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REVIEW PAPER/*PRACA POGLĄDOWA*

Cigarette smoking and oxidative stress

Palenie papierosów a stres oksydacyjny

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ABSTRACT

Cigarette smoke is a complex mixture of more than 6000 chemical compounds, including high concentrations of free radicals and other oxidants. Cigarette smoke is also a source of free radicals. It is known that free radicals and lipid peroxidation have roles in pathogenesis of cardiovascular and pulmonary disease such as coronary artery disease and chronic obstructive pulmonary disease. Cigarette smoking is the major cause of preventable morbidity and mortality in Poland and constitutes a major risk factor for atherosclerotic vascular disease. It is believed that smoking causes increased oxidative stress because of several mechanisms, including direct damage by radicals. Moreover, numerous studies have indicated greater levels of oxidative stress in cigarette smokers, which is most likely attributable to the high concentration of reactive oxygen species in cigarette smoke. Homeostasis of an organism and its proper functioning are determined by the oxidative-antioxidant balance. Its disorder is most often associated with overproduction of reactive oxygen species that cause oxidative stress. It is a condition where an imbalance exists between the production of reactive oxygen species and the body's ability to neutralize these intermediates, resulting in cellular damage. Cigarette smoke is known to be both a source and an inducer of cellular oxidative stress, which is a factor in many smoking-related diseases, and this oxidative stress initiates a variety of pathological processes which contribute to disease development. According to the World Health Organization, active smoking is one of the leading causes of death among people in the world through diseases caused by the toxic components of tobacco smoke.

KEY WORDS

oxidative stress, atherosclerosis, free radicals, NAD(P)H oxidase, mitochondrial reactive oxygen species.

STRESZCZENIE

Dym papierosowy to złożona mieszanina ponad 6000 związków chemicznych, zawierająca wysokie stężenie wolnych rodników i innych utleniaczy. Dym papierosowy jest głównym źródłem wolnych rodników. Wiadomo, że wolne rodniki i peroksydacja lipidów odgrywają ważną rolę w patogenezie chorób sercowo-naczyniowych i płuc, takich jak choroba wieńcowa czy przewlekła obturacyjna choroba płuc. Palenie papierosów jest główną przyczyną zachorowalności i śmiertelności, której można zapobiegać w Polsce i stanowi główny czynnik ryzyka wystąpienia miażdżycowej choroby naczyń. Uważa się, że palenie papierosów powoduje zwiększony stres oksydacyjny z powodu kilku mechanizmów, w tym bezpośredniego uszkodzenia przez rodniki. Ponadto liczne badania wskazują na wyższy poziom stresu oksydacyjnego u palaczy papierosów, co najprawdopo-

dobniej przypisuje się wysokiemu stężeniu reaktywnych form tlenu w dymie papierosowym. O homeostazie organizmu i jego prawidłowym funkcjonowaniu decyduje równowaga oksydacyjno-przeciwutleniająca. Jej zaburzenie jest najczęściej związane z nadprodukcją reaktywnych form tlenu, które wywołują stres oksydacyjny. Jest to stan, w którym istnieje brak równowagi między produkcją reaktywnych form utleniających a zdolnością organizmu do neutralizacji tych związków pośrednich, co prowadzi do uszkodzenia komórek. Wiadomo, że dym papierosowy jest zarówno źródłem, jak i induktorem komórkowego stresu oksydacyjnego, który jest czynnikiem w wielu chorobach związanych z paleniem. Stres oksydacyjny inicjuje różnorodne procesy patologiczne, które przyczyniają się do rozwoju choroby. Według Światowej Organizacji Zdrowia aktywne palenie jest jedną z głównych przyczyn zgonu ludzi na świecie poprzez choroby wywołane toksycznymi składnikami dymu tytoniowego.

SŁOWA KLUCZOWE

stres oksydacyjny, miażdżyca, wolne rodniki, oksydaza NAD(P)H, mitochondrialne reaktywne formy tlenu.

ADDRESS FOR CORRESPONDENCE

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INTRODUCTION

Homeostasis of an organism and its proper functioning are determined by the oxidative-antioxidant balance. This disorder most often occurs as a result of the overproduction of reactive oxygen species (ROS). It is a condition where an imbalance exists between the production of ROS and the body's ability to neutralize these intermediates, resulting in cellular damage. There are many factors that may increase the risk of long-term oxidative stress, mainly cigarette smoking. Treatment of oxidative stress is still controversial even among experienced doctors. Oxidative stress does not give clear symptoms. They can be easily attributed to another disease or infection. The organs particularly exposed to oxidative stress are: the respiratory system, the circulatory system, the brain and the organ of vision [1–9]. Important elements in rebalancing the body are hydration, a diet rich in vegetables and fruits, and physical activity.

A better understanding of the processes underlying the initiation and development of oxidative stress could improve the results of treatment. Influence of the type of smoked cigarettes could play a primary role.

OXIDATIVE STRESS AND SMOKING

Cigarette smoke is known to be both a source and an inducer of cellular oxidative stress, which is a factor in many smoking related diseases [2, 6–8]. Oxidative stress initiates a variety of pathological processes which contribute to disease development.

According to the World Health Organization (WHO), active smoking is one of the leading causes of death among people in the world through diseases caused by the toxic components of tobacco smoke.

Tobacco smoke, which is a mixture of nearly 6,000 chemical compounds, is classified as a direct toxic agent with proven carcinogenic properties. Among the thousands of toxic compounds identified so far in cigarette smoke there are free radicals [10, 11]. Smoking may enhance oxidative stress not only through the production of reactive oxygen radicals in smoke but also through weakening of the antioxidant defense systems.

FREE RADICALS

Free radicals are one of the groups of toxic substances found in cigarette smoke. They arise as a result of combustion processes, i.e. vigorous oxidation, and pyrolysis processes, i.e. thermal decomposition. Both of the above-mentioned processes take place during the smoking of a cigarette, in the area known as the glow cone.

Free radicals, i.e. atoms or groups of atoms containing one or more unpaired electrons, are significant constituents of tobacco smoke that contribute to its toxic proper-

ties. Radicals are generated during complex pyrolysis and combustion reactions in burning a cigarette cone.

Free radicals are found in both the partial smoke phase (often referred to as tar) and the gas phase. Firstly, both the particulate and gas phases of the cigarette smoke are direct and rich sources of exogenous free radicals of many different species.

Considerable *in vivo* studies support the role of free radical reactions in atherogenesis and atherosclerotic related coronary heart disease. Free radicals are involved throughout the atherogenic process, from endothelial dysfunction to the rupture of a lipid-rich atherosclerotic plaque, which further leads to acute myocardial infarction or sudden death [12].

MITOCHONDRIAL REACTIVE OXYGEN SPECIES

Mitochondria and NAD(P)H oxidase are major ROS sources which contribute to atherogenesis. Perhaps they do not alone account for all ROS produced and other cell enzyme systems may also provide a source of oxidative stress.

A recent study showed that cigarette smoke induced mitochondrial ROS production, transcription factor activation, upregulation of inflammatory markers, DNA damage and apoptosis in endothelial cells [13].

Mitochondrial enzymes produce superoxide anions at physiological levels and can become pathologic due to mitochondrial dysfunction leading to excess ROS production or due to failure of antioxidant mechanisms. Madamanchi and Runge observed accelerated atherosclerosis and elevated mitochondrial ROS in experiments involving the deletion of antioxidant systems in ApoE-KO mice, suggesting a role for mitochondrial ROS in atherogenesis [14].

Mitochondria are also important sources of ROS in the cardiovascular system. There is growing evidence that cigarette smoke constituents impair mitochondrial function and elicit mitochondrial oxidative stress in various cell types [15–20], including cardiovascular tissues [21].

Research has shown that acrolein, a major toxicant in cigarette smoke, causes oxidative mitochondrial damage [16]. *In vitro* treatment with cigarette smoke extract (CSE) caused loss of cellular ATP and rapid depolarization of mitochondrial membrane potential, followed by apoptotic cell death [17]. In smokers a higher level of oxidative mtDNA damage has been observed [21–23]. These data support the hypothesis that cigarette smoke-induced mitochondrial damage and dysfunction may contribute to an increased risk for cardiovascular disease in smokers.

It was also observed that in addition to cigarette smoke, electronic cigarette (ecig) aerosols and copper nanoparticles induce mitochondrial ROS production, mitochondrial stress (reduced stability of OxPhos electron transport chain complex IV subunit) and DNA fragmentation in lung fibroblasts [24].

It is worth emphasizing that mitochondria consume 90% of the oxygen used by the body, and 1–2% of the oxygen metabolized by the mitochondria is converted to ROS [25]. Therefore, mitochondria are the most important cellular source of ROS and may be susceptible to oxidative damage. Impaired mitochondrial function may lead to impaired electron transport and enhanced production of ROS. Increased mitochondrial mass may also lead to the increased production of ROS.

OXIDATIVE STRESS AND ATHEROSCLEROSIS

Atherosclerosis is a chronic inflammatory disease characterized by accumulation of lipids and inflammatory cells in the walls of medium sized and large arteries [26].

The pathogenesis of atherosclerosis involves activation of pro-inflammatory signaling pathways, expression of cytokine/chemokine, and increased oxidative stress. Growing evidence indicates that chronic and acute overproduction of ROS under pathophysiologic conditions is integral to the development of cardiovascular diseases (CVD).

ROS mediate various signaling pathways that underlie vascular inflammation in atherogenesis from the initiation of fatty streak development through lesion progression to ultimate plaque rupture.

ROS production in the vessel wall is increased in all conditions considered risk factors for atherosclerotic CVD such as hypertension, diabetes, smoking, and dyslipidemia [27].

Thus, hypercholesterolemia, diabetes, hypertension, smoking, aging, and nitrate intolerance all increase production of ROS, and these have been shown to initiate several processes involved in atherogenesis, including expression of adhesion molecule, stimulation of vascular smooth muscle proliferation and migration, apoptosis in the endothelium, oxidation of lipids, activation of matrix metalloproteinases, and altered vasomotor activity.

Pathological and epidemiological evidence suggests that proinflammatory cytokines play a central role orchestrating the pathological processes underlying the development of the atherosclerotic plaque. The aforementioned findings clearly demonstrate that cigarette smoke components are able to elicit a proatherogenic microenvironment in the vascular wall in the absence of circulating factors and immunocytes.

Various animal models of oxidative stress support the notion that ROS have a causal role in atherosclerosis and other cardiovascular diseases. Human investigations also support the oxidative stress hypothesis of atherosclerosis. A main source of ROS in vascular cells is the reduced

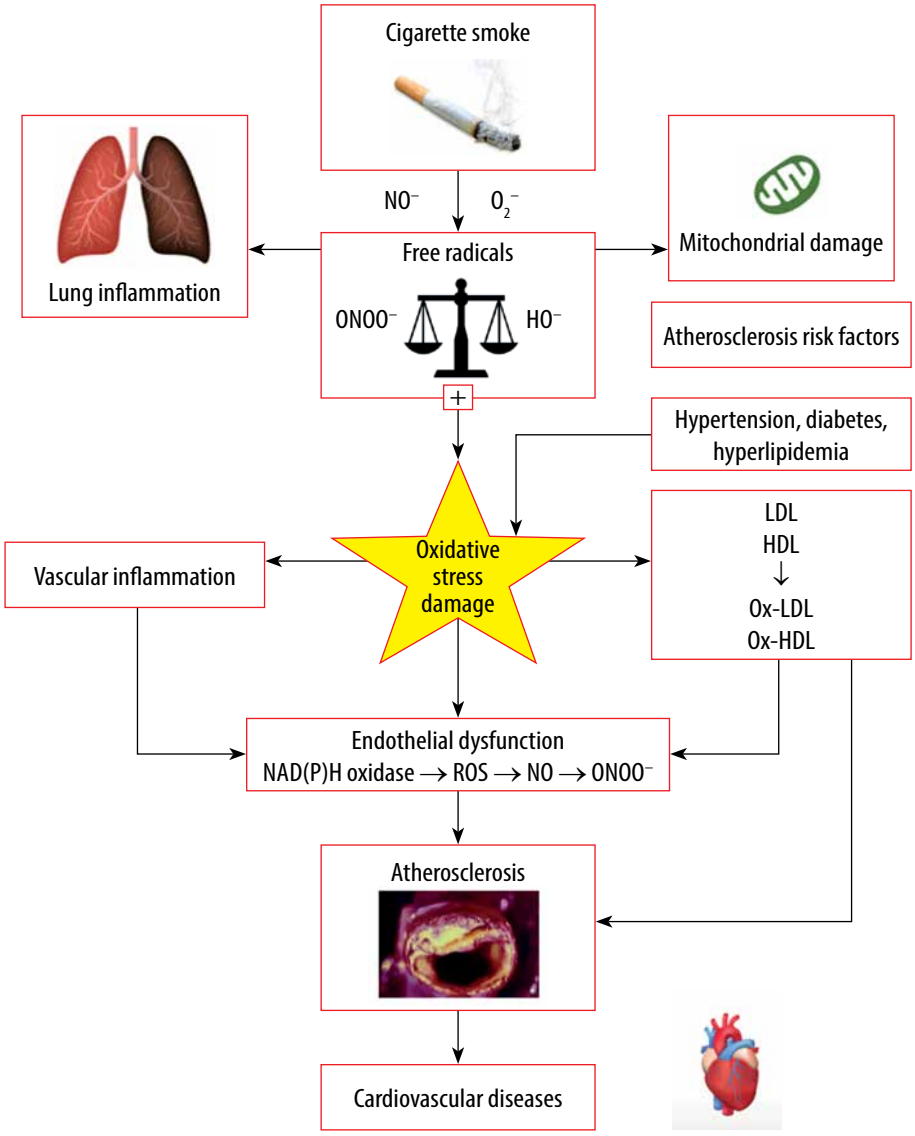

FIGURE 1. Effects of cigarette smoking and oxidative stress

nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate NAD(P)H oxidase system. In short, oxidative stress and inflammation, which are markers of atherosclerosis, promote the progression of atherosclerosis (Figure 1).

LOW-DENSITY LIPOPROTEIN AND OXIDATIVE STRESS

The initial event in the development of atherosclerosis is endothelial injury. This causes infiltration into and accumulation of low-density lipoprotein (LDL) cholesterol in the subendothelial space. LDL becomes oxidized to form oxidized LDL (ox-LDL) in pathologic states [28]. Clinical and epidemiological studies show that increased levels of LDL cholesterol promote premature atherosclerosis. The most plausible and biologically relevant modification of LDL is oxidation. LDL can be oxidatively modified by all major cells of the arterial wall [29, 30]. Oxidized LDL has several biological effects [29–34]; it is pro-inflammatory, it causes inhibition of endothelial nitric oxide synthase (eNOS), it promotes vasoconstriction and adhesion, stimulates cytokines such as interleukin-1 (IL-1) and increases platelet aggregation. In addition, ox-LDL stimulates vascular SMC proliferation [34]. Thus, intimal thickening further reduces the lumen of blood vessels, leading to further potentiation of hypertension and atherosclerosis.

According to the theory of oxidative stress, atherosclerosis is the result of the oxidative modification of LDLs in the arterial wall by ROS.

Growth factors released by these cells as well as ROS stimulate smooth muscle cell migration and collagen deposition, leading to the development of an atheromatous plaque.

ROS also induce release of matrix metalloproteinases (MMPs) that degrade the fibrous wall of the atheromatous plaque and basement membrane of the endothelial cells, resulting in physical disruption of the plaque.

F2-ISOPROSTANES AND OXIDATIVE STRESS

More direct evidence for the role of oxidative stress in atherosclerosis comes from studies with apoE−/− mice, an accepted model of atherosclerosis with high cholesterol concentration, increased lipid peroxidation, low nitric oxide bioavailability and spontaneous development of atherosclerosis similar to that found in humans. F2-isoprostanes, prostaglandin-like products of the free radical-catalyzed peroxidation of arachidonic acid and an established biomarker of *in vivo* lipid peroxidation [35–37], have been found to localize in foam cells in atherosclerotic lesions of humans [38, 39] as well as animals, and are significantly increased in the tissue, plasma, and urine of apoE knockout mice. In addition to serving as biomarkers of *in vivo* oxidative stress, F2-isoprostanes, including 8-epiPGF2, exert pathophysiological effects such as vasoconstriction [37].

ENDOTHELIUM AND OXIDATIVE STRESS

The production of free oxidative radicals is believed to induce endothelial dysfunction, an initial step of atherogenesis.

Evidence suggests that common risk factors for atherosclerosis increase the risk of the production of free ROS, not only from the endothelial cells, but also from the smooth muscle cells and the adventitial cells. Importantly, several processes are triggered by those risk factors, including the expression of adhesion molecules, the proliferation and migration of smooth muscle cells, the apoptosis of endothelial cells, the oxidation of lipids, the activation of metalloproteinases and the alteration of vasomotor activity [31, 40].

Because of the unique localization between circulating blood and the vessel wall, the endothelium has been suggested to play a crucial role in development and progression of atherosclerosis. Therefore, endothelial dysfunction is clearly associated with the disease process. Among factors that damage the endothelium, reactive oxygen species are increasingly recognized as the major factor responsible for compromising endothelial cell function [41, 42].

Endothelial dysfunction predisposes to long-term atherosclerotic lesions and has been proposed as an important diagnostic and prognostic factor for coronary syndromes [43].

Furthermore, the reduction of endothelial produced NO and O_2^- is able to blunt normal endothelial dysfunction as a result of the decreased endothelial NO production. The increased production of ROS reduces the production and consequently the bioavailability of NO, leading to vasoconstriction, platelet aggregation and adhesion of neutrophils to the endothelium. In fact, oxidative stress by hydrogen peroxide (H_2O_2) increases phosphorylation of tyrosine kinases, which leads to stronger binding of neutrophil cells on the endothelium and alteration of vessel permeability. Another mechanism through which oxidative stress (by H_2O_2) affects atherogenesis is the production of transcription factors such as nuclear factor kappaB (NF-kappaB) and activator protein 1 (AP-1), which participate in the expression of adhesion molecules such as vascular cellular adhesion molecules (VCAM-1), intracellular adhesion molecules (ICAM-1), E-selectin and other cytokines.

A large number of studies in experimental animals have shown that the common risk factors for atherosclerosis increase production of free oxygen radicals, not only by endothelial cells but also by vascular smooth muscle cells (VSMCs) and adventitial cells [44].

Orosz *et al.* in 2007 reported that both *in vivo* chronic cigarette smoke exposure and *in vitro* treatment with aqueous CSE elicit significant endothelial dysfunction in rat carotid arteries, which could be reversed by inhibition of the NAD(P)H oxidase [45].

In addition to the increased levels of O_2^- and H_2O_2 which have been implicated in proatherogenic vascular phenotypic alterations [46–48], including induction of proinflammatory gene expression [49–55], a large body of experimental evidence accumulated over the past 15 years indicates that peroxynitrite ($ONOO^-$) generation from NO and O_2^- represents a major threat to the functional integrity of the vascular endothelium [56–59].

Orosz *et al.* also found that both endothelial cells and VSMCs exhibited up-regulated O_2^- generation in vessels of cigarette smoke-exposed animals [45].

Also additional studies have reported that ecig exposed human lung vascular endothelial cells and umbilical vein endothelial cells develop oxidative stress [60, 61] with increased inflammation, cytotoxicity and endothelial cell permeability [60–64].

According to Aoshiba *et al.* [65], cigarette smoke exposure imposes oxidative stress primarily on bronchiolar epithelial and alveolar type II cells.

NAD(P)H OXIDASE

Cigarette smoke contains more than 4000 known components, and at present it is unclear which components activate NAD(P)H oxidase.

It is now well established that NAD(P)H oxidase is a major source of ROS in vascular cells and increased NAD(P)H oxidase activity is responsible for enhanced endothelial O_2^- production in aging and in pathophys-

iological conditions associated with accelerated vascular aging [66], such as hyperhomocysteinemia [56] and hypertension [67, 68].

CIGARETTE SMOKE AND OXIDATIVE STRESS

Cigarette smoking is the major cause of morbidity and mortality in Poland and constitutes a major risk factor for atherosclerotic vascular disease. It is believed that smoking causes increased oxidative stress because of several mechanisms, including direct damage by radical species and the inflammatory response caused by cigarette smoking [69].

Cigarette smoke can be divided into 2 phases – particulate matter and gas phase smoke – which contain high concentrations of ROS, NO, peroxynitrite and free radicals of organic compounds [70]. In addition to these short-lived, highly reactive substances, inhaled particles encountered in cigarette smoke, especially in the presence of ROS [71], may evoke an inflammatory response in the lung, activating immunocytes to produce ROS and promoting the production of proinflammatory cytokines.

Clinical studies and animal studies show that cigarette smoke produces generalized endothelial dysfunction in virtually every vascular bed [72–77], which is usually an indicator of increased oxidative stress. Studies have shown that cigarette smoke activates leukocytes to release reactive oxygen and nitrogen species and secrete pro-inflammatory cytokines, increases the adherence of monocytes to the endothelium and elicits airway inflammation.

Although the precise molecular basis of smoking-induced vascular injury remains unclear, increasing evidence supports the hypothesis that oxidative-nitrosative stress and inflammation provide the pathophysiological link between cigarette smoking and coronary artery disease (CAD) [72, 78].

Cigarette smoke contains reactive oxidants, which can enter the bloodstream and cause macromolecular damage in the endothelial cells. Cigarette smoking also elicits marked activation of platelets, which can also contribute to the oxidative vascular damage in smokers. Circulating cigarette smoke constituents were also shown to induce and activate ROS producing enzyme systems within the vascular wall.

Marangon *et al.* [79] have focused on oxidative stress as a potentially clinically relevant factor where cigarette smoke is associated with cancer and atherogenesis. They noted that smokers are exposed to a triple threat: first as they actively smoke cigarettes, second because of unhealthy nutrition with reduced intake of antioxidants, and finally because of consumption of large amounts of alcohol during smoking [80], which increases oxidative stress and reduces antioxidant protection.

The study of Kamcewa *et al.* showed that active smokers who smoke more than 40 cigarettes per day have higher oxidative stress than those who smoke 1–20 cigarettes per day or do not smoke, which means the number of cigarettes smoked is a significant risk factor for increased oxidative stress [81].

Moreover, research by MacNee *et al.* showed that cigarette smokers have a higher level of oxidative stress [2, 3], which can most likely be attributed to the high concentration of ROS in cigarette smoke [4].

CORONARY VESSELS AND OXIDATIVE STRESS

Csiszar *et al.* have published considerable evidence that cardiovascular aging in various tissues is associated with increased oxidative-nitrosative stress and impaired bioavailability of vasoprotective NO [58, 59, 82–84]. Based on their research, we can assume that aged arteries are more susceptible to cigarette smoke-induced oxidative stress and also more sensitive to the pro-inflammatory effects of cigarette smoke.

Kunitomo's study proved that smoking accelerates atherogenesis in the aorta of apoE- deficient mice and this acceleration can be ameliorated by administration of vitamin E [85].

Lander *et al.* found that in coronary arteries expression of TNF-α, which orchestrates pro-atherogenic vascular phenotypic changes [86], is frequently up-regulated in conditions associated with increased O_2^- and $ONOO^-$ production, such as hyperhomocysteinemia [56], aging [82] and hypertension.

Their research also showed that *in vivo* exposure of rats to cigarette smoke provokes an increase in the expression of pro-inflammatory cytokines (including IL-6, TNF-α and IL-1β) and cytokine sensitive inflammatory mediators (iNOS) in the vascular wall [45].

Meanwhile Lander *et al.* in their research found that NF-κB is activated by increased levels of ROS in many cell types [86–92], providing an important link between oxidative stress and pro-inflammatory cytokine expression in blood vessels. NF-κB is thought to induce the transcription of a large range of genes implicated in inflammation, including cytokines [93–95] which predispose arteries to atherosclerosis [96].

A recent study conducted by Van den Berg *et al.* also showed that NF-κB activity in peripheral blood mononuclear cells of smokers compared to non-smokers is significantly higher [97].

IQOS AND OXIDATIVE STRESS

Observations by Yoko *et al.* indicated that IQOS induces an oxidative stress response in rat AECs, which

suggests that heat-not-burn (HNB) cigarettes have the potential to induce oxidative stress in the airways and cause development of oxidative stress-related respiratory diseases [98].

As oxidative stress is involved in the occurrence and development of various respiratory diseases including COPD, idiopathic pulmonary fibrosis and lung cancer [99], it was also shown that HNB cigarettes can lead to these diseases by inducing oxidative stress in AECs, while Sohal *et al.* found that IQOS aerosol and conventional cigarette smoke have a similar potential to increase oxidative stress, inflammation, airway remodeling and the extracellular acidification rate [100].

Based on the above research, we can speculate that IQOS might induce oxidative stress at similar levels as conventional cigarette exposure, but induction of other stresses might be higher with conventional cigarettes than with IQOS.

NOXS

NOXs represent an important and widely expressed enzyme family with ROS generation as its primary function. Vendrov et al. reported that NOX-4 mediates cardiovascular disease in hyperlipidemic mice and expression of NOX-4 in the wall of the human artery is related to atherosclerotic severity [101].

NOX-4 expression and activity during the aging process enhance cellular and mitochondrial oxidative stress, vascular inflammation, dysfunction, and atherosclerosis. Lozhkin *et al.* observed the enhanced expression and activation of NOX-4 in Apoe−/− mice, which they ascribed to the pro-inflammatory phenotype in the VSMCs that was induced by an age-related increase in transforming growth factor β1, thus enhancing atherosclerosis [102].

CONCLUSIONS

Cigarette smoke is a major source of oxidative stress, which is one of the main factors contributing to the development of atherosclerosis. Oxidative stress undoubtedly plays an important role in the development of diseases such as COPD, lung cancer and atherosclerosis. Several studies have shown that elevated ROS levels affect the development of atherosclerosis. The development of atherosclerosis is a multifactorial process in which both elevated plasma cholesterol levels and proliferation of smooth muscle cells play central roles [32]. Free radicals are involved throughout the atherogenic process, from endothelial dysfunction to the rupture of a lipid-rich atherosclerotic plaque. These free radicals could potentially arise directly from cigarette smoke and indirectly from endogenous sources as well.

There are still studies ongoing that will allow us to identify newer therapeutic modalities selectively targeting oxidative stress in atherosclerosis and other conditions. Therefore, we believe that the evaluation of oxidative stress would be useful in the diagnosis of atherosclerosis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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