Review article

**Buerger’s disease: A Bench-to-Bedside Review**

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**Abstract**

Buerger’s disease or thromboangiitis obliterans is a non-atherosclerotic vascular disease that causes inflammation of the blood vessels and arterial occlusion in the extremities, resulting in impaired distal perfusion. Tobacco use is the main etiologic factor and is responsible for the progression and recurrence of the symptoms. Also, several contributing factors to the pathogenesis of the disease have been suggested, such as immunologic mechanisms and genetic predisposition. The disease is more prevalent in the Middle East and the Far East than in North America and Western Europe. Patients are often young male smokers, who may present with burning pain and paresthesia, cold sensitivity, purple discoloration, superficial thrombophlebitis, intermittent claudication, ischemic rest pain, ulcer, or gangrene. The diagnosis is based on the clinical criteria, such as Shionoya, Olin, Papa, and Mills criteria. Smoking cessation is the only effective treatment for pain relief, blood flow improvement, and limb salvage. However, additional therapeutic options have been proposed, such as sympathectomy, prostaglandin infusion, endovascular angioplasty, and surgical revascularization. If treatment measures fail, amputation may be inevitable.

**Keywords:** Buerger's disease, Thromboangiitis obliterans, Vascular disease

**1. Introduction**

Buerger’s disease also known as thromboangiitis obliterans, is a non-atherosclerotic obstructive disorder, involving small- to medium-sized arteries and veins of the upper and lower limbs [1]. The disorder was first described in 1879 by Felix von Winiwarter [2]. A detailed description of the condition was reported by Leo Buerger later in 1908 [3]. Although Buerger’s disease has been first described over a century ago, the condition remains poorly understood. This review aims to provide an overview of the current basic and clinical knowledge about Buerger’s disease.

**2. Epidemiology**

Although the disease typically occurs in young male smokers, the incidence among women has relatively increased during the last few decades. Buerger’s disease has a global distribution [4]. However, the disease is more prevalent in the Middle East and the Far East than in North America and Western Europe [4]. The prevalence of the disease among all patients with the peripheral arterial disease has been reported as follows: Western European countries: 0.5 to 5.6%, India: 45 to 63%, Japan: 16 to 66%, and Ashkenazi Jews: 80%. In addition, Buerger’s disease usually occurs in patients with low social economic status [5, 6].

**3. Risk factors**

Tobacco exposure is proved to be an essential factor for the onset and progression of thromboangiitis obliterans [7]. Although smoking is the most common risk factor, the disease may also be caused by chewing tobacco or marijuana consumption [8]. In general, there is a close relationship between tobacco use and the onset, clinical manifestations, and recurrence of Buerger’s disease. Thus, tobacco is recognized as a major risk factor [9]. Other important risk factors after tobacco use include male gender, race, age between 20 and 45 [10, 11].

**4. Immunologic Mechanisms**

Many researchers have examined specific pathological mechanisms in Buerger’s disease. Inflammatory cells such as CD3+ T cells, CD4 cells, and CD20 B cells respond to the elastic layer of vessels involved in Buerger's disease in the subacute stage [12]. Small abscesses are observed in the acute stage of Buerger’s disease, which can be associated with acute inflammation in the intima and thrombus [11]. The chronic stage of Buerger's disease usually includes obstruction and is characterized by prominent arterial and perivascular fibrosis. In general, the structure of the vascular wall and the elastin layer, unlike atherosclerosis and other types of vasculitis, are not damaged in Buerger’s disease [13]. Endothelial cells seem to play a crucial role in the initiation and persistence of the inflammatory response in Buerger’s disease [14]. A further expression of adhesive molecules, such as VCAM-1, ICAM-1, and selectin on the endothelial cell surface has been confirmed in patients with Buerger’s disease [15]. Some researchers believe that Buerger’s disease is an endarteritis caused by some antigens. CD8+ T cells may be involved in the onset of Buerger’s disease [15]. The activity of CD4+ T cells is at least as evident as CD8+ T cells during the progression of Buerger’s lesions [16] CD68+ macrophages and S-100-positive dendritic cells can be seen in the intima layer in acute and subacute stages of patients with Buerger’s disease [17]. Immunoglobulins and complement factors are present in the elastic layer in the acute or subacute stage of the disease [17].

**5. Genetic Predisposition**

Genetic analysis of TAO patients showed that the prevalence of HLA A-9 and HLA B-5 is higher and the prevalence of HLA-B12 is lower in patients with Buerger’s disease than in healthy individuals [18, 19] Variations in the expression of the HLA genes occur in Buerger’s disease and this change in gene expression varies in different racial populations [20, 21]. According to a study conducted in Mashhad on Buerger’s disease and their relationship with HLA showed that HLA class one and two were associated with Buerger’s disease [21]. The MyD88 signaling pathway is one of the most important innate safety signaling pathways in Toll-like receivers (TLRs). A study by Chen et al. indicated that rs7744 single nucleotide polymorphism (SNP) in the MyD88 gene was significantly lower in Japanese patients with Buerger’s disease than in the healthy group [22]. Besides, Adigozel et al. found that the occurrence of endothelial nitric oxide synthase (eNOS) gene on position 894 is related to a reduced incidence of Buerger’s disease. It was, therefore, suggested that the eNOS gene polymorphism of the 894G → T gene polymorphism plays a protective role against the TAO development. Also, Chen et al. reported that the frequency of genotype CD14 TT, HLA-DRB1 1501, and HLA-DPB1 0501 was significantly higher in patients with Buerger’s disease than in healthy individuals [23]. A case-control study to identify genetic factors involved in the development of Buerger’s disease demonstrated that SNPs rs376511 in IL17RC and rs7632505 in SEMA5B are associated with a significant risk of developing Buerger’s disease. It was shown in a study, performed in China, that Buerger’s disease is controlled by genes involved in innate and acquired immunity [3].

**6. Histopathology**

A biopsy is rarely indicated, and clinical assessment is usually sufficient to diagnose Buerger’s disease. Histological specimens can be obtained from amputated limbs or a superficial inflamed vein in patients with Buerger’s disease [24]. Biopsy from an ischemic limb is not recommended due to the risk of causing chronic non-healing ulcers [25]. The pathological findings of specimens from Buerger's patients are different from those of other vascular patients [26]. Thus, Buerger’s disease can be differentiated from atherosclerosis, idiopathic arterial thrombosis, or vasculitis. The pathological stages of Buerger’s disease can be categorized into acute, intermediate, or subacute, and chronic stages [27]. Acute phase lesions include inflammatory thrombosis with a low rate of vascular wall inflammation, polymorphonuclear leukocytes, and multinucleated giant cells. A progressive thrombus can be seen in the intermediate stage [17]. In the chronic stage, only thrombosis and fibrosis will be observed [28].

**7. Diagnostic criteria**

The diagnosis of Buerger's disease is mainly based on clinical criteria. For instance, the Shionoya criteria include the history of smoking, the onset of disease before the age of 50, infrapopliteal artery disease, upper extremity involvement or migratory thrombophlebitis, and no risk factors for atherosclerosis other than smoking [29]. There is no specific diagnostic test and serological marker for definitive diagnosis of Buerger's disease [29]. In addition to Shionoya's diagnostic criteria, Olin [30], Papa [31], and Mills [32] have proposed diagnostic criteria for Buerger's disease. There are differences in defining the diagnosis for Buerger's disease by these people, the is less than 50 years in Shionoya's diagnostic criteria, less than 45 years in Olin’s diagnostic criteria. Raynaud’s phenomenon is not present in Shionoya’s and Olin’s diagnostic criteria, and the female sex is present as a negative criterion only in Papa’s diagnostic criteria [30, 32].

**8. Clinical presentations**

Patients usually present with signs and symptoms of distal extremity ischemia [33]. The disease progression can be observed over time with the involvement of more proximal arteries. However, the involvement of the large arteries is unusual[34]. Multiple limb involvement is common, and more than one limb is usually involved [29]. Early findings include cold sensitivity and sensory disturbance such as paresthesia. Sometimes, migratory superficial thrombophlebitis can be an early sign. Also, the disease may be manifested with burning pain in the feet and hands, the Raynaud phenomenon, purple discoloration, intermittent claudication of the foot and/or calf or hand and/or arm. As the disease progresses, rest pain, ischemic ulcers, and gangrene develop. The vascular examination may reveal absent distal pulses and abnormal Allen’s test [35]. Rarely, cerebral, coronary, or visceral arteries can be involved, leading to the development of atypical symptoms [36]. Photos of Buerger's and angiogenesis patients in Figures 1 (A-B) and 2 (A-B).

**9. Diagnostic Evaluation**

As discussed before, the diagnosis is mainly based on the diagnostic criteria. In addition to a detailed physical examination, laboratory tests and imaging studies are beneficial in confirming the diagnosis, determine the severity of the disease, and excluding differential diagnoses. Digital plethysmography and ankle-brachial index measurement are recommended. In arteriography, segmental distal occlusions, normal proximal arteries, corkscrew collaterals, and absence of arterial wall calcification are suggestive of Buerger’s disease. Duplex ultrasound can reveal distal occlusive disease and exclude atherosclerosis. Additionally, echocardiography and abdominal ultrasonography may be done to exclude the proximal source of emboli. Several laboratory tests are also suggested, such as inflammatory markers and autoantibodies to rule out connective tissue disease and coagulation profile for the exclusion of thrombophilia [32, 37, 38].

**10. Buerger's disease in Iran**

In a retrospective study in Mashhad, Modaghegh et al. examined 225 patients with Buerger's disease from 2000 to 2010. During the study period, patients' clinical characteristics, family history, and tobacco use were reviewed. The patients included 222 males (98.7%) and 3 females (1.3%). The mean age of patients was 40.7 years, and 88.9% of them were smokers. The clinical manifestations were chronic ulcer (80%), claudication (63.6%), Rest pain (60%), finger gangrene (57.8%), cold sensitivity (44%), purple discoloration (40.4%), paresthesia (28.4%) and migratory thrombophlebitis (18.7%). Both upper and lower limbs were involved in 98 patients (43.6%). Seventeen patients (7.6%) received prostaglandin infusion. A total of 150 sympathectomy procedures were performed, while surgical bypass was done in only 4 patients (1.8%). Also, 113 (50.2%) and 41 (18.4%) patients underwent minor and major amputations, respectively [6]. Another study by Salimi et al. was conducted on 116 male smoker patients in Tehran during 1997-2002 to determine the clinical course of Buerger’s disease. All hospitalized patients were diagnosed according to Shionoya clinical criteria. The patients’ involvement was found to be as follows: Lower limb involvement in 102 patients (87.9%), upper limb involvement in 3 patients (2.6%), and both lower and upper limbs involvement in 11 patients (5.9%). The most common reasons for hospitalization included ischemic ulcers (90.5%), limping (87.9%), paresthesia (75.9%), rest pain (66.4%), gangrene (60.3%), Raynaud's phenomenon (23.3%), and thrombophlebitis (9.5%). In general, upper extremity involvement, thrombophlebitis and Raynaud's phenomenon were rarely seen among the subjects [39]. An Iranian Scoring System for Diagnosing Buerger's Disease by Ramin et al. suggested age, sex, smoking, Raynaud's phenomenon, abnormal proximal Doppler, diabetes mellitus and hyperlipidemia as diagnostic criteria for Buerger's Disease. According to this study, the sensitivity and specificity of the criteria were respectively 95.1% and 78.7% [40]. A study by Tavakoli et al. on the range of clinical symptoms of burger patients during 10 years (2005-2006) in Tehran showed that out of 198 patients with burgers, all male patients had a mean of 40.5 1 10.1 and were smokers. Their range of clinical symptoms included 91.4% lower limb involvement, 2% upper limb involvement, 6.6% lower and upper limb involvement. Sympathectomy, amputation and bypass surgery were the treatments performed for these patients [41]. A study conducted in northeastern Iran estimated the prevalence of the disease as 3 per 100,000 people [42]. In addition, other studies have been performed in Mashhad such as HLA study [21], surgical Therapy [43] and immunological factors [12] in burger patients.

**11. Treatment**

Smoking cessation is the basis of treatment for Buerger's disease. However, when ulcer or gangrene occurs, smoking cessation alone may not be enough to relieve the pain and improve wound healing. [44]. The therapeutic goals include improving distal flow, alleviating pain, healing the ulcer, preventing amputation, and treating concomitant infections Table 1 [45-47]. Oral medications such as antiplatelets, calcium channel blockers for vasospasm, folic acid supplements, and analgesics are suggested to be prescribed [27, 48]. When there is a superimposed infection, administration of antibiotics and wound care is of utmost importance. Therapeutic measures such as sympathectomy, prostaglandin infusion, surgical bypass, and endovascular therapy are considered for patients with ischemic rest pain or tissue loss [49]. Often, bypass surgery is not feasible, because a distal target vessel is usually not available [50]. Sympathectomy is effective temporarily, but symptoms usually recur after several weeks or months. Therefore, sympathetic denervation cannot be considered a long-term treatment [51, 52]. Prostaglandin analogs have shown promising results. However, a relatively prolonged hospital stay is necessary for the infusion of prostaglandins. In patients with critical limb ischemia, percutaneous angioplasty is a potential alternative to sympathectomy and prostaglandin infusion Table 2[43].

**12. Conclusion**

Although Burger's disease has been diagnosed for more than a century, the mechanism of the disease and specific diagnostic markers have not yet been fully identified, so the disease can only be diagnosed using specialists familiar with diagnostic criteria. On the other hand, there is no single treatment for the disease. Although pharmacological and cell therapies have yielded good results, in many cases, the patient does not respond to existing treatments and the only solution for vascular surgeons is limb amputation.

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**Author contribution**

All authors contributed equally and also approving the final version of the manuscript.

**Conflict of Interest**

The authors declare no conflicts of interest.

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