BULLETIN OF STOMATOLOGY AND MAXILLOFACIAL SURGERY
Volume 21, Issue 3

DOI:10.58240/1829006X-2025.3-223

COMPARATIVE ASSESSMENT OF SALIVARY ENDOTHELIN-1 LEVELS PERIODONTITIS SUBJECTS FOLLOWING NON-SURGICAL PERIODONTAL THERAPY (NSPT) WITH ADJUNCTIVE PHOTOBIOMODULATION AND NSPT ALONE: A PROSPECTIVE INTERVENTIONAL STUDY

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Received: Mar 6, 2025; **Accepted:** Mar.26, 2025; **Published:** Apr.5, 2025

ABSTRACT

Background: Non-surgical periodontal therapy (NSPT) effectively reduces microbial load and inflammation in Periodontitis; however, adjunctive therapies such as photobiomodulation (PBM) have been proposed to enhance outcomes. Endothelin-1 (ET-1), an inflammatory biomarker, has been associated with periodontal disease progression, yet its levels in saliva remain under-investigated, thus we aimed to comparatively assess salivary ET-1 levels in periodontitis patients undergoing NSPT alone versus NSPT combined with photobiomodulation.

Material and methods: This prospective, randomized, single-blinded study involved 96 subjects divided equally into three groups: healthy controls, generalized periodontitis treated with NSPT alone, and periodontitis treated with NSPT and photobiomodulation. Clinical periodontal parameters and levels of salivary ET-1 were recorded at baseline and on the 21st day.

Results: Results demonstrated significantly elevated levels of ET-1 in periodontitis patients in comparison to healthy individuals (p=0.002). Both treatment modalities showed improvements in clinical parameters; however, NSPT combined with photobiomodulation significantly reduced ET-1 levels (p=0.048) and improved periodontal outcomes.

Conclusion: Adjunctive photobiomodulation enhances the efficacy of NSPT, with salivary ET-1 proving to be promising as a biomarker to monitor periodontal disease and therapeutic response.

Keywords: non-surgical periodontal therapy, endothelin-1, photobiomodulation, periodontitis

INTRODUCTION

Chronic Periodontitis (CP) is an inflammatory disorder affecting tissues supporting teeth. The standard treatment for CP is nonsurgical periodontal therapy (NSPT) as it can reduce bacterial load and microbe induced inflammatory responses, targeting subgingival biofilm elimination[1]. Therapeutic efficacy of this method is well-documented, and scaling and root planing(SRP) are the standard in CP treatment[2]. To improve the results of NSPT, additional therapies including photobiomodulation have been suggested. Photobiomodulation (PBM) is a therapeutic approach that employs appropriate dosages of laser photonic radiation. It is advocated for its anti-inflammatory properties, analgesic benefits, and promotion of wound healing[3].

Endothelin-1 (ET-1) is a commonly studied element of the Endothelin system in the human body, expressed in tissues during inflammatory states[4]. Evidence-based literature indicates a robust correlation between ET-1 and the aetiology of periodontitis[5,6]. Furthermore, ET-1 levels are considered a pivotal component in the outcomes of periodontitis.

Existing literature has assessed ET-1 concentrations

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in gingival crevicular fluid(GCF) and serum in CP and NSPT effects on these levels[7–9]. To our knowledge, just a single study has evaluated Salivary ET-1 levels in CP. This study aimed to assess Salivary ET-1 levels in individuals with periodontitis and to compare these levels before and after NSPT combined with PBM in CP patients. This will facilitate the investigation of Endothelin-1 as a salivary biomarker in periodontitis.

2. MATERIAL AND METHODS

2.1 Study design and Patient Selection

This prospective, randomised, single blinded interventional trial was executed in Department of Periodontology.

The sample size was determined using the subsequent formula:

$$n = \frac{Z1\text{-}\alpha/22\ SD2}{(M\ X\ \varepsilon)2}$$

A minimum sample of 29 was necessary in each category according to the given calculation. Nevertheless, given the likelihood of dropouts, a total of 32 patients were included in each of the groups. A selective sample method was employed for assigning a total of 96 patients for 3 groups. Group 1 comprised 32 periodontally and systemically healthy individuals, Group 2 included 32 individuals with generalised periodontitis undergoing NSPT exclusively, Group 3 consisted of 32 individuals with generalised periodontitis getting both NSPT and PBM. Subjects with periodontitis were selected based on 2017 AAP World Workshop on Classification of Periodontal and Peri-implant Diseases and Conditions. Participants in the study included systemically healthy individuals, those exhibiting bleeding on probing at≥10 % of sites, a Simplified Oral Hygiene Index of ≥ 1.2, Gingival Index (GI)≥1, Periodontal Probing Depth (PPD)≤5mm at over 30% of sites, Clinical Attachment Loss (CAL) of 3-4 mm at over 30% of sites, radiographic evidence of bone loss, and individuals aged between 30 and 65 years. Patients with systemic diseases, recent infections, pregnant or lactating females, individuals having previous history of periodontal therapy within the past six months, tobacco users, those using any drugs that affect periodontal tissues, and patients who did not provide consent for study enrolment were excluded.

A flowchart illustrating the recruitment and allocation of the research population (Figure 1).

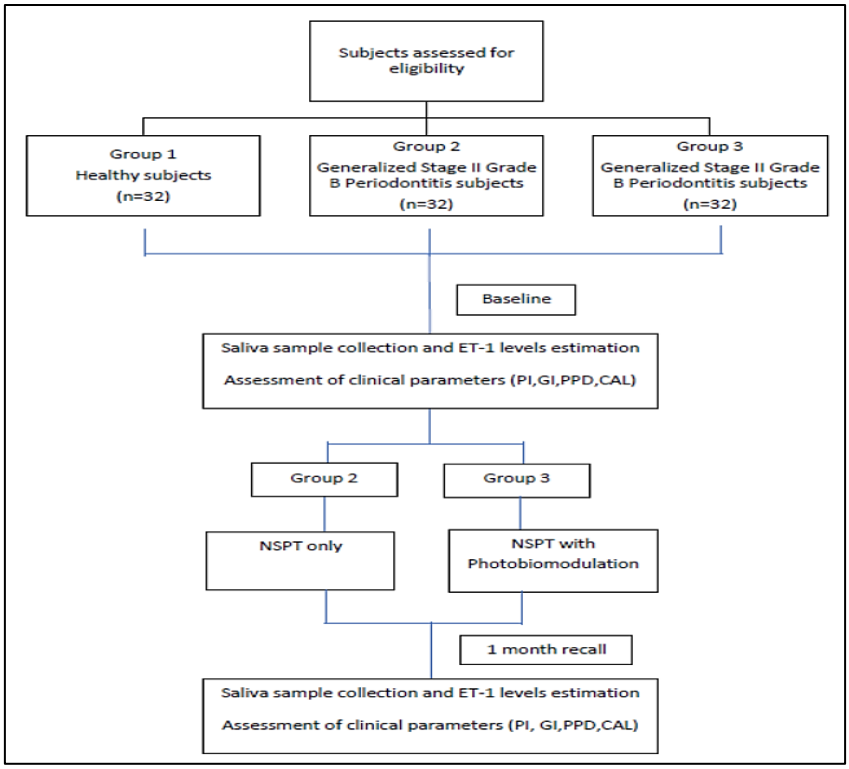

Figure 1. Recruitment and allocation of the study population

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2.2 Collection of Saliva samples

Under aseptic conditions, 2ml of unstimulated whole saliva was collected via the spitting method two hours postprandially, between 10 am and 12 pm for standardising our collection. 2 millilitres of saliva sample were transferred into an Eppendorf tube. Cell debris was eliminated by centrifuging the samples at 1000 rpm for 20 minutes at a temperature of 2-8°C. For subsequent examination, 0.5ml supernatant was preserved in a 1.5ml plastic Eppendorf tube at -80°C in the Department of Genetics. The tubes were labelled and a tracking number was allotted.

2.3 Assessment of clinical parameters

Our study involved NSPT, which included a single-session scaling with a piezo-electric ultrasonic scaling unit (EMS PM100, Guangxi Ehall Medical Technology Co., Ltd.) and root planing using Standard Gracey Curettes (HuFriedy, Chicago, IL, USA), conducted after the collection of saliva samples in groups 2 and 3 by a blinded, trained operator. The operator provided self-administered plaque control techniques and oral hygiene instructions. The patients were called for follow up after 3 weeks for the reassessment of periodontal markers.

2.4 Photobiomodulation

Laser specifications and Laser irradiation: Indium Gallium Arsenic based diode laser (Photonplus diode laser®, ZolarTechnology and Mfg.Co.Inc.Canada) was utilised, featuring a 980nm wavelength, 100mW output power, .5cm²spot size area, and an irradiance of 0.2 W/cm². Cumulative energy administered was 8J. The provided dosage (energy density) was 2 J/cm² per application location. The laser functioned in continuous wave mode for 10 seconds/point. Laser tip was positioned perpendicular to tooth's long axis at four locations around the teeth, specifically at interdental papilla on buccal and lingual/palatal aspects, both mesially and distally. Standard postoperative directives were provided. All LASER safety protocols and measures were meticulously adhered to. The patients were summoned after 21 days for the re-evaluation of periodontal markers.

2.5 Estimation of salivary Endothelin-1 level

ET-1 levels were assessed utilising the Fine Test® Human Endothelin-1 enzyme linked immunosorbent assay (ELISA) kit. Assay was conducted with an ELISA reader (Lisa Quant, Department of Microbiology) in accordance with manufacturer's guidelines.

2.7 Statistical analysis

After obtaining all necessary information, the data was analysed to identify the impact of NSPT and PBM on ET-1 levels in saliva samples of Stage II Grade B Periodontitis. Data was imported into an MS Excel spreadsheet and subsequently evaluated using the statistical software application SPSS, IBM, INDIA 20.0. Variations in salivary ET-1 levels was assessed via Quadratic Regression Equation. A thorough comparative analysis of clinical parameters and Salivary ET-1 levels was conducted using a One-way ANOVA test, with Tukey's post hoc test applied for intergroup comparisons. The threshold for statistical significance was established at $p < 0.05$.

2.8 Study Ethics And Safety

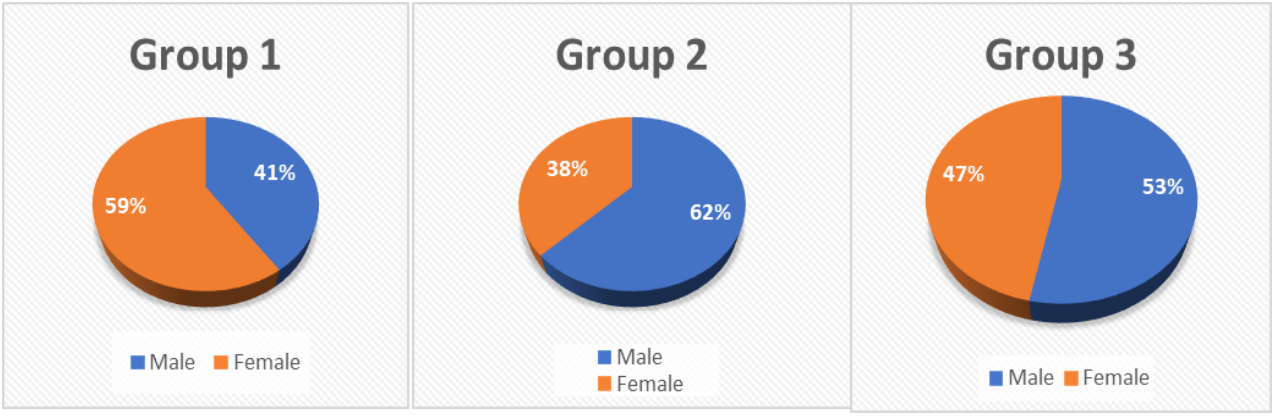
This clinical investigation received approval from the Ethical Committee and Institutional Review Board (No. 233/2020-2021). Participants were explained about study procedures and included upon receiving their agreement.

3. RESULTS

The current study was conducted among 96 subjects which were equally distributed among, the Healthy group (n=32), NSPT group (n=32), and NSPT along with the Photobiomodulation group (n=32).

3.1 Age and Gender wise distribution

Graph 1 shows gender-wise distribution of study population. The mean age was 41.65 years in group 1, in group 2 it was 48.43 years whereas for group 3 the average age was 53.37 years.



Graph 1. Age and Gender-Wise Distribution of the study population

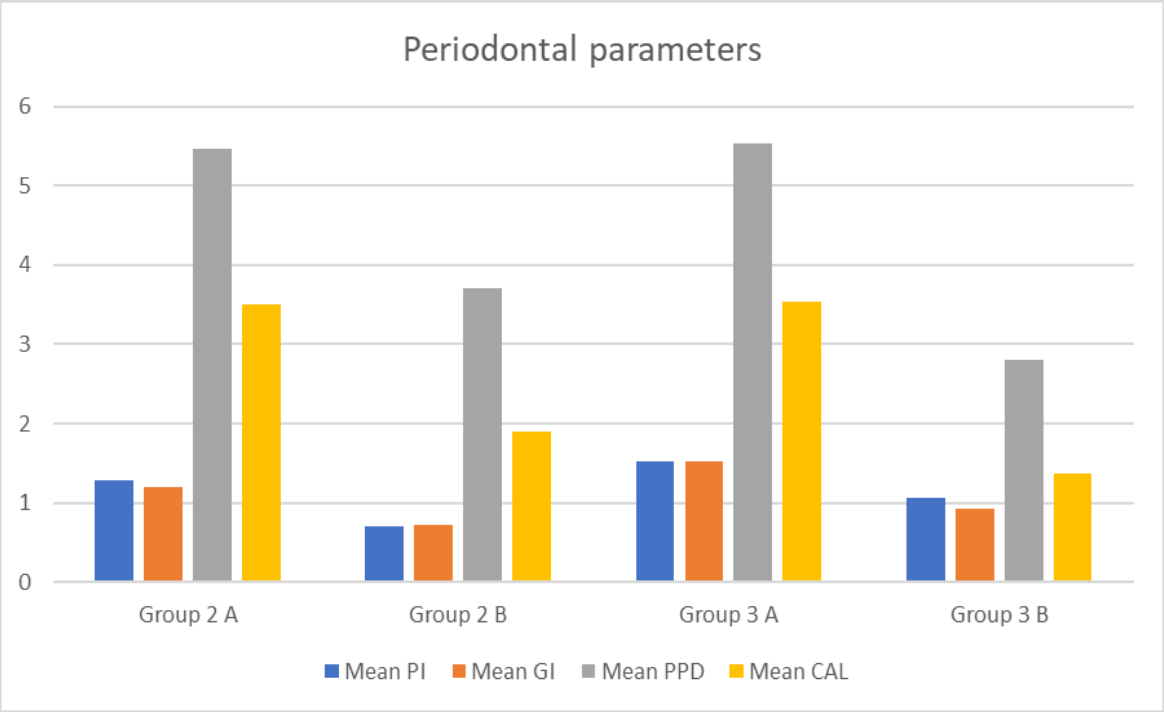
3.2 Comparison of Plaque index (PI) and Gingival Index (GI) at baseline and post 21 days in NSPT and NSPT with Photobiomodulation group

Graph 2 describes mean value of PI and GI while **Table 1** describes mean difference between PI and GI at baseline and after 3 weeks. A significant reduction in PI and GI was noted among both groups when compared to baseline scores. Intergroup comparative analysis revealed a dec decrease in PI score was significantly better in group 2 than in group 3. Results showed that in both groups there was a statistically significant reduction in mean GI values from the baseline to the 21st day ($p<0.001$). On comparison of both the study groups, the mean difference NSPT along with PBM showed more reduction in GI as compared to NSPT alone.

Table 1. Overall comparative statistics of mean PI and GI score in 3 groups

Group	Comparison Group	Plaque index		Gingival index	
		Mean Difference	P value, Significance	Mean Difference	P value, Significance
Group 2A (NSPT- Pre) vs	Group 2B (NSPT -Post)	0.571	p<0.001**	0.481	p<0.001**
Group 2B (NSPT -Post) vs	Group 3B (NSPT+PB Post)	0.346	p =0.009*	0.212	p <0.001**
Group 3A (NSPT+PB Pre) vs	Group 3B (NSPT+PB Post)	0.468	p<0.001**	0.6	p<0.001**

p>0.05-no statistically significant difference *p<0.05-significant **p<0.001-highly significant



Graph 2. Mean PI, GI, PPD, and CAL score at baseline and post 21 days in group 2 and group 3

3.3 Comparison of PPD and CAL at baseline and post 21 days in NSPT and NSPT with Photobiomodulation group

Graph 2 explains mean value of PPD and CAL while **Table 2** describes mean difference between PPD and CAL at baseline and on the 21st day. It was found that PPD reduced significantly from the baseline to the 21st day in both groups ($p<0.001$). Also, it was observed that the PPD reduced significantly for NSPT and PBM group than NSPT alone group. On intragroup comparison, it was found in both groups that there was a statistically significant difference from the baseline to the 21st day ($p<0.001$). Also, CAL gain was more significant in Group 3 than in Group 2 suggesting beneficial effects of PBM adjunctive to NSPT.

Table 2. Overall comparative statistics of mean PPD and CAL in 3 groups

Group	Comparison Group	PPD		CAL	
		Mean Difference	p value, Significance	Mean Difference	p value, Significance
Group 2A (NSPT- Pre) vs	Group 2B (NSPT -Post)	1.75	p<0.001**	1.59	p<0.001**
Group 2B (NSPT -Post) vs	Group 3B (NSPT+PB Post)	0.90	p =0.001*	0.53	p =0.062
Group 3A (NSPT+PB Pre) vs	Group 3B (NSPT+PB Post)	2.625	p<0.001**	2.15	p<0.001**

p>0.05 – no statistically significant difference *p<0.05 -significant **p<0.001 – highly significant

3.4 Comparison of Endothelin-1(pg/ml) Levels in group 1 and at baseline and post 21 days in group 2 and group 3

Table 3 and 4 summarizes the mean values of ET-1. For healthy group mean ET-1 levels were 201.74 pg/ml. At baseline and on 21st day for Group 2 it was 224.27 pg/ml and 208.94 pg/ml respectively. For Group 3, the mean

value at baseline was 226.31 pg/ml and 210.39 pg/ml at 21 days. Overall comparative analysis of all three groups reported higher levels of salivary ET-1 in CP patients than in healthy subjects (p =0.002). Intragroup comparison for Group 2 revealed that salivary ET-1 levels did not reduce significantly after NSPT alone (p=0.276). Whereas salivary ET -1 levels were significantly reduced post-NSPT with PBM (p=0.048). This suggested beneficial results of photobiomodulation as an adjunctive therapy to NSPT. Further intergroup comparative analysis suggested a statistically insignificant differences between Group 2 (p=0.828), Group 3(p=0.709) postoperatively.

Table 3. Overall comparative statistics of salivary endothelin-1 levels in 3 groups

	Mean (pg/ml)	SD	One-way Anova F test	p value, Significance
Group 1 (Healthy)	201.74	35.16	F = 4.448	p=0.002*
Group 2A (NSPT- Pre)	224.27	32.16		
Group 2B (NSPT -Post)	208.94	17.71		
Group 3A (NSPT+PB Pre)	226.31	30.78		
Group 3B (NSPT +PB Post)	210.39	13.24		

p>0.05 – no statistically significant difference *p<0.05 -significant **p<0.001 – highly significant

Table 4. Intergroup comparison of salivary endothelin -1 levels in 3 groups

Group	Comparison Group	Mean Difference	p value, Significance
Group1 (Healthy) vs	**Group 2 A (Pre)**	20.74	p=0.023*
	Group 2 B (Post)	7.19	p=0.828 (NS)
	Group 3 A (Pre)	24.56	p=0.004*
	Group 3 B (Post)	8.65	p=0.709 (NS)
Group 2A (NSPT- Pre) vs	**Group 2B (NSPT -Post)**	13.54	p=0.276 (NS)
	Group 3 A (Pre)	3.82	p=0.980 (NS)
Group 2B (NSPT -Post) vs	**Group 3B (NSPT+PB Post)**	1.45	p =1.000
Group 3A (NSPT+PB Pre) vs	**Group 3B (NSPT+PB Post)**	15.91	p=0.048*

4.DISCUSSION

ET-1 has been demonstrated to mediate the immune response at the endothelium level during periodontal disease by facilitating the generation of cross-reactive T cells through specific heat shock proteins[10,11]. ET-1 is a critical modulator that influences the host's defence system in this context. It subsequently induces the formation of endothelial cells, which increases the likelihood of future tissue injury caused by periodontal pathogenic bacteria in a variety of oral disorders[12]. The correlation between CP and levels of ET-1 in serum, GCF, & gingival tissues were evaluated in a few studies. However, based on our understanding, only one study has analysed ET-1 levels in saliva[13].

Concentrations of mean salivary ET-1 in NSPT and NSPT with PBM groups was significantly higher than the healthy group. Similarly, prior research has suggested that ET-1 levels have increased in periodontal and gingival tissues that are inflammatory. In comparison to the periodontally healthy group, Yamamoto E et al., Selvan T et al. and Ansai T et al., observed elevated levels of ET-1 in gingival tissue samples from CP cohort[14–16]. The Fujioka study observed that the ET-1 levels were higher in CP cases compared to those with periodontal health[15]. Nevertheless, Pradeep AR et al. were unable to identify ET-1 in GCF in their investigation[17].

The adoption of plaque management techniques in periodontitis treatment, in addition to the outstanding results associated with SRP, have been extensively documented[18].

Our study findings demonstrated substantial decline in CP metrics, such as PI, GI, PPD, and CAL. These results are in agreement with previous research that demonstrated NSPT to significantly increase CAL levels and decrease PPD in CP patients.

Kaur PK et al. and Gay IC et al. observed that PPD was increased at subsequent follow-up intervals following SRP[19,20]. In a similar vein, Smiley et al. conducted a meta-analysis of 11 RCTs and concluded that SRP was correlated with a statistically significant improvement in CAL of 0.49 mm in comparison to no therapy, as assessed at 6 months follow up[21]. A systematic review conducted by Needleman et al. observed correlation between SRP and a reduction in plaque levels[22].

Khare N et al. and Tawfig A et al. observed the changes in GI that occurred after SRP treatment from the baseline and showed a significant improvement in the SRP in 90days[23,24]. These findings are consistent our results, which similarly demonstrated a considerable reduction in PI, PPD, and GI, as well as a substantial increase in CAL, as a result of NSPT alone.

In CP patients, our study noted substantial decrease in salivary ET-1 post NSPT is similar to Khalid study, that reported a significant decrease in blood ET-1 levels of CP patients following NSPT[7]. A direct comparison of our findings is not feasible due to the lack of research that compares salivary ET-1 levels before and after therapy in CP.

PBM has been acknowledged for its anti-inflammatory, wound healing, alongwith analgesic properties[25,26]. Constituents of cellular metastatic chain are considered to be the primary mechanism of PBM at cellular level, as they absorb monochromatic visible light and near-infrared radiation[27]. Proton electrochemical potential, ATP synthesis, protein and RNA synthesis, mitochondrial membrane potential, synthesis of NADH, oxygen consumption, and ATP are all enhanced by PBM in mitochondria[28]. The dissociation of intracellular reserves, such as nitrosothiols, may result in the generation of a small quantity of nitric oxide from mitochondria during the transmission of laser light[29]. The modest concentration of NO produced by illumination is believed to be advantageous via cellular signalling pathways[30]. Consequently, PBM alters cellular behaviour by modulating mitochondrial respiratory chains or membrane calcium channels, thus promoting the angiogenesis, synthesis of collagen, release of growth factors, etc thereby expediting wound healing[31,32]. In periodontal practice, diode lasers can be securely employed for PBM.

Our study findings indicated both groups to have experienced statistically significant enhancements in clinical parameters following the implementation of NSPT in conjunction with PBM. The PI score and GI score showed a statistically significant decrease in both groups from baseline to 21 days post-intervention in the current study. In comparison to the NSPT along with photobiomodulation group, the PI score experienced a significant decline in NSPT group. These findings are consistent with the Michelli GD study[33]. In comparison to SRP alone, the photobiomodulation group demonstrated statistically significant improvements in GI levels for our study. This suggests that the supplementary use of photobiomodulation is more effective than SRP alone in reducing GI and PI scores. These results are consistent with the research by M Sopi et al., Gandhi et al., and Qadri et al[34–36].

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The present study's intergroup comparison of mean PPD in the NSPT and NSPT with photobiomodulation groups, both pre- and post-intervention, demonstrated a substantial reduction in PPD for both groups. However, the comparative analysis determined that the photobiomodulation group experienced a significantly greater PPD reduction and CAL gain. The current study reported both groups to show a statistically significant increase in CAL from baseline to 21 days. After 21 days, photobiomodulation resulted in a statistically significant increase in CAL. A potential explanation is that laser irradiation increases cellular ATP production and decreases PGE2 levels[37,38]. These results are consistent with the research conducted by several authors. In periodontitis patients, NSPT + PBM showed significantly greater reduction in both clinical and microbiological parameters at 60 days follow up[35,39]. Our results are also consistent with the research conducted by Jiang et al. and Samulak R et al[40,41].

According to a study by Özdemir et al., PBMT + SRP groups exhibited a statistically significant decrease in PPD and CAL, but not in GI and PI, when contrasted with SRP alone[42].

On the other hand, Makhlouf et al., Lai et al., and Euzebio Alves et al. did not observe any substantial reduction in clinical measures following NSPT with photobiomodulation in comparison to NSPT alone[43–45]. According to Angiero et al., both groups demonstrated considerable clinical improvement when compared to controls; however, no statistically significant difference was observed[46]. Chandra et al. conducted a study that showed a statistically significant increase in PI. Although, there was no significant decrease in GI, PPD, and CAL gain in either laser or NSPT groups[47].

Dakhil et al. reported a statistically significant improvement in CAL, despite the absence of significant differences between cases and controls, which is in contrast to our results[48]. While Nguyen et al. & Hatipoğlum et al. observed a statistically significant decrease in PPD and an increase in CAL in a clinical trial, no significant differences were observed between the groups[49,50].

Our primary goal was to examine the function of ET-1 as a salivary biomarker in periodontitis. The results of this investigation will be beneficial to dentists in their evaluation of patients' periodontitis by evaluating salivary ET-1 levels. ET-1 is essential for regulation of blood pressure and vascular tone in healthy individuals, as previously mentioned. As a result, the sublingual evaluation of ET-1 in the dental context may aid in the prediction of cardiovascular issues and the facilitation of appropriate referrals to primary care specialists.

The current investigation has been limited by a relatively small sample size. In order to ascertain the precise role of ET-1 in CP aetiology and its influence on other systemic disorders, it is imperative to conduct additional interventional studies with a larger sample size. Additionally, research may be conducted using modified study designs, extended follow-up periods, and comparisons of different diode laser wavelengths with or without NSPT versus NSPT alone. This will enable the extrapolation of standardised laser techniques across a wide range of wavelengths.

CONCLUSION

The data that was previously discussed suggests that periodontitis is associated with elevated salivary ET-1 levels. Periodontitis can be effectively managed through conventional NSPT. Conventional NSPT is supplemented by photobiomodulation, which is a therapeutic approach that is advantageous. Salivary Endothelin-1 levels were significantly reduced by the combined use of NSPT and photobiomodulation. As a result, ET-1 may be identified as a diagnostic and prognostic indicator in assessment of therapy outcomes in CP cases.

DECLARATIONS

Funding
No Funding

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Declaration of competing interest
The authors declare None of the authors have any relevant financial relationship(s) with a commercial interest.

Data Availability
Not applicable

Acknowledgments

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