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Electronic cigarette aerosol increases the risk of organ dysfunction by enhancing oxidative stress and inflammation

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Electronic Cigarette Aerosol Increases the Risk of Pulmonary Dysfunction by Enhancing Oxidative Stress and Inflammation

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None

Abstract

An electronic cigarette is a rechargeable device that produces an inhaled aerosol containing varying levels of nicotine, and inorganic and organic toxicants and carcinogenic compounds. The aerosol is generated by heating a solution of propylene glycol and glycerin with nicotine and flavoring ingredients at a high temperatures. The e-cigarette was developed and marketed as a safer alternative to the regular cigarette which is known to be injurious to human health. However, published studies suggest that the aerosol of e-cigarette can also have adverse health effects. The main objective of this review is to briefly describe some consequences of e-cigarette smoking, and to present data showing that the resulting increased oxidative stress and inflammation are likely to be involved in effecting to lung damage. The aerosol contains varying amounts of organic and inorganic toxicants as well as carcinogens, which might serve as the source of such deleterious events. In addition, the aerosol also contains nicotine, which is known to be addictive. E-cigarette smoking releases these toxicants into the air leading to inhalation by non-smokers in residential or work place areas. Unlike regular tobacco smoke, the long-term consequences of direct and secondhand exposure to e-cigarette aerosol have not been extensively studied but based on available data, e-cigarette aerosol should be considered harmful to human health

1. Introduction

In 2003, Hon Lik, a Chinese pharmacist patented an electronic-cigarette (e-cigarette), which initially was marketed in China, and then entered the USA market in 2007. The e-cigarette is a rechargeable lithium battery powered device, which produces an aerosol that can be inhaled. The aerosol is produced by heating a solution of propylene glycol and glycerin with or without nicotine at high temperatures (186-292ºC) that are required to produce the aerosol (1). This type of smoking device was developed and marketed as an alternative to tobacco cigarettes that could lead to cessation of tobacco cigarette smoking. E-cigarettes are widely perceived as a safer alternative to conventional cigarettes (2, Buchanan et al., 2020). Between 2014 and 2017, marketing strategies by British and US company led to an increase in the sale of e-cigarettes by 146%. However, JUUL laboratories, an American e-cigarette company, developed an e-cigarette resembling a USB flash drive. This device which delivers much high levels of nicotine than other devices therefore, poses a greater risk of addiction (3) led to a 640% increase in sales. The use of e-cigarettes by high school students has risen dramatically, from 13% in 2014 to 27.5% in 2019 (4, Cullen et al., 2019). However, rather than constituting a less harmful substitute for regular cigarettes, e-cigarettes have been found to act as a complementary product in 14-17 year olds (5,Kinnunen et al., 2021).

Because of potential health concerns, a number of studies have investigated adverse health effects of e-cigarette aerosol on both smokers and non-smokers who received aerosol from secondhand exposure. E-cigarette aerosol led to severe lung injury and 12 deaths among e-cigarette smokers in the USA (CDC 2019). In addition to pulmonary dysfunction, the use of e-cigarettes caused defects in the heart (6), eye (7), and oral cavity (8). There have been several reports that e-cigarette aerosol can lead to increased oxidative stress and inflammation and this may in part account for the reported pathogenesis of acute respiratory distress, heart, and eye defects (9-11).

Both inorganic and organic toxicants, and carcinogens in the aerosol may contribute to oxidative and inflammatory damage to the lung (described in separate section ~~later~~). Since the aerosol releases many potentially harmful substances in the air, there is a likelihood that deleterious secondhand exposure of non-smokers of e-cigarettes may occur. The long-term consequences of secondhand exposure to aerosol remain unknown. There are no studies on the tissue levels of markers of oxidative damage and inflammation after exposure to aerosol. Animal models have provided useful information concerning the role of free radicals and inflammation in the pathogenesis of aerosol-induced damage (12, Gotts et al., 2019, 13 Kleinman et al., 2020).

A comparative analysis of the toxicants of e-cigarette aerosol and tobacco cigarette smoke found that a number of toxic constituents were lower in the aerosol than in the smoke of tobacco cigarettes (14)Goniewicz. However, the size of particles in e-cigarette aerosols is smaller than those in the smoke of regular cigarettes [15Mikheev]. This is important as very fine particles can deposit deep in the lung and can result in chronic inflammatory diseases such as COPD (16Traboulsi et al., 2020). While toxicological reports suggest that e-cigarettes may be safer than conventional cigarettes (17Hussein et al., 2019), the potential long-term effects of e-cigarette consumption have not been extensively studied (18Marques et al., 2021).

2. Health Effects of e-Cigarette Aerosol

2.1 The Respiratory System

Human studies: The presence of nicotine in e-cigarette aerosol can lead to addiction in e-cigarette smokers (19Drazen et al., 2019). The Centers for Disease Control and Prevention (CDC) summarizing input from 25 State Health Departments documented reported 213 cases of severe pulmonary disease associated with e-cigarette vaping (20Schier). Harmful constituents of the aerosol can cause throat and mouth irritation, cough, nausea, and vomiting (21Chen). The use of e-cigarettes leads to constriction of airways, and this may aggravate the symptoms of asthma, emphysema or chronic bronchitis (22 Varfarvas). It has been suggested that the risk of cardiac arrhythmias and hypertension may be increased due to the presence of toxicants in the aerosol of e-cigarettes, in addition to the elevated risk of lung disease (23 Lippi). e-cigarette

smokers who used tetrahydrocannabinol (THC) in e-cigarette devices were found to have bilateral infiltrates in the lung, 94% of these were hospitalized and 32% underwent intubation and mechanical ventilation, and one death occurred (24Layden). In addition, 98% of patients showed respiratory distress, 81% had gastrointestinal problems, and all had systemic symptoms such as weight loss, fevers, headache, and malaise.

Since 2019, over 2600 cases and 60 deaths of E-cigarette or vaping-product associated lung injury (EVALI) have been reported in the USA. A significant proportion of these patients required hospitalization and admission in the intensive care unit. Older patients and those with pre-existing diseases such as heart disease and pulmonary damage were at a higher risk for mortality and morbidity (25Cherian). A further analysis of EVALI patients with respect to clinical characteristics (26Heinzi) found 46% of 156 patients with EVALI, were admitted to an intensive care unit, while 29% required mechanical ventilation, and 4 died in the hospital. Of the 86 patients in this group who were interviewed EVALI, used THC-containing e-cigarettes, 66 used cannabinol (CBD) containing e-cigarettes, and 41 used nicotine-containing only vaping products. A major cause of EVALI was attributed to the presence of Vitamin E or vitamin E acetate found in many THC-containing products in studies conducted by the Centers for Disease Control and Prevention (CDC) (27 Boudi et al., 2019). This form of α-tocopherol is used as a condensing agent in e-cigarettes, and has been found in lung fluid samples of their users. Since vitamin E acetate in the presence of oxidizing agents such as inorganic and organic toxicants can be oxidized and then act as a pro-oxidant rather than as an antioxidant, this may be the mechanism by which vitamin E acetate could facilitate the pathogenesis of lung injury (28,29 Burkitt and Milnes 1996, Kanane et al., 2017). However, significant lung injury by a vaping product, can occur even in the absence of a-tocopherol, tetrahydrocannabinol or nicotine (13 Kleinman et al., 2021). Other chemicals produced by use of electronic cigarettes, likely to contribute to lung injury, include silica, heavy metals, benzaldehyde, diacetyl, propylene glycol, glycerin, acetaldehyde and formaldehyde (30Winnika and Shenoy, 2020).

Acute exposure to nicotine-free e-cigarettes transiently impaired endothelial function in healthy volunteers (31 Caporal). e-cigarette aerosol containing nicotine elevated the levels of circulating

extracellular vesicles of endothelial and platelet origin in the blood of healthy volunteers suggesting further vascular damage (32 Mobarrez).

A cross-sectional random-dial telephone survey of 8,087 adults who had asthma or chronic obstructive pulmonary disease, found an association between smoking e-cigarettes and exacerbation of adverse respiratory events (33Wills). This epidemiologic study does not establish a causal relationship between e-cigarette smoking and further aggravation of asthma or chronic obstructive respiratory disorder. To answer this question, it is important to perform an intervention study with e-cigarette on patients using e-cigarettes who have developed these lung diseases.

Animal and Cell Culture studies: E-cigarette aerosols studied in a variety of rodent model systems have been found to be damaging to a variety of organ systems. In addition to the inevitable CNS mediated onset of addiction to nicotine, the respiratory, cardiovascular and immune systems appear to be especially impacted by electronic nicotine delivery devices (ENDS) (34Millano et al., 2020).

Inhalation of nanoparticles of nickel hydroxide induced oxidative stress and inflammation in the lung and heart of mice (35Kang). In another mouse model, extended exposure to e-cigarette aerosol increased infiltration of inflammatory cells including eosinophils into the airways, stimulated the production of inflammatory cytokines interleukin-4 (IL-4), IL-5 and IL-13 in the lung, and increased airway hyper-responsiveness. In humans, e-cigarettes could in this manner exacerbate allergy-induced asthma (36 lim).

E-cigarette aerosol condensate was cytotoxic to alveolar macrophages in culture at lower concentrations than unvaped e-cigarette liquid, and led to increased apoptosis and necrosis (18). The elevation of stress response genes in primary rat alveolar epithelial cells caused by smoke extracts from either e-cigarettes or regular cigarettes did not differ (37Ito et al., 2020).

3. Effects on Other Organ systems

3.1 Cardiovascular system

Human studies: A comparative study between the effects of smoking e-cigarettes or regular cigarettes, found ~~that~~ the levels of peripheral systolic blood pressure to rise significantly for 45 minutes after vaping nicotine-containing liquid, but only for 15 minutes after regular cigarette smoking (3Franzen). Furthermore, the heart rate was elevated for 45 minutes after vaping an e-cigarette with nicotine-containing liquid, while it was unchanged after cigarette smoking. Using these indices of impairment of function, e-cigarette smoking appears to be more detrimental than smoking of regular cigarettes. Most reports on cardiovascular effects of e-cigarettes are based on acute exposures and the consequences of extended e-cigarette exposure remains an important gap to be filled (40Buchanan et al., 2020).

Animal Studies: Exposure of mice to nicotine-containing e-cigarette aerosol led to decreased left ventricular fractional shortening, a reduced ejection fraction, and increased atherosclerosis in the aortic root compared to controls (41).

3.2. Ocular System

Human studies: e-cigarette aerosol induced moderate to severe dry eye symptoms resulting from poor quality of tears (7).

3.3 Oral cavity

A prior review has evaluated the effects of e-cigarette aerosol on oral cavity lesions and indicated that adverse consequences to oral health may be associated with e-cigarette use (42Yang et al., 2021).

3.4 Carcinogenicity

Vapor from e-cigarette condensate enhanced metastatic lung colonization and increased levels of several tumorigenic factors of breast cancer cells in a mammary fat pad model (43Pham et al., 2020).

4. Evidence for Increased Oxidative Stress and Inflammation

Human studies: The aerosol of e-cigarette contains organic and inorganic toxicants. Ultrafine heavy metal particles accumulate primarily in the lung. Since these toxicants cannot rapidly be removed from the lung, they can act as an irresolvable source of inflammation.

Markers of oxidative stress and inflammation were elevated 1-2 hours after smoking e-cigarette aerosol without nicotine, and returned to normal levels at 6 hours after exposure to aerosol. Habitual e-cigarette users have also been found exhibit a shift in the cardiac autonomic balance toward sympathetic predominance. The susceptibility of apolipoproteins B-containing lipoproteins to oxidation was also significantly increased in e-cigarette users. These changes have all been associated with increased risk of cardiovascular disease (44). Acute e-cigarette inhalation may induce vascular pathologies (45). The soluble components of e-cigarette, including nicotine, triggered dose-dependent loss of lung epithelial barrier function. This was attributed to increased levels of oxidative stress and inflammation (6schweitzer). The levels of exhaled nitric oxide, a quantitative measure of airway inflammation, increased in nine volunteers using e-cigarettes (34mobarrez). Enhanced production of nitric oxide can lead to elevated levels of peroxynitrite, a very reactive free radical. The levels of markers of inflammation and of oxidative damage were elevated in plasma, urine, and saliva samples of e-cigarette users (8). In general, use of e-cigarettes has been associated with increased levels of biomarkers of inflammation and oxidative stress (38Singh et al., 2019).

Animal and Cell Culture studies: E-cigarette aerosol exposure of mice enhanced vascular, pulmonary and cerebral oxidative stress and inflammation. These effects were not observed in mice lacking NADPH oxidase -2 (NOX-2) suggesting that they were mediated via NOX-2 (39). Exposure of mice to e-cigarette aerosol during pregnancy increased markers of renal oxidative stress and inflammation, and fibrosis in adult offspring (40). Such exposure also induced inflammatory responses that damage the lung. These changes were exacerbated in the presence of flavoring agents. Detrimental effects were at least comparable to, and in many cases greater than those obtained following exposure to cigarette smoke (41). However, some of the adverse changes due to e-cigarettes are often less pronounced than parallel changes effected by regular cigarettes. Thus smoke from regular cigarettes produced more severe increases than e-cigarette

aerosol in indices of oxidative stress and inflammation in exposed mice (42). Also, cigarette smoke led to a greater increase in rat immune cell number than did e-cigarette aerosol (43).

In vitro exposure to e-cigarette aerosol led to increased oxidative stress, inflammation, and DNA damage together with reduction in histone deacetylase-2 activity in human gingival epithelial cells and human periodontal ligament fibroblasts (44). Exposure to e-cigarette aerosol also triggered excessive production of reactive oxygen species (ROS), inflammatory cytokines and chemokines, and reduced phagocytic activity in cultured alveolar macrophages in culture (45). E-cigarette aerosol induced reactive oxygen species (ROS) and increased DNA damage, and reduced viability in a dose-dependent manner in human umbilical vein endothelial cells in culture (46).

5. Levels of Nicotine and Organic and Inorganic Toxicants in e-Cigarette Aerosol

In order to evaluate the risk of e-cigarette smoking on human health, it is important to determine the levels of toxicants in the aerosol. Due to variable quality control by the manufacturers and the use of a range of formulations, the levels of organic toxicants (47) and inorganic metal toxicants (22) as well as nicotine in the aerosol vary markedly (48).

Nicotine levels: E-cigarettes have the potential to deliver equal or more nicotine compared to a tobacco cigarette and this constitutes a major component of overall health risks.(49 Voos et al., 2019).

Organic toxicants: The levels of carcinogenic organic compounds in the aerosol of e-cigarettes were 1-2 orders of magnitude lower than in the tobacco cigarette smoke, but higher than in nicotine inhaler (9). The aerosol of e-cigarettes contains propylene glycol and/or glycerol (45-48) and acrolein (a product of heated glycerin), which can cause irritation in the upper respiratory tract (49). Significant levels of nitrosamine metabolites are found in the urine of e-cigarette users (Kankanamage et al., 2020) ~~aerosol of e-cigarettes (50).~~ The aerosol of e-cigarettes also contains low levels of formaldehyde, acetaldehyde, isoprene, acetic acid, 2-

butanodione, acetone, propanol, propylene glycol, and diacetin; however, the levels are much lower than in tobacco cigarette smoke (51). A comparative analysis of potentially carcinogenic compounds, such as carbonyls, and volatile organic compounds, nitrosamines in the aerosol of e-cigarettes found that their levels were also lower than those in tobacco cigarette smoke (9).

The urine levels of certain organic compounds such as propylene oxide, crotonaldehyde, acrylonitrile, acrolein, and acrylamide were higher in e-cigarette smokers than in non-smoking controls (52). Yet, levels of many metabolites including as benzene, ethylene oxide, acrylonitrile, acrolein, and acrylamide were higher in the urine of smokers, who used both tobacco cigarettes and e-cigarettes in relation to those who smoke only e-cigarettes.

Inorganic toxicants: E-cigarettes contain metals, such as copper wire coated with Ag,Sn, Ni, Cr Al, and Cu which occur in the aerosol of e-cigarettes as particles (22).

These metal particles constitute a unique hazard of e-cigarettes as they are not found in regular cigarettes. E-cigarettes generate high concentrations of nanoparticles and fewer bigger particles (<10 μm) when compared to smoke from conventional cigarettes (Schripp et al., 2013). Smaller particle size is associated with a greater ability to produce free radicals (Abdal Dayem et al., 2017). Such particles can induce inflammation in tissues especially in the lung. Furthermore, nanoparticles from the aerosol can gradually distribute systemically and accumulate in other tissues including the liver, kidney, heart, and brain (52Ruszkiewicz et al., 2020) where they can promote inflammation.

The role of constituents of e-cigarettes on facilitating levels of oxidative stress and inflammation has not been adequately investigated. These studies could be conducted by measuring the levels of oxidative and inflammatory markers in plasma, urine and saliva.

6. Secondary Exposure to e-cigarette Aerosol

The aerosol released increased levels of 1, 2-propanediol, glycerin, nicotine, carcinogenic polycyclic aromatic hydrocarbons, carbonyls, and ultrafine metal particles in the surrounding indoor air (29). The aerosol also releases inorganic toxicants in the surrounding indoor air (29).

This suggests that potential hazard of exposure to secondhand e-cigarette aerosol exists albeit at lower concentrations than regular tobacco smokers (Gallart-Mateu et al., 2016). The serum levels of cotinine (a biomarker of nicotine levels) were lower in subjects passively exposed to aerosol of e- cigarettes than in those who were exposed to smoke of tobacco cigarette (53). The transition from regular cigarettes to e-cigarettes in the home has been reported to improve indoor air quality (Oh and Kacker, 2014). Nevertheless, tobacco-specific nitrosamines have been detected in the urine samples of people exposed to secondhand aerosol from a smoker of e-cigarettes.

Hazards of gestational exposure to e-cigarette use are well-documented. Use of e-cigarettes during pregnancy increase the risk of use during pregnancy increased the risk of deficits in weight of offspring at birth (Cardenas et al., 2019).-There is evidence for widespread developmental deficits incurred after fetal exposure to nicotine (McGrath-Morrow et al., 2020). Consideration of the nicotine content of e-cigarettes alone, gives concern, as parents, who generally understand the need for protection of children from secondhand cigarette smoke, do may not have the same concern about exposure to e-cigarettes, which are perceived as safer (Buchanan et al., 2020). In the USA, the nicotine content of e-cigarettes has been progressively rising since 2013 (Romberg et al., 2019). The long-term effects of secondhand exposure to e-cigarette aerosol are largely unknown and this is an important gap in our understanding. In order to document this, epidemiologic studies need to be performed by evaluating pulmonary damage, and abnormalities of other organs ~~such as eye, and oral cavity~~ among those who have been exposed to secondhand aerosol from smokers of e-cigarettes for a long period of time (Li et al., 2020). In addition, the incidence of cancer among various organs among those passively exposed to e-cigarette smoke should be documented**.**

7. Public Policy with Respect to Secondhand Exposure to e-Cigarette Aerosol

There are many smoke-free zone protection policies in place due to the well-established health hazard from secondhand tobacco cigarette smoke. These include restriction of tobacco cigarette smoking at work places, public transport, restaurants, and homes. Pubic policies regulating

secondhand exposure from aerosol of e-cigarette smokers are slowly being instituted in a manner similar to those of tobacco cigarette smoking .

Contrasting views of the tobacco industry with those of professional societies are marked (Bhatt et al., 2020). One major review concluded that while e-cigarette use is increasing , it "poses substantially less harm to smokers than cigarettes" (Glasser et al., 2017). It is stated while " that some liquids and vapors contain potentially toxic constituents, but in far fewer numbers and at much lower or trace levels than found in smoke" and that adverse health effects are "generally mild". This optimistic perspective is based on relatively few long term studies and ignores the hazards of a growing proportion of the population addicted to nicotine. It is also in contrast to reports that e-cigarettes have a worse acute toxicity than regular cigarettes (Bhatt et al., 2020). The qualitive difference in composition between e-cigarettes and regular cigarettes needs to be considered as well as the relative content of those chemicals common to both.

Conclusion

There are many critical variables regarding the hazard of e-cigarettes which have contributed to the lack of consensus concerning their toxicity. Factors such as the exact nicotine content, types of flavoring agent used and varying content of toxic metals, vaping style, can all influence the extent of damage (Ganguly et al., 2020, Kaur et al., 2020). Suspected chemicals produced by use of electronic cigarettes, likely to contribute to related lung injury, include silica, heavy metals, benzaldehyde, diacetyl, propylene glycol, glycerin, acetaldehyde and formaldehyde (Winnika and Shenoy, 2020). This renders generalized conclusions concerning the exact extent of their harmfulness difficult. However, overall, there is unequivocal evidence that e-cigarettes cause a significant degree of injury to their users. An important population group for epidemiological study is that without a long history of smoking of regular cigarettes since the residual damage and health effects of such prior smoking can confound findings.

The aerosol of e-cigarette induced acute respiratory distress, functional abnormalities of heart, eye, and oral cavity. Increased oxidative stress and inflammation appear to contribute to the pathogenesis of these adverse health effects. Organic and inorganic toxicants contribute to

increased oxidative damage and inflammation. There is evidence that the levels of toxicants derived from e-cigarettes are also present in the serum of those who received secondhand exposure to e-cigarette. Although the acute and late adverse health risk of direct exposure and secondary exposure to tobacco cigarette smoke has been established, no data on the-long term health effects of direct exposure or on effects of secondary exposure to e-cigarettes are available. Animal studies as well as epidemiologic and intervention studies with e-cigarettes on human health should be conducted to evaluate these issues. While the toxicity of some tobacco constituents is reduced by their absence or lower levels in e-cigarettes, the presence of distinctive metal particles in aerosol gives e-cigarettes a characteristic profile of toxicity that is quantitively and qualitatively different from that of regular cigarettes. The overall nature of the two products is sufficiently divergent so that their toxicity cannot readily be compared.

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Conflicts of Interest

The authors declare no conflicts of interest relating to this review.

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