Smoking and cardiovascular diseases

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ABSTRACT

Currently, cardiovascular diseases (CVD) are the leading cause of morbidity and mortality worldwide. Some of the CVD with higher incidence and prevalence are coronary artery disease (CAD), heart failure, angina, acute myocardial infarction (AMI), valve diseases, arrhythmias, systemic arterial hypertension (SAH), and peripheral vascular disease. Some studies on risk factors associated with CVD indicate smoking as the main predictor of sudden cardiac death due to myocardial ischemia, increased peripheral arterial disease, and stroke. According to the World Health Organization (WHO), smoking kills around 5.4 million people in the world each year, more than the sum of the victims of tuberculosis, malaria, and AIDS. In Brazil, smoking accounts for approximately 45% of deaths in men aged under 65 years and 55% in women aged over 65 years. It is estimated to cause approximately six million premature deaths worldwide, i.e., deaths caused by diseases related to smoking in people who, without smoking, would have another cause of death. The first disease associated with tobacco use was lung cancer; however, not only lung diseases, but other health problems are currently related to smoking, such as CVD.

KEY WORDS: Smoking, cardiovascular diseases, cause of death.
Introduction

Cardiovascular disease (CVD) can be defined as a disease affecting the heart or blood vessels, including coronary heart disease (disease of the blood vessels that supply the heart muscle), cerebrovascular disease (disease of the blood vessels that supply the brain), peripheral arterial disease (disease of the blood vessels that supply the upper and lower limbs), rheumatic heart disease (damage to the heart muscle and heart valves due to rheumatic fever caused by streptococcal bacteria), congenital heart disease (heart structure malformations existing from birth), deep vein thrombosis and pulmonary embolism (blood clots in the leg veins, which can dislodge and move to the heart and lungs) (1).

Currently, CVD are the leading cause of morbidity and mortality worldwide. Some of the CVD with higher incidence and prevalence are coronary artery disease (CAD), heart failure, angina, acute myocardial infarction (AMI), valve diseases, arrhythmias, systemic arterial hypertension (SAH), and peripheral vascular disease (1,2).

Several risk factors are related to CVD, both modifiable and non-modifiable. Non-modifiable factors are related to family history, age, sex, and race. Modifiable factors can be eliminated by lifestyle changes such as dyslipidemia, alcohol consumption, hyperglycemia, obesity, sedentary lifestyle, and smoking (3).

Smoking, defined in psychopathology as a drug addiction characterized by psychological dependence on tobacco consumption (4), is considered one of the most relevant risk factors for CVD. Being actively practiced by about 1.4 billion people and passively by other 2 billion people worldwide, it is considered one of the main preventable causes of disease and premature death (5).

The origin of tobacco

Tobacco is a product of natural origin extracted from the processing of leaves of plants of the species Nicotiana tabacum, originating in Central America and discovered near the city of Tobacco, Yucatán region, around 1520 (6,7). It was recreationally used by indigenous people as a straw cigarette to scare mosquitoes away and in religious rituals, being taken by European explorers to spread throughout the world (9).

Smoking as a chronic disease

Since 1997, smoking is classified as a chronic non-communicable disease (NCD), being included in the International Classification of Chronic Diseases (ICD-10) of the World Health Organization (WHO) (9), due to the high influence of nicotine dependence, a substance that has a strong power to remodel brain biology and physiology (10,11). Cigarette smoke is a mixture of more than 4,000 substances, having two phases, a gaseous and a particulate one (10,11). The gas phase is composed of carbon monoxide (CO), ammonia, formaldehyde, acetaldehyde, acrolein, among others (12). The particulate phase contains nicotine and tar, which is composed of more than 40 carcinogens (5).

Substances found in cigarettes and their harmfulness

The consumption of tobacco in the form of cigarettes exposes users to more than 4,720 components, from pesticide residues to elements to improve its appearance, such as humectants (propylene glycol, glycerol, sorbitol), flavoring and enhancing agents (cocoa, licorice, menthol, fruit extracts), in addition to several sugars and ammonium compounds (7).

In addition to nicotine and tar, which are well known, cigarettes contain other components that are extremely harmful to human health, such as plutonium, a metal with carcinogenic potential also harmful to kidney function. Cigarettes also have other radioactive components such as carbon 14, uranium, and lead. Pesticide residues are also found, including dichlorodiphenyltrichloroethane (DDT), which is associated with gastritis, ulcers, and digestive system cancers (6).

Chemical dependency is associated with nicotine. When aspirated, it reaches the brain in eight seconds (9). Tar is a compound of more than 40 substances known to be carcinogens, formed from the combustion of tobacco derivatives. These include arsenic, nickel, benzopyrene, cadmium, pesticide residues, radioactive substances such as Polonium 210, acetone, naphthalene, and even phosphorus P4/P6 (13).

The epidemiology of smoking

The WHO estimates smoking-related deaths at around 5.4 million a year, more than the sum of tuberculosis, malaria, and AIDS victims.
According to the survey, this number could almost double in approximately another decade (13).

The regular consumption of tobacco began in America and spread throughout the world through Europe, which includes rich and highly developed countries. It is precisely in these countries that there has recently been a decreased tobacco consumption due to very high cigarette taxes that have almost doubled its gross price, in addition to a large investment in educational actions, health, and regulations restricting the use of this drug in closed environments (10).

In Brazil, with the sixth cheapest cigarette sold in the world, approximately 45% of deaths of men under 65 and 55% of women over 65 were caused by smoking in 2014. An anti-smoke law eliminated smoking from indoor environments, but it was not strongly associated with a significantly decreased tobacco consumption and, unlike developed countries, consumption has increased in poor and developing countries, especially in people with lower educational level (10,11).

**Harmful effects on general health**

Smoking is estimated to cause, by diseases related to smoking, approximately six million premature deaths worldwide in people who, without smoking, would have another cause of death (14). The first disease associated with tobacco use was lung cancer, in 1950. Currently, not only cancer, but other health problems are related to smoking, such as cardiovascular and pulmonary diseases (15).

According to the American Heart Association, smoking is one of the seven controllable behavioral factors that can prevent the development of CVD (14). In addition, smoking is the main preventable risk factor for the development of atherosclerosis (16), closely linked to CAD and stroke, the two main causes of death worldwide (17).

Of the approximately 4,800 components of the cigarette, approximately 100 have carcinogenic and/or mutagenic properties, highlighting its relationship with the development of neoplasms. The types of cancer that have been linked to smoking are lung, bladder, oral cavity, esophagus, colon, pancreas, breast, larynx, and kidney cancers, in addition to acute myeloid leukemia (18).

Pulmonary disorders such as chronic obstructive pulmonary disease (COPD), chronic bronchitis, and pulmonary emphysema are also associated with cigarette smoking. Complementarily, smoking increases oxidative stress (15) and is a risk factor for blindness, deafness, pain, osteoporosis, peripheral vascular disease, Alzheimer’s disease, vascular dementia, erectile dysfunction, infertility, spontaneous miscarriage, and neonatal death (18), being considered an important global health problem (19).

**Impacts on cardiovascular health**

Tobacco increases the risk of cardiovascular disease, doubling the risk of death for smokers and considerably increasing for passive smokers. Some studies on risk factors associated with cardiovascular disease show smoking as one of the predictors of sudden cardiac death caused by myocardial ischemia, increased peripheral arterial disease, and stroke due to the acceleration of the atherosclerotic process not only in the coronary arteries but also in different arterial territories (1,20). In May 2018, on the World Against Tobacco Day, the WHO issued an alert to the important link between cigarette consumption and its harm to the general health, especially to cardiovascular health, showing the importance of educational actions to make the population aware of the risks not only of cancer, but of the development of CVD.

**Pathophysiological mechanisms of tobacco in cardiovascular diseases**

Nicotine, the largest organic substance present in cigarettes, increases plasma catecholamines that modify the vascular tone, generating hemodynamic changes. Carbon monoxide (CO) comes from the gaseous phase (combustion) and has a certain affinity with hemoglobin (Hb), which carries oxygen to all organs of the body. The binding of CO with hemoglobin forms a compound called carboxyhemoglobin, which hinders blood oxygenation, depriving some organs of oxygen and being directly related to atherogenesis (13,14).

As for the deleterious effects on arterial vasomotor response, previous studies demonstrated an immediately decreased epicardial coronary artery constriction and increased vessel resistance (21).

Other studies on arterial elastic properties show
decreased carotid and brachial artery compliance (1,21).

Atherosclerotic disease

Atherosclerosis is a chronic inflammatory disease (22) characterized by the deposition of atheromatous plaques in the tunica intima that progressively reach the media and adventitia layers (23). Its multifactorial etiology is mainly related to environmental factors and lifestyle habits (24,26).

The endothelium is structurally a simple tissue that has a complex and fundamental functionality in the integrity of blood vessel walls. Its activity makes it an active component in the maintenance of the arterial wall and vascular homeostasis, acting as a selective permeability barrier in the synthesis, metabolism, and secretion of substances (26,27). There is an important role of the inflammatory response against endothelial injury, which generates response signals to different immune system cells, subsequently contributing to endothelium changes such as vascular wall stiffening and atherosclerotic plaque formation (6).

Some of the most evidenced risk factors in the literature are dyslipidemia, SAH, smoking, obesity, diabetes mellitus (DM), family history, metabolic syndrome, and alcohol consumption, which corroborate increased endothelial dysfunction and atherosclerotic disease progression (20,25,26).

The onset of lesions occurs with the accumulation of lipoprotein aggregates in sites predisposed to injury in the tunica intima (30).

The oxidized low density lipoprotein (LDL, OxLDL) participates in the formation of these aggregates since it is not recognized by the LDL receptor when undergoing an oxidative modification by reactive oxygen species. Thus, OxLDL tends to accumulate in tissues, acquiring more pro-inflammatory and pro-atherogenic properties (31).

Subsequently, monocytes adhere to the endothelium surface, transmigrate from the endothelium to the intima, proliferate, differentiate into macrophages, and cause local lipoprotein endocytosis, generating foam cells or macrophages saturated with cholesterol. The death of these cells expose their lipid content, forming the necrotic nucleus of the lesion. These necrotic core sites accumulate smooth muscle cells that migrate from the vascular medial layer and secrete fibrous elements. Subsequently, occlusive plaques that initially grow toward the tunica adventitia are developed and expand toward the endothelium, compromising the vascular lumen (30).

Thus, the atherosclerotic or atheroma plaque is formed by a continuous and dynamic process, which again stimulates monocytes to adhere and migrate, increasing the lesion area (30). It has a variable composition, but mostly presents a fibrous cover, smooth muscle cells, mononuclear leukocytes (12), cell debris, cholesterol, foam cells, calcium, extracellular matrix components, and the necrotic nucleus. Variations in its composition can make it more susceptible to rupture, predisposing to thrombotic events (32).

Dyslipidemia and smoking comprise approximately two-thirds of the risk of developing atherosclerotic disease (24), with smoking being the largest preventable risk factor for its development. It increases vascular inflammation and loss of endothelial homeostasis. Nicotine, one of the main components of cigarettes, promotes the release of catecholamines, increasing heart rate and systemic blood pressure, hemodynamically contributing to atherosclerosis progression (16). In addition, nicotine also increases endothelial cell proliferation, induces the formation of capillary networks (neovascularization), increases platelet aggregation, and contributes to the proliferation of vascular smooth muscle cells, processes involved in the progression of the atherosclerotic plaque (16).

As a consequence, atherosclerosis can lead to thrombosis and stenosis (23), occluding arteries and obstructing cardiac, cerebral, and lower limb blood flow, generating, respectively, CAD, ischemic stroke, and peripheral vascular disease (PVD) (33), and culminating in ischemic lesions of high clinical repercussion (23). As a result, quitting smoking is beneficial and reduce the risk of mortality from atherosclerotic disease by 70% (29).

Coronary artery disease

Smoking is significantly and independently associated with the presence and extent of coronary atherosclerosis, as well as an increased risk of non-obstructive and obstructive CAD compared to non-smokers (34). According to Duarte et al. (35), the risk factors mostly associated with CAD are age and sex, with the most expressive association being for older age.
and male patients. Of the modifiable risk factors, those with the greatest association with the presence of coronary events are DM and dyslipidemia in men, and DM in women. The separation by specific age groups highlight smoking for young men (< 40 years old), and DM and smoking for women aged between 40 and 50 years. Exposure to cigarettes seems to change the balance of antithrombotic, prothrombotic, and pro-fibrinolytic/anti-fibrinolytic factors by affecting the functions of endothelial cells (EC), platelets, fibrinogen, and coagulation factors (36,37).

EC are greatly important in vascular homeostasis, maintaining the balance between vasodilation and vasoconstriction factors, thrombotic and antithrombotic factors, and fibrinolytic and anti-fibrinolytic factors. Of the vasodilator molecules, nitric oxide (NO) seems to be reduced in humans exposed to cigarettes, changing endothelial expression and activity. NO also helps regulate inflammation, leukocyte adhesion, platelet activation, and thrombosis. Therefore, a changed NO biosynthesis would have primary and secondary effects on the progression of thrombotic events (21,37).

In addition, smokers have presented higher extracellular lipid content in atherosclerotic plaques. Cigarette exposure or smoking seem to increase the inflammatory process and neovascularization within the plaque, leading to hemorrhage and increased necrotic nucleus (21). Smokers seem to have higher triglyceride levels than non-smokers and former smokers and lower HDL cholesterol levels (34).

Furthermore, exposure to cigarettes can increase sympathetic activity, leading to increased blood pressure, heart rate, and vasospasm, creating a zone of high mechanical stress near a vulnerable region. The association of these factors can cause plaque instability, contributing to its rupture and initiation of a pathological thrombosis process depending on the local balance of platelet activation, antithrombotic and prothrombotic factors, and pro-fibrinolytic and anti-fibrinolytic factors (21).

Active or passive exposure to cigarettes causes thrombosis in multiple vascular beds, affecting the function of EC, platelets, fibrinogen, and coagulation factors. Although the mechanisms responsible for these changes remain uncertain, current evidence points to greater oxidative stress mediated by free radicals and the loss of the protective effect of NO playing a central role in thrombotic diseases due to cigarette exposure (21). A study showed that high-sensitivity C-reactive protein values ≥ 3 mg/L and particularly a calcium score > 100 identified smokers at high risk for cardiovascular disease, and that these people may benefit more from smoking cessation (36).

**Peripheral venous disease**

Chronic venous insufficiency (CVI) can be defined as a set of clinical presentations caused by peripheral venous system (superficial, deep or both) abnormalities (reflux, obstruction or both), generally affecting the lower limbs (38,39). The most common CVD symptoms are pain, heaviness or fatigue in the legs, lower limb edema, especially in the afternoon, burning, nocturnal cramps, and itching (39).

CVI has a high worldwide prevalence and morbidity, with an important impact on the patients’ quality of life (38,40). International studies show that up to 80% of the population may have milder degrees of CVI, with intermediate degrees ranging from 20 to 64%, and progression to more severe degrees between 1 and 5%. This prevalence may vary between countries, as it depends on exposure to intrinsic and extrinsic risk factors in each region (38,39).

Some important risk factors are having a positive family history of CVD, higher body mass index (BMI), age, being a female, not exercising regularly, number of pregnancies, hormone replacement, number of hours standing or sitting in a day, use of birth control pills, and smoking (38,39).

Smoking is considered an important factor in oxidative stress, tissue hypoxia, and endothelial damage. The pathophysiological mechanism involved in the development of venous insufficiency in the lower limbs caused by tobacco exposure is still not fully understood. It is believed that tissue hypoxia through CO and NO fixation in hemoglobin may be the path to clarification (41).

Some authors suggest that hypoxia would activate EC, leading to the production of pro-inflammatory factors within the vessel wall and resulting in increased capillary permeability, inflammatory changes, and edema. Furthermore, many harmful effects of tobacco smoke would be due to direct oxidative damage to biological substances and phagocytic cell activation, which, in turn, would generate reactive oxygen species, increasing the endothelial and local inflammation responsible for microvascular disorders in venous insufficiency (41).
Cerebrovascular disease

The vascular aggression promoted by smoking is related to several chemical substances, mainly due to the increased production of free radicals present in cigarette smoke, promoting vascular endothelium inflammation and dysfunction and the development of the atherosclerotic process (22). Smoking also promotes a procoagulant state marked by increased fibrinogen, platelet aggregation, and hematocrit levels and reduced fibrinolytic activity (22). In addition, smoking reduces cerebral blood flow, which can further increase the risk of clot formation and consequently of ischemic stroke (23).

Scientific evidence showed that nicotine acts on the central nervous system through several neurochemical pathways and different receptors, stimulating the release of catecholamines and leading to important cardiovascular consequences. Furthermore, it leads to increased LDL, decreasing high-density lipoprotein through the mobilization of free fatty acids, intensifying vasoconstriction and accelerating blood epithelial cell damage and atherosclerosis progression (24,25).

CO, which is inhaled through smoke, binds to hemoglobin to induce hypoxia, increasing the number of red blood cells and blood viscosity and having a direct impact on thrombosis and atherosclerosis (26). Given the above, smoking not only causes coronary heart disease, but also induces structural arterial wall damage, being associated with ischemic stroke caused by atherosclerosis and by non-traumatic subarachnoid hemorrhage, caused by aneurysm formation and rupture27.

Conclusion

Smoking is the main preventable risk factor for the development of atherosclerosis, closely linked to CAD and stroke, the two main causes of death worldwide. Therefore, it is relevant that health professionals at different levels of care emphasize the importance of smoking cessation as a way to prevent CVD.

References


