

## ⇒ Review Article



# Thromboangiitis Obliterans: A Multifactorial Disease With an Immunological Basis

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## Abstract

The aim of this review was to assess several factors associated with Buerger's disease or thromboangiitis obliterans (TAO), especially the immunological basis of this disease. We found that an established etiology for TAO has not been agreed on so far, but no one denies the strong association between TAO and tobacco consumption. Another possible etiology for this disease is bacterial infections such as *Porphyromonas gingivalis* and *Rickettsia* and their possible role via inflammatory processes. TAO was more common in low socioeconomic societies with poor hygiene. It may be attributable to the prevalence of *Rickettsia* infection because of the tick bite in these societies. In case of autoimmunity, it should be noted that T 17 cells keep the body away from autoimmune processes. The number of infiltrated CD4<sup>+</sup> T cells in the arterial wall is higher than B cells. In fact, this may propose the significant role of T cells in the immunopathology of patients with TAO. The disease is also associated with tumor necrosis factor (TNF- $\alpha$ ), interleukin (IL)-1 $\beta$ , IL-4, IL-17 and IL-23, as inflammatory cytokines. Antiphospholipid antibodies, anti-CL, anti-TLRVYK, anti-TLRIYT, anti-TLALYK, and anticardiolipin may also play a role in this disease. Further evidence is needed to shed light on the condition, especially in case of T cell lymphocytes' role.

**Keywords:** Buerger's disease, Thromboangiitis obliterans, T cells

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## Background

Buerger's disease or thromboangiitis obliterans (TAO) is a non-sclerotic obliterative disorder of small and medium-sized arteries and veins in the upper and lower extremities (1). The etiology of the disease includes clot formation and recurrent, progressive inflammation of the vessels (2). Tobacco consumption plays a large role in this setting. Clinical signs and symptoms of TAO include painful ulcers on the tip of phalanges and intermittent phalangeal pain (3, 4). Currently, there is no cure for TAO; amputation is often needed in the course of the disease. However, tobacco consumption cessation can notably reduce TAO progression (4). The main risk factor of TAO includes any form of tobacco consumption, but the exact cause of the disease is still unknown (3). Further evidence is needed to shed light on the condition, especially in the case of T cell lymphocytes' role.

## Methods

Our study search was conducted through reviewing PubMed, Scopus, Embase, Web of Science, and also Google Scholar using the keywords "Buerger's disease", "thromboangiitis obliterans", "immune system", "cytokines", "T-cell", and "pathophysiology". There was

no time limitation for literature review; however, only English and Persian articles were reviewed. All clinical and laboratory experiments were reviewed, and the articles that reviewed Buerger's disease pathophysiology and the role of the immune system were included. To assess the quality of the included studies, Joanna Briggs checklists (5) were used, and the eligible studies were reviewed.

## Results

### Buerger's Disease

Buerger's disease is typically found in 20-40-year-old men and is highlighted by recurrent, progressive vessel failure that leads to gangrene and amputation (6). The disease owes its name to the Austrian pathologist Leo Buerger, who named the disease TAO (7). The disease is differentiated from atherosclerosis by a positive Allen's test (8). The underlying vasculitis in this disease is present in small and medium vessels, and the involvement of large arteries is rare (9).

### Disease Risk Factor and the Cause of the Disease

#### Tobacco Consumption

Several risk factors have been proposed for Buerger's

disease so far. Previous studies have shown a strong relationship between TAO and tobacco consumption, especially cigarette smoking (10). It is often stated that Buerger's disease is related to heightened sensitivity to glycoproteins that are present in tobacco (11); however, the only approved pathogenesis with this regard is that cigarettes can cause platelet, leukocyte, and endothelial cells malfunction leading to thrombosis and inflammation (12, 13). Several studies have shown the close relationship between TAO progress and smoking; this relationship is so close that only quitting cigarette smoking, even in the acute phase of TAO, can subside the disease (14-16). Rare cases of TAO have been reported among non-smokers (7). Furthermore, a study on Iranian Buerger's cases showed a significant increase in oxidative cytokine levels in smokers compared to healthy non-smokers (17).

### Infection

Shortly after Leo Buerger, two scientists named Allen and Brown hypothesized that infectious bacteria or viruses might play a role in TAO pathogenesis (18, 19). Soon after, in 1923, gram-negative bacilli were cultured from TAO patients' blood samples; however, after two years, it was proposed that this role was not confined to the gram-negative bacteria, and gram-positive organisms such as *Staphylococcus aureus* may have a role in this disease (19). Buerger found that intravenous injection of samples obtained from the amputated limbs of patients with TAO can induce thrombophlebitis migrans in these patients. In 1980s, an Italian scientist named Bartolo hypothesized a possible role of *Rickettsia* in Buerger's disease. He found antibodies against different strains of *Rickettsia* in 101 patients with TAO (20). *Rickettsia* is an intracellular pathogen causing infection in humans via tick and other insect bites. The bacteria attach to the endothelial walls of vessels and attack the DNA of the endothelial cells that ultimately leads to platelet activation and thrombus formation (21-23). This feature of *Rickettsia* may be the cause of specific pathological findings of the disease, such as endothelial cell proliferation that further causes vessels occlusion (19). *Rickettsia* infection can also explain the thrombo-occlusive nature of the disease and inflammation of the vessels. Accordingly, in a recent study on 25 vein samples obtained from TAO patients' amputated limbs, the extracted DNA underwent polymerase chain reaction (PCR) to see whether the *Rickettsia* genome was present or not. The *Rickettsia* genome was present in three samples, but the strain of *Rickettsia* was not specified (23).

In 2005, a group of Japanese researchers investigated the infectious nature of Buerger's disease by using PCR. They extracted the DNA of oral bacteria such as *Porphyromonas gingivalis* from the thrombosis in the occluded vessels of patients with TAO (24). Bacteria of the normal mouth flora, including *P. gingivalis* can generally induce macrophages to produce interleukin

(IL)-23 (25). This cytokine can trigger the differentiation of primary T-cells to Th17 cells. The role of these cells in autoimmune inflammatory diseases has been proven (26, 27). Furthermore, the lipopolysaccharide (LPS) of gram-negative bacteria such as *P. gingivalis* can induce platelet aggregation and reduce thrombomodulin expressed in endothelial cells and thus lead to thrombosis and vascular inflammation (28). *P. gingivalis* can activate TLR4 receptor on the surface of endothelial cells, leading to the induction of pro-inflammatory molecules, such as the IL-8, IL-1, IL-6, IL-8, MCP-8, ICAM-1, VCAM-1, E-Selectin, on the surface of endothelial cells (24, 28-30). Despite all these findings, the infectious etiology of Buerger's disease has not been proven yet, and still, it is open for debate.

### Sex

TAO was initially diagnosed in men and was believed to be a disease of men and not women; however, more recent reports demonstrated women with TAO with lower incidence (1). In the past, smoking was a prevalent habit in men and not women but now a growing trend toward smoking is observed in women, as well. Moreover, sex hormones are also responsible for this difference as testosterone increases platelet aggregation by expressing more thromboxane A2 receptors in the male sex that causes subsequent arterial thrombosis (31). Therefore, it is a combination of hormonal basis and smoking habits that makes young men more prone to the thrombotic and inflammatory processes that lead to TAO.

### Personality

A study in 1988 showed that patients with Buerger's disease have similar personalities and behavioral traits. It was even claimed that the discovery of the role personalities could be a part of the diagnostic criteria for Buerger's disease. Patients with Buerger's disease are erratic, ambitious but are also frustrated and pessimistic. On the other hand, they are not satisfied with their condition (7). Perhaps this is one of the reasons for their tendency toward smoking (drug abuse is also higher among them). Moreover, they are not knowledgeable enough to understand the close relationship between smoking and their condition, and thus they have no urge to quit smoking. These patients usually have impulsive and aggressive behaviors, and after these behaviors they usually become very regretful. Suicidal tendencies and unsuccessful attempts are usually high in these patients (32).

### Genetic Predisposition

One of the important aspects that need to be discussed is the genetic basis of the disease and especially HLA typing. Many studies have addressed this issue (33-35). Chen and colleagues (35) discovered a relationship between HLA-DRB1\*1501, B54, with Buerger's disease in Japan. Also, in this study, CD14 TT genotype, DRB1\*1501

and DPB1\*0501 HLAs were more prone to TAO. Mehra and Jaini (36) investigated the immunological basis of Takayasu and TAO and found a positive relationship between HLA-B5 molecule and Takayasu's arteritis and also a powerful positive correlation between HLA-DRB1\*1501 and Buerger's disease. They proposed that these HLAs may make the patients more prone to vasculitis. In recent years, eNOS-786C mutations have been reported in patients with Buerger's disease that cause disorders in the synthesis of nitric oxide in endothelial cells (37). Not only is nitric oxide a vasodilator, but also inhibits platelet aggregation and binding of inflammatory cells to endothelial cell (38). A disorder in the synthesis of nitric oxide can have a significant role in the pathogenesis of TAO.

### **Epidemiological Findings**

It seems that TAO is more prevalent in patients with low socioeconomic class and it is also higher in developing nations than in developed countries. For example, a dramatic increase in the prevalence of the disease was observed in low socioeconomic populations during World War II in many parts of the world, especially Japan and Jewish residents of Europe. However, the condition subsided after the war ended. In recent years, the prevalence of the disease has reached its lowest level in North America, Japan, and West Europe (39).

### **Clinical Course and Signs of the Disease**

The subacute phase of the disease is characterized by progressive thrombosis in the upper and lower extremities. In this phase of the disease, there is no fibrinoid necrosis in the arterial wall, and no major abnormalities can be seen. The chronic phase is characterized only by the presence of organized thrombosis and vascular fibrosis without any inflammatory signs. The pathological manifestations of the chronic phase are similar to other occlusive arterial diseases (1).

Compared with patients with atherosclerosis, claudication is rare in Buerger's disease, but if this condition is present in patients with TAO, it will be a sign of the involvement of specific regions such as the soles of the feet or distal regions. The most common clinical sign is at rest pain and ischemic ulcers at the dorsal part of the foot. Unlike atherosclerosis, involvement of the upper part of the foot is common in patients with TAO. Nearly 50% of the patients with TAO have only lower extremity involvement, 30%-40% of the cases have both lower extremity and upper extremity involvement, and only 10% of cases have pure upper extremity involvement (40). Upper extremity involvement can present itself as Raynaud's syndrome or Frank's fingered ischemia. Another useful clue in detecting TAO cases is a positive history of superficial thrombophlebitis. This sign is present in approximately 40% of patients with TAO (1, 40).

### **Immunological Literature of the Disease**

A study in 2012 by Dellalibera-Joviliano and colleagues (41) evaluated the level of tumor necrosis factor (TNF- $\alpha$ ) and interleukins such as IL-1 $\beta$ , IL-4, IL-17 and IL-23 in patients with Buerger's disease. Their results showed increased production of these cytokines in patients with Buerger's disease compared with the normal controls, which could be related to an inflammatory response in the vascular level. Furthermore, Smolen et al (42) compared the humoral and cellular immune status and HLA antigens level in patients with TAO and a normal control group. They concluded that autoimmune mechanisms might be involved in the pathogenesis of Buerger's disease. Maslowski et al (43) also evaluated antiphospholipid antibodies such as anticardiolipin antibodies (aCLa) in Buerger's disease. They concluded that the presence of high levels of these antibodies was associated with increased morbidity, including major amputations. With this regard, patients with TAO should be screened for aCLa.

Kobayashi and colleagues (44) studied the arterial wall of patients with Buerger's disease through pathology assessments. They found that the structure of the arterial wall was preserved, and immunological infiltration was mainly seen in the thrombus and intima. CD3<sup>+</sup> B cells were much more prevalent in the infiltrate compared to the CD20<sup>+</sup> B cells. Moreover, CD68<sup>+</sup> macrophages or S-100 positive dendritic cells were seen in the vascular intima during the acute or subacute phases of the disease. In all cases except one, infiltration of the intima was via HLA-DR antigen-bearing macrophages and dendritic cells. Immunoglobulin (Ig) A, IgG, IgM, IgD and C4 complement factor were found as immunological deposits in the internal elastic lamina.

There is pooling evidence that supports the autoimmune nature of Buerger's disease. An increase in the number of free radicals, the release of intracellular antigens, increased levels of neutrophils, increased activity of B cells and CD4<sup>+</sup> T cells leads to an autoimmune status in these patients (45). The presence of auto-antibodies further supports the immunological basis of TAO. Halacheva and colleagues (46) compared serum levels of anti-neutrophil cytoplasmic antibodies (ANCA), myeloperoxidase, lactoferrin, and elastase between patients with TAO and normal controls. There was a significant difference in ANCA serum level between the patients and the control group; however, this was not consistent for other mentioned auto-antibodies. Schellong and colleagues (47) also assessed the ANCA serum level in patients with TAO using immunofluorescence and ELISA methods. In this study, ANCA was found not to have a role in active or inactive forms of TAO.

In another (48), the immunogold-silver staining technique was used for immunopathology assessment of patients with TAO. They used this technique to find

immune complex deposition in the vessels of 18 patients and found anti-vascular autoantibodies in the serum sample of 28 patients. The immune complex deposition was present in all cases, and intravascular antibodies were present in 86% of the cases. Moreover, Chen and colleagues (34) reported that periodontitis was more prevalent in patients with Buerger's disease. aCLa, anti-TLRVYK, anti-TLRIYT, anti-TLALYK serum antibodies were also increased in these cases. De Godoy and Braile (49) concluded that aCLa can be associated with TAO and may worsen the thrombotic events in these patients. Thus, the auto-inflammatory basis is an important controversial issue in patients with TAO. Especially, the role of T cell lymphocytes should not be ignored in this regard.

### **The Role of T Cells**

Normally, in the presence of the tolerance phenomenon, the body does not react to self-antigens. Self-antigen sequestration, lymphocyte activity regulation by suppressor T cells, and elimination of T cells which are sensitive to self-antigens are factors that maintain tolerance phenomenon in the body (50). Alteration of any of the above factors or self-antigens causes self-antigen reacting antibodies and causes autoimmune diseases such as Buerger's disease (51, 52).

The immunological analysis further proved the presence of T cells, both CD4<sup>+</sup> and CD8<sup>+</sup> T cells in the arterial wall of patients with Buerger's disease (53). Kobayashi et al (44) reported that the predominant cell lineage in the arterial intima was CD8<sup>+</sup> T cells. However, Lee and colleagues (53) reported that CD4<sup>+</sup> T cells are infiltrated in the intima and adventitia of affected arteries in Buerger's disease. With this regard, it is postulated that antigen presentation to T cell lymphocytes can cause autoimmunity in patients with TAO, and T cells play a crucial role in this regard (54). However, still, this role is not fully investigated, and further studies are needed. The crucial role of CD8<sup>+</sup> T cells is confirmed in the pathogenesis of giant cell arteritis (55) Takayasu's arteritis (56), lupus (57), and abdominal aortic aneurysm; however, the role of this cell lineage is not fully investigated in TAO patients. Future studies might prove its fundamental role in TAO (58).

### **Complications**

The long-term consequences of the disease are related to minor and major amputations and may even lead to mortality (59-61). These studies proposed a rate of 27% for limb amputations. However, this risk can be proposed as 25% for the first 5 years, 38% for the first 10 years, and 46% for a time of 20 years. Also, the involvement of the upper extremity has increases (60, 62). Very rare cases of coronary (63), renal (64), retinal (65), splenic (66), or mesenteric (67) arteries involvement in the setting of Buerger's disease have been reported.

### **Diagnosis**

Researchers from Japan proposed a five clinical criteria list for TAO: 1) Smoking, 2) Onset of disease before the age of 50, 3) Blockage of an artery below the popliteal artery, 4) Upper extremity involvement or phlebitis migrans, and 5) The absence of atherosclerotic risk factors other than smoking (3). Mills and Porter, in a cohort study, proposed stricter criteria need to be present for Buerger's disease (40). Different angiographic findings were also reported. Atheroma and arterial calcification are not seen in these patients. Multiple blockages of the ulnar arteries, radial or both, can be seen (2). Most types of immune arthritis involve necrotizing of the upper extremities. Therefore, in all patients suspected of Buerger's disease, four segmental arterial pressure is taken, and digital plethysmography is performed.

In severe cases of the disease, histopathological findings can be used for diagnosis. General surgeons first take a biopsy from the ischemic organ; amputation is generally done when Long-term efforts to stop smoking and attempts to control the disease with medication have failed. But in a small number of patients with clinical criteria, the histopathological examination can show problems in the following vessels: aortic, iliac, cerebral, coronary, mesenteric, pulmonary, and even the spermatic artery (68). The variant of the disease which affects the spermatic cords was first reported by Buerger himself (69). Most studies have proposed that diseases with similar symptoms to Buerger's disease should be checked and ruled out. Blood coagulation is one of the factors for diagnosis; its prevalence is on the rise. Therefore patients should be evaluated on it regularly. Buerger's disease is considered far worse than atherosclerosis and other types of necrosis because of the amputation of limbs (40, 70). 19% of amputations are of the foot, and 6.3% are of the fingers (40).

### **Treatment**

There is no standard and effective treatment for the recovery of TAO. The first line of treatment and the most important is the stoppage of all types of tobacco products and avoiding second-hand tobacco smoke. The strict avoidance of tobacco is essential. This must be told to the patient, and if necessary medical and psychological support should be available to the patient. Despite the severe risks and warnings, a significant proportion of patients with TAO continue to smoke cigarettes (71). Evidence supporting treatment with antiplatelet or lipid-lowering therapy for patients with TAO does not exist. Immunosuppressive therapy may be useful in some patients with TAO (72).

New insights concerning the role of lymphocytes and inflammation dependent on TNF- $\alpha$  in the pathogenesis of TAO, have led to new treatment options such as anti-TNF- $\alpha$  or anti-CD20, such as the use of rituximab (anti-

CD20 chimeric antibody) (73).

Sympathectomy is used in the treatment of many different disorders; However, although it might be effective, the clinical impact in most cases is limited. Currently, cutting the sympathetic innervation of the area has minimal side effects and is done via the destruction of the second thoracic ganglia using a thoracoscope (74).

Angioplasty usually is not successful (75-77). In a study on 46 cases of surgery in patients with Buerger's disease, the grafted artery stayed open in 54% of cases after a year, in 47% of the cases after 5 years, and in 39% of cases after 10 years. Also, 14% of the unsuccessful grafts led to amputation (59).

### Conclusion

Buerger's disease can be predisposed by several factors, including tobacco consumption, sex, infection, personality, and socioeconomic factors. However, the immunological basis of the disease still needs further investigations and is an important part of the disease which is not fully understood. Our review showed that T cell infiltration and activity play a significant role in the pathogenesis of the disease. The immunological balance that keeps the body away from autoimmune processes is based on the T 17 cells. The infiltration of CD 3 positive T cells in the arterial wall is much more than B cells. The disease is also associated with TNF- $\alpha$ , IL-1 $\beta$ , IL-4, IL-17, and IL-23. Antiphospholipid antibodies, anti-CL, anti-TLRVYK, anti-TLRIYT, anti-TLALYK, and anticardiolipin may play a role in the disease. There is also controversy about ANCA in the disease.

### Authors' Contribution

ADT, HR and MS contributed to the arrangement of the study, and served as the lead author of the manuscript. ADT, MS, AO, MMM and SS wrote some parts of the draft, and finalized the manuscript. All authors read and approved the final manuscript.

### Conflict of Interests

None to declared.

### Ethical Approval

Not applicable.

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