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VASCULAR HEALTH IN BEHÇET'S DISEASE: THE ROLE OF UROTENSIN II AND SCLEROSTIN

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Abstract

Aim: Behçet's disease (BD) is characterized by the presence of skin and mucosal lesions, systemic inflammation, and vasculitis. The objective of this study was to examine changes in urotensin II (UII) and sclerostin levels in patients with BD and to assess their correlation with atherosclerosis.

Material and Methods: The study population comprised 32 patients with BD, 39 with systemic lupus erythematosus, and 30 healthy controls. A series of clinical examinations were conducted, and blood samples were obtained to analyze UII and sclerostin levels by enzyme-linked immunosorbent assay. The carotid intima-media thickness (cIMT) was evaluated using Doppler ultrasonography.

Results: UII levels were significantly elevated in the BD group compared with the other groups ($p<0.001$). Conversely, sclerostin levels were markedly diminished in the BD group ($p<0.001$). In the BD group, UII levels were positively correlated with cIMT ($r=0.513$, $p<0.001$), whereas sclerostin levels were negatively correlated with cIMT ($r=-0.270$, $p=0.020$).

Conclusion: Elevated UII and reduced sclerostin levels are crucial biomarkers of atherosclerosis risk in individuals with BD. These findings help to elucidate the cardiovascular complications associated with BD.

Keywords: Behcet disease, atherosclerosis, urotensin, sclerostin

INTRODUCTION

Behçet's disease (BD) is a multisystemic chronic inflammatory vasculitis characterized by skin and mucosal lesions. Although its etiopathogenesis is not fully understood, it involves major organs such as the eyes, joints, central nervous system, and gastrointestinal system. BD can affect any vessel and artery of any size. Endothelial dysfunction is a hallmark of BD and is considered an initial lesion in the development of atherosclerosis. Furthermore, the relationship between BD and atherosclerosis is emphasized by the observation that patients with BD frequently display elevated levels of inflammatory markers and endothelial progenitor cells, which are linked to disease activity and vascular complications (1). This inflammatory state not only exacerbates endothelial dysfunction but also promotes atherogenesis, suggesting that individuals with BD may be at increased risk of cardiovascular disease, including myocardial infarction and stroke (2).

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The presence of these vascular complications not only signifies a poor prognosis but also suggests a potential link between BD and increased cardiovascular risk, including atherosclerosis (3). For instance, the increased thickness of the epicardial adipose tissue and carotid intima-media thickness (cIMT) observed in patients with BD are indicative of heightened cardiovascular risk factors associated with atherosclerosis (4).

Urotensin II (UII) is a cyclic undecapeptide that has attracted considerable attention for its significant role in cardiovascular physiology and pathology, particularly in the context of atherosclerosis. The urotensinergic system, which encompasses the UII and its receptor (UTR), has been linked to several cardiovascular disorders, including atherosclerosis. In this context, UII has been shown to play a role in vascular remodeling and endothelial dysfunction. Some studies have shown that UII enhances human macrophage foam cell formation and vascular smooth muscle cell proliferation (5). There are studies reporting the association of this molecule with BD, diabetes, diabetic retinopathy, and systemic sclerosis. Sclerostin, a glycoprotein primarily secreted by osteocytes, plays a significant role in the regulation of bone metabolism and has emerged as a critical factor in vascular health, particularly with regard to atherosclerosis. Its primary function as an inhibitor of the Wnt signaling pathway has implications for both bone and vascular tissues, influencing processes such as cell proliferation, migration and calcification (6). The relationship between sclerostin and atherosclerosis is complex, and various mechanisms contribute to vascular calcification and cardiovascular risk (7).

The objective of this study was to determine the changes in UII and sclerostin levels and their correlation with atherosclerosis in patients with BD.

MATERIALS AND METHODS

The present study included patients diagnosed with BD and systemic lupus erythematosus (SLE) and healthy controls. The study was conducted in accordance with the ethical standards determined by the Fırat University Non-Interventional Research Ethics Committee and the Helsinki Declaration (approval no: 350179, date: 26/09/2019). Patients were provided with comprehensive information about the study and were included in the study only after providing informed consent to participate. All participants were evaluated comprehensively, including a clinical examination and medical history assessment.

cIMT measurements were conducted using Doppler ultrasonography. This non-invasive technique is widely employed for the early detection of atherosclerosis and cardiovascular diseases (8). cIMT was measured at the thickest points of both carotid arteries and evaluated independently by two experienced physicians. Plaque was defined as localized thickening of the cIMT compared to adjacent wall segments, with a thickness of at least 1.5 mm, protruding into the lumen, and consisting of calcified or non-calcified components. The cIMT of the right and left common carotid arteries was measured within a 1 cm segment proximal to the dilation of the carotid bulb. All measurements were performed manually on the static images obtained during sonographic scanning.

The levels of UII and sclerostin were quantified from blood samples collected from the patients. The measurement of UII and sclerostin was conducted using a specific and sensitive enzyme-linked immunosorbent assay kit, which was provided by a commercial source.

Statistical Analysis

Analyses were conducted using the SPSS 22 software package. Descriptive data are presented as n, % for categorical data, and mean ± standard deviation (mean ± SD) for continuous data. The chi-square test (pearson chi-square) was used to compare categorical variables between groups. The suitability of continuous variables for normal distribution was evaluated using the Kolmogorov-Smirnov test. The Student's t-test was used to compare normally distributed variables between the two groups, and the Mann-Whitney U test was used for non-normally distributed variables. One-way analysis of variance was used for more than two normally distributed variables, and the Kruskal-Wallis test for those not normally distributed. The Spearman correlation test was used to examine the relationship between continuous variables. A p-value of <0.05 was considered statistically significant.

RESULTS

Demographic Data and General Characteristics

A total of 101 participants were included in the study. Of the participants, 32 were diagnosed with BD, 39 with SLE, and 30 were healthy controls. No statistically significant differences were observed between the groups regarding gender and age (Table 1). A higher proportion of individuals with BD (28.1%) and SLE (15.4%) were smokers than the control group (0%). A significant difference was identified between the three groups in terms of smoking status ($p=0.004$). Additionally, notable discrepancies were observed in systolic ($p<0.001$) and diastolic ($p<0.001$) blood pressure between the groups. This disparity can be attributed to the divergence between the SLE and other groups (Table 1).

Laboratory Parameters

Significant differences in sedimentation values were observed between the groups. However, only the SLE and healthy control groups exhibited statistically significant differences (p=0.001). Significant differences were observed in C-reactive protein (p=0.002), urotensin (p=0.005) and sclerostin levels (p<0.001) between the groups. These differences were attributed to the comparison between the control group and the other two groups (Table 2).

Differences within the Different Behçet's Clinical Involvements A notable disparity was observed in UII concentrations among the different BD subgroups (p=0.001). The aforementioned discrepancy was identified between the articular and vascular groups, as well as between individuals in the mucocutaneous, uveitis, and neuro behçet groups. The UII levels of smokers were significantly higher than those of non-smokers (p=0.013). Additionally, a notable discrepancy was observed in sclerostin levels between the BD and non-BD groups. This disparity was attributed to the contrast between the vascular and mucocutaneous, uveitis, and neuro Behçet groups (p=0.023) (Table 3).

Table 1. Comparison of demographic data of the groups

	BD (n=32)	SLE (n=39)	HC (n=30)	p-value
Gender (Females), n (%)	14 (43.8)	26 (66.7)	18 (60)	0.143*
Mean age (years)	40.4±11.7	39.0±12.1	35.5±11.0	0.236**
BMI, kg/m^2	24.6±4.7	24.8±4.2	25.1±5.0	0.894**
SBP, mmHg	114.8±18.8^a	124.7±19.9^b	107.8±10.6^a	**<0.001****
DBP, mmHg	71.1±11.0^a	81.3±14.0^b	67.0±7.9^a	**<0.001****

*Chi-square analysis, **One-way analysis of variance (ANOVA) analysis was applied. ^{a,b}Group where the difference originated, BD: Behçet's disease, SLE: Systemic lupus erythematosus, HC: Healthy controls, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 2. Comparison of laboratory parameters among the study groups

	BD (n=32)	SLE (n=39)	HC (n=30)	p-value
Total cholesterol (mg/dL)	173.4±39.4	181.3±49.8	169.0±32.5	0.516*
Triglyceride (mg/dL)	122.1±44.1	135.7±65.3	110.8±67.3	0.264*
LDL (mg/dL)	108.8±36.6	113.9±41.5	93.7±20.5	0.102*
HDL (mg/dL)	46.3±9.8	46.4±13.5	60.7±35.4	0.116**
ESR (mm/h)	19.0±18.6$^{a.b}$	28.2±21.0^a	11.8±8.7^b	**0.001***
CRP (mg/L)	5.2±5.6^a	7.6±9.1^a	3.9±1.7^b	**0.002****
GFR (mL/min)	86.2±15.3	88.7±5.1	90.0±.0	0.088**
Urotensin (ng/mL)	14.3±14.8^a	10.8±11.6^a	4.7±2.8^b	**0.005****
Sclerostin (ng/mL)	14.4±7.8^a	11.2±7.2^a	25.6±25.0^b	**<0.001***

*One-way ANOVA analysis, **Kruskal-Wallis test was performed. ^{a,b}Group where the difference originated, BD: Behcet disease, SLE: Systemic lupus erythematosus, HC: Healthy control, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, GFR: Glomerular filtration rate

Correlation Analysis

A significant positive correlation was observed between urotensin levels and several cardiovascular risk factors, including duration of diagnosis, systolic and diastolic pressure, right and left cIMT, Framingham vascular age, and vascular risk. A significant inverse correlation was observed between urotensin levels and the glomerular filtration rate (GFR). A significant negative correlation was identified between sclerostin and age, body mass index (BMI), systolic and diastolic pressure, right and left cIMT, total cholesterol, low-density lipoprotein (LDL) and Framingham vascular age.

A significant difference in UII levels among the BD groups was due to differences between the articular and vascular group and the mucocutaneous, uveitis, and neuro group (p=0.001). UII levels in smokers were significantly higher than in non-smokers (p=0.013). Sclerostin levels differed significantly among the BD groups, particularly between the vascular group and the mucocutaneous, uveitis, and neuro Behçet group (p=0.023). Sclerostin levels were significantly lower in those with a cardiovascular history (p=0.010) and those using mycophenolate mofetil (p=0.011). Sclerostin levels in those using TNF inhibitors were significantly higher than in those not using them (p=0.010).

Table 4 illustrates the correlation between urotensin and sclerostin levels and a number of other variables, including age, BMI, disease duration, blood pressure, and laboratory data. A positive correlation was observed between urotensin levels and

Table 3. Comparison of urotensin and sclerostin levels in patients with Behçet's disease

Clinical Involvements	Urotensin (ng/mL)		Sclerostin (ng/mL)	
	Mean ± SD	p-value*	Mean ± SD	p-value*
Mucocutaneosis (n=14)	7.2±6.3^a	**0.001***	15.0±7.1^a	**0.023****
Uveitis (n=6)	7.1±3.7^a		18.5±7.7^a	
Articular (n=5)	30.3±22.6^b		10.5±4$^{a.b}$	
Vascular (n=5)	30.9±7.9^b		7.8±2.5^b	
Neuro-Behçet's (n=2)	4.2±1.5^a		24.9±15.3^a	

*One-way ANOVA analysis. $^{a.b}$Group where the difference originated

Table 4. Correlation between urotensin and sclerostin levels

	Urotensin		Sclerostin	
	r*	p-value	r*	p-value
Mean age (years)	0.144	0.150	**-0.229**	**0.021**
BMI (kg/m)^2	0.110	0.273	**-0.231**	**0.020**
Duration of diagnosis (month)	**0.241**	**0.043**	-0.137	0.255
Systolic blood pressure	**0.273**	**0.006**	**-0.381**	**<0.001**
Diastolic blood pressure	**0.233**	**0.019**	**-0.362**	**<0.001**
Right cIMT (mm)	**0.513**	**<0.001**	**-0.27**	**0.020**
Left cIMT (mm)	**0.530**	**<0.001**	**-0.323**	**0.006**
Total cholesterol (mg/dL)	0.054	0.604	**-0.24**	**0.018**
Triglyceride (mg/dL)	-0.059	0.571	-0.038	0.712
LDL (mg/dL)	0.071	0.499	**-0.244**	**0.018**
HDL (mg/dL)	0.016	0.880	-0.079	0.459
ESR (mm/h)	0.037	0.711	-0.180	0.073
CRP (mg/L)	-0.095	0.346	-0.131	0.194
Glucose (mg/dL)	-0.153	0.203	0.002	0.988
Uric acid (mg/dL)	0.046	0.706	-0.045	0.708
GFR (mL/min)	**-0.243**	**0.014**	0.188	0.060
Duration of corticosteroid treatment (month)	0.092	0.473	-0.211	0.097

BMI: Body mass index, cIMT: Carotid intima-media thickness, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, GFR: Glomerular filtration rate

disease duration, systolic and diastolic blood pressure, right and left carotid intima thickness, Framingham vascular age, and vascular risk; a negative correlation was observed with GFR. A negative correlation was observed between sclerostin levels and age, BMI, systolic and diastolic blood pressure, right and left cIMT, total cholesterol, LDL, and Framingham vascular age.

DISCUSSION

The main pathological finding of BD is vasculitis, which affects vessels of all sizes in both the arterial and venous systems. Venous involvement is more frequent than arterial involvement (up to 80%). Vascular involvement is observed in up to 40% of Behçet patients, especially in young males, and is a significant cause of mortality and morbidity (9). BD is considered a natural model of thrombosis caused by inflammation, driven by an impaired immune-inflammatory response rather than traditional cardiovascular risk factors. Neutrophils promote thromboinflammation through various mechanisms, leading to platelet activation, endothelial dysfunction, and impaired fibrinolysis.

Endothelial dysfunction and neutrophilic vascular inflammation mediate thrombosis in patients with BD. High-resolution B-mode ultrasonography is commonly used to evaluate endothelial function. Arterial intima-media thickness is a sensitive marker of early atherosclerotic vessel wall changes, particularly in the main carotid artery (10). The hypothesis that inflammatory processes in BD can lead to endothelial dysfunction and increased arterial IMT has emerged. Previous studies on Turkish cohorts have shown increased cIMT in patients with BD compared with healthy controls (11).

Our study revealed no difference in cIMT values between patients with BD and healthy controls. Differences in patient characteristics, such as disease duration and age, may influence these results (12). A study by Messedi et al. (11) indicated that cIMT is affected in patients with BD, regardless of symptoms, disease duration, or corticosteroid treatment, and is potentially linked to subclinical atherosclerotic changes.

This study evaluated the serum levels of two peptides involved in the vascular pathogenesis associated with atherosclerosis: UII and sclerostin. The U-II is a potent vasoconstrictor peptide that stimulates cell proliferation. Inflammation increases urotensin receptor expression, leading to endothelial and smooth muscle cell proliferation, foam cell formation, and chemotaxis. UII also produces reactive oxygen species in vascular smooth muscle cells, inducing proliferation and accelerating atherosclerosis (13).

UII receptor interaction stimulates calcium release in vascular smooth muscle cells, leading to cellular proliferation and activation of Ca2+-dependent kinases. Recent studies have suggested that UII adversely affects vascular remodeling by influencing vascular endothelial growth factor expression in adventitial fibroblasts (14). The upregulation of UII in endothelial cells within atherosclerotic plaques suggests that UII directly contributes to disease progression by promoting a pro-inflammatory and pro-thrombotic environment (15).

Our study found higher serum UII levels in patients with BD with vascular involvement than in the other subgroups. Additionally, cIMT was significantly increased in all patients with BD and positively correlated with serum UII levels. High UII levels in patients with articular involvement may be related to its role in synovial fibrosis (16).

Sclerostin, a Wnt pathway modulator, affects endothelial dysfunction, vascular smooth muscle cell (VSMC) proliferation, and intimal thickening. Wnt signaling's role in atherogenesis was first reported in families with coronary artery disease linked to *LRP6*

gene mutations (17). Studies have shown varying effects of Wnt levels on atherosclerotic plaques (18). The negative relationship between sclerostin and cIMT contradicts the findings of Morales-Santana et al. (19), possibly because of differences in patient groups. Agostino et al. also showed an inverse relationship in diabetic patients. Furthermore, sclerostin's function is not merely correlative; it actively participates in the modulation of VSMC behavior. Sclerostin downregulates matrix metalloproteinases and other factors involved in vascular remodeling, thereby influencing the progression of atherosclerosis (20). In conditions of low sclerostin, an increase in VSMC proliferation and migration has been observed, which can lead to structural changes in blood vessels that promote atherosclerosis (21). Conversely, in conditions of elevated sclerostin, the inhibition of Wnt signaling may result in the reduction of VSMC activity and the potential mitigation of vascular calcification (22). If high sclerostin levels have a protective vascular effect, further research is needed to elucidate the Wnt/β-catenin pathway's role in atherosclerosis. This study is the first to reveal the relationship between serum sclerostin levels and IMT.

The interplay between urotensin and sclerostin may also be influenced by the systemic inflammatory response. BD is characterized by elevated levels of pro-inflammatory cytokines that can affect both urotensin and sclerostin levels. For instance, inflammatory cytokines can stimulate the production of urotensin while downregulating sclerostin expression in osteocytes (23). This dual effect may create a feedback loop in which increased urotensin exacerbates endothelial dysfunction, while decreased sclerostin a limitation of this study is that it did not include patients who had not previously undergone any treatment.

The relationship between UII and sclerostin levels and cIMT in patients with BD offers insight into the underlying pathophysiology of this systemic inflammatory condition. BD is typified by vasculitis, which can result in significant vascular complications, including atherosclerosis and increased cIMT, which serve as markers of cardiovascular risk. The presence of elevated UII levels and decreased sclerostin levels has been documented in this patient population, suggesting a potential correlation with the vascular alterations observed in BD.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the ethical standards determined by the Fırat University Non-Interventional Research Ethics Committee and the Helsinki Declaration (approval no: 350179, date: 26/09/2019).

Informed Consent: Patients were provided with comprehensive information about the study and were included in the study only after providing informed consent to participate.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.Ö., A.K., Concept: B.Ö., A.K., Design: A.D.K., Y.D., Data Collection or Processing: M.K., Analysis or Interpretation: İ.G., Literature Search: G.Y., Writing: G.Y.

Conflict of Interest: The authors have no conflicts of interest to declare.

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REFERENCES

1. Arica DA, Akşan B, Örem A, et al. High levels of endothelial progenitor cells and circulating endothelial cells in patients with Behçet's disease and their relationship to disease activity. An Bras Dermatol. 2019;94:320-6.
2. Acikgoz N, Kurtoğlu E, Yagmur J, et al. Elevated monocyte to high-density lipoprotein cholesterol ratio and endothelial dysfunction in Behçet disease. Angiology. 2018;69:65-70.
3. Balta S, Balta I, Demirkol S, et al. Endothelial function and Behçet disease. Angiology. 2014;65:657-9.
4. Yuksel M, Yildiz A, Oylumlu M, et al. Novel markers of endothelial dysfunction and inflammation in Behçet's disease patients with ocular involvement: epicardial fat thickness, carotid intima media thickness, serum ADMA level, and neutrophil-to-lymphocyte ratio. Clin Rheumatol. 2016;35:701-8.
5. Ames RS, Sarau HM, Chambers JK, et al. Human urotensin-II is a potent vasoconstrictor and agonist for the orphan receptor GPR14. Nature. 1999;401:282-6.
6. Catalano A, Bellone F, Morabito N, et al. Sclerostin and vascular pathophysiology. Int J Mol Sci. 2020;21:4779.
7. Clarke BL, Drake MT. Clinical utility of serum sclerostin measurements. Bonekey Rep. 2013;2:361.
8. Carpenter M, Sinclair H, Kunadian V. Carotid intima media thickness and its utility as a predictor of cardiovascular disease: a review of evidence. Cardiol Rev. 2016;24:70-5.
9. Alibaz-Oner F, Direskeneli H. Management of vascular Behçet's disease. Int J Rheum Dis. 2019;22(Suppl 1):105-8.
10. Rhee MY, Chang HK, Kim SK. Intima-media thickness and arterial stiffness of carotid artery in Korean patients with Behçet's disease. J Korean Med Sci. 2007;22:387-92.
11. Messedi M, Frigui M, Ben Mahfoudh K, et al. Intima-media thickness of carotid artery in patients with Behçet's disease. Arch Med Res. 2011;42:398-404.

12. Keser G, Aksu K, Tamsel S, et al. Increased thickness of the carotid artery intima-media assessed by ultrasonography in Behçet's disease. Clin Exp Rheumatol. 2005;23(Suppl 38):71-6.

13. Watanabe T, Arita S, Shiraishi Y, et al. Human urotensin II promotes hypertension and atherosclerotic cardiovascular diseases. Curr Med Chem. 2009;16:550-63.

14. Şatıroğlu Ö, Durakoğlugil ME, Çetin M, et al. The role of urotensin II and atherosclerotic risk factors in patients with slow coronary flow. Interv Med Appl Sci. 2016;8:158-63.

15. Cirillo P, De Rosa S, Pacileo M, et al. Human urotensin II induces tissue factor and cellular adhesion molecules expression in human coronary endothelial cells: an emerging role for urotensin II in cardiovascular disease. J Thromb Haemost. 2008;6:726-36.

16. Gögebakan B, Uruc V, Ozden R, et al. Urotensin II (U-II), a novel cyclic peptide, possibly associated with the pathophysiology of osteoarthritis. Peptides. 2014;54:159-61.

17. Abou Ziki MD, Mani A. Wnt signaling, a novel pathway regulating blood pressure? State of the art review. Atherosclerosis. 2017;262:171-8.

18. Poznyak AV, Sukhorukov VN, Popov MA, et al. Mechanisms of the Wnt pathways as a potential target pathway in atherosclerosis. J Lipid Atheroscler. 2023;12:223-36.

19. Morales-Santana S, García-Fontana B, García-Martín A, et al. Atherosclerotic disease in type 2 diabetes is associated with an increase in sclerostin levels. Diabetes Care. 2013;36:1667-74.

20. Fehervari L, Frigy A, Kocsis L, et al. Serum osteoprotegerin and carotid intima-media thickness are related to high arterial stiffness in heart failure with reduced ejection fraction. Diagnostics. 2021;11:764.

21. Kirkpantur A, Balci M, Turkvatan A, et al. Independent association between serum sclerostin levels and carotid artery atherosclerosis in prevalent haemodialysis patients. Clin Kidney J. 2015;8:737-43.

22. Frysz M, Gergei I, Scharnagl H, et al. Circulating sclerostin levels are positively related to coronary artery disease severity and related risk factors. J Bone Miner Res. 2020;37:273-84.

23. Pelletier S, Dubourg L, Carlier MC, et al. The relation between renal function and serum sclerostin in adult patients with CKD. Clin J Am Soc Nephrol. 2013;8:819-23.