ISSN NO: 2770-2936
January, 2026

Oral Health And Diabetes Mellitus: Bidirectional Biochemical Relationships

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ABSTRACT
This article analyzes the bidirectional biochemical relationships between diabetes mellitus and oral health based on scientific literature from the past five years. The relationship between periodontitis and diabetes mellitus has been demonstrated to occur through inflammatory processes, oxidative stress, advanced glycation end products (AGEs) and their receptors (RAGE), cytokine cascades, and oral microbiota dysbiosis. Meta-analysis results indicate that non-surgical periodontal treatment can reduce HbA1c levels by 0.4–0.6%, which has significant practical implications for diabetic patients. Furthermore, integrated approaches to managing oral health alongside diabetes mellitus are discussed.

Keywords: diabetes mellitus, periodontitis, AGE-RAGE, oxidative stress, cytokines, oral microbiota, HbA1c, bidirectional relationship.

INTRODUCTION

Diabetes mellitus (DM) is one of the most pressing challenges facing global healthcare today, affecting more than 460 million adults worldwide [1]. DM not only affects blood glucose regulation but is also directly associated with oral health conditions, particularly periodontal and peri-implant diseases [2]. Recent studies have demonstrated that this relationship is not only strong but also bidirectional in nature: while diabetes exacerbates oral diseases, oral infections negatively impact glycemic control [3].

Periodontitis is a chronic inflammatory disease that develops under the influence of bacterial biofilm (dental plaque) and damages the tooth-supporting apparatus, namely the periodontal ligaments and alveolar bone [4]. According to epidemiological data, the risk of developing periodontitis in diabetic patients is three times higher than in healthy individuals [5]. Moreover, there is a direct correlation between hyperglycemia levels (measured via HbA1c) and periodontitis severity, with chronic elevated blood glucose being a more significant risk factor than the type of diabetes itself [6].

Although all mechanisms underlying this bidirectional relationship have not been fully elucidated, they have been identified as closely linked to immune function, neutrophil activity, and cytokine biology [5]. Inflammation resulting from periodontitis elevates systemic markers such as C-reactive protein, which worsens glycemic control and increases insulin resistance [7]. Conversely, hyperglycemia in diabetes weakens the immune system, delays wound healing, and intensifies oxidative stress, thereby deepening inflammation and damage in periodontal tissues [8].

The aim of this review article is to analyze the molecular basis of the bidirectional biochemical relationships between oral health and diabetes mellitus based on recent scientific literature and to evaluate the impact of periodontal treatment on glycemic control.

MATERIALS AND METHODS

The study was conducted using a systematic literature review methodology. Electronic databases including PubMed, Web of Science, Scopus, and Google Scholar were searched for articles published between 2020 and 2025. Keywords and their various combinations used in the search included "diabetes mellitus," "periodontitis," "oral health," "bidirectional relationship," "AGE-RAGE," "oxidative stress," "cytokines," "oral microbiome," and "HbA1c."

Inclusion criteria for the study were: original research, meta-analyses, and systematic reviews published in English, Russian, or Uzbek; studies examining biochemical relationships between diabetes mellitus and periodontitis; and randomized clinical trials investigating the effect of periodontal treatment on glycemic control. Exclusion criteria included conference abstracts, dissertations, and articles without full-text access.

ISSN NO: 2770-2936
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The initial search yielded 156 articles, of which 45 fully met the specified criteria and were included in the analysis. Literature review was conducted in accordance with PRISMA guidelines.

RESULTS

Effect of Diabetes Mellitus on Periodontitis: Molecular Mechanisms

The conducted studies demonstrated that diabetes mellitus significantly increases susceptibility to periodontitis through several molecular mechanisms [9]. Under hyperglycemic conditions, production of reactive oxygen species (ROS) sharply increases and oxidative stress intensifies, further deepening damage to periodontal tissues [10].

Advanced Glycation End Products (AGE) and RAGE Interaction. Prolonged hyperglycemia promotes AGE formation, which accumulates in periodontal tissues [11]. When AGEs bind to their receptors (RAGE), NF-κB and MAPK signaling pathways are activated. This results in increased production of pro-inflammatory cytokines—TNF-α, IL-1β, and IL-6 [12]. Thus, a self-perpetuating inflammatory cycle is established, accelerating the chronicity of periodontitis [13].

Oxidative Stress and Antioxidant Defense. Neutrophils in diabetic patients produce significantly more superoxide compared to healthy individuals [14]. The imbalance between ROS production and antioxidant defense leads to increased oxidative stress. Additionally, AGE accumulation further intensifies oxidative stress in periodontal tissues [15]. Certain ROS, such as superoxide and hydrogen peroxide, activate osteoclasts and promote new osteoclast formation, leading to alveolar bone resorption [4].

Cytokines and Inflammatory Mediators. Diabetes mellitus significantly alters the expression of inflammation-related cytokines such as TNF-α, IL-6, and IL-1β [16]. These cytokines disrupt the RANKL/OPG ratio, activate osteoclasts responsible for bone resorption, and impair polymorphonuclear leukocyte function, thereby accelerating periodontitis progression [1].

Effect of Periodontitis on Glycemic Control

Inflammation resulting from periodontitis elevates systemic markers such as C-reactive protein, worsens glycemic control, and increases insulin resistance, creating conditions for diabetes progression [7]. Recent systematic reviews have also confirmed the bidirectional epidemiological relationship between periodontitis and diabetes: the prevalence of type 2 DM is significantly higher in patients with periodontitis (OR = 4.04; $p < 0.001$), and vice versa (OR = 1.58; $p < 0.001$) [17].

Systemic Inflammation and Insulin Resistance. Systemic inflammation precedes type 2 diabetes, leading to decreased pancreatic β-cell function, apoptosis, and insulin resistance [5]. When periodontal pathogens and their virulence factors enter the bloodstream, systemic inflammation (acute phase proteins and oxidative stress biomarkers) is further intensified. This serves as the biological basis for periodontitis affecting diabetes [8].

Oral-Gut Axis. Recent studies have demonstrated that oral pathogens also affect the gut microbiota. For example, when Porphyromonas gingivalis is ingested orally, it disrupts gut microflora balance, weakens the intestinal barrier, and allows bacteria and their products to spread throughout the body [6]. This process further exacerbates metabolic diseases, including type 2 DM pathology.

Oral Microbiota Dysbiosis and Diabetes Mellitus

Metagenomic and metabolomic analyses have shown significant changes in the oral microflora of patients with type 2 DM [18]. Periodontal pathogens—Porphyromonas gingivalis, Treponema denticola, Fusobacterium nucleatum, and Prevotella melaninogenica—are found in significantly higher numbers in type 2 DM patients. Interestingly, no significant differences were observed in the levels of dental caries pathogens such as Streptococcus mutans and Streptococcus sobrinus [18].

In diabetic patients, the genera Veillonella, Prevotella, Porphyromonas, Leptotrichia, Lactobacillus, and Streptococcus predominate, while Capnocytophaga and Neisseria are more common in healthy individuals [19]. Common taxa such as Fusobacterium and Porphyromonas present in both type 2 DM and periodontitis groups are associated with pro-inflammatory environments and periodontal disease. This suggests that type 2 DM may increase susceptibility to periodontitis through common pro-inflammatory microbial profiles [19].

Effect of Periodontal Treatment on Glycemic Control: Meta-Analysis Conclusions

Recent meta-analyses confirm that periodontal treatment has a positive effect on glycemic control. A systematic review and meta-analysis published in 2025, analyzing 11 studies, reported that periodontal

ISSN NO: 2770-2936
January, 2026

therapy reduced HbA1c levels by –0.64% (95% CI = –0.96 to –0.32) at three months and –0.33% (95% CI = –0.65 to –0.01) at six months [20]. C-reactive protein (CRP) also decreased significantly, indicating reduced systemic inflammation [20].

A Cochrane review analyzed 35 randomized clinical trials. Results showed that periodontal treatment with subgingival instrumentation reduced HbA1c by an average of 0.43% at 3–4 months, 0.30% at six months, and 0.50% at 12 months compared to routine care [3]. The certainty of evidence was assessed as moderate.

An additional meta-analysis examined 23 randomized clinical trials. Periodontal therapy significantly reduced HbA1c levels at 3 months (WMD –0.514; 95% CI –0.730, –0.298; $p < 0.001$) and 6 months (WMD –0.548; 95% CI –0.859, –0.238; $p < 0.001$). The effectiveness of periodontal treatment was particularly pronounced in patients with higher baseline HbA1c levels [3].

DISCUSSION

This literature analysis has elucidated the complex nature of the bidirectional biochemical relationship between oral health and diabetes mellitus. This relationship operates through several key mechanisms: inflammatory processes, AGE-RAGE interaction, oxidative stress, and oral microbiota dysbiosis [5, 9, 11].

Under hyperglycemic conditions, AGE accumulation and interaction with RAGE activates the NF-κB signaling pathway, which increases production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [12, 13]. These cytokines not only intensify local periodontal inflammation but also contribute to systemic inflammation, increase insulin resistance, and worsen glycemic control [7, 16].

Changes in the oral microbiota are also of great importance. The proliferation of P. gingivalis and other periodontal pathogens not only damages local tissues but also affects the gut microbiota and creates conditions for the development of metabolic diseases through the oral-gut axis [6]. These findings demonstrate that maintaining oral health is important not only from a dental perspective but also from a general health standpoint.

According to meta-analysis results, non-surgical periodontal treatment can reduce HbA1c levels by 0.3–0.6% [3, 20]. This is clinically significant because each 1% reduction in HbA1c can decrease diabetes complications by up to 21% over 10 years. Furthermore, the effectiveness of periodontal treatment can be compared to adding a second medication to the pharmacological regimen [5].

However, insufficient collaboration between medical and dental specialists remains a challenge [6]. Physicians often neglect oral health assessment, while dentists may miss opportunities for early detection of undiagnosed diabetes. Therefore, integrated care models incorporating bidirectional screening protocols are necessary.

CONCLUSION

The results of this literature analysis clearly confirm the bidirectional relationship between oral health and diabetes mellitus. This relationship manifests through inflammatory processes, AGE-RAGE interaction, oxidative stress, and oral microbiota dysbiosis. Periodontal treatment can serve as an effective adjunctive measure for improving glycemic control in diabetic patients.

For the future, larger-scale randomized trials based on long-term follow-up are recommended to further investigate the bidirectional relationship and evaluate the impact of periodontal therapy on diabetes. Development of practical guidelines for medical specialists, dentists, and patients regarding periodontal care and oral health management for diabetic patients or individuals at risk of diabetes is essential.

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ISSN NO: 2770-2936
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