Relationships Between Symptoms and Venous Disease

The San Diego Population Study

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Background: The associations between symptoms and venous disease of the lower extremities are poorly characterized.

Methods: We conducted a cross-sectional study to evaluate relationships between symptoms associated with venous disease and prevalent disease in 2408 men and women aged 29 to 91 years who were employees, retirees, or spouses at a large state university. Index participants were randomly selected within strata by age, sex, and ethnicity. A structured interview assessed the prevalence of aching, itching, heaviness, tired legs, cramping, swelling, and nighttime restless legs. A comprehensive standardized examination determined the prevalence of visible disease (normal, telangiectasias, varicose veins, and trophic changes) and functional disease (normal, superficial, and deep disease). We related symptoms to disease with attention to modification by sex, ethnicity, and age.

Results: Aching, itching, heaviness, tired legs, cramping, and swelling were related to both superficial and deep functional disease. The same symptoms were related to varicose veins and trophic changes. Swelling and heaviness were related to telangiectatic disease. Except for restless legs and trophic changes, the prevalence of symptoms across each category was greater in women than men. Aching was the most common symptom but was relatively nonspecific. Swelling was the most specific marker for prevalent visible and functional disease. Heaviness and itching also helped to distinguish prevalent disease.

Conclusions: Venous symptoms were more prevalent in study participants with both visible and functional disease and in women. Swelling was the most specific predictor; heaviness, itching, and aching also helped to distinguish cases.

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CHRONIC VENOUS DISEASE IS common, and its symptoms generate a substantial number of health care visits.[1-3] However, data on the associations between major forms of venous disease and symptoms are extremely limited. Techniques for assessing venous disease have improved with developments in noninvasive methods, particularly duplex ultrasonography. However, few reports have been published on the prevalence of venous disease in representative populations assessed with contemporary methods.[4-6]

The San Diego Population Study was established to obtain a comprehensive assessment of putative symptoms and risk factors for venous disease in a free-living population, to relate these to findings from a comprehensive examination with visual inspection and duplex ultrasonography, and to provide prevalence estimates of venous disease by sex, age, and ethnicity.[7] The present analyses were conducted to evaluate the relationship between symptoms and venous disease.

METHODS

The San Diego Population Study enrolled 2408 adults who were randomly selected from an ethnically diverse population of current and retired employees of the University of California, San Diego (UCSD). Random selection was made within strata defined by age, sex, and ethnicity. For age, the categories were 40 through 49 years, 50 through 59 years, 60 through 69 years, and 70 through 79 years. We oversampled women to provide additional power for certain female-specific hypotheses, including the effects of pregnancy and hormonal therapy on venous disease. We also oversampled 3 ethnic minorities (Hispanic, African American, and Asian individuals) to provide statistical power for contrasts by ethnicity. The spouse or significant other of each randomly selected participant was invited to participate in the study; partners did not need to meet the specified age criteria. We also enrolled a few volunteers who had heard about the study and asked to participate.

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At the study visit, trained interviewers used a standard questionnaire to obtain information on demographics, relevant medical history, family history, symptoms potentially related to venous disease, and lifestyle. Certified vascular technologists conducted a limited physical examination following a standardized protocol. The remainder of the examination focused on the vascular system in the lower extremities and also followed a standardized protocol. The venous examination included visual inspection for visible disease with the participant standing and photographic documentation of major abnormalities. Technologists noted simple telangiectasias (spider veins), reticular telangiectasias, simple varicosities, and reticular varicosities on each leg in 5 anatomical regions: thigh, knee, calf, ankle, and foot. Visual evidence of trophic changes (TCs) (ie, hyperpigmentation, lipodermatosclerosis, or healed or active ulcer) at the level of the calf or below was also recorded. The presence of edema (calf or below) was recorded but was not considered a trophic change.[7]

For functional disease, both the superficial and deep venous systems were examined for reflux and obstruction using an Acuson model 128 duplex ultrasonograph with a 5-MHz transducer (Acuson Corporation, Mountain View, Calif). Duplex measurements were recorded at prespecified anatomical levels with the participants on a tilt table in a 15° reverse Trendelenburg position, with the legs slightly flexed in minimal external rotation. A probe was used to determine vein wall compressibility with the participant at rest. Standardized pressure using an automatic cuff inflator (DE Hokanson Inc, Bellevue, Wash) with rapid inflation and deflation of cuffs placed sequentially at midthigh, midcalf, and foot levels was used to identify reflux. For Valsalva reflux testing, a pressure-monitoring system was used to maintain 40 mm Hg for 3 seconds of participant effort.

Reflux duration of 0.5 second or more or Valsalva reflux duration of 0.5 second or more was considered evidence of valvular insufficiency.[8] The duration of reflux was a quantitative estimate of the severity of valvular incompetence. Partial and complete venous obstruction were assessed by the degree of compressibility of venous walls, where complete compressibility was normal.[9,10] The reproducibility of these measurements in our study has previously been published.[11]

For all study procedures, participants provided signed informed consent following a detailed introduction to the study. The study was approved by the Committee on Investigations Involving Human Subjects of UCSD, with annual reviews and renewals.

VENOUS SYMPTOMS

As part of the standard interview, participants were asked whether they had symptoms of aching, itching, heaviness, tired legs, cramping, swelling, or nighttime restless legs individually for each leg, both currently and in the past. Because substantial overlap existed across periods, for the present analyses past and current symptoms were combined into a single variable, indicating the presence of that symptom ever. Since symptoms and functional disease were recorded for each leg, analyses were conducted by leg rather than by person.

DISEASE CLASSIFICATION

Visible Categories

Visible classification was based on visual inspection of each leg separately. This inspection was conducted before duplex ultrasonography so that functional and visible diagnoses were independent of one another. Visible disease was classified hierarchically: normal, telangiectasias or spider veins (TSVs), varicose veins (VVs), and TCs. Normal legs were free of TSVs, VVs, and TCs; legs classified as having TSVs were free of VVs and TCs; legs with VVs may or may not have also had TSVs but were free of TCs; and legs with TCs could have had TSVs or VVs present. Legs with a normal visible examination result but with a history of sclerotherapy were arbitrarily classified as having TSVs (n=7). Legs with a history of vein stripping but a visible examination finding consistent with normal or TSVs categories were classified as having VVs (n=23). This classification parallels the clinical picture, etiology, anatomical distribution, and pathophysiology (CEAP) algorithm.[12] Normal corresponds to class 0, TSVs to class 1, VVs to class 2, and TCs to classes 4, 5, and 6.

Functional Categories

Functional classification was determined independent of visible findings using duplex ultrasonography criteria. The initial hierarchical classification categories were normal, superficial functional disease (SFD), perforator disease, and deep functional disease (DFD). We defined SFD as reflux or abnormal compression (ie, partial or complete obstruction) in the long or short saphenous veins or in another superficial vein noted by a technologist. We defined DFD as reflux or abnormal compression in the common femoral, superficial femoral, popliteal, or posterior tibial veins or at the saphenofemoral or saphenopopliteal junctions, abnormal compression at the peroneal vein, or abnormal Valsalva response at the common femoral vein or saphenofemoral junction. Because of the hierarchical nature of these categories, legs with DFD were likely to also have SFD. Preliminary analyses showed that less than 1% of all examined legs had perforator reflux without DFD; therefore, those legs were grouped with SFD. Legs that were functionally normal but had a history of vein stripping were also classified as SFD. Thus, there were 3 hierarchical functional categories: normal, SFD, and DFD. These functional categories correspond to a combination of the CEAP anatomical (superficial, deep, or perforating veins) and pathophysiologic classification (reflux, obstruction, or both) categories.[12]

STATISTICAL ANALYSIS

Data were entered into a relational database created in Microsoft Access (Microsoft Corp, Redmond, Wash) with screens that reflected the paper forms. The screens included range and validity checks. The data required for these analyses were extracted using DBMS/Copy software (Conceptual Software, Inc, Houston, Tex) into a file usable by SPSS statistical software for Windows version 6.02 (SPSS Inc, Chicago, Ill), which was used for all statistical analyses.[13] Descriptive analyses were conducted to look for outliers, and these were adjudicated against the original record. Categorical differences were tested using χ^2 statistics, and odds ratios (ORs) for disease based on the presence of a symptom with adjustment for appropriate factors were obtained by multiple logistic regression. All *P* values reflect 2-tailed tests.

RESULTS

A total of 6115 persons were randomly selected to receive an invitation to participate in the study. They were asked to extend the invitation to their spouses or significant others. From these invitations, we enrolled 2209 participants. An additional 199 people who learned of the study volunteered to participate and were enrolled, yielding a total study population of 2408 individuals who were 29 to 91 years old. Four participants did not complete the duplex ultrasonography examination, leaving 2404 persons for this report. Accordingly, examinations were conducted on 4808 legs. After exclusion for missing symp-

tom data (3% of the sample), 1598 legs from men and 3058 legs from women remained for these analyses.

Table 1 gives the mean age and ethnic distribution by sex for all legs examined. The deliberate oversampling of women is evident, and women were slightly younger than men, with mean ages of 58.4 and 59.7 years, respectively. The study also had greater representation of ethnic minorities among women (45%) than men (32%). The distribution of venous disease in functional and visible categories has been described in detail in another report.[7] Briefly, visible disease was present in 84% of women and 57% of men. The most common form of visible disease was TSVs, which were present in 56% of women and 44% of men. Varicose veins were twice as common in women as men, at 28% and 15%, respectively. Conversely, TCs were slightly more prevalent in men than women, at 8% compared with 5%. Functional disease was present in 30% of women and 24% of men. However, SFD was more common in women than men (22% vs 13%), and DFD was more common in men than women (11% vs 8%).

Aching was the most commonly reported venous symptom, with an overall prevalence of 17.7% (**Table 2**). Cramping was present in 14.3%, tired legs in 12.8%, and swelling in 12.2% of legs. Heaviness and restless legs had similar prevalences at 7.5% and 7.4%, respectively. Itching was the least commonly reported symptom, affecting 5.4% of legs. With the exception of restless legs, all of these symptoms increased in prevalence with increasing severity of venous functional disease. The rate was lowest in normal legs, increased in legs with SFD, and highest in legs with DFD. These differences were statistically significant ($P<.001$) for all symptoms except for restless legs ($P=.56$). Although each symptom was more common in women than men, trends were similar in both sexes (**Figure 1**).

Escalating rates of symptoms were also found across categories of visible venous disease (**Table 3**). However, symptom prevalence in participants with TSVs, the most common category of visible disease, was only marginally greater than in those with normal legs. Symptoms were generally about twice as common when VVs were present. Rates were further increased in the presence of TCs. Again, with the exception of restless legs ($P=.06$), these differences were highly statistically significant ($P<.001$). **Figure 2** shows the prevalence rates by symptom and visible category for each sex. Similar to functional disease, symptom prevalence was uniformly greater in women, although trends were similar in both sexes. Again, the symptom of restless legs had the least consistent association with disease categories.

Approximately 17% of the population had a high school equivalent education or less. Lower educational level was generally associated with a slightly greater likelihood of symptoms when disease was present. This trend was reversed for trophic disease. Typically, the reported prevalence of a symptom was 1% to 3% greater in the lower so-

Table 1. Population Distribution by Sex, Age, and Ethnicity

Characteristic	Male	Female
No. of legs	1598	3058
Age, mean (SD), y	59.7 (11.2)	58.4 (11.3)
Ethnicity, No. (%)		
Non-Hispanic white	1090 (68.2)	1688 (55.2)
Hispanic	164 (10.3)	522 (17.1)
African American	156 (9.8)	484 (15.8)
Asian	188 (11.8)	364 (11.9)

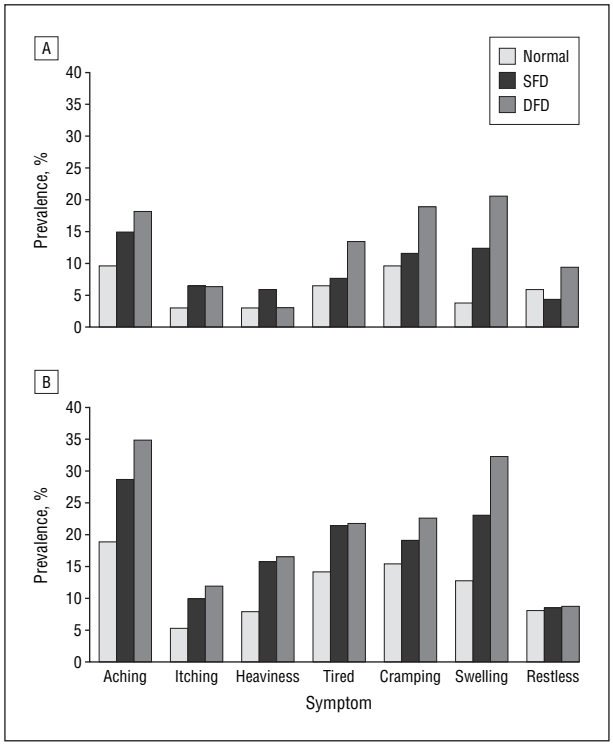

Figure 1. The prevalence of symptoms and functional venous disease by sex. A, Prevalence in men. B, Prevalence in women. SFD indicates superficial functional disease; DFD, deep functional disease.

Table 2. Percentage of Participants With Leg Symptoms by Functional Disease

Symptom	All	Normal	SFD	DFD	*P* Value*
Aching	17.7	15.5	25.5	27.2	<.001
Itching	5.4	4.5	9.0	9.3	<.001
Heaviness	7.5	6.2	13.5	10.4	<.001
Tired	12.8	11.3	18.2	17.9	<.001
Cramping	14.3	13.2	17.4	20.8	<.001
Swelling	12.2	9.5	20.5	26.9	<.001
Restless	7.4	7.3	7.6	9.0	.56

Abbreviations: DFD, deep functional disease; SFD, superficial functional disease.
*Pearson χ^2.

Table 3. Percentage of Participants With Leg Symptoms by Visible Disease

Symptoms	All	Normal	TSVs	VVs	TCs	*P* Value*
Aching	17.7	14.2	15.7	25.5	29.1	<.001
Itching	5.4	4.0	4.3	8.7	13.1	<.001
Heaviness	7.5	4.4	6.7	11.8	16.0	<.001
Tired	12.8	10.6	11.1	18.3	21.1	<.001
Cramping	14.3	12.9	13.2	17.7	19.7	<.001
Swelling	12.2	7.2	10.1	19.1	35.7	<.001
Restless	7.4	5.8	7.5	9.0	8.0	.06

Abbreviations: TCs, trophic changes; TSVs, telangiectasias or spider veins; VVs, varicose veins.
*Pearson χ^2.

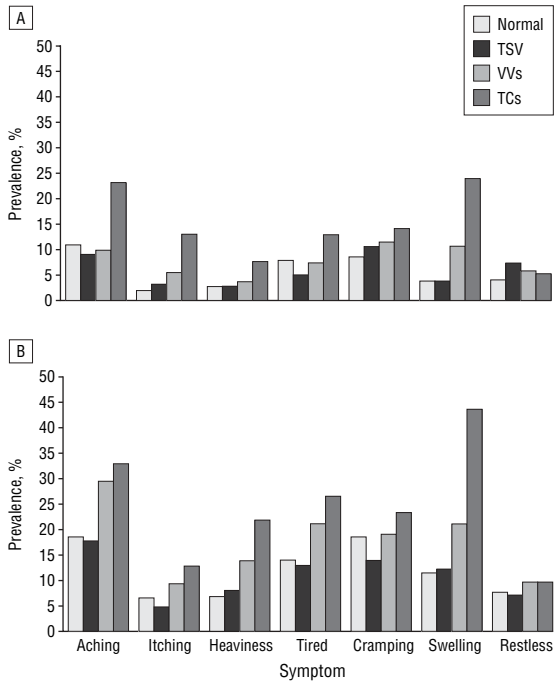

Figure 2. The prevalence of symptoms and visible venous disease by sex. A, Prevalence in men. B, Prevalence in women. TSVs indicates telangiectasias or spider veins; VV, varicose veins; and TCs, trophic changes.

cioeconomic status group, with a maximum difference of 6% (data not shown). To estimate the relative importance of each symptom to the clinical picture of venous disease, we evaluated the ORs for each symptom in each of the 12 categories of venous status formed by crossing the 3 categories of functional disease with the 4 categories of visible disease using logistic regression adjusted for age, sex, body mass index (calculated as weight in kilograms divided by the square of height in meters), racial/ethnic group, and educational level (**Table 4**). Aching (OR, 2.20) and swelling (OR, 2.99) were significantly associated with DFD even in participants without visible disease. These 2 symptoms were significantly associated with DFD across all categories of visible disease, with the strongest association in participants with TCs. Aching was significantly associated with VVs regardless of venous functional status and was associated with TCs except in those with normal functional examinations. Itching followed a similar pattern and was significantly associated with VVs regardless of visible

Table 4. Odds Ratios for Symptoms by Functional Disease Category Adjusted for Sex, Age, Ethnicity, Education, and Body Mass Index

Category	Normal	TSVs	VVs	TCs
No. of legs				
Normal	1024	2519	184	58
SFD	5	22	591	117
DFD	39	87	107	55
Aching				
Normal	Referent	1.11	2.05*	0.85
SFD	0.03	1.56	2.29*	3.90*
DFD	2.20*	1.93*	2.82*	6.17*
Itching				
Normal	Referent	1.11	1.98*	2.63
SFD	0.04	5.88*	2.33*	4.81*
DFD	1.10	0.32	5.31*	6.94*
Heaviness				
Normal	Referent	1.33	1.60	0.02
SFD	0.01	1.44	2.69*	5.68*
DFD	0.59	1.65	2.82*	5.27*
Tired				
Normal	Referent	1.09	1.63*	0.42
SFD	0.01	0.30	2.07*	3.80*
DFD	1.52	1.04	2.95*	4.79*
Cramping				
Normal	Referent	0.95	1.45	0.46
SFD	0.03	1.36	1.41*	1.82*
DFD	1.53	1.57	1.44	3.82*
Swelling				
Normal	Referent	1.15	1.91*	5.41*
SFD	0.02	4.13*	2.31*	6.73*
DFD	2.99*	2.57*	5.82*	11.61*
Restless				
Normal	Referent	1.44*	2.36*	1.13
SFD	0.03	1.50	1.64*	0.95
DFD	2.32	0.82	1.18	3.78*

Abbreviations: DFD, deep functional disease; SFD, superficial functional disease; TCs, trophic changes; TSVs, telangiectasias or spider veins; VVs, varicose veins.
*$P<.05$.

status and with TCs except in those with normal functional examination results. However, the OR for itching with VVs and DFD was nearly twice the level of the parallel ratio for aching (5.31 and 2.82, respectively). Swelling had associations similar to itching for VVs but was associated with much higher ORs when TCs were present (ORs, 11.61, 6.94, and 6.17 for swelling, itching, and aching, respectively, in participants with DFD and TCs). Heaviness, tired legs, and cramping each had modest associations with disease in the presence of both functional and visible abnor-

malities. Although the symptom of restless legs was associated with disease for participants with both DFD and TCs, it did not consistently distinguish disease, because rates were elevated in participants who had normal venous functional status but either TSVs or VVs. In general, a combination of visible and functional venous findings tended to increase the OR compared with only a visible or a functional finding.

COMMENT

In this population-based study, aching was the most commonly reported symptom related to venous disease. However, it was relatively nonspecific, because it was reported by approximately 15% of participants with normal legs (assessed by either functional or visible status). Swelling was a more specific marker for prevalent disease, with less than 10% of participants with normal results reporting this symptom and at least a 2-fold higher rate associated with functional disease or any visible disease besides TSVs. Likewise, heaviness and itching were reported in legs with functional or visible findings at more than twice the rate reported in normal legs. Tired legs and cramping were also increased in legs with functional or visible findings, but the contrasts with normal legs were not as strong. In the multivariate analysis, symptoms were most frequent when both functional and visible venous findings were present in the same leg.

Our finding that swelling is a strong predictor is concordant with several other reports. A study[14] of patients who attended a vascular clinic found an association between vascular endothelial growth factor and CEAP classification and between vascular endothelial growth factor and swelling. The Edinburgh Vein Study,[15] conducted in patients from clinical practices, evaluated associations by leg as in the present report. Disease was defined by the presence of superficial and deep reflux. For isolated superficial reflux, associations were found for heaviness and itching in women; there were no significant associations in men. For venous disease defined as combined superficial and deep reflux, associations were found among swelling, cramps, and itching for men and between aching and cramps in women. A study[5] of a large employed population found swelling and nocturnal cramps to be the most common symptoms of venous disease. Surprisingly, in that population the strongest association was found for people with small cutaneous veins, the equivalent of TSVs in our study. In a clinical population evaluated by color-flow duplex ultrasonography, the strongest associations were found for aching and swelling, which were associated with below-knee reflux.[6]

Women were more likely to report symptoms than men. Similar results have been reported by other investigators.[5,16] This is not simply an artifact of the greater prevalence of visible disease and SFD in women,[7] since it was evident on a percentage basis for each category and was also found for DFD, which was more prevalent in men. Lower educational attainment was associated with a slightly greater level of symptoms when disease was present. Although this study enrolled participants in all job classifications, the average educational level was higher than in the community at large, with more than 80% having some college or more advanced education. Accordingly, our estimates of symptom associations by disease category may be conservative. The symptom of restless legs was not predictive of functional or visible disease and thus had no utility in this population.

Leg symptoms of swelling, aching, heaviness, and itching are reasonably good predictors of clinically verifiable functional or visible venous disease. The presence of both aching and swelling or aching and tiredness in a limb may further qualify this association. These symptoms may be useful in clinical assessment and may be helpful in estimating the population prevalence of venous disease. Symptoms are more common when both functional and visible venous diseases are present.

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