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BRIEF REPORT

Venous vessel wall thickness in lower extremity is increased in male patients with Behcet's disease

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Abstract

Vascular involvement, especially in young males, is seen in up to 40% of the patients with Behcet's disease (BD) and is a major cause of mortality and morbidity. In this study, we investigated vessel wall thickness (VWT) and dilatation in lower extremity veins with Doppler ultrasound (US) in male BD patients. Sixty-one male patients with BD, 37 healthy male controls (HC) and 27 male patients, with ankylosing spondylitis (AS), were included in the study. Venous Doppler US was performed by an experienced radiologist blinded to cases. Bilateral common femoral vein (CFV) wall thickness and great/small saphenous vein (SV) dilatations were assessed. All venous measurements were significantly higher in BD compared to AS and HC ($p < 0.001$ for all). Both right and left extremity CFV thicknesses had a high area under the ROC curve (> 0.8). Cut-off values for right and left CFV thicknesses for BD was 0.49 and 0.48 mm, respectively. High sensitivity and specificities are observed for both measurements (right CFV: sensitivity 81%, specificity 78.4%; left CFV: sensitivity 82.8%, specificity 81.1%). We found increased CFV thickness in BD patients independent of vascular involvement. As a similar change was not observed in controls, increased CFV thickness may be a specific sign of venous inflammation in BD. Our acceptable sensitivity and specificity values of CFV measurements suggest that assessment of femoral vein thickness with US may be a candidate diagnostic tool, especially in young males suspected of BD.

Keywords Behcet's disease · Male · Venous wall thickness

Introduction

Behcet's disease (BD) is a multi-systemic, inflammatory disorder with both arterial and venous involvement, named as a "variable-vessel vasculitis" in Chapel Hill classification. [1] Venous wall inflammation presenting as deep venous thrombosis and superficial thrombophlebitis is the most common vascular clinical form, whereas arterial wall inflammation presents as thrombosis and aneurysms in arteries of any size [2, 3].

Vascular involvement (VBD) is observed in up to 40% of the patients with BD. Young males have the highest risk, as the major cause of morbidity and mortality in young ages. Lower extremity vein thrombosis is the most frequent form of venous involvement [4], however many other sites including inferior and superior vena cava, pulmonary arteries, suprahepatic vessels, and cardiac cavities may be involved [5].

There is no reliable assessment tool to identify high-risk patients or vascular wall inflammation in BD, except detecting ongoing intravascular thrombosis with US. Previous studies investigated arterial vessel wall thickness with US (mostly in carotid arteries) in BD. In a recent meta-analysis of nine

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studies assessing endothelial dysfunction with flow-mediated dilation (FMD) and intima-media thickness (IMT) of arterial wall, FMD was found to be impaired in BD even in inactive disease, suggesting a low-level chronic inflammation [6].

There is very limited data assessing venous wall inflammation in BD. We previously reported that a significant subset of BD patients has venous insufficiency without a history of vascular involvement [7]. In a study from the UK, magnetic resonance imaging (MRI) of popliteal veins demonstrated increased popliteal vein thickness in BD [8]. In this study, we investigated venous wall thickness and dilatation in lower extremity veins with Doppler ultrasound (US) as an easier and cost-effective way of performing vascular assessment to identify venous wall inflammation in male patients with BD which have the highest risk for vascular disease.

Material and methods

Patients and controls

In this cross-sectional study, 61 male patients with BD (mean age 32.6 ± 5.9 years) classified according to the International Study Group Criteria and followed in Marmara University Behcet's Clinics, 27 male patients with ankylosing spondylitis (AS) (mean age 30.5 ± 5.5 years) fulfilling the modified New York criteria as the disease control group and 37 healthy male controls (mean age 30.1 ± 5.1 years) were included.

Routine laboratory tests for all patients and healthy controls, including complete blood count, fasting plasma glucose, and liver and renal function tests were in normal ranges. There were also no known histories of hypertension, hyperlipidemia, and diabetes mellitus in study groups. Thrombophilic risk factors or antiphospholipid antibodies were not screened, as these were not part of the routine assays in BD patients in our clinic. History of venous thrombosis or varicose veins were only present in vascular BD group. When these were detected in control group cases (AS and healthy controls), they were excluded from the study.

BD patients with mucocutaneous involvement ($n = 31$) were treated with non-immunosuppressive (IS) medications. Other BD patients ($n = 30$) with vascular involvement (VBD) were under IS-based treatment protocols. Some patients in VBD group had also neurological ($n = 11$, 36.6%) and ocular involvement ($n = 7$, 23.3%). Behcet's Syndrome Activity Score (BSAS) was used to assess general disease activity in BD [9].

Venous Doppler ultrasonography

Bilateral lower extremity venous Doppler ultrasonography was performed by an experienced radiologist blinded to cases, the same day with clinical assessment. Superficial and deep lower extremity veins (the common femoral vein, superficial and deep femoral vein, popliteal vein, and great and small saphenous vein are examined) were examined with a high-resolution ultrasound Doppler system (İu22 Philips, Philips Health Care, Bothell, WA, USA) equipped with a high-resolution linear transducer (8–12 MHz).

All veins were studied in both longitudinal and transversal sections to visualize venous thrombosis, width, wall thickness, collateral veins, or dilated perforating veins. Venous insufficiency is evaluated after Valsalva maneuver both in the saphenofemoral junction and popliteal veins in supine and prone positions. Vessel wall thickness (VWT) was the main assessment in common femoral veins (CFV) and vein dilatations in great/small saphenous veins. In ten patients, CFV wall thickness was measured by two different radiologists (RE, RA) on the same day to calculate "inter-observer reliability." Correlation between the radiologists was observed to be good ($r = 0.765$, $p < 0.001$). Study protocol was approved by Marmara University Local Ethics Committee (approval number: 09.2017.529) and a written informed consent was obtained from each patient. The study was performed according to the Declaration of Helsinki.

Statistical analysis

Data were analyzed by using SPSS 16.0 statistic program (SPSS Inc., Chicago, IL, USA). The unpaired sample t test, ANOVA test, and chi-square test were used for comparisons of data. Spearman correlation test was used to analyze inter-observer reliability. Receiver operating characteristic (ROC) curve method was used to determine the sensitivity and specificity of all venous wall measurements. Positive predictive values were also calculated.

Results

Age and body mass index (25.4 ± 3.7) of patients with BD were observed to be similar in AS (23.9 ± 2.4) and HC (25.3 ± 3.7)($p = 0.192$ and $p = 0.156$ respectively). Smoking rate was also similar among groups (Table 4 in supplement file). Mean disease duration was 9.6 ± 6 years and BSAS score was 24.3 ± 17.7 in BD patients. BSAS score negatively correlated with age in BD patients ($r = -0.3$ $p = 0.029$).

All venous wall measurements were significantly higher in BD compared to AS and healthy controls ($p < 0.001$ for all, Table 1). In contrast, venous measurements were similar between AS and HC ($p > 0.05$). When a ROC curve analysis was performed, area under the curve was higher than 0.80 for all measurements (0.801–0.858). Cut-off points generated from ROC curve analysis were shown in Table 2 (Supplement).

As an assessment tool of imaging, sensitivity, and specificities were reasonably high for both right CFV (cut-off 0.49 mm, sensitivity 81%, specificity 78.4%) and left CFV

Table 1 Venous wall measurements of lower extremity in study groups

Venous wall measurements (mm)	BD ($n = 59$) Mean ± SD	AS ($n = 27$) Mean ± SD	HC ($n = 37$) Mean ± SD	BD vs HC p	BD vs AS p
Right common femoral venous wall thickness	0.8 ± 0.3	0.3 ± 0.2	0.4 ± 0.2	< 0.001	< 0.001
Left common femoral venous wall thickness	0.8 ± 0.3	0.3 ± 0.1	0.4 ± 0.2	< 0.001	< 0.001
Right freat saphenous width	3.3 ± 1.2	2.5 ± 0.6	2.2 ± 0.6	< 0.001	< 0.001
Left great saphenous width	3.3 ± 1.2	2.4 ± 0.9	2.3 ± 0.6	< 0.001	< 0.001
Right small saphenous width	3 ± 1.2	1.9 ± 0.6	1.6 ± 0.6	< 0.001	< 0.001
Left small saphenous width	2.9 ± 1.2	1.9 ± 0.6	1.6 ± 0.6	< 0.001	< 0.001

thickness measurements (cut-off 0.48 mm, sensitivity 82.8%, specificity 81.1%) (Table 2, Fig. 1). Cut-off values also performed well against AS (sensitivity 79.6%, specificity 96.2% for right CFV; sensitivity 83.1%, specificity 96.2% for left CFV). Positive and negative predictive values in our tertiary clinical setting were also acceptable (PPV 78.6–87.5%, NPV 68.2–75%) for all venous assessments.

Although all measurements were higher in patients with vascular involvement (Table 3), only left CFV thickness [0.7 (0.03–1.2) vs 0.9 (0.2–1.6), $p = 0.028$] and width of right great saphenous vein [2.6 (0.12–5.1) vs 3.8 (2.2–6.4), $p < 0.001$] reached statistical significance. All patients with vascular involvement were under IS treatments, whereas the others were not.

No correlation was observed between bilateral CFV thickness and acute phase reactants and BSAS (for left CFV between BSAS and CRP, $r = -0.184$, $p = 0.170$; $r = -0.68$, $p = 0.633$, respectively) (for right CFV between BSAS and CRP, $r = -0.230$, $p = 0.250$; $r = -0.56$, $p = 0.689$, respectively).

According to the cut-off value of 0.49 mm, 82% ($n = 50$) of BD patients had increased femoral vein thickness. When we compared the BD patients with and without increased femoral vein thickness, there were no differences between the groups regarding age, BMI, disease duration, C-reactive protein (CRP), and erythrocyte sedimentation (ESR) rate levels ($p < 0.05$ for all). BSAS was observed to be significantly higher in BD patients without increased femoral vein thickness which is a small group ($n = 11$) compared to patients with increased thickness (32 vs 21, $p = 0.019$) (Table 4 in supplement).

Discussion

Results of our present study demonstrate an increased venous wall thickness in Behcet's disease that can be measured non-invasively by Doppler US. As similar increased VWT measurements were not observed in AS, our observations seem unassociated with systemic inflammation.

Inflammation may lead to thickness in vessel walls, especially in arterial system and imaging of arterial system; modalities, such as MRI or PET-CT, are widely used especially in large-vessel vasculitides (LVV) to demonstrate the presence of vessel wall inflammation. Venous vasculature, even major vein walls are thinner and more deformable compared to the arterial system. Pressure in venous system is also lower and is sensible to respiration and muscle activity around vessels which makes venous imaging more challenging.

There is only one previous study directly assessing venous wall inflammation in BD. Ambrose N. et al. in a small group of BD patients ($n = 5$) used MRI to assess venous inflammation. With a ranking based on wall thickness and signal enhancement, popliteal vein scores were demonstrated to be increased in BD [8]. However, as in LVV, using MRI wall enhancement to assess vascular system is difficult to perform, costly for routine clinical practice, and hard to standardize. Therefore, other techniques should be studied. Recently, Boulon C. et al published a BD case with a history of recurrent deep venous thrombosis in lower extremity. In this case, increased wall thickness in right great saphenous vein without a

Table 2 Diagnostic performance of venous vessel measurements in Behcet's disease

Venous vessel measurements	AUC	95 CI %	Cut-off (mm)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Right common femoral venous wall measurements	0.858	0.780–0.936	0.49	81	78.4	85.7	72.5
Left common femoral venous wall measurements	0.852	0.771–0.933	0.48	82.8	81.1	87.5	75
Right great saphenous width	0.816	0.729–0.902	2.25	85.7	64.8	78.6	75
Left great saphenous width	0.801	0.711–0.891	2.65	76.7	75.6	82.7	68.2
Right small saphenous width	0.857	0.777–0.938	1.70	82.1	78.3	85.1	74.3
Left small saphenous width	0.847	0.766–0.929	1.85	78.5	81	86.3	71.4

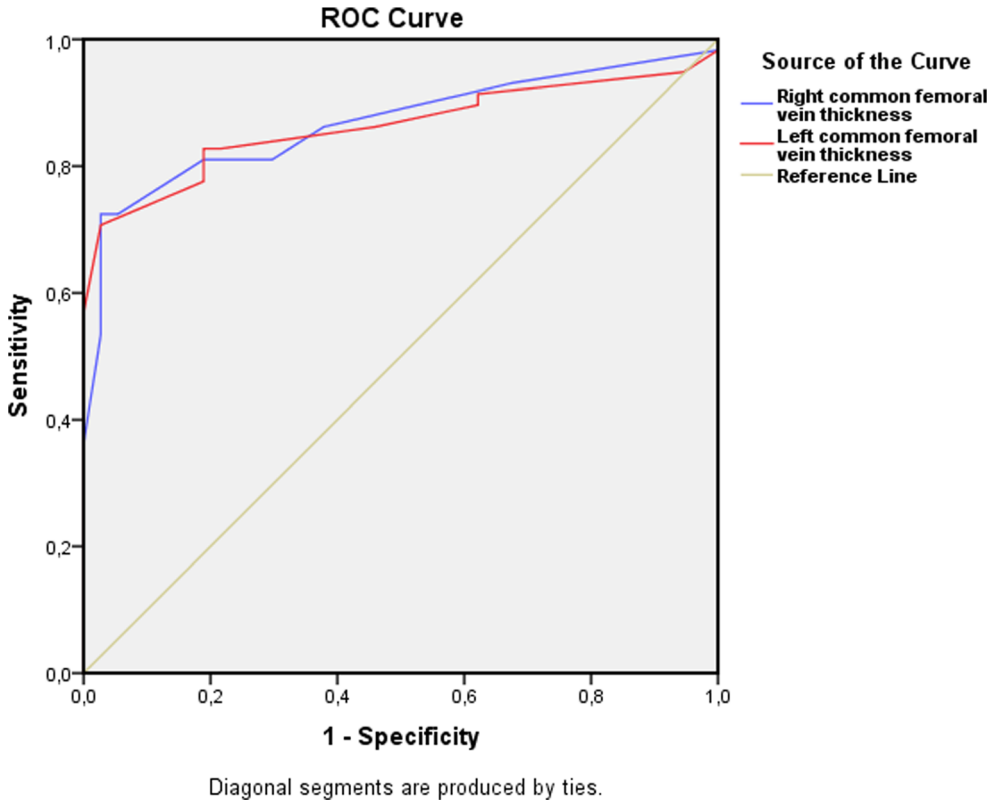

Fig. 1 Receiver operating characteristic curve for right and left common femoral vein thicknesses

thrombosis was observed with venous Doppler US. A dramatic decrease in VWT was also observed after corticosteroid treatment [10].

Diagnosing BD is a challenge, especially in countries with a low prevalence. International Study Group Criteria, which is accepted to be a diagnostic one, has a low sensitivity, especially in early cases when a major organ involvement such as uveitis or deep vein thrombosis presents without other major manifestations [11]. Similarly, incomplete BD is increasing in recent years in Far East countries such as Japan and Korea [12]. Pathergy test, the only diagnostic tool, has a low sensitivity in recent years due to less traumatic needle use. Acute-phase reactants, such as CRP, also have a much limited value compared to systemic inflammatory disorders in BD.

Ultrasonography is the most commonly used non-invasive, cost-effective, and easily accessible radiological modality with high patient compliance. Our data suggests that with sensitivity and specificity values above > 70%, lower extremity venous wall assessment with US, which can be performed in less than 10 min by an experienced radiologist, can be a possible candidate for the imaging diagnosis of BD.

Contrary to our expectations, in our study, we did not observe a consistent association with venous wall thickness and venous thrombotic disease in vascular BD patients. This observation can be explained by the systemic nature of venous inflammation in BD. Our results suggest that most patients with BD may have a tendency for venous inflammation, but secondary factors increasing intravascular thrombotic tendencies such

Table 3 Venous wall measurements of lower extremity in patients with Behçet's disease

Venous wall measurements (mm)	Mucocutaneous BD ($n = 30$) Mean ± SD	Vascular BD ($n = 29$) Mean ± SD	p
Right common femoral venous wall thickness	0.68 ± 0.30	0.81 ± 0.30	0.089
Left common femoral venous wall thickness	0.66 ± 0.30	0.85 ± 0.30	0.028
Right great saphenous width	2.70 ± 1.0	3.88 ± 1.0	< 0.001
Left great saphenous width	3.03 ± 1.20	3.63 ± 1.10	0.056
Right small saphenous width	2.80 ± 1.35	3.11 ± 1.39	0.309
Left small saphenous width	2.71 ± 1.20	3.11 ± 1.03	0.194

BD, Behcet's disease

as pro-coagulant mutations (Factor V Leiden etc) or other factors affecting viscosity might trigger venous/arterial thrombosis. Similarly, overall disease activity assessed by BSAS is mildly higher in BD patients without increased femoral vein thickness compared to patients with increased thickness (32 vs 21, $p = 0.019$). The small number of the group ($n = 11$) without increased femoral vein thickness makes the interpretation of this result difficult. Overall activity assessment is a controversial issue in BD due to the multi-systemic nature of the disease and use of all current assessment tools in clinical studies of BD is controversial. Therefore, this result needs to be confirmed with larger sample size.

Our main limitations are the cross-sectional design of the study and not including female gender. A longitudinal study might show whether our observations persist during the disease course and whether therapeutic approaches affect VWT. We chose not to study females in this first study due to milder course in most female patients and a higher prevalence of venous insufficiency in females starting from young ages.

In conclusion, we observed an increased lower extremity vessel wall thickness in BD patients independent of vascular involvement. As a similar change was not observed in controls, increased VWT may be a sign of continuous venous inflammation in most patients with BD. Common femoral veins, easily and reliably visualized by Doppler ultrasound, may be the choice of vessel for US assessment. Our cut-off values of 0.48–0.49 mm seem quite sensitive and specific for BD and can be used as a surrogate marker for diagnosis. We think Doppler US may, therefore, be used as a possible diagnostic test in especially young males suspected of BD. Prospective follow-up studies are started, focusing on females, longitudinal changes during the disease course and whether femoral vein thickness can predict future vascular or other major organ involvements in BD.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-Suarez LF, Gross WL, Guillevin L, Hagen EC, Hoffman GS, Jayne DR, Kallenberg CGM, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DGI, Specks U, Stone JH, Takahashi K, Watts RA (2013) 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 65:1–11
2. Calamia KT, Schirmer M, Melikoglu M (2011) Major vessel involvement in Behçet's disease: an update. Curr Opin Rheumatol 23:24–31
3. Yazici H, Yurdakul S, Hamuryudan V (2001) Behçet disease. Curr Opin Rheumatol 13:18–22
4. Kural-Seyahi E, Fresko I, Seyahi N, Ozyazgan Y, Mat C, Hamuryudan V, Yurdakul S, Yazici H (2003) The long-term mortality and morbidity of Behcet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. Medicine (Baltimore) 82:60–76
5. Saadoun D, Wechsler B, Desseaux K, Le Thi Huong D, Amoura Z, Resche-Rigon M et al (2010) Mortality in Behcet's disease. Arthritis Rheum 62:2806–2812
6. Merashli M, Ster IC, Ames PR (2016) Subclinical atherosclerosis in Behcet's disease: a systematic review and meta-analysis. Semin Arthritis Rheum 45:502–510
7. Alibaz-Oner F, Karatay E, Akpinar IN, Ergun T, Direskeneli H (2014) Evaluation of asymptomatic venous disease by venous Doppler ultrasonography in patients with Behcet's disease without overt thrombosis. Clin Rheumatol 33:277–280
8. Ambrose N, Pierce IT, Gatehouse PD, Haskard DO, Firmin DN (2014) Magnetic resonance imaging of vein wall thickness in patients with Behçet's syndrome. Clin Exp Rheumatol 32:S99–S102
9. Yilmaz S, Simsek I, Cinar M, Erdem H, Kose O, Yazici Y et al (2013) Patient driven assessment of disease activity in Behçet's syndrome: cross-cultural adaptation, reliability and validity of the Turkish version of the Behçet's Syndrome Activity Score. Clin Exp Rheumatol 31:77–83
10. Boulon C, Skopinski S, Constans J (2016) Vein inflammation and ultrasound in Behçet's syndrome. Rheumatology (Oxford) 55:1750
11. Blake T, Pickup L, Carruthers D, Damato EM, Denniston A, Hamburger J et al (2017) Birmingham Behçet's service: classification of disease and application of the 2014 International Criteria for Behçet's Disease (ICBD) to a UK cohort. BMC Musculoskelet Disord 18:101
12. Kirino Y, Ideguchi H, Takeno M, Suda A, Higashitani K, Kunishita Y, Takase-Minegishi K, Tamura M, Watanabe T, Asami Y, Uehara T, Yoshimi R, Yamazaki T, Sekiguchi A, Ihata A, Ohno S, Ueda A, Igarashi T, Nagaoka S, Ishigatsubo Y, Nakajima H (2016) Continuous evolution of clinical phenotype in 578 Japanese patients with Behçet's disease: a retrospective observational study. Arthritis Res Ther 18:217