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Smoking and Vascular Disease

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ABSTRACT

Background: Smoking is considered a crucial predisposing factor for the development of carotid diseases, cardiovascular disease, and peripheral artery disease. Around 10% of Americans have peripheral artery disease that is most likely related to smoking, and smoking is strongly associated with abdominal aortic aneurysms. The most important cause of death among smokers continues to be cardiovascular diseases. **Methodology:** We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: smoking, cardiovascular diseases, abdominal aortic aneurysms, peripheral vascular diseases, tobacco chemicals, smoking effects on blood vessels **Aim:** In this review, we aim to study the pathophysiology and mechanism of adverse effects caused by cigarette smoking upon the vascular system. **Conclusion:** Exposure to smoking both directly and indirectly is associated with significant increase in strokes, coronary heart diseases, aneurysms, and peripheral artery diseases. Atherosclerosis is also strongly associated with cigarette smoking. Smoking cessation will rapidly improve the overall health status and decrease the risk of cardiovascular diseases. More studies are needed to evaluate and assess mechanisms associated with smoking-related cardiovascular diseases.

Keywords: cardiovascular diseases, abdominal aortic aneurysms, peripheral vascular diseases, tobacco chemicals, smoking as a culprit.

INTRODUCTION

About 16% of adults in the United States are smokers with higher prevalence among men than women. Moreover, up to 24% of school students are smokers. However, smoking rates have been decreasing recently. Smoking is considered a crucial predisposing factor for the development of carotid diseases, cardiovascular disease, and peripheral artery disease. Actually, about 10% of Americans have peripheral artery disease that is most likely related to smoking. Additionally, smoking is strongly associated with abdominal aortic aneurysms that can occur in up to 7% of male smokers.

The most important cause of death among smokers continues to be cardiovascular diseases. About 7,357 toxic chemical compounds have been documented to be present in tobacco smoke, of which nicotine is the most important. Smoking has been associated with higher active cellular process that is suggested to play a role in the pathogenesis of atherosclerosis and abdominal aortic aneurysm. Regarding costs, smoking causes large costs to health care system, and its prevention will be associated with significant decrease in costs [1].

METHODOLOGY

- **Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: smoking, cardiovascular diseases, abdominal aortic aneurysms, peripheral vascular diseases, tobacco chemicals, smoking effects on blood vessels. **The study was done after approval of ethical board of Imam Abdulrahman Bin Faisal university**.

- **Data Extraction**

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were

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resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

Cigarette Smoke

The most important addictive chemical present in smoking is nicotine, which can rapidly reach the brain after inhalation. Nicotine's molecular structure is somewhat similar to the structure a natural neurotransmitter known as acetylcholine. Acetylcholine has several effects in the brain that include areas responsible for arousal and reward. This is the mechanism in which nicotine causes euphoria, causing reinforcement for tobacco use [2].

Chemicals other than nicotine include carbon dioxide (CO_2), CO, hydrogen cyanide (HCN), acrolein, ammonia, acetaldehyde, methane, nitric acid, gas phase nitrosamines, phenols, water, humectants, carboxylic acids, nicotine, acetone, hydrogen sulfide (H_2S), carbonyl compounds, methanol, hydrocarbons, paraffin waxes, terpenoids, tobacco-specific nitrosamines, catechols, and polyaromatic hydrocarbon (PAHs) [3].

A review conducted by the tobacco products scientific advisory committee, concluded that smoking is associated with the following vascular effects: vasospasticity caused by the inhalation of arsenic, ischemic effects caused by oxidizing gases and carbon monoxide, lipid peroxidation caused by exposure to aldehydes, endothelial dysfunction and elevated blood pressure due to lead exposure, and atherosclerosis which is accelerated by PAHs [4].

The variations between smoking styles create a relatively important difference in smoking-related chemicals exposure-levels. For example, each draw's depth, time between puffs, the size of the cigarette, the inhaled amount into the lungs, and puffs number, all play a role in determining the level of exposure of each individual [1].

Free Radicals

Two different types of free radicals are associated with cigarette smoking. The tar phase constitutes mainly of the quinone/hydroquinone (Q/QH_2) complex, which can produce superoxide, by actively reducing oxygen molecules. These radicals have a long half-life. On the other hand, the gas phase has nitric oxide (NO) and nitrogen dioxide (NO_2), which are oxidized by the reaction with isoprene and other reactive species in smoke, to produce small oxygen and carbon radicals. These radicals have a relatively very short half-life [5].

Studies of electron resonance showed that the production of hydroxyl and superoxide radicals occurs simultaneously along with hydroquinone and catechol-related auto-oxidation within aqueous compounds of tar. Up to 500 million parts of nitric oxide can be present in fresh cigarette smoke. The production of nitric oxide radical occurs slowly using peroxinitrite, amine complexes, and other nitrogen oxides-including reactants. The reaction of hydrogen peroxide with nitric oxide can produce oxygen which also mediates endothelial damage. Ample evidence is present that supports the involvement of nitric oxide in the smoking-induced oxidative damage. Moreover, reactive nitrogen species are also involved in smoking-induced DNA damage, along with oxygen species. Polyphenols constitute the main source of hydrogen and oxygen in cigarette smoke. These polyphenols interact synergistically with nicotine. Another factor is also responsible for the production of reactive oxygen species, and is shown to be present in the vapor phase. These free radicals include mainly alkyl and alkoxyl free radicals [5].

Filters that contain hemoglobin can sometimes prevent the passage of nitrogen oxides, hydrogen peroxide, nitric oxide, aldehydes, carbon monoxide, and carcinogenic nitrosocompounds. Interestingly, smokers' RBCs contain more glutathione when compared to non-smokers, and thus can provide higher in-vitro protection of endothelial cells [6].

Vascular Disease in Smokers

Since 1900, the leading cause of death in the United States has been cardiovascular diseases. Of these diseases, smoking can enhance for carotid artery disease, peripheral artery disease (PAD), and abdominal artery aneurysms, as it predisposes to atherosclerosis. Up to 12 million Americans (about 12% to 20% of the Americans age 60 and older) have a peripheral artery disease, which is equally distributed between men and women. Some studies reported higher prevalence of peripheral artery disease among Hispanics, when compared to non-Hispanics white. Of people older than 60 years, up to 20% can have peripheral artery disease. Smoking is considered the most important predisposing factor for the development of peripheral artery disease, and the risk increases proportionally with the number of cigarettes [7, 8].

In the United States, stroke is considered a major cause of morbidity and disability. Most stroke cases occur as a result of occlusion. Smoking is directly and indirectly related to stroke as it contributes to obstruction of blood flow by affecting coagulability. Moreover, it is associated with thick intima-media, and atherosclerosis progression. Current male smokers aged between 60 and 64 years were found to have the highest risk of stroke occurrence. Second-hand smoke also increases the risk of stroke by 30%. In fact, more than 8,000 deaths occur annually due to strokes caused by second-hand smoke exposure [9].

Another important disease is abdominal aortic aneurysm, which is linked to atherosclerosis and mostly prevalent among smoking males. It can occur in up to 7% of old male smokers. A Swedish study has found that the prevalence of abdominal aortic aneurysm can be high even among females who are smokers, and can reach 2% in current smokers. Early smoking is strongly associated with early occurrence of atherosclerosis leading to aneurysms. In 2013, the National Vital Statistic Reports reported that more than 17 thousand deaths that occurred in 2009 in the United States were associated either directly or indirectly with aortic aneurysms [10].

Aneurysm dilation will consequently cause an increased risk of vessel rupture, and the risk is proportionally correlated with size of the aneurysm. Wide variation in pathophysiology exists when it comes to aneurysms. Common etiologies include atherosclerosis and degenerative disorders that affect the medial layer [11].

Smoking is strongly associated with both atherosclerosis and aneurysms, especially in the abdominal descending aorta. The duration and amount of smoking is important to determine the possible risk of abdominal aneurysms development, expansion, and risk of rupture. In fact, current smokers have double the risk of aneurysm rupture than on-smokers. About 90% of aneurysms are present in the infrarenal aorta, and are associated directly or indirectly with smoking [12].

Normally, collagen and elastin are present in the extracellular matrix of arterial walls and provide a strong layer to protect against pressure. In aneurysms, degenerated elastin is present. Smoking contributes to this mechanism by increasing levels of MMP-1. These alterations have been suggested to play a significant role in impaired angiogenesis, and disrupted matrix, leading to aneurysms [12].

Smoking and Endothelial Dysfunction

The first evidence to support the theory of smoking involvement in endothelial injury was from observational studies on the umbilical arteries of smoking mothers. Later, several other studies confirmed this association with altered endothelial morphology that causes the endothelium to be irregular with disturbed membranes that show blebs (microvillous-like projections). Animal models showed that exposure to cigarettes smoke caused altered morphology thoracic aorta endothelium of rats. These morphological changes were associated with a decrease in the production of endothelial prostacyclin [13].

The impairment of endothelium can cause a dose-dependent possibly-reversible dilation of arteries. This will be associated with endothelial dysfunction, and will lead to vasoconstriction of distal and proximal coronary arteries along with an increased coronary vessel tone, despite the presence of high oxygen demands [14].

Nitric Oxide and Endothelial Dysfunction

The synthesis of nitric oxide in the endothelium is also affected by cigarette smoke, causing a decrease in nitric oxide exhaled. This decrease is suggested to be caused by the inhibition of nitric oxide synthase enzyme [13].

In the pulmonary artery, smoking can lead to irreversible nitric oxide synthase inhibition within the endothelium. This was observed and documented in animal models.

However, animal models have also documented an elevated expression of the nitric oxide synthase gene. As a result, nitric oxide concentrations in the lower respiratory tract have been shown to be increased after smoking. In humans, levels of nitrate (either in plasma or in urine) were observed to stay unchanged. This suggests that humans do not absorb nitric oxide following smoking [15].

The endothelial vasodilation dysfunction related to smoking can be partially explained by the decreased activity of nitric oxide synthase. The same hypothesis can also explain the increased risk of vascular and pulmonary diseases among smokers. The coronary artery tone is also influenced by smoking, which impacts the coagulation mechanisms dependent on nitric oxide. In animal models, it was found that chronic smoking can potentially cause an age-independent high blood pressure with a significant decline in nitric oxide synthesis in the penis [16].

Carbon Monoxide and Free Radicals

Animal models have shown that when pulmonary artery endothelium was exposed to carbon monoxide, this resulted in elevated nitric oxide levels. Exposure of isolated aortas to smoking caused a dose-dependent inhibition of relaxation. This is thought to be due to decreased production of nitric oxide, causing dysfunctional endothelial relaxation. This theory was proven using cultured endothelial cells extracted from humans. Another study on rabbits' femoral veins also showed a significant decrease in relaxation after exposure to smoking, despite the absence of apparent muscle injury. In the same study, authors found that ascorbic acid may be beneficial and protective against endothelial injury related to smoke [17].

Hypoxia

Hypoxia along with exogenous nitric oxide, will together cause endothelial vasorelaxation, and consequently will cause augmented endothelial relaxation in animal models. Moreover, smoking has been associated with increased regeneration of aortic endothelium, and higher nitric oxide levels after aortic injury. Acute hypoxia is also associated with constriction of pulmonary vessels. This happens along with high replication of smooth muscles on the long term, which is associated with accumulation of extracellular matrix, consequently leading to remodeling of vessels wall. Oxidation of LDL, cytokines, and hypoxia, all play a role in the induction of oxygenase activity in smooth muscles and endothelium [18].

LDL Oxidation

Endothelial cells of smokers showed a significantly increased LDL conversion into atherogenic forms. This LDL conversion was found to be associated with thiol and superoxide. Some evidence suggests that LDL impaired with smoking caused dysfunctions in endothelial relaxation in isolated arteries [19].

Glutathione

Intracellular glutathione is present in higher doses in smokers when compared to non-smokers. This observation may be due to increased production of superoxide, which will consequently cause cardiovascular diseases. Several papers suggested that glutathione modification is involved in the damage caused by filtered cigarette smoke, despite the relatively lower levels of free radicles. The production of cGMP by endothelium is also reduced after exposure to smoking, and the detachment endothelial cells is increased. When adding thiols from external sources, endothelial cells show higher levels of protection. Thiols are suggested to express binding with several components causing this protection. In humans, this dysfunction in endothelial cells is observed for hours after exposure to smoking, and is not decreased following repeat exposures [20].

Endothelial Cell Proliferation

Increased proliferation of endothelium has been associated with cigarette smoking in rats. This phenomenon was associated with the presence of high levels of nitric oxide in the blood. Current evidence suggests that proliferation of pulmonary vessels that is induced by smoking can be partially caused by endothelin-A receptors stimulation. However, angiogenesis in rats was found to be decreased after exposure to cigarette smoke. Additionally, the exposure to smoke was found to associate with higher blood levels of endothelin-1 only ten minutes following smoking [13].

Smoking and Atherosclerosis

The development of atherosclerosis has been found to strongly associate with both smoking and chronic inflammation. The role of smoking is most likely attributed to the smoking-related exposure to several toxic chemicals that have inflammatory effects. These chemicals include aldehydes, arsenic, and PAHs. The length of exposure to these chemicals is an essential factor in determining the extent of inflammation. Cellular pathways linked with atherosclerosis have been found to strongly correlate with smoking, with significant increased atherosclerotic proliferation among smokers. A recent report found atherosclerotic proliferation to show a 50% elevation in smokers, with a 20% elevation in second-hand smokers [21].

Lipid Profile Modification

Smoking predispose to atherosclerosis by affecting the lipid profile. This effect include a significant increase in cholesterol, LDL, and triglyceride blood levels, along with decreased HDL levels. The exact mechanisms that cause these changes in lipid profile following smoking are not well understood. Moreover, it is not known if the diet variations between smokers and non-smokers affect these changes. Recent studies have suggested that insulin resistance may play a role in the pathophysiology of smoking-related cardiovascular diseases [22].

The modification of LDL is also increased with smoking, and higher levels of oxidized LDL are found in smokers. Researchers in 1988 found that exposure to smoke led to LDL modifications causing the formation of foam-cells. It was also found that smoke exposure caused human plasma to show more oxidation of LDL. Moreover, plasma cells exposed to smoke showed decreased paraoxonase activity, leading to weaker protection of LDL particles against oxidation. Studies on animal models showed that smoking initiated atherosclerosis by oxidizing LDL particles [22].

Mean serum levels of cholesterol, LDL, and triglycerides are also shown to be increased in smokers. Some theories suggest than platelets consumption is increased in vessels with atherosclerosis with the production of larger more-active platelets. Substance P-induced tissue plasminogen is also inhibited by smoking. It was also found that von Willebrand factor was present in higher levels in the serum of smokers when compared to non-smokers [23].

Inflammation

Atherosclerosis is strongly associated with inflammation, with many studies demonstrating up to 25% increase in leukocytes count in the blood of smokers. Other than leukocytes, smoking was found to cause elevation of several inflammatory markers like interleukin-6, tumor necrosis factor alpha, and C-reactive protein [24].

Atherosclerosis starts with leukocytes recruitment on the endothelium causing increased proinflammatory cytokines levels. This in turn will lead to more recruitment of leukocytes due to the interaction of cytokines with endothelium. Soluble ICAM-1, VCAM-1, and E-selectin levels increase significantly [25].

It was found that monocytes adhesion was increased by 90% with smoking. This was attributed to more adhesion molecules expressed following smoking. The rates of endothelial migration also increased by 200% after smoking. Molecules that increased after smoking include integrin CD 11b/CD 18, and ICAM-1 [24].

CONCLUSION

In conclusion, exposure to smoking (either directly or indirectly) is associated with significant increase in strokes, coronary heart diseases, aneurysms, and peripheral artery diseases. Atherosclerosis is also strongly associated with cigarette smoking. This increase in risk is influenced by the duration and amount of cigarette smoking. However, even low levels of exposure can lead to high risks. Smoking cessation will rapidly improve the overall health status and decrease the risk of cardiovascular diseases. More studies are needed to evaluate and assess mechanisms associated with smoking-related cardiovascular diseases.

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