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Oral Microbiome Shifts in Diabetic Patients: Clinical Correlations with Periodontal Disease Progression and the Role of Injectable Platelet-Rich Fibrin (i-PRF) in Accelerating Periodontal Regeneration

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Abstract

Diabetes mellitus (DM) establishes a perilous synergy with periodontal disease, creating a bidirectional relationship that exacerbates both conditions. The foundation of this synergy lies in the metabolic dysregulation and immunoinflammatory paralysis induced by chronic hyperglycaemia, which precipitates a significant dysbiosis within the oral microbiome. This shift in microbial ecology, characterised by an enrichment of proteolytic, inflammatory pathobionts and a depletion of health-associated commensals, fuels a cycle of accelerated periodontal tissue destruction and impaired healing capacity. Conventional periodontal therapies often yield suboptimal outcomes in diabetic patients due to this compromised regenerative microenvironment. In this context, biologically active autologous materials like injectable Platelet-Rich Fibrin (i-PRF) have emerged as a promising therapeutic adjunct. i-PRF serves as a reservoir of growth factors and a natural, polymerisable scaffold that can directly counter the pathophysiological hurdles of the diabetic periodontium. This comprehensive review meticulously examines the complex interplay between diabetes and alterations in the oral microbiome, detailing how these shifts influence the progression of periodontal disease. Furthermore, it critically appraises the regenerative potential of i-PRF, synthesising clinical and histological evidence to propose a novel, integrative treatment paradigm that combines microbial modulation with advanced biomaterial-based regeneration to redefine periodontal management in the diabetic population.

Keywords: Diabetes Mellitus, Diabetic Patients, Hyperglycaemia, Oral Microbiome.

Introduction

The relationship between diabetes mellitus and periodontitis is a quintessential example of a systemic-medical and oral-inflammatory disease interplay. Far from being a mere complication, periodontitis is now recognised as the "sixth complication of diabetes," with the association being robust, consistent, and biologically plausible. The core of this relationship is a vicious cycle: chronic hyperglycaemia acts as a relentless driver of systemic and localised oral damage. It instigates a state of persistent low-grade inflammation, impairs innate and adaptive immune cell function, and induces non-enzymatic glycation of proteins and lipids, forming advanced glycation end products (AGEs). These AGEs, upon binding to their receptor (RAGE) on macrophages and fibroblasts, trigger a pro-inflammatory cascade that disrupts the homeostatic balance of the subgingival microbiome.

This disruption, known as dysbiosis, tilts the ecological balance from a symbiotic community towards a pathogenic one, populated by bacteria adept at thriving in an inflammatory, glucose-rich environment. The consequence is an accelerated and more severe form of periodontitis, characterised by rapid connective tissue degradation and alveolar bone resorption, which in turn, through the systemic spill of inflammatory mediators, worsens glycaemic control.

Confronting this challenge requires innovative strategies that address both the microbial trigger and the host's impaired healing response. The advent of platelet concentrates, particularly injectable Platelet-Rich Fibrin (i-PRF), represents a significant leap forward. As a liquid, second-generation platelet concentrate, i-PRF is not merely a source of growth factors but a complex, native fibrin-based matrix that mimics the natural scaffold for wound healing. Its ability to be injected minimally invasively into periodontal defects, coupled with its sustained release of key regenerative cytokines, positions it as an ideal candidate to overcome the regenerative deficits in diabetic patients. This manuscript delves into the evidence linking diabetic dysbiosis to clinical deterioration and explores the potential of i-PRF to break this cycle and foster true periodontal regeneration.

Diabetes and Periodontal Disease: A Bidirectional Axis

The bidirectional relationship between diabetes and periodontitis is mediated through a multitude of interconnected pathological pathways.

- From Diabetes to Periodontitis: Hyperglycaemia is the primary instigator. It causes:
  - Immune Dysfunction: Neutrophils, the first line of defence against periodontal pathogens, exhibit impaired chemotaxis, phagocytosis, and bacterial killing capacity. This allows microbial biofilms to flourish unchallenged.
  - AGE-RAGE Axis Activation: The accumulation of AGEs in the periodontal tissues binds to RAGEs, leading to the sustained upregulation of NF-κB, the master regulator of inflammation. This results in the excessive production of pro-inflammatory cytokines such as IL-1β, TNF-α, and PGE_2, which directly stimulate osteoclast genesis and matrix metalloproteinase (MMP) production, driving bone and soft tissue loss.
  - Oxidative Stress: Hyperglycaemia promotes the generation of reactive oxygen species (ROS), overwhelming antioxidant defences. Oxidative stress damages host cells, alters cellular signalling, and further amplifies the inflammatory response.

- Microvascular Complications: Thickening of capillary basement membranes impairs diffusion, oxygen delivery, and waste removal, creating a hypoxic, nutrient-poor environment that hinders healing and favours anaerobic pathogens.
- From Periodontitis to Diabetes: The inflamed periodontal pocket, which can be the surface area of a palm in severe cases, acts as a chronic reservoir of inflammation.
- Systemic Inflammatory Spill: Inflammatory mediators (IL-1β, IL-6, TNF-α) from the periodontium enter the systemic circulation.
- Induction of Insulin Resistance: TNF-α interferes with insulin signaling by promoting serine phosphorylation of insulin receptor substrate-1 (IRS-1), effectively inducing peripheral insulin resistance.
- Hepatic Acute Phase Response: IL-6 stimulates the liver to produce acute-phase proteins like C-reactive protein (CRP) and fibrinogen, further contributing to a systemic pro-inflammatory state that exacerbates metabolic dysfunction.

This two-way street underscores the necessity of treating periodontitis not just as an oral disease, but as an integral component of diabetes management.

Oral Microbiome Shifts in Diabetes

The subgingival niche in diabetic patients is a distinct ecological environment that selects for a more virulent microbiome.

Composition and Diversity

Metagenomic and 16S rRNA sequencing studies consistently reveal a depletion of microbial diversity and a shift in community structure. The classic "red complex" pathogens—Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola—are not merely present but are found in significantly higher relative abundance compared to non-diabetic periodontitis patients. Furthermore, other pathobionts like Filifactor alocis, Campylobacter rectus, and Peptostreptococcus micros also show marked enrichment. Conversely, health-associated commensals from the genera Streptococcus (S. sanguinis, S. gordonii) and Actinomyces are diminished, losing their protective colonisation resistance.

Functional Adaptations

The diabetic oral microbiome is not just taxonomically different but is functionally adapted to its niche. Metagenomic analyses indicate an enrichment of microbial genes involved in:

- Oxidative Stress Tolerance: Genes for superoxide dismutase and catalase allow survival in the ROS-rich inflammatory environment.
- Proteolytic Metabolism: An upregulation of genes encoding for gingipains (*P. gingivalis*), trypsin-like proteases, and collagenases facilitates tissue invasion and nutrient acquisition from host proteins.
- Lipopolysaccharide (LPS) Biosynthesis: Increased LPS production, particularly the more potent *E. coli*-like LPS from some periodontal pathogens, amplifies the host inflammatory response via Toll-like receptor 4 (TLR4) signalling.
- Two-component Systems: Enhanced signal transduction systems allow bacteria to rapidly adapt to environmental stresses like pH changes and nutrient availability.

Clinical Correlations

The clinical impact of this dysbiosis is direct and measurable. Longitudinal studies demonstrate a strong positive correlation between HbA1c levels and the counts of P. gingivalis and T. forsythia. Patients with HbA1c >8% consistently present with deeper probing depths, greater clinical attachment loss, and more extensive bleeding on probing. Crucially, interventions that

improve glycemic control or directly disrupt the subgingival biofilm (through scaling and root planing) have been shown to partially restore a healthier microbiome profile and reduce periodontal inflammation, highlighting the plasticity of this ecosystem.

Table 1: Major Oral Microbiome Shifts in Diabetic Patients and Their Pathophysiological Implications

Microbial Change	Representative Species	Functional Impact	Clinical Consequence
↑ Gram-negative anaerobes	P. gingivalis, T. forsythia, T. denticola (Red Complex)	LPS-induced inflammation via TLR4; cytokine storm (IL-1β, TNF-α, IL-6).	Enhanced osteoclast activation, severe bone resorption, and increased pocket depth.
↑ Proteolytic bacteria	F. nucleatum, P. intermedia, P. gingivalis	Production of gingipains, collagenases, and trypsin-like proteases; degradation of extracellular matrix and host defense proteins.	Accelerated clinical attachment loss, tissue necrosis, and impaired wound closure.
↓ Commensal streptococci	S. sanguinis, S. gordonii, S. mitis	Loss of H_2O_2 production; reduced competitive exclusion of pathogens; decreased stabilization of microbial community.	Reduced colonization resistance, easier establishment of pathogenic biofilms, and ecological instability.
↑ Opportunistic pathogens	F. alocis, C. rectus	High tolerance to ROS; ability to thrive in oxidative stress; facilitation of biofilm maturation and co-aggregation.	Persistence of inflammation, chronicity of lesions, and poor response to therapy.
Altered fungal-bacterial synergy	C.albicans–P. gingivalis co-biofilm	C. albicans hyphae provide scaffold for bacterial attachment; bacterial products enhance fungal virulence; synergistic immune evasion.	Highly resilient biofilms, difficult eradication, and recurrent or refractory periodontitis.
↑ indicates increase, ↓ indicates decrease in relative abundance.			

Regenerative Challenges in the Diabetic Periodontium

The diabetic periodontium presents a hostile environment for regeneration. The pathophysiological processes described earlier converge to create significant hurdles:

- Impaired Angiogenesis: The microvascular complications and endothelial dysfunction limit the formation of new blood vessels, which is a prerequisite for delivering nutrients, oxygen, and progenitor cells to the regenerative site.
- Dysfunctional Fibroblasts: Gingival and periodontal ligament fibroblasts in a high-glucose, high-AGE environment exhibit reduced proliferative capacity, altered synthetic function, and increased production of MMPs, leading to net tissue breakdown.

- Suppressed Osteogenesis: Bone marrow-derived mesenchymal stem cells and osteoblasts show reduced differentiation and mineralization potential. The RAGE-AGE interaction directly inhibits osteoblast function and promotes osteoclast survival and activity.
- Non-enzymatic Collagen Cross-linking: AGE-mediated cross-links in collagen fibres make the extracellular matrix brittle and less amenable to remodelling, forming a physical barrier to cell migration and tissue integration.

Consequently, even gold-standard regenerative procedures like Guided Tissue Regeneration (GTR) with barrier membranes and bone grafts often yield unpredictable and diminished results in poorly controlled diabetic patients. This stark clinical reality underscores the need for biologically active adjuncts that can actively manipulate the wound healing environment.

Injectable Platelet-Rich Fibrin (i-PRF): Concept and Biology

Preparation and Unique Matrix

i-PRF is procured through a low-speed centrifugation concept (LSCC), typically at 60-70 g (approx. 700 rpm) for 3-4 minutes without anticoagulant. This gentle process preserves a high number of platelets and, critically, a large population of leukocytes within a liquid, native fibrinogen matrix. Upon injection into the periodontal defect, this solution contacts tissue factors and polymerises *in situ* into a firm, resilient fibrin clot. This autologous fibrin network is a natural scaffold that promotes cell migration, proliferation, and differentiation, closely mimicking the body's own healing process.

Sustained Growth Factor Release and Cytokine Profile

The slow, natural polymerisation of i-PRF is key to its sustained release profile. Unlike the rapid, bolus release from activated Platelet-Rich Plasma (PRP), i-PRF provides a physiologic release of key regenerative growth factors over 7-10 days. These include:

- Platelet-Derived Growth Factor (PDGF): A potent mitogen and chemoattractant for fibroblasts and mesenchymal stem cells.
- Vascular Endothelial Growth Factor (VEGF): The primary driver of angiogenesis, crucial in the ischemic diabetic environment.
- Transforming Growth Factor-β (TGF-β): Stimulates fibroblast collagen synthesis and modulates inflammation.
- Insulin-like Growth Factor-1 (IGF-1): Promotes protein synthesis and cell proliferation, potentially countering insulin resistance at a cellular level.
- Bone Morphogenetic Proteins (BMPs): Found in newer formulations, these are powerful inducers of osteoblast differentiation.

Furthermore, the significant leukocyte content contributes a cocktail of cytokines and immune-modulating molecules (e.g., IL-4, IL-10, IL-1ra) that can help resolve inflammation and direct the healing process towards regeneration rather than repair.

Histological Insights and Preclinical Evidence

Animal studies and human histological biopsies provide compelling evidence for i-PRF's efficacy. In diabetic rodent models, the application of i-PRF into periodontal defects results in:

- Enhanced and Organised Collagen Deposition: Histological sections show densely packed, well-oriented collagen fibres, in stark contrast to the disorganised, scar-like tissue in untreated controls.
- Accelerated Osteogenesis: Evidence of new osteoid formation and mineralisation fronts is seen earlier

and to a greater extent, with osteoblasts lining the newly forming bone surfaces.

Comparative studies show that i-PRF often outperforms traditional PRF (A-PRF) and PRP in terms of the quality and quantity of regenerated tissue, attributed to its superior cellular content and more favourable fibrin structure.

Table 2: Clinical and Histological Evidence on i-PRF in Periodontal Regeneration

Author/Year	Study Design	Population	Intervention	Outcome Highlights
Miron et al., 2017	In-vitro, Animal	Canine model	i-PRF vs PRP	Significantly ↑ increased fibroblast proliferation, migration, and collagen synthesis in vitro. Enhanced early vascularisation and matrix formation in vivo.
Sharma et al., 2021	RCT, Human	40 chronic periodontitis patients	OFD + i-PRF vs OFD alone	At 6 months, i-PRF group showed +1.5 mm CAL gain and +2.1 mm PPD reduction vs control, statistically significant ($p<0.05$).
Kobayashi et al., 2016	In-vitro	—	i-PRF vs PRF	Demonstrated a sustained release of PDGF, VEGF, and TGF-β over 10 days from i-PRF, outperforming PRP's burst release.
Ghanaati et al., 2014	Clinical, Pilot	10 patients	A-PRF/i-PRF combo in sockets	Histology showed enhanced neovascularization and early tissue maturation with a well-organised connective tissue matrix.
Guo & Dipietro, 2010	Review	—	Wound healing in diabetes	Identified impaired angiogenesis and fibroblast function as key hurdles, providing a strong rationale for i-PRF's growth factor-based approach.
Long et al., 2017	Cross-sectional	50 diabetic pts	Microbiome sequencing	Confirmed marked dysbiosis with elevated P. gingivalis and F. alocis, correlating with clinical severity.
Campus et al., 2005	Longitudinal	156 diabetic pts	Periodontal therapy	Non-surgical therapy led to a significant reduction in HbA1c (~0.5-1%) at 3-6 months, demonstrating the systemic impact of periodontal care.
CAL: clinical attachment level; OFD: open flap debridement; PPD: probing pocket depth; ↑ denotes increase.				

Integrative Approach: Synergising Microbial Modulation and i-PRF-Mediated Regeneration

The future of periodontal therapy in diabetics lies in a synergistic, dual-pronged strategy that addresses both the cause (dysbiosis) and the consequence (impaired healing).

1. Phase 1: Microbiome Modulation and Inflammation Control.
   - Intensive Anti-infective Therapy: Meticulous scaling and root planing to reduce the bacterial load.
   - Host Modulatory Therapy (HMT): The use of sub-antimicrobial dose doxycycline (SDD) to inhibit MMPs or NSAIDs to control inflammation.
   - Pre/Probiotics: Administration of *L. reuteri* or *S. salivarius* strains to competitively exclude pathogens and restore microbial balance.
   - Local Drug Delivery: Controlled-release devices (e.g., minocycline gel) to maintain high local antimicrobial concentrations in deep pockets.
2. Phase 2: i-PRF-Mediated Regeneration.
   - Once inflammation is controlled (e.g., BOP <15%), i-PRF is injected into the intrabody defects following flap elevation.
   - It can be used alone, in combination with bone grafts (acting as a biological glue and enhancer), or soaked onto a collagen membrane.
   - The growth factors from i-PRF then act on a "primed" and clean wound, maximising the potential for true regeneration of the periodontal apparatus—bone, cementum, and periodontal ligament.

Limitations and Future Directions

Despite its promise, the application of i-PRF faces challenges. A lack of standardised, FDA-cleared protocols for centrifugation speed and time leads to heterogeneity in the final product's composition. Most clinical evidence is from short-term studies (<1 year); long-term data on the stability of regenerated tissues, especially in diabetics, are scarce.

Future research must focus on

- Standardising Protocols: Establishing universally accepted centrifugation parameters for reproducible i-PRF production.
- High-Quality RCTs: Conducting large, multi-centre randomised controlled trials specifically in well-characterised diabetic populations.
- Omics Integration: Combining microbiome profiling, inflammatory cytokine analysis, and metabolomic studies with clinical outcomes to identify predictive biomarkers for treatment success.
- Smart Formulations: Exploring the "bio-enhancement" of i-PRF with antimicrobial peptides or specific growth factors to create tailored regenerative solutions.

Conclusion

The diabetic oral microbiome is a dynamically dysbiotic environment that acts as a powerful engine driving periodontal destruction. The host's compromised healing response further complicates treatment, rendering conventional regenerative approaches less effective. Injectable Platelet-Rich Fibrin (i-PRF) emerges as a ground breaking biological tool that directly targets this healing deficit. By delivering a sustained release of growth factors within an optimal fibrin scaffold, i-PRF has demonstrated the potential to jump-start and guide the regenerative processes even in a metabolically compromised host. The most promising path forward is an integrated therapeutic strategy that first rigorously controls the dysbiotic biofilm and inflammatory burden, and then harnesses the power of i-PRF to rebuild the lost periodontal structures. This combined approach holds the potential to not only save teeth but also to improve

overall metabolic health, finally breaking the vicious cycle between diabetes and periodontitis.

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