Increased vein wall thickness in Behçet disease

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ABSTRACT

Objective: Lower extremity (LE) deep venous thrombosis (DVT) is the main feature of vascular involvement in Behçet disease (BD). We thought that vein wall thickness (VWT) could be a surrogate marker for venous inflammation and hence predict future vascular involvement. We assessed VWT in proximal LE veins in BD patients without DVT, BD patients with DVT, and healthy controls in a formal, masked protocol.

Methods: We studied 50 (43 male and 7 female) BD patients with LE DVT (group 1), 50 (43 male and 7 female) BD patients without any vascular involvement (group 2), and 50 (43 male and 7 female) age- and sex-matched apparently healthy controls (group 3). Two radiologists blinded to the diagnosis of BD used ultrasound to measure VWT of common femoral vein, femoral vein, and great saphenous vein in both legs. Interobserver reliability was assessed using the intraclass correlation coefficient and Bland-Altman plots.

Results: There was good agreement between the two observers. The mean VWT was significantly increased in both BD patients with LE DVT and those without apparent vascular involvement compared with the healthy controls, whereas those with LE DVT had the highest VWT.

Conclusions: VWT of proximal deep and superficial LE veins is increased among the BD patients without any clinical and radiologic vascular involvement. This information, after prospective work, might be useful in management and elucidating disease mechanisms in vascular BD. (J Vasc Surg: Venous and Lym Dis 2019;7:677-84.)

Keywords: Behçet disease; Lower extremity venous thrombosis; Doppler ultrasound; Vein wall thickness; Vascular involvement

Vascular involvement can be seen in up to 40% of the patients with Behçet disease (BD), leading to significant morbidity.[1] Lower extremity (LE) deep venous thrombosis (DVT) is its most common manifestation. LE DVT occurs early in the disease course and usually precedes major vascular involvement, such as vena cava thrombosis, Budd-Chiari syndrome, or pulmonary artery involvement.[1] Compared with idiopathic DVT, DVT in BD affects mostly young men, runs a more relapsing course, and tends to be more frequently bilateral.[2] It is associated with significantly less recanalization, more collateral formation, and more thrombotic occlusions.[2] As a result, severe post-thrombotic syndrome occurs in about half of the patients.[2] The main treatment of DVT is immunosuppression.[1,3] Anticoagulation alone or in addition to immunosuppressive treatment does not prevent relapses.[3]

Typical ultrasound findings of chronic DVT include resistance to compression, absence of flow, and presence of thrombotic changes or residue in the vessel wall and the lumen.[2,4] Vein wall thickness (VWT) is proposed to be a surrogate marker of venous disease. It can be increased because of remodeling in venous insufficiency and venous hypertension and also because of inflammation in acute and chronic thromboses.[5-7]

A pilot magnetic resonance study of seven BD patients and controls reported increased VWT and signal enhancement in the LE veins of BD patients without clinical venous disease.[8] Another study, this time using ultrasound, reported that VWT was increased in BD patients without vascular disease compared with patients with ankylosing spondylitis and healthy controls.[9] These studies[8,9] had not compared differences in VWT between BD patients with and without clinical vascular disease. Using gray-scale ultrasound to evaluate VWT, we aimed to assess this difference. In a formal, masked protocol, we measured VWT in the proximal LE veins in BD patients without LE DVT and suitable positive (BD patients with a history of chronic DVT) and healthy negative controls.

METHODS

We studied consecutive BD patients aged ≤45 years who attended the dedicated BD outpatient clinic at Cerrahpaşa Medical Faculty of University of Istanbul between July 2017 and May 2018. All BD patients had fulfilled the International Study Group criteria for the diagnosis of BD.[10] The study included two subsets of BD patients (group 1 and group 2) and healthy controls (group 3).

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Group 1 included patients with LE DVT, who were defined as having a documented chronic thrombotic event in any (superficial or deep) LE vein based on Doppler ultrasound. Group 2 included patients without vascular disease who had no recorded vascular involvement, defined as any venous thrombosis or insufficiency or any arterial thrombosis or aneurysms. These patients were rescreened with Doppler ultrasound and considered eligible for group 2 only if they had normal results. Group 3 included apparently healthy individuals of the hospital staff who were age and sex matched to the patients and had no history of autoimmune or autoinflammatory disease.

Information on clinical characteristics, disease duration, and current medications was obtained from the medical records. Height and weight were measured. Comorbidities and smoking habits were prospectively recorded.

Doppler ultrasound assessment. Two independent radiologists, blinded to the identity of study participants, used B-mode ultrasound to measure VWT of common femoral vein (CFV), femoral vein (FV), and great saphenous vein (GSV) from both legs. They also evaluated the presence or absence of chronic thrombotic changes in the proximal and distal LE veins. The ultrasound examination started with the patient in the supine position. External rotation of the hip and slight rotation of the knee were used to help decrease muscle tension and to expose deep veins. The veins were examined from cranial to caudal direction. The thickest part of the venous wall was determined, and VWT was measured from the posterior wall of the vein and recorded in millimeters. Anterior wall examination would cause reverberation artifacts that would cause imperfect delineation. Wall thickening was usually symmetric; most of the time, radiologists measured the posterior wall. Because vein wall could not be differentiated when acute or subacute thrombotic changes occurred, we did not include patients with acute or subacute thrombosis. Ultrasound examination consisted of the investigation of echogenic thrombus in the lumen, response to compression, presence or absence of flow on Doppler examination, hyperechogenic linear septation in the lumen, and recanalization in the flow pattern. Reflux or collateral formations were not specifically evaluated. Fig 1 shows a B-mode ultrasound picture of a left CFV posterior wall measurement on a longitudinal plane in a patient with chronic thrombotic changes. Fig 2 shows a B-mode ultrasound picture of a right CFV posterior wall measurement on a longitudinal plane in a patient without DVT.

The Institutional Review Board of Cerrahpaşa Medical School approved the study. All participants gave informed consent.

Statistical analysis. Continuous data were given as the mean and standard deviation. Data with non-normal distribution were expressed as median (interquartile range). Comparisons of continuous variables were made by using Student *t*-tests or one-way analysis of variance. Continuous variables with non-normal distributions were

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective, blinded, case-control study
- **Key Findings:** Mean vein wall thickness (VWT) of proximal lower extremity veins in 50 Behçet disease (BD) patients with unilateral deep venous thrombosis was significantly larger on ultrasound measurements on the affected side compared with the unaffected side ($P < .001$). VWT on the unaffected side was similar to that measured in 50 BD patients without vascular involvement ($P > .05$) but still larger than in 50 healthy controls ($P < .001$).
- **Take Home Message:** The study indicates that venous wall inflammation is a feature of BD with or without clinically overt vascular disease and suggests further evaluation of VWT as a risk factor for deep venous thrombosis in BD patients.

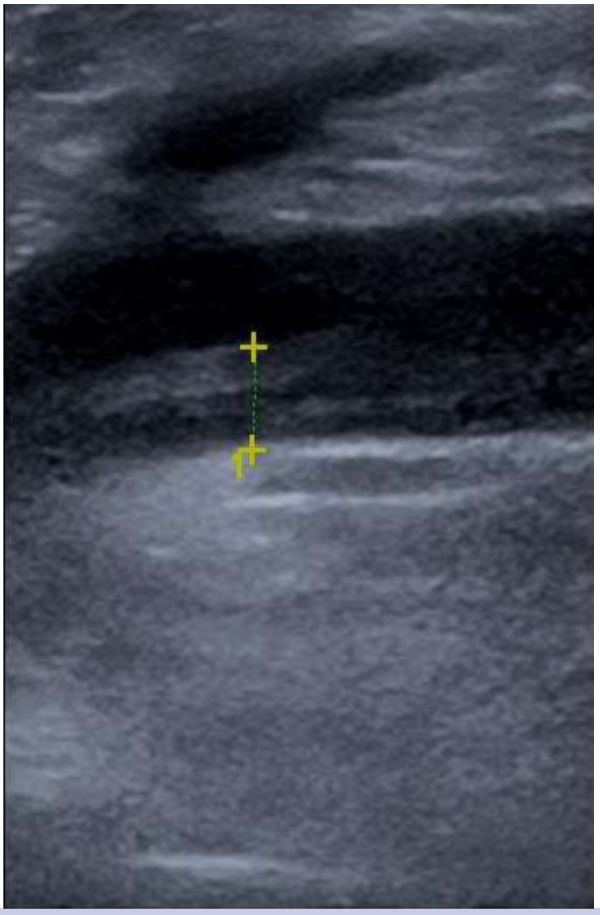

Fig 1. B-mode ultrasound picture of a left common femoral vein (CFV) on a longitudinal plane showing posterior wall vein wall thickness (VWT) measurement in a patient with chronic thrombotic changes.

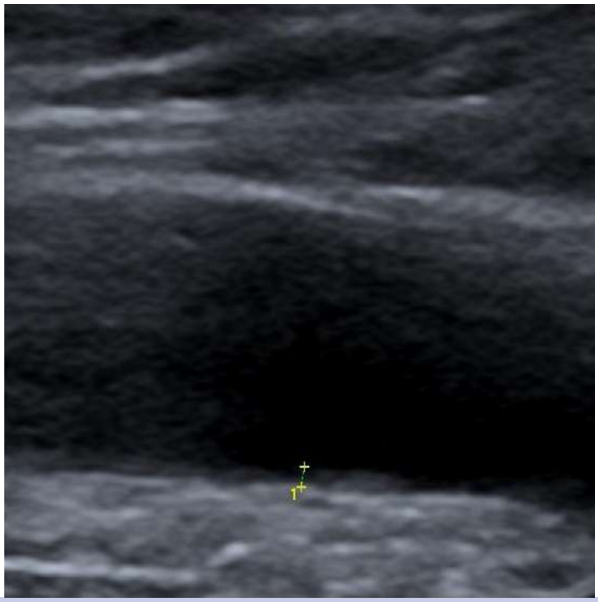

Fig 2. B-mode ultrasound picture of a right common femoral vein (CFV) on a longitudinal plane showing posterior wall measurement in a patient without deep venous thrombosis (DVT).

compared by Mann-Whitney *U* and Kruskal-Wallis tests. Categorical variables were compared by the Pearson χ^2 test or the Fisher exact test. Interobserver reliability was assessed using the intraclass correlation coefficient and Bland-Altman plots. Receiver operating characteristic (ROC) curve was plotted to select the appropriate cutoff value of VWT to discriminate BD patients with no vascular disease from healthy controls. All tests were performed using version 22.0 of SPSS software for Windows (IBM Corp, Armonk, NY).

RESULTS

We studied 50 (43 male and 7 female) BD patients with LE DVT (group 1), 50 (43 male and 7 female) BD patients without vascular disease (group 2), and 50 (43 male and 7 female) healthy controls (group 3). Demographic and clinical characteristics of the patients and the healthy controls are shown in Table I. The mean disease duration was similar between the BD study groups. Body mass index and frequency of smoking were similar between the study groups. The frequency of BD manifestations, such as eye, joint, or neurologic involvement, was similar between those with and those without vascular disease (Table I). The frequency of comorbid conditions also did not differ between the study groups. Whereas nonbiologic immunosuppressive agents were used significantly more by patients with LE DVT, it was colchicine that was significantly more used by patients with no vascular disease. The frequency of those using glucocorticoids, interferon alfa, and anti-tumor necrosis factors was

Table I. Demographic and clinical characteristics of Behçet disease (*BD*) patients and healthy controls

	Patients with LE DVT (n = 50; 43 male, 7 female)	Patients with no vascular involvement (n = 50; 43 male, 7 female)	Healthy controls (n= 50; 43 male, 7 female)	*P*
Age, years	37.2 ± 5.2	37.0 ± 4.5	36.0 ± 6.8	.558
Disease duration, years	11.0 ± 6.5	10.0 ± 5.9	–	.809
Body mass index, kg/m^2	25.7 ± 3.7	26.1 ± 3.6	26.5 ± 3.4	.562
Current or past smoking	36 (72)	29 (58)	38 (76)	.125
BD manifestations				
Eye involvement	25 (50)	26 (52)	–	.841
Joint involvement	14 (28)	17 (34)	–	.517
Neurologic involvement	2 (4)	1 (2)	–	.390
Comorbidities				
Hypertension	4 (8)	2 (4)	5 (10)	.503
Diabetes mellitus	0	0	3 (6)	–
Hyperlipidemia	1 (2)	0	2 (4)	–
Current drugs				
Nonbiologic immunosuppressive agents	30 (60)	17 (34)	–	.002
Colchicine	12 (24)	32 (64)	–	<.001
Steroids	7 (14)	7 (14)	–	.267
Interferon	8 (16)	3 (6)	–	.111
Anti-tumor necrosis factors	4 (8)	3 (6)	–	.707
Anticoagulant	1 (2)	0	–	–

DVT, Deep venous thrombosis; *LE*, lower extremity.
Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation.

Table II. Vein wall thickness (VWT) of common femoral vein (*CFV*), femoral vein (*FV*), and great saphenous vein (*GSV*) on both legs measured by two radiologists between the study groups

	BD with vascular involvement (n = 50; 43 male, 7 female)	BD without vascular involvement (n = 50; 43 male, 7 female)	Healthy controls (n = 50; 47 male, 3 female)	*P* value
Right CFV				
First observer	0.90 ± 0.65	0.69 ± 0.15	0.55 ± 0.10	<.001[a,b]
Second observer	0.92 ± 0.74	0.70 ± 0.18	0.57 ± 0.08	<.001[a,b]
Left CFV				
First observer	1.03 ± 0.83	0.66 ± 0.11	0.56 ± 0.07	<.001[a,b]
Second observer	1.07 ± 0.81	0.69 ± 0.16	0.57 ± 0.07	<.001[a,b]
Right FV				
First observer	0.78 ± 0.37	0.60 ± 0.12	0.49 ± 0.9	<.001[a,b,c]
Second observer	0.79 ± 0.41	0.62 ± 0.13	0.51 ± 0.08	<.001[a,b,c]
Left FV				
First observer	0.86 ± 0.37	0.62 ± 0.12	0.48 ± 0.09	<.001[a,b,c]
Second observer	0.88 ± 0.40	0.63 ± 0.13	0.49 ± 0.07	<.001[a,b,c]
Right GSV				
First observer	0.59 ± 0.22	0.52 ± 0.11	0.44 ± 0.07	<.001[a,b,c]
Second observer	0.63 ± 0.25	0.53 ± 0.13	0.46 ± 0.09	<.001[a,b,c]
Left GSV				
First observer	0.66 ± 0.24	0.53 ± 0.11	0.43 ± 0.09	<.001[a,b,c]
Second observer	0.64 ± 0.26	0.53 ± 0.11	0.43 ± 0.06	<.001[a,b,c]

BD, Behçet disease.
All measurements are expressed in millimeters as mean ± standard deviation.
[a]BD with vascular involvement vs BD without vascular involvement: $P < .05$.
[b]BD with vascular involvement vs healthy controls: $P < .001$.
[c]BD without vascular involvement vs healthy controls: $P < .05$.

similar between group 1 and group 2. Only one patient with DVT was using anticoagulants, and 14 were taking aspirin (28%).

Clinical characteristics of the patients with LE DVT (group 1)

The mean age of the patients with LE DVT at the time of thrombosis onset was 26.4 ± 5.8 years. The DVT was bilateral in 18 of 50 (36%) patients. FVs were most frequently involved (FV, 70%; CFV, 48%; deep FV, 22%), followed by popliteal vein (62%) and GSV (32%). In addition, patients had thrombosis of iliac veins (n = 5), superior vena cava (n = 3), inferior vena cava (n = 2), hepatic vein (n = 1), and cerebral sinus veins (n = 2). Apart from the venous involvement, four patients had pulmonary artery aneurysms or thrombosis.

VWT

Interobserver variability. There was good concordance between the two observers (Supplementary Table, online only). Interobserver variability analysis obtained a mean difference of −0.016 mm, −0.023 mm, −0.016 mm, −0.014 mm, −0.023 mm, and 0.004 mm for right CFV, left CFV, right FV, left FV, right GSV, and left GSV, respectively, with zero included in the confidence intervals, indicating no significant difference between observers (Supplementary Table, online only). The Bland-Altman plots (Supplementary Fig, online only) similarly indicated good agreement between observers (a mean VWT difference of −0.02 mm, −0.04 mm, −0.05 mm, −0.03 mm, 0.02 mm, and −0.02 mm, for right CFV, left CFV, right FV, left FV, right GSV, and left GSV, respectively).

Measurements (Table II; Fig 3). The mean VWT was significantly increased in both BD patients with DVT and those without any vascular involvement compared with the healthy controls, whereas those with DVT had the thickest veins (Table II; Fig 3). This was true for FV, CFV, and GSV for both right and left sides and as measured by two radiologists (Table II; Fig 3). Mean ± standard deviation and ranges of combined measurements obtained by calculating the average of four measurements (that of radiologists 1 and 2 for both right and left sides) are shown for each vein in Table III. We performed ROC analysis to obtain the cutoff value of VWT to make discrimination between BD patients with no vascular disease and healthy controls. The area under the ROC curve of 0.62 mm for CFV, 0.56 mm for FV, and 0.45 mm for GSV achieved the best discriminatory performances. Table IV shows sensitivity and specificity values of the cutoff values for each vein.

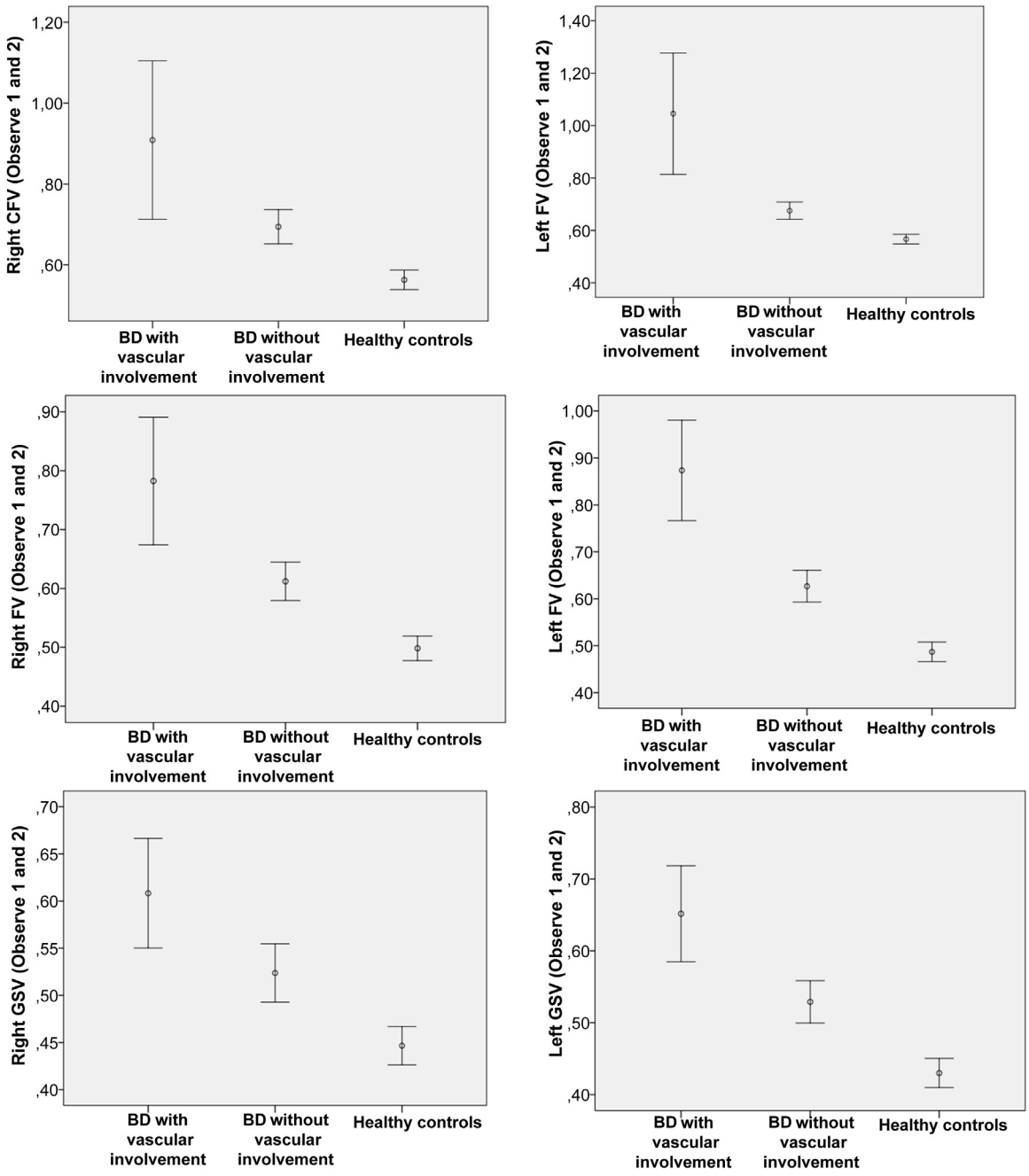

Fig 3. The 95% confidence levels of mean vein wall thickness (VWT) measurements of right and left common femoral vein (*CFV*), femoral vein (*FV*), and great saphenous vein (*GSV*) obtained by calculating the mean of two observers' measurements. *BD*, Behçet disease; n = 50 in all study groups (BD with vascular involvement, BD without vascular involvement, and healthy controls).

There was no correlation between VWT and disease duration or severity of BD complications or level of C-reactive protein in both patients with and without DVT.

In another post hoc analysis, we wanted to compare VWT of the ipsilateral affected leg veins with that of unaffected contralateral leg veins. Hence, we excluded 18 patients who had bilateral involvement among patients with LE DVT and studied 32 patients with unilateral involvement. As shown in Fig 4, the four groups included in this analysis were described as follows: ipsilateral affected leg veins (32 veins; 19 on the left, 13 on the right); contralateral unaffected leg veins (32 veins; 19 on the right, 13 on the left); patients with no vascular involvement (all 100 veins, 50 bilateral); and healthy controls (all 100 veins, 50 bilateral).

The mean VWT was significantly ($P < .001$) increased on the thrombotic leg vein side compared with the contralateral unaffected side (Fig 4). The VWT of the contralateral

Table III. Mean and ranges of common femoral vein (*CFV*), femoral vein (*FV*), and great saphenous vein (*GSV*) in the study groups

	BD patients with vascular involvement (n = 50; 43 male, 7 female)	BD patients without vascular involvement (n = 50; 43 male, 7 female)	Healthy controls (n = 50; 43 male, 7 female)
CFV			
Mean ± SD, mm	0.98 ± 0.57	0.68 ± 0.11	0.56 ± 0.05
Range, mm	0.46-3.41	0.51-1.06	0.42-0.68
FV			
Mean ± SD, mm	0.83 ± 0.28	0.62 ± 0.10	0.49 ± 0.06
Range, mm	0.45-1.83	0.44-0.89	0.34-0.70
GSV			
Mean ± SD, mm	0.63 ± 0.17	0.53 ± 0.09	0.44 ± 0.06
Range, mm	0.37-1.14	0.39-0.82	0.32-0.61

BD, Behçet disease; *SD*, standard deviation.

unaffected side was similar ($P > .05$) to that of BD patients with no vascular involvement but significantly thicker ($P < .001$) than that of healthy controls.

DISCUSSION

There is ample clinical evidence indicating that venous inflammation is a key feature in BD. Not only is there a distinctly increased frequency of LE DVT,[1] but this is associated with involvement of larger veins, dural sinuses, and pulmonary arteries, vessels structurally similar to veins.[1,2] Moreover, the DVT in BD differs from idiopathic DVT in that large segments of the vessel wall are involved in BD.[2] The associated thrombi are taken to be more adherent to long segments of the wall with less propensity for the development of emboli.[11,12] Moreover, retinal vasculitis that occurs in patients with posterior uveitis primarily involves the retinal veins,[13] and autopsy studies and biopsy specimens of the central nervous system (CNS) lesions are consistent with venous involvement as well.[14] Finally, a magnetic resonance imaging study from our group revealed that spinal cord involvement associated with CNS lesions demonstrates evidence of thrombus in the venous collateral network with surrounding edema.[15] Another magnetic resonance imaging study using a special method that allows visualization of veins (susceptibility weighted imaging), again from our group, observed that CNS parenchymal lesions were hemorrhagic in appearance, caused possibly by venous ischemia, which supports the venous theory in pathology.[16]

The difference in VWT that we showed between group 1 and group 2 patients and between the clinically affected and not affected legs of group 1 patients with unilateral disease strongly confirms that venous wall inflammation is common in BD with or without clinical vascular disease. Because the unaffected leg and the nonaffected patients have significantly increased thickness compared with healthy controls but have almost the same thickness, we cannot tell whether the thickness is a precursor to DVT; it most probably demonstrates a systemic inflammation. Although we do not have histologic or serologic evidence, we believe that the wall thickening results from diffuse vascular inflammation. The important corollary to this contention would be the hypothesis that among those patients with more inflammation (greater VWT), the thrombotic disease would be more clinically manifested.

In vivo studies addressing VWT in conditions other than BD have been few as well.[5-7,17-21] It has been reported that VWT may increase also among patients with venous insufficiency and during post-thrombotic vein wall remodeling,[5-7,17-19] and it has been suggested that VWT along with deep venous valve dysfunction could be an anatomic sequela of a previous DVT.[19] On the other hand, an increased VWT detected before hip fracture surgery helped define a potentially high risk population for LE DVT after surgery.[21]

Table IV. Results of the receiver operating characteristic (ROC) curve analyses

	Cutoff, mm	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC	*P*
CFV	>0.617	72	90	87.8	76.3	0.833	<.001
FV	>0.557	74	94	92.5	78.3	0.859	<.001
GSV	>0.447	82	66	70.7	78.6	0.805	<.001

AUC, Area under the curve; *CFV*, common femoral vein; *FV*, femoral vein; *GSV*, great saphenous vein; *NPV*, negative predictive value; *PPV*, positive predictive value.

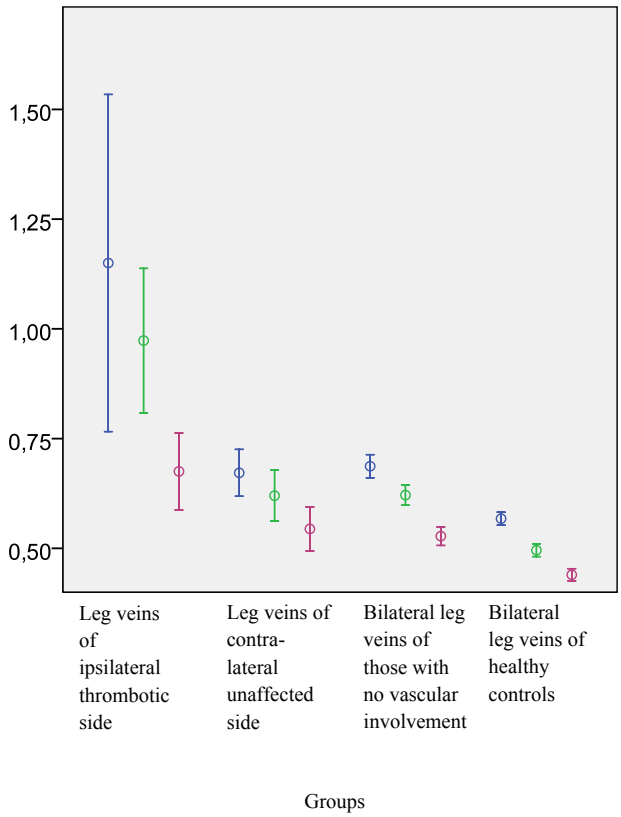

Fig 4. Mean vein wall thickness (VWT) in millimeters with 95% confidence interval (*CI*) among the study groups: ipsilateral thrombotic side (n = 32), contralateral unaffected side (n = 32), Behçet disease (BD) patients with no vascular involvement (n = 100), and healthy controls (n = 100). Common femoral vein (CFV), *blue*; femoral vein (FV), *green*; and great saphenous vein (GSV), *purple*.

Our observation and that of others[8,9] that VWT is increased in BD without any previous clinical history strongly suggests that this increased venous thickness is indeed a surrogate for vascular inflammation or perhaps a precursor of DVT or other vascular diseases in BD. On the other hand, our findings cannot rule out that the increased VWT is a result of a preceding thrombosis.[6,18,19] These considerations mandate a prospective study to assess the onset of thrombotic complications among thrombosis-free patients with differing degrees of increased VWT. Hence, we believe that cutoff VWT values (0.62 mm for CFV, 0.56 mm for FV, and 0.45 mm for GSV) that we found in this study would be helpful in the future while planning prospective research. These would also be helpful in routine practice while planning the management strategy in individual patients. Whether those BD patients with VWT with greater cutoff measurements would require intensified immunosuppressive treatment should also be the subject of a future project.

Magnetic resonance venography could be another useful option to study vein wall characteristics in BD besides ultrasound. Apart from the pilot study[8] that showed increased enhancement in seven patients with BD that we mentioned earlier, there are no magnetic resonance venography studies in BD. Recent developments enabled the acquisition of high-quality images, and it has become a valuable technique in detecting venous disease, distinguishing effectively between acute and chronic thrombus and giving detailed information about wall morphology.[22,23]

Whereas our study has the strength of inclusion of positive and negative control groups and its assessment of interobserver variability, it also has some limitations. The sample size of the female patients was too small to make a proper comparison between sexes in a condition in which sex differences are important in disease expression. Interobserver agreement was good; however, we did not test the intraobserver variability. Finally, further studies including patients with another rheumatic disease or idiopathic thrombosis should be planned to re-evaluate our observations.

CONCLUSIONS

VWT of proximal deep and superficial LE veins was found to be significantly increased in BD patients without any clinical or radiologic evidence of vascular involvement. Although we believe that our pioneering work with clinically and biologically important findings would shed light on the pathogenesis of inflammatory thrombosis in BD, it needs further assessment by prospective studies.

AUTHOR CONTRIBUTIONS

Conception and design: ES, IM, HY
Analysis and interpretation: ES
Data collection: ES, MG, ED, SA, NS, AD, IM
Writing the article: ES
Critical revision of the article: ES, MG, ED, SA, NS, AD, IM, HY
Final approval of the article: ES, MG, ED, SA, NS, AD, IM, HY
Statistical analysis: ES, NS
Obtained funding: Not applicable
Overall responsibility: ES

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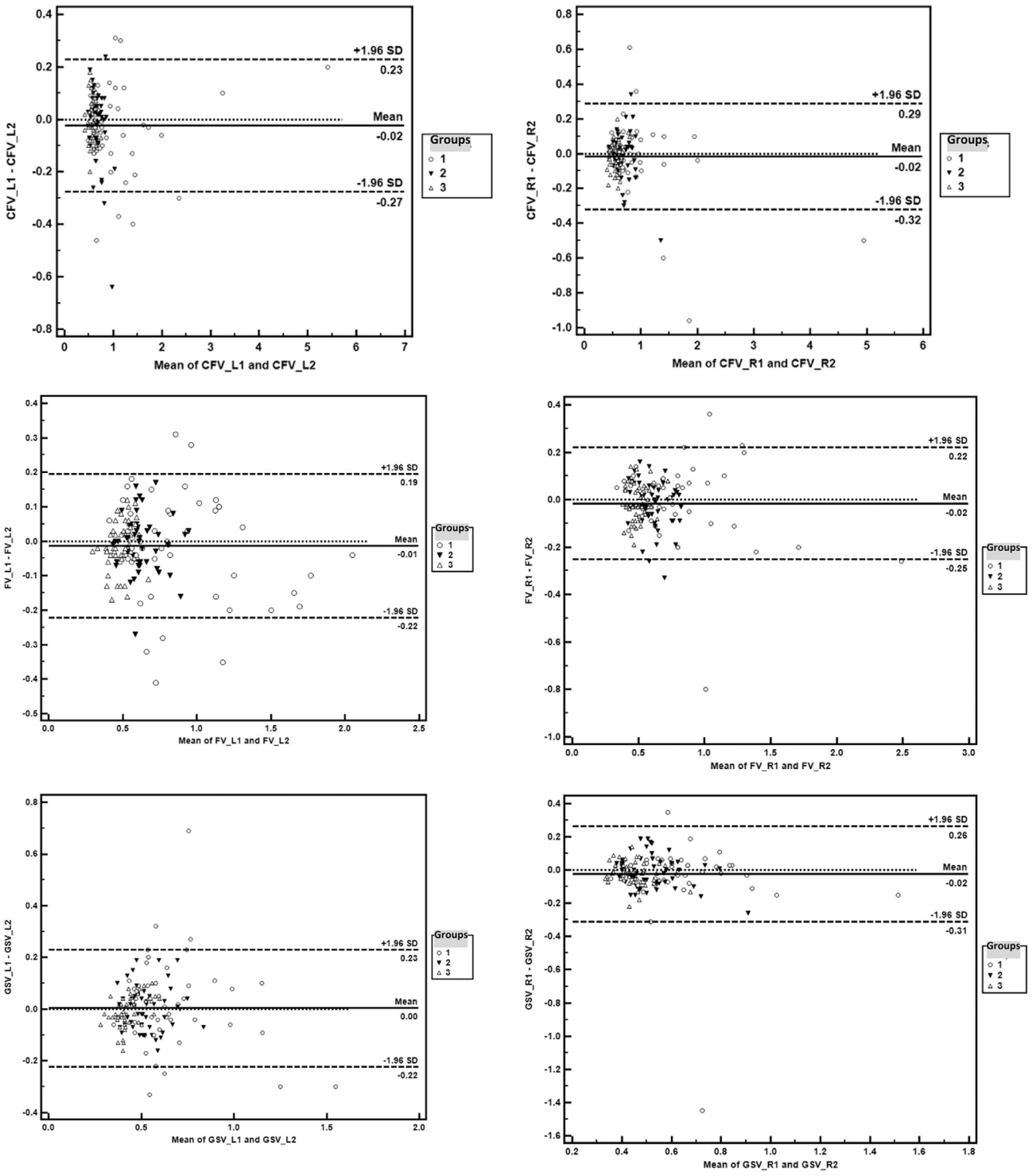
Supplementary Table (online only). Interobserver variability and reliability between first and second observers

	Interobserver variability			Interobserver reliability			
		95% Confidence interval			95% Confidence interval		
	Mean ± standard deviation	Lower	Upper	Intraclass correlation	Lower	Upper	*P*
Right CFV, first-second observer	−0.016 ± 0.155	−0.041	0.009	0.968	0.956	0.977	<.001
Left CFV, first-second observer	−0.023 ± 0.129	−0.044	−0.002	0.985	0.979	0.989	<.001
Right FV, first-second observer	−0.016 ± 0.120	−0.036	0.003	0.946	0.926	0.961	<.001
Left FV, first-second observer	−0.014 ± 0.106	−0.031	0.003	0.964	0.951	0.974	<.001
Right GSV, first-second observer	−0.023 ± 0.147	−0.047	0.0004	0.774	0.687	0.836	<.001
Left GSV, first-second observer	0.004 ± 0.116	−0.015	0.022	0.894	0.854	0.923	<.001

CFV, Common femoral vein; *FV,* femoral vein; *GSV,* great saphenous vein.
Variability defines the difference of the measurements of the two observers and was expressed as mean ± standard deviation and 95% confidence intervals. Reliability refers to the agreement of the two observers and was expressed as intraclass correlation and 95% confidence intervals.



Supplementary Fig (online only). Bland-Altman plots indicate the mean percentage difference (*solid line*) between first (*1*) and second (*2*) observers' measurements and upper and lower 95% limits of agreement (*dashed lines*). *CFV,* Common femoral vein; *FV,* femoral vein; *GSV,* great saphenous vein; *L,* left; *R,* right; *SD,* standard deviation.