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From clouds to clarity: Understanding the real consequences of e-cigarettes and EVALI

De las nubes a la claridad: comprendiendo las verdaderas consecuencias de los cigarrillos electrónicos y EVALI

Carlos Silva Paredes[1,2], Marien Semprún[3], Juan Lauretta[2,4], Omar Ross[5], Jennifer Rojas[5], Luis Rincón[5], Valmore Bermúdez[6,7]

SUMMARY

Electronic cigarettes are devices that heat liquid into aerosols for inhalation. According to the CDC and FDA, a 2022 survey found that 14.1 % of high school students and 3.3 % of college students in the U.S. used these devices, totaling 2.55 million young users. This growing trend gained serious attention in 2019 with the emergence of EVALI (E-cigarette or Vaping Product Use-Associated Lung Injury), predominantly affecting teenagers and young adults. EVALI presents with acute respiratory symptoms, often requiring hospitalization, and by February 2020, it had caused approximately 2 800 hospitalizations and 68 deaths. Although vitamin E acetate (VEA) was strongly implicated, other factors (including solvents, psychoactive substances, heavy metals, and flavorings) are under investigation. Compounding the issue, the COVID-19 pandemic has posed diagnostic challenges due to symptom overlap. The long-term health effects of electronic cigarette use remain uncertain, but research has linked it to chronic respiratory diseases like COPD, cancer, and systemic and cardiovascular conditions. Additionally, its use poses unique risks for younger populations due to the potential for addiction and developing complications. This review consolidates current research to explore the short- and long-term effects of electronic cigarette use, its pathophysiology, clinical manifestations, and effective diagnostic approaches. By broadening

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ORCID: https://orcid.org/0000-0002-8483-0276[1,2]
ORCID: https://orcid.org/0009-0004-2807-2118[3]
ORCID: https://orcid.org/0009-0004-4617-5380[2,4]
ORCID: https://orcid.org/0009-0004-3852-9716[5]
ORCID: https://orcid.org/0009-0000-4374-9749[5]
ORCID: https://orcid.org/0009-0009-1531-7047[5]
ORCID: https://orcid.org/0000-0003-1880-8887[6,7]

[1,2]MD, PhD E-mail: csilva_paredes@hotmail.com
[3]MD E-mail: dramariensemprun@gmail.com
[2,4]MD, PhD E-mail: jflauretta@gmail.com
[5]Bsc E-mail: omarrosschacon@hotmail.com
[5]Bsc E-mail: luismax9913@gmail.com
[6,7]MD, MSc, MPH, PhD E-mail: valmore.bermudez@unisimon.edu.co

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[1]University of Zulia. Faculty of Medicine. Chair of Human Physiology
[2]Zulia Academy of Medicine
[3]University of Zulia. Maracaibo, Venezuela
[4]University of Zulia. Maracaibo, Venezuela. Postgraduate Chest Surgery
[5]Endocrine and Metabolic Diseases Research Center. School of Medicine. University of Zulia. Maracaibo, Venezuela
[6]Simón Bolívar University, Faculty of Health Sciences, Barranquilla, Colombia.
[7]Life Sciences Research Center (CICV). Simon Bolivar University, Barranquilla, Colombia.

Autor de Correspondencia: Carlos Silva Paredes. Médico Internista- Neumonólogo Doctor en Ciencias Médicas. Profesor Asociado de LUZ- Facultad de Medicina- Cátedra de Fisiología. Miembro del Comité Académico del Postgrado de Medicina Interna "Hospital Central de Maracaibo". Miembro Titular de la Academia de Medicina del Estado Zulia (N°2). E-mail: csilva_paredes@hotmail.com

understanding beyond VEA as the primary cause of EVALI, this study highlights the need to consider the complex interplay of multiple chemical components involved in e-cigarette use. Advancing knowledge in this area is crucial for improving diagnosis, treatment, and prevention strategies while addressing the broader public health challenges posed by electronic cigarettes.

Keywords: *Electronic cigarettes, vaporizer, EVALI, vitamin E acetate, lung health, propylene glycol, vegetable glycerin, lung cancer, COPD, COVID-19, dual smokers.*

RESUMEN

Los cigarrillos electrónicos son dispositivos que calientan líquido hasta convertirlo en aerosol para inhalarlo. Según los CDC y la FDA, una encuesta de 2022 descubrió que el 14,1 % de los estudiantes de secundaria y el 3,3 % de los estudiantes universitarios en EE.UU usaban estos dispositivos, lo que suma un total de 2,55 millones de usuarios jóvenes. Esta tendencia creciente ganó mucha atención en 2019 con la aparición de EVALI (lesión pulmonar asociada al uso de cigarrillos electrónicos o productos de vapeo), que afecta predominantemente a adolescentes y adultos jóvenes. La EVALI se presenta con síntomas respiratorios agudos, que a menudo requieren hospitalización, y en febrero de 2020 había causado aproximadamente 2 800 hospitalizaciones y 68 muertes. Aunque el acetato de vitamina E (VEA) estuvo fuertemente implicado, se están investigando otros factores (incluidos solventes, sustancias psicoactivas, metales pesados y saborizantes). Para agravar el problema, la pandemia de COVID-19 ha planteado desafíos de diagnóstico debido a la superposición de síntomas. Los efectos a largo plazo del uso de cigarrillos electrónicos en la salud siguen siendo inciertos, pero las investigaciones lo han vinculado con enfermedades respiratorias crónicas como EPOC, cáncer y afecciones sistémicas y cardiovasculares. Además, su uso plantea riesgos únicos para las poblaciones más jóvenes debido al potencial de adicción y desarrollo de complicaciones. Esta revisión consolida la investigación actual para explorar los efectos a corto y largo plazo del uso de cigarrillos electrónicos, su fisiopatología, manifestaciones clínicas y enfoques de diagnóstico efectivos. Al ampliar la comprensión más allá de VEA como la causa principal de EVALI, este estudio destaca la necesidad de considerar la compleja interacción de múltiples componentes químicos involucrados en el uso de cigarrillos electrónicos. Avanzar en el conocimiento en esta área es crucial para mejorar el diagnóstico, el tratamiento y las estrategias de prevención, al tiempo que se abordan los desafíos de salud pública más amplios que plantean los cigarrillos electrónicos.

Palabras clave: *Cigarrillos electrónicos, vaporizador, EVALI, acetato de vitamina E, salud pulmonar, propilenglicol, glicerina vegetal, cáncer de pulmón, EPOC, COVID-19, fumadores duales.*

INTRODUCTION

Electronic cigarettes, originally introduced as a presumably safer alternative to conventional smoking, have seen a notable increase in popularity, especially among younger populations. Between 2010 and 2014, there was a 24.4 % increase in the prevalence of device use among teenagers in Central and Eastern Europe (1). According to data published by the Centers for Disease Control and Prevention (CDC) in 2022, approximately 2.55 million high school and college students in the United States were using electronic cigarettes. One in four of these users reported daily use, highlighting that a considerable number of young people have had prior experience with these devices (2). However, this emerging trend has also brought to light significant concerns about the health implications associated with vaping. One of the most alarming issues is the emergence of "E-cigarette or Vaping Product Use-Associated Lung Injury" (EVALI), which reached epidemic levels in 2019 in the United States (3). This disease, characterized by acute pulmonary symptoms and severe dyspnea, highlights the immediate dangers associated with vaping (4,5). Although initial research attributed EVALI predominantly to vitamin E acetate, recent studies suggest a more complex etiology that includes a wide range of chemicals and additives present in e-liquids. These compounds, including solvents, flavorings, and psychoactive substances, interact to create chemical byproducts that pose significant health risks (6,7). Moreover, successive generations of electronic cigarettes significantly reflect the evolution of these devices, which exhibit a remarkable capacity for customization, encompassing aspects such as vaporization temperature, flavor diversity, and chemical compound concentration (8). While these innovations enhance the appeal of vaping, they also lead to a proliferation of chemical

products and their interactions, creating greater complexity in their effects on health (9).

Beyond the immediate concern of EVALI, the long-term effects of electronic cigarettes have also begun to emerge. There is growing evidence linking vaping with chronic respiratory diseases such as Chronic Obstructive Pulmonary Disease (COPD) and the development of lung cancers (10). Moreover, the impact of vaping extends far beyond the respiratory system, also affecting the cardiovascular system (11). This multifaceted impact directs toward a comprehensive investigation of the pathophysiological effects of electronic cigarettes, especially given their growing prevalence among young populations (12). In addition, the simultaneity between the outbreak of EVALI and the onset of the COVID-19 pandemic has further complicated the scenario, as the similarity of symptoms between the two conditions and the lung injury mechanism produced by EVALI, which involves acute alveolar damage and a marked inflammatory process, can mimic the manifestations of COVID-19 in radiological images (13). Therefore, this creates greater difficulties for the diagnosis of EVALI, increasing the risk of inappropriate treatments and delays in proper care (14).

In light of these complexities, this review aims to provide a clearer and more comprehensive pathophysiological perspective on the pathological effects of electronic cigarettes, emphasizing the need for a detailed understanding of the health risks associated with vaping to inform the scientific community better. This understanding is crucial for improving the prevention and diagnosis of EVALI and addressing the increasing prevalence of these devices among younger populations, ultimately aiming to mitigate their short-term, medium-term, and long-term consequences.

ELECTRONIC CIGARETTES

Electronic cigarettes are devices designed to convert liquid into aerosol or vapor by applying heat, thereby facilitating inhalation. Originating in 1979, these devices emerged as an alternative to traditional cigarettes, introducing the term "vaping," which remains in use. However, the first model created was not commercially successful due to the bitter taste of the nicotine aerosol (5). In 2003, a more advanced design was launched in Beijing, marking a turning point with several key improvements that ensured its market acceptance. This new model was introduced in the United States in 2006, triggering a steady increase in the popularity of electronic cigarettes, particularly among young people. This boom is attributed to the introduction of disposable cartridges with flavored nicotine solutions, which eliminated the bitter taste and significantly expanded the variety of products available (15).

Additionally, data from the National Youth Tobacco Survey, the Youth Risk Behavior Surveillance System, and the Monitoring the Future study reveal an exponential increase in the use of these devices among high school and college students since 2014. For example, in 2018, 13.5 % of eighth-grade students reported having tried nicotine vaping products at some point in their lives, with an increase to 34 % among twelfth-grade students, and up to 40.5 % reporting their use in September 2019. These figures underline the growing prevalence of vaping among youth, a phenomenon driven by aggressive marketing and a variety of appealing flavors (16-18).

The nomenclature and characteristics of electronic cigarettes have undergone considerable evolution, reflecting both their diversification and widespread use. Commonly described as "e-cigs," "cigalikes," "e-hookahs," "mods," "vape pens," "vapes," and "tank systems," these devices have introduced specific terminology such as "vape juice" or "e-liquid," and verbs like "to rip," "to juul," "to puff," or "to hit" to describe the action of vaping (15,4). Historically, electronic cigarettes are classified into four generations, each with distinctive features that reflect technological advances and adaptations to consumer markets. The first generation, known as "cigalikes," mimics the aesthetics of conventional cigarettes and are generally disposable devices (8,19,20). The second generation resembles a pen and offers enhanced features such as rechargeable batteries and increased vapor production (8,20). The third generation, or "tank style," allows personalized adjustments in vapor temperature and a greater e-liquid storage capacity, thus offering a more intense and personalized experience (21). The fourth generation, or "Pod Mod," includes devices

that are often disguised as everyday objects, such as USB drives, and utilize nicotine pods that allow for more concentrated inhalation with reduced irritation, which is particularly appealing to young audiences (22,23).

STRUCTURE AND COMPONENTS

In general terms, electronic vaping devices consist of several essential components that work together to convert liquid into vapor. These include a lithium battery that supplies power, an atomizer located within a vaporization chamber, a reservoir that stores the e-liquid, and a mouthpiece through which the user inhales the vapor. The interaction between these components begins when the user draws air through the mouthpiece, activating a sensor which, in turn, ignites the atomizer. This component heats the e-liquid until it vaporizes, thus allowing the inhalation of the resulting aerosol (22).

The control of the device's activation is facilitated by an on/off button, which, along with the inhalation sensor, enables the user to manage the electronic cigarette's operation. In some designs, the device eliminates a physical button and activates automatically when it detects user inhalation, making the sensor a critical component in the system's operability. The battery, whether rechargeable or non-rechargeable, is crucial as it provides the necessary energy to heat the atomizer to reach temperatures around 400 degrees Fahrenheit in just seconds. The battery's power can range from 5W to 200W and plays an important role in determining the range of vaporization temperatures, which can influence the integrity of the atomizer and the chemical composition of the liquid, resulting in the generation of potentially harmful byproducts during the vaporization process (19,22,24,25). Likewise, the atomizer, another vital component, consists of heavy metal coils that convert the e-liquid into vapor. The configuration and resistance of these coils are crucial for the size of the vapor particles, which can vary from ultrafine, less than 0.1 micrometers (μm), to micrometric particles of approximately 4 μm. This variability in particle size is significant as it determines how they deposit in the respiratory system and the proportion that reaches the airways, which is fundamental for understanding the pulmonary effects of vaping (24,26).

Regarding the cartridge, which is responsible for containing the e-liquid, it can be prefilled or designed for the user to fill. Often, this component is combined with the atomizer to form a single unit and is made of plastic or metal. Some models even include a transparent cover that allows users to monitor the remaining liquid level (22). The e-liquids used in these devices feature a complex variety of ingredients, including psychoactive substances such as nicotine, tetrahydrocannabinol (THC), cannabinoids (CBD), and solvents like vitamin E acetate (VEA), propylene glycol (PG), and vegetable glycerin (VG). Although PG and VG are classified by the Food and Drug Administration (FDA) as safe for consumption and topical applications, their inhalation poses significant risks, including the production of harmful aldehydes such as formaldehyde, acetaldehyde, acrolein, and methylglyoxal, which raise concerns due to their potentially carcinogenic effects (17,27).

VEA, often used as a diluent in e-liquids containing more viscous substances like THC and CBD, has been linked with severe lung injuries. Additionally, nicotine, a stimulant known for its addictive and cardiovascular effects, is often combined with these solvents and other additives, creating a complex chemical profile that may include impurities and carcinogenic substances such as tobacco-specific nitrosamines (TSNAs) (15,20,18,28). Finally, the complexity is further increased by the presence of between 8 000 and 15 000 different flavorings used in e-liquids, including diacetyl, which imparts a buttery flavor; ethyl maltol, which provides a sweet caramel touch; vanillin, which introduces a warm vanilla flavor; and menthol, which offers a refreshing and cleansing sensation. These additives, while enriching the sensory experience of vaping, are not without controversy due to their potential negative impact on lung health when inhaled. For example, diacetyl, safe for food consumption, has been linked to severe lung diseases in inhalation contexts. Similarly, ethyl maltol, when interacting with metals present in the aerosols of electronic cigarettes, can increase the absorption of harmful substances such as heavy metals (7,29-32). The inclusion of these

flavorings in e-liquids demonstrates an effort to satisfy a wide range of consumer preferences, yet also highlights the need for careful evaluation of their safety when inhaled, given the various health implications they may have.

E-CIGARETTE OR VAPING PRODUCT USE-ASSOCIATED LUNG INJURY (EVALI)

The use of electronic cigarettes has been linked to a wide range of adverse health effects, primarily derived from exposure to toxic and potentially carcinogenic substances commonly found in the liquids and flavorings of these devices, as well as from the oxidation of their compounds during the vaping process, which leads to the generation of harmful chemicals. This began to be observed more than a decade ago, specifically starting in 2012, when cases of lung damage linked to vaping began to be documented, with patients presenting symptoms such as persistent cough and ground-glass opacities observed in computed tomography (CT) images, and lipid-laden macrophages (LLM) detected in bronchoalveolar lavage (BAL) samples (33,34).

In the subsequent years, between 2013 and 2018, multiple studies were conducted, and numerous case reports were collected that demonstrated a variety of acute lung injuries linked to the use of electronic cigarettes. These included lipid pneumonia, acute eosinophilic pneumonia, cases of pneumonitis with pleural effusion, respiratory bronchiolitis, interstitial lung diseases, bronchiolitis obliterans organizing pneumonia, and in extreme cases, diffuse alveolar hemorrhage (37-45). However, despite these observations that clearly indicated the potential dangers associated with the use of these electronic devices, it was not until the outbreak of a mysterious and severe respiratory disease in 2019 in the United States that electronic cigarettes began to receive due attention. This outbreak, which quickly reached epidemic levels by the end of September 2019, led to approximately 2 800 hospitalizations and 68 deaths by February 2020 (3,46). The Centers named this disease for Disease Control and Prevention (CDC) as "E-cigarette or Vaping Product Use-Associated Lung Injury" (EVALI), which is characterized by an acute pulmonary inflammatory process that causes alveolar collapse and a severe disruption of gas exchange, resulting from damage to the pulmonary endothelial and epithelial barriers exposed to toxic vapor particles (26,47).

CDC research identified that vaping products containing THC and vitamin E acetate (VEA) were particularly associated with the EVALI outbreak. The presence of these substances in the BAL of patients pointed to their role in the etiology of the disease. However, the detection of other toxic agents in vaping products, including pesticides, oils, thinners, and plasticizers, and the continuation of EVALI cases even after the prohibition of illicit products containing THC and VEA, underscore the need for a more thorough and comprehensive analysis of the physicochemical and toxicological properties of e-liquids, as well as the underlying mechanisms in the pathogenesis of EVALI (6,48-50).

PATHOPHYSIOLOGY

Five years after the EVALI epidemic, scientific research has made significant advances in understanding its pathophysiology. The complexity of the e-liquids used in electronic cigarettes, which include solvents such as PG (propylene glycol), VG (vegetable glycerin), and VEA (vitamin E acetate), along with psychoactive components like nicotine, THC, and CBD, as well as flavorings like diacetyl and vanillin, has been a central focus of these studies. Specifically, a key study conducted by Blount et al. in 2019 analyzed BAL (bronchoalveolar lavage) samples from 51 patients affected by EVALI, identifying the presence of VEA and THC in 94 % of these samples (6). These findings were crucial in establishing these components as the main causative agents of the disease. It is essential to note that this study not only highlighted the direct association between these additives and EVALI but also guided further research towards a more detailed examination of how these chemicals interact with lung tissues (9,12).

VEA-THC

VEA is the ester of vitamin E (α-tocopherol). It can affect the physiological processes of the lungs in multiple ways, such as the function of

pulmonary surfactant, mucociliary clearance, the immune system, and its role in the phagocytosis of inhaled particles.

Effects on Pulmonary Surfactant

Pulmonary surfactant is a complex mixture of phospholipids, with phosphatidylcholines, particularly dipalmitoyl phosphatidylcholine (DPPC), being the most abundant, constituting approximately 90 % of its composition. This substance is essential for pulmonary stability as it reduces surface tension in the alveoli during the cycles of inspiration and expiration, preventing alveolar collapse. The impact of VEA on pulmonary surfactant is particularly detrimental because this component acts as a "surfactant disruptor," given its structure with a long aliphatic tail, which allows it to integrate and align parallel with the surfactant phospholipids, specifically with the molecules of DPPC, causing the surfactant to transition from a gel phase to a liquid crystalline phase, drastically altering its elastic properties (51). This structural modification not only diminishes the surfactant's efficacy in reducing surface tension but also negatively affects the lung's compression-expansion cycle during breathing, thereby playing a fundamental role in EVALI (52-54).

Alteration in the Immune System

The inhalation of aerosols containing VEA has a considerable impact on the innate immune system, particularly affecting the respiratory epithelium. This component interferes with the function of primary immune system cells, such as alveolar macrophages (AM) and polymorphonuclear leukocytes (PMN), which are essential for pulmonary defense. AMs, in particular, show an increase in their rate of apoptosis and a notable reduction in their ability to phagocytize and degrade pathogens, aerosol particles, and apoptotic cells (55).

These alterations have been demonstrated in various studies, including one conducted by Bhat et al., which analyzed bronchoalveolar lavage (BAL) samples and performed anatomopathological examinations on a group of 30 mice exposed to VEA aerosols. The results of this study showed an increase in leukocyte concentration in lung tissue, indicating an acute inflammatory response. Additionally, a notable accumulation of lipid-laden alveolar macrophages, identified as foam cells, was observed near the alveolar epithelial pneumocytes and exhibited intense oil red O staining, demonstrating an alteration in the cellular environment (56). Similarly, further research conducted by Matsumoto et al., revealed an increase in the levels of certain chemokines and pro-inflammatory cytokines in BAL, such as monocyte chemokine MCP-3, neutrophil chemokine KC, and cytokines IL-6 and IL-8, without a corresponding increase in IL-10, an anti-inflammatory cytokine, maintaining a pro-inflammatory state (57-59). At the same time, damage to the integrity of the alveolar-capillary barrier was documented, evidenced by an increase in protein concentration in the BAL of vaping patients, including albumin, suggesting compromised capillary permeability (60).

Harmful Agents by Pyrolysis

Electronic cigarettes operate at temperatures ranging from 110 to 1 000 °C, acting as miniature pyrolysis devices. Factors such as the resistance of the heating coil, applied voltage, the composition of the vape liquid, and user practices directly influence the temperature at which the e-liquid is heated. Particularly, the pyrolysis of VEA in these devices can be harmful, as it produces gases such as ketene, alkenes, and benzene, all of which are known for their toxic and carcinogenic properties. Ketene formation is especially likely at temperatures above 500 °C, or under "dry puff" conditions, a term describing situations where the vape liquid is scarce and concentrated, which can lead to overheating. This scenario is more common when using counterfeit or modified vaping devices (53,61).

During the pyrolysis of VEA, two main pathways can be followed: in the first, ketene is initially released, triggering the breakage of the C-C and C-O bonds of the dihydropyran ring, resulting in the production of duroquinone and alkene. The second pathway produces a different

sequence where the dihydropyran ring is cleaved before ketene is released. These byproducts, particularly benzene, are recognized carcinogens that are also present in tobacco smoke and pose a significant health risk (62), as it has been documented that exposure to 200 ppm of ketene can be lethal within just 10 minutes. More recent studies have recalibrated the lethal concentration to just 0.24 ppm, highlighting the extreme toxicity of these compounds even at minimal levels (53,63). Thus, it is highly concerning that these substances have already been identified at high concentrations in studies examining teenage users of electronic cigarettes (64).

Cellular Damage and Epigenetic Changes

Type II pneumocytes (NT II), cells responsible for surfactant production, can undergo cell death upon contact with aerosols containing VEA, indicating its direct toxicity. This toxicity was demonstrated by Matsumoto et al. in a study where these cells were exposed to VEA aerosols for periods of 10 and 120 minutes per day over three consecutive days. The results revealed cytotoxicity that increased with the administered dose, exhibiting a clear dose-response pattern (58). Similarly, in another study conducted by Soto et al., it was observed that NT II cells absorbing VEA exhibited alterations in 752 genes, identified with a false-positive rate of less than 0.1 %. This finding unveiled a high activation in signaling pathways of IL-17, MAPK, and TNFα, which are associated with the expression of inflammatory genes, as well as genes involved in osteoclast differentiation (53).

Additionally, research conducted by Marrocco et al. shed light on how exposure to VEA aerosol differentially affects various cell types. For instance, while in human pulmonary epithelial cells (Calu-3), no significant increase in the production of reactive oxygen species (ROS) was observed, human monocyte cells (THP-1) experienced a notable increase in ROS production that was proportional to the dose. Additionally, it was found that VEA aerosol could disrupt the mitochondrial membrane potential in pulmonary epithelial cells, which in turn activated caspase-3, leading to cellular apoptosis (65).

FLAVORINGS

Flavorings have been fundamental to the success of electronic cigarettes, as they have enabled the bitter taste of nicotine to be overcome. Currently, there is a wide variety of these flavorings, designed to appeal to young consumers, particularly. However, the diversity of options available complicates their study, since many have been approved for food use, but not for inhalation. This raises significant concerns about their safety when consumed in this manner.

Ethyl maltol (EM) is a flavoring with a caramel taste frequently found in e-liquids. It has been observed that EM, in conjunction with residues of heavy metals from the components of electronic cigarettes, has the potential to be highly cytotoxic by increasing the absorption of iron, copper, lead, and zinc (66-68). This was recorded in a study by Durrani et al., where the cytotoxic effects of aerosols containing ethyl maltol (EM) and heavy metals on various pulmonary cell lines, including Calu-6 and A549 (lung epithelial cells), as well as HEK293 and IMR-90 (fibroblasts), were evaluated. The results revealed that exposure to aerosols enriched with copper (Cu) and EM significantly reduced the viability of Calu-6 and A549 cells due to an increase in the generation of reactive oxygen and nitrogen species, which activated the expression of genes related to the Nrf2 antioxidant pathway. Despite this antioxidant response, oxidative stress still occurred, causing DNA damage and activating the ATM protein kinase (Ataxia Telangiectasia Mutated), which is crucial for damage repair. When damage is irreparable, the cells initiate apoptosis processes. On the other hand, cells exposed to aerosols with EM and iron (Fe) maintained their viability thanks to high levels of metallothionein (MT), which provided effective defense by neutralizing potential damage. However, in fibroblast cell lines HEK293 and IMR-90, exposure to aerosols with Cu and EM did not affect their viability. In contrast, aerosols with Fe and EM did reduce their viability, indicating that the cellular response to metal exposure varies significantly between different types of cells (32,66-68).

Menthol, cherished in the world of electronic and conventional cigarettes for its refreshing mint flavor, has gained popularity, especially among new users. However, its use is surrounded by controversy due to its potential impact on lung health, as it has been associated with several adverse effects, including reduced cell proliferation, increased oxidative stress, promotion of inflammatory processes, and damage to the respiratory epithelium (7,69). In the study by Nair et al., it was observed that menthol binds to the TRPM8 receptor (Transient Receptor Potential Melastatin 8), an ion channel that prefers calcium. This binding causes a rapid increase in intracellular calcium levels, generating vesicles originating from the endoplasmic reticulum. These vesicles migrate towards the cell membrane, although they do not fuse with it. Excess cytosolic calcium is expelled by calcium exporters located on the cell surface, such as Ca^{2+}-ATPase and the Na^{+}/Ca^{2+} exchanger. This calcium increase can also extend to the mitochondria through the mitochondrial uniporter channel (MCU), inducing the oxidation of mitochondrial proteins and the mitochondrial antioxidant enzyme SOD2, which triggers the production of reactive oxygen species (ROS) and results in oxidative stress (7,30,69).

The nuclear factor kappa B (NF-κB), an essential signaling pathway activated by oxidative stress, plays a crucial role in the bronchiolar epithelium, where it facilitates the activation and expression of NF-κB-dependent inflammatory mediators. Additionally, it regulates the expression of genes responsible for neutralizing reactive oxygen species (ROS) to promote cell survival, as well as the production of cytokines with immunomodulatory functions. Elevated levels of NF-κB and increased production of proinflammatory cytokines such as IL6 and IL8, which are common in inflammatory lung disorders, underscoring that both acute and chronic inflammation are fundamental elements in the pathogenesis of various lung diseases (7,30,69).

Diacetyl, also known as 2,3-butanedione, has an intense buttery flavor. It is classified as "generally recognized as safe" (GRAS), although there is limited data on its safety when inhaled. It has been found that high-voltage vaping with diacetyl significantly increases levels of acetaldehyde, acrolein, and formaldehyde, which are classified as primary irritants of the respiratory tract. Diacetyl is a dicarbonyl and tends to cross-link proteins and thus is considered reactive. In this regard, it has been considered to inactivate proteins by reacting with an amino acid, arginine, to cause bronchiolitis obliterans or "popcorn lung," resulting in a decrease in forced expiratory volume in the first second (FEV1) and the FEV1/ forced vital capacity (FVC) ratio (31,70,71). Moreover, the electrochemical activity of diacetyl alters the normal electron transfer, leading to the production of ROS that can cause cell necrosis. Diacetyl also causes significant changes in gene expression, including those genes involved in cilia formation, which can lead to a reduction in the number of ciliated cells. These cells are crucial for effective mucociliary transport, and their dysfunction has been associated with chronic lung diseases, including chronic obstructive pulmonary disease (COPD) and asthma (70,72).

Vanillin, known for imparting the popular vanilla flavor, can negatively influence the metabolic processes of the respiratory epithelium. This impact is manifested in various metabolic pathways, including those related to fatty acids, lipids, mitochondrial function, and the metabolism of numerous amino acids such as glutamate, tyrosine, methionine, cysteine, arginine, proline, aspartate, glycine, serine, alanine, threonine, as well as branched-chain amino acids (valine, leucine, isoleucine) and lysine. On the other hand, ethyl vanillin, another derivative of vanilla flavoring, has been shown to have detrimental effects on the lungs, specifically reducing the ability of neutrophils to generate an oxidative burst, thereby compromising immune function (73,74).

Other compounds frequently used as flavoring additives include cinnamaldehyde, which imparts the distinctive cinnamon flavor, and benzaldehyde, found in cherry and almond aromas. Additionally, linalool is used to provide sweet and floral notes. The presence of these and thousands of other compounds in electronic cigarettes significantly complicates the research on the harmful effects that flavorings can have on the respiratory epithelium and, therefore, on lung injury associated with the use of electronic cigarettes (7).

PG, VG, AND VG/PG

The most commonly used solvents in e-liquids are PG (propylene glycol) and VG (vegetable glycerin), which the FDA has approved as safe for consumption and topical application in cosmetics due to their lipophilic solvent properties. However, this approval did not consider their inhalation. When these components are used in a vaporizer, their vaporization process generates toxic byproducts, including carbon monoxide, acetylene, methane, and aldehydes (75,76). They have also been shown to contribute to alterations in essential processes for normal mucociliary clearance, as they affect ion channels such as the large conductance K^+ channel (BK) and the cystic fibrosis transmembrane conductance regulator (CFTR). These ion channels are essential for maintaining liquid volumes on the surface of the airways (LSA) for proper ciliary beating and mucus transport in the airway epithelium (77,78).

In a series of three studies conducted by Kim et al., the effects of e-liquids composed mainly of VG, PG, and VG/PG, respectively, were evaluated. In the first study, carried out in 2022, the effects of exposure to aerosols composed mainly of VG on airway inflammation and ion channel function were investigated. It was recorded that there was a reduction in CFTR function in non-smoking, non-vaping human volunteers after just one week of vaping with e-liquids containing VG. This change in CFTR function was accompanied by elevated levels of mRNA expression of inflammatory mediators, such as interleukin 6 (IL6), interleukin 8 (IL8), matrix metalloproteinase 2 (MMP2), matrix metalloproteinase 9 (MMP9), and transforming growth factor beta 1 (TGFB1). These results aligned with *in vitro* experiments, where human bronchial epithelial cells (HBEC) not exposed to cigarette smoke but to electronic cigarette aerosols containing VG for seven days, and showed reduced function of the CFTR channel (79-81). The second study, conducted in 2023, focused mainly on the effects of e-liquids composed of PG and their impact on both *in vivo* and *in vitro* models of BK and CFTR ion channels, as well as the detection of inflammatory markers in the airway, resulting in a significant decrease in BK activity. The effect on BK is mediated by methylglyoxal (MGO), an α-dicarbonyl compound produced from the thermal decomposition of PG by the atomizer coil. This substance can modify the arginine residues in the C-terminal tail of LRRC26 to form irreversible adducts, thus preventing the interaction between Slo1 (the main α subunit of the BK channel) and LRRC26 (Slo1/LRRC26), and thereby inhibiting BK function. Interestingly, exposure of sheep to PG aerosols did not affect CFTR, nor did it induce an increase in plasma levels of inflammatory markers, including IL-6, IL-8, and TGF-β1, after 5 days (10,17,82-84).

Finally, the last study, conducted in 2024, focused on the alterations caused by e-cig aerosols containing propylene glycol (PG) and vegetable glycerin (VG) in equal proportions (PG/VG). As a result, it was concluded that the PG/VG combination clearly affects mucociliary function, causes inflammation in the airway epithelium, alters the normal function of CFTR and BK channels, further reducing ciliary beating, and increases the expression of MUC5AC, possibly inducing hyperplasia of goblet cells. PG/VG aerosols from electronic cigarettes also increased mucus concentration and the activity of MMP-9 in the airways of sheep *in vivo*. Together, these data provide clear evidence of the harmful effects of PG, VG, and PG/VG on the airways (85).

CLINICAL PRESENTATION

The clinical presentation of EVALI is varied and nonspecific, often leading to its confusion with an infection. Although tests do not demonstrate the presence of the causative pathogen, approximately 72 % of patients who are hospitalized report having been seen in outpatient settings before admission for related symptoms, and 45 % of these patients received antibiotics with no improvement. According to recent studies, approximately 80 % to 95 % of patients present with respiratory conditions, including cough, breathing difficulties, and pleuritic chest pain. Additionally, approximately 87 % of patients experience constitutional symptoms, such as fever, fatigue, and generalized weakness, and 73 % exhibit gastrointestinal symptoms, including nausea, vomiting, and abdominal pain (4,15,86-89). Regarding the duration of symptoms before a hospital presentation, the median is approximately 6 days, although in some cases, it can last from 0 to 61 days. When assessing

the initial vital signs of these patients, it was recorded that 64 % presented with tachycardia, 43 % with tachypnea, and 38 % of patients had an oxygen saturation between 89 % and 94 % while breathing room air, whereas 31 % had an oxygen saturation below 89 %. Additionally, fever was documented in 29 % of patients during triage (90).

IMAGING PRESENTATION

Since the 2019 epidemic of electronic cigarettes, a substantial amount of data has been collected on the imaging findings of EVALI. Despite this, precise descriptions of these findings, particularly in computed tomography (CT), positron emission tomography (PET), radiography (RX), and magnetic resonance imaging (MRI), continue to be limited and occasionally restricted to presumptive cases, with limited correlation with the histopathological findings of this condition (91,92).

CT is the most commonly used imaging technique to assess pulmonary abnormalities in EVALI. According to Hofmann et al., acute pulmonary lesions are observed in 98 % of the affected patients, while the remaining 2 % present chronic pulmonary lesions (93). Various studies, such as those conducted by Henry et al. (94,95) and Kligerman et al. (4), predominantly describe diffuse alveolar damage (DAD) on CT scans. However, Panse et al., in 2020 (96), suggested that the appropriate term to describe these lesions was "Acute Lung Injury" (ALI). This is because one of the defining histopathological characteristics of DAD, the presence of hyaline membranes, was present in only a minority of patients (24 %). ALI is the most common CT pattern of EVALI, consisting of multifocal or diffuse ground-glass opacities, observed in 96 % of the patients, and/or consolidation, which affects most or all lobes bilaterally, with or without mild interlobular septal thickening, and there may even be subpleural preservation (96-98). The distribution of pulmonary parenchymal abnormalities is observed to be multifocal in 54 % of EVALI patients and diffuse in 46 % of cases. Additionally, 17 % of the cases are also characterized as peripheral and predominantly central in 8 %. Likewise, infiltrative abnormalities of the pulmonary parenchyma show subpleural preservation in 45 % of affected patients (92,94,96-98).

On the other hand, in chest X-rays, patients often present with diffuse and hazy opacity, more pronounced centrally, with notable preservation of the cardiac border and subpleural portions of the lung. The abnormalities are usually predominant in the upper, middle, or lower part of the lung. Kerley lines may also be observed due to septal thickening. These findings tend to coincide with those observed in CT, showing diffuse ground-glass opacities that are generally bilateral and relatively symmetrical. Even in cases where consolidation is present, it tends to be mild. Another common finding is the presence of subpleural spread areas both centrally and peripherally, as well as lobular spread areas (4).

DIAGNOSIS

The diagnosis of EVALI presents a considerable challenge for healthcare professionals, given the absence of specific tests that directly confirm the disease. Therefore, to correctly diagnose EVALI, a comprehensive approach is required that encompasses the evaluation of the patient's clinical symptoms, their history of using vaping devices, and the identification of pulmonary infiltrates in diagnostic imaging such as X-rays (RX) or computed tomography (CT) scans of the chest (4,99). This process is based on the principle that EVALI must be considered a diagnosis of exclusion, which implies that other possible causes of the patient's respiratory symptoms must be ruled out through a variety of tests that include analysis for respiratory viruses such as influenza or SARS-CoV-2, sputum cultures, and specific tests for other pathogens present in the urine. Additionally, a complete blood count that includes differential and liver transaminase levels, as well as inflammatory markers such as the erythrocyte sedimentation rate and C-reactive protein, is essential. Toxicological tests in urine, with proper informed consent, to detect substances like THC should also be conducted (100,101).

In terms of imaging, findings may vary but commonly show evidence of ALI, which includes diffuse bilateral opacities or ground-glass opacities, without unique characteristics

that clearly differentiate them from other lung diseases (88,91,92,96). In situations where imaging findings are inconclusive or when other infectious causes are suspected, procedures such as bronchoscopy may be indispensable to ensure an accurate diagnosis in the presence of atypical symptoms or the suspicion of alternative infections (100).

To standardize the diagnosis of EVALI, the CDC formulated guidelines in 2019 that continue to be a cornerstone in the definition and management of this disease, providing clear criteria for the identification and reporting of confirmed and probable cases. According to these criteria, a confirmed case involves the use of vaping products within 90 days prior to the onset of symptoms, the presence of pulmonary infiltrates on a chest CT scan, and the absence of pulmonary infection or any other plausible disease in the initial evaluation. A probable case is defined similarly but allows some flexibility when an infection is detected that is not believed to be the sole cause of lung damage, or when not all the minimum criteria to rule out a pulmonary infection have been met (99,101).

Given the ongoing evolution in the understanding of EVALI, it is essential that diagnostic criteria be reviewed and regularly updated based on the most recent evidence. This ensures an effective diagnostic and management approach, enabling the delivery of evidence-based care for patients affected by this condition.

ELECTRONIC CIGARETTES AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production, and/or exacerbations) due to abnormalities in the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction. This disease is commonly associated with the chronic inhalation of harmful gases such as cigarette smoke, leading to irreversible airflow obstruction (102).

The Burden of Obstructive Lung Diseases (BOLD) program used a standardized methodology that included questionnaires and pre- and post-bronchodilator spirometry to assess the prevalence and risks of COPD worldwide. Based on BOLD and other large-scale epidemiological studies, the global prevalence of COPD is estimated at 10.3 %. However, with the increasing prevalence of smoking in low and middle-income countries and the aging population in high-income countries, the prevalence of COPD is expected to rise significantly in the coming years. This disease is one of the leading causes of death globally, and according to the World Health Organization (WHO), as of June 22, 2021, it is the third leading cause of death worldwide, causing more than 3 million deaths by 2024 (103-107).

A distinctive feature of COPD related to the use of electronic cigarettes is the dehydration of the mucosa, caused by an imbalance in sodium and water homeostasis and hypersecretion of mucin. This situation is exacerbated by exposure to aerosols from electronic cigarettes containing vegetable glycerin (VG) and propylene glycol (PG). These components alter essential ion channels such as CFTR, BK, and the epithelial sodium channel (ENaC), which are crucial in regulating the hydration of the airway surface and fluid balance (10,79,85).

The aerosols generated during vaping sessions contain oxidants and ROS, produced by heating the liquid in the coil. Even unvaporized e-liquids can induce oxidative effects; however, flavor additives, especially sweet and fruity flavors, are the most oxidizing. Vaping has been linked with an increased risk of lung diseases by inducing oxidative stress, inflammation, and mitochondrial dysregulation, crucial for the production of reactive oxygen and ATP. This link was supported by a study by Li et al., which demonstrated that vaping electronic cigarettes induces the upregulation of Toll-like receptor 9 (TLR9), associated with mitochondrial DNA damage and inflammatory processes (108-111).

Additionally, the NRF2 protein plays a vital role in the cellular antioxidant response. Under normal conditions, NRF2 is found in the cytoplasm bound to KEAP1, which, along with CUL3 and RBX1, forms a ubiquitin ligase

complex that marks NRF2 for degradation and prevents its accumulation. However, when ROS levels increase, NRF2 is released from KEAP1, allowing it to translocate to the nucleus, where it initiates the transcription of antioxidant genes. Interestingly, flavoring agents, such as acrolein, induce carbonyl deposition and affect the expression of KEAP1 in the lungs, interfering with NRF2's antioxidant function (111-113).

Lastly, it has been observed that heavy metal particles present in electronic cigarettes can alter mitochondrial reactive oxygen species (mtROS) and the stability of the electron transport chain complex. This could lead to a significant reduction in the stability of subunit II of the cytochrome C oxidase complex IV, resulting in inefficient electron transfer and the potential formation of mtROS and mitochondrial DNA damage (112-114).

Together, these alterations promote mucosal dehydration, increase inflammation, excessive mucus production, and degradation of alveolar cells, contributing significantly to the obstruction of the airways and exacerbating the adverse effects of using electronic cigarettes, leading to the progression of COPD.

COVID-19 AND EVALI

SARS-CoV-2, the etiological agent of the COVID-19 pandemic, has caused over 6 million deaths worldwide, establishing itself as one of the most devastating and well-known diseases of our time (115). Its dramatic and destructive emergence at the end of 2019 coincided with the end of the EVALI epidemic. In addition, the clinical presentation of COVID-19 is often confused with that of other respiratory diseases due to the nonspecificity of its symptoms and similarities in radiological images, as is the case with EVALI, since both diseases share common symptoms, such as cough, fever, dyspnea, chest pain, and gastrointestinal issues (13).

EVALI was first identified in 2019, almost simultaneously with the emergence of COVID-19 at the end of that year, further complicating the differential diagnosis due to the overlap in the chronology and symptoms of both diseases. EVALI is a form of acute lung disease characterized by pathological findings that include fibrosis, pneumonitis, and diffuse alveolar damage, which can progress to pneumonia. This similarity in symptomatic presentation with COVID-19 poses a considerable diagnostic challenge, often resulting in delays in administering appropriate and timely treatment (116,117).

There are documented cases where COVID-19 and EVALI coexist, further complicating the clinical diagnosis. EVALI is often established as a diagnosis of exclusion in these scenarios. The respiratory symptoms of patients, along with paraclinical findings such as chest computed tomography angiographies, may indicate mild progression of a bilateral infiltrative lung disease, which increases the suspicion of COVID-19 pneumonitis. Additionally, chest X-rays of these patients may reveal diffuse bilateral pulmonary infiltrates and ground-glass interstitial opacities, making it even more challenging to distinguish between these two conditions (99,118,119).

CARDIOVASCULAR EFFECTS

Numerous clinical studies have assessed the impact of electronic nicotine delivery systems, commonly known as electronic cigarettes, on cardiovascular health. These studies have become significant due to the notable increase in the incidence of heart diseases and cerebrovascular illnesses among young adults and adolescents. This demographic previously exhibited lower rates of these diseases prior to the widespread adoption of electronic cigarettes (11).

The cardiovascular effects of electronic cigarettes have primarily been studied through short-term research, as their introduction to the market is relatively recent, and the long-term effects of their continuous use over years or decades are still not fully understood (120). Initial findings suggest acute hemodynamic changes after using these devices, including slight increases in systolic and diastolic blood pressure, approximately by 2 mmHg, and a mild increase in heart rate by about 2 beats per minute, particularly with versions that contain nicotine (121). These variations in heart rate seem to be related to alterations in sympathetic tone following recent consumption of electronic cigarettes, whether

with or without nicotine (122). These changes can influence ventricular repolarization, affecting the diastolic phase of the heart. Moreover, it has been observed that the use of electronic cigarettes can compromise endothelium-mediated dilation function, evidencing a reduction in the bioavailability of nitric oxide, essential for vascular health (11).

Several studies have also documented that the consumption of electronic cigarettes can decrease blood flow velocity, a result of oxidative stress that induces endothelial dysfunction, enhancing the development of cardiovascular diseases. This oxidative stress can increase arterial stiffness in electronic cigarette users, an effect that might persist even after cessation of use. Additionally, there could be a reduced responsiveness of myocardial blood flow to physical exertion, affecting coronary circulation without altering myocardial contraction and relaxation (121,123).

Lastly, recent research has demonstrated that the smoke from electronic cigarettes intensifies platelet activation, aggregation, and adhesion, which could lead to ischemic heart diseases, including acute myocardial infarction (AMI). This increase in platelet aggregation is primarily associated with aerosols containing nicotine. However, nicotine-free aerosols have also shown adverse effects on the endothelial barrier due to other components, such as acrolein. Furthermore, it has been noted that oxidative stress may remain elevated even after discontinuing the use of electronic cigarettes, suggesting a prolonged residual impact on inflammatory and oxidative processes (124).

DUAL USERS: VAPING AND SMOKING

The emergence of devices such as electronic cigarettes has introduced a new dimension in the management of smoking, presenting itself as an option to reduce the harm associated with conventional cigarettes in adults who cannot quit tobacco. However, the phenomenon of "dual users," those who consume both electronic and traditional cigarettes, complicates the scenario (125, 126). Although for some, dual use may be a temporary phase towards the total abandonment of tobacco, this transition period can be prolonged indefinitely, often without achieving complete cessation of tobacco use (127). A study conducted by Patel et al., described that common reasons why conventional smokers do not quit smoking conventional cigarettes include the lack of authenticity of vaping compared to smoking, resulting in an unsatisfactory experience which leads many to opt for electronic cigarettes especially in public places because it is currently more socially acceptable, while in the company of other smokers, smoking is often preferred due to the social context of the moment (128).

It is well known that cigarette smoke contains a mixture of harmful chemicals such as heavy metals, volatile organic compounds, compounds with carcinogenic properties, nicotine, carbon monoxide, cyanide, among others, so smoking even one cigarette a day is enough to reach exposure thresholds that have multiple harmful effects on health (129). This indicates that dual use does not always lead to a significant reduction in exposure to harmful substances, particularly if the consumption of conventional cigarettes remains prominent. Additionally, it has been observed that users who predominantly vape and only smoke conventional cigarettes intermittently achieve a significant reduction in levels of potent carcinogens and carbon monoxide (128). Therefore, the dual-use pattern could be a key predictive factor for overall toxin exposure, highlighting its importance for future research in the field (130). Thus, although there is evidence supporting that dual users can minimize harm by completely transitioning to the use of electronic cigarettes, many remain dual users for long periods, facing the health risks associated with both the toxins of traditional cigarettes and the potential risks of vaping. Understanding and managing this phenomenon requires a thorough analysis of the characteristics of electronic cigarette products to continue making progress in this area (131,132).

ELECTRONIC CIGARETTES AND LUNG CANCER

The current evidence on the relationship between electronic cigarette use and lung cancer (LC) is ambiguous. This uncertainty is due to several limiting factors in existing research, including the lack of appropriate respiratory

models, insufficient sample sizes, variable exposure methods, and inconsistent study results. Furthermore, as electronic devices are relatively new technology, their long-term health effects are not yet clearly defined, complicating the determination of their role as a risk factor for lung cancer (28,133,134). However, it is indisputable that electronic cigarettes can generate toxic products with carcinogenic potential (135).

According to the International Agency for Research on Cancer (IARC), electronic cigarettes produce acetaldehyde, metals, nitrosamines, and carbonyl compounds, including acrolein and formaldehyde, which are human carcinogens. Although the quantities of these byproducts produced by electronic cigarettes are lower than those of tobacco smoke, they are sufficient to contribute to carcinogenesis, especially as they contain recognized carcinogens such as formaldehyde and acrolein (136). This is due to the thermal decomposition of various compounds, including flavorings, solvents (PG, VG, and VEA), nicotine, and the presence of heavy metals from the atomizer (133,137).

Aldehydic compounds, including acetaldehyde, formaldehyde, and acrolein, exhibit significant inflammatory activity. This activity derives from the activation of macrophages, chemotaxis, and the production of reactive oxygen species. These elements together modulate the immune response and contribute to the activation of adverse inflammasomes. This sequence of events is closely linked to oncogenic processes, directly linking inflammation with lung cancer. The negative activation of inflammasomes by macrophages creates an immunosuppressive environment, which is hostile to T cells and is essential in the progression and malignancy of lung cancer (136,137). Additionally, aldehydes can interfere with DNA replication, cause DNA damage (by creating DNA adducts), and disrupt DNA repair mechanisms, reducing the efficacy of repair proteins such as XPC and OGG1/2. Particularly, acrolein has been observed to generate DNA adducts at key mutational sites of the TP53 gene, similar to those detected in lung cancers associated with tobacco use (136).

In another context, nicotine can be converted into nitrosamines through nitrosation. Compounds such as nitrosaminoketone (NNK) and nitrosonornicotine (NNN) are well-known carcinogens in both humans and animals, capable of inducing DNA adducts and interfering with DNA repair in human cells (138). This substance also plays a promoting role in the oncogenesis of various cancers through interaction with nicotinic receptors, as its effects can amplify the survival and proliferation of cancer cells, as well as promote metastasis, invasion, and epithelial-mesenchymal transition, in addition to angiogenesis, directly affecting the tumor microenvironment. It can also decrease apoptosis of cancer cells induced by oncological treatments such as chemotherapy, radiotherapy, or tyrosine kinase receptor inhibitors (139). The ability of nicotine to increase susceptibility to mutations and tumorigenic transformation was demonstrated in a study by Tang et al. in which mice exposed to electronic cigarettes with nicotine developed lung adenocarcinoma and urothelial hyperplasia of the bladder (138).

Certain flavorings require particular mention, such as menthol, which exerts possible oncogenic effects through the modulation of nicotine metabolism and its effect on increasing the expression of the nicotine receptor and the direct pro-inflammatory effects mediated through TRPM8, leading to increased oxidative stress (136). Given the oncogenicity of nicotine, it leads to greater tissue exposure and potential DNA damage. This demonstrated an increase in epithelial-mesenchymal transition (EMT), with the consequent increase in invasive potential, following exposure in electronic cigarettes with menthol and nicotine (133). On the other hand, ethyl maltol, when interacting with iron and copper (present in the heating element) to form hydroxypyrone complexes, results in greater generation of ROS (140). It also facilitates the passage of heavy metals through the cell membrane, which in turn can carry oxidative stress through the generation of free radicals (at the level of the electron transport chain in mitochondria), direct genotoxicity by metals/metallic ions, and alterations in the genetic expression of stem cells (141). However, ethyl maltol does not only do this; it induces an inflammatory response, alters local immune function, and compromises the function and

integrity of the epithelial barrier, promoting additional pro-inflammatory effects and greater systemic exposure to inhaled substances (133).

In general, the relationship between cancer and electronic cigarettes is based on three molecular mechanisms: First, the epithelial-mesenchymal transition to acquire motility, invasion capability, and metastasis; Second, oxidative stress and mitochondrial dysfunction leading to inflammation and genotoxicity, giving a critical role for mitochondria and mitochondrial subversion in cancer; and third, the breakage and fragmentation of DNA, as cancer is an inherently genetic disease associated with genomic instability and clonal evolution. Therefore, although there is no conclusive evidence that a connection between electronic cigarettes and LC exists, there are excellent scientific foundations suggesting a significantly higher risk of developing lung cancer (133,142).

CONCLUSION

The accumulated evidence highlights that the use of electronic cigarettes is not a safe alternative to conventional cigarettes, as was initially promoted. Contrary to this, it is irrefutable that vaping is directly associated with serious lung injuries such as EVALI, and a clear connection between the use of electronic cigarettes and COPD has been established. It is crucial to recognize that electronic cigarettes not only compromise lung health but also induce significant adverse effects on the cardiovascular system.

From a public health perspective, recent findings underline the urgent need for stricter regulations and guidelines on the use of electronic cigarettes, particularly among young people and vulnerable populations. The constant innovation in vaping products and the emergence of new e-liquid formulas with potentially harmful components demand rigorous supervision and a detailed assessment of the health risks associated with their use. Understanding how each component interacts within the e-liquid mixture, as well as its impact on the respiratory system and cardiovascular level, requires a multidisciplinary approach that incorporates specialties such as toxicology, physiology, and analytical chemistry. This understanding is essential to tailor prevention strategies and health education appropriately. Furthermore, it is vital that health professionals are properly equipped with the knowledge and tools necessary to identify and manage EVALI cases, applying a high index of suspicion in young patients who present with nonspecific respiratory symptoms and report recent use of electronic cigarettes. Given this scenario, ongoing research and education are indispensable to address and mitigate the adverse effects of this concerning trend in public health, thus ensuring a proactive approach in protecting collective health against the risks of electronic cigarette use.

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