Electronic Cigarettes

Subjects: Pathology

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Electronic cigarettes (EC) are a novel product, marketed as an alternative to tobacco cigarette. Its effects on human health have not been investigated widely yet, especially in specific populations such as patients with asthma.

Keywords: electronic cigarette ; asthma ; review ; asthma pathogenesis ; lung function ; airway inflammation ; asthma control ; smoking cessation

1. Introduction

Asthma is a chronic inflammatory airway disease characterized by exacerbations and remissions, affecting 1–18% of the population in different countries [1]. Airway inflammation in asthma is typically eosinophilic, but can also be neutrophilic, mixed, or non-granulocytic [1]. Different factors are involved in aggravating airways inflammation in asthmatic patients, with cigarette smoke being one of the main ones [1][2]. Smoking prevalence in patients with asthma approximates that of the general population [3]. Even in severe asthma, the percentages of asthmatic smokers could reach or even exceed these of the general population [4]. The percentage of severe asthmatics that were using e-cigarettes (ECs) in the same study was 2% and was higher than in the general population in many countries [4]. Asthmatic smokers suffer from more symptoms and exacerbations, develop a more rapid decline in pulmonary function and have a worse prognosis than non-smoking asthmatics [5][6][7]. In addition, they usually present with a higher proportion of neutrophils in induced sputum, reduced pH, and heterogenous inflammatory mediator profiles in exhaled breath condensate (EBC) [8][9][10][11].

Since 2003, the EC has become very popular as it was advertised as a tool for smoking cessation. Clinical experience has shown that smokers attempting to quit smoking use the EC as an alternative [12][13][14][15]. However, ECs' safety has not been scientifically demonstrated, especially in asthmatic patients.

2. The Role of EC Compounds in the Pathogenesis of Asthma

The constitution of EC aerosol is defined by temperature, and by the contents in the heated liquid as propylene glycol (PG), glycerin, flavoring agents, nicotine in variable concentrations and other non-nicotine substances [16]. Laboratory, observational, and clinical studies have revealed that EC aerosols contain numerous respiratory irritants and toxins and that may have a cytotoxic effect on lung tissue, analogous to that of the tobacco cigarette [17][18]. More than 80 compounds (including known toxins—e.g., formaldehyde, acetaldehyde, metallic nanoparticles, and acrolein) have been found in e-liquid and aerosols and as a result, ECs have been linked with an increase in symptoms in individuals with asthma [16]. Additionally, ECs were found to contain not only formaldehyde but also formaldehyde-forming hemiacetals and potentially toxic particulate matter that deposits on surfaces [19]. The novel-generation high-power electronic nicotine delivery systems (ENDS) which seem to be particularly user-adaptive, produce droplets with a diameter at 0.78 ± 0.03 μm [20][21]. Exposure of the airway epithelial cells to certain liquid flavorings reaches toxicity thresholds. The chocolate flavoring 2,5-dimethypyrazine activates the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel [22]. Work-related inhalation of several usual food-safe flavoring substances has been related with occupational asthma and asthma symptoms deterioration [23]. More specifically, work-related inhalation exposures to the flavoring substance diacetyl was found to cause irreversible obstructive airway disease in healthy workers. The thermal decomposition of PG and vegetable glycerin (VG), the key elements of EC liquids, generates reactive carbonyls, including acetaldehyde, formaldehyde, and acrolein which have well-known lung toxicities [23]. PG vapor has been found to induce respiratory irritation and increase asthma risk, despite the fact that EC use improved home indoor air quality compared with secondhand tobacco smoke [24]. Long-term exposure to EC was found to change the human bronchial epithelial proteome promoting its damage [25]. Heavy EC smoking promotes inflammatory processes (activator of transcription and nuclear factor-κB signaling, Janus tyrosine kinase/signal transducer, and mitogen-activated protein kinase), in a similar way to tobacco smoke. Protracted exposure to some components of EC vapor results in respiratory complications as asthma [26].

Chronic EC exposure also seems to result in increased neutrophil elastase and matrix metalloprotease levels in the lung, abnormal activation of the lung epithelial cells, β-defensins and neutrophilic response (NETosis), activation of transient receptor potential ankyrin 1 (TRAP1), alternations in the normal respiratory microbiota, induced proteolysis and in general impaired respiratory innate immune system, all associated with allergies and asthma [27][28]. Respiratory innate immune cell function has also been found to be impaired by flavored EC liquids and more specifically, by cinnamaldehyde which suppresses phagocytosis by macrophages [29], and provisionally represses ciliary mobility of bronchial epithelial cells through dysregulation of mitochondrial function [30]. These dysregulations of the respiratory immunity by EC could impact asthma development, severity, and/or exacerbations [31].

3.What Is the Effect of EC Use on Lung Function and on Airway Inflammation in Patients with Asthma?

Asthmatic patients exhibited a significant increase in respiratory system total impedance at 5 Hz (Z5), respiratory resistance at 5, 10, and 20 Hz (R5, R10, and R20), resonant frequency and reactance area measured by impulse oscillometry (IOS) after EC use, compared with healthy controls [32]. Mean airway resistance along with the slope of the phase III curve on the single breath nitrogen test increased immediately after short-term EC use in a group of asthmatic smokers, thereby demonstrating airway dysfunction, particularly in small airways [33]. Apart from airway resistance, asthmatic patients also exhibited impaired pulmonary function tests (PFTs) after vaping for five minutes, with the decrease in forced expiratory volume in 1 s to forced vital capacity ratio (FEV1/FVC) and peak expiratory flow (PEF) being more significant [34]. Furthermore, patients who recovered from electronic vapor acute lung injury (EVALI), a condition more commonly observed in asthmatic patients, exhibited chronic irreversible airflow obstruction, markedly abnormal ^{129}Xe MRI ventilation heterogeneity, abnormal lung clearance index and oscillometry measures and decreased diffusing capacity of the lung for carbon monoxide (DLCO), all persistent after their discharge [35][36]. Studies in animals with allergen-induced airway disease demonstrated not only increased airway hyperresponsiveness after EC vapor inhalation, but also increase in mucus and airway wall thickening which are hallmark features of allergic asthma [37][38][39][40].

The effects of EC use on inflammation have been studied in cell lines, animal models, and humans. In all three, EC use led to inflammation and oxidative stress [41]. However, specifically in asthmatic patients, the studies that evaluate the effects of ECs on airway inflammation are limited [42]. ECs free of nicotine were found to cause heterogenous effects depending on their flavor, while ECs containing nicotine suppressed airway inflammation but not airway remodeling in mice with allergic airway disease [39]. Eosinophilic inflammation is accompanied by an increased fraction of exhaled nitric oxide (FeNO) and correlates with other indices of inflammation in asthmatic patients [43]. FeNO is increased during asthma exacerbations, while it decreases with recovery or inhaled corticosteroids [44][45]. There is conflicting evidence on the effect of EC on the FeNO of asthmatics. There are studies where FeNO significantly decreased after an EC session [32], whereas the opposite result was exhibited in another study [34]. In the latter study, Th2 cytokines such as interleukins (IL) IL-4 and IL-13 in the EBC of asthmatics were found to be significantly increased after vaping for five minutes, reflecting increased eosinophilic inflammation, and supporting the finding of increased FeNO [34]. Apart from Th2 inflammatory mediators, an increase in IL-1β and tumor necrosis factor alpha (TNF-α) was observed. Both are proinflammatory cytokines that amplify and orchestrate the inflammatory response in asthma and determine its severity; IL-10, a cytokine derived from Th2 cells and 8-Isoprostane (ISO8) a biomarker of oxidative stress were also increased [34]. Additionally, in three experimental studies on mice with allergen-induced airway disease, EC inhalation increased infiltration of what by inflammatory cells, including eosinophils, into airways from blood, increased the number of all types of inflammatory cells in Bronchoalveolar lavage fluid (BALF), stimulated the production of Th2 cytokines such as IL-4, IL-5, and IL-13 and allergen-specific immunoglobulin E (IgE) and reduced the levels of transforming growth factor (TGF)-β1 and matrix metalloproteinase (MMP)-2 in lung tissue homogenate [38][40][46].

4. What Is the Effect of EC on the Clinical Characteristics of Asthma?

Thirty-nine observational studies including 2,111,023 participants, six case studies, two opinion articles, eight reviews, and five systematic reviews with four meta-analyses investigated the effects of EC use in asthmatics. Several investigators have concluded that EC could be associated with the development of pulmonary disorders, including asthma and might increase asthma severity and exacerbations [18][31][47][48][49][50]. Numerous cross-sectional studies with a large number of participants have described the significant association between EC use and even secondhand exposure and asthma diagnosis and severity [51][52][53][54][55][56][57][58][59][60], compared to the few studies which found no association [61][62], or even negative association between EC use and asthma [63][64]. A prospective cohort study also found that EC use was associated with an increased risk of developing respiratory disease, including asthma, independent of cigarette smoking [65]. A study from Korea demonstrated that adolescent EC users presented the highest adjusted odds ratio for

severe asthma, which was reflected by the number of days absent from school due to asthma symptoms [66]. EC use was found to be positively correlated with asthma, or even more, to increase the probability of an adolescent being diagnosed with asthma and also enhanced the adverse effects of tobacco cigarettes in asthma [66][67][68]. A study from Sweden which comprised patients with obstructive lung diseases, mostly asthmatics, showed that all respiratory symptoms were most common among dual users (electronic plus tobacco cigarette), former smokers and nonsmokers who used ECs rather than tobacco cigarette smokers-alone [69]. Furthermore, two studies from France and Canada also found that asthma was more commonly associated with EC use [70][71]. A large epidemiological study from the USA including more than 400,000 participants showed that current EC use was associated with 39% higher odds of self-reported asthma, compared to never EC use and that there was a graded increased odds of having asthma with increased EC use intensity, from occasional to daily EC users [72]. Five more studies from the USA also concluded that EC is an independent risk factor for respiratory disease including asthma, after controlling for covariates [73][74][75][76][77]. EC had an additive effect for asthma beyond smoking [77]. Dual use, which is the most common usage pattern, is riskier than using either product alone [73]. Dual use, with even passive exposure to EC, was identified as significant predictor for asthma in two more cross-sectional studies [59][78] and one meta-analysis [79]. A recently published systematic review concluded that evidence up to now suggests that the side effects of ECs may be exaggerated in people with asthma [42]. Additionally, asthma symptoms were among the most frequently reported side effects associated with EC use, second to headaches [80]. Moreover, EC use was associated with lower general health scores, higher breathing difficulty scores and a greater proportion of reporting asthma [81]. A large epidemiological study in USA with a weighted sample size of 31,721,603 adults between 18 and 24 years (2,503,503 with former and 3,200,681 with current asthma) found that the prevalence of EC use was significantly higher among young adults with current or former asthma and that asthma combined with EC use was significantly associated with worse mental health [82], a finding similar to that of another study from Korea [58].

5. Discussion

Most studies indicate the negative effects of vaping on asthma indirectly by the increased likelihood of a vaper being also an asthmatic, with a dose-dependent manner. However, most of the studies were cross-sectional, thus they could not establish a cause-and-effect relationship between EC use and asthma. Nevertheless, they provide excellent epidemiological data to assess trends and note areas where interventions are needed. Studies suggesting that EC improves asthma control presented serious concerns about a possible selection bias, as they were based on online surveys data, or included a small number of asthmatics. Recently published systematic reviews with meta-analyses tally with the above conclusions [79][83][84][85]. More research is needed in order to study the effects of EC on lung function and airway inflammation of asthmatic patients.

As nicotine dependence remains while vaping, most studies reflect the ineffectiveness of EC as a smoking cessation tool by pointing out that patients with asthma could more easily become addicted to EC than non-asthmatics and that asthmatics who are dual users smoke a greater number of tobacco cigarettes per day, while the most alarming finding on this aspect is the ‘gateway effect’. On the contrary, there are also studies suggesting that EC could in fact promote smoking cessation [86][87]. Nonetheless, the study with the most participants supporting that was based on an online survey [87], thus there are serious concerns of a possible selection bias.

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