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THE EFFECT OF NON- SURGICAL PERIODONTAL THERAPY ON PERIOSTIN LEVEL IN THE GINGIVAL CREVICULAR FLUID OF TYPE II DIABETIC PATIENTS WITH PERIODONTITIS

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ABSTRACT

Background and Objective: Periostin is a protein highly expressed within extracellular matrix of bone and periodontal ligament responsible for tissue integrity and play significant role in wound repair and bone remodeling. The present study designed to estimate the effectiveness of non surgical periodontal therapy (NSPT) on level of periostin in the gingival crevicular fluid (GCF) of diabetic patient with periodontitis.

Materials and Methods: 36 subjects were admitted in this study. The subjects allocated into 3 groups, Group I involve 12 periodontally healthy subjects, Group II involve 12 participants with periodontitis. Group III: involve 12 participants with periodontitis diagnosed with diabetes mellites type II. Group II and III were received conventional periodontal treatment scaling and root planning (S&RP). Clinical parameters: pocket depth (PD), clinical attachment loss (CAL), gingival index (GI), plaque index (PI) were measured and the GCF samples were gathered for assessment of periostin at baseline and at 3 months postoperatively.

Results: Periostin level in the GCF were significantly increased in healthy subjects ($P \leq 0.001$) compared to those with diabetic patients with periodontitis and patients with periodontitis only. NSPT in group II and III resulted in significant increase ($P \leq 0.001$) in periostin level at 3 months postoperatively.

Conclusion: NSPT can significantly increase the level of periostin in the GCF of diabetic patients with periodontitis and those with periodontitis only. Moreover, periostin suggested to be inflammatory marker reliable for diagnosis and evaluation of the outcome of periodontal treatment.

KEYWORDS: Periodontitis, diabetes mellites, gingival crevicular fluid, periostin, non-surgical periodontal therapy.

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INTRODUCTION

Periodontitis, is a disease of periodontium triggered by specific microorganisms or groups of microorganisms, and is characterized by advanced clinical attachment loss, periodontal pocketing, gingival inflammation and alveolar bone resorption. [1] During the progress of periodontal disease, host mechanisms that were initially meant to defend against the bacterial challenge get involved into an uncontrolled catabolic process that leads to destruction of the supporting tissues, tooth mobility and finally tooth loss. [2]

Diabetes mellitus (DM) is a highly dominant metabolic syndrome. The more common form, type 2 diabetes, results from a combination of diminished insulin production and insulin resistance. [3] Severe and rapid periodontal tissue destruction is commonly related to DM due to the increased production of proinflammatory cytokines associated with this metabolic disorder; equally, periodontal inflammation worsens the glycemic control, leading to a two-way relationship. The inflammatory response can further be upregulated by existence of both diseases. [4,5]

Advanced glycation end products (AGEs) accumulate excessively in the gingiva of diabetic patients and interact with its receptors (RAGEs) resulting in microangiopathy, loss of barrier function and tissue integrity.[6] DM is also associated with compromised wound healing and the possible mechanism consists of failure of polymorphonuclear leukocytes (PMNLs) chemotaxis to the area of wound healing and altered cellular activity of PMNLs. [7]

Periostin is among the most significant proteins that play a main role in the healing of wounds and periodontal defects. It assists as a modulator of homeostasis in the PDL produced by fibroblasts and is essential for health and growth of tissues. [8,9] periostin is also released in the periosteum and plays a serious role in collagen fibrillogenesis pathway. [10] In chronic periodontal disease, the proliferation and differentiation of the PDL cells are expressively reduced, the tissue integrity is compromised and tissue regeneration and healing are totally impaired. Under such situations, periostin aids as a marker for reconstructive cellular matrix interactions and cell behaviour in matrix biomechanics. [8]

To the best of our knowledge, there were no studies that evaluated the effect of non-surgical periodontal therapy on periostin level in the GCF of periodontitis in subjects with diabetes mellitus type 2. Accordingly, this study hypothesizes that non-surgical periodontal treatment of periodontitis in patients with diabetes mellites type 2 will upregulate periostin production and increase its level in the GCF.

MATERIALS AND METHODS

Study population

This clinical trial was implemented on thirty-six patients with or without diabetes mellitus type II and who complained of periodontitis. Their ages ranged between 35-60 years. The participants were chosen from the out-patient clinic of Oral Medicine and Periodontology Department, Faculty of Dentistry, Suez Canal University from January 2020 to May 2020. Written informed consent was signed by the participants in this study after detailed discussion of the procedures and follow up visits. The protocol of this clinical trial was approved by the Research Ethics committee (REC) of the Faculty of Dentistry, Suez Canal University.

Inclusion criteria: [11]

According to the new classification 2017 the participants included in this clinical trial involved:

- Patients with healthy periodontium (grade A stage I with clinical attachment loss (CAL) 1-2 mm and pocket depth (PD) ≤ 4mm)
- Patient with periodontitis (grade B or C and stage II (with CAL ≥3-4 mm and PD ≤ 5 mm with no

tooth loss from periodontitis) or stage III (with CAL≥5 and tooth loss from periodontitis ≤4)

- Patients with Type 2 diabetes and the diagnosis of diabetes should not exceed 2 years, under oral hypoglycemic medications and diet control, with good or fair glycemic control confirmed with hemoglobin A1C [HbA1C] (<8%).

Exclusion criteria: [11]

- Patients that received antibiotic within past 6 months should be excluded from the study.
- Patients under drug that could affect periodontal status long-term anti-inflammatory drugs or contraceptives.
- Smokers & chronic alcoholic patients.
- Pregnant or lactating women.
- Subjects with any acute, chronic or allergic diseases.
- Patients with poorly controlled DM (HbA1C >8%) with a history of diabetic complications.

Sample-size calculation:

On the basis of the study of **Burra *et al*., 2019.**[12] calculation of the sample size was fulfilled. Based on the power analysis with α error of 5% and 95% power, G-power software utilized for calculating sample size and the sample size expected for this study was 36. The individuals were allocated into three groups on the basis of specific criteria as the following: Group I included 12 periodontally healthy patients, Group II included 12 patients with periodontitis and Group III included 12 participants with periodontitis diagnosed with diabetes mellites type II.

Study design:

Participants were first be assigned for a screening visit to assess research eligibility. If the participants fit the research criteria, a full-mouth series of x-rays (FMX) were performed to assess bone loss. Participants were then appointed for additional visits. Visit 1 (baseline visit): collection of the GCF was carried out to assess the periostin concentration. The periodontal evaluation consisted of plaque index (PI), [13] gingival index (GI),[13] probing depths (PD), and clinical attachment level (CAL). After visit 1, participants were reappointed for the treatment visit (S&RP) in which anaesthetic was administered, if the patients requested it. Full-mouth supragingival and subgingival (S&RP) were performed for all participants. The treatment has taken an average of four sessions. following (S&RP), a professional plaque-control plan was fulfilled twice a month for 3 months, encompass removal of supragingival plaque and oral hygiene procedures reinstruction. Thereafter, clinical re-examination of all participants was carried out and collection new GCF samples were performed at third months to assess the effect of the NSPT on the formerly estimated clinical and biochemical parameter.

Collection of GCF samples:

In all groups, the GCF samples were collected from the distobuccal or mesiobuccal surface of the teeth with infrabony defects. The sites were isolated with cotton rolls before GCF sampling, the supragingival plaque was eliminated by a sterile curette. Sterile filter paper strips (periopaper® Amityville, NY, USA) were positioned into the gingival sulcus until mild resistance was encountered, and remained in position for 30 seconds. The paper points tainted with saliva or blood were excluded. The samples were put into a sterile polypropylene tube and stored at - 70°C until analysis. [14]

Biochemical assay:

Periostin concentration in samples was analysed by a commercially available Periostin Enzyme Immunoassay kit (Uscn Life Science Inc., Wuhan, China) after following the manufacturer's

prescript. The biochemical assay was performed in the Department of Microbiology, Faculty of Medicine, Suez Canal University, Egypt. Prior to using the reagents, they were conditioned at room temperature (18-25°C) for at least 30 minutes. The kit contained anti- Periostin antibodies with a minimum detection sensitivity < 5 pg/mL. All samples and standards were turned on at least in duplicate as it was recommended based on the manufacturer's instructions. The addition of a 50 mL stop solution to each well was the last step in the enzyme linked immunosorbent assay (ELISA), and after 10 minutes an ELISA reader (Molecular Dynamics, Sunnyvale, CA) was used to read the absorbance of the substrate colour reaction under 450nm wavelength. The concentration of Periostin was recorded as picogram per milliliter (pg/mL) in each sample.

Statistical analysis:

Data were collected, compared then statistically analyzed. Numerical data were explored for normality by checking the distribution of data and using tests of normality (Kolmogorov-Smirnov and Shapiro-Wilk tests). All values were presented as means ± standard deviations.

Analysis of variance (ANOVA): The data collected for each variable and subjected to two-ways ANOVA (3 groups and 2 intervals) with 12 replications. [15] Analysis of variance was done using the computer program SPSS software for windows version 22.0 (Statistical Package for Social Science, Armonk, NY: IBM Corp). Duncan`s post hoc tests was performed for the evaluation of statistical significances among factors. P value ≤ 0.05 is considered be statistically significant

RESULTS

36 participants were involved in this research and allocated into 3 groups, group I included 12 healthy subjects, group II: included 12 subjects with periodontitis and group III: included 12 diabetic patients type 2 with periodontitis. Periodontal clinical parameters were recorded and GCF samples were collected at baseline and at 3 months after NSPT. All secondary outcomes (PD, CAL, PI and GI) were shown in table 1 & 2. There was statistically significant improvement (P≤0.001) in the clinical parameters at 3 months after NSPT in both group II& III compared to baseline with no statistical significant difference (P≥ 0.05) between both group. The mean values of periostin concentration in the GCF (pg/mL) was illustrated in table 3. The periostin concentration was statistically significant increase (P≤0.001) in healthy group compared to group II & III. NSPT resulted in significant increase in the periostin in the GCF at 3 months in both group II & III with no statistically significant difference (P≥ 0.05) between the two groups.

TABLE (1) Results of repeated-measures analysis of variance for the effect of NSPT and time on PD & CAL

PD				
Groups	**Base**	**3Ms**	**Means**	**Percentage of change**
Group 1 control	2.250± 0.75	2.250±0.75	2.250b	0.0%
Group 2	5.083±0.79	3.667±0.89	4.375a	27.86**%**
Group 3	5.167±0.94	3.917±1.16	4.542a	24.19**%**
Means	**4.17a**	**3.28b**		
Sig	**Groups (G)**	**Interval (I)**	**G×I**	
P values	0.00**	0.00**	0.015*	
CAL				
Group 1 control	0.167±0.39	0.167±0.39	0.167b	0.0%
Group 2	2.833±0.72	1.750±0.62	2.292a	38.23%
Group 3	3.00 ±0.60	1.833±0.39	2.417a	38.9**%**
Means	**2.00 a**	**1.25 b**		
Sig	**Groups (G)**	**Interval (I)**	**G×I**	
P values	0.000**	0.000**	0.00**	
***a,b;** means significant differences at P-value<0.05*				

TABLE (2) Results of repeated-measures analysis of variance for the effect of NSPT and time on GI& PI

GI				
Groups	Base	3Ms	Means	Percentage of change
Group 1 control	0.258±0.27	0.258±0.27	0.258b	0.00%
Group 2	1.417±0.51	0.525±0.44	0.971a	69.42%
Group 3	1.392±0.54	0.500±0.48	0.946a	6.08%
Mean	1.02a	0.43b		
Sig	Groups (G)	Interval (I)	G×I	
P values	0.00**	0.00**	0.00**	
PI				
Groups	Base	3Ms	Means	Percentage of change
Group 1 control	0.417±0.51	0.417±0.51	0.417b	0.00%
Group 2	1.583±0.51	0.500±0.52	1.042a	68.41%
Group 3	1.750±0.62	0.500±0.52	1.125a	71.43%
Means	1.25a	0.47b		
Sig	Groups (G)	Interval (I)	G×I	
P values	0.00**	0.00**	0.00**	
***a,b;** means significant differences at P-value<0.05*				

TABLE (3) Results of repeated-measures analysis of variance for the effect of NSPT and time on the concentration of periostin in the GCF:

Groups	Base	3Months	Means	Percentage of change
Group 1	100.39±5.93[a]	100.39±5.93[a]	**100.39[A]**	0.0%
Group 2	51.37±4.67[c]	73.56±4.17[b]	**62.46[B]**	43.20%
Group 3	47.64±4.48[c]	69.81±4.10[b]	**58.73[C]**	46.54%
Means	**66.47[B]**	**81.25[A]**		
Sig	**Groups (G)**	**Interval (I)**	**G×I**	
P values	0.000**	0.000**	0.000**	

*[A'B';**] means significant differences for main factors at P-value<0.05*

[a,b;] means significant differences for interaction at P-value<0.05

DISCUSSION

Periodontal tissue homeostasis, wound repair and bone and tooth remodeling is regulated by periostin which has been considered as the most specific protein expressed in the periodontal ligament. [16] It has crucial role in maintaining the connective tissue integrity in both health and disease. [17] Detection of the activity of the disease, future prediction of disease progression and evaluation of the response of periodontal therapy can be identified by detection of changes in these protein molecules. [18] Accordingly, this study evaluated the GCF level of periostin in patient with type 2 diabetes mellitus after nonsurgical periodontal therapy (NSPT).

In the present research, GCF level of periostin in healthy sites were statistically significantly increased ($P < 0.001$) compared to the diseased sites in group II and group III at baseline suggesting its role in periodontal tissue homeostasis preserving its health as well as presence of inflammation down regulate its expression that may be attributed to the decreased fibroblast numbers or due to overexpression of proinflammatory cytokines leading to reduction in periostin secretion. [9, 19]

The findings of the current research were compatible with the study of **Balli et al., 2015**[14] in which the levels of periostin in the GCF and serum of patients with periodontitis were estimated and compared to those with healthy periodontal condition. It was concluded that the level of periostin in the GCF decreased significantly ($P < 0.05$) as the disease progressed from the healthy state to gingivitis and periodontitis. Moreover, periostin levels in the GCF were negatively correlated with the clinical parameters as GI and CAL. Likewise, in a study of **Aral et al., 2016** [20] it was confirmed that the expression of periostin was diminished in diseased periodontium.

Nonetheless, the current results are partially consistent with the research of **Radhika et al., 2019** [21] who reported that periostin levels in the GCF were increased in healthy group, lower in periodontitis group, and least in periodontitis with diabetes mellitus with significant difference ($P < 0.001$) between the three groups but in the present study periostin level in the GCF of periodontitis patients with diabetes mellitus were less than non diabetic periodontitis group but with no statistically significant difference between groups.

It has been suggested that the production of periostin was downregulated when subjecting human periodontal ligament fibroblasts to tumor necrosis factor-alpha (TNF-α) and *Porphyromonas gingivalis*(P.g) lipopolysaccharide which are

implicated in the pathogenesis of periodontal disease. [9] These may explain the decreased level of periostin in the GCF of periodontitis patient with DM where the advanced glycation end products (AGEs) are accumulated in the tissue and interact with its receptors RAGEs on the monocytes leading to excessive production of proinflammatory mediators such as IL-1β, TNF-α, and IL–6, with subsequent destruction of bone and connective tissue.[22,23]

Negative correlation between GCF level of periostin and TNF-α was confirmed by the study of **Radhika et al., 2019.** [21] Consequently, it can be concluded that the increased expression of periostin in the GCF was associated with the absence of inflammation or reduced inflammation, and the decrease in the level of TNF-α in the, and vice versa in presence of inflammation.

Actually, periostin may exaggerate the inflammatory response in systemic diseases by promoting the release of proinflammatory mediators and by initiating fibrosis as it has the ability to act as anabolic or a catabolic protein due to its versatile nature. [24] It was documented that periostin concentration in the serum of diabetic patients was positively correlated with diabetes and its complication. [25,26] Moreover, a study of **Luo et al., 2016** [27] showed increase in the serum level of periostin in diabetic patients, in addition subjects with both obesity and diabetes showed maximum serum concentration of periostin and its level was associated with the increase in serum level of inflammatory cytokines TNF-α and IL-6. The conflicts between systemic and periodontal disease with regard to periostin expression are supposed to be due to the entirely dissimilar environmental condition which persist in these diseases. Also, the unique phenotypic nature of gingival fibroblasts and their ability to sustain inflammation affect the expression of periostin. [28]

In the present study, NSPT resulted in statistically significant increase ($P \leq 0.001$) in the GCF level of periostin at 3 months postoperatively within group II &III and no statistical significant difference ($P \geq 0.05$) between group II & III. The possible explanation of these results might be due to the effectiveness of NSPT in reducing the levels of proinflammatory cytokines in the GCF of patients with periodontitis with and without type 2 diabetes. [11]

The findings of current study were compatible with the study of **Kumaresan et al., 2016** [10] which investigated the effect of NSPT with adjunctive application of low level laser therapy on the level of periostin in the GCF of patients with periodontitis. It was concluded that the GCF level of periostin was lower in periodontitis than healthy subjects at baseline and its level showed statistically significant increase at 3 months following NSPT and following NSPT combined with LLLT confirming the role of inflammatory condition in reducing the expression of periostin in the GCF. Therefore, it was proposed that periostin could act as a marker for detection of the activity and progression of the disease and estimate the response following periodontal treatment.

On the other hand, detection of the changes of periostin in the GCF following periodontal therapy were investigated in the research by **Padial-Molina et al. 2015** [16]. Their study included periodontitis patients treated with open flap debridement and the GCF samples were collected at 24 h, 48 h, 2 wk and 4 wk . They concluded that periostin level in the GCF significantly increased at 48 h and 2 weeks after surgery compared to baseline as well as it was significantly increased at different time points suggesting its correlation with the healing process. As a consequence of periodontal surgery, there was a reduction of inflammatory response and bacterial stimuli which explain its increase after periodontal surgery. Periostin increased to support healing process by enhancing migration and proliferation of the cells to construct a firm extracellular matrix. At 4 weeks after periodontal surgery the level of periostin returned back to baseline level, as collagen

fibres became mature, the periostin was deposited within the extracellular matrix. Therefore, periostin may have a key role in restoring periodontal tissue function and architecture and can be considered as crucial regenerative agent during wound healing.

The present study have some limitations including short follow up interval and small number of participants enrolled in it. Moreover, microbiologic analysis and its correlation with biochemical and clinical findings were not assessed. Therefore, more longitudinal prospective studies with a longer follow up intervals and larger number of participants are required to support the findings of the current study as well as more immunohistochemical trials are recommended to realize the precise function of periostin in periodontal disease.

From current clinical trial, it was concluded that periostin can be considered as effective biomarker for assessment of disease activity and response to periodontal therapy.

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