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PERSPECTIVES

Oral Health and Diabetic Cardiomyopathy: Mechanisms, Biomarkers, and Early Screening Approaches

Junhao Fang[1,*], Yanlin Wu[2,*], Han Wang[1], Jiale Zhang[3,4], Liangzhen You[5]

[1]College of Stomatology, Hangzhou Normal University, Hangzhou, People's Republic of China; [2]School of Clinical Medicine, Hangzhou Normal University, Hangzhou, People's Republic of China; [3]Institute of Basic Theory for Chinese Medicine, China Academy of Chinese Medical Sciences, Beijing, People's Republic of China; [4]China Science and Technology Development Center for Chinese Medicine, Beijing, People's Republic of China; [5]Key Laboratory of Chinese Internal Medicine of Ministry of Education, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jiale Zhang; Liangzhen You, Email zhang_tcm@163.com; youliangzh@126.com

Abstract: Diabetic Cardiomyopathy (DCM) is a common cardiovascular complication in patients with diabetes. In recent years, the association between oral health and diabetic heart disease has gained increasing attention. This perspective reviews the potential mechanisms of oral diseases in diabetic heart disease, oral indicators for early screening of diabetic heart disease, and proposes future research directions. The potential mechanisms of oral diseases in diabetic heart disease primarily involve abnormal activation of inflammatory responses, dysregulation of the oral microbiome, and immune system disorders. In the context of early screening for diabetic heart disease, oral health indices, salivary biomarkers, and the oral microbiome serve as critical oral indicators with significant clinical value for early diagnosis. Future research should promote interdisciplinary diagnosis and collaboration, develop non-invasive early screening technologies, integrate multimodal and multi-omics oral data, leverage large-scale multicenter clinical data to comprehensively evaluate the association between oral health indicators and diabetic cardiomyopathy, and simultaneously train and validate precise artificial intelligence models. This perspective integrates existing research findings on the role of oral health in diabetic heart disease, highlights current research limitations, and emphasizes the need for further studies to clarify causal relationships and facilitate widespread clinical application.

Keywords: diabetic cardiomyopathy, oral health status, mechanism, screening indicators, machine learning

Introduction

Diabetic Cardiomyopathy (DCM) is a prevalent cardiovascular complication observed in individuals with diabetes, encompassing conditions such as myocardial infarction, heart failure, and various other cardiovascular disorders. The pathogenesis of DCM is intricate and primarily associated with prolonged hyperglycemia, which triggers metabolic disturbances, chronic inflammation, and endothelial dysfunction.[1] Research indicates that the mortality rate from coronary heart disease in diabetic patients is two to four times higher than that of non-diabetic individuals; approximately two-thirds of deaths among diabetic patients are attributable to cardiovascular diseases, with around 40% due to ischemic heart disease, 15% due to other cardiac conditions, primarily congestive heart failure, and about 10% from stroke.[2] Given that the early identification and intervention for diabetic patients can significantly reduce the risk of severe health complications, enhance patient prognosis, and lower the incidence of cardiovascular events,[3,4] early warning systems become particularly crucial in this context.

Growing evidence has established a significant association between oral health status and diabetic cardiomyopathy. A study focusing on Chinese patients with type 2 diabetes identified a correlation between inflammatory markers, periodontal indices, and increased risks of coronary heart disease, suggesting that periodontitis may influence cardiac

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health via inflammatory pathways.[5] In addition, red complex bacteria, including Porphyromonas gingivalis and Fusobacterium nucleatum, may also play an important role in the pathogenesis of cardiovascular diseases in patients with periodontal disease and diabetes. For example, various oral bacteria (such as Streptococcus mutans, Streptococcus sanguinis, Actinomyces, and Aggregatibacter actinomycetemcomitans) have been directly detected in aortic valve specimens.[6] Research has shown that two or more periodontal bacteria are frequently detected in heart valve samples from patients with high rates of dental caries and periodontal disease.[7] This evidence directly indicates a causal relationship between oral bacteria and cardiovascular diseases. Periodontal bacteria may contribute to cardiovascular diseases through mechanisms such as direct arterial infection, platelet aggregation, systemic inflammation, and cross-reactivity. Additionally, a prospective cohort study revealed that oral diseases, indicated by tooth loss, were associated with elevated all-cause mortality as well as heightened risks of both cardiovascular and non-cardiovascular deaths in type 2 diabetic patients.[8] Early interventions targeting oral health in diabetic individuals were shown to mitigate cardiovascular complications. A retrospective cohort study demonstrated that advanced periodontal therapy in patients with type 2 diabetes significantly reduced the incidence of myocardial infarction and heart failure, highlighting the dual benefits of periodontal treatment for both oral and cardiovascular health.[9] Research also emphasized the impact of lifestyle factors on oral health as mediators of systemic health in diabetic patients, reducing risks of chronic conditions such as cardiovascular complications. Implementing systemic disease risk assessments in dental settings provides a framework for dental professionals to enhance patient outcomes.[10] A Swedish study found that general dental practitioners could effectively identify patients at risk of fatal cardiovascular events within a set timeframe, enabling timely intervention for those unaware of their CVD-related risks.[11] Collectively, these findings underscore the importance of oral health management for early detection and intervention of cardiovascular complications in diabetic patients, ultimately improving prognosis.

Current research on the oral-systemic axis in diabetic cardiomyopathy (DCM) reveals several critical knowledge gaps requiring urgent investigation. While observational studies have identified preliminary associations between periodontal indices, salivary biomarkers, oral microbiome profiles and DCM, their small sample sizes and cross-sectional designs preclude definitive conclusions about temporal relationships or causal mechanisms—necessitating large-scale multicenter prospective cohorts. The precise quantification of how socioeconomic and lifestyle confounders modulate DCM progression through oral-inflammatory pathways remains undefined. A standardized analytical framework integrating multimodal omics data (clinical parameters, imaging features, genomics, transcriptomics, proteomics, metabolomics) with optimized AI model weighting schemes is conspicuously absent. Salivary diagnostics face translational challenges including lack of standardized collection protocols, unvalidated longitudinal monitoring utility, and underdeveloped cost-effective detection technologies. Crucially, evidence regarding the long-term cardioprotective effects and cost-effectiveness of oral health interventions (eg, periodontal therapy) on DCM outcomes remains insufficient. Addressing these gaps will require interdisciplinary efforts combining advanced bioinformatics, precision medicine approaches, and health economics analyses.

To enable clinical doctor to identify patients with diabetic cardiomyopathy at an early stage and intervene promptly, we reviewed the mechanisms by which oral health influences the development of diabetic heart lesions. We also summarized potential oral biomarkers for early screening of diabetic cardiomyopathy and outlined future research directions in this field. Ultimately, our goals are to promote the conduct of large-scale multicenter cohort studies and intervention trials in the future to validate the biological performance of multiple oral indicators, facilitate the development of unified multi-omics and multimodal artificial intelligence models to improve diagnostic and predictive efficiency, advance the development of saliva-based noninvasive early diagnostic technologies and standardized sample collection methods to reduce biases from different detection approaches, and extend the application of oral multi-omics indicators in diagnostic and predictive models to other systemic diseases.

Potential Mechanisms of Oral Diseases in Diabetic Heart Disease

In a high blood sugar environment, the oral cavity primarily triggers cardiovascular events through abnormally activated inflammatory responses, dysregulation of the oral microbiota, and immune modulation disorders (Figure 1). The specific mechanisms are as follows:

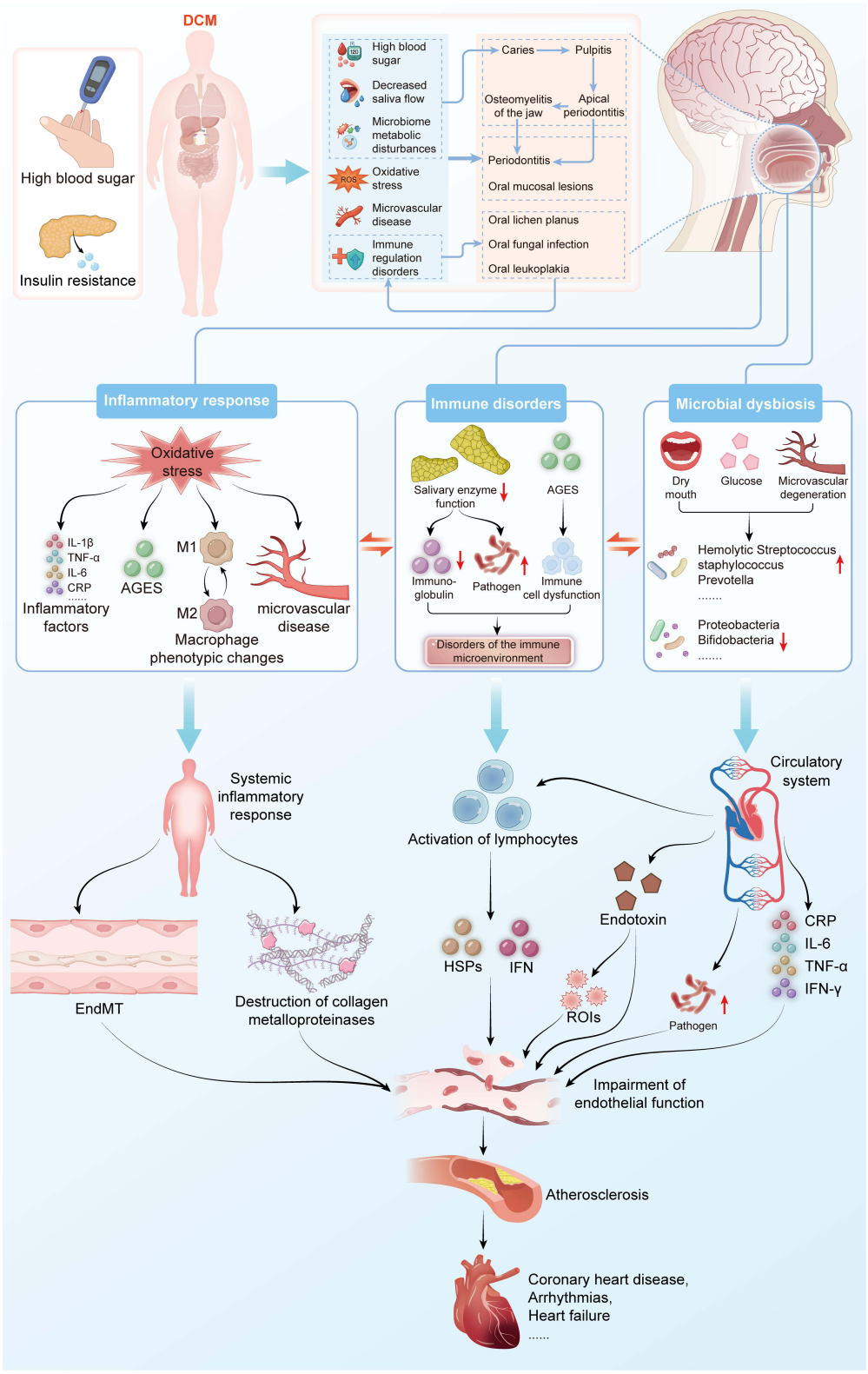

Figure 1 Potential Mechanisms of Oral Diseases in Diabetic Heart Disease.
Abbreviations: DCM, Diabetic Cardiomyopathy; AGEs, Advanced Glycation End-products; HSPs, Heatshock Proteins; CRP, C-reactive Protein; EndMT, Endothelial-mesenchymal transition; IFN, Interferon; ROIs, Reactive Oxygen Intermediates; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-alpha; IFN-γ, Interferon-γ.

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Abnormal Activation of the Inflammatory Response

Recent studies have established a close relationship between diabetes and localized oral inflammation. Research indicates that the prevalence of periodontitis in patients with type 1 diabetes mellitus (T1DM) is 18.5%, with an odds ratio (OR) of 2.51 compared to the general population.[12] The oxidative stress and reactive oxygen species generated by hyperglycemia in diabetic patients may exacerbate localized damage to periodontal tissues.[13] This condition leads to elevated levels of inflammatory markers such as IL-1β, TNF-, IL-6, C-reactive protein (CRP), RANKL/OPG, and oxygen metabolites in periodontal tissues.[14] Additionally, there is a significant increase in advanced glycation end products (AGEs) within the periodontal tissues.[15] Increased vascular permeability and microvascular lesions damage vascular walls, facilitating the invasion of pathogenic microorganisms and their toxins, which in turn triggers inflammation.[16,17] These factors contribute to the onset and progression of periodontitis.

Consequently, localized periodontitis can further induce systemic inflammation, influencing the development of cardiovascular complications. Experimental results show that levels of pro-inflammatory mediators, such as IL-1, IL-6, CRP, amyloid A, and MMP-9, are elevated in patients with severe periodontitis compared to healthy controls, along with an increase in neutrophil counts in the bloodstream.[18–20] Studies using mouse models have found a significant correlation between systemic inflammation induced by periodontitis and the formation of arterial plaques,[21] indicating that severe periodontitis can lead to systemic diseases through the initiation of widespread inflammation.

Systemic inflammation may further promote atherosclerosis through endothelial-mesenchymal transition (EndMT), enhancing platelet aggregation and thrombosis. Research has demonstrated that pro-inflammatory cytokines released by macrophages, such as TNF-α, IL-1β, and IL-6, can induce EndMT in human umbilical vein endothelial cells (HUVECs) in a periodontitis mouse model. During this process, endothelial cells lose their barrier integrity, allowing monocytes and macrophages to infiltrate the vascular intima. Furthermore, mesenchymal-like cells derived from EndMT destabilize atherosclerotic plaques by altering the balance of collagen and matrix metalloproteinases, thereby promoting the progression of atherosclerosis through these endothelial dysfunctions.[21] Studies have shown that thrombotic and hemostatic markers, such as fibrinogen, plasminogen activator inhibitor-1, von Willebrand factor, and selectins, are significantly elevated in patients with periodontitis.[20] These factors play a crucial role in atherosclerosis and thrombosis by facilitating platelet aggregation and clot formation.[22]

A series of studies have demonstrated that successful localized periodontal treatment reduces systemic inflammatory markers, thereby attenuating systemic inflammatory responses. This highlights the potential for oral disease interventions to improve overall systemic inflammation,[14,18,23] providing new ideas and insights for future treatment plans to diabetic cardiomyopathy.

Oral Microbiome and Metabolic Disorders

Diabetes exhibits a profound correlation with oral dysbiosis, significantly influencing bacterial and fungal infection dynamics. The oral cavity, being highly vascularized and innervated, is particularly susceptible to diabetic perturbations.[24] Diabetes modulates oral microbiome composition through multifaceted mechanisms, including xerostomia, reduced salivary flow, elevated glucose levels, and microvascular degeneration, ultimately disrupting microbial homeostasis and predisposing to oral infections.[25] In diabetic conditions, predominant microbial shifts involve increased Gram-positive bacterial species like hemolytic Streptococcus, Staphylococcus, Propionibacterium, Lactobacillus, and Veillonella, alongside elevated oral Candida species. Conversely, Proteus and Bifidobacterium genera experience significant negative metabolic impacts.[26]

Building upon microbiome metabolic dysregulation, diabetes exacerbates pathogenic oral microbiota's virulence through enhanced inflammatory processes, osteoclastogenesis, and accelerated periodontal bone loss.[27] These mechanisms intensify local inflammatory responses in periodontitis patients, facilitating bacterial dissemination.[28] The gingiva's highly vascularized characteristics enable periodic bacterial and endotoxin entry into systemic circulation, directly triggering and amplifying inflammatory responses while accelerating atherosclerotic progression. This phenomenon manifests through direct endotoxemia and indirect cellular modulation via inflammatory cytokines, including C-reactive protein (CRP), interleukin-6, tumor necrosis factor-α, and interferon-γ.[29] Bacterial endotoxin release

ultimately induces endothelial cell damage through direct mechanisms and cellular activation of superoxide radical generation, thereby precipitating further endothelial injury and potentially triggering cardiovascular events.[30]

Immune Regulation Disorder

The intricate pathological association between diabetes, oral immunological dysregulation, and cardiovascular damage represents a complex immunometabolic interaction. Research substantiates significantly elevated immunoglobulin IgG and IgA levels in diabetic patients' saliva,[31] with these aberrant immune responses not only exacerbating periodontal disease progression but potentially triggering broader systemic diseases.[32]

Diabetic patients exhibit profound immunological microenvironment dysregulation in oral tissues. Hyperglycemia, as the core pathological hallmark, profoundly modulates oral immune equilibrium through multifaceted mechanisms. Primarily, elevated glucose levels suppress salivary gland function, dramatically reducing salivary secretion and decreasing pH, consequently creating an optimal environment for pathogenic bacterial proliferation.[33] Concurrently, immunoglobulin secretion and functionality become severely compromised, substantially weakening local immune defensive capacities.[34] Moreover, advanced glycation end-products (AGEs) generated through hyperglycemic pathways directly interfere with immune cell normal functioning. These end-products disrupt phagocytic capabilities, activate pro-inflammatory cytokines, and significantly alter immunological response homeostasis.[35] Critically, diabetic patients experience substantial oral microbiome compositional shifts, particularly increased proportions of Gram-negative bacteria, intimately associated with immunological microenvironment perturbations, establishing a vicious pathogenic cycle.[36]

Oral bacterial translocation through bloodstream exposure can induce chronic systemic immune responses. While potentially protective, this process simultaneously poses cardiovascular risks, potentially precipitating coronary atherosclerosis and myocardial infarction.[30,37] The local oral immunological microenvironment recruits polymorphonuclear and monocytic cells, releasing various immune factors that generate reactive oxygen intermediates (ROIs) through arachidonic acid cascade reactions, ultimately causing endothelial damage and cardiovascular complications.[38] Oral pathogens like Porphyromonas gingivalis stimulate heat shock protein (HSP) expression in oral lymphocytes, inducing both specific and non-specific immune responses.[39,40] Elevated HSP levels may trigger detrimental autoimmune reactions, potentially leading to myocardial injury and arrhythmias.[41] Moreover, neutrophil and macrophage functional abnormalities in diabetic patients can exacerbate periodontal disease progression. Macrophage dysfunction impairs pathogen clearance, perpetuating oral health complications, while gingival fibroblasts demonstrate immunoregulatory imbalances further exacerbating oral health deterioration.[35,42] These immunological alterations not only unveil potential interconnections between oral microbiota and cardiovascular diseases but also provide novel theoretical perspectives on diabetic cardiovascular complication mechanisms.

Based on the evidence presented, we propose a model in which hyperglycemia, decreased salivary flow, and dysregulated microbiome metabolism induce caries, subsequently leading to the development of pulpitis, apical periodontitis, and osteomyelitis of the jaw. Apical periodontitis and osteomyelitis can further progress to periodontal disease. All these conditions, including hyperglycemia, reduced salivary flow, microbiome metabolism disturbances, oxidative stress, and microvascular complications, contribute to the development of periodontal disease and oral mucosal lesions. Furthermore, dysregulation of oral immune responses can lead to the onset of immune-related oral conditions such as oral lichen planus, oral fungal infections, and oral leukoplakia. Persistent and recurrent manifestations of these diseases may promote the risk of oral cancer. This cascade of conditions exacerbates the deterioration of overall oral health. As oral health declines, it primarily impacts endothelial function and accelerates atherosclerosis through three major pathways: hyperglycemia, decreased salivary flow, and dysregulated microbiome metabolism, as well as disturbances in the oral microbiome and immune regulation. These processes ultimately contribute to the development of cardiovascular diseases such as coronary heart disease, atrial fibrillation, and myocardial infarction.

Oral Indicators for Early Screening of Diabetic Heart Disease

Recent studies have identified the crucial role of oral health indices, salivary biomarkers, and oral microbiomes in the screening of diabetic heart disease. For example:

Oral Health Status

The assessment of oral health status has shown significant clinical value in the early diagnosis of diabetic cardiomyopathy. Several studies have demonstrated that specific oral diseases, such as recurrent aphthous ulcers, xerostomia, and oral leukoplakia, are significantly associated with the occurrence of systemic diseases. For instance, recurrent aphthous ulcers are closely related to the systemic inflammatory state in diabetic patients,[43] which can promote the incidence of systemic cardiovascular events; the symptoms of xerostomia and decreased salivary flow indicate that type 1 diabetic patients may face a higher risk of neurogenic complications,[44] which could further increase the likelihood of cardiovascular events. Furthermore, oral leukoplakia, recognized as a precancerous lesion, has a higher incidence among diabetic patients, indicating an elevated risk of cardiovascular disease for these individuals.[45]

Additionally, the periodontal index has been utilized in the development and application of diagnostic models for diabetes and cardiovascular complications. For example, Amr Sayed Ghanem et al[46] examined the impact of the periodontal index—which includes gingival bleeding, active caries, tooth mobility, and tooth loss—on the prevalence of diabetes and constructed a logistic regression model for comprehensive risk assessment and prediction of diabetes. In research conducted by Huiyuan Zhang et al, the periodontal indices, including the plaque index by Silness and Löe and the bleeding points index by Ainamo and Bay, were employed to evaluate periodontal health in diabetic patients and served as crucial indicators for the early diagnosis of diabetic cardiomyopathy.[47] Moving forward, it may be feasible to predict the risk of diabetic cardiomyopathy based on specific diseases and oral health conditions, although further experimental work and data validation are required to confirm the predictive role of oral health in diabetes and its complications.

Salivary Biomarkers

Recent studies have indicated that biomarkers in saliva and gingival crevicular fluid are considered effective tools for early diagnosis. Various salivary biomarkers, such as glucose, glycosylated hemoglobin (HbA1c), cytokines (eg, TNF-α), C-reactive protein (CRP), IL-6, advanced glycation end-products (AGEs), α-defensins, and insulin-like growth factor (IGF), not only reflect inflammatory states and insulin resistance,[48] but also provide crucial information for the early diagnosis of diseases such as diabetic cardiomyopathy.[49] Furthermore, the mRNA transcriptome in saliva possesses potential diagnostic value for diabetic cardiomyopathy; studies have identified elevated expression levels of KRAS, SAT1, SLC13A2, and TMEM72, as well as decreased expression of EGFR and PSMB2, all associated with type 2 diabetes mellitus (T2DM).[50] These molecules may serve as significant targets for future research and clinical applications.

Salivary biomarkers are widely utilized in the diagnosis and monitoring of diabetes, demonstrating disruptive potential due to their non-invasive nature. However, their role in the diagnosis and prognostic models of diabetes-related cardiovascular events remains in early developmental stages. Raphael-Enrique Tiongco et al applied Pearson correlation and linear regression models, finding that salivary glucose exhibits comparability to blood glucose in diagnosing and monitoring T2DM, and due to its non-invasiveness, it is considered more advantageous than blood sampling.[51] Priya Desai et al noted that salivary biomarkers (such as 1,5-AG, CRP, IL-6) show promise for early diagnosis and risk prediction of diabetes; these markers have demonstrated consistent positive results in diabetic patients, though further research is needed to standardize analytical processes.[52] Ekhosuehi Theophilus Agho et al discovered that inflammatory biomarkers in saliva (eg, TNF-α, IL-6) correlate with glycemic control, inflammatory status, and cardiovascular disease risk in diabetic patients, serving as important indicators for assessing their health status.[53] A review of published data concerning salivary molecular diagnostics for cardiovascular events revealed significant associations between certain salivary biomarkers and cardiovascular disease (CVD), although some existing study details are conflicting.[54] While the clinical application of salivary biomarkers for diagnosing and predicting heart disease related to diabetes is promising, it remains in the early stages of development. Further research is essential to validate these findings, establish diagnostic thresholds, and compare them with other established biomarkers currently in clinical use.[55]

Oral Microbiome

Changes in the oral microbiome are closely associated with the development of diabetic cardiomyopathy. Research indicates that the oral microbiota in diabetic patients differs significantly from that in healthy individuals. For instance, children and adolescents with type 1 diabetes exhibit a characteristic composition of oral microbiota, showing a high proportion of cariogenic and periodontal pathogens from an early age.[56] In patients with poor glycemic control, the oral presence of characteristic microbial communities associated with diabetic cardiomyopathy (DCHD), such as Fusobacterium nucleatum, Streptococcus australis, and Lachnospiraceae bacterium oral taxon 096, is more pronounced.[56] In a study involving adults with type 1 diabetes receiving continuous insulin pump therapy, significant differences in the oral microbiota were observed, with a higher relative abundance of Streptococcus, S. oralis, and Actinomyces in the mouths of diabetic patients.[36]

Currently, the oral microbiome has been utilized for the diagnosis of diabetes and its cardiovascular complications. Selvasankar Murugesan et al[57] employed machine learning models to analyze oral microbiome data, categorizing diabetic patients into "low-risk CVD" and "high-risk CVD" groups. This indicates that integrating oral microbiome data with machine learning techniques can enhance the accuracy of cardiovascular disease risk predictions in diabetic patients. Furthermore, Gregorczyk-Maga et al[36] identified three optimal sampling sites for oral microbiota in a large cohort of individuals with type 1 diabetes: buccal and palatal mucosa, tooth surfaces, and gingival pockets, providing a standardized approach for the future large-scale application of oral microbiome diagnostics in diabetes. Lastly, Shaalan A et al[58] proposed that when abnormal microbial communities such as Fusobacterium nucleatum and Streptococcus are detected, patients should undergo further testing for diabetes indicators and cardiovascular diseases to facilitate early diagnosis. In summary, monitoring changes in the oral microbiome in the future may offer new insights for the early diagnosis of diabetic cardiomyopathy.

Future Research Directions

In future research, applying machine learning and artificial intelligence technologies, developing non-invasive early screening methods, and promoting interdisciplinary collaboration will provide new perspectives and solutions for the early diagnosis and management of diabetic heart disease (Figure 2).

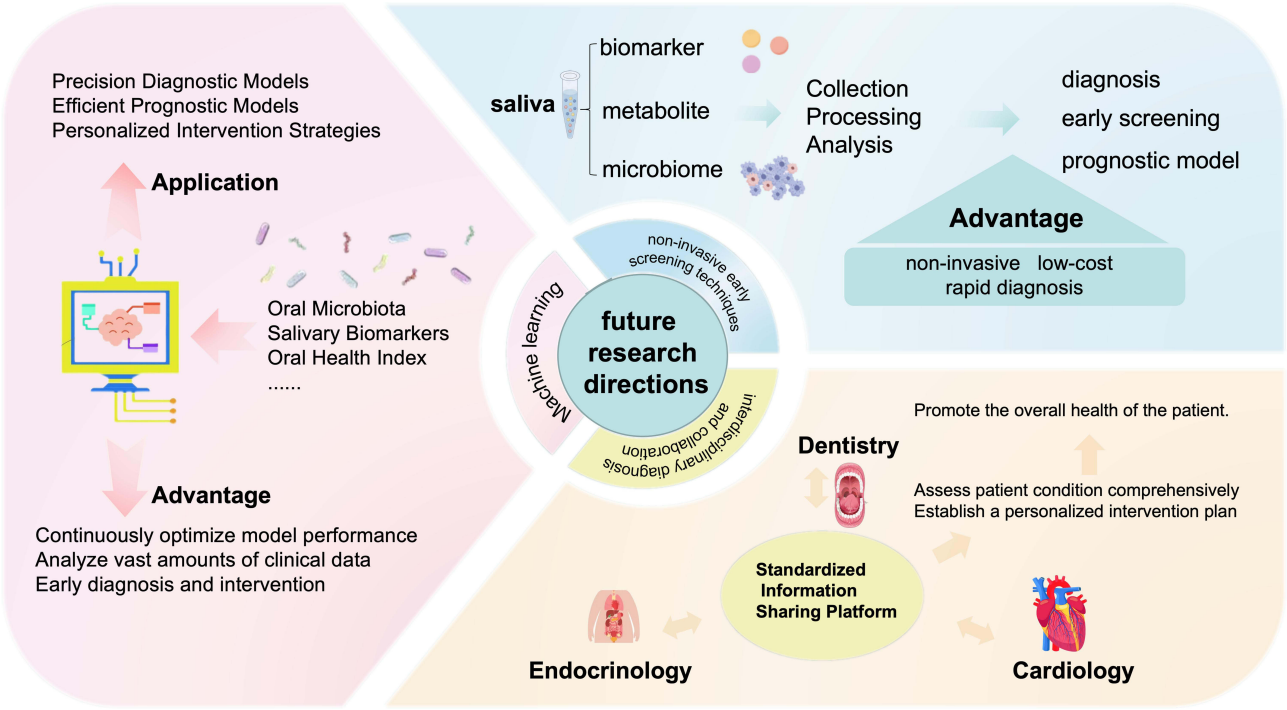

Figure 2 Future Research Directions on the Role of Oral Health in Diabetes Cardiomyopathy.

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Applications of Machine Learning Models and Artificial Intelligence Technologies

In future research directions, the application of machine learning and artificial intelligence technologies is expected to facilitate early precise diagnosis of diabetic cardiomyopathy through the assessment of oral health status, predict disease prognosis, and develop personalized intervention strategies. Although there are currently machine learning models based on other systemic indicators used in the early diagnosis and prevention of diabetic cardiomyopathy, such as blood biomarker analysis[59] and standard retinal imaging in patients with type 2 diabetes,[60] the "oral indicators for early screening of diabetic cardiomyopathy" discussed in this paper also demonstrate significant potential for utilizing oral metrics in constructing profiles for diabetes and cardiovascular complications. However, there is still a lack of standardized machine learning models specifically designed to evaluate oral health in relation to diabetes and cardiovascular complications.

Future studies should focus on designing comprehensive risk assessment models that integrate oral health-related indicators, including oral health indices, salivary biomarkers, and oral microbiomes, as this approach can significantly enhance the convenience and accuracy of risk assessment for diabetic cardiomyopathy. Leveraging machine learning techniques, these models can analyze large amounts of clinical data to identify potential risk factors and provide personalized early warning systems.[46] Additionally, the deep learning capabilities of artificial intelligence can process extensive patient data rapidly, optimizing model performance and making early diagnosis and interventions more precise and efficient.[61] Dentists can utilize these developed risk assessment tools to promptly identify high-risk patients and make appropriate referrals, thereby improving clinical outcomes.[62] Therefore, ongoing research and development in this area will pave the way for new insights into the early diagnosis and management of diabetic cardiomyopathy, showcasing significant application potential and clinical value.

Develop Non-Invasive Early Screening Technologies

In recent years, saliva and oral tissues have emerged as non-invasive biological samples with significant potential for early diagnosis and monitoring of diabetes and its cardiovascular complications. Compared to traditional venipuncture, saliva collection has proven to be a non-invasive, convenient, and cost-effective method. Saliva is rich in proteins, DNA, RNA, and microbial communities, which can serve as biomarkers for cardiovascular diseases and diabetes.[52,63] For instance, 1,5-anhydroglucitol (1,5-AG) and C-reactive protein (CRP) in saliva have been identified as clinical biomarkers for diabetes, demonstrating good consistency and predictive value.[52] Additionally, biomarkers associated with cardiovascular diseases, such as Irisin and ischemia-modified albumin, have also been detected in saliva.[63]

Future research should focus on utilizing metabolites, biomarkers, and microbiome data from saliva to develop non-invasive early screening technologies through high-throughput sequencing and machine learning modeling.[57] This includes standardizing the collection, processing, and analysis of saliva samples to minimize inconsistencies and errors across different studies. Although the significance of metabolites, biomarkers, and microbiome data in relation to diabetic cardiomyopathy has been established, diagnostic and prognostic models for cardiovascular events in diabetes are still in the early stages of development, and their efficacy and outcomes require further investigation and validation. By integrating biomarkers and microbiome data from saliva with advanced machine learning techniques, it is possible to develop more precise and efficient non-invasive early screening technologies. This not only aids in increasing the early diagnosis rates of diabetes and its complications but also provides personalized prevention and treatment strategies for patients, ultimately improving overall health outcomes.[64]

Interdisciplinary Diagnosis and Treatment Collaboration

Research indicates a bidirectional relationship between oral health and diabetes;[65] oral health not only has the potential to exacerbate the condition of diabetes but may also serve as an early warning signal for the disease.[66] Therefore, interdisciplinary collaboration is particularly important in the prevention and management of diabetic cardiomyopathy.[67] Specifically, it is essential to establish a referral mechanism among departments such as dentistry, endocrinology, and cardiology, as well as standardized information sharing and multidisciplinary collaboration platforms to ensure that patients' oral and systemic health information is shared in a timely manner.[68] Dentists hold a unique

advantage in identifying high-risk patients; through regular oral examinations, they can promptly detect potential periodontal issues in diabetic patients and refer them to relevant healthcare professionals for further diagnosis and treatment.[69] This bidirectional referral mechanism not only enhances the oral health of diabetic patients but also effectively reduces their risk of cardiovascular diseases, facilitating the implementation of comprehensive prevention and treatment strategies. Moreover, interdisciplinary collaboration can promote a comprehensive evaluation of patients' health status, integrating expertise from various disciplines to formulate personalized treatment plans. Finally, ongoing education and training, along with relevant institutional policies in hospitals, are critical factors in advancing interdisciplinary collaboration, helping healthcare teams better understand the connection between oral health and systemic health, and take appropriate preventive measures for early intervention and comprehensive treatment.

Discussion

Emerging evidence underscores oral health as both a critical modulator in diabetes progression and a potential early warning biomarker for diabetic cardiomyopathy (DCM). The pathophysiological triad of abnormal activation of the inflammatory response, oral microbiome and metabolic disorders constitutes the principal mechanistic framework linking oral pathologies to DCM development. These insights advocate for systematic oral health surveillance in diabetic populations to mitigate cardiovascular complications.

The landmark identification of Porphyromonas gingivalis within coronary thrombi of acute myocardial infarction (AMI) patients[70] provides definitive histopathological evidence establishing the causal link between periodontal pathogens and cardiovascular events. Expanding beyond previously characterized mechanisms—including virulence factor-induced endothelial inflammation with subsequent plaque destabilization and pro-inflammatory cytokine-mediated fibrous cap degradation (IL-1β/TNF-α upregulation)—contemporary research delineates three novel pathogenic pathways: First, gingipain-mediated proteolytic cleavage of autophagy regulators VAMP8/STX17 disrupts autophagosome-lysosome fusion, precipitating cardiomyocyte proteotoxic stress and programmed cell death that heightens post-infarction cardiac rupture risk.[71] Second, bacterial outer membrane vesicles (OMVs) orchestrate NF-κB-driven transcriptional activation, exacerbating ischemic myocardial injury through TNF-α/IL-6 hyperexpression and neutrophil extracellular trap-mediated endothelial barrier disruption.[71] Third, a dual thrombogenic mechanism emerges via TLR2/4-dependent platelet hyperreactivity coupled with complement system evasion through C3/C5 convertase degradation, establishing a self-perpetuating cycle of immunothrombosis.[72] These multilayered pathomechanisms—spanning subcellular autophagy dysregulation, paracrine inflammatory amplification, and thromboinflammatory crosstalk—collectively redefine the oral microbiome's role in cardiovascular pathogenesis, providing a molecular rationale for targeted periodontal interventions in secondary cardiovascular prevention strategies.

It is additionally worth noting that in patients with diabetes mellitus complicated by periodontal disease, the synergistic effect of persistent hyperglycemia and periodontal inflammation can significantly exacerbate glucolipotoxic damage to the myocardium. In a hyperglycemic environment, myocardial cells increase their uptake of free fatty acids (FFAs), leading to the accumulation of lipid intermediates such as diacylglycerol and sphingosine, which in turn trigger oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress—thereby impairing myocardial cell function.[72] The presence of periodontal disease amplifies this process through multiple mechanisms: firstly, lipopolysaccharide (LPS) from *Porphyromonas gingivalis* induces upregulation of macrophage ACAT1 expression, promoting cholesterol esterification and foam cell formation while inhibiting ABCG1-mediated cholesterol efflux, thus increasing the instability of atherosclerotic plaques;[73] secondly, periodontal inflammation-induced systemic low-grade inflammation exacerbates insulin resistance, prompting a shift in FFA metabolism from β-oxidation to non-oxidative pathways and accelerating lipotoxic damage to myocardial cells;[74] additionally, clinical studies show that periodontitis patients exhibit significantly elevated serum triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) levels, coupled with reduced high-density lipoprotein cholesterol (HDL-C)—this dyslipidemic profile is closely associated with diastolic dysfunction in diabetic cardiomyopathy.[72] Notably, *P. gingivalis* infection can also exacerbate myocardial fibrosis and coronary microvascular endothelial dysfunction by inducing excessive angiotensin II (Ang II) secretion, forming a vicious cycle of glucolipotoxicity-inflammation-fibrosis.[75] Therefore, alleviating glucolipotoxicity may confer therapeutic benefits in diabetic heart disease patients with periodontitis and related oral local inflammation. In early

screening, oral health indices, salivary biomarkers, and oral microbiome analysis have shown significant clinical value. While mounting evidence demonstrates significant associations between oral health parameters and diabetic cardiomyopathy (DCM), several methodological challenges persist in establishing definitive links. First, the predominance of observational studies limits causal inference, as these designs cannot establish temporal relationships or direct causation.[76] Second, multiple confounding variables - including socioeconomic status, education level, lifestyle factors, smoking habits, alcohol consumption, and dietary patterns may simultaneously influence both oral and cardiovascular health,[77,78] necessitating rigorous statistical control in analytical approaches. Furthermore, current research suffers from sampling limitations, with many studies employing small cohorts restricted to specific diabetic populations,[66] thereby compromising generalizability. In addition, from a clinical examination perspective, while existing dental protocols adequately assess localized oral pathologies, they prove insufficient for evaluating systemic conditions like DCM. Current oral health assessment methods lack standardized, multidimensional parameters with sufficient diagnostic precision for comprehensive systemic disease evaluation.

To address the current research limitations, future investigations should prioritize several key methodological advancements: First, large-scale prospective cohort studies should be conducted to establish temporal relationships and causal pathways between oral health parameters and diabetic cardiomyopathy (DCM), employing multicenter collaborations to enhance sample diversity across geographic, ethnic, and socioeconomic strata, thereby improving the validity and generalizability of findings. Second, standardized protocols must be implemented for covariate collection and analytical procedures, utilizing stratified analyses or multivariate regression models to adjust for confounding variables including socioeconomic status and lifestyle factors. In addition, a unified sampling framework should be established for oral health assessment in DCM and systemic complications, specifying operational standards for core indicators such as periodontal indices, salivary biomarkers, oral microbiome profiling, and radiographic evaluations. Methodologically, integrating multi-omics approaches (metagenomics, proteomics, metabolomics) with artificial intelligence algorithms will enable construction of robust predictive models, while leveraging electronic health records for longitudinal validation of these predictive tools.

Future research should focus on investigating the relationship between various oral health indicators and diabetic cardiomyopathy, utilizing multi-omics and multimodal data to train machine learning and artificial intelligence models, thereby enhancing the accuracy of early diagnosis (Figure 3). Specifically, current studies are limited to assessing the

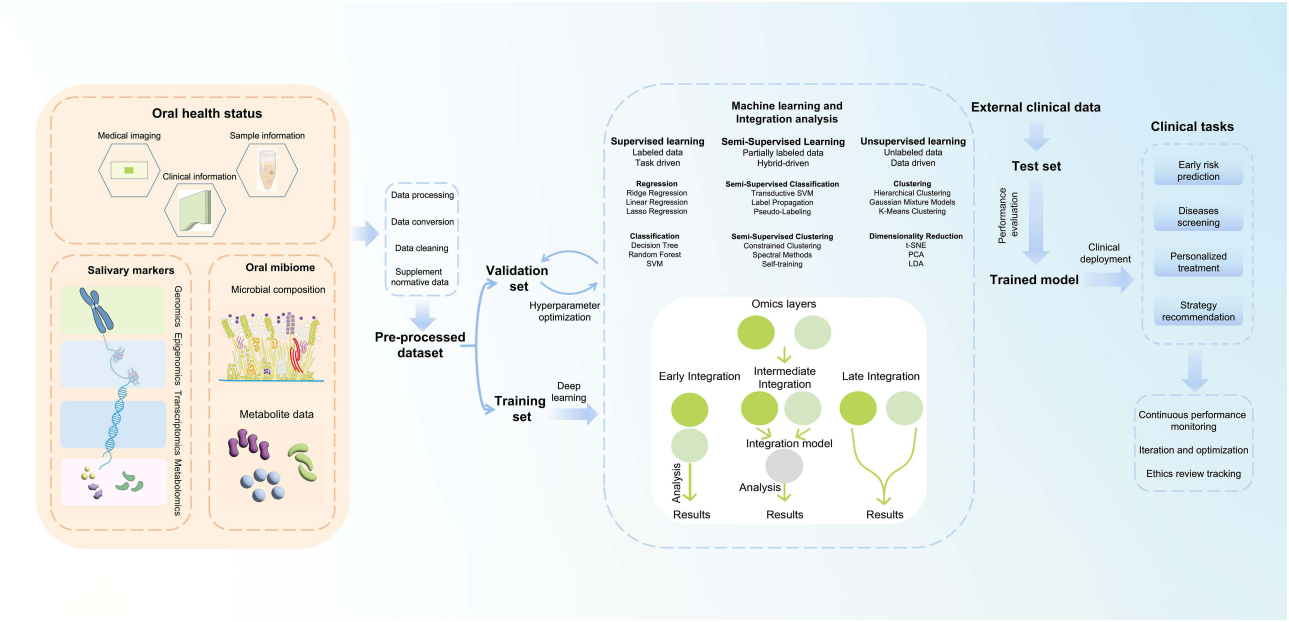

Figure 3 Machine Learning Models Integrating Multi-omics and Multimodal Data via Comprehensive Oral Health Indicators for Early Diagnosis and Prediction of Diabetic Cardiomyopathy.

effects of a single oral health indicator on diabetic heart disease. Our previous research has demonstrated that a comprehensive evaluation of overall oral health status, a variety of biomarker profiles in saliva, and information from omics and microbiomics can effectively diagnose and assess the prognosis of diabetic heart disease. Therefore, future methodologies should integrate multimodal and multi-omics technologies for training artificial intelligence models.[79] In particular, multimodal data can encompass clinical data, imaging data, and genomic information, while multi-omics data should include genomics, transcriptomics, proteomics, metabolomics, and emerging omics fields. Given the increasing data dimensions and predictive indicators, larger-scale and multi-center clinical data will be necessary for model training. Moreover, before utilizing machine learning or oral biomarkers as standard diagnostic tools, extensive multi-center data must validate the trained artificial intelligence models to enhance the reliability, applicability, and robustness of the research outcomes.[80] Ultimately, by integrating these vast multimodal and multi-omics data, more precise diagnostic models and risk prediction models can be constructed, and corresponding intervention strategies can be proposed, utilizing electronic health records for long-term follow-up to verify predictive effectiveness.

A noteworthy challenge in the field is the issue of cost-effectiveness, as both the acquisition of multi-omics data and the training of machine learning models entail significant expenses. The costs associated with multi-omics data collection include genomic sequencing with Illumina NovaSeq, transcriptome sequencing with 10x Genomics, epigenomic sequencing with ATAC-seq, proteomics using LC-MS/MS, metabolomics via GC-MS, and microbiome sequencing through 16S rRNA sequencing. Additionally, expenses related to the machine learning model training process encompass investments in computational hardware, data acquisition and processing, human resources, experimental and clinical validation, as well as ongoing maintenance and updates. These high costs represent potential barriers to the development of effective models in the future. However, from a long-term perspective, advanced systems may significantly reduce healthcare costs by enhancing diagnostic efficiency, decreasing misdiagnosis rates, streamlining detection methods, and optimizing treatment plans. Moreover, advancements in sequencing technologies consistently yield lower costs and higher throughput solutions, enabling more rapid data generation while reducing expenses.[80,81] Furthermore, governments are increasingly providing funding and incentives to support multi-omics and artificial intelligence research, thereby laying a solid foundation for large-scale clinical trials. To effectively minimize costs, future efforts could establish collaborative networks across multiple centers, combining data resources and technologies to distribute expenses, enabling research teams to engage in comprehensive studies. Actively participating in and developing public databases for multi-omics can also decrease data acquisition costs while enhancing the reproducibility and reliability of research. During the model training phase, implementing dimensionality reduction techniques can help streamline the data by extracting the most relevant biomarkers from complex multi-omics datasets, thereby reducing the complexity of data collection and analysis while constructing more efficient and effective models.[82]

Although this study does not involve human participants, we still believe that integrating machine learning into healthcare raises critical ethical issues, primarily concerning the ethics of future human trials and the protection of patient data. First, the lack of a comprehensive informed consent process may lead to insufficient transparency, causing patients to feel uneasy about how their data is being used. Therefore, obtaining informed consent from patients regarding data usage is essential for ensuring transparency and maintaining ethical standards. To address this issue, it is crucial to implement a clear and flexible consent process that informs patients of their rights and the specific applications of their data. At the same time, as machine learning technology evolves, interdisciplinary collaboration among healthcare professionals, ethicists, and data scientists should be encouraged to develop guidelines that inform responsible research practices and ethical frameworks. Secondly, protecting patient privacy is vital, as unauthorized access to or misuse of sensitive health information can lead to significant harm. To tackle these issues, robust data protection measures must be implemented, including data anonymization, secure storage, and strict access controls. By prioritizing ethical considerations, we can harness the potential of machine learning to improve healthcare outcomes while minimizing risks to patient privacy and autonomy.

Our previous research indicates that developing a non-invasive early screening method using saliva to detect diabetic cardiomyopathy is crucial for reducing associated diagnostic costs and may represent a significant direction for future advancements. However, there are several challenges in standardizing saliva diagnostics. First, the lack of uniform protocols for the collection and processing of saliva samples can lead to reduced comparability of results across different

studies. Evidence suggests that the composition of saliva may vary depending on the collection method and timing,[83] thus affecting the concentration of salivary biomarkers. Establishing standardized operating procedures encompassing sample collection, storage, and analysis is essential for ensuring the reliability of these biomarkers. Furthermore, continuous monitoring may offer greater insights than single-point measurements, thereby enhancing the analysis of salivary biomarkers.[84]

Currently, the clinical application of salivary biomarkers is still in its nascent stages. Existing studies primarily focus on the associations between individual biomarkers and diabetic heart disease; however, a single biomarker is insufficient to comprehensively explain disease mechanisms. The optimal diagnostic model for saliva may emerge from a combination of biomarkers tailored to each pathological condition. Constructing diagnostic models utilizing multiple biomarkers appears to be the most promising approach, likely enhancing clinical efficacy alongside accuracy and specificity. To identify specific salivary biomarkers for distinct diseases, extensive cohort studies and long-term follow-up investigations are necessary to verify their accuracy. Future research should emphasize multicenter collaborative studies and large-scale clinical trials to validate the effectiveness and feasibility of salivary biomarkers, thereby facilitating their application in clinical practice.

In addition, it is important to note that while considerable research has been conducted on saliva diagnostics, the development of relevant assay kits is still in its exploratory phase. On one hand, further investigation is required to identify salivary biomarkers associated with specific diseases; on the other hand, accurate detection of salivary biomarkers necessitates advanced nanoscale devices that possess high sensitivity and specificity. Additionally, current gold standard detection methods, such as PCR, gel electrophoresis, chromatography, and microarrays, are time-consuming and require skilled personnel for analysis.[85] These factors significantly hinder the commercialization of saliva-based diagnostic kits for disease detection. Therefore, developing rapid, convenient, and cost-effective testing methodologies should be a central focus of future research in salivary diagnostics, advancing the field further.

This study is a perspective article focusing on an emerging field where substantial literature support is lacking, conducted through a systematic literature search via PubMed and Web of Science. The selection process prioritizes studies published within the past five years to capture the latest advancements, with the timeframe extended to the past decade and further as needed when recent evidence is insufficient, ensuring a comprehensive foundation for the discussion. Adopting a narrative review framework, the analysis synthesizes and interprets core thematic areas within the field, though it does not adhere to the standardized methodological protocols of systematic reviews. This approach inherently involves potential limitations, including risks of selection bias and possible omissions of relevant literature due to the reliance on subjective inclusion criteria and non-transparent search strategies. To address the identified knowledge gaps—particularly in contentious topics or under-investigated domains—future research could benefit from conducting systematic reviews integrated with meta-analyses to quantitatively assess the strength of available evidence, thereby enhancing the robustness of conclusions and providing a more definitive basis for guiding both research and clinical applications in this evolving area.

Ultimately, based on the oral multimodal machine learning model framework proposed in this paper, future research can expand its diagnostic scope from diabetic cardiomyopathy to various systemic diseases, such as breast cancer, gastric cancer, and Alzheimer's disease. For instance, Assad et al conducted untargeted metabolomic analyses of saliva samples from breast cancer patients and healthy controls, identifying 31 compounds that were upregulated in the breast cancer group.[86] Similarly, Huang et al utilized 16S rRNA sequencing to compare the salivary microbiome profiles of patients with gastric cancer, superficial gastritis, and atrophic gastritis. By constructing a random forest model, they achieved an impressive AUC of 0.91 in accurately distinguishing gastric cancer patients from non-gastric cancer patients.[87] Additionally, salivary lactoferrin levels are significantly reduced in Alzheimer's disease (AD) patients, which can differentiate between preclinical AD/AD and healthy controls, indicating promising detection performance for AD.[88] By employing machine learning algorithms for feature selection and weight optimization of oral characteristics and indicators, the model can establish a diagnostic prediction system applicable across multiple diseases while retaining its core advantages—non-invasive sampling, multimodal data integration, and real-time monitoring capabilities. Notably, achieving cross-disease applications necessitates the development of a large-scale disease-specific oral biomarker database and addressing the challenges of heterogeneity among different disease datasets, ultimately leading to the

formation of adaptable risk assessment, intelligent diagnostic platforms, prognostic analysis, and treatment plan design systems suitable for various clinical scenarios.

Conclusion

Oral health is closely intertwined with diabetic cardiomyopathy, primarily inducing the latter through three mechanisms: Abnormal Activation of the Inflammatory Response, Oral Microbiome and Metabolic Disorders, and Immune Regulation Disorder. Early oral health interventions exert favorable effects on diabetic cardiomyopathy. In the future, oral health is poised to play a pivotal role in the early screening and prevention of diabetic cardiomyopathy. Currently, several categories of oral biomarkers, including Oral Health Status, Salivary Biomarkers, and Oral Microbiome, have been validated as relevant to diabetic cardiomyopathy, demonstrating utility in its diagnosis and prognostic prediction. However, the existing research is predominantly observational and conducted on small scales. To enhance the validity and generalizability of findings, we advocate for future large-scale multicenter cohort studies and interventional trials. Future directions include integrating multi-omics and multimodal data to develop unified artificial intelligence models for improved diagnostic and predictive efficiency; advancing saliva-based noninvasive early diagnostic technologies alongside standardized sample collection methodologies; and promoting interdisciplinary diagnosis and treatment collaboration while extending the application of oral multi-omics indicators in diagnostic and predictive models to other systemic diseases.

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Disclosure

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