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Comparative Evaluation of Adipolin Expression in Gingival Crevicular Fluid and Serum of Healthy Subjects and Periodontitis Patients with and without Type 2 Diabetes Mellitus †

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Abstract: Background: Adipokine is a huge family of cytokines which are cell-signaling proteins secreted by adipose tissue released by white adipose tissue (WAT), and adipolin (FAM132A/CTRP12 gene) is the newest member added to the adipokine family. This research marks the first attempt to estimate and compare the gingival crevicular fluid (GCF) and serum levels of adipolin in healthy subjects and periodontitis patients with and without type-2 diabetes mellitus (T2DM). Methods: The study population consisted of 10 patients each with healthy subjects and periodontitis with and without T2DM. GCF and serum samples were collected from each patient before non-surgical periodontal therapy. All the samples underwent an enzyme-linked immunosorbent assay (ELISA) test with an antibody specific to adipolin. Results: The mean GCF and serum adipolin levels were high in Groups I and III compared with Groups II and IV. Comparison of adipolin levels between the groups showed no statistically significant difference either in GCF ($p = 0.68$) or serum ($p = 0.85$). The comparison between GCF and serum adipolin levels in Group IV showed a statistically significant difference ($p < 0.031$). The mean values showed a decrease in adipolin values as the disease rate progressed. A negative correlation was seen in serum and GCF adipolin with HbA_{1C}. Conclusion: As the GCF and serum concentration of adipolin show a gradual positive relation with disease severity, within the limitations of the current study, it can be postulated adipolin could be a possible anti-inflammatory biomarker of periodontal disease.

Keywords: adipolin; adipokines; periodontitis; type 2 diabetes mellitus

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1. Introduction

Periodontitis results from the interaction between bacteria and the host response to bacterial challenge. Various environmental and acquired risk factors and genetic susceptibility can modify the disease. The clinical signs result from the host inflammatory response that develops to combat the biofilm [1–3].

Microbial products trigger the release of cytokines, the dysregulation of which, in serum, saliva, and gingival crevicular fluid (GCF), lead to the disease. The role of cytokines

such as interleukin-1, tumor necrosis factor-alpha (TNF-α), interferon-γ (INF), adipocytokines, and many others have been proven in the progression of periodontitis [4–7]. The increased level of cytokines seen in periodontitis can aggravate existing conditions, like atherosclerosis, diabetes, or rheumatoid arthritis [8].

The two-way relationship between periodontitis and diabetes was originally established in the year 1996 by Harald Loe, and an improvement in HbA_{1c} levels in type 2 diabetes mellitus (T2DM) patients after periodontal therapy has been observed [9]. Recent studies indicate that chronic low-grade inflammation is associated not only with the pathogenesis of T2DM but also with periodontal diseases where adipocytokines play an essential role in the host's response to periodontal biofilm [10]. Thus, adipolin is considered a candidate for linking inflammation to other metabolic disorders such as T2DM [11].

Adipokine or adipocytokine is a huge family of cytokines that are cell-signaling proteins released by white adipose tissue. They are modulator proteins derived from adipose tissue that regulate various metabolic functions such as immune cell migration, adipocyte metabolism, inflammation, etc. They include leptin, adiponectin, omentin, chemerin, interleukin-6, visfatin, and adipolin. These adipokines affect insulin resistance and may also have an impact on inflammation and immune responses [12].

Adipolin (FAM132A/CTRP12 gene) is the newest member added to the adipokine family in the year 2011 by Takashi Enomoto, which is involved in glycemic control and insulin sensitization. Similar to adiponectin, Takashi Enomoto found that the circulating levels of adipolin decreased substantially in obese mice and that administering adipolin resulted in an improvement in insulin sensitivity and glucose tolerance and a decrease in adiposity and inflammation in obese and diabetic animal models [13]. It functions by acting as an anti-inflammatory by decreasing pro-inflammatory gene expression like TNF-α and IL-β, which are potent mediators of periodontitis, and acts by decreasing the macrophage cell count [14].

An in vitro study showed that adipolin acts as an insulin sensitizer in diabetic patients by suppressing glucogenesis and promoting glucose uptake in hepatocytes and adipocytes [15]. Many theories explain the increased severity of periodontal disease in individuals with T2DM. Monitoring persisting low-grade inflammation using the levels of cytokine and adipokine activity may have a possible application for assessing the diabetic condition and development of periodontitis [16]. This research marks the first attempt to estimate and compare the GCF and serum levels of adipolin in healthy subjects and periodontitis patients with and without T2DM.

2. Materials and Methods

2.1. Participant Selection

Forty individuals (20 females and 20 males) aged 20 to 50 years were selected and recruited from the outpatient section of the Department of Periodontics at an institution. The patients were divided into 4 groups viz. 10 healthy subjects (Group I), 10 healthy subjects with T2DM (Group II), 10 periodontitis patients without T2DM (Group III), and 10 periodontitis patients with T2DM (Group IV).

Individuals with aggressive periodontitis, type 1 diabetes mellitus, pregnancy, human immunodeficiency virus (HIV) infection, smoking and alcoholism, hematological and immune system disorders, and bone disorders; patients on contraceptives or antibiotic therapy in the last 6 months; and those receiving any periodontal treatment were excluded.

The periodontitis patients who were showing radiographic evidence of bone loss and clinical attachment loss (CAL) $\geq$ 5 mm (severe), with a minimum of 6 teeth with a pocket probing depth (PD) of $\geq$5 mm; bleeding on probing (BOP) in at least 2 separate quadrants; a gingival index (GI) > 1 and a plaque index (PI) $\geq$ 1; a minimum of 14 teeth; and an age of >20 years were included. Healthy subjects were approved if the full-mouth probing pocket depth (PPD) was $\leq$3 mm, clinical attachment loss (CAL) = 0, GI $\leq$ 1, and PI $\leq$ 1 (absence of clinical inflammation). Radiographic bone loss was recorded dichotomously to differentiate between periodontitis patients and healthy subjects.

The diabetic patients diagnosed with T2DM were screened, and their glycemic condition was evaluated using glycated hemoglobin A1c (HbA1c) levels. Patients with HbA1c levels between 7 and 8% (moderately controlled) were recruited [17]. It was determined that none of the participants changed their prescription over the past 3 months preceding this study.

Ethical clearance for this study was obtained from the institutional ethical review board. The study procedure was explained to the patients, and informed consent was obtained from those who agreed to participate voluntarily in this study. Two examiners were trained to check for clinical parameters. Calibration was performed and reliability was checked with a kappa value of 0.8 agreement.

2.2. Selection of Site and Sample Collection

On the first day, clinical and radiological examinations, group allocation, and sampling site selections were completed, and samples were collected on the following day. This was performed to prevent the contamination of GCF with blood from probing the inflamed sites. In Groups I and II, multiple sites with the absence of inflammation were sampled by pooling GCF to ensure an adequate amount for the study. In Groups III and IV, sites with the highest clinical signs of inflammation, attachment loss, and >5 mm probing depth were selected. The area was dried with a blast of air, and then the supragingival plaque was removed without touching the marginal gingiva. The GCF samples were collected in 30 s using the intracrevicular method. The GCF obtained was immediately transferred into plastic vials and stored at −70 °C until the time of assay.

For serum collection, the skin over the antecubital fossa was disinfected and two ml of blood was collected by venipuncture using a 20-gauge needle with a 2 mL syringe and immediately transferred to the laboratory. Samples were allowed to clot at room temperature and after one hour, the samples were centrifuged at 3000× *g* rpm for 15 min to separate serum components. Serum was extracted from the blood and stored at −70 °C until the assay procedure.

2.3. Adipolin Assay

The supernatants were then collected, and the adipolin concentration was evaluated with a sandwich enzyme-linked immunosorbent assay (ELISA) using standard commercial equipment (Bioassay Technology, Shanghai Biotech Ltd., Shanghai, China). The recommended detection parameters for adipolin by the manufacturers were 0.05–20 ng/mL. The measurement of absorbance of each well was obtained under the 450 nm wavelength, which was carried out within 10 min after adding the stop solution. The concentration of adipolin in the samples was then determined by comparing the optical density (OD) values for each well, which were calculated with a standard curve using MyAssays software version 9.2.26.586.

3. Statistical Analysis

The data were entered and analyzed using the Statistical Package for Social Sciences (SPSS) for Windows, Version 28.0. (Armonk, NY, USA: IBM Corp). Confidence intervals were set at 95%, and a p-value ≤ 0.05 was considered statistically significant. One-way Analysis of Variance (ANOVA), Pearson's correlation coefficient test, and Chi-square tests were carried out to compare adipolin levels among groups. Spearman's correlation coefficient test was used to correlate adipolin levels to clinical parameters.

4. Results

There were no statistical differences in age or gender distribution between the groups. The full mouth parameters and sample sites PI, GI, PPD, and CAL showed a notable increase as the disease severity increased viz. from Group I to Group IV (Table 1)

Table 1. Demographic data of the study population.

	Gender Male: Female	Mean Age (in Years)
Group I	5:5	32.3
Group II	5:5	40.3
Group III	5:5	41.2
Group IV	6:4	37.1

The comparison of mean PI, GI, PPD, and CAL between Groups I and III, Groups I and IV, Groups II and III, and Groups II and IV, respectively, showed statistically significant differences ($p < 0.0001$). There was no statistically significant difference ($p > 0.05$) between Groups I and II and Groups III and IV (Table 2).

Table 2. Clinical parameters of the study groups.

	PI	GI	PPD (in mm)	CAL (in mm)
Group I	0.66 ± 0.26	0.61 ± 0.24	1.6 ± 0.96	0
Group II	0.57 ± 0.26	0.50 ± 0.27	1.2 ± 0.69	0
Group III	1.90 ± 0.53	1.74 ± 0.52	5.3 ± 0.74	5.85 ± 0.84
Group IV	1.91 ± 0.42	1.94 ± 0.55	5.5 ± 0.35	6.04 ± 0.43

PI: plaque index; GI: gingival index; PPD: probing pocket depth; CAL: clinical attachment loss.

The mean GCF adipolin values in Groups I, II, III, and IV were 10.71 ± 6.76 ng/mL, 8.27 ± 5.09 ng/mL, 9.02 ± 3.38 ng/mL, and 8.75 ± 2.7 ng/mL. The mean GCF adipolin levels were high in Groups I and III compared with Groups II and IV. The comparison of adipolin levels between the groups showed no statistically significant difference ($p = 0.68$).

The mean serum adipolin values in Groups I, II, III, and IV were 7.68 ± 6.5 ng/mL, 5.89 ± 5.7 ng/mL, 6.37 ± 5.25 ng/mL, and 5.93 ± 2.76 ng/mL. The mean serum adipolin levels were high in Groups I and III compared with Groups II and IV. The comparison of adipolin levels between the groups showed no statistically significant difference ($p = 0.85$). The comparison between GCF and serum adipolin levels in Groups I, II, and III showed no statistically significant difference ($p = 0.32$, $p = 0.33$, and $p = 0.97$), respectively. Whereas Group IV showed a statistically significant difference ($p < 0.031$) (Table 3).

Table 3. Comparison of serum and GCF adipolin levels in all the groups.

Group	Serum Adipolin (ng/mL)	GCF Adipolin (ng/mL)	*p*-Value
Group I	7.68	10.71	0.32
Group II	5.89	8.27	0.33
Group III	6.37	9.02	0.97
Group IV	5.93	8.75	0.031 *

* indicates a statistically significant difference ($p < 0.05$).

The Spearman's correlation test was used to observe the correlation in the adipolin levels of GCF and serum and clinical parameters, i.e., PPD and CAL in Groups III and IV. In Group III, the correlation between adipolin (GCF) and PPD and CAL showed no statistically significant difference with $p = 0.86$ and $p = 0.46$. The correlation between adipolin (serum) and PPD and CAL also showed no statistically significant difference with $p = 0.93$ and $p = 0.72$. In Group IV, the correlation between adipolin (GCF) and PPD and CAL showed no statistically significant with $p = 0.52$ and $p = 0.35$, and the correlation between adipolin (serum) and PPD and CAL also showed no statistically significant difference with $p = 0.46$ and $p = 0.32$. (Tables 4 and 5). The HbA1c results showed a negative correlation with serum

and GCF adipolin levels in all the groups. However, there was a statistically significant difference ($p < 0.05$) in Group IV (Table 6).

Table 4. Correlation between the change in levels of adipolin (GCF) and adipolin (serum) and the change in clinical parameters of periodontitis severity (PPD, CAL) in Group III.

Adipolin	*p*-Value for PPD	rho Coefficient	*p*-Value for CAL	rho Coefficient
GCF	0.86	0.06	0.46	0.26
Serum	0.93	0.03	0.72	−0.13

Table 5. Correlation between the change in levels of adipolin (GCF) and adipolin (serum) and the change in clinical parameters of periodontitis severity (PPD, CAL) in Group IV.

Adipolin	*p*-Value for PPD	rho Coefficient	*p*-Value for CAL	rho Coefficient
GCF	0.52	−0.23	0.35	−0.33
Serum	0.46	−0.26	0.32	−0.35

PPD: probing pocket depth; CAL: clinical attachment level.

Table 6. Correlation between the change in levels of adipolin (GCF) and adipolin (serum) and the change in HbA1c levels.

Groups		Mean	SD	rho Coefficient	*p*-Value
Group I	GCF adipolin	10.71	6.76	−0.39	0.26
	Serum adipolin	7.68	6.50	−0.11	0.76
	HbA1c	4.56	0.38		
Group II	GCF adipolin	8.27	5.09	−0.57	0.08
	Serum aAdipolin	5.89	5.70	−0.32	0.35
	HbA1c	6.18	0.26		
Group III	GCF adipolin	9.02	3.38	−0.12	0.72
	Serum adipolin	6.37	5.25	−0.01	0.96
	HbA1c	5.03	0.26		
Group IV	GCF adipolin	8.75	2.70	−0.79	0.006 *
	Serum adipolin	5.90	2.76	−0.28	0.42
	HbA1c	7.66	0.40		

* indicates a statistically significant difference ($p < 0.05$).

5. Discussion

Adipolin (FAM132A/CTRP12/Clq/TNF-related protein gene) is a novel adipokine that is influenced by a decrease in Kruppel-like factor-15 (KLF-15) and in T2DM patients, insulin resistance disrupts the insulin–adipolin homeostatic response, which could lead to lower adipolin levels [18,19]. Predominantly macrophages and almost all major types of immune cells are involved in the linkage of endocrine function of adipose tissue in systemic metabolic regulation [20].

The metabolic disarrangement found in diabetic conditions is related to alterations in adipocyte metabolism. The loss of periodontal attachment and alveolar bone started early in the diabetic population. Along with being a passive reservoir of triglycerides, adipose tissue produces high levels of adipokines that can result in the initiation and progression of disease through dysregulated immune responses. These adipocytokines play an important role in periodontal disease activity by stimulating monocytes, which increases the production of inflammatory cytokines by altering the host immune response and results in a higher susceptibility to bacterial infections [14]. Thus, the present study

was undertaken to study the GCF and serum levels of adipolin in healthy subjects and periodontitis patients with and without T2DM.

Considering the inclusion of an equal number of males and females in each group and the selection of individuals within the age range of 20–50 years, the gender and age of the subjects had no impact on the adipolin concentration in the present study. It is possible that the varying concentrations seen within each group are the result of the disease being in a different stage when the GCF and serum samples were taken, which would explain the wide range of values.

Our study found that the subjects included in Groups II and IV had moderate levels of HbA_{1c} ranging from 7 to 8%. This criterion was used to avoid the bias that could have occurred in the case of extreme values. This range of HbA_{1c} is in accordance with the diabetes diagnosis criteria of the American Diabetes Association [17]. Values measuring $HbA_{1c} < 7\%$ are good control subjects, and the detection of biomarkers may not be feasible. Previous studies found a link between high HbA_{1c} and periodontitis, in which it was stated that HbA_{1c} was significantly associated with pocket depth, the clinical attachment level, the plaque index, and insulin resistance [21–23]. To avoid a shift in biomarker values resulting from fluctuation in HbA_{1c}, all patients with moderate HbA_{1c} levels were included. The prevalence of advanced periodontal disease was significantly higher among T2DM persons as compared with non-diabetic persons of the Pima Indian community, and the rate of periodontal disease progression in T2DM was three times that in non-diabetic persons [24].

The PI and GI scores show a gradual rise from Group I to Group IV. The evaluation of PPD and CAL values is an important indicator of periodontal diseases. The inter-group comparison of mean PPD and CAL values showed statistically significant differences indicating higher periodontal destruction in Groups III and IV than in Groups I and II. This suggested that Groups III and IV had "severe" periodontitis according to the American Academy of Periodontology's classification [25].

Adipolin, though, is predominantly seen in adipose tissue, and its mRNA profiles are also expressed in various tissues when using quantitative real-time PCR analysis. Minor quantities are also found in the liver, kidneys, leukocytes, and cardiac tissues. The source of cytokine has an impact on the regulation of biomarkers and the interaction with the glycemic index [15].

In the current study, the presence of adipolin in the serum of diseased and healthy conditions was seen. The mean serum adipolin levels ranged from 5.89 ng/mL to 7.68 ng/mL, indicating that the severity of periodontitis in T2DM patients is associated with a decreased level of adipolin.

This biomarker showed an anti-inflammatory curve in the serum. A similar observation was found by Enomoto (2011) [13], where adipolin administration in diet-induced obese mice ameliorated insulin resistance and increased insulin sensitivity. Its supplementation further reduced the accumulation of macrophages and pro-inflammatory gene expression in adipose tissue. It had an inhibitory impact on the production of cytokines that contribute to inflammation in response to lipopolysaccharides and TNF-. This points to the fact that insulin-resistant states are characterized by decreased amounts of the adipokine that suppresses inflammation [26].

Our study is the first to discover the presence of adipolin in GCF. The mean GCF adipolin values in Groups I, II, III, and IV were 10.715 ± 6.76 ng/mL, 8.27 ± 5.09 ng/mL, 9.02 ± 3.38 ng/mL, and 8.75 ± 2.7 ng/mL, respectively. The mean values showed a steady downward inclination, representing the decrease in adipolin values as the disease rate progresses. As a result, the anti-inflammatory property of adipolin was proven. No statistically significant difference was observed in the adipolin levels in the four groups. This speculation might be explained by the study undertaken by Mehrdadi (2016) [27], which hypothesized that variations in adipolin levels, as well as the consequences that are associated with them, are dependent on the metabolic and genetic makeup of the participants.

This study recorded a peculiar characteristic of adipolin levels between the diabetic and non-diabetic groups. Adipolin levels were found to be decreased in Groups II and

Group IV as compared with Group I and Group III, and the serum adipolin and GCF adipolin levels were lower in patients with T2DM than patients without T2DM. This suggests a systemic effect of diabetes on the periodontal status, which affects adipolin levels, and the diabetic condition aggravates the periodontal disease.

Wei et al. (2012) [15] showed that after the administration of the anti-diabetic drug rosiglitazone to mice models, adipolin exerted its insulin-sensitizing action by suppressing gluconeogenesis and thereby increasing glucose uptake in hepatocytes. A similar action was reported by Tan et al. (2013) [28], who documented that the concentration of serum adipolin in polycystic ovary syndrome (PCOS) was lower compared with a healthy group. This action might be due to metabolic disorders that accompany PCOS like obesity, insulin resistance, and inflammation. Additionally, adipolin levels were increased in PCOS patients after the administration of Metformin [29].

Another interesting fact observed was in the comparison of adipolin concentration in GCF and serum in Group IV, which showed a statistically significant difference. Group IV included periodontitis with T2DM, and the status of one condition is influenced by another, i.e., the presence of periodontitis enhanced the T2DM condition, and vice versa. This suggested that the combined dual effect of periodontitis as well as T2DM on the level of adipolin is significant and thus shows the resultant difference in comparison. A similar study conducted by Zimmerman G. (2013) [30] checked the levels of adiponectin in obese and non-obese subjects with and without periodontitis in serum and GCF and concluded that adiponectin levels were lower in the periodontitis group than in the non-periodontitis group.

The levels of adipolin observed in GCF were higher than the serum levels. These elevated levels of this adipokine in GCF might be attributed to the systemic "spill" of cytokine via the circulation. Offenbacher (1996) was the first person to propose this theory. He stated that cytokines produced within the tissues work locally to trigger specific cellular targets and are destroyed within a localized zone. However, if the stressor continues, the cellular cytokine receptors may become overloaded, which will result in decreased cytokine clearance and a "spill" of systemic cytokines via the circulation [31,32].

This study also tried to show the correlation between PPD, CAL, and levels of Adipolin. This association shows a constant relation. The mean values of PPD and CAL increased with rising disease intensity. Congruently, the mean levels of adipolin in the serum and GCF also rose. Though there was no statistically significant correlation found, it gave similar results to the study conducted by P Bharti (2013), which showed that with a decrease in PPD, the levels of adiponectin increased. The negative correlation observed in GCF adipolin levels with HbA1c in periodontitis and T2DM patients could be due to increased local and systemic inflammatory burden [33].

This study is the first of its kind to have detected adipolin in the periodontium. This study showed that decreased concentrations of adipolin are detected in the serum and GCF of T2DM patients with and without periodontitis compared with healthy subjects and periodontitis patients.

In addition, the change in the trend of the expression of a biomarker was also studied, and a steady correlation was obtained, i.e., with increasing disease severity, a decrease in the biomarker level was observed. This showed that adipolin levels change according to the level of inflammatory burden present in different stages of the disease. Thus, suggesting adipolin is a potential biomarker of inflammation in periodontitis and T2DM.

Additional longitudinal studies are recommended to be carried out with a larger subject population. Later, an evaluation of the levels of adipolin in GCF and serum before and after periodontal therapy should be carried out to confirm the role of adipolin as an anti-inflammatory biomarker in periodontal disease.

6. Conclusions

Adipolin is an anti-inflammatory biomarker that could be a possible connecting link between periodontitis and other inflammatory conditions like obesity, atherosclerosis, and

hypertension. Adipolin levels in periodontitis are a predictive parameter in the progression of systemic conditions like obesity, T2DM, and metabolic syndrome. Futuristic chair-side diagnostic kits can be devised to assess adipolin levels as possible biomarkers for periodontitis and obesity-related conditions.

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