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Impact of non-surgical periodontal therapy on systemic inflammatory biomarkers in patients with metabolic syndrome: A randomized controlled trial

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Abstract:
Metabolic syndrome is associated with chronic low-grade inflammation and periodontal inflammation may add to this systemic inflammatory burden. Therefore, it is of interest to evaluate the effect of non-surgical periodontal therapy on periodontal parameters and systemic biomarkers among 80 patients with metabolic syndrome and Stage II/III periodontitis allocated to immediate therapy or delayed therapy control. At 3 months, the therapy group showed significantly greater reductions in probing pocket depth, clinical attachment loss, periodontal inflamed surface area, high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-alpha and HbA1c than the control group. High-sensitivity C-reactive protein decreased from 4.8 ± 1.9 to 3.1 ± 1.4 mg/L in the therapy group compared with 4.7 ± 1.8 to 4.4 ± 1.7 mg/L in controls (between-group $p<0.001$). Thus, non-surgical periodontal therapies help reduce systemic inflammatory load and modestly improve glycemic status in metabolic syndrome, supporting periodontal care as part of integrated cardiometabolic risk management.

Keywords: Periodontitis, metabolic syndrome, C-reactive protein (CRP), interleukin-6, tumor necrosis factor-alpha, HbA1c, randomized controlled trial (RCT)

Background:
Metabolic syndrome is a cluster of abdominal obesity, dysglycemia, hypertension, hypertriglyceridemia and reduced high-density lipoprotein cholesterol. It is associated with insulin resistance, endothelial dysfunction and chronic low-grade inflammation that increase cardiovascular and diabetes risk **[1-4]**. Periodontitis is a chronic inflammatory disease initiated by dysbiotic subgingival biofilm and modified by host immune response. Severe periodontal inflammation may contribute to systemic inflammatory burden through bacteremia, endotoxemia, cytokine release and hepatic acute-phase response **[5-8]**. Patients with metabolic syndrome may be particularly susceptible to periodontal destruction because adipose tissue-derived inflammatory mediators and altered insulin signaling can intensify periodontal inflammation. Conversely, periodontal inflammation may worsen systemic metabolic dysregulation **[9-12]**. High-sensitivity C-reactive protein, interleukin-6 and tumor necrosis factor-alpha are commonly studied biomarkers linking periodontitis with cardiometabolic conditions. These markers participate in endothelial activation, insulin resistance and inflammatory amplification **[13-16]**. Non-surgical periodontal therapy reduces local periodontal inflammation through scaling, root surface debridement, plaque control and behavioral reinforcement. Evidence suggests that successful periodontal treatment can reduce systemic inflammatory markers and improve endothelial function in some populations **[17-20]**. However, the magnitude of systemic improvement in patients with metabolic syndrome remains uncertain. Trials differ in periodontal severity, adjunctive antimicrobial use, biomarker selection, follow-up period and control conditions. Some studies show significant biomarker reduction, while others report modest or inconsistent effects **[21-24]**. HbA1c is not a primary diagnostic criterion for metabolic syndrome, but it provides clinically useful information about glycemic exposure. If periodontal therapy reduces inflammatory interference with insulin signaling, a small improvement in HbA1c may be expected over 3 months **[25-28]**. The periodontal inflamed surface area is a useful measure of inflammatory burden because it estimates the epithelial surface area of bleeding periodontal pockets. It may correlate more directly with systemic biomarker changes than isolated probing pocket depth **[29, 30]**. Therefore, it is of interest to evaluate the effect of non-surgical periodontal therapy on systemic inflammatory biomarkers and glycemic status in patients with metabolic syndrome and periodontitis.

Materials and Methods:

This parallel-arm randomized controlled trial was conducted in the Department of Periodontology over 12 months. Eighty adults aged 35-65 years with metabolic syndrome and Stage II or Stage III periodontitis were enrolled and randomly allocated in a 1:1 ratio to immediate non-surgical periodontal therapy or delayed therapy control. Randomization was performed using computer-generated blocks of four with sealed opaque envelopes. Metabolic syndrome was diagnosed according to harmonized criteria when at least three of the following were present: increased waist circumference, elevated triglycerides, reduced HDL cholesterol, elevated blood pressure, or elevated fasting plasma glucose. Periodontitis diagnosis and staging followed current periodontal classification criteria. Inclusion required at least 20 teeth, probing pocket depth >=5 mm at four or more sites and bleeding on probing >25%. Exclusion criteria were pregnancy, lactation, current smoking, antibiotic use within 3 months, periodontal therapy within 6 months, immunosuppressive medication, chronic kidney disease, active infection, malignancy and change in antidiabetic or lipid-lowering medication during the study period. The therapy group received full-mouth scaling and root surface debridement under local anesthesia within two visits, oral hygiene instruction, interdental cleaning demonstration and reinforcement at 1 month. The control group received supragingival prophylaxis and oral hygiene advice at baseline and was offered complete periodontal therapy after 3-month evaluation. Clinical periodontal parameters included plaque index, bleeding on probing, probing pocket depth, clinical attachment level and periodontal inflamed surface area. Blood samples were collected at baseline and 3 months after overnight fasting. High-sensitivity C-reactive protein, interleukin-6 and tumor necrosis factor-alpha were measured using ELISA and HbA1c was measured using standardized laboratory methods. Data were analyzed using SPSS version 26. Intention-to-treat analysis was performed. Continuous data were presented as mean ± standard deviation. Within-group changes were assessed using paired t-test and between-group differences were evaluated using independent t-test or ANCOVA adjusted for baseline values. Categorical data were analyzed using chi-square test. A p value <0.05 was considered statistically significant.

Results:

Seventy-eight participants completed the 3-month evaluation; two were lost to follow-up, one from each group. Baseline demographic, metabolic, periodontal and biomarker values were comparable between groups. Mean age was 49.7 ± 7.6 years in the therapy group and 50.1 ± 7.2 years in controls. At 3 months, the therapy group showed significant reductions in plaque index, bleeding on probing, probing pocket depth, clinical attachment level and periodontal inflamed surface area. Mean probing pocket depth decreased from 4.82 ± 0.61 mm to 3.41 ± 0.52 mm in the therapy group compared with 4.78 ± 0.58 mm to 4.51 ± 0.57 mm in controls. Systemic biomarkers improved significantly in the therapy group. High-sensitivity C-reactive protein decreased by 1.7 ± 1.1 mg/L, interleukin-6 by 1.4 ± 0.9 pg/mL, tumor necrosis factor-alpha by 2.8 ± 1.7 pg/mL and HbA1c by 0.32 ± 0.28%. Reductions in biomarkers correlated with reductions in periodontal inflamed surface area.

Table 1: Baseline characteristics of randomized groups

Variable	Therapy group (n=40)	Control group (n=40)	p value
Age (years)	49.7 ± 7.6	50.1 ± 7.2	0.809
Male sex, n (%)	23 (57.5%)	22 (55.0%)	0.821
BMI (kg/m2)	29.4 ± 3.6	29.1 ± 3.4	0.704
Waist circumference (cm)	98.6 ± 8.8	97.9 ± 8.4	0.716
HbA1c (%)	6.82 ± 0.54	6.79 ± 0.58	0.812
Mean PPD (mm)	4.82 ± 0.61	4.78 ± 0.58	0.764
PISA (mm2)	1042 ± 318	1016 ± 304	0.708

Table 2: Changes in periodontal parameters at 3 months

Parameter	Therapy baseline	Therapy 3 months	Control baseline	Control 3 months	Between-group p
Plaque index	2.34 ± 0.38	1.18 ± 0.31	2.29 ± 0.40	2.04 ± 0.36	<0.001
Bleeding on probing (%)	58.6 ±12.4	24.2 ± 8.7	56.9 ± 11.8	49.6 ±10.5	<0.001
Mean PPD (mm)	4.82 ± 0.61	3.41 ±0.52	4.78 ± 0.58	4.51 ± 0.57	<0.001
Mean CAL (mm)	5.21 ± 0.74	4.16 ± 0.68	5.18 ± 0.71	5.02 ± 0.69	<0.001
PISA (mm2)	1042 ± 318	482 ± 206	1016 ± 304	862 ± 276	<0.001

Table 3: Changes in systemic inflammatory biomarkers and HbA1c

Marker	Therapy baseline	Therapy 3 months	Control baseline	Control 3 months	Between-group p
hs-CRP (mg/L)	4.8 ± 1.9	3.1 ± 1.4	4.7 ± 1.8	4.4 ± 1.7	<0.001
IL-6 (pg/mL)	5.6 ±2.1	4.2 ± 1.7	5.5 ± 2.0	5.2 ±1.9	0.002
TNF-alpha (pg/mL)	12.9 ± 4.6	10.1 ± 3.8	12.6 ± 4.3	12.0 ± 4.1	0.004
HbA1c (%)	6.82 ± 0.54	6.50 ± 0.48	6.79 ± 0.58	6.70 ± 0.55	0.001
Fasting glucose (mg/dL)	126.4 ± 17.8	118.2 ± 15.6	124.9 ± 18.1	122.7 ± 17.2	0.034

Discussion:

The present randomized trial showed that non-surgical periodontal therapy significantly improved clinical periodontal status and reduced systemic inflammatory biomarkers in patients with metabolic syndrome. The reduction in high-sensitivity C-reactive protein, interleukin-6 and tumor necrosis factor-alpha suggests that periodontal inflammatory control can reduce systemic inflammatory load **[31, 32]**. The decrease in

periodontal inflamed surface area was strongly correlated with biomarker improvement. This supports the concept that the inflamed pocket epithelium represents an active interface through which microbial products and inflammatory mediators may enter the circulation **[33, 34]**. High-sensitivity C-reactive protein showed the largest and most consistent reduction. This is clinically relevant because C-reactive protein is a downstream acute-phase marker stimulated by interleukin-6 and is associated with cardiometabolic risk. The magnitude of reduction observed in this study is compatible with the hypothesis that periodontal treatment can reduce systemic inflammatory burden in susceptible patients **[35]**. Interleukin-6 and tumor necrosis factor-alpha also decreased significantly. These cytokines are biologically relevant in metabolic syndrome because they interfere with insulin signaling, adipocyte function, endothelial homeostasis and hepatic inflammatory response. Periodontal therapy may reduce one source of cytokine stimulation, although adiposity and metabolic factors remain important drivers **[1-4]**. The HbA1c reduction was modest but statistically significant. This effect is plausible because inflammatory reduction may improve insulin sensitivity and improved oral health may support better dietary and self-care behavior. However, periodontal therapy should be viewed as an adjunct rather than a substitute for standard metabolic management **[17-20]**. The delayed therapy control design allowed ethical provision of periodontal treatment while providing a meaningful short-term comparison. The control group received oral hygiene advice and supragingival prophylaxis, which may explain the small improvement in periodontal and biomarker values, but the between-group differences, remained significant **[21-24]**. The strengths of this study include randomized design, assessor blinding, standardized biomarker measurements and use of periodontal inflamed surface area. Limitations include a 3-month follow-up, single-center setting and exclusion of smokers and patients with unstable medication regimens. Longer follow-up is required to determine durability of systemic improvement **[25-28]**. The findings support integrating periodontal assessment into care pathways for metabolic syndrome. Collaboration between physicians and dental professionals may improve recognition of oral inflammatory burden as a modifiable component of cardiometabolic risk **[29, 30]**. The clinical importance of this trial lies in the possibility of reducing one modifiable inflammatory source in patients already burdened by cardiometabolic risk. Periodontal therapy did not normalize systemic biomarkers, but it produced measurable improvement over a short follow-up. This suggests that periodontal care can complement weight reduction, glycemic control, lipid management and antihypertensive therapy rather than compete with them. The reduction in HbA1c was modest but clinically meaningful at a population level. Even a small glycemic improvement may be relevant when achieved through a non-pharmacological intervention that also preserves teeth, improves chewing, reduces bleeding and enhances oral hygiene. The finding should be interpreted cautiously because medication adherence and diet may influence HbA1c, but randomization reduces the likelihood that these factors fully explain the between-group difference. The response pattern also suggests that patients with larger baseline periodontal inflamed surface area may experience greater systemic biomarker reduction. This observation can help identify patients most likely to benefit from intensive periodontal therapy. Future studies should examine whether baseline inflammatory burden, obesity phenotype, glycemic status, or microbial profile modifies treatment response. Implementation in routine care requires sustained maintenance. Non-surgical periodontal therapy produces initial improvements, but recolonization and relapse may occur without plaque control, risk factor modification and supportive periodontal therapy. Therefore, systemic biomarker benefits are likely to depend on long-term periodontal stability rather than a single episode of debridement. This trial also supports closer communication between physicians and periodontists. Patients diagnosed with metabolic syndrome should be informed that oral inflammation is relevant to general health and dental referral should be considered when bleeding gums, tooth mobility, or halitosis are present. Similarly, dental clinics can screen for cardiometabolic risk indicators and encourage medical evaluation when appropriate. The inflammatory biomarker response should be interpreted in the context of periodontal wound healing. Short-term increases in bacteremia or inflammatory mediators may occur immediately after instrumentation, but the 3-month assessment reflects a stable post-treatment phase with reduced pocket bleeding and microbial load. This timing is clinically meaningful because HbA1c also reflects glycemic exposure over approximately the same period. Patient adherence likely influenced the magnitude of periodontal improvement. Oral hygiene reinforcement was provided at follow-up, but long-term success depends on daily plaque control, interdental cleaning and regular maintenance visits. For metabolic syndrome patients, motivational counseling may be particularly useful because diet, exercise, oral hygiene and medication adherence all require sustained behavior change. The study did not include adjunctive systemic antibiotics, which strengthens the interpretation that mechanical periodontal therapy and oral hygiene improvement were sufficient to produce measurable systemic effects. Avoiding routine antibiotics is also consistent with antimicrobial stewardship, especially when chronic periodontitis can often be managed effectively with debridement and supportive care. A recent systematic review of randomized trials in patients with metabolic syndrome and periodontitis reported modest benefits of periodontal treatment for systolic blood pressure and fasting glucose, while effects on C-reactive protein and several other metabolic parameters were inconsistent [5].

Conclusion:

Non-surgical periodontal therapy significantly reduced periodontal inflammation, high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-alpha and HbA1c over 3 months in patients with metabolic syndrome and periodontitis. The reduction in systemic biomarkers correlated with improvement in periodontal inflamed surface area. Periodontal therapy may be a valuable adjunct in multidisciplinary

management of metabolic syndrome-related inflammatory burden.

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