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Smoking and cardiovascular diseases

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ABSTRACT

Cardiovascular diseases are the foremost cause of morbidity and mortality in the world and in our country. What is favorable in terms of epidemic cardiovascular diseases is that they are substantially "preventable". Smoking is one of the leading preventable risk factors. Smoking causes development and progression of cardiovascular diseases through different pathophysiological processes such as endothelial dysfunction, development and progression of atherosclerosis, hemodynamic effects, inflammation, hypercoagulable state, and dyslipidemia. Cardiologists, who encounter the clinical consequences of smoking, play a central role in informing patients regarding the hazards of smoking, supporting them for smoking cessation, providing psychological and pharmacological treatments as well as cardiovascular effects of these treatments. Starting the fight against smoking, which seriously threatens public health, seems to be the most appropriate start regarding fight for the prevention and control of cardiovascular diseases.

1. Introduction

Cardiovascular diseases are the foremost cause of morbidity and mortality in the world and in our country. According to Turkish Statistical Institute and based on the main ICD 10 codes, diseases of the circulatory system were by far the leading cause of death with a rate of 40.3% in 2015 (TİK, 2015). Of the deaths resulting from circulatory system disorders, 40.5% were due to ischemic heart disease, 24.3% were due to cerebrovascular disease, 20.4% were due to other cardiac diseases and 9.7% were due to hypertensive diseases (TİK, 2015).

According to 2012 World Health Organization (WHO) data, 46.2% (17.5 million) of all deaths globally were the result of cardiovascular diseases. Among these, 7.4 million were associated with ischemic cardiac diseases while 6.7 million were due to stroke. Cardiovascular diseases are responsible for 37% of deaths below the age of 70 years. Deaths due to cardiovascular diseases are estimated to be 22.2 million in 2030, 8 million of which are related directly to smoking. Furthermore, cardiovascular diseases are estimated to remain the leading cause of death for a long period of time (http://www.sbu.saglik.gov.tr; www. apps.who.int/iris.com; www.who.int/healthinfo/globalburdendisease). However, what is favorable in terms of cardiovascular diseases is that they are substantially "preventable". WHO stated that the incidence of cardiovascular diseases may be reduced by half with the control of unfavorable behaviors such

as smoking, sedentary lifestyle, and unhealthy nutrition (http://www.sbu.saglik.gow.tr; www.apps.who.int/iris. com.; www.whqlibdoc.who.int/publications/2011).

In pathophysiology and development of cardiovascular diseases, smoking is the leading factor among preventable risk factors. In risk calculation systems for cardiovascular diseases and mortality, particularly in the most frequently used SCORE system, the risk doubles in smokers (http://www.sbu.saglik.gov.tr). Nearly half of regular smokers die due to diseases associated with smoking. Life expectancy decreases by 10 years on average in smokers compared to non-smokers (Rigotti and Clair, 2013). Twenty-nine percent of deaths associated with cardiovascular diseases are attributed directly to smoking (Piepoli et al., 2016). According to 2012 data, 1.1 billion individuals are known to be smokers worldwide (www. apps.who.int/iris.com). Six million individuals die due to tobacco use or passive smoking each year (www. apps.who.int/iris.com).

According to the results of a 2012 survey on global tobacco use among adults in Turkey, 14.8 million individuals (27.1%) were found to be users of tobacco products in 2012. Frequency of tobacco use is 41.5% in men, and 13.1% in women. Among all tobacco users, 23.8% (37.3% in men and 10.7% in women) use tobacco every day. Age of onset for smokers who smoke everyday is 17.1 years. Of all users of tobacco products, 94.8% use manufactured cigarettes and 1% use hookah (http://www.sbu.saglik.gov.tr; KYTA, 2012). Current data may provide an explanation why all kinds of cigarettes must be avoided owing to the destructive effects of smoking and the incidence of cardiovascular disease.

Cardiovascular diseases such as coronary heart disease (CHD) [including myocardial infarction (MI) and sudden death], cerebrovascular disease (stroke), peripheral artery disease (PAD) and abdominal aortic aneurysm, and hypertension are identified to be directly related to smoking (Rigotti and Clair, 2013). Development of heart failure increases by two-fold in smokers compared to non-smokers. Prognosis is even worse in smoking patients with heart failure (Rigotti and Clair, 2013). Additionally, smoking may trigger cardiac arrhythmia or increase existing arrhythmia (D'Alessandro et al., 2012).

Tobacco and smoking

Tobacco was discovered in America and Australia followed by a rapid spread across the world. In Turkey, tobacco use and cultivation was started in 1600s (Yetkin, 1992). More than 90% of tobacco is used in manufacturing cigarettes; and only small amounts are used for medicinal purposes in veterinary medicine, agriculture and medicine (Yetkin, 1992). After the discovery of cigarette rolling machine in 1881, it became cheaper and resulted in a more widespread use. Tobacco was provided to American soldiers free of charge during World War I and II. Precautions against smoking because of increasing cardiovascular diseases were initiated between 1940 and 1960 (http://www.healthliteracy.worlded. org/docs/tobacco). Cigarettes contain more than 4000 cytotoxic, carcinogenic and mutagenic chemical substances, particularly nicotine, carbon monoxide (CO) and oxidant chemical gases (Behr and Nowak, 2002). There are several substances such as nitrosamines, polycyclic hydrocarbons and inorganic compounds, which enter the body in the form of particles with cigarette smoke. With each cigarette consumed, 2-3 mg nicotine and 20-30 ml CO enter the body. One g of tar of cigarette smoke contains 1018 oxygen radicals while the gas phase of the smoke contains 1015 oxygen radicals (Behr and Nowak, 2002). Free oxygen radicals result in DNA mutations with oxidative stress, progression of atherosclerosis, and chronic inflammation. These chemical substances cause endothelial dysfunction, insulin resistance, dyslipidemia, inflammation, hemodynamic changes, hypercoagulable state and atherothrombosis associated with smoking (Salahuddin et al., 2012).

Pathophysiological changes induced by smoking

Nicotine, CO and oxidant chemical substances which generate free oxygen radicals are involved in the pathophysiology of cardiovascular diseases resulting from smoking. These factors increase atherothrombosis and its progression through several mechanisms (Salahuddin et al., 2012; Fig. 1).

Endothelial dysfunction and Atherosclerosis

Nicotine causes structural changes in vascular endothelium. It stimulates DNA synthesis in vascular endothelial cells and causes vascular proliferation (Benowitz, 2003). Free oxygen radicals increase in endothelium via the oxidant toxic molecules in cigarette. The increase in cytokines as well as increased inflammation, lipid oxidation, platelet activation and vasospasm due to increased endothelium are observed alongside the decrease in production and levels of endothelial vasodilator nitric oxide (NO). Endothelial damage plays a significant role in the development and acceleration of atherosclerosis with the migration of lymphocytes, macrophages, monocytes and smooth muscle cells into the intima as well as increased chemotaxis molecules and thrombocyte adhesion leading to accumulation of oxidized LDL in intima and foam cell formation (Smith and Fischer, 2001; Benowitz, 2003; Salahuddin et al., 2012).

Hemodynamic effects of smoking

Nicotine increases the heart rate, blood pressure, cardiac output, myocardial oxygen demand and

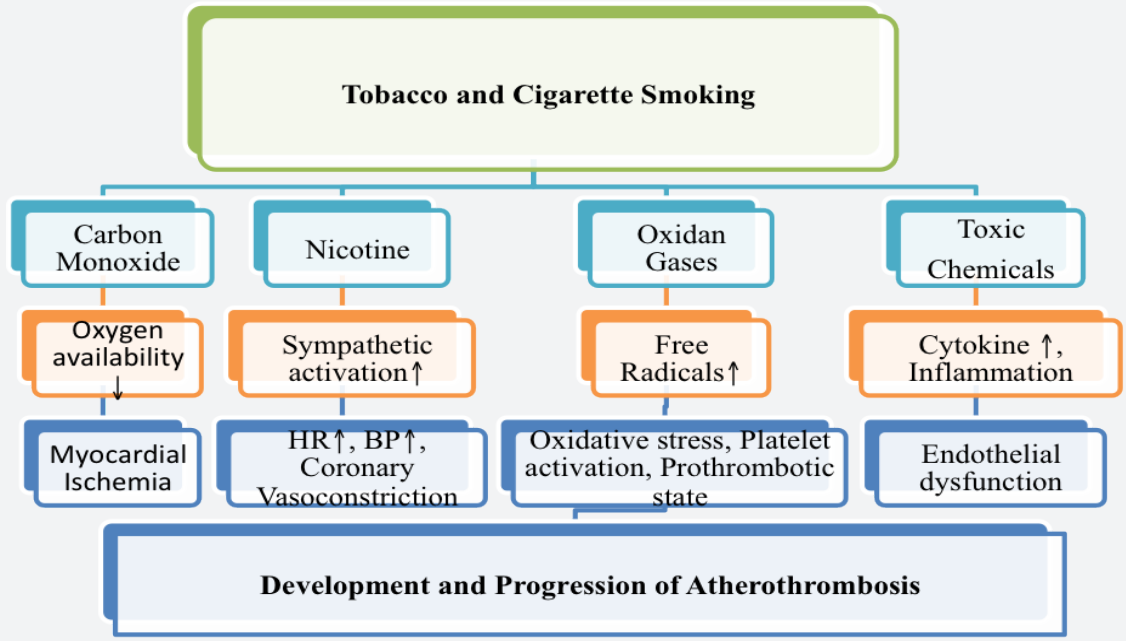

Fig. 1. Pathophysiological effect of cigarette smoking on cardiovascular disease. **HR:** Heart rate; **BP:** Blood pressure; **NO:** Nitrogen monoxide. Figure reprinted with permission from Salahuddin, S., Prabhakaran, D., Roy, A. Pathophysiological mechanisms of tobacco-related CVD. Global Heart. 2012. 7, 113-119

consumption via sympathetic activation. It causes coronary vasoconstriction. CO decreases oxygen transfer to all tissues, particularly to myocardium by binding proteins such as hemoglobin, myoglobin, and cytochrome oxidase (Benowitz, 2003; Salahuddin et al., 2012). For this reason, diastolic and systolic myocardial functions are affected by chronic smoking and are shown in clinical researchs. (Gulel et al., 2007).

Inflammation

Smoking causes chronic inflammation, which is also the basis of atherosclerosis. Smoking increases proinflammatory cytokines and adhesion molecules such as interleukin-6, C-reactive protein (CRP), tumor necrosis factor alpha (TNF-a), soluble vascular cell adhesion molecule 1, intracellular adhesion molecule 1 and E-selectin (Mazzone et al., 2001; Bermudez et al., 2002; Salahuddin et al., 2012).

Hypercoagulable state

Smoking creates a predisposition to thrombosis with the increase in thrombocyte activation, adhesion, and aggregation. It leads to a prothrombotic state by increasing plasma viscosity, coagulation factors and serum fibrinogen levels while decreasing the levels of fibrinolytic molecules such as tissue plasminogen activators. The thrombosis/fibrinolysis balance on endothelium shifts in favor of thrombosis (Benowitz, 2003; Salahuddin et al., 2012).

Lipid abnormalities

Serum cholesterol, triglyceride, very low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C) levels are high in smokers while serum high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-1 levels tend to be lower. Again, endothelial permeability and subendothelial accumulation increase with the increase of oxidized LDL-C (Craig et al., 1989; Salahuddin et al., 2012).

Smoking and insulin-resistance

Smoking is thought to cause insulin resistance by various mechanisms such as the increase in corticosteroids, growth hormone, endothelial dysfunction and oxidative stress by means of sympathetic nervous system activation. Smoking increases visceral fat. Also, waist/hip ratio is detected to be higher in smokers (Tahtinen et al., 1998; Canoy et al., 2005; Salahuddin et al., 2012).

Passive smoking and cardiovascular effects

It is called passive smoking when non-smokers inhale the smoke in smoking zones. The CO in cigarette smoke, nicotine, nitrosamines, heavy metals, polycyclic hydrocarbons are involved in the development of cardiovascular diseases. Passive smoking is known to create risks for cardiovascular diseases at least as much as smokers (Rigotti and Clair, 2013).

Water-pipe smoking and cardiovascular effects

The waterpipe tobacco smoking, also known as narghile, shisha, hookah, goza, and hubble bubble, has become prevalent in the world, especially among youth (Shihadeh et al., 2015). Waterpipe users are exposed to significant levels of carbon monoxide, nicotine, nitrosamines, carcinogenic aromatic hydrocarbons and volatile aldehydes over the duration of the smoking session, despite a common opion that waterpipe smoking is less harmful than cigarette smoking (Neergaard et al., 2007; Shihadeh et al., 2015). So waterpipe smoking has create risks for cardiovascular diseases at least as much as smokers. Using waterpipe to smoke is not a safe alternative to cigarette smoking and less harmful (Neergaard et al., 2007).

Electronic cigarettes and cardiovascular effects

Complete smoking cessation is the best outcome for smokers, but the powerful addictive effects of nicotine and the ritualistic behavior of smoking create a huge obstacle. Electronic cigarettes are devices that can vaporize a nicotine solution combined with liquid flavors and as marketed to help smoking cessation that require further investigation for advers effects (Nelluri et al., 2016). But their benefits in smoking cessation still have not been proven by adequate scientific evidence, also, they uphold nicotine addiction and may increase the risk of starting conventional cigarette. Electronic cigarettes have sympathomimetic cardiovascular effects related to nicotine exposure, also contain other chemicals that require further investigation for advers effects (Farsalinos and Polosa, 2014; Nelluri et al., 2016).

Smoking cessation treatment and cardiovascular effects

Smoking cessation must be recommended to all smokers regardless of period and amount of smoking, age, and existence of diseases (Rigotti and Clair, 2013). Quitting smoking before the age of 40 years may reduce deaths associated with smoking by 90% (Jha et al., 2013). In a survey conducted in USA, 70% of adult smokers stated that they wanted to quit smoking and more than half of these individuals reported trying to quit; however, only 6% of them were successful (Jamal et al., 2012). The major hindrance for smoking cessation is related to the addictive effect of nicotine. Cardiovascular symptoms may also be clinically apparent as well as irritability, anger, restlessness, anxiety, depressed mood, difficulty concentrating, insomnia, and increased hunger as nicotine withdrawal symptoms (Rigotti and Clair, 2013). Pharmacological treatments and psychosocial treatments are used for smoking cessation treatment. NRT (nicotine replacement therapy) such as patch, gum, and spray as well as varenicline and bupropion are the main pharmacological agents used for smoking cessation (Rigotti and Clair, 2013).

Nicotine replacement therapy (NRT) reduces nicotine withdrawal symptoms. Different results have been obtained with its use in patients with cardiovascular diseases. Nicotine patches are reported to be not as thrombogenic as cigarettes and they also do not contain CO (Rigotti and Clair, 2013). They are reported to be safely used in patients with stable cardiovascular disease, and may also be used by taking into consideration the benefit/risk ratio in patients who experienced myocardial infarction, unstable angina or and ventricular arrhythmia in the last 2 weeks (Rigotti and Clair, 2013).

Varenicline is the partial agonist of the alpha4-beta2 nicotine receptor. While it reduces nicotine withdrawal symptoms by binding nicotine receptors, it also blocks nicotine from binding to receptors again. It is reported to be safely used in patients with cardiovascular disease (Rigotti and Clair, 2013).

Bupropion is an atypical antidepressant which exerts its effects by increasing the levels of dopamine and norepinephrine. It is reported to be safely used in stable CVD. Bupropion is metabolized with the cytochrome P450 2B6 enzyme; and caution should be exercised with this agent as it may result in increased drug levels when used with medications metabolized through the same pathway, especially clopidogrel (Rigotti and Clair, 2013).

Conclusions and recommendations: Cardiologist's role

Smoking is involved in the development and progression of cardiovascular diseases through various pathophysiological mechanisms and is also the leading preventable risk factor. Cigarettes are addictive and have serious effects on individual and public economy due to treatment of resulting diseases, smoking costs, early deaths as well as the costs of behavioral and pharmacological treatments used for smoking cessation. Cardiovascular effects may be reversed by preventing cigarette use, and by smoking cessation among smokers. Cardiologists, who encounter the clinical consequences of smoking, must have a leading role in informing patients about the harms of smoking at every stage including medical and pharmacological support for smoking cessation. Starting the fight against smoking, which seriously threatens public health, seems to be the most appropriate start regarding fight for the prevention and control of cardiovascular diseases.

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