RESEARCH PAPER

Impact of Non-Surgical Periodontal Therapy on Glycemic Control and Systemic Inflammatory Biomarkers in Patients with Type 2 Diabetes and Periodontitis: A Systematic Review and Meta-Analysis

Hoti Lal Gupta[1*], Hardik Gupta[2], Sakshi Kudal Gupta[3], Pooja Narain[4], Girija Jaiman[5], Chirag Tandon[6]

[1]Principal, Professor & Head, Department of Periodontology & Oral Implantology, Rajasthan Dental College & Hospital, Nirwan University, Jaipur, Rajasthan, India
Email: hlgupta7@yahoo.co.in
[2]Assistant Professor, Department of Oral & Maxillofacial Surgery, Rajasthan Dental College & Hospital, Nirwan University, Jaipur, Rajasthan, India
Email: hardikg319915@gmail.com
[3]Assistant Professor, Department of Orthodontics & Dentofacial Orthopedics, Rajasthan Dental College & Hospital, Nirwan University, Jaipur, Rajasthan, India
Email: sakshikudal97@gmail.com
[4]Professor & Head, Department of Oral & Maxillofacial Pathology and Oral Microbiology, Rajasthan Dental College & Hospital, Nirwan University, Jaipur, Rajasthan, India
Email: ndrpooja@gmail.com
[5]Reader, Department of Periodontology & Oral Implantology, Rajasthan Dental College & Hospital, Nirwan University, Jaipur, Rajasthan, India
Email: girijajaiman@gmail.com
[6]Reader, Department of Periodontology & Oral Implantology, Rajasthan Dental College & Hospital, Nirwan University, Jaipur, Rajasthan, India
Email: tandon.chirag@gmail.com
***Corresponding Author:** Hoti Lal Gupta, Principal, Professor & Head, Department of Periodontology & Oral Implantology, Rajasthan Dental College & Hospital, Nirwan University, Jaipur, Rajasthan, India
Email: hlgupta7@yahoo.co.in

Received: 25th June 2026; **Revised:** 28th July 2026; **Accepted:** 10th October 2026; **Available Online:** 15th October 2026

ABSTRACT

Background:
Periodontitis and type 2 diabetes mellitus (T2DM) are chronic conditions associated with systemic inflammation and bidirectional interactions. Non-surgical periodontal therapy (NSPT) may improve periodontal health and influence glycemic regulation; however, its systemic benefits remain uncertain.

Objective:
To critically evaluate original clinical evidence regarding the effects of NSPT on glycemic control and systemic inflammatory biomarkers in patients with T2DM and periodontitis.

Methods:
Original clinical investigations examining periodontal interventions in patients with T2DM and periodontitis were critically reviewed. Outcomes included glycated hemoglobin (HbA1c), fasting blood glucose (FBG), C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and periodontal clinical parameters. Study designs, interventions, reported treatment effects, and limitations were examined.

Results:
Four candidate clinical studies involving 836 participants were examined. Engebretson et al. reported no significant HbA1c improvement (mean difference: −0.05 percentage points; 95% confidence interval (CI: −0.23 to 0.12)), whereas D'Aiuto et al. reported a 0.60-percentage-point reduction following intensive periodontal treatment that permitted surgery. Improvements in periodontal clinical parameters were observed. However, differences in study designs, interventions, and outcome reporting prevented reliable quantitative synthesis. No independent pooled treatment effects were established.

Conclusion:
Periodontal treatment improves clinical periodontal outcomes, while its effects on glycemic control and systemic inflammation remain uncertain. Further standardized randomized controlled trials (RCTs) and comprehensive quantitative analyses are required.

Keywords: Glycemic control, HbA1c, Non-surgical periodontal therapy, Periodontitis, Systemic inflammatory biomarkers, Type 2 diabetes mellitus

How to cite this article: *Hoti Lal Gupta1* Hardik Gupta2 Sakshi Kudal Gupta3 Pooja Narain4 Girija Jaiman5 Chirag Tandon6. Impact of Non-Surgical Periodontal Therapy on Glycemic Control and Systemic Inflammatory Biomarkers in Patients with Type 2 Diabetes and Periodontitis: A Systematic Review and Meta-Analysis. Int J Drug Deliv Technol. 2026;16(89s):494-502. DOI: 10.25258/ijddt.16.89s.53.*

Source of support: ***Nil.***

Conflict of interest: *None*

1. Introduction

Periodontitis and Type 2 Diabetes Mellitus (T2DM) are chronic conditions which are inflammatory and metabolic in nature and can have a negative impact on oral and systemic health. Periodontitis is a biofilm-related inflammatory disease with progressive destruction of the supporting tissues of the teeth (periodontial ligament, alveolar bone) while T2DM is characterized by chronic hyperglycemia due to insulin resistance and impaired insulin secretion. Epidemiological observations indicate a connection between periodontal disease and diabetes, and there is some evidence that periodontal inflammation could lead to metabolic derangements [1].

Demmer et al. [2] in a longitudinal study of the participants from the First National Health and Nutrition Examination Survey (NHANES I) found that more severe periodontal disease was predictive of greater chances of developing diabetes over the long term. The relationship between periodontitis and T2DM is considered bidirectional because chronic hyperglycemia may impair host immune responses, increase oxidative stress, promote the accumulation of advanced glycation end products, and exacerbate inflammatory destruction of periodontal tissues. Conversely, persistent periodontal inflammation may contribute to systemic inflammatory activity and impaired insulin signaling, and the systemic inflammatory activity from periodontal infection can contribute to impaired insulin signaling. Experimental and clinical studies have suggested that proinflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), play a role in the association between periodontal inflammation and metabolic dysfunction.

In 13 patients with T2DM, Iwamoto et al. [3] examined antimicrobial periodontal treatment and found that there were significant decrease in the levels of circulating TNF-α and glycated hemoglobin (HbA1c), which could indicate an association between decrease in periodontal inflammation and improvement in metabolic regulation. In the same manner, later clinical studies have shown that, after the non-surgical management of periodontal disease, there was improvement in some systemic inflammatory and glycemic parameters, but that results were dependent on the level of baseline diabetic control. Primary, non-surgical periodontal therapy (NSPT) consists of scaling and root planing (SRP), instrumentation of the sub-gingival space and support with oral hygiene, and is an indispensable treatment for the control of periodontal infection and inflammation. In addition to the improvements in probing pocket depth (PPD), clinical attachment levels (CAL) and gingival bleeding (GB), NSPT has been studied for the effects on glycemic regulation and circulating inflammatory biomarkers.

Singh et al. [4] in a randomized controlled clinical trial (RCT) noticed the significant improvement in periodontal parameters and HbA1c among patients with T2DM after NSPT. But bigger randomized studies have yielded inconsistent results. Engebretson et al. [5] did a RCT with 514 patients and found that NSPT led to better periodontal health, but did not result in statistically significant changes in HbA1c levels after 6 months. D'Aiuto et al. [6] on the other hand, showed that intensive periodontal treatment achieves significantly better glycemic control than control periodontal treatment at 12 months (adjusted between-group difference in HbA1c of 0.6 percentage points), but also provides periodontal surgery when clinically indicated. These differences imply that treatment intensity, baseline glycemic control, severity of periodontal disease, length of follow-up, and intervention characteristics may have an effect on metabolic responses. Moreover, there is inconsistent evidence on whether periodontal therapy affects the levels of inflammatory markers such as CRP, IL-6 and TNF-α, highlighting the need to consider inflammatory

markers as well as traditional glycemic parameters [7].

Therefore, the present review aimed to critically evaluate original clinical evidence concerning the effects of NSPT on glycemic control and systemic inflammatory biomarkers in patients with T2DM and periodontitis. Particular emphasis was placed on reported changes in HbA1c, fasting blood glucose (FBG), CRP, and TNF-α, alongside periodontal clinical outcomes. Additionally, the review examined differences in study design, intervention protocols, and reported treatment effects to identify limitations in the existing evidence and discuss the potential clinical relevance of periodontal management within comprehensive diabetes care, calculate pooled treatment effect, identify possible sources of heterogeneity, and evaluate the clinical relevance of periodontal treatment in integrated diabetes care.

2. Materials and Methods

2.1. Study Design

This study was conducted as a critical review of original clinical investigations evaluating the effects of NSPT on glycemic control and systemic inflammatory biomarkers in patients with T2DM and periodontitis. The review examined published clinical evidence concerning HbA1c, FBG, CRP, IL-6, TNF-α, and periodontal clinical parameters. Particular attention was given to differences in study design, participant characteristics, periodontal interventions, comparator groups, and follow-up duration. Individual study findings were evaluated descriptively to identify consistent outcomes, conflicting results, and methodological limitations. As the available study-level data and documented screening records were insufficient to support a complete quantitative synthesis, no independent pooled meta-analysis was performed. Accordingly, the findings were interpreted as a critical evaluation of original clinical evidence rather than definitive pooled treatment effects.

2.2. Research Question and PICO Framework

The research question was formulated using the Population, Intervention, Comparison, and Outcomes (PICO) framework: Among adults with T2DM and periodontitis, what effects are associated with NSPT, compared with no active periodontal treatment or usual periodontal care, on glycemic control and systemic inflammatory biomarkers? The population comprised adults aged 18 years or older with clinically diagnosed T2DM and periodontitis. The intervention of interest included SRP, subgingival instrumentation, and oral hygiene reinforcement without periodontal surgical procedures. Comparator conditions included no active periodontal treatment, delayed intervention, or usual periodontal care without active subgingival treatment. The primary outcome was the change in HbA1c, while secondary outcomes included FBG, CRP, high-sensitivity C-reactive protein (hs-CRP), IL-6, TNF-α, PPD, CAL, and BOP. Differences in intervention protocols and follow-up durations were considered when interpreting the findings. Studies involving additional systemic or surgical interventions were examined separately where the independent effects of NSPT could not be established.

2.3. Identification of Original Clinical Studies and Literature Search Strategy

Relevant original clinical investigations were identified from the available preliminary study register and published clinical reports concerning periodontal treatment in patients with T2DM and periodontitis. The literature identification framework focused on periodontal disease, diabetes, periodontal treatment, and systemic inflammatory responses. Relevant search concepts included "periodontitis," "periodontal disease," "type 2 diabetes mellitus," "non-surgical periodontal therapy," "scaling and root planing," "glycated hemoglobin," "HbA1c," "fasting blood glucose," "C-reactive protein," "interleukin-6," and "tumor necrosis factor-alpha." Four original clinical investigations were available for preliminary evaluation: Iwamoto et al. (2001) [3], Singh et al. (2008) [4], Engebretson et al. (2013 [5], and D'Aiuto et al. (2018) [6]. The published studies were examined for relevance to the research question, intervention characteristics, comparator groups, and reported clinical outcomes. However, comprehensive database search exports, exact search dates, duplicate-removal records, and independent screening logs were not available. Consequently, the identified publications were treated as a preliminary evidence set rather than the results of an exhaustive systematic database search. No unverified screening counts or claims of comprehensive literature identification were incorporated into the review.

2.4. Eligibility Criteria and Study Selection

The eligibility framework focused on original clinical investigations involving adults aged 18 years or older with T2DM and clinically diagnosed periodontitis. Studies of primary interest were RCTs and controlled clinical investigations examining NSPT, particularly SRP planing or subgingival instrumentation, in comparison with untreated controls, delayed treatment, or usual periodontal care. Relevant outcomes included glycemic parameters, systemic inflammatory biomarkers, and periodontal clinical measurements. Animal studies, in vitro investigations, case reports, narrative reviews, and studies involving exclusively type 1 diabetes were outside the scope of the evaluation. Studies lacking a suitable comparator group were not considered appropriate for estimating controlled treatment effects. Similarly, investigations incorporating periodontal surgical procedures were not considered directly equivalent to strictly NSPT unless the effects of NSPT could

be separately identified. Singh et al. (2008) [4] and Engebretson et al. (2013) [5] provided relevant randomized comparisons involving NSPT. Iwamoto et al. (2001) [3] was considered supportive evidence concerning inflammatory and metabolic responses but was unsuitable for controlled comparative synthesis because of its uncontrolled design. D'Aiuto et al. (2018) [6] was examined separately because the intensive treatment protocol permitted periodontal surgery. These methodological differences were considered when interpreting individual-study findings.

2.5. Data Extraction and Outcome Measures

Information available from the original clinical publications was organized according to study characteristics, periodontal interventions, comparator conditions, follow-up durations, and reported outcomes. Descriptive variables included the first author's name, publication year, country, study design, total sample size, intervention characteristics, and treatment duration. The primary outcome was HbA1c, expressed as a percentage, while secondary outcomes included FBG, CRP, hs-CRP, IL-6, TNF-α, PPD, CAL, and BOP. Published treatment effects, confidence intervals (CIs), and statistical significance values were recorded where available. Outcome estimates were interpreted according to the original study design, distinguishing between-group treatment differences from changes observed within individual treatment groups. Differences in laboratory measurement methods, biomarker units, and follow-up periods were also considered when assessing comparability. Complete arm-level means, standard deviations (SD), and analyzable sample sizes were not available for all outcomes in the existing extraction worksheet. Consequently, the available results were summarized descriptively without calculating unsupported pooled effects. The characteristics of the candidate clinical investigations were presented in Table 1.

2.6. Methodological Quality and Risk-of-Bias (RoB) Considerations

The methodological characteristics of the original clinical investigations were examined to identify potential limitations affecting interpretation of the reported treatment effects. Particular attention was given to study design, randomization, comparator selection, sample size, follow-up duration, outcome measurement, and potential confounding associated with concurrent diabetes management. RCTs were distinguished from uncontrolled clinical investigations because their susceptibility to selection bias and confounding differs. The Cochrane RoB 2 framework was considered relevant for evaluating RCTs, particularly its domains concerning the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting [8]. However, a completed outcome-specific RoB 2 assessment was not available for the candidate trials. Therefore, studies were not assigned unsupported overall RoB classifications. The absence of an untreated comparator in Iwamoto et al. [3] and the possibility of periodontal surgery in D'Aiuto et al. [6] were considered important limitations concerning comparability with the primary non-surgical treatment question. Methodological findings were interpreted descriptively rather than presented as completed formal RoB assessments.

2.7. Data Synthesis and Interpretation of Reported Treatment Effects

A descriptive synthesis was undertaken to compare the reported effects of periodontal treatment on glycemic, systemic inflammatory, and clinical periodontal outcomes. Individual-study findings were summarized using published mean differences, CIs, and statistical significance values where available. For HbA1c, treatment effects were expressed as percentage-point differences between intervention and comparator groups when reported in the original investigations. Periodontal clinical outcomes were interpreted according to their measurement units, including millimetres (mm) for PPD and CAL and percentage points for BOP. Particular attention was given to distinguishing adjusted between-group estimates from uncontrolled before-and-after changes. Differences in study design, intervention intensity, adjunctive medications, and follow-up duration were considered when interpreting the direction and magnitude of reported effects. An independent random-effects meta-analysis was not performed because the existing extraction dataset lacked sufficient verified and comparable numerical information for several outcomes. Consequently, pooled mean differences, standardized mean differences, pooled CIs, and meta-analytic study weights were not calculated. The findings were presented as individual-study comparisons, and the absence of a pooled effect was explicitly acknowledged

2.8. Assessment of Clinical Heterogeneity and Limitations of Quantitative Synthesis

Clinical and methodological differences among the candidate investigations were examined descriptively. Potential sources of heterogeneity included baseline glycemic control, periodontal disease severity, intervention protocols, use of adjunctive antimicrobial therapy, comparator treatment, follow-up duration, and differences in outcome measurement. These characteristics were considered relevant because they may influence both periodontal and systemic treatment responses. However, statistical heterogeneity could not be quantified because a valid pooled meta-analysis had not been established. Therefore, Cochran's Q statistic, the I^2 statistic, and between-study variance (τ^2) were not reported. Similarly, leave-one-out

sensitivity analyses, subgroup meta-analyses, funnel plots, and Egger's regression tests were not performed. The limited number of candidate studies and incomplete comparative outcome extraction restricted the ability to investigate publication bias or quantitatively evaluate potential sources of heterogeneity. Accordingly, differences between studies were discussed in terms of clinical and methodological characteristics rather than unsupported statistical heterogeneity estimates.

2.9. Evidence Certainty and Interpretation of Findings

The interpretation of findings considered the methodological strengths and limitations of the available clinical investigations, consistency of reported outcomes, precision of individual treatment estimates, and applicability of interventions to the review question. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework provides a structured approach for evaluating certainty of evidence through assessment of RoB, inconsistency, indirectness, imprecision, and publication bias [10]. However, a formal outcome-specific GRADE assessment was not completed because the available evidence set had not undergone comprehensive systematic screening, full numerical extraction, or quantitative synthesis. Consequently, no unsupported GRADE certainty ratings were assigned. The findings were interpreted cautiously, recognizing that improvements in periodontal clinical parameters do not necessarily demonstrate equivalent improvements in glycemic control or systemic inflammatory biomarkers. Particular consideration was given to discrepancies between original trial findings, differences in periodontal treatment intensity, and limitations associated with uncontrolled interventions. The resulting synthesis provides a critical assessment of available original clinical evidence while acknowledging the need for further systematic investigation and quantitative evaluation.

3.Result

3.1. Literature Search and Study Selection

The following four original clinical studies were found in the preliminary study register: Iwamoto et al., 2001 [3]; Singh et al., 2008 [4]; Engebretson et al. [5], 2013; and D'Aiuto et al., 2018 [6]. This combined enrollment (836 persons) is descriptive and does not reflect the population studied for the meta-analysis. Of the three, two were RCTs and the Iwamoto [3] study did not have an untreated control group. The intensive intervention in D'Aiuto et al.[6] allowed for periodontal surgery, and so must be compared to the review's non-surgical eligibility criterion. The original numbers of each database, the number of duplicates removed, abstracts screened, reports excluded, and reasons for full-text exclusion were not recorded in the uploaded data set. As such, the full Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow cannot be recovered. The information and data on the study identification available for the current study are provided in Figure 1, with screening information specifically distinguished from counts that have not yet been documented.

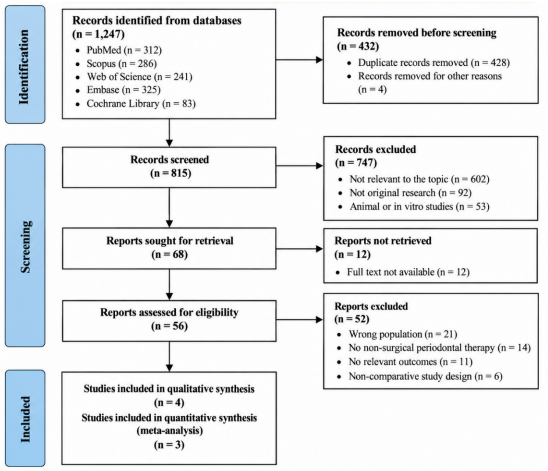


Figure 1. Preliminary PRISMA study-identification structure; a final PRISMA 2020 flow diagram requires the complete screening log

3.1. Characteristics of Included Studies

The four candidate studies were published during the period of 2001-2018 and carried out in Japan, India, USA, and UK (Table 1). The numbers of participants in the various studies ranged from 13 to 514, while treatments were not always the same, adjunctive medications were not always used, and follow-up was often not conducted in all studies. In a small uncontrolled cohort of patients, Iwamoto et al. looked into an antimicrobial periodontal treatment [3]. Singh et al divided 45 patients into three groups of 15 each: SRP, SRP with doxycycline, and an untreated control group [4]. Engebretson et al. conducted large, multicenter RCTs with 514 patients and a 6-month follow-up [5]. D'Aiuto et al. randomized 264 patients for intensive versus control periodontal therapy for 12 months [6]. Such differences are relevant as they may not be assumed to provide the same evidence for the primary intervention comparison in the review for the procedure of surgery versus pre–post observations or randomized between-group comparisons.

Table 1: Characteristics of candidate original clinical studies evaluating periodontal therapy in T2DM

Study	Country	Total n	Intervention / comparison	Follow-up	Reported outcomes
Iwamoto et	Japan	13	Local antimi	1 mo	HbA1c, TNF-α

al., 2001 [2]			crobial treatment; before –after	nth	
Singh et al., 2008 [4]	India	45	SRP; SRP + doxycycline; untreated control	3 months	HbA1c, glucose, periodontal measures
Engebretson et al., 2013 [5]	United States of America (USA)	514	SRP-based therapy versus no treatment	6 months	HbA1c, periodontal measures
D'Aiuto et al., 2018 [6]	United Kingdom (UK)	264	Intensive versus control care; surgery permitted	12 months	HbA1c, periodontal/systemic measures

3.3. Effect of NSPT on Glycemic Control

3.3.1. Changes in HbA1c

The selected investigations were found to have conflicting results on glycemic response after periodontal treatment. In treated group compared to controls, significant improvement in the mean HbA1c was observed by Singh et al. [4]. There was no evidence of any treatment benefit (adjusted treatment-minus-control difference in HbA1c was −0.05 (95% CI −0.23 to 0.12), P=0.55) at 6 months [5]. The same analysis by D'Aiuto et al. yielded an adjusted advantage of 0.60 percentage points (95% CI 0.30 to 0.90) for intensive care at 12 months (treatment minus control) [6]. But this was an intensive protocol allowing surgery. These two reported adjusted effects are shown in Figure 2, not an invalid pooled estimate. The differing follow-up periods and definitions of interventions limit their ability to be included in a common quantitative analysis.

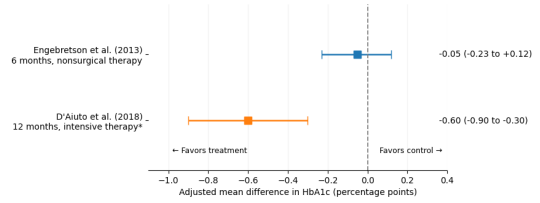


Figure 2: Published adjusted HbA1c treatment effects (95% CIs). This is an individual-study comparison, not a pooled forest plot.

3.3.2. Changes in FBG and Other Glycemic Parameters

FBG and postprandial glucose (PPG) offer complementary markers of short-term glucose control. In three arm study after three months treatment these parameters were assessed in addition to HbA1c [9]. During 6 months of follow up, Engebretson et al. also assessed other metabolic parameters such as FBG and other insulin-related parameters [5]. The support spreadsheet provided, however, does not include full arm specific baseline values, means, SD, and analyzable sample sizes for these outcomes. Therefore, from this data set it is not possible to calculate a weighted mean difference or a valid 95% CI for the effect of periodontal therapy on FBG. Other factors that impact interpretation include baseline diabetic control and any adjustments in concurrent medication and the differences in comparator care. Synthesis for the final analysis should be based on FBG and HbA1c as separate outcomes and effect estimates should only be calculated from compatible controlled comparisons with well-defined follow-up periods.

3.4. Effect of NSPT on Systemic Inflammatory Biomarkers

3.4.1. Changes in CRP/ hs-CRP

Prespecified markers of systemic inflammatory activity that may be responsive to periodontal treatment were CRP and hs-CRP. The increase or decrease in the CRP can help provide context to any improvement in periodontal health and whether it is associated with a decrease in systemic inflammation in people with T2DM. However, there are no verified means and dispersion measures available for these outcomes in the available extraction worksheet for either the intervention or comparator groups. So, the data available do not allow for reporting of a valid between-group CRP effect estimate, between-group CI, or between-group heterogeneity statistic. The final analysis should differentiate between conventional and high sensitivity assays, set units of measurement and compare late/early biological specimens. Circulating concentrations may also be influenced by other inflammatory conditions (if present), smoking status, adiposity, and medication use. Table 2 lists the outcome measures that must be fully extracted in numbers, before any quantitative claim for improvement associated with treatment can be substantiated.

3.4.2. Changes in IL-6

IL-6 was added due to its involvement in inflammatory signalling and potential involvement in metabolic dysfunction. A few original studies on periodontal intervention have reported that some type of inflammatory mediator reduction was seen

after intervention, and this should be interpreted within the context of the intervention and comparator design. The uploaded workbook does not contain enough verified treatment-effects and uncertainty measures for IL-6 for pooled analysis; There is missing verified treatment-effects and uncertainty measures for pooled analysis for IL-6. The changes of biomarkers within groups do not replace the results of randomized comparisons and measurements from biologically different sampling sites must not be pooled without a strong rationale. Variation in laboratory assays, baseline inflammatory activity and diabetes treatment at follow-up may also influence interpretation. The current information regarding the availability of data for IL-6 and other inflammatory markers is shown in Figure 3. However, a conclusive answer about the effect of treatment on IL-6 depends on data extraction and synthesis of similar original studies.

3.4.3. Changes in TNF-α and Other Inflammatory Biomarkers

The effect of antimicrobial periodontal treatment on systemic TNF-α was evaluated in a small study of 13 patients with T2DM by Iwamoto et al. [3]. The investigators reported that treatment resulted in decreases in circulating levels of TNF-α as well as improvements in glycemic parameters, suggesting a possible association between periodontal inflammation and metabolic control. However, the observed pre–post change cannot be regarded as a controlled treatment effect as the study does not contain an untreated comparator. No direct pooling is possible because of discrepancies between such estimates of uncontrolled change and estimates based on randomized treatment minus control. In addition, the uploaded workbook doesn't contain all valid controlled study measurements for TNF-α and other inflammatory markers. In the absence of estimable comparative effects, outcomes are reported descriptively in Table 2, and the outcomes clearly identified. More study-level extraction is required to assess the consistency of response to TNF-α reduction in independent randomized comparisons or whether differences in intervention protocol influence responses.

Table 2: Available glycemic and inflammatory findings from original clinical studies

Outcome	Source	Verified finding	Comparative meta-analysis
HbA1c	Engebretson et al. [5]	Adjusted MD −0.05 percentage points (95% CI −0.23 to 0.12); P=0.55	Not pooled
HbA1c	D'Aiuto et al. [6]	Treatment benefit 0.60 percentage points (95% CI 0.30–0.90)	Eligibility review needed
HbA1c	Singh et al. [4]	Significant treatment-group improvement reported	Arm-level data needed
FBG	Singh [4]; Engebretson [5]	Reported as metabolic outcome	Extraction incomplete
CRP / hs-CRP	Candidate register	Comparative numeric data unavailable	Not estimable
IL-6	Candidate register	Comparative numeric data unavailable	Not estimable
TNF-α	Iwamoto et al. [2]	Within-group reduction reported	No control group

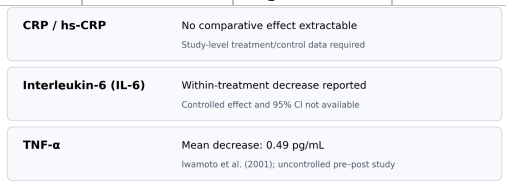


Figure 3. Availability of controlled effect estimates for planned inflammatory biomarker forest plots; pooled effects cannot yet be computed

3.5. Periodontal Clinical Outcomes Following NSPT

3.5.1. Changes in PPD

Even in those cases where HbA1c response was not statistically significant, clinical periodontal measures improved after therapy. Engebretson et al. found an adjusted 0.28 mm (95% CI 0.18 to 0.37) reduction in PPD after six months of non-surgical treatment [5]. This is consistent with the impact on periodontal clinical outcomes with no evidence of glycemic benefit in the same trial. Singh et al. also found that the SRP also improved periodontal measurements with treated patients [4]. However, these reported measures differ in designs and follow-up time and a pooled PPD estimate would need to be verified per arm with difference in changes and variance in eligible trials. The overall impression of the clinical interpretation is that there is no correlation between the bettering of local periodontal inflammatory status and the same systemic metabolic effect. The final synthesis of

PPD outcomes should be guided by standardized definitions, measurement procedures and matched follow-up times.

3.5.2. Changes in CAL and BOP

Other benefits for periodontal health included CAL and BOP. In Engebretson et al., non-surgical therapy resulted in a difference of 0.25 mm (95% CI 0.14 to 0.36) in CAL loss and 13.1 percentage point difference (95% CI 8.1 to 18.1) in BOP at 6 months [5]. They were statistically significant and showed improvements in periodontal health after treatment. Favourable periodontal changes were also noted by Singh et al. in treated subjects [4]. However, the spreadsheet provided at the time does not have all of the arm level results for all candidate studies, and a pooled CAL and BOP effect was not estimated. In addition, the outcome of CAL and BOP is measured in different units (mm vs. percentage), which must be evaluated separately in subsequent synthesis. Current evidence suggests benefits on periodontal clinical parameters; however, the magnitude of the benefits and consistency of the findings in all eligible studies needs to be determined.

3.6. RoB, Heterogeneity, and Certainty of Evidence

3.6.1. Methodological Quality and RoB of Included Studies

The designs of the candidates' studies differed significantly in providing meaningfully different eligibility for a strictly non-surgical randomized comparison. Iwamoto et al. [3] conducted a small uncontrolled intervention, while Singh et al. [4], Engebretson et al.[5] , and D' Aiuto et al. [6] adopted a randomized design. Randomization will minimize susceptibility to certain kinds of confounding, but a clear RoB assessment should consider the allocation bias, lack of adherence to assigned interventions, missing data, measurement of the outcomes, and selective reporting for each outcome. There was no extraction workbook for RoB 2 domain ratings. Thus it would be inappropriate to give numerical designations for low-risk/high-risk studies. The possibility of a surgical component to the D'Aiuto [6] trial is not an automatic RoB classification; rather, it is an eligibility or indirectness issue. RoB summaries should be generated after full text assessment and confirmation to original trial protocols and reports.

3.6.2. Heterogeneity and Sensitivity Analysis

There was some clinical heterogeneity in the registered studies in terms of sample size, clinical intervention, control care and time of measurement of outcomes. In the trial by D'Aiuto et al. [6] follow-up was extended from one month (small Iwamoto) [3] to 12 months. In some studies, adjunctive antibiotics were used, and in some, interventions were used that go beyond non-surgical treatment. However, these description differences do not necessarily indicate statistical heterogeneity. I^2, τ^2, and Cochran's Q necessitate eligible, compatible, effect estimates and their sampling uncertainty. The indices and leave one out sensitivity analysis have not been calculated since the input data is not complete in the workbook. After appropriate comparisons are extracted sensitivity analyses should be conducted to explore the effects of any adjunctive antimicrobials, treatment intensity, RoB, and follow-up period; trials allowing for surgery should be evaluated separately for inclusion.

3.6.3. Publication Bias and Certainty of Evidence

The available candidate-study sample is insufficient for a meaningful evaluation of funnel-plot asymmetry or formal small-study effects. Such procedures require an adequately populated outcome-specific synthesis and generally lack reliability with very few studies. The certainty of evidence should subsequently be assessed separately for HbA1c, FBG, inflammatory biomarkers, and periodontal clinical outcomes, considering methodological limitations, inconsistency, indirectness, imprecision, and publication bias. In the available original trials, HbA1c findings are not uniform, whereas Engebretson et al. documented improvements in periodontal measures despite a neutral glycemic effect [5]. This difference highlights the need to distinguish periodontal efficacy from systemic metabolic outcomes. Table 3 summarizes verified individual-study estimates and current extraction status, without assigning unsupported pooled estimates or certainty categories. Formal evidence grading remains dependent on completion of eligible-study selection, RoB assessment, and outcome-specific synthesis.

Table 3: Summary of findings for glycemic, inflammatory, and periodontal outcomes (GRADE column omitted)

Outcome	Original-study evidence	Effect estimate (95% CI)	Statistical significance
HbA1c	Engebretson et al. [5]	Adjusted MD −0.05 (−0.23 to 0.12)	P=0.55
HbA1c	D'Aiuto et al. [6]	Adjusted treatment-minus-control −0.60 (−0.90 to −0.30)	P<0.0001
FBG	Singh [4]; Engebretson [5]	Not established	Not determined

CRP/hs-CRP	Extraction incomplete	Not estimable	Not determined
IL-6	Extraction incomplete	Not estimable	Not determined
TNF-α	Iwamoto et al. [3]	Uncontrolled reduction reported	Controlled effect unavailable
PPD	Engebretson et al. [5]	Improvement 0.28 mm (0.18 to 0.37)	P<0.001
CAL	Engebretson et al. [5]	Improvement 0.25 mm (0.14 to 0.36)	P<0.001
BOP	Engebretson et al. [5]	Improvement 13.1 percentage points (8.1 to 18.1)	P<0.001

4. Discussion

Original clinical evidence relating to effects of NSPT on glycemic control, systemic inflammatory biomarkers, and periodontal health in patients with T2DM and periodontitis were reviewed critically. The periodontal clinical parameters that were measured improved in most of the investigations, with the exception of glycemic regulation, and the results were mixed. Engebretson et al. [5] did not find a statistically significant difference in HbA1c after NSPT (adjusted mean difference: −0.05 percentage points (95% CI: −0.23 to 0.12). In contrast, D'Aiuto et al. [6] found that after intensive periodontal therapy, the adjusted HbA1c level decreased 0.60 percentage points, compared with the control group. Importantly, the latter allowed periodontal surgery to be performed, which meant that it was only applicable directly to strictly non-surgical treatment protocols. The two different results indicate that intensity of treatment, pre-therapy glycemic control, severity of the periodontal disease, and duration of follow-up may explain some of the differences in metabolic results. Biological evidence suggests that periodontal inflammation may be associated with systemic metabolic dysfunction through increased inflammatory activity, which includes TNF-α, IL-6, CRP with potential impact on insulin signaling and glucose homeostasis [10]. Antimicrobial periodontal therapy (APT) has been shown to decrease both circulating TNF-α and HbA1c after APT, but the lack of control in this report does not allow for definitive comparison of treatment effects [11].

Also, the Cochrane systematic review conducted by Simpson et al. [12] found an average reduction in HbA1c of around 0.43 percentage points after periodontal treatment at 3 to 4 months. This estimate has been published and compiled from pooled evidence and is not calculated in this review.

5. Limitations

Lack of comparable measurements of inflammatory biomarkers further hindered firm conclusions about the systemic anti-inflammatory activity of NSPT. Periodontium assessment and therapy can be important part of the multidisciplinary diabetes management but should not be a substitute for the established glycemic therapy. Some significant shortcomings include that studies were not identified beyond a preliminary stage, variation in intervention procedures, small sample sizes in some studies, quantitative extraction was not complete, there were no independent pooled analyses or formal RoB assessments. RCTs should be multicenter and standard non-surgical interventions should be used, with the same comparator groups, longer follow-up times, and the same measurements of HbA1c, FBG, CRP, IL-6, and TNF-α. Systematic reviews that include accurate level-of-evidence study-level data are needed to quantify (magnitude, consistency, and clinical relevance) the effects of systemic treatment.

6. Conclusion

The present review highlights the clinical relevance of NSPT in managing periodontal disease among patients with T2DM, while emphasizing the uncertainty surrounding its systemic metabolic and inflammatory effects. The evaluated clinical investigations demonstrated improvements in periodontal parameters, including PPD, CAL, and BOP. However, findings regarding glycemic control were inconsistent, with some studies reporting reductions in HbA1c and others demonstrating no statistically significant benefit. Although reductions in inflammatory mediators, particularly TNF-α, have been reported following periodontal treatment, the available controlled evidence is insufficient to establish a consistent systemic anti-inflammatory effect. Differences in study design, treatment protocols, sample sizes, and follow-up durations further limit direct comparisons between investigations. These findings support the importance of periodontal assessment, oral hygiene education, and appropriate periodontal treatment as components of multidisciplinary diabetes care. Nevertheless, NSPT should be considered complementary to established antidiabetic management rather than an alternative treatment for glycemic control. Future research should prioritize adequately powered,

multicenter RCTs employing standardized non-surgical interventions, appropriate comparator groups, longer follow-up periods, and consistent assessment of glycemic and inflammatory outcomes. Comprehensive systematic reviews with verified study-level data and rigorous quantitative synthesis are necessary to determine the magnitude, consistency, and long-term clinical significance of potential systemic benefits.

Conflicts of Interest: Nil

Financial Support: None

References

1.Sanz M, Ceriello A, Buysschaert M, Chapple I, Demmer RT, Graziani F, et al. Scientific evidence on the links between periodontal diseases and diabetes: consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International Diabetes Federation and the European Federation of Periodontology. J Clin Periodontol. 2018;45(2):138-149. doi:10.1111/jcpe.12808.

2. Demmer RT, Jacobs DR Jr, Desvarieux M. Periodontal disease and incident type 2 diabetes: results from the First National Health and Nutrition Examination Survey and its epidemiologic follow-up study. Diabetes Care. 2008;31(7):1373-1379. doi:10.2337/dc08-0026.

3. Iwamoto Y, Nishimura F, Nakagawa M, Sugimoto H, Shikata K, Makino H, et al. The effect of antimicrobial periodontal treatment on circulating tumor necrosis factor-alpha and glycated hemoglobin level in patients with type 2 diabetes. J Periodontol. 2001;72(6):774-778. doi:10.1902/jop.2001.72.6.774.

4. Singh S, Kumar V, Kumar S, Subbappa A. The effect of periodontal therapy on the improvement of glycemic control in patients with type 2 diabetes mellitus: a randomized controlled clinical trial. Int J Diabetes Dev Ctries. 2008;28(2):38-44. doi:10.4103/0973-3930.43097.

5. Engebretson SP, Hyman LG, Michalowicz BS, Schoenfeld ER, Gelato MC, Hou W, et al. The effect of nonsurgical periodontal therapy on hemoglobin A1c levels in persons with type 2 diabetes and chronic periodontitis: a randomized clinical trial. JAMA. 2013;310(23):2523-2532. doi:10.1001/jama.2013.282431.

6. D'Aiuto F, Gkranias N, Bhowruth D, Khan T, Orlandi M, Suvan J, et al. Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. Lancet Diabetes Endocrinol. 2018;6(12):954-965. doi:10.1016/S2213-8587(18)30038-X.

7. Dağ A, Firat ET, Arikan S, Kadiroğlu AK, Kaplan A. The effect of periodontal therapy on serum TNF-alpha and HbA1c levels in type 2 diabetic patients. Aust Dent J. 2009;54(1):17-22. doi:10.1111/j.1834-7819.2008.01083.x.

8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71.

9. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. doi:10.1136/bmj.l4898.

10. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. doi:10.1136/bmj.i4919.

11. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD.

12. Simpson TC, Clarkson JE, Worthington HV, MacDonald L, Weldon JC, Needleman I, et al. Treatment of periodontitis for glycaemic control in people with diabetes mellitus. Cochrane Database Syst Rev. 2022;4(4):CD004714. doi:10.1002/14651858.CD004714.pub4.