

Behcet's Disease – Endothelial Function

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SUMMARY

Endothelial cells form a multifunctional cell lining that covers all of the inner surface of blood vessels and regulates several important physiological and pathological reactions. These include inflammation/immune reaction, blood vessel tonus, hemostasis/thrombosis, angiogenesis and so on. Behçet's Disease (**BD**) is a chronic, relapsing, multisystemic disorder characterized by urogenital ulcers and ocular inflammation with cutaneous, musculoskeletal, vascular and nervous system manifestations. People from the Far East, the Middle East and the Mediterranean basin are more commonly affected than those from other parts of the world. In Northern Europe, Central Africa and the United States the disease is infrequent. Affection for all ages with male predominance is a well-known clinical entity.

Vasculitis as well as endothelial dysfunction are principal pathological findings in BD although the etio-pathogenesis of the disease remains obscure.

In this review, we aimed to cover BD and endothelial function in terms of endothelial dysfunction mechanisms.

Keywords: Behçet's Disease (**BD**); Endothelium; Endothelial Function.

Endothelial cells play a wide variety of critical roles in the control of vascular function. Indeed, since the early 1980s, the accumulating knowledge of the endothelial cell structure as well as of the functional properties of the endothelial cells shifted their role from a passive membrane or barrier to a complex tissue with complex functions adaptable to needs specific in time and location.

Endothelial cells form a multifunctional cell lining that covers all of the inner surface of blood vessels and regulates several important physiological and pathological reactions. These include inflammation/immune reaction, blood vessel tonus, hemostasis/thrombosis, angiogenesis and so on. Thus, abnormalities of endothelial function may play crucial roles in the development of angitis syndrome, thrombosis/embolism, bleeding Disseminated Intravascular Coagulation (**DIC**), and neovascularization in some pathological states including tumor growth and diabetic retinopathy. Research on endothelial cells now forms a new frontier termed “Endotheliology.”

The endothelial lining of blood vessels in different organs differs with respect to morphology and permeability and is classified as ‘continuous’, ‘fenestrated’ or ‘discontinuous’. The endothelial cell is thought to arise from the splanchnopleuric mesoderm. Endothelial cells form the inner lining of a blood vessel and provide an anticoagulant barrier between the vessel wall and blood. In addition to its role as a selective permeability barrier, the endothelial cell is a unique multifunctional cell with critical basal and inducible metabolic and synthetic functions.

The endothelial cell reacts with physical and chemical stimuli within the circulation and regulates hemostasis, vasomotor tone, and immune and inflammatory responses. In addition, the endothelial cell is pivotal in angiogenesis and vasculogenesis. Endothelial cell injury, activation or dysfunction is a hallmark of many pathologic states including atherosclerosis, loss of semi-permeable membrane function, and thrombosis [1].

Endothelium consists of approximately $(1-6) \times 10^{13}$ endothelial cells forming an almost 1 kg organ. [2] They uniquely contain Weibel-Palade bodies, 0.1 microm wide, 3 microm long membrane-bound structures that represent the storage organelle for Von Willebrand Factor (**vWF**). [3] The endothelial cell is not only a permeability barrier but also a multifunctional paracrine and endocrine organ. It is involved in the immune response, coagulation, growth regulation, production of extracellular matrix components, and is a modulator of blood flow and blood vessel tone.

Inflammation is a localized protective response elicited by injury or destruction of tissues, which serves to destroy, dilute, or wall-off both the injurious agent and the injured tissue. It is characterized in the acute form by the classical signs of pain (dolor), heat (color), redness (rubor), and swelling (tumor, edema). Inflammation is aimed to be life preserving. However, it needs to be tightly tuned since inappropriate, excessive, or chronic inflammation leads to pathological situations.

Endothelial cells coordinate the recruitment of inflammatory cells to sites of tissue injury or infection and produce and release cytokines and growth factors serving as communication signals to leukocytes. The migration of leukocytes from the vascular system to sites of injury or pathogenic exposure is a key event in the process of inflammation. The entry of leukocytes into sites of injury or infection requires molecular mechanisms, which enable them to recognize

such sites from within the vasculature and to establish contact with the endothelium in order to exit and migrate through the endothelium of post-capillary venules. Monocytes, lymphocytes, and neutrophils all migrate by these similar, sequence-dependent mechanisms but differ in their response to chemotactic and inflammatory signals, particularly in their qualitative and quantitative expression of adhesion molecules.

Behçet's Disease (**BD**) is a chronic, relapsing, multisystemic disorder characterized by urogenital ulcers and ocular inflammation with cutaneous, musculoskeletal, vascular and nervous system manifestations [4]. The etio-pathogenesis of the disease remains obscure, although genetic predisposition, environmental factors and immunological abnormalities have been implicated [5,6]. It has recently been proposed that BD is an autoinflammatory disorder, although there is no consensus [7,8]. People from the Far East, the Middle East and the Mediterranean basin are more commonly affected than those from other parts of the world [9]. In Northern Europe, Central Africa and the United States the disease is infrequent [10]. All ages may be affected, although the frequency is higher in persons in the 3rd or 4th decade. The sex predominance varies widely among the diseased population in different geographical areas [9,10]. Earlier studies suggested a male predominance in high prevalence areas, but more recent surveys indicate equal involvement of the sexes. In Western countries females predominate. Behçet's disease is included in the wide spectrum of vasculitits [11].

Vasculitis is a principal pathological finding in BD and vessels of all sizes are involved, both in arterial and venous systems. Large vessel vasculitis is not a rare manifestation of BD and it was proposed that this be one of the diagnostic criteria of the disease [12]. The prevalence of large vessel vasculitis varies according to the authors and the population. The vascular involvement in BD is predominantly seen in the venous system rather than arterial system. Venous lesions of the BD are superficial thrombophlebitis, and deep vein thrombosis of the lower extremities; arterial lesions consist of true and/or false aneurysms. In general, BD patients with major vessel involvement have worse prognosis [13-15].

The etiology of endothelial dysfunction in BD is probably multifactorial and includes high homocysteine levels as well as oxidative stress, although all of the mechanisms that underlie this dysfunction are not clearly known.

Several markers can be used to evaluate ED and vascular involvement in BD. Mean platelet volume, neutrophil-lymphocyte ratio, red cell distribution width, gamma glutamyl transferase activity and uric acid levels. However, these markers can be affected by hypertension (HT), diabetes mellitus (DM), thyroid dysfunction, or malignancy [16-21].

ED can also be assessed by hsCRP, tHcy, ADMA, VEGF and endocan levels [19-27].

VASCULAR ENDOTHELIAL FUNCTION IN BEHÇET'S DISEASE

Mechanisms

Oxidative stress

The mechanisms underlying endothelial dysfunction in Behçet's syndrome are not known. It is previously hypothesized that endothelial dysfunction is mediated by increased oxidative stress and are consistent with previous observations of elevated levels of lipid peroxides, as well as increased neutrophil production of superoxide, in patients with Behçet's syndrome [1,2]. Oxidative stress is a key factor in vascular injury. Previous studies have shown that oxygen-derived free radicals, including superoxide anion, react with nitric oxide, thus reducing its availability [3].

Homocysteine

Hyper-homocysteinemia was reported to be significantly higher in patients with active disease than in patients with inactive disease and in control subjects [28]. Moreover, high levels of homocysteine were reported in 64% of patients with BD with thrombosis as compared to 9% in those without thrombosis [29]. It is previously hypothesized that homocysteine had a deleterious effect on endothelial cells, causing endothelial cell damage, smooth muscle cell proliferation, and increased oxidative stress. An alternate mechanism for induction of vascular disease and thrombosis could be the interference with coagulation mechanisms. Other researchers blame the generation of superoxide and hydrogen peroxide by homocysteine for this effect, both of which may induce endothelial damage [30]. Homocysteine may have a deleterious effect in BD by decreasing NO levels and also through immune system effects. Homocysteine activates T cells and increases the interaction of monocytes and T cells with endothelial cells [31]. Homocysteine finally does not yield a complete answer to the mechanism underlying endothelial dysfunction in BD.

Vascular endothelial growth factor

Higher serum levels of Vascular Endothelial Growth Factor (**VEGF**) were found in patients with BD compared to normal controls, particularly at the active stage of the disease and in patients with vascular manifestations and ocular involvement [26, 27, 32, 33]. The production of VEGF may be subject to genetic control [27]. The association of VEGF gene polymorphism with BD was studied in patients and controls [34]. Carriers of -634C and allele 1 are associated with susceptibility to developing BD. VEGF activates endothelial cells and causes the release of vasoactive substances inducing vascular thrombosis and inflammation. VEGF also up-regulates NO synthase which may induce damage to host cells and tissue symmetric dimethylarginine (**ADMA**) and NO levels may reflect signs of endothelial dysfunction in BD [33,35]. The endothelial NO synthase gene polymorphism Glu - 298 Asp of exon 7 is associated with BD when compared to controls [36].

Anti-endothelial cell antibodies

These antibodies have been found in the serum of BD patients, particularly during the active stage of the disease. However, the exact role of these antibodies in the disease has not been clarified [37-39]. Endothelial cell antibodies were detected in 18-37% of patients with BD [40,41]. However, other investigators have not found any statistically significant difference between patients and controls [42].

Cytokines

The serum levels of several cytokines were determined in 94 BD patients, 74 with active disease, and 75 healthy individuals matched for age and sex who served as controls. Increased levels in the serum of IL-8 were found in patients with active disease with oral ulcers and neurological manifestations compared to the patients with inactive disease and controls. IL-8 secretion by dermal microvascular endothelial cells is stimulated in the presence of Behçet serum. It is also postulated that circulating anti-endothelial cell antibodies may be responsible for this effect [43].

High sensitivity C-reactive protein (hsCRP) hsCRP reflects systemic inflammation and is related to ED.

It may contribute to ED in BD [45,46].

Increased plasma asymmetric dimethylarginine (ADMA) levels (which is an endogenous inhibitor of NO synthase-NOS) and decreased plasma NO levels have been reported in patients with BD [46].

Inhibition of NOS by ADMA and oxidant/antioxidant imbalance may contribute to decreased bioavailability of NO in BD [46].

Endocan is a novel human endothelial cell-specific molecule. BD patients also have significantly higher levels of endocan which is an endothelial immunoinflammatory marker [47].

Besides these biochemical markers, some noninvasive methods have been developed to assess ED. Flow Mediated Dilatation (**FMD**) is one of these methods. FMD is mainly influenced by nitric oxide from endothelial cells [14]. This technique utilizes FMD of the brachial artery [15].

Another method is the measurement of carotid intima media thickness. Recent studies have demonstrated a significant correlation between increased IMD and ED, which is consistent with BD and endothelial dysfunction [48, 49].

In conclusion, BD is a disease of vascular system. Venous system is generally affected rather than the arterial system. Endothelial dysfunction plays a major role in the pathogenesis of the vasculitis and atherogenesis is an important consequence of this complex clinical entity.

References

1. Mege JL, Dilsen N, Sanguedolce V, Gul A, Bongrand P, et al. Overproduction of monocyte derived tumor necrosis factor alpha, interleukin (IL) 6, IL-8 and increased neutrophil superoxide generation in Behçet's disease: a comparative study with familial Mediterranean fever and healthy subjects. *J Rheumatol.* 1993; 20: 1544–1549.
2. Freitas JP, Filipe P, Yousefi A, Emerit I, Guerra Rodrigo F. Oxidative stress in Adamantiades-Behçet's disease. *Dermatology.* 1998; 197: 343-348.
3. G Kojda, D Harrison. Interactions between NO and reactive oxygen species: pathophysiological importance in atherosclerosis, hypertension, diabetes and heart failure. *Cardiovasc Res.* 1999; 43: 562–571.
4. Kaklamani VG, Vaiopoulos G, Kaklamanis PG. Behçet's Disease. *Semin Arthritis Rheum.* 1998; 27: 197-217.
5. Gül A. Behçet's disease: an update on the pathogenesis. *Clin Exp Rheumatol.* 2001; 19: S6-12.
6. Direskeneli H. Behçet's disease: infectious aetiology, new autoantigens, and HLA-B51. *Ann Rheum Dis.* 2001; 60: 996-1002.
7. Gül A. Behçet's disease as an autoinflammatory disorder. *Curr Drug Targets Inflamm Allergy.* 2005; 4: 81-83.
8. Yazici H, Fresko I. Behçet's disease and other autoinflammatory conditions: what's in a name? *Clin Exp Rheumatol.* 2005; 23: S1-2.
9. Zouboulis CC. Epidemiology of Adamantiades-Behçet's disease. In: Zierhut M, Ohno S, editors. *Immunology of Behçet's Disease.* Amsterdam: Grafisch Produktiebedrijf Gorter. 2003: 1-16.
10. Christos C Zouboulis, Ina Kötter, Djalil Djawari, Wilhelm Kirch, Peter K Kohl, et al. Adamantiades-Behçet's disease: Epidemiology in Germany and in Europe. In: Lee S, Bang D, Lee E-S, Lee S, editors. *Behçet's disease: A guide to its clinical understanding Textbook and Atlas.* Berlin: Springer. 2001: 157-169.
11. Koç Y, Güllü I, Akpek G, Akpolat T, Kansu E. Vascular involvement in Behçet's disease. *J Rheumatol.* 1992; 19: 402-410.
12. Schirmer M, Calamia KT, O'Duffy JD. Is there a place for large vessel disease in the diagnostic criteria of Behçet's disease? *J Rheumatol.* 1999; 26: 2511-2512.
13. Hong SN, Park JC, Yoon NS, Lee SR, Kim KH, et al. Carotid artery intima-media thickness in Behçet's disease patients without significant cardiovascular involvement. *Korean J Intern Med.* 2008; 23: 87-93.
14. Ulusoy RE, Karabudak O, Kilicaslan F, Kirilmaz A, Us MH, et al. Noninvasive assessment of impaired endothelial dysfunction in mucocutaneous Behçet's disease. *Rheumatol Int.* 2008; 28: 617-621.
15. Oflaz H, Mercanoglu F, Karaman O, Kamali S, Erer B, et al. Impaired endothelium-dependent flow-mediated dilatation in Behçet's disease: more prominent endothelial dysfunction in patients with vascular involvement. *Int J Clin Pract.* 2005; 59: 777-781.
16. Ekiz O, Balta I, Sen BB, Rifaioglu EN, Ergin C. Mean platelet volume in recurrent aphthous stomatitis and Behçet disease. *Angiology.* 2014; 65: 161-165.
17. Balta S, Demirkol S, Celik T, Kucuk U, Unlu M. Association between coronary artery ectasia and neutrophil-lymphocyte ratio. *Angiology.* 2013; 64: 627-632.
18. Demirkol S, Balta S, Celik T, Arslan Z, Unlu M. Assessment of the relationship between red cell distribution width and cardiac syndrome X. *Kardiol Pol.* 2013; 71: 480-484.
19. Cakar M, Balta S, Demirkol S, Altun B, Demirbas S. Serum gamma-glutamyltransferase (GGT) should be evaluated together with other inflammatory markers in clinical practice. *Angiology.* 2013; 64: 401.
20. Cakar M, Sarlak H, Balta S, Unlu M, Demirbas S, et al. Serum uric acid still carries controversies about its role in endothelial dysfunction. *J Clin Hypertens.* 2013; 15: 296.
21. Balta S, Balta I, Demirkol S, Ozturk C, Demir M. Endothelial function and Behçet Disease. *Angiology.* 2014; 65: 657-659.
22. Unlu M, Karaman M, Ay SA, Balta S, Cakar M. The comparative effects of valsartan and amlodipine on vascular microinflammation in newly diagnosed hypertensive patients. *Clin Exp Hypertens.* 2013; 35: 418-423.
23. Ozdemir R, Barutcu I, Sezgin AT, Acikgoz N, Ermis N. Vascular endothelial function and plasma homocysteine levels in Behçet's disease. *Am J Cardiol.* 2004; 94: 522-525.
24. Sahin M, Arslan C, Naziroglu M, Tunc SE, Demirci M. Asymmetric dimethylarginine and nitric oxide levels as signs of endothelial dysfunction in Behçet's disease. *Ann Clin Lab Sci.* 2006; 36: 449-454.
25. Cekmen M, Evreklioglu C, Er H, Inalöz HS, Doganay S. Vascular endothelial growth factor levels are increased and associated with disease activity in patients with Behçet's syndrome. *Int J Dermatol.* 2003; 42: 870-875.

26. Marumo T, Schini-Kerth VB, Busse R. Vascular endothelial growth factor activates nuclear factor-Kappa B and induces monocyte chemoattractant protein -1 in bovine retinal endothelial cells. *Diabetes*.1999; 488: 1131-1137.
27. Balta I, Balta S, Demirkol S, Mikhailidis DP, Celik T. Elevated serum levels of endocan in patients with psoriasis vulgaris: correlations with cardiovascular risk and activity of disease. *Br J Dermatol*. 2013; 169: 1066-1070.
28. Mungan AG, Can M, Açikgöz S, Eştürk E, Altinyazar C. Lipid peroxidation and homocysteine levels in Behçet's disease. *Clin Chem Lab Med*. 2006; 44: 1115-1118.
29. Aksu K, Turgan N, Oksel F, Keser G, Ozmen D. Hyperhomocysteinaemia in Behçet's disease. *Rheumatology (Oxford)*. 2001; 40: 687-690.
30. Er H, Evereklioglu C, Cumurcu T, Türköz Y, Ozerol E. Serum homocysteine level is increased and correlated with endothelin-1 and nitric oxide in Behçet's disease. *Br J Ophthalmol*. 2002; 86: 653-657.
31. Ozkan Y, Yardim-Akaydin S, Sepici A, Engin B, Sepici V. Assessment of homocysteine, neopterin and nitric oxide levels in Behçet's disease. *Clin Chem Lab Med*. 2007; 45: 73-77.
32. Cekmen M, Evereklioglu C, Er H, Inalöz HS, Doganay S. Vascular endothelial growth factor levels are increased and associated with disease activity in patients with Behçet's syndrome. *Int J Dermatol*. 2003; 42: 870-875.
33. Shaker O, Ay El-Deen MA, El Hadidi H, Grace BD, El Sherif H. The role of heat shock protein 60, vascular endothelial growth factor and antiphospholipid antibodies in Behçet disease. *Br J Dermatol*. 2007; 156: 32-37.
34. Salvarani C, Boiardi L, Casali B, Olivieri I, Cantini F. Vascular endothelial growth factor gene polymorphisms in Behçet's disease. *J Rheumatol*. 2004; 31: 1785-1789.
35. Sahin M, Arslan C, Naziroglu M, Tunc SE, Demirci M. Asymmetric dimethylarginine and nitric oxide levels as signs of endothelial dysfunction in Behçet's disease. *Ann Clin Lab Sci*. 2006; 36: 449-454.
36. Kim JU, Chang HK, Lee SS, Kim JW, Kim KT. Endothelial nitric oxide synthase gene polymorphisms in Behçet's disease and rheumatic diseases with vasculitis. *Ann Rheum Dis*. 2003; 62: 1083-1087.
37. Aydintug AO, Tokgöz G, D'Cruz DP, Gürler A, Cervera R. Antibodies to endothelial cells in patients with Behçet's disease. *Clin Immunol Immunopathol*. 1993; 67: 157-162.
38. Cervera R, Navarro M, López-Soto A, Cid MC, Font J. Antibodies to endothelial cells in Behçet's disease: cell-binding heterogeneity and association with clinical activity. *Ann Rheum Dis*. 1994; 53: 265-267.
39. Lee KH, Bang D, Choi ES, Chun WH, Lee ES. Presence of circulating antibodies to a disease-specific antigen on cultured human dermal microvascular endothelial cells in patients with Behçet's disease. *Arch Dermatol Res*. 1999; 291: 374-381.
40. Triolo G, Accardo-Palumbo A, Triolo G, Carbone MC, Ferrante A. Enhancement of endothelial cell E-selectin expression by sera from patients with active Behçet's disease: moderate correlation with anti-endothelial cell antibodies and serum myeloperoxidase levels. *Clin Immunol*. 1999; 91: 330-337.
41. Direskeneli H, Keser G, D'Cruz D, Khamashta MA, AkoÄYlu T. Anti-endothelial cell antibodies, endothelial proliferation and von Willebrand factor antigen in Behçet's disease. *Clin Rheumatol*. 1995; 14: 55-61.
42. Dinc A, Takafuta T, Jiang D, Melikoglu M, Saruhan-Direskeneli G. Anti-endothelial cell antibodies in Behçet's disease. *Clin Exp Rheumatol*. 2003; 21: S27-30.
43. Zouboulis CC, Katsantonis J, Ketteler R, Treudler R, Kalamani E. Adamantiades-Behçet's disease: interleukin-8 is increased in serum of patients with active oral and neurological manifestations and is secreted by small vessel endothelial cells. *Arch Dermatol Res*. 2000; 292: 279-284.
44. Unlu M, Karaman M, Ay SA, Balta S, Cakar M. The comparative effects of valsartan and amlodipine on vascular microinflammation in newly diagnosed hypertensive patients. *Clin Exp Hypertens*. 2013; 35: 418-423.
45. Öztürk MA, Unverdi S, Oktar SO, Bukan N, Gülbahar O. Vascular endothelial growth factor and carotid intima-media thickness in patients with Behçet's disease. *Clin Rheumatol*. 2008; 27: 961-966.
46. Sahin M, Arslan C, Naziroglu M, Tunc SE, Demirci M. Asymmetric dimethylarginine and nitric oxide levels as signs of endothelial dysfunction in Behçet's disease. *Ann Clin Lab Sci*. 2006; 36: 449-454.
47. Balta I, Balta S, Koryurek OM, Demirkol S, Mikhailidis DP. Serum endocan levels as a marker of disease activity in patients with Behçet disease. *J Am Acad Dermatol*. 2014; 70: 291-296.
48. Hong SN, Park JC, Yoon NS, Lee SR, Kim KH, et al. Carotid artery intima-media thickness in Behçet's disease patients without significant cardiovascular involvement. *Korean J Intern Med*. 2008; 23: 87-93.
49. Juanula M, Vikari JS, Laitinen T, Marniemi J, Helenius H, et al. Interrelations between brachial endothelial function and carotid intima-media thickness in young adults: the cardiovascular risk in young Finns study. *Circulation*. 2004; 110: 2918-2923.