

## Original Article

# Gingival crevicular fluid periostin levels in chronic periodontitis patients following nonsurgical periodontal treatment with low-level laser therapy

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## ABSTRACT

**Objective:** Periostin is a matricellular protein highly expressed in periosteum, periodontal ligament and is essential for tissue integrity and maturation. It plays a role in collagen fibrillogenesis and is downregulated in periodontal disease. Biostimulation utilizing low-level laser therapy (LLLT) influences periodontal ligament fibroblast proliferation. This study was conducted with the objective of estimating periostin levels in chronic periodontitis (CP) patients following LLLT as an adjunct to root surface debridement (RSD). **Materials and Methods:** Thirty periodontally healthy participants (Group I) and sixty CP participants were recruited. Based on the therapeutic intervention, CP patients were allocated to either RSD (Group II) or to RSD with LLLT (Group III) group. Clinical parameters and gingival crevicular fluid (GCF) periostin levels were assessed at the baseline and at the 3<sup>rd</sup> month. **Results:** Periostin levels were significantly lower in CP patients when compared to healthy individuals at the baseline ( $P < 0.01$ ). Following nonsurgical periodontal treatment (NSPT), periostin levels significantly increased in both Group II and III, when compared to baseline values ( $P < 0.001$ ). Comparison of mean periostin levels between both the treatment groups showed a significant increase in LLLT group than RSD at the 3<sup>rd</sup> month ( $P < 0.05$ ). **Conclusion:** Within the limitations of the present study, LLLT application was found to have additional benefits over RSD with respect to clinical periodontal parameters and GCF periostin levels. Moreover, periostin may be used as a possible biomarker to evaluate the outcome following NSPT.

**Key words:** Enzyme Linked Immunosorbent Assay, fibrillogenesis, gingival crevicular fluid, low-level laser, periostin

## INTRODUCTION

Periodontitis is an inflammatory disease caused by specific microorganisms resulting in progressive destruction of the supporting tissues of the teeth. The host response causes the release of inflammatory mediators and cytokines leading to periodontal breakdown.<sup>[1]</sup>

Periostin a matricellular protein earlier termed osteoblast specific factor - 2 belongs to the Fasciclin - I

family. It influences cell matrix interactions, cell functions, tissue remodeling, wound repair, and type I collagen fibrillogenesis in periodontal ligament.<sup>[2,3]</sup> It is induced by transforming growth factor-beta (TGF- $\beta$ ) and modulates matrix-cell interactions relevant to connective tissue repair.<sup>[4-6]</sup>

Periostin knock-out mice experiments have shown defective remodeling in periodontal ligament

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and periodontal disease like phenotype.<sup>[5]</sup> Its expression is downregulated in human periodontal ligament fibroblasts when exposed to tumor necrosis factor-alpha (TNF- $\alpha$ ) and *Porphyromonas gingivalis* (P.g) lipopolysaccharide both of which are present abundantly in periodontitis.<sup>[7]</sup>

Removal of bacterial deposits and their toxins from the root surface and within the periodontal pockets is not completely achieved with conventional mechanical nonsurgical debridement alone. Hence, adjunctive therapies like low-level laser therapy (LLLT) have been developed.

LLLT biostimulation causes fibroblast proliferation, maturation and stimulates the production of basic fibroblast growth factor (bFGF), reduces plaque levels, gingival inflammation, enhances wound healing, and increases bone deposition.<sup>[8-10]</sup>

The use of noninvasive biomarker diagnostic techniques can help us further understand if any improvement does occur at the molecular level to further support the use of adjuvant laser therapy. To the authors' knowledge, there is no clinical study to evaluate the changes in periostin levels following LLLT as an adjunct to root surface debridement (RSD).

The aim of the present case-control clinical study was to evaluate the periostin levels in chronic periodontitis (CP) patients following LLLT as an adjunctive to RSD. The hypothesis was that application of LLLT along with RSD could improve periostin levels in patients with CP.

## MATERIALS AND METHODS

### Study population

The study protocol was approved by the institutional review board of SRM Dental College (SRMU/MandHS/SRMDC/2013/M.D.S-PG Student/508). Ninety participants of Indian origin were recruited for this prospective, case-control clinical study. Thirty patients were allocated to systemically and periodontally healthy group (Group I) and sixty patients were allotted to the CP group (Group II and III).

Patients with generalized CP with a probing depth of  $\geq 4$  mm, with at least 24 teeth remaining were included in the study. Patients with a history of systemic diseases, smoking, intake of systemic antibiotics in the previous 3 months, and history of periodontal surgery in the last 6 months were excluded from the study.

### Study design

The study period was between December 2013 and August 2015. All patients were subjected to full-mouth periodontal examination and radiographic evaluation. CP patients recruited were randomly assigned to either of the two treatment groups - RSD group (Group II) or RSD with LLLT group (Group III) by a coin toss method. A single examiner completely blinded to the study recorded the baseline clinical parameters, and gingival crevicular fluid (GCF) samples were collected after 24 h (AB). After sample collection, complete oral prophylaxis, full-mouth RSD within 24 h was done for patients in Group II and III. LLLT was done after a week following RSD for patients in Group III once a week for 6 consecutive weeks. A single operator (DK) blinded to the baseline parameters performed RSD and LLLT in the same controlled environment. All measures were taken to eliminate bias in the study design.

Following RSD analgesics were prescribed, however patients were instructed to take the medicine only if required. The clinical parameters and GCF were collected at the 3<sup>rd</sup> month in Group II and III. During the study period, the participants were instructed to brush twice a day.

### Application of low-level laser therapy

A diode laser (AMD Picasso, 810 nm diode laser, Indianapolis, USA) with the power of 0.7 watts in continuous mode was applied over the gingival margin with the tip (0.5 mm) pointed into the sulcus. The laser was applied at about 0.5-1 mm away from the gingival margin for 20 s over each surface covering the entire oral cavity.

### Clinical evaluation

Probing pocket depth (PPD), clinical attachment level (CAL), and sulcular bleeding index (SBI) were assessed at the baseline for all the three groups, and after 3 months in Group II and III.

### Gingival crevicular fluid sample collection

GCF samples were collected with a microcapillary pipette (Hirschmann, Sigma-Aldrich, USA) from all the ninety study patients (Group I, II, and III) at the baseline and at the 3<sup>rd</sup> month in Group II and III following nonsurgical treatment from the deepest probing site. The collected GCF was stored at  $-80^{\circ}\text{C}$  until analyzed for periostin using Enzyme Linked Immunosorbent Assay (Aviscera Biosciences, Santa Clara, California, USA). The sensitivity of the kit was 5 ng/mL. Intra-assay precision was 4-6% and inter-assay precision was 8-12%.

## Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics for windows, Version 22.0, (IBM Corp., Armonk, NY). Quantitative data were recorded as a mean  $\pm$  standard deviation. One-way ANOVA followed by "Tukey's (honest significant difference [HSD])" *post hoc* was performed to check for significance between the three groups at the baseline. Independent sample *t*-test was performed to check for significance between mean values of Group II and III at the 3<sup>rd</sup> month. Paired *t*-test was done to compare the mean values between Group II and III at different time points. Periostin levels at the baseline and after 3 months were correlated with all the clinical parameters in both Group II and III using Pearson's correlation.

## RESULTS

The patient's characteristics such as age, "mean PPD, CAL, and SBI" and periostin levels are represented in Table 1.

### Assessment of periostin level in gingival crevicular fluid

Group II and III periostin levels were lesser than Group I at the baseline. Following nonsurgical periodontal treatment (NSPT), the periostin values increased in both Group II and III. The mean periostin level in Group III was higher when compared to Group II at 3<sup>rd</sup> month [Table 1].

Comparison of baseline periostin levels between the three groups showed statistically significant difference between the groups ( $P < 0.001$ ). "Tukey's HSD" *post hoc* showed that periostin levels were significantly higher in Group I when compared to Group II and III ( $P < 0.001$ , statistics not represented in table).

Comparison of periostin levels between baseline and 3<sup>rd</sup> month in Group II and III was statistically significant ( $P < 0.05$ ). Comparison of periostin levels between Group II and III at 3<sup>rd</sup> month was found to be statistically significant ( $P < 0.001$ ) [Table 2].

### Assessment of clinical parameters and periostin at the 3<sup>rd</sup> month

Comparison of mean PPD, CAL, and SBI at baseline and 3 months following NSPT in Group II and III showed statistically significant difference ( $P < 0.001$ ) [Table 3]. Similarly, intergroup comparison of clinical parameters at the 3<sup>rd</sup> month between Group II and III showed statistically significant difference ( $P < 0.001$ ) [Table 4].

There was a significant correlation between periostin and PPD at the baseline in Group II. No correlation was found at both baseline and after 3 months between periostin and the clinical parameters in Group III [Table 5].

## DISCUSSION

In this study, LLLT was used as an adjunct to RSD to observe the changes in the levels of periostin. To our knowledge, this is the first study in which periostin

**Table 1: Mean and standard deviation values of age, sex; clinical parameters and periostin levels at baseline and after 3 months**

|                              | Group I          | Group II           | Group III         |
|------------------------------|------------------|--------------------|-------------------|
| Number of participants       | 30               | 30                 | 30                |
| Male                         | 15               | 18                 | 17                |
| Female                       | 15               | 12                 | 13                |
| Age in years (mean $\pm$ SD) | 26.97 $\pm$ 4.74 | 39.60 $\pm$ 11.866 | 41.03 $\pm$ 12.06 |

SD: Standard deviation

**Table 2: Comparison of mean periostin (ng/ml) at baseline and 3 months**

|  | Group I         | Group II           | Group III         |
|--|-----------------|--------------------|-------------------|
| Mean periostin level at baseline (ng/ml)   | 6.54 $\pm$ 1.82 | 3.46 $\pm$ 1.31    | 3.57 $\pm$ 1.02   |
| ANOVA compare mean periostin levels between groups at baseline   |                 | F=45.61<br>P<0.001 |                   |
| Mean periostin level   |                 |                    |                   |
| Baseline   | 6.54 $\pm$ 1.82 | 3.46 $\pm$ 1.31    | 3.57 $\pm$ 1.02   |
| 3 months   | -               | 4.49 $\pm$ 2.10    | 5.79 $\pm$ 1.89   |
| Paired <i>t</i> -test to compare mean periostin level within groups at different time points                 | -               | t=2.41<br>P=0.02   | t=6.19<br>P<0.001 |
| Independent <i>t</i> -test to compare mean periostin level between Group II and III at 3 <sup>rd</sup> month | -               |                    | t=2.51<br>P=0.1   |

**Table 3: Intragroup comparison of clinical parameters at baseline and at 3<sup>rd</sup> month**

|   | Group I         | Group II           | Group III          |
|---|-----------------|--------------------|--------------------|
| Mean PPD at baseline (mm)                                 | 2.25 $\pm$ 0.20 | 4.59 $\pm$ 0.46    | 3.55 $\pm$ 0.30    |
| Mean PPD at 3 months                                      | -               | 3.54 $\pm$ 0.78    | 2.29 $\pm$ 0.63    |
| Intragroup comparison of mean PPD (paired <i>t</i> -test) | -               | t=8.66<br>P<0.001  | t=13.44<br>P<0.001 |
| Mean CAL at baseline                                      | 0.0             | 3.81 $\pm$ 0.71    | 2.65 $\pm$ 0.34    |
| Mean CAL at 3 months                                      | -               | 2.44 $\pm$ 0.51    | 1.75 $\pm$ 0.52    |
| Intragroup comparison of mean CAL (paired <i>t</i> -test) | -               | t=12.60<br>P<0.001 | t=9.29<br>P<0.001  |
| Mean SBI at baseline                                      | 0.26 $\pm$ 0.05 | 2.38 $\pm$ 0.48    | 2.57 $\pm$ 0.81    |
| Mean SBI at 3 months                                      | -               | 0.8120 $\pm$ 0.11  | 0.4863 $\pm$ 0.43  |
| Intragroup comparison of mean SBI (paired <i>t</i> -test) | -               | t=18.17<br>P<0.001 | t=15.09<br>P<0.001 |

PPD: Probing pocket depth, CAL: Clinical attachment level, SBI: Sulcular bleeding index

**Table 4: Intergroup comparison of clinical parameters and periostin levels**

| Variable  | Group     | Mean      | t     | P      |
|-----------|-----------|-----------|-------|--------|
| PPD       | Group II  | 3.54±0.78 | 6.836 | <0.001 |
|           | Group III | 2.29±0.63 |       |        |
| CAL       | Group II  | 2.44±0.51 | 5.167 | <0.001 |
|           | Group III | 1.75±0.52 |       |        |
| SBI       | Group II  | 0.81±0.11 | 4.001 | <0.001 |
|           | Group III | 0.48±0.43 |       |        |
| Periostin | Group II  | 4.49±2.10 | 2.510 | 0.015  |
|           | Group III | 5.79±1.89 |       |        |

PPD: Probing pocket depth, CAL: Clinical attachment level, SBI: Sulcular bleeding index

**Table 5: Correlation of periostin levels with clinical parameters in Group II and III**

| Group     | Clinical parameters   | Periostin levels Pearson correlation | P              |
|-----------|-----------------------|--------------------------------------|----------------|
| Group II  | Baseline              |                                      |                |
|           | PPD                   | -0.423                               | 0.020<br><0.05 |
|           | CAL                   | -0.181                               | 0.337          |
|           | SBI                   | -0.181                               | 0.339          |
|           | 3 <sup>rd</sup> month |                                      |                |
|           | PPD                   | -0.269                               | 0.151          |
| Group III | Baseline              |                                      |                |
|           | PPD                   | 0.295                                | 0.114          |
|           | CAL                   | 0.059                                | 0.755          |
|           | SBI                   | 0.114                                | 0.549          |
|           | 3 <sup>rd</sup> month |                                      |                |
|           | PPD                   | 0.021                                | 0.912          |
|           | CAL                   | 0.104                                | 0.584          |
|           | SBI                   | 0.04                                 | 0.83           |

PPD: Probing pocket depth, CAL: Clinical attachment level, SBI: Sulcular bleeding index

has been used to evaluate the outcome of nonsurgical periodontal therapy using LLLT as an adjuvant to RSD.

At the 3<sup>rd</sup> month, periostin level was increased when compared to the baseline in both Group II and III. Moreover, there was a greater increase in GCF periostin and improvement in clinical parameters in Group III than Group II at the 3<sup>rd</sup> month ( $P < 0.05$ ).

The outcome of periodontal therapy is conventionally based on an assessment of clinical parameters. Laser biostimulation brings about a marginal improvement of such clinical parameters.<sup>[9,10]</sup> To understand the dynamics at the molecular level, periostin was estimated along with the clinical parameters.

Connective tissue homeostasis is maintained by signaling molecules in extracellular matrices.<sup>[11]</sup>

Identification of changes in these molecules can help us to detect the presence of active disease, predict future disease progression, and evaluate the response to periodontal therapy. Periostin regulates collagen fibrillogenesis, wound repair, angiogenesis, improves cell survival and is downregulated in periodontal disease.<sup>[3,4,12]</sup> Similar effects are seen with LLLT biostimulation as well. Qadri *et al.*, Yu *et al.*, and Almeida-Lopez *et al.* in their studies have shown that LLLT induces fibroblast proliferation, and the stimulated fibroblasts are organized in parallel bundles.<sup>[9,13,14]</sup> In addition, LLLT promotes collagen synthesis, angiogenesis, and release of growth factors thereby accelerating wound healing.<sup>[8-10]</sup> Hence, periostin was chosen to evaluate the adjuvant effects of LLLT in this study. Furthermore, to identify site-specific changes, GCF was assessed.

Periostin levels significantly reduced in CP patients when compared to healthy individuals ( $P < 0.001$ ). This is in agreement with the studies by Padial-Molina *et al.*, Aral *et al.*, Balli *et al.*<sup>[15-17]</sup> Aral *et al.* found a significant decrease in GCF periostin levels in aggressive and CP patients when compared to nonperiodontitis patients.<sup>[16]</sup> In a similar study, Balli *et al.* analyzed GCF and serum periostin levels in healthy, gingivitis and CP patients and concluded that GCF periostin concentration decreased with the periodontal disease severity.<sup>[17]</sup>

Periostin levels were significantly higher at the 3<sup>rd</sup> month when compared to the baseline values in both the Groups (II, III) ( $P < 0.05$ ). CP is initiated by complex microbes in plaque biofilm. The red complex organisms comprising of P.g, *Treponema denticola*, and *Tannerella forsythia* are considered periodontal pathogens and are expressed at the sites of progressing periodontitis.<sup>[18]</sup> An *In vitro* study by Padial-Molina *et al.* showed decreased expression of periostin in periodontal ligament fibroblast when exposed to P.g and TNF- $\alpha$ .<sup>[7]</sup> Long-term studies have shown that there is a reduction in the levels of bacteria such as *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia*, P.g, and proinflammatory cytokines following LLLT application.<sup>[10,19]</sup> The increase in periostin levels in Group II and III from the baseline was perhaps due to the effects of LLLT causing a reduction in P.g and TNF- $\alpha$  both of which decrease the expression of periostin. However, lack of microbial profile in the present study is a possible limitation.

LLLT with RSD produced a greater increase in periostin levels and improvement in clinical parameters when compared to RSD alone. This agrees with Qadri

*et al.* and Padial-Molina *et al.*<sup>[9,15]</sup> Qadri *et al.* in their controlled clinical trial evaluated the effects of LLLT as an adjunct to RSD and concluded that significant improvement in clinical parameters and GCF MMP-8 levels were seen following adjuvant biostimulation.<sup>[9]</sup> An increase in periostin levels was also seen following open flap debridement in CP patients by Padial-Molina *et al.*<sup>[15]</sup> The improvement in periostin levels seen in this study may be attributed to increased motility of gingival and periodontal ligament fibroblasts, stimulation of cellular adenosine triphosphate, wound healing promotion, angiogenesis, and production of bFGF and TGF- $\beta$  expression by LLLT.<sup>[8-10,20]</sup>

However, conflicting outcomes were reported by Schwarz *et al.* and Sgolastra *et al.*<sup>[21,22]</sup> Schwarz *et al.* in their systematic review suggest that there is only a marginal increase in clinical parameters following LLLT as an adjunct to mechanical debridement.<sup>[21]</sup> Further, Sgolastra *et al.* in their meta-analysis concluded that LLLT as an adjunct to RSD using diode laser showed no significant improvement in clinical parameters.<sup>[22]</sup>

There was a negative correlation seen between periostin level and baseline PPD in Group II. This concurs with the findings of Aral *et al.* and Balli *et al.* wherein they found a negative correlation between GCF periostin and clinical parameters in CP patients ( $P < 0.05$ ).<sup>[16,17]</sup> The results of our study show that periostin levels are reduced in diseased sites indicating its protective role in the homeostasis of periodontium, and there is an improvement in its level following NSPT.

## CONCLUSION

Periostin holds promise as a reliable inflammatory biomarker for diagnosis and to evaluate the outcome following therapeutic interventions. Moreover, additional treatment with LLLT improves clinical parameters and increases periostin levels in CP patients.

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### Conflicts of interest

There are no conflicts of interest.

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