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The Effects of E-cigarette/Vaping Nicotine Delivery System on Periodontal Health

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Abstract: *E-cigarettes have gained popularity among adolescents and adults and are either used as alternatives to traditional cigarettes or to help in smoking cessation. Their impact on one's systemic and periodontal conditions is a growing concern among health and oral health professionals. This review investigated the evidence of the effect of electronic nicotine delivery systems on periodontal health. A systematic search of available literature in three areas of interest: intraoral microbiome alterations, impact on periodontal disease markers, and comparisons of the e-cigarette population to conventional smokers. Results indicate that the use of e-cigarettes modifies the oral microbiome, increases inflammatory reactions and affects salivary composition. These changes are a contributing factor to tissue damage and increased susceptibility to periodontal disease. Comparative studies have also shown that cigarette smoke and e-cigarette aerosol increase the levels of oxidative stress and inflammatory cytokines, causing cellular damage in the periodontium. It has been proven from the evidence that e-cigarettes have negative effects on periodontal health. Finally, longitudinal studies of exclusive e-cigarette users are needed to establish the chronic influence and severity of these effects.*

Keywords: e-cigarettes, vaping, nicotine delivery systems, periodontal health, oral health

INTRODUCTION

The popularity of e-cigarettes has increased and is rising at an alarming rate and has emerged as a growing public health concern in the United States (Centers for Disease Control and Prevention, 2020). E-cigarettes are battery-operated devices that heat a liquid which usually contains nicotine, flavorings, and other chemicals to create an inhalable aerosol (U.S. Food and Drug Administration, n.d.). Unlike conventional cigarettes, they do not include tobacco while some formulas have cannabis. These devices are also known as vape pens, e-hooks or electronic nicotine delivery devices (ENDS) (Centers for Disease Control and Prevention, 2022).

In 2018, an estimated 3.2% of US adults were active users of e-cigarettes, with the majority being aged 18-24 years (Centers for Disease Control and Prevention, 2020). Of those who quit in the past year, 57.3% of adults had tried e-cigarettes, but only 25.2% of the adults were regular users. Adolescents and young adults were the population with the largest rate of increase between 2017 and 2019, which fell slightly in 2020 (Centers for Disease Control and Prevention, 2021). The percentage of middle-school students using disposable e-cigarettes increased from 3% to 15.5% from 2019 to 2020, while

the percentage of high-school students using disposable e-cigarettes increased from 2.4% to 26.5% in the same period (Centers for Disease Control and Prevention, 2021). According to Silverstein (2020), estimates suggested that 9.1 million adults in the U.S. used e-cigarettes or vaping products, with 36.9% using them and regular cigarettes, 39.5% using them instead of cigarettes, and 23.6% having no previous cigarette use (Centers for Disease Control and Prevention, 2022).

E-cigarettes are frequently presented as a healthier choice to conventional tobacco products (Truth Initiative, 2021). Manufacturers state they will help smokers reduce or quit tobacco consumption and have increased oral health in comparison with standard cigarettes. However, the views of health professionals are still conflicting. Some see e-cigarettes as a harm-reduction device for smokers who are not able to quit, while others see them as a threat to population health (Farsalinos and Le Houezec, 2015; Fairchild et al., 2014). In response to these issues, e-cigarettes were added to the regulatory reach of the U.S. Food and Drug Administration (FDA) in 2013, and the long-term efficacy and safety of e-cigarettes continue to be under review (U.S. Food and Drug Administration, 2019).

Research has indicated that tobacco smoking is still the greatest risk factor for periodontal disease and is responsible for more than half of adult cases in the United States (Borojevic, 2012; American Academy of Periodontology, 2020). Some emerging data suggest that e-cigarettes are also toxic to oral tissues. In vitro work has demonstrated that e-cigarette vapor causes inflammation in all-gingival epithelial cells that is equivalent to that caused by conventional cigarette smoke (Beklen and Uckan, 2021). Other studies show that e-cigarette use interferes with the oral microbiome and encourages dysbiosis associated with periodontal disease (Ganesan et al., 2020; Xu et al., 2022; Thomas et al., 2022). Wilson et al. (2022) further found that e-cigarette aerosol exposure binds the generation of inflammatory cytokines in gingival fibroblasts and progenitor cells, a pathway today (2022) believed to play a role in periodontal tissue damage.

The prevalence of e-cigarette use and its potential effects on periodontal health require a biological and clinical understanding of its effects. This review discusses the existing peer-reviewed literature to ensure the effects of electronic nicotine delivery systems on the periodontium and how this process contributes to the development of periodontal disease.

LITERATURE REVIEW

The Relationship between Smoking and Periodontal Health

Tobacco smoking is a major cause of periodontal disease, which is responsible for more than 50% of cases of periodontal disease among adults in the United States (Borojevic, 2012; American Academy of Periodontology, 2020). Smoking impairs the immune response, exerts a destructive effect on the periodontal vasculature and inhibits host defense mechanisms, all of which increase the rate of periodontal tissue destruction (Kang, 2018). Studies have demonstrated that nicotine has an effect of diminishing the gingival blood flow and masking inflammatory symptoms resulting in delayed early detection (Johnson and Guthmiller, 2007, cited in Borojevic, 2012). Other studies have also shown that smoking impairs the production of cytokines and reduces tissue oxygenation, making one more vulnerable to bacterial infection and poor wound healing (Kinane et al., 2017; cited in Borojevic, 2012).

The Relationship between E-cigarette Use and the Oral Microbiome

The oral microbiome refers to the ecosystem of the microorganisms in the oral cavity that affect oral and systemic health (Sharma et al., 2018; Deo and Deshmukh, 2019). Maintaining a healthy balance between beneficial and harmful microorganisms of the human gastrointestinal system, a balanced microbiome, is essential for normal immune function and tissue integrity, whereas an altered balance, called dysbiosis, is associated with diseases such as dental caries and periodontal disease (Sedghi et al., 2021; American Academy of Periodontology, 2020). Tobacco use is one of the most important factors that can influence the oral microbiota and its detrimental long-term effects on periodontal health are well documented (Borojevic, 2012; Kang, 2018). As the amount of electronic nicotine delivery systems (eNDS) is increasing, the critical point has been on the understanding of whether the e-cigarette has the same microbial and inflammatory reactions (World Health Organization, 2022; U.S. Food and Drug Administration, 2019).

Ganesan et al. (2020) performed a cross-sectional study on 123 adults to investigate the effects of E-cigarette exposure on the subgingival microbiome and host immune response. It was found that e-cigarette users had a greater number of pathogenic bacteria including those associated with periodontitis and higher levels of inflammatory processes but without clinical signs. The authors noted that the propylene glycol and glycerin used in e-liquids changed the microbial community composition within 24 hours which promoted pro-inflammatory biofilm formation (Ebersole et al., 2020).

Thomas et al. (2022) have expanded this work in a six-month longitudinal study involving e-cigarette users, cigarette smokers and non-smokers. Hence, each group had unique microbiome signatures, but microbial diversity evolved in an identical way in each group. The oral microbiome of e-cigarette smokers was close to that of smokers, and there was a significantly higher level of inflammatory cytokines IL-4, IL-1b, and TNF-α, indicating an underlying pro-inflammatory transition for vaping (Atuegwu et al., 2019).
Xu et al (2022) examined saliva from 101 subjects with mild periodontitis and observed that e-cigarette users had higher amounts of Treponema, Fusobacterium, and Tannerella spp., as well as higher amounts of pro-inflammatory cytokines like IL-1, TNF-α, and IFN-γ. The scientists found that the dysbiosis caused by the use of e-cigarettes is similar to that caused by traditional smoking.

Rouabhia et al. (2020) used an in vitro model to test the effects of e-cigarette vapor on Streptococcus mutans. They noticed that, following repeated exposure to the vapor, there was more bacterial growth and replication, the formation of biofilms and expression of genes associated with virulence. Although the study was laboratory-based, it showed that short-term exposure to vapors of chemicals can modify microbial behavior associated with the risk of caries (Beklen and Uckan, 2021).

El-Mouelhy et al. (2022) compared the cellular impact of e-cigarette, cannabis, and cigarette aerosols on the gingival fibroblasts. Cigarette and cannabis smoke decreased mitochondrial potential and cell viability while e-cigarette aerosol had minimal effects similar to non-smokers. While the results indicate less cytotoxicity in the case of e-cigarette vapor, the research does still confirm such items cause measurable evidence of cellular stress (Briggs, Bell and Breik, 2021).

Sundar et al. (2016) exposed oral epithelium and periodontal ligament cells to flavored and flavorless e-cigarette aerosols and found an increase in oxidative stress, DNA damage, and pro-inflammatory

response. These reactions were seen for nicotine, as well as non-nicotine flavorings, suggesting that flavoring agents are also a cause of oral tissue inflammation.

Overall, clinical, longitudinal and in silico studies have demonstrated that the use of e-cigarettes causes alterations in oral microbiota, an increase in inflammatory cytokines and promotes the pathogenesis associated with periodontal disease (Vohra et al., 2020; Javed et al., 2017). Although the cytotoxicity of e-cigarette aerosols is often deemed to be lower than that of traditional smoke, several reports confirm that e-cigarette aerosols negatively affect oral microbial ecology and immune homeostasis. A broader adequacy investigation is required to find out whether the effects are more or less reversible step by step and just how they modify particular final long-term periodontitis effects (Pierce et al., 2021; World Health Organization, 2022).

Table 1: The Relationship between E-cigarette Use and The Oral Microbiome

Author/year/country	Study Design	Sample Size	Results
Ganesan et al. 2020 USA	Case-Control Study, In Vitro Study	123 participants (25CS,25NS, 20ES, 28 DS, 25 FSES)	• E-cigarette use negatively impacted the inflammatory immune response and oral microbial dynamics. (Leading to an overrepresentation of punitive periodontal pathogens in the subgingival microbiome, rapidly increased pro-inflammatory signals, and increased bacterial virulence profiles similar to those observed in patients with severe periodontitis) • Carbon and glycol/glycerol encouraged significant changes in the structure of the oral biofilm after 24 hours.
Thomas et al. 2022 USA	Longitudinal Study	84 Participants (27 CS,28 ES, 29 NS)	• E-cigarette users had oral microbiomes similar to regular smokers and few similarities to nonsmokers. • E-cigarette vapor has a different microbial community than tobacco smoke. • There was a difference in periodontal microbiome between smokers and nonsmokers.
Rouabhia and Semlali 2021 Canada	In Vitro Study	-	• E-cigarette vapor significantly enhanced the growth and adherence of S. mutans more strongly to exposed teeth.

Xu et al. 2021 USA	Longitudinal Clinical Study	101 participants (31CS,32ES, 38 NS)	• E-cigarette usage increased the prevalence of *Treponema*, *Fusobacterium taxa*, and *Tilifactor* in oral microbiomes of periodontitis. • E-cigarettes may have comparable effects to traditional cigarettes by changing the bacterial composition of saliva which leading to develop of periodontal disease. • pro-inflammatory cytokines in e-cigarette users contribute to oral dysbiosis and disease development
El-Mouelhy et al. 2021 Egypt	In Vitro Study	32 participants (8 CS, 8 ES, 8 cannabis)	• Cigarette and cannabis smokers had fewer CFU-F than e-cigarette users. • E-cigarettes did not increase gene expression, unlike cannabis and conventional cigarettes. • E-cigarette aerosol had a low impact on the GF/G-MSCs of nonsmokers than cannabis and cigarette smoke.
Sundar et al. 2017 USA	In Vitro Study	-	• E-cigarette use raises protein carbonylation, pro-inflammatory responses in HPdLFs and HGEPp, and IL-8 production in HPdLF cells. • E-cigarettes increase oxidative/carbonyl stress, inflammation, DNA damage, and histone deacetylase 2 (HDAC2) reductions in the gingival epithelium. • Damage caused by e-cigarette flavored aerosols on the periodontal tissues used in this study could compromise periodontal health

The Effects of E-cigarettes on Periodontal Disease

E-cigarette consumption has been reported to cause periodontal conditions that resemble those of traditional smokers. The Population Assessment of Tobacco and Health (PATH) survey provides data that there was a major correlation between e-cigarette usage and increased gum disease risk. In a study, Atuegwu et al (2019) observed that among continuous users, the odds of being self-diagnosed with gum disease (odds ratio = 1.76) and bone loss (odds ratio = 1.67) were higher than those in never users. Although the large-scale study provided good evidence of a potential relationship, it relied on self-reported data and lacked clinical confirmation, which could have introduced bias.

A small prospective study by Wadia et al. (2016) investigated the impact of switching from smoking to VAP after the former. After 2 weeks, transition smokers demonstrated a significant increase in BOP ($P < 0.001$) and little change in plaque level. Conclusions: The findings indicated that the conversion to vaping could lead to gingival inflammation, which might develop into periodontitis if left untreated. However, their limited strength was due to the lack of a control group.

A systematic review was conducted by Wilson et al. (2022) on 18 studies on the impact of e-cigarette aerosols on oral and periodontal cells. The majority of studies found that exposure to e-cigarettes decreased cell viability, induced DNA harm and also wound healing retardation in fibroblasts. Especially menthol-flavored aqueous liquids were related to lower myofibroblast differentiation and higher inflammatory cytokine release. The review showed the need for more long-term and homogeneous clinical trials that include never-smokers to verify these effects.

Beklen and Uckan (2021) studied the effects of the primary e-cigarette solvents, propylene glycol and vegetable glycerin, on the gingival epithelial cell. The result was that after 24-hour exposure, cell viability was decreased but inflammatory markers IL-6, IL-8 and MMP-9 were increased. The effects were enhanced by the addition of nicotine, suggesting both basal solutions and nicotine have an etiological role in periods of gingival inflammation. The study concluded that e-cigarettes are not harmless alternatives to tobacco use, since the basic ingredients of e-cigarettes cause cytotoxic and inflammatory effects in oral tissues.

Sancilio et al. (2016) found similar cytotoxic effects in human gingival fibroblasts treated with nicotine-free and nicotine-containing e-cigarette fluids up to 72 hours. The study demonstrated elevated reactive oxygen species, activation of Bax gene and activation of apoptosis. These results revealed that oxidative stress and apoptosis are independent of the nicotine content and indicated that flavor chemicals and solvents are also important for periodontal tissue damage.

Alqahtani et al. (2020) explored e-cigarette users and non-smokers for differences in inflammatory biomarkers in saliva, by including 14 e-cigarette users and 16 non-smokers. The amounts of IL-1β and TNF-γ were elevated in e-cigarette users, and significant alterations in 368 metabolites involved in inflammation and tissue decomposition were noticed. Prostaglandins and leukotrienes are biomarkers that have been reported to be responsible for periodontal pathogenesis. Although this was a small study with mixed tobacco usage in cohort subjects, the study showed an inflammatory profile that was compatible with periodontal tissue stress.

The study by Tatullo et al. (2016) is an observational study over a period of 120 days that compared the oral health outcomes of smokers following their transition to e-cigarette use and those of the patients who continued to use conventional cigarettes. Plaque index, bleeding index, and papillary bleeding index in patients were significantly improved from baseline to day 120. Participants also reported improved taste, smell and improved overall health. Researchers credited a decrease in exposure to toxins from combustion and a lower level of nicotine consumption as the causes of these improvements. However, the results may have been affected by confounders such as the lack of a control group of smokers who did not want to quit smoking and possibly behavior change bias.

AlQobaly et al. (2022) used data of 8,129 adults from the National Health and Nutrition Examination Survey (NHANES) and reported that e-cigarette users had a higher prevalence of periodontal disease when compared to non-users (OR: 1.85). When smoking status was added the association was higher and showed that both smoking and vaping were related to self-reported periodontitis. The authors concluded that e-cigarette use is associated with increased periodontal risk, but their inability to demonstrate that it was causal due to a cross-sectional design and a lack of data regarding a duration effect.

Taken together, the clinical, laboratory, and epidemiological evidence indicate that e-cigarette aerosols modify inflammatory responses, impair healing, and also may cause an increased susceptibility to periodontal disease (Atuegwu et al., 2019; Beklen and Uckan, 2021; Wilson et al., 2022). While some data exist to indicate short-term benefits from switching from smoking to vaping (Tatullo et al., 2016), no evidence has yet shown the biological impact of e-cigarette exposure on periodontal tissues, other than disease progression markers, not disease recovery.

Table 2: The Effects of E-cigarettes on Periodontal Disease

Author/year/country	Study Design	Sample Size	Results
Atuegwu et al. 2019 USA	Survey Study	18.289 Participants	• The long-term use of e-cigarettes raised the risk of bone loss and periodontal disease.
Wadia et al. 2016 UK	A pilot longitudinal study	20 participants (20 ES)	• BOP locations increased significantly (P=< 0.001) when smokers converted to vaping. • Two weeks after switching to vaping, the gingival inflammation of smokers increased significantly. • E-cig had small differences in plaque levels. • E-cigarettes may develop gingivitis, which may proceed to periodontitis if untreated.
Wilson et al. 2022 USA	Systematic Review	-	• (16/18) of articles showed that head, neck, and cells from the periodontium had significant negative alterations when exposed to e-cig aerosols. • periodontal ligament fibroblasts exhibited significantly decreased cell growth after exposure to menthol e-cigarette liquid and delayed periodontal healing. • E-cigarette vapor induced periodontal fibroblasts and gingival progenitor cells to create more inflammatory cytokines, potentially contributing to periodontal disease.

Beklen and Uckan 2021 Turkey	In Vitro Study	-	• The gingival epithelial cell viability was significantly decreased. • the higher the concentration of VG/PG with or without nicotine, the less viable the gingival epithelial cells were. • All the PG/VG mixtures with or without nicotine had significant cytokines (IL-6, IL-8) and MMP-9 expression. • E-cigarettes are not safer alternatives to conventional cigarettes because of the cytotoxicity and increased cytokine production by gingival epithelial cells.

Sancili et al. 2016 Italy	In Vitro Study	-	• Nicotine and nicotine-free fluids raised reactive oxygen species(ROS)after 48 hours. • Nicotine and the nicotine-free liquids are linked to human gingival fibroblast cytotoxicity.
ALQahtani et al. 2020 USA	Pilot Randomized controlled trial	30 Participants (14ES, 16NS)	• ENDS users' saliva had 368 metabolites that significantly differed from non-smokers • ENDS users had increased inflammatory markers and salivary metabolites, which associated with periodontal disease at a young age compared to young non-smokers
Tatullo et al. 2016 Italy	An observational pilot study	110 former CS switched to ES. 60 less than 10 years CS, 50 more than 10 years CS.	• PI score was significantly decreased in both groups. • BI showed improvement in periodontal health in over 90% of participants across all groups. • PBI was improved and exhibited a significant positive impact in this group. • Clinical dental examinations showed improved periodontal parameters and self-perception of health after switching to e-cigarettes. • ES are better than CS for general and oral health.

AlQobaly et al. 2022 UK	Cross sectional Study	8,129 participants 1471 current S, 2168 ever use ES, 4490NS	• ES and ever use ES reported considerably increased risks of periodontal disease than non-users with OR = 1.43 • ES and ever use ES had more significant risks of periodontal disease and bone loss than NS. • Association between ES and periodontal diseases exhibited higher odds of self-reported periodontal disease than NS, with odds ratios of 2.05 and 1.65.

Periodontal Health in E-cigarette Smokers and Conventional Cigarette Smokers

Several studies have compared the periodontal health outcomes of e-cigarette users and conventional cigarette smokers and have provided some evidence of common effects shared by e-cigarettes and conventional cigarettes, as well as effects that are unique to e-cigarettes.

Jeong et al. (2019) performed a secondary data analysis of the South Korean National Health and Nutrition Examination Survey (2013-2015) for 13,551 adults. Participants were divided into e-cigarette smokers, traditional cigarette smokers, ex-smokers and non-smokers. Using the Community Periodontal Index (CPI), the study found that periodontal disease was present in 35.8% of men and 28.6% of women who used e-cigarettes compared to 44.0% of men and 35.3% of women who used conventional cigarettes. Both e-cigarette and traditional cigarette users showed a significantly higher probability of periodontal disease as compared to non-smokers with an odds ratio of 2.34 and 2.17 respectively. The authors concluded that users of e-cigarettes are at similar risk of periodontal disease as traditional smokers. However, the cross-sectional study design and reliance on self-reported data prevented cause-and-effect interpretation.

Xu et al. (2021) conducted a longitudinal study amongst 101 participants who were separated into cigarette smokers, e-cigarette users, and non-smokers over a 6-month period. Periodontal health parameters, namely probing depth (PD), clinical attachment loss (CAL) and bleeding on probing (BOP) were recorded. Traditional cigarette smokers had the highest concentrations of cotinine and carbon monoxide and CAL increased significantly among e-cigarette users. Severe periodontitis in both groups of smokers was higher than in non-smokers. The varying ages and ethnicities between groups may have affected the results, and the researchers advised future studies to be longer and ethnically balanced.

Javed et al. (2017) have conducted a pilot cohort study in 33 smokers, 31 exclusive e-cigarette users, and 30 non-smokers. Cigarette smokers had significantly higher plaque index (PI), marginal bone loss (MBL) and probing depth (PD) than e-cigarette users and non-smokers. Interestingly, the amount of bleeding on probing was higher in patients who were non-smokers which can be considered to be an indicator for resolution of inflammation in non-exposed tissues. The study did not report any differences in levels of attachment loss or the number of missing teeth in groups. The conventional cigarette smokers showed greater gingival swelling and oral discomfort compared to the e-cigarette users. Other limitations included the small groups and short periods of use for E-Liquid.

Karaaslan et al. (2020) treated clinical and biochemical indicators of 19 subjects who were e-cigarette users (former smokers) and traditional smokers (former smokers). While plaque index, attachment loss and probing depth did not differ significantly between the groups, gingival index scores were higher in recent quitters. E-cigarette users had abnormal inflammatory and oxidative stress markers with increased IL-8 and TNF-α compared to the former smokers, implying a background inflammatory stress. The authors concluded that both forms of smoking have a negative effect on the balance of cytokines and oxidative stress although e-cigarettes may generate a less potent response.

Vohra et al. (2020) conducted an observational study comparing 28 cigarette smokers, 26 e-cigarette users, and Juul users, and 26 non-smokers. Cigarette smokers said they experienced more tooth pain, bad breath, and periodontal pain than e-cigarette or Juul users. However, the e-cigarette users still experienced more tooth pain and bleeding gums than the non-smokers. Clinically, it was found that the plaque and probing depth values for smokers and e-cigarette users were greater and the bleeding on probing was lower than for non-smokers. No significant difference was found in loss of attachment or missing teeth. The small number of e-cigarette users and the short duration of exposure to e-cigarettes were major limitations of the study.

Ye et al. (2020) investigated biochemical indicators of periodontal stress in saliva and gingival crevicular fluid of e-cigarette smokers, cigarette smokers, dual users, and non-smokers (n=48). Cigarette smokers had higher prostaglandin E2 (PGE2) levels than all other groups (but IL-1b levels proved to be no different). Both the cigarette and e-cigarette users showed reduced oxidative stress markers; however, the e-cigarette users showed the lowest levels. E-cigarette users also had lower concentrations of growth factors, which could mean damage to tissue repair abilities. In spite of its limited statistical power, the results strengthened suggestive evidence of the inflammatory and oxidative bona fides of vaping.

Shah et al. (2022) performed a retrospective study evaluating 220 periodontitis patients who received non-surgical periodontal therapy. E-Cigarette users along with cigarette smokers showed less good healing response and more surgical interventions compared to non-smokers. Although differences between e-cigarette and conventional smokers were not statistically significant, both groups had higher rates of residual probing depths ([5mm]). The retrospective nature and previous smoking history of e-cigarette users had limitations on the conclusions.

In comparison, Mokeem et al (2018) did a comparison of 154 participants between cigarette, waterpipe, e-cigarette and non-smoker participants. While cotinine levels did not differ between any groups of smokers, the IL-1 and IL-6 levels in cigarette and waterpipe smokers were significantly higher than those in e-cigarette users and non-smokers. Periodontal parameters such as depth of probing, amount of attachment and bone loss were similar for e-cigarette users compared to non-smokers but were worse for traditional and waterpipe smokers. These results indicated that e-cig exposure may potentially cause less (severe) periodontal damage than conventional smoking, although the inflammatory markers were confirmed to have biological activity.

From the reviewed literature, we can conclude that both e-cigarette and traditional cigarette use are linked to poor periodontal health. While there are some studies that show less severe effects for e-cigarettes, there is overwhelming evidence that shows inflammatory changes, tissue damage, and higher treatment failure rates compared to non-smokers (Jeong et al., 2019; Xu et al., 2021; Karaaslan

et al., 2020; Shah et al., 2022). The extent of harm seems to be related to time and intensity of exposure, which would indicate that e-cigarettes are not a risk-free alternative for periodontal health.

Table 3: Periodontal Health in E-cigarettes User and Conventional Smoker

Author/year/ country	Study Design	Sample Size	Results
Jeong et al. 2019 South Korean	Secondary data	13,551 participants (222 ES, 2320 CS, 2667ex-CS, 8342 NS)	• E-cigarette users were 2.34 times more likely to have periodontal disease, while traditional smokers were 2.17 times more likely compared to non-smokers. • Both cigarette smoking and e-cigarette use were linked to tooth discomfort, caries, and enamel degradation.
Xu et al. 2021 USA	longitudinal design study	101 Participants (32 ES, 31CS, 38 NS)	• Traditional smokers' saliva contained the most cotinine and carbon monoxide. • E-cigarette users had higher CAL. • Smokers and e-cigarette users had more severe periodontitis than nonsmokers.
Javed et al. 2017 USA	Pilot Cohort study	94 participants 33 CS, 31ES 30 NS	• CS had higher PI, PD,MBL, and clinical periodontal parameters than other groups. • NS had more bleeding than cigarette and e-cigarette users. • Clinical attachment loss, tooth loss, and marginal bone loss were all similar. • CS reported more self-perceived gingival swelling than ES and NS.
Karaaslan et al. 2020 Turkey	Cohort study	57 participants (19ES, 19CS, 19ex-S)	• CS had lower levels of IL-8 than ES and lower in ex-S. • Tumor Necrosis Factor-α (TNF-α) levels were higher in CS than in ES and lower in ex-S. • Clinically, PI, AL, and PD were not significantly different in all three groups. • CS and ES negative impacted on inflammatory cytokines and oxidative stress.
Vohra et al. 2020 Saudi Arabia	Observational study	105 participants 28CS, 51ES, 26 NS	• CS reported more often higher periodontal pain and poor breath than ENDS users. • No significant difference between CS and ENDS users in bleeding gums. • ES had a higher odds ratio for tooth pain and bleeding gums than NS.

Ye et al. 2020 USA	Cross-sectional pilot Study	48 participants 12 ES, 12 CS 12DS, 12NS	• CS had higher saliva PGE2 levels than all the other groups. • interleukin-1 (IL-1) was not significantly different across groups • ES and CS showed statistically significant reductions in oxidative stress than NS,
			• ES showed reductions in oxidative stress than DS. • ES had lower growth factors than other groups.
Shah et al. 2022 UK	Retrospective Study	220 participants 20 ES, 20 CS 60 ex-S, 120 NS	• ES had poorer PMPR treatment responses than NS., by increasing need of surgery. • ES had more PD sites than non-smokers. • CS and ES were not significantly different. • Ex-S responded better to therapy, PD sites, and probing depth than ES.
Mokeem et al. 2018 Saudi Arabia	Cross - sectional study	154 Participants 39 CS, 37 ES, 38NS 40 waterpipe smoker	• NS have significantly less cotinine than All groups. • ES users and NS had lower IL-1 and IL-6 than CS and waterpipe smokers. • ES users and NS exhibited comparable PPD, CAL, MBL, IL-1, and IL-6 levels. • CS and waterpipe smokers showed worse periodontal inflammatory indices than ES and NS

DISCUSSION

The piece of evidence discussed proves that the use of e-cigarettes plays a role in the occurrence and worsening of periodontal diseases like gingivitis and periodontitis. The pathogenesis involves two major mechanisms: alteration of the oral microbiome and stimulation of the host's inflammatory response (Deo and Deshmukh, 2019; Sharma et al., 2018; Xu et al., 2022). Although the link between e-cigarette use and periodontal health is a popular one, studies differ in how pronounced and severe the effects can be (Javed et al., 2017; Karaaslan, Dikilitas and Yigit, 2020). A comparison of smokers who switched to e-cigarettes with complete quitting smokers showed a tendency toward increased gingival inflammation during the early stages of smoking cessation. Wadia et al. (2016) reported an increase in bleeding on probing and gingival inflammation in three to five days after quitting smoking. This raises the possibility that some of the inflammatory effects reported in the literature in e-cig users could be an effect of nicotine withdrawal in the short term, rather than the effects of vaping. A longitudinal study, however, has indicated that frequent e-cigarette consumption still had an impact on periodontal parameters, including the probing depth and the attachment loss (Atuegwu et al. 2019; AlQobaly et al. 2022).

Inflammation has been a regular effect of e-cigarette use. In these studies, high levels of cytokines, including interleukin (IL)-1b, IL-6, IL-8, tumor necrosis factor-alpha (TNF-a), and matrix metalloproteinase-9 (MMP-9), were strongly associated with periodontal tissue destruction (Sundar et al., 2016; Ye et al., 2020; Ebersole et al., 2020). These inflammatory reactions are accompanied by elevated oxidative stress and apoptosis, and improved appearance of Bax that takes part in cell death and damage to the tissues (Sancilio et al., 2016; Beklen and Uckan, 2021).

Another significant finding is that there are changes in the oral microbiota. E-cigarette smokers exhibit elevated numbers of pathogenic bacteria, which include Streptococcus mutans, Fusobacterium, Treponema, and Filifactor (Rouabhia and Semlali 2020; Xu et al. 2022; Thomas et al. 2022). These microorganisms are associated with biofilm formation and synthesis of glucan-binding proteins and glucosyl transferases, which facilitate plaque accumulation (Rouabhia and Semlali 2020). In another study (Xu et al. 2022), microbe diversity, inflammatory potential (IR), and periodontal pathogen-enriched e-cig compared with non-smokers were also reported. Results from in vitro studies validated e-cigarette aerosol and showed a facilitative role on bacterial adhesion and biofilm formation as cornerstones of periodontal pathogenesis (Ganesan et al., 2020; Wilson et al., 2022).

The liquid content of the e-cigarettes plays a major role in these effects. Vegetable glycerine and propylene glycol (the two common solvents contained in E-Liquids) cause an inflammatory process in gingival epithelial cells (Beklen & Uckan, 2021). Nicotine (Nic), both containing and nicotine-free e-liquids induce ROS (Sancilio et al., 2016; El-Mouelhy et al., 2022), expression of Bax, and apoptosis. These data suggest that the injurious cellular responses were insensitive to the presence of nicotine content and that the solvents in themselves cause tissue stress and inflammation.

Comparative studies demonstrate that both conventional cigarette smokers and e-cigarette users have greater incidences of gingivitis and periodontitis than do non-smokers (Mokeem et al., 2018; Jeong et al., 2020). However, conventional smokers tend to have more severe forms of periodontal disease. Javed et al. (2017) studied that the destruction was more extensive in the cigarette smokers and the groups exhibited more probing depth and attachment loss. Contrastingly, AlQobaly et al. (2022) showed the clinical attachment loss to be higher among e-cigarette users as well, suggesting that vaping carries potentially similar or greater risks based on the level of exposure as well as the type of device used.

Progesterone use also varies among users in regard to clinical outcomes after periodontal treatment. Shah et al (2022) found that e-cigarette smokers had a worse response to non-surgical periodontal therapy when compared with non-smokers and/or had to undergo the surgical intervention more frequently. This suggests a reduced healing ability similar to that of cigarette smokers, which may be linked to reduced vascularization and chronic inflammation in the gingival tissues (Briggs, Bell, and Breik, 2021).

Despite obvious associations, a number of methodological issues constrain current research. Most studies have small sample sizes, a cross-sectional design, or are based on self-reported smoking status (Atuegwu et al., 2019; Javed et al., 2017). Some studies are not accessible for comparison due to the absence of control groups, and the presence of different age and lifestyle differences between

participants adds bias (AlQobaly et al., 2022; Karaaslan, Dikilitas and Yigit, 2020). The World Health Organization (2022) and the Center of Disease Control and Prevention (2022) acknowledge the rapid increase in e-cigarette use, especially among adolescents, pointing to the importance of conducting large-scale longitudinal studies on the effects of e-cigarettes in the long-term benefits on oral health. Overall, there is evidence of e-cigarettes modifying the oral microbiome, increasing oxidatory stress and elevated inflammatory markers, which are all factors in periodontal tissue destruction. Whereas some short-term studies have suggested partial restoration of the oral health of smokers switching to e-cigarettes (Caponnetto et al., 2011; Farsalinos and Le Houezec, 2015), chronic exposure to e-cigarette aerosol seems to sustain chronic inflammation and inhibit healing. In addition, more longitudinal studies are required to elucidate the long-term impact of exclusive use of such devices, especially in youth who have no history of smoking.

CONCLUSION

This review considered available evidence on the effect of e-cigarette use on periodontal health. Findings have never ceased to reveal how e-cigarettes contribute to biological damage of the periodontal tissue through three primary mechanisms: direct cytotoxic effect of aerosols on gingival and periodontal cells, disturbed oral microbiome leading to dysbiosis and increased production of inflammatory mediators, such as interleukins and matrix metalloproteinases. In combination, these mechanisms trigger and maintain the development of inflammation and tissue destruction of the periodontium.

Although e-cigarettes have been marketed as safer alternatives to traditional tobacco, available data show that they are not much safer for the mouth than traditional tobacco. Several studies showed structural and functional changes of gingival tissues, increased probing depth, and attachment loss among e-cigarette users compared with non-smokers. Both nicotine-containing and nicotine-free e-liquids cause oxidative stress and apoptosis, indicating that the matter inducing the pathogenesis may be the solvents and additives themselves.

There continues to be weak evidence in the current literature due to flaws in study design. Most of the studies are cross-sectional, small samples, or those that have current or former tobacco smokers, so it is often hard to tell the effect of vaping on its own. Longitudinal prospective studies with larger populations devoted to only using e-cigarettes are needed to help clarify dose-response relationships and long-term effects.

The current e-cigarette use should not be viewed as harmless for periodontal health. The beginning of the emergence of evidence to measure biological and clinical changes consistent with early periodontal disease. Public health measures in this direction should therefore incorporate education on the possible oral risks of vaping and emphasize cessation/prevention in adolescents and young adults. Future research will also need to evaluate the reversibility of periodontal damage following cessation of e-cigarette use and compare the effectiveness of periodontal therapy in people with this disease.

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