1 (n=108)	Case Group 2 (n=122)	Case Group 3 (n=46)	Case Group 4 (n=32)
Factor VIII, %	92 (68–120)	93 (70–119)	99 (70–131)	119 (83–144)	99 (78–145)
von Willebrand Factor, %	94 (72–119)	94 (77–114)	106 (87–143)	114 (79–155)	94 (81–141)
D-dimer, ug/ml	0.21 (0.12–0.37)	0.21 (0.14–0.32)	0.31 (0.16–0.49)	0.32 (0.21–0.49)	0.34 (0.14–1.05)
Factor V Leiden, n (%; 95% CI) [†]	14 (4%, 2%–7%)	3 (3%, 1%–8%)	5 (4%, 1%–9%)	3 (7%, 1%–18%)	2 (6%, 1%–21%)
Prothrombin 20210A, n (%; 95% CI) [‡]	8 (2%, 1%–5%)	2 (2%, 0%–7%)	1 (1%, 0%–5%)	1 (2%, 0%–12%)	2 (6%, 1%–21%)

* Values shown are median (interquartile range) or n (%; 95% confidence interval). Missing values: factor VIII (5 controls, 7 cases), von Willebrand factor (8 controls, 8 cases), D-dimer (5 controls, 7 cases), factor V Leiden (2 controls, 5 cases), prothrombin 20210A (2 controls, 5 cases).

[†] 5 of 27 affected were homozygotes (2 controls, 3 cases).

[‡] 0 of 14 affected were homozygotes.

Table 4

Odds ratios of peripheral venous disease by hemostasis factors*

	Odds ratio of venous disease, 308 cases, 346 controls		
	Tertile 1	Tertile 2	Tertile 3
Factor VIII			
Age, sex race	1.0 (ref)	1.1 (0.7–1.6)	1.6 (1.1–2.4)
+ BMI	1.0 (ref)	1.0 (0.7–1.5)	1.4 (1.0–2.1)
+ FH Ulcer	1.0 (ref)	1.0 (0.7–1.5)	1.4 (0.9–2.1)
von Willebrand Factor			
Age, sex race	1.0 (ref)	1.5 (1.0–2.3)	1.7 (1.1–2.5)
+ BMI	1.0 (ref)	1.5 (1.0–2.2)	1.6 (1.0–2.3)
+ FH Ulcer	1.0 (ref)	1.4 (0.9–2.1)	1.5 (1.0–2.3)
D-dimer			
Age, sex race	1.0 (ref)	1.4 (0.9–2.2)	2.0 (1.2–3.1)
+ BMI	1.0 (ref)	1.4 (0.9–2.1)	1.7 (1.1–2.8)
+ FH Ulcer	1.0 (ref)	1.3 (0.8–2.0)	1.7 (1.1–2.8)

* 33rd and 66th percentile (tertile) cutpoints: Factor VIII 75, 107%. von Willebrand factor 80, 110%. D-dimer 0.13, 0.31 ng/ml. Odds ratios compare the second or third tertile to the first tertile.