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Electronic Cigarettes, Diabetes, and Cardiovascular Disease

Mini Review

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Abstract

Conventional tobacco smoking is well known to cause type 2 diabetes and cardiovascular diseases. Smokers have switched to using electronic cigarettes as a smoking cessation tool. However, electronic cigarette use is rapidly increasing in adolescents and young adults, although the safety research of electronic cigarettes on human health impact is extremely limited. The widely using of electronic cigarettes raises alarming public health concerns. The current review summarizes the recent research data about the adverse effects of electronic cigarettes on metabolic diseases and cardiovascular diseases, which will help to develop more-feasible regulations on electronic cigarettes for protecting human health.

Keywords: *Electronic Cigarettes; Tobacco Smoking; Nicotine; Diabetes; Cardiovascular Disease*

Introduction

The conventional and combustible tobacco cigarettes contain much more toxic substances, which lead to the well-known serious health issues, including cancer, cardiovascular diseases, and metabolic disease. Many smokers have switched to electronic cigarette (E-cigarette) [1], a novel battery-powered nicotine delivery device, as a presumably less harmful alternative. The extensive marketing and advertising campaigns and imaginary safety have triggered an exponentially increased use of E-cigarettes not only by adults but also by middle and high school students [2]. The rapid increase in using of E-cigarettes among youth has emerged as an alarming public health issue [3]. Significant health implications of E-cigarette use in adolescent populations may include acute and chronic effects on neuron development, exposure to harmful carcinogens, and life-long nicotine addiction that can lead to metabolic disease, hypertension, arterial stiffness, stroke, cardiovascular disease, and cancer. Although the prevalence of E-cigarette use is dramatically increasing, there remains a lack of sufficient research regarding its toxicity and addiction potential, as well as no final policy on E-cigarette till August in 2016. Review from the published data will have significant implications for developing future regulations for E-cigarettes or other alternative nicotine delivery devices in the United States and worldwide.

Major components in e-liquids and aerosols of E-cigarettes

E-cigarettes use batteries to heat a liquid, known as e-liquid or e-juice. Heat transforms the e-liquid into a vapor, or aerosol that can be inhaled. Analyses of e-cigarette liquids using gas or liquid chromatography coupled with mass spectroscopy have unraveled the

components of e-liquid. E-liquid usually contains a mixture of the following compounds: water, solvents (including propylene glycol (PG), vegetable glycerin (VG), or a combination of the two), flavorings (for example aldehydes from fruit, nitrosamines from tobacco, and diacetyl from Peach Schnapps) [4,5], and variable dose of nicotine (0, 8, 12, 18, 24, or 36 mg/mL) [6]. The combination of VG and PG as the vehicle facilitates delivery of more nicotine to the human body than VG alone, whereas the menthol flavor in the e-liquid does not lead to more nicotine delivery to human body [7]. Also, the e-liquid flavors and pH value may affect nicotine absorption [8].

Heating e-liquid with metal coil powered by the battery of E-cigarettes will generate aerosols, which are inhaled by the user and are more directly associated with adverse health events. Constituents of the E-cigarette aerosols include nicotine [9,10], acrolein, acetaldehyde, formaldehyde [11-13], and metal particles (including nickel, cadmium, lead, chromium, manganese, or arsenic) [14,15] (Table 1). Although research on the biological effects of E-cigarette liquids and aerosols is still limited, it appears that E-cigarette aerosols do have adverse effects on a variety of humans or mouse cell types.

Major constituents	Mechanisms	Associated diseases	References
Nicotine	ROS↑, inflammation↑	Atherosclerosis, AAA	[16,17]
Acetaldehydes	N/A	Heart rate↑	[11,18]
Formaldehyde	Oxidative stress↑	Cardiovascular dysfunction	[19,20]
Acrolein	Irritant and oxidant	Cardiomyopathy, Atherosclerosis	[21,22]
Metal particles (nickel, cadmium, lead, chromium, manganese, or arsenic)	Oxidative stress↑, inflammation↑, mitochondrial DNA damage↑	Respiratory disease, Atherosclerosis	[14,23]

Table 1: *Major constituents in E-cigarette aerosol and their adverse effects*

AAA: Abdominal Aorta Aneurysm, N/A: Not Available

E-cigarettes and metabolic disease

There is less study on the effect of E-cigarettes on metabolic diseases till now. Most E-cigarettes contain nicotine in a concentration of 6~24 mg/mL. Since nicotine inhibits lipogenesis [24], enhances lipolysis, and increases circulating free fatty acid [25], which strongly induces metabolic insulin resistance and the following type 2 diabetes in humans and animal model [26]. Thus nicotine-containing E-cigarettes would lead to the development of type 2 diabetes in humans. In addition, a recent study was conducted with neonatal mice being exposed to E-cigarette cartridges containing either 18 mg/mL nicotine in PG or PG vehicle alone for the first ten days of life. Mice exposed to 18 mg/mL nicotine with PG have a 13.3% reduction in total body weight, while PG-exposed mice have an 11.5% decrease in total body weight when compared with age-matched room air mice [27]. These studies indicate that exposure to E-cigarette PG emissions during the neonatal period negatively impacts weight gain. However, it is unknown whether the body weight reduction is due to the impaired development of fat mass or lean mass mediated by E-cigarette-altered metabolism. All these reported studies further suggest that nicotine replacement products, such as E-cigarettes or patches, are not good smoking cessation tools for people with diabetes.

E-cigarettes and cardiovascular dysfunction

It has been scientifically proven that nicotine enhances atherosclerosis formation [17] and plaque instability, increases blood pressure, as well as accelerates the formation of abdominal aorta aneurysm in the animal model and humans [16]. Likewise, nicotine-containing E-cigarettes may also adversely impact the integrity of cardiovascular system [28]. There are several types of research on the effects of acrolein, acetaldehyde, or formaldehyde on the cardiovascular systems [29], but they are not directly focused on E-cigarettes. Interestingly, nicotine-containing E-cigarettes acutely increase diastolic and systolic blood pressure, as well as heart rate in humans [7]. E-cigarette users have higher mitral annulus diastolic velocities and diastolic strain rate, and lower isovolumetric relaxation time corrected-to-heart rate, myocardial performance index calculated from Doppler flow and tissue Doppler [30]. These data suggest that E-cigarettes impair myocardial function. Moreover, use of E-cigarettes does not present statistically significant alternations in the stiffness index (SI) and reflection index (RI), two parameters of arterial stiffness, although smoking of a conventional cigarette increases arterial

stiffness [31]. Later, it was reported that E-cigarette does increase aortic stiffness and blood pressure in young smokers [32]. E-cigarette aerosols contain chromium and nickel nanoparticles, which instigate atherosclerosis in apoprotein E-knockout (ApoE-/-) mouse model [23]. E-cigarette vapor dramatically increases the permeability of microvascular endothelial cells in vitro [33]. Baboon abdominal aortic rings treated with e-liquid for five days presents increased elastin fiber fragmentation, reduced elastin fiber density, and decreased smooth muscle cell density when compared with vehicle (serum–free Dulbecco's modified Eagle medium) treatment [34]. A recent study indicates that habitual E-cigarette users have significantly decreased high-frequency component, an indicator of vagal activity, as well as significantly increased low-frequency component, a mixture of both vagal and sympathetic activity, and the low-frequency to high-frequency ratio, reflecting the cardiac sympathovagal balance, when compared with control nonusers [35]. E-cigarette users have increased oxidative stress, demonstrated by elevated low-density lipoprotein oxidizability in plasma, as compared with nonuser individuals [35]. These results imply that E-cigarette increases oxidative stress and cardiac sympathetic activity contributing to cardiovascular disease. Also, E-cigarette extracts inhibit the expression of tight junctional protein ZO-1 in cultured mouse primary brain microvascular endothelial cells, and E-cigarette vaping enhances mouse brain vascular inflammation and stroke injury, suggesting E-cigarette has a detrimental effect on the cerebrovascular system [36].

Perspectives

E-cigarette exposure may be one of the most prevalent and preventable environmental risk factors for metabolic and cardiovascular disease in future. However, there is an absence of sufficient data that directly address the long-term effects on health outcomes of E-cigarette use and the underlying mechanisms. Now, it is warranted to 1) Determine the short- and long-term effects of constituents of E-cigarette aerosols on lipid, glucose, and amino acid metabolism; 2) Validate the involvement of specific E-cigarette components in acute and chronic endothelial cytotoxicity and endothelial dysfunction; 3) Evaluate and understand the relative cardiovascular toxicity of vapors from E-cigarette of varying nicotine levels and vehicle chemical composition, using an innovative physiological assay; 4) More research is needed to evaluate the efficacy of E-cigarettes as a smoking-cessation products [37]. Even as these investigations are underway, regulations that make active or passive E-cigarette exposure unavailable to children is required. It is warranted that discourage nonsmokers from using E-cigarettes. Clinical and epidemiological studies are also needed to clarify the impact of E-cigarette use among persons with pre-existing metabolic and cardiovascular diseases.

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Disclosures

The authors declare that there are no conflicts of interest.

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