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REVIEW ARTICLE

BONE METABOLISM-RELATED BIOCHEMICAL BIOMARKERS IN DIABETIC ORAL MANIFESTATIONS: A SCOPING REVIEW OF PATHOGENETIC MECHANISMS AND CLINICAL IMPLICATIONS

Hakob Khachatryan[1], Elene Aghajanova[2]
[1]Department of Oral and Maxillofacial Surgery Yerevan State Medical University,Yerevan,Armenia
[2]Professor, Head of the Department of Endocrinology of the Yerevan State Medical University, Yerevan,Armenia
***Corresponding authors:** Hakob Khachatryan, Department of Oral and Maxillofacial Surgery Yerevan State Medical University,Yerevan, Armenia, e-mail: hakobsurgeon@gmail.com
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Abstract

Background: Diabetes mellitus is a chronic metabolic disorder associated with numerous oral complications, including periodontal disease, impaired wound healing, increased susceptibility to infection, and progressive alterations in periodontal supporting tissues. The pathogenesis of diabetic oral manifestations is strongly influenced by persistent hyperglycemia, oxidative stress, accumulation of advanced glycation end products (AGEs), and dysregulation of inflammatory and bone remodeling pathways. In recent years, biochemical biomarkers involved in bone metabolism have attracted increasing attention as potential indicators of the molecular mechanisms underlying diabetic-associated oral tissue alterations. Understanding changes in bone formation, bone resorption, and inflammatory biomarkers may provide new insights into the mechanisms linking systemic metabolic dysfunction with periodontal destruction and impaired alveolar bone homeostasis.

Objective: The aim of this scoping review was to map the current evidence regarding the role of bone metabolism-related biochemical biomarkers in the pathogenetic mechanisms of oral manifestations associated with diabetes mellitus and to identify current research trends, clinical implications, and knowledge gaps.

Methods: This scoping review was conducted according to the Joanna Briggs Institute (JBI) methodology and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. A comprehensive literature search was performed in electronic databases, including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. Studies published between **2000 and 2026** were considered eligible. The review included clinical, observational, and experimental studies investigating biochemical biomarkers related to bone metabolism in patients with diabetes mellitus and oral manifestations, including diabetic periodontitis, alveolar bone loss, impaired periodontal healing, and alterations in periodontal tissue remodeling.

Results: The initial literature search identified **79 records**. After screening and eligibility assessment, studies that did not meet the inclusion criteria were excluded. Following full-text evaluation, **40 studies were included in the final scoping review**.The identified biomarkers were categorized into several major groups, including bone formation markers such as osteocalcin, bone-specific alkaline phosphatase, and procollagen type I N-terminal propeptide; bone resorption markers including receptor activator of nuclear factor kappa-B ligand (RANKL), osteoprotegerin (OPG), C-terminal telopeptide (CTX), and N-terminal telopeptide (NTX); and inflammatory mediators associated with diabetic periodontal destruction, including interleukin-1β, interleukin-6, tumor necrosis factor-alpha, and matrix metalloproteinases. The available evidence indicates that diabetes mellitus disrupts normal bone remodeling by promoting an imbalance between osteoblastic bone formation and osteoclastic bone resorption. Hyperglycemia-induced oxidative stress, AGE accumulation, inflammatory activation, increased RANKL expression, reduced OPG activity, and altered cellular signaling pathways contribute to impaired alveolar bone metabolism and increased susceptibility to periodontal tissue destruction.

Conclusions: Bone metabolism-related biochemical biomarkers represent important molecular indicators involved in the pathogenesis of diabetic oral manifestations. Their evaluation provides valuable insights into the mechanisms responsible for periodontal destruction, impaired bone remodeling, and delayed tissue repair in patients with diabetes mellitus. Although current evidence highlights their potential diagnostic and prognostic value, further longitudinal clinical studies are required to determine their applicability in early detection, risk assessment, and personalized periodontal management of diabetic patients.

Keywords: Diabetes mellitus; Bone metabolism biomarkers; Osteocalcin; Bone resorption; Bone formation; Osteoprotegerin; RANKL); Periodontal tissue remodeling; Oxidative stress; Advanced glycation end products (AGEs).

1.INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia and progressive alterations in multiple physiological systems. Beyond its well-established systemic complications, diabetes exerts a profound influence on oral health, contributing to increased susceptibility to periodontal disease, impaired wound healing, altered immune responses, and disturbances in hard tissue metabolism. Among oral complications, periodontitis represents one of the most clinically relevant manifestations of diabetes and has been recognized as the sixth major complication associated with this metabolic disease. The relationship between diabetes and periodontal disease is bidirectional, as hyperglycemia increases periodontal susceptibility, while periodontal inflammation may negatively influence glycemic control through systemic inflammatory pathways.[1–5]

Periodontitis is a chronic inflammatory disease initiated by dysbiotic microbial communities within the subgingival biofilm; however, tissue destruction is primarily mediated by an exaggerated host immune-inflammatory response rather than microbial infection alone. In individuals with diabetes, metabolic abnormalities amplify this inflammatory response through mechanisms involving oxidative stress, advanced glycation end products (AGEs), impaired leukocyte function, endothelial dysfunction, and altered cytokine production. These pathological changes contribute to accelerated connective tissue degradation, periodontal attachment loss, and alveolar bone destruction.[4,5]

Alveolar bone homeostasis depends on a highly coordinated balance between bone formation by osteoblasts and bone resorption mediated by osteoclasts. Under physiological conditions, remodeling processes maintain skeletal integrity through tightly regulated cellular communication. Diabetes disrupts this equilibrium by impairing osteoblast differentiation, increasing osteoclast activation, and modifying intracellular signaling pathways involved in bone turnover. Chronic hyperglycemia promotes accumulation of AGEs within periodontal tissues, activation of the AGE receptor (RAGE), increased reactive oxygen species production, and stimulation of inflammatory pathways that ultimately enhance osteoclastogenesis and suppress regenerative responses.[7,15,16]

The molecular mechanisms linking diabetes with periodontal bone destruction are strongly associated with dysregulation of the receptor activator of nuclear factor kappa-B (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) pathway. RANKL is a critical regulator of osteoclast differentiation and activation, whereas OPG functions as a decoy receptor that inhibits RANKL-mediated osteoclastogenesis. An increased RANKL/OPG ratio has been reported in inflammatory conditions characterized by accelerated bone loss and is considered an important molecular mechanism contributing to periodontal bone destruction, particularly in the context of diabetes.[6,8,9]

In recent years, biochemical biomarkers associated with bone metabolism have received increasing attention as potential indicators of periodontal disease activity and systemic metabolic influence. Unlike conventional clinical parameters, including probing depth, clinical attachment loss, and radiographic bone loss, biochemical biomarkers provide information regarding biological processes occurring during bone remodeling. Their evaluation may improve understanding of disease mechanisms, facilitate early risk identification, and support the development of personalized periodontal management strategies.[10–12]

Bone formation biomarkers represent an important group of indicators reflecting osteoblastic activity and mineralized tissue development. Osteocalcin, bone-specific alkaline phosphatase (BALP), and procollagen type I N-terminal propeptide (P1NP) are widely investigated markers associated with osteoblast differentiation, collagen synthesis, and bone matrix mineralization. Alterations in these biomarkers may reflect impaired bone formation capacity in diabetic conditions and may contribute to the reduced regenerative potential observed in periodontal tissues affected by metabolic dysfunction.[10–12]

Conversely, biomarkers associated with bone resorption provide insight into osteoclastic activity and periodontal tissue breakdown. C-terminal telopeptide of type I collagen (CTX) and N-terminal telopeptide (NTX) represent degradation products released during collagen breakdown and have been investigated as indicators of increased bone turnover. In periodontal disease, alterations in resorption-related biomarkers may reflect enhanced osteoclastic activity associated with inflammatory stimulation and metabolic disturbances.[10–12]

Inflammatory mediators represent another essential component connecting diabetes with periodontal bone metabolism abnormalities. Hyperglycemia promotes increased production of pro-inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). These cytokines stimulate osteoclast differentiation, regulate RANKL expression, and enhance extracellular matrix degradation

through activation of matrix metalloproteinases (MMPs). Therefore, inflammatory biomarkers provide important information regarding the interaction between immune dysregulation and periodontal destruction in diabetic patients.[13],[14]

Advanced glycation end products represent a central molecular pathway involved in diabetic periodontal complications. Chronic hyperglycemia promotes non-enzymatic glycation of proteins and lipids, resulting in AGE accumulation within periodontal tissues and bone. Binding of AGEs to RAGE activates nuclear factor-kappa B (NF-κB)-dependent inflammatory signaling, increases oxidative stress, and promotes expression of inflammatory mediators involved in periodontal tissue destruction. This mechanism provides an important link between metabolic abnormalities and impaired periodontal regeneration.[15],[16]

Vitamin D-related pathways have also emerged as potential regulators of periodontal bone metabolism. Vitamin D receptors are expressed in osteoblasts, immune cells, and periodontal tissues, where vitamin D influences calcium metabolism, immune regulation, antimicrobial activity, and inflammatory control. Lower serum 25-hydroxyvitamin D concentrations have been associated with greater gingival inflammation, suggesting a potential role for vitamin D status in periodontal health and bone metabolism.[17]

Despite increasing scientific interest, current knowledge regarding bone metabolism-related biomarkers in diabetic oral manifestations remains fragmented. Previous studies have frequently focused on individual inflammatory markers or isolated molecular pathways, whereas the interaction between osteogenic markers, osteoclastic mediators, inflammatory cytokines, oxidative stress pathways, and metabolic alterations has not been comprehensively synthesized. Furthermore, variability exists among studies regarding diabetes type, periodontal diagnosis, biomarker sampling methods, analytical techniques, and clinical outcome measures.

A scoping review methodology is particularly appropriate for this field because it enables comprehensive mapping of heterogeneous evidence, identification of emerging biomarker patterns, and recognition of research gaps. By integrating available evidence regarding biomarkers involved in bone formation, bone resorption, inflammation, and metabolic regulation, such an approach may provide a broader understanding of the molecular mechanisms underlying diabetic oral manifestations.

Therefore, the aim of this scoping review was to map the current evidence regarding bone metabolism-related biochemical biomarkers associated with diabetic oral manifestations, with particular emphasis on their role in periodontal bone remodeling disturbances, inflammatory regulation, tissue destruction, and potential clinical applications in risk assessment and personalized periodontal care.

2. MATERIALS AND METHODS

2.1 Study Design and Reporting Framework

This scoping review was conducted according to the methodological framework proposed by the Joanna Briggs Institute (JBI) for scoping reviews and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines.

The primary objective of this review was to map the available scientific evidence regarding the role of bone metabolism-related biochemical biomarkers in the pathogenetic mechanisms of diabetic oral manifestations, with particular emphasis on periodontal tissue destruction, alveolar bone remodeling, inflammatory regulation, and potential clinical implications.

A scoping review methodology was selected due to the broad and multidisciplinary nature of the research question, including clinical studies, observational investigations, and experimental studies evaluating different biomarker categories and their involvement in diabetic-associated oral alterations.

2.2 Review Question and PCC Framework

The review question was formulated according to the Population–Concept–Context (PCC) framework recommended by the Joanna Briggs Institute.

Population:
Patients with diabetes mellitus presenting with oral manifestations, including periodontal disease, alveolar bone loss, impaired periodontal healing, and other diabetes-associated oral tissue alterations.

Concept:
The role of biochemical biomarkers associated with bone metabolism, including markers of bone formation, bone resorption, inflammatory regulation, and metabolic pathways involved in periodontal tissue destruction.

Context:
Clinical, biological, and molecular studies investigating the relationship between diabetes mellitus, oral

manifestations, and bone metabolism-related biochemical alterations.

The primary review question was:

"What is the current evidence regarding the role of bone metabolism-related biochemical biomarkers in the pathogenetic mechanisms of oral manifestations associated with diabetes mellitus?"

2.3 Search Strategy and Information Sources

A comprehensive literature search was performed using electronic databases, including:

- PubMed/MEDLINE
- Scopus
- Web of Science
- ScienceDirect
- Google Scholar

The search strategy was developed using combinations of controlled vocabulary terms (MeSH terms) and free-text keywords related to diabetes mellitus, oral manifestations, periodontal disease, bone metabolism, and biochemical biomarkers.

The main search terms included:

"diabetes mellitus",
"diabetic oral manifestations",
"periodontitis",
"periodontal disease",
"alveolar bone loss",
"bone metabolism",
"bone biomarkers",
"osteocalcin",
"bone alkaline phosphatase",
"RANKL",
"osteoprotegerin",
"CTX",
"NTX",
"inflammatory biomarkers",
"cytokines",
"advanced glycation end products".

Studies published between **2000 and 2026** were considered eligible to capture contemporary evidence regarding molecular biomarkers and their clinical relevance.

2.4 Eligibility Criteria

Studies were selected according to predefined inclusion and exclusion criteria.

Inclusion criteria

Studies were included if they:

- investigated patients with diabetes mellitus;
- evaluated oral manifestations associated with diabetes, particularly periodontal disease and alveolar bone alterations;
- assessed biochemical biomarkers related to bone metabolism or tissue remodeling;
- investigated biomarkers involved in bone formation, bone resorption, inflammation, or metabolic regulation;
- included clinical, observational, experimental, or translational study designs;
- were published in English.

Exclusion criteria

Studies were excluded if they:

- did not evaluate diabetic populations;
- focused exclusively on systemic bone diseases without oral manifestations;
- did not investigate biochemical biomarkers;
- were unrelated to periodontal or oral tissue outcomes;
- consisted of case reports, editorials, conference abstracts, or non-original publications;
- lacked sufficient methodological information.

2.5 Study Selection Process (PRISMA-ScR Flow)

The study selection process was conducted according to the PRISMA-ScR recommendations.

The initial database search identified a total of **79 records**. After screening of titles and abstracts, studies that did not correspond to the predefined eligibility criteria were excluded. Potentially relevant articles were subsequently retrieved for full-text evaluation.

Following full-text assessment, studies lacking relevant information regarding bone metabolism-related biomarkers and diabetic oral manifestations were excluded.

Finally, **40 studies were included in the final scoping review** and underwent data extraction and qualitative synthesis.

The complete study selection process is illustrated in the **PRISMA-ScR flow diagram (Figure 1).**

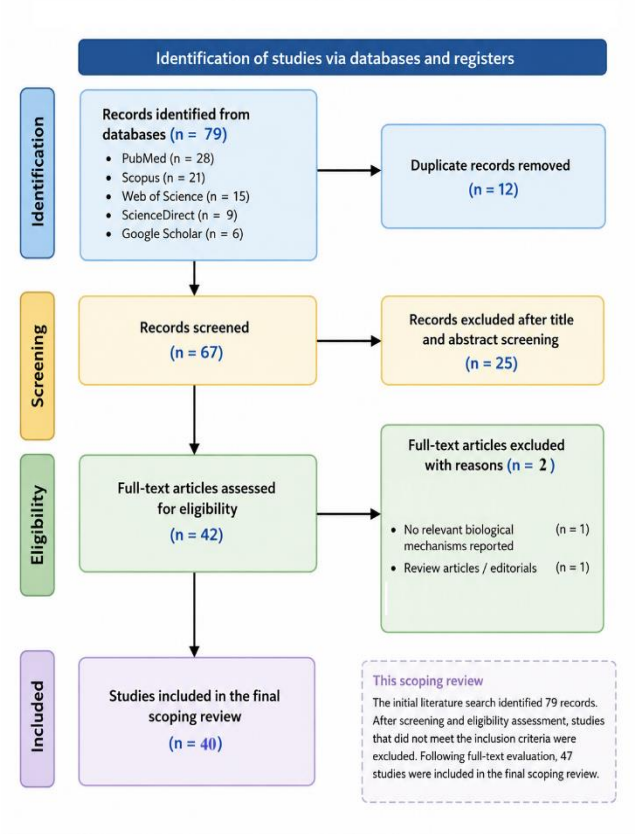


Figure 1 PRISMA-ScR flow diagram illustrating the study selection process.

2.6 Data Extraction and Charting Process

Data extraction was performed using a standardized data-charting form developed according to JBI scoping review recommendations.

The following information was extracted from each included study:

- first author and year of publication;
- country of study;
- study design;
- characteristics of the study population;
- type of diabetes mellitus;
- investigated oral manifestation;
- evaluated biochemical biomarkers;
- biological pathway associated with the biomarker;
- main findings and clinical implications.

The extracted data were systematically organized to identify major biomarker categories and their potential contribution to diabetic oral pathogenesis.

2.7 Data Synthesis and Presentation

The extracted evidence was synthesized descriptively and presented in narrative form and summary tables.

Biomarkers were categorized according to their primary biological function:

1. **Bone formation biomarkers**
   - Osteocalcin
   - Bone-specific alkaline phosphatase (BALP)
   - P1NP
2. **Bone resorption biomarkers**
   - RANKL
   - Osteoprotegerin (OPG)
   - CTX-I
   - NTX
3. **Inflammatory and tissue destruction biomarkers**
   - IL-1β
   - IL-6
   - TNF-α
   - MMP-8/MMP-9
4. **Metabolic and regulatory biomarkers**
   - Advanced glycation end products (AGEs)
   - Vitamin D-related pathways
   - Oxidative stress-related markers

The findings were mapped to clarify the mechanisms linking diabetes mellitus with altered bone metabolism, periodontal destruction, and impaired oral tissue repair.

3. RESULTS

3.1 Study Selection and Characteristics of Included Studies

The initial literature search identified **79 records** from the selected electronic databases. After removal of irrelevant publications during title and abstract screening, potentially eligible studies underwent full-text assessment according to predefined inclusion and exclusion criteria. Studies were excluded when they did not investigate biochemical biomarkers associated with bone metabolism, lacked evaluation of diabetic oral manifestations, or did not provide sufficient information regarding biomarker-related mechanisms.

Following the eligibility assessment, a total of **40 studies were included in the final scoping review**. The included studies were published between **2000 and 2026** and represented a heterogeneous body of evidence consisting of observational clinical studies, case-control investigations, cross-sectional analyses, longitudinal studies, and experimental research.

The majority of included studies focused on diabetic periodontitis and explored molecular mechanisms associated with periodontal inflammation, alveolar bone remodeling, and impaired tissue regeneration. The

evaluated biomarkers were categorized according to their biological function into: (1) markers of bone formation, (2) markers of bone resorption, (3) inflammatory mediators regulating bone destruction, and (4) metabolic biomarkers associated with diabetic tissue alterations.

3.2 Osteocalcin as a Biomarker of Osteoblastic Activity and Bone Remodeling in Diabetic Oral Manifestations

Osteocalcin (OC), also known as bone γ-carboxyglutamic acid-containing protein, is one of the most extensively studied non-collagenous proteins associated with bone metabolism. It is synthesized predominantly by mature osteoblasts during the mineralization phase of bone formation and is considered an important indicator of osteoblastic differentiation, matrix maturation, and bone remodeling activity. Beyond its traditional role in skeletal mineralization, osteocalcin has been recognized as a multifunctional molecule involved in the regulation of systemic metabolism, including glucose homeostasis and insulin sensitivity. [17,18,31]

The included studies demonstrated that alterations in osteocalcin expression may reflect impaired bone remodeling processes in patients with diabetes mellitus and periodontal disease. Diabetes-associated metabolic abnormalities, particularly chronic hyperglycemia, oxidative stress, and persistent inflammatory activation, negatively influence osteoblast proliferation, differentiation, and functional activity. These mechanisms may contribute to reduced bone formation capacity within periodontal tissues, where continuous remodeling is essential for maintaining alveolar bone integrity. [19,20,30]

Experimental and clinical investigations suggest that hyperglycemic conditions may suppress osteoblast activity through accumulation of advanced glycation end products (AGEs), increased production of reactive oxygen species, and disruption of osteogenic signaling pathways. These alterations may result in decreased synthesis of bone matrix proteins, including osteocalcin, and may contribute to delayed periodontal regeneration and impaired healing following periodontal injury. [25,30]

The relationship between osteocalcin and diabetes appears to be bidirectional. Osteocalcin has been proposed as an endocrine regulator linking skeletal metabolism with glucose metabolism by influencing insulin secretion and peripheral insulin sensitivity. Therefore, reduced osteocalcin activity in diabetic individuals may represent both a marker of impaired osteoblast function and a component of the pathological interaction between metabolic dysfunction and periodontal tissue destruction. [17,18,20,31]

Within diabetic periodontal disease, osteocalcin alterations may reflect an imbalance between destructive inflammatory processes and regenerative mechanisms. While inflammatory mediators stimulate osteoclast activation and alveolar bone resorption, insufficient osteoblastic activity may limit compensatory bone formation. Consequently, evaluation of osteocalcin may provide additional molecular information regarding the biological status of periodontal tissues beyond conventional clinical parameters. [13,21,34]

The available evidence indicates that osteocalcin represents a potentially valuable biomarker for evaluating osteoblast-related changes in diabetic oral manifestations. However, interpretation of current findings remains limited by heterogeneity among studies, including differences in diabetes type, disease duration, periodontal status, biological sample collection, and analytical methodology. Further longitudinal studies are required to determine whether osteocalcin can predict periodontal disease progression, healing capacity, or response to periodontal therapy in patients with diabetes.

The characteristics and main findings of studies evaluating osteocalcin in diabetic oral manifestations are summarized in **Table 1**.

Table 1. General characteristics and scope of the evidence identified in the review

Evidence domain	Characteristics identified
Population	Predominantly adult patients with diabetes mellitus, particularly type 2 diabetes mellitus
Oral conditions	Periodontitis, periodontal inflammation, periodontal tissue destruction, alveolar bone loss, impaired periodontal healing, and selected diabetes-related oral conditions
Study designs	Clinical, observational, population-based, experimental, translational, and mechanistic studies
Biological specimens	Serum, plasma, gingival crevicular fluid, periodontal tissues, and experimental tissue samples
Bone formation markers	Osteocalcin, bone-specific alkaline phosphatase, procollagen type I N-terminal propeptide

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Evidence domain	Characteristics identified
Bone resorption markers	C-terminal telopeptide of type I collagen, N-terminal telopeptide
Osteoclast regulatory markers	Receptor activator of nuclear factor kappa B ligand and osteoprotegerin
Inflammatory mediators	Interleukin-1 beta, interleukin-6, tumor necrosis factor alpha
Tissue-destructive mediators	Matrix metalloproteinase-8 and matrix metalloproteinase-9
Metabolic pathways	Advanced glycation end products, receptor for advanced glycation end products, oxidative stress, vitamin D-related pathways
Principal biological outcomes	Altered bone formation, enhanced bone resorption, inflammatory activation, osteoclastogenesis, extracellular matrix degradation, and periodontal tissue destruction
Principal clinical outcomes	Periodontal inflammation, periodontal tissue destruction, alveolar bone loss, bone turnover, and impaired tissue remodeling
Overall evidence pattern	Interconnected alterations in metabolic, inflammatory, and bone-remodeling pathways
Major limitation	Substantial methodological and clinical heterogeneity between studies

Note: Table 1 presents the principal characteristics of the evidence mapped in the review and is not intended to imply that every biomarker or outcome was evaluated in every included study.

3.3 Bone-Specific Alkaline Phosphatase (BALP) as an Indicator of Osteoblast Differentiation and Alveolar Bone Formation

Bone-specific alkaline phosphatase (BALP) is one of the most widely investigated biochemical markers reflecting osteoblast differentiation, extracellular matrix maturation, and mineralization activity. BALP represents an osteoblast-derived isoenzyme of alkaline phosphatase that participates in phosphate metabolism and hydroxyapatite crystal formation, thereby playing an essential role in bone matrix mineralization. Because of its relatively specific expression by active osteoblasts, BALP is considered an important indicator of bone-forming activity and osteogenic capacity. [10–12,22]

The studies included in this review indicate that diabetes mellitus may negatively influence BALP-associated osteogenic processes through multiple interconnected mechanisms. Persistent hyperglycemia, insulin resistance, oxidative stress, and chronic inflammatory activation contribute to impaired osteoblast proliferation and differentiation, resulting in reduced bone formation potential. These alterations are particularly relevant in periodontal tissues, where continuous alveolar bone remodeling is required to maintain structural stability and compensate for inflammatory-mediated tissue injury. [19,30]

Hyperglycemia-induced accumulation of advanced glycation end products (AGEs) represents one of the major mechanisms responsible for impaired osteoblast function in diabetes. AGE formation alters extracellular matrix properties, activates oxidative pathways, and stimulates inflammatory signaling through the AGE–RAGE axis.

These molecular changes may suppress osteogenic gene expression and decrease the activity of bone formation-related enzymes, including BALP, thereby contributing to delayed periodontal regeneration and compromised alveolar bone repair. [15,24,25,33]

The role of BALP is particularly important in diabetic periodontitis because periodontal destruction is characterized by an imbalance between excessive bone resorption and insufficient bone regeneration. While inflammatory mediators such as IL-1β, IL-6, and TNF-α stimulate osteoclast differentiation and periodontal bone loss, impaired osteoblast activity limits the ability of periodontal tissues to restore damaged bone. Therefore, reduced BALP activity may represent a molecular indicator of decreased regenerative capacity within diabetic periodontal lesions. [13,21,34]

Several clinical and experimental studies have demonstrated associations between altered BALP expression and impaired bone remodeling in metabolic disorders. Although BALP is not a disease-specific marker for periodontal pathology, changes in its activity may provide additional information regarding the biological status of bone-forming cells and the balance between destructive and reparative mechanisms. [10–12,22,23]

From a clinical perspective, BALP measurement may have potential value in monitoring periodontal healing responses, particularly in patients with diabetes who demonstrate impaired regenerative capacity. Restoration of periodontal tissues following surgical or regenerative procedures requires activation of osteogenic pathways, and biochemical markers such as BALP may provide complementary information alongside conventional clinical and radiographic assessments. [11,26,28,29]

However, interpretation of BALP levels requires consideration of systemic factors that influence bone metabolism, including age, renal function, diabetes duration, glycemic control, medication use, and overall skeletal turnover. Furthermore, differences in biomarker detection methods and patient populations contribute to heterogeneity among available studies. Consequently, although BALP represents a valuable indicator of osteoblast-related activity, further longitudinal clinical investigations are required to clarify its prognostic significance in diabetic periodontal disease. [10–12,22,23]

Overall, current evidence suggests that BALP reflects an important component of the molecular mechanisms responsible for diabetes-associated alterations in periodontal bone metabolism. Reduced BALP activity may indicate impaired osteoblast differentiation, decreased alveolar bone formation, and limited regenerative potential in individuals affected by diabetes mellitus.

The main characteristics of studies evaluating BALP in relation to diabetic bone metabolism are summarized in **Table 2**.

Table 2. Demographic and diabetes-related characteristics considered in the evidence mapping

Characteristic	Findings from the available literature	Interpretation
Age	Predominantly adult and middle-aged populations	Age may influence bone turnover and periodontal susceptibility
Approximate mean age in studies reporting this characteristic	Approximately 55 years	Descriptive literature-derived characteristic; not a pooled estimate
Diabetes type	Predominantly type 2 diabetes mellitus	Consistent with the primary focus of the review
Duration of diabetes	Approximately 5–6 years in several reported clinical populations	Descriptive characteristic; not uniformly reported
Glycemic status	Variable between studies	Potential source of biomarker heterogeneity
Periodontal status	Ranged from periodontal inflammation to established periodontitis and periodontal tissue destruction	Differences in disease definition limit direct comparison
Other potentially relevant factors	Age, smoking, obesity, medication use, vitamin D status, systemic bone health, and other metabolic characteristics	Important potential confounders
Interpretation of demographic data	No patient-level pooling was performed	Findings should not be interpreted as characteristics of a single cohort

Note: The values presented in this table describe characteristics reported in the available literature and should not be interpreted as pooled demographic estimates.

3.4 Procollagen Type I N-Terminal Propeptide (P1NP) as a Marker of Bone Matrix Formation and Periodontal Regenerative Capacity

Procollagen type I N-terminal propeptide (P1NP) is a biochemical marker directly associated with type I collagen synthesis and represents an important indicator of osteoblast-mediated bone matrix formation. Type I collagen constitutes the major organic component of bone extracellular matrix and provides the structural framework required for subsequent mineral deposition. During collagen type I biosynthesis, procollagen molecules undergo enzymatic cleavage, resulting in the release of P1NP into the extracellular environment and circulation. Therefore, P1NP concentration reflects osteoblastic synthetic activity and is considered a reliable marker of bone-forming processes. [27,28,29]

Within the context of diabetes mellitus, alterations in P1NP levels may indicate impaired osteoblast function and reduced regenerative capacity of periodontal tissues. Chronic hyperglycemia, oxidative stress, inflammatory activation, and accumulation of advanced glycation end products (AGEs) negatively affect collagen metabolism and extracellular matrix organization. These mechanisms

may interfere with normal type I collagen synthesis and compromise the structural integrity of periodontal supporting tissues, including alveolar bone and periodontal ligament. [19,25,30]

The available evidence suggests that diabetic conditions are associated with disturbances in bone matrix metabolism characterized by reduced anabolic activity and impaired repair responses. Hyperglycemia-induced cellular stress may suppress osteoblast differentiation, alter collagen production, and reduce expression of genes involved in extracellular matrix formation. Since periodontal regeneration requires coordinated collagen matrix synthesis followed by mineralization, reduced P1NP activity may reflect an unfavorable biological environment for tissue reconstruction. [19,27,30]

The importance of P1NP in diabetic periodontal disease is related to the balance between inflammatory destruction and regenerative mechanisms. Periodontitis is characterized by progressive degradation of periodontal ligament components and alveolar bone caused by inflammatory mediators and osteoclast activation. Although cytokines such as IL-1β, IL-6, and TNF-α promote tissue destruction, restoration of periodontal structures requires adequate osteoblast activity and extracellular matrix production. Therefore, P1NP may provide molecular information regarding the regenerative potential of periodontal tissues affected by diabetes. [13,21,34]

Several studies evaluating bone metabolism in diabetic patients have demonstrated alterations in bone formation markers, suggesting impaired anabolic responses associated with metabolic dysfunction. Compared with conventional clinical parameters, P1NP provides specific information regarding collagen matrix synthesis and osteoblastic activity, making it a potentially valuable complementary biomarker when interpreted together with markers of bone resorption and inflammation. [10–12,27–29]

From a clinical perspective, P1NP may have potential application in evaluating biological responses following periodontal regenerative procedures. Successful regeneration requires not only elimination of bacterial infection and control of inflammation but also restoration of osteogenic activity. Monitoring changes in bone formation markers may provide additional information regarding healing capacity and may assist in identifying patients with compromised regenerative potential, particularly among individuals with poorly controlled diabetes. [26,28,29]

However, current evidence regarding P1NP in diabetic oral manifestations remains limited compared with other biomarkers, including RANKL, OPG, and osteocalcin. Variability among studies related to diabetes type, disease duration, glycemic control, periodontal status, systemic bone metabolism, and laboratory methodology limits direct comparison of findings. Furthermore, most available studies remain observational, and prospective longitudinal investigations are required to determine whether P1NP has predictive value for periodontal progression or treatment outcomes.

Overall, the available evidence indicates that P1NP represents an important biomarker reflecting osteoblast-mediated extracellular matrix synthesis and bone-forming capacity. Evaluation of P1NP together with other bone remodeling and inflammatory biomarkers may provide a more comprehensive understanding of the molecular mechanisms underlying diabetes-associated periodontal destruction and impaired regeneration.

3.5 RANKL/OPG System and Osteoclast-Mediated Alveolar Bone Destruction in Diabetic Periodontal Disease

The receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegerin (OPG) pathway represents one of the most important molecular regulatory mechanisms controlling osteoclast differentiation, activation, and survival. This signaling system plays a central role in physiological bone remodeling by regulating the balance between bone formation and bone resorption. RANKL acts as a key stimulator of osteoclastogenesis through binding to its receptor RANK on osteoclast precursor cells, whereas OPG functions as a soluble decoy receptor that prevents RANKL–RANK interaction and inhibits excessive osteoclastic activity. Therefore, the relative balance between RANKL and OPG determines the overall intensity of bone resorption and represents a critical determinant of skeletal and periodontal bone homeostasis. [8,34–37]

The findings of the included studies indicate that diabetes-associated periodontal destruction is strongly influenced by dysregulation of the RANKL/OPG pathway. Persistent hyperglycemia, oxidative stress, and chronic inflammatory activation characteristic of diabetes create a biological environment favoring osteoclast activation and accelerated alveolar bone loss. Increased RANKL expression and reduced OPG availability have been reported in diabetic periodontal conditions, suggesting that disruption of this regulatory axis contributes significantly to periodontal tissue breakdown. [32,33,35,36]

Under physiological conditions, RANKL is produced by osteoblasts, periodontal ligament cells, fibroblasts, and activated immune cells. Binding of RANKL to RANK on osteoclast precursor cells activates intracellular signaling pathways, particularly nuclear factor-kappa B (NF-κB),

resulting in osteoclast differentiation, maturation, and activation. OPG counteracts this mechanism by binding to RANKL and preventing excessive osteoclast formation, thereby maintaining normal bone turnover. [8,34–37]

In diabetes mellitus, this balance becomes significantly disturbed. Hyperglycemia-induced formation of advanced glycation end products (AGEs) activates the AGE–RAGE pathway, leading to oxidative stress and enhanced inflammatory signaling. Activation of NF-κB promotes increased production of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, which stimulate RANKL expression and amplify osteoclast-mediated bone destruction. [15,24,33]

The clinical importance of RANKL/OPG imbalance is particularly evident in diabetic periodontitis, where excessive alveolar bone resorption represents a major determinant of disease progression. Unlike conventional periodontal inflammation, diabetic periodontal disease is characterized by an exaggerated inflammatory response combined with impaired tissue repair mechanisms. Increased RANKL activity contributes to enhanced osteoclastogenesis, progressive periodontal attachment loss, and reduced stability of alveolar bone structures. [1,3,4,21,32]

Several investigations have demonstrated associations between increased RANKL levels, decreased OPG expression, and more severe periodontal destruction among diabetic patients. Elevated RANKL/OPG ratios have been reported in individuals with greater periodontal pocket depth, increased clinical attachment loss, and radiographic evidence of alveolar bone loss. These findings suggest that the RANKL/OPG ratio may provide more clinically meaningful information than either biomarker alone because it reflects the balance between destructive and protective bone remodeling mechanisms. [35,36,38] The RANKL/OPG system also represents an important molecular connection between systemic metabolic abnormalities and local periodontal tissue changes. Diabetes-related immune dysfunction alters activity of macrophages, T lymphocytes, and other inflammatory cells within periodontal tissues, promoting increased RANKL production and sustaining osteoclast activation. Consequently, metabolic dysregulation may directly influence periodontal bone remodeling through immune-mediated pathways. [32,34,37] From a therapeutic perspective, modulation of the RANKL pathway represents a potential strategy for controlling pathological bone resorption. However, clinical application in periodontal therapy requires careful consideration because physiological osteoclast activity is essential for normal bone adaptation and remodeling. Further studies are necessary to determine whether targeted regulation of RANKL/OPG signaling may improve periodontal outcomes without interfering with normal skeletal metabolism. [24,37] Despite substantial biological evidence supporting the importance of the RANKL/OPG pathway, current clinical studies demonstrate considerable heterogeneity. Differences in diabetes type, duration of disease, glycemic control, periodontal diagnosis, sampling methods, and laboratory techniques limit direct comparison between investigations. Furthermore, most available studies are cross-sectional, making it difficult to establish whether RANKL/OPG alterations represent early pathogenic events or secondary consequences of established periodontal destruction. Overall, current evidence indicates that the RANKL/OPG pathway represents a central mechanism linking diabetes mellitus with periodontal alveolar bone destruction. Increased RANKL activity together with reduced OPG-mediated inhibition promotes osteoclast activation, accelerates bone resorption, and disrupts periodontal tissue homeostasis. Evaluation of RANKL, OPG, and their ratio, combined with inflammatory and metabolic biomarkers, may provide valuable molecular information for future risk assessment and personalized periodontal management in diabetic patients. The main characteristics of studies evaluating the RANKL/OPG system are summarized in **Table 3**.

Table 3. Classification of biomarkers investigated in relation to diabetes and oral manifestations

Biomarker or pathway	Principal biological role	Relationship relevant to periodontal disease	Potential interpretation in T2DM
Osteocalcin	Bone formation and osteoblast-related activity	May reflect altered bone formation and remodeling	Potential relationship with systemic glucose and bone metabolism
Bone-specific alkaline phosphatase	Osteoblastic differentiation and mineralization	Reflects bone-forming activity	May indicate altered bone formation
Procollagen type I N-terminal propeptide	Type I collagen synthesis	Reflects bone matrix formation	Potential indicator of altered osteoblastic activity
C-terminal telopeptide of	Collagen degradation	Reflects osteoclasti	May provide information

Biomarker or pathway	Principal biological role	Relationship relevant to periodontal disease	Potential interpretation in T2DM
type I collagen	and bone resorption	c bone resorption	on systemic bone turnover
N-terminal telopeptide	Type I collagen degradation	Indicator of bone resorption	May reflect altered skeletal turnover
Receptor activator of nuclear factor kappa B ligand	Osteoclast differentiation and activation	Important mediator of periodontal bone resorption	May be influenced by inflammation and diabetes-associated pathways
Osteoprotegerin	Inhibitor of receptor activator of nuclear factor kappa B ligand-mediated osteoclastogenesis	Counter-regulates osteoclast activity	Altered balance with receptor activator of nuclear factor kappa B ligand may favor bone resorption
Interleukin-1 beta	Pro-inflammatory cytokine	Promotes periodontal inflammation and bone destruction	May contribute to enhanced inflammatory osteoclastogenic activity
Interleukin-6	Pro-inflammatory cytokine	Associated with inflammatory tissue destruction	May influence osteoclastogenesis
Tumor necrosis factor alpha	Pro-inflammatory cytokine	Contributes to periodontal connective tissue and bone destruction	May amplify inflammatory bone resorption
Matrix metalloproteinase-8	Extracellular matrix degradation	Associated with collagen degradation in periodontal tissues	May reflect periodontal tissue destruction
Matrix metalloproteinase-9	Extracellular matrix remodeling	Associated with periodontal tissue degradation	May contribute to tissue remodeling and destruction
Advanced glycation end products	Products of chronic non-enzymatic glycation	Promote inflammatory and oxidative responses	Important consequence of chronic hyperglycemia
Receptor for advanced glycation end products	Mediates advanced glycation end product-related signaling	Promotes inflammatory activation and tissue destruction	Potential link between hyperglycemia and periodontal bone loss
Vitamin D-related pathways	Calcium metabolism, bone remodeling, immune regulation	May influence periodontal inflammatory status	Potential modifier of periodontal and bone homeostasis
Oxidative stress-related pathways	Cellular stress and inflammatory signaling	May contribute to periodontal tissue destruction	Important mechanism associated with chronic hyperglycemia

3.6 C-Terminal Telopeptide of Type I Collagen (CTX-I) and N-Terminal Telopeptide (NTX): Biomarkers of Osteoclastic Bone Resorption in Diabetic Oral Manifestations

Bone resorption represents a fundamental component of skeletal and periodontal remodeling, and biochemical markers reflecting collagen degradation provide important information regarding osteoclastic activity. Among these biomarkers, **C-terminal telopeptide of type I collagen (CTX-I)** and **N-terminal telopeptide of type I collagen (NTX)** are widely recognized indicators of type I collagen breakdown and have been extensively investigated as markers of bone turnover. Because type I collagen constitutes approximately 90% of the organic

matrix of alveolar and skeletal bone, increased concentrations of collagen degradation products may reflect enhanced osteoclastic activity and accelerated bone resorption. [10–12,22,23,28,29]

The findings of the included studies indicate that diabetes mellitus is associated with significant alterations in bone turnover, characterized by an imbalance between bone formation and bone resorption. In diabetic oral manifestations, particularly periodontal disease, increased osteoclastic activity contributes to progressive alveolar bone loss and deterioration of periodontal supporting tissues. CTX-I and NTX may therefore serve as biochemical indicators reflecting the destructive phase of diabetic-associated periodontal remodeling. [19,21,30,38]

CTX-I is generated during enzymatic degradation of mature type I collagen by activated osteoclasts. Due to its specificity for collagen degradation, CTX-I is considered a sensitive marker of bone resorption activity. Several studies included in this review demonstrated increased CTX-I concentrations in individuals with metabolic disorders associated with impaired bone homeostasis. In diabetic patients with periodontal disease, elevated CTX-I levels may indicate enhanced collagen breakdown within alveolar bone and increased osteoclastic remodeling activity. [10–12,22,28,29]

The mechanisms responsible for increased CTX-I release in diabetes are closely related to chronic inflammatory activation and metabolic dysregulation. Persistent hyperglycemia promotes oxidative stress and the accumulation of advanced glycation end products (AGEs), which modify extracellular matrix proteins and impair normal bone metabolism. AGE accumulation within periodontal tissues activates the AGE-RAGE signaling pathway, resulting in increased production of inflammatory cytokines such as IL-1β, IL-6, and TNF-α. These mediators stimulate osteoclast differentiation and activation, leading to increased degradation of type I collagen and elevated CTX-I levels. [15,24,25,33]

NTX represents another biochemical marker derived from the degradation of type I collagen. Similar to CTX-I, NTX reflects osteoclastic bone resorption and increased turnover of mineralized tissues. Although NTX has been investigated less frequently than CTX-I in periodontal research, available evidence suggests that it may provide valuable information regarding systemic and local alterations in bone metabolism among diabetic patients. [22,23,28]

The clinical relevance of CTX-I and NTX in diabetic oral manifestations is related to their potential ability to detect active bone destruction before extensive radiographic changes become apparent. Conventional periodontal assessment methods, including probing depth, clinical attachment loss, and radiographic evaluation, primarily identify established structural damage. In contrast, biochemical markers may provide insight into ongoing biological processes responsible for tissue destruction and may contribute to earlier identification of patients at increased risk for periodontal progression. [9–12,38]

The relationship between CTX-I, NTX, and periodontal disease severity appears to be influenced by multiple factors, including glycemic control, duration of diabetes, systemic inflammation, age, and concomitant metabolic disorders. Poorly controlled diabetes may intensify inflammatory responses and increase osteoclastic activity, resulting in greater collagen degradation and accelerated alveolar bone loss. Therefore, interpretation of these biomarkers requires consideration of the broader metabolic and clinical context. [4,5,19,30]

From a therapeutic perspective, monitoring changes in CTX-I and NTX may provide additional information regarding the biological response to periodontal treatment. Successful periodontal therapy aims not only to reduce microbial inflammation but also to restore a favorable balance between bone resorption and regeneration. A reduction in bone resorption biomarkers after treatment may indicate decreased osteoclastic activity and improved periodontal stability, particularly when accompanied by improved glycemic control. [28,29,38]

However, current evidence regarding CTX-I and NTX in diabetic periodontal disease remains heterogeneous. Differences in study methodology, sample size, biomarker detection methods, diabetes characteristics, and periodontal diagnostic criteria limit direct comparison among investigations. Furthermore, most available studies provide associative data rather than longitudinal evidence demonstrating that changes in CTX-I or NTX predict future periodontal destruction.

Overall, the available evidence suggests that CTX-I and NTX represent important biochemical indicators of osteoclastic activity and collagen degradation in diabetic oral manifestations. Their evaluation, together with bone formation markers such as osteocalcin and BALP and regulatory markers such as RANKL/OPG, may provide a comprehensive understanding of the dynamic processes responsible for diabetic-associated alveolar bone alterations. [10–12,21,22,28,38]

The main findings regarding CTX-I and NTX are summarized in **Table 4**.

Table 4. Biomarker–biological pathway relationships

identified in the reviewed evidence

Biomarker/pathway	Biological process	Potential effect of diabetes-related alterations	Periodontal implication
Osteocalcin	Osteoblast activity and bone formation	Altered bone and glucose metabolism	Potential alteration of periodontal bone remodeling
Bone-specific alkaline phosphatase	Osteoblastic differentiation and mineralization	Possible impairment of bone-forming activity	Potential reduction in regenerative capacity
Procollagen type I N-terminal propeptide	Type I collagen synthesis	Altered bone matrix formation	May reflect changes in periodontal bone formation
C-terminal telopeptide of type I collagen	Collagen degradation	Altered systemic bone turnover	Potential association with increased bone resorption
N-terminal telopeptide	Collagen degradation	Altered skeletal turnover	May provide complementary information regarding resorption
Receptor activator of nuclear factor kappa B ligand	Osteoclast differentiation	May be enhanced by inflammatory and metabolic signals	Increased osteoclastogenesis and alveolar bone resorption
Osteoprotegerin	Inhibition of osteoclastogenesis	Altered regulation may reduce inhibition of receptor activator of nuclear factor kappa B ligand	Potential shift toward bone resorption
Receptor activator of nuclear factor kappa B ligand/osteoprotegerin balance	Regulation of osteoclast activity	Potential shift toward osteoclastogenesis	Important mechanism of periodontal bone loss
Interleukin-1 beta	Inflammatory signaling	Enhanced inflammatory activity	Connective tissue destruction and osteoclast activation
Interleukin-6	Inflammatory signaling	Increased inflammatory burden	Potential contribution to osteoclastogenesis
Tumor necrosis factor alpha	Inflammatory signaling	Enhanced inflammatory response	Periodontal tissue and bone destruction
Matrix metalloproteinase-8	Collagen degradation	Increased tissue-destructive activity	Periodontal connective tissue destruction
Matrix metalloproteinase-9	Extracellular matrix remodeling	Increased tissue remodeling and inflammation	Periodontal tissue degradation
Advanced glycation end products/receptor for advanced glycation end products	Hyperglycemia-related inflammatory signaling	Increased oxidative stress and inflammatory activation	Potential enhancement of periodontal bone destruction
Vitamin D	Bone and immune regulation	Possible metabolic insufficiency	Potential modification of periodontal inflammatory status
Oxidative stress	Cellular and inflammatory signaling	Increased under chronic hyperglycemia	May promote tissue destruction and osteoclastogenic activity

3.7 Inflammatory Biomarkers Regulating Bone Metabolism in Diabetic Periodontal Disease

Inflammatory biomarkers represent a critical molecular link between diabetes mellitus, immune dysregulation, and periodontal tissue destruction. Although microbial biofilm represents the initiating factor of periodontal disease, the severity and progression of tissue damage are largely determined by the magnitude and duration of the host inflammatory response. In individuals with diabetes mellitus, persistent hyperglycemia creates a pro-inflammatory environment characterized by increased production of cytokines, oxidative stress, and impaired resolution of inflammation. These alterations directly

influence bone remodeling processes by stimulating osteoclast differentiation, enhancing extracellular matrix degradation, and disrupting periodontal tissue homeostasis. [2–5,14,15]

The included studies demonstrated that inflammatory mediators play a central role in the pathogenesis of diabetic oral manifestations, particularly periodontal disease and alveolar bone loss. Among the most extensively investigated inflammatory biomarkers were interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and matrix metalloproteinases (MMPs). These mediators participate in interconnected pathways regulating immune activation, connective tissue degradation, osteoclastogenesis, and periodontal remodeling. [3–5,9,13–15]

3.7.1 Interleukin-1β (IL-1β) and Osteoclast Activation

Interleukin-1β (IL-1β) is one of the most potent pro-inflammatory cytokines involved in periodontal tissue destruction and regulation of bone metabolism. It is mainly produced by activated macrophages, monocytes, and other immune cells in response to microbial stimulation and metabolic stress. IL-1β contributes to periodontal pathology by promoting inflammatory cell recruitment, stimulating extracellular matrix degradation, and enhancing osteoclast-mediated bone resorption. [13–15]

The available evidence demonstrates increased IL-1β expression in diabetic patients with periodontal disease compared with metabolically healthy individuals. Hyperglycemia-associated oxidative stress and accumulation of advanced glycation end products (AGEs) activate intracellular inflammatory pathways, particularly NF-κB signaling, resulting in increased IL-1β production. [4,5,15,24,33]

A major mechanism through which IL-1β contributes to alveolar bone destruction is stimulation of the RANKL/OPG pathway. IL-1β enhances RANKL expression in periodontal ligament cells, osteoblasts, and immune cells, thereby promoting differentiation and activation of osteoclast precursors. Excessive IL-1β activity may also reduce the protective effects of OPG, shifting bone metabolism toward increased resorption. [8,13,14,34–36]

3.7.2 Interleukin-6 (IL-6) and Regulation of Bone Remodeling

Interleukin-6 (IL-6) is a multifunctional cytokine involved in chronic inflammation, immune regulation, and bone remodeling. Increased IL-6 levels have been reported in diabetic patients with periodontal inflammation and are associated with poor metabolic control and increased periodontal disease severity. [3–5]

IL-6 contributes to periodontal bone destruction primarily through stimulation of osteoclastogenesis. It enhances RANKL expression and promotes differentiation of osteoclast precursor cells, resulting in increased bone resorption. Furthermore, IL-6 interacts synergistically with IL-1β and TNF-α, maintaining a chronic inflammatory environment that accelerates periodontal tissue breakdown. [13–15,34–36]

In diabetic conditions, persistent elevation of IL-6 may contribute to a pathological shift from physiological bone remodeling toward excessive bone resorption, increasing susceptibility to alveolar bone loss and impaired periodontal stability. [4,5,14]

3.7.3 Tumor Necrosis Factor-Alpha (TNF-α) and Inflammatory-Mediated Bone Destruction

Tumor necrosis factor-alpha (TNF-α) represents one of the major inflammatory mediators involved in periodontal destruction and diabetes-associated inflammation. It is produced primarily by activated macrophages and T lymphocytes and plays an essential role in amplification of inflammatory responses. [13–15]

The reviewed evidence indicates that TNF-α levels are elevated in diabetic individuals with periodontal disease and are associated with increased inflammatory activity and tissue destruction. Hyperglycemia, insulin resistance, and AGE-RAGE pathway activation stimulate TNF-α production, resulting in prolonged inflammatory signaling. [4,5,15,24,33]

TNF-α affects bone metabolism through dual mechanisms: stimulation of osteoclast differentiation via increased RANKL expression and suppression of osteoblast-mediated bone formation. Therefore, increased TNF-α activity contributes simultaneously to enhanced bone resorption and reduced regenerative capacity of periodontal tissues. [4,13–15,34–36]

3.7.4 Matrix Metalloproteinases (MMP-8 and MMP-9) and Extracellular Matrix Degradation

Matrix metalloproteinases (MMPs) are proteolytic enzymes responsible for degradation of extracellular matrix components, particularly collagen, which is essential for periodontal tissue integrity. Among these enzymes, MMP-8 and MMP-9 are considered important biomarkers of periodontal connective tissue destruction. [9,13]

MMP-8, also known as neutrophil collagenase, plays a major role in degradation of type I collagen within periodontal tissues, whereas MMP-9 contributes to extracellular matrix remodeling and inflammatory cell migration. Increased activity of these enzymes has been demonstrated in periodontal disease and is further enhanced under diabetic metabolic conditions. [9,13–15]

Hyperglycemia-induced oxidative stress and inflammatory cytokine activation stimulate MMP expression, resulting in accelerated degradation of periodontal ligament fibers, connective tissue structures, and bone matrix components. Furthermore, MMP-mediated tissue degradation generates inflammatory signals that may further enhance osteoclast activation and contribute to progressive alveolar bone loss. [3–5,13–15]

Summary of Inflammatory Biomarkers

Overall, the available evidence indicates that inflammatory biomarkers represent essential molecular mediators connecting diabetes mellitus with periodontal destruction and dysregulation of bone metabolism. In diabetic individuals, persistent hyperglycemia, oxidative stress, and accumulation of advanced glycation end products (AGEs) contribute to chronic inflammatory activation, resulting in enhanced production of pro-inflammatory cytokines and proteolytic enzymes involved in periodontal tissue breakdown. [2–5,14,15]

Among the investigated inflammatory mediators, IL-1β, IL-6, and TNF-α demonstrate a central role in regulating osteoclast activity through activation of the RANKL signaling pathway. These cytokines stimulate osteoclast differentiation, enhance bone resorption, and contribute to progressive alveolar bone loss. In parallel, MMP-8 and MMP-9 participate in extracellular matrix degradation by promoting collagen breakdown and destruction of periodontal connective tissues, thereby amplifying the inflammatory cascade associated with diabetic periodontitis. [8,13–15,34–36]

The interaction between inflammatory pathways and bone remodeling mechanisms represents a key feature of diabetic periodontal disease. Increased cytokine production shifts the physiological balance between bone formation and bone resorption toward a destructive phenotype characterized by enhanced osteoclastogenesis, impaired osteoblast function, and reduced regenerative capacity. Consequently, inflammatory biomarkers may provide valuable molecular information regarding disease activity, periodontal tissue instability, and susceptibility to accelerated bone loss in patients with diabetes mellitus. [3–5,13–15]

Although inflammatory biomarkers demonstrate significant potential as indicators of diabetic periodontal alterations, their clinical application remains limited by heterogeneity among studies, differences in sampling methods, variations in diabetes control, and lack of standardized reference values. Future longitudinal investigations integrating inflammatory biomarkers with bone formation and resorption markers may contribute to improved risk assessment and personalized periodontal management strategies in diabetic patients.

The main findings regarding inflammatory biomarkers involved in diabetic periodontal bone destruction are summarized in **Table 5**.

Table 5. Inflammatory, metabolic, and osteoclast-regulatory pathways associated with periodontal bone destruction

Pathway or mediator	Principal mechanism	Relationship with diabetes	Potential periodontal consequence
Receptor activator of nuclear factor kappa B ligand	Stimulates osteoclast differentiation and activation	May be influenced by chronic inflammation and metabolic dysfunction	Increased alveolar bone resorption
Osteoprotegerin	Inhibits receptor activator of nuclear factor kappa B ligand-mediated osteoclastogenesis	Altered regulation may disturb bone homeostasis	Reduced inhibition of bone resorption
Receptor activator of nuclear factor kappa B ligand/osteoprotegerin balance	Determines relative osteoclastogenic activity	May shift toward resorption in inflammatory conditions	Periodontal bone loss
Interleukin-1 beta	Promotes inflammatory signaling and bone resorption	Increased inflammatory activity may occur in diabetes	Periodontal connective tissue and bone destruction
Interleukin-6	Regulates inflammation and may promote osteoclastogenesis	May be increased in chronic inflammatory conditions	Enhanced periodontal inflammatory response

Pathway or mediator	Principal mechanism	Relationship with diabetes	Potential periodontal consequence
Tumor necrosis factor alpha	Promotes inflammation and osteoclast activity	Diabetes may amplify inflammatory signaling	Periodontal tissue destruction
Advanced glycation end products	Accumulate during chronic hyperglycemia	Increased formation with persistent hyperglycemia	Tissue dysfunction and inflammatory activation
Receptor for advanced glycation end products	Mediates advanced glycation end product-induced signaling	Activation associated with diabetes-related inflammation	Oxidative stress and periodontal tissue destruction
Oxidative stress	Promotes cellular injury and inflammatory signaling	Increased in chronic hyperglycemia	May enhance inflammatory and osteoclastogenic pathways
Matrix metalloproteinase-8	Degrades periodontal collagen	May participate in enhanced tissue destruction	Connective tissue breakdown
Matrix metalloproteinase-9	Extracellular matrix degradation and remodeling	May be associated with inflammatory activity	Periodontal tissue destruction
Vitamin D-related regulation	Influences bone and immune homeostasis	Deficiency or insufficiency may coexist with metabolic abnormalities	Potential modification of periodontal inflammation and bone metabolism

3.8 Advanced Glycation End Products (AGEs), Oxidative Stress, and Their Interaction with Bone Remodeling in Diabetic Oral Manifestations

Advanced glycation end products (AGEs) represent one of the central molecular mechanisms linking chronic hyperglycemia with periodontal tissue destruction and impaired bone metabolism in patients with diabetes mellitus. AGEs are formed through non-enzymatic glycation reactions between reducing sugars and proteins, lipids, and nucleic acids. Because periodontal tissues contain abundant extracellular matrix proteins, including collagen type I, they are particularly susceptible to AGE accumulation and subsequent structural and functional alterations. [15,25,33]

The included studies indicate that AGE accumulation contributes significantly to the pathological changes observed in diabetic periodontal disease by affecting both inflammatory regulation and bone remodeling processes. Binding of AGEs to their cellular receptor, the receptor for advanced glycation end products (RAGE), activates intracellular signaling cascades, particularly nuclear factor-kappa B (NF-κB), resulting in increased expression of pro-inflammatory cytokines and oxidative stress-related molecules. [15,24,25,33]

In periodontal tissues, AGE-RAGE interaction promotes sustained production of inflammatory mediators, including IL-1β, IL-6, and TNF-α, which subsequently enhance osteoclast differentiation through activation of the RANKL pathway. This mechanism creates a pathological cycle in which metabolic dysfunction amplifies inflammation, inflammation stimulates bone resorption, and progressive tissue destruction further compromises periodontal homeostasis. [4,8,15,24,33,34–36]

AGE accumulation also directly affects osteoblast function. Experimental evidence has demonstrated that AGEs may induce osteoblast apoptosis through activation of intracellular stress pathways, including mitogen-activated protein kinase (MAPK) and caspase-dependent mechanisms. This results in reduced osteogenic activity, impaired extracellular matrix formation, and decreased capacity for periodontal bone regeneration. [25]

Oxidative stress represents another important mechanism involved in diabetic-associated periodontal alterations. Persistent hyperglycemia increases reactive oxygen species production, resulting in cellular damage, impaired immune regulation, and disruption of normal bone remodeling. Excessive oxidative stress negatively influences osteoblast differentiation while simultaneously enhancing osteoclast activation, thereby shifting the remodeling balance toward bone destruction. [3–5,14,15]

Therefore, AGEs and oxidative stress should be considered upstream regulators that integrate metabolic abnormalities with inflammatory activation and bone remodeling disturbances. Their interaction with RANKL/OPG signaling, inflammatory cytokines, and osteogenic pathways provides a comprehensive explanation for accelerated periodontal destruction observed in diabetic patients. [8,15,24,25,33–36]

No separate table is required for this subsection, because the principal mechanisms of AGEs, RAGE, oxidative stress, and NF-κB signaling are already incorporated into the integrated biomarker network presented in **Table 6**.

3.9 Vitamin D/Vitamin D Receptor (VDR) Pathway and Regulation of Bone Metabolism in Diabetic Oral Manifestations

Vitamin D metabolism represents an additional regulatory mechanism involved in maintaining periodontal tissue stability and bone homeostasis. Vitamin D exerts its biological effects primarily through binding to the vitamin D receptor (VDR), which is expressed in osteoblasts, immune cells, periodontal ligament cells, and other periodontal tissues. Through genomic and immunomodulatory mechanisms, vitamin D contributes to regulation of bone mineralization, inflammatory responses, and host defense mechanisms. [16]

The available evidence suggests that alterations in vitamin D status may influence periodontal susceptibility among individuals with diabetes mellitus. Diabetes-related metabolic disturbances, including chronic inflammation and impaired immune regulation, may interact with vitamin D signaling pathways and contribute to abnormal bone remodeling processes. [16,19,30,32]

Vitamin D deficiency has been associated with impaired osteoblast function, altered calcium metabolism, and reduced mineralization capacity. Since diabetic periodontal destruction involves both increased bone resorption and compromised repair mechanisms, disruption of vitamin D-mediated regulation may further contribute to alveolar bone instability. [16,19,30]

Furthermore, vitamin D influences inflammatory responses by modulating immune cell activity and reducing excessive production of pro-inflammatory cytokines. Impaired vitamin D signaling may therefore enhance inflammatory activation, increase osteoclastogenic stimulation through the RANKL pathway, and promote periodontal tissue destruction. [8,16,32]

Although vitamin D-related biomarkers have not been investigated as extensively as RANKL, OPG, or inflammatory mediators, current evidence indicates that vitamin D/VDR signaling represents an important component of the complex network regulating diabetic periodontal bone metabolism. [16,32,40]

A separate table for Vitamin D/VDR was removed to avoid unnecessary duplication. Its biological role is incorporated into the integrated biomarker fram

Table 6. Integrated biological model linking type 2 diabetes mellitus, inflammation, bone metabolism, and periodontal tissue destruction

Biological level	Principal factor	Biological effect	Potential periodontal consequence
Metabolic	Chronic hyperglycemia	Increased metabolic stress	Increased susceptibility to periodontal dysfunction
Metabolic	Advanced glycation end product accumulation	Altered protein and tissue function	Periodontal tissue dysfunction
Signaling	Receptor for advanced glycation end products activation	Inflammatory and oxidative signaling	Amplification of periodontal inflammation
Cellular stress	Oxidative stress	Cellular injury and altered signaling	Enhanced tissue destruction
Inflammatory	Interleukin-1 beta	Pro-inflammatory and osteoclastogenic activity	Periodontal connective tissue and bone destruction
Inflammatory	Interleukin-6	Inflammatory signaling and osteoclast regulation	Enhanced inflammatory bone remodeling
Inflammatory	Tumor necrosis factor alpha	Inflammatory activation and bone resorption	Periodontal tissue and alveolar bone destruction
Osteoclast regulatory	Receptor activator of nuclear factor kappa B ligand	Osteoclast differentiation and activation	Increased alveolar bone resorption
Osteoclast regulatory	Osteoprotegerin	Inhibition of osteoclastogenesis	Protective regulation of bone remodeling
Osteoclast regulatory	Receptor activator of nuclear factor kappa B ligand/osteoprotegerin imbalance	Shift toward osteoclast activity	Periodontal bone loss
Bone formation	Osteocalcin	Osteoblast-related bone formation	Altered regenerative and remodeling capacity
Bone formation	Bone-specific alkaline phosphatase	Osteoblastic differentiation and mineralization	Potential impairment of bone formation
Bone	Procollagen type I	Type I collagen	Altered

Biological level	Principal factor	Biological effect	Potential periodontal consequence
formation	N-terminal propeptide	synthesis	bone matrix formation
Bone resorption	C-terminal telopeptide of type I collagen	Collagen degradation	Increased systemic bone turnover when elevated
Bone resorption	N-terminal telopeptide	Collagen degradation	Indicator of bone resorption
Tissue destruction	Matrix metalloproteinase-8	Collagen degradation	Periodontal connective tissue breakdown
Tissue destruction	Matrix metalloproteinase-9	Extracellular matrix remodeling	Periodontal tissue destruction
Metabolic regulation	Vitamin D	Bone and immune regulation	Potential modification of periodontal inflammation
Final tissue outcome	Combined metabolic, inflammatory, and remodeling disturbances	Imbalance between tissue destruction and repair	Periodontal attachment loss and alveolar bone destruction

4. DISCUSSION

The present scoping review provides an updated synthesis of current knowledge regarding the contribution of bone metabolism-related biochemical biomarkers to the pathogenesis of diabetic oral manifestations, with particular emphasis on periodontal tissue alterations and alveolar bone remodeling disturbances. The findings from the included literature indicate that periodontal complications associated with diabetes mellitus cannot be explained solely by increased susceptibility to microbial challenge. Instead, they represent the consequence of a complex interaction between chronic metabolic imbalance, dysregulated host immune response, persistent inflammation, oxidative stress, and impaired mechanisms of tissue repair and bone homeostasis. [1–5]

The association between diabetes mellitus and periodontal disease has been extensively investigated, and current evidence supports a bidirectional relationship in which diabetes increases the risk and severity of periodontal destruction, while periodontal inflammation may further contribute to systemic metabolic dysregulation. Previous studies have demonstrated that hyperglycemia affects periodontal tissues through multiple mechanisms, including impaired neutrophil function, increased inflammatory mediator production, endothelial dysfunction, and altered collagen metabolism. [1,2,5,7] However, recent advances in molecular biology have expanded this concept by highlighting the importance of bone remodeling pathways as key determinants of periodontal breakdown in diabetic individuals. [3,4,8]

The present review emphasizes that diabetic periodontal disease should be considered not only an inflammatory disorder but also a disease characterized by disturbed bone metabolism. Although inflammation initiates and amplifies periodontal tissue destruction, the ultimate clinical outcome depends on the balance between osteoclastic bone resorption and osteoblastic bone formation. Alterations in this balance may determine the rate of alveolar bone loss, the potential for periodontal regeneration, and the long-term response to therapeutic interventions. Therefore, evaluation of biomarkers associated with bone formation, bone resorption, and regulatory signaling pathways provides a more comprehensive understanding of diabetic periodontal pathology. [8–12,21–23]

One of the most important mechanisms identified in the reviewed literature is the effect of chronic hyperglycemia and advanced glycation end products (AGEs) on periodontal bone metabolism. Persistent elevation of glucose levels promotes the formation and accumulation of AGEs, which modify extracellular matrix proteins and activate the AGE receptor (RAGE). This interaction stimulates oxidative stress and activates nuclear factor-kappa B (NF-κB)-dependent inflammatory pathways, resulting in increased production of pro-inflammatory cytokines and disruption of tissue homeostasis. [15,24,25,33] Experimental studies have demonstrated that AGE accumulation negatively affects osteoblast viability and function, contributing to reduced bone formation capacity and impaired periodontal repair. [25]

An important aspect emerging from this review is the recognition that diabetes affects both sides of bone remodeling: it enhances destructive mechanisms while simultaneously suppressing regenerative processes. Previous research has primarily focused on increased osteoclast activity as the main explanation for accelerated alveolar bone loss in diabetic patients. However, evidence regarding osteoblast dysfunction suggests that impaired bone formation is equally relevant. Reduced osteocalcin expression, decreased bone-specific alkaline phosphatase

activity, impaired collagen matrix synthesis, and altered mineralization processes may compromise the ability of periodontal tissues to restore structural integrity following inflammatory injury. [18–20,25,27,30]

Osteocalcin represents an important example of the complex relationship between skeletal metabolism and systemic glucose regulation. Originally considered primarily a marker of osteoblastic activity, osteocalcin has been shown to participate in endocrine regulation of energy metabolism. Experimental and clinical studies have suggested that osteocalcin levels are associated with glucose metabolism and insulin sensitivity, indicating a potential reciprocal relationship between metabolic dysfunction and bone remodeling abnormalities. [17,18,20,31] These observations are particularly relevant in diabetes, where impaired metabolic control may contribute to reduced osteogenic activity and compromised periodontal healing. [19,30]

The RANKL/OPG signaling system represents one of the central regulatory mechanisms connecting inflammation with osteoclastic bone destruction. Under physiological conditions, the balance between RANKL-mediated osteoclast activation and OPG-mediated inhibition maintains normal bone turnover. [8,34–36] However, diabetic conditions may disturb this equilibrium through chronic inflammatory stimulation, AGE-RAGE activation, and increased production of cytokines such as IL-1β, IL-6, and TNF-α. [8,13–15,24,33] The resulting increase in osteoclastogenesis contributes to accelerated alveolar bone resorption and progression of periodontal attachment loss. [32,34–37]

The role of inflammatory biomarkers identified in this review further supports the concept that inflammation functions as a regulator of bone metabolism rather than merely a marker of disease activity. IL-1β and TNF-α have been shown to stimulate osteoclast differentiation and enhance RANKL expression, while IL-6 contributes to osteoclast maturation and sustained inflammatory signaling. [13–15] In addition, matrix metalloproteinases, particularly MMP-8 and MMP-9, participate in degradation of extracellular matrix components, including collagen, thereby accelerating periodontal tissue destruction. [9,13–15] These findings indicate that inflammatory mediators represent critical molecular intermediates linking metabolic disturbances with structural periodontal damage.

Biochemical markers of bone resorption, including CTX-I and NTX, provide additional insight into the destructive phase of diabetic periodontal disease. These biomarkers reflect degradation of type I collagen, the major organic component of bone matrix, and may indicate increased osteoclastic activity. [22,23,28,29] Although most available studies evaluating these markers originate from skeletal metabolism research, their potential application in periodontal monitoring is increasingly recognized. Their combination with inflammatory and bone formation biomarkers may provide a more complete evaluation of periodontal disease activity. [10–12,22,23,28,29]

An important clinical implication of the current findings is the potential role of biomarker-based approaches in improving periodontal risk assessment among diabetic patients. Traditional periodontal parameters, including probing depth, clinical attachment loss, and radiographic bone loss, remain essential for diagnosis but primarily reflect established structural damage. In contrast, biochemical biomarkers may provide information regarding active biological processes preceding clinically detectable deterioration. This may be particularly valuable in diabetic patients, where metabolic status influences inflammatory response, healing capacity, and treatment outcomes. [9–12,38,39]

The present scoping review differs from previous publications by integrating multiple biomarker categories into a unified framework. Earlier reviews have primarily focused on the epidemiological relationship between diabetes and periodontitis or on individual inflammatory mechanisms. [1–5,7] In contrast, this review highlights the interconnected nature of bone formation markers, bone resorption markers, inflammatory mediators, AGEs, oxidative stress pathways, and metabolic regulators. [8–16,18–25,32–38] Such an integrated approach reflects the biological complexity of diabetic periodontal disease and provides a more comprehensive explanation of why affected patients frequently experience accelerated periodontal destruction and reduced regenerative potential.

Despite these advances, several limitations within the current evidence base should be acknowledged. Most available investigations remain observational, limiting conclusions regarding causal relationships between biomarker alterations and periodontal progression. Furthermore, substantial heterogeneity exists regarding diabetes type, duration of disease, glycemic control, periodontal classification systems, biological samples analyzed, and laboratory methodologies. These differences make direct comparison between studies challenging and currently prevent establishment of clinically applicable reference values for most biomarkers. [10–12,22,23,38]

Another important limitation is the predominance of single-marker investigations. Diabetes-associated periodontal destruction represents a multifactorial process involving simultaneous activation of inflammatory,

metabolic, and skeletal pathways. Therefore, future research should focus on multidimensional biomarker panels rather than isolated measurements. Combining bone turnover markers such as osteocalcin, BALP, P1NP, RANKL, OPG, CTX-I, and NTX with inflammatory mediators and metabolic indicators may provide a more accurate assessment of individual disease risk and therapeutic response. [10–12,18,21–23,27–29,32–38]

Future directions should include prospective longitudinal studies evaluating biomarker changes over time and their relationship with periodontal progression, response to periodontal therapy, and maintenance of periodontal stability. Integration of advanced analytical approaches, including proteomic and metabolomic profiling, may further facilitate identification of molecular signatures associated with diabetic periodontal complications. In addition, artificial intelligence-based analysis of complex biological datasets may contribute to the development of predictive models for personalized periodontal medicine.

Overall, the available evidence demonstrates that bone metabolism-related biochemical biomarkers represent important molecular components of diabetic oral manifestations. Diabetes mellitus creates a pathological environment characterized by enhanced inflammatory activation, increased osteoclastic activity, impaired osteoblast function, and reduced regenerative potential. Understanding these interconnected mechanisms provides new perspectives for early risk identification, monitoring of disease activity, and development of biologically targeted approaches for periodontal management in patients with diabetes mellitus. [3–5,8,13–16,18–25,32–39]

5. CONCLUSIONS

This scoping review highlights the important role of bone metabolism-related biochemical biomarkers in understanding the pathogenesis of diabetic oral manifestations, particularly periodontal tissue destruction and alveolar bone remodeling disturbances. The available evidence demonstrates that diabetes mellitus affects periodontal homeostasis through a complex interaction between chronic hyperglycemia, oxidative stress, advanced glycation end product accumulation, inflammatory activation, and altered bone turnover regulation. [1–5,15,24,25,33]

Biomarkers reflecting bone formation, including osteocalcin, bone-specific alkaline phosphatase, and P1NP, indicate impaired osteoblast activity and reduced regenerative capacity, whereas bone resorption markers such as RANKL, CTX-I, and NTX reflect enhanced osteoclastic activity and accelerated alveolar bone loss. [18–23,27–29,34–38] Inflammatory mediators, including IL-1β, IL-6, TNF-α, and MMPs, act as important regulators connecting metabolic dysfunction with periodontal tissue destruction. [13–15]

Although current findings support the potential clinical value of these biomarkers for understanding disease mechanisms and improving risk assessment, their routine application in periodontal practice remains limited due to methodological heterogeneity and the lack of standardized reference values. [10–12,22,23,38] Future longitudinal studies are required to validate integrated biomarker profiles and determine their prognostic value in diabetic periodontal management.

Overall, a better understanding of molecular alterations in bone metabolism may contribute to the development of personalized preventive and therapeutic strategies aimed at improving periodontal outcomes in patients with diabetes mellitus. [3,4,8,10,11,18,21–23,32,38,39]

DECLARATION

Conflict of interest

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