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REVIEW

PERIPHERAL ARTERIAL DISEASE

EDITOR'S CHOICE

Smoking and lower extremity artery disease

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ABSTRACT

Cigarette smoking is a major preventable risk factor for lower extremity arterial disease (LEAD) and is strongly associated with a higher risk of disease progression, worse post-procedural outcomes, and increased healthcare utilization. Smoking provokes the development of atherosclerotic through different mechanisms. Endothelial cell dysfunction, oxidative stress, inflammation, and arterial stiffness are among the key factors related to the development of atherogenesis due to smoking. Smoking cessation among patients with LEAD and the use of smoking cessation methods, including pharmacological treatment, are mandatory. Given that smoking cessation interventions remain underutilized. Therefore, in this narrative review we highlight the importance of incorporating smoking cessation treatments as part of the medical management of LEAD. Regulatory approaches to reduce tobacco use and support smoking cessation have the potential to reduce the burden of LEAD.

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Key words: Smoking; Peripheral arterial disease; Atherosclerosis.

Lower extremity arterial disease (LEAD) represents one of the major atherosclerotic cardiovascular (CV) diseases which is related to high risk of mortality and major cardiovascular events.[1] Smoking is an independent and modifiable risk factor for peripheral arterial disease (PAD), carrying three to four-fold increased risk for the development of PAD.[2, 3] Hughson *et al.* demonstrated that male and female smokers have even a five-to-seven-fold higher risk of developing intermittent claudication compared to male and female non-smokers, respectively.[4] More than 200 million people worldwide are affected by LEAD, and many of them smoke.[5] Therefore, the aim of this narrative review is to expose the importance of this strong and removable risk factor of LEAD.

PubMed/Medline, Embase and the Cochrane databases were searched by authors until March 31, 2024 to identify studies focusing on the association between LEAD and smoking, as well as the mechanisms involved.

The following combinations of search terms were used: "Lower limb arterial disease and smoking, pathophysiological mechanism of smoking, smoking related atherosclerosis, smoking cessation and LEAD, substitutes of tobacco smoking.

Evidence of the relationship between smoking and LEAD

Given that smoking cessation remains underutilized, we highlight the importance of incorporating smoking cessation as a part of medical management of patients with LEAD.

Numerous studies have confirmed the link between smoking and LEAD. A systemic review showed that half of LEAD cases are due to smoking.[6]

In a study published by the American Heart Association, more than a third of LEAD patients were active smokers.[1] This study highlights the importance of knowing the risk factors of smoking to aid in the diagnosis of conditions such as LEAD. They also had about twice the risk of stroke and coronary heart disease (CHD). There is also a relationship between the intensity of smoking and PAD. A clear dose- response relationship with a strong increase in risk for LEAD in heavy smokers was observed.[7, 8] Also, the risk of intermittent claudication increases with the duration and intensity of smoking.[4]

Smoking is a much stronger risk factor for the development and progression of LEAD than for CHD. In the Edinburgh Artery Study the incidence of LEAD was two times higher than for coronary artery disease (5.1% *vs.* 11.1%).[9] The difference of risk of LEAD or coronary artery disease in smokers could be the consequence of morphologic characteristics of arterial wall in different circulatory beds and hemodynamic forces.[10] LEAD patients also have an increased risk of stroke. The meta-analysis showed that smokers had 1.9 higher risk of cerebral infarction than non-smokers.[11]

Patients with LEAD are often heavy smokers and are less likely to successfully quit smoking compared to CHD patients.[8] In addition, people who have smoked have an even higher risk of developing LEAD compared to non-smokers.[5] Passive smoking also increases the risk of vascular damage and atherosclerotic LEAD.[12]

Persistent smoking is associated with a significant increase in hospital admissions, revascularization procedures and healthcare costs related to PAD, and the 5-year mortality rate for active smoking and chronic symptomatic PAD is 4050%.[13]

Figure 1, 2 show the recommendations of the latest guidelines.[13, 15]

Therefore, cigarette smoking is an important preventable risk factor for LEAD and is strongly associated with a higher risk of disease progression, poorer outcomes after intervention and increased healthcare utilization. Endothelial cell dysfunction, oxidative stress, inflammation and arterial stiffness are among the key events in the development of atherosclerosis provoked by smoking.[16]

Pathogenesis of LEAD in smokers

The pathophysiologic mechanisms by which tobacco smoke accelerates vascular disease are numerous and complex, in part because smoke contains more than 4000 different chemicals.[17] Exposure to cigarette smoke activates a number of mechanisms, including thrombosis,

Ongoing smoking and use of other farms of tabacco.	80%-90% of patients revascularized for severe limb symptoms are current smokers. OR 2.4 for developing symptomatic LEAD incurrent smokers.	Ongoing smoking is associated with a significant increase in LEAD-related hospitalizations, revascularization procedures, and health care costs. The 5-y mortality rate with active smoking and chronic symptomatic LEAD is 40-50%.

Figure 1.—LEAD-Related Risk Amplifiers. Effects of smoking on the symptoms of LEAD and the results of treatments (modified from Changeux JP[14]).

Smoking cessation for LEAD		
COR	LOE	Recommendations
1	A	1. Patients with LEAD who smoke cigarettes or use any other forms of tobacco should be advised at every visit to quit or encouraged to maintain cessation.
1	A	2. Patients with LEAD who smoke cigarettes or use any other forms of tobacco should be assisted in developing a pian for quitting that includes pharmacotherapy (*i.e.*, varenicline, bupropion, and/or nicotine replacement therapies) combined with counseling, and/or referral to a smoking cessation program.
1	B-NR	3. Patients with LEAD should be advised to avoid exposure to secondhand tobacco smoke in all indoor or enclosed spaces, including work, home, transportation vehicles, and public places.

Figure 2.—Recommendations for Smoking Cessation for LEAD (modified from Changeux JP[14]).

insulin resistance and dyslipidemia, vascular inflammation, abnormal vascular growth and angiogenesis, and loss of endothelial homeostatic and regenerative functions.[18] Several studies have shown that harmful substances can induce various phenotypic changes and dysfunctions of macrophages, endothelial cells and smooth muscle cells upon long-term exposure to smoke.[19-21]

Also, some of the substances such as polycyclic aromatic hydrocarbons, oxidizing agents and nicotine have been identified in cigarette smoke and are considered to be potential contributors to atherogenesis.[21] In addition, nicotine also accelerates vascular disease by inducing the release of catecholamines and increasing heart rate and blood pressure.[15] These adverse hemodynamic effects are associated with the progression of atherosclerosis, particularly LEAD.

In addition, nicotine-induced release of catecholamines increases platelet aggregability.[15]

Platelets contribute to plaque growth through the release of growth factors (such as platelet-derived growth factor) that stimulate vascular smooth muscle cell proliferation.[20] Nicotine and other substances also have direct effects on the cellular elements involved in plaque formation.[17]

While acetylcholine stimulates both types of cholinergic receptors (muscarinic and nicotinic), nicotine preferentially stimulates the nicotinic receptor.[15]

Plaque progression and neovascularization as an effect of nicotine was independent of plasma lipid levels and was blocked by rofecoxib, a known inhibitor of angiogenesis.[14] The effect of nicotine (or endogenous acetylcholine) and other substances on endothelial cells appears to be largely mediated by the homomeric α7-n acetylcholine receptor (α7-n AChR).[22-24] Pharmacological antagonism (by alpha-bungarotoxin), genetic knockout or suppression of the α7-nAChR by short interfering RNA (siRNA) significantly inhibits nicotine-induced activation of endothelial cells and angiogenic processes.[25]

Endothelial dysfunction is one of the earliest abnormalities observed in the development of atherosclerosis, and endothelial nitric oxide (NO) synthase (eNOS), which plays a critical role in regulating endothelial function, is reduced in smokers.[24-26] The extent of endothelial dysfunction is related to the intensity and duration of smoking.[27]

According to some studies, plasma levels of asymmetric dimethylarginine (ADMA) are significantly higher in smoking patients than in non-smokers.[28] ADMA, a metabolite of L-arginine, is an endogenous inhibitor of eNOS.[29] Studies have also confirmed that cigarette extract not only inhibits the uptake of L-arginine but also reduces the expression of the cationic L-arginine amino acid transporter (CAT1), thereby reducing NO production.[30, 31]

Various chemokines and proinflammatory cytokines activated by nicotine and other harmful substances promote the adhesion of monocytes to endothelial cells, stimulate monocytes to invade the endothelium and lead to phenotypic changes. The most important regulatory factor is the CC chemokine receptor 2 (CCR2) and its ligands monocyte chemoattractant protein 1 (MCP-1) and monocyte chemoattractant protein 3 (MCP-3).[32-34] Activated protein kinase C (PKC) promotes increased expression of the monocyte adhesion ligand CD11b in peripheral blood and the endothelial cell counter-receptors vascular cell adhesion molecule 1 (VCAM1), intercellular adhesion molecule 1 (ICAM-1) and endothelial leukocyte adhesion molecule 1 (ELAM-1).[35]

When white cells are stimulated by pathologic factors such as nicotine, phenotypic changes in smooth muscle cell proliferation, migration, and apoptosis occur that are

critical to the pathologic process of atherosclerosis.[36, 37] Nicotinic acetylcholine receptors (nAChRs) belong to the superfamily of cys-ligand-gated ion channels (cysLGICs) and are widely distributed transmembrane proteins in vascular smooth muscle cells. They are involved in the regulation of homeostasis and cause functional changes in blood vessels.[37-39] Nicotine in cigarette smoke is an important ligand for the a1 nicotinic acetylcholine receptor, which directly induces the conversion of vascular smooth muscle cells (VSMCs) from a contractile phenotype to a synthetic phenotype *via* the nicotinic acetylcholine receptor and the G-protein-coupled receptor.[40, 41]

Substitutes of tobacco smoking

The only effective measure to reduce the risk of smoking-related atherosclerosis is to completely stop smoking. However, after quitting smoking, the lingering effects caused by smoking are not completely eliminated[42] and with the change of tobacco marketing methods, some new types of tobacco substitutes, such as electronic cigarettes (E-cig), heated tobacco products (HTPs), water pipes, etc., have gradually developed into new forms of smoking consumption and are increasingly used also by young people.[43] The various tobacco substitutes contain hundreds of different chemical components.[44-47] Qualitative and quantitative comparisons of the composition of e-cigarettes, heated tobacco products, waterpipe aerosols and cigarette smoke have been carried out; the risks of consuming e-cigarettes, heated tobacco products and waterpipe aerosols are estimated to be lower than those of cigarette consumption.[48-50]

Smoking cessation

Smoking cessation is an important component of LEAD's secondary prevention guidelines and has been recognized as an effective preventive measure.[51, 52] American guidelines for the management of PAD even provide a Grade IA recommendation for the assessment of a LEAD patient's smoking status at each examination and offer smoking cessation support to all those who actively smoke.[53] The 2024 European Society for Cardiology guidelines on peripheral arterial and aortic diseases state that E-cig may be considered as an aid to quit tobacco smoking, but it is advisable to limit their use and avoid simultaneous use with conventional cigarettes due to unknown long-term effects.[54]

Despite the key role attributed to smoking as a risk factor in LEAD and the availability of effective smoking cessation treatments, there is surprisingly little current data describing the current prevalence of smoking in LEAD patients and the efforts of clinicians to promote smoking cessation.[55-58] There is also little evidence on how the habits of smokers with LEAD change after they consult their physician for symptoms related to LEAD.

Smoking cessation has the potential to improve intermittent claudication. In a study examining ankle pressure, intermittent claudication and exercise capacity, the cohort of patients with LEAD who continued to smoke showed a significant decrease in ankle pressure and no change in maximal treadmill walking distance. However, the cohort who stopped smoking showed a significant improvement in maximal treadmill walking distance over an average period of 10 months.[59]

Several studies have shown the negative impact of smoking on the patency of bypass grafts for LEAD.[60] A meta-analysis of 29 studies investigating the association between smoking and lower extremity bypass graft patency found that smoking leads to an increased risk of graft failure after lower extremity bypass surgery. There was a clear dose-response relationship. It was also reported that smoking cessation restored patency rates compared with the never-smoker group.[60]

There was no difference between the patency of autogenous or polyester grafts in smoking patients. The lack of graft material preference is not unexpected. However, in a meta-analysis, there was no clear evidence of a possible preference for femoropopliteal graft materials.[61]

Armstrong *et al.* investigated the relationship between smoking cessation and mortality and amputation-free survival. In a retrospective cohort of 739 patients with claudication or critical limb ischemia (CLI) using the PAD-University of California Davis Registry, mortality was lower in the successful smoking cessation cohort than in the cohort of continued smokers (14% *vs.* 31% at five years). The decrease in mortality was more pronounced in the cohort of patients with CLI (18% and 43%, respectively).[11] In addition, improved amputation-free survival was seen in the cohort of successful ex-smokers compared with the cohort of continued smokers, with a hazard ratio of 0.43 (95% CI, 0.22-0.86). A recent study by Reitz *et al.* examined 14,350 patients with intermittent claudication who underwent revascularization between 2011 and 2019 as part of the Veterans Affairs Surgical Quality Improvement Program.[62] They reported that 30-day mortality was higher in the smoking cohort (0.6% *vs.* 0.1%), regardless of the type of procedure: endovascular, open or hybrid revascularization. Graft failure was also higher in the smoking cohort (2.2% *vs.* 0.7% P=0.001).

In a registry of 739 LEAD patients who underwent angiography, those who continued to smoke had higher mortality at 5-year follow-up (31% *vs.* 14%; P<0.05). In the same registry, the amputation rate was significantly higher in survivors who continued to smoke (40% *vs.* 19%; P<0.05).[62, 63]

Patients with LEAD who smoke cigarettes or use other forms of tobacco should be assisted in developing a smoking cessation plan that includes pharmacotherapy (*i.e.*, varenicline, bupropion, and/or nicotine replacement therapies) in combination with counseling and/or referral to a smoking cessation program.[42, 63]

Patients with LEAD should be advised to avoid exposure to secondhand smoke in all enclosed spaces, including at work, at home, on transportation, and in public places.[63]

A randomized clinical trial reported that patients with LEAD with active smoking who received an intensive intervention (medical advice, smoking cessation advice and pharmacological treatment) had a 6-month abstinence rate of 21.3, compared with 6.8% in the less intensive treatment group who received only verbal advice on smoking cessation.[64] Kalbaugh *et al.* reported that smokers with LEAD were offered smoking cessation counseling or pharmacological treatment in only about one-third of visits.[65] An analysis of the PORTRAIT Registry (Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories registry) assessed smoking rates and smoking cessation interventions offered to patients with LEAD who presented with new or worsening PAD symptoms and examined changes in smoking behavior at 1-year follow-up.[1] Of the 474 patients with LEAD who were active smokers, fewer than one in five were referred to a smoking cessation counseling program and only one in ten had received pharmacologic treatment. Of the patients who quit smoking, more than a third relapsed, highlighting how difficult it is for patients to quit smoking permanently.[1]

There are several approved smoking cessation methods that can be used either alone or in combination with pharmacological therapies and behavioral approaches with smoking cessation counseling programs. E-cig have been proposed as a smoking cessation aid, but there is a need for more information on their efficacy and safety.[16, 66-69]

Clinicians caring for patients who smoke should use a four-step plan to support smoking cessation.[70]

As reported in a consensus document of ACC, a comprehensive smoking cessation program that combined counseling and pharmacological agents increased the rates of smoking cessation to 21%, compared with 7% with standard advice alone.[63] But for smokers who are not ready to quit, the consensus document is advising discussing the use of smoke-free products (*e.g.* E-cig or HTPs) if smokers are not interested in using stop smoking medications. This is among the first recognition of the so-called Tobacco Harm Reduction approach applied to those who would decide to otherwise continue to smoke.

Recent data have shown that electronic nicotine delivery systems have a positive effect on smoking cessation rates.[16, 67-71] However, the long-term health-related outcomes (MACE and MALE) of using electronic nicotine delivery systems have not been studied.

According to the conclusion of the Cochrane review on E-cig for smoking cessation, nicotine E-cig can help people to stop smoking for at least six months.[67] Evidence

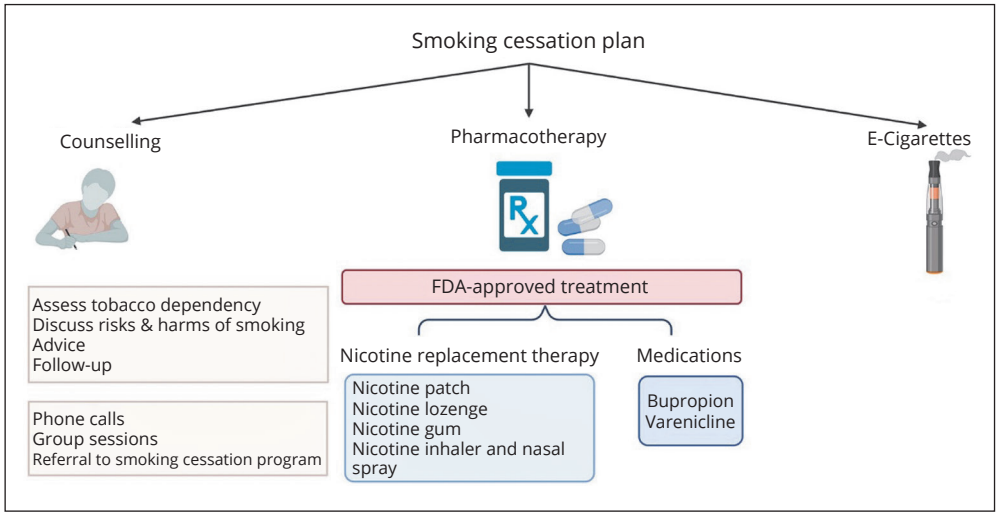

Figure 3.—Approach to promoting smoking cessation in patients with LEAD.

shows they work better than nicotine replacement therapy, and probably better than e-cigarettes without nicotine. They may work better than no support, or behavioral support alone, and they may not be associated with serious unwanted effects. However, we still need more evidence, particularly about the effects of newer types of E-cig that have better nicotine delivery than older types of E-cig, as better nicotine delivery might help more people quit smoking (Figure 3).

Conclusions

In terms of the efficacy of e-cigarettes for promoting smoking cessation, the evidence is limited to the research setting. We should obtain more data on their effectiveness in real-life setting.

Importantly, patients in the e-cigarette group had a high rate of continued E-cig use.

As to HTPs the only data available on their use as a smoking cessation tool (even if they were not developed for such scope but for providing adult smokers, who would otherwise continue smoking, with a relatively less risky alternative) there is at least one randomized clinical trial showing their efficacy in the short term and in the clinical setting.[69]

In conclusion, smoking is one of modifiable risk factors for the development and progression of LEAD. Tobacco smoke which contains different harmful substances damage endothelium and increases its permeability via the formation of reactive oxygen species, which favors the deposition of cholesterol and other proatherogenic substances in the vessel wall.

The degree of this effect is clinically evident, because according to a comprehensive study, the incidence of LEAD is 2-4 times higher in current smokers than in non-smokers. Patients with LEAD suffer from smoking-related comorbidities and increased mortality. Smoking is a modifiable risk factor. Therefore, smoking cessation should be incorporated in the treatment as a part of the medical management of patients with LEAD.[72]

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The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
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