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Impact of Electronic Cigarettes on the Liver

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Abstract

E-cigarettes (ECs) can affect several organs in the body. On the liver, it causes toxic and immunological effects associated with many inflammatory processes and oxidative stress. E-cigarettes may cause hepatic fibrosis, steatosis, cell dysfunction, injury with the elevation of liver enzymes, and cancer. On the other hand, it also causes hepatic DNA damage and mitochondrial dysfunction. Nicotine affects both cellular and humoral immune responses.

Keywords: ECs; E-Cigarettes; Nicotine; Propylene Glycol; Glycerol; Liver

Introduction

Electronic cigarettes, also known as e-cigarettes, electronic vaping devices electronic nicotine delivery systems or ECs, are battery-operated devices with the function to vaporize nicotine [1].

There are several types of ECs; more than 460 e-cigarette brands and 8000 different flavorings. The products available on the market are mainly of three types; first, second, and third generations [2]. First-generation devices have a similar appearance, shape and size as tobacco cigarettes. These were the first ECs released to the market. They comprise a little lithium battery and a cartomizer. Examples of the first generation are cigalikes, vape sticks and vape pen. Second-generation devices are characterized by higher-capacity lithium batteries and atomizers with the ability to refill them with liquid (sold in separate bottles). Third-generation devices are composed of a lithium battery with an integrated circuit that allows the user to adjust the energy delivered to the atomizer. They are also called mods. Box Mod is a crate formed e-cigarette, named as its shape is like a case. Mech Mod is a mechanical smoke and, an e-cigarette gadget that doesn't contain a control chip, and its security relies upon the information on the player. Pod Mod is a shut e-cigarette with replaceable cartridges [3]. Most variety of ECs comes from the difference in nicotine presented in e-liquids, different volumes of e-liquids per product, different carrier compounds, additives, flavors, and battery voltage [4].

Components identified in e-cigarette liquids and aerosols include nicotine, humectants (propylene glycol and glycerol), polycyclic aromatic hydrocarbons, tobacco alkaloids, tobacco-specific nitrosamines, phenolic compounds, water, aldehydes, citric acid, heavy metals, flavoring agents, and volatile organic compounds [5]. Users of ECs often report that propylene glycol produces better "throat hit" and carries flavor better than glycerol while glycerol is much smoother than propylene glycol. Propylene glycol is physically much thinner than glycerol. Some of the key metals include iron, nickel, lead, tin, aluminum, manganese and chromium. All metals except cadmium, are found at a markedly higher level than in combustible tobacco cigarettes [2].

Heating this liquid produces an aerosol (e-vapor), which is toxic, oxidative, and induces inflammation [6]. Nicotine causes dependence and addiction, and exposure to it from ECs likely elevates the cardiovascular disease risk in people with pre-existing cardiovascular diseases, but the cardiovascular risk in people without cardiovascular diseases is uncertain [7]. There are more than 8000 different flavoring agents (e.g. menthol, fruit, vanilla, caramel, and coffee) of e-liquid available. Some flavorings resemble the taste of cigarettes [1]. The majority of them are assigned as commonly perceived as safe by FDA, however, those assignments are for oral utilization in food and do not apply to flavorings used in ECs; most of these were never studied for toxicity via the inhalation route [2].

By the end of 2021, the number of e-cigarette users may reach almost 55 million worldwide [1]. Youths aged between 15 and 25 years had the highest rate of using e-cigarette [3]. 5.3% of all users are middle school students, and 16% are high school students. This is very dangerous because the brain is only fully developed by the age of mid-twenties, and youths' exposure to nicotine may disrupt their brain development and, hinder attention and learning with elevating susceptibility for addiction to nicotine or other drugs such as cocaine [8].

The use of ECs among the young is essentially connected to their curiosity and the "appealing" flavored nature of e-liquids. Former smokers primarily use ECs to discontinue smoking because they perceive them to be safety perceptions, current trends, and reduced costs compared with tobacco cigarette smoking [9]. Users believe that the negative effects of ECs use can only become apparent after many years. However, there are certain differences of opinion about its long-term effects on health. In particular, some people assert that it is less harmful than traditional cigarettes, but others assert the opposite [10].

Users claim safety aid because ECs purportedly do not involve tobacco combustion; which reduces toxicant exposure for e-cigarette users as compared to traditional cigarettes, but these data are not conclusive. ECs may provide a less harmful source of nicotine than traditional cigarettes, but evidence of decreased harm with long-term use is not available. Some proof suggests that e-cigarette use may facilitate smoking cessation, but definitive data are lacking. E-cigarette has not been approved by FDA as a cessation aid [11].

The use of ECs mainly affects the respiratory tract, cardiovascular system, central nervous system, reproductive system, immune system, mouth, eye, nose, throat and skin. Also, ECs can damage the digestive system. On the oral cavity, ECs cause oral tissue dehydration, a decrease of the flow of gingival fluid, a decrease of enamel hardness, a decrease of lysozyme levels in saliva and elevation levels of lactoferrin in saliva. ECs also cause reflux esophagitis and cancer of the esophagus. In addition, ECs also destroy insulin-secreting cells which lead to diabetes mellitus [3].

Because of these contemplations, it is clear that there are many unanswered questions regarding the overall safety, efficacy of harm reduction, and the long-term health impact of these devices. This article aims to give a critical review of the existing studies on the health consequences of vaping of ECs on the liver.

The Hepatic Effects of ECs

The liver is a significant organ that has numerous functions. The liver is responsible for removing drugs, alcohol and other toxins from the body. Also, it has a function for nicotine transformation, and nicotine exerts several adverse physiological effects on the liver [12].

Various chemical substances and ultrafine particles known to be toxic, carcinogenic, and/or to cause liver disease have been identified in e-cigarette aerosols, cartridges, refill liquids, and environmental emissions. The toxicity of ECs is not only attributed to nicotine but also by aldehydes, metals, volatile organic compounds, phenolic compounds, polycyclic aromatic hydrocarbons, tobacco alkaloids and flavoring agents' mixture in e-liquid [13]. Indeed, exposure to humectants aerosols in concentrations found in ECs has no hepatic effect but several hazardous compounds have been found in liquids and in the heated aerosol produced by ECs, including formaldehyde, acetaldehyde, and acrolein, which are known as carcinogenic toxicants [2].

The exposure to ECs chemical substances is highly variable and depends on product characteristics and how the device is operated. Nicotine is a volatile substance consisted of a pyridine and a pyrrolidine ring and has a molecular weight of 162.2. The concentration of nicotine in ECs in most cases ranges from 0 mg/ml to 36 mg/ml. The amount of nicotine absorbed is affected by the device and the amount of e-liquids vaporized [14]. Smoking an ECs with a 30s interval for 10 times leads to a significant increase in the serum nicotine concentration in 5 min, indicating that nicotine in ECs is rapidly absorbed [15]. During smoking, nicotine is absorbed by the lungs and is rapidly metabolized in the liver, which induces three major adverse effects on the liver: toxic, immunological, and oncogenic effects [16].

The use of ECs may induce hepatic fibrosis, steatosis, cell dysfunction, injury with the elevation of liver enzymes and cancer [17].

The toxic effect of ECs may be multifactorial. It is due to the increase in the formation of reactive oxygen species/oxidative stress, anti-inflammatory cytokines, DNA damage, hepatocyte apoptosis and necrosis, excess free fatty acids delivery (possibly through adipose tissue lipolysis), perturbations of cholesterol and lipid metabolism and epigenetic changes [15].

Oxidative stress is associated with many inflammatory diseases. It can cause membrane lipid rupture, protein denaturation, DNA damage, mitochondrial dysfunction and other cellular macro-molecular damage, thus severely altering signal transduction and cell metabolism. The use of ECs causes endothelial/ vascular dysfunction and, nitric oxide deficiency. The use of ECs increases serum and hepatic iron which induces oxidative stress and lipid peroxidation that leads to activation of stellate cells and development of fibrosis [18]. On the other hand, nicotine-free e-liquid can cause depression in the activity of antioxidant enzymes which lead to increased oxidative stress. Oxidative stress seems to play a crucial role, and the Nrf2 (nuclear factor erythroid-2-related factor 2) signaling pathway plays a very important role in the process of oxidative stress [3].

Some chemicals present in ECs (e.g., nicotine, formaldehyde and acrolein) are capable of causing DNA damage and mutagenesis. ECs induce hepatic DNA damage, decreasing levels of NAD+, elevated NADH levels and mitochondrial dysfunction [19].

Infiltration of inflammatory cells and cell death are also present. Nicotine increases the pro-inflammatory cytokines (IL-1, IL-6, IL-8 and tumor necrosis factor alpha) which are involved in liver cell injury [16]. Protein kinase C alpha signaling pathway appears to play an important role in the inflammatory response triggered by ECs containing nicotine [3].

The immunologic effect of nicotine is the disturbance of both cell-mediated and humoral immune responses. Nicotine decreases lymphocyte proliferation and differentiation including suppression of antibody-forming cells by inhibiting antigen-mediated signaling in T-cells and ribonucleotide reductase [20]. Furthermore, smoking induces apoptosis of lymphocytes by increasing the production of Fas (CD95) death receptor which permits them to be slaughtered by different cells communicating a surface protein called Fas ligand (FasL). Smoking induces decreased CD4+ cells, increased of CD8+ lymphocytes, impaired natural killer cell activity and increases the production of pro-inflammatory cytokines [16].

Nicotine-containing ECs may alter the expression of genes related to cholesterol biosynthesis and lipid metabolism in liver. It can increase the level of free fatty acids by direct stimulation of lipolysis in adipocytes. These free fatty acids cause the accumulation of triglycerides in the liver [16].

Smoking has carcinogenic chemicals that increase the risk of hepatocellular carcinoma. The use of ECs has been implicated in disruption of the normal pathways of cell cycle control, which may affect both immune competence and tumor progression. Smoking-induced fibrosis may favor the development of hepatocellular carcinoma [16]. Some chemicals present in e-cigarette aerosols (e.g., formaldehyde, acrolein) are capable of causing hepatic DNA damage and cancer [2]. Research data suggest that both the M1 and M2 subunits of ribonucleotide reductase participate in cellular functions that are important for determining malignant potential, and aberrant levels of ribonucleotide reductase expression and enzyme activity have been reported in human tumors [20]. Nicotine has been associated with the suppression of p53 (tumor suppressor gene) [16]. Thus, ECs may provide a selective advantage to malignant cells by promoting tumor cell growth and suppressing the immune response to those cells [20].

While evidence in humans for associations between ECs use and liver cancer is extremely sparse, more abundant data have been generated in the in vitro and in vivo settings, including some positive data and some negative data on mutagenesis of e-cigarette parts. Due to the mixed results across different experimental conditions and for different outcomes, clear, consistent signals have yet to be observed [2].

Despite the known negative consequences of tobacco smoking, numerous pregnant females keep on utilizing ECs dependent on their wellbeing insight as contrasted and tobacco. Nicotine can cross the placenta and has effects on fetal development. Therefore, during pregnancy smoking can result in multiple adverse consequences, including sudden infant death syndrome, and could result in altered corpus callosum, deficits in auditory processing, and obesity. Pregnant women must avoid ECs even if it is free of nicotine as it may cause increased oxidative stress, induce inflammation that may lead to multiple organs injury in mother and offspring [21].

Future Research

Most of the studies included in this review were talking about the effect of nicotine on the liver. So, we recommend more studies in the future on the effect of other ECs components as propylene glycol, glycerol and flavorings. Also, we recommend more studies using ECs with zero or low concentration of nicotine because many studies in our review used a high concentration of nicotine. There is a need also to know the effect of ECs on humans as there is a lack of human studies. We recommended studying the effect of long-term exposure to ECs.

Conclusion

The biggest problem of ECs lies in the presence of nicotine in its composition as it causes many problems including liver toxicity, immunological effect and cancer. Pregnant women are advised to avoid ECs as their components may affect their newborns' liver.

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