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Effect of Electronic Cigarette use on Severity of Chronic Rhinosinusitis

(1) Maytham Lafta Kareem (2)Witwit Uday H.K.AL-Janabi

(1)Department of otolaryngology,College of Medicine ,University of Babylon.Iraq

(2)Department of Microbiology / College of Medicine / Babylon University.Iraq

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Abstract :

Chronic rhinosinusitis (CRS) is a chronic inflammatory disorder of the sinonasal mucosa characterized by dysfunctional epithelial clearance systems, defective mucociliary clearance, and chronic immune activation that have a great impact on quality of life and morbidity. The rising global use of e-cigarettes, especially among adolescents and young adults, creates concern for their role in the pathogenesis of CRS. This review presents experimental, clinical, and epidemiological evidence linking vaping exposure with CRS onset and severity. E-cigarette aerosols injure sinonasal epithelial cells by oxidative stress, mitochondrial damage, and disruption of critical tight junctions, leading to increased mucosal permeability and chronic inflammation. Increased mucus secretion and reduced ciliary function lead to impaired mucociliary clearance, ultimately encouraging pathogen colonization and recurrent infections. In addition, reactive oxygen species prime the signaling pathways of inflammation, such as NF-κB, worsening any damage of tissues. Immune dysregulation characterized by altered cytokine expression, impaired macrophage function, and neutrophilic-eosinophilic inflammation amplifies chronic mucosal inflammation. Alterations within the microbiome may serve to perpetuate chronic infection and diminished treatment response. Clinical evidence has found that e-cigarette users have greater symptomatology of CRS in terms of amount and severity, with more severe endoscopic and radiological signals than non-users. Current evidence suggests a biologically plausible relationship between e-cigarette use and the development of CRS; however, further long-term studies are necessary to establish a cause and effect relationship between the two and to develop prevention strategies.

Keywords:
Electronic cigarettes, Vaping, Chronic rhinosinusitis, Sinonasal inflammation, Oxidative stress, Mucociliary dysfunction

Introduction:

Chronic rhinosinusitis (CRS) constitutes an intricate and heterogeneous inflammatory illness that affects the mucosa of both the nasal cavity and paranasal sinuses. CRS is now recognized to be one of the most prevalent types of chronic conditions encountered by physicians working in both otolaryngology and respiratory health [1]. CRS can be differentiated from acute rhinosinusitis by its chronic inflammation because the inflammatory response continues for at least 12 consecutive weeks, even with good medical management. CRS is caused by the interaction of multiple pathogenic processes including dysfunction of the epithelial barrier, dysregulation of the immune system, microbial imbalance, exposure to the environment and ongoing chronic inflammation. Generally, CRS is classified into two major subtypes or phenotypes based on whether or not nasal polyps are present; CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). The two types have distinct immunological and inflammatory characteristics. Recent research supports that CRS should no longer be considered a purely infectious disease but rather a chronic inflammatory disease of the airways with close ties to asthma, allergy, and other systemic inflammatory disorders [2,3].

The definition of CRS is based upon a combination of clinical signs and symptoms plus actual evaluation of paranasal sinuses findings to determine the level of inflammation. Per the International Consensus Statement on Allergic Rhinitis and CRS, a diagnosis of CRS must be made if two or more cardinal signs have been present for 12 or more weeks and there is also objective evidence to document the presence of inflammation [4]. Four cardinal signs for CRS are: nasal obstruction; nasal discharge; facial pain/pressure; anosmia. There are objective methods to document the presence of nasal mucosal edema, nasal polyps, mucopurulent discharge and CT findings that indicate thickening and opacity of the sinus mucosa [5, 6].

Clinically, CRS is associated with a variety of sinonasal and systemic symptoms, which can significantly affect the quality of life of patients with CRS. The most commonly reported symptoms include a troublesome, ongoing nasal obstruction; thick nasal drainage; facial fullness/pressure; post-nasal drip; and reduced sense of smell (olfaction). In addition to these symptoms, many patients with CRS will also report symptoms of fatigue, sleep disturbance, headache, cough, cognitive difficulties and emotional distress, particularly in those with severe or refractory disease [7]. Olfactory dysfunction is often considered to be among the most characteristic features of CRS, especially in patients with nasal polyps and noted eosinophilic inflammation [8]. The chronic state of inflammation will further lead to degradation of mucosal tissue, disruption of the epithelial surface, and decreased mucociliary clearance, which may lend itself to the development/recurrence of infections and occurring symptoms. In the most severe forms of CRS, patients can develop

orbital or intracranial complications, although these are relatively rare (occurring less often) in the era of antibiotics. In addition, the severity of symptoms does not always closely correlate to the degree of abnormalities seen on imaging studies, which indicates the heterogeneity and complex nature of CRS [9].

CRS represents a significant burden on global health as well as a significant socioeconomic burden on a global scale. Epidemiological studies suggest that CRS approximately affects about 11% of the European population [10].

There is a strong association between the development of CRS and the presence of multiple comorbidities, such as asthma, allergic rhinitis, atopic dermatitis, obstructive sleep apnea, and both depression and anxiety disorders [11]. Environmental pollutants; tobacco smoke; and exposure to electronic cigarettes contribute significantly to the onset and worsening of CRS by exacerbating inflammation and oxidative damage to the sinonasal epithelium [12, 13].

Through an evaluation that examines both contemporary scientific data associated with vaping and chronic rhinosinusitis (CRS), both with a focus on evidence-based medicine will be discussed as a primary goal of the present review as follows: Assessing the current level of research on the impact electronic cigarette (e-cig) usage poses on chronic rhinosinusitis through the use of electronic cigarettes (ECGs), determining how these products contribute to the symptoms, severity, and progression of chronic rhinosinusitis through various mechanisms, establishing a comparison between the e-cigarette and conventional combustible cigarette using clinical evidence including epidemiologic studies, identifying where future study would be warranted. Lastly, this review has the goal of integrating and analyzing all of the current available evidence related to electronic cigarettes and chronic rhinosinusitis and making recommendations for future research.

Data collection:

Data for this review was gathered by conducting a comprehensive search for literature via primary scientific electronic databases: PubMed, Scopus, Web of Science, Google Scholar. The search strategy was based on combinations of keywords and Medical Subject Heading (MeSH) terms such as "e-cigarettes," "vaping," "chronic rhinosinusitis," "sinonasal inflammation," "nasal polyps," "oxidative stress," and "mucociliary dysfunction," that were published in the English language during the years 2015 - 2026. In addition, additional studies were located from manual screening of reference lists of selected articles. Eligible publications included original research articles; clinical studies; epidemiological studies; experimental studies; systematic reviews; and meta-analyses demonstrating evidence of the association between electronic cigarette exposure and sinonasal or upper airway inflammatory diseases. Articles that were not scientifically relevant; duplicate studies; conference abstracts with no full text; and or other non-peer-

reviewed sources were excluded in order to provide the data that was collected with high reliability and scientific validity.

1. Classification of CRS

The chronic and persistently long-lasting inflammatory condition known as chronic rhinosinusitis (CRS) can be classified by both an individual's symptoms, through the pattern of inflammation, and their immunological disorder's background mechanism. When classifying CRS phenotypically, chronic rhinosinusitis with nasal polyps (CRSwNP) is categorized separately from chronic rhinosinusitis without nasal polyps (CRSsNP); however, many recent studies have also started classifying CRS into particular endotypes based upon the inflammatory process underlying the individual's CRS. One endotype of CRS is identified as allergic fungal rhinosinusitis (AFRS) which is characterized as an allergic-type reaction to mold, resulting in eosinophilic inflammation as well as the development of hyperplastic polyp formation within the nasal cavity or paranasal sinuses [4, 5].

CRSwNP is characterized by the formation of benign, non-cancerous, inflammatory polyps that form in either the nasal cavity or paranasal sinuses. The development of polyps in people with this type of CRS is often an indication of type 2 inflammation, characterized by eosinophils, mast cells, and excess production of interleukins, particularly IL-4, IL-5, and IL-13. Many patients suffering from this form of CRS present with chronic, severe nasal blockage, loss of smell, multiple occurrences of infectious-related complications, and have a significantly higher incidence of obstructive airway disease (asthma) and/or are aspirin-exacerbated respiratory disease patients. Histologically, CRSwNP can usually be recognized by histopathological changes to the epithelium (i.e., subepithelial edema), significant eosinophilic infiltration, increased number of goblet cells, and extensive tissue remodelling. In addition, it has been shown that biologic therapies aimed at interfering with type 2 inflammation can greatly improve overall success of CRS management for patients with severe CRSwNP [14].

CRS-NP is characterized by the absence of polyps, predominately neutrophilic/mixed inflammation, and signs and symptoms such as facial pain/pressure, mucoid drainage, nasal congestion, and thickening of the sinus mucosa with fibrosis and basement membrane thickening. Histologically compared to CRW-NP, CRS-NP shows more prominent features of fibrosis and basement membrane thickening. CRSSNP was previously thought to be less as severe than PP disease; however, there is now considerable variability in clinical presentation and significant impairment of quality of life in CRS individuals [15, 16].

Allergic fungal sinusitis is a unique subtype of CRS caused by excessive immune response to a fungus in the sinonasal cavity. AFRS is associated with the presence of an eosinophilic mucinous exudate containing fungal hyphae and nasal polyps, elevated serum IgE levels, and radiographic evidence of eosinophilic tissue involvement with heterogeneous opacification on CT or MRI scans [17].

Patients tend to show extensive sinonasal involvement and suffer from recurrent disease, as well as aggressive inflammatory changes, which may lead to bone destruction or orbital complications (the latter being associated with severe forms of the disease). Aspergillus and dematiaceous fungi are the two main fungal types implicated in the disease process. AFRS is more common in warm and humid climates, affects a greater number of youth who are atopic, and is referred to as the "hot" Turkish disease in this patient group [18].

Recent research has focused on the inflammatory endotypes of chronic rhinosinusitis (CRS) with relative emphasis on the eosinophilic versus the non-eosinophilic subtypes. Eosinophilic CRS is characterized by a high density of eosinophils, the predominance of type II cytokines, and elevated IgE levels; in addition, there may be marked mucosal inflammation, nasal polyps, and asthma associated with this form of CRS. The eosinophilic subtype tends to have higher rates of recurrence, worse disease severity, and may be more responsive to corticosteroid and biologic therapy [19, 20]. In contrast, the non-eosinophilic CRS (or neutrophilic CRS) group is generally associated with neutrophils, bacteria, Th1/Th17 immune responses, and fibrosis [21].

2. Electronic Cigarettes: Definition and Evolution

E-cigarettes, known as electronic nicotine delivery systems (ENDS), are battery-powered gadgets for the inhalation of nicotine and other substances in aerosol form, rather than smoke from combustible tobacco products. Originally marketed as a replacement for regular cigarettes, e-cigarettes have quickly gained widespread acceptance and use worldwide by adolescents and young adults. The operation of e-cigarettes is accomplished by heating up a liquid substance, commonly known as e-liquid or vape juice, that generally consists of nicotine, propylene glycol (PG), glycerin (VG), flavoring agents, and chemicals used for making the vaping process easier. While the manufacturers of e-cigarettes claim that they are a safer alternative to smoking tobacco, numerous studies are confirming that the aerosols produced by e-cigarette devices include significant amounts of toxic compounds as well as inflammatory materials; thus, exhibiting potential respiratory and sinonasal injury [22, 23, 24].

The modern e-cigarette was created in 2003 by Hon Lik, a Chinese pharmacist, and was introduced to the international market in the mid-2000s. Since then, e-cigarettes have undergone significant technological advancements that have produced multiple generations. The first-generation cigalikes resembled standard cigarettes in form and provided relatively low concentrations of nicotine. Generation two vape pens used refillable tanks or cartridges and had larger battery sizes than generation one devices [25]. Third-generation mods allowed users to set the parameters of the device (voltage, wattage, and temperature) to produce more aerosol than the previous generation's devices. More recently, fourth-generation pod systems such as JUUL have become popular because they are small in size, contain higher concentrations of nicotine salts, and are easily used without drawing attention. These technological advancements have changed the ways in

which e-cigarette users engage and are exposed to nicotine by increasing nicotine addiction, dependence, and exposure to the aerosolized toxic substances [26].

E-cigarettes contain five main parts: a rechargeable lithium battery; a heating element or atomizer; a cartridge or reservoir with e-juice; a wick system to send e-juice to the atomizer; and a mouthpiece. When the device is turned on, the battery sends electricity to the metal coil in the atomizer; this heats up and quickly vaporizes the e-liquid, creating an aerosol that can be inhaled. Ultrasonic particles, nicotine, volatile organic compounds, heavy metals, carbonyl compounds (such as formaldehyde and acrolein), and toxins from flavorings are included in the aerosol. The amount of these chemicals in the aerosol depends on a variety of factors: the power of the device; the temperature of the coil; the length of puffs; the chemical makeup of the e-liquid used; and the user's inhalation patterns. E-cigarettes that operate at higher temperatures are associated with much higher levels of oxidative and/or toxic compounds than e-cigarettes that operate at lower temperatures, and the compounds may be capable of damaging airway epithelial cells and inhibiting mucociliary function [27, 28, 29].

E-cigarettes produce aerosol in a different way than traditional cigarettes do. Traditional cigarettes rely on the burning of tobacco leaves while E-cigarettes depend on heating liquid solutions (e-liquids) to form an aerosol that is then inhaled into the lungs. While E-cigarettes do not contain combustion products, studies have shown that the thermal breakdown of propylene glycol and glycerine when heated can produce reactive compounds, such as aldehydes, free radicals and compounds that induce cellular oxidative stress. In addition, flavoring additives in e-liquids, like; cinnamaldehyde; menthol, and diacetyl; may have toxic and pro-inflammatory effects on lung cells. Recent research has suggested that repeated exposure to e-cigarette aerosol may lead to altered immune responses, impaired integrity of the epithelial barrier, and increased risk of developing respiratory infections and chronic inflammatory lung diseases including chronic rhinosinusitis [30, 31].

2.1Global Epidemiology of Electronic Cigarette Use

In the past 10 years, the number of people using electronic cigarettes has grown rapidly around the world. These products were developed as a safer alternative to regular cigarettes and to help people stop smoking. However, their rapid increase in popularity has been due to their availability in a variety of flavored products, advertising on social media, and because consumers think that they're less harmful than smoking [23]. In many locations, including the US and Canada, many adults are using e-cigarettes instead of traditional tobacco products, even though they are still using regular cigarettes along with e-cigarettes. As a result, a number of adults are using both products at once and therefore are continuing to expose themselves to nicotine [32]. Vaping by adolescents and young adults represents one of today's greatest public health challenges. Numerous flavors, sleek designs, and ease of availability have all added to the increased rate of addiction to nicotine by these younger people. Pod-based devices (e.g., JUUL) have become very

popular among adolescents and young adults because they can deliver high levels of nicotine and are very discreet [33, 34].

3. Anatomy and Physiology of the Sinonasal Tract

The sinonasal tract is a very complicated area anatomically and immunologically because it includes both the nasal cavities and the para-nasal sinuses workingly for air conditioning, filtration, humidification and protecting from diseases. The para-nasal sinus system consists of the maxillary sinus, ethmoid sinus, frontal sinus and sphenoid sinus; all of which contain respiratory mucosa lining and connect to the nasal cavity through a series of narrow holes (ostia). The maxillary sinus is the largest sinus in the body, drains into the middle meatus (middle nasal passage) via the osteomeatal region - this area is very important in CRS etiology. Ethmoid sinuses consist of many air cells that are closely related to the lateral nasal wall and the orbit, whereas the frontal and sphenoidal sinuses drain through small canals leading them to obstruction and chronic inflammation [35, 36].

Mucosal barriers in the sinonasal cavity serve as the first line of defense against inhaled pathogens, allergens, and environmental pollutants. The sinonasal mucosa consists of a pseudo-stratified ciliated columnar epithelium which contains basal, goblet, and ciliated epithelial cells. The integrity of the epithelium and its permeability is maintained by tight junction proteins (claudins, occludins, and junctional adhesion molecules). Disruption of these junctions increases epithelial permeability leading to pathogen entry and chronic inflammation. Goblet cells play a role in secreting mucus; thus contributing to trapping inhaled particles and providing a means for mucosal defense. Recent studies are beginning to identify that a dysfunctional epithelial barrier may play an important role in the development and persistence of CRS [35, 37].

Mucociliary clearance is an essential physiological function that removes inhaled pathogens and particulate matter from the sinonasal cavity. Mucociliary clearance relies on coordinated ciliary activity and optimal mucus rheology. Cilia transport mucus toward the nasopharynx, where it is either expelled or swallowed. Mucins (MUC5AC and MUC5B), antimicrobial peptides, immunoglobulins, and electrolytes are among the constituents of the mucus layer that provide an innate defense. Mucociliary dysfunction—caused by epithelial injury, dehydration, or inflammatory damage leads to mucus stasis, microbial colonization, and chronic inflammation, which are characteristics of CRS [38, 39] .

The sinonasal mucosa also has a highly specialized immune defense system that combines elements of both innate and adaptive immunity. Innate immunity is mediated by epithelial cells, macrophages, dendritic cells, and pattern recognition receptors (PRRs)—including Toll-like receptors (TLRs)—that recognize components of microorganisms and activate inflammatory signaling pathways. Adaptive immunity is mediated by T and B lymphocytes, which generate antigen-specific responses and develop an immunologic memory. In addition, epithelial cells produce antimicrobial peptides, such as defensins, lysozyme, and lactoferrin, which act quickly against bacteria, viruses, and fungi.

Dysfunction in the regulation of these immune systems results in chronic inflammation, tissue remodeling, and a prolonged sinonasal condition [35, 40, 41].

4. Pathophysiology of Chronic Rhinosinusitis

4.1 Inflammatory Mechanisms in CRS

Chronic rhinosinusitis (CRS) is an inflammatory disorder that consists of multiple factors that lead to constantly activating the immune system and cause different types of inflammation in the body. The current data categorize CRS by inflammation patterns based on the types of cytokines produced in the body and the cells that migrate to these sites of inflammation. The three types of CRS inflammation are Type 1, Type 2, and Type 3, with Type 1 inflammation primarily using the cytokines interferon-gamma and tumor necrosis factor-alpha (TNF-α), while neutrophils and macrophages are the predominant cells participating in the Type 1 inflammation response. Type 2 inflammation is the most researched CRS Type 2 inflammation and can occur with or without nasal polyps; however, this type of inflammation consists of predominantly eosinophils migrating to the inflammation site with elevated levels of interleukin (IL)-4, IL-5, and IL-13, which leads to mucus production, tissue swelling, and polyp development. Type 3 inflammation consists of IL-17 and IL-22 cytokine signaling and is usually associated with neutrophilic inflammation and damage to the epithelial cells above the site of inflammation. Since each type of inflammation may contain characteristics of overlapping inflammation patterns, this leads to varied results from treatment options [42, 43].

Cytokine Networks are Central to CRS Pathogenesis. The cytokine network is responsible for regulating the following aspects of CRS pathogenesis: inflammatory cell recruitment, epithelial dysfunction, and tissue remodelling. Cytokines that have been shown to be elevated in sinonasal tissue from CRS Patients include the following: IL-4, IL-5, IL-13, TNF-α, IL-17, TSLP, and TGF-β. These cytokines are key contributors to the development of both chronic mucosal inflammation by promoting eosinophil survival; neutrophil activation; mucus production; and fibroblast proliferation. Prolonged (persistent) inflammatory signalling ultimately results in prolonged damage to the epithelium and lack of healing to the mucosa [44, 45].

4.2 Epithelial Barrier Dysfunction

The epithelial barrier of the sinonasal region protects against inhaled pathogens and allergens and is a major protective mechanism against damage due to inhaled environmental irritants. Dysfunction of the sinonasal epithelial barrier is one of the important factors in the pathogenesis of chronic rhinosinusitis (CRS) and contributes to the development of chronic rhinosinusitis due to chronic inflammatory processes. Integrity of the sinonasal epithelium and regulation of the paracellular permeability properties of the sinonasal epithelium are maintained by tight junction proteins, which include the claudins, occludins, and zonula occludens. Tight junction proteins have been shown to be reduced in expression and structurally disrupted in patients with chronic

rhinosinusitis, resulting in dysfunctional sinonasal epithelial barrier function and increased sinonasal mucosal permeability [46, 47].

Increased sinonasal epithelial permeability provides a conduit for allergens, microbial antigens, pollutants, and harmful particles to breach the sinonasal epithelial barrier and enter deeper layers of the sinonasal mucosa, resulting in persistent immune activation and chronic activation of inflammatory signalling pathways. Damage to the sinonasal epithelium also impairs the mucociliary clearance mechanism, and creates conditions that promote chronic colonization of sinonasal mucosal tissues by microbial agents, thereby further perpetuating sinonasal inflammation. Recent studies have indicated that exposure to environmental agents, such as tobacco smoke and e-cigarette aerosol, may directly induce sinonasal epithelial barrier injury via the activation of oxidative and inflammatory signalling pathways [48, 49].

4.3 Oxidative Stress in CRS

CRS pathogenesis and progression largely depend on oxidative stress. Inflammatory cells and damaged epithelial cells in chronic inflammation generate reactive oxygen species (ROS), which include superoxide anions, hydroxyl radicals, and hydrogen peroxide. Overproduction of ROS contributes to epithelial damage, mitochondrial failure, DNA damage, and activation of pro-inflammatory transcription factors such as NF-κB [50, 51]. Under physiological conditions, sinonasal tissues have antioxidant defense mechanisms that include superoxide dismutase, catalase, glutathione peroxidase, and non-enzymatic antioxidants to regulate redox balance. CRS patients frequently have significant depletion of antioxidants in sinonasal tissues and/or impaired redox homeostasis, resulting in a continual state of oxidative injury and chronic mucosal inflammation. Additionally, in CRS, oxidative stress has been associated with excessive amounts of mucus, ciliary dysfunction, tissue remodeling, and particularly in eosinophilic phenotype CRS [52].

4.4 Microbial Dysbiosis and Biofilms

CRS is characterized by microbial dysbiosis (loss of the normally diverse and healthy microbial communities that comprise the sinonasal mucosa) contributing to CRS pathogenesis. The sinonasal mucosa in a healthy individual typically contains multiple taxa of microbes that are essential in maintaining homeostasis of the mucosal environment while preventing excess growth of pathogenic microbes. In CRS, these communities are disrupted, resulting in excessive colonization of pathogenic bacteria (e.g., S. aureus, P. aeruginosa, and anaerobic organisms), among other things [53, 54].

Another critical factor that plays a role in CRS and persistent sinonasal inflammation is biofilm formation. Biofilms are structured microbial communities that produce an extracellular polymeric matrix (EPM) surrounding the microbial cells, thus providing them with protection against the host's immune response and antibiotics. Biofilms have been linked to severe CRS cases, recurrent infection, poorer surgical outcomes, and elevated levels of mucosal inflammation. Fungus has also been implicated in selected CRS subtypes, especially allergic fungal rhinosinusitis (AFRS) where the immune response to

fungal antigens causes significant eosinophilic cellular responses and chronic inflammation of the sinonasal mucosa [55, 56].

4.5 Role of Allergens and Environmental Pollutants

CRS development and severity are greatly affected by environmental exposures. Air pollution such as PM2.5, ozone, nitrogen dioxide, and industrial chemicals can harm the sinonasal epithelium, disrupt mucociliary clearance, and cause oxidative stress. Recent studies have shown a correlation between smoking and CRS development, with the level of tobacco smoke exposure being a major risk factor. When compared to other known environmental risk factors for developing CRS related to smoking, nicotine is found to have significantly less impact on CRS development than other environmental pollutants [57].

Tobacco smoke is an environmental risk factor that plays a significant role in CRS pathogenesis. Cigarette smoke is made up of many toxic compounds that can create epithelial damage and cause oxidative stress, mucus hypersecretion, and chronic inflammation throughout the body. Recent research has suggested that the aerosol from electronic smoking devices can also cause similar damage to tissues in the sinonasal area. Another environmental risk factor for CRS is occupational exposure to dust, chemicals, fumes, and agricultural pollutants, which has been linked to CRS due to chronic inflammation of the sinonasal tissue and an increased incidence of CRS for individuals exposed to these substances on the job [58].

4.6 Tissue Remodeling in CRS

CRS causes long-lasting inflammation that leads to changes to the actual structure of the nasal cavity and paranasal sinuses, known collectively as tissue remodelling. This includes fibrosis (scar tissue), excess extracellular matrix, thickening of the basement membrane, hyperplasia (overgrowth) of mucus-producing glands, swelling (edema), and formation of new blood vessels (angiogenesis). TGF-β and MMPs are two important mediators of remodelling processes and fibroblast activation in the paranasal sinuses [59, 60].

Edema occurs when fluid leaks out of blood vessels, which happens due to increased permeability of tissues, a result of the chronic inflammation process. In CRSwNP, the persistent eosinophilic inflammation and increased amount of extracellular fluid in the submucosa both result in the development of nasal polyps, which are abnormal protrusions of the chronically inflamed mucosa. Thus, polyps will often contain many inflammatory cells, plasma proteins and extracellular matrix elements that will perpetuate the chronic disease. The degree of tissue remodelling is related to the severity, recurrence, and poor response to medication in patients with CRS [3, 61, 62].

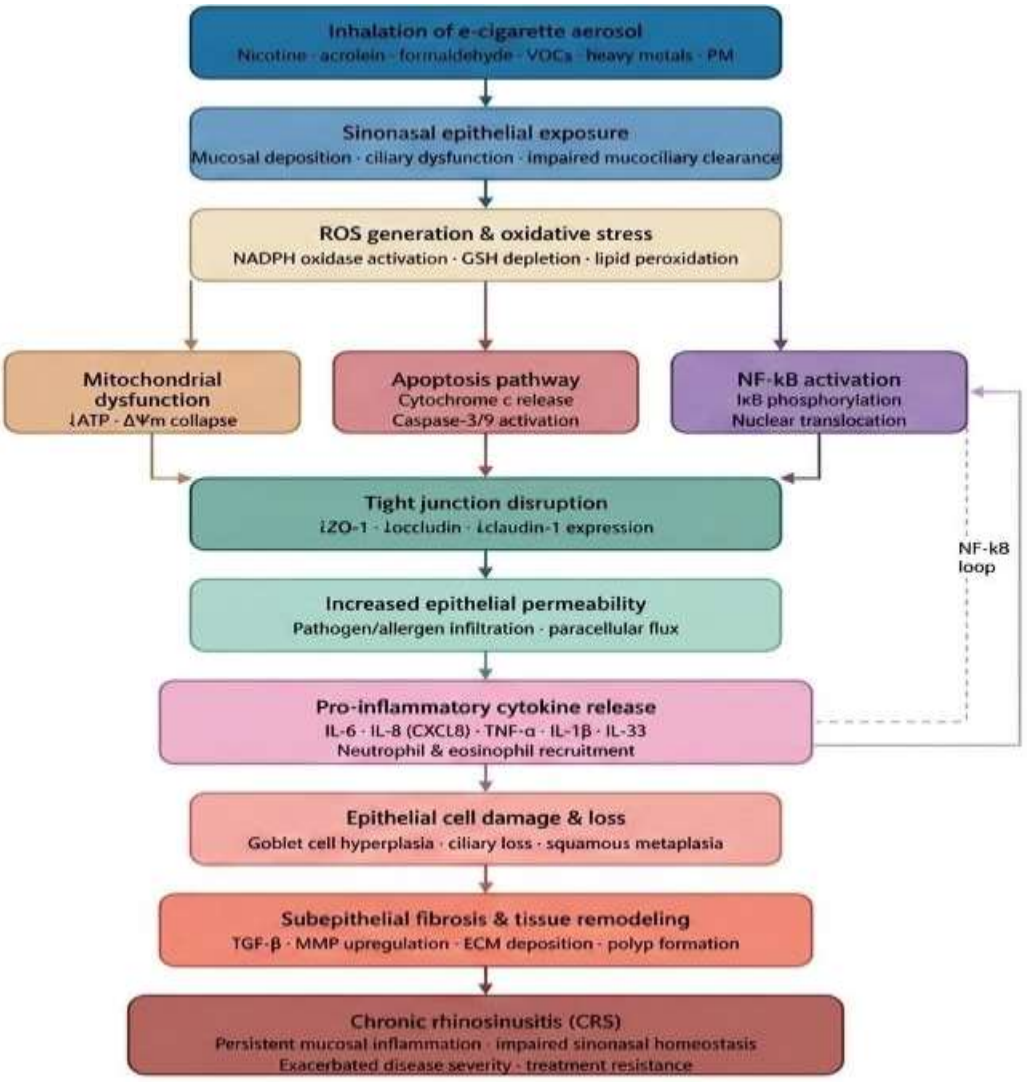

Figure 1: Pathophysiology of CRS.

5. Composition and Toxicology of Electronic Cigarettes

5.1 Structure and Working Mechanism of Electronic Cigarettes

Nicotine is delivered using electronic cigarettes (e-cigs), which are devices used to deliver nicotine via liquid vaporized in an aerosol form. E-cigs consist of three primary components: a rechargeable lithium battery; heating coil; and a reservoir containing e-liquid. The battery provides the necessary power to heat the coil within the atomizer, which transforms the liquid from the reservoir into an aerosol or vapor that can be easily inhaled through the mouthpiece and into the lungs [24, 27].

E-cigs have undergone numerous generational transformations and innovations in design with respect to performance, nicotine delivery profile, and overall aerosol output. Due to significant improvements in product design and new technologies, modern e-cig use has resulted in much larger aerosol quantities and concentrations of many harmful byproducts than prior generation e-cigs. The voltage from the e-cig battery, temperature at the coil,

and manner in which one puffs on the e-cig all contribute to the chemical composition and toxicity of the generated aerosol [22, 23].

5.2 Chemical Constituents of E-Liquids

Typically e-liquids have a combination of nicotine, propylene glycol (solvent) and vegetable glycerin (aerosol) as well as other flavorings. Nicotine is the primary drug responsible for the addictive properties of vaping and may be made of either free-base or salt formulation for the purpose of delivering more nicotine with less irritation to the throat. Chronic exposure to nicotine has been shown to create oxidative stress, cause damage to blood vessels, promote inflammation, and suppress immune function [23].

Propylene glycol and vegetable glycerin both act as solvent carriers and aerosol producers during the act of vaping. While propylene glycol and vegetable glycerin are considered safe to consume when not heated, upon heating, thermal decomposition can produce toxic aldehydes and reactive oxygen species which can be harmful to the respiratory epithelium. There are thousands of different flavorings that may be included in e-liquids that serve as flavor enhancements and some examples include menthol or vanillin. Many of these chemicals exhibit properties that are damaging to the cells lining the airway and have the ability to promote inflammation [63, 64].

5.3 Toxic Compounds Generated During Vaping

Vaping, or e-cigarettes are a source of harmful chemicals, including carbonyl compounds such as formaldehyde and acetaldehyde, which result from the thermal breakdown of propylene glycol and glycerol as they are heated and aerosolized. These carbonyl compounds can cause oxidative stress, damage DNA inside cells, injure epithelial cells, and lead to chronic inflammation [28, 65]. Additionally, vaping has been shown to produce heavy metals such as nickel, chromium, lead, tin, and cadmium, which enter e-cigarette aerosols primarily from the metal coils used to heat the e-liquid and from other metallic pieces of the e-cigarette. Long-term exposure to these metals through inhalation may cause injury to the airways and be toxic to the lungs. Finally, vaping aerosols contain volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons, and ultrafine particulate matter, which infiltrate the deeper parts of your respiratory system, leading to oxidative stress as well as impairing normal immune function [66, 67].

5.4 Flavoring Chemicals and Respiratory Toxicity

The flavoring chemicals in e-cigarette products are a major area of concern due to their potential to cause respiratory toxicity. Diacetyl, a flavoring compound that imparts a buttery flavour to certain e-liquids, has been associated with bronchiolitis obliterans and severe injury to the epithelial tissues of the airways when inhaled. Cinnamaldehyde is an additional flavouring compound commonly used to provide flavour to cinnamon-based products. Cinnamaldehyde may impair the function of cilia, disrupt epithelial integrity, and suppress innate immune responses in respiratory tissues. Furthermore, menthol-flavoured products may lead to changes in cellular calcium signaling; may enhance the risk of addiction to nicotine; and may promote the development of inflammation in the airway epithelium [68]. Flavoured e-cigarette aerosols have also demonstrated increased cytotoxicity compared to unflavoured products due to the combined effects of the flavouring additive and the thermal degradation (i.e., breakdown of the aerosolised aerosol) products. The flavouring compounds in flavoured e-cigarette aerosols have been shown to impair mucociliary clearance; increase oxidative stress; and induce chronic airway inflammation, raising significant concerns about their potential contribution to the development of chronic respiratory diseases such as chronic rhinosinusitis [65, 69].

5.5 Comparison Between Conventional Smoking and Vaping

E-cigarettes are often promoted as "safer" alternatives to traditional cigarettes; however, they have many of the same toxicological properties as traditional cigarettes. Conventional cigarettes are considered to be among the most toxic products a person could use, containing thousands of toxic products, including carbon monoxide, reactive oxidants, carcinogens (cancer-causing agents), and tar from combustion. While e-cigarettes generally expose the user to lower concentrations of certain toxic substances compared to traditional cigarettes, the aerosol produced from e-cigarettes includes many of the same harmful substances described above, including nicotine, aldehydes, metals, oxidants, and inflammatory particles, present in sufficient concentrations to cause damage to the lungs and heart [22, 23]. Both smoking conventional cigarettes and using e-cigarettes result in dysfunction of the epithelial barrier, oxidative stress, immune dysfunction, impaired mucociliary clearance, and chronic inflammation within the lungs. In addition, misconceptions about the safety of e-cigarettes have led to an increase in use among adolescents and non-smokers. Current research indicates that chronic e-cigarette exposure can have significant effects on the lungs, particularly if users utilize high wattage devices, flavored e-cigarette products, or have a longer duration of e-cigarette use. Dual users of traditional cigarettes and e-cigarettes may incur greater cumulative toxic exposures and have a higher risk of developing tobacco-related illnesses than exclusive users of traditional cigarettes or e-cigarettes [31, 65].

6. Mechanisms by Which Electronic Cigarettes May Exacerbate Chronic Rhinosinusitis

6.1 Epithelial Cell Injury and Barrier Dysfunction

The sinonasal epithelium is directly injured by e-cigarette aerosol, damaging the integrity of the mucosal barrier. The exposure of epithelial cells to vaping aerosol has been demonstrated to cause epithelial cytotoxicity, inflammatory activation, and decreased cellular viability as a result of oxidative and metabolic stress pathways[70]. More recently, studies have demonstrated that e-cigarette exposure leads to disruption of epithelial tight junction proteins and increased epithelial permeability which allows for the penetration of allergens, pathogens and toxic particles into the underlying tissues [71]. Moreover, chronic exposure of epithelial tissue to aerosol may induce epithelial apoptosis and airway remodeling leading to worsening of persistent mucosal inflammation and the progression of CRS [72].

6.2 Impairment of Mucociliary Clearance

The mucociliary clearance mechanism is a crucial defensive tool that helps clear inhaled pathogens and particles from the respiratory airway. Research indicates that exposure to electronic cigarette vapor can cause a decrease in both the frequency of ciliary beating and the coordination of these cilia as well as structural changes to the ciliated epithelial cells. Other experimental data have shown that certain flavoring agents (i.e., cinnamaldehyde and menthol) used in electronic cigarettes may significantly decrease ciliary activity and adversely affect the functioning of the airway epithelium[68, 73]. It is also believed that the use of electronic cigarettes may cause excess mucous secretion through stimulation of the goblet cells in the airway and through the release of inflammatory cytokines. Retained mucous with increased viscosity from decreased ciliary function can lead to obstruction of the nasal cavity and sinuses. Long-term exposure to the toxins in electronic cigarette aerosol can lead to ciliary dyskinesia, which can decrease the effectiveness of pathogen clearance and cause an individual to be at an increased risk for repeated infections and chronic inflammation due to chronic rhinosinusitis [66, 70].

6.3 Oxidative Stress and Reactive Oxygen Species Production

The primary cause of e-cigarette-based lung damage is oxidative stress, which means that e-liquids that are heated produce reactive oxygen species (ROS), aldehydes (carbonyl compounds), and free radicals that can cause damage at the cellular level. Overproduction of ROS has been shown to damage the mitochondria, leading to disruption of ATP synthesis and the activation of pro-inflammatory transcription factors such as NF-kB [63, 74]. Vaping exposure-induced mitochondrial dysfunction also contributes to epithelial damage/apoptosis, as well as ongoing pro-inflammatory activation in the sinonasal mucosa. Oxidative stress is additionally thought to exacerbate pro-inflammatory cytokine production and lead to prolonged tissue damage. Increasing evidence indicates that inhaled e-cigarette aerosol may also alter the body's antioxidant defense mechanisms; ultimately leading to long-term oxidative imbalance and increased risk for chronic inflammatory airway disorders such as CRS [75].

6.4 Immune Dysregulation

Inhalation of vapor from electronic cigarettes (e-cigarettes) can dramatically change both innate and adaptive immune responses in the respiratory tract. The chemicals found in e-cigarettes produce unregulated levels of cytokines; many of these cytokines have been found to be involved in the production of pro-inflammatory cytokine compounds, such as interleukin (IL)-6 and IL-8, tumor necrosis factor-alpha (TNF-α), and numerous additional cytokines, leading to chronic mucosal inflammation and immune dysfunction [70, 76]. In addition to impairing cytokine activity in the respiratory tract, evidence shows that e-cigarettes can cause both neutrophilic and eosinophilic inflammatory responses

depending on the duration of exposure, type of e-cigarette device, and composition of the e-cigarette aerosol. Neutrophilic inflammatory responses are frequently correlated with injury to epithelial lining and development of chronic infections; whereas an eosinophilic inflammatory response contributes to secretion of excess amounts of mucus and development of tissue edema. Moreover, aerosol exposure from e-cigarettes results in decreased macrophage phagocytosis, which will reduce the ability of immune cells to clear pathogens. Dysfunctional macrophages can lead to an increased risk for developing chronic sinonasal infections and chronic inflammation [27, 77].

6.5 Microbiome Alterations

Maintaining mucosal homeostasis and regulating local immune responses relies heavily on the sinonasal microbiome. Exposure to electronic cigarettes may change the microbial diversity of the sinonasal cavity and cause dysbiosis of the upper respiratory tract [78]. Vaping has been associated with an increased prevalence of pathogenic organisms, while also having a detrimental effect on the colonization of protective commensal bacteria[79]. Changes in the microbiome via these exposures may lead to chronic inflammation and epithelial dysfunction, and may create an increased risk of CRS developing and progressing [80].

6.6 Biofilm Enhancement and Persistent Infection

Biofilm is a group of microorganisms (biofilm) within a matrix of polysaccharides that protect and enhance their ability to persist and resist antibiotics. E-cigarettes can promote biofilm development through epithelial cell death and disruption of the clearance mechanism [81].Increased biofilm development is associated with chronic colonization and recurrent infections and leads to less favourable treatment responses in CRS patients [82]. The pathogens, Staphylococcus aureus and Pseudomonas aeruginosa are associated with biofilms in CRS and may become more persistent after long-term use of e-cigarettes [81].

6.7 Allergic and Hypersensitivity Responses

The flavor chemicals used in some e-cigarettes could cause allergic and hypersensitivity reactions to the mucosa of the lungs. When chemicals are aerosolized or vaped, they can activate IgE-mediated inflammation and create eosinophilic inflammatory processes from an increased production of: Th2 cytokines (e.g., IL-4; IL-5; IL-13) [83]. Cinnamaldehyde and other flavors could also disrupt the epithelial immune defences of the airways and promote hyperreactivity [68]. Therefore, chronic use of vaping aerosols may create more allergic inflammation and exacerbate CRS among susceptible individuals [70].

6.8 Nicotine-Induced Inflammatory Effects

Nicotine has a number of biological effects that may contribute to CRS pathogenesis and progression. Nicotine-induced vasoconstriction reduces blood flow and oxygen supplying to sinonasal tissues, therefore affecting the healing of mucosae and increasing tissue hypoxia[84]. In addition to these effects, nicotine modifies both inflammatory and immune signalling pathways, modifies macrophage activity, and contributes to long-term inflammatory responses within respiratory tissues [77]. Recent data also shows that aerosols that contain nicotine can enhance oxidative stress and dysregulation of the immune system, thus further enhancing the development of chronic sinonasal inflammatory disease [23].

Table 1. Mechanisms by Which Electronic Cigarettes May Exacerbate Chronic Rhinosinusitis

	Pathophysiological Effects	Clinical Consequences in CRS	Key Findings	References
Epithelial Cell Injury and Barrier Dysfunction	E-cigarette aerosols induce epithelial cytotoxicity, oxidative stress, mitochondrial dysfunction, apoptosis, and disruption of tight junction proteins, leading to increased epithelial permeability.	Enhanced penetration of allergens, pathogens, and toxic particles into sinonasal tissues; persistent mucosal inflammation; airway remodeling; CRS progression.	Chronic vaping exposure alters epithelial proteome, disrupts barrier integrity, and promotes inflammatory activation.	Ghosh et al., 2018; Raduka et al., 2023; Cao et al., 2024; Assiri et al., 2024
Impairment of Mucociliary Clearance	Vaping aerosols reduce ciliary beat frequency, impair ciliary coordination, damage ciliated epithelial cells, and induce mucus hypersecretion	Mucus retention, chronic nasal obstruction, impaired pathogen clearance, recurrent infection, and chronic sinonasal inflammation.	Flavoring chemicals such as cinnamaldehyde and menthol suppress ciliary motility and	Clapp et al., 2019; Kim et al., 2024; Xie et al., 2020; Ghosh et al., 2018

	through goblet cell stimulation.		impair epithelial function.	
Oxidative Stress and ROS Production	Heating of e-liquids generates reactive oxygen species (ROS), aldehydes, and free radicals that damage mitochondria and activate NF-κB inflammatory pathways.	Persistent epithelial injury, apoptosis, amplified cytokine production, chronic tissue damage, and increased susceptibility to CRS.	E-cigarette aerosols impair antioxidant defense systems and promote prolonged oxidative imbalance.	Assiri et al., 2024; Muthumalage et al., 2020; Taylor et al., 2021
Immune Dysregulation	E-cigarettes alter innate and adaptive immunity through increased IL-6, IL-8, TNF-α, neutrophilic activation, eosinophilic inflammation, and impaired macrophage phagocytosis.	Chronic mucosal inflammation, persistent infections, impaired antimicrobial defense, tissue edema, and worsening CRS severity.	Vaping induces unique inflammatory responses involving neutrophilic activation and altered mucin secretion.	Reidel et al., 2018; Ghosh et al., 2018; Madison et al., 2020; Bozier et al., 2020
Microbiome Alterations	Vaping exposure alters sinonasal microbial diversity, promotes dysbiosis, increases pathogenic colonization, and reduces protective commensal bacteria.	Persistent inflammation, epithelial dysfunction, recurrent infection, and enhanced CRS progression.	E-cigarette use is associated with nasal microbiome dysbiosis and altered airway cytokine profiles.	Hickman et al., 2025; Hwang et al., 2016; Stewart et al., 2018
Biofilm Enhancement and Persistent Infection	E-cigarette exposure promotes bacterial adhesion and biofilm formation through epithelial damage and impaired mucociliary function.	Increased bacterial persistence, antibiotic resistance, recurrent infection, and poor CRS treatment outcomes.	Biofilms involving Staphylococcus aureus and Pseudomonas aeruginosa may become more persistent in vaping individuals.	Kalininskiy et al., 2021; Karunasagar et al., 2026

Allergic and Hypersensitivity Responses	Flavoring chemicals activate IgE-mediated pathways and stimulate Th2 cytokines including IL-4, IL-5, and IL-13.	Eosinophilic inflammation, airway hyperreactivity, worsening CRS symptoms, and enhanced allergic responses.	Menthol and cinnamaldehyde-containing aerosols impair innate immunity and induce allergic inflammation.	Clapp et al., 2017; Ghosh et al., 2018; Li et al., 2026
Nicotine-Induced Inflammatory Effects	Nicotine causes vasoconstriction, tissue hypoxia, altered macrophage function, oxidative stress, and chronic inflammatory signaling.	Delayed mucosal healing, chronic sinonasal inflammation, increased oxidative stress, and CRS progression.	Nicotine-containing aerosols worsen inflammatory and immune dysregulation in respiratory tissues.	Banks et al., 2023; Madison et al., 2020; Mihălțan et al., 2026

7. Clinical Evidence Linking Electronic Cigarette Use and Chronic Rhinosinusitis Severity

7.1 Epidemiological Studies

There is increasing epidemiologic evidence that electronic cigarette (e-cigarette) use is associated with chronic rhinosinusitis (CRS) - related respiratory symptoms. Population-based studies have demonstrated that e-cigarette users report higher rates of chronic nasal symptoms and sinonasal irritation and inflammation of the upper airways when compared with non-e-cigarette users [73 ,85]. Additionally, cross-sectional analyses of national health surveys indicate that e-cigarette use is associated with a variety of increased rates of CRS symptoms, particularly among dual use of conventional and e-cigarettes[86]. Cohort studies have also suggested that long-term exposure to e-cigarette aerosol may contribute to the persistence of airway inflammation and a gradual decline in respiratory health status. Although studies supporting this relationship are limited, there is emerging evidence that vaping frequency is positively correlated with the severity of sinonasal symptoms in a dose-dependent manner [31, 87]. The cumulative evidence suggests that exposure to e-cigarette aerosol may be one of several environmental factors involved in the pathophysiology and progression of CRS.

7.2 Clinical Symptoms Associated with Vaping

Inhalation of electronic nicotine delivery systems (ENDS) may lead to symptoms in the upper respiratory system. Many users of e-cigarettes or ENDS experience many symptoms such as nasal congestion or nasal obstruction which may be caused by inhaling aerosols from these devices, leading to inflammation. Both nasal obstruction and sinonasal mucosal swelling affect an individual's ability to breathe through their nose [22]. By

affecting mucociliary clearance and leading to the production of excessive mucus, symptoms such as nasal discharge (rhinorrhea) and the sensation of mucus being present in the throat develope [70]. In addition, mucosal inflammation and impaired sinus drainage can lead to pain and pressure in the face. Olfactory dysfunctions such as hyposmia (decreased sense of smell) and hyposmia (loss of sense of smell) have also been reported in vape users, possibly due to severe injury to the epithelial tissue and resultant inflammatory process on the olfactory neuroepithelium [88, 89].

7.3 Impact on CRS Severity Scores

There is extensive literature investigating the link between smoking and vaping exposure and validated measures of CRS severity; most notably, the Sinonasal Outcome Test-22 (SNOT-22) is one of the most commonly used patient-reported outcome measures for CRS, wherein it has consistently shown that the symptom burden is significantly greater in both traditional and electronic cigarette smokers compared to non-smokers. Among electronic cigarette smokers, elevated SNOT-22 scores may correlate with an increase in nasal obstruction, sleep disturbance, nasal pain, and loss of sense of smell [90, 91].

The Lund-Mackay computed tomography scoring system is used to objectively assess radiological severity, and there is evidence to suggest that people exposed to commercially produced tobacco, including e-cigarette aerosol, show increased Lund-Mackay scores. There have also been reports that individuals who use e-cigarettes demonstrate an increase in endoscopic findings of mucosal edema, thickened secretions, crusting, and inflammatory polypoid change compared to individuals who do not use e-cigarettes, suggesting that e-cigarettes further increase the risk of developing mucosal inflammation and/or worsening epithelial damage [92].

7.4 Vaping and Nasal Polyp Formation

Recent studies have indicated that exposure to e-cigarettes may cause the onset and worsening of chronic rhinosinusitis with nasal polyps (CRSwNP). Exposure to the aerosol produced from e-cigarette vapor could cause damage to the cells lining the nasal cavity, increased oxidative stress, and Th2-driven inflammatory reactions, which are indicated by an increase in eosinophils and the production of multiple inflammatory cytokines, including interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13) [70, 93].

These inflammatory pathways are associated with the creation of polyps in the nasal passages and with the creation of new tissue in the nasal passages. It is therefore possible that continued exposure to vaping-related health hazards is likely to produce or worsen eosinophil-related inflammation or fluid buildup in the mucous membranes, leading to the formation of polyps and extension of the duration of the disease. Although there is insufficient evidence directly correlating vaping and CRSwNP, the available information on the pathophysiology and inflammation associated with vaping provides a logical basis for the relationship between vaping and the severity of CRSwNP [62].

7.5 Comparison Between Smokers, Vapers, and Non-Users

According to research comparing the effects of smoking versus using e-cigarettes, both groups have more respiratory symptoms and sinonasal symptoms than people that do not use either form of nicotine. Smokers usually have the longest duration of exposure to burning chemicals that harm mucous membranes; therefore, they usually have the most injury/inflammation to their mucosa. E-cigarette smokers also have substantial inflammation in the airway, epithelial dysfunctions, and reduced ability to clear mucus from their airways [22, 94].

Quality-of-life (QOL) assessments show that smokers and e-cigarette users suffer from poorer QOL related to the sinonasal region compared with people that do not smoke or vape; specifically, smokers or vapers have more sleep problems, fatigue, nasal obstruction, and smell problems [87, 95].

Table 2. Clinical Evidence Linking Electronic Cigarette Use and CRS Severity

Clinical Aspect	Major Findings	CRS-Related Outcomes	Supporting Evidence	References
Epidemiological Studies	Population-based studies demonstrate increased sinonasal irritation, upper airway inflammation, and CRS symptoms among e-cigarette users.	Increased prevalence of chronic nasal symptoms and worsening sinonasal inflammation.	Dual users exhibit greater CRS symptom burden compared with non-users.	Cha et al., 2023; Kim et al., 2024; Lee et al., 2020; Wills et al., 2021; Alamri et al., 2026
Dose-Dependent Respiratory Effects	Increased vaping frequency correlates with worsening respiratory symptoms and persistent airway inflammation.	Greater CRS severity and disease progression over time.	Long-term exposure may contribute to chronic respiratory morbidity.	Wills et al., 2021; Alamri et al., 2026

Nasal Obstruction and Congestion	E-cigarette users commonly report mucosal edema, epithelial irritation, and chronic congestion.	Nasal blockage, impaired airflow, and chronic discomfort.	Aerosol-induced inflammation contributes to sinonasal dysfunction.	Gotts et al., 2019; Ghosh et al., 2018
Rhinorrhea and Postnasal Drip	Increased mucus production and impaired mucociliary clearance are commonly observed.	Persistent rhinorrhea and postnasal drainage.	Goblet cell stimulation and mucus hypersecretion are key contributors.	Ghosh et al., 2018
Olfactory Dysfunction	Vaping exposure may damage olfactory neuroepithelium and induce inflammatory changes.	Hyposmia, anosmia, and impaired quality of life.	Chronic epithelial injury may affect olfactory sensory pathways.	Majchrzak et al., 2020; AlMatrouk et al., 2021
Increased SNOT-22 Scores	Smokers and e-cigarette users demonstrate significantly worse symptom scores compared with non-users.	Greater sleep disturbance, facial pain, fatigue, and olfactory dysfunction.	Elevated SNOT-22 scores reflect increased CRS severity.	Hung et al., 2025; Masuda et al., 2026
Radiological and Endoscopic Findings	Vaping exposure is associated with mucosal thickening, edema, crusting, inflammatory secretions, and polypoid changes.	Increased radiological severity and chronic sinonasal inflammation.	Lund-Mackay scores may be elevated among vaping users.	Cha et al., 2023; Mukhopadhyay et al., 2020

Nasal Polyp Formation	Vaping induces epithelial injury and Th2-mediated eosinophilic inflammation associated with nasal polyp development.	Increased CRSwNP severity and persistent tissue remodeling.	IL-4, IL-5, and IL-13 pathways play major roles in polypogenesis.	Yang et al., 2025; Stevens et al., 2016; Ghosh et al., 2018
Smokers vs Vapers vs Non-Users	Both smokers and vapers exhibit greater respiratory and sinonasal symptoms than non-users.	Worse quality of life, congestion, fatigue, and olfactory impairment.	Conventional smokers generally exhibit the highest inflammatory burden, but vapers also show significant epithelial dysfunction.	Gotts et al., 2019; Chen et al., 2025; Alamri et al., 2026

8. Special Populations and Risk Factors

8.1 Adolescents and Young Adults

The adolescent and young adult population is one of the most highly impacted groups by exposure to e-cigarettes and vaping products. The ease of purchasing flavored vaping with high abuse potential, aggressive marketing through social media outlets, and mistakenly thinking that vaping products are safe for you or have no risk have all contributed to the rapid rise in young people using e-cigarettes and vaping products [96]. As adolescents develop their respiratory and immune systems, they may be at an increased risk for the adverse effects of inhaling vaping aerosol including injury to the epithelial lining, oxidative stress, and long-term inflammation of the airways [26].

Growing evidence shows that adolescent e-cigarette users often exhibit respiratory symptoms such as chronic cough, nasal obstruction (congestion), runny nose (rhinorrhea), and problems with smell (olfaction). During adolescence, exposure to nicotine may affect the immune system causing long-term changes that could contribute to developing chronic inflammatory airway disease including CRS. Adolescent vaping is also a significant public health issue because many adolescents who begin vaping will become dependent on nicotine and continue to be exposed to the respiratory toxicants due to continued vaping [31].

8.2 Patients with Allergic Rhinitis or Asthma

Individuals who have existing allergies such as asthma or allergy rhinitis are more susceptible to inflammatory effects associated with electronic cigarette aerosol exposure than those without allergies. Evidence has demonstrated that electronic cigarette vapor can increase the hyperresponsiveness of the airway, eosinophilic inflamation, increased mucus production, and altered epithelial barrier function through the activation of Th2 type immune responses [97]. Furthermore, flavoring chemicals and aerosolized particles can potentially act as irritants to the airways and may lead to an allergic reaction in those who are sensitive to these substances [68].

E-Cigarettes expose asthmatics to an increased rate of respiratory symptoms and decreased lung function compared to non-e-cigarette users. This is supported by evidence that those who use e-cigarettes have increased rates of exacerbation compared to non-users [98].

8.3 Immunocompromised Individuals

Vaping related lung issues may be more likely in immunocompromised people since they have weakened defense mechanisms against infections. The inhalation of vapour from electronic cigarettes can affect innate immunity, impair macrophage activity, decrease the antimicrobial ability of the epithelial cells, and change the signaling pathways of cytokines. This immune system dysfunction could therefore increase your risk of developing a chronic infection and/or being colonized with microorganisms. In addition, this type of dysfunction may increase your risk of suffering from chronic sinonasal inflammation [77].

8.4 Dual Users (Smoking + Vaping)

Individuals who use both traditional cigarettes and electronic cigarettes are at heightened risk for cumulative exposure to harmful chemicals from both sources. Studies show that dual users tend to have more nicotine dependence than individuals who only use one type of product alone as well as higher levels of inflammatory biomarkers and more serious respiratory symptoms [23]. Simultaneously exposing yourself to cigarette smoke and e-cigarette aerosol can cause greater epithelial injury, increase oxidative stress, weaken mucociliary function, and create ongoing inflammation in the sinonasal tissue. Additionally, dual users have shown to experience greater coughing, more nasal obstruction, poorer overall quality of life,and more chronic respiratory disease exacerbations [31].

8.5 Occupational and Environmental Co-Exposures

Environmental and occupational exposure can create greater long-term health repercussions from electronic cigarette use for individuals using electronic cigarettes frequently. Chronic exposure to airborne pathogens such as microbiological (fungal) entities, chemical vapors (including solvents), construction materials (dust), agriculture-related irritants (herbicides), and volatile organic species (i.e., things made of carbon; like

the methane produced while heating a furnace) can cause epithelial damage and eventually lead to chronic respiratory issues [99].

The combined effects of chronic exposures to above-named toxins and habitual use of electronic cigarettes may increase the amount of inflammation by causing additional inflammation via the synergistic effect of using another of the chemicals mentioned above, leading to the generation of additional oxygen radicals, which are involved in tissue damage, and depleting the ability of the mucosal defence to prevent the development of anything that can damage your mucosa [77].

Individuals exposed to diesel exhaust (industrial fumes from commercial transportation), construction (particulate matter in construction), or the vapour created from using any of the solvents contained in e-liquid created for electronic cigarettes may also be at an increased risk for developing electrocution or recurrent sinus infection due to their use of e-cigarettes. Urban air quality, as well as indoor environmental conditions, may also contribute to the severity of sinus symptoms of individuals to using an electronic cigarette [100].

9. limitations and Knowledge Gaps

While there is an increasing amount of research investigating the association between vaping and respiratory disease, including chronic rhinosinusitis (CRS), there is still no conclusive or robust evidence. The literature is inconsistent, and there are disagreements between studies on what the relationship is, as some demonstrate a significant relationship between the two, while others show no independent relationship when adjusted for confounding variables (e.g., history of smoking and other environmental factors) [22, 27]. One of the reasons for inconsistency in literature is due to the lack of a standard definition for exposure, as well as the lack of uniformity in the populations under study, and variation in how outcomes were defined across studies.

A major limitation of research on this topic is the absence of long-term, longitudinal data to assess chronic exposure to e-cigarettes, and how CRS changes over time. Most of the current research on this topic consists of cross-sectional studies, limiting the ability to determine temporal or causal associations between vaping and the development of sinonasal disease [21]. The rapid evolution and development of the e-cigarette manufacturing industry introduces considerable variability in the devices themselves (i.e., e-cigarettes), the amount of nicotine contained in them, and the types of flavorings used in e-cigarettes, making it difficult to interpret findings from various studies on different user groups (Banks et al., 2023). The high degree of variability across user groups further complicates risk assessment and limits the ability to compare the results of such studies.

Methodological issues have limited the current body of research regarding vaping, including self-reported behavior of those who vape, under-reported use as a dual user of conventional cigarettes, and not having enough consideration of the potential environmental and occupational confounding factors. Many of the experimental studies are done in vitro or on animal models which do not replicate how humans are exposed to

e-cigarettes in everyday life and lack real-world applicability[33]. Furthermore, because of CRS being a multifactorial disease, it has been difficult to establish causality since CRS is affected by a person's genetic predisposition, a dysbiosis of microbes, allergy conditions, and environmental influences. Therefore, there is no clear separation of the independent effect of e-cigarette use from the many factors that can contribute to the development of and/or the extent of the disease, indicating the need for further well-designed prospective cohort studies and standardisation of exposure assessments [22, 27].

10. Future Research Directions

Studies that follow human cohorts over a long period of time are necessary to clarify how long between when someone began using electronic cigarettes and the development or worsening of chronic rhinosinusitis. This work is needed to help bridge the gap between cross-sectional studies and if using electronic cigarettes is an independent or contributing risk factor in the development of CRS. In addition, advanced molecular methods (e.g., transcriptome, proteomics, metabolomics) will be necessary to further clarify the specific pathways that mediate the injury to the sinonasal cavity from vaping. These technologies can be used to identify key inflammatory, oxidative stress, and epithelial remodeling markers that are associated with the chronic effects of e-cigarette aerosol exposure.

Research examining the microbiome will also be important in understanding how vaping affects the diversity of sinonasal microbiota, the dysregulated microbial growth (dysbiosis), and biofilm formation in the sinonasal cavity, all of which may contribute to chronic inflammation and resistance to treatment for CRS. Moreover, future studies should focus on the development of personalized medicine for patients with asthma using genetic predispositions, immune phenotypes and environmental exposures to better identify high-risk groups, including patients with atopy, asthma and dual-use, and to develop more effective prevention and management strategies. Lastly, identifying new potential treatment targets is an ongoing priority, with an emphasis on identifying targets that restore epithelial barrier integrity, reduce oxidative stress and adjust dysregulated immune and microbial responses to vaping exposure.

Conclusion:

This review discusses recently published data supporting a link between e-cigarette use and the pathophysiology of CRS as well as its severity. Overall, exposure to e-cigarettes may initiate sinonasal inflammation through various interrelated mechanisms such as the dysregulation of the epithelial barrier function, impaired mucociliary clearance, oxidative

stress (OS), immune dysregulation, and changing microbiome composition. Additionally, e-cigarette use may increase an individual's susceptibility to chronic infection and formation of biofilms. All of these biological effects, when taken together, may lead to an exacerbation of existing CRS or an increased likelihood of long-term symptoms or progression of CRS among the exposed. Patients with CRS should consider vaping and e-cigarettes to be an important contextual issue when assessing patients with CRS, particularly those with refractory CRS or patients who are not responding well to standard therapies. By recognizing the potential role of vaping in causing inflammation of the sinonasal cavity, diagnostic accuracy may be improved, appropriate risk stratification may be better able to be achieved, and more individualized treatment approaches can be developed. Otorhinolaryngologists should routinely assess smoking and vaping history during their evaluation of CRS. Adolescents, atopy, and dual users should be counseled about the negative effects on sinonasal health of e-cigarettes. In terms of public health, the data presented in this study supports the need for awareness campaigns about e-cigarette use and for strategies to decrease the prevalence of e-cigarette use among adolescents. In summary, while the evidence that exists is limited to date, the data from mechanistic studies and emerging clinical data to date suggest that the use of electronic cigarettes may be a factor that contributes to both the severity and persistence of CRS. However, to determine how vaping and e-cigarette use affect CRS, larger longitudinal studies and innovative translational research are needed to provide insights into how to prevent and treat patients with CRS.

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