REVIEW

Effects of E-Cigarettes (Vaping) on the Oral Microbiome – a Narrative Review

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Abstract

Introduction: E-cigarettes, also referred to as electronic cigarettes, are gaining popularity as an alternative to tobacco use. Although their use has significantly increased recently, there is still much debate over their effectiveness and safety as smoking cessation aids.

Objective: This review paper's objective is to offer an inclusive evaluation of the body of research about the impact of e-cigarettes on the oral microbiome and oral health.

Methodology: Data was extracted from PubMed, Google Scholar, and Scopus to compile scientific evidence for a narrative review article on the effects of e-cigarettes on the oral microbiome. The investigation was restricted to published research articles from 2001 to 2022, using pre-defined search phrases for e-cigarettes, vaping, quitting smoking, oral microbiota, and oral health.

Results: The chemicals in e-cigarettes, including nicotine, propylene glycol, vegetable glycerin, flavorings, and chemical additives, cause a dysbiosis that can lead to a variety of conditions, including dental caries, periodontal diseases, and a variety of mental health issues, such as bone loss, gingival tissue inflammation, and increased plaque accumulation. The chemical toxicity of e-cigarettes, including nicotine and other components present in e-cigarette aerosols, has been implicated in various oral health problems that lead to systemic complications.

Conclusion: A wide range of oral health sequelae may be associated with e-cigarette use. Future investigation should focus on elucidating the long-term effects of e-cigarette use on oral microbiomes, and overall health and exploring potential strategies for minimizing the adverse impacts on oral health.

Keywords: e-cigarettes, ENDS, e-aerosol, microbiome, oral health, periodontitis, saliva, vapingTop of Form

Introduction

Since the Chinese chemist Hon Lik created electronic cigarettes in the early 2000s, they are also referred to as e-cigarettes or EC. These items function by heating a solution called vape juice/e-juice that often contains glycerin or propylene glycol (propylene glycol), nicotine, and flavorings to create a nicotine aerosol, also known as vapor[1]. This aerosol contains several potentially harmful chemicals, like heavy metals, volatile organic compounds, and ultrafine particles, in particular, nicotine, a highly addictive substance that can have many negative health effects causing inflammation in lung cells[2,3]. Each "puff" of the heating element causes a tiny volume of liquid to vaporize. In this scenario, instead of smoking, the ENDS (Electronic Nicotine Delivery Systems) user inhales a nicotine aerosol or vapor (up to 24-100 mg). As a result, ENDS will deliver significantly more nicotine than other tobacco cessation products on the market. E-liquids typically have nicotine concentrations between 0 mg/ml (nicotine-free) and higher levels like 3 mg/ml, 6 mg/ml, 12 mg/ml, 18 mg/ml, and even more [4,5].

At least 32 nations have laws that forbid the trade of nicotine-containing e-cigarettes, whereas 79 nations, including Australia, have laws that either entirely or partially permit it[6]. The remaining 84 nations do not have any laws governing electronic cigarettes[6]. There are millions of e-cigarette users globally, however, usage prevalence varies greatly between nations. Younger people tend to use e-cigarettes more regularly. While recent use varies from 1% in Hong Kong and

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Mexico to 33% in Guam, its use is greater among those aged 8 to 19 years, ranging from 2% in Cambodia to 52% in France [6].

Additionally, e-cigarettes have been promoted as a superior substitute to traditional tobacco smoking, and some even assert that they may help people cut back on their cigarette consumption or quit altogether. In the last ten years, the use of e-cigarettes has rapidly expanded. In the US, the percentage of adults who said they had ever used an e-cigarette rose from 3.7% in 2014 to 6.3% in 2019. When everyday or irregular use is taken into account, the percentage increased from 1.8% in 2014 to 3.2% in 2019[7,8]. In 2019, 5.5% of youngsters between the ages of 18 and 24 years, and 12.5% reported smoking e-cigarettes. Recent use of e-cigarettes among high school students increased from 1.5% in 2011 to 27.5% in 2019, with greater rates among male students, White students of Hispanic and non-Hispanic descent, and students in the 11th and 12th grades. These studies demonstrated that e-cigarette usage is becoming more and more common, specifically among young adults and adolescents[9].

The ability to "smoke anywhere" using e-cigarettes has also been touted as a technique to get around smoke-free restrictions[10]. The popularity of EC has led to major multinational tobacco companies entering the market in 2013[1]. Although e-cigarettes are becoming more and more popular, there is still a lot of debate about their safety and effectiveness as a smoking cessation tool. Ample literature has claimed that e-cigarettes were found to be less toxic than conventional cigarettes since they don't comprise the tar and other dangerous compounds contained in tobacco smoke[11]. However, some studies have raised questions about the long-term health consequences of EC use, particularly in light of the absence of industry regulation[12]. In addition, the long-term implications of e-cigarette usage on the oral microbiome and oral health outcomes are little understood. With the increase in EC popularity and the absence of regulation and standardization, safety concerns have been raised. Therefore, it is necessary to conduct a thorough evaluation of EC components and look at specific health issues connected to them. In this respect, our review endeavored to examine EC-linked adversities on oral health by analyzing a range of studies, including human trials.

Methodology

This narrative review was conducted using Cochrane Library, Embase, PubMed, and Web of Science. The research was limited to articles in English, published between January 2001 and December 2022. A search was conducted to compile scientific evidence for a review article on the effects of e-cigarettes on the oral microbiome and the investigation was restricted using pre-defined search phrases for e-cigarettes, vaping, quitting smoking, oral microbiota, and oral health. For possible inclusion, pertinent research that was cited in the publications that were retrieved was also examined. One or more authors searched, and a consensus was reached over the final list of articles to be included. The selected articles were examined and synthesized to facilitate a thorough summary of the state of research on the subject, including how e-cigarettes affect the composition, variety, and stability of the oral microbiome. The review identified gaps in the current knowledge and discussed potential future research directions.

Results and Discussion

Although the data indicate that e-cigarettes are less dangerous than traditional cigarettes, it is crucial to note that e-cigarette use provides a greater vulnerability to the formation of changes in oral biological tissues than ex-smokers or non-smokers.[10-12] The popularity of e-cigarettes may be related to the general belief that they are less harmful than regular tobacco products.[12]

a. Oral Microbiome- the Habitat of Oral Cavity

The oral microbiome plays a significant part in retaining oral health by contributing to various physiological and biochemical processes, including digestion, immunity, oral tissue development, and homeostasis[13,14]. It refers to the microbial community that inhabits the oral cavity, consisting of bacteria, fungi, viruses, and archaea that interact with the host in a symbiotic relationship. The oral microbiome is dominated by four major phyla, including *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria*[15]. According to a study, more than 700 species of microorganisms are found in the oral cavity, with bacteria being the most abundant group. The bacterial communities in the oral cavity can be categorized into several groups, including *Streptococcus*, *Actinomyces*, and *Prevotella*, with each having a distinct role in maintaining oral health. *Firmicutes*, *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, *Bacteroidetes*, and *Spirochaetes* make up around 96% of the overall bacterial population in the oral cavity[16].

Among the other oral microbes, gram-positive bacteria have a significant impact on the preservation of oral health. For example, *Streptococcus* species, including *Streptococcus* mutants and *Streptococcussanguinis*, are important for dental health as they participate in producing dental biofilms (plaque) and contribute to the initial stages of dental plaque formation. *Actinomyces* species also have a beneficial role in maintaining oral health by competing with potentially harmful bacteria and contributing to the stability of the oral microbiota. Additionally, some gram-positive bacteria, such as Lactobacillus species, are involved in maintaining a healthy balance in the oral cavity. These bacteria can produce antimicrobial substances and help in preventing the overgrowth of pathogenic bacteria. Depletion of gram-positive bacteria in the oral cavity can contribute to the emergence of oral diseases such as dental caries, periodontal disease, and oral candidiasis. These beneficial bacteria play a vital part in sustaining oral health by preventing the overgrowth of harmful pathogens and contributing to the balance of the oral microbiota. Maintaining a diverse and balanced oral microbiota, including the presence of gram-positive bacteria, is essential for optimal oral health[17]. However, dysbiosis (disruption of the equilibrium of the oral microbiome) results in a range of diseases, including periodontal disease, dental caries, and cardiovascular disease[18]. The onset of periodontal disease causes an upsurge in the pathogenic bacteria and diminishes the proportion of beneficial bacteria. *Streptococcus* and *Actinomyces* are involved in the initial colonization of the tooth surface, contributing to biofilm formation (dental plaque), and are associated with dental caries (tooth decay). In addition, some *Prevotella* species are considered opportunistic pathogens. Prevotella intermedia, for example, is considered an opportunistic pathogen and has been involved in the development and progress of periodontal disease.[19] Other bacteria commonly found

in the oral cavity include *Porphyromonasgingivalis*, *Fusobacteriumnucleatum*, and *Treponemadenticola*, which are related to the development of periodontal disease (PD)[20]. A chronic inflammatory illness known as PD affects the gums and tissues that protect the teeth. *Fusobacteriumnucleatum* and *Treponemadenticola* are also thought to be involved in the development of the disease. *Porphyromonasgingivalis* is regarded as a crucial pathogen in the development of periodontitis[21].

Researchers analyzed the oral microbiomes of e-cigarette consumers and non-users and found accumulating indications that the use of e-cigarettes can be detrimental to the oral microbiome. Oral biofilms' composition changed as an outcome of e-cigarette use, involving an increase in the number of potentially dangerous bacteria[22]. They discovered that e-cigarette users exhibited potentially hazardous bacteria, such as *Lactobacillus, Staphylococcus, and Streptococcus species*, in their mouths[23]. Furthermore, exposure to e-cigarette vapor led to increased virulence of Streptococcus mutants, a major cause of tooth decay[24].

b. ChemicalToxicity of E-cigarettes on the Oral Health

Nicotine, propylene glycol, vegetable glycerin, flavorings, and other substances are all included in e-cigarettes. Nicotine is highly addictive and may impair developing brains, respiratory systems, and cardiovascular systems. Vegetable glycerin and propylene glycol are usually regarded as safe substances, however, research into the long-term effects of inhalation is ongoing. Flavorings, particularly those containing aldehydes, have been linked to respiratory irritation and lung damage. Chemical additives like formaldehyde and acetaldehyde can contribute to oxidative stress and inflammation. The specific involvement of these chemicals in various diseases requires a comprehensive analysis of multiple studies, as their effects can vary based on concentration, duration, and individual factors[25,26].

Furthermore, propylene glycol and glycerol in EC, encourage water absorption that may result in xerostomia (dry mouth), raising the risk of dental caries. Among the young adults who reported ever using e-cigarettes, approximately 29% reported experiencing dry mouth symptoms[27]. According to the study, 0.5% of the students surveyed used EC daily, 1.9% only sometimes (between 1 and 29 times in the previous month), and 5.9% had never used them. From a sizable percentage of students, 18.5% reported having gingival pain and/or bleeding, 11.0% tongue and/or inside-cheek pain, and 11.4% a cracked or fractured tooth. The likelihood of having a cracked or fractured tooth was higher among EC users (daily, occasional, and former) compared to those who had never used EC, with daily users having the highest risk (adjusted odds ratio [OR] of 1.65). A higher incidence of tongue and/or inside-cheek soreness was also seen among daily EC users (adjusted OR of 1.54). However, no meaningful connection was found[28].

Streptococcusmutans adherence to enamel and the development of biofilms can be facilitated by the flavors added to EC liquids, which contain sugars including sucrose, sucralose, and sugar alcohol. Additionally, flavored e-cigarette aerosols contain several compounds that might irritate nearby tissues, lessen the hardness of the enamel, and start the demineralization of the enamel[29]. In comparison to people who have never used EC, those who use them now or in the past are more likely to report bone loss and periodontal disease. The risks of periodontal disease and bone loss were found to be 1.43 and 1.80 times greater for EC users after controlling for smoking and other potential variables[30].

Besides, EC users experience a shift from a commensal to a pathogenic microbial community by any unfavorable trigger like vapors of e-cigarettes, which drives inflammatory responses and tissue destruction[31], resulting in various oral diseases, such as dental caries, oral cancer, and PD. Periodontitis is a widespread epidemic affecting a significant proportion of the global population accounting for 40% to 90% of individuals worldwide[32]. Taking into consideration the impact of smoking and controlling for other confounding variables, people who had ever used e-cigarettes had 1.43 times greater chances of self-reported periodontal disease compared to non-users[33].

Javed et al. accentuated a higher prevalence of oral infection in smokers compared to non-smokers. About 32% of e-cigarette users had oral infections compared to 15% of non-smokers[34]. In addition, EC-users exhibited 18% incidences of oral sub-mucosal fibrosis (OSMF) compared to 5%in non-smokers. These studies validate that EC smokers are at a greater dearth of emerging various diseases linked to oral health[35].

c. E-cigarettes alter the Balance of the Oral Cavity

EC users were found to have a greater prevalence of symbiotic flora and other microorganisms in the oral cavity of individuals who use alternative tobacco products compared to those who smoke traditional cigarettes and individuals who do not smoke at all. A study found that EC users exhibited higher co-occurrence of potentially pathogenic bacteria, indicating that EC users had a higher percentage (27.5%) of gram-negative bacteria compared to traditional cigarette smokers (4.6%). Nonetheless, no substantial difference was perceived in the presence of gram-positive bacteria[36]. Consistently, an alternative study found a higher percentage of gram-negative bacteria in the users of e-cigarettes compared to the individuals who use traditional cigarettes, as well as a higher co-occurrence of potentially pathogenic bacteria in the oral cavity among e-cigarette users. This animal trial study comprised two groups: Group 1 was a control group, while Group 2 was subjected to EC aerosol exposure. When collated with the control group, EC aerosol exhibited a decrease in obliging microorganisms and an increase in atypical species such as *Candidaalbicans* (p=0.0337), *Acinetobacterlwoffii* (p=0.0001), and Klebsiella pneumonia (p=0.0456). The duration of EC exposure was found to be significantly associated with the presence of these opportunistic pathogens. Overall, the study found that EC aerosol exposure had a negative impact on the oral microbiota, leading to dysbiosis categorized by an imbalance in microbial species and an upsurge in potentially harmful pathogens. Additionally, there was a reduction in the total microbial count. This indicates that the use of e-cigarettes influences the oral microbiota composition and increases the presence of certain bacteria types, potentially affecting oral health[37]. A contrasting study showed that the use of electronic smoking systems and tobacco heating systems resulted in a decrease in the number of resident plaque microflora. Specifically, the heating tobacco group showed a decrease in *S. mitis* from 35.7% to 23.9% and an increase in *S. aureus* from 0% to 13%. Among the vape systems users, *S. pneumoniae* showed the highest increase from 0% to 17.9%. Overall, the study suggests that the use of ENDDs

may result in a higher rate of excretion and the appearance of transient streptococci with opportunistic tendencies, such as *S. pneumoniae* and *S. pyogenes*, which can have an epidemiologically substantial level of colonization[38].

E-cigarette users and tobacco smokers exhibit decreased levels of lysozyme, an enzyme with bacteriolytic properties in their saliva. Additionally, tobacco smokers display reduced levels of IgA and lactoferrin in their saliva. Conversely, saliva from e-cigarette users shows elevated levels of lactoferrin and no alterations in IgA concentration. According to the study, e-cigarette users had lower IgA levels (201 ± 118 μg/mL) compared to traditional cigarette smokers (164.7 ± 95 μg/mL) and the control group (515.8 ± 430 μg/mL). Traditional cigarette smokers also had lower IgA levels compared to the control group. Additionally, e-cigarette users had lower lysozyme levels (1.7 ± 0.9 μg/mL) compared to both traditional cigarette smokers (1.8 ± 1.4 μg/mL) and the control group (6.5 ± 4.8 μg/mL). Furthermore, e-cigarette users had higher lactoferrin levels (9.5 ± 10.6 μg/mL) compared to traditional cigarette smokers (2.7 ± 3.5 μg/mL) and the control group (7.0 ± 8.8 μg/mL). Both the users of e-cigarettes and traditional cigarettes showed significant differences compared to the control group[39].

Lactoferrin is an important protein with antimicrobial properties that play a part in the body's defense against infections. It helps to inhibit the growth of bacteria and fungi and also has anti-inflammatory effects. A reduction in lactoferrin levels may compromise the immune response in the oral cavity, making individuals more prone to oral infections, including periodontal disease and dental caries. Additionally, lactoferrin deficiency has been connected with an augmented risk of systemic conditions, such as anemia and gastrointestinal infections. On the other hand, the impact of reduced IgA (Immunoglobulin A) levels in saliva also poses a significant impact. IgA serves as a pivotal antibody in the immune protection of mucous membranes, encompassing vital areas such as the oral cavity. It helps to neutralize pathogens and prevent their colonization on mucosal surfaces. A decrease in IgA levels can weaken the immune response, leaving individuals more susceptible to infections and inflammatory conditions in the oral cavity. It can also compromise protection against respiratory and gastrointestinal infections[40].

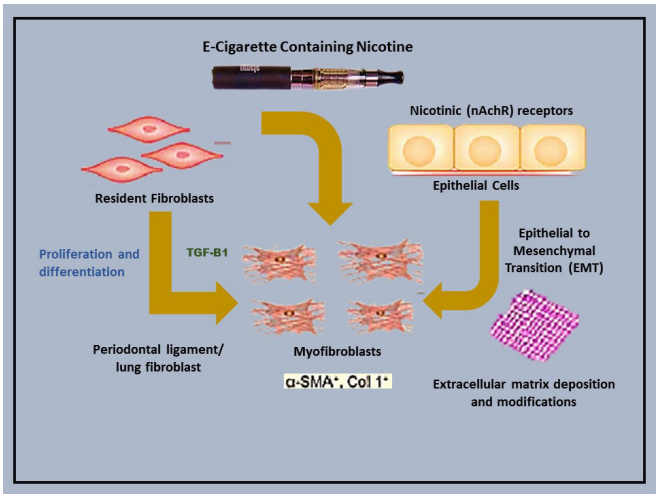

Fig. 1: Inflammatory Responses in the Periodontal Tissues

d. E-Cigarette Use and Dysbiosis Linked With Other Complications

The dysbiosis in the oral microbiome is related to various systemic disorders, such as cardiovascular disease, diabetes, and Alzheimer's disease[41]. According to current scientific opinion, oxidative stress (OS) and pathways involving reactive oxygen species (ROS) are important in developing cerebrovascular and neurological illnesses such as stroke and Alzheimer's disease. The production of ROS, inflammation, and BBB (Blood-brain barrier) disruption are the characteristics of these pathways. Numerous investigations have revealed a strong link between vascular endothelial dysfunction and tobacco smoking (TS), both actively and passively. The negative effects of TS on endothelial function are causal, dependent on the quantity and frequency of smoking, and are mainly related to the release of ROS[42]. Research has shown that dental dysbiosis, which results in periodontal disease, can raise the risk of cardiovascular disease[43,44]. According to a recent study, *Porphyromonasgingivalis*, a bacterium connected to periodontal illness, was found in the brains of Alzheimer's patients, revealing a correlation between the two diseases[45]. It was also observed that e-cigarette users had impaired wound healing as compared to non-smokers. The study showed that the users of e-cigarettes took significantly longer to heal their wounds compared to non-smokers[46]. This is also a reason for various implant failures in EC smokers. The inflammation and breakdown of the bone and soft tissues around the implant can increase the complexities in the clinical profile of the patient. Furthermore, e-cigarettes can affect the radiographic profile of dental implants. Radiographs are commonly used by dentists to monitor the health and stability of implants over time. However, the aerosols from e-cigarettes can leave residues on the implant surface, causing artifacts or changes in the radiographic appearance. This can make it more challenging for dentists to accurately assess the bone level around the implant, detect early signs of bone loss, and evaluate the overall health and stability of the implant[47,48].

E-Cigarettes Induce Damage to Epithelial Cells

Epithelial cells are vulnerable to infection when exposed to EC aerosols. Premalignant Leuk-1 and cancerous cell lines were exposed to EC aerosols using an in vitro infection model and were then challenged with *Porphyromonasgingivalis* and *Fusobacteriumnucleatum*. These results show that EC aerosols can alter the oral microbiota and raise the risk of infection by harming the epithelial linings of the oral cavity. This exposure led to a greater inflammatory response[49]. E-cigarettes and their flavorings have been found to induce oxidative and carbonyl stress in oral cells, leading to protein carbonylation, inflammation, DNA damage, and stress-induced premature senescence (SIPS). This type of stress causes long-lasting inflammation and may have an impact on the emergence of oral illnesses. Pro-inflammatory cytokines are also released by e-cigarettes, and gingival epithelium and tissue levels of prostaglandin-E2, cyclooxygenase-2, and the receptor for advanced glycation end products (RAGE) all rise as a result[50]. Nicotine has been shown to negatively impact wound healing by interfering with the differentiation of myofibroblasts and/or the epithelial-mesenchymal transition (EMT). Myofibroblasts play a crucial role in

wound healing by promoting tissue contraction and collagen deposition, whereas the epithelial-mesenchymal transition is a cellular process involved in wound healing. Epithelial cells acquire mesenchymal characteristics to facilitate migration and tissue repair. One study conducted by Heeschen et al. (2001) investigated the effects of nicotine on wound healing in a mouse model. The researchers found that nicotine administration impaired wound healing by inhibiting the recruitment and differentiation of myofibroblasts. The study suggested that nicotine's interference with myofibroblast function led to delayed wound closure and impaired tissue repair[51](Figure 1). The periodontal tissues may become inflamed as a result of the oxidative stress and vascular remodeling carried on by inhaled nicotine. Oxidative stress can cause the extracellular matrix to carbonylate, which can further promote the deposition of the modified matrix and ultimately aid in the emergence of oral submucosal fibrosis[52].

E-cigarettes may also have negative effects on nasal epithelial cell growth and function and may contribute to inflammation by escalating the secretion of pro-inflammatory cytokines in the nasal passages[53], consequently causing a significant increase in cell growth and Ki67 expression, promoting cellular proliferation in nasal passages. E-cigarette vapor can additionally inflame the head and neck parts of the body[54].

Conclusion

E-cigarette use negatively affects the oral microbiome and oral health due to the presence of nicotine, propylene glycol, vegetable glycerin, flavorings, and chemical additives. Dysbiosis caused by these components leads to various oral health disorders, including dental caries, periodontal infections, inflammation, and increased plaque buildup. This can be caused by the dysregulation of a healthy oral microbiome and the growth of pathogenic bacteria like *Lactobacillus*, *Staphylococcus*, and *Streptococcus* species. In addition, EC toxicity may lead to systemic complications including, CVD, AD, bone loss, compromised immunity, delayed wound healing, and implant failures. Therefore, to ensure the safety of the product, regulations, and standardization in the e-cigarette sector are substantial.

Further research is required to understand the impact of e-cigarette use on the oral microbiome, especially in non-EC users when exposed to secondhand vapor. Long-term studies are necessary to evaluate its effects on dental implant outcomes, periodontitis, and oral cancer.

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