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Non-Surgical Periodontal Therapy and High-Sensitivity C-Reactive Protein in Type 2 Diabetes: Secondary Analysis of a Randomized Trial

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Highlights

What are the main findings?

- Non-surgical periodontal therapy (NSPT) did not significantly reduce hsCRP at 3 months compared with oral hygiene instructions alone, but by 6 months the NSPT group had a clearly lower hsCRP, corresponding to about a 19% reduction.
- Periodontal clinical parameters improved more in the NSPT group, but changes in these local measures were not independently associated with the change in hsCRP after adjusting for treatment group.

What are the implications of the main findings?

- The sustained reduction in hsCRP at 6 months suggests that NSPT may contribute to lowering systemic low-grade inflammation in patients with type 2 diabetes and periodontitis, supporting its potential role in integrated diabetes and cardiometabolic care.
- Because hsCRP changes only became evident after 6 months and were not tightly linked to individual periodontal improvements, longer-term maintenance and larger trials with clinical endpoints are needed before this effect can be confidently translated into cardiovascular or diabetes-complication risk reduction.

Abstract

Background: Type 2 diabetes mellitus (T2DM) and periodontitis are chronic inflammatory conditions. Periodontitis may amplify low-grade systemic inflammation in people with T2DM. High-sensitivity C-reactive protein (hsCRP) reflects this inflammatory burden, but the effect of non-surgical periodontal therapy (NSPT) on hsCRP in T2DM remains uncertain. **Objective:** To evaluate whether NSPT changes hsCRP at 3 and 6 months compared with oral hygiene instructions alone in patients with T2DM and periodontitis. **Methods:** Predefined secondary analysis of a 1:1 parallel-group randomized trial with assessments at baseline, 3 months, and 6 months. Participants received scaling and root planing plus oral hygiene instructions (intervention) or oral hygiene instructions only (control). Fasting hsCRP (mg/L) was analyzed on the log scale using mixed-effects models; effects are presented as exponentiated ratios with 95% confidence intervals. Sensitivity analyses included baseline-adjusted analysis of covariance (ANCOVA) and covariate-adjusted mixed models. An exploratory group-adjusted regression examined associations between periodontal changes and hsCRP change. **Results:** Eighty-nine participants were randomized (45 control, 44 intervention), with hsCRP available for most participants through 6 months. There was no between-group difference at

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3 months (ratio 0.958; 95% CI 0.875–1.049; p=0.358). At 6 months, hsCRP was lower in the NSPT group than in controls (ratio 0.809; 95% CI 0.738–0.887; p<0.001), corresponding to ~19% lower hsCRP; the model-based geometric mean hsCRP at 6 months was 2.66 mg/L versus 3.26 mg/L. Periodontal measures improved more with NSPT, but changes in periodontal measures were not independently associated with hsCRP change after group adjustment. **Conclusions:** In patients with T2DM and periodontitis, NSPT was associated with lower hsCRP at 6 months, suggesting a potential systemic anti-inflammatory benefit. These findings support periodontal care as part of integrated management in T2DM.

Keywords: type 2 diabetes mellitus; periodontitis; high-sensitivity C-reactive protein

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic condition characterized by low-grade systemic inflammation, which contributes to insulin resistance and cardiometabolic complications. High-sensitivity C-reactive protein (hsCRP) is a sensitive biomarker of systemic low-grade inflammation, produced predominantly in the liver and regulated by pro-inflammatory cytokines (notably interleukin-6 [IL-6], with contributions from interleukin-1β [IL-1β] and tumor necrosis factor-alpha [TNF-α]) [1]. Unlike conventional CRP assays, hsCRP allows detection of subtle elevations in circulating CRP concentrations, making it particularly suitable for assessing chronic inflammatory burden. Elevated hsCRP levels have been consistently associated with increased cardiovascular morbidity and mortality and are considered a reliable marker of systemic inflammatory activity [2–4].

Periodontitis is a chronic, biofilm-induced inflammatory disease characterized by persistent bacterial challenge and dysregulated host immune response. Periodontal pathogens and their virulence factors, including lipopolysaccharides (LPS), can enter the systemic circulation, promoting transient bacteremia and endotoxemia. This systemic dissemination stimulates hepatic acute-phase response pathways and amplifies cytokine production, contributing to elevated hsCRP levels. In patients with type 2 diabetes mellitus (T2DM), chronic hyperglycemia leads to the formation of advanced glycation end products (AGEs), oxidative stress, and activation of inflammatory signaling pathways such as NF-κB. These mechanisms exacerbate systemic inflammation and impair immune regulation. The bidirectional relationship between periodontitis and diabetes further intensifies inflammatory burden, creating a pathogenic feedback loop characterized by increased IL-6, TNF-α, and CRP production [5–7]. Consistent with this oral–systemic link, consensus reports and clinical guidance support periodontal care as part of comprehensive diabetes management [6,7]. Non-surgical periodontal therapy (NSPT), by reducing subgingival bacterial load and resolving local periodontal inflammation, may attenuate systemic cytokine levels and modulate the acute-phase response. Consequently, assessing changes in hsCRP following NSPT provides valuable insight into the systemic anti-inflammatory potential of periodontal treatment, particularly in patients with T2DM, who represent a high-risk group for both periodontal destruction and cardiovascular complications [8,9].

The aim of this study was to determine whether NSPT reduces systemic inflammation, as measured by hsCRP, in patients with T2DM and periodontitis compared with a control group. The primary objective was to evaluate the effect of NSPT on hsCRP levels at 6 months. Secondary objectives were to assess changes in hsCRP at 3 months and to examine the pattern of systemic inflammatory response over the study period.

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2. Materials and Methods

2.1. Study Design and Participants

This study was a single-centre, parallel-group randomized controlled clinical trial (1:1 allocation) conducted to evaluate the effect of non-surgical periodontal therapy on systemic inflammation in patients with T2DM and periodontitis. It was approved by the Ethics Committee of the University of Medicine of Tirana, and all participants provided written informed consent before enrollment. The trial had a longitudinal design with assessments at baseline, 3 months, and 6 months. The study protocol followed SPIRIT recommendations, and reporting adheres to CONSORT guidance. The trial was registered in the ISRCTN registry (ISRCTN12954826). A total of 89 participants meeting the eligibility criteria were enrolled and randomized to the intervention or control group; participant flow is presented in the CONSORT diagram (Figure 1). Eligible participants were adults aged 18–70 years with a diagnosis of T2DM, HbA1c ≥7%, and periodontitis defined as ≥4 teeth with at least one site with probing depth (PD) ≥5 mm and full-mouth bleeding on probing (BOP) ≥10%, and with ≥10 natural teeth. Exclusion criteria included periodontal treatment within the previous 6 months, systemic antibiotic use within the previous 3 months, systemic conditions affecting periodontal response, pregnancy or breastfeeding, and inability to attend follow-up visits.

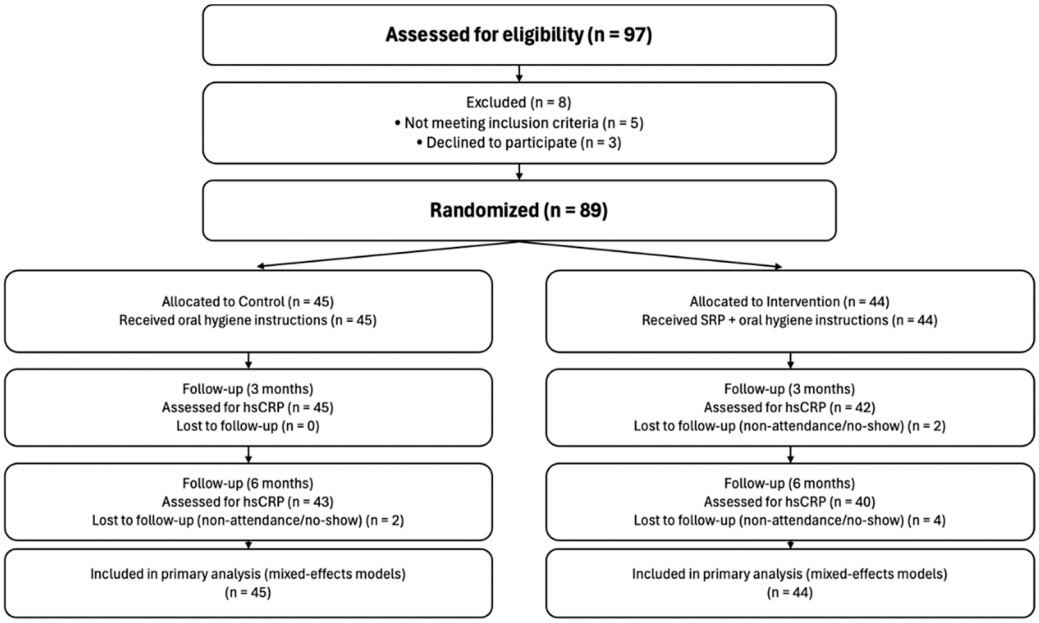

Figure 1. CONSORT flow diagram. Note: Mixed-effects models included all available hsCRP observations at each time point. Baseline-to-6-month change analyses were restricted to participants with hsCRP at baseline and 6 months (n = 83: Control 43; Intervention 40).

2.2. Randomization, Masking, and Clinical Procedures

Participants were randomized after completion of baseline assessments using a computer-generated 1:1 allocation sequence prepared by an independent operator who was not involved in enrollment, treatment delivery, or outcome assessment. Group assignment was concealed using consecutively numbered sealed envelopes that were prepared in advance and opened only after enrollment. Periodontal examinations were performed by a single examiner and as the intervention was procedural, neither participants nor clinicians could be masked to group allocation. Periodontal examinations were performed using a standardized protocol. PD and clinical attachment level (CAL) were recorded at six sites per tooth. BOP was recorded and expressed as the percentage of sites with bleeding. Gingival index (GI) and plaque index (PI) were recorded on a 0–3 scale. Fasting venous

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blood samples were collected at baseline, 3 months, and 6 months. Laboratory personnel were blinded to treatment allocation. Sampling and hsCRP analyses were outsourced to an accredited laboratory. The assay platform/manufacturer was not provided in the laboratory report.

2.3. Interventions

Participants in the intervention group received full-mouth NSPT consisting of scaling and root planing (SRP) using manual and ultrasonic instruments, together with oral hygiene instructions. Treatment was delivered as full-mouth therapy in a single visit (one session). Supportive periodontal therapy was provided at 3 and 6 months and included reinstrumentation of residual sites as needed, professional polishing, and reinforcement of oral hygiene instructions. The control group received oral hygiene instructions only during the study period. For ethical reasons, full non-surgical periodontal therapy was offered to control group participants after completion of the 6-month follow-up.

2.4. Statistical Analysis

Analyses were conducted according to randomized treatment allocation. All available hsCRP measurements from randomized participants were analyzed using linear mixed-effects models (participant-level random intercept) with fixed effects for group, time (baseline, 3 months, 6 months), and group x time interaction. Given the skewed distribution of hsCRP, analyses were performed on the log scale; results are presented as exponentiated effects (ratios) with 95% confidence intervals. The primary contrast was the between-group difference in change from baseline at 6 months; the 3-month contrast was prespecified as secondary. Sensitivity analyses included baseline-adjusted analysis of covariance (ANCOVA) at each follow-up (log[hsCRP] at follow-up adjusted for baseline log[hsCRP]) and a covariate-adjusted mixed model including baseline age, sex, BMI, smoking status, statin use, baseline HbA1c, and diabetes duration. Values >10 mg/L were prespecified to indicate possible acute inflammation. Periodontal outcomes (PD, CAL, BOP, GI, PI) were analyzed using analogous mixed-effects models. Exploratory analyses (restricted to participants with hsCRP at baseline and 6 months) assessed associations between Δlog (hsCRP) and changes in periodontal measures (ΔBOP, ΔPD, ΔCAL) using linear regression adjusted for treatment group. Mixed-effects models used all available observations and implicitly accommodated incomplete follow-up under a missing-at-random assumption; we did not impute missing hsCRP values. Analyses were performed using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Participant Flow and Baseline Data

Participant flow is shown in the CONSORT diagram (Figure 1). A total of 89 participants were randomized (Control n=45; Intervention n=44).

hsCRP measurements were available at baseline for all participants (n=89), at 3 months for n=87 (Control n=45; Intervention n=42), and at 6 months for n=83 (Control n=43; Intervention n=40) (Table 1).

Table 1. Number of participants with available hsCRP measurements.

Group	Baseline	3 months	6 months
Control	45	45	43
Intervention	44	42	40

Baseline demographic and clinical characteristics were comparable between groups (Table 2), and baseline hsCRP values were similar (median [IQR] 3.36 [2.36–4.76] mg/L in the control group vs 3.34 [2.48–4.60] mg/L in the intervention group).

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Table 2. Baseline characteristics.

Variable	Control	Intervention
Participants, n	45	44
Sex: Female	22 (48.9%)	23 (52.3%)
Sex: Male	23 (51.1%)	21 (47.7%)
Smoking: Current	10 (22.2%)	7 (15.9%)
Smoking: Former	18 (40.0%)	17 (38.6%)
Smoking: Never	17 (37.8%)	20 (45.5%)
Statin use	30 (66.7%)	29 (65.9%)
Age	49.80 ± 10.79	53.23 ± 10.88
BMI (kg/m²)	28.88 ± 4.10	30.44 ± 4.72
HbA1c percent	8.21 ± 0.80	8.33 ± 0.59
Diabetes Duration years	8.82 ± 4.54	8.76 ± 5.07
PD mm	5.94 ± 0.59	5.93 ± 0.55
CAL mm	7.21 ± 0.67	7.12 ± 0.66
BOP percent	62.18 ± 13.17	60.44 ± 16.38
GI index	2.08 ± 0.51	2.04 ± 0.46
PI index	2.09 ± 0.45	1.92 ± 0.61
hsCRP mg L	3.36 [2.36–4.76]	3.34 [2.48–4.60]

Missing hsCRP at follow-up occurred because participants did not attend the visit and/or did not provide a blood sample (3 months: 0/45 control, 2/44 intervention; 6 months: 2/45 control, 4/44 intervention).

3.2. hsCRP Outcomes

Model-based geometric mean hsCRP values (95% CI) are shown in Table 3 and Figure 2.

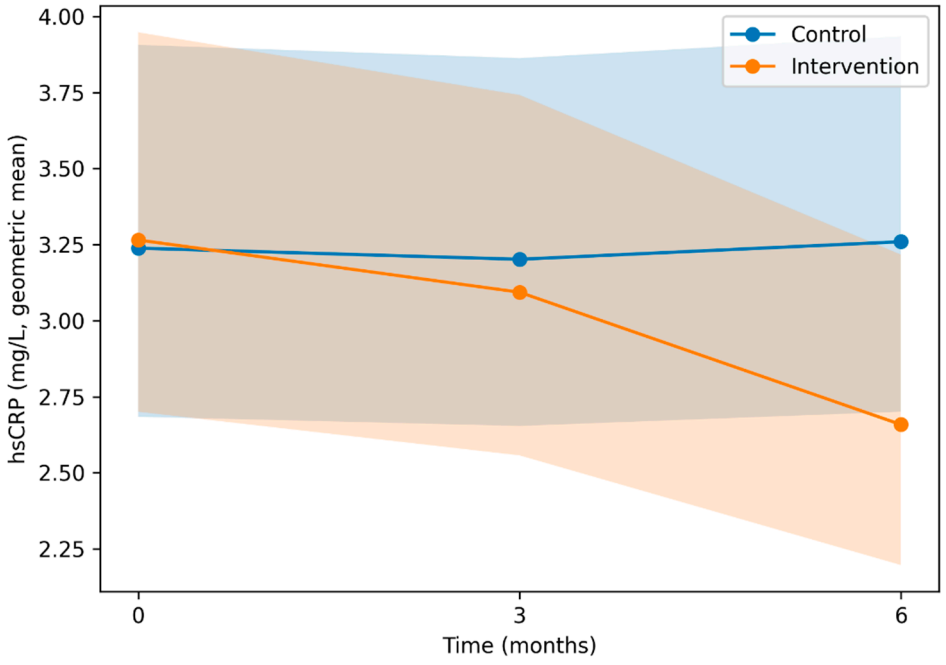

Figure 2. hsCRP over time (model-based geometric mean ±95% CI).

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Table 3. hsCRP by group and time (mixed model; geometric mean + 95% CI).

Group	Time_Months	Geometric mean (mg/L)	95% CI
Control	0	3.24	2.68–3.91
Control	3	3.20	2.65–3.86
Control	6	3.26	2.70–3.93
Intervention	0	3.27	2.70–3.95
Intervention	3	3.09	2.56–3.74
Intervention	6	2.66	2.20–3.22

In the primary log-scale mixed-effects model, there was no evidence of a between-group difference in hsCRP change at 3 months (ratio 0.958; 95% CI 0.875–1.049; p=0.358) (Table 4).

Table 4. Between-group difference in change in hsCRP (ratio; mixed model).

Time (months)	Ratio (95% CI)	% difference	p
3	0.958 (0.875–1.049)	-4.2%	0.358
6	0.809 (0.738–0.887)	-19.1%	<0.001

At 6 months, the intervention group demonstrated a significantly greater reduction in hsCRP compared with control (ratio 0.809; 95% CI 0.738–0.887; p<0.001), corresponding to an approximately 19% lower hsCRP relative to control. In absolute terms, the model-based geometric mean hsCRP at 6 months was 2.66 mg/L (95% CI 2.20–3.22) in the intervention group versus 3.26 mg/L (95% CI 2.70–3.93) in the control group (difference in model-based geometric means −0.60 mg/L). From baseline to 6 months, geometric mean hsCRP remained essentially stable in the control group (3.24 to 3.26 mg/L) but decreased in the intervention group (3.27 to 2.66 mg/L). No hsCRP values exceeded 10 mg/L at any time point. Sensitivity analyses were consistent with the primary model. Baseline-adjusted ANCOVA yielded similar results, including a significant effect at 6 months (ratio 0.809; 95% CI 0.727–0.899; p<0.001) (Table 5), and results were consistent in covariate-adjusted mixed-effects models (Table 6).

Table 5. Sensitivity ANCOVA (ratio at 3 and 6 months).

Time (months)	n	Ratio (95% CI)	p
3	87	0.958 (0.900–1.020)	0.1766
6	83	0.809 (0.727–0.899)	<0.001

Table 6. Sensitivity covariate-adjusted mixed model (ratio).

Time (months)	Ratio (95% CI)	p
3	0.958 (0.875–1.050)	0.3597
6	0.809 (0.738–0.887)	<0.001

3.3. Periodontal Outcomes and Exploratory Associations

Periodontal parameters improved over follow-up, with greater improvements in the intervention group (Table 7; Figures 3–7).

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Table 7. Between-group differences in change in periodontal outcomes.

Outcome	Time (months)	Between-group difference in change (95% CI)	p
PD (mm)	3	-0.22 (-0.34–-0.10)	0.0003
PD (mm)	6	-0.34 (-0.46–-0.22)	<0.001
CAL (mm)	3	-0.19 (-0.33–-0.05)	0.0081
CAL (mm)	6	-0.39 (-0.53–-0.25)	<0.001
BOP (%)	3	-9.78 (-13.43–-6.13)	<0.001
BOP (%)	6	-14.72 (-18.44–-11.01)	<0.001
GI (0–3)	3	-0.38 (-0.47–-0.28)	<0.001
GI (0–3)	6	-0.38 (-0.47–-0.28)	<0.001
PI (0–3)	3	-0.28 (-0.39–-0.18)	<0.001
PI (0–3)	6	-0.39 (-0.49–-0.28)	<0.001

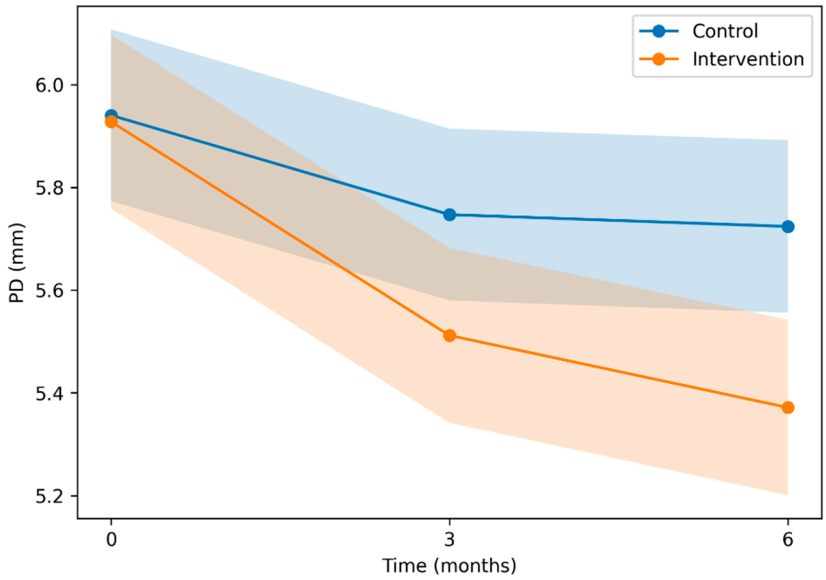

Figure 3. Mean probing depth over time (±95% CI).

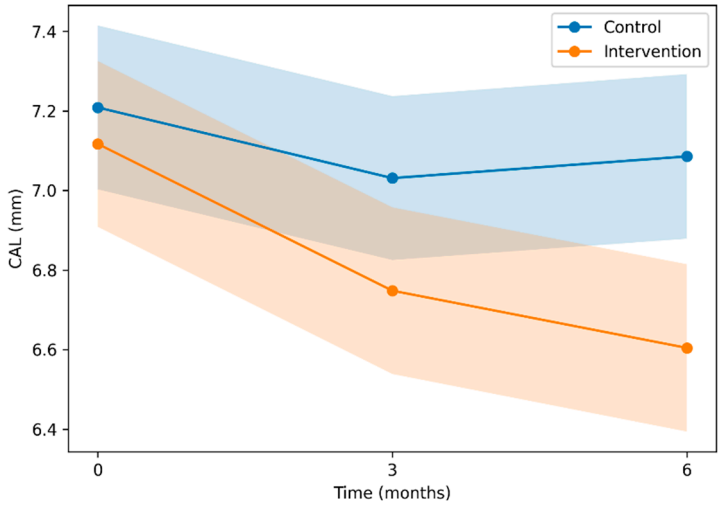

Figure 4. Mean clinical attachment level over time (±95% CI).

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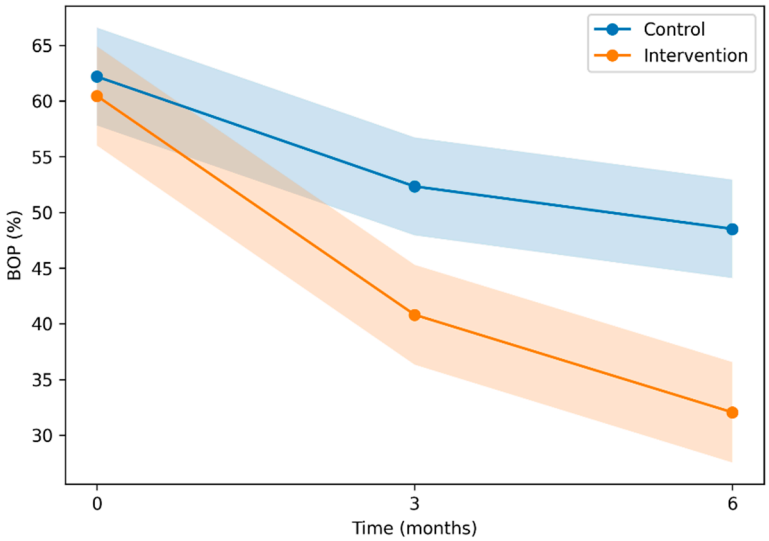

Figure 5. Bleeding on probing over time (±95% CI).

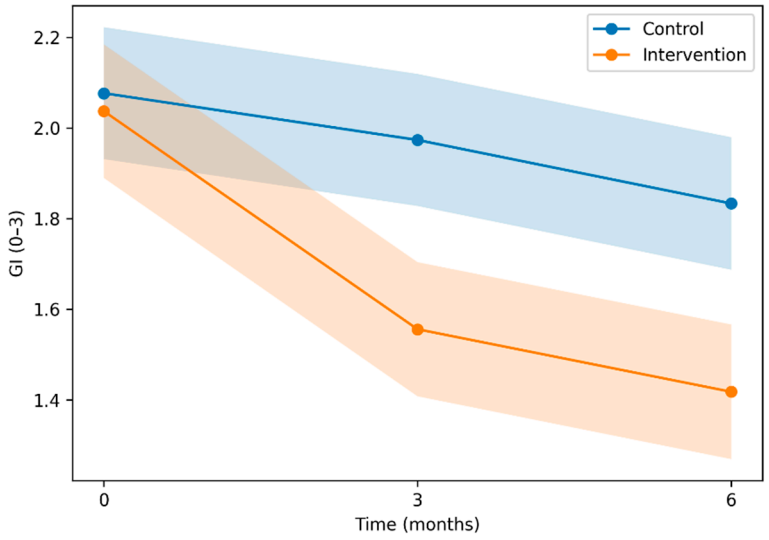

Figure 6. Gingival index over time (±95% CI).

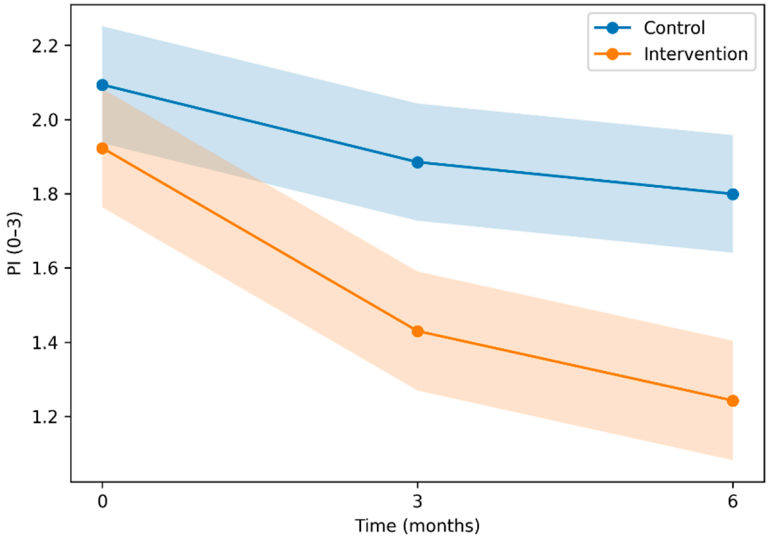

Figure 7. Plaque index over time (±95% CI).

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In exploratory analyses (baseline to 6 months), changes in periodontal measures were not independently associated with changes in hsCRP after adjusting for treatment group (all $p \geq 0.417$) (Table 8).

Table 8. Exploratory associations (Δlog hsCRP vs Δperiodontal measures).

Predictor	Effect (95% CI)	p	N
ΔBOP	0.002 (-0.005–0.009)	0.5582	83
ΔPD	-0.039 (-0.244–0.166)	0.7068	83
ΔCAL	-0.071 (-0.244–0.102)	0.4171	83

Scatterplots of change in log(hsCRP) versus change in BOP and PD are shown in Figures 8 and 9.

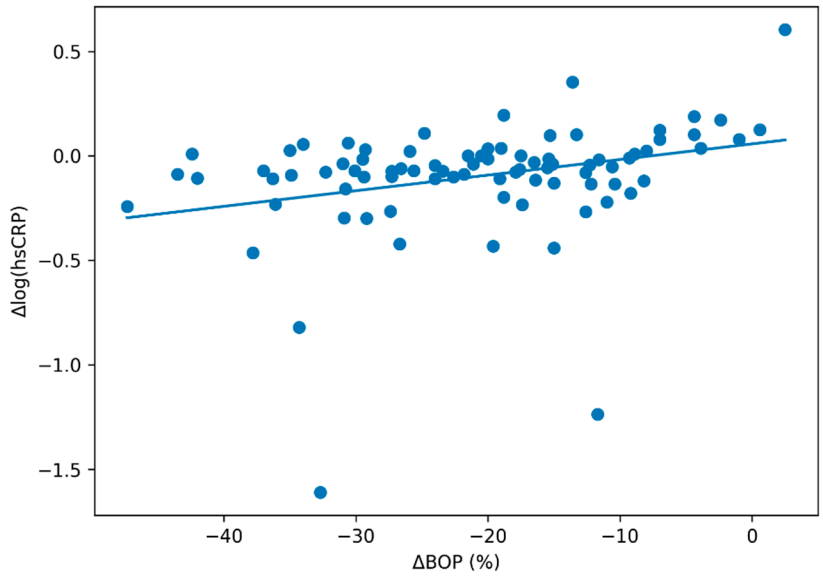

Figure 8. Change in log(hsCRP) vs change in BOP (baseline to 6 months).

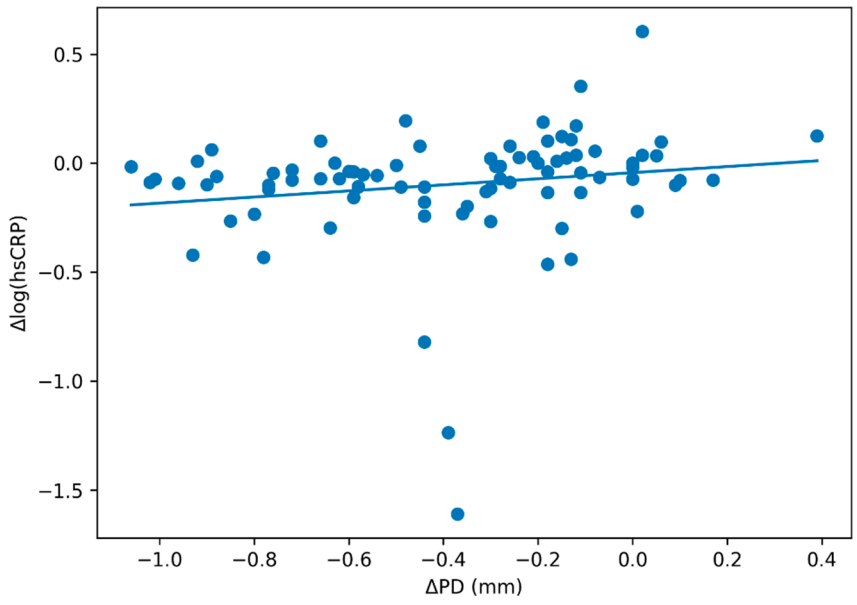

Figure 9. Change in log(hsCRP) vs change in PD (baseline to 6 months).

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4. Discussion

In this predefined secondary analysis of a randomized controlled trial in adults with T2DM and periodontitis, non-surgical periodontal therapy was associated with lower hsCRP at 6 months compared with oral hygiene instructions alone, whereas no clear between-group difference was observed at 3 months. Findings were consistent across sensitivity analyses. As expected, periodontal clinical measures improved more in the intervention group, confirming effective local disease control. Exploratory analyses did not demonstrate a clear association between the magnitude of periodontal improvement and hsCRP change after accounting for treatment assignment. This may reflect limited power to detect dose–response relationships and/or that hsCRP is influenced by factors not captured by individual clinical periodontal measures.

The absence of a detectable between-group difference at 3 months, followed by a clear separation at 6 months, is biologically plausible in a chronic inflammatory setting such as T2DM. Periodontal healing and stabilization may require sustained suppression of the subgingival inflammatory burden and maintenance before systemic inflammatory signaling decreases sufficiently to be detected by hsCRP, a biomarker with substantial within-person variability. In addition, supportive periodontal therapy and reinforcement of oral hygiene during follow-up may contribute to a more durable reduction of periodontal inflammation over time. Nonetheless, alternative explanations should be considered. The intervention group had more clinical contact than controls, which could influence oral-health behaviors and other health behaviors, and hsCRP can be affected by intercurrent conditions and other unmeasured factors. Therefore, the observed temporal pattern should be interpreted as consistent with a lagged systemic response, while acknowledging potential behavioral and non-specific influences.

The between-group difference corresponds to an approximate 19% relative reduction and an absolute separation of ~0.6 mg/L at 6 months. In clinical risk frameworks, hsCRP values are often interpreted as low (<1 mg/L), intermediate (1–3 mg/L), and high (>3 mg/L) inflammatory risk [8], and hsCRP ≥2 mg/L is frequently used as a risk-enhancing threshold in cardiovascular risk assessment [1,2]. In our cohort, baseline hsCRP values were in a range typically considered elevated, and the intervention group's model-based geometric mean decreased from an elevated range toward lower values within commonly used risk categories. While this magnitude of change suggests a downward shift in systemic inflammatory burden, it does not by itself justify changes in cardiometabolic management, nor does it demonstrate reduced cardiovascular events. Rather, it supports hsCRP as a responsive systemic biomarker following periodontal treatment in this high-risk population.

Although periodontal clinical measures improved more in the intervention group, we did not detect an independent linear association between change in individual periodontal parameters and change in hsCRP after adjustment for treatment group. This finding cautions against a simple dose–response interpretation in which larger local clinical improvements necessarily translate into proportionally larger systemic hsCRP reductions. Several explanations are possible, including limited power for within-group dose–response analyses, measurement variability in both periodontal indices and hsCRP, and the likelihood that systemic inflammation in T2DM reflects multiple concurrent drivers (e.g., adiposity, glycemic control, medication use, and intercurrent conditions). While our models adjusted for key covariates (including statin use), residual confounding cannot be excluded, and hsCRP should be interpreted as a non-specific biomarker rather than a direct proxy for periodontal inflammation.

Evidence supports a two-way association between diabetes and periodontitis, likely mediated by overlapping inflammatory and immune-metabolic pathways linking periodontal inflammation to systemic inflammation [5–7]. CRP reflects hepatic acute-phase responses to inflammatory cytokine signaling and is sensitive to low-grade inflammation [1]. Consistent with this oral–systemic interface, observational studies and meta-analyses report higher circulating CRP/hsCRP in periodontitis than in periodontal health [8], and mechanistic reviews describe potential pathways linking periodontal inflammation to systemic inflammatory comorbidities [10], supporting hsCRP as a relevant systemic outcome in periodontal intervention studies.

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Meta-analyses of randomized trials in mixed populations suggest that non-surgical periodontal therapy can reduce circulating CRP/hsCRP, although effect sizes vary by population, comparator intensity, adjunctive measures, and follow-up duration [9]. Evidence specific to T2DM cohorts is more limited and heterogeneous: systematic reviews report modest and variable effects on glycemic outcomes [14–17,19], and findings for inflammatory biomarkers such as CRP/hsCRP are less consistent across diabetes-focused trials and syntheses [11,17]. Individual randomized trials in T2DM cohorts have reported variable changes in systemic inflammatory markers after periodontal treatment [12,18], and recent systematic reviews suggest that HbA1c improvements after periodontal therapy are modest and heterogeneous [19]. Overall, systemic responses may depend on multiple factors such as baseline inflammation, adiposity, concomitant medications, periodontal severity, and maintenance intensity [5–7]. Within this context, our findings add randomized evidence that hsCRP showed clearer between-group separation at 6 months than at 3 months, consistent with the possibility that sustained periodontal stabilization and maintenance are required before biomarker changes become detectable in patients with T2DM. Compared with mixed-population RCTs, trials in T2DM cohorts have reported more variable systemic responses after NSPT, likely reflecting differences in baseline inflammation and glycemic control, concomitant cardiometabolic therapies (including statins), periodontal severity, and variation in treatment intensity and maintenance protocols [11,12,17,18]. In this context, our findings support hsCRP as a responsive systemic biomarker at 6 months in T2DM while underscoring that effect sizes may be context-dependent and heterogeneous across trials.

CRP is an acute-phase reactant synthesized in the liver, largely regulated by cytokine signaling (notably IL-6), and hsCRP assays capture lower concentrations relevant to chronic inflammation and cardiometabolic risk [1,2]. Periodontitis is a chronic biofilm-driven inflammatory disease with ulcerated pocket epithelium and potential for recurrent bacteremia/endotoxemia, which can increase systemic inflammatory signaling [20]. In T2DM, hyperglycemia-related immune dysfunction, oxidative stress, and advanced glycation end-products may amplify periodontal inflammation and impair resolution, contributing to heightened systemic inflammation [5–7]. Non-surgical periodontal therapy reduces subgingival bacterial load and local inflammation and may thereby attenuate systemic inflammatory responses [9,11,12,18]. Although hsCRP is non-specific, a reduction in this marker may be relevant because hsCRP is widely used to quantify low-grade inflammation and inform cardiometabolic risk assessment [2–4]. Beyond inflammatory biomarkers, periodontal treatment has also been associated with improvements in endothelial function in systematic reviews and meta-analyses, supporting the plausibility of broader cardiometabolic benefits [13]. However, the present results should be interpreted as biomarker improvement rather than evidence of reduced cardiovascular events or diabetes complications, and studies with clinical endpoints are required.

In our study, hsCRP was available for most participants, and mixed-effects models maximized use of repeated measures while accounting for within-participant correlation. hsCRP analyses were performed by personnel blinded to treatment allocation, limiting outcome measurement bias. Nevertheless, several limitations should be considered. The trial was conducted at a single center, which may limit generalizability. Blinding of participants and treating clinicians was not feasible, and periodontal examinations were performed by a single examiner who was not blinded to allocation; moreover, the intervention group received more clinical contact than the control group. These factors may introduce performance bias and potential assessment bias despite the use of a standardized protocol. hsCRP is a non-specific biomarker influenced by adiposity, smoking, intercurrent illness, and concomitant medications (e.g., statins), which are common in T2DM populations [1,2,4]. Although no hsCRP values exceeded 10 mg/L, residual confounding and biological variability cannot be excluded. The modest sample size also limits precision in secondary and exploratory analyses and reduces power to detect treatment-effect heterogeneity. Because participants and clinicians were not blinded and the intervention involved greater clinical contact than the control, performance effects (behavior change) and detection bias in clinical periodontal measures are possible despite standardized assessments.

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Finally, while the sample size supported the primary longitudinal comparison, it may have been insufficient to detect modest dose–response relationships or treatment effect heterogeneity; exploratory associations between periodontal changes and hsCRP should therefore be interpreted as hypothesis-generating rather than causal. Future trials should include longer follow-up with clearly defined maintenance protocols and consider stratification by baseline inflammatory status and glycemic control. Broader biomarker panels (e.g., IL-6, TNF-α) may help clarify underlying inflammatory pathways. Studies incorporating clinical endpoints or validated surrogate outcomes are also needed to determine whether improvements in inflammatory biomarkers translate into reduced cardiometabolic risk.

5. Conclusions

In patients with T2DM and periodontitis, NSPT was associated with a greater reduction in hsCRP at 6 months than oral hygiene instructions alone, with consistent findings across sensitivity analyses. Exploratory analyses did not demonstrate an independent dose–response relationship between changes in clinical periodontal status and hsCRP. These findings are hypothesis-generating for systemic inflammatory benefit and should not be interpreted as evidence of reduced cardiovascular events or diabetes complications; adequately powered multicenter trials with longer follow-up and clinical endpoints are needed.

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Abbreviations

The following abbreviations are used in this manuscript:

AGEs	advanced glycation end products
ANCOVA	analysis of covariance
BMI	body mass index
BOP	bleeding on probing
CAL	clinical attachment level
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRP	C-reactive protein
GI	gingival index
HbA1c	glycated hemoglobin

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hsCRP	high-sensitivity C-reactive protein
IL-1β	interleukin-1 beta
IL-6	interleukin-6
IQR	interquartile range
ISRCTN	International Standard Randomised Controlled Trial Number
LPS	lipopolysaccharides
NF-κB	nuclear factor kappa B
NSPT	non-surgical periodontal therapy
PD	probing depth
PI	plaque index
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SRP	scaling and root planing
T2DM	type 2 diabetes mellitus
TNF-α	tumor necrosis factor-alpha

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