



www.bioinformation.net
Volume 22(9)



Research Article

Received September 1, 2026; Revised September 30, 2026; Accepted September 30, 2026, Published September 30, 2026

DOI: 10.6026/973206300226130

SJIF 2026 (Scientific Journal Impact Factor for 2026) = 8.478

2022 Impact Factor (2023 Clarivate Inc. release) is 1.9

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Edited by P Kanguane

Citation: Rameshwar *et al.* Bioinformation 22(9): 6130-6135 (2026)

Impact of non-surgical periodontal therapy on salivary soluble neuropilin-1 among periodontitis patients with and without metabolic syndrome: An interventional study

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Abstract:

Salivary soluble neuropilin-1 (sNRP1) levels were estimated in both the groups via PCR along with the estimation of the various parameters related to metabolic syndrome and periodontitis. Therefore, it is of interest to evaluate the levels of salivary soluble neuropilin-1 (sNRP1) in periodontally healthy and metabolic syndrome patients with stage II/III grade B periodontitis. Thirty six subjects with metabolic syndrome showed significantly higher anthropometric, biochemical and periodontal parameters compared to systemically healthy individuals. Salivary sNRP1 levels were elevated in the metabolic syndrome group at baseline and decreased after non-surgical periodontal therapy in both groups. sNRP1 showed positive correlations with blood pressure, fasting glucose, triglycerides and periodontal parameters, but not with HDL-c. Thus, data shows that sNRP1 may serve as a potential salivary biomarker linking periodontal inflammation with systemic metabolic risk.

Keywords: Type II diabetes, obesity, periodontitis, salivary biomarkers, enzyme-linked immunosorbent assay (ELISA)

Background:

Periodontitis is a chronic inflammatory disease affecting connective tissue and bone, initiated by microbial dysbiosis. Its initiation and progression depend on pathogenic microorganisms and the host immune response [1]. Bacterial irritants from supra- and subgingival plaque are essential for gingivitis and periodontitis development [2]. Effective therapy requires anti-infective measures to eradicate plaque-associated pathogens, with professional cleaning recommended for long-term stability [3]. Diagnostic research is advancing toward biomarker-based methods that objectively assess periodontal risk and disease activity [4]. Radiographic and clinical data detect prior disease but fail to predict future risk, highlighting the need for improved diagnostic tools. Periodontitis is linked to systemic disorders including rheumatoid arthritis, renal disease, respiratory conditions, obesity and cognitive decline, with metabolic syndrome receiving growing attention [5]. Metabolic syndrome involves deregulated glucose and lipid metabolism, elevated IL-6 and TNF- α and oxidative stress, which may connect it to periodontal inflammation [6]. Salivary neuropilin-1 is a novel biomarker whose role in metabolic syndrome and periodontitis remains largely unexplored, particularly in response to non-surgical therapy [6]. Therefore, it is of interest to evaluate the impact of non-surgical periodontal therapy on salivary soluble neuropilin-1 among periodontitis patients with and without metabolic syndrome.

Materials and Methods:**Study design:**

A total of 36 patients (Group I and Group II) were selected from Department of Periodontics, Meenakshi Ammal Dental College and Hospital, MAHER, Chennai based on the inclusion and exclusion criteria during the study period from December 2023 to November 2024 after the approval by the "Institutional Ethical Committee", MAHER - Deemed to be University, Chennai (MADC/IEC-II/026/2023). Written and informed consent was obtained from each patient before enrolment in the

study. The selected 36 subjects were divided into two groups based on inclusion and exclusion criteria. GROUP I - 18 Stage II/III Grade B Periodontitis patients with no systemic diseases. GROUP II - 18 Stage II/III Grade B Periodontitis patients with metabolic syndrome.

Inclusion criteria:

The inclusion criteria for the study comprised individuals who were willing to participate, specifically patients diagnosed with stage II or III Grade B periodontitis, both with and without metabolic syndrome. Eligible participants were required to be within the age range of 35 to 65 years and to have at least 20 natural teeth. For Group 1- Patients with stage II/III Grade B periodontitis with generalized interdental CAL $\geq$ 3-5mm with radiographic bone loss extending to middle third of the root and beyond, tooth loss due to periodontitis present $\leq$ 4 teeth, probing pocket depth (PPD) $\geq$ 5mm, vertical bone loss $\geq$ 3mm with class II/III furcation and moderate ridge defect and with no associated systemic diseases. For Group 2 - Patients with stage II/III Grade B periodontitis with generalized interdental CAL $\geq$ 3-5mm with radiographic bone loss extending to middle third of the root and beyond, tooth loss due to periodontitis present $\leq$ 4 teeth, probing pocket depth (PPD) $\geq$ 5mm, vertical bone loss $\geq$ 3mm with class II/III furcation and moderate ridge defect and diagnosed with metabolic syndrome for over 5 years [6].

Diagnostic criteria for metabolic syndrome (AHA/NHLBI 2005): [7]

Metabolic syndrome was diagnosed based on the presence of three or more of the following five criteria: Waist circumference of at least 102 cm (40 inches) in men or 88 cm (35 inches) in women; blood pressure equal to or greater than 130/85 mmHg; fasting glucose level of 100 mg/dL or higher; HDL cholesterol less than 40 mg/dL in men or less than 50 mg/dL in women; and triglyceride levels of 150 mg/dL or above.

Exclusion criteria:

The exclusion criteria for the study included patients with a history of antibiotic use, non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressant, bisphosphonates, or systemic steroid therapy within the previous six months. Individuals with salivary gland disorders or systemic conditions such as respiratory, renal, or liver disease, rheumatoid arthritis, allergies, advanced malignancies, Human Immunodeficiency Virus (HIV), or hepatitis infection were also excluded. Pregnant and lactating women, as well as those with a history of radiation therapy, were not eligible. Additionally, current and former smokers, alcoholic patients, individuals who had undergone periodontal therapy within the preceding months and those taking nutritional supplements such as docosahexaenoic acid, polyunsaturated fatty acids, or monounsaturated fatty acids were excluded from participation.

Sample size estimation:

Sample size was determined based on prior research and local hospital records, accounting for the prevalence of metabolic syndrome and periodontitis in the region. Power analysis showed a 95% confidence level with a minimum sample size of 15 subjects per group. To account for potential dropouts, 36 subjects per group were included.

Demographic and biochemical assessments:

A single calibrated investigator (JM) collected dental and medical histories. Another examiner (TS), blinded to the study, assessed demographic parameters including age, gender, height, weight, body mass index (BMI), waist circumference (WC) and socioeconomic status (based on monthly income). Biochemical parameters such as fasting blood glucose, high-density lipoprotein (HDL-C), triglycerides (TG), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded for all participants.

Collection of unstimulated saliva samples:

Unstimulated whole saliva samples were collected at baseline and on the 30th day from both groups using the standard spit method prior to periodontal examination. Participants were instructed to avoid food, beverages and oral hygiene for two hours before sample collection, avoid large meals two hours prior and abstain from alcohol for 12 hours before collection. Samples were collected between 8:00 A.M. and 12:00 P.M. to standardize conditions. Participants rinsed their mouths with water to remove food

particles before the collection. Saliva samples were stored at -80°C for salivary soluble neuropilin-1 analysis.

Assessment of periodontal parameters and Non-Surgical periodontal therapy (NSPT):

Periodontal parameters oral hygiene index-OHI modified gingival index- MGI, probing pocket depth (PPD) and clinical attachment level (CAL) were assessed at baseline. Full-mouth scaling and root planing (SRP) were performed, followed by full-mouth subgingival debridement (SGD). Standard oral hygiene instructions (tooth brushing twice daily using the modified Bass technique and interdental cleaning once daily) were provided to all participants. On the 30th day, periodontal parameters were re-evaluated and saliva samples were collected again.

Molecular analysis of salivary soluble neuropilin-1 using enzyme-linked immunosorbent assays (ELISA):

Salivary soluble neuropilin-1 levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA), following the manufacturer's instructions, based on a double-antibody sandwich technique. After thawing, saliva samples were analyzed in duplicate. Plates were pre-coated with monoclonal antibodies specific for salivary soluble neuropilin-1 incubated with sample diluent and horseradish peroxidase (HRP)-conjugated antibody for 90 minutes, followed by development with substrate reagent. Absorbance was measured at 450 nm. The assay standard curve ranged from 0.156 to 10 ng/mL, with a sensitivity of 0.094 ng/ml.

Statistical analysis:

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 26.0, Armonk, NY: IBM Corp. Released 2019. Inferential statistics was done by using one way ANOVA followed by post-hoc test to assess the pair wise comparison. To compare proportions between groups Chi-Square test is applied. To assess the difference among 0-day and 30th day following scaling and root planing, independent sample t test and unpaired t-test is used. Correlation analysis was done using Pearson correlation to assess the correlation between the determinants. In the present study, $p < 0.05$ was considered as the level of significance.

Table 1: Comparison of mean demographic variables among group I and Group II at 0-day

Variables	Groups	Mean ± Std. Deviation	p-value
Age (years)	Group I	43.44±6.50	0.119 ^{NS}
	Group II	47.05±6.73	
Height (cm)	Group I	161.22±6.22	0.872 ^{NS}
	Group II	161.61±8.16	
Weight (kg)	Group I	67.83±22.24	<0.001 ^{**}
	Group II	75.05±6.25	
BMI (kg/m ²)	Group I	23.92±1.36	<0.001 ^{**}
	Group II	28.81±1.64	
Waist circumference (cm)	Group I	76.72±5.08	<0.001 ^{**}
	Group II	91.16±7.48	
Monthly income (Rs)	Group I	10905.55±4695.51	<0.001 ^{**}
	Group II	20388.88±4146.42	

*P< 0,05 is considered to be statistically significant
**P<0.001 is considered to be highly statistically significant NS- Statistically non-significant

Table 2: Comparison of gender among Group I and Group II at 0-day

Variable		Group						p-value
		Group I		Group II		Total		
		N	%	N	%	N	%	
GENDER	Male	11	61.2	8	44.4	19	52.8	0.914 ^{NS}
	Female	7	38.9	10	55.6	17	47.2	
	Total	18	100.0	18	100.0	36	100.0	

Table 3: Comparison of Mean blood pressure and biochemical parameters among Group I and Group II at 0-day

Variables	Groups	Mean ± Std. Deviation	p value
Systolic Blood Pressure (mm Hg)	Group I	119.44±7.25	<0.001**
	Group II	128.33±4.85	
Diastolic Blood Pressure (mm Hg)	Group I	77.22±4.60	<0.001**
	Group II	131.66±7.47	
Fasting blood glucose level (mg/dL)	Group I	83.05±2.26	<0.001**
	Group II	89.22±5.19	
High-Density Lipoprotein (mg/dL)	Group I	53.33±3.71	<0.001**
	Group II	41.11±3.19	
Total Triglycerides (mg/dL)	Group I	159.22±22.55	<0.001**
	Group II	198.50±4.96	

Table 4: Intragroup and intergroup comparison of periodontal parameters among Group I and Group II 0-day and 30th day following non-surgical periodontal therapy

Variables	Groups	0-day	30 th day	p-value (Intragroup)
		Mean ±Std. deviation	Mean ±Std. deviation	
Oral hygiene index simplified (OHI-S)	Group I	3.26±0.50	1.48±0.43	<0.001**
	Group II	3.53±0.69	1.94±0.48	<0.001**
	p-value (intergroup)	0.189	<0.001**	-
Modified gingival index (MGI)	Group I	1.16±0.13	0.30±0.14	<0.001**
	Group II	2.53±0.22	1.63±0.29	<0.001**
	p-value (intergroup)	<0.001**	<0.001**	-
Probing pocket depth (PPD) (mm)	Group I	5.09 ±0.27	2.42±0.29	<0.001**
	Group II	7.86 ±0.17	4.4±0.34	<0.001**
	p-value (intergroup)	<0.001**	<0.001**	-
Clinical attachment Level (CAL) (mm)	Group I	5.61 ±0.27	2.89±0.39	<0.001**
	Group II	9.37±0.24	4.88±0.31	<0.001**
	p-value (intergroup)	<0.001**	<0.001**	-

Table 5: Intragroup and intergroup comparison of mean expression of salivary soluble neuropilin-1 among Groups I and II at 0-day and 30th day following non- surgical periodontal therapy

Variables	Groups	0-day	30 th day	p-value (intragroup)
		Mean ±Std. deviation	Mean ±Std. deviation	
Salivary Soluble neuropilin 1 (ng/mL)	Group I	65.03±13.16	40.17±15.19	<0.001*
	Group II	85.57±14.52	52.85±12.93	<0.001*
	p-value (intergroup)	<0.001*	<0.001*	-

Table 6: Correlation of overall variables with salivary soluble neuropilin- 1 Expression at 0-day

Variables		Soluble neuropilin 1 (ng/ml)
Systolic Blood Pressure (mm Hg)	Correlation	0.406
	P-value	0.014*
Diastolic Blood Pressure (mm Hg)	Correlation	0.592
	P-value	0.001*
Fasting glucose (mg/dl)	Correlation	0.495
	P-value	0.002*
High-Density Lipoprotein (mg/dL)	Correlation	-0.449
	P-value	0.006*
Triglycerides (mg/dL)	Correlation	0.536

Oral hygiene index simplified (OHI-S)	P-value	0.001*
	Correlation	0.061
Modified gingival index (MGI)	P-value	0.725 ^{NS}
	Correlation	0.583
Probing pocket depth (mm)	P-value	0.001*
	Correlation	0.588
Clinical attachment level (mm)	P-value	0.001*
	Correlation	0.602
	P-value	0.001*

Results and Discussion:

When comparing demographic variables between the two groups, weight, BMI, waist circumference and monthly income were significantly higher in the periodontitis patients with metabolic syndrome (P+MS) compared to those without systemic disease (P), while no significant differences were observed in height and age (Table 1). Patients with periodontitis without any systemic diseases (group I) were mainly males whereas females were found to be more in number in group II (Periodontitis with metabolic syndrome) (Table 2). Systolic and diastolic blood pressure, fasting blood glucose, HDL-c and triglycerides were significantly elevated in the P+MS group, consistent with the metabolic abnormalities that characterize this syndrome (Table 3). At 0-day, periodontal parameters including modified gingival index (MGI), probing pocket depth (PPD) and clinical attachment level (CAL) were also significantly higher in the P+MS group. Following scaling and root planing (SRP) and subgingival debridement (SGD), both groups showed significant improvements in oral hygiene index, MGI, PPD and CAL by the 30th day (Table 4). Salivary soluble neuropilin-1 (sNRP-1) levels were significantly higher in the P+MS group at baseline and decreased in both groups after therapy, through levels remained comparatively higher in the P+MS group (Table 5). Correlation analysis revealed that sNRP-1 was positively associated with systolic and diastolic blood pressure, fasting glucose, triglycerides, MGI, PPD and CAL, while showing a negative correlation with HDL-c. At 30 days post-therapy, sNRP-1 continued to correlate positively with MGI, PPD and CAL, whereas its correlation with oral hygiene index simplified was positive but not statistically significant (Table 6). These findings reinforce the established link between periodontitis and metabolic syndrome, both of which share common inflammatory pathways [8]. Elevated BMI, waist circumference, blood pressure and dyslipidemia in the P+MS group highlight the systemic inflammatory burden that exacerbates periodontal tissue destruction. The worse periodontal parameters observed in these patients are consistent with previous reports, while the improvements following non-surgical therapy confirm the efficacy of SRP and SGD in reducing local inflammation even in the presence of systemic disease [9]. The novel aspect of this study lies in the evaluation of salivary sNRP-1, a biomarker implicated in immune modulation, angiogenesis and chronic inflammation. Elevated baseline levels in patients with metabolic syndrome and their significant reduction after therapy suggest that sNRP-1 reflects both systemic and periodontal inflammatory status. These results align with earlier studies linking sNRP-1 to disease severity and support its potential as a non-invasive biomarker for monitoring periodontal health and systemic metabolic conditions.

Similarly, salivary sNRP-1 levels showed significant intragroup changes between stage I-II periodontitis group and healthy group; however, intergroup comparison revealed a more pronounced reduction in biomarker levels in the periodontitis group compared to the healthy group [10]. Barbato *et al.* (2026) reported that periodontitis was associated with an increased risk of developing at least one metabolic syndrome component (RR 1.18), with a stronger association observed in severe periodontitis (RR 1.34), although the risk of developing full metabolic syndrome was not statistically significant [11]. In summary, salivary sNRP-1 shows diagnostic and prognostic value and future longitudinal studies with larger cohorts are warranted to validate its role in clinical practice and personalized treatment strategies [12].

Conclusion:

Periodontitis patients with metabolic syndrome showed high systemic and periodontal parameters. Salivary soluble neuropilin-1 levels were increased at baseline and decreased after non-surgical therapy. SNRP-1 correlated positively with systemic and periodontal variables. Thus, we show sNRP-1 as a promising biomarker linking periodontitis and metabolic syndrome.

Advancement to knowledge:

This study is highly relevant in today’s scenario where metabolic syndrome, diabetes, obesity and cardiovascular diseases are rapidly increasing worldwide. It highlights the close relationship between periodontal inflammation and systemic metabolic disturbances through the role of salivary soluble neuropilin-1 (sNRP1) which may serve as a promising non-invasive salivary biomarker for monitoring both oral and systemic inflammatory status. The findings also reinforce the concept of periodontal medicine, emphasizing the importance of oral health in overall systemic wellbeing and supporting early diagnosis, risk assessment and multidisciplinary patient care.

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