

COVID-19 and the role of e-cigarette use: An evidence-based review

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ABSTRACT: While the world is grappling with one of the biggest pandemics in history, the role that personal preferences or lifestyles can play in the development of this pandemic should not be overlooked. One of these preferences is the use of electronic cigarettes (e-cigarettes). COVID-19 is a disease that primarily attacks the lungs. Thus, factors that cause pre-existing lung disease such as e-cigarette use may increase the risk for critical complications from COVID-19. Promoted as an alternative to conventional cigarettes, e-cigarettes induce inflammation of human airways and possibly increase susceptibility toward pneumonia because of an increase of pneumococcal adherence to airway cells. Lung damage caused by flavorings contained in e-cigarettes can increase health risks, especially from COVID-19. When compared to nonsmokers, e-cigarette users had a five times increased risk while dual users with tobacco had a seven times increased risk of COVID-19 infection. Recent research supports that many medical consequences such as lung inflammation and increased susceptibility to pulmonary viral and bacterial infections in smokers and people with COVID-19 disease may also develop due to e-cigarette use. The aim of this article is to investigate whether there is a role for e-cigarette use in the development of respiratory diseases caused by the COVID-19 virus. With the help of our experience of working on e-cigarettes for many years and various scientific databases (PubMed, Scopus, etc.), the health risks experienced by people who both use e-cigarettes and have a COVID-19 virus infection, and the role of respiratory system symptoms, in particular, were investigated.

KEYWORDS: SARS-CoV-2; COVID-19; electronic cigarette; EVALI.

1. INTRODUCTION

The main problems of humanity, including climate change and global warming; air, water and soil pollution; population growth estimated to exceed nine billion by 2050; loss of biodiversity; microplastics; energy sustainability; excessive consumption of resources and waste management; lack of food; and poverty have almost been replaced with the threats of coronavirus disease 2019 (COVID-19) that has affected all societies and caused the death of more than 1 million people in a short time. Humanity's current main goal is to develop vaccines and drugs that can defeat COVID-19 as soon as possible. In other words, humanity is trying to save the day by ignoring the traditional large-scale threats that will gradually destroy itself, for which they were seeking a solution until a year ago.

The pandemic of COVID-19, troubling the world for more than a year, is caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Besides the systemic symptoms such as fever, fatigue, and myalgia, several upper and predominantly lower respiratory tract symptoms including dry cough, sore throat, sneezing, rhinorrhea, dyspnea, chest pain, and respiratory problems develop after infection with SARS-CoV-2. In addition, acute respiratory distress syndrome (ARDS), hypoxemia, shock, arrhythmia, acute cardiac injury, and acute renal failure have been observed among COVID-19 patients [1]. The disease might lead to shortness of breath, possibly accompanied by or progressing to hypoxemia for some patients. The development of ARDS from respiratory injury is a feared complication that occurs in 10-20 % of severe cases. Also, non-cardiogenic pulmonary edema and a requirement for mechanical ventilation might be encountered in some patients. Interestingly, many of these conditions also resemble the health risks that can be seen in long-term smokers. Risk factors for disease severity are underlying comorbidities (for instance, hypertension, cardiovascular diseases, diabetes, and cerebrovascular disease) and advanced age [2]. Furthermore, lifestyle factors such as smoking and obesity might be a key factor in the progression of the disease.

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According to the Centers for Disease Control and Prevention (CDC), smokers are at increased risk of severe COVID-19 illness as well as adults of any age with certain underlying medical conditions such as cancer, chronic obstructive pulmonary disease (COPD), chronic kidney disease, coronary artery disease or cardiomyopathies, cardiac diseases such as heart failure, immunodeficiency from solid organ transplantation, sickle cell disease, obesity, pregnancy, and type 2 diabetes mellitus. The first systematic review examining five studies from China by Vardavas and Nikitara concluded that smoking is most likely associated with the progression and negative outcomes of COVID-19 as noted in previous influenza and MERS-CoV outbreaks [3]. Furthermore, Patanavanich and Glantz, as a result of their meta-analysis to determine the relationship between COVID-19 and cigarette smoking, reported that "smokers have about 2 times the odds of severe COVID-19 outcomes than never smokers" and concluded that cigarette smoking was an independent risk factor for disease progression [4]. The banned sales of tobacco products during the lockdown periods to mitigate the COVID-19 pandemic in countries such as South Africa and India clearly reveal the negative role of tobacco products in this pandemic [5]. With an increasing number of scientific data on the role of cigarettes in COVID-19, the question arises whether e-cigarettes, the consumption of which is escalating in societies, also have a detrimental effect on the disease caused by the COVID-19 virus.

2. E-CIGARETTES

During the last decade, the tobacco and cigarette industry has been in an effort to introduce new products to the market against the measures taken by the governments, especially against cigarettes, and the most popular product among these new products has been e-cigarettes [6]. The variety of products called e-cigarettes is changing daily and different products are included in this range. Most of these new products utilize heating instead of burning, some use nicotine liquids, and some use specially prepared tobacco itself, similar to cigarettes. For example, "Ploom", "IQOS", "Ifuse", "Glo", and "JUUL" are the trade names of these products and they are offered to nicotine addicts with different mechanisms (fired, heated, etc.). Studies investigating the number and diversity of chemical substances released by e-cigarettes report that the level of toxic compounds in e-cigarette vapor is lower compared to conventional cigarettes [7,8]. The interpretation of this situation as "not being exposed to any chemicals or carcinogenic substances" due to e-cigarette use is misleading consumers and the general public in terms of health risks that may arise.

Scientific studies demonstrated the presence of carbonic compounds, volatile constituents, especially acetaldehyde, tobacco-specific nitrosamines, phenolic compounds, tobacco alkaloids, flavorings, illicit drugs (e.g., Tetrahydrocannabinol-THC), and at least 20 human carcinogens and teratogens such as formaldehyde, benzaldehyde, acrolein, and polycyclic aromatic hydrocarbons in e-liquids and e-cigarette vapor [9]. Today, there is substantial evidence showing that vitamin E acetate and heavy metals such as lead and arsenic are important components of some e-cigarettes [10]. Our knowledge of the health effects of e-cigarette exposure is still in its infancy and the consequences of chronic exposure are undetermined. In this environment of uncertainty, our lack of information about the extra health risks that COVID-19 may pose in e-cigarette users prevents the optimal management of the disease.

E-cigarettes have gained popularity among adults and adolescents worldwide. For example, approximately 3 million high school age adolescents and over 10 million adults are active electronic nicotine delivery system (ENDS) users in the USA and this number is increasing daily [11]. Adolescents constitute a risk group with the greatest increase in use. For example, e-cigarettes were the most commonly used tobacco product among high school students (11.7%), followed by cigars (7.7%), cigarettes (7.6%), smokeless tobacco (5.5%) and hookah (3.3%) in 2017 in USA [12]. The findings of the 2018 National Youth Tobacco Survey conducted in the USA indicates as a high popularity of e-cigarette usage among high school youth, increasing up to 75% between 2017 and 2018 [13].

2.1. E-cigarettes and lung diseases

Since the introduction of e-cigarettes to the marketplace, it has been suggested that the inhalation of various toxic compounds and microparticles produced by the vaping process could cause damage to the lungs. Various health effects are expected, especially on the respiratory system, due to e-cigarette use. The first evidence that the usage of e-cigarettes could lead to a serious and life-threatening lung disease was revealed with isolated lung injury reports starting in 2012 [14]. Other studies, especially studies in adolescents, have begun to reveal a relationship between bronchitis symptoms (chronic cough, sputum production, or bronchitis) and the frequency of e-cigarette use [15,16].

Today we have a growing body of epidemiological data from several cross-sectional studies that have found associations between respiratory symptoms and e-cigarette use. These studies report an increase in the prevalence and severity of symptoms in asthma, especially among adolescents, due to e-cigarette use. According to a survey, conducted in Hong Kong with participation of approximately 45,000 adolescents, recent usage of e-cigarette of previous month was associated with an increased odds of reporting chronic cough or sputum (odds ratio 2.1, 1.8 to 2.5) [16]. Results of a study on 2,086 students, who are attending final grades of high school (11th and 12th grade) based in Southern California show that both current and past use of e-cigarettes is associated with a nearly two-fold increase in the risk of chronic bronchitis symptoms (bronchitis chronic, cough or phlegm,). Another survey of 35,904 Korean high school students found that, after adjusting for potential confounders like exposure to cigarette smoke, student's self-reported doctor diagnosis of asthma in the past 12 months increased in current e-cigarette users compared to those who never used it (odds ratio 2.7, 1.3 to 5.8). Additionally, this study has proven the fact that e-cigarette usage also triggers asthma severity, which causes absence from school due to asthma symptoms [17]. The researchers conducted a cross-sectional survey on covariates and smoking with participation of 8,087 Hawaiian adults through random dialing on telephone in 2016. According to those surveys, serious links of chronic pulmonary disorder in the total sample of e-cigarette users were detected [18]. A cross-sectional study of a random sample of 30,272 Swedish adults found an association of e-cigarette use with respiratory symptoms such as long-standing cough, recurrent wheezing. Moreover, the prevalence of respiratory symptoms was highest among the current smokers who also used e-cigarettes [19]. After 142 cases reported from Illinois and Wisconsin related to e-cigarette and vaping-product use associated lung injury (EVALI) was first described in 2019 by the CDC [20]. Furthermore, different cross-sectional surveys have found associations of e-cigarette use with a history of asthma and with asthma exacerbations in young people in USA [21,22]. According to the study, conducted by Health eHeart with participation of 40,000 individuals, usage of e-cigarette increases case numbers of dyspnea and reports of asthma and COPD [23].

Recently, various studies have revealed the damage caused by the use of e-cigarettes to the respiratory system. These studies have shown that exposure to vapour of e-cigarettes can disrupt pulmonary homeostasis with increased airway inflammation, oxidative stress and risk of respiratory infection, decreased lung function and immunity. [15,18,24-26]. Moreover, e-cigarettes cause a significant induction of inflammation in the lungs through a different dysregulated immune landscape. Thus, in addition to tobacco, e-cigarettes can also worsen the inflammation in COVID-19 [27] and might cause an increased susceptibility toward pneumonia due to the facilitation of pneumococcal adherence to airway cells. Furthermore, e-cigarettes could cause damage to lung epithelium (Table 1) [28]. Among various types of e-cigarettes, those containing nicotine and flavors are related to oxidative stress, epithelial barrier dysregulation, DNA damage, and enhanced inflammation [27].

Table 1. Effects of e-cigarette/e-liquids on the lung.

Effects	Tissue/cell type			
	Endothelia	Epithelia	Fibroblasts	Inflammatory cells BALF
<i>Cytotoxicity</i>		↑	↑	
<i>Cell Viability</i>	↓	↓	↓	
<i>Infection</i>		↑		↑
<i>Inflammation</i>		↑		
<i>Electrical Resistance</i>	↓			
<i>Cytokine Secretion</i>				↑
<i>Macrophages</i>				↑
<i>Altered morphology</i>			✓	

Madison et al. (2019) [11] demonstrated in animal studies that e-cigarette exposure, independent of nicotine, caused changes in lipid metabolism and profiles in alveolar macrophages and epithelial cells. They have found aberrant phospholipids in alveolar macrophages and an increase in surfactant-associated phospholipids in the airways. In addition to e-cigarette-induced lipid deposition, chronic e-cigarette vapor exposure downregulates innate immunity against viral pathogens in those macrophages. Also in the extension of their study, e-cigarette exposed mice infected with influenza virus demonstrated augmented and persistent tissue damage and lung inflammation, independent of nicotine, resulting in increased morbidity and mortality. E-cigarette vapor aberrantly changes the physiology of local immune cells and lung epithelial cells and leads to a weak response against infectious agents. Since the alterations in immune dysfunction and lipid homeostasis also take place in the absence of nicotine, more comprehensive studies of the vehicle solvents

used in e-cigarettes are warranted, which were considered safe until recently and are still not evaluated by regulatory authorities.

3. COVID-19 AND E-CIGARETTES

Smoking has been recognized as one of the risk factors for COVID-19 in several studies and by the WHO [3,4,29]. This is an expected finding because smoking is a major determinant leading to vulnerability conditions for COVID-19, such as cardiovascular disorders and chronic lung disease. Based on this fact, scientific attention has focused on whether there is any potential relationship between COVID-19 morbidity and e-cigarettes. Various hypotheses have been generated about the greater tendency of e-cigarette users to exhibit a worse prognosis of COVID-19, yet there is limited information on this subject. Although the risk of young people getting infected by COVID-19 is relatively lower compared to older adults, considering the proportion of young people using e-cigarettes and the dual use of cigarettes and e-cigarettes in youth, it may be one of the major risk factors for health problems caused by COVID-19.

In fact, the findings obtained by Gaiha and coworkers (2020) [30] from the online national screening results from the 50 U.S. states, which were performed on 4351 13-24 years old teenagers and young adults in the USA in May 2020, confirm this situation. They highlighted that not only dual users but also e-cigarette users had an increased risk factor of having COVID-like symptoms in the past 30 days. One key result of this study, after findings were adjusted for number of major confounders such as sex, age, and obesity, is that those who only reported e-cigarette use or dual use with tobacco were at a five (95% CI: 1.82-13.96) or seven (95% CI: 1.98-24.55) times higher risk, respectively, of having a diagnosis of COVID-19 compared to non-users.

Previous studies have shown that smokers are twice as likely as nonsmokers to contract influenza and have more severe symptoms. Moreover these studies indicated that smokers also experienced higher mortality in the past MERS-CoV outbreak [31,32]. The smokers are believed to be prone in terms of showing COVID-19 symptoms and likely to be taken to the intensive care. In this regards, compared to nonsmokers, smokers have been identified as 1.4 times more likely to have severe COVID-19 and 2.4 times been to the intensive care unit by requiring assisted ventilation, or die [3]. Studies conducted in the last year, when COVID-19 was widespread, report that many findings previously obtained for cigarettes are similar to those for e-cigarettes, both of which may cause lung inflammation and increased susceptibility to pulmonary viral and bacterial infections. Tobacco e-cigarette use is a possible COVID-19 risk factor [33].

Similar to tobacco smoker's chronic exposure, e-cigarettes disrupt renin-angiotensin system (RAS) homeostasis by inhibiting local compensatory mechanisms, resulting in an increased susceptibility to pulmonary and cardiovascular distress thereby potentially increasing the risk of COVID-19. Reidel and coworkers (2018) found that among e-cigarette users, there is an important increase in MUC4, a membrane-anchored mucin, and an increase in the ratio of secretory mucins MUC5AC to MUC5B compared to non-users [34]. Tsai and coworkers (2018) investigated whether e-cigarette use may promote apoptosis-associated speck-like protein containing caspase activation and recruitment domain (ASC) release into the lungs. ASC in bronchoalveolar lavage fluid (BALF) is higher in e-cigarette users and cigarette smokers. No statistical difference was seen between ASC levels of e-cigarette users and cigarette smokers. Levels of Caspase-1 and IL-1 β are higher in smokers compared to e-cigarette users and nonsmokers [35].

The role of $\alpha 7$ nicotinic acetylcholine receptor (nAChR $\alpha 7$) might be substantial in the inflammatory responses induced by e-cigarette aerosols containing nicotine. Wang and coworkers (2020) investigated whether sub-chronic exposure to e-cigarettes induces an inflammatory response and dysregulated repair/extracellular matrix (ECM) remodeling, which takes place through nAChR $\alpha 7$. In this study, adult wild-type (WT), lung epithelial cell-specific KO (nAChR $\alpha 7$ CreCC10) and nAChR $\alpha 7$ knockout (KO) mice were used and BALF and lung tissues were examined. Sub-chronic exposure to e-cigarettes containing nicotine increased the inflammatory cellular influx of macrophages and T-lymphocytes and pro-inflammatory cytokines in BALF and caused an increase in the SARS-CoV-2 ACE2 receptor. However, in nAChR $\alpha 7$ KO mice, a reduction in inflammatory responses associated with decreased ACE2 receptor was seen. Wang and coworkers (2020) concluded that e-cigarette aerosols containing nicotine cause lung inflammation because of an altered repair response and ECM remodeling mediated by nAChR $\alpha 7$, which is thought to be an important target [36].

Lee and coworkers (2020) investigated the potential association between vaping/smoking and the dysregulation of key genes and pathways related to COVID-19. It was reported that smoking, but not vaping, upregulates ACE2. Both smoking and nicotine and flavor-containing e-cigarettes result in the upregulation of pro-inflammatory cytokines and inflammasome-related genes. Chemokines including CXCL8 and CCL20 are

upregulated in smokers, whereas CCR1 and CCL5 are upregulated in flavor/nicotine-containing e-cigarette users. In addition, genes implicated in inflammasomes, such as CXCL1, CXCL2, NOD2, and ASC, are upregulated in smokers and e-cigarette users. In contrast, vaping flavor and nicotine-free e-cigarettes did not cause significant cytokine dysregulation or inflammasome activation. It is concluded that smoking or vaping might substantially worsen COVID-19-associated inflammation or increase susceptibility to COVID-19 [27].

4. VAPING-INDUCED LUNG INJURY (EVALI) AND COVID-19

Acute eosinophilic pneumonia (AEP), lipid pneumonia, and acute lung injury (ALI) induced by e-cigarette use have been reported [14,37,38]. EVALI is a condition of acute or subacute lung injury with various findings ranging from mild respiratory symptoms to severe lung disease like organizing pneumonia to diffuse alveolar damage. A total of 2,807 EVALI cases have been reported to the CDC as of February 18, 2020, and among those, there have been 68 deaths [39]. EVALI is most often associated with the use of cannabis-based ENDS products. Results of recent EVALI cases have shown that vitamin E acetate, an additive found in some tetrahydrocannabinol containing vaping products, is strongly linked to EVALI outbreaks. It may present with new onset respiratory symptoms linked to vaping-related behavior within 90 days before symptom onset and a new infiltrative finding on either CT scan or chest radiograph [40]. Other infectious or plausible causes should be excluded. Pathophysiological processes of EVALI patients show heterogeneity [41]. EVALI is encountered as a spectrum of illnesses involving diffuse alveolar hemorrhage, respiratory-bronchiolitis interstitial lung disease, lipid pneumonia, and acute eosinophilic pneumonia [42]. Similar clinical and radiographical findings can be found both in COVID-19 and EVALI. Findings of EVALI can overlap with COVID-19 pneumonia, which is why it is important for clinicians to consider this possibility [43].

It has been reported very recently that pulmonary imaging findings from e-cigarette users, EVALI, and COVID-19 may be similar [44]. Though COVID-19 and EVALI have related characteristic CT manifestations that mostly can be differentiated in their classic forms, when presented with overlapping imaging features, the distinction is of great importance, which might be hard due to symptoms common in both disorders such as shortness of breath, cough, fever and gastrointestinal symptoms [43]. When typical COVID-19 chest CT images are considered, ground glass opacities in a peripheral and subpleural distribution, multilobular involvement, and a slightly lower lung predominance are seen. The presence and increase in number and size of consolidation areas might be seen through the course of the disease. Interlobular septal thickening along with ground glass opacities is a common finding. Imaging patterns of EVALI can be variable, which are classified as acute eosinophilic pneumonia, hypersensitivity pneumonitis, diffuse alveolar damage, lipid pneumonia, and organizing pneumonia, but among these, organizing pneumonia is the imaging pattern that most overlaps with COVID-19. Involvement of the lung periphery and general lack of pleural effusion can be seen in both cases but the existence of significant subpleural sparing suggests considering the organizing pneumonia subtype of EVALI rather than COVID-19 [43].

Pulmonary diseases with inflammatory characteristics generally increase serum CRP levels in response to inflammatory cytokines such as IL-1, IL-6, or TNF- α . Recently, it is claimed that in patients with COVID-19, admission CRP levels correlated with disease severity and tended to be a good predictor of adverse outcomes [45]. Similarly, high CRP concentrations were detected in EVALI patients [46].

5. COVID-19, E-CIGARETTES, AND SOCIAL FACTORS

Sussman and coworkers (2021) [47] reported in their review that there is a possibility of aerial virus transmission through exhaled bioaerosols including from e-cigarettes and it could translate into an extra risk of COVID-19 contamination. Indirect transmission via aerosols may occur across longer distances than conventional droplets. Aerial transmission of the coronavirus through environmental e-cigarette aerosols exhaled by infected vapers has not been studied comprehensively yet, but this issue remains a serious potential area for discussion. During the course of the pandemic, people were obliged to share limited indoor and outdoor spaces at various levels of home confinement and mobility constraints. While this situation decreased personal contacts in large populations, it also increased close contact both in space and time within small groups such as families.

The consumption of e-cigarettes entails frequent repetitive physical contact between the users' hands, mouth, and e-cigarette device. They have to remove their face masks to be able to use an e-cigarette in a public setting. Because of these factors, the person would be at higher risk of both contracting the virus when exposed to a contaminated environment and transmitting it to others. When individuals share a device with others, the

risk amplifies further [48]. There are also behavioral changes influenced by the various aspects of the psychological impacts of the pandemic. Forced isolation has led to anxiety and depression, possibly leading to a rise in the intake of psychoactive substances, including nicotine products and e-cigarettes. At the same time, the COVID-19 pandemic has caused some direct behavioral changes in e-cigarette consumption patterns. Some of the most common alterations are: stocking up and bulk purchasing, changes in obtaining e-cigarette supplies, alternative purchasing procedures, increased e-cigarette usage, and disruption of routine and e-cigarette use. The authors concluded that users of e-cigarette may experience or perceive additional COVID-19 impacts, such as increased exposure, health risks, stress and financial burdens [49]. Some countries, such as Spain and Turkey (as of 12 November 2020), reacted to this situation by imposing smoking and vaping bans in outdoor public open spaces [50].

6. CONCLUSION

The global COVID-19 pandemic, which was declared a worldwide epidemic in March 2020, is an important public health problem that threatens men and women in all societies. Because there are several animal reservoirs of coronaviruses other than humans, it is unlikely that the disease will be eradicated, at least in the near future. In contrast, a former major killer, smallpox, only had a reservoir in humans and was declared eradicated in 1980. However, the coronavirus problem will stay with us for a time. Therefore, it is important to apply preventive measures and prepare by keeping immunity high and avoiding various risk factors that may weaken resilience and increase vulnerability to threatening infectious agents. Rationally, the COVID-19 epidemic should be perceived as a great opportunity for all societies to quit the usage of tobacco and its products, especially cigarettes and e-cigarettes. The relationship between COVID-19 and e-cigarette use is a multifaceted problem. First, e-cigarette consumption may make users vulnerable to SARS-CoV-2 infection and its complications. Secondly, the aerosols exhaled by vapers may enhance the aerial viral transmission as a vehicle. And thirdly, the pandemic itself may promote the intensified utilization of e-cigarettes because of the peculiar psychological stress burden. It should also be considered as an opportunity for health authorities, governments, and non-governmental organizations to motivate efforts to quit tobacco products in society.

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