INTRODUCTION

Thromboangiitis obliterans (TAO) or Buerger’s disease is an uncommon but not rare relapsing-remitting, segmental, inflammatory, occlusive, peripheral vascular disease with an unknown etiology which can lead to multiple amputations and limb loss [1]. TAO usually occurs in young male smokers from the low-income segment of a society [2], and it is more prevalent in the Middle East, Far East, Southeast Asia, Eastern Europe and potentially southern America, according to several publications regarding TAO with a considerable sample size from southern America [1]. The disease is more prevalent in men than in women [3], but there is no evidence that the disease is more benign in women and there is no difference in clinical presentation of the disease in male and female patients [4].
The aetiology of TAO remains unknown [2]. However, the close relationship between smoking and TAO has been emphasised since early after the definition of the disease [5]. It has been implied that favourable prognosis cannot be expected unless the patient stops smoking and that patients who continue smoking may undergo several amputations and experience limb loss [1,5,6]. Recently, the effects of tobacco use on the functions of platelets, leukocytes, and the vascular endothelium as the main components of thrombosis, inflammation, and vascular tone have been demonstrated [3]. This combined evidence has pointed to smoking as the main aetiology of TAO for many years and, since 1986, TAO has been called ‘smoker’s leg’ in Germany [7].

Nonetheless, it is still unknown why, amongst millions of smokers all around the world, only a small number develop TAO. It is also unknown why, of TAO patients who continue smoking, only half [6,8] show aggravation and undergo amputations or experience limb loss. The aims of this review are to investigate evidence in support of or against the relationship between TAO and smoking, and to discover the possible role of smoking in TAO pathophysiology.

HISTORY

In 1908, Leo Buerger reported the details of clinical manifestation and vascular pathology of a group of cases then called ‘spontan-gangran’ by German physicians or ‘endarthritis obliterans’ by Von Winiwarter. Buerger’s report was based on observing the clinical presentation of 30 patients and a histology evaluation of 11 amputated limbs [9]. According to histological findings, he suggested the term thromboangiitis obliterans for the disease. At the time of his report in 1908, Buerger had no idea about the causes of extensive thrombosis of the arteries and veins, but he suggested external influences such as ‘toxic conditions of blood’ [9]. He also implied that syphilis may play a role in the production of vascular lesions in TAO, although he could not demonstrate Spirochete Pallidum in any of the histology section [9].

Notably, in 1913, Weber called TAO ‘non-syphilitic arteritis obliterans’ and indicated that most of his patients had been employed in cigarette factories, and tobacco-smoking might be suspected of being a contributory factor [10].

In 1914, Lilienthal emphasized the relationship between smoking and TAO [5]. Meyer, in 1916, concurred that TAO is caused by tobacco use, but he found that the clinical manifestation of TAO was no different in heavy smokers (e.g., 70–80 cigarettes per day) in comparison with patients who were not tobacco-addicted (i.e., using spontaneously) [11].

In 1924, Leo Buerger considered tobacco smoking a predisposing factor for developing TAO [11]. However, he clarified that tobacco may make the vessels susceptible to a special agent, such as a toxic or infectious agent, but that tobacco cannot be the only cause of TAO [12]. Only a few years later, in 1927, Silbert called TAO Buerger’s disease and stated that he had never seen a patient with a diagnosis of TAO who was not a habitual smoker [13].

In 1928, Allen and Brown found that only three out of two hundred TAO patients were totally non-smokers, in comparison to the control group of sex- and age-matched patients with other diseases. However, the authors warned against jumping to a hasty conclusion that smoking is the cause of TAO and merely pointed out that smoking is more common in TAO patients [14].

In 1931, Barker studied the records of 350 TAO patients and suggested that nicotine plays a role in TAO relapse [14]. He also found that TAO patients who stopped smoking improved much faster than those who continued smoking. In addition, he noted that the severity of TAO is greater in heavy tobacco users than in non-users or moderate tobacco users [15].

The suggestion that prolonged vasoconstriction due to tobacco use for a considerable period of time affects peripheral arterioles, capillaries, and venules was offered by Maddok in 1933 [12]. He further emphasised that smoking can make changes in the peripheral arteries and veins because of poor nutrition of the vascular wall resulting from vasoconstriction of the vasa vasorum. Maddok implied that the vasoconstriction effects of tobacco smoking can diminish the benefits of all conservative treatments. Then, in 1938, Horton reported that 7% of his TAO patients were non-smokers [16]. In 1943, Homans emphasised that the disease persists or aggravates in patients who fail to stop smoking [16].

As a result of his study of 100 TAO patients with long-term follow-up [5], in 1945, Silbert stated that TAO could be completely ‘arrested’ with smoking cessation. He implied that tobacco use is the ‘sole’ factor associated with both occurrence and progression of TAO and he reported that 50% of the patients who continue smoking underwent amputation [5]. Silbert further stated that a diagnosis of TAO cannot be made in non-smokers. However, he also implied that, amongst millions of smokers, only a few develop TAO. Silbert concluded that
a special sensitivity of the blood vessels to tobacco must be present to develop TAO [5].

As late as 1947, de Takats suggested diagnostic criteria for TAO that did not include tobacco use [17]. However, in 1953, Richards suggested adding tobacco smoking and male gender as supportive criteria for TAO diagnosis [18]. In 1960, Wessler et al. offered the opinion that there is no clear correlation between TAO and smoking. They reached this conclusion based on the fact that the disease does not progress in all TAO patients who continue smoking and because disease progression in a particular patient cannot be predicted. Wessler et al. claimed this clinical evidence was the same as for heart disease and atherosclerosis [19]. Finally, in 1980, Shionoya presented diagnostic criteria for TAO including smoking; these criteria were universally accepted [20]. From that point forward, other suggested diagnostic criteria included smoking as one of the main criteria for TAO diagnosis [21–23]. However, in 1986, Lee suggested that smoking is a necessary but not sufficient cause for developing TAO [24].

TOBACCO USE AND TAO

EPIDEMIOLOGY

It has been implied that TAO is more common in countries with a higher rate of smoking, such as the Middle East and India, than in North America and Western Europe [25]. Notably, according to the report by the World Health Organization (WHO) on the prevalence of tobacco use in 2015, the mean percentage of smokers in Western Europe, including Belgium, France, Germany, Luxembourg, the Netherlands, and Switzerland, is 27.93%, and in the United States it is 19.5% [26]. The data regarding the prevalence of tobacco use in other countries in Western Europe has not been known in the WHO report in 2015 [26]. The mean prevalence of tobacco use in Middle Eastern countries including Egypt, Iran, Turkey, Saudi Arabia, Israel, Jordan, Lebanon, Oman, and Bahrain as recorded in 2015 is 40.6%, and in India it is 20.4% [26]. Data regarding the prevalence of tobacco use in other Middle Eastern countries is not readily available in 2015 [26]. Additionally, a study in Poland demonstrated a decrease in the incidence of TAO as well as the diagnosis of more cases of TAO in women after 1995, parallel with a reduction in the prevalence of male smokers after 1995 and a relative increase in female smokers in Poland [27].

In the United States, the prevalence of TAO patients at the Mayo Clinic declined from 104 to 13.5 per 100,000 patients from 1947 to 1987 [28]. During this same time, the prevalence of smokers in the United States between 25 and 45 years of age also declined from 63% to 35.6% [29,30]. However, the steady decline in the prevalence of smoking does not run parallel to the sharp decline in the number of TAO patients (Figure 1) and, notably, the number of TAO patients slightly increased between 1976 and 1987, whereas the prevalence of young smokers decreased during that time [28,29]. Moreover, only 11% of the registered TAO patients at the Mayo Clinic in 1987 were female [4]. The prevalence rates of male and female smokers in the United States between 1985 and 1990 were 32.6%/28.4% and 27.9%/22.8%, respectively [29]. On the other hand, TAO was reported to be eight times more prevalent in males than females, a ratio not in parallel with the prevalence of smokers in each gender.

DIFFERENT TYPES OF TOBACCO USE

It has been implied that TAO can also be developed in smokeless tobacco users and that the substitution of chewing tobacco for cigarette smoking cannot prevent limb loss in TAO patients [31–33]. Moreover, passive smoking can keep TAO active or even aggravate the disease [32, 34]. Owing to the fact that TAO is more common in countries such as India or Bangladesh, where smokers usually smoke unprocessed and filterless cigarettes [35] and where TAO is less reported amongst cigar and pipe users [36], the quality of the cigarettes may contribute to TAO development. Rahman et al. demonstrated that 65% of the TAO patients in their study smoked filterless and handmade cigarettes (known as bidi cigarettes, or bidis), which compared to 30% of smoker patients admitted to their hospital for other causes [37]. However, Jindal and Patel implied that the higher prevalence of bidi smokers amongst TAO patients in India is secondary to the low socioeconomic status of...
such patients [38]. On the other hand, Jindal and Patel implied that TAO development may be related to malnutrition as a consequence of low socioeconomic status and not precisely to the quality of cigarettes [38].

In addition, several studies have suggested that TAO patients should avoid nicotine patches as a means of smoking replacement, because nicotine patches can induce vasoconstriction or vascular hypersensitivity and keep the disease active [28,39,40]. However, in 1992, when humoral response and cellular sensitivity to tobacco glycoprotein antigen were evaluated in TAO patients, healthy smokers, and non-smokers [41], no significant difference in humoral response was observed amongst the three groups. Moreover, cellular hypersensitivity was the same in TAO patients and healthy smokers, whereas the non-smokers did not show a cellular response [41]. Additionally, a study was conducted in 2006 of 27 TAO patients who received nicotine patches and nicotine gum as part of their smoking cessation program [42]. According to this study, 40% of the patients successfully abstained from smoking using nicotine patches and nicotine gum, and TAO symptom improvement was observed in all the abstainers. Furthermore, none had undergone amputation after one year’s follow-up. However, 50% of the patients who continued smoking underwent one or more amputations during the follow-up period [42].

**TOBACCO DEPENDENCY AND TAO**

It has been claimed for years that TAO patients are heavy smokers [43]. In 1969, Kjeldsen and Mozes demonstrated that patients with TAO had significantly higher tobacco consumption and carboxyhemoglobin levels than patients with atherosclerosis and the control group [44]. However, in 2006, a study on tobacco dependence in TAO patients compared with patients with coronary artery disease (CAD) was conducted. In contrast to the researchers' hypothesis, no significant difference in the Fagerstrom Test to Nicotine Dependence (FTND) score was observed between the TAO and CAD patients. Additionally, the TAO patients smoked significantly fewer cigarettes per day than the CAD patients (p = 0.003) [45].

According to a study of 86 TAO patients in 2010, their level of cigarette smoking ranged from 2 to 80 cigarettes per day, and the duration of smoking before disease onset ranged from two months to 35 years [2]. In 2014, it was demonstrated that 45% of TAO patients smoked 5–15 cigarettes per day for 5–10 years duration, and there was no correlation between the number of cigarettes smoked per day and the duration of smoking with early presentation of the disease [46]. Finally, several studies have demonstrated that TAO can also occur in non-smokers [14,47]. In 1973, Stojanovic et al. observed that 5% of TAO patients in their study had never smoked [48].

**TOBACCO USE AND TAO PROGNOSIS**

Early after the definition of TAO, several studies suggested that smoking cessation is the most important treatment factor for better prognosis of such patients [5,15,16]. In 1974, in his study on the prognostic factors of TAO, Hill stated that heavy and continued smoking was associated with worse prognosis in TAO patients [47]. He demonstrated that 60% of disease exacerbation was correlated with increased tobacco consumption, 23% of exacerbation was the result of cold exposure, and the remainder of the exacerbation occurred owing to inexplicable reasons [47]. During 15 years of follow-up, Hill also demonstrated that approximately 60% of the patients who underwent major amputation were heavy smokers (i.e., smoking more than ten cigarettes per day) and suggested that better prognosis could be achieved if the patients who could not give up smoking would instead reduce the number of cigarettes smoked per day to less than five [47].

However, a study based on the urinary cotinine level in TAO patients showed that, amongst patients with disease aggravation, urine cotinine levels varied widely. The researchers further emphasised that it is impossible to predict worsening prognosis in TAO patients according to the number of cigarettes smoked per day [34]. They also demonstrated that approximately 7.5% of the patients experienced worsening of the disease despite their urinary cotinine levels remaining within a non-smoker’s or passive smoker’s range [34].

Different studies also reported that 18.8%–50% of patients who continued smoking underwent amputations, and 94%–100% of the patients who were successful in smoking cessation avoided amputation. Furthermore, disease activity presented as intermittent claudication, rest pain, ischemic ulcers, and thrombophlebitis was much less in TAO patients who stopped smoking [21,42,49,50]. A study in Poland also demonstrated that TAO patients who stopped smoking had a 50% decrease of disease exacerbation [27]. However, the researchers emphasised that, although smoking cessation improved the clinical course of TAO, it cannot stop further recurrences of the disease [27].

Moreover, according to a study of 103 TAO patients, no significant difference in the long-term limb salvage rate
was found between ex-smokers and current smokers. It was noticed, however, that some patients who achieved remission through smoking cessation, but who resumed smoking after remission, remained in remission despite smoking resumption [51].

During their study of 287 TAO patients, Shigematsu H and Shigematsu K did not find any significant correlation between the continuity of TAO clinical symptoms and smoking [8]. They also did not discover any significant correlation between smoking and limb loss in their case series, but they did find a significant correlation between smoking and minor amputation [8].

However, a survival analysis of 108 TAO patients demonstrated that smoking for more than 20 years is significantly related to a major amputation event [52]. In this study, the multivariate analysis also demonstrated that the duration of smoking but not the number of cigarettes smoked per day had a significant relationship with major amputation (Hazard Ratio [HR] 2.73; P=0.004) [52]. The researchers further demonstrated that smoking cessation had a highly protective effect in terms of avoiding limb loss (Relative Risk [RR] 0.057), whereas decreasing the number of cigarettes smoked per day did not have any effect on the disease outcome (RR 1) [52].

**SMOKING,ATHEROSCLEROSIS, AND AUTOIMMUNE DISEASES**

The effects of smoking on the initiation, process, and severity of atherosclerosis have been under study for years. Critchely and Capewell showed a 36% decrease in relative risk (RR) of mortality for patients with coronary artery disease (CAD) who discontinued smoking compared with those who continued smoking (RR 0.64) [53]. A study conducted by Kumanan et al. of the results of a meta-analysis of 12 cohort studies showed a decrease in the mortality rate accompanied with smoking abstinence. The combined Odds Ratio (OR), based on the random effects model for death after myocardial infarction, was 0.54 in those who quit smoking, and the relative risk reductions across the studies ranged from 15% to 61% [54]. Interestingly, it has been reported that passive smoking is associated with a 30% increase in the risk of CAD, compared with an 80% increased risk of CAD in active smokers [55, 56].

It appears that smoking is also a notable risk factor for developing rheumatoid arthritis (RA). It has been demonstrated that smoking is associated with an increased incidence of rheumatoid factor-seropositive RA [57]. The relative risk of seropositive RA is 2.6 in male ex-smokers and 3.8 in current smokers, in comparison with men who have never smoked [57]. Smoking is also a risk factor for an unfavourable treatment response in patients with RA. [58]. Moreover, it has been reported that current smokers have the highest—and never-smokers the lowest—disease activity, as determined by Swollen Joint Count (SJC) and Tender Joint Count (TJC) scores (P < 0.001 and P = 0.02, respectively) [57].

It has also been demonstrated that smoking is associated with dsDNA autoantibody production in systemic lupus erythematosus (SLE), and a significantly high risk of dsDNA seropositivity in current smokers over never smokers (OR = 4.0) has been observed [59]. It has been found that cigarette smoking before SLE diagnosis, versus ex-smoking before SLE diagnosis, significantly increased the risk of developing SLE (OR 6.69 and 3.62, respectively) [59]. It has also been demonstrated that current smokers have a significantly higher SLE disease activity index score than ex-smokers and never-smokers [60]. Miot et al. revealed that cigarette smoking was significantly associated with Discoid Lupus Erythematosus (DLE) development. A higher smoking outbreak was noted in DLE (84.2%) than in controls (33.5%), and OR for smokers compared with non-smokers was 14.4 [57]. Smoking also appears to have a negative influence on the disease activity and quality of life of Ankylosing Spondylitis (AS) [61]. However, it appears that smoking is not a risk factor for developing systemic sclerosis (SSc) (OR 1.02), although smoking can influence SSc severity [62].

Surprisingly, several studies have shown that cigarette smoking may be favourable toward the symptoms of Behçet disease (BD), and that discontinuance of smoking can activate or exacerbate BD [63, 64]. Soy et al. showed that smoking cessation can activate mucocutaneous symptoms, particularly oral aphthous lesions, in BD patients [65]. Smoking is also not associated with the types of BD uveitis (OR 1.01, 0.96, and 1.80 for anterior uveitis, posterior uveitis, and panuveitis, respectively) [65]. However, a study conducted by Aramaki et al. concluded that the frequency of HLA-B51 with smoking—but not that of smoking alone—was significantly higher in chronic progressive neuro-Behçet syndrome (NB) than in acute NB [66]. In ulcerative colitis, as in BD, the risk of developing the disease is significantly lower in smokers than in non-smokers [67].

**CONCLUDING REMARKS**

Although Buerger did not report the relationship between TAO and smoking [9], early after disease definition, it
was noticed that TAO patients were almost always tobacco smokers [5]. Even after documenting this relationship, Buerger stressed that smoking is not the cause of TAO; it simply increases the risk of TAO [11]. According to the vascular histopathology of TAO patients, Buerger suggested an infectious pathogen such as spirocheta species as the main aetiology of TAO [68]. However, since he could not culture any precise pathogen from the blood or tissue of TAO patients, focus shifted from his hypothesis to smoking as the main aetiology of TAO.

Notably, in 2005, Iwai et al., inspired by the findings of Buerger, reported the presence of a type of spirochete—so-called *Treponema denticola*—in the vascular lesions of TAO patients [69]. *Treponema denticola* is one of the subgingival microflora found in smokers, and, in this way, Iwai et al. made a connection between smoking and this particular spirochete species [69]. Recently, Iwai et al. also developed an animal model of TAO using *Treponema denticola* [70, 71].

Unfortunately, the findings of Iwai et al. have not yet been evaluated in other regions. Moreover, the exact mechanism of movement of *Treponema denticola* from subgingival plaques to microcirculation of the extremities and the means of inducing inflammation in tissues and microenvironments other than the oral cavity remains unknown. Also, it is not yet clear why *Treponema denticola* might induce disease in the vessels of the extremities but not the visceral vessels.

Recently, several polymorphisms in TAO patients have been demonstrated which lead to high oxidative stress, vasoconstriction and impairment in thrombolysis [72, 73]. Notably, smoking can have an exaggerated effect on vascular endothelium function in patients carrying such polymorphisms [72, 73].

However, none of these hypotheses explains the relapsing-remitting nature of TAO, in particular in patients who had not changed their smoking habit during the natural history of their disease.

In this review, we presented a number of antithetical reports, some of which support the close relationship between smoking and TAO, and some of which cast doubt on smoking as the main aetiology for TAO (Table 1).

### Table 1. Evidence on tobacco use and TAO

| PROS | CONTRAS |
|------|---------|
| TAO is more common in countries with a higher rate of smoking [25]. | The smoking rate of some countries in which TAO is more common is less than several countries of Western Europe, where TAO is less common [26]. |
| In Poland and the US, a decrease in the incidence of TAO was parallel with a reduction in the prevalence of male smokers [27-30]. | The steady decline in the prevalence of smoking does not run parallel to the sharp decline in the number of TAO patients [28,29]. |
| An increase in the incidence of TAO in women is in parallel with a relative increase in female smokers in Poland [27]. | TAO is about eight times more prevalent in males than females, a ratio not in parallel with the prevalence of smokers in each gender [4, 29]. |
| TAO may develop in smokeless, chewing tobacco users, and passive smokers. In active smokers, substitution of cigarette smoking with chewing tobacco or exposure to cigarette smoke may keep the disease active or even exacerbate it [28, 39, 40]. | According to several studies, TAO can also occur in non-smokers. There is no correlation between the number of cigarettes smoked per day and the duration of smoking with early presentation of TAO [2, 14, 46, 48]. |
| There is a close relationship between smoking cessation and TAO clinical improvement and avoiding amputation [5,15,16,52]. | About 50%, but not all, of the patients who continued smoking underwent one or more amputations. About 7.5% of the patients who gave up smoking experienced worsening of the disease according urinary cotinine levels. Patients who achieved remission through smoking cessation, but who resumed smoking after remission, remained in remission despite smoking resumption [34, 42]. |
The faith in the relationship between smoking and TAO distinguished smoking as the main aetiologcal factor of TAO. While this belief was helpful in terms of convincing patients to adopt a healthier lifestyle, it also prevented achieving a better prognosis for patients who could not stop smoking. It appears that smoking is a predisposing rather than an aetiologic factor (Figures 2 and 3; Artworks by Masoudian M). Further studies are necessary regarding the main aetiology of TAO with the aim of determining appropriate treatment and medical management for patients who fail to stop smoking.

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**DISCLAIMER**
The authors declare that no part of this review, including ideas, text and graphics, is copied or published elsewhere in whole or in part in any languages. Also, the authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Целью этого обзора является исследование доказательств в поддержку или опровержение взаимосвязи между ТАО и курением на основании литературных источников, посвященных ТАО, опубликованных с 1908 г. по январь 2022 г. На основании выполненного анализа можно сделать вывод, что курение является основной этиологией ОАС, открывая тем самым путь для выявления истинной основной этиологии ТАО, для определения надлежащего лечения и медикаментозного ведения пациентов, которым не удалось бросить курить.

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