Thromboangiitis obliterans: a review

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ABSTRACT

Buerger's disease was initially described by von Winiwarter in 1879 where he described it as thromboangiitis obliterans (TAO), detailing the case of spontaneous gangrene secondary to intimal proliferation. In 1908, Leo Buerger published a complete pathological description based on the amputation of a group of people who later suffered short-term gangrene. Buerger's disease or TAO is defined as a non-atherosclerotic inflammatory vasculitis that affects the small and medium vessels (including arteries and veins) of the lower and upper extremities. Although there are hypotheses about its etiopathogenesis such as the association with exposure to tobacco, few biomedical investigations have been carried out, so its direct causality remains unknown. Diagnosis continues to be a challenge, since the findings tend to be non-specific or inconsistent with suspicion, which is why it is currently based on ruling out other causes such as atherosclerosis and vasculopathies. With current evidence, there are many types of treatments, both pharmacological and non-pharmacological, with the cessation of tobacco consumption having greater evidence of results. It is essential to strengthen basic research as well as clinical trials to standardize management in this type of patient, since it is a disease with a high impact on quality of life.

Keywords: Buerger's disease, TAO, Vasculitis, Non-atherosclerotic inflammatory vasculitis, Vasculopathies

INTRODUCTION

Buerger's disease was originally described by von Winiwarter in 1879 where he described it as TAO and detailed a case of spontaneous gangrene secondary to intimal proliferation.¹ Later, the disease was named after Leo Buerger, who in 1908 published a complete pathological description based on the amputation of a group of people, including smokers, with neuropathic pain, trophic changes in the skin and annexes such as distal coldness, loss of hair, onychodystrophy, with absence of posterior pedis and tibial pulses, lasting months to years, and which later presented with gangrene in the short term.²,³

LITERATURE REVIEW

A search was performed using the MeSH and alternative terms “TAO”, “Buerger's disease”, “MicroRNAs”, “MiRNA”, “diagnosis” “sympathectomy” in the databases PubMed, ScienceDirect, Scopus and SpringerLink where it was initially obtained. 3646, 6138, 3296 and 2165 results respectively. Subsequently, a filter was carried out by English and Spanish language, where
1919 results were found in SpringerLink, 1674 in Scopus, 1862 in PubMed and 5871 in ScienceDirect. A review of the articles found was carried out, the most current ones were analyzed in a period from 2002-2024 with emphasis on articles from the last 5 years, scientific articles from observational and analytical studies were included, with a total of 37 articles.

**DEFINITION**

Buerger's disease or TAO is defined as a non-atherosclerotic inflammatory vasculitis that affects the small and medium vessels (including arteries and veins) of the lower and upper extremities. Although there are hypotheses about its etiopathogenesis such as the association with exposure to tobacco, few biomedical investigations have been carried out, so its direct causality remains unknown.\(^1\)

**EPIDEMIOLOGY**

Buerger's disease has a worldwide distribution; However, a higher prevalence is observed towards the Middle East and far East than what is reported in North America and Europe. The prevalence of the disease in patients with peripheral arterial disease depends on the place where it is described, in Western Europe it varies from 0.5-5.6% to 45-63% in India, 16-66% in Korea and Japan and 80% In Israel.\(^5\) Although it was considered that the disease was almost exclusive to men under 45 years of age, for several years an increasing pattern has been observed in women, possibly related to the increase in cigarette consumption.\(^1\) On the other hand, not many studies have been documented in Latin America on the prevalence of the disease in this region; there is a descriptive study from 2009 where the epidemiology of primary vasculitis in Colombia was studied and it was observed that Buerger's disease it ranked second with a prevalence of 11.2% after Takayasu disease.\(^6\)

**ETIOPATHOGENESIS**

The etiology of Buerger's disease remains unknown. It has been shown that it can predominantly affect young men under 45 years of age and has a high relationship with smoking and with other substances such as cannabis.\(^7\) Cannabis has classically been linked to a particular disease called cannabis arteritis and had previously been routinely considered a subtype of TAO because the reported cases of cannabis arteritis were mostly men without cardiovascular risk factors with similar symptoms. Buerger's disease such as claudication, Raynaud's phenomenon, absence of distal pulses, subacute distal ischemia of the lower limbs and in more advanced cases distal necrosis or gangrene of the lower limbs and venous thrombosis. However, the greatest difference is found in the anatomopathological examination of cannabis arteritis where a clear acute pattern is not found. However, Sterne and Ducastaingt did studies in late lesions where thrombosis was observed without inflammation of the vascular wall.\(^8,9\)

At the moment, four processes are recognized that are related to the pathogenesis of Buerger's disease: a secondary variant due to atherosclerosis; immunological arteritis; bacterial thrombosis; hyper-homocysteinemia; despite this, a higher percentage of patients have been seen where immune-mediated arteritis is representative according to immunocytochemistry reports where accumulation of immunoglobulins IgG, IgM and IgA is observed in addition to complement factor C4 in the vessel wall and the presence of antibodies. Anti-endothelial cells as markers of immune response against the endothelium, so a special focus is placed on these pathological mechanisms.\(^10\) The existence of autoantibodies has been described in some patients, including anti-endothelial cell antibodies, anti-elastin, and anti-collagen I and III antibodies. Subsequently, the presence of antineutrophil cytoplasmic antibodies (ANCA) was reported, showing a significantly higher level of ANCA in patients with more severe clinical manifestations compared to patients with mild disease and patients without the disease. Additionally, high levels of anti-cardiolipin and anti-beta 2 glycoprotein antibodies were found. However, because fluctuation is observed in these levels, a diagnosis of antiphospholipid syndrome could not be established in these patients.\(^11\) From another pathophysiological point, the interaction of cytokines and chemokines, adhesion molecules, *Rickettsia rickettsii* and *Porphyromonas gingivalis*, angiogenic factors, catecholamines, inflammation of lymph nodes, T lymphocytes, macrophages, dendritic cells and among others was proposed; as possible effectors of the response, higher concentrations of pro-inflammatory cytokines such as TNF-a, INF-gamma, IL-1, IL-6, IL-12, IL-4 were found; in patients with severe form elevations of complement C4.\(^12\) Various studies have shown that oxidative stress favors the dysfunction of endothelial cells with a direct influence on vascular tone by decreasing the availability of nitric oxide, generating a vicious circle in the pathological process because the non-functional endothelium is a direct source of oxidative stress. Oxidative stress has been found to be significantly higher in people with OAD and smoking. On the other hand, a significant increase in intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), which are key regulators of vascular permeability, has been demonstrated in patients with TO, compared to healthy non-smokers.\(^11\) Additionally, in a study carried out by Tamai and collaborators to see the possible participation of NOTCH signaling in the pathogenesis of Buerger's disease, it was observed that certain genetic pathways that produce activation of JAG1 and Notch1 are very active in the endothelium of the vasa vasorum and the cells of the tunica media in patients with Buerger's disease and in some cases of atherosclerosis.\(^13\) In 2022, a meta-analysis was carried out to assess whether plasma homocysteine concentrations had an effect on vascular damage, where they found that despite the scarcity of studies and other limitations in the study, the data are consistent in a participation of the plasma...
homocysteine in vascular damage, however, making it clear that it is unlikely to be genetically triggered. However, they point out that the increase in oxidative stress that accompanies Buerger’s disease, whether mainly due to smoking or not, can inhibit cystathionine B-synthase, the first enzyme that catalyzes the transformation of homocysteine to cystathionine, so it can perpetuate and increase the homocysteine increasing oxidative stress and vascular damage; Therefore, they conclude that elevated homocysteine is more an effect of the inflammation that often accompanies Buerger's disease and is less likely to be a primary cause. The pathological processes of Buerger's disease are not completely defined, but it is proposed to be multifactorial with the predominance of an immune response together with oxidative stress that triggers an inflammatory response and endothelial dysfunction with a procoagulant state (Figure 1).

![Figure 1: Mechanisms involved in the pathogenesis of Buerger's disease.](image)

The processes related to oxidative stress in Buerger's disease are described.

**MICRO-RNA AND BUERGER'S DISEASE**

MicroRNAs (miRNAs) have been studied in relation to different pathologies, recently they have been sought as a possible etiology in systemic vasculitis. Micro RNAs often have almost 22 nucleotides and are responsible for controlling the translation and stabilization of mRNA molecules; They do this through the interaction with proteins by targeting the 3' untranslated regions, which can affect post-transcriptional genetic silencing and in this way, an interruption in the circuit can contribute to the pathogenesis of vasculitis. However, in the case of Buerger's disease the regulatory mechanisms and alterations have not yet been completely defined. In a study carried out by Chen and collaborators, the presence of several regulatory networks that can be associated with the progression of TAO, such as the NEAT1/miR-1-3p/GNA 12 pathway, was demonstrated, in addition to identifying the involvement of 16 miRNAs (3 downregulated and 13 upregulated) that would also have implications in the pathogenesis of the disease. In 2021, a study was carried out with the aim of exploring the effects of exosomal miRNAs associated with TAO in human vascular smooth muscle cells and the presence of 39 miRNAs was demonstrated compared to controls (10 downregulated and 29 upregulated) with particular importance in miRNA 233-5p since the results of the study suggest that the overexpression of this miRNA generates a suppression of the cell viability of vascular smooth muscle cells and, conversely, the suppression of the miRNA 233-5p was related to greater cell viability. However, other molecules have been identified such as miRNA 100, which has an anti-inflammatory function in chronic inflammation, so the hypothesis of its possible activity in TAO was raised through a study where it was demonstrated that the overexpression of miRNA 100 manages to reduce H₂O₂ apoptosis and inflammatory damage in human umbilical vein endothelial cells through the inactivation of signaling pathways that mainly involve the Notch pathway, which could be considered a therapeutic target in the future. miRNAs have not only been studied as therapeutic targets, but they can also be used for diagnosis, as in a study where it was observed that miRNA 155 is overexpressed in patients with TAO, so it may have high diagnostic value, in addition to the implication that this molecule has in the activation of platelets and subsequent generation of thrombosis.

**CLINICAL PRESENTATION**

Buerger's disease is characterized by periods of exacerbation and remission; The manifestations tend to worsen at 30 to 40 years of age with a subsequent period...
of decrease in symptoms and even recurrence is rarely seen in people over 60 years of age. The symptoms presented by patients with Buerger's disease are essentially generated by the stenosis and occlusion of small blood vessels; initially the involvement occurs in small distal arteries and veins, then as the disease progresses it involves proximal arteries (Table 1). When the occlusion is marked, it produces ischemia of the upper and lower extremities, this represented as intermittent claudication initially in the arch of the foot, which is usually an early sign and as it progresses, it compromises the calf until it generates pain at rest, Raynaud's phenomenon, skin color changes, tingling, numbness of the fingers and toes, and ultimately ulcers and gangrene. In severe cases, amputation may be necessary although compared to patients with atherosclerosis it is much less. Death in patients with Buerger's disease is very unusual and is not an expected complication. Patients often present superficial thrombophlebitis, it has been reported that up to 40-60% of cases are migratory, tend to be recurrent and affect arms and legs; In young patients this manifestation is highly suggestive of TAO. Systemic manifestations are not frequently observed in patients with TAO, except for some rheumatic manifestations such as non-erosive arthritis. Although it is not the most frequent, because the disease affects the blood vessels in a general way, involvement of the visceral vessels has been described, producing a varied clinical picture depending on the affected bed, generating various symptoms such as abdominal pain, mesenteric ischemia, chest pain, heart attack, acute myocardium, coronary artery stenosis, hemiparesis, aphasia, hemianopsia, seizures, retinal artery involvement, gangrenous glans of the penis, erythema nodosum in extensors, among others. The main manifestations reported in different studies are summarized in Table 1.

### Table 1: Clinical manifestations of Buerger's disease.

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical manifestations</th>
</tr>
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<tbody>
<tr>
<td>Olin et al&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Initially claudication of extremities, ischemic ulcerations in the distal portion of the fingers. Routinely it almost always involves two or more limbs.</td>
</tr>
<tr>
<td>Malecki et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Intermittent claudication, superficial thrombophlebitis, paresthesias, pain at rest, necrosis, ulceration and Raynaud's phenomenon. Important to take into account an atypical course.</td>
</tr>
<tr>
<td>Vijayakumar et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Signs of arterial insufficiency in the extremities such as intermittent claudication, pain at rest, ulcers or migratory thrombophlebitis. Joint symptoms prior to the classic ones.</td>
</tr>
<tr>
<td>Fakour et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>In addition to the signs of ischemia, they present diffuse abdominal pain, weight loss, hemiparesis, aphasia, cognitive impairment, headache, retinal artery involvement, among others.</td>
</tr>
<tr>
<td>Szydelko-Paško et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Intermittent claudication of the upper and lower extremities, paresthesias, pain at rest, change in skin color up to ulcers and gangrene. Varied manifestations in other organs such as gastrointestinal tract, heart, central nervous system, eye, kidneys, among others.</td>
</tr>
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### DIAGNOSIS

The diagnosis is primarily clinical based on the history, anamnesis regarding clinical manifestations, and a directed physical examination. Now there are no cost-effective and simple tests that guide the diagnosis, since biochemical alterations are usually non-specific, so the request for tests such as serum creatinine, blood glucose, CRP, ESR and certain antibodies such as ANCA and anticiemoterone have more value in ruling out differential diagnoses. It has been described that patients with high antitumour necrosis pateriters are mainly young and report a higher rate of amputations. Malowski and collaborators in a group of 47 patients evaluated between 1990-1996 with Buerger's disease reported high titers of antitumor necrosis antibodies and with the association that the greater their presence there could be a greater tendency to produce thrombosis and therefore more requirements for amputation. However, this is still a topic under study, so its diagnostic and prognostic value remains in doubt. The initial step is usually to exclude atherosclerosis or risk factors for other occlusive vasculopathies; The initial image is usually a Doppler ultrasound as it details the level of occlusion, luminal occlusion and quality of blood flow. Subsequently, tomography or magnetic resonance arteriography can be considered, where lesions have classically been described as corkscrew-shaped collaterals defined as Martorell's sign which denotes changes in the vasa vasorum, presence of segmental lesions or can also be found in occlusions of the distal extremity. For several years, several criteria have been proposed to suspect the disease, such as the Shionoya, Olin, Papa and Mills criteria, (Table 2). However, the most accepted in countries where the disease is more prevalent are the Shionoya criteria, which are preferred in patients where the use of images is not cost-effective. To make the diagnosis, the presence of all 5 criteria is required; however, if all the criteria are not met, the diagnosis can be made if other diseases are excluded and the imaging findings in addition to pathology are consistent with the disease.

Biopsy is not usually indicated initially, only in cases in which the patient presents atypical symptoms, is very old, or when involvement of large arteries is suspected; In this case, the histopathological findings include the presence of an inflammatory thrombus with polymorphonuclear cells and multinucleated giant cells with involvement of arteries and veins.
Table 2: Shionoya and Olin diagnostic criteria for Beuguer's disease.

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Shionoya clinical criteria</th>
<th>Olin criteria</th>
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<tbody>
<tr>
<td>1.</td>
<td>Smoking history</td>
<td>Current or past tobacco use</td>
</tr>
<tr>
<td>2.</td>
<td>Onset before age 50 years</td>
<td>Onset before age 45 years</td>
</tr>
<tr>
<td>3.</td>
<td>Infrapopliteal arterial occlusions</td>
<td>Distal limb ischemia (infrapopliteal or intrabrachial), such as claudication, pain at rest, ischemic ulcers, and gangrene documented with non-invasive testing)</td>
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<tr>
<td></td>
<td></td>
<td>Laboratory tests to rule out autoimmune or connective tissue diseases and diabetes mellitus</td>
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<tr>
<td>4.</td>
<td>Upper limb involvement or migratory thrombophlebitis</td>
<td>Exclusion of proximal source of emboli with echocardiography and arteriography</td>
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<tr>
<td>5.</td>
<td>Absence of cardiovascular risk factors other than smoking</td>
<td>Demonstrate consistent arteriographic findings in affected and clinically uninvolved extremities</td>
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Figure 2: Diagnosis of Beuguer's disease.

*Consider arterial or venous vessel biopsy in atypical presentation, very advanced age or involvement of large arteries.
DIFFERENTIAL DIAGNOSIS

Once Buerger's disease is considered, the differential diagnosis is not very broad, so diseases such as atherosclerosis obliterans, popliteal impingement syndrome and systemic vasculopathies such as systemic lupus erythematosus (SLE) and kidney disease must be ruled out. Behcet. Atherosclerosis obliterans is defined as a chronic arterial disease that produces symptoms of ischemia such as intermittent claudication, pain at rest, tissue loss secondary to obstruction of the arteries secondary to atherosclerosis, for which risk factors are often present. Thus, the presence of risk factors or evidence of an atheroma usually excludes TAO. Popliteal artery entrapment syndrome occurs more in young, athletic people without atherosclerotic risk factors; It is defined as a disorder in which the popliteal artery is compressed by aberrant muscular and tendon structures in the popliteal fossa, which causes intermittent claudication, pain in the feet and calves, mainly after performing physical activity and which resolves when resting or changing positions. SLE is a multisystem autoimmune disease with a multifactorial origin of genetic, sociodemographic, and infectious factors. It is more prevalent in young women and the symptoms are very varied with a significant deterioration in quality of life. Behcet's disease is an inflammatory disorder in which patients present with skin symptoms, oral thrush, ophthalmic lesions, and genital ulcers. Occasionally, they may present vascular alterations such as deep vein thrombosis and arterial occlusion, which is why they may also present ischemic symptoms.

TREATMENT

The fundamental basis of the treatment and the one that has had the best results is the suspension of tobacco consumption, although this alone has not shown evidence of being the solution in all cases. Different pharmacological treatments have been proposed, however, most of them have been inefficient, so the functioning of pharmacological treatment with anticoagulants, thrombolitics, vasodilators and anti-inflammatory agents is still questioned. Among the different pharmacological treatment options, aspirin from the class of non-steroidal anti-inflammatory drugs is described, which blocks the production of the thromboxane A2 pathway, which generates an inhibition of platelets and reduces thrombosis. Cilostazol is usually indicated initially since it acts as a phosphodiesterase inhibitor, which has an additional particular mechanism of action, since it is proposed to reduce the expression of IL-1B, IL-6 and TNF-a, which would have a double effect by impacting its pathophysiology and on the other hand increasing cAMP in platelets and endothelial cells; ioprost is a prostacyclin I2 analogue that generates a vasodilatory effect and is usually indicated in patients with severe ischemia of the lower extremities. In a recent publication in Cochrane, they evaluated how effective intravenous and oral therapies could be, where they found that when the use of aspirin and intravenous ioprost were compared, effective results were obtained in healing ulcers and eradicating pain at rest after 28 days of treatment; However, there was no effect on the amputation rate 6 months after treatment was instituted. Due to the above, other arterial revascularization therapies were proposed, whether surgical or endovascular, sympathectomy and the mobilization and implantation of bone marrow cells, which is usually indicated mainly in the most serious cases. Revascularization therapies are indicated when the patient presents symptoms despite having instituted non-pharmacological and pharmacological treatment. For its part, open surgery is considered a standard strategy to generate revascularization in patients with TAO and advanced limb ischemia; however, its biggest problem is bypass occlusion. Because TAO involves different pathophysiological mechanisms than atherosclerosis, endovascular therapy has been proposed as one of the best alternatives through angioplasty with advantages in terms of high safety, no in-hospital mortality reported, low rate of perioperative complications and late results such as vascular permeability which favored a lower rate of limb amputations. Sympathectomy is indicated in patients who have symptomatic ulcers in the fingers of the extremities and revascularization is not possible.

DISCUSSION

Buerger's disease is a vasculitis of small and medium vessels that has been very little studied and still has little clarity regarding etiology and treatment. It has been seen that it may predominate more in 45-year-old men from the East and smoking is a possible trigger; however, other factors such as cannabis consumption and genetic factors have been raised. Diagnosis continues to be a challenge, since the findings tend to be non-specific or inconsistent with suspicion, which is why it is currently based on ruling out other causes such as atherosclerosis and vasculopathies. With current evidence, there are many types of treatments, both pharmacological and non-pharmacological, with the greatest evidence of results being the suspension of tobacco consumption. The prognosis tends to be good for patients, although it has been reported that up to 70% of patients will experience an ischemic ulcer or necrosis. In some long-term studies it was reported that between 2.7 and 10.5% required major limb amputations; However, in a multicenter study of 224 patients, it was found that 34% of patients may require amputation 15 years after diagnosis. A flow chart is proposed as an algorithm regarding suspicion and treatment (Figure 2).

CONCLUSION

Currently, since there are no definitive and specific management guidelines or protocols for Buerger's disease regarding its diagnosis and treatment, it is essential to strengthen basic research as well as clinical trials to
standardize management in this type of patient, since it is a disease with high impact on quality of life.

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