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Periodontal Healing Dynamics and Biomarker Responses Following Non-Surgical Periodontal Therapy in Type 2 Diabetes Mellitus: A Narrative Review

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ABSTRACT

Type 2 diabetes mellitus (T2DM) and periodontitis share a well-established bidirectional relationship, with glycemic control playing an important role in periodontal healing following periodontal therapy. This narrative review summarizes the current clinical evidence on periodontal healing in patients with T2DM, with particular emphasis on the influence of glycemic control and the potential role of biological biomarkers in monitoring treatment response. A literature search was conducted using PubMed, ScienceDirect, and Google Scholar, focusing primarily on human clinical studies and systematic reviews of clinical studies. Current evidence indicates that patients with well-controlled T2DM generally achieve favorable periodontal healing following non-surgical periodontal therapy, whereas poorer glycemic control may result in less pronounced improvements in some clinical parameters and an increased risk of disease progression. Clinical studies further demonstrate that periodontal healing is a dynamic biological process involving inflammatory resolution, tissue remodeling, and systemic responses that may not fully reflected by conventional clinical parameters. Biomarkers derived from gingival crevicular fluid, saliva, and serum have the potential to complement clinical assessment by providing insights into these biological processes. However, further well-designed longitudinal clinical studies are needed to validate their routine clinical application in patients with T2DM.

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1. INTRODUCTION

Periodontitis is an irreversible chronic inflammatory disease that destroys the tooth supporting structures. It results from a complex interaction between dysbiotic dental biofilm and a dysregulated host immune response, which is further influenced by an individual's susceptibility to disease (Cullinan *et al*., 2001; Seymour & Taylor, 2004). Beyond the oral cavity, periodontitis shares a well-established bidirectional relationship with systemic health, whereby systemic conditions can influence periodontal disease progression, while periodontitis may adversely affect systemic health (Falcao & Bullón, 2019; Iacopino & Cutler, 2000).

Type 2 diabetes mellitus (T2DM) is a common chronic metabolic disorder characterized by insulin resistance and progressive impairment of pancreatic β cell function (American Diabetes Association, 2010). Extensive evidence indicates that T2DM is associated with an increased prevalence, extent, and severity of periodontitis, supporting a well-established bidirectional relationship between the two conditions(Chávarry *et al*., 2009; Hugoson *et al*., 1989; Soskolne & Klinger, 2001; Taylor *et al.*, 2013).

Although periodontal therapy consistently improves clinical periodontal outcomes, its effect on glycemic control remains inconsistent. While some studies have reported modest improvements in glycated haemoglobin following treatment, others, including a large multicentre randomized clinical trial, found no significant benefit (Engebretson *et al.*, 2013; Madianos & Koromantzos, 2018; Simpson *et al*., 2022). These conflicting findings highlight the complex relationship between periodontitis and T2DM. Furthermore, periodontal healing involves dynamic biological processes that are not fully captured by conventional clinical parameters, highlighting the need to better understand the biological response to periodontal therapy.

2. SEARCH STRATEGY AND SCOPE OF REVIEW

This narrative review provides an overview of the current clinical evidence on periodontal healing in patients with T2DM, with particular emphasis on the biological processes underlying healing and the potential role of biomarkers in monitoring treatment response following periodontal therapy.

A literature search was conducted using PubMed, ScienceDirect, and Google Scholar to identify relevant publications. Search terms included combinations of *periodontitis*, *type 2 diabetes mellitus*, *periodontal therapy*, *non-surgical periodontal therapy*, *periodontal surgery*, *periodontal healing*, *biomarkers*, *gingival crevicular fluid*, *saliva*, *serum*, *inflammation*, *tissue remodeling*, *glyaemic control*, and *treatment response*. Additional relevant publications were identified through manual screening of the reference lists of selected articles.

The review primarily included human clinical studies, including randomized controlled trials, prospective and longitudinal studies, observational studies, and systematic reviews and meta-analyses of human clinical studies. Seminal clinical studies published before 2000 were also included where they provided foundational evidence on periodontal healing and the influence of glycemic control on treatment outcomes. Experimental animal studies, in vitro studies, conference abstracts, editorials, and non-English publications were excluded unless they were considered essential for explaining the biological mechanisms discussed.

3. PERIODONTAL HEALING IN TYPE 2 DIABETES MELLITUS

3.1. Molecular Mechanisms Linking Hyperglycemic Dysregulation to Periodontal Breakdown

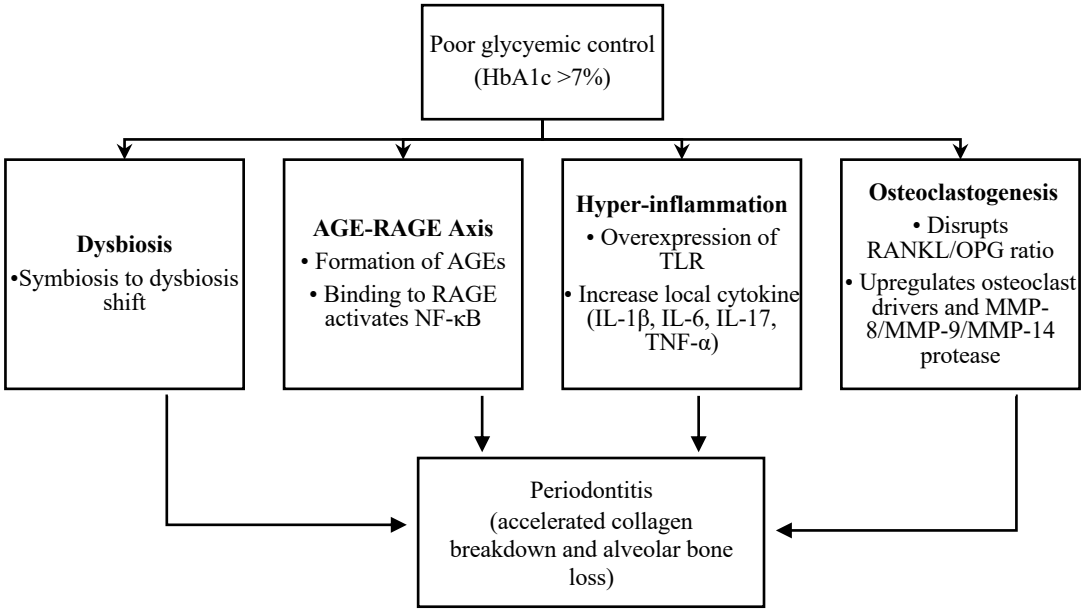


Fig. 1. Pathways detailing how poor glycemic control drives accelerated soft tissue and alveolar bone loss.

Source: Polak *et al*. (2020)

Polak *et al*. (2020) outlined plausible molecular mechanisms that may link diabetes with periodontitis deriving evidence from clinical, animal, and cell culture studies. The mechanisms are summarized in Figure 1.

Under chronic hyperglycemic conditions associated with uncontrolled diabetes, periodontal tissue destruction is accelerated through several parallel pathobiological pathways. First, hyperglycemia disrupts oral homeostasis, triggering a subgingival microbiome shift from symbiosis to dysbiosis. This dysbiotic state, combined with hyperglycemia-induced upregulation of pattern recognition receptors, specifically Toll-like receptors 2 and 4 (TLR-2 and TLR-4) which drives host cells into a hyper-responsive state.

Second, elevated glucose levels initiate the non-enzymatic formation of advanced glycation end-products (AGEs). The binding of AGEs to their receptor (RAGE) on leukocytes and periodontal ligament fibroblasts activates inflammatory signaling, exacerbates oxidative stress, and induces endoplasmic reticulum stress.

Consequently, these activated pathways stimulate a massive local upregulation and secretion of pro-inflammatory cytokines and chemokines which include IL-1β, IL-6, IL-12, IL-17, IL-23, and TNF-α, alongside C-reactive protein (CRP). This intense inflammatory cascade stimulates fibroblasts and hyper-

reactive leukocytes to release tissue-destructive matrix metalloproteinases (MMPs), which directly degrade the extracellular matrix and periodontal ligament.

Concurrently, bone homeostasis is severely altered. AGE-RAGE signaling and the local cytokine storm upregulate the local RANKL/OPG ratio and stimulate key bone-resorption mediators, including RANK. This imbalance drives osteoclast differentiation and hyper-activation. Ultimately, these parallel microbial, inflammatory, and osteolytic pathways converge to accelerate soft tissue degradation and alveolar bone loss, resulting in progressive periodontal breakdown.

3.2. Biological Basis of Periodontal Healing in T2dm

Periodontal healing following NSPT is not a simple event but a complex, multi-phase biological process. It encompasses the resolution of inflammation, the repair of soft connective tissues, and the stabilization or remodeling of alveolar bone (Bartold & Ivanovski, 2025). In patients with T2DM, this finely tuned healing cascade is often dysregulated. Chronic hyperglycemia and insulin resistance drive a series of metabolic and immune disturbances that can impair the resolution of inflammation, disrupt the formation of new blood vessels, and hinder crucial cellular repair mechanisms (Dasari *et al*., 2021; Vaibhav *et al*., 2024). The diabetic state is characterized by several factors known to compromise healing, including impaired neutrophil function, increased oxidative stress, endothelial dysfunction, and the accumulation of advanced glycation end products (AGEs) in tissues (Burgess et al., 2021). For these reasons, understanding how diabetes and glycemic control influence periodontal healing outcomes has become a major focus of periodontal research.

3.3. Early Clinical Evidence On Glycemic Control On Periodontal Healing

Early clinical evidence from case reports and longitudinal studies suggested that poor glycemic control compromises periodontal healing and long-term periodontal stability, resulting in more severe periodontal destruction and less favourable treatment outcomes in individuals with poorly controlled diabetes. For example, (Ainamo *et al*., 1990) reported rapid periodontal breakdown in adults with longstanding uncontrolled diabetes that persisted despite comprehensive periodontal therapy, with periodontal stability observed only after metabolic control improved. Similarly, (Seppälä & Ainamo, 1994) demonstrated significantly greater alveolar bone loss over one and two years in patients with poorly controlled insulin dependent diabetes than in those with good glycemic control, despite both groups receiving periodontal therapy.

However, subsequent evidence demonstrated that periodontal healing in individuals with diabetes is strongly influenced by the level of glycemic control rather than the presence of diabetes alone. Interventional studies showed that patients with well controlled diabetes achieved comparable improvements in probing pocket depth, levels of periopathogenic bacteria, and markers of neutrophil hyperactivity following non-surgical periodontal therapy to those observed in systemically healthy individuals (Christgau *et al*., 1998; Smith *et al.*, 1996; Tervonen & Karjalainen, 1997). These findings indicate that satisfactory periodontal healing can be achieved when diabetes is adequately controlled. Supporting this observation, (Westfelt et al., 1996) reported that individuals with well controlled diabetes who received appropriate supportive periodontal care maintained long-term periodontal stability, with recurrence rates comparable to those of non-diabetic individuals.

3.4. Recent clinical evidence on periodontal healing following NSPT

Recent clinical studies have further clarified the influence of T2DM on periodontal healing following NSPT. Mirnic *et al*. (2013) and mirnić *et al*. (2021) reported that NSPT produced comparable improvements in most periodontal parameters among patients with well-controlled T2DM, poorly-controlled T2DM, and non-diabetic individuals. However, both studies found significantly smaller reductions in probing pocket depth in patients with diabetes than in non-diabetic controls. Similarly, kaur *et al.* (2015) observed comparable improvements in periodontal parameters among patients with controlled and poorly controlled T2DM following NSPT, although nondiabetic individuals demonstrated greater reductions in gingival inflammation, bleeding on probing, and deep periodontal pockets. Meanwhile, in the untreated control groups, periodontal deterioration over six months occurred in both diabetic groups but was significantly greater in patients with poorly controlled diabetes, highlighting the importance of glycemic control in limiting disease progression.

Evidence from systematic reviews further supports these clinical findings. Hsu *et al*. (2019) concluded that diabetes with glycated haemoglobin (HbA1c) levels of ≤8.5% was not associated with poorer clinical periodontal outcomes following NSPT. Instead, baseline probing pocket depth and patient age had a greater influence on treatment response than diabetic status. Likewise, Kang et al. (2024) reported that individuals with well controlled T2DM achieved probing pocket depth reduction comparable to that of systemically healthy individuals following NSPT. However, systemically healthy individuals demonstrated greater clinical attachment level gain than both well controlled and poorly controlled T2DM groups.

Overall, the available evidence suggests that favourable periodontal healing following NSPT can be achieved in patients with T2DM. However, the magnitude of improvement in certain clinical parameters, particularly probing pocket depth, may be less pronounced than in systemically healthy individuals.

3.5. Implications For Contemporary Periodontal Care

Current evidence supports diabetes as an important modifying factor rather than an independent predictor of poor periodontal outcomes. This concept is reflected in the 2017 World Workshop Classification of Periodontal and Peri Implant Diseases and Conditions, which incorporates diabetes into the grading system as a systemic risk factor influencing the estimated rate of disease progression and the anticipated response to periodontal therapy (Jepsen *et al.*, 2018; Papapanou *et al*., 2018).

This risk-based approach is consistent with clinical evidence showing that patients with well-controlled T2DM can achieve favourable periodontal healing following NSPT, whereas poorer glycemic control is associated with less pronounced improvements in some clinical parameters and greater periodontal deterioration in the absence of treatment. Consequently, diabetes should be considered as one component of a comprehensive periodontal risk assessment together with baseline periodontal status, patient related factors, and long term supportive periodontal care to optimise treatment outcomes.

4. BIOLOGICAL BIOMARKERS OF PERIODONTAL HEALING

4.1. Limitations of Conventional Clinical Parameters

Conventional clinical parameters, including probing pocket depth, clinical attachment level, and bleeding on probing, remain the cornerstone for diagnosing periodontitis and evaluating treatment outcomes. However, they have limited ability to detect current disease activity or predict future progression, as they primarily reflect previous tissue destruction rather than ongoing biological processes (Tonetti *et al*., 2005). While the absence of bleeding on probing has a high negative predictive value for disease progression, confirmation of progression requires longitudinal assessment (Lang *et al*., 1990; Preshaw, 2015).

These limitations are particularly relevant in patients with T2DM, who may exhibit clinical improvement following periodontal therapy yet remain at increased risk of disease progression *(Costa et al.*, 2013; Kaur *et al*., 2015; Preshaw *et al*., 2020). This suggests that underlying biological dysregulation may persist despite favorable clinical outcomes.

Consequently, biological biomarkers have emerged as potential valuable adjuncts to conventional clinical assessment (Buduneli *et al.*, 2024). They may provide objective and quantifiable information on inflammatory and tissue repair processes that cannot be detected by clinical examination alone, thereby improving the assessment of disease activity, treatment response, and long-term periodontal stability, particularly in patients with T2DM.

4.2. Biomarkers Across the Phases of Periodontal Healing

Table 1. Phases of periodontal healing after NSPT

Healing Phase	Primary Biological Source	Key Representative Biomarkers	Expected Trend with Successful NSPT	Clinical Interpretation	References
1. Inflammatory Resolution	GCF	IL-1β, IL-6, TNF-α;	↓ Rapid Decrease	Suppression of destructive inflammation & activation of pro-resolving pathways.	Krasniqi *et al*., 2025; Ma *et al*., 2024
		Specialized Pro-Resolving Mediators (e.g., LXA4)	↑ Increase		
2. Tissue Turnover & Remodelling	GCF Saliva	Breakdown: MMP-8, MMP-8/TIMP-1 ratio; Repair: Periostin, TGF-β Bone: RANKL/ OPG ratio	Breakdown ↓; Repair ↑; Bone RANKL/OPG: Ratio ↓	Shift from tissue degradation to active ECM repair, organization, and bone stabilization.	Correa *et al*., 2008; Gursoy *et al*., 2010; López Roldán *et al*., 2020; Morsy & Ali, 2020; Ribeiro *et al*., 2011 Umeizudike *et al*., 2022
3. Systemic Echo	Serum	High-sensitivity CRP, HbA1c	Modest ↓	Reduction in systemic inflammatory burden and potential metabolic improvement.	Corbella *et al*., 2025; Luthra *et a*l., 2023

To be clinically useful, biomarkers should be interpreted within the context of the biological processes that occur during periodontal healing rather than in isolation. Based on the conceptual framework proposed by Bartold & Ivanovski (2025), successful healing following NSPT progresses through a series of overlapping biological phases. Table 1 summarizes representative biomarkers associated with each phase, drawing exclusively on evidence from human clinical studies and systematic reviews of clinical studies.

Clinical studies have demonstrated that different classes of biomarkers provide complementary information throughout the healing cascade, enabling a more comprehensive assessment of periodontal recovery than conventional clinical parameters alone. The first phase, Inflammatory Resolution, is characterized by suppression of the destructive host inflammatory response. Human interventional studies have consistently shown reductions in pro inflammatory mediators such as IL 1β, IL 6, and TNF α, together

with an increase in specialized pro resolving mediators such as lipoxin A4 following successful NSPT, reflecting restoration of inflammatory homeostasis (Krasniqi et al., 2025; Ma et al., 2024).

Clinical intervention studies further demonstrate that healing progresses to the Tissue Turnover and Remodeling phase, during which extracellular matrix degradation is gradually replaced by tissue repair and bone stabilization. Biomarkers of tissue breakdown, including MMP 8 and the MMP 8/TIMP 1 ratio, generally decrease, whereas reparative markers such as periostin and TGF β increase, reflecting collagen maturation and extracellular matrix remodeling (Correa *et al*., 2008; Gursoy *et al*., 2010; Morsy & Ali, 2020; Ribeiro *et al*., 2011; Umeizudike *et al.*, 2022). Concurrently, reductions in the RANKL/OPG ratio indicate suppression of osteoclast activity and restoration of bone homeostasis (López Roldán *et al*., 2020). Although the magnitude and timing of these biomarker changes vary among studies, the overall pattern consistently supports a transition from tissue destruction toward periodontal repair following NSPT.

Evidence from clinical trials and systematic reviews of clinical studies also suggests that successful periodontal therapy may produce systemic effects beyond the periodontal tissues. During this Systemic Echo phase, modest reductions in circulating inflammatory markers such as high sensitivity C reactive protein and, in some patients, improvements in glycemic control have been reported following NSPT (Corbella *et al*., 2025; Luthra *et al*., 2023). Although these systemic responses are generally less pronounced and more variable than local biomarker changes, they indicate that serum biomarkers may provide complementary information regarding the systemic impact of periodontal therapy.

5. CONCLUSION

NSPT consistently improves clinical periodontal outcomes in patients with T2DM. Current evidence suggests that periodontal healing is influenced primarily by the level of glycemic control, with well controlled T2DM generally achieving more favourable treatment outcomes than poorly controlled disease.

Periodontal healing in T2DM is a complex biological process that extends beyond improvements in conventional clinical parameters. Evidence from human clinical studies indicates that biomarkers derived from gingival crevicular fluid, saliva, and serum have the potential to complement clinical assessment by providing insights into inflammatory resolution, tissue remodeling, and systemic responses following therapy. However, further longitudinal clinical studies are needed to validate their routine clinical application in monitoring periodontal healing and guiding personalised periodontal care in patients with T2DM.

6. LIMITATION AND CLINICAL IMPLICATIONS

This narrative review is limited by its non-systematic methodology and the heterogeneity of the included clinical studies in terms of study design, patient populations, periodontal therapies, biomarkers evaluated, biological sample sources, and follow up periods. Consequently, the findings should be interpreted with caution. Nevertheless, current evidence supports NSPT as an effective treatment for periodontitis in patients with type 2 diabetes mellitus, with periodontal healing being influenced primarily by glycemic control. While conventional clinical parameters remain the cornerstone of treatment evaluation, biological biomarkers have the potential to complement clinical assessment by providing additional information on the underlying healing process. However, further well-designed longitudinal clinical studies and standardized biomarker assessment protocols are needed before their routine clinical application.

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None

8. CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflict of interest.

9. AUTHORS' CONTRIBUTIONS

Mastura Norman: Conceptualisation, methodology, investigation, formal analysis and writing of original draft, **Mohd Faizal Hafez**, **Fouad Hussain** and **Hasidah Abdul Hamid**: Supervision, writing- review and editing and validation, **Najwa Baharudin**: Conceptualisation.

10. DECLARATION OF GENERATIVE AI IN THE WRITING PROCESS

During the preparation of this work, the author(s) used scispace to assist in paper summarization and refine language readibility. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

11. DATA AVAILABILITY/SUPPLEMENTARY MATERIALS

Data sharing is not applicable to this article as no new datasets were generated or analysed during the current study.

12. ETHICS STATEMENT

Ethical approval was not required for this study as it is a narrative review of previously published literature and did not involve human participants or animal subjects.

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