Immune Dysregulation Linking Type 1 Diabetes Mellitus and Periodontal Disease: The Roles of Neutrophil Dysfunction and Cytokine Signaling in Pediatric Populations

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Introduction / Background

- Periodontal disease is a chronic inflammatory condition affecting the gingiva, periodontal ligament, and alveolar bone, driven by interactions between microbial biofilms and host immune responses.
- Begins as gingivitis (reversible inflammation) ➔ Progresses to periodontitis (irreversible bone and connective tissue loss)
- While traditionally considered a localized oral condition, periodontal disease is now recognized as part of a broader oral-systemic inflammatory axis.
- Type 1 Diabetes Mellitus (T1DM) known to increase susceptibility to periodontal inflammation and accelerate disease progression.

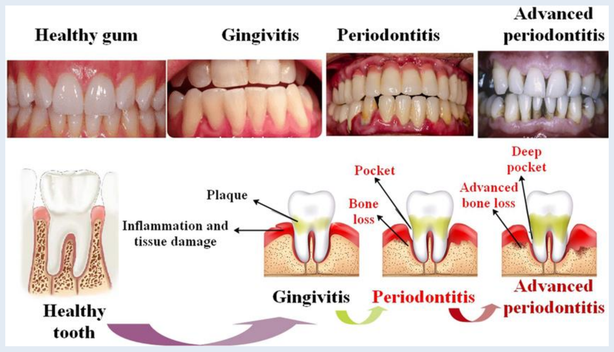

Figure 1. Clinical progression of periodontal disease from health to advanced periodontitis. This figure illustrates the sequential stages of periodontal disease progression, beginning with healthy gingival tissue, followed by gingivitis characterized by reversible inflammation, and advancing to periodontitis marked by connective tissue degradation, periodontal pocket formation, and alveolar bone loss. As disease severity increases, bacterial plaque accumulation and host inflammatory responses intensify, leading to irreversible structural damage to the tooth-supporting apparatus (Kiarashi, Mohammad, et al. 2024).

Why It Matters (Systemic Relevance)

- T1DM induces chronic hyperglycemia, resulting in: 1.) accumulation of AGEs (harmful compounds formed by sugar-protein bonds that accelerate tissue degradation and inflammation) & 2.) activation of the RAGE-NF-κB pathway (key pro-inflammatory signaling cascade causing alveolar bone loss, particularly in diabetic patients).

- A.) Signaling cascade promotes sustained production of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IL-17) ➔ B.) Immune dysregulation altering neutrophil function ➔ C.) Impaired bacterial clearance & Excessive inflammatory responses

- Bidirectional disease relationship formed between T1DM and periodontal inflammation

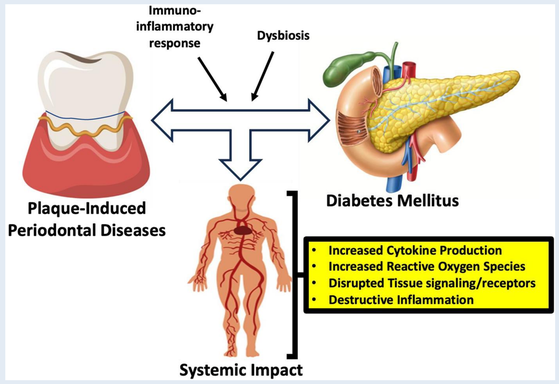

Figure 2. Bidirectional relationship between Type 1 Diabetes Mellitus and periodontal disease. This conceptual diagram illustrates the reciprocal interactions between systemic metabolic dysfunction and periodontal inflammation. Diabetes-associated hyperglycemia promotes increased cytokine production, oxidative stress, and immune dysregulation, which exacerbate periodontal tissue damage. In turn, periodontal inflammation contributes to systemic inflammatory burden, further impairing metabolic control and reinforcing disease progression (Khammissa, R. A. G., & Andriankaja, O. M. 2025).

Thesis / Research Focus

“Chronic systemic inflammation associated with Type 1 Diabetes Mellitus alters immune regulation within periodontal tissues by promoting neutrophil dysfunction and cytokine dysregulation, leading to impaired microbial clearance, sustained inflammation, and accelerated periodontal tissue destruction in pediatric populations.”

Methods / Analytical Approach

- Conducted as a structured literature review integrating clinical, experimental, and mechanistic studies.
- Relevant articles selected using keywords related to T1DM, periodontal disease, neutrophils, cytokines, pediatric patients, and the oral microbiome.
- Data extracted into a comparative evidence table including study design, sample type, immune markers, and key findings.

References	Type of Study	Methodology	Types of Samples & Immune Analysis	Results	Conclusions
Dakovic & Pavlovic, 2008	Cross-sectional case-control study	187 children and adolescents with T1DM (ages 6-18) were compared with 178 non-diabetic controls. Periodontal parameters measured included plaque index (PI), gingival index (GI), gingival bleeding index (GBI), probing depth (PD), and clinical attachment level (CAL).	Clinical periodontal examination Analysis of diabetes-related variables including HbA1c levels and disease duration	i.) Children with T1DM had significantly higher plaque accumulation, gingival inflammation, periodontal destruction, and more affected teeth compared to non-diabetic controls. ii.) Periodontal destruction was also correlated with higher HbA1c levels and longer duration of diabetes.	Periodontal disease is more prevalent and widespread within the pediatric population with T1DM, and its severity level increases with poor metabolic control and longer disease duration.
Salvi et al., 2010	Clinical experimental study	Patients with periodontitis, both with and without diabetes, were evaluated to determine differences in inflammatory mediator production within periodontal tissues. Periodontal examinations were conducted to assess disease severity, and gingival crevicular fluid samples were collected from periodontal pockets.	Gingival crevicular fluid (GCF) samples were collected from inflamed periodontal sites and analyzed using immunoassays (ELISA) to quantify pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α	i.) Diabetic patients demonstrated significantly higher levels of inflammatory cytokines within gingival crevicular fluid compared with non-diabetic individuals with periodontitis. ii.) Elevated cytokine levels were associated with increased periodontal inflammation and tissue destruction.	Hyperglycemia and metabolic dysregulation enhance inflammatory cytokine production in periodontal tissues, contributing to exaggerated inflammatory responses and increased periodontal tissue damage in diabetic patients.
Graves et al., 2011	Experimental animal study	Diabetic mouse models were used to investigate inflammatory responses and alveolar bone loss during experimentally induced periodontitis. Periodontal inflammation was induced using bacterial inoculation, and bone loss was assessed using histological and imaging techniques.	Gingival tissues were collected for molecular analysis of inflammatory cytokine expression, including IL-1β, TNF-α, and IL-6 Bone loss was evaluated using micro-computed tomography (micro-CT) and histological examination of periodontal tissues.	Diabetic mice exhibited significantly elevated inflammatory cytokine expression and greater alveolar bone loss compared with non-diabetic controls during experimental periodontitis.	Diabetes amplifies inflammatory signaling pathways within periodontal tissues, leading to increased osteoclast activity and accelerated periodontal tissue destruction.

Key Results

Neutrophil Dysfunction

- Impaired chemokine signaling (↓ CXCL1) delays neutrophil recruitment
- Reduced bacterial clearance allows for pathogen persistence
- Hyperactivated neutrophils release excessive cytokines and ROS
- Persistent inflammation leads to connective tissue damage and bone loss

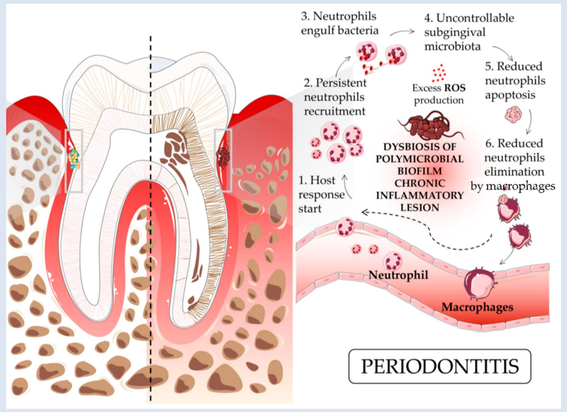

Figure 4. Progression of periodontal disease showing how persistent neutrophil activity, impaired immune regulation, and microbial dysbiosis lead to chronic inflammation, excessive reactive oxygen species (ROS) production, and tissue destruction in the gingiva (Bassani et al. 2023).

Cytokine Dysregulation

- A.) Elevated # of cytokines (IL-1β, IL-6, TNF-α, IL-17) ➔ B.) RANKL signaling triggered, a pathway that activates osteoclasts (bone-resorbing cells) ➔ C.) Increased bone breakdown around the teeth
- A.) RAGE-NF-κB pathway sustains chronic inflammation ➔ B.) Proper healing prevented

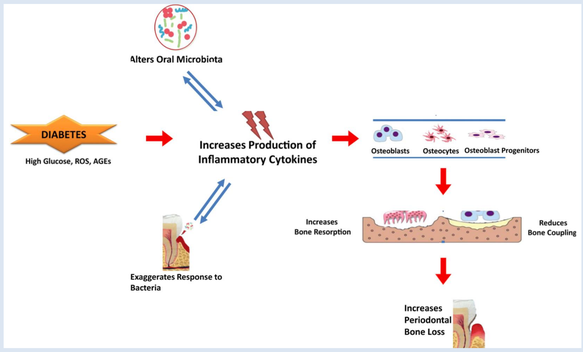

Figure 5. AGE-RAGE signaling and its role in impaired tissue repair and periodontal destruction. Illustratese how accumulation of advanced glycation end products (AGEs) in diabetic conditions activates RAGE signaling pathways, leading to sustained inflammatory responses and impaired tissue repair. The combined effects of microbial dysbiosis, exaggerated inflammation, and reduced regenerative capacity result in enhanced periodontal tissue breakdown and disease progression [Figure generated by Woo with BioRender].

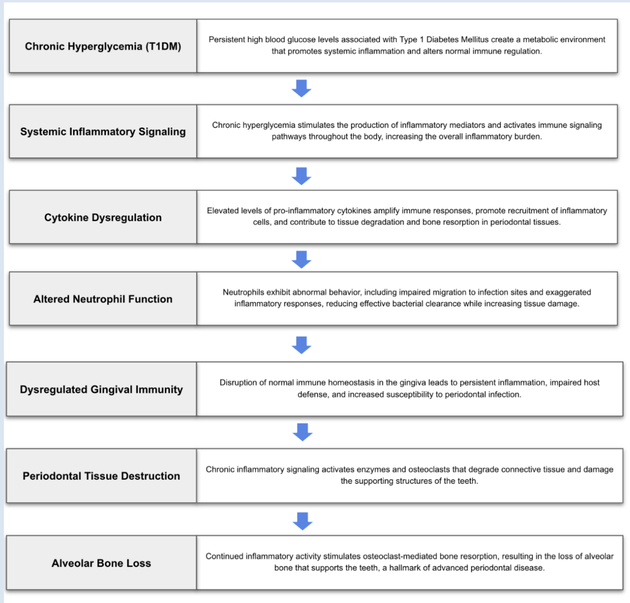

Figure 6. Integrated mechanistic model linking T1DM-associated hyperglycemia to periodontal disease progression through cytokine dysregulation, neutrophil dysfunction, and immune-mediated tissue destruction [Figure generated by Woo with BioRender].

Conclusion

“T1DM promotes periodontal disease through interconnected mechanisms, including systemic inflammation, cytokine dysregulation, neutrophil dysfunction, and microbial imbalance. Together, these processes create a self-sustaining inflammatory environment that drives tissue destruction and bone loss, highlighting that periodontal disease is a result of systemic immune dysregulation rather than a purely localized condition.”

Next Steps

- Conduct longitudinal clinical studies to track disease progression
- Explore targeted treatments aimed at immune regulation rather than bacterial control alone
- Medical + Dental care approach