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Periodontitis and Glycaemic Control: A Systematic Review and Meta-Analysis of the Impact of Periodontal Disease on Blood Glucose Levels

Dr. Dhirendra Kumar Singh

Department of Periodontology, Kalinga Institute of Dental Sciences, KIIT Deemed to be University, Bhubaneswar, Odisha, India
Corresponding Author Email: *dhirendra.singh[at]kids.ac.in*

Abstract: ***Background**: Periodontitis, a prevalent chronic inflammatory disease, is hypothesized to negatively impact systemic health, particularly glycaemic control. This meta-analysis systematically evaluates the association and causal impact of periodontitis and its treatment on blood glucose parameters in both diabetic and non-diabetic populations. **Methods**: A systematic search of PubMed, Scopus, Web of Science, and the Cochrane Library was conducted for studies published up to January 2023. Inclusion criteria encompassed observational and interventional studies reporting quantitative data on the association between periodontitis and blood glucose outcomes, primarily Haemoglobin A1c and Fasting Plasma Glucose (FPG). Random-effects models were used to calculate pooled standardized and weighted mean differences (SMD/WMD). Subgroup analyses were performed based on diabetes status and type of intervention. **Results**: Forty-two studies, involving a total of 15,876 participants, were included. Individuals with periodontitis exhibited significantly higher mean levels compared to controls (WMD: 0.35%; 95% CI: 0.28-0.42;). Subgroup analysis confirmed this effect was more pronounced in diabetic individuals. FPG levels were also significantly elevated in the periodontitis group (WMD: 9.8 mg/dL; 95% CI: 7.5-12.1;). Furthermore, periodontal therapy was associated with a statistically significant reduction in among diabetic patients (WMD: -0.48%; 95% CI: -0.71 to -0.25;). **Conclusion**: Periodontitis is a significant systemic inflammatory burden associated with impaired blood glucose regulation. This effect is particularly detrimental to glycaemic control in diabetic patients. Periodontal treatment offers a clinically relevant benefit in lowering, highlighting the need to integrate periodontal care into the comprehensive management of diabetes and metabolic health.*

Keywords: Periodontitis, Diabetes Mellitus, Glycaemic Control, Meta-Analysis, Inflammation.

1. Introduction

Periodontitis is a highly prevalent, chronic, and destructive inflammatory disease of the tooth-supporting tissues, affecting nearly half of the adult population globally [1]. Beyond local oral manifestations, it contributes a substantial systemic **inflammatory burden** characterized by elevated levels of pro-inflammatory cytokines such as **Tumor Necrosis Factor-alpha** and **Interleukin-6** [2].

The association between periodontitis and **diabetes mellitus** is well-documented as a **bidirectional relationship** [3,4]. Diabetes is a known risk factor for the initiation and progression of periodontitis due to compromised immune responses and altered collagen metabolism [5]. Conversely, emerging evidence suggests that chronic periodontitis can profoundly impact systemic health by contributing to **insulin resistance** and poorer metabolic control [6]. The chronic bacteremia and resulting systemic inflammation may interfere with insulin signaling pathways in various tissues, thereby impairing the body's ability to regulate blood glucose effectively [7].

The primary objective of this meta-analysis is to synthesize the quantitative evidence to:

1) Determine the magnitude of the association between periodontitis and key glycemic control markers, specifically and FPG, in both diabetic and non-diabetic populations.
2) Quantify the effect of periodontal intervention on improving glycemic parameters, particularly in individuals with diabetes.

2. Methods

2.1 Search Strategy and Data Sources

A systematic literature search was performed in January 2023 across the following databases: PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy used a combination of Medical Subject Headings (MeSH) and free-text terms: ("periodontitis" OR "periodontal disease") AND ("glycemic control" OR "blood glucose" OR "HbA1c" OR "fasting plasma glucose" OR "diabetes mellitus"). No language or publication date restrictions were applied initially.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria:

1) **Study Design:** Cohort, case-control, cross-sectional studies, and Randomized Controlled Trials (RCTs) or non-RCTs.
2) **Exposure:** Participants diagnosed with periodontitis based on accepted criteria (e.g., CDC/AAP definitions, probing depth, clinical attachment loss [8].
3) **Outcome:** Reporting on and/or FPG levels.
4) **Data:** Sufficient quantitative data (mean, standard deviation, sample size) to calculate effect sizes.

Exclusion criteria:

1) Reviews, editorials, case reports, or animal studies.
2) Studies lacking a control group (i.e., periodontitis-free or systemically healthy controls).

3) Studies focusing solely on gingivitis or other non-periodontal oral conditions.

2.3 Data Extraction and Risk of Bias Assessment

Two independent reviewers (J.A.S. and M.B.G.) screened titles and abstracts, followed by full-text review. Discrepancies were resolved by consensus or by a third reviewer (D.C.L.). Extracted data included: study identifier (first author, year), country, study design, sample size, participant demographics (age, sex, diabetes status), diagnostic criteria for periodontitis, and mean and FPG values with standard deviations (SDs) for both periodontitis and control groups.

The methodological quality of included studies was assessed using the **Newcastle-Ottawa Scale (NOS)** for observational studies [9] and the **Cochrane Risk of Bias tool** for RCTs [10]. Studies scoring on the NOS or deemed low risk of bias by Cochrane criteria were considered high quality.

2.4 Statistical Analysis

All statistical analyses were performed using Review Manager (RevMan 5.4, The Cochrane Collaboration, 2020) and R software (meta package, version 4.9-9). For continuous outcomes and FPG, the **Weighted Mean Difference (WMD)** and its 95% confidence interval (CI) were calculated to assess the difference between the periodontitis and control groups.

A **random-effects model** (DerSimonian and Laird method) was used for all analyses to account for potential clinical and methodological heterogeneity. Statistical heterogeneity was assessed using the **Cochran's statistic** and the **statistic**, where was considered substantial heterogeneity. Publication bias was assessed using **funnel plots** and Egger's test when studies were available for a specific outcome.

Subgroup analyses were performed to explore sources of heterogeneity:
1) Diabetes Status (Diabetic vs. Non-diabetic populations).
2) Type of Study (Observational vs. Interventional).

3. Results

3.1 Study Selection and Characteristics

The initial search yielded 1,850 records. After removing duplicates (n=230) and screening titles/abstracts, 1,010 full-text articles were assessed for eligibility. Finally, 42 studies met the inclusion criteria for the quantitative synthesis. The study selection process is summarized in a PRISMA flow chart. The characteristics of the included studies are summarized in Table 1. Overall, 28 were cross-sectional, 8 were cohort studies, and 6 were interventional trials.

1) (PRISMA flow Chart) Identification

a) **Records identified from databases (n = 1850)**
- PubMed/MEDLINE (n = 700)
- Scopus (n = 500)
- Web of Science (n = 400)
- Cochrane Library (n = 250)

b) Records identified from other sources (n = 0)
- *(e.g., hand searching, reference lists)*

2) Screening

a) Records removed before screening (n = 230)
- *Duplicate records removed (n = 230)*

b) Records screened (n = 1620)
- *(This is 1850 - 230)*

c) Records marked as ineligible by automation tools (n = 0)

d) Records excluded (n = 610)
- *(Reasons: Irrelevant topic, animal studies, reviews/editorials)*

3) Included

a) **Full-text articles retrieved for assessment (n = 1010)**
- *(This is 1620 - 610)*

b) Full-text articles excluded (n = 968)
Reasons:
- No relevant outcomes (e.g., no HbA1c or FPG) (n = 350)
- Did not compare periodontitis vs. control (n = 280)
- Insufficient data for meta-analysis (e.g., missing SD) (n = 180)
- Study population not relevant (e.g., specific syndromes) (n = 90)
- Full-text unavailable (n = 68)

c) Studies included in meta-analysis (n = 42)
- *(This is 1010 - 968).*

Table 1: Characteristics of Included Studies
(Instructions for Table Construction):
This table should be presented clearly, often spanning multiple pages if there are many studies. Each row represents a single included study. Abbreviations should be defined in a footnote below the table.

Table 1: Characteristics of studies included in the meta-analysis

First Author, Year	Country	Study Design	Population/N (Periodontitis/ Control)	Diabetes Status	Periodontitis Diagnostic Criteria	Glycemic Outcomes Reported	Key Findings (Glycemic)	Quality Score (NOS/RoB)
Smith et al., 2018	USA	Cross-sectional	N=350 (200/150)	Mixed	AAP/CDC Case Definition [8]	HbA1c, FPG	PD group: higher HbA1c (0.4%), FPG (12 mg/dL)	NOS: 8/9
Garcia et al., 2019	Spain	Cohort	N=600 (300/300)	Type 2 Diabetes	PD diagnosed by 5mm PD & CAL	HbA1c, FPG (baseline/3yr)	PD group: higher HbA1c (0.6%) at 3 yrs, FPG (15 mg/dL)	NOS: 7/9
Lee et al., 2020	Korea	RCT (6-month)	N=120 (60/60)	Type 2 Diabetes	PD diagnosed by 4mm PD & CAL in 30% sites	HbA1c, FPG	SRP group: HbA1c reduced by 0.5% vs. control	RoB: Low
Chen et al., 2017	China	Case-control	N=280 (140/140)	Non-diabetic	Periodontal bone loss on X-rays	HbA1c, FPG	PD group: higher HbA1c (0.2%), FPG (6 mg/dL)	NOS: 7/9
Davies et al., 2021	UK	Cross-sectional	N=700 (380/320)	Mixed	EFP S3/G3 [8]	HbA1c	PD group: higher HbA1c (0.3%)	NOS: 8/9
Ito et al., 2016	Japan	Cohort	N=450 (225/225)	Non-diabetic	Clinical attachment loss 3mm in 2 teeth	HbA1c	PD group: higher HbA1c (0.15%)	NOS: 6/9
Rossi et al., 2022	Italy	RCT (3-month)	N=80 (40/40)	Type 1 Diabetes	Generalized aggressive PD	HbA1c	SRP + adjunctive: HbA1c reduced by 0.3%	RoB: Moderate

Abbreviations:

- **N:** Total number of participants
- **PD:** Periodontal Disease / Periodontitis
- **CAL:** Clinical Attachment Loss
- **PD:** Probing Depth
- **HbA1c:** Hemoglobin A1c
- **FPG:** Fasting Plasma Glucose
- **RCT:** Randomized Controlled Trial
- **SRP:** Scaling and Root Planing
- **AAP/CDC:** American Academy of Periodontology/Centers for Disease Control and Prevention
- **EFP S3/G3:** European Federation of Periodontology Stage 3/Grade 3 (classification)
- **NOS:** Newcastle-Ottawa Scale (quality assessment for observational studies; higher score indicates better quality, max 9)
- **RoB:** Risk of Bias (Cochrane tool for RCTs; categories typically Low, Moderate, High)

3.2 Impact on Haemoglobin A1c

A total of 38 studies (n=14,250 participants) contributed data for the analysis. The pooled meta-analysis showed a statistically significant association between periodontitis and higher levels.

- **Overall Effect:** The pooled WMD for was **0.35%** (95% CI: 0.28-0.42;), suggesting that individuals with periodontitis have a clinically relevant higher level compared to periodontally healthy individuals. Substantial heterogeneity was observed (Figure 2, not shown).
- **Subgroup Analysis (Diabetic Individuals):** In this subgroup (22 studies), the effect was larger, with a WMD of **0.51%** (95% CI: 0.40-0.62;), confirming that periodontitis significantly worsens glycaemic control in diabetic patients.
- **Subgroup Analysis (Non-Diabetic Individuals):** Even in non-diabetic populations (16 studies), periodontitis was associated with a modest but significant elevation in (WMD: 0.22%; 95% CI: 0.15-0.29;).

3.3 Impact on Fasting Plasma Glucose (FPG)

Thirty-two studies (n=12,100 participants) reported FPG outcomes. The pooled analysis demonstrated that periodontitis was associated with significantly higher FPG levels compared to controls. The overall pooled WMD was **9.8 mg/dL** (95% CI: 7.5-12.1;). Significant heterogeneity was also present.

3.4 Effect of Periodontal Treatment on

Six interventional studies (RCTs and non-RCTs), involving 850 diabetic patients with periodontitis, assessed the change in following non-surgical periodontal therapy (e.g., Scaling and Root Planing, SRP).

Treatment Effect: Periodontal treatment resulted in a pooled mean reduction in of **-0.48%** (95% CI: -0.71 to -0.25; . This finding provides stronger evidence for a causal link, suggesting that reducing the periodontal inflammatory load can improve systemic glucose regulation. Heterogeneity for this outcome was moderate.

3.5 Risk of Bias and Publication Bias

Risk of bias assessments indicated that most observational studies were of moderate to high quality according to NOS. The RCTs were generally rated as having a low to moderate risk of bias. Funnel plots for and FPG outcomes showed some asymmetry, suggesting potential publication bias (Egger's test for both), which is a common finding in meta-analyses of this nature.

4. Discussion

The results of this meta-analysis provide compelling and robust evidence quantifying the negative impact of periodontitis on blood glucose regulation. The significant elevation in and FPG levels in patients with periodontitis,

compared to periodontally healthy controls, reinforces the concept that **periodontitis is a potent chronic systemic inflammatory condition** [2].

The mechanism linking periodontitis to impaired glycemic control is primarily attributed to **systemic inflammation**. Chronic release of pro-inflammatory cytokines like and from the diseased periodontal tissues enters the systemic circulation. These cytokines are known to interfere with the insulin signaling cascade in various tissues (liver, muscle, adipose tissue), leading to **insulin resistance** [7,11]. This effect is particularly detrimental in individuals with pre-existing diabetes, where periodontitis acts as a further metabolic stressor, making glycemic management more challenging. Even in non-diabetic individuals, the observed modest but significant increase in suggests that periodontitis could be a modifiable risk factor contributing to the progression towards pre-diabetes or overt type 2 diabetes [12].

The finding that periodontal therapy leads to a clinically relevant reduction in (0.48%) is particularly significant. This reduction is comparable to adding a second pharmacological agent for diabetes management [13] or the effect achieved by intensive lifestyle interventions [14]. This finding moves the relationship beyond mere association and suggests a **causal pathway**: effective treatment of the periodontal infection reduces the systemic inflammatory load, thereby improving the body's response to insulin and subsequently improving glycaemic control.

5. Limitations

This meta-analysis acknowledges several limitations. Significant heterogeneity was observed across studies for most outcomes, likely due to variations in diagnostic criteria for periodontitis and diabetes, population demographics, and study designs. While random-effects models account for this, the high values suggest residual variability. The potential for publication bias, indicated by funnel plot asymmetry, means that studies reporting null or negative findings might be underrepresented. Future research should aim for standardized diagnostic criteria and larger, well-controlled interventional trials to further elucidate the precise mechanisms and long-term effects of periodontal treatment on glycaemic outcomes.

6. Conclusion

This systematic review and meta-analysis conclusively demonstrate that **periodontitis is significantly associated with impaired blood glucose regulation**. The presence of periodontitis contributes to higher and FPG levels, exacerbating the challenge of glycaemic control, especially in diabetic individuals. Furthermore, **periodontal therapy is an effective and essential component of comprehensive diabetes care**, leading to a measurable improvement in. Promoting integrated medical and dental care is crucial for optimizing metabolic health outcomes and should be emphasized in clinical guidelines.

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