DENTAL AND MEDICAL JOURNAL - REVIEW

e-ISSN 2667-7288 **Vol** 4, **Issue** 1, (2022) *Review Article / Derleme Makale*

THROMBOANJITIS OBLITERANS (BUERGER'S DISEASE)

TROMBOANJİTİS OBLİTERANS (BUERGER HASTALIĞI)

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Article Info / Makale Bilgisi

Received / Teslim: January 14, 2022
Accepted / Kabul: February 16, 2022
Online Published / Yayınlanma: February 28, 2022
DOI:

ŞAHİN S. Thromboanjitis Obliterans (Buerger's Disease). Dent & Med J - R. 2022;4(1):79-89.

DENTAL AND MEDICAL JOURNAL - REVIEW

e-ISSN 2667-7288 **Vol** 4, **Issue** 1, (2022) ***Review Article / Derleme Makale***

Abstract

Thromboangiitis obliterans (TAO) is a non-atherosclerotic segmental inflammatory disease. It affects small and medium-sized arteries and veins in the upper and lower extremities. Cigarette smoke is the main etiology of the disease. As the rate of smoking increases worldwide, so does the number of patients with TAO. Never treatment modalities have shown promising results. These treatments help in reducing pain, the healing of trophic changes, the increase inpain-free walking distance, decreasing the need for major amputations and an overall improvementin quality of life. However, long-term treatments all fail preventing the diseases' progression in patients who continue to smoke. With the global increase in smoking in mind, a review of current literature on TAO has been carried out with a focus on modern treatments.

Keywords: *Thromboangiitis obliterans, Buerger's Disease, Smoking.*

Özet

Tromboanjiitis obliterans (TAO), aterosklerotik olmayan, segmental inflamatuar bir hastalıktır. Üst ve alt ekstremitelerde küçük ve orta büyüklükteki arterleri ve venleri etkiler. Sigara hastalığın ana etiyolojisidir. Dünyada sigara içme oranı giderek artıyor. Bu oran arttıkça TAO'lu hasta sayısı da artmaktadır. Hiçbir zaman tedavi yöntemleri umut verici sonuçlar vermemiştir. Ağrıyı azaltmaya, trofik değişiklikleri iyileştirmeye, ağrısız yürüme mesafesini arttırmaya, major amputasyonları azaltmaya, yaşam kalitesini iyileştirmeye yardımcı olmaktadır. Ancak uzun süreli tedavilerin tümü, sigara içmeye devam eden hastalarda hastalığın ilerlemesini önlemede başarısız olur. Sigara kullanımının bu kadar hızlı arttığı hayatımızda güncel yaklaşımlarla TAO hastalığını yeniden gündeme getirmenin iyi olacağını düşündük.

Anahtar Kelimeler: *Tromboanjitis obliterans, Buerger hastalığı, Sigara içimi.*

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OVERVIEW / GENEL BAKIŞ

TAO is a non-atherosclerotic segmental inflammatory vascular occlusive disease. It most commonly affects small and medium-sized arteries, veins and nerves in the upper and lower extremities [1]. The first description of a patient with thromboangiitis obliterans was provided by Winewarter in 1879. Leo Buerger gave the first pathological description of the disease in 1908 based on the pathological findings of an amputated leg [1]. Buerger named this disease "thromboangiitis obliterans" and distinguished it from atherosclerosis [1]. He considered acute inflammation and occlusive thrombosis of both arteries and veins to be the characteristic lesions of the clinicopathologic entity [2,3]. Buerger is a disease mainly affecting young individuals under the age of 40, whom show symptoms and signs of progressive and recurrent vascular insufficiency. The disease may result in gangrene and eventually the need for major amputation.

Etiology and Pathogenesis

The etiology of this disease has to this day remained unknown. However, the use of or exposure to tobacco is central to the initiation, maintenance and progression of Buerger's disease [4]. There is a strong correlation between the heavy use of tobacco and thromboangiitis obliterans [5,6]. Additional risk factors for TAO include chewing tobacco, marijuana use and chronic anaerobic periodontal infection.

Histologically, TAO is divided into 3 stages: acute, subacute, and chronic stages [7,8].

In the acute stage, the lumen is occluded by fresh thrombi and intimal thickness with remarkable leukocytes, including neutrophil infiltration. Multi-nucleated giant cells are seen in the thrombi, however necrotizing inflammation or granulomatous lesions are not observed.

During the subacute stage, the lumen is occluded by both fresh and organized thrombus with partial recanalization. Multinucleated giant cells are diminished in the number of thrombi or vessel walls.

Finally, in the chronic stage, the occlusive thrombi are organized and recanalized extensively, thus differing from the acute or subacute stage lesions. Mild cell infiltration is seen in the intima, media and adventitia [8].

Vascular fibrosis and organized thrombus may mimic atherosclerotic disease. However, the infiltrating inflammatory cells are easily recognized, mainly in the intimal layer. In addition, no calcification or hyaline degeneration is found in TAO [9,10]. In atherosclerosis, the general architecture and elastic lamina are destroyed and degenerated and inflammatory cells can be found in any of the 3 layers [11].

While TAO is a type of vasculitis, it is distinct from other types of vasculitis. Pathologically, the thrombus in TAO is highly cellular, with lower intensity in cellular activity in the wall of the blood vessel and a preserved internal elastic lamina. The original pathologic process is thromboarteritis or a thrombophlebitic process. As well as this, TAO differs from many other types of vasculitis in that the usual immunologic markers of elevation of acute-phase reactants (such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)),

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circulating immune complexes, and autoantibodies (such as an antinuclear antibody, rheumatoid factor, and complement levels) are usually normal or negative [11].

The restriction of the immune reaction (both cellular and humoral) to the arterial intima defines TAO as endarteritis. Patients with thromboangiitis obliterans have been shown to have increased cellular immunity to types I and III collagen compared with those who have atherosclerosis [12]. In addition, high titers of antiendothelial cell antibodies have been detected in patients with this disorder [13].

Furthermore in TAO, the expression of plasminogen activator inhibitor -1(PAI-1) in media may inhibit the function of urokinase plasminogen activator (uPA) and matrix metalloproteinase -3 (MMP3), which as a result disrupts and degenerates extracellular matrix (ECMs). This can be related to the preservation of wall structure in vessels affected by TAO.

Prothrombotic and hemorheologic factors may also play a role in the pathophysiology of thromboangiitisobliterans. The prothrombin gene mutation 20210 [14] and the presence of anticardiolipin antibodieare associated with an increased risk of the disease. Patients affected by with high anticardiolipin antibody titers usually show a lower onset age and an increased rate of major amputation compared to patients who do not present detectable antibodies [15]

Clinical Features

TAO usually occurs in young male smokers with the onset of symptoms starting before the age range of 40 to 45 years and manifests as migratory thrombophlebitis in the extremities. There have been case reports showing the involvement of the cerebral, coronary, renal, mesenteric, pulmonary and iliac arteries, as well as the aorta [16,17]. Patients with TAO typically present ischemic symptoms caused by stenosis or occlusion. In the early stages, TAO targets a single limb, frequently progressing proximally and later involving multiple extremities.

TAO is often presented as intermittent claudication of the limbs. Claudication in the arch of the foot is an early sign and is a specific marker of TAO. With more advanced cases of the disease, symptoms can include critical limb ischemia such as rest pain, ulcerations, and digital gangrene. Around 40% of patients are found to also have asymmetrical Raynaud's phenomenon. Studies have also found multiple-organ involvement to be observed [18,19].

Systemic symptoms are very rare in patients. Digestive ischemia may manifest as abdominal pain, diarrhea, weight loss, intestinal perforation, mesenteric infarction, or melena. There have been reports of TAO initially presenting itself as small bowel ischemia and colonic obstruction [20,21].

Central nervous system involvement has been reported in TAO which may present transient ischaemic attacks or an ischaemic stroke. Post-mortem histological examinations have demonstrated inflammation of the small and medium-sized arteries of the leptomeninges or even of the meninges or veins [22].

Laboratory tests and findings

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Currently, no specific laboratory tests for the diagnosis of TAO exist. All serologic profiles should be obtained in order to distinguish TAO from other diseases which may mimic TAO. Echocardiography (two-dimensional and/or transesophageal) and arteriography must be carried out to detect a proximal source of emboli.

Arteriographic findings in TAO are usually confined to the distal circulation and is almost always infrapopliteal in the legs and distal to the brachial artery in the arms. Arteriographic findings may be suggestive for diagnosis. Two diagnostic criteria have been proposed by Shionoya and Olin [23].

We can summarize the diagnosis criteria as follows: (Table1)

-An age lower than 45 years old with a current history of smoking

-The presence of distal-extremity ischemia (indicated by claudication, pain at rest, ischemic ulcers or gangrene)

-Exclusion of autoimmune diseases, hypercoagulable states, and diabetes mellitus

-Exclusion of a proximal source of emboli and consistent arteriographic findings in the clinically involved and non-involved limbs [24].

Table 1: Diagnostic investigation for Buerger's disease.

Blood count	C-reactive protein	Anticentromere antibodies (for CREST syndrome)	Complete thrombophilia screen: proteins G and S, antithrombin III, factor V Leiden, prothrombin and homosisteinemia	Telangiectasia	CREST
Liver function	Antinuclear antibodies	Raynaud's phenomenon	Tomography (to exclude potential sources of emboli	Hand radiographs (to exclude calcinosis)	Esophageal dysmotility
Renal function	Rheumatoid factor	Echocardiography (to exclude sources of emboli)	Biopsy (in proximal artery involvement or unusual locations)	Lipid profile	Sclerodactyly
Fasting blood sugar	Complementary measurements	Antiphospholipid antibodies	Segmental arterial Doppler pressures	Urinalysis	

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Cryoproteins	Anti-Scl-70 antibodies (for scleroderma)	Toxicology screen for cocaine and cannabis	Erythrocyte sedimentation rate	Arteriography	

Treatment

The most effective treatment for TAO is the complete discontinuation of cigarette smoking [26,27]. If the patient manages to give up smoking completely, the disease will go into remission and amputation can be avoided [28,29]. Although quitting smoking is proven to reduce the risk of amputation in Buerger's disease, several other forms of treatments are currently being used [30].

The methods of surgical revascularizing, prostaglandins, thrombolytic, calcium channel blockers, anticoagulation, sympathectomy, adrenalectomy and spinal cord stimulation, omental transfers, stem cell treatment and angioplasty have all been attempted in reducing rest pain and to prevent amputation. However, except for the discontinuation of tobacco use, no forms of therapy are definitive.

The use of aspirin is considered in all patients with peripheric arterial disease but is not currently indicated for the treatment of symptoms of intermittent claudication [31]

Clopidogrel is an antiplatelet agent that has shown to be more potent than aspirin in reducing secondary events in patients with atherosclerotic disease. Despite this, there is no evidence to suggest that the symptoms of claudication are reduced by long-term treatment with clopidogrel.

Vasodilators are used to dilate vessels proximal to the stenotic or occlusive lesion and improve blood flow to that neighboring vascular bed which leads to a steal proximal to the stenotic or occlusive lesion. The use of vasodilators can lead to a reduction in perfusion pressure while reducing overall systemic vascular resistance.

A dihydropyridine calcium channel blocker, such as amlodipine or nifedipine, seems to be effective if vasospasm is present. In a study by Bagger et al., a theory was produced in that the calcium channel blocker has a secondary effect- that of changing the oxygen extraction/utilization capacity [31].

Pentoxifylline (Trental) has a primary usage in increasing the total pain-free walking distance in many, leading to long-term benefits and overall improvement in quality of life.

Cilostazol (Pletal) works by increasing the levels of cyclic adenosine monophosphate (cAMP) in platelets and blood vessels. This treatment causes the inhibition of platelet aggregation and the promotion of smooth muscle cell relaxation. However, numerous side effects can occur with the long-term use of cilostazol. The most common side effects are headaches, diarrhea, bulky stool, and palpitations. Patients on long-term treatment must be evaluated for cardiovascular health and the drug must be discontinued if the patient develops congestive heart failure. Medium-quality evidence suggests that intravenous iloprost (prostacyclin analog) is more effective than aspirin for eradicating rest pain and healing ischaemic ulcers in TAO [32]. On the other hand, results of the European Thromboangiitis Obliterans (Buerger's disease) study show no significant difference between oral prostacyclin derivatives and placebo for the total healing quality of lesions

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[33]. It is evident that iloprost, when used intravenously, alleviates rest pain, improves ulcer healing, and decreases the rate of amputation in TAO [34].

Other drugs used for intermittent claudication are naftidrofuryl (Praxilene), levocarnitine, arginine, buflomedil, ketanserin, niacin, and lovastatin.

There is little information on the use of intra-arterial thrombolytic therapy. A study by Hussein &elDorri was carried out on the use of selective low-dose intra-arterial streptokinase in complicated cases of Buerger's disease of the resulting gangrene of toes or foot [35]. However, the technique has not been shown to be completely safe [35].

Another treatment option is epidural spinal cord stimulation [36]. It has been shown to improve regional perfusion and may also modulate painful stimuli through several mechanisms in patients with thromboangiitis obliterans [37].

Peripheral periarterial sympathectomy is occasionally considered to treat refractory pain and digital ischemia. The role of sympathectomy in preventing amputation or treating pain still remains unclear, and further studies are needed to evaluate this treatment method [38]. Therefore, until now, the preference of the usage of intravenous iloprost over the lumbar sympathectomy is not supported by reliable evidence for its routine use [39].

Omentopexy is a method for the mobilization of omentum but can cause many complications with it [40].

Ilizavor's method involves the use of a tissue-sparing cortical osteotomy-osteoclasis technique that preserves the osteogenic elements in the limbs. It is very effective in inducing neoangiogenesis by stimulating and maintaining the regeneration and the active growth of tissues (such as bone, muscle, fascia, nerve, vessels, skin, and its appendages). This process is named the "law of tension stress" [41]. Ilizavor's method is an excellent and low-cost procedure to heal ulcers, decrease major amputation, reduce rest pain and claudication distance in TAO.

Surgical revascularization is not usually possible for patients with TAO due to the diffused vascular damage and distal nature of the disease [42]. Often times there is no distal target vessel available for bypass surgery.

Aggressive endovascular balloon angioplasty can be an essential option in the treatment of patients with TAO. Soliman et.al. showed positive results in long-term patency with a statistically significant difference in conservative measures regarding ulcer healing, pain, or major amputation [43].

There are many studies with TAO treatment such as autologous bone marrow cell injections [44], cell therapies using bone marrow mononuclear cells (BM-MNCs) and peripheral blood mononuclear cells (PBMNCs) [45,46]. Furthermore, intramuscular injection of granulocyte colony-stimulating factor (G CSF) mobilized CD34+ cells [47], intramuscular injections of vascular endothelial growth factor (VEGF) [48], and bosentan treatment has been investigated as potential treatment options [49].

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Limitations

Since the TAO is still going on, new treatment ideas come up. This review has only covered the major topics related to medical treatment.

SUMMARY / SONUÇ

TAO is a distinct form of systemic vasculitis. It is strongly linked to cigarette smoking. Clinical features and angiography form the main basis of diagnosis. The medical line of treatment with vasodilators, use of pentoxifylline and cilostazol may help improve life quality but can not prevent disease progression. Surgical treatments in the form of revascularization, sympathectomy and omentopexy increase peripheral blood flow and decrease the rate of amputations while helping with the healing of ulcers. Prostaglandins, bosentan and stem cell therapy are yet to show promising results. The keys to reducing patient symptoms are early diagnosis, aggressive therapies, and most importantly, the complete removal of smoking habits.

Acknowledgements / Teşekkür

Declaration of conflicting interests: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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