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Review Article

The Effect of Electronic Cigarettes on Periodontal Tissues and Alveolar Bone Loss: A Narrative Review

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Abstract

Electronic cigarettes are widely promoted as a safer alternative to combustible tobacco, yet their effect on the periodontium and on alveolar bone remains unsettled. This narrative review appraises the clinical, radiographic, microbiological and immunoinflammatory evidence on electronic nicotine delivery systems (ENDS) in relation to periodontal health and alveolar bone loss, comparing ENDS users with conventional cigarette smokers and non-smokers. Across comparative studies and meta-analyses, cigarette smokers consistently show the poorest periodontal indices, while ENDS users occupy an intermediate position and are frequently indistinguishable from non-smokers for plaque index and probing depth. Bleeding on probing is lowest in ENDS users, a finding attributable to nicotine-mediated vasoconstriction rather than to periodontal health. Pooled estimates of marginal bone loss show no significant difference between ENDS users and non-users, but rest on cross-sectional studies with short vaping histories, pervasive confounding by prior smoking and heterogeneity exceeding 85%; cohorts with longer exposure report bone loss equivalent to that of smokers. The molecular evidence is more consistent. Crevicular and salivary RANKL, interleukin-1β, interleukin-15 and interleukin-18 are elevated in ENDS users to levels comparable with smokers even when clinical parameters are not; the salivary RANKL/osteoprotegerin ratio remains disturbed three months after non-surgical therapy; and e-cigarette vapour condensate suppresses osteoblast osteoprotegerin secretion at sub-cytotoxic doses. ENDS users also respond less favourably to non-surgical periodontal therapy than non-smokers. E-cigarettes are plausibly less injurious to the periodontium than combustible cigarettes, but they are not periodontally inert, and the available evidence is not of a design capable of excluding an effect on alveolar bone.

Keywords: Electronic Nicotine Delivery Systems; Vaping; Periodontitis; Alveolar Bone Loss; RANK Ligand; Osteoprotegerin

Introduction

Periodontal diseases are among the most prevalent chronic inflammatory conditions of the oral cavity, and tobacco smoking is one of their most firmly established modifiable risk factors. Cigarette smoke impairs the host response to the dental biofilm, heightens the production of destructive inflammatory cytokines and enzymes, promotes a more pathogenic subgingival microbiome, and diminishes the reparative capacity of periodontal tissues, thereby worsening periodontal status independently of plaque levels and reducing the predictability of periodontal and implant therapy [1].

Over the past decade, electronic cigarettes (e-cigarettes) have emerged as the most widespread of a growing class of novel nicotine products. Marketed by industry as a "safer" alternative to combustible tobacco and promoted as a smoking-cessation aid, their use has risen sharply, particularly among adolescents and young adults [1]. These electronic nicotine delivery systems (ENDS) operate by heating an e-liquid typically composed of a propylene glycol or Vegeta

Ble glycerin carrier, nicotine, and flavouring agents into an inhalable aerosol [1,2]. Because this aerosol passes in close proximity to the periodontal and mucosal tissues, and because nicotine exerts vasoconstrictive effects while other constituents induce oxidative stress, inflammatory responses, and shifts in the oral microbiome, adverse periodontal effects are biologically plausible even in the absence of combustion [2,3].

Despite this plausibility, the clinical evidence remains mixed and inconclusive. Systematic reviews and network meta-analyses consistently rank traditional cigarette smokers as having the poorest periodontal indices, while e-cigarette users tend to occupy an intermediate position and are frequently statistically indistinguishable from non-smokers for plaque index and probing depth [2,3]. Bleeding on probing is often paradoxically reduced in both cigarette and e-cigarette users relative to non-smokers, a finding widely attributed to the vasoconstrictive action of nicotine masking underlying gingival inflammation [2,3,4]. Meta-analytic data indicate a lower likelihood of a positive bleeding-on-probing result in e-cigarette users than in cigarette smokers; nonetheless, harmful effects of

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ENDS on periodontal health are still evident, and the absence of randomised controlled trials precludes a definitive conclusion [3].

Crucially, apparent clinical similarity between e-cigarette users and non-smokers may be misleading. Several investigations report that, even when clinical parameters are comparable, cigarette and e-cigarette users exhibit elevated gingival crevicular fluid advanced glycation endproducts, raised whole-salivary interleukin-15 and -18, and higher cotinine concentrations, biomarkers that signal an ongoing, yet latent, periodontal inflammatory process, particularly in individuals with a short exposure history [4,5,6]. Consistent with this, e-cigarette users have been shown to present with more acidic salivary pH and cotinine levels comparable to those of cigarette smokers [6]. Analogous concerns extend to peri-implant tissues, where umbrella-level evidence suggests that, although e-cigarettes may reduce or leave unchanged the clinical inflammatory signs of peri-implantitis relative to combustible tobacco, they still deliver nicotine and can adversely affect peri-implant health [7].

Interpretation of this body of literature is further constrained by recurring methodological limitations: a predominance of cross-sectional designs, relatively short vaping histories, confounding by prior or concurrent combustible-tobacco use, wide heterogeneity and non-standardisation of e-liquids and devices, and the aforementioned lack of randomised controlled trials [3,7]. Given the rapid uptake of e-cigarettes, the discordance between clinical and molecular findings, and the persistent uncertainty regarding their true periodontal impact, a focused synthesis of the current evidence is warranted. The aim of the present review is therefore to critically appraise how e-cigarette use affects periodontal health, comparing clinical, radiographic, and immunoinflammatory outcomes with those of conventional cigarette smokers and non-smokers.

Search Strategy

A narrative review was conducted to examine the effects of electronic cigarettes on alveolar and marginal bone loss in periodontology. Relevant publications were identified through manual searches of the PubMed/MEDLINE database. The search strategy combined the following keywords using Boolean operators: ("electronic cigarette" OR "e-cigarette" OR "vaping" OR "electronic nicotine delivery system" OR "ENDS") AND ("alveolar bone loss" OR "marginal bone loss" OR "periodontal bone loss" OR "peri-implant bone loss" OR "RANKL" OR "osteoprotegerin" OR "bone resorption" OR "periodontitis"). Reference lists of retrieved articles and relevant reviews were also manually examined to identify additional publications.

The literature search, study selection, reference checking, and verification of bibliographic information were performed manually by the researchers. Each included publication was checked against its PubMed entry and the publisher's DOI record to verify authorship, journal, publication year, volume, pagination, and editorial status. Publications were also screened for retractions, corrections, and expressions of concern. Artificial intelligence (AI) tools were used solely for language editing, translation, and manuscript editing, and were not used to conduct the literature search, select studies, or analyze or interpret the scientific evidence.

Priority was given to peer-reviewed articles published in English, with an emphasis on publications from the preceding six years. Eligible sources included systematic reviews, meta-analyses, clinical and observational studies, and laboratory-based investigations reporting radiographic or molecular outcomes related to bone loss among e-cigarette users, conventional cigarette smokers, and non-smokers. Publications were selected according to their relevance to the aims of the review rather than through formal quality scoring, consistent with the narrative nature of the review.

Composition of Electronic Cigarettes and Differences from Conventional Cigarettes

Electronic cigarettes, or electronic nicotine delivery systems (ENDS), are battery-powered devices that generate an inhalable aerosol by heating a liquid ("e-liquid") rather than by burning tobacco [1]. Although designs have evolved rapidly and vary widely in appearance, most share a common architecture comprising a battery, a heating element (coil or atomiser), and a reservoir holding the e-liquid, delivered as refillable "tanks" or pre-filled "pods" in a broad range of flavours and nicotine strengths [1]. Activation of the battery heats the coil, which vaporises the surrounding liquid; the vapour immediately condenses into a fine aerosol of liquid droplets that is inhaled by the user [10]. This vaporisation occurs at substantially lower temperatures than tobacco combustion (typically around 300 °C, compared with the roughly 800 °C reached at the burning tip of a conventional cigarette), so many of the thermal degradation processes that dominate cigarette smoke chemistry are, in principle, avoided [2].

The e-liquid itself is comparatively simple, comprising three main components: a carrier or humectant solution of propylene glycol (PG) and/or vegetable glycerin (VG), nicotine (unless a nicotine-free formulation is used), and flavouring agents [1]. Quantitative analysis of 150 chemical measurands in one e-cigarette aerosol detected only 25 constituents, of which 16 were generated wholly or partly by the device; these comprised the major e-liquid constituents (nicotine, propylene glycol and glycerol),

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together with recognised impurities of pharmacopoeia-quality nicotine and eight thermal decomposition products of the humectants, whereas approximately 100 measurands were detected in mainstream cigarette smoke [11]. Nicotine content is highly variable and device- and liquid-dependent, and the declared concentration is an unreliable guide to the actual one: across 32 refill liquids sampled from retail outlets, measured nicotine ranged from undetectable to 17.5 mg/mL and differed from the labelled value by -32.2% to +3.3%, while a product sold as "pure nicotine" contained 150.3 ± 7.9 mg/mL [9].

Nevertheless, the aerosol is not chemically inert. Several compounds detected in e-cigarette aerosols are absent from the parent e-liquid and are instead generated in situ, primarily through the thermal decomposition of the humectants PG and VG and of flavouring compounds during heating [10]. These reaction products include carbonyls such as formaldehyde, acetaldehyde, and acrolein. In addition, the device hardware itself contributes contaminants, as heavy metals and silicate particles, including chromium, nickel, lead and copper, can leach from the heating coil and other components into the aerosol [10]. Aerosol chemistry is therefore not fixed but is strongly modulated by device operating parameters and by e-liquid composition. Testing four device types under controlled vaping conditions, Son and colleagues found that applying higher power raises coil temperature and so facilitates thermal decomposition of e-liquid components, that carbonyl and carbon monoxide emissions increased nearly linearly with puff duration, and that flavoured e-liquids generated more carbonyls and carbon monoxide than unflavoured ones; a top-coil device produced the highest formaldehyde yields, such that daily carbonyl exposure from e-cigarette use could still exceed acute exposure limits [8]. This dependence on both product and user behaviour is a recurring source of heterogeneity that complicates any general safety assessment [1].

The defining distinction between the two products is combustion. Conventional cigarette smoke is a highly complex mixture arising from tobacco combustion, containing thousands of chemical constituents, including a substantial burden of established carcinogens and toxicants such as polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines, and carbon monoxide [1]. By bypassing combustion, e-cigarettes avoid the generation of much of this cocktail, and their aerosols are consequently both compositionally simpler and lower in toxicant concentration. Comprehensive comparative analyses report that emissions of regulated toxicants are reduced by approximately 82 to more than 99% on a per-puff basis relative to a reference tobacco cigarette, rendering the aerosol compositionally far less complex than cigarette smoke [11]. It is on this basis that e-cigarettes are frequently framed, by industry and by some public health bodies, as a "less harmful" alternative for nicotine-dependent smokers [1].

This reduction, however, is neither absolute nor uncontested. E-cigarette aerosols still deliver nicotine, carbonyl decomposition products, flavour-derived toxicants, and metals, and their toxicant profile differs qualitatively from that of cigarettes rather than being simply a diluted version of it [10]. Toxicological analyses suggest that e-cigarettes may be safer than conventional cigarettes, yet harmful effects of even short-term use have been described, and the potential long-term consequences remain scarcely investigated [10]. Reduced exposure to a given set of measured biomarkers does not necessarily translate into a proportionate reduction in biological risk. For the periodontium specifically, the relevance of this composition lies in the constituents that reach the oral tissues directly: nicotine, with its vasoconstrictive and cytotoxic potential; carbonyls and flavourings capable of inducing oxidative stress and inflammatory responses in gingival cells; and metal particulates, all delivered in close proximity to the gingival and periodontal tissues, and each a plausible contributor to the alveolar bone changes examined in this review [1].

The Effect of Cigarette and E-Cigarette Nicotine on Salivary pH

Saliva is a principal determinant of oral homeostasis, and its pH, normally maintained near neutrality by bicarbonate and other buffering systems, governs the balance between demineralization and repair, modulates the subgingival microbial ecology, and reflects the secretory function of the salivary glands. A shift towards a more acidic salivary environment has been consistently associated with both cigarette smoking and, more recently, with e-cigarette use, and is regarded as a marker of a disturbed oral milieu conducive to periodontal disease [6].

In cigarette smokers, the reduction in salivary pH is well documented and appears to arise through several converging mechanisms. Chronic smoking is frequently accompanied by hyposalivation and a thicker, more serous salivary consistency, which lowers the basal salivary flow rate; the consequent reduction in bicarbonate delivery diminishes the buffering capacity of saliva and drives the pH downward. In a cohort of 259 male smokers and 251 non-smokers, both salivary pH (7.42 ± 0.48 versus 7.52 ± 0.43; $p = 0.018$) and buffering capacity (3.41 ± 0.54 versus 4.17 ± 0.71; $p = 0.001$) were significantly lower in smokers [14]. In parallel, smoke impairs salivary proteins and enzymes directly. In vitro exposure of whole saliva to nine puffs of gas-phase smoke raised protein carbonyls by some 400% and reduced amylase, lactate dehydrogenase and acid phosphatase activities by approximately 34%, 57% and 71%, while alkaline phosphatase and aspartate

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aminotransferase were unaffected; glutathione and N-acetylcysteine largely prevented the amylase and lactate dehydrogenase losses, implicating aldehyde attack on protein sulfhydryl groups. Salivary pH itself stayed between 7.0 and 7.4 throughout, indicating that the acidification seen clinically arises from reduced flow and buffering rather than direct chemical action on saliva [13]. This acidification sits within the broader picture of smoking-associated periodontal risk.

Although e-cigarettes lack the combustion products of tobacco, their aerosol is not inert with respect to salivary chemistry. In a recent comparative study, unstimulated whole salivary pH was significantly more acidic in both cigarette smokers and e-cigarette smokers than in never-smokers, with no significant difference between the two smoking groups, indicating that vaping produces an acidifying effect on saliva comparable in magnitude to that of conventional smoking [6]. The mechanism necessarily differs from that of combustible tobacco, since no combustion products are involved. Comparing 40 e-cigarette users, 39 cigarette smokers and 49 non-smokers, Cichońska and colleagues found salivary pH lower, and total protein, calcium and phosphate concentrations higher, in e-cigarette users than in non-smokers, though the difference reached statistical significance only for calcium. This is evidence that the aerosol alters salivary physicochemistry, albeit modestly, in the absence of combustion [12]. Nicotine itself is common to both products and contributes indirectly through its vasoconstrictive and secretomotor effects, which can reduce salivary flow and, by extension, buffering capacity. The clinical relevance of this shared acidification lies in its downstream consequences. A persistently lowered salivary pH favours the proliferation of acidogenic and periodontopathogenic microorganisms, weakens the mineral stability of hard tissues, and reflects a reduced capacity of saliva to neutralise the inflammatory and oxidative challenges imposed on the periodontium. That e-cigarette users display salivary acidification indistinguishable from that of cigarette smokers despite frequently exhibiting milder clinical periodontal signs reinforces a recurring theme of this review: the apparent "safety" of vaping at the level of clinical indices may conceal biochemical disturbances of the oral environment that are themselves plausible contributors to periodontal and alveolar bone changes [6].

Clinical Periodontal Parameters in E-Cigarette Users

The clinical examination remains the foundation of periodontal diagnosis, and it is here that the evidence on e-cigarettes is at once most abundant and most ambiguous. Across the available comparative studies a consistent gradient emerges: conventional cigarette smokers display the poorest periodontal indices, never-smokers the most favourable, and e-cigarette users an intermediate position that frequently fails to separate statistically from that of non-users [2,3,15].

The network meta-analysis of Pesce and colleagues quantified this gradient most explicitly. Pooling five studies comprising 512 participants, probing depth differed significantly between cigarette smokers and non-smokers (effect size 3.297; 95% CI 2.142-4.454; p = 0.001) and between cigarette smokers and e-cigarette users (effect size 2.507; 95% CI 1.351-3.663; p = 0.001). Plaque index followed the same pattern, differing significantly between cigarette smokers and non-smokers (21.34; 95% CI 13.41-29.27; p = 0.001) and between cigarette smokers and e-cigarette users (15.67; 95% CI 7.73-23.62; p = 0.001), while the comparison between e-cigarette users and non-smokers was non-significant (5.67; 95% CI -2.23 to 13.56; p = 0.160). On the surface under the cumulative ranking curve, non-smokers ranked most favourably for both probing depth and plaque index, followed by e-cigarette users, with tobacco smokers unambiguously last [2].

Bleeding on probing inverts this hierarchy. Both e-cigarette users and cigarette smokers bled significantly less than non-smokers (-16.22; 95% CI -22.85 to -9.59; p < 0.001 and -14.47; 95% CI -21.103 to -7.848; p < 0.001, respectively), such that in the cumulative ranking e-cigarette users occupied the most "favourable" position and non-smokers the least [2]. The meta-analysis of Thiem and co-workers reached a concordant conclusion by a different route, identifying a 0.33-fold lower likelihood of a positive bleeding-on-probing result in e-cigarette users compared with cigarette smokers (p = 0.03) and a 0.01-fold decreased likelihood compared with non-smokers (p < 0.01) [3]; the more recent meta-analysis of Shabil and colleagues, pooling twelve studies, similarly recorded a substantially lower mean bleeding score in e-cigarette users than in non-users (pooled mean difference -14.233; 95% CI -20.424 to -8.043) [15]. This convergence across three independent syntheses makes the finding robust, but it should not be mistaken for evidence of periodontal health. Nicotine produces acute vasoconstriction in the human microvasculature, and the association between smoking and gingival bleeding is dose-dependent with a plateau at approximately ten to twenty cigarettes daily [2]. Suppressed bleeding in a nicotine-exposed periodontium therefore represents a blunted vascular response to an inflammatory stimulus rather than its absence: a masking phenomenon of direct clinical consequence, since the clinician's most routine screening sign is the one that nicotine silences.

Findings for attachment loss are less consistent. Thiem and colleagues identified two studies reporting significantly greater attachment loss in cigarette smokers than in the other groups, while two further studies detected no

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intergroup differences [3]. In the pooled analysis of Shabil and co-workers, neither clinical attachment loss (mean difference 0.120; 95% CI -0.045 to 0.285) nor probing depth (0.056; 95% CI -0.070 to 0.182) differed significantly between e-cigarette users and non-users [15]. The scoping review of Charde and colleagues, by contrast, concluded that vaping may be associated with greater attachment loss relative to non-smokers, alongside unfavourable effects on periodontal microbial counts and on biomarkers of inflammation and oxidative stress [16]. The discrepancy reflects not only genuine variation between studies but the near-uniform statistical heterogeneity of the pooled estimates, which exceeded 85% for every parameter in the Shabil analysis [15] and renders a single summary figure difficult to interpret.

Two further syntheses weigh against a benign reading of these pooled nulls. The systematic review of Figueredo and colleagues, which weighted eight case-control studies comprising 582 participants according to their risk of bias rather than pooling them conventionally, estimated that vaping was associated with increased plaque, clinical attachment loss, probing depth and marginal bone loss together with reduced bleeding on probing, and concluded that the available results point toward increased destruction of the periodontium [25]. D'Ambrosio and co-workers, synthesising 18 studies comparing conventional cigarettes, heat-not-burn tobacco and e-cigarettes, concluded that e-cigarettes may attenuate the clinical inflammatory signs of periodontitis and, hypothetically, of peri-implantitis relative to conventional smoke, but that both alternative products, because they deliver nicotine, may nonetheless exert negative effects on periodontal and peri-implant health [26]. At population level the picture differs again: in wave 4 of the Population Assessment of Tobacco and Health Study (33,643 United States adults), combustible smoking was consistently associated with adverse oral outcomes including self-reported bone loss around the teeth, whereas exclusive use of non-cigarette products such as electronic nicotine delivery systems was not. This is an important null, though one qualified by the authors' observation that most such users were dual or poly-users and that the cross-sectional design precludes causal inference [27].

The cross-sectional study of Hasan and colleagues illustrates how exposure history shapes these comparisons. Among 144 age-matched male participants, probing depth, the proportion of sites with probing depth of at least 4 mm, and clinical attachment loss were all significantly higher in cigarette smokers than in never-smokers ($p < 0.05$), while gingival index was significantly lower in the smoking groups. Critically, the e-cigarette users had smoked conventional cigarettes for a mean of 6.04 ± 6.57 years before switching and had vaped for only 4.15 ± 2.76 years thereafter [6]. Their periodontal status thus reflects a composite and relatively brief exposure, a confounding structure that recurs throughout this literature and biases comparisons toward the null.

Immunoinflammatory Mediators and the Subclinical Inflammatory Burden

Where clinical indices converge, molecular markers diverge, and it is here that the most coherent signal of e-cigarette-associated periodontal harm is found. Destruction of the attachment apparatus is mediated not by the biofilm directly but by the host's cytokine and proteinase response to it; markers of that response therefore register pathological activity before it becomes clinically or radiographically apparent.

Thiem and colleagues documented significantly raised concentrations of interleukin-1β, interleukin-6, interferon-γ, tumour necrosis factor-α, matrix metalloproteinase-8, and matrix metalloproteinase-9 in cigarette smokers relative to non-smokers. Decisively for the present question, interleukin-1β was also significantly elevated in e-cigarette users compared with non-smokers ($p < 0.001$), establishing that vaping is not immunologically silent [3]. The investigation of Ali and co-workers extends this to a longer exposure window. Comparing cigarette smokers, individuals using electronic nicotine delivery systems for a mean of 12.5 ± 0.8 years, non-smokers with periodontitis, and periodontally healthy controls, the authors found plaque index, clinical attachment loss, probing depth, mesial and distal marginal bone loss, and the number of missing teeth to be significantly higher in all three affected groups than in controls ($p < 0.001$) yet statistically comparable among themselves. Whole-salivary interleukin-15 and interleukin-18, however, were significantly higher in both cigarette smokers and e-cigarette users than in either non-smokers with periodontitis or healthy controls ($p < 0.001$), with no difference between the two nicotine-exposed groups, and levels correlated significantly with increasing attachment loss [5]. Clinically indistinguishable periodontal status therefore coexisted with a measurably amplified immunoinflammatory burden attributable to nicotine exposure rather than to periodontitis itself.

Laboratory models of the gingival tissues themselves corroborate this picture while qualifying its magnitude. Delivering standardised puff topography to air-liquid interface cultures of human gingival epithelial cells by means of an automated smoking instrument, Ramenzoni and colleagues found that e-cigarette aerosol and conventional cigarette smoke produced comparable dose-dependent cytotoxicity and cell death, with inflammatory cytokine genes upregulated up to three-fold ($p < 0.05$) [30]. Wilson and co-workers, synthesising eighteen studies of head, neck and oral cells, reported significant aberrant

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Libyan Journal of Medical Research

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morphology, cytotoxicity, oxidative stress, reduced viability, delayed fibroblast migration and genotoxicity after e-cigarette exposure, while noting that most included studies found cigarette smoke the more toxic of the two [32]; a parallel review of DNA damage reached the same dual conclusion, documenting oxidative stress, double-strand breaks and genotoxicity in oral cells in vitro alongside raised acrolein-DNA adducts in e-cigarette users [33]. The comparison is not uniformly unfavourable to vaping: in human gingival epithelial cells, four commercially available e-cigarette aerosol condensates produced no significant loss of viability at nicotine concentrations at which cigarette smoke condensate did, with lower matrix metalloproteinase-1 and -3, cyclooxygenase-2 and inflammatory factor levels and higher type I collagen [31]. The in vitro literature thus supports harm that is real but generally smaller in magnitude than that of combustible smoke.

The same dissociation appears at shorter exposure durations and in a different biological compartment. Ali and colleagues assessed advanced glycation endproducts (highly oxidant glycotoxins whose interaction with their receptor induces oxidative stress in periodontal tissues) in the gingival crevicular fluid of young cigarette smokers and waterpipe users with a history of approximately five pack-years. Clinicoradiographic outcomes showed no significant difference between groups, yet crevicular fluid volume was significantly greater in both exposed groups ($p < 0.001$) and glycation endproduct levels were nearly three times higher than in never-smokers, which the authors interpreted as signalling an ongoing yet latent inflammatory process [4]. Although this cohort examined combustible and waterpipe exposure rather than vaping, the methodological lesson transfers directly: a null clinical finding in a young cohort with brief exposure is weak evidence of biological safety.

The Effect of E-Cigarettes on Alveolar and Marginal Bone Loss

Alveolar bone loss is the defining irreversible sequela of periodontitis and the outcome against which any claim of relative safety must ultimately be tested. The evidence derives from two largely separate bodies of work, radiographic observation in human users and cellular investigation of bone metabolism, which point in somewhat different directions.

Radiographic evidence. Marginal bone loss, conventionally measured as the distance from a point 2 mm below the cemento-enamel junction or implant platform to the crestal alveolar bone, was assessed in five of the studies synthesised by Thiem and colleagues. Cigarette smokers consistently demonstrated significantly greater mesial and distal bone loss than non-smokers ($p < 0.01$ and $p < 0.05$ across studies), and significantly greater loss than e-cigarette users. For e-cigarette users compared with non-smokers, however, the included literature was frankly inconsistent: two studies found no difference, while two others reported significantly increased bone loss, one yielding an odds ratio of 1.67 (95% CI 1.06-2.63) and the other reaching significance at $p < 0.01$ [3]. The pooled estimate of Shabil and colleagues found no significant difference in marginal bone loss between e-cigarette users and non-users (mean difference -0.052; 95% CI -0.168 to 0.064), though with substantial heterogeneity ($I^2 = 88\%$) and an explicit caveat that the available research is limited and that longitudinal study is required [15]. The earlier review of Figueredo and colleagues, using risk-of-bias weighting in place of conventional pooling, reached the opposite estimate and reported increased marginal bone loss among vapers [25]. Individual cohorts point the same way: Ibraheem and colleagues recorded mesial and distal marginal bone loss of 4.4 mm in ENDS users against 1.5 and 1.4 mm in non-smokers ($p < 0.01$), the highest values of any group in that study, cigarette smokers included [17]. Set against these pooled nulls, the cohort of Ali and co-workers, whose e-cigarette users had vaped for more than twelve years, recorded mesial and distal marginal bone loss significantly greater than in healthy controls and statistically indistinguishable from that of cigarette smokers [5]. Exposure duration thus appears a decisive and under-appreciated modifier: analyses dominated by short vaping histories report no association, whereas the one cohort with a decade or more of exposure reports bone loss equivalent to that of smokers.

The RANKL-osteoprotegerin axis. Alveolar bone homeostasis is governed principally by the receptor activator of nuclear factor-κB (RANK), its ligand (RANKL), and the soluble decoy receptor osteoprotegerin; RANKL drives osteoclast differentiation and activation, osteoprotegerin sequesters it, and the RANKL/osteoprotegerin ratio therefore determines the net direction of bone remodelling [18]. Ibraheem and colleagues measured both mediators in the gingival crevicular fluid of 120 men, 30 each of cigarette smokers, waterpipe users, ENDS users and non-smokers. Crevicular RANKL was significantly higher in all three exposed groups than in non-smokers (ENDS users 11.5 ± 8.4 versus 3.5 ± 0.7 pg/mL; $p < 0.01$), with no difference between the exposed groups, and plaque index, probing depth, attachment loss and marginal bone loss were likewise raised. Osteoprotegerin, however, rose in parallel rather than falling (77.5 ± 3.4 versus 21.5 ± 10.7 pg/mL; $p < 0.01$), and neither mediator correlated with attachment loss. The study therefore establishes heightened bone-remodelling activity in nicotine-product users but not a shift in the RANKL/osteoprotegerin balance towards resorption, and every ENDS user in it was a former smoker

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who had quit some six years earlier [17]. More recently, the prospective observational cohort of Teodorescu and co-workers followed 236 participants (72 non-smokers, 83 heated-tobacco users and 81 e-cigarette users) before and three months after non-surgical periodontal therapy. At baseline, both product-user groups showed significantly greater probing depth ($p = 0.005$) and clinical attachment loss ($p = 0.001$) than non-smokers, and salivary RANKL was significantly higher, while osteoprotegerin did not differ. All parameters improved after scaling and root planing, yet at three months both groups retained higher probing depth, attachment loss, and salivary RANKL than non-smokers ($p < 0.001$), and the RANKL/osteoprotegerin ratio remained significantly altered specifically in the e-cigarette group [18]. That a disturbed bone-remodelling ratio persisted in vapers after successful mechanical therapy is among the most direct clinical indications that e-cigarette exposure maintains an osteoclastogenic bias within the periodontium.

Cellular mechanisms. Laboratory work provides a plausible mechanistic basis for these observations, and implicates more than nicotine alone. Human bone cells express nicotinic receptors, and nicotine at high concentrations reduces the viability and impairs the function of both osteoblasts and osteoclasts; aldehydes and flavouring chemicals likewise diminish osteoblast viability and the capacity to form bone, with the caveat that much of this work has used immortalised cell lines such as MG-63 or Saos-2 rather than primary human cells [20]. The most pertinent evidence for this review comes from Nicholson and colleagues, who exposed human primary osteoblasts to e-cigarette vapour condensate generated from second- and third-generation devices. Twenty-four hours of exposure reduced osteoblast viability in a dose-dependent manner, with condensate from the more powerful third-generation device proving the more toxic. The effect was mediated only in part by nicotine, since nicotine-free condensate of equivalent concentration was significantly less toxic, and was rescued by co-treatment with the antioxidant N-acetyl-L-cysteine, implicating reactive species generated during device operation. Most importantly for the bone-resorption pathway, doses that were themselves non-toxic significantly blunted osteoblast osteoprotegerin secretion within 24 hours, an effect sustained for up to seven days [19]. Reduced osteoprotegerin output at sub-cytotoxic exposure levels offers a plausible cellular correlate of the disturbed salivary RANKL/osteoprotegerin ratio that persists in e-cigarette users after therapy [18], and indicates that bone metabolism can be perturbed at concentrations producing no overt cell death.

Reactive oxygen species appear central to this mechanism. Vaporisation of e-liquids generates substantial quantities of short-lived, highly reactive free radicals, in excess of 10^{13} molecules per puff, and atomisation of flavouring compounds such as linalool, dipentene, and citral independently generates free radicals. Since reactive oxygen species both activate osteoclasts and stimulate RANKL expression in human osteoblast-like cells, flavour-derived radicals constitute a nicotine-independent route to bone resorption [20]. Consistent with this, the only in vivo investigation of e-cigarette vapour on bone architecture to date reported microfractures in the femora of exposed mice after three hours of daily exposure for up to six months, with the effect occurring in response to aerosols containing propylene glycol and vegetable glycerin alone, that is, in the absence of both nicotine and flavourings [20]. This observation is of considerable conceptual importance: it indicates that the humectant carriers assumed to be inert excipients may themselves be skeletally active, and that nicotine-free e-liquids cannot be presumed safe for bone. The same principle has since been demonstrated in oral tissue: aerosols generated from a nicotine-free, unflavoured propylene glycol/glycerin base alone induced significantly greater cytotoxicity and DNA damage in gingiva-derived oral keratinocytes than the corresponding non-aerosolised liquid, identifying the aerosolisation process itself, rather than nicotine or flavourings, as the critical determinant of injury [34].

E-Cigarettes and the Subgingival Microbiome

Because alveolar bone loss is ultimately driven by the host response to a dysbiotic subgingival biofilm, any agent that reshapes that community has an indirect route to bone. Chaffee and colleagues noted that e-cigarette aerosol exposure appears to induce adverse changes in the oral microbiome that are distinct from those observed with cigarette smoking [1], and subsequent sequencing work has substantiated this.

Thomas and co-workers characterised the subgingival plaque microbiome of e-cigarette users, conventional smokers, and non-smokers, and concluded that the vaper's community is a unique amalgamation sharing features with both comparison groups while being enriched in periodontal pathogens in a distinctly dysbiotic manner. Several taxa showed habit-specific distributions: Actinomyces species, known hosts for Saccharibacteria, were most abundant in e-cigarette users and relatively depleted in both smokers and non-smokers, suggesting that vaping shifts the balance between Saccharibacteria and their bacterial hosts in a direction favouring dysbiosis. Pro-inflammatory mediators including interferon-γ, interleukin-1β, and tumour necrosis factor-α, all elevated in chronic periodontitis, have been reported as raised in e-cigarette users relative to non-smokers. The authors' formulation is precise and worth preserving: e-cigarette use may promote a healthier subgingival microbiome than that of conventional smokers, but not a healthier one than that

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associated with never having smoked at all [21]. This framing captures the broader pattern of the present review with unusual economy.

The mechanisms proposed for this shift are consistent with the aerosol chemistry outlined earlier. The oral cavity and its microbial community are the first tissues exposed to the aerosol [21], and the salivary acidification documented in e-cigarette users [12] establishes an environment favouring acidogenic and periodontopathogenic organisms. The resulting dysbiosis has been advanced as a principal mediator of e-cigarette-associated damage to the oral soft tissues [22], and by extension of the inflammatory bone resorption that follows sustained dysbiotic challenge; reviews of e-cigarette aerosol exposure have correspondingly identified altered periodontal microflora, raised inflammatory and oxidative biomarkers, and increased susceptibility to periodontal disease among the oral consequences of vaping [23,24].

Peri-Implant Bone Loss

Peri-implant tissues lack the periodontal ligament and its vascular and reparative capacity, and crestal bone around implants is therefore an informative, if more vulnerable, analogue of the alveolar response. The umbrella review of Fathi and colleagues pooled five systematic reviews and meta-analyses and reported acceptable, high-quality evidence that, relative to combustible tobacco, e-cigarettes may reduce or leave unchanged the clinical inflammatory signs of periodontitis and peri-implantitis: bleeding on probing, probing depth, peri-implant bone loss and treatment response. The authors nonetheless concluded that e-cigarettes deliver nicotine capable of harming periodontal and implant health, and identified vaping as a potential risk factor for impaired healing and for implant therapy outcomes [7]. The pattern mirrors the dentate periodontium precisely: an apparent clinical advantage over smoking, no demonstrated equivalence to non-use, and an intact mechanism of harm.

Response to Periodontal and Implant Therapy

A distinct and clinically consequential question is whether e-cigarette use compromises the response to treatment. For combustible tobacco the answer is established: smoking perturbs the host response to periodontal pathogens, alters the subgingival microbial communities and compromises the healing potential of the tissues, and is associated with inferior outcomes of both periodontal and implant therapy [29]. For vaping the evidence is newer, but points the same way. In a retrospective study of 220 patients with periodontitis treated by professional mechanical plaque removal, Shah and colleagues found that e-cigarette users responded significantly less favourably than non-smokers, showing a greater need for surgery, more sextants and sites with probing depth of at least 5 mm, and greater mean probing depth. Their response did not differ significantly from that of current smokers, and former smokers responded significantly better than they did [28]. Read alongside the persistence of a disturbed RANKL/osteoprotegerin ratio in vapers three months after scaling and root planing [18], this suggests that e-cigarette use attenuates the benefit of non-surgical therapy to a degree approaching that of continued smoking, a finding of more immediate practical relevance to the clinician than the contested cross-sectional comparisons of baseline indices.

Limitations of the Current Evidence

Four limitations recur consistently enough across this literature to constrain every conclusion drawn from it.

Study design is the foremost. No randomised controlled trial has examined the periodontal effects of e-cigarettes, and the absence of such evidence is explicitly cited by two of the major syntheses as precluding a definitive conclusion [3,7]. The field is dominated by cross-sectional investigations, which cannot establish temporality in a disease whose natural history unfolds over decades.

Exposure duration is the second. Vaping histories in most cohorts are short relative to the latency of periodontal bone loss, and the daily frequency of nicotine inhalation among e-cigarette users has been reported as roughly half that of conventional smokers in the same analyses [2]. Current null findings may therefore reflect insufficient follow-up rather than genuine absence of effect; the interpretation is reinforced by the contrast between short-exposure cohorts reporting no bone loss [3,15] and the long-exposure cohort reporting loss equivalent to smokers [5].

Confounding by prior or concurrent combustible tobacco use is the third and most intractable. E-cigarette users are frequently former or current smokers [1], and in the cohort of Hasan and colleagues the mean duration of prior cigarette smoking exceeded that of subsequent vaping [6]. Some studies excluded e-cigarette users with a smoking history while others did not report it at all, a divergence acknowledged as capable of influencing pooled results [2].

Product heterogeneity is the fourth. Device generation, coil power and temperature, puffing topography, humectant ratio, nicotine concentration, and flavour composition all modulate aerosol chemistry [10], and nicotine content is frequently mislabelled [9]. That third-generation condensate is more cytotoxic to osteoblasts than second-generation condensate [19] confirms device class as a biologically meaningful variable, yet it is rarely reported clinically. Pooling such exposures under the single label "e-cigarette use" imposes heterogeneity that no statistical adjustment can resolve, as the uniformly high I^2 values of the available meta-analyses attest [15]. To this must be added the reliance of mechanistic work on cell lines and short-term models [20] and the difficulty of translating in vitro doses into clinically relevant exposures [1].

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Clinical Implications and Future Directions

E-cigarette use must be recorded explicitly within the tobacco history, since patients frequently do not report vaping when asked about smoking [1]. Suppressed bleeding on probing in a vaping patient should be read as a masked rather than an absent inflammatory response, with diagnosis resting correspondingly more on probing depth, attachment level, and radiographic bone assessment. Because e-cigarette users respond less favourably to non-surgical therapy than non-smokers and comparably to current smokers [28], re-evaluation intervals and maintenance frequency are better planned on the assumption of a smoker-like than a non-smoker-like response. Patients deserve a balanced account: that e-cigarettes deliver markedly lower concentrations of combustion toxicants than cigarettes and rank more favourably than smoking on most periodontal indices, but that they are not equivalent to non-use, that nicotine, carbonyls, flavour-derived radicals, and metals continue to reach the periodontium, and that long-term consequences remain unestablished. A smoker motivated to attempt cessation through vaping should not be discouraged, but should be offered the full range of evidence-based cessation options; non-smokers, and young people in particular, should be advised against initiating use [1].

The research priorities follow directly. Prospective longitudinal cohorts of exclusive e-cigarette users with no prior combustible exposure, followed long enough for radiographic bone change to manifest, represent the single most valuable missing design. Such studies should characterise device generation, power, and e-liquid composition rather than treating vaping as a uniform exposure; should pair clinical and radiographic parameters with molecular endpoints, the RANKL/osteoprotegerin ratio in particular, given the discordance demonstrated between these levels; and should test whether the altered bone-remodelling profile that persists after therapy in e-cigarette users [18] translates into poorer long-term treatment outcomes. Mechanistic work using primary human osteoblasts, osteoclasts, and periodontal ligament cells at physiologically relevant aerosol concentrations is needed to apportion responsibility between nicotine, humectant degradation products, and flavourings, and to determine whether nicotine-free formulations offer any genuine skeletal advantage.

Conclusion

The evidence assembled here supports a position that is neither reassuring nor alarmist. Measured by conventional clinical indices, e-cigarette users fall between cigarette smokers and non-smokers and are frequently indistinguishable from the latter, while bleeding on probing is paradoxically lowest of all three groups owing to nicotine-mediated vasoconstriction. Pooled analyses show no significant difference in marginal bone loss between e-cigarette users and non-users, but those estimates rest on cross-sectional studies with short vaping histories, pervasive confounding by prior smoking, and heterogeneity exceeding 85%.

Against this apparent clinical equivalence stands a consistent body of molecular and cellular evidence. Salivary and crevicular mediators, among them interleukin-1β, interleukin-15 and interleukin-18, are elevated in e-cigarette users to levels comparable with those of cigarette smokers even when clinical parameters are not. Crevicular and salivary RANKL is significantly raised in vapers; osteoprotegerin rises alongside it in crevicular fluid, so the direction of the balance is not settled there, but the salivary RANKL/osteoprotegerin ratio remains disturbed after non-surgical therapy, and e-cigarette vapour condensate suppresses osteoblast osteoprotegerin secretion at sub-cytotoxic doses. Their subgingival microbiome is uniquely dysbiotic, healthier than that of smokers but not than that of never-smokers, and salivary pH is acidified to a degree indistinguishable from that produced by combustible tobacco. Reactive species and humectant degradation products provide nicotine-independent routes to bone resorption: both the only in vivo study of vapour on bone architecture and the aerosolised humectant base tested on oral keratinocytes caused damage without nicotine or flavourings. E-cigarette users also respond less favourably to non-surgical periodontal therapy than non-smokers, and no better than current smokers.

E-cigarettes are therefore plausibly less injurious to the periodontium than combustible cigarettes, but they are not periodontally inert, and the present clinical evidence is not of a design capable of excluding an effect on alveolar bone. The discordance between quiescent clinical signs and active molecular markers is the central finding of this literature, and it argues that the apparent safety of vaping as judged at the chairside may represent a latent process rather than an absent one. Until prospective longitudinal data on exclusive, long-duration users become available, the prudent clinical position is to regard vaping as a modifiable periodontal risk factor of uncertain magnitude rather than a safe alternative to smoking.

Declarations

Author Contributions. Samer Mahroos Mkhailef Al-Shammari: conceptualisation, literature search and screening, data extraction, writing — original draft. Samer Mahroos Mkhailef Al-Shammari: literature screening, data extraction, writing — review and editing. Ahmed S. Mikael: interpretation, writing — review and editing. Ali Çekici: supervision, interpretation, writing — review and editing. All authors have read and agreed to the published version of the manuscript.

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