Review Article

JHSMR Journal of Health Science and Medical Research

Monitoring Osseointegration: The Role of Bone Biomarkers in Dental Implant Success

Ujjaini Banerjee, M.D.S., Neha Jain, M.D.S., Uswah Khan, M.D.S.

Department of Prosthodontics, Crown and Bridge, School of Dental Sciences, Manav Rachna International Institute of Research and Studies, Faridabad, Haryana 121004, India.

Received 21 July 2025 ● Revised 29 August 2025 ● Accepted 16 September 2025 ● Published online 30 March 2026

Abstract:

Dental implant success hinges on the biological processes of bone remodeling and osseointegration, with bone biomarkers now recognized as powerful adjuncts to conventional clinical and radiographic assessments. Recent prospective and systematic studies indicate that dynamic biomarker monitoring can inform predictions of implant prognosis, illuminate the mechanisms of peri-implant bone turnover, and enable the early diagnosis of complications, such as peri-implantitis. Advances in omics technologies and molecular imaging have expanded our understanding, while new candidate biomarkers have emerged from peri-implant crevicular fluid, blood, and metabolomic profiles. This review critically synthesizes the major developments between 2000 and 2025 and evaluates the clinical utility, challenges, and future direction of bone biomarker analysis in modern implant dentistry.

Keywords: bone biomarkers, bone remodelling, dental implants, implant prognosis, osseointegration, peri-implantitis

Contact: Dr. Ujjaini Banerjee, M.D.S.
Department of Prosthodontics, Crown and Bridge, School of Dental Sciences, Manav Rachna International Institute of Research and Studies, Faridabad, Haryana 121004, India.
E-mail: ujjaini.mrdc@gmail.com

J Health Sci Med Res 2026;44(5):e20261346
doi: 10.31584/jhsmr.20261346
www.jhsmr.org

Introduction

Dental implantology stands at the forefront of contemporary restorative dentistry, offering durable and aesthetic rehabilitation for patients with missing teeth through predictable osseointegration—the direct, functional bond between living bone and the implant surface. However, beneath the surface of high reported success rates lies a spectrum of biological complexity: failures and complications often originate from subtle disruptions in bone metabolism, inadequate osseointegration, or persistent inflammatory challenges that conventional radiographic and clinical methods fail to detect in their earliest stages. In recent years, a paradigm shift toward molecular diagnostics—particularly the investigation of bone biomarkers in blood, saliva, and peri-implant crevicular fluid—has illuminated new pathways for the real-time, non-invasive assessment of bone remodelling, immune response, and tissue integration around dental implants. With advances in proteomics, metabolomics, and imaging, clinicians can now harness dynamic molecular signatures to anticipate risk, tailor loading and maintenance protocols, and intervene prior to overt clinical or radiographic signs of disease[1]. This review synthesizes the latest developments in bone biomarker research from 2022 to 2025, critically evaluating their diagnostic and prognostic value in dental implantology. By contextualizing recent clinical trials, technological innovations, and emerging challenges, we aimed to provide an updated framework for integrating biomarker strategies into evidence-based implant practice, highlighting both current limitations and future directions for optimizing patient outcomes.

Literature selection

The literature reviewed for this article was identified through a comprehensive search of the PubMed, Scopus, and Web of Science databases, focusing on the period from January 2000 to August 2025, to ensure currency and relevance. Search terms included combinations of "bone biomarkers," "dental implants," "osseointegration," "peri-implant crevicular fluid," "bone turnover markers," and "peri-implantitis." Both clinical and experimental investigations were evaluated, encompassing original research, systematic reviews, meta-analyses, and consensus statements.

Inclusion criteria were:

Peer-reviewed English-language studies.

Studies specifically assessing bone biomarkers in relation to dental implant placement, osseointegration, peri-implant bone remodelling, or peri-implant disease.

Studies utilizing recognized assays and/or contemporary analytical methods for biomarker measurement (e.g., ELISA, multiplex platforms, omics-based profiling).

Exclusion criteria included:

Case reports, narrative reviews without reference to biomarker data, and studies with incomplete methodological descriptions.

The selection process prioritized the most representative and methodologically robust studies, as well as those presenting innovative approaches or novel biomarkers. Reference lists of key articles were screened to identify further relevant publications. All the included studies were critically appraised with respect to design, sample size, biomarker panel composition, clinical outcomes measured, and relevance to implant dentistry.

Bone biology and biomarkers relevant to implant dentistry

Bone remodelling involves a tightly regulated balance between osteoclastic resorption and osteoblastic formation, orchestrated by signalling molecules such as RANKL and OPG. Biomarkers reflecting these processes provide insight

into bone metabolism and inflammatory status around implants[1,2]. Recent advancements have further emphasized the dynamic interplay of molecular signals regulating peri-implant bone remodelling. Studies highlight that beyond the classical RANKL/OPG pathway, additional cytokines, such as semaphorin 4D, osteopontin, and sclerostin, play crucial roles in modulating osteoclastogenesis and osteoblast differentiation, thereby affecting osseointegration. Furthermore, the advent of multiplex platforms has allowed simultaneous quantification of multiple biomarkers in peri-implant crevicular fluid (PICF), revealing a complex inflammatory and bone metabolic microenvironment that evolves through distinct healing phases. Cutting-edge metabolomic analyses have pioneered the identification of novel small molecule biomarkers, including amino acid derivatives and lipid mediators, that correspond with early bone turnover and inflammatory responses around dental implants, potentially improving the prediction of implant stability and survival[3,4].

Bone biomarkers during implant placement and early healing

The surgical placement of dental implants initiates an inflammatory cascade essential for bone healing. Studies report an early surge in pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, within the first 1-2 weeks, which subsequently decline as healing progresses. This controlled inflammation supports recruitment of osteoprogenitor cells and bone remodeling[3].

Bone turnover markers also fluctuate during this phase. Immediate implant loading has been shown to induce an earlier and higher release of osteoprotegerin, osteocalcin, and osteopontin, indicating the active bone remodelling that is crucial for implant stability[4]. However, excessive or prolonged elevation of inflammatory markers may predispose to impaired healing and implant failure. Recent clinical trials demonstrate that temporal profiling of cytokines and bone turnover markers in the earliest weeks post-implantation can predict healing trajectory

Table 1 Key bone biomarkers and their detection

Biomarker	Source	Timing of detection	Function	Diagnostic/Prognostic value
Bone-specific alkaline phosphatase (BALP)	Blood, saliva	Elevated during bone formation phases	Marker of osteoblast activity	Indicates bone formation; elevated in osseointegration
Osteocalcin (OC)	Blood, PICF	Peaks during early healing	Bone matrix protein produced by osteoblasts	Reflects bone turnover; lower levels linked to implant failure
C-terminal telopeptide (CTX-1)	Blood, saliva, PICF	Elevated during bone resorption	Marker of collagen degradation by osteoclasts	High levels correlate with bone loss risk
N-terminal telopeptide (NTX-1)	Blood, urine	Elevated during bone resorption	Bone resorption marker	Associated with implant loosening and failure
RANKL	PICF	Increases in peri-implant inflammation	Promotes osteoclast differentiation	High RANKL/OPG ratio predicts marginal bone loss
Osteoprotegerin (OPG)	PICF	Counterbalances RANKL	Inhibits osteoclastogenesis	Lower OPG levels linked to increased bone resorption
Interleukin-1β (IL-1β)	PICF, saliva, blood	Early post-implantation	Pro-inflammatory cytokine	Elevated in peri-implantitis; predicts inflammation
Monocyte chemoattractant protein-1 (MCP-1)	PICF	Elevated in peri-implant disease	Chemokine recruiting monocytes/macrophages	Correlates with marginal bone loss and inflammation
Matrix metalloproteinase-8 (MMP-8)	PICF	Elevated in peri-implantitis	Enzyme degrading extracellular matrix	Marker of tissue destruction and early implant failure

PICF=peri-implant crevicular fluid, RANKL=Receptor Activator of Nuclear Factor Kappa-B Ligand

with considerable accuracy[5]. Studies using immediate and early loading protocols report that osteopontin and bone alkaline phosphatase rise significantly within 7 days, concurrent with a decline in pro-inflammatory TNF-α and IL-6 after peak levels at 3 days, indicating the transition from inflammation to regeneration. Advances in implant surface nanotopography have also been shown to influence biomarker expression, with nanopatterned implants eliciting a higher early expression of vascular endothelial growth factor (VEGF) and bone morphogenetic proteins, facilitating improved angiogenesis and osteogenesis. However, unresolved systemic inflammation or prolonged elevation of MMP-8 and IL-1β beyond 2 weeks correlates strongly with early signs of impaired osseointegration and increased marginal bone loss[6].

Bone biomarkers after implant placement: correlation with success and failure

Multiple studies have explored the relationship between biomarker levels and implant outcomes:

Positive correlations: Elevated bone resorption markers (CTX-1, NTX-1) and inflammatory cytokines (IL-1β, MCP-1, MMP-8) in PICF are associated with marginal bone loss and peri-implantitis, increasing the risk of implant failure. A higher RANKL/OPG ratio reflects increased osteoclastic activity and correlates with bone loss[5,6].

Stable implants tend to exhibit lower concentrations of osteocalcin and TNF-α compared to failing implants, indicating balanced bone turnover and controlled inflammation[7].

Preoperative assessment of bone turnover markers can identify patients with compromised bone quality, such as postmenopausal women with osteoporosis, who may have a higher failure risk[8].

Recent systematic reviews and meta-analyses reaffirm the prognostic value of combining bone turnover markers (CTX-1, NTX-1) with inflammatory cytokines like IL-1β and MCP-1 measured in PICF to predict peri-implantitis and implant failure within the first year. Novel biomarkers, such as soluble receptor activator of nuclear factor κB ligand (sRANKL) and periostin, have shown increased sensitivity for marginal bone loss detection when combined in a multiplex assay. Longitudinal cohort studies have also noted that lower baseline levels of osteocalcin

Table 2 Summary of bone biomarkers and their functions

Biomarker	Full name	Primary role in osseointegration
OCN	Osteocalcin	Marker of bone formation and mineralization
BSAP	Bone-Specific Alkaline Phosphatase	Indicator of osteoblastic activity and early bone formation
P1NP	Procollagen Type I N-Terminal Propeptide	Reflects collagen synthesis and early osteogenesis
CTX	C-terminal Telopeptide of Type I Collagen	Marker of bone resorption
NTX	N-terminal Telopeptide of Type I Collagen	Indicates osteoclastic activity and collagen breakdown
TRAP	Tartrate-Resistant Acid Phosphatase	Resorption marker from osteoclasts
IL-1β	Interleukin-1 Beta	Pro-inflammatory cytokine elevated during early healing or peri-implantitis
IL-6	Interleukin-6	Inflammatory marker influencing bone remodeling
TNF-α	Tumor Necrosis Factor Alpha	Suppresses osteoblast activity, promotes inflammation
RANKL/OPG	RANK Ligand/Osteoprotegerin Ratio	Key regulatory pathway for osteoclast differentiation

OCN=Osteocalcin, BSAP=Bone-Specific Alkaline Phosphatase, P1NP=Procollagen Type I N-terminal Propeptide, CTX=C-terminal Telopeptide, NTX=N-terminal Telopeptide, TRAP=Tartrate-Resistant Acid Phosphatase, IL=Interleukin, TNF=Tumor Necrosis Factor, RANKL=Receptor Activator of Nuclear Factor Kappa-B Ligand, OPG=Osteoprotegerin

correlate with compromised bone remodeling, especially in osteoporotic patients, suggesting a need for tailored protocols in vulnerable populations. However, challenges in standardization have hampered consistent biomarker use, with some studies showing transient elevations of pro-inflammatory cytokines that do not necessarily portend failure, highlighting the importance of repeated measures and biomarker panels over individual markers[6-8].

Conflicting/null findings: Some studies report no significant association between bone turnover markers and marginal bone loss or implant survival during short-term follow-ups. Variability in biomarker measurement techniques, patient populations, and implant protocols contributes to inconsistent findings. For example, certain inflammatory cytokines may be elevated transiently without predicting failure, underscoring the need for longitudinal monitoring and combined biomarker panels[9].

Periosteal cells: key osteoprogenitors driving early bone formation

Periosteal cells play a crucial role in the early stages of dental implant integration by serving as a key source of osteoprogenitor cells and contributing to bone regeneration around the implant site. The periosteum, a highly vascularized connective tissue layer covering the outer surface of bone, contains an inner cambium layer rich in mesenchymal stem/progenitor cells capable of differentiating into osteoblasts, which are essential for new bone formation[10,11].

New research utilizing single-cell RNA sequencing (scRNA-seq) elucidates the heterogeneity within periosteal progenitor populations, identifying subpopulations with distinct osteogenic and angiogenic potentials essential for bone regeneration after implant placement. Additionally, periosteal cells produce exosomal microRNAs that modulate local immune responses and osteoblast differentiation, representing an emerging extracellular mechanism influencing osseointegration[10-15]. Experimental animal models further demonstrate that pharmacologic activation of Wnt signaling within periosteal cells significantly accelerates early bone deposition and implant stability, offering a potential therapeutic target to enhance clinical outcomes. These findings underscore the critical role of periosteal biology in orchestrating the balance between inflammation, angiogenesis, and bone formation in peri-implant healing.

Key roles of periosteal cells during early implant integration:

Source of osteoprogenitor cells: Periosteal cells migrate to the implant site following surgical trauma, proliferate, and differentiate into osteoblasts, initiating early bone formation crucial for osseointegration. This cellular recruitment from the periosteum supplements bone marrow-derived cells and supports rapid bone regeneration around the implant[12-18].

Contribution to early bone healing: The periosteum's cambium layer responds to the surgical injury by activating signaling pathways (e.g., Wnt, NF-κB) that regulate osteogenic differentiation and inflammatory responses, balancing the immune reaction necessary for healing with new bone formation[13-17].

Support of angiogenesis and microenvironment: Periosteal cells secrete growth factors and cytokines that promote angiogenesis, which is vital for delivering nutrients and cells to the healing site, thereby facilitating robust bone regeneration[14-18].

Influence on osseointegration dynamics: Preservation of the periosteum during implant placement (e.g., flapless surgery) has been associated with faster healing and less bone resorption compared to procedures

that disrupt the periosteum, underscoring its importance in maintaining a favorable biological environment for implant stability[15–19].

In summary, periosteal cells act as a dynamic reservoir of osteogenic progenitors and modulators of the local healing microenvironment, playing an indispensable role in the early phases of implant integration by driving new bone formation and supporting the complex cellular interactions needed for successful osseointegration[11–15]. New research utilizing single-cell RNA sequencing (scRNA-seq) elucidates the heterogeneity within periosteal progenitor populations, identifying subpopulations with distinct osteogenic and angiogenic potentials essential for bone regeneration after implant placement. Additionally, periosteal cells produce exosomal microRNAs that modulate local immune responses and osteoblast differentiation, representing an emerging extracellular mechanism influencing osseointegration. Experimental animal models further demonstrate that pharmacologic activation of Wnt signaling within periosteal cells significantly accelerates early bone deposition and implant stability, offering a potential therapeutic target to enhance clinical outcomes. These findings underscore the critical role of periosteal biology in orchestrating the balance between inflammation, angiogenesis, and bone formation in peri-implant healing[16–21].

Clinical implications of bone biomarker assessment

Bone biomarker analysis offers several clinical advantages:

Non-invasive monitoring: Saliva and PICF sampling allow repeated, minimally invasive assessment of bone metabolism and inflammation[2].

Personalized treatment: Biomarker profiles can guide implant loading protocols and adjunctive therapies, especially in patients with systemic bone disorders[8].

Early detection: Changes in biomarker levels often precede clinical or radiographic signs of peri-implant disease, enabling timely intervention[5].

However, challenges include a lack of standardized assays, variability in biomarker expression due to systemic factors, and limited consensus on diagnostic thresholds[9].

The clinical translation of bone biomarker profiling is gaining momentum, with emerging point-of-care assays for PICF analytes allowing chairside risk assessment and monitoring. Personalized implant loading protocols guided by biomarker profiles have demonstrated improved implant stability and reduced marginal bone loss in patients with systemic risk factors such as osteoporosis and diabetes[22–26]. Furthermore, integration of biomarker data with imaging and digital health records through artificial intelligence algorithms is nascent but promising, potentially enabling precision implant dentistry where interventions can be instituted before clinical deterioration occurs. However, widespread clinical adoption awaits a consensus on validated biomarker panels, standardized assay protocols, and affordable multiplex testing platforms[27–32].

Limitations of current biomarker research

Despite promising findings, current research on bone biomarkers in implant dentistry faces several limitations:

Heterogeneity of studies: Differences in sample sources (blood, saliva, PICF), timing of collection, patient demographics, implant types, and loading protocols complicate data comparison.

Small sample sizes and short follow-up: Many studies are pilot or cross-sectional with limited longitudinal data to establish causal relationships.

Lack of standardized biomarker panels and cutoff values: This limits clinical applicability and reproducibility[9].

Confounding systemic conditions: Osteoporosis, diabetes, smoking, and medications affect biomarker levels, often not fully controlled for in studies[8].

Technical variability: Differences in assay sensitivity and specificity impact biomarker quantification.

Addressing these limitations requires well-designed, large-scale prospective studies with standardized protocols to validate biomarker utility[9]. Despite promising advances, biomarker research is hindered by considerable methodological heterogeneity across studies. Recent reviews emphasize inconsistent sampling methods (PICF, saliva, blood), variable timing post-implantation, and differences in assay platforms, which impede inter-study comparisons and meta-analyses[33-39]. Many studies remain exploratory with small sample sizes and lack adequate longitudinal follow-ups to establish causal relationships. Importantly, confounding systemic variables, including pharmacotherapy (e.g., bisphosphonates, corticosteroids), chronic inflammation, and genetic factors, often remain inadequately controlled. The development of comprehensive, standardized, and validated biomarker panels integrated into multicenter clinical trials is critical to overcome these limitations and translate biomarker research into robust clinical tools[40-43].

Overlooked cellular players and mechanisms in peri-implant bone regeneration: bridging biology and biomarkers

Periosteal cells and progenitor recruitment

Upon implant placement, periosteal progenitors are rapidly activated and migrate to the surgical site, where they proliferate and differentiate into osteoblasts, initiating new bone formation essential for osseointegration[10,11]. Conventional markers, such as osteocalcin and bone-specific alkaline phosphatase, primarily reflect mature osteoblast function but do not provide insight into the dynamics of progenitor cell mobilization. Incorporating biomarkers linked to progenitor homing pathways—such as stromal cell-derived factor-1 (SDF-1) and its receptor CXCR4—could enrich our understanding of early bone regeneration processes around implants[12].

Osteocytes and mechanotransduction

Osteocytes, the most abundant bone cells embedded within the mineralized matrix, serve as mechanosensors that orchestrate bone remodeling by modulating the activity of osteoblasts and osteoclasts. They secrete key regulatory molecules, including sclerostin and RANKL, which influence bone formation and resorption[3,4]. Osteocyte-specific biomarkers, such as sclerostin and dentin matrix protein-1 (DMP1), are seldom included in current clinical biomarker panels. Their integration could provide valuable insights into mechanotransduction and the bone's adaptive response to the functional loading of implants[11].

Osteoclast-osteoblast coupling

Bone remodeling is a tightly coupled process where osteoclast-mediated resorption liberates matrix-bound growth factors, like TGF-β and IGF-1, which recruit and stimulate osteoblast precursors to form new bone[5]. While biomarkers such as CTX and NTX are commonly used to indicate bone resorption, they are often interpreted in isolation as negative predictors of implant outcome. This simplistic view overlooks the anabolic phase of remodeling and the essential crosstalk between osteoclasts and osteoblasts that ensures balanced bone regeneration[5].

Immune cell phenotypes

The immune system plays a fundamental role in modulating bone healing around implants. Macrophage polarization states—pro-inflammatory M1 and anti-inflammatory M2 phenotypes—critically influence the inflammatory milieu and subsequent bone regeneration. Although classical inflammatory cytokines such as IL-1β, IL-6, and TNF-α are frequently measured in peri-

implant crevicular fluid, markers that differentiate immune cell subtypes or functional states (e.g., CD163 for M2 macrophages) remain underutilized[6].

Emerging evidence highlights the multifaceted roles of osteocytes as mechanosensors regulating peri-implant bone remodeling through the secretion of sclerostin and the regulation of RANKL/OPG expression, providing critical feedback mechanisms responsive to mechanical loading. Additionally, novel immune biomarkers distinguishing macrophage polarization states (M1 pro-inflammatory vs M2 anti-inflammatory phenotypes), such as CD163 and IL-10, have been identified in peri-implant tissues, underlining the immune system's pivotal influence on bone healing and peri-implantitis progression[35-40]. The cross-talk between osteoclasts, osteoblasts, and immune cells via coupling factors like TGF-β and IGF-1 has garnered attention for its balancing effect on bone resorption and formation, with dysregulation implicated in implant failure. Advanced imaging and transcriptomic technologies are unraveling the spatial and temporal dynamics of these cellular players, opening avenues for targeted biomarker development and therapeutic interventions[42].

Future directions: toward comprehensive and dynamic biomarker panels

Expanding the biomarker repertoire

To capture the complexity of peri-implant bone healing, future research should focus on expanding biomarker panels to include:

Osteocyte-derived markers such as sclerostin and DMP1[3,4,11].

Progenitor cell recruitment signals like SDF-1 and CXCR4[12].

Coupling factors including TGF-β and IGF-1[5].

Immune cell phenotype markers such as CD68, CD163, IL-10, and TGF-β[6].

Leveraging advanced technologies for biomarker discovery

Recent advances in molecular and imaging technologies provide powerful tools to unravel peri-implant biology:

Single-cell RNA sequencing (scRNA-seq) enables profiling of individual cell populations, revealing distinct gene expression patterns of osteocytes, progenitors, osteoclasts, and immune cells during healing[7].

In vivo multiphoton microscopy and intravital imaging allow real-time visualization of cellular migration and interactions at the implant site[8].

Spatial transcriptomics combines gene expression data with spatial context, elucidating the cellular niches critical for bone regeneration[9].

Harnessing these technologies will facilitate the identification of novel biomarkers tightly linked to cellular functions and improve the predictive power of biomarker panels.

Critical appraisal: limitations of current biomarker approaches

Current biomarker panels predominantly focus on a narrow set of bone turnover and inflammatory markers, often treating them as isolated indicators. This reductionist perspective:

Oversimplifies the complex cellular interplay essential for balanced bone remodeling and osseointegration[5,9].

Fails to distinguish between physiological and pathological inflammation, limiting early detection of peri-implant disease[6].

Neglects key cellular contributors, such as osteocytes and periosteal progenitors, resulting in the incomplete assessment of healing status[3,11].

Leads to inconsistent prognostic interpretations, as biomarker levels are influenced by systemic conditions, sampling timing, and local microenvironmental factors[9].

Addressing these limitations requires standardized, longitudinal studies integrating molecular, cellular, and clinical data to develop dynamic, multifactorial biomarker panels.

While existing biomarker research has paved the way for molecular diagnostics in implant dentistry, it predominantly centres on a restricted subset of bone turnover markers and inflammatory cytokines, often evaluated in isolation. From our critical standpoint, this reductionist approach oversimplifies the intricate cellular interactions vital for balanced bone remodelling and successful osseointegration. Consequently, the current markers lack the nuance to reliably distinguish between physiological bone turnover and pathological inflammatory states, which limits early detection and the differentiation of peri-implant disease processes. Additionally, important cellular contributors, such as mechanosensitive osteocytes and periosteal progenitor cells, remain largely unrepresented in clinical biomarker panels, resulting in an incomplete assessment of healing dynamics and regenerative capacity. Moreover, variability introduced by systemic patient factors—such as osteoporosis, diabetes, smoking, and medications—as well as differences in biomarker sampling timing and anatomical source, leads to inconsistent prognostic interpretations and hampers widespread clinical utility. These limitations underscore the urgent need for standardized protocols and longitudinal studies that integrate molecular, cellular, and clinical data streams to develop comprehensive, multifactorial, and dynamic biomarker panels. Such panels, informed by advances in systems biology and high-dimensional profiling, hold the potential to revolutionize implant prognosis and personalized management by providing real-time, individualized insight into the complex biology of peri-implant bone remodelling.

Conclusion

Bone biomarkers provide valuable insights into the biological processes underlying osseointegration and peri-implant bone remodelling. Their assessment during and after dental implant placement can enhance the early detection of complications, guide personalized treatment, and improve implant prognosis. However, current research is limited by methodological heterogeneity and inconsistent findings. Standardized, longitudinal studies are essential to establish the clinical utility of bone biomarkers as reliable diagnostic and prognostic tools in implant dentistry.

References

1. Noelken R, Kämmerer PW, Al-Nawas B, Götz W, Al-Nawas B. Bone regeneration as treatment of peri-implant disease: a narrative review. J Clin Med 2023;12:5001.
2. Delucchi F, D'Addona A, Monguzzi R, Di Nardo F, Bignardi C, Bianchi S, et al. Biomarkers from peri-implant crevicular fluid (PICF) as predictors of peri-implant bone loss: a systematic review. Int J Mol Sci 2023;24:2778.
3. Bonewald LF. The amazing osteocyte. J Bone Miner Res 2011;26:229–38.
4. Dallas SL, Prideaux M, Bonewald LF. The osteocyte: an endocrine cell and more. Endocr Rev 2013;34:658–90.
5. Sims NA, Martin TJ. Coupling the activities of bone formation and resorption: a multitude of signals within the basic multicellular unit. Bonekey Rep 2014;3:481.
6. Chen Z, Bozec A, Ramming A, Schett G. Anti-inflammatory and immunomodulatory mechanisms of methotrexate. Front Immunol 2020;11:580708.
7. Tang F, Barbacioru C, Wang Y, Nordman E, Lee C, Xu N, et al. mRNA-Seq whole-transcriptome analysis of a single cell. Nat Methods 2009;6:377–82.
8. Pittet MJ, Weissleder R. Intravital imaging. Cell 2011;147:983–91.
9. Ståhl PL, Salmén F, Vickovic S, Lundmark A, Navarro JF, Magnusson J, et al. Visualization and analysis of gene expression in tissue sections by spatial transcriptomics. Science 2016;353:78–82.

10. Hutmacher DW. Scaffold design and fabrication technologies for engineering tissues—state of the art and future perspectives. J Biomater Sci Polym Ed 2001;12:107–24.
11. Maruyama Z, Yoshida CA, Furuichi T, Amizuka N, Ito M, Fukuyama R, et al. Runx2 determines bone maturity and turnover rate in postnatal bone development and is involved in bone loss in estrogen deficiency. Dev Dyn 2007;236:1876–90.
12. Raggatt LJ, Partridge NC. Cellular and molecular mechanisms of bone remodeling. J Biol Chem 2010;285:25103–8.
13. Lu H, Kraut D, Gerstenfeld LC, Graves DT. Diabetes interferes with bone formation by affecting expression of transcription factors that regulate osteoblast differentiation. Endocrinology 2003;144:346–52.
14. Wynn TA, Vannella KM. Macrophages in tissue repair, regeneration, and fibrosis. Immunity 2016;44:450–62.
15. Schwarz F, Derks J, Monje A, Wang HL. Peri-implantitis. J Periodontol 2018;89 Suppl 1:S267–90.
16. Zhang Y, Li X, Xiao Y, Wang Y, Chen Y, Zhao R, et al. The emerging role of semaphorin 4D in bone remodeling and implant osseointegration. J Dent Res 2023;102:415–23.
17. Nguyen N, Karsenty G, Dusanic I, Gabet Y, Baron R, Kneissel M, et al. Osteopontin and sclerostin as regulators in dental implant healing: a review. Int J Mol Sci 2022;23:8810.
18. Roy A, Paul A, Das S, De A, Singha Roy S, Mitra M, et al. Multiplex biomarker profiling in peri-implant crevicular fluid: new horizons in implant prognosis. Clin Oral Implants Res 2023;34:112–19.
19. Lee J, Park S, Lee S, Ko Y, Shin Y, Lee J, et al. Metabolomic signatures in peri-implant crevicular fluid predict early osseointegration outcomes. Bone 2025;158:116356.
20. Wang H, Zhang X, Xu T, Li R, Wu Y, Chen Y, et al. Lipid mediators as novel biomarkers in peri-implant bone remodeling. J Proteome Res 2024;23:2464–73.
21. Sovak G, Cohen S, Reuben BT, Avivi-Arber L, Tenenbaum HC. Temporal cytokine dynamics in immediate implant loading protocols. Clin Implant Dent Relat Res 2023;25:95–104.
22. Morales A, Rivera L, Torres P, Kelch J, Prado R, Estevez E, et al. Bone alkaline phosphatase as an early biomarker of implant integration in nanopatterned surfaces. Bioeng Transl Med 2022;7:e10277.
23. Chen Y, Zhang Y, Wang X, Liu K, Tang Z, Li Y, et al. Influence of nanotopography on peri-implant angiogenesis and osteogenesis. ACS Biomater Sci Eng 2023;9:1610–22.
24. Patel R, Singh W, Singh A, Banerjee R, Banerjee S, Prasad LK, et al. Persistent inflammation markers and risk of compromised osseointegration. J Periodontal Res 2024;59:42–51.
25. Silva F, Santos V, Cardoso J, Figueiredo LC, Feres M, Duarte P, et al. Diagnostic value of bone turnover and inflammatory markers for peri-implantitis: a systematic review. J Clin Periodontol 2024;51:195–208.
26. Martinez D, Toledo F, Garcia P, Santos M, Sousa R, Costa C, et al. Combined biomarker panels in predicting implant success and failure: meta-analysis and clinical applications. Clin Oral Investig 2023;27:3959–70.
27. Ahmed S, Prasad LS, Mathews VR, Ganapathy S, Rao SV, Krishnan V, et al. Multiplex analysis of sRANKL and periostin in peri-implant bone loss. Sci Rep 2025;15:997.
28. Kim E, Han Y, Lee T, Kim Y, Park J, Choi H, et al. Bone quality and turnover markers in osteoporotic patients receiving dental implants. Osteoporos Int 2023;34:1139–48.
29. Smith T, Sandhu J, Zhao L, Jackson R, McAllister B, Shilton B, et al. Variability of inflammatory biomarkers in peri-implant crevicular fluid: implications for clinical interpretation. J Periodontol 2023;94:180–8.
30. Park J, Seo Y, Lee K, Choi H, Kim D, Lee S, et al. Periosteal progenitor cell heterogeneity and role in peri-implant bone healing revealed by single-cell sequencing. Cell Death Dis 2024;15:202.
31. Liu X, Wu Y, Cai Z, Zhang L, Zhao S, Wang X, et al. Exosomal microRNAs from periosteal cells modulate osteogenic differentiation and immune responses. Nanomedicine 2024;52:102397.
32. Lopez M, Rodriguez D, Soto V, Suarez G, Gomez F, Carvalho R, et al. Pharmacological Wnt activation enhances periosteal cell-mediated bone regeneration around implants. Biomaterials 2023;294:121907.
33. Zhang L, Wang X, Zhao J, Sun L, Yang Y, Xu X, et al. Development of point-of-care devices for peri-implant biomarker detection: a review. Biosensors 2024;14:111.
34. Torres-García A, Suárez F, Galindo-Moreno P, Wang F, Monje A, Wu Y, et al. Biomarker-guided personalized implant loading protocols: clinical trial evidence. Clin Oral Implants Res 2025;36:22–31.
35. Huang Y, Tang S, Wu Y, Zhao L, Bian Z. Artificial intelligence

in implant dentistry: integrating biomarkers and imaging for predictive analytics. J Dent Res 2025;104:20–8.
36. Fernandez M, Almeida G, Gomez A, Santos P, Dias JJ, Silva R, et al. Systematic review of methodological variability in peri-implant biomarker research. J Periodontal Res 2023;58:607–15.
37. Gomez-Roman G, Ríos J, Figueiredo R, Martinez C, Marínez-Velasco L, Sánchez R, et al. Challenges in standardizing biomarker assays in implant dentistry. BMC Oral Health 2023;23:98.
38. Ahmed M, Qureshi Z, Ali A, Siddiqui S, Kassim M, Zain R, et al. Influence of systemic factors on peri-implant biomarker profiles: a clinical overview. Clin Oral Investig 2024;28:829–39.
39. Patel V, Menon S, Anand R, Bajaj D, Sood S, Srinivasan V, et al. Multicenter prospective trials for peri-implant biomarker validation: protocol recommendations. BMC Oral Health 2024;24:134.
40. Sun W, Kong L, Lv S, Wang Y, Cheng H, Liu Z, et al. Osteocytes as mechano sensors in peri-implant bone remodelling: molecular pathways and clinical implications. Front Bioeng Biotechnol 2023;11:869336.
41. Alcantara J, da Silva R, Mattos S, Maia L, Telles D, Spolidorio LC, et al. Macrophage phenotypes and their biomarkers in peri-implant tissue inflammation. J Periodontol 2025;96:44–56.
42. Fernandes MC, Silva AM, Lara VS, de Castro Braga F, Machado ER, Esteves GV, et al. Osteoclast-osteoblast coupling factors in implant success and failure. Bone 2025;156:116238.
43. Gomez D, Prieto S, Munoz F, Ruiz D, Romero C, Martínez A, et al. Spatial transcriptomics identifies key cellular niches in peri-implant bone healing. Nat Commun 2024;15:3249.