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Review Article

Smoking: A High Risk Factor of Atherosclerosis and its Serious Consequences

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ABSTRACT

Cigarette smoking is a major modifiable risk factor for cardiovascular disease (CVD), including coronary artery disease (CAD), heart attacks, stroke, peripheral vascular disease, and congestive heart failure. The hazardous effects of smoking on the cardiovascular system are multiple and synergistic. Mechanisms include mainly vascular endothelial and smooth cell dysfunction, enhanced platelet aggregability, disturbed lipid profile, thrombosis, and hemodynamic changes. These effects, both, increase the likelihood of an acute event as well as contribute to long-term development of CAD. Tobacco smoke may also cause insulin resistance, a risk factor for diabetes and CVD**.** The same mechanisms responsible for CVD in active smokers are nearly as large in passive smokers**.** The specific ingredients of cigarette smoke responsible for its cardiovascular effects include mainly the polycyclic aromatic hydrocarbons, nicotine, oxidizing agents and particulate matter. Although smoking has been well clarified as the leading cause of cardiovascular morbidity and mortality worldwide, still a large scale of population continues to smoke while others start to smoke adding more victims to this bad habit. The death toll from tobacco is expected to climb to about 10 million people per year within next 25 years. 70% of victims will be in low- and middle-income countries**.** It is estimated that eventually 50% of all smokers will be killed by direct or indirect effects of tobacco. This review highlights atherosclerosis as one of the serious complications of smoking with discussion of its mechanisms and detrimental consequences particularly peripheral arterial disease, stroke and coronary artery disease.

Key words: Smoking, nicotine, endothelial cells, atherosclerosis, peripheral arterial disease, stroke, coronary artery disease.

INTRODUCTION

The morbidity and mortality resulting from smoking have been extensively documented. Prolonged use of tobacco or its products, as smoke or chew, endows significant risk of developing various diseases. Tobacco consumption affects every major organ of the body; particularly lung, heart and blood vessels.[1] More dangerously, death toll from tobacco use is on the rise.

Although tobacco consumption is the leading preventable agent of death in the world, its use is still increasing especially in developing countries, in teenagers and in women, despite governmental & WHO warnings and intervention by other statutory bodies. The number of cigarette smokers in the world is exceeding 1.3 billion and this figure is expected to rise to 1.7 billion by 2025.[2]

Tobacco smoke contains over 7000 different chemicals, some of which are known to be toxic or mutagenic**.**[3] Examples include the polycyclic aromatic hydrocarbons, N-nitrosamines, 1,2 butadiene, cyanide, arsenic, cresols, oxidizing agents and particulate matter.[4] Further, there is concrete evidence that cigarette smoke promotes pathophysiological processes that contribute to atherosclerosis including thrombosis, insulin resistance, dyslipidemia, vascular inflammation, and endothelial cell dysregulation**.**[5]

ACTION OF NICOTINE ON VASCULAR CELLS

A preponderance of evidence indicates that cigarette smoking aggravates and accelerates the development of atherosclerosis. The interaction of toxic substances especially nicotine with vascular wall cells namely endothelial and smooth muscle cells seems to be a key mechanism of nicotine-induced atherosclerosis.

Smoking & endothelial cell function:

While endogenous endothelial progenitor cell function is disrupted in the setting of smoking, nicotine content of cigarette smoke also induces a rise in intra-cytoplasmic filaments in endothelial cells and enhances endothelial cell proliferation, migration and tube formation.[6-8] This constitutes an important contributing role of nicotine in the pathophysiology of atherosclerosis.

Smoking & vascular smooth muscle cells:

Nicotine induces degenerative or necrotic changes in the arterial wall leading to arterial damage producing typical atherosclerotic plaques.[9] Development of intimal hyperplasia after vessel wall injury is initiated by the activation and proliferation of smooth muscle cells in the tunica media. Subsequently, the smooth muscle cells migrate to the sub-endothelial space, where they proliferate and synthesize the extracellular matrix.[10]

In vivo studies clarified the role of basic fibroblast growth factor and platelet-derived growth factor (PDGF) in the formation of intimal lesions. In fact, nicotine directly induces the proliferation of vascular smooth muscle cells (VSMCs), in part by stimulating their release of fibroblast growth factor.[11] On the other hand nicotine stimulates the release of catecholamines that promote platelet aggregability. Platelets contribute to the growth of plaque through the accretion of thrombus and release of certain growth factors (most importantly PDGF) that further induce vascular smooth muscle cell proliferation.[10]

Under the influence of PDGF, VSMCs migrate into the intima. Matrix metalloproteinases breakdown the extracellular content before the cell migration(MMPs). The major groups of MMPs are collagenases, stromelysins, and gelatinases. The collagenases digest collagen types I, II, and III, whereas the stromelysins degrade collagen type IV, basal laminins, and basement membranes. The gelatinases degrade denatured collagens and collagen style IV.[10] In the sub-endothelial space VSMCs undergo phenotypic modulation into myofibroblasts and osteoblast-like cells, elaborate extracellular matrix (collagen and osteopontin), and even take up lipid to resemble macrophage-derived foam cells.[12]

SMOKING-INDUCED PROINFLAMMATORY RESPONSES AND ATHEROSCLEROTIC PROCESS

The relationship between smoking, oxidative stress, and inflammation is well established, but complex. Cigarette smoke contains multiple agents contributing directly to inflammation. Lipid soluble smoke particles consisting of DMSO-soluble particles (DSP), nicotine, and lipopolysaccharides (LPS), upregulate G protein-coupled receptors for potent contractile agents, endothelin and thromboxane, which contribute to endothelial dysfunction.[13] In addition to up-regulating contractile receptors, LPS exposure simultaneously increases activation of inflammatory and contractile thromboxane and angiotensin I receptors while inhibiting anti-inflammatory and dilatory prostacyclin and acetylcholine receptors.[14]

Smoking increases oxidative stress markers malondialdehyde and isoprostanes through free-radical catalyzed peroxidation of arachidonic acid (AA) and AA metabolites as well as inflammatory markers tumor necrosis factor-α, interleukin-6 and C-reactive protein.[15-18] Elevated circulating levels of homocysteine are also associated with smoking and constitute a strong risk for endothelial dysfunction and associated cardiovascular events.[19] Smoking alone increases risk of CAD and amplifies that risk in presence of other risk factors e.g. hypertension and diabetes.[20] Homocysteine is generated through methionine metabolism with elevated levels most commonly associated with vitamin B deficiencies.[21] Elevated homocysteine increases thromboxane synthesis and isoprostane formation, enhancing platelet activity.[22-24]

Particular pro-inflammatory role of nicotine:

Nicotine is the predominant chemical in cigarette smoke and has been suspected to be a causative agent of atherosclerosis for decades. There is strong evidence that nicotine damages vascular endothelial cells through overstimulation or desensitization of the nicotinic acetylcholine receptors $\alpha_4\beta_2$ (nAChR).[25, 26] Prolonged exposure to nicotine leads to nAChR desensitization, causing cell bulking and, eventually, detachment, implicating that nicotine effects are caused by direct injury to the arterial wall.[27]

The postulated molecular mechanism of nicotine action on atherogenesis has ranged from initiation to angiogenesis.[8] Nicotine augments the synthesis and secretion of pro-inflammatory cytokines and inducible nitric oxide synthase (iNOS). It also amplifies the generated oxidative stress by monocytes and macrophages and their secondary effects on

endothelial and smooth muscle cells in vascular lesions. This is mediated by the molecular crosstalk between macrophages and endothelial and smooth muscle cells, which occur in the lesion.[28]

Nicotine directly induces iNOS and tumor necrosis factor (TNF)-expression in monocytes and macrophages via the nicotinic acetylcholine receptors. In turn, the activated macrophages, after they infiltrate the lesion, activate the NF-ʁB transcriptional factor in macrophages, smooth muscle cells, and endothelial cells with their secreted pro-inflammatory cytokines and generated oxidative stress. Of the NF-ʁB target genes stimulated by nicotine, activation of vascular cell adhesion molecule (VCAM-1) and cyclooxygenase-2 (COX-2) occurs first, followed by platelet-derived growth factor-β (PDGFβ) at a later stage. [28]

The nicotine-accelerated expression of VCAM-1 helps promote macrophage trans-endothelial migration. The concurrent increase of COX-2, which facilitates the progression of atherosclerosis, enhances vascular permeability, cell proliferation, chemotaxis, and influx of white blood cells, including phagocytes and lymphocytes, from the circulation into the tissue.[29,30] Subsequently, nicotine additionally stimulates PDGFβ synthesis in the lesion, which promotes enhancement of angiogenesis and thrombosis. Interestingly, PDGF A- and B-chain mRNA levels are increased in monocytes from hypercholesterolemia patients.[31-33] The growth factor can additionally promote smooth muscle cell migration, as well as enhance nicotine-induced proliferation of endothelial cells at the later stages.[28]

EFFECT OF SMOKING ON LIPID PROFILE

Lipid levels and inflammation, both key players in the atherosclerotic process, are affected by tobacco smoke.[34] Cigarette smokers have a more atherogenic lipid profile than non-smokers. The anti-atherogenic sub-fraction HDL_2 is lower in smokers and passive smokers.[35] Smokers and passive smokers have higher levels of products of lipid peroxidation and oxidized LDL compared to nonsmokers.[36] Smoking-induced endothelial injury may result from oxidative damage caused by lipid peroxidation and production of free radicals.[37]

EFFECTS OF TIMING & EXTENT OF SMOKING, CIGARETTE TYPE AND CONCOMITANT RISK FACTORS ON ATHEROSCLEROSIS

Smoking-induced atherosclerosis with its negative effect on cardiovascular health is well established nevertheless, many people continue or even start to smoke.[38-41] Carotid intima-media thickness (C-IMT), a marker of subclinical atherosclerosis, has been used as a surrogate end point to investigate the effects of cigarette smoking. Some studies have failed to report a difference in C-IMT between former and current smokers suggesting that the effect of smoking on vascular walls is irreversible.[40]

However, categorizations that do not take into account the extent and timing of smoking may yield misleading conclusions. For example, an individual with a 40-year history of cigarette smoking who stopped smoking 1 year ago is classified as a former smoker, but his/her C-IMT may well not differ from that of a current smoker. Conversely, a current smoker is included in this category even if he/she started smoking only a few months ago with an effect of smoking still negligible. Other factors potentially modifying the effect of smoking on the arterial walls are the cigarette contents of tar, nicotine, and carbon monoxide (CO) as well as the possible interactions with other common vascular risk factors.

Many smokers use light cigarettes in the belief that this may reduce the risks of smoking or as a first step toward stopping smoking.[42] Interestingly no relevant difference in C-IMT has been significantly detectable between consumers of “light” and “regular” cigarettes.[43] Consequently, there is no support of the hypothesis that light cigarettes have a less unfavorable effect than regular cigarettes. Although previous reports showed that switching from regular to light cigarettes does not reduce tobacco related cardiovascular morbidity mistaken beliefs about the possible benefits of light cigarettes are still widespread even in countries where considerable efforts have been made to educate people about the misconception of “light”.[44-46]

Diabetes and hypertension interact with smoking in determining C-IMT. The effect of cigarette smoking on C-IMT progression rate in diabetic patients is almost twice that observed in non-diabetic patients. On the other hand, smoking habit and hypertension are both independent determinants of C-IMT, with a significant interaction between hypertension and smoking habit. Thus, the identification of atherogenic interactions warrant intensified efforts to promote smoking cessation in patients with diabetes or hypertension.[43]

Age- and sex-adjusted C-IMTs increase with the number of pack-years, in both former and current smokers, thus confirming a direct dose-dependent relationship between smoking and C-IMT. However, the atherogenic effect of smoking is equally strong in both sexes.[43]

CONSEQUENCES OF ATHEROSCLEROSIS

Tobacco in any form trebles the risk of cardiac

disease. About 30% of all deaths from heart disease are due to smoking. Cardiovascular effects of smoking occur within minutes with rise in heart rate up to 30 % in first 10 rains. This is short lived, but since most individuals smoke cigarettes several times a day, these occur often, leading to long-term problems including atherosclerosis or atherothrombosis (AT).[47,48] AT is a complex inflammatory disease of the arterial wall in which a sclerotic plaque of lipid and fibrous tissue is deposited over time, often leading to rupture and thrombus formation.[49] Recently, it has been reported that nicotine promotes atherosclerotic cardiovascular disease, in part by promoting plaque neovascularization.[12]

Atherosclerotic disease is the leading cause of morbidity and mortality globally.[50,51] It is a systemic disease that affects all arterial beds and can present with multiple clinical manifestations according to the end organ supplied. In fact, atherosclerosis is a normal aging process but smoking accelerates it particularly in presence of other risk factors as male sex, advanced age, hypertension, diabetes, and hyperlipidaemia.[52]

Coronary vessel sclerosis leads to ischemic heart disease or myocardial infarction. Smokers develop coronary thrombosis 10 years earlier than non-smokers. Nine out of ten patients who undergo coronary artery bypass surgery are smokers. CO in smoke damages the heart muscle and increases myocardium's susceptibility to viral infections, cardiomyopathy and congestive cardiac failure.

Atherosclerosis of peripheral arteries enhances chance of peripheral arterial disease (Burgers disease, Raynaud's phenomenon), and gangrene. Peripheral arterial disease (PAD) is a serious vascular disorder characterized by ischemia of the limbs secondary to atherosclerotic occlusion, so it is a marker of advanced atherosclerosis. The clinical consequences of occlusive PAD include intermittent claudication, that is, pain with walking, and critical limb ischemia which includes pain at rest and loss of tissue integrity in the distal limbs, which may ultimately lead to amputation of a portion of the lower extremity.

PAD is a highly prevalent and debilitating condition, estimated to affect >25 million patients in Europe and North America alone.[53] Unfortunately, PAD is associated with a four-fold increased risk of myocardial infarction.[54] Indeed, the risk of cardiovascular mortality and morbidity in patients with PAD is comparable to that in patients with CAD.[50] Additionally, PAD is associated with a two to three-fold increased risk of stroke.[55]

A role for nicotine in the pathophysiology of atherosclerosis is supported by recent genomic evidence, which indicates that a sequence variant in the cluster of genes on chromosome 15 that encode nicotinic acetylcholine receptors is associated with increased risk of PAD.[56] It is possible that this genetic variation affects the vascular response to nicotine, and/or nicotine dependency.

Atherosclerosis may also be complicated by renal hypertension or renal failure due to renal artery sclerosis. Furthermore, atherosclerotic process may result in serious ocular disturbances, blindness, optic neuropathy and macular degeneration.[57] Cerebral vessel sclerosis causes collapse, subarachnoid hemorrhage, stroke, paralysis, coma and death. With the aging of the population and the steep association of stroke risk with age, the numbers of patients with stroke are expected to increase dramatically. Overall, total annual costs of stroke are projected to increase to $240.67 billion by 2030, an increase of 129%.[58]

CONCLUSIONS

Hastening of atherosclerosis due to smoking is attributed to a number of mechanisms: direct endothelial damage, increased proliferation of smooth muscle in atherosclerotic lesions, decreased endothelium-dependent coronary vasodilatation, and reduced levels of high-density lipoprotein cholesterol. There is evidence that inflammation and hyper-homocysteinemia may be important mechanisms by which smoking promotes atherosclerotic disease.[20]

Subclinical and clinical atherosclerosis has been consistently associated with smoking in a dose-response relationship. Subclinical atherosclerosis, measured as the C-IMT, was increased in smokers in the Atherosclerosis Risk in Communities Study.[59] Clinical atherosclerosis, manifested as intermittent claudication, is increased in smokers.[60]

The threat posed by a recent transient ischemic attack or stroke presents a special “teachable moment” for smokers who may not previously have been ready to quit. In the setting of recent myocardial infarction, 70% of smokers could be persuaded to quit.[61] Smoking increases risk of stroke six-fold, while quitting smoking greatly reduces that risk.[62]

A crucial role of successful management of smoking as a serious health problem is to understand how difficult sometimes for the patient to quit. However the treating physician should show the patient that he is on his side and that there are various valuable solutions that can be offered to help. Many patients (and many physicians) are under the impression that nicotine replacement is hazardous; however, continuing to smoke is much more hazardous. Patients need permission to use as much nicotine replacement as it takes. A 21 mg nicotine patch delivers about as much nicotine as smoking half a

pack of cigarettes a day, so some patients may need two patches at first, and in addition they can use nicotine gum, nicotine spray, or nicotine inhaler (or a combination of these) in as large a quantity as it takes to deal with the addiction. Medications such as bupropion and varenicline are helpful in combination with nicotine replacement. Varenicline is probably more effective than bupropion, but the latter might be more appropriate for patients with a history of depression. Lastly, counseling definitely improves quit rates.[58]

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