The Mechanisms of Vascular Thrombosis in Behcet’s Disease

Emel Koseoglu*

Department of Neurology, Faculty of Medicine, University of Erciyes, Kayseri-Turkey

*Corresponding author: Emel Koseoglu, Department of Neurology, Faculty of Medicine, University of Erciyes, Kayseri-Turkey, Email: emelk@erciyes.edu.tr

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ABSTRACT

Behcet’s disease is a systemic vasculitis of every kinds and sizes of vessels. The prevalence of vascular involvement in BD has been reported as up to % 51.5. Vascular involvement includes superficial thrombophlebitis, deep venous thrombosis, arterial thrombosis, aneurysms and pseudoaneurysms.

The inflammation induced endothelial injury seems to be the main mechanism underlying vascular thrombosis in BD. However, because of higher prevalence of thrombosis in BD in comparison to other vasculitic disease, some other possible trombotic mechanisms have been suspected to take role in the pathogenesis of vascular thrombosis in Behcet’s disease; for this reason the roles of coagulant and anticoagulant factors, fibrin and fibrinolytic pathway, and of thrombocytes have been studied for many years. In recent years, there are some studies confirming an existence of protrombotic state due to alterations in platelet activity and changes in coagulation mechanisms like increased hypofibrinolysis, altered fibrinogen structure and impaired fibrinogen function. The possible roles of thrombophilic factors like the mutations in factor V, prothrombin and MTHFR genes seem to be not confirmed by recent studies. The studies performed on homocysteine, Lipoprotein (a) and antiphospholipid antibodies have been evaluated with a careful approach.
In this review, all possible mechanisms under vascular thrombosis in BD are evaluated considering their possible contribution to the treatment. The mechanisms of inflammation induced endothelial injury and, of prothrombic state due to thrombophilic factors, alterations in platelet activation and coagulation mechanisms are discussed thoroughly.

**Keywords:** Behcet’s disease; Vascular thrombosis; Endothelial injury; Thrombophilia; Platelet activation; Fibrinogen function

**INTRODUCTION**

Behcet’s Disease (BD) is a systemic vasculitis of every kinds and sizes of vessels, characterized by recurrent oral and/or genital aphthous ulcerations, uveitis and skin lesions. It can practically affect every tissue and organ of the body. International diagnostic criteria for BD was first published in 2006 and recently revised so that vascular involvement is added as a diagnostic criterion [1].

Vascular involvement in BD varies depending on the ethnic group and its prevalence has been reported as up to % 51.5 [2-5]. Vascular involvement includes superficial thrombophlebitis, deep venous thrombosis, arterial thrombosis, aneurysms and pseudoaneurysms. Compared to other types of vasculitic disorders, vascular involvement is more common in BD patients. The reason of this is not clearly known. Venous thrombosis is more common than arterial thrombosis, with relative frequencies of % 90 and % 10 respectively [6]. Deep and superficial venous thromboses in the lower extremities are the common sites of thrombosis. Nevertheless, because of the tightly adherence of the thrombus to vessel wall, thromboembolism is rare despite the high frequency of venous disease [7].

The treatment of vascular thrombosis in BD involves mostly immunosuppressive agents against inflammation of vessel wall. But the roles of antiaggregant or anticoagulant treatment are being evaluated. Because there can be some factors causing a prothrombotic state that contribute to the pathogenesis of thrombosis in BD. If thrombosis in BD is due to the vascular inflammation itself, why do not all of the patients show vascular involvement? Why is vascular thrombosis in BD more common than those in other vasculitic disorders?

Inflammation induced endothelial injury seems to be main mechanism underlying vascular thrombosis in BD similar the the other vasculitic diseases. Nevertheless, the roles of coagulant and anticoagulant factors, fibrin and fibrinolytic pathway, and of thrombocytes are under debate. If there is a thrombophilic tendency in BD, it is also important to clarify that if is it transient or a stable one and if there is a need for prophylactic treatment against vascular thrombosis in BD?

In order to make an accurate approach to vascular thrombosis in BD, it is obligatory to understand the underlying mechanisms. In this review, we tried to discuss these mechanisms to better evaluate therapeutic options for vascular thrombosis in BD.
Inflammation Induced Endothelial Injury

Vascular endothelium has anticoagulant and fibrinolytic properties. Vascular endothelial cells take the most critical part in the defence mechanism against thrombosis [8]. Different mechanisms of inflammation may affect endothelial cells. Anti-endothelial cell antibodies (AECA) have been described as a possible link between immune response and endothelial dysfunction particularly in BD [9]. Endothelial cell injury activates coagulation cascade by exposing subendothelial collagen, by releasing pro-coagulant endothelial agents, and by reducing activity of anti-thrombotics. A very important link between inflammation and thrombosis is tissue factor (TF) expression. As a result of vessel wall disruption due to inflammation; TF, which is expressed only in tissue cells, directly contacts with the blood. In sequence, it binds to activated factor VII, leading factor X activation and thrombin generation. In turn, thrombin converts fibrinogen to fibrin and, also activates platelets [10]. Inflammation also increases the synthesis and expression of TF, mainly by endothelial cells, macrophages and platelets [11]. Apart from TF, in result of the interactions between platelets, leukocytes and endothelial matrix, other procoagulant endothelial agents are released including von Willebrant factor (vWF), E-selectin, P-selectin and other adhesion molecules, thromboxane A2 (TxA2), the type-1 inhibitor of plasminogen activators (PAI-1) and platelet activator factor (PAF) [12]. Moreover, increased levels of vascular endothelial factor (VEGF) and endothelin-1, which is a vasoconstrictor product of endothelial cells, accompany with the active state of the disease and contribute to the thrombosis formation [13,14].

Inflammation induced endothelial injury also reduces the activities of anti-thrombotics, such as prostacyclin (PGI2), nitric oxide (NO), thrombomodulin, tissue plasminogen activator (t-PA), urokinase-type plasminogen activator (u-PA), tissue factor pathway inhibitor (TFPI) [12].

Currently, the vascular thrombosis in BD is accepted to be the result of the inflammation of the vessel wall. For this reason, the European League against Rheumatism (EULAR) recommendations suggest immunosuppressive therapy in the treatment [15].

Prothrombic State Due to Thrombophilic Factors, Alterations in Platelet Activation and Coagulation Mechanisms

Endothelial injury itself, common to all vasculitic diseases, cannot clearly explain the higher prevalence rate of vascular thrombosis in BD in comparison with other vasculitic diseases. So, a protrombotic state has been suspected and investigated intensively in BD. All observed values of the thrombin-antithrombin complex and the prothrombin fragments 1+2 in BD indicate a prothrombin clotting activation [16]. Moreover, as observed in other inflammatory diseases, fibrinogen level, which is an acute phase reactant, were increased in patients with BD.
**Thrombophilic Factors**

Data from the studies of thrombophilic risk factors in patients with BD have recently been evaluated in which the association between the incidence of thrombotic events and the presence of G1691A mutation in the factor V gene (factor V Leiden), the G20210A mutation in the prothrombin gene, and the previously mentioned C677T mutation of the MTHFR gene was evaluated. In this systematic review and meta-analysis, an increased risk of thrombosis was observed only in the presence of the factor V Leiden but with a frequency similar to the healthy population [17]. Factor V Leiden mutation was reported to be more prevalent in Turkish [18,19], but not in Italian, Spanish and Israeli patients [20-22].

Other classic trombophilic risk factors such as deficiency in protein C, protein S and Antithrombin (AT) were also studied in BD with contradictory results. Although some studies found an association between these risk factors and thrombosis in BD [23-26], many other studies did not find any of these risk factors to be associated with BD [16,27-31]. Protein Z, being a relatively unknown anticoagulant, is a vitamin K-dependent protein acting as a co-factor in the pathway of activated factor X (FXa) inhibition. In one small case-control study, it was found to be decreased in BD patients with vascular involvement [32].

Antiphospholipid antibodies (aPL) are a heterogenous group of antibodies that include antibodies directed against pure phospholipids, coagulation related phospholipid binding proteins (β2-glycoprotein I, prothrombin, annexin V, protein S), and against complexes of phospholipids and phospholipid binding proteins [33]. It is well known that aPLs are associated with arterial and venous thrombosis [34]. In most of the studies, nearly 30 % of BD patients had raised levels of anticardioliopin antibody (aCL). However, these levels were not significantly associated with thrombotic events [35-38].

Lipoprotein 'Lp (a)' has both atherogenic and anti-fibrinolytic effects [39]. Lp (a) level in BD was found to be negatively correlated with tissue plasminogen activator (t-PA) and D-dimer product of fibrin [40]. Its concentrations in patients with BD and its relation to the disease activity and procoagulant state were investigated in some studies. In these studies, Lp (a) concentrations were found to be higher in active phase than in the remission phase [38,40,41]. In one of these studies, it was detected that there was not any significant difference between inactive BD patients and healthy controls with regards to Lp (a) levels. Most of the studies concluded that Lp (a) behaved as an acute phase reactant in the disease, as it related with CRP, ESR and polymorphonuclear leukocyte elastase activity [38,41]. Only in one study, it was reported that increased serum Lp (a) level might contribute to the increased incidence of vascular complications in BD [42].

Homocosyteine is a structural intermediate generated during the synthesis of cysteine from methionine. Mechanistic studies have shown that hyperhomocysteinemia can lead to vascular endothelial damage and generation of a prothrombotic state by inducing an increase in the expression of adhesion molecules, cytokines, TF and blood coagulation factor V; an inhibition
of fibrinolysis; a disruption of NO metabolism; an increase in platelet reactivity and lipid peroxidation [43]. The association between hyperhomocysteinemia and thrombosis in BD has been investigated for several years. Many of these studies are small in size with conflicting results. In a recent meta-analysis including sixteen studies comprising a total of 979 patients with BD, hyperhomocysteinemia was more prevalent in patients with thrombosis than in those without. Mean levels of homocysteine were significantly higher in patients with thrombosis in comparison with patients without. As a result, it was concluded that hyperhomocysteinemia was associated with thrombosis in BD patients. Considering the fact that vitamin supplementation reduces homocysteine level but not cardiovascular events, the authors thought that hyperhomocysteinemia might be a marker for but not a cause of vascular disease [44]. In one study, the patients with thrombophlebitis showed a less frequent positivity of HLA-B5 antigen than the patients without thrombophlebitis [45]. In a previous report from Iranian patients with BD, a possible negative association between HLA-B51 and increased plasma homocysteine levels was suggested [46]; but this finding was not verified in another study [47].

Nowadays, it is generally accepted that the protrombotic state found in BD is not related to the thrombophilic risk factors in spite of some studies with contradictory results. In a recent study, combined thrombophilic factors in patients with BD have been reported to may have a role in the development of recurrent thrombotic events [48].

**Alterations in Platelet Activation**

Prothrombotic state in BD can be due to platelets and their activation. One study [49] found that mean platelet volume (MPV), being an independent risk factor of recurrent vascular events, was higher in patients with BD than controls. MPV was larger in patients with thrombosis than those without thrombosis. Furthermore, there was no significant difference in MPV between BD patients with active and inactive states. In another study using flow cytometry, inactive BD patients had significantly higher CD62P-expressing platelets and CD62P⁺platelet microparticles as compared with healthy controls [50]. Studies performed on the platelet activation markers in BD yielded contradictory results. Some authors reported that platelets from patients with BD were activated [51-54], but in a recent study, no difference in the presence of platelet activation markers (exposure to P-selectin, binding of PAC1, and formation of platelet-leukocyte aggregates) was found between patients with BD and the healthy control group [55]. Importantly, in one small study, it was found that the prevalence of 807TT genotype and 807T allele of the platelet glycoprotein Ia C807T/G873A gene polymorphism was higher in patients with BD as compared with healthy controls, which might suggest genetically determined platelet hyperfunction in BD [56]. However, it should be noted that this result is to be confirmed with more robust investigations.

**Alterations in Coagulation Mechanisms**

Recently in two studies, two global coagulation tests, namely rotational thromboelastometry (ROTEM) and calibrated automated thrombogram (CAT), have been used to evaluate the
hypercoagulable condition in inactive state of BD [57,58]. Maximum clot firmness (MCF) increased in both of the studies indicating a prothrombotic state in this disease. In one of these studies using only ROTEM parameters, clot formation time was not significantly changed [58]. The authors of this study thought that abnormalities in platelets rather than coagulation cascade might play role in the pathogenesis of thrombosis in BD. In the other study, clot formation time decreased significantly and the ROTEM test showed that increased levels of fibrinogen and plasminogen activator inhibitor type (PAI-1) might be involved in protrombotic state of the pathology, while platelets did not significantly involved [57]. Moreover, CAT assay demonstrated that plasma from BD patients was able to generate more thrombin than controls in response to the same stimulus and this effect was shown to be independent of disease activity and endothelial impairment.

Decreased fibrinolysis is another mechanism that has long been recognized as a key factor implicated in coagulopathy in BD [59,60]. Plasmin, the key enzyme of the fibrinolytic system, is effectively inhibited by $\alpha 2$ antiplasmin, forming a plasmin- $\alpha 2$-antiplasmin complex (PAP), a molecular marker of fibrinolytic activity. Significantly higher plasma levels of PAP were found in patients with BD, and even higher plasma levels of PAP were found in patients with vascular manifestations [61].

Many case-control studies on tissue plasminogen activator (t-PA) in BD found conflicting results, indicating its decreased [40], increased [62] or unchanged activity [16,63]. In a study evaluating BD patients who were with and without thrombosis both in acute and chronic phases of the disease, along with suitable diseased and healthy controls; the t-PA levels in BD with acute deep vein thrombosis (ADVT) were significantly lower than those in the patients with ADVT due to other causes. PAI-1 levels did not show significant differences among the groups [64]. However, the majority of studies on PAI-1 showed increased levels of this inhibitor of plasminogen activation in BD patients with or without thrombosis [40,65].

Thrombin activatable fibrinolysis inhibitor (TAFI), associated with venous thromboembolism in general population, was detected to be increased in one study performed in the patients with BD [65]. This increase was found not due to inflammation. PAI-1 and TAFI genetic polymorphisms were also assessed in this study, but no associated polymorphism was found. The increased fibrinogen levels observed in BD patients may increase thrombin generation due to fibrin’s ability to protect thrombin from inhibition by antithrombin [66].

Additionally, in a recent study performed on the patients in the inactive state of BD, it has been found that systemic redox imbalance and circulating neutrophil hyperactivation in BD has been associated with altered fibrinogen structure and impaired fibrinogen function. This mechanism has been thought to be responsible for impaired coagulation in the disease by increasing fibrin resistance to lysis [67].
The Uses of the Mechanisms in the Treatment

Currently, the treatment of vascular thrombosis in BD patients is based on immunosuppressive therapy, because the thrombosis generally is accepted to be the result of the inflammation of the vessel wall [15]. This acceptance is highly concordant with the localization of a sticky thrombus near the inflammation site and with the low rate of embolism [68]. Anticoagulation treatment alone is not recommended except central nervous system venous thrombosis [15,69,70]. The discordant data on the relation of coagulation abnormalities to thrombosis, the possibility of life threatening coexistence of pulmonary artery aneurysm and thrombosis and, the low efficacy of the anticoagulants reported in some retrospective studies [71,72] are the main reasons for not using anticoagulants in BD. However, the association of thrombophilic factors in BD, especially when they are multiple, necessitates examinations of these factors in the patients.

Considering the role of platelet hyperactivity in the thrombosis observed in BD patients, anti platelet therapy can take place in the treatment. Fibrinolytic treatment may be a measure against the hypofibrinolysis. Currently, only anti-platelet therapy with acetyl salicylic acid is used in the most cases without adverse effects. Experience with fibrinolytic therapy is scarce and has also been unsuccessful [15]. The effect of prophylactic treatment with antiplatelet agents or anticoagulants is yet to be clarified.

CONCLUSION

The role of endothelial injury due to inflammation is certain in the pathogenesis of vascular thrombosis in BD. In the treatment of thrombosis, immunosuppressive therapy is recommended by the European League. However, because of higher prevalence of thrombosis in BD in comparison to other vasculitic disease, the roles of some other possible mechanisms have been studied for many years. In these studies, BD patients and BD patient subgroups designated with regards to the activity state of the disease and presence of vascular thrombosis history were compared with healthy controls. The studies are mostly small in size with patient number less than 50.

Because of the limitations of the studies, the results are inconclusive and even contradictory. So, there is a need for larger and more elaborated studies to clear the roles of the possible mechanisms, even including comparisons with other vasculitic diseases and idiopathic thrombosis cases. Increasing our knowledge about underlying mechanisms of vascular thrombosis is necessary for our improvement in the treatment approaches.

References


