The Relationship of Cigarette Smoking to Peripheral Arterial Disease

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Cigarette smoking is one of the most important risk factors for peripheral arterial disease (PAD). Smoking increases the risk of PAD by several fold and is a more influential risk factor for PAD than for coronary artery disease. Multiple pathophysiologic mechanisms may account for the prevalence of atherosclerosis in cigarette smokers. These include abnormalities of endothelial function, lipoprotein metabolism, coagulation, and platelet function. Smoking cessation decreases the risk of cardiovascular morbidity and mortality, and may improve functional capacity in patients with PAD. Therapies to promote smoking cessation include counseling, nicotine replacement, and bupropion. Healthcare providers must enhance their efforts and target smoking cessation as a modifiable risk factor in patients with PAD and other manifestations of atherosclerosis.
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A correlation between peripheral arterial disease (PAD) and smoking was reported early in the twentieth century.[1] Today, smoking remains one of the most important risk factors for the development of PAD, as well as its only avoidable risk factor.[2,3] This association is relevant for both genders and occurs at every age.[2] Approximately 90% of patients with PAD have a history of smoking.[4–6] Smoking elevates the risk of PAD several fold.[7–10] Taking into account other risk factors, such as hypercholesterolemia and diabetes, approximately 75% of PAD is attributable to smoking.[2,10]

Whereas smoking is a risk factor for all regional manifestations of atherosclerosis, it carries a greater risk for PAD than for coronary artery disease.[2,11,12] In the Framingham Study population, the risk of intermittent claudication was doubled in smokers compared to non-smokers and the odds ratio of developing intermittent claudication was 1.4 per 10 cigarettes smoked daily.[2,8,13] The Edinburgh Artery Study found that the odds ratios of intermittent claudication, major asymptomatic PAD, and minor asymptomatic PAD in current smokers was 3.7, 5.6, and 2.4, respectively.[11] In ex-smokers, the odds ratios for each level were 3.0, 2.8, and 1.8, respectively. The risk of PAD in smokers is strongly dose-dependent, related to both the amount of cigarettes smoked per day and number of years smoked.[2,9,10,12]

Smoking reduces high-density lipoprotein cholesterol and increases low-density lipoprotein and very low-density lipoprotein cholesterol, as well as triglyceride levels.

Pathophysiology of Vascular Disease in Smokers

Cigarette smoke contains more than 4000 compounds, many of which are toxic. The effects of most of these compounds have not been fully explored. There is considerable debate over the specific pathological mechanisms caused by each component.[14] The compounds that have drawn the most attention are nicotine and carbon monoxide, although some studies have recently posited that components of cigarette smoke other than these may be the true culprits in atherosclerosis.[15] The toxins found in cigarette smoke cause damage along different biochemical pathways, and together, these injuries can contribute synergistically to the worsening of PAD.[16]

Endothelial function, lipoprotein metabolism, coagulation pathways, and platelet function are adversely affected by smoking cigarettes. Endothelium-dependent vasodilation, which reflects the bioavailability of nitric oxide, is impaired in smokers and may contribute to endothelial dysfunction.[17–21] Moreover, there is an association between the severity of endothelial dysfunction and total pack-years smoked.[17] Also, the risk of coronary artery disease is increased in smokers with a polymorphism of the endothelial nitric oxide synthase gene.[22] Oxidative stress is increased in smokers. Compared to nonsmokers, the urinary excretion of 8-epi-prostaglandin F2 alpha, a stable byproduct of lipid peroxidation, is increased in smokers.[23] Reactive oxygen species may inactivate nitric oxide and potentially reduce its synthesis from nitric oxide synthase.[24,25] Administration of the antioxidant vitamin, ascorbic acid, restores endothelium-dependent vasodilation in smokers, supporting the notion that smoking-induced oxidative stress impairs endothelial function.[26]

Cigarette smoking increases monocyte adhesion to endothelial cells, an initial process in atherogenesis.[27] Smoking also affects lipoprotein and cholesterol homeostasis.[14] Smoking reduces high-density lipoprotein cholesterol and increases low-density lipoprotein and very low-density lipoprotein cholesterol, as well as triglyceride levels,[28] and also facilitates the peroxidation of low-density lipoprotein molecules.[18,20,29–32] These modifications also impair endothelial function and contribute to atherosclerosis and plaque instability.

Cigarette smoking may contribute to a prothrombotic predisposition. Cigarettes increase levels of fibrinogen, factor VII, and other factors involved in the fibrin clotting cascade and decrease the concentration of plasminogen.[33–35] Cigarette smoke activates platelets, increasing their reactivity and their ability to adhere to the vessel wall.[29,36] Urinary excretion of platelet-derived thromboxane B2, a metabolite of thromboxane A2, and plasma concentrations of platelet factor 4 and beta thromboglobulin are increased in healthy, chronic smokers. Nicotine, in particular, decreases the synthesis of prostacyclin and also the availability of nitric oxide, both inhibitors of platelet aggregation,[37–39] whereas it increases the concentration of thromboxane A2, a cofactor for platelet aggregation.[27,38,40] Thus, cigarette smoke contributes to thrombus formation via its effects on the coagulation cascade and platelets.

Smoking adversely affects the myocardial oxygen demand/supply relationship. Nicotine is an amine that crosses the blood-brain barrier and stimulates the central and peripheral nervous systems through dopamine release from the nucleus accumbens.[20] As a stimulant, nicotine creates a hyperadrenergic state, resulting in increased heart rate and myocardial contractility as well as vasoconstriction, all of which may[41,42] increase myocardial oxygen demand. Carbon monoxide has an affinity for hemoglobin that is approximately 200 times higher than that of oxygen, and thus, smoking increases the proportion of carboxyhemoglobin, leading to hypoxia.[43–45] This effectively reduces the blood oxygen concentration and amount of oxygen delivery.[46]

Smoking Cessation and Reduction of PAD Risk

Smoking cessation decreases the risk

of cardiovascular morbidity and mortality to levels that approach those of people who have never smoked.[47] The benefits of smoking cessation become apparent soon after stopping smoking. Abstention from cigarette smoking for as little as 8 weeks causes a gradual normalization of both blood and plasma viscosity, as well as hematocrit.[48] Endothelium-dependent vasodilation improves, although normal levels (such as would be seen in people who have never smoked) may not be attained.[17]

Smoking cessation increases long-term survival in patients with PAD. In one study, the 10-year survival rate was 82% in former smokers compared with 46% in continuing smokers.[49] Myocardial infarction occurred in 53% of PAD patients who continued to smoke versus 11% of PAD patients who had quit, and 43% of smokers eventually suffered cardiac death, as opposed to only 6% of former smokers.[49] Similarly, following vascular surgery, the survival rate is greater in former smokers than in those who continue smoking (66% vs 36%, respectively), approaching a 2-fold difference at 5 years.[6,50] Also, vascular patency following venous bypass graft for PAD is improved by smoking abstinence.[51,52]

In addition to increased survival rate, some studies have suggested that symptoms of PAD improve. In one study, exercise tolerance improved more often in those who quit smoking, but worsened in those who continued to smoke. Maximal treadmill walking distance was 18% greater in former smokers than in current smokers.[53] Also, the onset of claudication and maximal claudication distances occur earlier in continuing smokers than in former smokers, and it may take longer for the pain to subside.[54] The incidence of rest pain, a manifestation of critical limb ischemia, decreases after smoking cessation. In one study, 16% of continuing smokers developed rest pain over the course of 7 years whereas none of the former smokers developed it during that time.[49] Similarly, the amputation rates in those who continue to smoke are higher than in those who quit.[4,50]

Treatment and Intervention

Counseling, nicotine replacement, and bupropion have been utilized to help patients quit smoking. Counseling is only partially successful, as without an acute adverse event, many patients fail to fully grasp the damaging effects of smoking.[47] Approximately 10% of all smokers who try to quit are able to do so, but 25% of PAD patients successfully quit after 10 months.[53] Among PAD patients who are candidates for surgery, the success rate for smoking cessation is between 30–50%.[50,51]

For many patients, however, counseling is insufficient to curb the psychological and physiological needs of nicotine dependence. Two current pharmacotherapies are nicotine replacement by transdermal patch or gum, and bupropion, an antidepressant. Nicotine replacement therapy is an effective intervention for smoking cessation.[55,56] Nicotine replacement by gum or transdermal patch delivers less nicotine than does cigarette smoking, and provides this nicotine over a longer time period, avoiding the extreme highs and lows that come with the administration of a bolus of nicotine during each cigarette smoked.[57] Platelet activation and overproduction of clotting cascade factors seen in cigarette smoking are not evident in users of the transdermal nicotine patch.[58] Nicotine replacement does not involve the inhalation of carbon monoxide, thereby lowering carboxyhemoglobin content and decreasing myocardial work. Finally, blood pressure is lower because the decreased nicotine release results in a lower sympathetic activation. Although it was shown that endothelium-dependent vasodilatory response is still partially impaired in those who were using nicotine gum, the degree of impairment is significantly less in nicotine gum chewers than in cigarette smokers.[59] There is no increase in acute cardiovascular events during treatment with nicotine replacement

Main Points

- Taking into account other risk factors, such as hypercholesterolemia and diabetes, approximately 75% of peripheral arterial disease (PAD) is attributable to smoking, its only avoidable risk factor.
- The toxins found in cigarette smoke cause damage along different biochemical pathways, and together, these injuries can contribute to the worsening of PAD. Endothelial function, lipoprotein metabolism, coagulation pathways, and platelet function are all adversely affected by smoking cigarettes.
- In addition to increased survival rate, some studies have suggested that symptoms of PAD improve after a smoker quits.
- Two current methods that are used to supplement counseling to facilitate smoking cessation are nicotine replacement therapy and sustained-release bupropion.

patches compared with placebo.[60] Thus, nicotine replacement therapy may be considered to promote smoking cessation in patients with cardiovascular disease.[46]

Bupropion is an antidepressant that stimulates dopamine release and curbs the severe withdrawal symptoms of smoking cessation.[47] In a double-blind placebo-controlled clinical trial the success rate for smoking cessation was 15.6% with placebo, 16.4% with a nicotine patch, 30.3% with bupropion, and 35.5% with combined bupropion and nicotine patch.[61] The difference between the bupropion and bupropion plus nicotine groups was not significant, implying that the increase in success rate is due largely to the effects of bupropion. Whereas all groups suffered from withdrawal symptoms, they were not as severe in the nicotine patch, bupropion, and bupropion plus patch conditions as in the placebo group. The dosage of bupropion affects the success of smoking cessation. Administration of bupropion 300 mg or 150 mg per day over 7 weeks is associated with a significant rate of smoking cessation (44.2% and 38.6%, respectively).[62] Yet, administration of 100 mg per day over that time caused a nonsignificant reduction in smoking rates compared to placebo (28.8% and 19.0%, respectively).

Components of cigarette smoke, including carbon monoxide and nicotine, affect the function of endothelial cells; increase the reactivity, aggregation, and adhesion of platelets; cause vasoconstriction; and permit the migration of smooth muscle cells and oxidized low-density lipoprotein-containing foam cells into the vessel lining.

Conclusion

Smoking is a major risk factor for PAD, a condition that can lead to great impairments in quality of life and decreased length of life. Components of cigarette smoke, including carbon monoxide and nicotine, affect the function of endothelial cells; increase the reactivity, aggregation, and adhesion of platelets; cause vasoconstriction; and permit the migration of smooth muscle cells and oxidized low-density lipoprotein-containing foam cells into the vessel lining. These processes accelerate the progression of atherosclerosis throughout the vascular system and increase the risk of limb loss, as well as acute coronary artery and cerebrovascular events. Smoking cessation has been shown to restore some of the normal physiological responses of the vascular system. Smoking cessation increases both life expectancy and the probability of limb viability in patients with PAD. Two current methods that are used to supplement counseling to facilitate smoking cessation are nicotine replacement therapy and sustained-release bupropion. Although smoking cessation is difficult, the benefits are substantial. Physicians should enhance their efforts directed at smoking cessation in their patients with PAD. ■

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