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THE ROLE OF FINE PARTICLES THAT POLLUTE AMBIENT AIR IN ATHEROSCLEROSIS PATHOGENESIS: A LITERATURE REVIEW

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ABSTRACT — Background. Atmospheric air pollution with fine particles (PM 2.5) is one of the global challenges having an impact on the disease rate, mortality, and disability of the earth's population. The optimal content of PM2.5 in the air is < 10 micrograms/m3 (according to WHO), however, this concentration is not completely safe. Currently the impact of fine particles that pollute ambient air on the progression of atherosclerosis and cardiovascular diseases (CVD) is being actively studied. Pathogenetic mechanisms enabling fine particles to partake in atherogenesis are being studied. Understanding specific fundamental mechanisms which underpin PM 2.5-induced atherogenesis allows to improve prevention-care intervention aimed to mitigate the negative impact of PM 2.5 on pathogeny of atherosclerosis and CVD.
Objective. Study of the impact of fine particles polluting ambient air on the development and progression of atherosclerosis and CVD, as well as discussion of the main pathogenetic mechanisms that underpin this phenomenon.
Methods. PubMed/Medline and Embase databases have been used for searching and analyzing modern-day literature. We looked at the terms «fine particles», and «PM 2.5» in combination «atmospheric air» with «atherosclerosis». The search for literary sources has been carried out over the past 15 years.
Results. Many experimental and clinical studies prove the connection between fine particles (PM 2.5) polluting ambient air and the risk of atherosclerosis progression and further CVD progression, all the way through to the increased risk of unfavorable cardiovascular events (acute myocardial infarction, cerebral vascular accidents) in persons inhabiting polluted areas. PM 2.5-induced atherosclerosis is underpinned by the following pathogenetic mechanisms: Induction of oxidative stress and enhancement of inflammatory reactions, progression of endothelial dysfunction, as well as dysfunction of vegetative nervous system, and imbalance of coagulative blood system.
Conclusion. According to the review conducted fine particles PM 2.5 play an important role in the pathogeny of atherosclerosis and CVD, and they partake in practically all the key pathophysiological mechanisms. PM 2.5-induced atherogenesis is underpinned by multiple mechanisms, the most important ones being oxidative stress and inflammation, endothelial dysfunction, dyslipidemia, dysfunction of vegetative nervous system and hemostatic system. Contribution of fine particles polluting ambient air in the progression of atherosclerosis is so much so great that it must be taken into account, and prevention-care intervention must be administered to persons residing in the most unfavorable areas.

KEYWORDS — Ambient air pollution, atherosclerosis, cardiovascular diseases (CVD), fine particles, PM 2.5, pathogenesis.

INTRODUCTION

The most recent report by the Global Burden of Disease (GBD), which analyzed mortality due to all causes and particular causes, stated that PM 2.5 was the fifth most important global risk factor that had caused 4.2 million deaths per year, and most of these deaths were accounted for by cardiovascular diseases (CVD) [15]. According to a statement by World Health Organization (WHO) only 18% of population are subjected to the impact of such annual average levels of fine particles (levels of fine particles (PM 2.5) that conform to the Air Quality Guidelines (AQG) (WHO, 2018) [38]. Epidemiological and toxicological studies have unambiguously demonstrated that the impact of PM 2.5 threatens human health and causes increased rate of cardiovascular diseases and mortality of human population [3, 7, 34, 39]. Atherosclerosis was a pathological foundation for practically all known CVD [2, 5, 6, 8–14]. Globally atherosclerotic CVD have long been considered the leading cause of death [2, 4, 30]. A number of published studies are indicative of the fact that PM 2.5 can promote the occurrence and progression of atherosclerosis in human organism [6, 13, 17]. The optimal content of PM2.5 in the air is ≤10 mcg/m^3 (according to WHO), however, several studies have reported that even lower levels of PM 2.5 can be associated with atherosclerosis and CVD [5, 8, 9].

The objective of this article is to study the impact of fine particles polluting ambient air on the development and progression of atherosclerosis and CVD, as well as identify the main pathophysiological mechanisms underpinning PM 2.5-induced atherogenesis.

METHODS

PubMed/Medline and Embase databases have been used for searching and analyzing modern-day literature. We looked at the terms «fine particles», and «PM 2.5» in combination «atmospheric air» with «atherosclerosis». The search for literary sources has been carried out over the past 15 years.

PM 2.5 AND ATHEROSCLEROSIS

Fine particulate matters (PM 2.5) are a complex mix of microscopic particular matters in the atmosphere that vary in terms of both size and composition. Volcano eruptions, water drops, sand storms, and plant sources are the relatively few main natural sources of PM formation. At the same time, human sources are more complex and diverse. They include fossil fuel incineration, emissions by industrial facilities, smoke, road dust, and vehicle exhaust fumes. The composition of atmospheric particulates is complex and it depends on various factors, such as emission sources and weather conditions [37]. Physical and chemical properties of PM and their effect on human body are determined by various factors relating with PM, primarily the size of particles, their concentration and composition. PM can be divided into four categories in accordance with their aerodynamic diameters (AD): large particles (AD ≤ 10 μ, PM 10), small particles (AD ≤ 2.5 μ, PM 2.5), PM 1 (AD ≤ 1 μ), and ultrafine particles (AD ≤ 0.1 μ, PM 0.1). Different-size particles can have varying impact on human health. For instance, PM 10–2.5 can be deposited in respiratory system causing diseases including cough, hyper sensitivity, and bronchitis [28]. PM 2.5 can move up and down respiratory passages and enter alveoli and stay deposited in alveoli thereby causing inflammation in the lungs. The finest components, especially ultrafine particulates, are able to enter blood circulation and blood cells via the vascular barrier, which testifies to the substantially increased number of studies that evaluate the impact of high and low concentrations of PM 2.5 on human health, which demonstrate negative effect on human health due to the impact of PM 2.5, even at the levels below those recommended by WHO standards [36]. There is a 'dose-effect' relationship between PM 2.5 concentration and the ability to cause inflammatory responses and oxidative stress, which positively correlates with disease rate and mortality rate due to CVD [6, 41]. In vitro и in vivo trials also provided evidence in support of this viewpoint [3, 15]. Release of inflammatory factors during atherosclerosis progression depends on PM concentration [41, 43]. Toxicity of a certain dose of PM 2.5 and its main components is based on the concentration of pollutants in the actual milieus, as well as frequency and duration of exposure of pollutants on human body [42, 43]. PM 2.5 composition substantially varies depending on particular areas and weather conditions which may have varying toxicological effect. At the same time, organic components of PM 2.5 can be more closely connected to CVD, while inorganic components can be more closely related to pneumopathy [25].

Although various components of PM 2.5 have varying degree of impact of human health, they nonetheless promote the occurrence and progression of atherosclerosis. A major study stated that long-term exposure to organic carbon which is part of PM 2.5 can cause the increase of Intima-media thickness (IMT) of carotid artery [20]. Another study also indicated that all the reviewed components of PM 2.5 were related with increased IMT of carotid arteries, and that organic carbon had the highest pathogenetic effect [32]. A recent study conducted in China stated that each increase of iron concentration by 0.51 μ/m3 and nickel-iron by 2.5 ng/m^3 in PM 2.5 resulted in the increased of oxidized LDL (ox-LDL) in blood by 1.9% (95% CI 0.2%–3.7%) and 1.8% (95% CI 0.2%–3.4%), correspondingly, which allows to suggest that the metal component of PM 2.5 can promote enhancement of oxidative stress related to PM 2.5-induced atherosclerosis [40].

THE KEY PATHOGENIC MECHANISMS OF PM 2.5 — INDUCED ATHEROSCLEROSIS

Oxidative stress and inflammation. PM 2.5 depositing in bronchi and alveoli after inhalation causes local and systemic inflammation, as well as oxidative stress, which as it has been widely acknowledged is one of the most important mechanisms favoring atherosclerosis [8, 10]. As PM 2.5 is a complex mix comprising a multitude of different aldehydes, polycyclic aromatic hydrocarbons (PAHs), transition metals, and other organic and inorganic components, they can enter into various chemical reactions, both between themselves and between chemical components of a human body. When these substances enter human body they are able to change initial oxidation-reduction homeostatic body state and oxidation-reduction processes by way of generating active oxygen species and nitrogen (AOS/ANS)[16, 35]. Inflammatory reaction and oxidative stress promote and enhance each other, promoting a number of reactions including generation and breakage of atherosclerotic patches. Thus PM 2.5 can indirectly promote and occurrence and progression of atherosclerosis via oxidative stress and inflammatory reaction.

Endothelial dysfunction. Endothelium damage is widely acknowledged as the initial event for

the progression of atherosclerosis. Endothelial cells release endothelial factors that cause constriction and relaxation of blood vessels and maintain balance between them using a complex regulatory mechanism. Reactive hyperemia, flow-mediated vasodilatation (FMD), vasoconstriction and baseline arterial diameter (BAD) are sensitive indicators of endothelium function [24]. An extensive incidence study showed that long-term exposure to PM 2.5 can substantially degrade endothelium function due to the reduction of FMD and enhancement of vasoconstriction [21]. In vivo and in vitro trials also provided the evidence of progression of PM 2.5-induced damage of endothelial cells and disruption of their normal operation. It has been demonstrated that dysfunction of endothelial cells caused by PM 2.5 was mostly implemented via indirect cytotoxic effected as caused by inflammatory cytokines and oxidative stress [29]. Thus, PM 2.5 can initiate damage and dysfunction of endothelial cells thereby causing a number of pathophysiological reactions in atherogenesis.

Lipid storage disease. Lipid storage disease is yet another important risk factor for atherosclerosis progression [10, 12, 17]. Randomized double blind cross-sectional study showed that the impact of PM 2.5 had resulted in significant changes in whey metabolites, including hormones, glucose, amino acids, and lipids [22]. Recent studies demonstrated that the impact of PM 2.5 can cause dyslipidemia, including the increase of concentration of total cholesterol, LDL and ox-LDL, levels of chylomicrons and triglycerides, as well as reduction of the level of antiatherogenic particles (high density lipoproteins (HDL)) [23]. These studies provided compelling evidence that PM 2.5 can accelerate congestion of lipids in plates changing the metabolism of lipids and the properties of lipoproteins, such as stimulation of acidification of LDL and their transformation into more atherogenic particles of ox-LDL.

Disruption of vegetative nervous system. Abnormal agitation of vegetative nervous system is one of the main mechanisms of malfunction of the cardiovascular system caused by PM 2.5. Parameters, such as heart rate, heart rate variability (HRV), and arterial tension, are governed by vegetative nervous system. HRV is a marker of vegetative nervous system of the heart [1]. Epidemiological studies showed that the impact of PM 2.5 can disrupt operation of vegetative nervous system of the heart, as well as change HRV [19]. The main mechanism lies in the fact that excessive oxidative stress and systemic inflammation aggravate the negative impact of PM 2.5 on cardiac vegetative function resulting in the reduction of HRV [27]. Besides, the impact of PM 2.5 can also cause dysfunction of sympathetic nervous system causing drastic variation of arterial tension. Elevated blood pressure can stimulate platelet-derived growth factor (PDGF) expression which, in turn, additionally induces proliferation of smooth muscle cells [27, 28]. In addition, hypertension can give rise to the formation of fibrous capsules and cause breakage of atherosclerotic patches [6, 10, 14].

Disruption of hemostatic system. Yet another possible mechanism of progression of atherosclerosis and CVD is agitation of hemostatic system caused by PM 2.5. Platelets and various coagulating albumens take part in the regulation of occurrence and development of atherogenesis and CVD by regulating inflammation, acidification, and immunoreactions. The impact of PM 2.5 is strongly correlated with changes in the concentration of blood coagulation markers, including fibrinogen, endogenic thrombin, tissue plasminogen activator (t-PA) and inhibitor of plasminogen activator-1 (PAI-1) in human blood serum, which is proves the connection between the hypercoagulation condition and the impact of PM 2.5 [18]. It has been shown that PM 2.5 inhibited t-PA and increase the release of PAI-1 from endothelial cells. Besides, PM 2.5 accelerates the formation of arterial thrombus due to enhanced agitation of platelets and aggregates of platelets-monocytes [33]. Long-term exposure of patients to high concentrations of PM 2.5 can result in the increased risk of progression of venous thrombosis and changes in the structure of atherosclerotic patches thereby increasing the probability of their breakage [26].

CONCLUSION

In view of the above ambient air pollution by fine particles (PM 2.5) must be considered one of the key risk factors in the development and progression of cardiovascular diseases. Of most concern is the information about excessive norms of impact of PM 2.5 on human body. PM 2.5-induced atherogenesis is underpinned by multiple mechanisms, the most important ones being oxidative stress and inflammation, endothelial dysfunction, dyslipidemia, dysfunction of vegetative nervous system and hemostatic system. Understanding specific pathophysiological mechanisms allows to recommend patients residing in the most unfavorable areas in terms of PM 2.5 pollution to allow prevention-care intervention aimed at restricting the negative impact of PM 2.5.

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