Serum and salivary calcitonin gene-related peptide, pentraxin-3 and interleukin-1β levels in patients with periodontitis suffering from migraines

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Abstract. Periodontitis is characterized by dysregulated host immune responses to Gram-negative anaerobes, resulting in local tissue destruction and systemic inflammatory spill-over. In parallel, neurovascular inflammation potentially influenced by mediators, such as interleukin-1β (IL-1β), calcitonin gene-related peptide (CGRP) and pentraxin-3 (PTX-3) is associated with migraine chronification. Given the biological overlap between mucosal and systemic inflammatory pathways, the present study assessed serum and salivary IL-1β, CGRP and PTX-3 levels in 96 individuals allocated to four groups as follows: Healthy controls, patients with chronic migraines without periodontitis, periodontitis without migraines, and patients with chronic migraines with periodontitis. Biomarker levels were quantified using validated ELISA protocols, and the periodontal status was evaluated using the plaque index, modified sulcular bleeding index, probing depth and clinical attachment level. Individuals with co-existing chronic migraines and periodontitis exhibited the highest salivary and serum biomarker concentrations. The salivary IL-1β level was consistently higher than the serum levels, whereas CGRP and PTX-3 levels were predominantly elevated in serum. Significant correlations were observed between the salivary and serum concentrations of all markers, and between biomarker levels and periodontal parameters. These findings indicate an amplified inflammatory burden in individuals with both conditions and support the concept of a shared neurovascular-immune axis. Although the cross-sectional design precludes causal inference, the results of the present study highlight the potential relevance of periodontal status in the inflammatory profile of chronic migraine.

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Introduction

Migraine is a chronic neurovascular disorder potentially influenced by the activation of the trigeminovascular system, neuropeptide release and systemic inflammatory sensitization. Calcitonin gene-related peptide (CGRP) mediates neurogenic inflammation and vasodilation, while interleukin (IL)-1β is released from activated glia and immune cells, and is associated with central sensitization and chronicity (1). Pentraxin-3 (PTX-3), an acute-phase protein produced by endothelial and immune cells, reflects vascular inflammation and endothelial dysfunction, linking systemic inflammation to migraine pathophysiology (2). Emerging evidence indicates that mucosal inflammatory sources, particularly gut barrier disruption, may elevate systemic pro-inflammatory mediators, such as IL-6 and lipopolysaccharide (LPS), lowering the threshold for trigeminal activation and promoting vascular dysregulation (3). Together, these mechanisms support an integrated model in which neurogenic, systemic and mucosal inflammation converge to be associated with recurrent attacks and the chronification of migraines (4,5). Individuals with both migraines and periodontitis exhibit elevated salivary IL-1β, (linked to periodontal severity) and high serum levels of PTX-3 and CGRP (linked to migraine chronicity), highlighting shared inflammatory mechanisms (6-8).

Periodontitis, characterized by a microbial shift towards Gram-negative anaerobes, induces a persistent immune-inflammatory response, evidenced by elevated levels of IL-1β, IL-6, CRP and PTX-3 (9-11). LPS from bacteria activate Toll-like receptor 4 (TLR4) and the NLRP3 inflammasome, potentially related to IL-1β production, neutrophil infiltration and MMP-9-mediated connective tissue breakdown. PTX-3, the expression of which is upregulated in response to IL-1β and LPS, plays a role in both local periodontal and systemic inflammatory processes (12,13). This systemic inflammatory milieu may potentiate migraine pathophysiology through the activation of the trigeminovascular system (14). Elevations in the levels of IL-1β, CGRP and PTX-3 associated with periodontitis can sensitize trigeminal neurons, promoting

neurogenic inflammation and vascular alterations characteristic of chronic migraines. Convergent inflammatory pathways and TLR-mediated immune dysregulation create a bidirectional feedback loop that may be associated with both conditions (15,16). While periodontitis is commonly observed in patients with chronic migraines and is associated with increased levels of biomarkers, such as CGRP, PTX-3 and soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) in blood, saliva and gingival crevicular fluid, to the best of our knowledge, no studies have yet examined the simultaneous association of serum and salivary IL-1β, CGRP and PTX-3 levels with periodontal status in individuals with periodontitis, chronic migraines, or both. Thus, the mechanistic link between periodontitis and migraine chronification remains incompletely understood.

Therefore, the present study aimed to evaluate and correlate salivary and serum IL-1β, CGRP and PTX-3 levels among individuals with periodontitis, chronic migraines, or both conditions. By integrating periodontal clinical parameters with systemic and mucosal biomarker profiles, the authors sought to elucidate whether shared inflammatory mediators could reflect a potential inflammatory axis linking the two conditions. The present study aimed to correlate the interrelationship between periodontal clinical parameters [probing pocket depth (PPD), clinical attachment level (CAL) and modified sulcus bleeding index (mSBI)] and the serum and salivary values of IL-1β, CGRP and PTX-3.

Patients and methods

Ethical statement. The present study intended to evaluate the serum and salivary levels of IL-1β, CGRP and PTX-3 in healthy, periodontally healthy patients with chronic migraines, systemically healthy subjects with periodontitis and in subjects with periodontitis with chronic migraines. All methodologies and experimental protocols received approval and were executed in compliance with the ethical standards and protocols of the SRM Dental College Institutional Review Board (IRB no SRMDC/IRB/2022/MDS/No. 507) in Chennai, India. The initial ethical approval for the commencement of the study was granted in December, 2022, which was formally renewed through a continuing review in June, 2023. Participant recruitment was initiated from February, 2023 till May, 2023, and biological sample collection (saliva and serum) was performed from June, 2023 to September, 2023 after obtaining the ethical renewal. Written informed consent was obtained from all participants prior to enrollment and sample collection.

Study population and design. A total of 96 subjects aged 18-70 years were recruited from the Outpatient Department of SRM Dental College and SRM General Hospital, Chennai, India. The sample size was calculated using G power version 3.1.9.2 with 90% power and 5% α error. A total number of 96 subjects was included, who were further categorized on their systemic and periodontal status with 24 members in each group. The groups were as follows: Group I, systemically and periodontally healthy subjects; group II, individuals with chronic migraine but without periodontitis; group III, subjects with only periodontitis and no migraines; and group IV, subjects with co-existing chronic migraines and periodontitis. Eligibility criteria included the presence of at least 15 teeth, a clinical diagnosis of chronic migraine, and/or periodontitis with a pocket depth ≥6 mm and CAL ≤5 mm in >30% of sites, corresponding to stage II or stage III periodontitis, as per the 2017 classification by the American Academy of Periodontology (17). Subjects were excluded if they had any systemic diseases (other than migraines) or were under medication, had undergone periodontal therapy in the prior 6 months, used tobacco (chewing or smoking), or were pregnant or lactating. A self-reported migraine-specific medication use within 3 months prior to sampling was recorded from the subjects with migraines; this is presented in Table I. Additionally, information on the body mass index, diet and lifestyle variables of the patients was recorded for all subjects (Table II).

Do you have frequent or intense headaches?	0. No 1. Yes
Do your headaches usually last more than 4 hours?	0. No 1. Yes
Do you usually suffer from nausea when you have a headache?	0. No 1. Yes
Does light or noise bother you when you have a headache?	0. No 1. Yes
Does headache limit any of your physical or intellectual activities?	0. No 1. Yes

Figure 1. Migraine screening questionnaire: This consists of all five questions which were used in the present study to assess frequency, intensity, duration, associated symptoms, sensitivity to light or noise and limitation of physical activities during the attack.

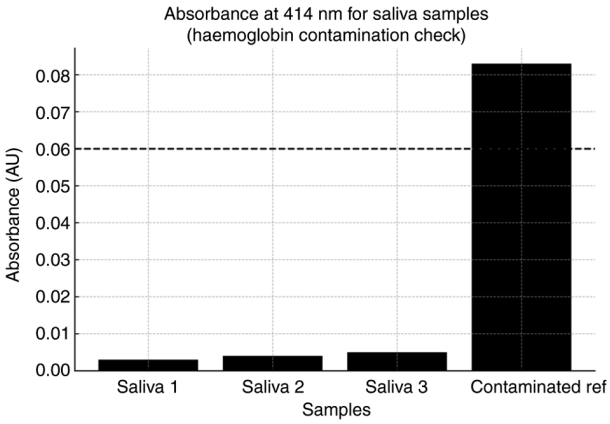

Figure 2. Absorbance at 414 nm for saliva samples: Three clean saliva samples show very low absorbance values (0.003-0.005 AU), well below the predefined contamination threshold of 0.06 AU. The contaminated reference sample displays a marked absorbance peak (0.083 AU), illustrating the sensitivity of the hemoglobin screening procedure.

Sample collection. Saliva and venous blood samples were collected from eligible participants, immediately following a clinical examination and prior to any periodontal or medical intervention.

Clinical examination. Periodontal parameters, including PPD, CAL, mSBI, and plaque index (PI) were recorded using a UNC-15 probe. All measurements were performed by a calibrated examiner (intra-examiner reliability κ=0.87).

Migraine screening questionnaire (MS-Q). Patients with chronic migraines, diagnosed by neurologists, were included in the present study. The MS-Q was used for the subjects with migraines (groups II and IV) using the MS-Q, a self-reported

Table I. Migraine-specific medication use within 3 months prior to sampling.

Medication class	Group II (n=24) (%)	Group IV (n=24) (%)	Total (n=48) (%)
Triptans	5 (20.8)	6 (25)	11 (22.9)
Gepants	1 (4.2)	1 (4.2)	2 (4.2)
NSAIDs (≥2x/month)	8 (33.3)	9 (37.5)	17 (35.4)
Acetaminophen	4 (16.7)	6 (25)	10 (20.8)
CGRP-mAbs	2 (8.3)	3 (12.5)	5 (10.4)
Preventive gepants	1 (4.2)	1 (4.2)	2 (4.2)
Beta-blockers	3 (12.5)	5 (20.8)	8 (16.7)
Topiramate	3 (12.5)	3 (12.5)	6 (12.5)
Antidepressants	2 (8.3)	3 (12.5)	5 (10.4)
Onabotulinumtoxin A	1 (4.2)	2 (8.3)	3 (6.3)
Acute medication ≥10 days/month	3 (12.5)	4 (16.7)	7 (14.6)
No migraine medication	4 (16.7)	3 (12.5)	7 (14.6)

Group II, patients with chronic migraine without periodontitis; Group IV, patients with chronic migraines and periodontitis; NSAIDs, non-steroidal anti-inflammatory drugs; CGRP-mAbs, calcitonin gene-related peptide monoclonal antibodies. Acute medications refer to drugs taken at the onset of a migraine attack to relieve pain or associated symptoms, including triptans, gepants, NSAIDs, acetaminophen and onabotulinumtoxin A. Preventive medications are taken regularly to reduce the frequency or severity of attacks.

Table II. BMI, diet and lifestyle variables of the patients.

Variable	Group I (n=24)	Group II (n=24)	Group III (n=24)	Group IV (n=24)	Comment
BMI (kg/m^2), mean ± SD	24.9±3.0	25.4±3.1	25.8±3.2	26.1±3.4	Groups matched
Diet score (Mediterranean 0-14), mean ± SD	6.1±1.8	5.8±2.0	5.7±1.9	5.6±1.9	No major differences
Vegetarian diet, n (%)	4 (16.7%)	3 (12.5%)	5 (20.8%)	4 (16.7%)	Self-reported
Alcohol (occasional), n (%)	5 (20.8%)	6 (25.0%)	6 (25.0 %)	7 (29.2%)	Not statistically different
Smoking status	0 smokers	0 smokers	0 smokers	0 smokers	Smoking excluded per protocol

Group I- Systemically and periodontally healthy; Group II, patients with chronic migraine without periodontitis; Group III- patients with only periodontitis and no migraine; Group IV, patients with chronic migraines and periodontitis; BMI- body mass index.

questionnaire (18) (Fig. 1). Each subject answered the following questions with a yes/no for each parameter. The intensity of the migraine was graded as 'moderate, severe and very severe'.

Saliva sample collection. Care was taken to avoid the collection of saliva contaminated by blood; ~5 ml unstimulated whole saliva was collected in a sterile container by asking the patient to spit in it. To objectively exclude blood contamination, the hemoglobin absorbance of all saliva samples was measured at 414 nm (Soret peak) using a microplate spectrophotometer (BioTek Epoch 2; BioTek; Agilent Technologies, Inc.); recorded absorbance values ranged from 0.002 to 0.008 AU, well below the predefined exclusion threshold (A_{414} >0.06), and therefore no samples were excluded (Fig. 2). All samples were centrifuged at 3,000 x g for 10 min at room temperature (22-25˚C), and the clarified supernatant was transferred into UV-transparent plates. The collected samples were then transferred to Tarsons conical end centrifuge tubes (Tarsons Products Limited) and centrifuged for 10 min at 2,700 x g at room temperature (22-25˚C). Following centrifugation, supernatants were collected and aliquoted into 0.5 ml Eppendorf tubes which were then preserved at -80˚C until ELISA was performed.

Serum sample collection. Using the venipuncture technique, 5 ml venous blood were withdrawn using a 5-ml syringe from the antecubital vein. The blood was then transferred into non-EDTA tubes and allowed to stand in a slanting position for 45 min following which the blood was allowed to coagulate naturally. The tube was then placed in a centrifuge and spun at 3,000 x g for 10 min at room temperature (22-25˚C). Serum was separated using a micropipette and stored in 0.5-ml Eppendorf tubes -80˚C until ELISA was performed.

Blinding and randomization procedures. All saliva and serum tubes were coded using non-identifiable numeric codes by a researcher independent of clinical data collection. Laboratory personnel performing ELISA were blinded to group allocation.

Table III. Migraine intensity based on the migraine screening questionnaire comparison in Groups II and IV.

Migraine Intensity	Group II (n=24)	Group IV (n=24)	Total (n=48)	P-value
Moderate	7 (29.2%)	6 (25.0%)	13 (27.1%)	0.0016
Severe	17 (70.8%)	9 (37.5%)	26 (54.2%)	
Very severe	0 (0.0%)	9 (37.5%)	9 (18.8%)	
Total	24 (100.0%)	24 (100.0%)	48 (100.0%)	

Data were analyzed using Fisher's exact test due to small expected cell counts. P<0.05 was considered statistically significant. Group II, patients with chronic migraine without periodontitis. Group IV, patients with chronic migraine with periodontitis.

Data entry and statistical analyses were performed using concealed codes until the analysis was complete.

ELISA and validation. Commercial sandwich ELISA kits (Abbkine Scientific Co., Ltd.) were used IL-1β (cat. no. KTE6013), PTX-3 (cat. no. KTE61036), and CGRP (Human CGRP ELISA Kit, cat. no. EH22808) for IL-1β, CGRP and PTX-3. Validation parameters were included as manufacturer-reported sensitivity and detection ranges. Standard curves (R^2 >0.98 for all assays) were reported. Duplicate measurements were performed for each sample. The intra-assay CV was <8% and the inter-assay CV was <12%. The analysis was performed with the use of internal controls, consisting of measured positive control samples with known concentrations of the target analyte (IL-1β, CGRP and PTX-3) and a zero-analyte (negative) control, along with blank wells, to ensure assay accuracy and reliability. Calibration was performed with known concentration controls and only assays meeting QC thresholds were included. Spike-recovery experiments were conducted for IL-1β, CGRP and PTX-3, and recovery rates between 92 and 106% were demonstrated in the saliva and serum samples, indicating good assay accuracy and minimal matrix interference. All saliva and serum samples for CGRP assessment were processed within 30 min of collection, supplemented with a broad protease-inhibitor cocktail (Abbkine PI-01; Abbkine Scientific Co., Ltd.), centrifuged immediately, at 3,000 x g for 10 min at 4˚C, aliquoted and stored at -80˚C. Samples underwent no more than one freeze-thaw cycle. Detection ranges were: IL-1β, 7.8--500 pg/ml; CGRP, 3.75-60 ng/l; PTX-3, 0.5-8 μg/l.

Statistical analysis. The Kolmogorov-Smirnov and Shapiro-Wilks tests were used to assess the normality of the data and parametric methods were applied as all variables exhibited a normal distribution. One-way ANOVA with Tukey's HSD post hoc tests were used to compare the mean values between groups. An independent samples t-test was used to compared the means, whereas the Chi-squared test assessed proportions between the study and control groups, with Fisher's exact test applied for expected cell frequencies <5. Karl Pearson correlations evaluated the linear correlations between variables. All tests were performed at a significance level of α=0.05. Data were analyzed using SPSS v26 software (Dotmatics). Effect size reporting (η^2 or ANOVA, Cohen's d), α error was adjusted to 0.05; two-tailed analyses were performed. Post hoc power analysis was performed for the primary outcome (serum IL-1β: Group IV vs. group II). Using the observed mean difference (45.67±10.97 vs. 11.84± 2.72 pg/ml), the calculated effect size was d=4.07, yielding a power of 1.00 at α=0.05. The Benjamini-Hochberg FDR correction was applied to ANOVA-derived biomarker comparisons; all remained significant (adjusted P<0.05). Correlation analyses were exploratory; therefore, effect sizes (r) and unadjusted P-values are presented.

Results

Study subjects. A total of 96 subjects were recruited for the study, including 38 males and 58 females, with a mean age of 44.84 years. All participants met the established inclusion criteria and completed the clinical and biochemical evaluations. The four study groups demonstrated comparable demographic characteristics, ensuring that observed differences in biomarkers and periodontal parameters were not attributable to age or sex distribution.

MS-Q assessment. The analysis of migraine intensity based on the MS-Q revealed marked differences among the groups. Group IV, representing individuals with chronic migraines and periodontitis, exhibited the greatest symptom burden. Notably, 37.5% of participants in this group reported 'very severe' migraine episodes, a proportion significantly higher than that observed in group II (those chronic migraines without periodontitis) (P=0.002; Table III). This trend highlights the potential amplifying effect of periodontal inflammation on migraine severity.

Groupwise differences in biomarker levels. Highly significant differences were observed across all groups for the salivary and serum levels of IL-1β, CGRP and PTX-3 (P<0.001), indicating distinct inflammatory and neurovascular profiles among the study categories. Group IV consistently demonstrated the highest concentrations of all biomarkers. For example, the serum IL-1β level increased from 5.51±1.19 pg/ml in group I to 11.84±2.72 pg/ml in group II and 45.67±10.97 pg/ml in group IV, while the salivary IL-1β level increased from 79.06±30.49 to 199.60±36.92 pg/ml in group II and 425.58±46.93 pg/ml in group IV. Similar graded increases were observed for CGRP and PTX-3 in both serum and saliva (Table IV).

Serum CGRP levels were higher than the salivary levels in all groups (P<0.001). Serum CGRP concentrations increased

Table IV. Groupwise comparisons of clinical parameters and biomarker levels in serum and saliva.

Parameter	Group I (n=24)	Group II (n=24)	Group III (n=24)	Group IV (n=24)	P-value
PPD (mm)	2.16±0.25	2.62±0.18	5.24±0.68	6.85±0.24	<0.001[a]
CAL (mm)	0.00±0.00	0.00±0.00	3.88±0.66	5.2±0.59	<0.001[a]
mSBI	1.37±0.20	1.63±0.33	2.41±0.23	2.77±0.11	<0.001[a]
PI	0.48±0.20	2.04±0.40	2.14±0.38	2.53±0.30	<0.001[a]
IL-1β (pg/ml)					
Serum	5.51±1.19	11.84±2.72	23.00±6.24	<0.001[a]	<0.001[a]
Saliva	79.06±30.49	199.60±36.92	349.58±58.67	425.58±46.93	<0.001[a]
CGRP (pg/ml)					
Serum	27.14±3.75	100.21±9.03	47.26±3.96	106.11±9.12	<0.001[a]
Saliva	27.08±1.74	42.05±5.85	32.15±1.60	73.85±4.33	<0.001[a]
PTX-3 (ng/ml)					
Serum	4.57±2.65	12.39±1.58	4.69±0.61	14.00±1.88	<0.001[a]
Saliva	0.80±0.26	10.09±2.76	1.37±0.22	12.38±3.03	<0.001[a]

Data are presented as the mean ± SD and were analyzed using one-way ANOVA. [a]P<0.05, statistically significant difference. Group I, healthy controls; Group II, patients with chronic migraine without periodontitis; Group III, patients with periodontitis without migraines; Group IV, patients with chronic migraines and periodontitis; PPD, probing pocket depth; CAL, clinical attachment level; mSBI, modified sulcular bleeding index; PI, plaque index; CGRP, calcitonin gene-related peptide; PTX-3, pentraxin-3; IL-1β, interleukin 1β.

Table V. Overall correlations between salivary and serum biomarker levels and clinical parameters. using Karl Pearson Correlation

		PI (n=96)		PPD (n=96)		CAL (n=96)	
Parameters		Correlation value	P-value	Correlation value	P-value	Correlation value	P-value
IL-1β (pg/ml)	Saliva	0.757	<0.001[a]	0.889	<0.001[a]	0.885	<0.001[a]
	Serum	0.669	<0.001[a]	0.873	<0.001[a]	0.846	<0.001[a]
CGRP (pg/ml)	Saliva	0.635	<0.001[a]	0.717	<0.001[a]	0.637	<0.001[a]
	Serum	0.717	<0.001[a]	0.411	<0.001[a]	0.305	0.003[b]
PTX-3 (ng/ml)	Saliva	0.600	<0.001[a]	0.369	<0.001[a]	0.269	0.008[b]
	Serum	0.551	<0.001[a]	0.341	<0.001[a]	0.233	0.22

Correlation analyses were performed using Pearson's correlation analysis. [a]P<0.01 and [b]P<0.05, statistically significant difference. PPD, probing pocket depth; CAL, clinical attachment level; mSBI, modified sulcular bleeding index; PI, plaque index; CGRP, calcitonin gene-related peptide; PTX-3, pentraxin-3; IL-1β, interleukin 1β.

from 27.14±3.75 pg/ml in group I to 100.21±9.03 pg/ml in group II and 106.11±9.12 pg/ml in group IV, whereas the salivary levels increased from 27.08±1.74 to 42.05±5.85 pg/ml in group II and 73.85±4.33 pg/ml in group IV (Table IV). The elevation in the serum CGRP levels among the chronic migraine groups supports its established involvement in the sensitization of the trigeminovascular system and migraine-related neurovascular activation.

The PTX-3 concentrations exhibited a similar pattern, with higher serum than salivary values across all groups (P<0.001). Serum PTX-3 levels increased from 4.57±2.65 ng/ml in group I to 12.39±1.58 ng/ml in group II and 14.00±1.88 ng/ml in group IV. Salivary PTX-3 values also increased from 0.80±0.26 ng/ml in group I to 10.09±2.76 ng/ml in group II and 12.38±3.03 ng/ml in group III. The higher concentrations in observed in groups II and IV align with the association of PTX-3 with systemic endothelial dysfunction and inflammatory activity relevant to migraines. Although group III exhibited elevated inflammatory markers due to periodontitis, groups II and IV demonstrated substantially higher serum CGRP and PTX-3 levels, suggesting that periodontal inflammation alone does not account for the systemic neurovascular elevations observed in subjects with chronic migraines.

Serum-saliva correlations of biomarkers. Karl Pearson's correlation analysis revealed significant positive correlations between the serum and salivary concentrations of IL-1β, CGRP and PTX-3 (P<0.001) (Table V). The correlation scatter plots for each of these biomarkers in saliva and serum are shown in Figs. 3 and 4, respectively. These associations indicate that local periodontal inflammatory activity parallels systemic inflammatory and neurovascular responses. Salivary

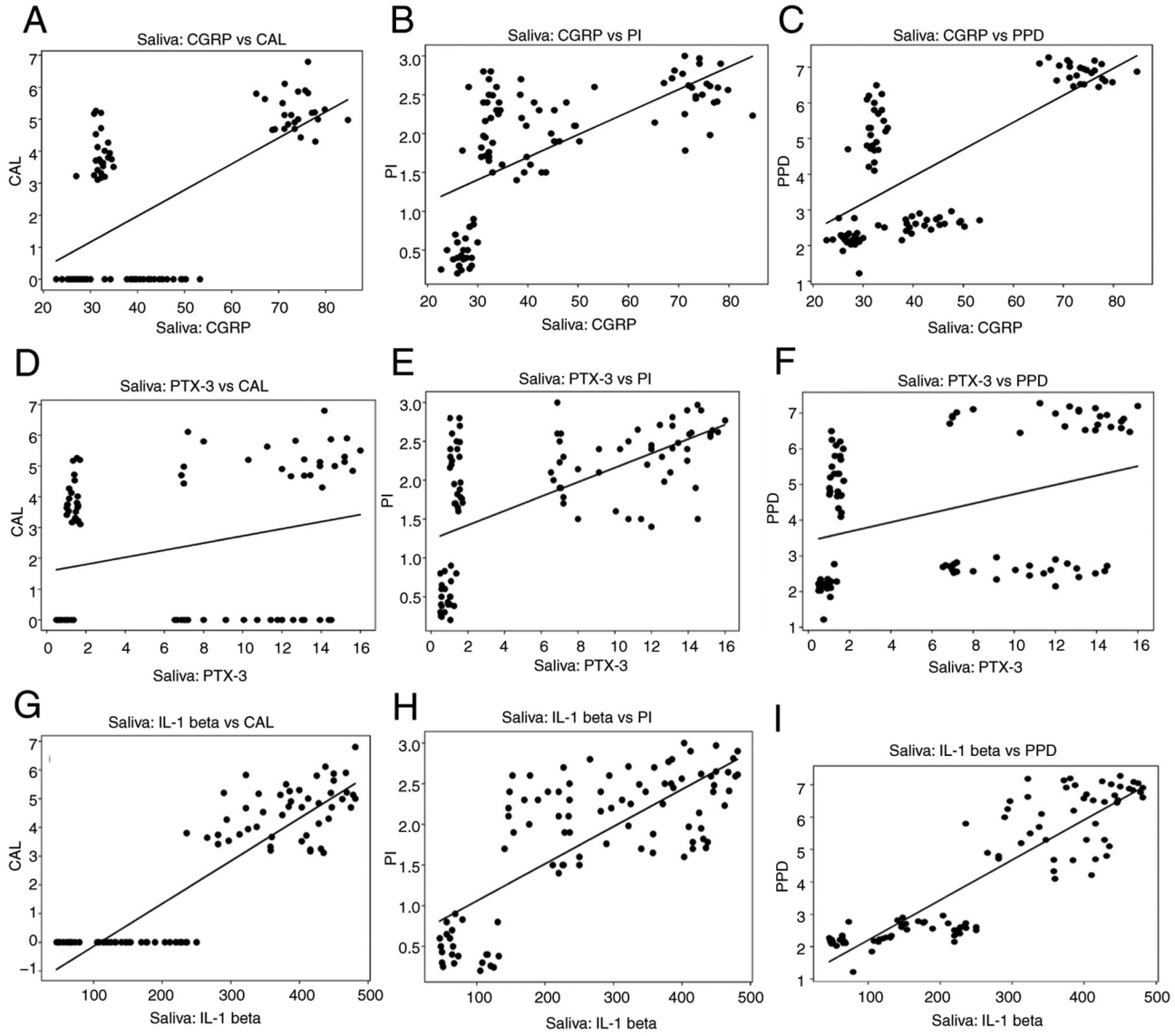

Figure 3. Scatter plots illustrating correlations between salivary biomarkers. (A-I) Pairwise associations among salivary IL-1β, CGRP and PTX-3 levels. Each panel displays individual data points with a fitted linear regression line; all correlations were statistically significant (P<0.001). CAL, clinical attachment level; PI, plaque index; CGRP, calcitonin gene-related peptide; PTX-3, pentraxin-3; IL-1β, interleukin 1β.

IL-1β demonstrated the strongest correlations, consistent with the oral cavity being a major source of IL-1β production in periodontitis, whereas serum CGRP and PTX-3 reflected broader systemic neurovascular involvement in migraine. The multivariate correlation matrix (Table VI) reinforced these findings, with significant positive correlations across all biomarker pairs. The scatter plots representing these correlations are depicted in Fig. 5. There was a sex-dependent variation in the biomarker levels and it was noted that salivary IL-1β and serum CGRP levels were higher in females than in males, although this was not statistically significant, while the other biomarker levels in serum and saliva were equally expressed in both males and females (Table VII).

Correlation between biomarkers and periodontal parameters. The levels of periodontal parameters in group IV were significantly elevated, reflecting more severe periodontal disease. The mean PPD was 6.85±0.24 mm in group IV, compared to 5.24±0.68 mm in group III, 2.62±0.18 mm in group II and

Table VI. Overall correlations between salivary and serum biomarkers.

Parameters	Correlation value	P-value
Saliva IL-1β vs. serum IL-1β	0.845	0.001[a]
Saliva IL-1β vs. serum CGRP	0.522	0.001[a]
Saliva IL-1β vs. serum PTX-3	0.405	0.001[a]
Saliva CGRP vs. serum IL-1β	0.811	0.001[a]
Saliva CGRP vs. serum CGRP	0.790	0.001[a]
Saliva CGRP vs. serum PTX-3	0.765	0.001[a]
Saliva PTX-3 vs. serum IL-1β	0.557	0.001[a]
Saliva PTX-3 vs. serum CGRP	0.901	0.001[a]
Saliva PTX-3 vs. serum PTX-3	0.861	0.001[a]

Correlation analyses were performed using Pearson's correlation analysis. [a]P<0.05, statistically significant difference. CGRP, calcitonin gene-related peptide; PTX-3, pentraxin-3; IL-1β, interleukin 1β.

Table VII. Sex-stratified biomarker levels (serum and saliva).

Biomarker	Compartment	Males (n=38), mean ± SD	Females (n=58), mean ± SD	P-value	Comment
IL-1β	Serum	21.8±14.9	24.5±15.7	0.42	No significant sex difference
IL-1β	Saliva	260±140	290±150	0.38	Higher variance in females
CGRP	Serum	63.4±37.9	69.8±42.3	0.47	Trending higher in females
CGRP	Saliva	41.2±18.4	46.5±21.1	0.33	Comparable overall
PTX-3	Serum	9.10±4.85	9.65±5.23	0.55	No sex effect
PTX-3	Saliva	6.85±4.32	7.40±4.67	0.51	No sex effect

CGRP, calcitonin gene-related peptide; PTX-3, pentraxin-3; IL-1β, interleukin 1β.

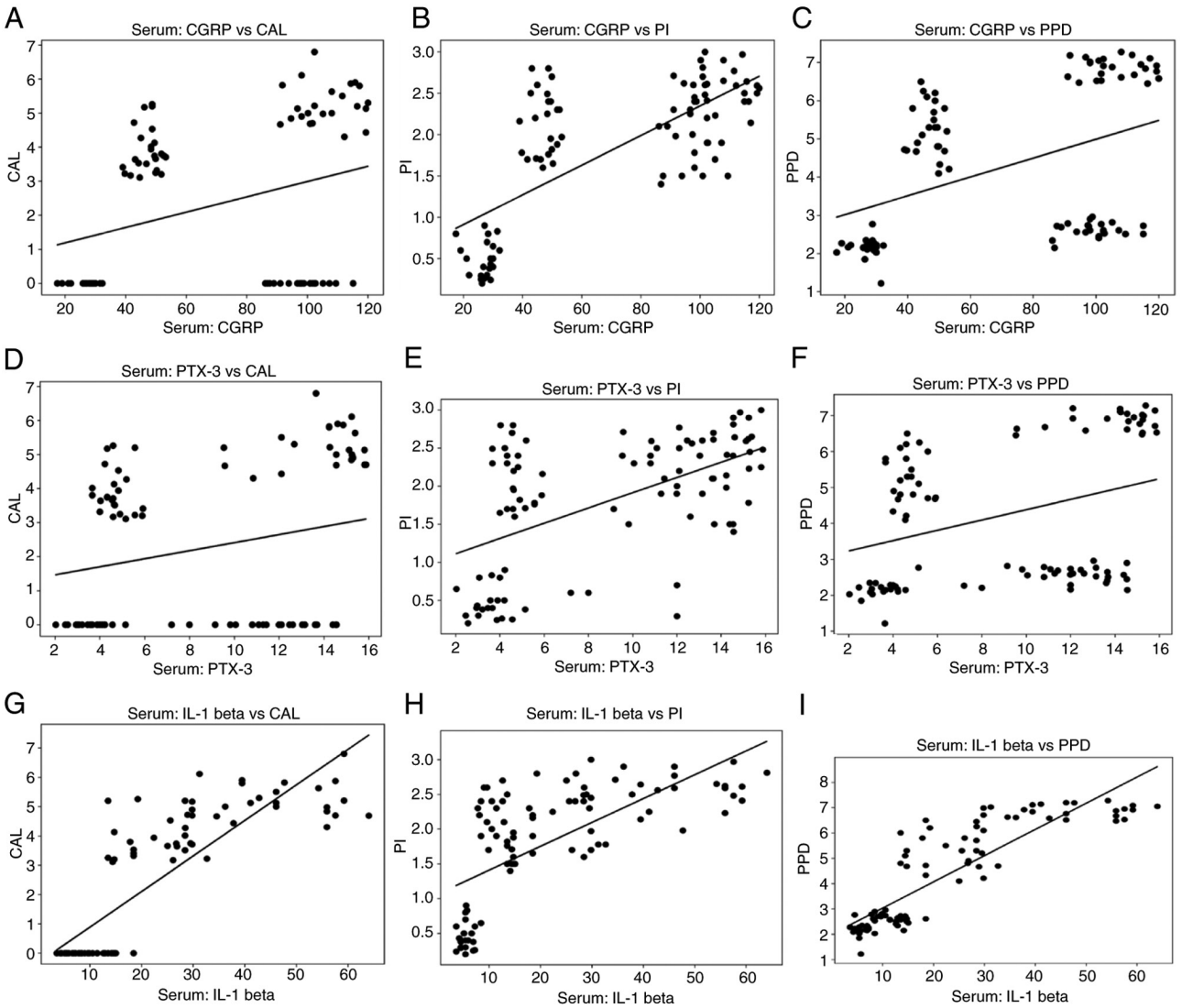

Figure 4. Scatter plots illustrating correlations between serum biomarkers. (A-I) Pairwise associations among serum IL-1β, CGRP and PTX-3 concentrations. Individual observations and linear regression lines are shown in each panel; all correlations were statistically significant (P<0.001). CAL, clinical attachment level; PI, plaque index; CGRP, calcitonin gene-related peptide; PTX-3, pentraxin-3; IL-1β, interleukin 1β.

2.16±0.25 mm in the healthy controls (P<0.001). Similarly, CAL in group IV was 5.2±0.59 mm, significantly higher than that in group III (3.88±0.66 mm) and absent in groups I and II (0.00±0.00 mm) (P<0.001). The m SBI and PI were also elevated in group IV (m SBI, 2.77±0.11; PI, 2.53±0.30), indicating an increased local inflammatory burden. Group-level analyses revealed significant positive correlations between both serum and salivary IL-1β, CGRP and PTX-3 levels, and

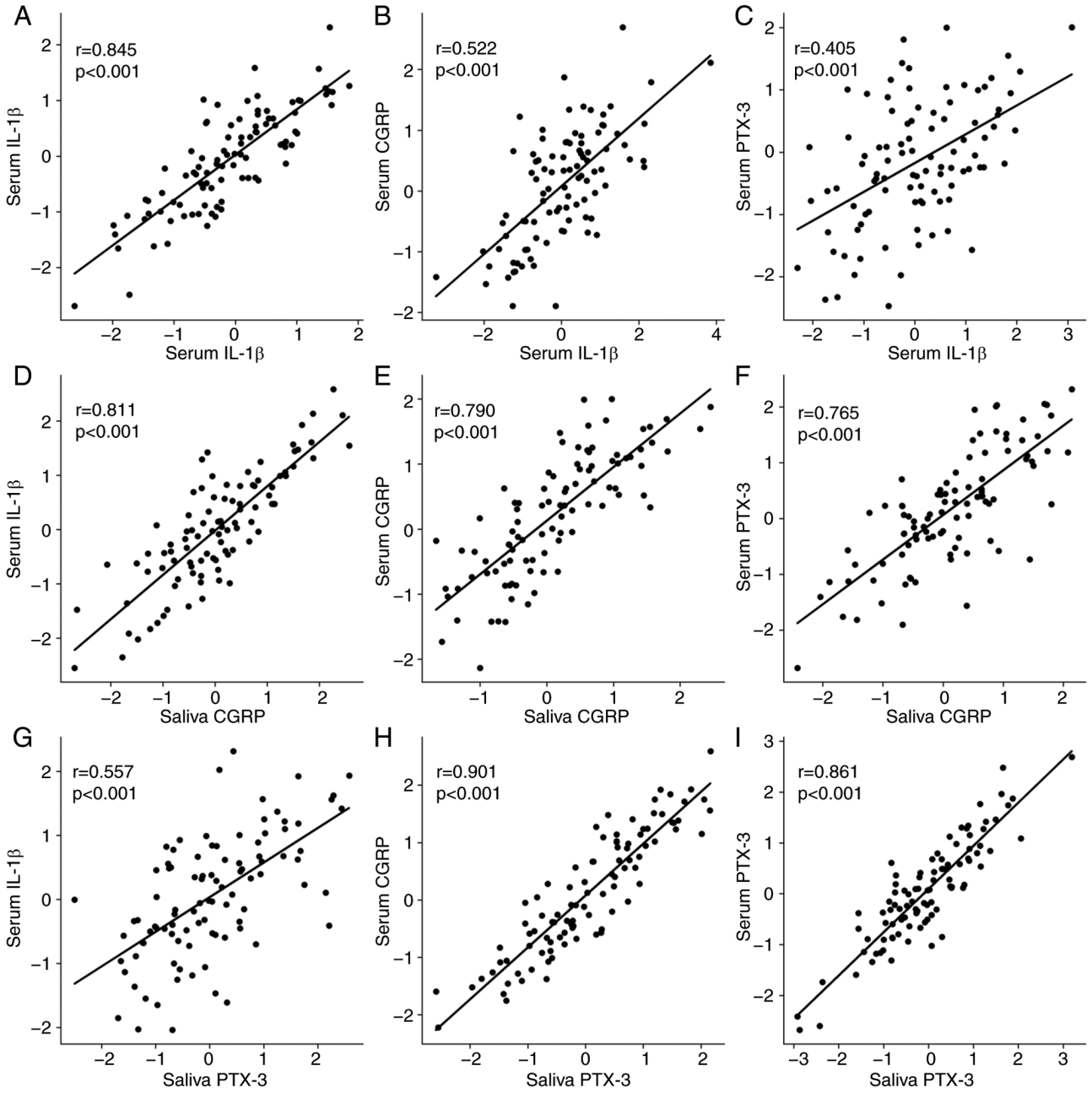

Figure 5. Scatter plots illustrating correlations between salivary and serum biomarker levels. (A-I) Pairwise correlations between salivary and serum IL-1β, CGRP and PTX-3. Each panel includes individual data points, a linear regression line, and Pearson's correlation coefficients (r). All correlations were statistically significant (P<0.001). CGRP, calcitonin gene-related peptide; PTX-3, pentraxin-3; IL-1β, interleukin 1β.

clinical periodontal measures, specifically PPD and CAL. Individuals with higher PPD and CAL values exhibited higher concentrations of all biomarkers. These correlations were strongest in group IV, where both periodontal inflammation and chronic migraine were present. These correlations are illustrated in Figs. 6 and 7, revealing clear upward trends between a worsening periodontal status and increasing biomarker concentrations in both saliva and serum.

Discussion

The present study provides novel insight into the inter-relationship between chronic migraines and periodontitis, highlighting the interplay of neurogenic and systemic inflammatory pathways. The findings indicated that individuals with co-existing chronic migraines and periodontitis (group IV) demonstrated a markedly higher migraine intensity, as assessed by the MS-Q, than those with chronic migraines but without periodontitis (group II), periodontitis alone (group III), or the healthy controls (group I). This observation supports the concept of a synergistic effect of systemic and local inflammation, potentially lowering the threshold for migraine initiation and exacerbating chronification (19-21).

The levels of periodontal parameters in group IV were significantly elevated, reflecting more severe periodontal disease, indicating an increased local inflammatory burden. These findings corroborate those of earlier studies by Leira *et al* (22) and Camps-Plomer *et al* (23) reporting heightened periodontal

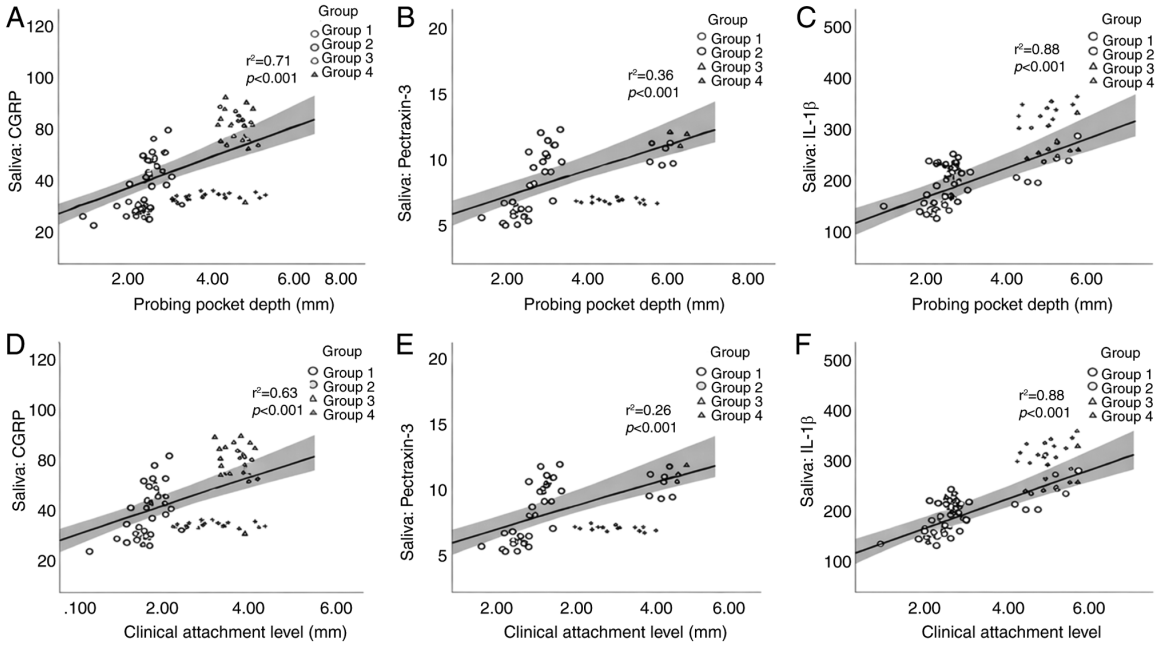

Figure 6. Correlation analysis scatter plots of saliva CGRP, PTX-3 and IL-1β levels in relation to probing pocket depth and clinical attachment level. (A) Saliva CGRP levels correlated with probing pocket depth. (B) Saliva PTX-3 levels correlated with probing pocket depth. (C) saliva IL-1β correlated with probing pocket depth. (D) Saliva CGRP levels correlated with clinical attachment level. (E) Saliva PTX-3 levels correlated with clinical attachment level. (F) Saliva IL-1β correlated with clinical attachment level. Linear regression lines with 95% confidence interval bands are displayed for each subplot. All correlations were statistically significant (P<0.001). CGRP, calcitonin gene-related peptide; PTX-3, pentraxin-3; IL-1β, interleukin 1β.

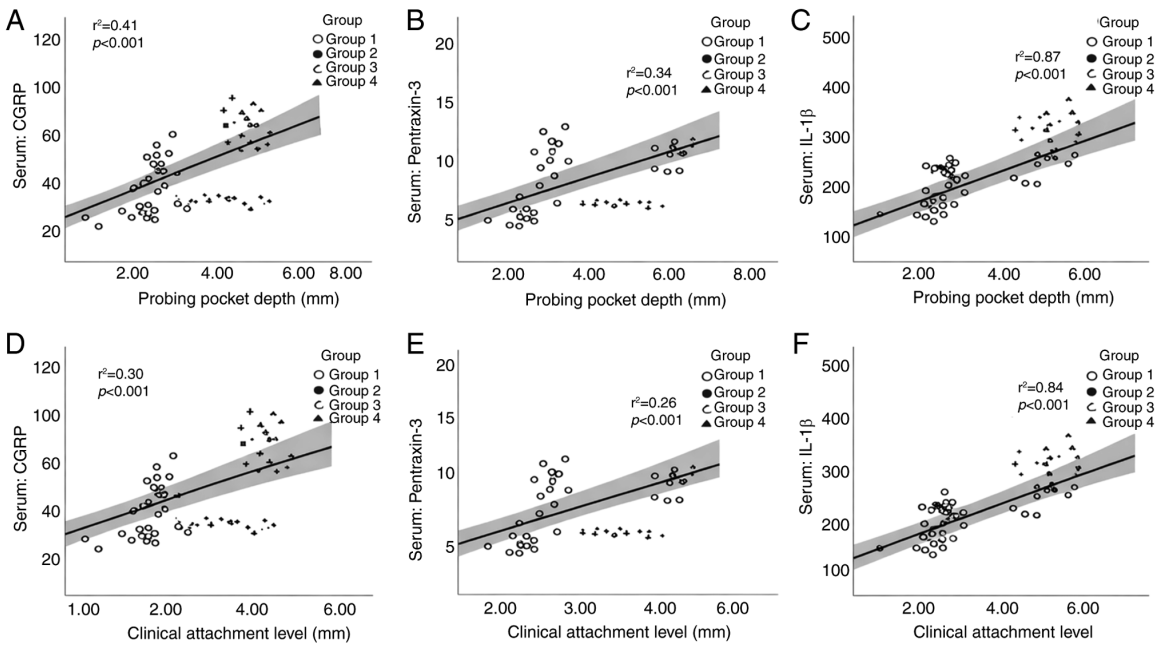

Figure 7. Correlation analysis scatter plots of serum CGRP, PTX-3 and IL-1β levels in relation to probing pocket depth and clinical attachment level. (A) Serum CGRP levels correlated with probing pocket depth. (B) Serum PTX-3 levels correlated with probing pocket depth. (C) Serum IL-1β correlated with probing pocket depth. (D) Serum CGRP levels correlated with clinical attachment level. (E) Serum PTX-3 levels correlated with clinical attachment level. (F) Serum IL-1β correlated with clinical attachment level. Linear regression lines with 95% confidence interval bands are displayed for each subplot. All correlations were statistically significant (P<0.001). CGRP, calcitonin gene-related peptide; PTX-3, pentraxin-3; IL-1β, interleukin 1β.

indices in patients with migraines and periodontitis. This suggests that chronic neurogenic inflammation may be associated with periodontal tissue breakdown or vice versa.

In the present study, the levels of IL-1β, a key pro-inflammatory cytokine, were significantly elevated in both the serum and saliva samples of patients in group IV. IL-1β values were elevated in group IV compared to the other groups and salivary IL-1β concentrations were substantially higher than serum values (P 0.001). The pronounced elevation in saliva reflects the predominant local production of

IL-1β within periodontal tissues and gingival crevicular fluid. Micro-bleeding or subclinical gingival inflammation may also increase salivary concentrations, consistent with the role of IL-1β as a locally acting pro-inflammatory cytokine in periodontal disease (24).

The elevated salivary concentrations of IL-1β likely reflect localized periodontal inflammation, whereas increased serum levels may indicate the systemic dissemination of inflammatory mediators, potentially via bacterial endotoxins entering the circulation. These findings have been reported by Sachelarie *et al* (24); Relvas *et al* (25) and Neurath and Kesting (26). Furthermore, Musubire *et al* (27) similarly reported elevated levels of IL-1β in patients with migraines, although the present study uniquely evaluated the concurrent effects of periodontal disease and migraine on both salivary and serum IL-1β levels.

In the present study, the leels of CGRP, a central mediator of the activation of the trigeminovascular system, were significantly higher in the migraine groups, with group IV exhibiting peak values. Elevated salivary levels of CGRP are indicative of local trigeminal activation and peripheral nociceptive signaling, while elevations in serum suggest systemic neurogenic inflammation that may perpetuate recurrent migraine episodes. The studies by Alpuente *et al* (28); Guo *et al* (29), Dholakia *et al* (30) and Oliveira *et al* (31) reported similar findings. These findings support the notion of a bidirectional neurovascular-inflammatory loop, where periodontal inflammation may amplify trigeminal activation and neuropeptide release, intensifying migraine severity.

Herein, the levels of PTX-3, an acute-phase protein upregulated by IL-1β and TNF-α, were highest in group IV, while PTX-3 mediates endothelial dysfunction, complement activation and neutrophil recruitment, linking vascular inflammation to periodontal tissue injury (32-34). The concurrent elevation of PTX-3, IL-1β and CGRP underscores a shared neurovascular-inflammatory axis between migraine and periodontitis.

Correlation analyses further reinforced the connection between biomarkers and clinical parameters. Salivary and serum CGRP, as well as PTX-3, demonstrated significant positive correlations with all clinical indices ($P<0.001$), highlighting the clinical relevance of these biomarkers in reflecting periodontal and neurogenic inflammation. Yaghobee *et al* (10), Relvas *et al* (35) and Leira *et al* (22,36) similarly observed the same trends in these biomarker values. Notably, serum PTX-3 exhibited a positive, but non-significant correlation with CAL, suggesting tissue-specific activity and potential compartmentalization of inflammatory signaling.

Mechanistically, IL-1β generated by periodontal inflammation can trigger the release of CGRP and PTX-3 synthesis, enhancing reactive oxygen species-mediated endothelial dysfunction, trigeminovascular sensitization, and systemic immune activation, as observed by Pradeep *et al* (37) Fujita *et al* (38) and Wang *et al* (39). Herein, IL-1β, CGRP and PTX-3 elevations in group IV suggested converging inflammatory pathways; however, these observations do not establish directional causality between periodontitis and migraine. The proposed IL-1β-CGRP/PTX-3 axis should therefore be considered hypothesis-generating. Alternative explanations include shared genetic predisposition to inflammatory hyper-responsiveness, systemic low-grade inflammation, hormonal influences, or behavioral confounders. Longitudinal and interventional studies are required to clarify temporal associations. CGRP, despite its inability to cross the blood-brain barrier, exerts potent peripheral nociceptive and vasodilatory effects, lowering the migraine threshold (40,41). PTX-3 amplification further augments vascular inflammation and chronicity risk, establishing a vicious cycle of bidirectional pathology, where periodontitis may intensify migraine attacks, and chronic migraine-associated neurogenic inflammation could reciprocally may be associated with periodontal disease.

When contextualized against previously published migraine-only and periodontitis-only cohorts, the magnitude of biomarker elevations observed in the present study, particularly in individuals with co-existing chronic migraines and periodontitis, appears greater than those typically reported. Prior migraine-focused studies have documented modest to moderate increases in serum CGRP (28,29,41) and PTX-3 (10,34,36,37), often within a narrower range and primarily during ictal phases or in highly selected chronic migraine populations. Similarly, periodontal studies generally report elevated levels of salivary IL-1β and PTX-3 (10,36,37) in periodontitis, although with lower absolute concentrations than those observed herein, particularly in saliva. The comparatively larger effect sizes in the present study cohort may reflect the cumulative and synergistic inflammatory burden imposed by the coexistence of two chronic inflammatory conditions, rather than either disease in isolation. Periodontitis represents a persistent peripheral inflammatory source capable of amplifying systemic cytokine spillover, endothelial activation and neurogenic sensitization, which may in turn augment CGRP release and PTX-3 expression in individuals already predisposed to migraine chronification. Additional factors that may contribute to the observed magnitude include the inclusion of patients with established chronic migraine, the assessment of both serum and saliva (capturing compartment-specific inflammatory activity), and the exclusion of confounding systemic diseases that could dilute disease-specific effects in broader cohorts. Differences in assay platforms, sample matrices, disease severity thresholds and the timing of sample collection relative to migraine activity may further explain variability across studies. Collectively, these considerations suggest that the larger observed biomarker changes likely reflect a biologically meaningful amplification of shared neurovascular-inflammatory pathways when migraine and periodontitis coexist, rather than methodological inflation alone.

Despite these compelling findings, certain limitations of the present study should be acknowledged, such as: The cross-sectional design precludes causal inference; single-center recruitment may limit generalizability; migraine-specific medication use, although recorded, may still exert residual confounding; absence of a low-frequency migraine group with healthy periodontium; the lack of an interventional periodontal-therapy arm; the absence of hormonal and menopausal stratification; in addition, correlations, although statistically significant, require validation in larger multicenter cohorts. Thus, further longitudinal, multicenter studies with interventional components are warranted to validate these findings and explore therapeutic targeting of shared inflammatory pathways.

In conclusion, chronic migraines with co-existing periodontitis are associated with higher serum and salivary IL-1β, CGRP and PTX-3 levels and a more severe periodontal destruction. However, although these findings support an association between periodontal status and neurovascular-inflammatory burden, they do not establish causality. The present study demonstrates that patients with co-existing chronic migraine and periodontitis exhibit markedly elevated serum and salivary levels of IL-1β, CGRP, and PTX-3, accompanied by worsened clinical periodontal parameters (PPD, 6.85±0.24 mm; CAL, 5.2±0.59 mm; PI, 2.53±0.30; mSBI, 2.77±0.11). These findings suggest a bidirectional, neurovascular-inflammatory link between the two conditions, with IL-1β functioning as a central mediator potentially related to CGRP release and PTX-3 expression. This inflammatory axis may be associated with the sensitization of the trigeminovascular system, vascular dysfunction, and migraine chronification. Salivary biomarkers, in particular, represent non-invasive surrogates for systemic inflammation. Further prospective and interventional studies are required to determine whether modifying periodontal inflammation influences migraine outcomes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SKG contributed to the conception and design of the study, investigation, data acquisition and in the writing of the original draft of the manuscript. DP played a central role in the conception and design of the study; developed and refined the study methodology; oversaw data acquisition, quality control, and data curation; supervised the overall conduct of the study; coordinated and figure preparation, contributed to data interpretation; and was responsible for writing, critical review, and substantive editing of the manuscript. CMA was involved in project administration, data curation, and in the writing, reviewing and editing of the manuscript. PSGP contributed to the conception and design of the study, provided critical intellectual input during study planning, oversaw study execution, guided data interpretation, and contributed to figure preparation and critical revision of the manuscript for important intellectual content. DJV contributed to the conception and design of the study, involved in study supervision and in the formal analysis. NV played a significant role in the preparation of the manuscript, including drafting. In addition, NV provided essential resources, including access to laboratory equipment, the provision of biological samples, and reagents necessary for conducting the assays used in this study. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Each experimental protocol and methodology was approved and carried out in accordance with the ethical guidelines of the Institutional Review Board of SRM Dental College, Chennai, India (IRB no: SRMDC/IRB/2022/MDS/No. 507). All individuals gave their written informed consent to participate in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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