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# The Role of HIF-1α in Gingival Hypoxia Induced by Smoking: A Scoping Review

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## Abstract

**Background:** Smoking is a well-established risk factor for periodontal disease, primarily due to its role in inducing hypoxia within gingival tissues. Hypoxia, defined as reduced oxygen supply, disrupts normal tissue homeostasis, exacerbates inflammation, and impairs healing. Chronic exposure to smoking-related toxins leads to microvascular dysfunction, reduced oxygen delivery, and an upregulation of hypoxia-inducible factor-1 alpha (HIF-1α). This molecular adaptation is associated with increased apoptosis, impaired angiogenesis, and delayed periodontal tissue regeneration, all of which contribute to disease progression. Understanding the role of hypoxia in smoking-related periodontal destruction is crucial for developing targeted therapeutic interventions.

**Methods:** This scoping review followed the Joanna Briggs Institute (JBI) protocol and PRISMA-ScR guidelines. A comprehensive search was performed in PubMed, EBSCOhost, Scopus, ScienceDirect, Google Scholar, and Web of Science using Boolean operators related to hypoxia, gingival health, and smoking. The Population-Concept-Context (PCC) framework guided the eligibility criteria, including observational and experimental studies that compared smokers and non-smokers. Extracted data included study design, sample size, periodontal parameters, and molecular findings.

**Results:** Out of 265 screened articles, 11 met the inclusion criteria. These included experimental, cross-sectional, cohort, and randomized controlled trial (RCT) studies involving 473 participants. Results demonstrated that smokers exhibited significantly higher levels of HIF-1α, VEGF, and inflammatory markers in periodontal tissues compared to non-smokers. Smoking-induced hypoxia disrupted angiogenesis, increased osteoclastogenesis, and altered vascularization, contributing to delayed healing and periodontal tissue degradation. Some studies reported no synergistic effect between smoking and periodontitis on HIF-1α expression; however, smoking independently impacted hypoxia-related pathways.

**Conclusion and Implications:** Smoking significantly contributes to periodontal disease by inducing hypoxia, disrupting angiogenic and inflammatory pathways, and impairing tissue regeneration. The upregulation of HIF-1α plays a central role in these mechanisms. Given these findings, integrating smoking cessation into periodontal management is essential. Future research should explore targeted interventions modulating HIF-1α activity to mitigate smoking-induced periodontal damage and improve treatment outcomes.

**Keywords:** Smoking, Hypoxia-Inducible Factor 1, gingiva, hypoxia, inflammation

## Introduction

Smoking is a major risk factor contributing to various health disorders, including periodontal disease. In the context of periodontal disease, smoking is known to elevate the risk of inflammation and tissue damage in the gingiva, one of the mechanisms being hypoxia. Hypoxia, a condition characterized by oxygen deficiency in tissues, plays a crucial role in the development and progression of periodontal disease by disrupting the healing process and triggering further inflammation. Additionally, smoking interacts with inflammatory factors and pathogenic microorganisms in the oral cavity, exacerbating the condition of periodontal tissues. Hypoxia occurs in individuals who smoke, including in the gingival tissue, and can worsen the condition of the periodontal tissues. Smoking interferes with the oxygen supply required by the gingival tissues, leading to impaired tissue function and delayed healing processes.[1–3]

Smoking has a significant impact on periodontal health by causing microvascular dysfunction and hypoxia in the gingival tissue. Studies indicate that smokers experience a reduction in blood flow to the gingiva, an increase in vascular density with smaller capillary diameters, and lower perfusion compared to non-smokers. Moreover, chronic smoking is associated with elevated levels of hypoxia-inducible factors and the expression of hypoxia-inducible factor 1α (HIF-1α) in gingival sulcus fluid. In smokers with periodontitis, there is an increase in inflammatory cell counts, apoptosis, and hypoxia markers when compared to healthy individuals. Although smokers tend to exhibit lower levels of gingival bleeding, they harbor more periodontal pathogens and demonstrate distinct host responses in experimental gingivitis conditions. Smoking also impacts the gingival epithelial structure, promoting changes such as dysplasia and reducing the inflammatory response. Overall, these microvascular and cellular changes induced by smoking contribute to an increased risk and severity of periodontal disease in smokers.[2,4–6]

A study by Bejna Bozyel et al. (2024) demonstrated that smoking and periodontitis induce comparable hypoxic effects on periodontal tissue, as evidenced by increased levels of HIF-1α, HIF-3α, and VEGF in gingival sulcus fluid. Both conditions lead to a reduction in fibroblast numbers and an increase in inflammatory cell counts within the periodontal tissue. Periodontitis lesions exhibit higher expression of HIF-1α and VEGF compared to healthy gingiva, indicating the activation of the HIF-1α pathway in advanced periodontal disease. Chronic smokers experience increased microvascular density in the gingiva with higher vascular density and smaller capillary diameters, which affects gingival perfusion. Furthermore, smoking suppresses gingival inflammation and angiogenesis in periodontal disease, largely due to local immunosuppression and oxidative stress. Although clinically appearing normal, the gingival tissue of smokers undergoes epithelial changes resembling early dysplasia and a reduced inflammatory response. [2,4–7]

Based on various studies, it is clear that smoking has a significant impact on periodontal health, particularly through the hypoxic mechanism that exacerbates gingival tissue conditions. Smoking-induced hypoxia contributes to microvascular dysfunction, increased oxidative stress, and impaired inflammatory responses that affect the progression of periodontal disease. Furthermore, altered vascularization patterns and increased expression of hypoxia-related factors further strengthen the role of smoking in worsening periodontal conditions. Therefore, a comprehensive understanding of the relationship between smoking and gingival hypoxia is crucial for developing more effective prevention and treatment strategies for periodontal disease in smokers. This scoping review aims to explore the current evidence regarding the impact of smoking on gingival hypoxia and compare it with non-smokers to provide a more comprehensive insight into periodontal health management.

## Material and Method

A scoping review was performed according to the protocol by the Joanna Briggs Institute[8] and the Preferred Reporting Items for Scoping Review (PRISMA-ScR). Article searches and analyses were conducted from January to February 2025. Six databases: PubMed, EBSCOhost, Scopus, ScienceDirect, Google Scholar, and Web of Science were searched for keywords and Boolean Operators as follows : (hypoxia inducible factor 1-alpha) AND (gingiva OR periodontal) AND (smokers OR smoker OR smoking OR cigarette OR cigarettes OR nicotine OR tobacco OR non smoker).

PCC (population, concept, context) guidelines were used to determine eligible articles. Population (P): smokers and non-smokers, concept (C) : The impact of smoking on gingival hypoxia conditions, a comparison of hypoxic conditions in smokers versus non-smokers and biological mechanisms associated with the effects of smoking on gingival blood circulation and periodontal tissue assessed by clinical and laboratory evaluation, and context (C) : smokers and non- smokers both female and male aged more than 18 years and above in all studies conducted in various countries contained in the publication. The inclusion criteria were articles with a study population of smokers and non-smokers, and articles that discussed. The impact of smoking on gingival hypoxia conditions, articles with observational (cross-sectional, case-control study) and experimental research designs, full-text articles, articles in English, and articles with year published since the first publication of literature discussing the relationship of smoking on gingival hypoxia conditions. Exclusion criteria included duplicate articles, scoping review, and narrative review.

All of the articles were transferred and screened, and duplicates were eliminated using Zotero software. Articles were screened by title and abstract, and potential articles were selected. Further selection was made after reading the full text of potential articles according to the inclusion and exclusion criteria. Articles that met the inclusion criteria were included in this study and then data extraction was carried out. The data information extracted is the author, year, title, research design, sample size, sample age, sample criteria, parameters, and study results.

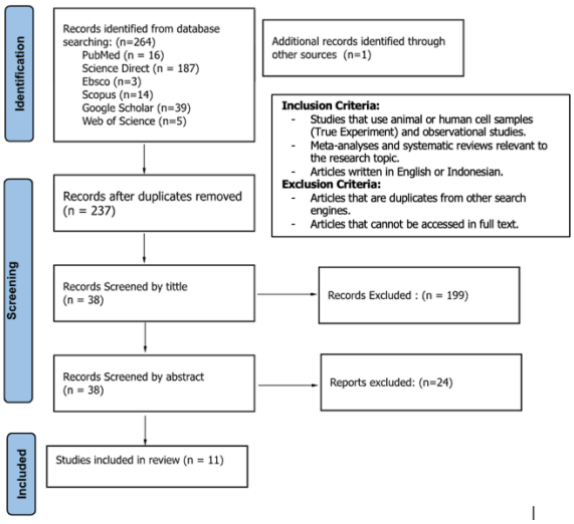


**Figure 1.** PRISMA-ScR

## Results

A total of 265 articles were identified from the databases, and 28 were duplicates and removed. The titles and abstracts of 237 articles were assessed, and 199 were excluded. The remaining 38 underwent full-text examination, and then 11 studies were finally included in the review.

### Study Characteristics

The reviewed articles discuss the effects of smoking on periodontal health and various related factors, published between 2003 and 2025. The research designs utilized in these studies include experimental, cross-sectional, cohort, and randomized controlled trials (RCTs). Among the studies, 4 were experimental, 2 were cross-sectional, 2 were cohort studies, 2 were RCT, and 1 was a non-RCT. The total number of participants across all studies is 473, with samples consisting of both smokers and non-smokers. The smallest sample size in the selected studies was 16 participants, and the largest sample size was 88 participants. Participants included in the studies were those with healthy gingiva, gingivitis, and periodontitis, and those undergoing orthodontic treatment or dental implant procedures. The smokers involved had an average smoking history ranging from 10 to 20 cigarettes per day, with an average duration of smoking exposure between 5 and 20 years.

The studies focused on a variety of periodontal conditions, from gingival inflammation to advanced periodontitis and implant osseointegration, examining the molecular and clinical effects of smoking on periodontal health. Markers such as HIF-1α, MMPs, COX-2, VEGF, and PGE2 were frequently measured, highlighting the inflammatory and destructive effects of smoking on periodontal tissues.

The reviewed studies consistently demonstrate that smoking significantly impacts HIF-1α expression in periodontal tissues, particularly in periodontitis. Smoking elevates HIF-1α levels, as seen in studies like those by Ullrich et al. (2020), Karatas et al. (2019), and Kirschneck et al. (2017), where nicotine exposure enhanced osteoclastogenesis, root resorption, and inflammatory responses, suggesting the induction of hypoxic conditions. Michaud et al. (2003) further highlight smoking's effect on angiogenesis and inflammation, with smoking elevating HIF-1α and suppressing markers like VEGF, impairing tissue repair and vascular responses. In bone healing, Sayardoust (2017) observed higher HIF-1α levels and increased inflammatory markers in smokers, leading to impaired osseointegration. Despite this, Bejna Bozyel et al. (2025) and Taş et al. (2024) found no synergistic effect of smoking and periodontitis on HIF-1α expression beyond each factor's individual impact. However, smoking still contributes to delayed healing and altered gene expression in osseointegration, as evidenced by Sayardoust et al. (2018). Additionally, Kim et al. (2012) revealed that nicotine and lipopolysaccharide (LPS) synergistically upregulated HIF-1α, COX-2, MMPs, and other inflammatory markers, exacerbating periodontal tissue degradation. Overall, smoking elevates HIF-1α and promotes inflammation, osteoclastogenesis, and tissue degradation, exacerbating periodontal disease and impeding healing processes.

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| No | Article identity (author, year,tittle) | Origin | Purpose | Research Design | Target Population/ Sample size and Statistical methods | Conceptual/ Theoretical Framework | Framework proposed/ Result/finding | Limitation | Summary points/ Conclusion |
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| 1. | Bozyel et al, 2025, "Hypoxic Responses in Periodontal Tissues: Influence of Smoking and Periodontitis" | Turkey | Investigate hypoxic changes in periodontal tissues caused by smoking and periodontitis. Analyze the levels of hypoxia-inducible factors (HIF-1α, HIF-2α, HIF-3α) and Vascular Endothelial Growth Factor (VEGF) in Gingival Crevicular Fluid (GCF). | Cross-sectional study, Data Collection Method: Biomarker measurement using Enzyme-Linked Immunosorbent Assay (ELISA). | Total participants: 88 individuals (22 per group).Statistical Analysis:One-way ANOVA for between-group comparisons.Kruskal-Wallis test for non-normally distributed data.Spearman's correlation analysis to examine relationships between variables. | Hypoxia in periodontal tissues is influenced by Smoking: Causes vasoconstriction, local hypoxia, and reduced inflammatory response. Periodontitis: Increases the expression of HIFs, which regulate cellular responses to oxygen deficiency. VEGF: Plays a role in angiogenesis, increasing oxygen supply to tissues. | HIF-1α, HIF-3α, and VEGF levels were significantly elevated in HS, P, and PS groups compared to H ($p < 0.05$). HIF-2α levels were significantly higher in HS and P groups compared to H ($p < 0.05$). Significant correlations were observed between hypoxia biomarkers and periodontitis and smoking, but no synergistic effect was found when both were present. Bleeding on probing (BOP) was lower in the PS group than in the P group, suggesting that smoking suppresses the clinical inflammatory response. | Relatively small sample size limits generalizability.Did not evaluate long-term effects of hypoxic changes in periodontitis.Further research is needed to understand the regulatory mechanisms of hypoxia in periodontitis. | Smoking and periodontitis independently induce hypoxia in periodontal tissues, as evidenced by elevated HIF-1α, HIF-2α, HIF-3α, and VEGF levels. Smoking alone can trigger hypoxic effects similar to those seen in periodontitis. When smoking and periodontitis coexist, their hypoxic effects are not synergistic, indicating different regulatory mechanisms. HIF-1α has potential as a therapeutic target for periodontitis management. |
| 2. | Karatas et al, 2019, "Evaluation of apoptosis and hypoxia-related factors in gingival tissues of smoker and non-smoker periodontitis patients" | Turkey | To evaluate apoptotic and hypoxic tissue alterations in smoker and non-smoker periodontitis patients | Cross-sectional study, with histological and immunohistochemical analysis | Sample Size: 60 participants (4 groups of 15). Statistical Methods: One-way ANOVA with Tukey's post hoc test, Chi-square test, and ANCOVA with Bonferroni correction. Significance set at $p < 0.05$. | Study based on hypoxia and apoptosis mechanisms in gingival tissue. Examined markers: HIF-1α, VEGF, MMP-8, TIMP-1, Bax, Bcl-2, Caspase-3 | Smoking and periodontitis decreased fibroblast counts while increasing inflammatory cell counts. - Higher expression of HIF-1α and Bax in smokers, indicating increased hypoxia and apoptosis. - No significant differences in MMP-8 and TIMP-1 expressions among groups | No biochemical validation beyond immunohistochemistry. - Limited sample size (n=60). - No longitudinal analysis to determine progression over time. | Smoking and periodontitis both increase inflammation and apoptosis in gingival tissues. - Hypoxia markers (HIF-1α) and apoptotic markers (Bax, Bcl-2) are significantly altered in smokers. - Further research is needed with molecular techniques and larger sample sizes. |
| 3. | Taş et al., 2024, "The effect of smoking on clinical and biochemical early healing outcomes of coronally advanced flap with connective tissue graft: Prospective cohort study" | Turkey & USA | To evaluate the impact of smoking on early (≤3 months) clinical and biochemical healing outcomes after root coverage surgery | Prospective cohort study | Sample Size: 36 patients (18 smokers, 18 non-smokers) with RT1 gingival recession. Statistical Methods: Student's t-test, Mann-Whitney U-test, Chi-square test, ANCOVA, repeated measures ANOVA, Bonferroni correction, and Spearman correlation. Significance set at $p < 0.05$. | Study based on angiogenesis and wound healing. Examined biomarkers: VEGF-A, HIF-1α, 8-OHdG, ANG in gingival crevicular fluid and wound fluid | No significant differences in clinical or molecular healing outcomes between smokers and non-smokers at 3 months. - Strong correlation among angiogenesis-related biomarkers (VEGF-A, HIF-1α, ANG) at 7 and 28 days post-surgery. - Root coverage success: Smokers 83%, Non-smokers 91% ($p = 0.069$). | Moderate smokers only (10-20 cigarettes/day), excluding heavy smokers. - Limited timeframe (≤3 months), no long-term data. - No molecular analysis of additional key inflammatory biomarkers. | Smoking does not significantly affect early healing outcomes of root coverage surgery. - Key angiogenesis markers peak at 7 days and return to baseline at 28 days. - Longer-term follow-up may reveal delayed smoking-related effects. |
| 4. | Du et al., 2019, "MicroRNA expression profiling of nicotine-treated human periodontal ligament cells" | China & South Korea | To investigate the microRNA (miRNA) expression profile in human periodontal ligament cells (PDLCs) exposed to nicotine and identify potential mechanisms in nicotine-induced periodontitis | Experimental in vitro study using cell culture and miRNA microarray analysis | Sample Size: Human PDLCs isolated from healthy volunteers. Statistical Methods: t-test for differentially expressed miRNAs ($p < 0.05$), hierarchical clustering, Gene Ontology (GO) analysis, and KEGG pathway analysis for functional and pathway enrichment | Study based on nicotine-induced molecular changes in periodontal cells, focusing on miRNA expression and signaling pathways | Nicotine inhibited PDLC proliferation in a time- and dose-dependent manner - 30 miRNAs were differentially expressed (16 upregulated, 14 downregulated) - Key affected pathways: Toll-like receptor signaling, HIF-1 signaling, TGF-beta pathway, and nicotine addiction pathway - qRT-PCR validated miRNA expression patterns | In vitro study may not fully represent in vivo periodontal conditions - Limited number of miRNAs validated by qRT-PCR - Lack of functional assays to confirm miRNA roles in periodontal disease | Nicotine alters miRNA expression in PDLCs, potentially contributing to periodontitis - Toll-like receptor and HIF-1 pathways may play key roles in nicotine-induced periodontal damage - Future studies needed to confirm functional roles of specific miRNAs in periodontal disease progression |

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| 5. | Sayardoust et al., 2017, "Clinical, radiological, and gene expression analyses in smokers and non-smokers, Part 2: RCT on the late healing phase of osseointegration" | Sweden | To investigate the effects of smoking on late-phase osseointegration using clinical, radiological, and gene expression analyses | Randomized Controlled Trial (RCT) | Sample Size: 32 patients (16 smokers, 16 non-smokers), each receiving 3 implant types (machined, oxidized, laser-modified). Statistical Methods: Chi-square test, ANOVA, Kolmogorov-Smirnov test, Kruskal-Wallis test, Mann-Whitney U test, and multivariate regression analysis ($p < 0.05$) | Study based on molecular and clinical differences in osseointegration between smokers and non-smokers, focusing on gene expression, marginal bone loss (MBL), and implant stability | No difference in implant survival at 90 days - Smokers had greater marginal bone loss (MBL), especially around machined implants - Higher IL-6 (inflammatory marker) and lower osteocalcin (bone formation marker) in smokers - HIF-1α expression was lower in smokers, particularly in the maxilla, and correlated with greater MBL - Higher implant stability quotient (ISQ) in smokers at 90 days | Short-term study (90 days), no long-term outcomes - Limited to patients with a history of periodontitis - No molecular-level protein validation beyond gene expression | Smoking increases inflammation and bone loss around implants - HIF-1α and IL-6 are key predictors of bone loss - Machined implants show the greatest MBL in smokers - Further studies needed on long-term effects |
| 6. | Ullrich et al., 2020, "The role of HIF-1α in nicotine-induced root and bone resorption during orthodontic tooth movement" | Germany | To investigate the role of HIF-1α in nicotine-induced root resorption and bone loss during orthodontic tooth movement (OTM) | Animal experimental (in vivo) & cell culture (in vitro) | Sample Size: 20 male Fischer-344 rats (10 nicotine, 10 control). Statistical Methods: Student's t-test, ANOVA, Games-Howell post hoc test ($p \leq 0.05$) | Study based on nicotine's effect on osteoclastogenesis and periodontal bone loss, focusing on HIF-1α, RANK-L, and OPG | Nicotine increased root resorption and osteoclastogenesis during OTM - Nicotine did not significantly upregulate HIF-1α expression, which was primarily influenced by mechanical force and hypoxia - Bone volume and trabecular thickness were reduced due to OTM, independent of nicotine | Short-term study (14 days), no long-term effects analyzed - Limited nicotine dose range used - No evaluation of systemic effects of nicotine | Nicotine accelerates root resorption and bone loss in OTM, but not through HIF-1α stabilization - HIF-1α expression was influenced by hypoxia and mechanical force, but not nicotine - Nicotine likely affects bone resorption through alternative mechanisms |
| 7. | Sayardoust, 2017, "The effect of tobacco exposure on bone healing and the osseointegration of dental implants" | Sweden | To analyze the clinical and molecular effects of smoking on osseointegration and bone healing around dental implants | Retrospective cohort & prospective controlled studies | Sample Size: Study I: 5-year retrospective (smokers & non-smokers); Study II-IV: 16 smokers, 16 non-smokers receiving machined, oxidized, and laser-modified implants. Statistical Methods: Chi-square test, ANOVA, Kruskal-Wallis test, Mann-Whitney U test, multivariate regression ($p < 0.05$) | Study based on the impact of smoking on inflammation, osseointegration, and implant stability, focusing on IL-6, HIF-1α, osteocalcin, and RANKL | Higher marginal bone loss (MBL) and implant failure in smokers, especially with machined implants - Smokers showed increased IL-6 and decreased osteocalcin expression - Baseline HIF-1α expression and IL-6 in peri-implant crevicular fluid were key predictors of MBL - Oxidized implants mitigated some smoking effects by improving bone healing | Short-term molecular analysis (90 days), lacks long-term biomarker validation - No assessment of systemic effects of smoking on bone metabolism - Limited to specific implant surfaces | Smoking negatively affects bone healing and increases implant failure risk - Oxidized implants perform better than machined surfaces in smokers - HIF-1α and IL-6 are key molecular markers of smoking-induced bone loss - Long-term follow-up needed to assess chronic effects of smoking on osseointegration |
| 8. | Kirschneck et al., 2017, "Regular nicotine intake increased tooth movement velocity, osteoclastogenesis and orthodontically induced dental root resorptions in a rat model" | Germany | To evaluate the effect of nicotine on orthodontic tooth movement (OTM), osteoclast activity, and root resorption | Animal experimental (in vivo study) | Sample Size: 63 male Fischer-344 rats, divided into 3 groups (Control, OTM, OTM+Nicotine). Statistical Methods: ANOVA, Tukey's post hoc test, Kruskal-Wallis test, Mann-Whitney U test ($p \leq 0.05$) | Study based on nicotine's effect on periodontal bone remodeling, focusing on HIF-1α, IL-6, osteoclast markers (CTSK, CLCN7), and orthodontic movement | Nicotine increased tooth movement velocity by 50-80% compared to controls - Nicotine enhanced osteoclast activity and bone resorption during OTM - Increased inflammatory cytokines (IL-1β, IL-6, IL-8) and osteoclast markers in nicotine-exposed rats - HIF-1α expression was elevated in compression areas of the periodontal ligament, suggesting hypoxia-driven bone resorption - Significantly greater root resorption observed in nicotine-treated rats | Short-term study (14-28 days), lacks long-term effects - Only one nicotine dose tested - Findings may not fully translate to human orthodontics | Nicotine accelerates orthodontic tooth movement but increases root resorption risk - Higher osteoclastogenesis, inflammatory cytokines, and HIF-1α expression contribute to periodontal breakdown - HIF-1α may play a role in nicotine-induced bone resorption through hypoxia-related mechanisms - Patients should be informed of potential risks of nicotine during orthodontic treatment |

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| 9. | Kim et al., 2012, "Nicotine and lipopolysaccharide stimulate the production of MMPs and prostaglandin E2 by hypoxia-inducible factor-1α up-regulation in human periodontal ligament cells" | South Korea | To investigate the role of HIF-1α in nicotine- and LPS-induced production of MMPs and prostaglandin E2 (PGE2) in periodontal ligament cells (PDLCs) | In vitro experimental study using human PDLC cultures | Sample Size: PDLCs exposed to nicotine and LPS. Statistical Methods: Western blot, enzyme immunoassay (ELISA), zymography, siRNA knockdown, and pharmacological inhibition assays | Study based on HIF-1α as a regulator of inflammation and tissue destruction, focusing on its role in upregulating MMPs and PGE2 in response to nicotine and LPS | Nicotine and LPS synergistically increased HIF-1α expression - HIF-1α upregulation led to increased COX-2, PGE2, MMP-2, and MMP-9 production - HIF-1α inhibition reduced nicotine- and LPS-induced MMP and PGE2 levels - PI3K/Akt, MAPK, PKC, and NF-κB signaling pathways mediated HIF-1α activation | In vitro study lacks in vivo validation - Limited to short-term effects - No analysis of long-term periodontal degradation | HIF-1α mediates nicotine- and LPS-induced periodontal tissue destruction - Targeting HIF-1α may help in managing smoking-induced periodontal disease - HIF-1α inhibitors could be potential therapeutic agents for periodontitis treatment |
| 10. | Savardoust et al., 2018, "Implant-associated gene expression in the jaw bone of smokers and nonsmokers: A human study using quantitative qPCR" | Sweden | To analyze gene expression differences in implant-adherent cells and peri-implant bone during early osseointegration in smokers and non-smokers | randomized controlled clinical trial (RCT), Clinical human study with qPCR analysis | Sample Size: 48 patients (24 smokers, 24 non-smokers) receiving machined and oxidized implants. Statistical Methods: ANOVA, Kruskal-Wallis, Mann-Whitney U, Wilcoxon signed-rank test ($p < 0.05$) | Study based on molecular effects of smoking on osseointegration, focusing on inflammation, bone remodeling, and HIF-1α expression | Smokers exhibited delayed osteoblast and osteoclast gene expression, particularly in machined implants - HIF-1α and VEGF were upregulated early (day 1) but decreased over time - Oxidized implants enhanced bone remodeling markers (CatK, RANKL, OPG) and mitigated smoking-induced delays - Machined implants had higher inflammatory cytokine expression (IL-8, TNF-α) compared to oxidized implants | Short-term analysis (28 days), lacks long-term evaluation - No protein-level validation of gene expression changes - Findings may not fully translate to clinical outcomes | Smoking delays early osseointegration by suppressing osteoblast and osteoclast activity - HIF-1α and VEGF are key regulators of early implant healing Oxidized implants may mitigate smoking-induced impairment of osseointegration - Further studies needed to assess long-term effects of smoking on implant stability |
| 11. | Michaud et al., 2003, "Inhibition of hypoxia-induced angiogenesis by cigarette smoke exposure: Impairment of the HIF-1α/VEGF pathway" | Canada | To investigate how cigarette smoke exposure affects hypoxia-induced angiogenesis and its molecular mechanisms | In vitro (cell culture) and in vivo (mouse model) experimental study | Sample Size: Human umbilical vein endothelial cells (HUVECs) and 31 mice (cigarette smoke-exposed vs. control). Statistical Methods: One-way ANOVA, Newman-Keuls post hoc test ($p < 0.05$) | Study based on the role of HIF-1α in angiogenesis under hypoxic conditions, focusing on VEGF regulation and cigarette smoke's inhibitory effects | Cigarette smoke exposure significantly reduced angiogenesis in vitro and in vivo - HIF-1α and VEGF expression were suppressed under hypoxic conditions in smoke-exposed cells and tissues - Adenoviral overexpression of HIF-1α/VP16 restored VEGF levels and reversed the inhibition of angiogenesis - Cigarette smoke reduced HIF-1α protein half-life, impairing its stabilization in hypoxia | Short-term study (28 days), lacks long-term effects - Did not analyze systemic impacts of smoking on vascular disease progression - Limited to HIF-1α/VEGF pathway without assessing other angiogenic regulators | Cigarette smoke impairs hypoxia-induced angiogenesis by downregulating HIF-1α and VEGF - HIF-1α degradation in hypoxia reduces VEGF expression, leading to poor vascularization - Therapeutic HIF-1α stabilization may counteract smoking-induced vascular damage |

## Discussion

Hypoxia-inducible factor-1 alpha (HIF-1α) plays a crucial role in regulating cellular responses to hypoxia across various tissues, including the periodontium. Its involvement in smoking-induced gingival hypoxia is multifaceted, affecting pathways related to inflammation, immune response, and wound healing. In smokers, hypoxia is a defining characteristic of periodontal tissues, primarily due to nicotine-induced vasoconstriction, which restricts blood flow and oxygen delivery to the gingiva. As a response to these hypoxic conditions, HIF-1α acts as a key regulator, coordinating inflammatory processes, angiogenesis, and tissue remodeling to mediate cellular adaptation.

### HIF-1α Expression in Smokers and Non-Smokers with Different Periodontal Conditions

Smoking is a recognized risk factor for periodontal disease, mainly because of its vasoconstrictive effects, which diminish oxygen levels in gingival tissues. Nicotine-induced constriction of blood vessels restricts oxygen supply, leading to hypoxic conditions in the periodontium. Bejna et al. (2025) demonstrated significantly elevated levels of HIF-1α, HIF-2α, and HIF-3α in the gingival crevicular fluid of smokers and periodontitis patients compared to healthy individuals, indicating a substantial role of hypoxia in periodontal pathogenesis. Similarly, Karatas et al. (2019) reported that HIF-1α expression was markedly higher in smokers with periodontitis than in non-smokers, correlating with increased inflammation and apoptosis of fibroblast cells. These findings indicate that smoking exacerbates hypoxic stress in the periodontium, potentially accelerating tissue destruction in periodontitis patients.[2,9] Interestingly, while HIF-1α is typically

upregulated in hypoxic conditions, some studies suggest that chronic smoking may lead to dysfunctional HIF-1α signaling**.** Sayardoust et al. (2018) found that in smokers, the delayed and reduced expression of HIF-1α in peri-implant tissues correlated with impaired osseointegration and increased marginal bone loss. This suggests that while acute hypoxia triggers HIF-1α activation, chronic nicotine exposure may lead to dysregulated or inadequate HIF-1α responses, ultimately impairing periodontal healing.[10]

**Impaired Angiogenesis and the HIF-1α/VEGF Axis in Smokers**

Several studies have linked smoking also has effects on angiogenesis**,** a process that relies on HIF-1α regulation through the activation of vascular endothelial growth factor (VEGF)**.** Michaud et al. (2003) demonstrated that cigarette smoke exposure inhibits angiogenesis by reducing the expression of both HIF-1α and VEGF under hypoxic conditions, affecting both in vitro endothelial cell migration and in vivo capillary formation. This inhibition of VEGF expression disrupts vascular adaptation and impairs healing processes. In clinical studies, Taş et al. (2024) reported that while VEGF-A levels increased following regenerative periodontal therapy, smokers exhibited a significantly lower response than non-smokers, further suggesting that smoking interferes with tissue recovery through HIF-1α dysregulation. These studies highlight how smoking-induced HIF-1α suppression leads to inadequate angiogenic responses, contributing to delayed healing and disease progression.[11,12]

**HIF-1α and Osteoclastic Activity: The Impact on Bone Resorption**

Smoking has a profound impact on alveolar bone metabolism, with HIF-1α playing a crucial role in osteoclastic activity. Smoking-induced hypoxia also promotes osteoclastogenesis and bone resorption, contributing to alveolar bone loss in smokers. Kirschneck et al. (2017) found that nicotine exposure significantly increased osteoclast activity, accelerated orthodontic tooth movement, and enhanced root resorption. These findings align with Kim et al. (2012)**,** who reported that nicotine and bacterial lipopolysaccharides (LPS) synergistically upregulate HIF-1α, leading to increased production of MMP-2, MMP-9, and PGE2, which exacerbate periodontal tissue degradation. These findings suggest that HIF-1α may enhance bone resorption under smoking-induced hypoxia, further exacerbating periodontal tissue breakdown. However, a contrasting finding comes from Ullrich et al. (2019)**,** who investigated the role of HIF-1α in nicotine-induced root and bone resorption during orthodontic tooth movement (OTM)**.** Their study revealed that while nicotine increased osteoclastogenesis and periodontal bone loss, these effects were not mediated by HIF-1α**,** suggesting the involvement of alternative pathways such as nicotine-induced oxidative stress or inflammatory cytokines**.**[13–15]

**Gene Expression Alterations in the Periodontal Ligament Under Nicotine Exposure**

At the molecular level, the effects of nicotine on gene expression in periodontal ligament cells have been well-documented. Du et al. (2019) performed microRNA profiling and identified that nicotine exposure disrupts the regulatory pathways of HIF-1α, potentially altering inflammatory responses and bone remodeling in smokers. This dysregulation is also evident in implant-related studies. Sayardoust et al. (2017) found that reduced HIF-1α levels in peri-implant tissues of smokers correlated with increased marginal bone loss. Furthermore, Sayardoust et al. (2018) demonstrated that smoking negatively affected the expression of osteogenic and inflammatory genes, impairing osseointegration, particularly in implants with unmodified surfaces.[10,16,17]

**Apoptosis and Inflammation in Gingival Tissues of Smoker**

Smoking also exacerbates apoptosis and inflammatory responses in the gingiva, further impairing tissue homeostasis. Karatas et al. (2019) reported that smokers with periodontitis exhibited increased fibroblast apoptosis and a higher degree of inflammatory cell infiltration compared to non-smoking periodontitis patients. These findings suggest that smoking-induced hypoxia not only impairs angiogenesis and enhances osteoclastogenesis but also accelerates tissue breakdown through heightened cellular apoptosis.[9]

**Potential Therapeutic Interventions: Targeting HIF-1α for Periodontal Regeneration**

Given the impact of smoking on periodontal healing via HIF-1α dysregulation**,** researchers have explored potential therapeutic strategies**.** Michaud et al. (2003) demonstrated that HIF-1α/VP16 gene therapy successfully restored VEGF expression and completely reversed the inhibitory effects of cigarette smoke on angiogenesis. This suggests that targeted modulation of HIF-1α and VEGF could serve as a therapeutic strategy to enhance periodontal healing and bone regeneration in smokers.[9,11]

## Conclusion

The significant impact of smoking-induced hypoxia on periodontal health is primarily mediated through HIF-1α dysregulation, which contributes to impaired angiogenesis, increased inflammation, osteoclastic activity, and delayed tissue healing**.** Smoking alters the HIF-1α/VEGF axis**,** leading to reduced vascularization and compromised periodontal regeneration, ultimately exacerbating periodontal disease progression. The findings emphasize the need for targeted therapeutic interventions focusing on HIF-1α modulation, VEGF-based therapies, and smoking cessation strategies to improve treatment outcomes in smokers. Given the role of HIF-1α in periodontal destruction, future research should explore molecular-based therapies, gene therapy, and pharmacological approaches to mitigate smoking-induced tissue damage. Clinically, integrating smoking cessation programs with periodontal therapy and developing personalized treatment strategies for smokers could enhance regenerative outcomes and implant success rates, ultimately improving long-term oral health in this high-risk population.

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## Author Contributions

All authors act as the guarantor of the manuscript. MYP is the main investigator of this study. SS and AA participated in the conception, data acquisition, data interpretation, writing of the study, data analysis and statistical analysis of the study.

## Conflict of Interest

None.

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