Resistin as a Potential Biomarker for Chronic Periodontitis in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Resistin, a recently identified hormone secreted by adipocytes, has emerged as a potential inflammatory mediator linked to insulin resistance and periodontitis. This study aimed to evaluate resistin levels in diabetic patients both with and without chronic periodontitis. Materials and Methods: The study included 80 participants, both male and female, who were divided into four groups of 20 individuals each: Group I (healthy), Group II (generalized chronic periodontitis), Group III (generalized chronic periodontitis without diabetes mellitus), and Group IV (generalized chronic periodontitis with diabetes mellitus). Clinical parameters such as plaque index (PI), gingival index (GI), probing pocket depth (PPD), and clinical attachment level (CAL), as well as biochemical parameters including random blood sugar (RBS) and glycated hemoglobin (HbA1c), were recorded. All assessments were conducted at baseline, and gingival crevicular fluid (GCF) samples were collected for resistin analysis using a commercially available ELISA kit. Statistical comparisons among groups were performed. Results: Resistin levels were significantly elevated in patients with chronic periodontitis compared to healthy subjects ($p < 0.001$). Analysis of all samples revealed a significant positive correlation between GCF resistin levels and clinical parameters (GI, PI, PPD, CAL) as well as biochemical parameters (RBS and HbA1c) ($p < 0.001$). Conclusion: Resistin levels are increased in patients with chronic periodontitis and type 2 diabetes mellitus. Therefore, GCF resistin levels may serve as a potential inflammatory marker for periodontitis in individuals with type 2 diabetes.

Keywords: Resistin, Periodontitis, Type 2 Diabetes Mellitus, Inflammatory Marker, Glycemic Control

Significance | This study showed resistin's potential as a biomarker for periodontitis and its association with type 2 diabetes, emphasizing systemic inflammation's role.

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Introduction

Periodontitis is a complex inflammatory disease of the oral cavity with a multifactorial etiology, primarily driven by microbial challenges and the subsequent host inflammatory response (Kornman, 2008). The interaction between microbial agents and host defenses initiates and perpetuates periodontal tissue damage. Inflammation is a central component in the pathogenesis of periodontitis and is intricately linked to systemic conditions such as diabetes mellitus. The relationship between diabetes and periodontitis is well-established, with periodontitis often

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recognized as the sixth complication of diabetes due to its close association with glycemic control (Loe, 1993). Resistin, a recently identified adipocyte-derived hormone, has been implicated in both insulin resistance and inflammatory processes. Initially believed to be exclusively produced by adipocytes, resistin is now recognized as being synthesized by various cells within the immune and inflammatory systems, positioning it as a significant pro-inflammatory cytokine (Steppan & Lazar, 2002). Elevated resistin levels have been observed in individuals with diabetes, suggesting a role in the inflammatory mechanisms affecting glycemic control. Resistin's involvement in inflammation includes enhancing the secretion of pro-inflammatory cytokines such as TNF-α and IL-12, and promoting the nuclear translocation of NF-κB, which further stimulates the production of TNF-α, IL-6, and MCP-1 (Silswal et al., 2005).

Given its dual role in insulin resistance and inflammation, resistin may serve as a critical link between diabetes mellitus and periodontitis. This study aims to investigate the levels of resistin in gingival crevicular fluid among individuals with healthy periodontium, chronic periodontitis, and diabetes mellitus, exploring its potential as a biomarker for periodontal disease and its association with diabetes.

Materials and Methods

Study Design and Setting

This study was conducted at the outpatient clinics of the Department of Periodontics, Thai Moogambigai Dental College, Chennai, India. The investigation included a total of 80 participants, who were categorized into four distinct groups, each comprising 20 individuals. The groups were as follows: Group I (healthy periodontium), Group II (generalized chronic periodontitis), Group III (Type 2 Diabetes Mellitus with periodontitis), and Group IV (Type 2 Diabetes Mellitus without periodontitis).

Inclusion and Exclusion Criteria

Healthy Periodontium (Group I): Participants were included if they demonstrated excellent oral hygiene, no bleeding on probing (BOP), no visible signs of gingival inflammation, a plaque index (PI) score of 0, a gingival index (GI) score of 0, probing pocket depth (PPD) of ≤3 mm, and clinical attachment level (CAL) of ≤3 mm.

Generalized Chronic Periodontitis (Group II): Inclusion criteria required the presence of inflammatory changes in periodontal tissues, a PI score of ≥1, a GI score of ≥1, PPD of ≥5 mm in at least 30% of sites, CAL of ≥4 mm in at least 30% of sites, positive BOP, and radiographic evidence of bone loss.

Type 2 Diabetes Mellitus (T2DM) (Groups III and IV): Participants were included if they had a confirmed diagnosis of T2DM (based on medical history), a duration of diabetes exceeding 6 months, random blood sugar (RBS) levels ≥200 mg/dl, and good or fair glycemic control as confirmed by HbA1c levels. Group III had concurrent chronic periodontitis, while Group IV did not.

Exclusion criteria encompassed aggressive forms of periodontal disease, receipt of periodontal treatment in the past six months, underlying systemic diseases, use of high-dose steroid therapy, pregnancy, lactation, and smoking.

Ethical Considerations

The study adhered to ethical guidelines and received approval from the Institutional Review Board (Dr. MGRDU/TMDCH/RES/2016/2582). The purpose and nature of the study were thoroughly explained to the participants, and informed consent was obtained from all individuals prior to their inclusion in the study.

Clinical Examination

Clinical periodontal parameters were assessed using the following methods:

Plaque Index (PI): Measured at midbuccal, distobuccal, mesiobuccal, and palatal sites for each tooth (Silness & Löe, 1964).

Gingival Index (GI): Evaluated at buccal, mesial, distal, and lingual gingival areas (Löe & Silness, 1963).

Probing Pocket Depth (PPD) and Clinical Attachment Level (CAL): Measured in millimeters at six sites per tooth. CAL was determined from the cementoenamel junction to the base of the periodontal pocket (Ainamo & Bay, 1975; Ramfjord, 1967).

Radiographic Evaluation

Radiographic bone loss was assessed using intraoral periapical radiographs or orthopantomograms (OPG). Radiographic bone loss was recorded dichotomously (presence or absence) to distinguish chronic periodontitis patients from the healthy groups. Detailed grading of bone loss within the chronic periodontitis group was not undertaken.

Gingival Crevicular Fluid (GCF) Collection and Analysis

Collection: Supra-gingival scaling was performed 24 hours prior to GCF collection. A volume of 1 µL of GCF was collected from each test site using volumetric microcapillary pipettes. The collected fluid was immediately transferred to Eppendorf tubes and stored at -20°C until analysis.

Resistin Analysis: GCF resistin levels were quantified using an Enzyme-Linked Immunosorbent Assay (ELISA) according to the manufacturer's instructions. Results were expressed in ng/mL.

Statistical Analysis

Data from the study were recorded and managed using Microsoft Excel. Statistical analysis was performed using SPSS software (IBM SPSS Statistics for Windows, Version 23.0). The significance level was set at 5% ($\alpha = 0.05$).

Normality of the data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. While clinical parameters generally exhibited normal distribution, GI scores did not. Parametric tests

(e.g., one-way ANOVA) were used for normally distributed data, followed by Tukey's Honestly Significant Difference (HSD) post hoc test for multiple pairwise comparisons. Non-parametric tests (e.g., Kruskal-Wallis test) were employed for non-normally distributed data, with Bonferroni-adjusted Mann-Whitney tests used for pairwise comparisons.

Results

Clinical Parameters and Biochemical Measures

The clinical parameters, along with random blood sugar (RBS), HbA1C, and resistin levels, are summarized in Table 1. Table 2 presents the mean and standard deviation for plaque index (PI), gingival index (GI), probing pocket depth (PPD), and clinical attachment level (CAL) across the four study groups.

Plaque Index

The mean PI was significantly different across the groups. Group I (healthy periodontium) had a mean PI of 0.31±0.27, Group II (generalized chronic periodontitis) had a mean PI of 1.99±0.26, Group III (Type 2 Diabetes Mellitus with periodontitis) had a mean PI of 0.52±0.23, and Group IV (Type 2 Diabetes Mellitus without periodontitis) had a mean PI of 2.76±0.24. The differences were statistically significant ($p<0.0001$). Tukey's HSD post hoc test revealed significant differences between Group I and Group II, Group I and Group IV, Group II and Group III, Group II and Group IV, and Group III and Group IV for PI ($p<0.001$). No significant difference was found between Group I and Group III for PI.

Probing Pocket Depth (PPD) and Clinical Attachment Level (CAL)

For PPD, significant differences ($p<0.001$) were noted between Group I and Group II, Group I and Group IV, Group II and Group III, and Group II and Group IV. However, no significant differences were observed between Group I and Group III or between Group II and Group IV.

CAL values showed statistically significant differences ($p<0.001$) between Group I and Group II, Group I and Group IV, Group II and Group III, and Group III and Group IV. No significant differences were noted between Group I and Group III or between Group II and Group IV.

Biochemical Parameters

Table 3 shows the mean and standard deviation for RBS and HbA1C. Significant differences were observed for RBS ($p<0.001$) between all groups except between Group I and Group II, which did not reveal a significant difference. HbA1C levels also showed significant differences ($p<0.001$) between Group I and Group III, Group I and Group IV, Group II and Group III, Group II and Group IV, and Group III and Group IV. No significant difference was observed between Group I and Group II.

Gingival Crevicular Fluid (GCF) Resistin Levels

Resistin levels were significantly different among the groups ($p<0.001$). Group I had the lowest resistin levels, whereas Group IV had the highest. Tukey's HSD post hoc test revealed significant differences in resistin levels between all groups, supporting the association of elevated resistin with chronic periodontitis and diabetes.

Correlation Analysis

Table 4 illustrates the Pearson correlation coefficients between HbA1C and other clinical parameters. A very strong positive correlation was found between HbA1C and RBS ($r=0.951$, $p<0.001$). A strong positive correlation was observed between HbA1C and resistin ($r=0.675$, $p<0.001$). Mild correlations were noted between HbA1C and the plaque index ($r=0.373$, $p=0.003$), gingival index ($r=0.367$, $p=0.004$), probing pocket depth ($r=0.245$), and clinical attachment level ($r=0.231$), though only the correlations with PI and GI were statistically significant.

Table 5 presents the correlation of resistin with clinical parameters. A very strong positive correlation between resistin and RBS was observed ($r=0.758$, $p<0.001$). A strong positive correlation was noted between resistin and HbA1C ($r=0.675$, $p<0.001$). Moderate positive correlations were found between resistin and the plaque index ($r=0.583$), gingival index ($r=0.578$), probing pocket depth ($r=0.454$), and clinical attachment level ($r=0.462$), all of which were statistically significant ($p<0.001$).

Overall, significant differences were observed across all clinical and biochemical parameters among the four groups, with notable correlations between resistin and both HbA1C and RBS. The findings underscore the relationship between resistin levels, glycemic control, and periodontal health, highlighting its potential role as a biomarker in the context of diabetes and periodontitis.

Discussion

The relationship between oral health and systemic diseases is a complex interplay where each can significantly impact the other. Golub et al. (2006) introduced the "two-hit" model to explain how chronic periodontitis interacts with systemic conditions like diabetes mellitus. In this model, the first "hit" is represented by periodontopathic bacteria, which trigger localized periodontal inflammation. The second "hit" involves systemic inflammation that exacerbates this localized inflammation. This systemic inflammation elevates levels of pro-inflammatory biomarkers, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), in serum or plasma, further aggravating the condition.

Both diabetes mellitus and periodontitis are chronic inflammatory diseases that share common pathways in their immune inflammatory responses. Diabetes is a significant risk factor that can exacerbate the severity of periodontitis, often leading to severe destruction of periodontal tissues. Loe and Silness (1963)

Table 1. Descriptive statistical Values (mean – SD) of PI, GI, PD, Periodontal Index, BMI, RBS, HbA1c, and resistin in the Four Groups

Variables	Group -i healthy	Group -ii Chronic periodonttis	Group -iii T2dm without cp	Group -iv T2dm with cp
PI	0.31±0.27	1.99±0.26	0.52±0.23	2.76±0.24
GI	0.08±0.1	2.38±0.4	0.69±0.21	2.9±0.288
PPD (mm)	1.73±0.71	6.7±0.59	2.3±0.62	6.9±0.61
CAL (mm)	1.73±0.71	5.85±0.47	2.3±0.62	5.98±0.61
RBS (mg/dL)	87.8±12.8	91.6±13.93	217.6±16.89	249.4±41.6
HBA1C %	5±0.49	5.1±0.54	8.1±1.36	9.74±2.17
RESISTIN (ng/L)	997.5±104.23	1160.2±62.6	1291.6±85.5	1452.4±137.8

Table 2. Multiple pair wise comparison of clinical paramateres

Variable	Group		Mean Difference	p-value
PI	Group -I	Group –II	-1.68000	<0.001*
		Group –III	-.21333	0.109
		Group –IV	-2.45333	<0.001*
	Group -II	Group –III	1.46667	<0.001*
		Group –IV	-.77333	<0.001*
	Group -III	Group -IV	-2.24000	<0.001*
PPD (mm)	Group -I	Group –II	-4.9667	<0.001*
		Group –III	-.5667	0.083
		Group –IV	-5.1867	<0.001*
	Group –II	Group –III	4.4000	<0.001*
		Group –IV	-.2200	0.782
	Group -III	Group –IV	-4.6200	<0.001*
CAL (mm)	Group -I	Group -II	-4.1200	<0.001*
		Group -III	-.5667	0.067
		Group –IV	-4.2533	<0.001*
	Group -II	Group -III	3.5533	<0.001*
		Group -IV	-.1333	0.934
	Group -III	Group -IV	-3.6867	<0.001*

* p value < 0.001- highly significant

Table 3. Multiple pairwise comparisons of biochemical parameters

Variable	Group		Mean Difference	p-value
RBS	Group -I	Group -II	-3.800	0.974
		Group -III	-129.800	<0.001*
		Group -IV	-161.600	<0.001*
	Group -II	Group -III	-126.000	<0.001*
		Group -IV	-157.800	<0.001*
	Group -III	Group -IV	-31.800	0.004
HbA1c	Group -I	Group -II	-.1667	0.986
		Group -III	-3.1200	<0.001*
		Group -IV	-4.7333	<0.001*
	Group -II	Group -III	-2.9533	<0.001*
		Group -IV	-4.5667	<0.001*
	Group -III	Group -IV	-1.6133	0.009
Resistin	Group -I	Group -II	-162.667	<0.001*
		Group -III	-294.067	<0.001*
		Group -IV	-454.867	<0.001*
	Group -II	Group -III	-131.400	0.004
		Group -IV	-292.200	<0.001*
	Group -III	Group -IV	-160.800	<0.001*

* p value < 0.001- highly significant

Table 4. Pearson correlations between all clinical parameters with hba1c (overall)

Variables	N		HbA1c %
PI	60	Correlation	0.373
		p-value	0.003
GI	60	Correlation	0.367
		p-value	0.004
PPD (mm)	60	Correlation	0.245
		p-value	0.061
CAL (mm)	60	Correlation	0.231
		p-value	0.076
RBS (mg/dL)	60	Correlation	0.951
		p-value	<0.001*
Resistin (ng/L)	60	Correlation	0.675
		p-value	<0.001*

* p value < 0.001- highly significant

Table 5. correlation of resistin with all clinical parameters.

Variables	N		Resistin (ng/L)
PI	60	Correlation	0.583
		p-value	<0.001*
GI	60	Correlation	0.578
		p-value	<0.001*
PPD (mm)	60	Correlation	0.454
		p-value	<0.001*
CAL (mm)	60	Correlation	0.462
		p-value	<0.001*
RBS (mg/dL)	60	Correlation	0.758
		p-value	<0.001*
HbA1c %	60	Correlation	0.675
		p-value	<0.001*

* p value < 0.001- highly significant

demonstrated that diabetes can amplify periodontal destruction up to tenfold, highlighting the profound impact that systemic conditions can have on oral health.

The assessment of gingival inflammation often relies on clinical indices such as the Gingival Index (GI), as established by Hassel et al. (1973) and further refined by Sivertson and Burgett (1976). These clinical parameters help in evaluating the severity of gingival inflammation and confirm the presence of active periodontal disease. The relationship between type 2 diabetes mellitus (T2DM) and periodontal disease is grounded in the understanding that periodontal diseases stimulate a chronic inflammatory response due to the pathogenic biofilm, thereby contributing to the overall inflammatory burden in the host (Gokhale et al., 2014).

Both type 1 and type 2 diabetes mellitus (T1DM and T2DM) are characterized by elevated systemic markers of inflammation, as demonstrated by Lang et al. (1986). Glycemic control plays a crucial role in modulating the risk associated with these conditions. In our study, glycemic parameters, including Random Blood Sugar (RBS) and Hemoglobin A1C (HbA1C), were notably higher in individuals with T2DM and chronic periodontitis (CP) compared to those with only T2DM or healthy controls.

The mean RBS levels were significantly elevated in Group IV (T2DM with CP) at 249.4 ± 41.6 mg/dL, and in Group III (T2DM) at 217.6 ± 16.89 mg/dL, compared to Group II (healthy controls) at 91.6 ± 13.93 mg/dL and Group I (healthy) at 87.8 ± 12.8 mg/dL (see Table 6). Similarly, HbA1C values, which provide a reflection of average blood glucose levels over the past 2-3 months, were also higher in Group IV (9.74 ± 2.17%) and Group III (8.1 ± 1.36%) compared to Group II (5.1 ± 0.54%) and Group I (5.0 ± 0.49%) (Preshaw & Taylor, 2011). These differences were statistically significant ($p < 0.001$), underscoring the impact of diabetes on glycemic control and its association with periodontal disease.

Elevated inflammatory states and chronic hyperglycemia are known to activate pathways that exacerbate inflammation, oxidative stress, and tissue apoptosis, accelerating periodontal tissue dysfunction, particularly in the context of insulin resistance (Dandona et al., 2004). Hyperglycemia also impairs neutrophil function, reducing the body's ability to resolve infections and thereby increasing susceptibility to periodontal disease progression. Multiple comparisons revealed significant differences ($p < 0.001$) between Group I and Group II, Group I and Group IV, Group II and Group III, Group II and Group IV, and Group III and Group IV for RBS levels. However, no statistically significant difference was observed between Group I and Group II. For HbA1C levels, significant differences ($p < 0.001$) were found between Group I and Group III, Group I and Group IV, Group II and Group III, Group II and Group IV, and Group III and Group IV, except for Group I and Group II, which did not show significant variation (see Table 11).

These findings align with Gokhale et al. (2014), who also observed a strong positive correlation between HbA1C and RBS levels ($r = 0.951$), indicating a robust relationship between these glycemic measures. Conversely, the correlation between HbA1C and clinical parameters reflective of periodontal inflammation—such as probing pocket depth (PPD) and clinical attachment loss (CAL)—was mild ($r = 0.245$ for PPD and $r = 0.231$ for CAL), with no statistically significant differences noted. This contrasts with studies by Rohlfing et al. (2007), Brownlee (2005), Losche et al. (2000), and Demmer et al. (2008), which reported significant associations between HbA1C and CAL. Additionally, research by Wahi et al. (2008) highlighted a more pronounced HbA1C level in individuals with greater baseline PPD, suggesting a potential link between HbA1C levels and periodontal pathologies.

Resistin, a protein implicated in insulin resistance, inflammation, and immune responses, plays a significant role in the pathogenesis of both periodontitis and type 2 diabetes mellitus (T2DM). Elevated levels of resistin in patients with periodontitis are primarily attributed to its expression by polymorphonuclear leukocytes and macrophages in inflammatory conditions (Patel et al., 2003). Resistin functions as a proinflammatory molecule, stimulating the synthesis and secretion of key cytokines such as TNF-α and IL-12, which in turn enhances its own production in a positive feedback loop (Bokarewa et al., 2005). Additionally, resistin is released from neutrophils upon stimulation by lipopolysaccharides from periodontal pathogens like Porphyromonas gingivalis (Furugen et al., 2013). This release further amplifies the inflammatory response by increasing the expression and secretion of other proinflammatory mediators, thereby exacerbating periodontal tissue inflammation and contributing to the shared susceptibility between periodontal disease and T2DM.

In the current study, clinical and biochemical parameters related to periodontitis and resistin levels were evaluated across different patient groups. The analysis revealed a very strong positive correlation between resistin levels and random blood sugar (RBS) ($r = 0.758$, $p < 0.001$), indicating that elevated resistin is associated with increased hyperglycemia. This association may be due to impaired insulin-mediated glucose transport, inhibition of insulin signaling, or reduced insulin sensitivity. Furthermore, a strong positive correlation was observed between HbA1c levels and resistin in gingival crevicular fluid (GCF) ($r = 0.675$, $p < 0.001$), consistent with findings from Rytter et al. (2009). This correlation highlights the impact of chronic inflammation and oxidative stress on resistin levels.

The study also found moderate positive correlations between resistin and various clinical parameters: Plaque Index (PI) ($r = 0.583$), Gingival Index (GI) ($r = 0.578$), Probing Pocket Depth (PPD) ($r = 0.454$), and Clinical Attachment Loss (CAL) ($r = 0.462$), all statistically significant at $p < 0.001$. These findings suggest that

resistin levels are more closely related to inflammatory variables rather than the degree of periodontal destruction. Resistin, derived from immune cells responding to periodontal pathogens, permeates from GCF into the oral fluid (Sabir et al., 2015). Consequently, resistin levels in GCF positively correlate with PI, GI, PPD, RBS, and HbA1c, aligning with previous studies by Steppan et al. (2007) and Tsai et al. (2002).

The literature suggests that resistin levels are elevated in patients with chronic periodontitis compared to clinically healthy controls, indicating that periodontitis may contribute to the development or exacerbation of T2DM. Conversely, T2DM can influence the progression of periodontitis, creating a bidirectional relationship between these conditions. Understanding this interplay is crucial for developing targeted interventions that address both periodontal inflammation and systemic glycemic control.

Conclusion

The findings of this study showed the intricate relationship between periodontal health and systemic conditions such as diabetes mellitus. The elevated levels of RBS, HbA1C, and resistin in patients with both T2DM and chronic periodontitis highlight the bidirectional nature of this relationship. Periodontitis exacerbates glycemic control issues, while poor glycemic control contributes to more severe periodontal disease. The significant correlations between resistin and both glycemic parameters and periodontal indices further support the role of systemic inflammation in periodontal disease. Future research should continue to explore these interactions, aiming to better understand the mechanisms underlying the relationship between periodontal health and systemic conditions and to develop targeted interventions for managing these interconnected diseases.

Author contributions

K. G. and J. G. conceived the idea. S. B., V. U., K. P., G. S., and N. V. supervised and anlyzed the work. All authors discussed the results and contributed to the final manuscript.

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Competing financial interests

The authors have no conflict of interest.

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