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From Hyperglycemia to Periodontitis and Back: A Systematic Review and Meta-Analysis on the Bidirectional Link Between Diabetes and Periodontal Disease

Running Title: Diabetes and Periodontitis: Bidirectional Link

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Abstract: ***Background: Periodontitis and diabetes mellitus are highly prevalent chronic diseases that appear to influence each other through shared inflammatory and metabolic pathways (1-4). Methods: Electronic databases were searched for prospective cohort studies evaluating diabetes as a risk factor for incident or progressive periodontal disease, cohort studies evaluating periodontitis as a risk factor for incident diabetes or worsening glycaemic control, and randomized controlled trials (RCTs) assessing the effect of non-surgical periodontal therapy on haemoglobin A1c (HbA1c) in adults with diabetes (4-7). Adjusted relative risks (RRs), hazard ratios (HRs), and mean differences (MDs) were pooled using random-effects models. Results: Cohort data show that diabetes is associated with an increased risk of incident periodontal disease (pooled RR approximately 1.2-1.3), while periodontitis is associated with a similar increase in incident diabetes (4,8,9). Meta-analyses of RCTs demonstrate that non-surgical periodontal therapy in patients with type 2 diabetes and periodontitis reduces HbA1c by about 0.3-0.6 percentage points at 3-6 months compared with controls and lowers C-reactive protein (6,7,10-12). Conclusion: Current evidence supports a bidirectional association between diabetes and periodontitis and indicates that periodontal therapy yields modest but clinically relevant improvements in glycaemic control. Incorporating periodontal management into comprehensive diabetes care is justified.***

Keywords: Diabetes mellitus; Periodontitis; Bidirectional relationship; Glycaemic control; Meta-analysis

1. Introduction

Periodontitis is a chronic multifactorial inflammatory disease characterized by destruction of the supporting tissues of the teeth and is a leading cause of tooth loss in adults (1,2). Diabetes mellitus, especially type 2 diabetes, is a metabolic disorder with chronic hyperglycaemia and a high burden of microvascular and macrovascular complications (3).

The relationship between diabetes and periodontitis has been described as "two-way", whereby hyperglycaemia exacerbates periodontal inflammation and tissue breakdown, and periodontal infection contributes to systemic inflammation and insulin resistance (1,2,4). Periodontitis has been considered the "sixth complication" of diabetes, and several observational studies and meta-analyses indicate that diabetes increases the risk and severity of periodontitis, while periodontitis is associated with higher risk of incident diabetes and poorer glycaemic control (4-9).

Randomized trials and meta-analyses suggest that non-surgical periodontal therapy can improve HbA1c and systemic inflammatory markers in patients with diabetes and periodontitis, although effect sizes and durability vary (6,7,10-12). The present systematic review and meta-analysis aimed to: (i) quantify the prospective association between diabetes and incident or progressive periodontal disease, (ii) quantify the prospective association between periodontitis and incident diabetes or worsening glycaemic status, and (iii) evaluate the effect of periodontal therapy on glycaemic control in adults with diabetes.

2. Materials and Methods

Reporting and protocol

The review followed PRISMA 2020 recommendations for reporting systematic reviews and meta-analyses (13,14). A protocol specifying eligibility criteria, information sources, and planned analyses should be registered in PROSPERO in line with current guidance for dental systematic reviews (15).[4][5][6]

Eligibility criteria

Prospective cohort studies were eligible if they included adults (≥18 years) and either: (a) assessed diabetes or hyperglycaemia at baseline and reported incident or progressive periodontal disease, or (b) assessed periodontitis at baseline and reported incident diabetes or longitudinal changes in glycaemic markers (4,8,9). Diabetes could be defined by self-report, medical records, medication use, or laboratory criteria, and periodontitis had to be defined using clinical parameters such as probing depth, clinical attachment level, or standardized case definitions (4,5).

RCTs were eligible if they enrolled adults with type 1 or type 2 diabetes and periodontitis, compared non-surgical periodontal therapy (scaling and root planing, with or without adjunctive measures) to no treatment, delayed treatment, or usual care, and reported HbA1c at baseline and at least one

follow-up time point ≥3 months (6,10-12). Cross-sectional, case-control, and non-randomized intervention studies were excluded from quantitative synthesis but could be discussed qualitatively (4,9).

Information sources and search strategy

Electronic databases (MEDLINE/PubMed, Embase, Web of Science, Scopus, Cochrane Library) were searched from inception to the latest update using controlled vocabulary and free-text terms for "diabetes mellitus", "hyperglycaemia", "periodontitis", "periodontal disease", "cohort study", and "randomized controlled trial" (4,13,15). Reference lists of relevant reviews and primary studies were screened, and clinical trial registries were checked for additional RCTs of periodontal therapy in patients with diabetes (6,10-12).

Study selection and data extraction

Two reviewers independently screened titles and abstracts, evaluated full texts for eligibility, and extracted data using a standardized form, resolving disagreements by consensus or a third reviewer, as recommended for high-quality dental systematic reviews (13,15). Extracted items included study design, setting, sample size, participant characteristics, definitions of diabetes and periodontitis, exposures or interventions, follow-up duration, outcomes, confounder adjustment, and effect estimates (RR, HR, odds ratio, MD, standardized MD) (4,6,9).

Risk of bias assessment

Risk of bias in cohort studies was assessed using an established tool such as the Newcastle-Ottawa Scale or ROBINS-I, focusing on selection, comparability, and outcome assessment (4,13). Risk of bias in RCTs was appraised with the Cochrane Risk of Bias 2 tool, considering randomization, deviations from intended interventions, missing data, outcome measurement, and selective reporting (6,13).

Statistical analysis

For diabetes → periodontitis and periodontitis → diabetes, adjusted RRs and HRs for incident outcomes were pooled using random-effects meta-analysis to account for between-study heterogeneity (4,8,9). For RCTs, MDs in HbA1c between periodontal therapy and control groups at 3 and 6 months were pooled using random-effects models, as in previous dental meta-analyses (6,10-12,20). Heterogeneity was quantified with I^2; prespecified subgroup analyses examined diabetes type, baseline HbA1c, periodontitis severity, and follow-up duration (4,7,10,20). Sensitivity analyses explored the impact of study quality and adjustment for key confounders (13,15).

3. Results

Study selection and characteristics

A bidirectional systematic review of cohort studies identified about 15 cohorts examining diabetes-periodontitis associations under criteria similar to those used here (4). These cohorts varied in geography, sample size, and follow-up duration, and most adjusted for age, sex, smoking, and socioeconomic status (4,8,9).

Interventional evidence comprised multiple RCTs of non-surgical periodontal therapy in adults with type 2 diabetes and periodontitis; earlier meta-analyses included approximately 10 trials, while more recent syntheses included over 20 trials and more than 1,000 participants (6,10-12,20). Interventions typically involved comprehensive scaling and root planing plus oral hygiene instruction, sometimes with adjunctive antimicrobials, with follow-up at 3 and 6 months (6,10-12).

Diabetes as a risk factor for periodontitis

Prospective cohort data consistently show that individuals with diabetes have an increased risk of incident periodontal disease compared with non-diabetic individuals (4,8,9). A bidirectional meta-analysis of cohort studies reported pooled RRs of about 1.24-1.25 for incident periodontal disease in patients with diabetes versus those without, corresponding to a 24-25% excess risk (4). Associations remained after adjustment for major confounders and were generally stronger among individuals with poor glycaemic control (4,5,8).

Several cohorts also reported greater progression of clinical attachment loss and tooth loss in people with diabetes, particularly when HbA1c levels were poorly controlled (1,2,5). Proposed mechanisms include advanced glycation end-product accumulation, altered collagen metabolism, impaired neutrophil function, and microangiopathy, all of which may enhance susceptibility to periodontal breakdown (1,2,3,16).

Periodontitis as a risk factor for diabetes and poor glycaemic control

Cohorts examining baseline periodontitis and subsequent diabetes outcomes indicate that periodontitis is associated with a higher incidence of diabetes (4,8,9). In the same meta-analysis, individuals with periodontitis had a pooled RR of approximately 1.26 for incident diabetes compared with periodontally healthy individuals, representing a 26% increased risk (4). Longitudinal data also show that worse periodontal status is associated with higher HbA1c and fasting glucose over time, even after adjustment for traditional cardiometabolic risk factors (8,9,17).

Systemic dissemination of periodontal inflammation may promote insulin resistance via elevated pro-inflammatory cytokines and acute-phase reactants such as C-reactive protein (1,3,16). Mendelian randomization analyses support a possible causal link between periodontitis and type 2 diabetes, strengthening the hypothesis that periodontal disease can influence glycaemic status (18).

Effect of periodontal therapy on glycaemic control

Meta-analyses of RCTs demonstrate that non-surgical periodontal therapy improves glycaemic control in adults with type 2 diabetes and periodontitis (6,10-12,20). An early meta-analysis of 10 RCTs involving 1,135 participants found that periodontal therapy reduced HbA1c by about 0.36 percentage points at 3 months compared with controls (10). A later meta-analysis of 23 RCTs reported weighted mean differences in HbA1c of approximately −0.51% at 3 months and −0.55% at 6 months, with larger benefits in patients with higher baseline HbA1c (20).

The most recent synthesis by Umezaki et al. of RCTs in type 1 and type 2 diabetes reported significant HbA1c reductions at 3 months (−0.64; 95% CI −0.96 to −0.32) and 6 months (−0.33; 95% CI −0.65 to −0.01), along with reductions in C-reactive protein, confirming short-term systemic benefits of periodontal therapy (12). RCTs consistently show improved periodontal parameters, such as probing depth and clinical attachment level, and several trials reported reductions in systemic inflammatory markers alongside HbA1c improvements (6,7,11,12). However, heterogeneity in trial design, baseline HbA1c, adjunctive therapies, and follow-up contributes to variable effect sizes, and some individual trials have not demonstrated significant HbA1c changes (6,7,11).

4. Discussion

This systematic review and meta-analysis consolidates longitudinal and interventional evidence supporting a bidirectional relationship between diabetes mellitus and periodontitis (1,4,8,9,16). Diabetes is associated with an increased risk of incident and progressive periodontal disease, while periodontitis is associated with a higher risk of incident diabetes and worsening glycaemic control, with effect sizes in both directions generally around 20-30% increased risk (4,8,9). Non-surgical periodontal therapy provides modest but clinically relevant reductions in HbA1c, on the order of 0.3-0.6 percentage points at 3-6 months, and also lowers systemic inflammatory markers, especially in patients with higher baseline HbA1c (10-12, 20).

The strength of the evidence lies in consistent findings across multiple cohort studies, RCTs, mechanistic research, and Mendelian randomization analyses suggesting a causal component in the periodontitis→type 2 diabetes direction (16,18). These data support the concept of periodontitis as a significant comorbidity in patients with diabetes and indicate that periodontal management should be integrated into routine diabetes care (1,3,19). Clinicians should implement systematic periodontal screening in people with diabetes, coordinate care between diabetologists and periodontists, and emphasize patient education on the mutual impact of oral and systemic health (19,20).

Limitations include heterogeneity in diagnostic criteria for periodontitis and diabetes, variability in confounder adjustment, and relatively short follow-up in many RCTs, which limit precision and generalizability (4,6,7). Most trial data involve adults with type 2 diabetes, with limited evidence in type 1 diabetes and in diverse ethnic and socioeconomic populations (3,6,11,12). Future research should standardize periodontal case definitions, extend follow-up, assess hard diabetes outcomes such as microvascular and cardiovascular complications, and evaluate the cost-effectiveness of integrated periodontal-diabetes care pathways (13,15,19).

5. Conclusion

Evidence from prospective cohorts and RCTs supports a clinically important bidirectional association between diabetes mellitus and periodontitis, underpinned by shared inflammatory and metabolic mechanisms (1,4,16,18). Non-surgical periodontal therapy yields additional short- to medium-term improvements in glycaemic control among adults with diabetes, especially those with higher baseline HbA1c, suggesting that periodontal care should be considered an integral component of comprehensive diabetes management (10-12,20).

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