Original Article

Thromboangiitis Obliterans Or Buerger's Disease: Important Characteristics

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Abstract

Thromboangiitis obliteration (TAO; Buerger's disease) is a relatively rare and obstructive inflammatory disease of peripheral blood vessels, the cause of which has not yet been adequately investigated. The diagnosis is based on clinical criteria such as smoking history, ischemic manifestations in the lower limbs, auto-immune diseases and clotting conditions. Treatment involves both surgical and non-surgical methods. The most important treatment procedure to prevent amputation is complete abstinence from smoking. This paper summarizes the characteristics of the disease, its clinical features, and its diagnostic and therapeutic approaches, with a focus on novel treatment options, such as stem cell-derived therapies.

Keywords: Thromboangiitis obliterans, Buerger's disease, Therapeutic Strategy, stem cells

1. INTRODUCTION

Obliterate Thromboangiitis or Buerger's disease is a non-atherosclerotic inflammatory disease most commonly found in small arteries and veins of the arms and legs . It was first reported in 1879 (Aqel and Olin 1997). Later, in 1908, Leo Burger described patient amputees as pathological (Watanabe, Miyata et al. 2020). Although much progress has been made in diagnosing autoimmune syndromes, the cause of Buerger's disease is not yet clear (Li, Wang et al. 2020). The etiology of Buerger's infection has been thought of to be related with autoimmunity and the impacts of tobacco on the immunity of individual (Ehteshamfar, 2020). Buerger's disease differs greatly from another vasculitis. In this condition, cell thrombosis and inflammation are very severe, but acute stage proteins are generally normal. The disease is globally distributed, but more cases have been reported in Asian countries than in western countries, possibly due to differences in methods of diagnosis. Among all peripheral artery diseases, the prevalence of Buerger's disease in different areas is different(Alwan & Afshari, 2022). The lowest prevalence occurs in Western Europe (0.5-5.6%), with the highest prevalence occurring in India (45-63%), Korea and Japan (16-66%) and Ashkenazi Jews in Israel (80%), respectively (Olin, 2000)(Shanmugam, 2016)(Fazeli, 2020). In the upper east of Iran, the predominance of TAO was accounted for to happen in each 3 of 100,000 individuals(Alwan et al., 2021). Among the distinctive genders, there are extreme contrasts in the predominance of TAO in the Iranian populace (98.7% guys and 1.3% females), which is normal across numerous populaces.

2. CAUSE AND PATHOGENESIS

The causes of Buerger's disease are poorly known. However, tobacco use or exposure to tobacco is very important in the development and progression of the disease (Chapman, Ballinger et al. 2020) And there are strong links between smoking and Buerger's disease (Klein-Weigel, Volz et al. 2016). As a result, the disease is most prevalent in high-smoking countries. In India, people who smoke cigarettes with raw tobacco (Bidis) are at higher risk of developing Buerger's disease. Cases of this disease were also reported among those who did not use tobacco (Abuse, US et al. 2020). While a limited number of researchers believe that the disease may also occur in non-smokers (Rodoplu, Yildiz et al. 2020), most researchers see smoking as one of the most important criteria for diagnosing Buerger in the past or present (Cacione 2018, Nas, Kandemirli et al. 2020).

In a survey of patients with Buerger's disease, patients with the active form of the disease had significantly higher anti-serum endothelial cell antibody titers (1857 units in 237 patients) compared with normal individuals (126 units in 30 patients) and patients in the recovery phase (461 units in 21 people) (Olin 2000). While the measurement of endothelial antibody titer may be considered as an appropriate method to assess disease activity in Buerger patients, further studies are needed to assess the sensitivity and specificity of this test. Individuals with Buerger's disease have altered vasorelaxation of the peripheral vascular endothelium (Igari, Kudo et al. 2017). Vasorelaxation of the peripheral vascular endothelium was studied by measuring the effect of endothelium-dependent (acetylcholine) and endothelium-independent (sodium nitroprusside) vasodilators on brachial blood flow (Akkoca, Usanmaz et al. 2018).

People with Buerger's disease had less blood flow into their arms as a result of acetylcholine than normal people. Even the dilatation of the endothelial vessels in the sick organs of Buerger's patients has been altered. However, in response to sodium nitroprusside, individuals with Buerger's disease showed no significant differences in brachial blood flow compared to healthy individuals. This indicates that the endothelial vasodilatory mechanisms are intact (Bergholm, Leirisalo-Repo et al. 2002). Bollinger's theory is that Buerger's disease is considered inactive collagenosis (Strölin and Kofler 2020). A study found that less than a quarter of patients with Buerger's disease had increased levels of C proteins. As a result, unlike other auto-immune diseases, systemic inflammatory responses are generally not observed in this disease (Dissemond 2020).

A pathological study looked at the morphology and number of inflammatory cells associated with arterial samples from patients with Buerger's disease. One of the most important characteristics of this disease which sets it apart from other vascularity's is the preservation of the internal elastic layer (Shapouri-Moghaddam, Modaghegh et al. 2019). At the acute stage of the disease, the first population of cells infiltrated into the internal lamina is made up of CD3+ T-cells with an equal number of CD4+ and CD8 cells. The second cell population consists of macrophages that are most common in thrombus and bones. CD20+ lymphocytes and dendritic cells are less frequent in acute lesions, environments, and adventitia, and are generally located in the intima. In the chronic stage of the disease, the predominant cells are CD20+ and a smaller population of CD3+ cells, macrophages, and dendritic cells are found (Ehteshamfar, Afshari et al. 2020).

In immunological studies, endothelial cells play a critical role in early and persistent inflammatory responses. The level of adhesion molecules such as VCAM-1, endothelium- 1, ICAM-1, P, L, and E-selectin increases in endothelial cells in patients with Buerger's disease (!!! INVALID CITATION !!! (Maruotti, Cantatore et al. 2008, Joviliano, Song, Ji et al. 2018, Wu, Sun et al. 2018)). Cytokines controlling inflammatory processes such as TNF, IL-6, IL-10, and IL-12 are also increasing (Slavov, Stanilova et al. 2005, Keramat, Sadeghian et al. 2019). In Buerger's immune response, an increase in leukocytosis independent of C proteins, decreased The lymphocytes and HLA-DR expression in B lymphocytes (Shapouri-Moghaddam, Mohammadi et al. 2019).

The effect of anti-neutrophilic cytoplasmic antibodies (ANCA) on the course of Buerger's disease has not been agreed upon. Some studies reported no ANCA (Zheng and Wang 2020), while others reported ANCA in patients. Patients with Buerger may be isolated from atherosclerotic disease through ANCA. Besides, the elevated level of endothelial cell antibody (AECA) in patients with Buerger supports the hypothesis of an allergic-hyperallergic immune reaction in these patients (Kwok, Seo et al. 2007).

One reason why prothrombotic factors are studied in patients with Buerger is the presence of thrombus in the arteries. A study investigated mutations related to hereditary thrombophilia in patients with Buerger's

disease. The presence of this mutation has been found to increase the relative risk (RR) of illness by 8.0 (SAPIAN, RACZKOWSKA et al.). In another study, prothrombotic factors were investigated in patients with Buerger, and prothrombin and XIII mutations were more frequent in the disease than in the general population (Brodmann, Renner et al. 2000). In general, the interaction of many factors plays a role in the etiology of Buerger's disease, including genetic susceptibility, smoking/exposure, and responses to immune coagulation (Figure.1).

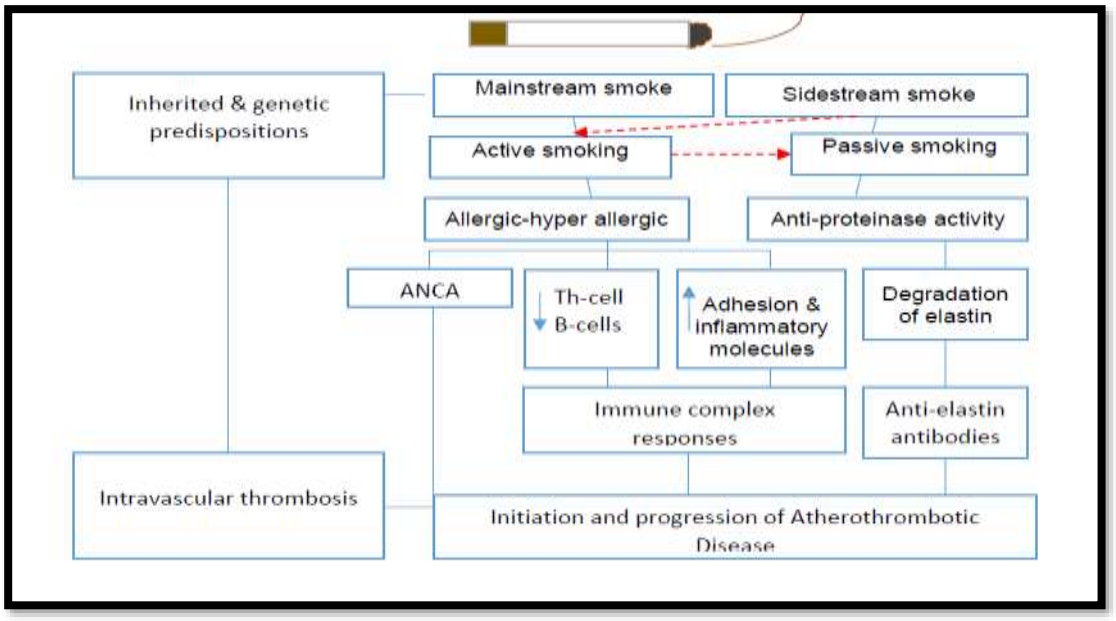

Figure.1. The interaction between genetic sensitivity, smoking/ exposure, and immune responses in the etiology of Buerger's disease

3. PATHOLOGICAL FINDINGS

The histopathological diagnosis of Buerger's disease is dependent on the duration of the disease and can usually be made in an acute stage. Because in the chronic stages, blood vessels develop thrombosis and fibrosis (Shionoya 1998).The histopathologic characteristic of the early-stage disease is obstructive inflammatory cellular thrombosis. At the middle stage of the disease, thrombus appears in the arteries and veins. In general, at every stage of the illness, the structure of the vessel wall remains healthy and normal (Figure.2).

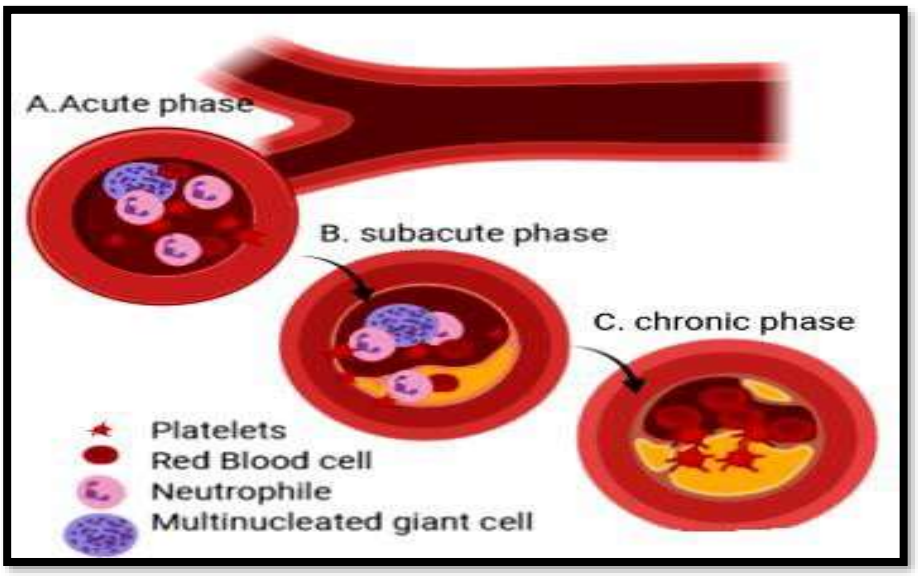

Figure.2. Histopathological stages of Buerger's disease. The histopathology of the blood vessels varies according to the stage of the disease. Histopathological diagnoses of the disease generally occur at the acute stage. The histopathology of the blood vessels varies according to the stage of the disease. Histopathological diagnoses of the disease generally occur at the acute stage. There are three stages in the histopathology of the disease: acute, sub-acute, and chronic phase. A. Acute phase: involves obstructive thrombosis with inflammatory cells. Neutrophils and multinucleated giant cells are often found around the margin of the thrombus. The presence of giant multi-nucleated cells is a feature of this step. B. Sub-acute phase: Inflammatory thrombosis occurs in the injured arteries and vessels. The vessel wall is mostly healthy. C. Chronic phase: Vascular fibrosis takes place.

This distinguishes Buerger's disease from other types of systemic vasculitis and atherosclerosis, where there is a significant disturbance of the artery wall (Sain, Bansal et al. 2020).
Although a characteristic of Buerger's disease is damage to the small and medium arteries and veins of the hands and feet, it has also been reported in many vascular beds. Brain, coronary, renal, mesenteric, aortic, pulmonary, and iliac artery damage have also been reported (Isobe, Amano et al. 2020).

4. CLINICAL FEATURES

Buerger's disease generally affects 40- to 45-year-old men who smoke. Various studies have reported a prevalence of 10-20% of illness among women (Olin, Young et al. 1990, Ariffin, Idris et al. 2019). The appearance of Buerger's disease is linked to ischemia of small arteries and distal arteries, and Large vessels are rarely present (Soliman, Mowafy et al. 2020). Patients may suffer from claudication in peripheral organs. This can be mistaken for an orthopedic problem. But as the disease progresses, the calf claudication causes ischemic pain at rest and ultimately ischemic wounds on the fingers and toes (Figure.3).

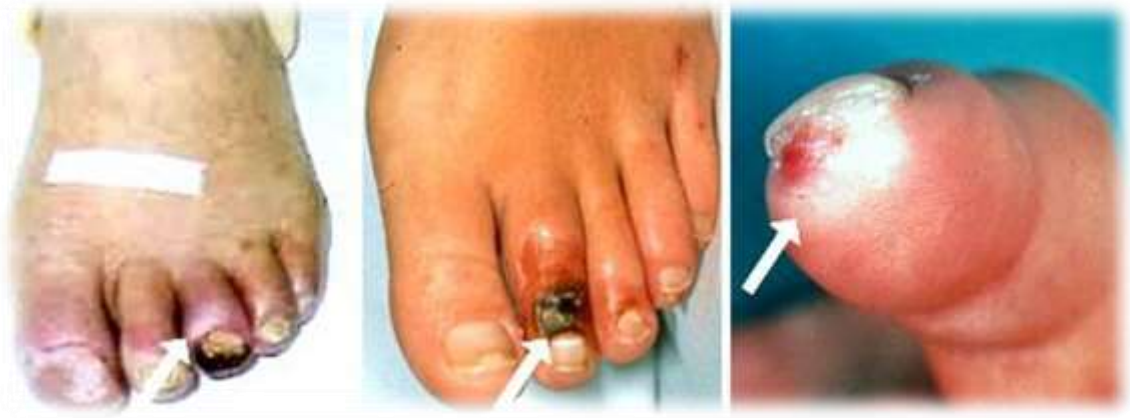

Figure.3. Ischemic injury of fingers and toes.

In a study of patients with Buerger's disease, 76 percent of patients had ischemic ulcers at the time of the exam (Olin, Young et al. 1990). Another study found that more than one limb was found in all patients with Buerger's disease and that two organs (16%), three organs (41%), and four organs (43%) were also found in the disease (Olin 2000). Therefore, for patients with limb disorders, it is recommended that an arteriogram be taken with two hands, two feet, and four limbs to avoid the possibility of other limbs being affected (Nas, Kandemirli et al. 2020).

However, it is not uncommon to see arteriographic abnormalities in organs that have not yet been clinically implicated. To assess the risk of Buerger's disease in people who have foot ulcers, the Allen test is conducted to assess blood flow in the hands and fingers (Agarwal, Agarwal et al. 2020). Among young smokers with foot ulcers, Buerger's disease is most likely to be suggested if an abnormal result is obtained by an Allen test. The distality of Buerger's disease and the damage to the legs and arms differentiate her from atherosclerosis (Figure.4).

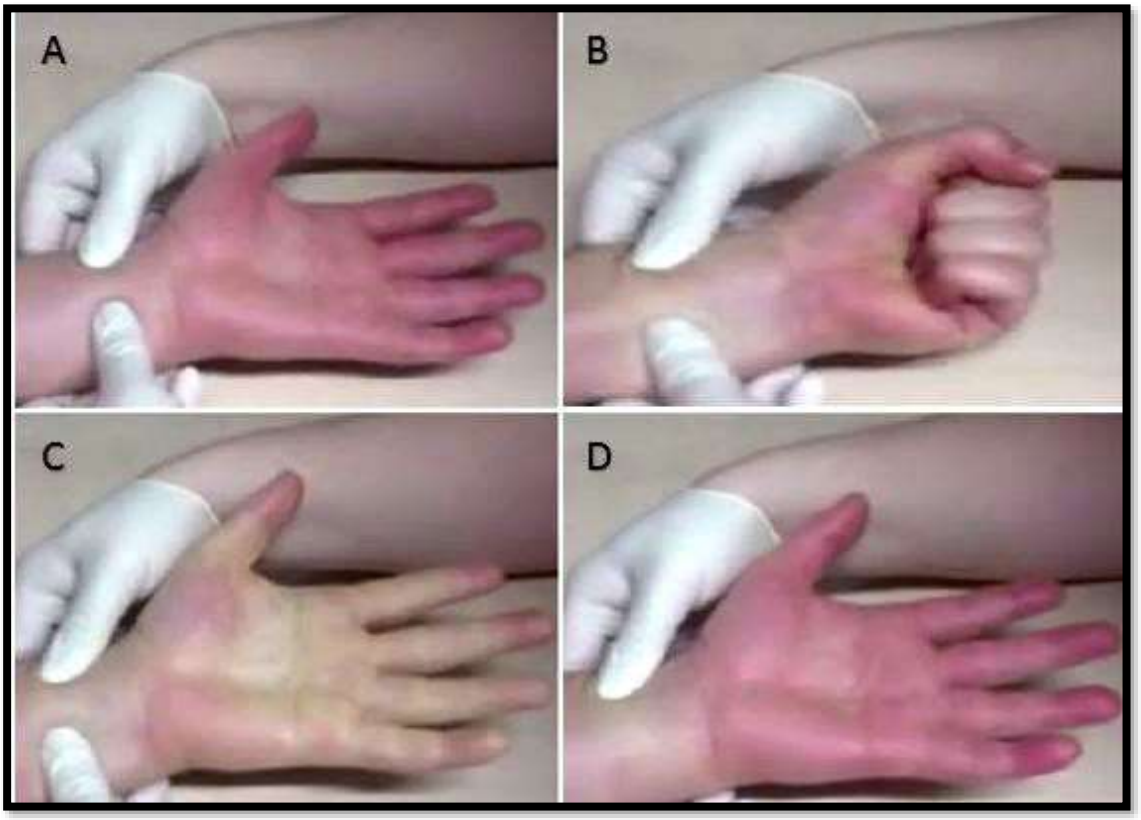

Figure.4. Allen test (A) the two ulnar arteries are contracted in the proximal fold of the wrist.
(B) When squeezing the two vessels, the person must open and close the hand 10 times.
(C) Following the opening, the palm is white. (D) The ulnar artery is cleared (Barner 2008).

5. LABORATORY AND ARTERIOGRAPHIC FINDINGS

At present, there are no specific tests for the diagnosis of Buerger's disease. For the laboratory diagnosis of this disease, it is necessary to develop a comprehensive serologic profile which includes a full number of different blood cells; a hepatic function test; Kidney; urine; fasting glucose; acute phase reagents; anti-nuclear antibodies, rheumatoid factor; CREST markers of scleroderma, and clotting tests are needed (Lazarides, Georgiadis et al. 2006).
Features of Buerger angiography include involvement of small and medium-sized arteries and digital arteries of the fingers and toes, segmental occlusion lesions, more severe distal arteries, normal proximal arteries without signs of atherosclerosis, collateralization around obstruction areas, and lack of an obvious source of emboli (Olin 2018). In Buerger's disease, arteriographic results are not diagnostic because they may be similar to scleroderma, CREST, systemic lupus erythematosus, rheumatoid vasculitis, joint connective tissue disease, and anti- phospholipid antibody syndrome (Michelotti, Rizzo et al. 2015).

6. DIAGNOSTIC CRITERIA

There are several criteria to diagnose Buerger's disease. For example, scoring systems which have different criteria of angiography, histopathology, and clinical (Papa, Rabi et al. 1996, Le Joncour, Soudet et al. 2018). In the scoring system (Table 1) (Małecki, Zdrojowy et al. 2009), if the patient has 6 points or more, the diagnosis is definitive, if he is 4-5 - probable, if he is 2-3 - suspect, and if he is 1 or less, the diagnosis is negative (Papa, Rabi et al. 1996). The main clinical criteria for Shionoya include a history of smoking, onset before

the age of 50, infrapopliteal arterial obstruction, arm injury or migraine phlebitis, and the lack of risk factors for non-smoking atherosclerosis. In rare cases, such as major arterial damage or in people older than 45 years, sampling is required.

In general, and taking into account the research conducted, useful criteria include the following: Age less than 45 years; Smoking; Presence of ischemia of the extremities; Lack of autoimmune diseases, coagulation, and diabetes; Removal of a proximal source of mobilization by echocardiography and coronary artery disease (Soudet, Le Joncour et al. 2020). An effective factor in diagnosing Buerger's disease is arteriography. Medium and small arteries, distally located in the elbow and/or knee, generally change and sudden obstructions with segmental lesions are observed. But before the vascular obstruction propagates(Ahmed & Jalil, 2022), the shape of the corkscrew (known as Martonell's sign), formed as collateral, also known as "tree roots" or "spider legs" (Suzuki, Mine et al. 1982). (Figure.5).

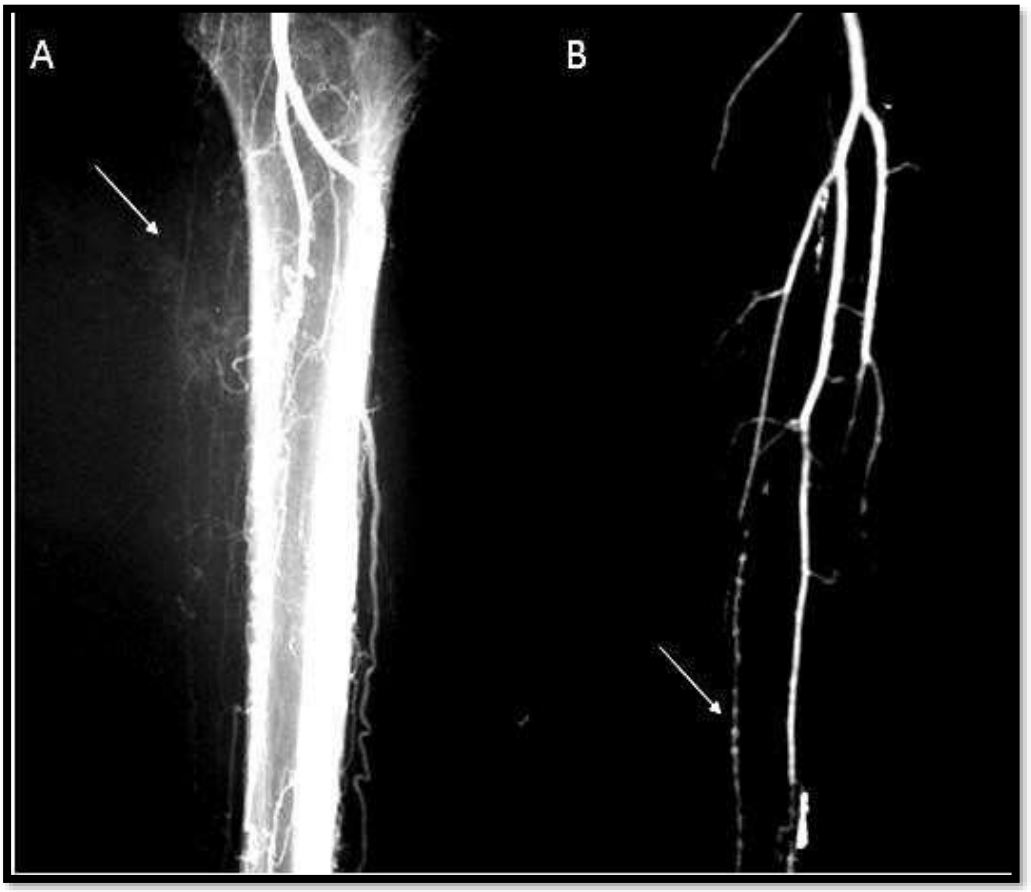

Figure.5. Left lower extremity arteriology. Collateral vessels in the shape of

(A) root and

(B) corkscrew (Del Conde and Peña 2014).

Table.1. diagnostic criteria of Olin, Shionoya and Papa (Shionoya 1998, Olin and Shih 2006).

	Positive criteria (+2/+1)	**Negative criteria (-1/-2)**
Age (years)	< 30; 30-40	
claudication	current/by history	-
Upper extremity involvement	Symptomatic/asymptomatic	-
Migrating superficial vein thrombosis	current/by history	-
Raynaud syndrome	current/by history	-

Angiography	biopsy Both typical/either	-
Location	-	Single limb/not in lower extremity
Absent pulses	-	Brachial/femoral
Arteriosclerosis, diabetes, hypertension, hyperlipidemia		Discovered later 5–10/2–5 years
Sex, tobacco use	-	Female/nonsmoker
Age (years)	-	45-50;> 50

7. TREATMENT

7.1. SMOKING CESSATION

Quitting smoking is the best treatment for this disease, which prevents the disease from progressing and ultimately amputation (Kiruba, Koranga et al. 2020). Tobacco use in all its forms (including chewing tobacco and nicotine replacement) causes the disease to progress. Therefore, these patients should stop smoking completely and not use other compounds and also not fall into contaminated environments. In individuals claiming to have quit smoking but presenting with serious symptoms, nicotine metabolism products can be detected in their urine. A prospective study shows that tobacco addiction in people with Buerger's disease is as high as in other patients with coronary heart disease (Hamid, Salam et al. 2016). Quitting smoking is also affected by socio-economic conditions, mental health problems and drug use (Imtiaz, Hossain et al. 2020). Therefore, it is important to reassure patients that their symptoms improve after quitting and that they do not have to have an amputation. Stopping smoking prevents amputation in more than 90% of patients, but causes amputation in more than 40% of people who do not quit (Olin 2000, Bhukebag 2006).

7.2. PROSTANOID THERAPY AND ANTIPLATELET DRUGS

One of the best treatments for the acute stage of the illness is the use of prostanoids. Several prospective studies investigated the effects of prostanoid compounds on aspirin, sympathectomy, and cessation of tobacco use (Rodoplu, Yildiz et al. 2020). Iloprost, an analog of prostaglandin, is the drug of choice. In a prospective, randomized, double-blind study, a 6-hour daily injection of the prostaglandin analog (Iloprost) was compared to aspirin. Only six percent of patients had a limb amputation. Consequently, it was useful for ischaemic patients during the quitting period (1998). However, in the next study, which included 319 patients, this result was not observed. The study took iloprost orally (Bozkurt, Köksal et al. 2006).

In another study, 158 patients were categorized as iloprost or lumbar sympathectomy. Pain reduction and wound healing were observed in more than 60% of patients treated with iloprost. During the study, the patient's injury size, pain, and clinical condition improved significantly (Bozkurt, Cengiz et al. 2013). In general, the oral composition of iloprost had no significant clinical effect in comparison with the injectable type. But has been more effective than lumbar sympathectomy. A study published in Cochrane investigated the quality of drug therapies in Buerger's disease (Cacione, Macedo et al. 2016, Cacione, Macedo et al. 2020). Another prostanoid called Alprostadil Alfadex, an E1 prostaglandin was effective in the treatment of Buerger (Vietto, Franco et al. 2018).

Although the use of prostanoids is recommended for the treatment of patients with ischemic vital organs by TASC II and ACC/AHA, and prostanoid injections are preventing the disease from spreading to people with more distal obstructive lesions. But it doesn't mean they're fully effective and some experiments have found them to be ineffective.

7.3 ANALGESIA

Patients with Buerger's disease generally suffer from severe ischaemic pain. Therefore, the use of analgesics is essential. Morphine-containing compounds and high-dose sedatives are commonly used to reduce pain. Anti-depressants, epidural anesthesia, and neuro- blockers are also used (D'Souza, Shen et al. 2020).(weigel2016)

7.4 REVASCULARIZATION PROCEDURES

As a rule of thumb, the distal nature of the disease limits vascular surgery in these patients. Because the distal vessel is not available and there is a high risk of rejection of coronary artery bypass grafting (CABG). However, in the case of acute ischemia, an autologous vein has been used in bypass surgery (Lee, Choi et al. 2018, Soliman, Mowafy et al. 2020) and about 4.6-17.7% revascularization rates have been –reported. These figures were reported in more specialized centers with more establishments, between 5 and 48 percent for 5 years and between 56 and 43 percent for 10 years (Sain, Bansal et al. 2020).

7.5. SYMPATHECTOMY

Due to difficulties in vascular surgery, surgical or chemical sympathectomy is often selected. In a study involving 216 patients, sympathectomy was found to be more effective than open surgery or CABG. Clinical findings of sympathectomy revealed an improvement of 52.3%, 27.8% unchanged, 19.8% disease exacerbation, and 19.19% amputation. According to some reports, lumbar sympathectomy is not as effective as injecting ilopraste68. Therefore, despite the widespread use of sympathectomy, no documented evidence exists on the effect of sympathectomy on Buerger disease (Klein-Weigel, Volz et al. 2016, Li, Wang et al. 2020).

7.6. PROGENITOR CELL THERAPY

Several studies have reported that cell therapy has a beneficial effect on ischemia in vital organs. Besides, patients with Buerger's disease responded better to cell therapy than patients with peripheral arteriosclerosis (Matoba, Tatsumi et al. 2008, Moriya, Minamino et al. 2009, Kinoshita, Fujita et al. 2012, C Dash, Peyvandi et al. 2020). In patients with Buerger's disease, cell therapy with bone marrow and peripheral blood mononuclear cells has shown effective results. Autologous injection of bone marrow cells into ischemic organs has shown beneficial effects (Ishida, Ohya et al. 2005). In a study to treat 42 patients, peripheral blood mononuclear stem cells were used and symptoms of recovery were observed in more than 60% of patients (Małecki, Zdrojowy et al. 2009, Moriya, Minamino et al. 2009, Kinoshita, Fujita et al. 2012). Also in 17 patients, CD34 cells were injected intramuscularly. 12 weeks after cell therapy, pain and wound size improved in all patients (Amann, Luedemann et al. 2009).Transfer of the gene from the vascular endothelial growth factor to muscle cells reduced pain and healed wounds (Shimamura, Nakagami et al. 2020). Endothelial progenitor cells (EPCs) are bone marrow mononuclear cells which are identified by CD34 and AC133 (MNC) surface markers and have the ability to differentiate into mature endothelial cells (Wang, Li et al. 2014, Yanishi, Shoji et al. 2020). The compounds G-CSF, GMCSF, vascular endothelial growth factor, estrogen, and tissue ischemia cause EPCs to enter the peripheral blood. The EPC migrates into areas where the arterial injury is present and help to blood vessel repairs (Friedrich, Walenta et al. 2006). In one study, vascular endothelial growth factor (VEGF) was injected intramuscularly to patients (Bobek, Taltynov et al. 2006, Nolfi, Behun et al. 2020) and improved ischemic sore in participants.

Adipose tissue is the ideal source of mesenchyme stem cells (ATMSC). These cells are similar to bone marrow stromal cells (BMSCs)(Suzuki, Fujita et al. 2015). They are also able to differentiate into endothelial cells (Kishimoto, Inoue et al. 2020). In one study, ATMSC was injected intramuscularly into 15 patients which resulted in clinical improvement in 66.7% of patients (Tsuji, Rubin et al. 2014).

People receiving bone marrow cells show an appropriate therapeutic response after a 4- to 8-week period

and this period is problematic when there is serious ischemia. Extensive research is needed to evaluate the long-term benefits of using stem cells (Vijayakumar, Tiwari et al. 2013).

7.7. IMMUNOADSORPTION

The use of the immune absorption (AI) method in many immune diseases has been approved to purify plasma from active antibodies. During the AI, the patient's plasma will be cleaned for five consecutive days for five to six hours(Mohammed Alwan et al., 2022). In treating the Buerger's disease, AI could be successes.100 this can be caused by the suppression of the vasoconstrictive α- and endothelin receptor agonist antibody which increase in the disease (Klein-Weigel, Köning et al. 2012, Klein-Weigel, Volz et al. 2016).

7.8. BOSENTAN

Endothelin-1 is elevated in Buerger patients' serum. In a survey of 13 patients, bosentan was used as an oral endothelin antagonist at doses of 65 and 125 mg and patients showed improvement of 92% (López de Maturana, Rodriguez et al. 2013).

7.9. PLATELET INHIBITORS

Aspirin is used for the prevention of side effects of Buerger's disease. Aspirin should not be prescribed in case of intermittent coagulation. Clopidogrel has been shown to be more effective than aspirin in atherosclerotic patients (Darnige, Helley et al. 2010).

7.10. DILATOR

When using the vasodilator, Systemic vessel strength decreases, the vessels next to the lesion are dilating, the arterial blood circulation Improves and the circulation system's getting better. Therefore, it reduces the bloodstream to the distal ischemic tissue. In case the vasospasm is present, a dihydropyridine calcium channel blocker such as amlodipine and nifedipine may be effective (Rodoplu, Yildiz et al. 2020). During a study, 44 Buerger patients participated and they were treated with a higher dose of verapamil. The results showed that 29% of individuals had less pain over longer distances. Calcium inhibitors have been shown to increase oxygen intake in the body. Pentoxifylline compounds, as a derivative of methylxanthines, increase red blood cell deformation, Reduces the viscosity of the blood. Also, it inhibits platelet aggregations and reduces levels of fibrinogens (Vijayakumar, Tiwari et al. 2013, Baran, Durdu et al. 2019). Cilostazole increases the level of cAMP in platelets and blood vessels inhibits platelet aggregate and loosens smooth muscle cells (Lee, Wu et al. 2020). Laparoscopic sympathectomy is used for the reduction of arterial spasms in patients with Buerger's disease (Nesargikar, Ajit et al. 2009, Conte, Bradbury et al. 2019). Spinal cord stimulator (SCS) regulates the pain mechanism in several ways. It also prevents peripheral blood vessels from contracting. The compounds include nitric oxide and aminobutyric acid (Vyshka 2011). SCS was used to study Buerger patients and it recovered the injuries and avoided amputations (Donas, Schulte et al. 2005, Saini, Shnoda et al. 2020). According to results from another study, SCS should be considered as a last resort for pain control (Fabregat, Villanueva et al. 2011). Vasoactive medications are not adapted to life- threatening ischemia patients.

8. CONCLUSION

Buerger's disease is vasculitis that involves the small and medium arteries and blood vessels of the limbs, and rarely the visceral and cerebral arteries. The diagnosis relies on the presence of a segmental thrombotic inflammatory obstruction and presents a histopathology different from atherosclerosis or necrotizing vasculitis. he illness is normally found in the infrapoplar and infrabrachial conduits of smoking youth. There are no fully accepted diagnostic criteria and quitting smoking is the only effective treatment for the disease (Kondo, Nakano et al. 2019, Kiruba, Koranga et al. 2020).

The illness is characterized by unpredictable periods of recovery and recurrence which may even result in idiopathic death at the age of 45-50. A major cause of relapse is tobacco use. Ratschof's (1934) theory states that the allergic and hyperergicimpact effects of smoking in Buerger's disease remain the leading cause of Buerger's disease (Małecki, Zdrojowy et al. 2009).

According to a recent literature review, the purpose of this review is to highlight some of the novel characteristics of treating this disease. In general, treatment with vasodilator

compounds may reduce pain, but the progression of the disease is not controlled. Surgical treatments also assist in increasing peripheral blood circulation and reducing amputation. Treatment with prostaglandin compounds, bosentan and using cellular therapy showed promising results. Currently, prostanoid compounds are mainly used to prevent the disease. And more studies are needed on anticoagulants.

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