

REVIEW

Connection between oral health and chronic diseases

Di Fu^{1,#} | Xingyue Shu^{1,#} | Ge Zhou¹ | Mengzhen Ji¹ | Ga Liao^{1,2}  | Ling Zou^{3,*}

¹State Key Laboratory of Oral Diseases, National Center for Stomatology, National Clinical Research Center for Oral Diseases, Sichuan University, Chengdu, Sichuan, China

²Department of Information Management, Department of Stomatology Informatics, West China Hospital of Stomatology, Sichuan University, Chengdu, Sichuan, China

³State Key Laboratory of Oral Diseases, National Center for Stomatology, National Clinical Research Center for Oral Diseases, Department of Conservative Dentistry and Endodontics, West China Hospital of Stomatology, Sichuan University, Chengdu, Sichuan, China

***Correspondence**

Ling Zou, State Key Laboratory of Oral Diseases, National Center for Stomatology, National Clinical Research Center for Oral Diseases, Department of Conservative Dentistry and Endodontics, West China Hospital of Stomatology, Sichuan University, Chengdu, 610041, Sichuan, China.

Email: zouling@scu.edu.cn

Funding information

National Natural Science Foundation of China, Grant/Award Number: 82071111; Project of the Science and Technology Department of Sichuan Province, Grant/Award Number: 2024YFHZ0042; Clinical Research Program, West China Hospital of Stomatology Sichuan University, Grant/Award Number: LCYJ-MS-202310

Abstract

Chronic diseases have emerged as a paramount global health burden, accounting for 74% of global mortality and causing substantial economic losses. The oral cavity serves as a critical indicator of overall health and is inextricably linked to chronic disorders. Neglecting oral health can exacerbate localized pathologies and accelerate the progression of chronic conditions, whereas effective management has the potential to reduce their incidence and mortality. Nevertheless, limited resources and lack of awareness often impede timely dental intervention, delaying optimal therapeutic measures. This review provides a comprehensive analysis of the impact of prevalent chronic diseases—such as diabetes mellitus, rheumatoid arthritis, cardiovascular disorders, and chronic respiratory diseases—on oral health, along with an exploration of how changes in oral health affect these chronic conditions through both deterioration and intervention mechanisms. Additionally, novel insights into the underlying pathophysiological mechanisms governing these relationships are presented. By synthesizing these advancements, this review aims to illuminate the complex interrelationship between oral health and chronic diseases while emphasizing the urgent need for greater collaboration between dental practitioners and general healthcare providers to improve overall health outcomes.

KEYWORDS

cardiovascular diseases, chronic diseases, chronic respiratory diseases, diabetes, oral health, rheumatoid arthritis

[#]Di Fu and Xingyue Shu contributed equally to this work.

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2025 The Author(s). *MedComm* published by Sichuan International Medical Exchange & Promotion Association (SCIMEA) and John Wiley & Sons Australia, Ltd.

1 | INTRODUCTION

Noncommunicable diseases (NCDs), including cardiovascular diseases (CVDs), diabetes mellitus (DM), chronic respiratory diseases, cancers, and obesity, are characterized by their prolonged nature and often incurability. According to the World Health Organization (WHO), NCDs account for 74% of global mortality, with approximately 17 million individuals succumbing before the age of 70 each year.¹ These diseases impose a substantial economic burden, with healthcare expenditures surpassing 85% of total global healthcare costs.² In the US healthcare system alone, over one trillion dollars are allocated annually to the management of chronic diseases.³ By 2030, the economic burden of major NCDs is projected to result in a loss of output amounting to \$47 trillion, equivalent to 75% of the global gross domestic product (GDP) in 2010.⁴ Moreover, aging populations and declining birth rates are anticipated to further exacerbate this burden.

The oral cavity, situated at the intersection of medicine and dentistry, serves as a critical indicator of overall health,

with its pathological conditions frequently exerting a more profound impact on systemic health than is commonly acknowledged by many healthcare providers.⁵ Ignoring oral health can not only exacerbate localized issues but also have significant repercussions on chronic diseases.^{6–9} Proactively managing oral health through regular dental examinations and the maintenance of proper oral hygiene can significantly enhance quality of life while aiding in the prevention and management of chronic diseases, thereby reducing their incidence and mortality rates.^{10–13} Regrettably, due to limited access to medical resources and dental care,¹⁴ many patients only recognize the close association between oral and systemic health after experiencing more severe health events, which subsequently delays optimal treatment and prevention. It is imperative to further explore this domain to enhance awareness of the critical role that oral health plays in the development of chronic diseases and to underscore its significance in the prevention and management of systemic conditions.

This review seeks to elucidate the relationships between oral health and prevalent chronic diseases (Figure 1),

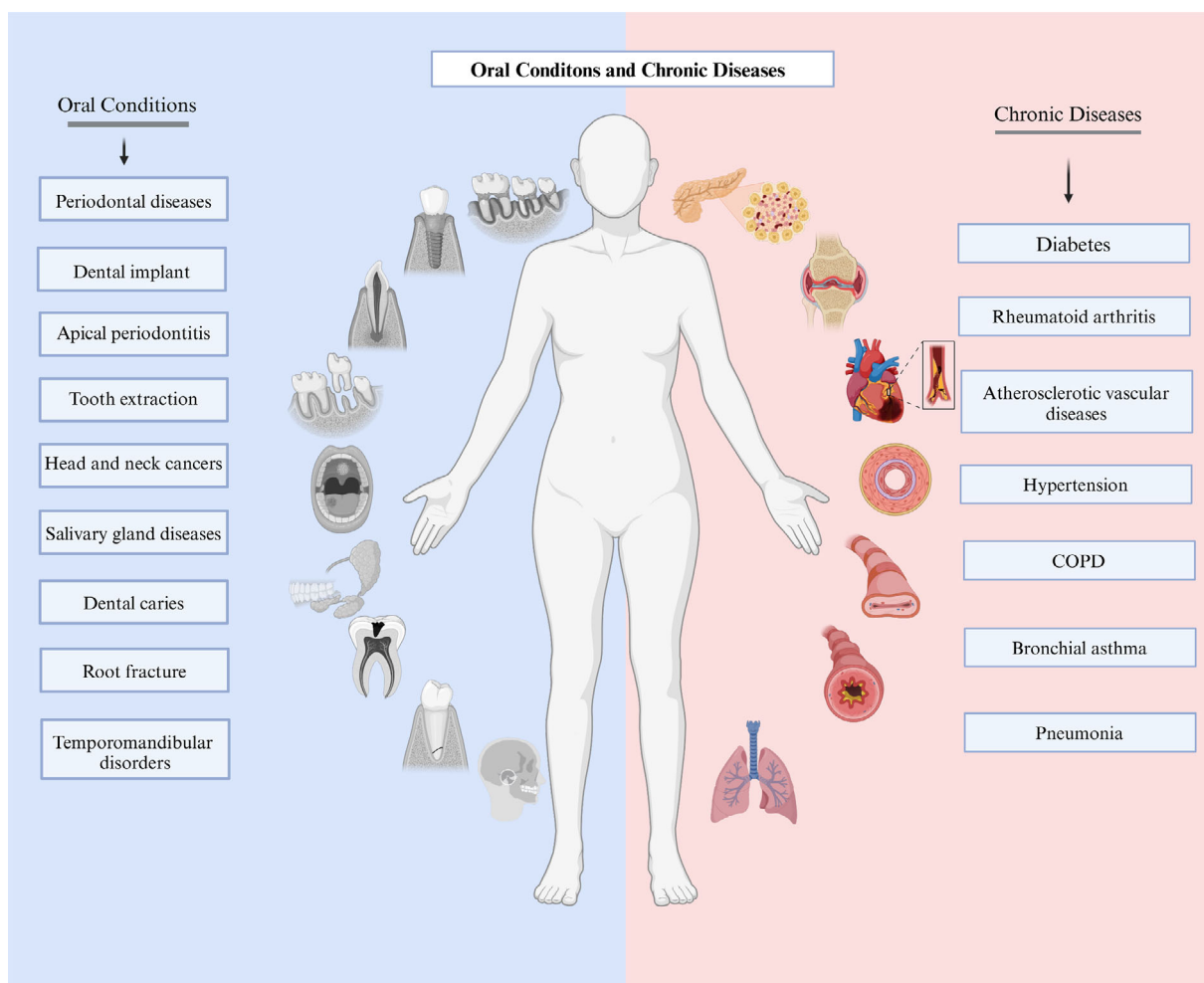


FIGURE 1 Oral conditions and chronic diseases. The left portion of the chart presents the common oral conditions referred to in this article, while the right portion exhibits the chronic diseases closely associated with oral conditions. Created with BioRender.com.

including DM, rheumatoid arthritis (RA), CVDs, and chronic respiratory diseases. It highlights recent advancements in understanding the mechanisms that connect oral health to these ailments and discusses strategies for enhancing oral care while managing chronic diseases.

2 | DIABETES MELLITUS AND ORAL HEALTH

DM encompasses a spectrum of metabolic disorders characterized by insufficient insulin secretion, insulin resistance, or a combination of both, leading to impaired regulation of blood glucose levels. It exhibits a complex and interdependent relationship with oral health. Hyperglycemia increases the risk of oral diseases, including periodontal diseases, apical periodontitis (AP), head and neck cancer (HNC), salivary gland diseases, dental caries, and root fracture, while also impeding the healing process of extraction sites. Glycemic control is intricately associated with the success rates of dental implants and root canal treatment (RCT) in patients with diabetes. Moreover, declining oral health conditions, such as periodontal disease, can increase the prevalence of diabetes and negatively impact glycemic control. Furthermore, diabetic patients frequently experience salivary gland dysfunction and chronic inflammation, resulting in complications such as xerostomia, infections, and oral mucosal lesions.

Consequently, the maintenance of oral health should be considered a vital component of comprehensive diabetes management to mitigate the incidence of related complications and enhance patients' quality of life. To facilitate readers' access to pertinent literature, we have summarized recent reviews, systematic evaluations, and meta-analyses regarding the relationship between diabetes and various oral diseases in the table (Table 1).

2.1 | Diabetes and periodontal diseases

Robust epidemiological and clinical evidence substantiates the association between the two.^{20–22} Diabetic patients exhibit a significantly higher prevalence of periodontitis and show worse periodontal parameters, including clinical attachment loss, periodontitis surface area, and the number of teeth lost.^{20,54–58} Conversely, individuals with periodontitis are at an increased risk of developing diabetes.⁶

A recent study delineated the pathophysiological mechanisms through which diabetes impacts periodontal disease, encompassing vascular alterations in the gingiva, immune responses, collagen metabolism disorders, and specific microbiological profiles within periodontal pock-

ets. Similarly, the mechanisms by which periodontal disease may affect diabetes include increased serum oxidative stress markers, elevated inflammatory markers, and enhanced insulin resistance.²¹ In 2023, Zhao et al. identified six potential mechanisms underlying the interaction between periodontitis and diabetes (Figure 2): (1) microbial factors; (2) enhanced inflammatory response through cytokines, adipokines, advanced glycation end product/receptor for advanced glycation end product (AGE/RAGE) pathways, and miRNAs; (3) host immune factors; (4) oxidative stress; (5) alveolar bone resorption damage; and (6) epigenetic changes.²⁴ Later, Enteghad et al. added that the uncoupling of resorptive and formative responses in connective tissue.²⁰ To provide a novel perspective on the interaction between diabetes and periodontitis, we reviewed the literature pertaining to the underlying mechanisms (Table 2) utilizing key molecules that may play significant roles in both diseases as indicators.

With the advancement of various saliva-based methodologies, markers, and models for the clinical screening of diabetes and prediabetes, saliva has emerged as a promising medium for this purpose. Dentists may leverage noninvasive chairside techniques to screen or diagnose diabetes and collaborate effectively with internists to manage the oral health of diabetic patients. Studies have demonstrated that placental growth factor (PlGF)⁵⁹ in gingival crevicular fluid (GCF) and microbial components⁶⁰ in saliva are correlated with blood glucose levels. These findings offer a promising avenue for the noninvasive auxiliary diagnosis of DM. In addition, researchers have developed diagnostic models capable of screening for prediabetes and diabetes in patients with periodontitis,⁶¹ demonstrating moderate to good discriminative ability. In the future, dental clinics may assume an increasingly vital role in diabetes screening.

2.2 | Diabetes and dental implants

Dental implants represent an effective solution for the replacement of missing teeth; however, their success is contingent upon both the local periodontal conditions and the overall health of patients, particularly with respect to a history of diabetes. Ongoing discussions examine how diabetes influences dental implant outcomes, with some researchers suggesting that diabetes may lead to complications surrounding implants and impede bone healing, ultimately resulting in a lower surgical success rate.^{109–111} Even if the initial success rates for implants in diabetic individuals can be quite high, the long-term results often seem less promising.¹¹² Conversely, other studies report differing results, indicating that the implant success rate

TABLE 1 Recent reviews/systematic reviews/meta-analyses on diabetes and oral diseases.

Topic	Author, year	Study type	Main contents
Overall oral health	Alqadi, 2024 ¹⁵	R	The oral manifestations of DM are delineated, along with essential dental considerations for the management of diabetic patients during treatment.
	Grisi, 2022 ¹⁶	R	The authors examine prevalent oral signs and symptoms of diabetes, highlighting the mechanisms that connect DM to oral diseases and the associated risks of inadequate oral health in patients with DM.
	Ahmad, 2021 ¹⁷	R	The relationship between DM and oral complications is reviewed.
	Borgnakke, 2021 ¹⁸	R	The relationship between oral diseases and DM, including the underlying mechanisms, is summarized. Additionally, prevalent risk factors are delineated.
	Negrini, 2021 ¹⁹	R	The principal oral manifestations of DM are summarized. The interactions among diabetes, its risk factors, the oral microbiome, and oral diseases are analyzed.
Periodontitis	Enteghad, 2024 ²⁰	R	Epidemiological and clinical evidence regarding the association between DM and periodontitis is summarized. The predictive value of periodontal parameters for identifying diabetes is emphasized, and the biological mechanisms through which diabetes induces periodontal disease are reviewed.
	Mirnic, 2024 ²¹	R	The clinical and epidemiological studies examining the bidirectional relationship between DM and periodontal disease, along with the pathogenesis and the role of oxidative stress, have been succinctly summarized.
	Vlachou, 2024 ²²	R	The bidirectional relationship between DM and periodontitis is investigated, with a focus on the cellular and molecular mechanisms underlying the interaction between the oral microbiome and the host immune response.
	Păunică, 2023 ²³	R	The most recent findings regarding the etiological factors, treatment, and prevention of both diseases are presented, with an emphasis on the role of diabetic microvascular complications, the oral microbiome, and inflammatory mediators.
	Zhao, 2023 ²⁴	R	The potential mechanisms underlying the interaction between periodontitis and diabetes are summarized into six points: (1) microbiome factors; (2) enhanced inflammatory responses through cytokines, adipokines, AGE/RAGE, and miRNAs; (3) host immune factors; (4) oxidative stress; (5) alveolar bone resorption damage; and (6) epigenetic changes.
	Nibali, 2022 ²⁵	R	The comorbidities associated with DM and periodontitis are summarized, and the underlying mechanisms are examined.
	Salhi, 2022 ²⁶	R	The data concerning the impact of periodontitis on diabetes and vice versa are summarized in a descriptive table.
	Genco, 2020 ²⁷	R	The role of diabetes as a risk factor for periodontal and other oral diseases is reviewed.
	Genco, 2020 ²⁸	R	Studies elucidating the adverse effects of periodontal disease and diabetes are discussed, with a summary of their implications for clinical practice and public health.
	Graves, 2020 ²⁹	R	The impact of DM on periodontal tissues, including periodontal ligament cells, osteoblasts, and osteocytes, is summarized. Furthermore, the effects of diabetes on the oral microbiome and its role in exacerbating periodontal bone loss are discussed.
	Polak, 2020 ³⁰	R	The progression from DM to periodontitis is delineated, with a focus on microbiome alterations and immune changes in poorly controlled diabetes. Both microbiological and immunological shifts contributing to this condition are summarized.
	Costa, 2023 ³¹	S	The prevalence and severity of periodontal disease are higher in individuals with T1DM compared to the healthy population.
	Maia, 2023 ³²	S	Fewer than half of diabetic patients are aware of their elevated risk for periodontal disease, and dentists frequently do not serve as the primary source encouraging them to seek this information.
	Nguyen, 2020 ³³	S	Patients with periodontal disease are at an increased risk of developing diabetes-related complications.
	Stöhr, 2021 ³⁴	SM	There exists a positive bidirectional association between periodontitis and DM, underscoring the necessity of screening diabetic patients for periodontitis and vice versa.
Baeza, 2019 ³⁵	SM	SRP significantly affects metabolic control and reduction of systemic inflammation in patients with T2DM.	

(Continues)

TABLE 1 (Continued)

Topic	Author, year	Study type	Main contents
Dental implants	Zhang, 2023 ³⁶	R	The structure of peri-implant soft tissue sealing, associated diseases and their treatments, as well as the regulatory mechanisms of T2DM in relation to soft tissue sealing damage, are comprehensively reviewed.
	Vijay, 2021 ³⁷	R	Recent advancements in the application of carbon-based nanomaterials for enhancing dental implants in diabetic patients are summarized.
	Bencze, 2024 ³⁸	SM	Within the constraints of this study, patients with poorly controlled T2DM or prediabetes may exhibit worse peri-implant conditions compared to individuals without diabetes and those with well-controlled T2DM. Furthermore, well-controlled T2DM does not serve as a risk indicator for peri-implant diseases.
	Al Ansari, 2022 ³⁹	SM	Implants in diabetic patients exhibit a higher risk of failure and increased marginal bone resorption compared to nondiabetic individuals, with T1DM demonstrating a greater failure rate than T2DM.
	Andrade, 2022 ⁴⁰	SM	With adequate blood glucose control, optimal oral hygiene, and strict adherence to procedural protocols, T2DM does not present a risk for immediate loading of implants.
	Lv, 2022 ⁴¹	SM	Diabetes or hyperglycemia upregulates negative regulators of bone metabolism, harming peri-implant health. HbA1c levels are dose related to advanced glycation end products, periodontal disease, and marginal bone loss.
	Shang, 2021 ⁴²	SM	BOP and PIBL were significantly higher in T2DM patients. However, strict oral hygiene reduced the impact of blood sugar levels on these parameters.
AP	Tibúrcio-Machado, 2017 ⁴³	R	Current literature suggests a positive correlation between diabetes and an increased prevalence of periapical lesions.
	Pérez-Losada, 2020 ⁴⁴	SM	There may be common pathophysiological factors underlying both AP and DM; however, the relationship between these two conditions necessitates further prospective studies.
	Liu, 2023 ⁴⁵	SM	DM may elevate the risk of AP in teeth that have undergone endodontic treatment. Furthermore, in cases where apical periodontitis is already established, DM may exacerbate the progression of this condition.
Head and neck cancer	Wang, 2020 ⁴⁶	R	Recent advancements in the research concerning the relationship between DM and the mechanisms underlying head and neck cancer development have been summarized.
	Ramos-Garcia, 2021 ⁴⁷	SM	The prevalence and risk of oral cancer, as well as potentially malignant oral diseases, are elevated in individuals with DM, and their associated mortality rate from oral cancer is significantly higher than that of nondiabetic individuals.
	Yan, 2021 ⁴⁸	SM	T2DM is associated with an increased risk of head and neck cancers in East Asia.
Salivary	Pérez-Ros, 2021 ⁴⁹	R	Salivary amylase and glucose concentrations represent potential noninvasive biomarkers for evaluating blood glucose control and clinical management in patients with DM.
Dental caries	Zhou, 2024 ⁵⁰	SM	T2DM may lead to an increased dental caries index in adults, along with reduced salivary flow rate, pH, and buffering capacity.
	Weijndijk, 2023 ⁵¹	SM	Compared to nondiabetic patients, diabetic patients have a higher DMF index score with moderate certainty.
	Coelho, 2020 ⁵²	SM	T1DM patients have a higher risk of dental caries.
	de Lima, 2020 ⁵³	SM	DM may increase the incidence of coronal and root caries in adults. Poor glycemic control makes diabetic patients more susceptible to dental caries.

Abbreviations: AGE, advanced glycation end product; AP, apical periodontitis; BOP, bleeding on probing; DM, diabetes mellitus; PIBL, peri-implant bone loss; R, review; RAGE, receptor for advanced glycation end product; S, systematic review; SM, systematic and meta-analysis; SRP, scaling and root planning; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

remains within an acceptable range.^{113–118} This inconsistency may stem from variations in diagnostic criteria and other influencing factors, particularly differences in the glycemic control of the studied patients.^{38–40,42,119} The evidence derived from two recently published meta-analyses

indicates that the management of blood glucose levels is a critical factor influencing the success of implants in diabetic patients.^{41,120}

The mechanisms through which diabetes influences dental implants are analogous to its effects on

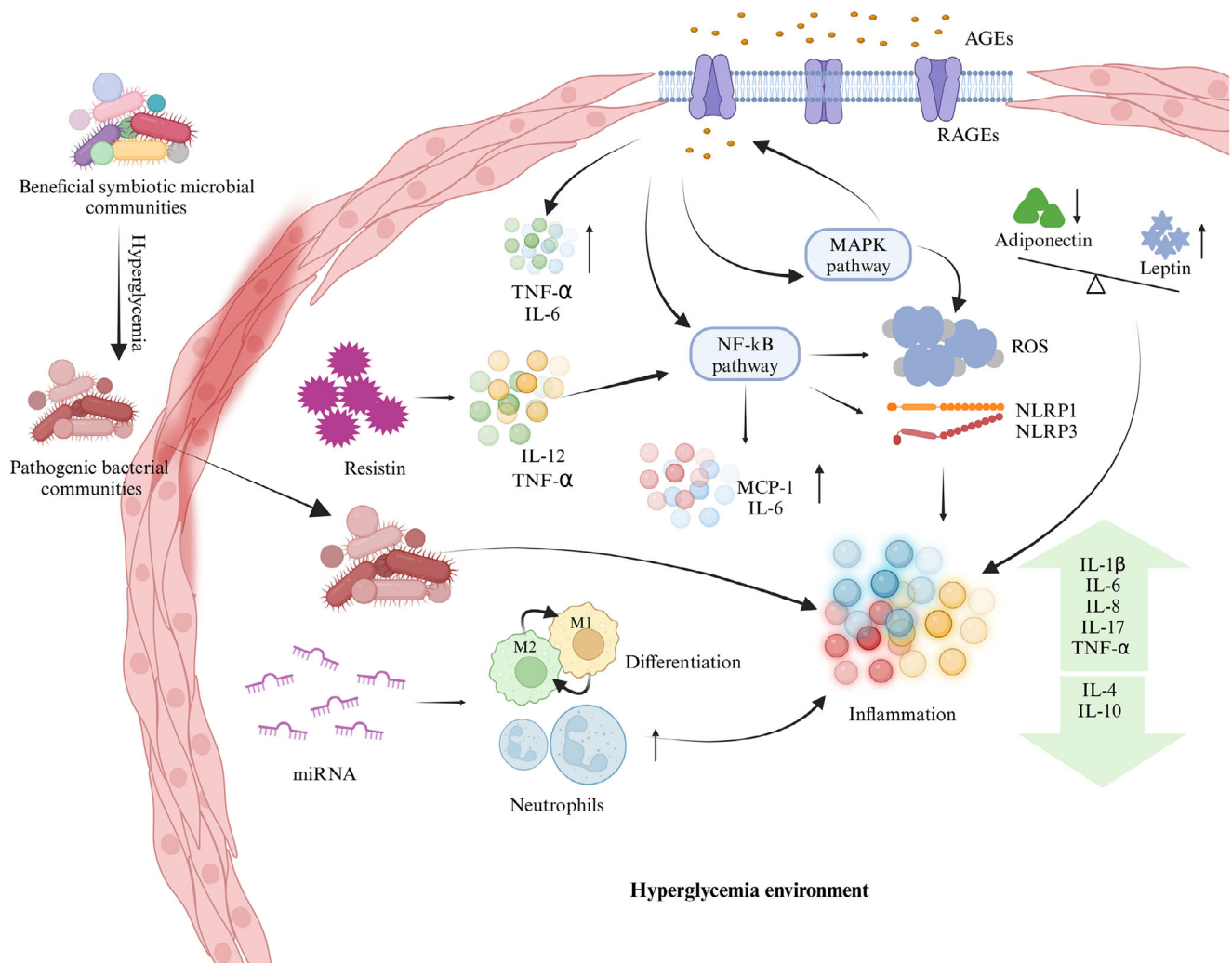


FIGURE 2 Mechanisms linking oral health and diabetes. Diabetes induces oral inflammation through multiple pathways, transforming beneficial microbial communities into pathogenic ones. Additionally, AGEs and resistin elevate inflammatory cytokines, thereby activating classical inflammatory pathways and generating ROS and inflammasomes. Dysregulation of adiponectin, leptin, and miRNA expression further drives immune cell differentiation and recruitment, exacerbating inflammation. AGEs, advanced glycation end products; IL-4, interleukin-4; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL-17, interleukin-17; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; M1, M1 macrophage; M2, M2 macrophage; NLRP1, NLR family pyrin domain containing 1; NLRP3, NLR family pyrin domain containing 3; RAGEs, receptor for advanced glycation end products; ROS, reactive oxygen species; TNF- α , tumor necrosis factor-alpha. Created with BioRender.com.

osteogenesis and osteoclastogenesis.¹²¹ A review conducted by de Oliveira et al. delineated these mechanisms as follows: (1) disrupting the balance between bone resorption and synthesis; (2) inducing microvascular disease; and (3) diminishing markers of bone formation while affecting collagen structure.¹²² Furthermore, AGEs-related NOX (NADPH oxidases)-mediated oxidative stress significantly impairs bone healing in diabetic patients.¹²³

Future improvements in the success rates of dental implants for diabetic patients are expected to focus on enhancing implant material properties,³⁷ refining implant coatings,¹²⁴ and advancing surgical techniques.¹²⁵

2.3 | Diabetes and apical periodontitis

AP manifests at the apex of the tooth root, leading to inflammation in both dental and periodontal tissues. Root canal therapy (RCT) serves as the primary treatment modality. Although evidence remains limited, existing studies indicate a positive correlation between diabetes and the prevalence of AP lesions.⁴³ Poor blood glucose control can lead to higher rates of AP and increased failure rates of RCT.^{126–129} The impact of RCT on blood glucose management in diabetic patients is still under debate.^{130–132} The discrepancies in findings may be

TABLE 2 Key molecules in the interaction between diabetes and periodontitis.

Core factors	Main findings	Clinical study	In vivo	In vitro	
IL-1 beta	Inflammatory cytokines play a role in the interplay between diabetes and periodontitis			62	
IL-6		63	64		
IL-10		65			
IL-12			66		
IL-17				67,68	
IL-21		69			
TNF-E		65,70,71	72–75	76	
Adiponectin	Adiponectin has anti-inflammatory effects and is linked to diabetes and glycemic control. After periodontal therapy, increased adiponectin can improve insulin resistance and lower HbA1c. The adiponectin receptor agonist, AdipoAI, may reduce tissue inflammation and damage, suggesting potential for treating diabetes-related periodontitis.	77	78		
Visfatin	Periodontal inflammation can upregulate proinflammatory cytokines such as IL-6 and IL-1b, leading to elevated visfatin expression in periodontal tissues. Visfatin may play a role in the pathogenesis of periodontitis by promoting the upregulation of matrix metalloproteinase-1 and chemokine CC-motif ligand 2 in periodontal ligament cells.	79			
ROS	ROS production induces MAPK and NLRP3-related protein expression in high glucose conditions. ROS act as upstream signals for MAPKs, NF-kappa B, and the NLRP3 inflammasome, leading to their activation. This process, along with increased oxidative damage and downregulation of Nrf2, contributes to the onset and progression of diabetic periodontitis.	58		62,76,80	
MAPK				80	
NLRP3				80	
NF-κB				81	80,81
Nrf2				82	
MMP	Elevated levels of MMP-8 and MMP-9 are associated with more severe periodontitis and an increased risk of diabetes mellitus.	56,83			
CRP	CRP affects periodontitis and diabetes by inhibiting osteoblast formation and promoting osteoclast formation through the PI3K/AKT signaling pathway, disrupting alveolar bone homeostasis.	84	85		
hBDs	The concentrations of hBD-2 and hBD-3 are closely related to periodontal health and diabetic status.	86,87			
GLUT1	GLUT1, a key glucose transporter in macrophages, is upregulated in the gingiva of diabetic mice. It contributes to high glucose-induced macrophage senescence and the SASP response, potentially worsening diabetic periodontitis.		88		
AGEs	In chronic hyperglycemic conditions, AGEs significantly increase and affect periodontal tissue cell function by binding to RAGE, correlating with the severity of periodontitis. Additionally, AGEs negatively impact the skeletal system by inhibiting the expression of osteoblast-related molecules, exacerbating periodontal disease in diabetic patients.	70,89	73	76,90–93	
WBC	WBCs worsen the development and progression of periodontitis in diabetic patients by amplifying inflammatory responses and impairing immune function.	84,94			
PMNs	The systemic effects of periodontal tissue inflammation may intensify the innate immune response of neutrophils, promoting the interaction between diabetes and periodontitis.		95		
RANKL	Oral infections and diabetes can upregulate osteoclast RANKL expression, increasing the number and activity of osteoclasts, which leads to bone loss. In diabetic patients, RANK and RANKL expression are elevated, while OPG expression is reduced.		96		

(Continues)

TABLE 2 (Continued)

Core factors	Main findings	Clinical study	In vivo	In vitro
Microbial change	Diabetes can alter the diversity and composition of the oral microbiome, particularly the subgingival microbiota.	97–99		
Gut microorganism	In PD patients, alterations in gut microbiota composition, particularly the reduction of butyrate-producing bacteria, are associated with elevated blood glucose levels and impaired glucose tolerance. Using antibiotics or fecal microbiota transplantation to eliminate gut bacteria can improve blood glucose levels and inflammation markers.		100	
miRNA	miR-146a and miR-155 may be novel biomarkers for periodontitis in both diabetic and nondiabetic patients. Additionally, miR-126, by targeting TRAF6 and reducing inflammation in gingival fibroblasts under high glucose conditions, could serve as a potential therapeutic target for treating periodontitis in diabetic patients.	101	102,103	103–106
SNPs	SNPs influence disease susceptibility and severity. SNPs in the IL-1, IL-4, and IL-6 genes are significantly associated with the risk of diabetes and periodontitis.	107		
25VD ₃	Patients with diabetes and periodontitis have lower levels of vitamin D and calcium, which are negatively correlated with RBS and HbA1c levels.		108	

Abbreviations: AGEs, advanced glycation end products; CRP, C-reactive protein; GLUT1, the glucose transporter 1; hBDs, human beta-defensins; IL, interleukin; MAPK, mitogen-activated protein kinase; MMP, metalloproteinase; NF- κ B, nuclear factor kappa-B; NLRP3, NOD-like receptor pyrin domain containing three; Nrf2, nuclear factor erythroid 2-related factor 2; OPG, osteoprotegerin; PD, periodontal diseases; PMNs, polymorphonuclear neutrophils; RAGEs, receptor for advanced glycation end products; RANK, receptor activator of nuclear factor- κ B; RANKL, receptor activator of nuclear factor- κ B ligand; RBS, random blood sugar; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SNP, single nucleotide polymorphisms; TNF- α , tumor necrosis factor-alpha; VD, vitamin D; WBC, white blood cell.

attributed to differences in criteria, limited sample sizes, or varying follow-up periods. Further well-structured, large-scale clinical trials are needed.

Existing evidence suggests that diabetes may exacerbate both the incidence and progression of AP by modulating levels of inflammatory factors, oxidative stress, and the prevalence of *Candida albicans* (*C. albicans*) within periodontal tissues. Several animal studies have underscored the significant roles of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and interleukin-17 (IL-17) in the pathogenesis and progression of both diabetes and AP.^{68,133} Furthermore, diabetes is known to disrupt the antioxidant balance by elevating malondialdehyde (MDA) and uric acid levels while concurrently decreasing albumin concentrations. The presence of AP exacerbates these diabetic effects, leading to further reductions in albumin and increases in uric acid levels.¹³⁴ Additionally, another investigation demonstrated that the presence of *C. albicans* in type 2 diabetes mellitus (T2DM) individuals correlates with a higher incidence of AP.¹³⁵

2.4 | Diabetes and tooth extraction

Persistent hyperglycemia and chronic inflammation associated with DM can adversely affect the healing process of extraction sockets.^{136–138} This underscores the importance

of blood glucose control for diabetic patients undergoing tooth extraction. However, many oral surgeons remain uncertain about the critical thresholds for blood glucose and HbA1c levels, as well as the point at which the risk of adverse complications significantly escalates.¹³⁹ A systematic review has provided new insights, indicating that a fasting blood glucose level of 240 mg/dL serves as the critical threshold for any dental treatment, as warning signs of diabetes begin to manifest at this level. For diabetic patients, the maximum acceptable blood glucose levels prior to tooth extraction are 180 mg/dL before meals and 234 mg/dL 2 h postprandially.¹⁴⁰ Moreover, the use of prophylactic antibiotics is not sufficiently supported by evidence. T2DM does not necessitate prophylactic antibiotics prior to tooth extraction in the absence of acute odontogenic infections.¹³⁸ A systematic review indicates that there is currently no scientific evidence to substantiate the efficacy of prophylactic antibiotic use prior to dental surgery in patients with diabetes.¹⁴¹

The characteristics of diabetic wounds encompass elevated levels of ROS, impaired M1/M2 macrophage polarization, and chronic inflammation driven by proinflammatory chemokines.¹³⁹ The challenges associated with healing postextraction wounds are linked to diminished osteogenic differentiation of mesenchymal stem cells (MSC),¹⁴² activation of matrix metalloproteinase-9 (MMP-9), persistent imbalance in the receptor activator of nuclear

factor- κ B ligand (RANKL)/osteoprotegerin (OPG) ratio.¹⁴³ Furthermore, the hyperglycemic environment disrupts the secretion of cytokines such as TNF- α , IL-6, and IL-1 β from macrophages,¹⁴⁴ resulting in functional impairments in neutrophils during the inflammatory response stages of wound healing, including migration, chemotaxis, and adhesion.¹³⁸

2.5 | Diabetes and head and neck cancer

HNCs encompass a range of malignancies originating in regions such as the oral cavity, pharynx, larynx, paranasal sinuses, nasal cavity, salivary glands, and lymph nodes within the head and neck area.¹⁴⁵ Among these, cancers directly impacting the oral cavity and adjacent areas, such as oral squamous cell carcinoma (OSCC) and oropharyngeal carcinoma, are of particular concern due to their profound implications for oral health and systemic well-being. Besides, for advanced-stage cancers, the application of high-energy radiation can lead to various potentially severe oral complications, including reduced salivary secretion causing xerostomia, oral pain, bacterial and fungal infections, taste disturbances, swallowing difficulties, discomfort, bleeding of periodontal tissues, and speech impairments.^{146,147} This section focuses on the relationship between the aforementioned cancers that directly affect oral health and chronic diseases, as well as the impact of cancer treatments and medications on chronic conditions.

DM has been associated with an increased risk of developing various cancers, including HNC.^{46,47,148} T2DM promotes proliferation, metastasis, and inhibits apoptosis in OSCC.¹⁴⁹ Patients with oral and oropharyngeal cancers who have a history of diabetes may have lower survival rates.¹⁵⁰

Researches indicate that antidiabetic medications such as metformin,⁴⁶ pioglitazone,¹⁵¹ and SGLT-2 inhibitors^{152,153} exhibit antitumor effects. A review has elucidated the mechanisms of action of SGLT-2 inhibitors and their applications in the management of type 2 diabetes and its associated complications. Both SGLT1 and SGLT2 are expressed in various tumors, where they facilitate euglycemic glycolysis by supplying tumor cells with glucose. Furthermore, the proliferation of carcinomas expressing SGLT2 can be effectively inhibited through the administration of an SGLT2 inhibitor.¹⁵⁴ Besides, the effects of GLP-1 receptor agonists (GLP-IRAs) on tumors remain ambiguous, with some studies suggesting a potential increase^{155,156} in cancer risk and others indicating otherwise.^{157,158} Additional experiments are warranted to investigate.

The association between diabetes and HNC may be attributed to shared risk factors inherent to both

conditions.¹⁵⁹ A review published in 2020 delineated the potential mechanisms by which diabetes may influence the occurrence, metastasis, and prognosis occ. These mechanisms include hyperglycemia, hyperinsulinemia, insulin resistance, chronic inflammation, and immune dysfunction.⁴⁶

2.6 | Diabetes and salivary gland diseases

In recent years, accumulating evidence has established a robust association between salivary gland diseases and diabetes.¹⁶⁰ Salivary gland dysfunction in diabetic patients is predominantly characterized by impaired salivary secretion, resulting in diminished saliva flow, a sensation of dry mouth, and an elevated risk of dental caries.^{161,162} Considering that the management of xerostomia should prioritize addressing its underlying causes,¹⁶³ effective blood glucose control is essential for diabetic patients experiencing this condition. When indicated, local saliva substitutes and/or stimulants may be utilized as adjunctive therapies.

Nitric oxide synthase (NOS) and its cofactor tetrahydrobiopterin (BH4) have been identified as promising targets for mitigating the reduced salivary secretion associated with diabetes-induced xerostomia.¹⁶⁴ Immunohistochemical analyses of diabetic rats further elucidate that inflammation and oxidative stress are critical contributors to the progression of this condition.¹⁶⁵ Additionally, acinar cell vacuolation,¹⁶⁶ intracellular structural damage,¹⁶⁷ and dysfunction of the cholinergic vasodilation pathway¹⁶⁸ have been implicated as potential mechanism.

Novel approaches have emerged to alleviate xerostomia and enhance salivary secretion in diabetic patients. Wu et al. reported that sialography-guided injection of pancreatic lipase into the salivary glands can effectively mitigate diabetes-related chronic obstructive parotitis.¹⁶⁹ Additionally, Muhamed et al. confirmed the efficacy of a topical saliva stimulant spray containing 1% malic acid for treating xerostomia in patients with T2DM.¹⁷⁰ Furthermore, animal studies have demonstrated that both atropine and metformin can ameliorate salivary gland damage in diabetic rats and alleviate symptoms of xerostomia, with effects being particularly pronounced when used in combination.¹⁷¹ These findings may offer new insights and strategies for the clinical management of diabetic xerostomia.

2.7 | Diabetes and dental caries

Diabetic patients exhibit a heightened risk of developing dental caries,¹⁷² which is influenced by their glycemic control and the duration of diabetes.¹⁷³ Two meta-analyses

TABLE 3 Clinical trials related to rheumatoid arthritis (RA) and oral health.

Diseases	Type of study	Aim	Sample	Sample	Molecule	Conclusions
Periodontitis	Cross-sectional study	Evaluate the relationship between periodontal parameters and the presence and levels of ACPAs.	164 RA patients	Blood	ACPA	In RA, the severity of periodontal conditions is linearly correlated with the presence and levels of ACPAs. ¹⁸⁵
	Retrospective cross-sectional study	Assess the production of NETs in patients with periodontitis and RA and their relationship with clinical parameters.	Early RA ($n = 24$), established RA ($n = 64$) and individuals without RA ($n = 76$)	Saliva and plasma	NETs	NETs may link PD and RA, with periodontal treatment significantly altering circulating NET levels. ¹⁸⁶
	Cross-sectional study	Investigate whether serum levels of TREM-1 and PGLYRP1 are associated with periodontitis in patients with RA.	154 participants with RA ($n = 55$), Behcet's disease ($n = 41$) and healthy controls ($n = 58$)	Serum and saliva	TREM-1 and PGLYRP1	Elevated serum TREM-1 is associated with PD and disease activity in RA. ¹⁸⁷
	Cross-sectional study	Examine the effects of periodontitis and RA on the serum and saliva concentrations of MCP-1, MIF, and fractalkine.	Periodontitis ($n = 21$), or with RA ($n = 23$), or with both diseases ($n = 23$), systemically and periodontally healthy individuals ($n = 22$)	Saliva and serum	MCP-1, MIF, fractalkine	In RA, saliva shows elevated levels of MCP-1, MIF, and fractalkine. ¹⁸⁸
	Case-control study	Investigate the genetic variations of PTPN22, PADI4, and CTLA4 and their impacts on RA and periodontitis.	111 RA patients and 256 systemically healthy controls	Blood, plaque	PTPN22, PADI4, CTLA4	Genetic variations may suggest a potential link between periodontitis and RA. ¹⁸⁹
	Cross-sectional study	Investigate salivary and serum IgA ACPA in a population-based cohort of elderly RA patients.	Patients with RA ≥ 61 years of age ($n = 132$)	Serum and saliva	Serum IgG ACPA and serum and saliva IgA ACPA	Serum and salivary IgA ACPA are not commonly found in RA patients with PD. ¹⁹⁰
	Retrospective cohort study	Explore the relationship between periodontal and serological indicators and disease activity in RA.	127 patients with RA	Serum	Anti-agalactosyl immunoglobulin G	PF is positively correlated with anti-agalactosyl IgG titers, and both show a positive association with disease activity in RA. ¹⁹¹
	Cross-sectional study	Investigate the relationship between antibody titers against fibrinogen-derived CCP and anti-CEP-1 in RA patients.	107 patients with RA	Plasma and plaque	Anti-CCP and anti-CEP-1 antibodies	In RA, PD may be a secondary risk factor for anti-CCP positivity. ¹⁹²
	Case-control study	Investigate whether the association between periodontitis and RA is influenced by SNPs in the genes encoding PAD2 and PAD4.	137 RA patients and 161 controls with self-reported periodontitis	Blood	rs2057094, rs2076616, rs2235912	Carriers of the alleles for SNPs rs2057094, rs2076616, and rs2235912 in the PADI2 gene may have an increased risk of developing RA in patients with periodontitis. ¹⁹³
	Case-control study	Quantify the relationship between periodontal clinical indicators, ABL, concentrations of antibodies against <i>Porphyromonas gingivalis</i> (<i>P. gingivalis</i>), <i>P. intermedia</i> , and <i>Fusobacterium nucleatum</i> (<i>F. nucleatum</i>), and the concentration of anti-MAA antibodies.	($n = 284$ RA cases, $n = 330$ OA controls)	Plasma	anti-MAA antibodies	MAA may play a role in the interaction between periodontal tissues and RA. ¹⁹⁴
	Case-controlled clinical trial	Investigate the levels of PRL in GCF, synovial fluid, and serum of patients with moderate active RA, both with and without periodontitis.	80	GCF, synovial fluid, and plasma	PRL	Local PRL levels in GCF and synovial fluid seem to be associated with the disease processes of periodontitis and RA, compared to serum levels. ¹⁹⁵

(Continues)

TABLE 3 (Continued)

Diseases	Type of study	Aim	Sample	Sample	Molecule	Conclusions
Sjögren's syndrome	Cross-sectional research	Investigate the relationship between NLRP3 gene polymorphisms and patients with RA and primary SS.	A total of 239 patients with RA, 285 patients with primary SS, and 170 controls	Blood	NLRP3 gene polymorphism	The NLRP3 genotype may affect clinical outcomes and progression in RA and primary SS. The activity of the NLRP3 inflammasome may explain the severity of these diseases. ¹⁹⁶

Abbreviations: ABL, alveolar bone loss; ACPA, anti-citrullinated protein antibody; anti-CCP, anti-cyclic citrullinated peptides; anti-CEP-1, anti-citrullinated α -enolase peptides; ARE, arylesterase; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GCF, gingival crevicular fluid; MAA, malondialdehyde-acetaldehyde; MCP-1, monocyte chemoattractant protein-1; MIF, migration inhibitory factor; NETs, neutrophil extracellular traps; OSI, oxidative stress index; PD, periodontitis; PGLYRP1, peptidoglycan recognition protein 1; PRL, prolactin; SNP, single nucleotide polymorphism; SS, Sjögren's syndrome; TAS, total antioxidant status; TMD, temporomandibular disorders; TOS, total oxidative status; TREM-1, triggering receptor expressed on myeloid cells 1.

have explored the relationship between diabetes and dental caries. One analysis revealed that the overall prevalence of dental caries in children and adolescents with type 1 diabetes was 67%, with the highest prevalence observed in South America and the lowest among patients maintaining good metabolic control.¹⁷⁴ The other study indicated that type 2 diabetes may contribute to an increase in the incidence of caries among adults.⁵⁰

The mechanisms underlying the association between diabetes and dental caries remain inadequately explored; however, they may be related to the effects of diabetes on saliva flow rate and buffering capacity, as well as alterations in the oral microbiota of affected individuals. Research has demonstrated that individuals with diabetes exhibit elevated levels of *Lactobacillus* alongside diminished saliva flow and buffering capacity. These factors facilitate the proliferation of *Streptococcus mutans*, thereby increasing the risk of dental caries.^{175,176}

2.8 | Diabetes and root fracture

Root fracture refers to a break or crack in the root of a tooth. The incidence of vertical root fracture (VRF) in diabetic patients is 2.67 times higher than that observed in nondiabetic individuals.¹⁷⁷ Furthermore, the resistance to root fracture in the premolars of diabetic patients is significantly lower compared to their nondiabetic counterparts.¹⁷⁸

The impact of diabetes on the physiological structure of teeth may be related to the increased incidence of root fracture in diabetic patients. Research has found that diabetes can disrupt enamel development, leading to alterations in its microstructure and mechanical properties.¹⁷⁹ Additionally, diabetes affects the nanostructure of dentin, with concentrations of elements such as magnesium, zinc, strontium, lithium, manganese, and selenium being significantly lower than those in nondiabetic patients, while copper concentrations are higher in diabetic patients.¹⁸⁰

3 | RHEUMATOID ARTHRITIS

RA is a chronic systemic autoimmune disorder that primarily targets the joints, resulting in pain, stiffness, and a decline in joint function.¹⁸¹ Patients with RA exhibit a heightened incidence of dental caries, pulpitis, gingivitis, periodontitis, and oral ulcers.¹⁸² The oral health-related quality of life (OHRQoL) in patients with RA is compromised, influenced by factors such as the type of RA and the severity of periodontitis.^{183,184} Consequently, understanding the relationship between RA and oral health, along with the underlying mechanisms, is crucial for the prevention and management of oral diseases in RA patients and may contribute to enhanced overall health outcomes.

To provide readers with a concise overview of the connections between RA and oral diseases, we summarize recent findings from relevant clinical studies in the table, highlighting key factors involved (Table 3).

3.1 | RA and periodontitis

Over the past decade, numerous studies worldwide have confirmed the correlation between RA and periodontitis.^{197–200} On one hand, certain RA medications appear to elevate the risk of periodontal inflammation and exacerbate periodontitis.^{201,202} Conversely, periodontal treatment has been shown to reduce RA activity.^{181,203,204} The mechanisms by which RA influences periodontitis primarily involve microbial factors, inflammatory mediators, and genetic associations (Figure 3).

Patients with periodontitis and RA often exhibit an abnormal abundance of specific microorganisms,^{205,206} along with limited variation in microbial taxa and gene functions between deep and shallow subgingival sites.²⁰⁷ These findings suggest that RA may influence the development and progression of periodontitis through alterations in the microbiome. Furthermore, specific oral pathogens such as *Porphyromonas gingivalis* (*P. gingivalis*) produce peptidyl arginine deiminase (PPAD),²⁰⁸ which can

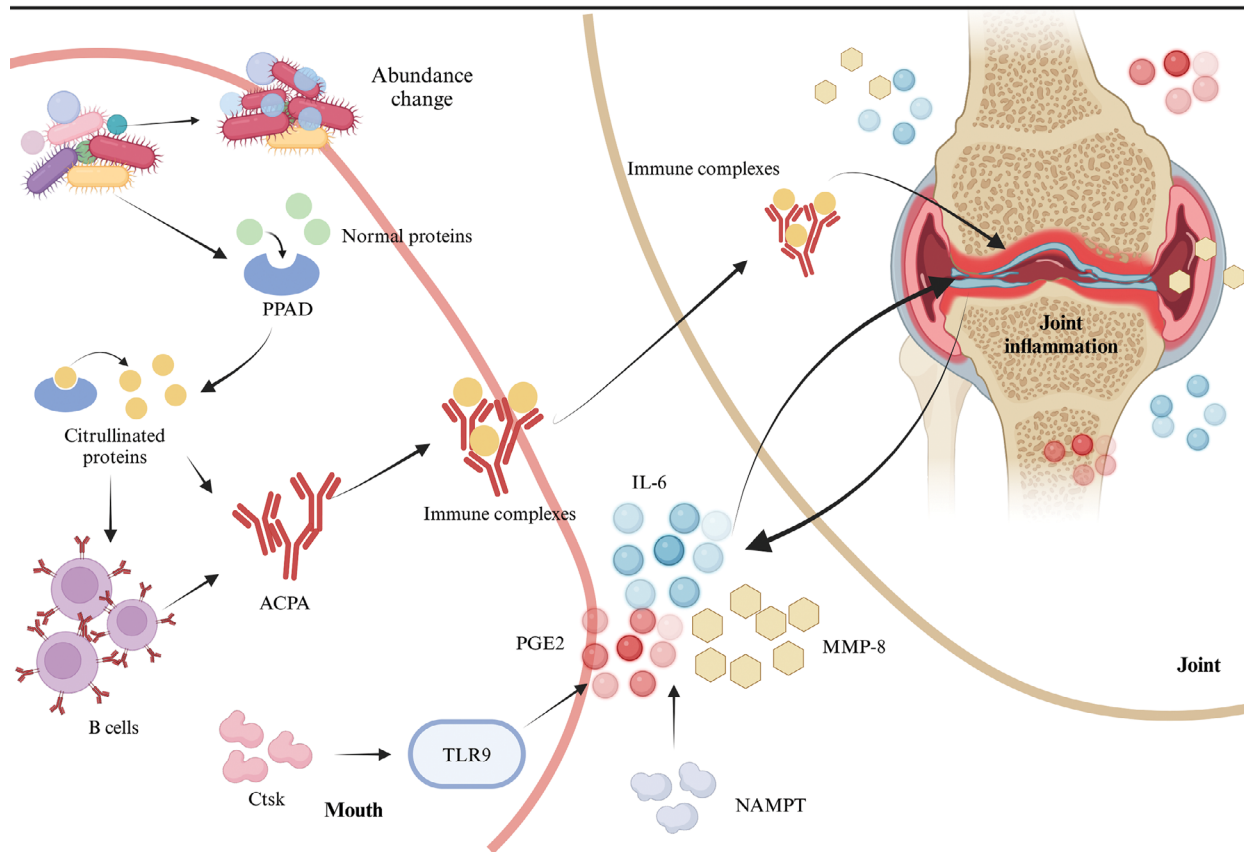


FIGURE 3 Mechanisms linking oral health and rheumatoid arthritis. Microorganisms such as *Porphyromonas gingivalis* (*P. gingivalis*) produce PPAD, which citrullinates proteins and stimulates B cells to generate ACPAs. These ACPAs form immune complexes that accumulate in the joints, contributing to the pathogenesis of rheumatoid arthritis. Additionally, NAMPT and Ctsk trigger inflammatory responses through distinct pathways, elevating levels of inflammatory cytokines and MMP-8, ultimately leading to joint tissue damage. Furthermore, the composition of oral bacteria is altered in patients with rheumatoid arthritis. ACPA, anti-citrullinated protein antibodies; Ctsk, cathepsin K; IL-6, interleukin-6; MMP-8, matrix metalloproteinase 8; NAMPT, nicotinamide phosphoribosyl transferase; PGE2, prostaglandin E2; PPAD, *P. gingivalis* peptidyl arginine deiminase. Created with BioRender.com.

citrullinate proteins, resulting in the formation of citrullinated autogenic antigens (CPAs) and subsequently leading to the production of anti-citrullinated protein antibodies (ACPAs).²⁰⁹

Furthermore, RA and periodontitis share common molecular mediators, such as MMP-8, IL-6, and prostaglandin E2.^{210,211} These same mediators may play a role in their interaction. RA can also influence periodontitis by regulating inflammatory factors through various upstream mediators. Studies have shown that nicotinamide phosphoribosyl transferase (NAMPT) expression is upregulated in the periodontal ligament tissues of RA mice, resulting in elevated levels of proinflammatory cytokines (IL-6), chemokines (IL-8, CCL5), and inflammatory mediators such as COX-2, MMP-1, and MMP-3 in periodontal ligament cells.²¹² Another study suggests that cathepsin K (Ctsk) influences the infiltration of dendritic cells and T cells, as well as the production of inflammatory factors through the TLR9 signaling pathway, serving as a key pathological regulator in both RA and periodontitis.

This mechanism contributes to enhanced erosion of periodontal bone and knee cartilage.²¹³

In addition to the aforementioned microbial and inflammatory factors, other studies have explored genetic associations. It was found that IL-1 α -889 C/IL-1 β -511a is positively correlated with RA.²¹⁴ Furthermore, another study indicated that a high incidence and severity of periodontitis in first-degree relatives (FDRs) of RA patients are associated with seropositivity for ACPAs, further supporting the hypothesis that periodontitis may serve as a risk factor for the development of RA.²¹⁵

3.2 | RA and other oral diseases

3.2.1 | Temporomandibular disorders

Many patients with RA exhibit clinical manifestations of temporomandibular joint (TMJ) inflammation, with the most common symptoms including pain in the TMJ area

during movement or stress, joint clicking, and impaired mandibular function.²¹⁶ A large-scale clinical study in Taiwan found that the risk of temporomandibular disorders (TMD) in patients with RA is 2.538 times higher than that in non-RA patients.²¹⁷ Bone resorption occurs within the TMJ of RA patients, potentially mediated by TNF through synovial fluid.²¹⁸ In terms of treatment, animal studies have demonstrated that bone marrow mesenchymal stem cells (BMSCs) significantly enhance the healing of TMJs in rats with induced RA.²¹⁹

3.2.2 | Sjögren syndrome and xerostomia

It has been reported that 51% of patients with RA experience dry mouth, and a statistically significant relationship exists between dry mouth and poor OHRQoL. The rates of whole-mouth saliva at rest and stimulated parotid saliva flow in RA patients are significantly lower than those observed in non-RA individuals.²²⁰ The OHRQoL of RA patients is adversely affected by dry mouth syndrome, which subsequently impacts their overall quality of life.¹⁸⁴ Regarding the underlying mechanism, a case-control study was conducted to investigate the role of viruses in the association between RA and Sjögren's syndrome (SS), revealing that Epstein-Barr virus (EBV) is more prevalent among RA patients and correlates with Schirmer test results.²²¹

3.2.3 | Dental caries and apical periodontitis

It has been observed that patients with RA exhibit a higher frequency and severity of dental plaque, with significantly elevated counts of *S. mutans* in the RA group.²²² There may also be an association between increased levels of systemic inflammatory cytokines induced by RA and AP. A cross-sectional study demonstrated that RA is significantly associated with a higher prevalence of AP, indicating that RA patients are more likely to develop this condition. However, RA does not appear to influence the outcomes of RCT.²²³

4 | CARDIOVASCULAR DISEASES

CVDs, encompassing conditions such as ischemic heart disease, stroke, heart failure, peripheral artery disease, and various other cardiac and vascular disorders, represent a leading cause of mortality worldwide and significantly impair quality of life.^{224,225} In 2019, CVDs accounted for 33% of all global deaths, with ischemic heart disease (9.1 million deaths) and stroke (6.6 million deaths) collec-

tively representing 85% of fatalities related to CVDs.²²⁶ There is a strong association between CVDs and oral health, particularly through the link between atherosclerosis and periodontitis. Additionally, an interplay exists between hypertension and periodontitis. Furthermore, patients with CVDs frequently exhibit higher rates of dental caries and tooth loss.

Consequently, it is imperative to underscore the critical role of clinical practitioners, dental professionals, and other healthcare providers in comprehending the relationship between periodontal disease and CVDs, identifying their risk factors, and recognizing the urgent need for timely referrals to specialized dental or periodontal care. Mitigating the prevalence and incidence of periodontal disease may contribute to a reduction in the associated risks of systemic diseases.

4.1 | Atherosclerotic vascular disease and periodontal diseases

Atherosclerotic vascular disease (ASVD) is a chronic condition characterized by the accumulation of lipids, cholesterol, and other substances within the arterial walls, leading to the formation of atherosclerotic plaques.²²⁷ There is a significant increase in risk associated with chronic periodontitis and ASVD, independent of other established cardiovascular risk factors.²²⁸ Meta-analyses encompassing prospective cohort studies, case-control studies, and cross-sectional studies consistently demonstrate a markedly elevated risk of coronary heart disease (CHD) in patients with periodontal disease.⁷ Furthermore, periodontal disease increases the incidence of myocardial infarction by two to four times,²²⁹ while severe periodontal disease can elevate the risk of stroke by 3.5%.²³⁰

The underlying mechanisms linking ASVD and periodontitis primarily involve infection, molecular mimicry, and systemic inflammation (Figure 4).²³¹ Furthermore, numerous lines of evidence suggest a potential association between *P. gingivalis* and atherosclerotic diseases related to periodontal disease. First, *P. gingivalis* can invade cardiovascular cells,²³² with its distant invasion correlating with an increased risk of acute myocardial infarction,²³³ indicating that it may exacerbate the severity of coronary artery disease through the induction of systemic inflammation. Second, *P. gingivalis* degrades platelet endothelial cell adhesion molecules (PECAM-1) and vascular endothelial cadherin (VE-cadherin), compromising the integrity of the endothelial barrier and enhancing vascular permeability.²³⁴ This disruption may promote platelet aggregation and the release of proinflammatory cytokines, potentially accelerating the progression of atherosclerosis.²³⁵ Additionally, the presence of *P.*

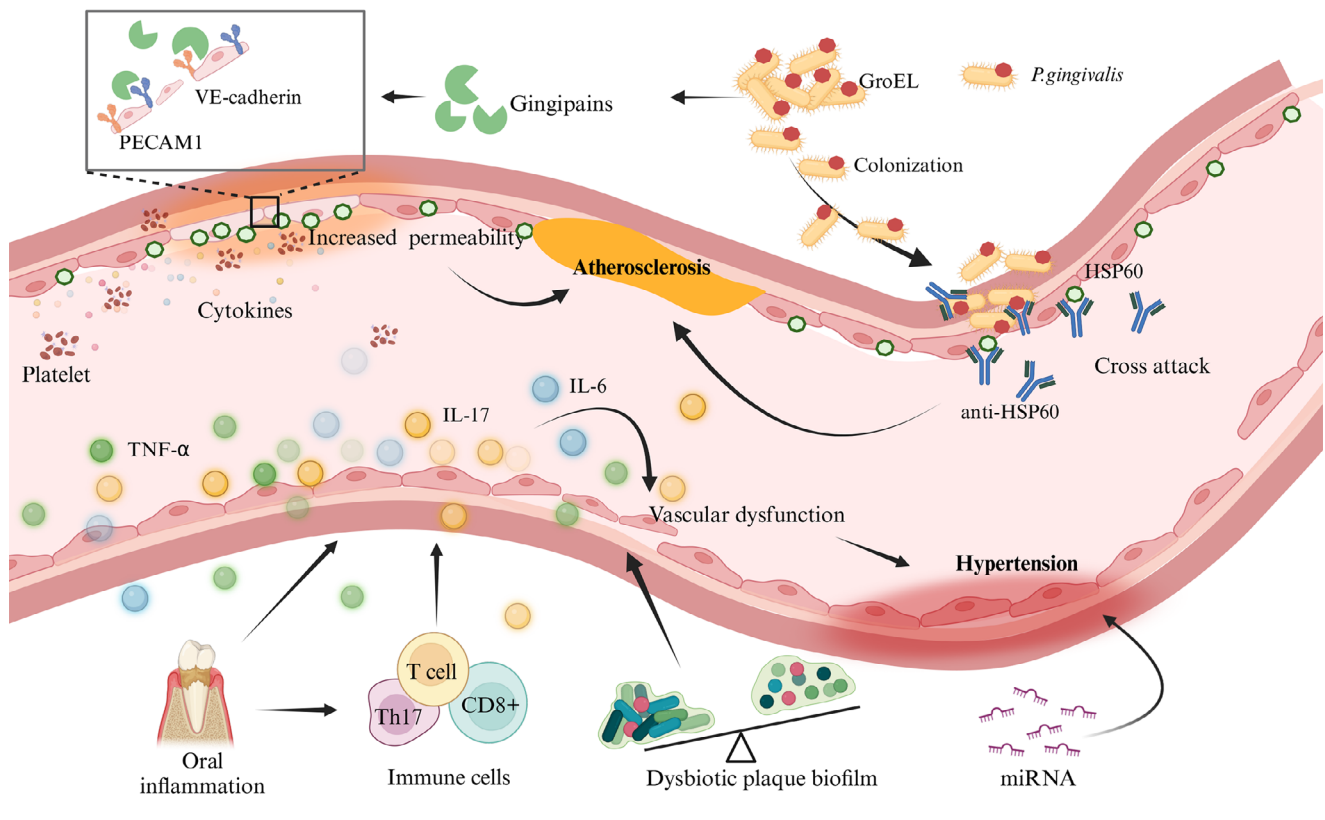


FIGURE 4 Mechanisms linking oral health and cardiovascular diseases. **Atherosclerosis:** *Porphyromonas gingivalis* (*P. gingivalis*) contains GroEL protein, which shares structural similarities with the HSP60 epitopes expressed by vascular endothelial cells. Consequently, antibodies against HSP60 may inadvertently target and damage these endothelial cells, thereby promoting the development of atherosclerosis. Additionally, *P. gingivalis* produces gingipains that degrade PECAM-1 and VE-cadherin, disrupting the integrity of the endothelial barrier, increasing permeability, promoting platelet aggregation, and triggering the release of proinflammatory cytokines—factors that may accelerate the progression of atherosclerosis. Created with BioRender.com. **Hypertension:** The inflammatory environment within the oral cavity releases cytokines such as TNF- α , IL-6, and IL-17, which can impair endothelial function and contribute to hypertension. Furthermore, this inflammatory milieu activates various immune cells, exacerbating cytokine release and resulting in vascular dysfunction. Additionally, dysbiosis of the oral microbiota may also be associated with hypertension. HSP60, heat shock protein 60; IL-6, interleukin-6; IL-17, interleukin-17; PECAM1, platelet endothelial cell adhesion molecule; TNF- α , tumor necrosis factor-alpha; VE-cadherin, vascular endothelial cadherin; WBC, white blood cell. Created with BioRender.com.

gingivalis is often associated with significantly elevated levels of antibodies against human heat shock protein 60 (HSP60).²³⁶ Under conditions characterized by endothelial dysfunction, HSP60 expression is observed; its epitopes share similarities with GroEL protein from *P. gingivalis*,²³⁷ which may lead to cross-reactivity that further exacerbates endothelial damage and accelerates atherosclerosis.

4.2 | Hypertension and periodontal diseases

Hypertension is a prevalent risk factor for CVDs, affecting approximately 45% of the global population, with prevalence rates increasing with age.²³⁸ Notably, about 50% of hypertensive patients fail to achieve effective blood pres-

sure control.^{239,240} This high prevalence can largely be attributed to a lack of public awareness regarding the classic triggers of hyperadherence to treatment recommendations among patients.²⁴¹ However, it is crucial to consider that nonclassical cardiovascular risk factors, such as periodontitis, may also contribute to the onset and poor management of hypertension.²⁴²

Clinical data and systematic reviews indicate that patients with periodontal disease exhibit significantly higher systolic and diastolic blood pressure compared to those without the condition,²⁴³ with a notable association between moderate to severe periodontal disease and an increased risk of hypertension.²⁴⁴ Furthermore, there is a significant correlation among periodontal disease, the number of missing teeth, and the experience of basic periodontal treatment concerning future incidence

of hypertension.²⁴⁵ Despite considerable heterogeneity across studies, current evidence suggests that periodontal treatment is associated with a marked reduction in C-reactive protein (CRP) levels and an improvement in endothelial function, along with varying degrees of blood pressure reduction.^{11,246,247}

The pathogenesis of hypertension in patients with periodontitis is complex and not yet fully elucidated, involving multiple interconnected mechanisms. For instance, inflammatory responses characterized by elevated levels of inflammatory molecules during periodontitis impair endothelial function and contribute to increased blood pressure (Figure 4).^{241,248,249} Immune cell responses are also significant; activated T cells migrate to vascular tissues, releasing proinflammatory cytokines that lead to vascular dysfunction.^{249–251} Additionally, microbial dysbiosis in the oral cavity, marked by pathogenic bacteria associated with periodontitis, correlates with elevated blood pressure.^{252–254} Finally, noncoding RNAs, particularly microRNAs, may serve as epigenetic regulators linking periodontitis and hypertension.²⁵⁵

4.3 | Other oral diseases

In addition to periodontitis, patients with CVDs demonstrate a higher incidence of dental caries and tooth loss.^{228,256,257} The loss of five or more teeth is significantly associated with an increased risk of CHD events and acute myocardial infarction. When the number of missing teeth reaches nine or more, there is a notable association with the risk of CVDs, diabetes, and all-cause mortality.²⁵⁸ A meta-analysis revealed a linear relationship between tooth loss and CHD mortality.²⁵⁹

5 | CHRONIC RESPIRATORY DISEASES

The primary function of the respiratory system is to facilitate the exchange of oxygen and carbon dioxide, thereby supporting the metabolic activities of the body's cells. Common respiratory diseases include chronic obstructive pulmonary disease (COPD), asthma, and pneumonia. According to the 2019 Global Burden of Disease study, chronic respiratory diseases ranked as the third leading cause of death, accounting for 4 million fatalities worldwide and affecting approximately 454.6 million cases (ranging from 417.4 to 499.1 million).²⁶⁰

The oral cavity is anatomically connected to the upper respiratory tract, and as air and food traverse the mouth into the pharynx, pathogens or inflammatory substances may enter the throat or lungs, potentially triggering or exacerbating respiratory diseases such as pneumonia,

COPD, asthma, and lung cancer.²⁶¹ Studies have demonstrated a significant degree of similarity between the oral and lung microbiomes in healthy individuals.²⁶²

Research shows that oral diseases are closely associated with various lung diseases, such as asthma, COPD, pulmonary fibrosis, and pneumonia.^{263,264} Patients with chronic respiratory diseases show a declining trend in OHRQoL.²⁶⁵

5.1 | COPD

Patients with COPD often exhibit poorer oral health, as evidenced by worse periodontal status, higher plaque indices, and elevated DMFT (decayed, missing, filled teeth) scores.²⁶⁶ Poor oral conditions or diseases, such as periodontitis,^{267,268} dental caries,²⁶⁴ and tooth loss²⁶⁹ can exacerbate airflow limitation in COPD patients, worsening daily respiratory symptoms like coughing and wheezing and potentially contributing to acute exacerbations that lead to increased hospitalization rates and higher mortality. Direct evidence demonstrating that oral care interventions can improve outcomes in COPD is currently limited; however, two small-scale trials have suggested that periodontal treatment may reduce the frequency of COPD exacerbations.^{12,270}

Research on the mechanisms linking COPD and various oral diseases is limited, with many studies conducted using animal models. These mechanisms may involve immune responses, microbial factors, and ferroptosis (Figure 5). Mutual exacerbation of periodontitis and COPD is associated with the activation of $\gamma\delta$ T cells and M2 macrophages, ultimately leading to increased expression of IL-17 and interferon gamma (IFN- γ), as well as M2 macrophage polarization.²⁷¹ Furthermore, *P. gingivalis* or *Fusobacterium nucleatum* (*F. nucleatum*) promoted the development of COPD and impaired lung function in mice.²⁷² Studies have also shown that periodontitis accelerates the progression of COPD by upregulating ferroptosis in lung tissue.²⁷³

5.2 | Bronchial asthma (asthma)

Patients with asthma exhibit altered salivary flow rates and composition, as well as poorer oral health, characterized by a higher prevalence of dental caries.^{274,275} Medications, such as inhaled corticosteroid (ICS) therapy used to treat bronchial asthma are also associated with an increased incidence of dental caries.²⁷⁶ The heightened risk of dental caries linked to ICS may be attributed to changes in salivary composition and flow rate.²⁷⁷ Furthermore, clinical data and systematic reviews indicate that asthma patients

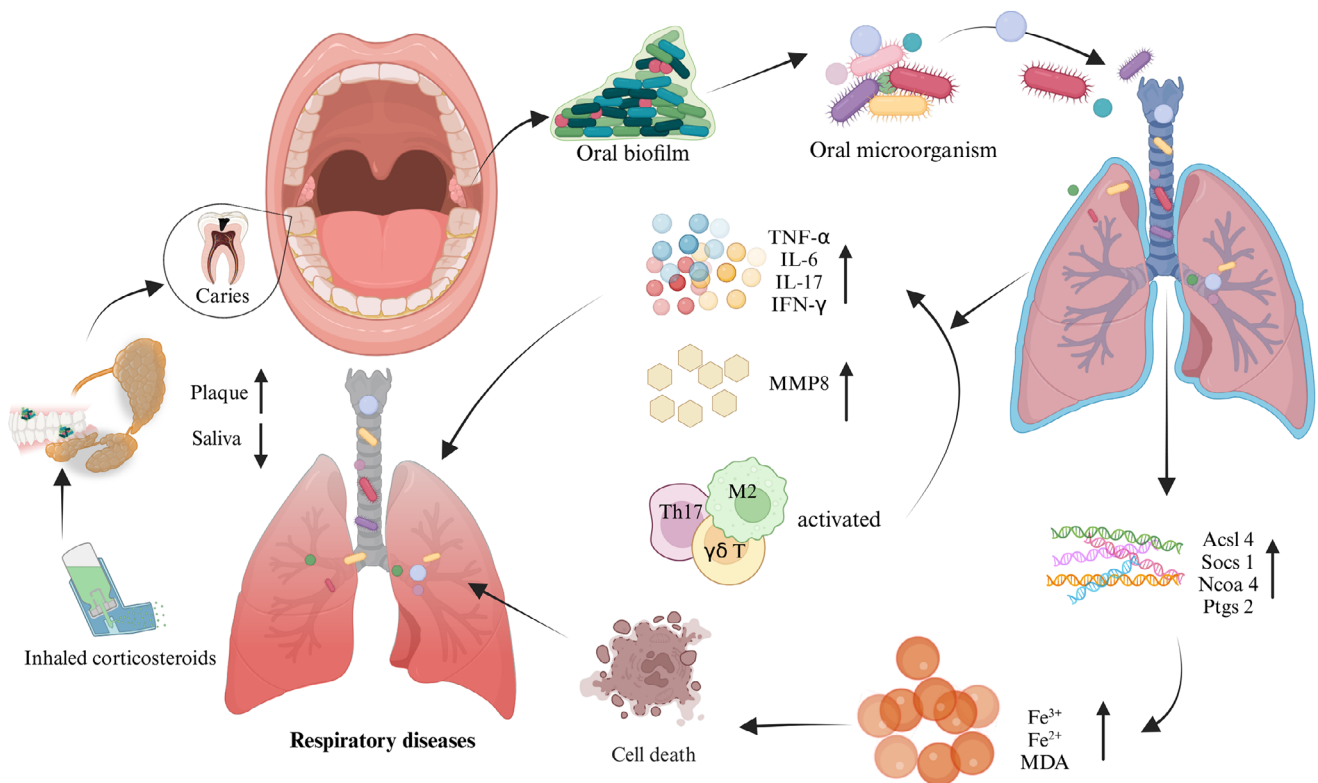


FIGURE 5 Mechanisms linking oral health and chronic respiratory diseases. Under specific conditions, oral bacteria can translocate to the respiratory tract and colonize the lungs. This may trigger immune and inflammatory responses, leading to the production of cytokines and MMPs that can damage lung tissue, potentially impacting oral tissues as well. Additionally, the expression of ferroptosis-promoting genes such as *Acsl4*, *Socs1*, *Ncoa4*, and *Ptgs2* are upregulated, inducing ferroptosis and contributing to chronic respiratory diseases. Furthermore, treatments for chronic respiratory diseases—such as inhaled corticosteroids—may increase plaque formation and reduce salivary flow rate, thereby elevating the risk of dental caries. *Acsl4/Socs1/Ncoa4/Ptgs2*, ferroptosis-related genes; IFN- γ , interferon-gamma; IL-6, interleukin-6; IL-17, interleukin-17; MDA, malondialdehyde; MMP-8, matrix metalloproteinase 8; TNF- α , tumor necrosis factor-alpha. Created with BioRender.com.

may have an elevated risk of periodontitis^{278,279} and tooth loss.²⁸⁰

Currently, there is no conclusive evidence establishing a direct biological link between periodontitis and asthma. The prevailing theoretical framework posits that these two inflammatory diseases may influence one another through microbial interactions, inflammatory factors, and immune responses (Figure 5). Research has shown that the periodontal pathogen *Prevotella* can induce the production of matrix metalloproteinases (MMPs), which adversely affect both periodontitis and asthma.²⁸¹ Additionally, MMPs can be produced by various inflammatory cells in the respiratory tract, potentially exacerbating periodontal inflammation.²⁸² On the immunological front, periodontal pathogens activate host immune cells to produce cytokines such as prostaglandin E2 (PGE2), interferon- γ , TNF- α , and several interleukins (IL-1, IL-6, IL-10, IL-11). These cytokines stimulate macrophages and osteoclasts to release hydrolases and collagenases—enzymes that degrade colla-

gen and elastic fibers in lung tissue—thereby contributing to bronchial remodeling processes in asthma.²⁸³ Moreover, Th17 cells are implicated in various immune-mediated inflammatory conditions such as psoriasis and RA; they serve as potent mediators of tissue inflammation. Interleukin 17A (IL-17A) can activate a range of inflammatory cascades that mediate the development and progression of periodontitis along with related systemic chronic inflammatory diseases like asthma.²⁸⁴

5.3 | Pneumonia

Epidemiological studies have demonstrated a correlation between oral health issues and the risk of developing pneumonia. Data from the Korean national population indicate that oral health problems, such as dental caries and tooth loss, significantly increase the risk of pneumonia; frequent tooth brushing and regular professional dental

cleanings are associated with a reduced incidence of this condition.²⁸⁵ In specific populations, including intensive care unit (ICU) patients,²⁸⁶ adults with severe and complex neurological disorders,²⁸⁷ postoperative cancer patients,²⁸⁸ and acute stroke patients,²⁸⁹ professional oral care has been linked to a decrease in pneumonia incidence. When examining specific types of pneumonia, evidence supporting the link between oral health is more consistent for hospital-acquired pneumonia (HAP),^{290,291} whereas the association with community-acquired pneumonia (CAP) remains controversial.²⁹²⁻²⁹⁵

Regarding the potential mechanisms linking oral health to the development of various types of pneumonia, Kim et al. proposed that the oral environment can serve as a reservoir for pneumonia pathogens, which may be aspirated into the lower respiratory tract under certain conditions, thereby creating a favorable environment for pneumonia development.²⁹³ Recent studies have reaffirmed that oral bacteria can act as a source of infection in aspiration pneumonia, with the quantity of oral bacteria identified as a significant risk factor for this condition.^{296,297} Furthermore, inflammatory cytokines induced by oral inflammatory diseases such as periodontitis play a crucial role in pneumonia pathogenesis.²⁹⁸ Recent animal experiments have demonstrated that *P. gingivalis* induces pneumonia in mice with periodontitis, significantly increasing levels of cytokines and neutrophils in peripheral blood and lung tissue.²⁹⁹ A recent study innovatively transplanted human oral commensal microbiota into germ-free mice to create human oral microbiota-associated (HOMA) mice; this study analyzed the impact of oral microbiota on lung immunity and systemic conditions during acute lung injury and acute respiratory distress syndrome (ALI/ARDS).³⁰⁰ The results indicated that HOMA mice exhibited systemic dysbiosis; compared to conventional (CNV) mice with sufficient microbial diversity, HOMA mice developed more severe ALI.

Mouthwash is a critical component of oral hygiene, and chlorhexidine mouthwash has been shown to reduce the incidence of respiratory infections; however, long-term use may result in side effects including altered taste, dry mouth, and tooth discoloration. Over the past decade, research has increasingly focused on exploring new mouthwashes derived from natural products. A study comparing a 6.66% clove extract mouthwash with a 0.2% chlorhexidine mouthwash demonstrated that the control group had a 2.06-fold higher risk of developing ventilator-associated pneumonia (VAP) than the intervention group.¹³ Additionally, a triple-blind randomized controlled trial investigating the effects of propolis mouthwash revealed that the intervention group experienced significantly lower incidences of VAP on days 3, 5, and 7 compared to the control group. Propolis mouthwash may

represent a viable alternative to chlorhexidine for patients in ICU.³⁰¹

6 | CONCLUSION

Chronic diseases and oral health are intricately linked, as conditions such as periodontitis, dental caries, and AP can potentially increase the risk of chronic illnesses through pathways like systemic inflammation and pathogen transmission. Addressing oral hygiene is not only crucial for dental health but also plays a significant role in reducing the burden of chronic diseases. Improving oral health management, raising public awareness, and providing accessible and cost-effective dental care can have a profound impact on public health outcomes. Medical institutions should consider integrating oral health into comprehensive patient care for individuals with CVDs, particularly during rehabilitation, by incorporating oral health education and preventive care. This holistic approach could mitigate long-term risks while enhancing the overall quality of life for these patients.

The intricate and intimate connection between chronic diseases and oral health offers an extensive array of exploration prospects for future research and clinical practice. Future research, for the first, will focus on uncovering the underlying mechanisms of these interactions, with the goal of identifying new therapeutic targets. For example, mechanistic studies on diabetes and periodontitis suggest future drug targets may involve proresolving pathways, host response modulation, Th17/Treg imbalance, antioxidant therapy, immune training, and genetic modifications.^{302,303} The integration of emerging technologies, such as multiomics approaches and artificial intelligence (AI), will be crucial for discovering new mechanism.^{304,305} In the future, noninvasive diagnostic tools, such as saliva-based rapid detection and continuous monitoring devices, will enable early detection and ongoing management of oral health issues linked to chronic diseases.^{306,307}

AUTHOR CONTRIBUTIONS

Di Fu: conception of the work; interpretation of data for the work; drafting the work. **Xingyue Shu:** conception and design of the work; Substantial contributions to acquisition and analysis of data for the work. **Ge Zhou:** revised the manuscript. **Mengzhen Ji:** revised the manuscript. **Ga Liao:** contributions to acquisition and analysis of data for the work; revised the manuscript critically for important intellectual content. **Ling Zou:** conception and design of the work; revising it critically for important intellectual content; acquisition of fundings. All the authors have read and approved the final manuscript.

ACKNOWLEDGMENTS

Image created with Biorender.com, with permission. This work was supported by grants from the National Natural Science Foundation of China (Grant No. 82071111), Project of the Science and Technology Department of Sichuan Province (Grant No. 2024YFHZ0042), and the Clinical Research Program, West China Hospital of Stomatology Sichuan University (Grant no. LCYJ-MS-202310).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data availability is not applicable to this review as no new data were created or analyzed in this review.

ETHICS STATEMENT

Not applicable.

ORCID

Ga Liao  <https://orcid.org/0000-0003-4327-0054>

REFERENCES

1. Network GBoDC. *Global Burden of Disease Study 2019 (GBD 2019) Results*. Institute for Health Metrics and Evaluation – IHME; 2020.
2. Prevention CfDca. *Chronic Disease Prevention and Health Promotion. Chronic Disease Overview*. Centers for Disease Control and Prevention; 2017.
3. Waters HGM, ed. *The Costs of Chronic Disease in the U.S.* 1st ed. Milken Institute; 2018.
4. Bloom DE, Cafiero E, Jané-Llopis E, et al. *The Global Economic Burden of Noncommunicable Diseases*. Program on the Global Demography of Aging; 2012.
5. Kane SF. The effects of oral health on systemic health. *Gen Dent*. 2017;65(6):30-34.
6. Wu CZ, Yuan YH, Liu HH, et al. Epidemiologic relationship between periodontitis and type 2 diabetes mellitus. *BMC Oral Health*. 2020;20(1):204.
7. Bahekar AA, Singh S, Saha S, et al. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. *Am Heart J*. 2007;154(5):830-837.
8. Sanz M, Marco Del Castillo A, Jepsen S, et al. Periodontitis and cardiovascular diseases: consensus report. *J Clin Periodontol*. 2020;47(3):268-288.
9. Ferreira MKM, Ferreira RO, Castro MML, et al. Is there an association between asthma and periodontal disease among adults? Systematic review and meta-analysis. *Life Sci*. 2019;223:74-87.
10. Preshaw PM, Taylor JJ, Jaedicke KM, et al. Treatment of periodontitis reduces systemic inflammation in type 2 diabetes. *J Clin Periodontol*. 2020;47(6):737-746.
11. Sharma S, Sridhar S, McIntosh A, et al. Periodontal therapy and treatment of hypertension-alternative to the pharmacological approach. A systematic review and meta-analysis. *Pharmacol Res*. 2021;166:105511.
12. Apeessos I, Voulgaris A, Agrafiotis M, et al. Effect of periodontal therapy on COPD outcomes: a systematic review. *BMC Pulmon Med*. 2021;21(1):92.
13. Jahanshir M, Nobahar M, Ghorbani R, et al. Effect of clove mouthwash on the incidence of ventilator-associated pneumonia in intensive care unit patients: a comparative randomized triple-blind clinical trial. *Clin Oral Investig*. 2023;27(7):3589-3600.
14. Sanchez P, Everett B, Salamonson Y, et al. Oral health and cardiovascular care: perceptions of people with cardiovascular disease. *PLoS One*. 2017;12(7):e0181189.
15. Alqadi SF. Diabetes mellitus and its influence on oral health: review. *Diabetes Metab Syndr Obes*. 2024;17:107-120.
16. Grisi DC, Vieira IV, de Almeida Lima AK, et al. The complex interrelationship between diabetes mellitus, oral diseases and general health. *Curr Diabetes Rev*. 2022;18(3):e220321192408.
17. Ahmad R, Haque M. Oral health messiers: diabetes mellitus relevance. *Diabetes Metab Syndr Obes*. 2021;14:3001-3015.
18. Borgnakke WS, Genco RJ, Eke PI, et al. *Oral Health and Diabetes*. National Institute of Diabetes and Digestive and Kidney Diseases (US); 2021.
19. Negrini TC, Carlos IZ, Duque C, et al. Interplay among the oral microbiome, oral cavity conditions, the host immune response, diabetes mellitus, and its associated-risk factors-An overview. *Front Oral Health*. 2021;2:697428.
20. Enteghad S, Shirban F, Nikbakht MH, et al. Relationship between diabetes mellitus and periodontal/peri-implant disease: a contemporaneous review. *Int Dent J*. 2024;74(3):426-445.
21. Mirnic J, Djuric M, Brkic S, et al. Pathogenic mechanisms that may link periodontal disease and type 2 diabetes mellitus—the role of oxidative stress. *Int J Mol Sci*. 2024;25(18):9806.
22. Vlachou S, Loumé A, Giannopoulou C, et al. Investigating the interplay: periodontal disease and type 1 diabetes mellitus—a comprehensive review of clinical studies. *Int J Mol Sci*. 2024;25(13):7299.
23. Păunică I, Giurgiu M, Dumitriu AS, et al. The bidirectional relationship between periodontal disease and diabetes mellitus—a review. *Diagnostics*. 2023;13(4):681.
24. Zhao M, Xie Y, Gao W, et al. Diabetes mellitus promotes susceptibility to periodontitis-novel insight into the molecular mechanisms. *Front Endocrinol*. 2023;14:1192625.
25. Nibali L, Gkrantias N, Mainas G, et al. Periodontitis and implant complications in diabetes. *Periodontol 2000*. 2022;90(1):88-105.
26. Salhi L, Reners M. Update on the bidirectional link between diabetes and periodontitis. *Adv Exp Med Biol*. 2022;1373:231-240.
27. Genco RJ, Borgnakke WS. Diabetes as a potential risk for periodontitis: association studies. *Periodontol 2000*. 2020;83(1):40-45.
28. Genco RJ, Graziani F, Hasturk H. Effects of periodontal disease on glycemic control, complications, and incidence of diabetes mellitus. *Periodontol 2000*. 2020;83(1):59-65.
29. Graves DT, Ding Z, Yang Y. The impact of diabetes on periodontal diseases. *Periodontol 2000*. 2020;82(1):214-224.
30. Polak D, Sanui T, Nishimura F, et al. Diabetes as a risk factor for periodontal disease-plausible mechanisms. *Periodontol 2000*. 2020;83(1):46-58.

31. Costa R, Ríos-Carrasco B, Monteiro L, et al. Association between type 1 diabetes mellitus and periodontal diseases. *J Clin Med*. 2023;12(3):1147.
32. Maia MB, Souza JGS, Bertolini M, et al. Knowledge of bidirectional relationship between diabetes and periodontal disease among diabetes patients: a systematic review. *Int J Dent Hyg*. 2023;21(1):28-40.
33. Nguyen ATM, Akhter R, Garde S, et al. The association of periodontal disease with the complications of diabetes mellitus. A systematic review. *Diabetes Res Clin Pract*. 2020;165:108244.
34. Stöhr J, Barbaresco J, Neuenschwander M, et al. Bidirectional association between periodontal disease and diabetes mellitus: a systematic review and meta-analysis of cohort studies. *Sci Rep*. 2021;11(1):13686.
35. Baeza M, Morales A, Cisterna C, et al. Effect of periodontal treatment in patients with periodontitis and diabetes: systematic review and meta-analysis. *J Appl Oral Sci*. 2020;28:e20190248.
36. Zhang Z, Ji C, Wang D, et al. The burden of diabetes on the soft tissue seal surrounding the dental implants. *Front Physiol*. 2023;14:1136973.
37. Vijay R, Mendhi J, Prasad K, et al. Carbon nanomaterials modified biomimetic dental implants for diabetic patients. *Nanomaterials*. 2021;11(11):2977.
38. Bencze B, Cavalcante BGN, Romandini M, et al. Prediabetes and poorly controlled type-2 diabetes as risk indicators for peri-implant diseases: a systematic review and meta-analysis. *J Dent*. 2024;146:105094.
39. Al Ansari Y, Shahwan H, Chrcanovic BR. Diabetes mellitus and dental implants: a systematic review and meta-analysis. *Materials*. 2022;15(9):3227.
40. Andrade CAS, Paz JLC, de Melo GS, et al. Survival rate and peri-implant evaluation of immediately loaded dental implants in individuals with type 2 diabetes mellitus: a systematic review and meta-analysis. *Clin Oral Investig*. 2022;26(2):1797-1810.
41. Lv X, Zou L, Zhang X, et al. Effects of diabetes/hyperglycemia on peri-implant biomarkers and clinical and radiographic outcomes in patients with dental implant restorations: a systematic review and meta-analysis. *Clin Oral Implants Res*. 2022;33(12):1183-1198.
42. Shang R, Gao L. Impact of hyperglycemia on the rate of implant failure and peri-implant parameters in patients with type 2 diabetes mellitus: systematic review and meta-analysis. *J Am Dent Assoc*. 2021;152(3):189-201.e181.
43. Tibúrcio-Machado CD, Bello MC, Maier J, et al. Influence of diabetes in the development of apical periodontitis: a critical literature review of human studies. *J Endod*. 2017;43(3):370-376.
44. Pérez-Losada FL, Estrugo-Devesa A, Castellanos-Cosano L, et al. Apical periodontitis and diabetes mellitus type 2: a systematic review and meta-analysis. *J Clin Med*. 2020;9(2):540.
45. Liu X, He G, Qiu Z, et al. Diabetes mellitus increases the risk of apical periodontitis in endodontically-treated teeth: a meta-analysis from 15 studies. *J Endod*. 2023;49(12):1605-1616.
46. Wang X, Wang H, Zhang T, et al. Diabetes and its potential impact on head and neck oncogenesis. *J Cancer*. 2020;11(3):583-591.
47. Ramos-García P, Roca-Rodríguez MDM, Aguilar-Diosdado M, et al. Diabetes mellitus and oral cancer/oral potentially malignant disorders: a systematic review and meta-analysis. *Oral Dis*. 2021;27(3):404-421.
48. Yan P, Wang Y, Yu X, et al. Type 2 diabetes mellitus and risk of head and neck cancer subtypes: a systematic review and meta-analysis of observational studies. *Acta Diabetol*. 2021;58(5):549-565.
49. Pérez-Ros P, Navarro-Flores E, Julián-Rochina I, et al. Changes in salivary amylase and glucose in diabetes: a scoping review. *Diagnostics*. 2021;11(3):453.
50. Zhou G, Shu X, Long Y, et al. Dental caries and salivary alterations in patients with type 2 diabetes: a systematic review and meta-analysis. *J Dent*. 2024;150:105321.
51. Weijndijk LPM, Van der Weijden GA, Slot DE. DMF scores in patients with diabetes mellitus: a systematic review and meta-analysis of observational studies. *J Dent*. 2023;136:104628.
52. Coelho AS, Amaro IF, Caramelo F, et al. Dental caries, diabetes mellitus, metabolic control and diabetes duration: a systematic review and meta-analysis. *J Esthet Restor Dent*. 2020;32(3):291-309.
53. de Lima AKA, Amorim Dos Santos J, Stefani CM, et al. Diabetes mellitus and poor glycemic control increase the occurrence of coronal and root caries: a systematic review and meta-analysis. *Clin Oral Investig*. 2020;24(11):3801-3812.
54. Roy M, Gastaldi G, Courvoisier DS, et al. Periodontal health in a cohort of subjects with type 1 diabetes mellitus. *Clin Exp Dent Res*. 2019;5(3):243-249.
55. Gogeneni H, Buduneli N, Ceyhan-Öztürk B, et al. Increased infection with key periodontal pathogens during gestational diabetes mellitus. *J Clin Periodontol*. 2015;42(6):506-512.
56. Chaparro A, Realini O, Hernández M, et al. Early pregnancy levels of gingival crevicular fluid matrix metalloproteinases-8 and -9 are associated with the severity of periodontitis and the development of gestational diabetes mellitus. *J Periodontol*. 2021;92(2):205-215.
57. Özçaka Ö, Ceyhan-Öztürk B, Gümüş P, et al. Clinical periodontal status and inflammatory cytokines in gestational diabetes mellitus. *Arch Oral Biol*. 2016;72:87-91.
58. Bunpeng N, Boriboonthirunsarn D, Boriboonthirunsarn C, et al. Association between gestational diabetes mellitus and periodontitis via the effect of reactive oxygen species in peripheral blood cells. *J Periodontol*. 2022;93(5):758-769.
59. Chaparro A, Zúñiga E, Varas-Godoy M, et al. Periodontitis and placental growth factor in oral fluids are early pregnancy predictors of gestational diabetes mellitus. *J Periodontol*. 2018;89(9):1052-1060.
60. Liu YK, Chen V, He JZ, et al. A salivary microbiome-based auxiliary diagnostic model for type 2 diabetes mellitus. *Arch Oral Biol*. 2021;126:105118.
61. Su N, Teeuw WJ, Loos BG, et al. Development and validation of a screening model for diabetes mellitus in patients with periodontitis in dental settings. *Clin Oral Investig*. 2020;24(11):4089-4100.
62. Vo TTT, Lee CW, Chiang YC, et al. Protective mechanisms of Taiwanese green propolis toward high glucose-induced inflammation via NLRP3 inflammasome signaling pathway in human gingival fibroblasts. *J Periodontol Res*. 2021;56(4):804-818.
63. Passoja A, Knuuttila M, Hiltunen L, et al. Serum interleukin-6 may modulate periodontal inflammation in type 1 diabetic subjects. *J Clin Periodontol*. 2011;38(8):687-693.

64. Matsuda Y, Kato T, Takahashi N, et al. Ligature-induced periodontitis in mice induces elevated levels of circulating interleukin-6 but shows only weak effects on adipose and liver tissues. *J Periodontol Res.* 2016;51(5):639-646.
65. Purnamasari D, Khumaedi AI, Soeroso Y, et al. The influence of diabetes and or periodontitis on inflammation and adiponectin level. *Diabetes Metab Syndr.* 2019;13(3):2176-2182.
66. Liu Y, Zhang Q. Periodontitis aggravated pancreatic β -cell dysfunction in diabetic mice through interleukin-12 regulation on Klotho. *J Diabetes Investig.* 2016;7(3):303-311.
67. Xiao E, Mattos M, Vieira GHA, et al. Diabetes enhances IL-17 expression and alters the oral microbiome to increase its pathogenicity. *Cell Host Microbe.* 2017;22(1):120-128.e124.
68. Cintra LT, Samuel RO, Azuma MM, et al. Apical periodontitis and periodontal disease increase serum IL-17 levels in normoglycemic and diabetic rats. *Clin Oral Investig.* 2014;18(9):2123-2128.
69. Ferreira RC, Simons HZ, Thompson WS, et al. IL-21 production by CD4+ effector T cells and frequency of circulating follicular helper T cells are increased in type 1 diabetes patients. *Diabetologia.* 2015;58(4):781-790.
70. Singhal S, Pradeep AR, Kanoriya D, et al. Human soluble receptor for advanced glycation end products and tumor necrosis factor- α as gingival crevicular fluid and serum markers of inflammation in chronic periodontitis and type 2 diabetes. *J Oral Sci.* 2016;58(4):547-553.
71. Türer ÇC, Durmuş D, Ballı U, et al. Effect of non-surgical periodontal treatment on gingival crevicular fluid and serum endocan, vascular endothelial growth factor-A, and tumor necrosis factor-alpha levels. *J Periodontol.* 2017;88(5):493-501.
72. Kim JH, Lee DE, Woo GH, et al. Osteocytic sclerostin expression in alveolar bone in rats with diabetes mellitus and ligature-induced periodontitis. *J Periodontol.* 2015;86(8):1005-1011.
73. Huang Y, Guo W, Zeng J, et al. Prediabetes enhances periodontal inflammation consistent with activation of toll-like receptor-mediated nuclear factor- κ B pathway in rats. *J Periodontol.* 2016;87(5):e64-e74.
74. Santamaria-Jr M, Bagne L, Zaniboni E, et al. Diabetes mellitus and periodontitis: inflammatory response in orthodontic tooth movement. *Orthod Craniofac Res.* 2020;23(1):27-34.
75. Grauballe MB, Østergaard JA, Schou S, et al. Effects of TNF- α blocking on experimental periodontitis and type 2 diabetes in obese diabetic Zucker rats. *J Clin Periodontol.* 2015;42(9):807-816.
76. Fang H, Yang K, Tang P, et al. Glycosylation end products mediate damage and apoptosis of periodontal ligament stem cells induced by the JNK-mitochondrial pathway. *Aging.* 2020;12(13):12850-12868.
77. Abdella NA, Mojiminiyi OA. Clinical applications of adiponectin measurements in type 2 diabetes mellitus: screening, diagnosis, and marker of diabetes control. *Dis Markers.* 2018;2018:5187940.
78. Qiu W, Wang Z, Chen Z, et al. The adiponectin receptor agonist AdipoAI attenuates periodontitis in diabetic rats by inhibiting gingival fibroblast-induced macrophage migration. *Br J Pharmacol.* 2023;180(18):2436-2451.
79. Wu Y, Chen L, Wei B, et al. Effect of non-surgical periodontal treatment on visfatin concentrations in serum and gingival crevicular fluid of patients with chronic periodontitis and type 2 diabetes mellitus. *J Periodontol.* 2015;86(6):795-800.
80. An Y, Zhang H, Wang C, et al. Activation of ROS/MAPKs/NF- κ B/NLRP3 and inhibition of efferocytosis in osteoclast-mediated diabetic osteoporosis. *Faseb J.* 2019;33(11):12515-12527.
81. Zheng J, Chen S, Albiero ML, et al. Diabetes activates periodontal ligament fibroblasts via NF- κ B in vivo. *J Dent Res.* 2018;97(5):580-588.
82. Li X, Sun X, Zhang X, et al. Enhanced oxidative damage and Nrf2 downregulation contribute to the aggravation of periodontitis by diabetes mellitus. *Oxid Med Cell Longev.* 2018;2018:9421019.
83. Bastos MF, Tucci MA, de Siqueira A, et al. Diabetes may affect the expression of matrix metalloproteinases and their inhibitors more than smoking in chronic periodontitis. *J Periodontol Res.* 2017;52(2):292-299.
84. Torrungruang K, Ongphiphadhanakul B, Jitpakdeebordin S, et al. Mediation analysis of systemic inflammation on the association between periodontitis and glycaemic status. *J Clin Periodontol.* 2018;45(5):548-556.
85. Zhou M, Xu X, Li J, et al. C-reactive protein perturbs alveolar bone homeostasis: an experimental study of periodontitis and diabetes in the rat. *J Clin Periodontol.* 2022;49(10):1052-1066.
86. Yilmaz D, Caglayan F, Buber E, et al. Gingival crevicular fluid levels of human beta-defensin-1 in type 2 diabetes mellitus and periodontitis. *Clin Oral Investig.* 2018;22(5):2135-2140.
87. Yilmaz D, Yilmaz N, Polat R, et al. Salivary levels of hBDs in children and adolescents with type 1 diabetes mellitus and gingivitis. *Clin Oral Investig.* 2022;26(7):4897-4904.
88. Wang Q, Nie L, Zhao P, et al. Diabetes fuels periodontal lesions via GLUT1-driven macrophage inflammaging. *Int J Oral Sci.* 2021;13(1):11.
89. Akram Z, Alqahtani F, Alqahtani M, et al. Levels of advanced glycation end products in gingival crevicular fluid of chronic periodontitis patients with and without type-2 diabetes mellitus. *J Periodontol.* 2020;91(3):396-402.
90. Mei YM, Li L, Wang XQ, et al. AGEs induces apoptosis and autophagy via reactive oxygen species in human periodontal ligament cells. *J Cell Biochem.* 2020;121(8-9):3764-3779.
91. Chiu HC, Fu MM, Yang TS, et al. Effect of high glucose, *Porphyromonas gingivalis* lipopolysaccharide and advanced glycation end-products on production of interleukin-6/-8 by gingival fibroblasts. *J Periodontol Res.* 2017;52(2):268-276.
92. Hiroshima Y, Sakamoto E, Yoshida K, et al. Advanced glycation end-products and *Porphyromonas gingivalis* lipopolysaccharide increase calprotectin expression in human gingival epithelial cells. *J Cell Biochem.* 2018;119(2):1591-1603.
93. Yi X, Zhang L, Lu W, et al. The effect of NLRP inflammasome on the regulation of AGEs-induced inflammatory response in human periodontal ligament cells. *J Periodontol Res.* 2019;54(6):681-689.
94. Pink C, Kocher T, Meisel P, et al. Longitudinal effects of systemic inflammation markers on periodontitis. *J Clin Periodontol.* 2015;42(11):988-997.
95. Fine N, Chadwick JW, Sun C, et al. Periodontal inflammation primes the systemic innate immune response. *J Dent Res.* 2021;100(3):318-325.
96. Graves DT, Alshabab A, Albiero ML, et al. Osteocytes play an important role in experimental periodontitis in healthy and

- diabetic mice through expression of RANKL. *J Clin Periodontol.* 2018;45(3):285-292.
97. Demmer RT, Breskin A, Rosenbaum M, et al. The subgingival microbiome, systemic inflammation and insulin resistance: the oral infections, glucose intolerance and insulin resistance study. *J Clin Periodontol.* 2017;44(3):255-265.
 98. Matsha TE, Prince Y, Davids S, et al. Oral microbiome signatures in diabetes mellitus and periodontal disease. *J Dent Res.* 2020;99(6):658-665.
 99. Shi B, Lux R, Klokkevold P, et al. The subgingival microbiome associated with periodontitis in type 2 diabetes mellitus. *Isme J.* 2020;14(2):519-530.
 100. Li L, Bao J, Chang Y, et al. Gut microbiota may mediate the influence of periodontitis on prediabetes. *J Dent Res.* 2021;100(12):1387-1396.
 101. Radović N, Nikolić Jakobina N, Petrović N, et al. MicroRNA-146a and microRNA-155 as novel crevicular fluid biomarkers for periodontitis in non-diabetic and type 2 diabetic patients. *J Clin Periodontol.* 2018;45(6):663-671.
 102. Byun JS, Lee HY, Tian J, et al. Effect of salivary exosomal miR-25-3p on periodontitis with insulin resistance. *Front Immunol.* 2021;12:775046.
 103. Li B, Xin Z, Gao S, et al. SIRT6-regulated macrophage efferocytosis epigenetically controls inflammation resolution of diabetic periodontitis. *Theranostics.* 2023;13(1):231-249.
 104. Wu Y, Song LT, Li JS, et al. MicroRNA-126 regulates inflammatory cytokine secretion in human gingival fibroblasts under high glucose via targeting tumor necrosis factor receptor associated factor 6. *J Periodontol.* 2017;88(11):e179-e187.
 105. Ou L, Sun T, Cheng Y, et al. MicroRNA-214 contributes to regulation of necroptosis via targeting ATF4 in diabetes-associated periodontitis. *J Cell Biochem.* 2019;120(9):14791-14803.
 106. He L, Liu C, Liu Y, et al. Circular RNA hsa_circ_0084054 promotes the progression of periodontitis with diabetes via the miR-508-3p/PTEN axis. *J Periodontol Res.* 2023;58(4):827-840.
 107. Cirelli T, Nepomuceno R, Rios ACS, et al. Genetic polymorphisms in the Interleukins IL1B, IL4, and IL6 are associated with concomitant periodontitis and type 2 diabetes mellitus in Brazilian patients. *J Periodontol Res.* 2020;55(6):918-930.
 108. Zhang P, Zhang W, Zhang D, et al. 25-Hydroxyvitamin D(3)-enhanced PTPN2 positively regulates periodontal inflammation through the JAK/STAT pathway in human oral keratinocytes and a mouse model of type 2 diabetes mellitus. *J Periodontol Res.* 2018;53(3):467-477.
 109. von Wilmsowky C, Stockmann P, Harsch I, et al. Diabetes mellitus negatively affects peri-implant bone formation in the diabetic domestic pig. *J Clin Periodontol.* 2011;38(8):771-779.
 110. Tang D, Wang E, Xu Y, et al. Is hyperglycemia the only risk factor for implant in type 2 diabetics during the healing period? *Oral Dis.* 2021;27(6):1551-1563.
 111. Liu J, Wu Z, He H, et al. Gallium and silicon synergistically promote osseointegration of dental implant in patients with osteoporosis. *Med Hypotheses.* 2017;103:35-38.
 112. Daubert DM, Weinstein BF, Bordin S, et al. Prevalence and predictive factors for peri-implant disease and implant failure: a cross-sectional analysis. *J Periodontol.* 2015;86(3):337-347.
 113. Aguilar-Salvatierra A, Calvo-Guirado JL, González-Jaranay M, et al. Peri-implant evaluation of immediately loaded implants placed in esthetic zone in patients with diabetes mellitus type 2: a two-year study. *Clin Oral Implants Res.* 2016;27(2):156-161.
 114. Al Amri MD, Abduljabbar TS. Comparison of clinical and radiographic status of platform-switched implants placed in patients with and without type 2 diabetes mellitus: a 24-month follow-up longitudinal study. *Clin Oral Implants Res.* 2017;28(2):226-230.
 115. Dögan ŞB, Kurtiş MB, Tüter G, et al. Evaluation of clinical parameters and levels of proinflammatory cytokines in the crevicular fluid around dental implants in patients with type 2 diabetes mellitus. *Int J Oral Maxillofac Implants.* 2015;30(5):1119-1127.
 116. Eskow CC, Oates TW. Dental implant survival and complication rate over 2 years for individuals with poorly controlled type 2 diabetes mellitus. *Clin Implant Dent Relat Res.* 2017;19(3):423-431.
 117. Abduljabbar T, Javed F, Malignaggi VR, et al. Influence of implant location in patients with and without type 2 diabetes mellitus: 2-year follow-up. *Int J Oral Maxillofac Surg.* 2017;46(9):1188-1192.
 118. Al Amri MD, Abduljabbar TS, Al-Johany SS, et al. Comparison of clinical and radiographic parameters around short (6 to 8 mm in length) and long (11 mm in length) dental implants placed in patients with and without type 2 diabetes mellitus: 3-year follow-up results. *Clin Oral Implants Res.* 2017;28(10):1182-1187.
 119. Oliveira LM, Zanatta FB, Antoniazzi RP, et al. Does diabetes mellitus affect guided bone regeneration outcomes in individuals undergoing dental implants? A systematic review and meta-analysis. *Front Dent Med.* 2024;5.
 120. Jiang X, Zhu Y, Liu Z, et al. Association between diabetes and dental implant complications: a systematic review and meta-analysis. *Acta Odontol Scand.* 2021;79(1):9-18.
 121. Retzepi M, Donos N. The effect of diabetes mellitus on osseous healing. *Clin Oral Implants Res.* 2010;21(7):673-681.
 122. de Oliveira P, Bonfante EA, Bergamo ETP, et al. Obesity/metabolic syndrome and diabetes mellitus on peri-implantitis. *Trends Endocrinol Metab.* 2020;31(8):596-610.
 123. Hu X-F, Wang L, Xiang G, et al. Angiogenesis impairment by the NADPH oxidase-triggered oxidative stress at the bone-implant interface: critical mechanisms and therapeutic targets for implant failure under hyperglycemic conditions in diabetes. *Acta Biomater.* 2018;73:470-487.
 124. Zafar MS, Fareed MA, Riaz S, et al. Customized therapeutic surface coatings for dental implants. *Coatings.* 2020;10(6):568.
 125. Yadav R, Agrawal KK, Rao J, et al. Crestal bone loss under delayed loading of full thickness versus flapless surgically placed dental implants in controlled type 2 diabetic patients: a parallel group randomized clinical trial. *J Prosthodont.* 2018;27(7):611-617.
 126. Sánchez-Domínguez B, López-López J, Jané-Salas E, et al. Glycated hemoglobin levels and prevalence of apical periodontitis in type 2 diabetic patients. *J Endod.* 2015;41(5):601-606.
 127. Smadi L. Apical periodontitis and endodontic treatment in patients with type II diabetes mellitus: comparative cross-sectional survey. *J Contemp Dent Pract.* 2017;18(5):358-362.
 128. Yip N, Liu C, Wu D, et al. The association of apical periodontitis and type 2 diabetes mellitus: a large hospital net-

- work cross-sectional case-controlled study. *J Am Dent Assoc.* 2021;152(6):434-443.
129. Limeira FIR, Arantes DC, de Souza Oliveira C, et al. Root canal treatment and apical periodontitis in a Brazilian population with type 1 diabetes mellitus: a cross-sectional paired study. *J Endod.* 2020;46(6):756-762.
 130. Davidović B, Krunić J, Mladenović I, et al. Effects of apical periodontitis treatment on hyperglycaemia in diabetes: a prospective cohort study. *Int Endod J.* 2024;57(8):1099-1109.
 131. Wang S, Wang X, Bai F, et al. Effect of endodontic treatment on clinical outcome in type 2 diabetic patients with apical periodontitis. *Heliyon.* 2023;9(3):e13914.
 132. Arya S, Duhan J, Tewari S, et al. Healing of apical periodontitis after nonsurgical treatment in patients with type 2 diabetes. *J Endod.* 2017;43(10):1623-1627.
 133. Prasetyo EP, Sampoerno G, Juniarti DE, et al. Effect of lipopolysaccharide-induced apical periodontitis in diabetes mellitus rats on periapical inflammation. *Eur J Dent.* 2023;17(4):1146-1152.
 134. Prieto AKC, Gomes-Filho JE, Azuma MM, et al. Influence of apical periodontitis on stress oxidative parameters in diabetic rats. *J Endod.* 2017;43(10):1651-1656.
 135. De la Torre-Luna R, Domínguez-Pérez RA, Guillén-Nepita AL, et al. Prevalence of *Candida albicans* in primary endodontic infections associated with a higher frequency of apical periodontitis in type two diabetes mellitus patients. *Eur J Clin Microbiol Infect Dis.* 2020;39(1):131-138.
 136. Gadicherla S, Smriti K, Roy S, et al. Comparison of extraction socket healing in non-diabetic, prediabetic, and type 2 diabetic patients. *Clin Cosmet Investig Dent.* 2020;12:291-296.
 137. Power DJ, Sambrook PJ, Goss AN. The healing of dental extraction sockets in insulin-dependent diabetic patients: a prospective controlled observational study. *Aust Dent J.* 2019;64(1):111-116.
 138. Fernandes KS, Glick M, de Souza MS, et al. Association between immunologic parameters, glycemic control, and post-extraction complications in patients with type 2 diabetes. *J Am Dent Assoc.* 2015;146(8):592-599.
 139. Yang S, Li Y, Liu C, et al. Pathogenesis and treatment of wound healing in patients with diabetes after tooth extraction. *Front Endocrinol.* 2022;13:949535.
 140. Gazal G. Management of an emergency tooth extraction in diabetic patients on the dental chair. *Saudi Dent J.* 2020;32(1):1-6.
 141. Sykara M, Maniatakos P, Tentolouris A, et al. The necessity of administering antibiotic prophylaxis to patients with diabetes mellitus prior to oral surgical procedures—a systematic review. *Diabetes Metab Syndr.* 2022;16(10):102621.
 142. Zhang S, Song S, Wang S, et al. Type 2 diabetes affects post-extraction socket healing and influences first-stage implant surgery: a study based on clinical and animal evidence. *Clin Implant Dent Relat Res.* 2019;21(3):436-445.
 143. Maftai G-A, Martu M-A, Martu M-C, et al. Correlations between salivary immuno-biochemical markers and HbA1c in type 2 diabetes subjects before and after dental extraction. *Antioxidants.* 2021;10(11):1741.
 144. Al Shehhi YI, Elemam NM, Alsaegh MA. The response of salivary proinflammatory biomarkers to tooth extraction in individuals with type II diabetes mellitus. *BMC Oral Health.* 2024;24(1):250.
 145. Daraei P, Moore CE. Racial disparity among the head and neck cancer population. *J Cancer Educ.* 2015;30(3):546-551.
 146. Liu S, Zhao Q, Zheng Z, et al. Status of treatment and prophylaxis for radiation-induced oral mucositis in patients with head and neck cancer. *Front Oncol.* 2021;11:642575.
 147. Shavi GR, Thakur B, Bhambal A, et al. Oral health related quality of life in patients of head and neck cancer attending cancer hospital of Bhopal city, India. *J Int Oral Health.* 2015;7(8):21-27.
 148. Ederaine SA, Dominguez JL, Harvey JA, et al. Survival and glycemic control in patients with co-existing squamous cell carcinoma and diabetes mellitus. *Future Sci OA.* 2021;7(5):Fso683.
 149. Hu X, Wu J, Xiong H, et al. Type 2 diabetes mellitus promotes the proliferation, metastasis, and suppresses the apoptosis in oral squamous cell carcinoma. *J Oral Pathol Med.* 2022;51(5):483-492.
 150. Xu W, Chen Z, Zhang L. Impact of diabetes on the prognosis of patients with oral and oropharyngeal cancer: a meta-analysis. *J Diabetes Investig.* 2024;15(8):1140-1150.
 151. Tseng CH. Pioglitazone and oral cancer risk in patients with type 2 diabetes. *Oral Oncol.* 2014;50(2):98-103.
 152. Sung HL, Hung CY, Tung YC, et al. Comparison between sodium-glucose cotransporter 2 inhibitors and dipeptidyl peptidase 4 inhibitors on the risk of incident cancer in patients with diabetes mellitus: a real-world evidence study. *Diabetes Metab Res Rev.* 2024;40(3):e3784.
 153. Hu WS, Lin CL. Patients with diabetes with and without sodium-glucose cotransporter-2 inhibitors use with incident cancer risk. *J Diabetes Complic.* 2023;37(5):108468.
 154. Koepsell H. The Na(+)-D-glucose cotransporters SGLT1 and SGLT2 are targets for the treatment of diabetes and cancer. *Pharmacol Ther.* 2017;170:148-165.
 155. Gier B, Matveyenko AV, Kirakossian D, et al. Chronic GLP-1 receptor activation by exendin-4 induces expansion of pancreatic duct glands in rats and accelerates formation of dysplastic lesions and chronic pancreatitis in the Kras(G12D) mouse model. *Diabetes.* 2012;61(5):1250-1262.
 156. Bjerre Knudsen L, Madsen LW, Andersen S, et al. Glucagon-like Peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. *Endocrinology.* 2010;151(4):1473-1486.
 157. Cao C, Yang S, Zhou Z. GLP-1 receptor agonists and risk of cancer in type 2 diabetes: an updated meta-analysis of randomized controlled trials. *Endocrine.* 2019;66(2):157-165.
 158. Liu Y, Zhang X, Chai S, et al. Risk of malignant neoplasia with glucagon-like peptide-1 receptor agonist treatment in patients with type 2 diabetes: a meta-analysis. *J Diabetes Res.* 2019;2019:1534365.
 159. Gallagher EJ, LeRoith D. Diabetes, cancer, and metformin: connections of metabolism and cell proliferation. *Ann N Y Acad Sci.* 2011;1243:54-68.
 160. Rohani B. Oral manifestations in patients with diabetes mellitus. *World J Diabetes.* 2019;10(9):485-489.
 161. Lima DLF, Carneiro S, Barbosa FTS, et al. Salivary flow and xerostomia in older patients with type 2 diabetes mellitus. *PLoS One.* 2017;12(8):e0180891.
 162. Hoseini A, Mirzapour A, Bijani A, et al. Salivary flow rate and xerostomia in patients with type I and II diabetes mellitus. *Electron Phys.* 2017;9(9):5244-5249.

163. Visvanathan V, Nix P. Managing the patient presenting with xerostomia: a review. *Int J Clin Pract.* 2010;64(3):404-407.
164. Stewart CR, Obi N, Epame EC, et al. Effects of diabetes on salivary gland protein expression of tetrahydrobiopterin and nitric oxide synthesis and function. *J Periodontol.* 2016;87(6):735-741.
165. Chen SY, Wang Y, Zhang CL, et al. Decreased basal and stimulated salivary parameters by histopathological lesions and secretory dysfunction of parotid and submandibular glands in rats with type 2 diabetes. *Exp Ther Med.* 2020;19(4):2707-2719.
166. Monteiro MM, D'Epiro TT, Bernardi L, et al. Long- and short-term diabetes mellitus type 1 modify young and elder rat salivary glands morphology. *Arch Oral Biol.* 2017;73:40-47.
167. Huang Y, Mao QY, Shi XJ, et al. Disruption of tight junctions contributes to hyposalivation of salivary glands in a mouse model of type 2 diabetes. *J Anat.* 2020;237(3):556-567.
168. Sato T, Mito K, Ishii H. Relationship between impaired parasympathetic vasodilation and hyposalivation in parotid glands associated with type 2 diabetes mellitus. *Am J Physiol Regul Integr Comp Physiol.* 2020;318(5):R940-R949.
169. Wu CB, Xue L, Zhou Q. Treatment strategy for chronic obstructive parotitis related to diabetes: a retrospective analysis of 12 cases. *Front Pharmacol.* 2022;13:869872.
170. Muhamed SA, Moussa EM, Aboasy NK, et al. Effect of 1% malic acid spray on diabetes mellitus-induced xerostomia: a randomized clinical trial. *Oral Dis.* 2024;30(2):631-638.
171. Zhang S, Li J, Nong X, et al. Artesunate combined with metformin ameliorate on diabetes-induced xerostomia by mitigating superior salivatory nucleus and salivary glands injury in type 2 diabetic rats via the PI3K/AKT pathway. *Front Pharmacol.* 2021;12:774674.
172. Shiferaw A, Alem G, Tsehay M, et al. Dental caries and associated factors among diabetic and nondiabetic adult patients attending Bichena Primary Hospital's Outpatient Department. *Front Oral Health.* 2022;3:938405.
173. Schmolinsky J, Kocher T, Rathmann W, et al. Diabetes status affects long-term changes in coronal caries—the SHIP study. *Sci Rep.* 2019;9(1):15685.
174. Wang Y, Xing L, Yu H, et al. Prevalence of dental caries in children and adolescents with type 1 diabetes: a systematic review and meta-analysis. *BMC Oral Health.* 2019;19(1):213.
175. Ferizi L, Dragidella F, Spahiu L, et al. The influence of type 1 diabetes mellitus on dental caries and salivary composition. *Int J Dent.* 2018;2018:5780916.
176. Latti BR, Kalburge JV, Birajdar SB, et al. Evaluation of relationship between dental caries, diabetes mellitus and oral microbiota in diabetics. *J Oral Maxillofac Pathol.* 2018;22(2):282.
177. PradeepKumar AR, JothiLatha S, Durvasulu A, et al. Impact of type 2 diabetes mellitus on the occurrence of vertical root fracture: a case control study. *J Endod.* 2024;50(4):450-455.e451.
178. Saghiri MA, Nath D, Rahmani B, et al. The effect of diabetes on fracture resistance of teeth: an in vitro study. *Aust Endod J.* 2021;47(3):499-505.
179. Abbassy MA, Watari I, Bakry AS, et al. Diabetes detrimental effects on enamel and dentine formation. *J Dent.* 2015;43(5):589-596.
180. Saghiri MA, Vakhnovetsky J, Samadi E, et al. Effects of diabetes on elemental levels and nanostructure of root canal dentin. *J Endod.* 2023;49(9):1169-1175.
181. Cosgarea R, Tristiu R, Dumitru RB, et al. Effects of non-surgical periodontal therapy on periodontal laboratory and clinical data as well as on disease activity in patients with rheumatoid arthritis. *Clin Oral Investig.* 2019;23(1):141-151.
182. Juan CY, Hsu CW, Lu MC. Increased dental visits in patients with rheumatoid arthritis: a secondary cohort analysis of population based claims data. *BMC Oral Health.* 2022;22(1):609.
183. Mühlberg S, Jäger J, Krohn-Grimberghe B, et al. Oral health-related quality of life depending on oral health in patients with rheumatoid arthritis. *Clin Oral Investig.* 2017;21(9):2661-2670.
184. Manzano BR, da Silva Santos PS, Bariquelo MH, et al. A case-control study of oral diseases and quality of life in individuals with rheumatoid arthritis and systemic lupus erythematosus. *Clin Oral Investig.* 2021;25(4):2081-2092.
185. González-Febles J, Rodríguez-Lozano B, Sánchez-Piedra C, et al. Association between periodontitis and anti-citrullinated protein antibodies in rheumatoid arthritis patients: a cross-sectional study. *Arthritis Res Ther.* 2020;22(1):27.
186. Oliveira SR, de Arruda JAA, Schneider AH, et al. Are neutrophil extracellular traps the link for the cross-talk between periodontitis and rheumatoid arthritis pathophysiology? *Rheumatology (Oxford).* 2021;61(1):174-184.
187. Inanc N, Mumcu G, Can M, et al. Elevated serum TREM-1 is associated with periodontitis and disease activity in rheumatoid arthritis. *Sci Rep.* 2021;11(1):2888.
188. Yilmaz D, Gönüllü E, Gürsoy M, et al. Salivary and serum concentrations of monocyte chemoattractant protein-1, macrophage inhibitory factor, and fractalkine in relation to rheumatoid arthritis and periodontitis. *J Periodontol.* 2021;92(9):1295-1305.
189. Schulz S, Zimmer P, Pütz N, et al. rs2476601 in PTPN22 gene in rheumatoid arthritis and periodontitis—a possible interface? *J Transl Med.* 2020;18(1):389.
190. Svärd A, Renvert S, Sanmartin Berglund J, et al. Antibodies to citrullinated peptides in serum and saliva in patients with rheumatoid arthritis and their association to periodontitis. *Clin Exp Rheumatol.* 2020;38(4):699-704.
191. Kaneko C, Kobayashi T, Ito S, et al. Association among periodontitis severity, anti-agalactosyl immunoglobulin G titer, and the disease activity of rheumatoid arthritis. *J Periodontol Res.* 2021;56(4):702-709.
192. Reichert S, Jurianz E, Natalie P, et al. Is periodontitis a prognostic factor in order to indicate antibodies against citrullinated peptides in patients with rheumatoid arthritis? *Clin Exp Rheumatol.* 2020;38(2):227-238.
193. Massarenti L, Enevold C, Damgaard D, et al. Peptidylarginine deiminase 2 gene polymorphisms in subjects with periodontitis predispose to rheumatoid arthritis. *Int J Mol Sci.* 2022;23(17):9536.
194. Lee JA, Mikuls TR, Sayles HR, et al. Associations between periodontitis and serum anti-malondialdehyde-acetaldehyde antibody concentrations in rheumatoid arthritis: a case-control study. *J Periodontol.* 2024;95:929-941.
195. El-Wakeel NM, Shalaby ZF, Abdulmaguid RF, et al. Local gingival crevicular fluid, synovial fluid, and circulating levels of prolactin hormone in patients with moderately active rheumatoid arthritis and stage III and IV periodontitis before and after non-surgical periodontal treatment—a controlled trial. *Clin Oral Investig.* 2023;27(6):2813-2821.

196. Li RN, Ou TT, Lin CH, et al. NLRP3 gene polymorphisms in rheumatoid arthritis and primary Sjogren's syndrome patients. *Diagnostics*. 2023;13(2):206.
197. Jung ES, Choi YY, Lee KH. Relationship between rheumatoid arthritis and periodontal disease in Korean adults: data from the Sixth Korea National Health and Nutrition Examination Survey, 2013 to 2015. *J Periodontol*. 2019;90(4):350-357.
198. Lee KH, Choi YY. Rheumatoid arthritis and periodontitis in adults: using the Korean National Health Insurance Service-National Sample Cohort. *J Periodontol*. 2020;91(9):1186-1193.
199. Karapetsa D, Consensi A, Castagnoli G, et al. Periodontitis in Italian patients with established rheumatoid arthritis: a cross-sectional study. *Oral Dis*. 2022;28(6):1715-1722.
200. Bolstad AI, Fevang BS, Lie SA. Increased risk of periodontitis in patients with rheumatoid arthritis: a nationwide register study in Norway. *J Clin Periodontol*. 2023;50(8):1022-1032.
201. Ziebolz D, Rupprecht A, Schmickler J, et al. Association of different immunosuppressive medications with periodontal condition in patients with rheumatoid arthritis: results from a cross-sectional study. *J Periodontol*. 2018;89(11):1310-1317.
202. Coat J, Demoersman J, Beuzit S, et al. Anti-B lymphocyte immunotherapy is associated with improvement of periodontal status in subjects with rheumatoid arthritis. *J Clin Periodontol*. 2015;42(9):817-823.
203. Moura MF, Cota LOM, Silva TA, et al. Clinical and microbiological effects of non-surgical periodontal treatment in individuals with rheumatoid arthritis: a controlled clinical trial. *Odontology*. 2021;109(2):484-493.
204. Nguyen VB, Nguyen TT, Huynh NC, et al. Effects of non-surgical periodontal treatment in rheumatoid arthritis patients: a randomized clinical trial. *Dent Med Probl*. 2021;58(1):97-105.
205. Schmickler J, Rupprecht A, Patschan S, et al. Cross-sectional evaluation of periodontal status and microbiologic and rheumatoid parameters in a large cohort of patients with rheumatoid arthritis. *J Periodontol*. 2017;88(4):368-379.
206. Manoil D, Bostanci N, Mumcu G, et al. Novel and known periodontal pathogens residing in gingival crevicular fluid are associated with rheumatoid arthritis. *J Periodontol*. 2021;92(3):359-370.
207. Lehenaff R, Tamashiro R, Nascimento MM, et al. Subgingival microbiome of deep and shallow periodontal sites in patients with rheumatoid arthritis: a pilot study. *BMC Oral Health*. 2021;21(1):248.
208. Laugisch O, Wong A, Sroka A, et al. Citrullination in the periodontium—a possible link between periodontitis and rheumatoid arthritis. *Clin Oral Investig*. 2016;20(4):675-683.
209. Bello-Gualtero JM, Lafaurie GI, Hoyos LX, et al. Periodontal disease in individuals with a genetic risk of developing arthritis and early rheumatoid arthritis: a cross-sectional study. *J Periodontol*. 2016;87(4):346-356.
210. Kirchner A, Jäger J, Krohn-Grimberghe B, et al. Active matrix metalloproteinase-8 and periodontal bacteria depending on periodontal status in patients with rheumatoid arthritis. *J Periodontol Res*. 2017;52(4):745-754.
211. Kurgan Ş, Fentoğlu Ö, Önder C, et al. The effects of periodontal therapy on gingival crevicular fluid matrix metalloproteinase-8, interleukin-6 and prostaglandin E2 levels in patients with rheumatoid arthritis. *J Periodontol Res*. 2016;51(5):586-595.
212. Kim D, Lee G, Huh YH, et al. NAMPT is an essential regulator of RA-mediated periodontal inflammation. *J Dent Res*. 2017;96(6):703-711.
213. Pan W, Yin W, Yang L, et al. Inhibition of Ctsk alleviates periodontitis and comorbid rheumatoid arthritis via downregulation of the TLR9 signalling pathway. *J Clin Periodontol*. 2019;46(3):286-296.
214. Domínguez-Pérez RA, Loyola-Rodríguez JP, Abud-Mendoza C, et al. Association of cytokines polymorphisms with chronic periodontitis and rheumatoid arthritis in a Mexican population. *Acta Odontol Scand*. 2017;75(4):243-248.
215. Loutan L, Alpizar-Rodríguez D, Courvoisier DS, et al. Periodontal status correlates with anti-citrullinated protein antibodies in first-degree relatives of individuals with rheumatoid arthritis. *J Clin Periodontol*. 2019;46(7):690-698.
216. Moccia S, Nucci L, Spagnuolo C, et al. Polyphenols as potential agents in the management of temporomandibular disorders. *Appl Sci*. 2020;10(15):5305.
217. Lin CY, Chung CH, Chu HY, et al. Prevalence of temporomandibular disorders in rheumatoid arthritis and associated risk factors: a nationwide study in Taiwan. *J Oral Facial Pain Headache*. 2017;31(4):e29-e36.
218. Ahmed N, Petersson A, Catrina AI, et al. Tumor necrosis factor mediates temporomandibular joint bone tissue resorption in rheumatoid arthritis. *Acta Odontol Scand*. 2015;73(3):232-240.
219. El Qashty RMN, Mohamed NN, Radwan LRS, et al. Effect of bone marrow mesenchymal stem cells on healing of temporomandibular joints in rats with induced rheumatoid arthritis. *Eur J Oral Sci*. 2018;126(4):272-281.
220. Silvestre-Rangil J, Bagán L, Silvestre FJ, et al. Oral manifestations of rheumatoid arthritis. A cross-sectional study of 73 patients. *Clin Oral Investig*. 2016;20(9):2575-2580.
221. Sorgato CC, Lins ESM, Leão JC, et al. EBV and CMV viral load in rheumatoid arthritis and their role in associated Sjögren's syndrome. *J Oral Pathol Med*. 2020;49(7):693-700.
222. Martinez-Martinez RE, Domínguez-Pérez RA, Sancho-Mata J, et al. The frequency and severity of dental caries, and counts of cariogenic bacteria in rheumatoid arthritis patients. *Dent Med Probl*. 2019;56(2):137-142.
223. Karataş E, Kul A, Tepecik E. Association between rheumatoid arthritis and apical periodontitis: a cross-sectional study. *Eur Endod J*. 2020;5(2):155-158.
224. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1736-1788.
225. GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1859-1922.
226. Di Cesare M, Perel P, Taylor S, et al. The heart of the world. *Glob Heart*. 2024;19(1):11.
227. Reynolds HR, Craig RG. Atherosclerotic vascular disease and periodontal disease. In: Craig R, Kamer A, eds. *A Clinician's Guide to Systemic Effects of Periodontal Diseases*. Springer; 2016:39-51.

228. Dietrich T, Webb I, Stenhouse L, et al. Evidence summary: the relationship between oral and cardiovascular disease. *Br Dent J*. 2017;222(5):381-385.
229. Gomes-Filho IS, Coelho JMF, Miranda SS, et al. Severe and moderate periodontitis are associated with acute myocardial infarction. *J Periodontol*. 2020;91(11):1444-1452.
230. Cho HJ, Shin MS, Song Y, et al. Severe periodontal disease increases acute myocardial infarction and stroke: a 10-year retrospective follow-up study. *J Dent Res*. 2021;100(7):706-713.
231. Behle JH, Papapanou PN. Periodontal infections and atherosclerotic vascular disease: an update. *Int Dent J*. 2006;56(suppl 41):256-262.
232. Curia MC, Pignatelli P, D'Antonio DL, et al. Oral *Porphyromonas gingivalis* and *Fusobacterium nucleatum* abundance in subjects in primary and secondary cardiovascular prevention, with or without heterozygous familial hypercholesterolemia. *Biomedicines*. 2022;10(9):2144.
233. Wu Y, Wang Y, Du L, et al. The link between different infection forms of *Porphyromonas gingivalis* and acute myocardial infarction: a cross-sectional study. *BMC Oral Health*. 2023;23(1):63.
234. Farrugia C, Stafford GP, Potempa J, et al. Mechanisms of vascular damage by systemic dissemination of the oral pathogen *Porphyromonas gingivalis*. *FEBS J*. 2021;288(5):1479-1495.
235. Gimbrone MA, Jr., García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. *Circ Res*. 2016;118(4):620-636.
236. Leishman SJ, Ford PJ, Do HL, et al. Periodontal pathogen load and increased antibody response to heat shock protein 60 in patients with cardiovascular disease. *J Clin Periodontol*. 2012;39(10):923-930.
237. Craig RG, Kamer AR. *A Clinician's Guide to Systemic Effects of Periodontal Diseases*. Springer; 2016.
238. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens*. 2018;36(10):1953-2041.
239. Wang YR, Alexander GC, Stafford RS. Outpatient hypertension treatment, treatment intensification, and control in Western Europe and the United States. *Arch Intern Med*. 2007;167(2):141-147.
240. Cutler JA, Sorlie PD, Wolz M, et al. Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988–1994 and 1999–2004. *Hypertension*. 2008;52(5):818-827.
241. Surma S, Romańczyk M, Witalińska-Łabuzek J, et al. Periodontitis, blood pressure, and the risk and control of arterial hypertension: epidemiological, clinical, and pathophysiological aspects—review of the literature and clinical trials. *Curr Hypertens Rep*. 2021;23(5):27.
242. Del Pinto R, Pietropaoli D, Muñoz-Aguilera E, et al. Periodontitis and hypertension: is the association causal? *High Blood Press Cardiovasc Prev*. 2020;27(4):281-289.
243. Franek E, Napora M, Blach A, et al. Blood pressure and left ventricular mass in subjects with type 2 diabetes and gingivitis or chronic periodontitis. *J Clin Periodontol*. 2010;37(10):875-880.
244. Muñoz Aguilera E, Suvan J, Buti J, et al. Periodontitis is associated with hypertension: a systematic review and meta-analysis. *Cardiovasc Res*. 2020;116(1):28-39.
245. Hwang SY, Oh H, Rhee MY, et al. Association of periodontitis, missing teeth, and oral hygiene behaviors with the incidence of hypertension in middle-aged and older adults in Korea: a 10-year follow-up study. *J Periodontol*. 2022;93(9):1283-1293.
246. Rodrigues JVS, Cláudio MM, Franciscan JPS, et al. The effect of non-surgical periodontal treatment on patients with combined refractory arterial hypertension and stage III, grade B periodontitis: a preliminary prospective clinical study. *J Clin Med*. 2023;12(13):4277.
247. Lanau N, Mareque-Bueno J, Zabalza MJ. Impact of nonsurgical periodontal treatment on blood pressure: a prospective cohort study. *Eur J Dent*. 2024;18(02):517-525.
248. Ozmeric N, Elgun S, Kalfaoglu D, et al. Interaction between hypertension and periodontitis. *Oral Dis*. 2024;30(3):1622-1631.
249. Czesnikiewicz-Guzik M, Osmenda G, Siedlinski M, et al. Causal association between periodontitis and hypertension: evidence from Mendelian randomization and a randomized controlled trial of non-surgical periodontal therapy. *Eur Heart J*. 2019;40(42):3459-3470.
250. Dutzan N, Kajikawa T, Abusleme L, et al. A dysbiotic microbiome triggers T(H)17 cells to mediate oral mucosal immunopathology in mice and humans. *Sci Transl Med*. 2018;10(463):eaat0797.
251. Dutzan N, Abusleme L. T helper 17 cells as pathogenic drivers of periodontitis. *Adv Exp Med Biol*. 2019;1197:107-117.
252. Gordon JH, LaMonte MJ, Genco RJ, et al. Is the oral microbiome associated with blood pressure in older women? *High Blood Press Cardiovasc Prev*. 2019;26(3):217-225.
253. Pietropaoli D, Del Pinto R, Ferri C, et al. Definition of hypertension-associated oral pathogens in NHANES. *J Periodontol*. 2019;90(8):866-876.
254. LaMonte MJ, Gordon JH, Diaz-Moreno P, et al. Oral microbiome is associated with incident hypertension among postmenopausal women. *J Am Heart Assoc*. 2022;11(6):e021930.
255. Rodriguez NM, Loren P, Paez I, et al. MicroRNAs: the missing link between hypertension and periodontitis? *Int J Mol Sci*. 2024;25(4):1992.
256. Ghanbari Z, Moradi Y, Samiee N, et al. Dental caries prevalence in relation to the cardiovascular diseases: cross-sectional findings from the Iranian Kurdish population. *BMC Oral Health*. 2024;24(1):509.
257. Wiener RC, Sambamoorthi U. Cross-sectional association between the number of missing teeth and cardiovascular disease among adults aged 50 or older: BRFSS 2010. *Int J Vasc Med*. 2014;2014:421567.
258. Liljestrand JM, Havulinna AS, Paju S, et al. Missing teeth predict incident cardiovascular events, diabetes, and death. *J Dent Res*. 2015;94(8):1055-1062.
259. Peng J, Song J, Han J, et al. The relationship between tooth loss and mortality from all causes, cardiovascular diseases, and coronary heart disease in the general population: systematic review and dose-response meta-analysis of prospective cohort studies. *Biosci Rep*. 2019;39(1):BSR20181773.
260. Momtazmanesh S, Moghaddam SS, Ghamari S-H, et al. Global burden of chronic respiratory diseases and risk factors, 1990–

- 2019: an update from the Global Burden of Disease Study 2019. *eClinicalMedicine*. 2023;59:101936.
261. Dong J, Li W, Wang Q, et al. Relationships between oral microecosystem and respiratory diseases. *Front Mol Biosci*. 2022;8:718222.
 262. Charlson ES, Bittinger K, Haas AR, et al. Topographical continuity of bacterial populations in the healthy human respiratory tract. *Am J Respir Crit Care Med*. 2011;184(8):957-963.
 263. Gupta A, Saleena LM, Kannan P, et al. The impact of oral diseases on respiratory health and the influence of respiratory infections on the oral microbiome. *J Dent*. 2024;148:105213.
 264. Kim S-H, Gu S, Kim J-A, et al. Association between oral health and airflow limitation: analysis using a nationwide survey in Korea. *J Korean Med Sci*. 2023;38(31):e241.
 265. Li S, Ning W, Wang W, et al. Oral health-related quality of life in patients with chronic respiratory diseases—results of a systematic review. *Front Med*. 2021;8:757739.
 266. Ciardo A, Simon MM, Eberhardt R, et al. Severe chronic obstructive pulmonary disease is associated with reduced oral health conditions. *Oral Dis*. 2024;30(5):3400-3412.
 267. Hayes C, Sparrow D, Cohen M, et al. The association between alveolar bone loss and pulmonary function: the VA Dental Longitudinal Study. *Ann Periodontol*. 1998;3(1):257-261.
 268. Scannapieco FA, Ho AW. Potential associations between chronic respiratory disease and periodontal disease: analysis of National Health and Nutrition Examination Survey III. *J Periodontol*. 2001;72(1):50-56.
 269. Gaeckle NT, Heyman B, Criner AJ, et al. Markers of dental health correlate with daily respiratory symptoms in COPD. *Chronic Obstr Pulm Dis*. 2018;5(2):97-105.
 270. Zhou X, Han J, Liu Z, et al. Effects of periodontal treatment on lung function and exacerbation frequency in patients with chronic obstructive pulmonary disease and chronic periodontitis: a 2-year pilot randomized controlled trial. *J Clin Periodontol*. 2014;41(6):564-572.
 271. Xiong K, Ao K, Wei W, et al. Periodontitis aggravates COPD through the activation of $\gamma\delta$ T cell and M2 macrophage. *mSystems*. 2024;9(2):e00572-e00523.
 272. Li W, Liu W, Yang H, et al. Oral infection with periodontal pathogens induced chronic obstructive pulmonary disease-like lung changes in mice. *BMC Oral Health*. 2024;24(1):850.
 273. Xiong K, Yang P, Wei W, et al. Periodontitis contributes to COPD progression via affecting ferroptosis. *BMC Oral Health*. 2023;23(1):664.
 274. Bairappan S, Puranik MP, Sowmya KR. Impact of asthma and its medication on salivary characteristics and oral health in adolescents: a cross-sectional comparative study. *Spec Care Dentist*. 2020;40(3):227-237.
 275. Moreira LV, Galvão EL, Mourão PS, et al. Association between asthma and oral conditions in children and adolescents: a systematic review with meta-analysis. *Clin Oral Investig*. 2023;27(1):45-67.
 276. Jan BM, Khayat MA, Bushnag AI, et al. The association between long-term corticosteroids use and dental caries: a systematic review. *Cureus*. 2023;15(9):e44600.
 277. Sag C, Ozden FO, Acikgoz G, et al. The effects of combination treatment with a long-acting beta2-agonist and a corticosteroid on salivary flow rate, secretory immunoglobulin A, and oral health in children and adolescents with moderate asthma: a 1-month, single-blind clinical study. *Clin Ther*. 2007;29(10):2236-2242.
 278. Lee SW, Lim HJ, Lee E. Association between asthma and periodontitis: results from the Korean National Health and Nutrition Examination Survey. *J Periodontol*. 2017;88(6):575-581.
 279. Moraschini V, Calasans-Maia JA, Calasans-Maia MD. Association between asthma and periodontal disease: a systematic review and meta-analysis. *J Periodontol*. 2018;89(4):440-455.
 280. Brasil-Oliveira R, Cruz AA, Souza-Machado A, et al. Oral health-related quality of life in individuals with severe asthma. *J Bras Pneumol*. 2020;47(1):e20200117.
 281. Lopes MP, Cruz AA, Xavier MT, et al. *Prevotella intermedia* and periodontitis are associated with severe asthma. *J Periodontol*. 2020;91(1):46-54.
 282. Hendrix AY, Kheradmand F. The role of matrix metalloproteinases in development, repair, and destruction of the lungs. *Prog Mol Biol Transl Sci*. 2017;148:1-29.
 283. Gueders MM, Foidart JM, Noel A, et al. Matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs in the respiratory tract: potential implications in asthma and other lung diseases. *Eur J Pharmacol*. 2006;533(1-3):133-144.
 284. Irie K, Azuma T, Tomofuji T, et al. Exploring the role of IL-17A in oral dysbiosis-associated periodontitis and its correlation with systemic inflammatory disease. *Dent J*. 2023;11(8):194.
 285. Son M, Jo S, Lee JS, et al. Association between oral health and incidence of pneumonia: a population-based cohort study from Korea. *Sci Rep*. 2020;10(1):9576.
 286. Ory J, Mourgues C, Raybaud E, et al. Cost assessment of a new oral care program in the intensive care unit to prevent ventilator-associated pneumonia. *Clin Oral Investig*. 2018;22(5):1945-1951.
 287. Prasad R, Daly B, Manley G. The impact of 0.2% chlorhexidine gel on oral health and the incidence of pneumonia amongst adults with profound complex neurodisability. *Spec Care Dentist*. 2019;39(5):524-532.
 288. Kurasawa Y, Maruoka Y, Sekiya H, et al. Pneumonia prevention effects of perioperative oral management in approximately 25,000 patients following cancer surgery. *Clin Exp Dent Res*. 2020;6(2):165-173.
 289. Ozaki K, Teranaka S, Tohara H, et al. Oral management by a full-time resident dentist in the hospital ward reduces the incidence of pneumonia in patients with acute stroke. *Int J Dent*. 2022;2022:6193818.
 290. Iinuma T, Arai Y, Abe Y, et al. Denture wearing during sleep doubles the risk of pneumonia in the very elderly. *J Dent Res*. 2015;94(suppl3):28s-36s.
 291. Cao Y, Liu C, Lin J, et al. Oral care measures for preventing nursing home-acquired pneumonia. *Cochrane Database Syst Rev*. 2022;11(11):Cd012416.
 292. de Melo Neto JP, Melo M, dos Santos-Pereira SA, et al. Periodontal infections and community-acquired pneumonia: a case-control study. *Eur J Clin Microbiol Infect Dis*. 2013;32(1):27-32.
 293. Kim S-J, Kim K, Choi S, et al. Chronic periodontitis and community-acquired pneumonia: a population-based cohort study. *BMC Pulmon Med*. 2019;19(1):268.

294. Sumi Y, Miura H, Michiwaki Y, et al. Colonization of dental plaque by respiratory pathogens in dependent elderly. *Arch Gerontol Geriatr.* 2007;44(2):119-124.
295. Yamasaki K, Kawanami T, Yatera K, et al. Significance of anaerobes and oral bacteria in community-acquired pneumonia. *PLoS One.* 2013;8(5):e63103.
296. Kikutani T, Tamura F, Tashiro H, et al. Relationship between oral bacteria count and pneumonia onset in elderly nursing home residents. *Geriatr Gerontol Int.* 2015;15(4):417-421.
297. Nishizawa T, Niikura Y, Akasaka K, et al. Pilot study for risk assessment of aspiration pneumonia based on oral bacteria levels and serum biomarkers. *BMC Infect Dis.* 2019;19(1):761.
298. Okuda K, Kimizuka R, Abe S, et al. Involvement of periodontopathic anaerobes in aspiration pneumonia. *J Periodontol.* 2005;76(suppl11):2154-2160.
299. Tian H, Zhang Z, Wang X, et al. Role of experimental periodontitis in inducing pulmonary inflammation in mice. *Oral Dis.* 2022;28(8):2294-2303.
300. Hayashi M, Mori M, Itsumi M, et al. Severity of acute lung injury in aspiration pneumonia model mice transplanted with human oral microflora. *Oral Sci Int.* 2024;21(1):121-130.
301. Darbanian N, Nobahar M, Ghorbani R. Effect of propolis mouthwash on the incidence of ventilator-associated pneumonia in intensive care unit patients: a comparative randomized triple-blind clinical trial. *BMC Oral Health.* 2024;24(1):636.
302. Zhao M, Xie Y, Gao W, et al. Diabetes mellitus promotes susceptibility to periodontitis—novel insight into the molecular mechanisms. *Front Endocrinol.* 2023;14:1192625.
303. Luong A, Tawfik AN, Islamoglu H, et al. Periodontitis and diabetes mellitus co-morbidity: a molecular dialogue. *J Oral Biosci.* 2021;63(4):360-369.
304. Kunath B, Hickl O, Queirós P, et al. Alterations of oral microbiota and impact on the gut microbiome in type 1 diabetes mellitus revealed by integrated multi-omic analyses. *Microbiome.* 2022;10(1):243.
305. Li J, Yuan P, Hu X, et al. A tongue features fusion approach to predicting prediabetes and diabetes with machine learning. *J Biomed Inform.* 2021;115:103693.
306. Taba M, Grant MM. Editorial: Salivary biomarkers for oral and systemic diseases. *Front Dent Med.* 2024;5:1429305.
307. Antony A. Flexible and wearable biosensors: revolutionizing health monitoring. In: Mathew R, Ajayan J, eds. *Biosensors: Developments, Challenges and Perspectives.* Springer Nature Singapore; 2024:237-258.

How to cite this article: Fu D, Shu X, Zhou G, Ji M, Liao G, Zou L. Connection between oral health and chronic diseases. *MedComm.* 2025;6:e70052. <https://doi.org/10.1002/mco2.70052>