Concise Review

Diabetic Retinopathy and Periodontitis: Implications from a Systematic Review and Meta-Analysis

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ABSTRACT

Background: Diabetes mellitus, a chronic metabolic disorder affecting millions worldwide, is associated with microvascular complications, including diabetic retinopathy (DR) and periodontitis. Understanding their interrelationship is crucial for comprehensive patient care.
Objective: This systematic review and meta-analysis aim to investigate the association between DR and periodontitis in patients with Type 1 and Type 2 diabetes.
Methodology: Using the PECO framework, we searched PubMed/MEDLINE, Scopus, EMBASE, Google Scholar, and Web of Science databases (Inception to April 2023) for studies on the association between DR and periodontitis. Ten studies (n = 1828 participants), including observational and cross-sectional studies, met the inclusion criteria. We conducted qualitative synthesis, risk of bias analysis using the ROBINS-E tool, Grading of Recommendations, Assessment, Development, and Evaluations assessment (GRADE), and random-effects meta-analysis.
Results: Eight studies found a significant association between severe periodontitis (pocket depth ≥5 mm) and DR, while two found no association. Meta-analysis of 843 participants showed diabetics with periodontitis had 4.48 times higher odds (95% confidence interval: 1.67-12.07, P = .003) of developing retinopathy compared to diabetics without periodontitis. High heterogeneity was observed (I^2 = 86%). Subgroup analysis by diabetes type showed no significant difference. The overall GRADE level of evidence was very low.
Conclusion: While most included studies suggest an association between severe periodontitis and increased DR risk, the overall certainty of evidence is low. These findings highlight the potential importance of periodontal health in diabetic patients. High-quality longitudinal studies with adequate control of confounders are required to determine if periodontitis contributes to the progression of DR or if the conditions are merely coincidentally related.

Introduction

Diabetes mellitus (DM) represents a significant global health challenge with far-reaching implications for systemic health. The worldwide prevalence of DM was estimated at 9.3% (463 million people) in 2019, with projections indicating a rise

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to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045.[1,2] This escalating prevalence underscores the importance of understanding and managing diabetes-related complications.

DM exerts a significant influence on oral health. It markedly elevates the risk of periodontal disease (PD) and results in severe periodontal complications if not meticulously managed.[3] PD, a chronic inflammatory condition affecting the tissues surrounding the teeth, has been recognized as both a complication and a potential risk factor for DM.[4,5] The relationship between PD and DM is bidirectional, with PD representing a persistent source of inflammatory mediators that may interfere with various organ systems.[6] These mediators can contribute to insulin resistance and increase the risk of diabetes-related complications.[7,8] Furthermore, hyperglycaemia, a hallmark of diabetes, can induce xerostomia, thereby increasing susceptibility to dental caries and oral infections. Diabetes also impairs wound healing, complicating oral surgical procedures and prolonging postoperative recovery periods.[9] Effective glycaemic control is imperative to mitigate these oral health challenges and to maintain optimal dental health in individuals with diabetes.

One of the most serious microvascular complications of DM is diabetic retinopathy (DR), a condition that poses a significant threat to vision. DR is classified into four stages based on the severity of vascular lesions: mild, moderate, severe, and proliferative DR.[10] Recent studies have reported that approximately 13.5% of diabetic patients develop DR, with nearly 10% of patients experiencing visual impairment within 15 years of Type 2 DM diagnosis.[11,12]

The pathogenesis of DR is complex, involving vascular disruption, oxidative stress, and inflammation.[13] Diabetic macular oedema (DME), a related condition, can occur concurrently with DR, resulting in increased retinal capillary permeability and blood-retinal barrier disruption.[14] While the incidence of DR and DME varies across populations, it is estimated that approximately one-third of individuals with diabetes will develop DR, and among those, about one-third will manifest signs of DME.[15] Emerging evidence suggests that inflammatory pathways play a crucial role in the aetiology of DR,[16] with studies demonstrating a correlation between systemic inflammatory markers and diabetic ocular complications.[17] This inflammatory link opens new avenues for exploring potential risk factors and comorbidities associated with DR.

While the pathogenesis of DR is well-documented, the variability in its occurrence among diabetic patients remains intriguing. Genetic factors alone failed to fully explain this discrepancy,[16] prompting researchers to explore other contributing factors. The systemic inflammation associated with conditions like PD has emerged as a possible link to ocular complications in diabetic patients.

Despite numerous epidemiological studies exploring the correlation between periodontitis and DR, there remains a significant gap in our understanding of this relationship.[18-20] Many existing studies have focused on either Type 1 or Type 2 diabetes exclusively, limiting our understanding of how this association might differ across diabetes types. There is a lack of comprehensive meta-analyses that synthesize data from studies examining the incidence of DR in diabetic patients with and without periodontitis. Furthermore, multiple studies have not systematically reviewed the potential confounding factors and mechanisms underlying this association. Importantly, the clinical implications of this association for patient care and screening practices remain unclear. These knowledge gaps highlight the need for more comprehensive research that addresses the relationship between periodontitis and DR across both types of diabetes, synthesizes existing data, explores underlying mechanisms, and examines the potential impact on clinical practice.

This systematic review and meta-analysis aim to address these gaps by synthesizing data from studies on both Type 1 and Type 2 diabetes, quantifying the strength of the association between periodontitis and DR, and exploring potential mechanisms and clinical implications. By doing so, we seek a more comprehensive understanding of this relationship and its relevance to clinical practice. The primary objective of this review is to determine if a significant correlation exists between PD and DR in diabetic patients. We aim to inform healthcare professionals and guide future research efforts by analysing the available evidence. Ultimately, this work seeks to enhance healthcare delivery for diabetic patients by elucidating potential risk factors and comorbidities associated with DR, potentially leading to improved preventive strategies and treatment approaches.

Methodology

Protocol and registration

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21] The protocol was registered with PROSPERO (CRD42023456276) before commencement.

Research question and eligibility criteria

The PECO framework was used to formulate the research question: 'In diabetic patients (P) with periodontitis (E), compared to healthy adults (C), is there an association between periodontitis and diabetic retinopathy (O)?'

The PECO framework was chosen for this systematic review for its suitability for observational healthcare studies. PECO stands for:

P (Population): Patients with DM
E (Exposure): Presence of periodontitis
C (Comparison): Absence of periodontitis
O (Outcome): Occurrence of DR

This framework was selected for several reasons: It allows for a clear and structured approach to formulating our research question, crucial in observational studies where interventions are not being assessed. PECO is particularly well-suited for studies investigating associations between exposures (in this case, periodontitis) and outcomes (DR), which aligns perfectly with our research aims. It facilitates the development of a comprehensive search strategy by clearly defining the key components of our research question.

The PECO framework aids in establishing explicit inclusion and exclusion criteria, ensuring consistency in study selection. It provides a logical data extraction and synthesis structure, allowing for more systematic comparison across studies. Using the PECO framework, we aim to enhance our systematic review's methodological rigour and transparency, ultimately leading to more reliable and clinically relevant findings.

Inclusion criteria:

1. Observational studies in diabetic patients with and without periodontitis reporting DR
2. Patients above 30 years of age
3. Diabetes reported based on HbA1c
4. Retinopathy assessment through ophthalmological examination
5. Studies published in English from inception to April 2023

Exclusion criteria:

1. Smokers
2. Comorbidities other than DM
3. Diabetic complications other than ocular ones
4. Studies evaluating gingivitis only
5. Case reports, animal studies, reviews, editorials, and consensus papers

Information sources and search strategy

Five databases (PubMed/MEDLINE, Scopus, EMBASE, Google Scholar, and Web of Science) were searched from inception to April 2023. The search strategy was developed using MeSH terms and keywords related to DM, DR, and periodontitis. Boolean operators were used to combine terms. A manual search of reference lists was also conducted.

Study selection

Two calibrated reviewers (BJ and SA) independently screened titles, abstracts, and full texts. Disagreements were resolved by consensus with a third reviewer (VS). The interexaminer Kappa coefficient was 0.9 for data extraction questions.

Data extraction

Two reviewers (BJ and SA) independently extracted data using a preformatted Excel sheet. Extracted information included author details, study design, sample characteristics, diagnostic criteria for diabetes and periodontitis, retinopathy assessment, statistical analyses, and key findings.

Addressing confounding factors

To enhance the validity of our findings, we carefully considered potential confounding factors throughout the study selection and data extraction processes:

Study selection: We prioritized studies that adjusted for known confounders in their analyses. Studies were assessed to consider key confounding variables such as age, gender, duration of diabetes, glycaemic control (HbA1c levels), hypertension, and smoking status. The quality of confounder adjustment was evaluated as part of the risk of bias assessment using the ROBINS-E tool.

Data extraction: We extracted information on all confounding factors considered in each study. For each included study, we documented which confounders were measured and how they were controlled for in the analysis (eg, stratification, multivariate analysis, propensity score matching). When available, we extracted both unadjusted and adjusted effect estimates to assess the impact of confounder control.

Analysis and interpretation: In our meta-analysis, we preferentially used adjusted effect estimates when available. Heterogeneity between studies was partly assessed based on differences in confounder adjustment. Sensitivity analyses were conducted to evaluate the impact of studies with different levels of confounder control. In the narrative synthesis, we explicitly discussed how different studies addressed confounding and how this might impact the interpretation of results.

Reporting: Our results and discussion clearly stated which confounders were consistently controlled for across studies and which often needed to be included.

We highlighted any unexpected or inconsistent findings related to confounding factors. By systematically addressing confounding factors at each stage of the review process, we aimed to minimize bias and enhance the reliability of our findings. However, residual confounding may still exist due to unmeasured or inconsistently measured factors across studies.

Risk of bias assessment

The Risk of Bias in Nonrandomized Studies-of Exposures (ROBINS-E) tool was used to assess the risk of bias.[22] Seven domains were evaluated, and bias was categorized as 'very high', 'high', 'low', 'unclear', or 'no information'.

Certainty of evidence

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach was used to assess the certainty of evidence.[23] Evidence was rated based on the risk of bias, indirectness, inconsistency, imprecision, and publication bias.

Meta-analysis

Meta-analysis was conducted using Review Manager (Review Manager (RevMan, Computer program; Version 5.4. The Cochrane Collaboration, 2020) software. Mean differences with 95% confidence intervals (CI) were calculated for continuous outcomes. Mantel–Haenszel pooled odds ratios (OR) were used for dichotomous outcomes. Heterogeneity was assessed using I^2 statistics, with $I^2 > 60\%$ considered significant. Fixed-effects models were used for low heterogeneity ($I^2 < 60\%$), and random-effects models for significant heterogeneity ($I^2 > 60\%$). Sensitivity analysis was performed by excluding studies with low methodological quality. P values $<.05$ were considered statistically significant. Publication bias

assessment using funnel plots and Egger's test was not performed due to the limited number of included studies (<10).

Results

Study selection

The initial search identified 210 primary studies. After removing duplicates and screening titles and abstracts, 37 articles were selected for full-text review. Ten studies met the inclusion criteria and were included in the qualitative synthesis (Figure 1). These studies were conducted primarily in Asian (n = 8) and European (n = 2) countries and published between 2013 and 2021.

Characteristics of included studies

Of the 10 included studies, nine were cross-sectional,[13,19,24-30] and one[29] was a cohort study, comprising 1828 participants. Eight studies outcomes[19,24-29,31] reported a statistically significant association between periodontitis and DR, while two[13,30] found no association (Table 1).

DM was diagnosed using glycated haemoglobin (HbA1c) tests. Retinopathy assessment methods included ophthalmological examination (n = 5),[13,27,29-31] an ophthalmoscopy (n = 2),[17,24] and fundus photography (n = 3).[24,25,28] Periodontitis was primarily diagnosed using probing pocket depth and clinical attachment level, with two studies[26,28] employing the community periodontal index. Three studies reported OR analyses, with two providing adjusted OR for the association between severe periodontitis and DR. Nitta et al[26] reported an adjusted OR of 1.3 (95% CI: 1.1-1.6, P = .01), while Song et al reported an adjusted OR of 2.206 (95% CI: 1.114-4.366).

Risk of bias assessment

Using the ROBINS-E tool, five studies[13,24,26,28,30] showed a low risk of bias, three[19,29,31] showed a high risk, and two[25,27] showed a very high risk of bias. Common issues included missing data, exposure classification, study population

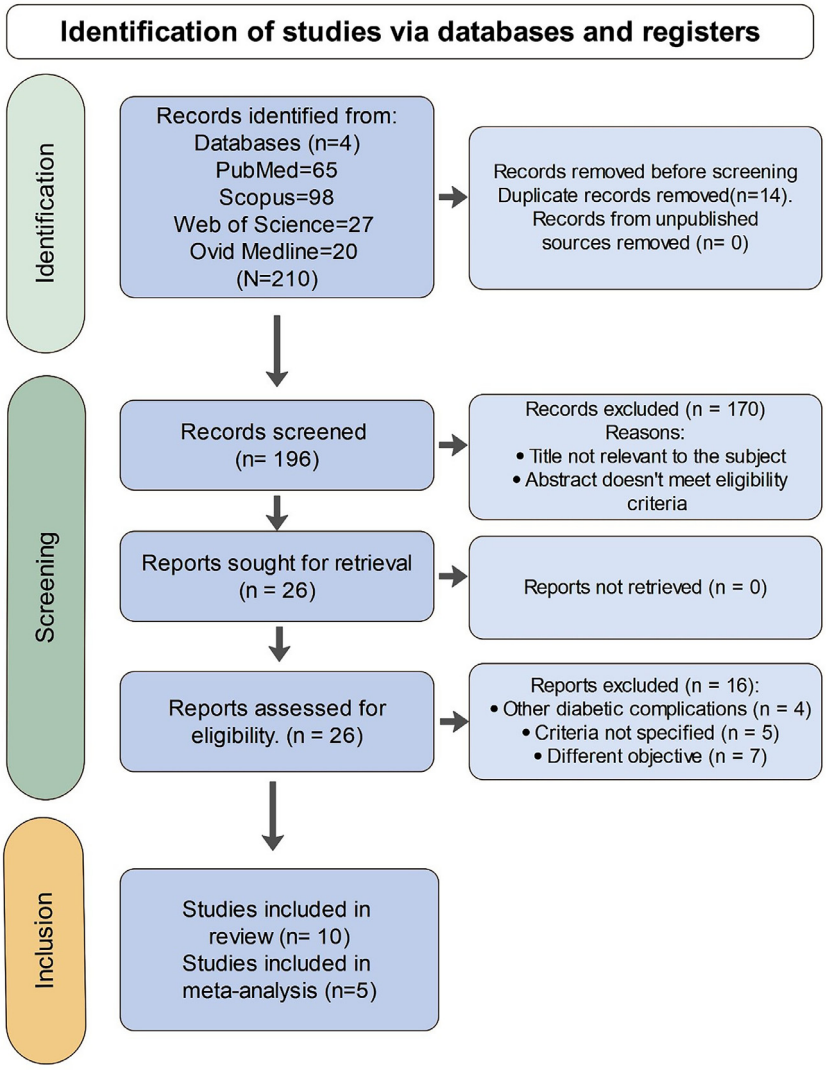


Fig. 1 – PRISMA 2020 flow diagram for the study selection process.

Table 1 – Characteristics of included studies on diabetic patients with retinopathy.

Study (author, country)	Sample size (T/C)	Mean age (y)	Diabetes type/ duration	Ocular disease	Periodontal diagnosis	Key findings
Lindner et al., Austria[25]	T = 46	62.6 ± 12.3	DM1 and DM2/17 ± 10 y	DME, DR	PI, PPD, CAL, BOP	Periodontitis and BOP associated with early DR in DME patients
Tandon et al., India[19]	T = 141 (PDR = 31, NPDR = 110), C = 72	56.1	DM2/5-15 y	DR	PI, GI, CAL	1.6 times higher risk of DR with severe periodontitis (95% CI: 0.953-2.782; P = .02)
Widen et al., Sweden[29]	T = 55, C = 30	42.3	DM1/12.6-27.8 y	DR	PI, GI, PPD, CAL	T1D associated with DR as age increases (OR: 7.3; 95% CI: 1.6-4.4; P < .01)
Yamamoto et al., Japan[30]	T = 36, C = 68	70.0 ± 1.2	DM2/13.6 ± 1.02 y	DR	PPD, BOP	Higher BOP in patients with DR
Veena et al., India[31]	T = 151 (G1 = 55, G2 = 44, G3 = 52), C = 49	30-65	DM2/4.8-10.3 y	DR	PI, GI, PPD, CAL	Significant correlation between DR severity and periodontitis severity (P < .001)
Ghadiri-Anari et al., Iran[13]	T = 87, C = 45	59.47 ± 9.5	DM2/10.5 ± 5.4 y	DR	Clinical examination	There is no association between diabetic complications and periodontitis severity
Song et al., Korea[28]	T = 90, C = 468	58.5 ± 1.6	DM2/10.9 ± 1.0 y	DR	CPI codes	DR risk is positively associated with periodontitis in nonobese diabetics (aOR: 2.206; 95% CI: 1.114-4.366)
Nitta et al., Japan[26]	T = 214, C = 40	55.1 ± 9.3	DM2/12.3 ± 8.5 y	DR	CPI codes	A significant association between severe periodontitis and DR (aOR: 1.3, 95% CI: 1.1-1.6, P = .01)
Amiri et al., Iran[24]	T = 84, C = 129	35-65	DM2/5-14 y	DR	PI, PPD, CAL, BOP	Periodontitis severity is significantly associated with DR (P > .011)
Ota et al., Japan[27]	T = 23 (PDR = 7, pre-PDR = 9, DR = 7)	55.4 ± 11.3	DM2/10.3 ± 8.8 y	DR	PPD, BOP, tooth mobility	Severe periodontitis (SD ± 7 mm) is significantly higher in DR patients

aOR, adjusted odds ratio; BOP, bleeding on probing; C, control group; CAL, clinical attachment loss; CI, confidence interval; CPI, community periodontal index; DM, diabetes mellitus; DME, diabetic macular oedema; DR, diabetic retinopathy; GI, gingival index; NPDR, nonproliferative diabetic retinopathy; OR, odds ratio; PDR, proliferative diabetic retinopathy; PI, plaque index; PPD, periodontal pocket depth; T, test group.

selection, outcome evaluation methods, and lack of confounding controls (Table 2, Figures 2 and 3).

While eight studies reported a significant association between severe periodontitis and DR, it's important to note that two studies found no such association: Ghadiri-Anari et al[13] from Iran and Yamamoto et al[30] from Japan. Both were cross-sectional studies focusing on Type 2 diabetes patients, with sample sizes comparable to some studies that did find an association. Ghadiri-Anari et al[13] used clinical examination for periodontitis diagnosis, which might have been less sensitive than quantitative measures in other studies. Yamamoto et al,[30] however, used standard measures (probing pocket depth and BOP), suggesting that diagnostic criteria alone don't explain the lack of association. Yamamoto et al[30] reported a mean HbA1c of 7.1%, indicating relatively good glycaemic control, which could potentially mitigate the impact of diabetes on periodontal health and retinopathy development. In contrast, Ghadiri-Anari et al[13] did not report specific HbA1c levels, making it difficult to assess the role of glycaemic control in their findings. These patterns suggest that

Table 2 – ROBINS-E risk of bias assessment for observational studies.

Study (author, country)	Confounding	Selection of participants	Classification of exposure	Deviations from intended exposure	Missing data	Measurement of outcomes	Selection of reported result	Overall bias
Tandon et al., India[19]	High	Low	Some concern	High	No information	Some concern	High	High
Lindner et al., Austria[25]	High	Low	High	High	No information	Low	Low	Very High
Widen et al., Sweden[29]	High	Low	Some concern	High	No information	Some concern	Low	High
Yamamoto et al., Japan[30]	Low	Low	Low	Low	No information	Low	Low	Low
Veena et al., India[31]	High	Low	Some concern	High	No information	Low	Low	High
Ghadiri-Anari et al., Iran[13]	Low	Low	Low	High	No information	Low	Low	Low
Nitta et al., Japan[26]	Low	Low	Some concern	Low	No information	Low	Low	Low
Song et al., Korea[28]	Low	Low	Some concern	Some concern	No information	Low	Low	Low
Amiri et al., Iran[24]	Low	Low	Low	Some concern	No information	Low	Low	Low
Ota et al., Japan[27]	High	Low	High	Very high	No information	Low	Low	Very high

geographic factors, patient age, diabetes duration, assessment methods, and glycaemic control might also play crucial roles in the observed relationship between periodontitis and DR. Both studies controlled for common confounders but may have differed in controlling for factors like glycaemic control or hypertension. Geographic and genetic factors specific to Iranian and Japanese populations might also have influenced the results. These conflicting findings highlight the complex relationship between periodontitis and DR. This underscores the need for further research to understand the conditions under which this association may or may not be observed and identify potential moderating factors.

GRADE evidence

The certainty of evidence for the association between DR and periodontitis was rated as very low, primarily due to the risk of bias, indirectness, imprecision, and potential publication bias inherent in observational studies (Table 3).

Meta-analysis

Five of the 10 studies were included in the meta-analysis.[13,19,24,29,31] High heterogeneity was observed among the included studies (I^2 = 86%). The pooled Mantel–Haenszel OR showed that subjects with diabetes and periodontitis had 4.48 times higher odds (95% CI: 1.67-12.07, P = .003) of developing retinopathy compared to subjects with diabetes without periodontitis (Figure 4). Sensitivity analysis, excluding studies with a high risk of bias, resulted in an OR of 4.63 (95% CI: 0.90-23.71, P = .07), with persistent high heterogeneity (I^2 = 93%) (Figure 5).

Similarly, when the studies with a high risk of bias were removed, I^2 value was high (93%), which implied increased heterogeneity across the studies. Figure 5 shows the Mantel–Haenszel OR of 4.63 (95% CI: 0.90-23.71) developing DR in subjects with diabetes and periodontitis than the control group when only studies with low risk of bias were considered.[13,24] However, this was not statistically significant (P value = .07).

Discussion

This systematic review evaluated the association between DR and periodontitis in patients with DM. Ten studies met the inclusion criteria, with eight reporting a positive association between DR and periodontitis, while two showed no association. The meta-analysis revealed that diabetic patients with periodontitis had 4.48 times higher odds of developing retinopathy compared to those without periodontitis. However, the GRADE analysis indicated very low certainty of evidence, highlighting the need for a cautious interpretation of these findings.

Interpretation of main findings

The observed association between DR and periodontitis aligns with the growing body of evidence suggesting a bidirectional relationship between diabetes and periodontal

disease.[5,8,27,32] Periodontitis has been identified as the sixth complication of diabetes,[18,33-35] providing a persistent source of inflammatory mediators that may impair glucose homeostasis and insulin sensitivity.[32,36]

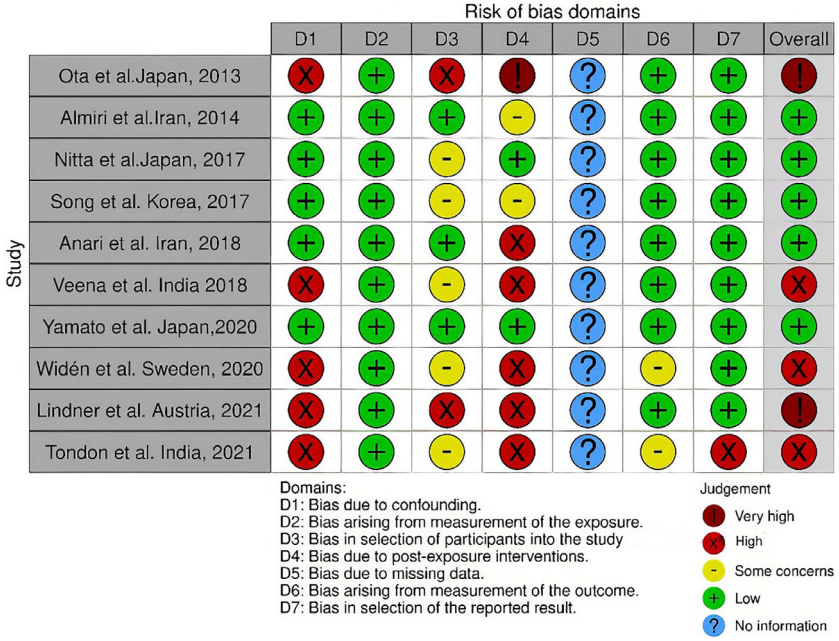
While these results provide valuable insights into the relationship between periodontitis and DR, it's important to understand the nuances of our statistical findings. To better grasp the implications of our analysis, let's break down the key statistical results in simpler terms. Our meta-analysis revealed that diabetic patients with periodontitis had about 4.5 times higher odds of developing retinopathy than those without periodontitis. In simpler terms, this means that among diabetic patients, those with periodontal disease were much more likely also to have eye problems related to their diabetes.[14,37] However, it is essential to understand that this finding showed much variation among the studies. We used a measure called I^2 to quantify this variation. Our I^2 value was 86%, which is considered high. To put this in perspective, if I^2 were 0%, it would mean all our studies showed the same thing. Our high I^2 of 86% means that the studies differed significantly in their findings.

We also looked at how reliable our evidence is using the GRADE approach. This is like a report card for scientific evidence. Our GRADE assessment showed that the overall certainty of evidence was very low. This doesn't mean our findings are wrong, but we need to be cautious about how sure we are of them. When we removed studies with a high risk of bias, we found that the link between periodontitis and retinopathy in diabetics became less clear. The OR dropped from 4.5 to about 4.6 but was no longer statistically significant. This means that when we only looked at the most reliable studies, we couldn't be as confident that there's a strong link between periodontitis and retinopathy in diabetics. These complex findings highlight why we need more high-quality research in this area. While our results suggest a connection between periodontitis and retinopathy in diabetics, we can't say how strong this connection is or if it applies to all diabetic patients. This interpretation of our statistical findings provides context for the strengths and limitations of our results. With this understanding, we can explore how these findings align with existing literature and their potential implications for clinical practice.

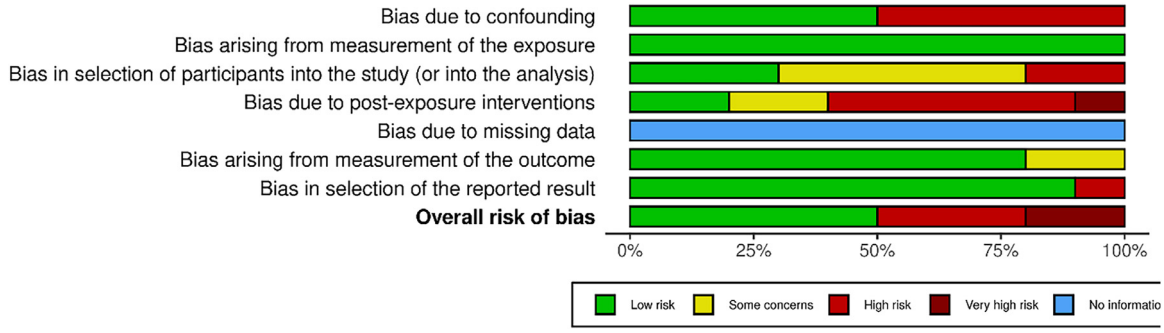
One of the included studies done in Indian diabetic patients demonstrated a significant positive association between DR and PD severity ($P = .02$), as indicated by increased plaque and gingival indices ($P < .001$). These findings highlight the importance of collaborative care between ophthalmologists and dentists for diabetic patients.[19] Another study in an Iranian population also showed that diabetic patients with retinopathy exhibited significantly higher periodontal disease severity ($P < .001$) and CPITN scores ($P < .001$) compared to those without retinopathy.[24]

A multicentric study done in a Japanese population found that patients with microvascular complications had more severe periodontitis, while poor glycaemic control increased the risk of both periodontitis prevalence and severity.[26] Another study found a strong association between early-stage DR and severe periodontal disease in Austrian patients. Patients with more severe periodontal inflammation required more frequent intravitreal injections.[25]

Identifying periodontal disease can be an early warning sign for other systemic conditions, prompting earlier screening and intervention. Healthcare providers, especially dentists, ophthalmologists, and endocrinologists, should collaborate to provide comprehensive care for patients with diabetes, focusing on both oral and systemic health. By



Figs. 2 and 3 – Risk of bias ROBINS-E tools.[22] Green: low risk of bias; yellow: some concerns; red: high risk of bias; grey: no information.



Figs. 2 and 3 Continued.

addressing both oral and systemic health issues, patients with diabetes may experience better overall health outcomes, including reduced risk of complications.

Given the established link between systemic inflammation and certain eye diseases, a potential link between periodontitis and ocular diseases warrants further discussion. Even without DM, people with periodontitis are at risk of many ocular complications. A review of the literature reveals multiple studies reporting such an association.[38] While the precise mechanisms underlying this relationship remain unclear, potential explanations include shared risk factors, innate immune response involvement, and choroidal thickness alterations.

A retrospective cohort study in Taiwan found that individuals with periodontitis had significantly higher rates of infectious keratitis, uveitis, and infectious scleritis compared to non-PD controls. The presence and duration of PD were moderately associated with an increased risk of developing infectious keratitis, uveitis, and infectious scleritis.[39] Another study investigated the association between periodontal disease and dry eye in 36,488 Japanese adults. Logistic regression analysis revealed a significant association between dry eye and periodontal disease (OR 1.12, 95% CI 1.03-1.22). These findings underscore the importance of comprehensive oral and ocular health management.[40] In yet another retrospective cohort study done using Taiwan's National Health Insurance Research Database, a significantly increased risk of developing glaucoma was found in individuals with periodontitis (adjusted HR 1.26, 95% CI 1.21-1.32). This association persisted across various subgroups and was specifically linked to primary open-angle glaucoma.[41]

Potential mechanisms

Shared inflammatory pathways may explain the link between periodontitis and DR. Both conditions are characterized by

Table 3 – GRADE certainty of evidence for the association between diabetic retinopathy and periodontitis.

Certainty assessment criteria	Evaluation
Number of studies	10
Study design	Observational studies
Risk of bias	Not serious*
Inconsistency	Serious†
Indirectness	Not serious
Imprecision	Serious†
Other considerations	Publication bias is strongly suspected; all plausible residual confounding would reduce the demonstrated effect

Outcome	Diabetic retinopathy and periodontitis	Healthy patients with diabetes	Relative effect (95% CI)	Absolute effect (95% CI)
Number of patients	1191/1828 (65.2%)	984/1828 (53.8%)	OR 4.48 (1.67-12.47)	301 more per 1000 (from 122 more to 397 more)

Overall certainty	Importance
⊕◯◯◯ Very low	Important

CI, confidence interval; OR, odds ratio.
Follow-up: median 2 months; assessed with mean, median.

* Methodological findings and results are not clearly mentioned.
† Different settings and cohorts of patients.
‡ Sample selection, results, and outcomes were not measured and registered properly.

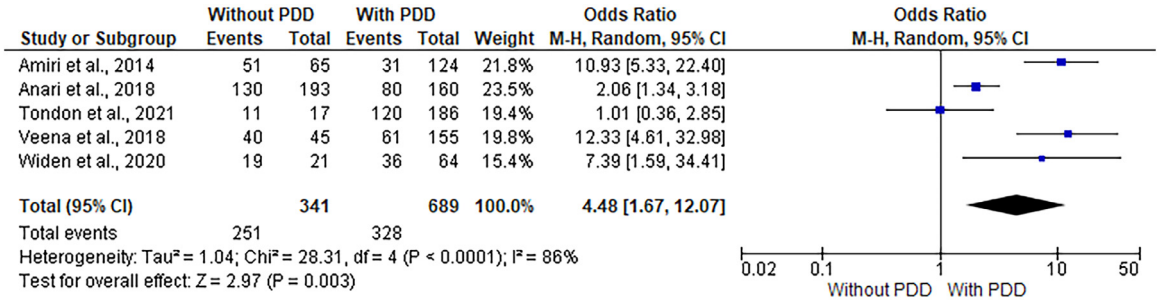


Fig. 4 – Forest plot for the Mantel–Haenszel odds ratio of developing diabetic retinopathy in subjects with diabetes and periodontitis compared to the control group.

elevated levels of inflammatory mediators such as IL-1β, IL-6, TNF-α, and CRP.[6,42] These mediators can promote endothelial damage and exacerbate diabetes-associated vascular pathology, potentially contributing to the development of DR.[16,43] Furthermore, the systemic inflammation associated with periodontitis may trigger atherosclerosis and retinal hypoxia, promoting retinal neovascularization.[44,45] Elevated inflammatory markers can also drive adipose tissue inflammation, causing dyslipidaemia and ectopic fat accumulation in the endothelium, further contributing to DR progression.[46,47]

Strengths and limitations

A key strength of this review is the comprehensive search strategy and rigourous methodology employed. Several limitations of this systematic review and meta-analysis must be acknowledged. Most included studies were cross-sectional, limiting our ability to establish a causal relationship between periodontitis and DR. The meta-analysis revealed high heterogeneity (I^2 = 86%) among studies, suggesting considerable variability that may be attributed to differences in study populations, diagnostic criteria, or uncontrolled confounding factors. Furthermore, the GRADE assessment indicated low to very low certainty of evidence, primarily due to the observational nature of the included studies, risk of bias, and imprecision in results. The limited number of included studies (less than 10) precluded a comprehensive assessment of publication bias using funnel plots and Egger's test.

The predominantly cross-sectional design (9 out of 10 studies) limits our ability to establish causality or temporal relationships between periodontitis and DR. Variable sample sizes, from relatively small (n = 23) to more substantial (n = 558), may have led to inconsistent statistical power across studies, affecting the reliability of our pooled estimates. Selection bias from hospital-based recruitment could have inflated the observed association by overrepresenting severe cases. Hospital-based recruitment may have introduced selection bias, potentially overrepresenting severe cases. Measurement bias could have arisen from variations in diagnostic criteria and methods across studies. Inconsistent control of confounding factors, particularly glycaemic control, could have masked or exaggerated the relationship between periodontitis and DR. The predominance of studies in Asian populations limits the generalizability of our findings to other ethnic groups, potentially overlooking important genetic or environmental factors. These limitations collectively suggest that our observed association may be subject to overestimation and should be interpreted cautiously.

To address these limitations and strengthen our understanding, future research should prioritize (1) longitudinal cohort studies to establish temporal relationships and explore potential causal mechanisms; (2) large-scale, multicentre studies with diverse ethnic representations to improve generalizability; (3) standardization of periodontitis and DR diagnostic criteria across studies; (4) comprehensive assessment and control of confounding factors, especially glycaemic control, hypertension, and lipid profiles; (5) investigation of potential mediating factors, such as inflammatory markers or microvascular changes; (6)

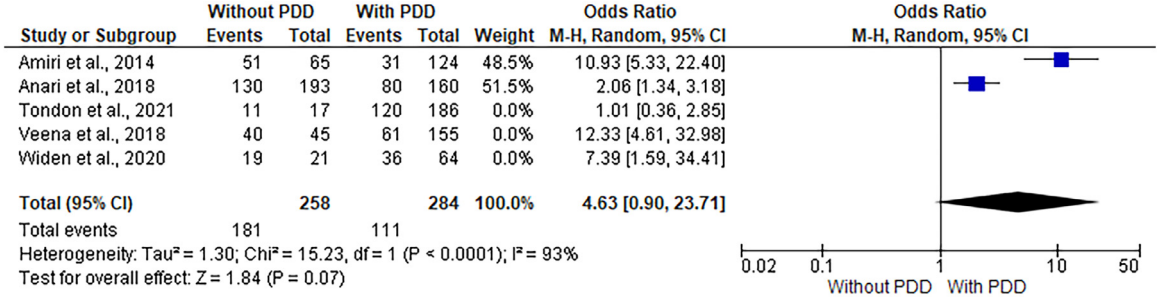


Fig. 5 – Mantel–Haenszel odds ratio of developing diabetic retinopathy in subjects with diabetes and periodontitis than the control group following sensitivity analysis.

exploration of the impact of periodontal interventions on DR progression; and (7) utilization of advanced statistical techniques, such as propensity score matching or instrumental variable analysis, to better account for confounding. By addressing these areas, future research can provide more robust evidence on the relationship between periodontitis and DR, potentially informing clinical practice and prevention strategies.

Implications for clinical practice and research

Despite the limitations, the consistent association observed across multiple studies suggests that the relationship between periodontitis and DR warrants clinical attention. Dental providers should consider the potential risk of retinopathy in managing diabetes patients with periodontitis and may consider referring them for ophthalmologic evaluation when indicated. Future research should focus on prospective studies with larger sample sizes, standardized diagnostic criteria for both periodontitis and DR, and careful control of potential confounders. Longitudinal studies examining the impact of periodontal treatment on DR progression could provide valuable insights into the causal nature of this relationship.

Conclusion

This systematic review and meta-analysis suggest a potential association between periodontitis and DR in patients with DM, with our analysis indicating higher odds of retinopathy in diabetic patients with periodontitis. However, it is crucial to interpret these findings with substantial caution due to significant limitations. The low to very low certainty of evidence, as determined by the GRADE assessment, and the high heterogeneity (I^2 = 86%) among included studies significantly complicate the reliability of our conclusions. These limitations, combined with the predominance of cross-sectional studies, prevent us from establishing causality or drawing firm conclusions about the nature or strength of the association. Nevertheless, the consistent trend observed across multiple studies suggests that this relationship warrants further investigation. While current evidence does not support definitive clinical recommendations, it underscores the importance of comprehensive care for diabetic patients, including oral and ocular health monitoring. Healthcare providers should be aware of this possible link but base clinical decisions on individual patient factors and more robust evidence as it becomes available. Our findings should be considered hypothesis-generating, pointing to the need for further rigourous research to elucidate the true nature and clinical significance of the relationship between periodontitis and DR.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

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Author contributions

Sukumaran Anil: Conceptualization, methodology, supervision, writing – original draft, writing – review and editing. Betsy Joseph: Data curation, formal analysis, writing – original draft. Merlyn Anjali Pereira: Investigation, data curation. Saket Arya: Investigation, data curation. Shirmila Syamala: Validation, writing – review and editing. Vishnupriya K. Sweety: Data curation, formal analysis. Ruwan Jayasinghe: Validation, writing – review and editing.

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