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ASSESSING THE LEVELS OF CHEMERIN: A NEOTERIC PRO INFLAMMATORY SALIVARY BIOMARKER IN PERIODONTITIS PATIENTS WITH AND WITHOUT DIABETES MELLITUS

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ABSTRACT

AIM AND OBJECTIVES: Currently, adipokines have been reported to be associated in chronic inflammatory response. Therefore aim of the study is to assess the level of pro inflammatory biomarker chemerin in saliva in periodontitis patients with and without diabetes mellitus and their association with periodontal health and disease.

METHODS: The study included 30 participants. Based on clinical and radiographic periodontal findings, they were categorised into 3 groups; the healthy group (group1; n=10), periodontitis without diabetes group (group 2; n=10), periodontitis with diabetes mellitus group (group 3; n=10). Salivary samples were collected from the participants and were quantified using an enzyme- linked immunosorbent assay.

RESULTS: The mean concentration of chemerin in saliva was increased consistently as the disease progressed from healthy state to periodontitis. It was highest in group 3 and lowest in group 1. Mean concentration of chemerin in group 1 was 115.32ng/ml, 475.71ng/ml in group 2 and 554.81ng/ml in group 3 respectively.

CONCLUSIONS: In all the three groups, chemerin concentrations were positively correlated. Therefore, chemerin can be used a diagnostic biomarker of inflammatory activity in periodontitis. However large scale studies are needed to confirm more positive associations.

KEY WORDS: Periodontitis; Saliva; Diabetes Mellitus

INTRODUCTION

Periodontitis is a chronic inflammatory disease driven by multiple factors, leading to the progressive degradation of the tooth-supporting structures, including the periodontal ligament and alveolar bone (1) This condition affects around 11% of the global population, representing a significant public health concern (2). Effective prevention and treatment hinge on precisely identifying its causes and mitigating modifiable risk factors. Research indicates that genetic variations affecting the inflammatory response can heighten susceptibility to periodontitis (3,4).

Diabetes mellitus is a metabolic and endocrine disorder characterized by disruptions in insulin secretion due to genetic or environmental factors. The condition encompasses various types including type 1 (T1DM), type 2 (T2DM), gestational diabetes mellitus (GDM), and other specific forms as defined by the American Diabetes Association (5). Diabetes is associated with several complications such as diabetic nephropathy, foot problems, and retinopathy, all of which significantly impact patients' overall well-being and health status (6,7). Notably, periodontitis remains a consistent sixth complication of diabetes (8). People with diabetes are more prone to develop periodontitis if their blood glucose levels are poorly regulated, whereas those with poor

oral hygiene develop insulin resistance, which leads to diabetes mellitus (9,10). Therefore there always exists a mutual two way connection between periodontitis and diabetes mellitus (11).

Periodontitis can induce persistent systemic inflammation, potentially leading to insulin resistance and elevated blood glucose levels. Genetic predispositions are a shared risk factor for both chronic periodontitis and type 2 diabetes mellitus. The chronic elevation of proinflammatory mediators, including interleukin-1 beta and tumor necrosis factor-alpha (TNF-α), in the bloodstream, resulting in insulin resistance, is the underlying mechanism connecting periodontitis with diabetes (12).

The activity of tissue defense mechanisms against microbiological agents in periodontitis, an inflammatory condition, results in the production of cytokines, chemokines, arachidonic acid metabolites, and other inflammatory mediators, including proteolytic enzymes. These substances contribute to the degradation of soft tissues and the resorption of bone in the host. Adipokines, proteins secreted by adipose tissue and defense cells, have recently been implicated in modulating inflammatory responses (13). Among these adipokines, leptin exhibits anti-inflammatory effects, resistin and visfatin are pro-inflammatory, and progranulin possesses both pro-inflammatory and anti-inflammatory properties(14,15).

Chemerin, also referred to as tazarotene-induced gene 2 and retinoic acid receptor responder 2 (RARRES2), is an adipokine predominantly found in adipose tissue. This newly identified adipokine plays a crucial role in the differentiation and development of adipocytes (16). It also affects glucose, cholesterol metabolism, and inflammatory levels. lt influences glucose and cholesterol metabolism as well as inflammatory levels. Chemerin is secreted by adipose tissue, liver, epithelial cells, endothelial cells, fibroblasts, and keratinocytes. It regulates adipocyte differentiation and adipogenesis via a receptor called chemokine-like receptor 1 (CMKLR1 or Chem-23) (17). The mechanism is hypothesized to be involved in both pro-inflammatory and anti-inflammatory responses.

One of the early findings regarding chemerin's function was its capacity to attract leukocytes to sites of inflammation. Additionally, it regulates proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) (18). Chemerin induces the migration of immature dendritic cells, monocytes, and macrophages to inflammatory sites through the ChemR23 receptor, exhibiting a chemoattractant effect. Consequently, it is present in inflamed tissues and inflammatory fluids. Chemerin has been associated with the pathogenesis of several conditions, including ulcerative colitis, Crohn's disease, osteoarthritis, psoriasis, and multiple sclerosis (19,20). Chemerin is currently being evaluated in the present study as a neoteric marker of systemic inflammation for the various reasons stated above. Therefore the aim of the current study was to investigate the influence of chemerin on periodontitis patients with and without diabetes mellitus and systemically healthy individuals.

MATERIALS AND METHODS

Study Population

The study was carried out in the Department of Periodontics at Saveetha Dental College, Chennai, Tamil Nadu, India. The study protocol received approval from the Institutional Human Ethics Committee at Saveetha Dental College, Chennai (ethical clearance number: IHEC/SDC/PERIO-2102/22/236). Total of 30 participants who were diagnosed with chronic periodontitis were included out of which 14 were males and 16 were females. The clinical features were obtained from the World Workshop classification system for periodontal Diseases 2017 (21). Group 1 (n=10) were systemically and periodontally healthy subjects with no gingival inflammation and with probing depth< 3mm. Group 2 (n=10) were patients with stage 2-4 periodontitis who were diagnosed both clinically and radiographically with interdental clinical attachment loss of 3 to >5mm in all the 4 quadrants, radiographic bone loss from coronal third extending to middle third of root and beyond it, tooth loss due to periodontitis of 5 or more than 5 teeth, probing depth of > 6mm. Group 3 (n=10) were patients with type 2 diabetes mellitus (glycated Hb range between 6.5 to 7.5 were included). Prior to participation, all individuals provided informed and comprehensive consent.

Inclusion and Exclusion Criteria

The inclusion criteria comprised patients with chronic periodontitis and systemic diseases such as diabetes mellitus. Exclusion criteria were smokers, those who had used anti-inflammatory medications in the past six months, those who received periodontal therapy within the last six months, individuals with systemic diseases other than diabetes mellitus, such as cardiovascular diseases, and pregnant or lactating women.

Collection of Saliva:

During the initial appointment, following an assessment of the overall periodontal status, gentle supragingival scaling was conducted. Subsequently, saliva collection took place in the next session early in the morning after isolating the field. Before collection, participants rinsed their mouths with water and waited 15 minutes before pooling saliva into the collection vessel. To mitigate diurnal fluctuations, saliva was ideally collected between 9 a.m. and 12 p.m. Participants were instructed to sit comfortably, swallow saliva, and then allow saliva to drain passively for approximately 20 minutes over the lower lip into a pre-labeled sterile container, with 5 ml of saliva being collected (Figure 1).

FIGURE 1: Salivary samples collection in eppendorf tubes

All salivary samples were centrifuged (10,000xg for 5 minutes) to eliminate cellular debris and to reduce saliva turbidity, which can impair assay accuracy (Figure 2). The salivary samples were aliquoted directly into 1.5 ml Eppendorf tubes and kept at 80 °C until the biochemical investigation.

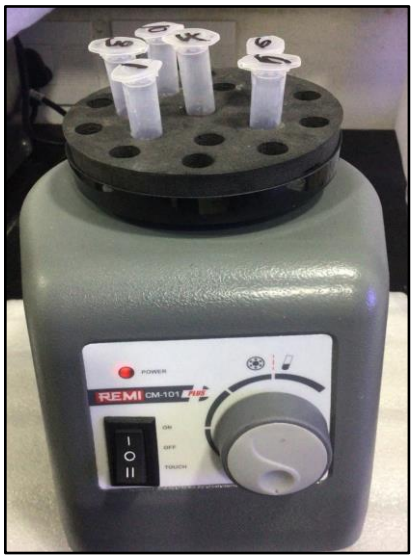

FIGURE 2: Salivary samples kept for centrifuge

Analysis of adipokines

Materials Required

- Microplate reader (wavelength 450nm)
- 37 °C incubator
- Automated plate washer
- Precision single and multi- channel pipette and disposable tips
- Clean tubes and eppendorf tubes with samples
- Deionized water pr distilled water

The enzyme-linked immunosorbent assay (ELISA) technique was employed to assess salivary chemerin levels, utilizing the Human CHEM (Chemerin) kit. The 96-well plates were pre-coated with anti-CHEM antibody, with biotin-conjugated anti-CHEM antibody serving as the detection antibody. Prior to conducting the test, all reagents, including the biotin detection antibody working solution and the preparation of streptavidin conjugate working solution, were prepared. Standards and samples were added to the microplate in duplicate, after which plates were washed twice before adding standard, sample, and control (zero) wells. Each well received 100 µl of standard or sample for 90 minutes at 37°C, followed by the addition of 100 µl of biotin detection antibody working solution to each well for 60 minutes at 37°C. Subsequently, the samples were aspirated and washed three times. The plate was then incubated for 30 minutes at 37°C. Using a wash buffer (250 µL) dispensed with a squirt bottle, manifold dispenser, or autowasher, each well was filled, leading to a color change from blue to yellow. If well color appeared green or the color shift was not uniform, the plate was gently tapped to ensure thorough mixing. Optical density (O.D) was measured at 450nm within 15 minutes using a microtiter plate reader (Figure 3).

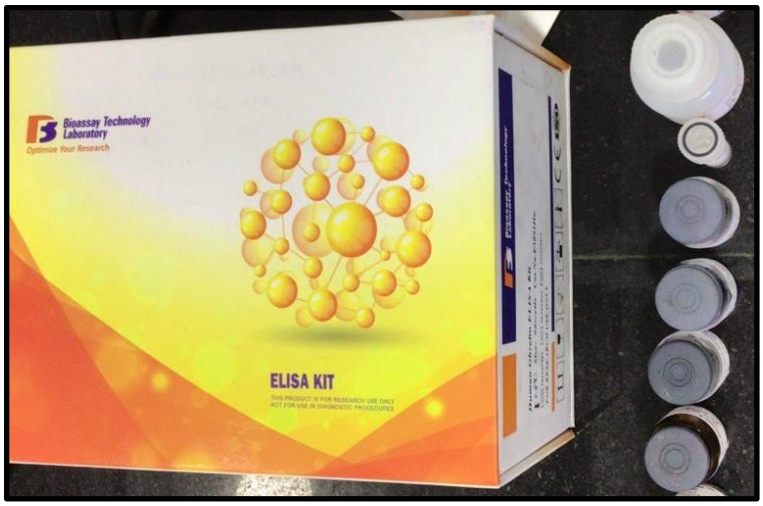

FIGURE 3: ELISA Kit

Statistical Analysis

The mean concentrations of chemerin were enumerated. For assessing the mean concentration of chemerin biomarker, a one-way ANOVA test was used to compare between the groups.The data was analysed using SPSS for windows (SPSS version 23.0, IBM Corp., Armonk, NY). Data was presented using graphs and tables. The level of significance was kept at $p< 0.05$.

RESULTS

The results of the current study reveals that mean chemerin concentration in saliva was highest in group 3. The study population consisted 30 participants with an age range of 25- 50 years, out of which 14 were males and 16 were females. The results indicated that there is a significant statistical difference in expression of marker between the groups ie, healthy vs only periodontitis ($p=0.001$),

between healthy subject vs periodontitis with diabetes mellitus (p=0.001), between periodontitis only vs periodontitis with diabetes mellitus (p=0.001). The highest mean concentration was recorded for the periodontitis with diabetes mellitus group (554.81 ng/ml) followed by periodontitis group. The lowest concentration was observed in the healthy group with a value of 115.32 ng/ml. The periodontitis group showed a mean concentration of 475.71 ng/ml (Table 1 and Figure 4).

S.no	Data	Mean	P-Value
1	Group I	115.32	
	Group II	475.71	0.001*
2	Group II	475.71	
	Group III	554.81	0.001*
3	Group III	554.81	
	Group I	115.32	0.001*

p value is less than 0.005, significant difference in mean values between groups

Group 1= Healthy subjects

Group 2= Periodontitis

Group 3= Periodontitis with diabetes mellitus

Table 1: Table depicting mean chemerin expression in healthy, periodontitis and periodontitis with diabetes mellitus groups

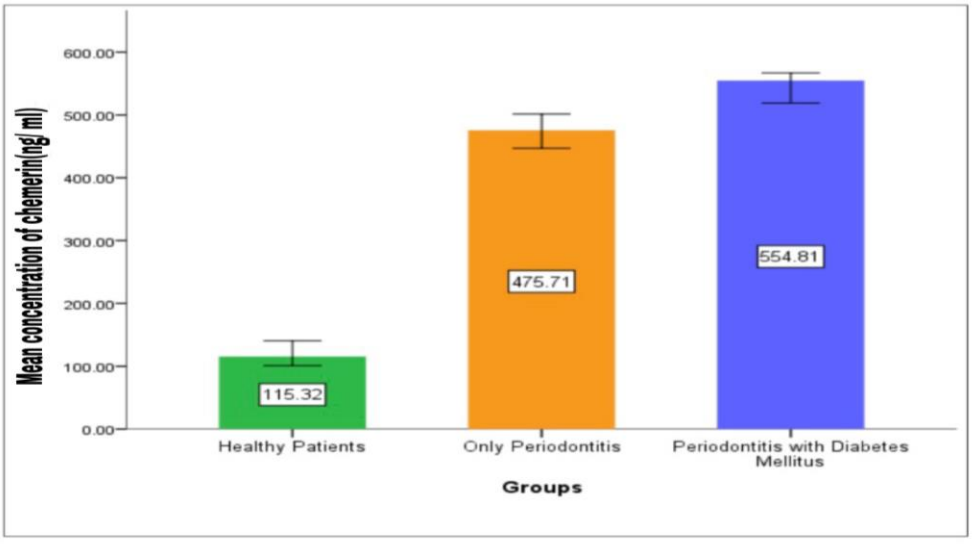

FIGURE 4: Bar graph depicting mean chemerin expression in healthy, periodontitis and periodontitis with diabetes mellitus groups.A statistically significant difference in concentration was observed between groups (p=0.01*). The highest concentration was recorded in periodontitis with diabetes mellitus group (554.81 ng/ml). The lowest concentration was observed in healthy group with a concentration of 115.32ng/ml. Periodontitis group exhibited a concentration of 475.71ng/ml.

DISCUSSION

The current study aimed to evaluate salivary chemerin levels in systemically healthy individuals, those with periodontitis, and those with both periodontitis and diabetes mellitus. Periodontitis, a chronic multifactorial inflammatory disease, involves an interplay between the host and microbes that activates proinflammatory cascade reactions. This activation leads to the production of TNF-alpha and interleukin-1 beta, resulting in soft tissue degradation and bone resorption (22). Adipokines play a role as immune regulators in chronic inflammatory conditions. Elevated adipokine levels contribute to insulin resistance and reduced insulin action, leading to the accumulation of pro-inflammatory adipokines.

To this end, saliva samples from patients were analyzed. Saliva assessment is a validated and reliable alternative to serum analysis (23). It is a highly adaptable biological fluid that can be collected non-invasively, and its analysis provides supplementary information to clinical and histological findings in the diagnosis of various disorders (24).

Salivary chemerin levels were considerably greater in the periodontitis group and even higher in the periodontitis with diabetes group in the current investigation. To the best of our knowledge, this is the first study to look at salivary chemerin levels in three different groups: systemically healthy, periodontitis, and periodontitis with diabetes mellitus. Chemerin is an adipokine that has been linked to inflammatory markers such as c-reactive proteins, IL-6, and TNF-alpha. Yamawaki et al. discovered that chemerin had anti-inflammatory characteristics in vascular endothelial cells by suppressing TNF-induced vascular cell adhesion molecule (VCAM)-1 expression and subsequent monocyte adherence by inhibiting the activation of NF kB and p38. In the same investigation, they discovered that chemerin exerts an inflammatory effect at high concentrations via activating endothelial nitric oxide synthase (eNOS) (25).

This reveals that chemerin functions as anti inflammatory adipokine in lower concentrations and as pro-inflammatory cytokine in higher concentrations. Chemerin can also be found in inflammatory fluids because it promotes chemotaxis of monocytes and macrophages to the site of inflammation. Chemerin, in addition to pro-inflammatory cytokines, causes irreparable tissue damage through raising MMP levels (26). Hah et al. discovered elevated levels of chemerin in serum in their research of patients with coronary artery disease (27). High serum chemerin concentrations have been found in several similar studies in various inflammatory and immunological diseases (28,29,30). In terms of chronic inflammatory state, our findings are consistent with the previous studies, since we detected increased amounts of salivary chemerin in periodontitis.

In the present study, it was found that mean concentration of chemerin was significantly higher in group 3 ie periodontitis with diabetes mellitus and lower concentration was detected in group 1 that is systemically healthy individuals. This proved that the concentration of salivary chemerin

consistently increased from healthy state to periodontitis individuals and even more higher in periodontitis with diabetes mellitus patients. In an previous research, researchers have investigated the relationship between serum chemerin levels in T2DM patients (31). In an another study by Yang et al, chemerin serum levels were shown to be greater in T2DM patients' serum than in normal-glucose-tolerant groups (32). Furthermore, in an another previous research , early periodontal therapy has been shown to reduce serum and GCF IL-6 levels in T2DM periodontitis patients (33). More importantly, variable chemerin quantities have been observed to strongly correlate with IL-6 and inflammatory markers. This study looked at the levels of IL-6 in GCF because it has been shown to have a pro-inflammatory effect in patients with CP and T2DM (33,34). These findings implicit why chemerin should be used as an diagnostic biomarker for the treatment of periodontitis.

Therefore results obtained from the above study implicits that chemerin is predominantly expressed in samples of subjects having periodontitis with diabetes mellitus than periodontitis subjects than healthy samples in a descending order.

CONCLUSION

Within the limitations of the study, it can be concluded that chemerin is a neoteric biomarker in diagnosis of periodontal disease. More research is needed to determine the involvement of chemerin in the aetiology of periodontal disease. Chemerin levels in saliva may be employed in the future to screen large populations for the risk of devastating periodontal disease. Furthermore, identifying the role of chemerin in periodontal inflammation can lead to new therapeutic techniques that include host modulation mechanisms.

CONFLICT OF INTEREST

None.

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