Pre-print
Journal of Angiotherpay
Vol 5 Issue 2

Evaluation of Resistin Levels in Gingival Crevicular Fluid in Diabetic Patients with And without Chronic Periodontitis

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Abstract

Background: Resisting, a newly identified adipocyte secreted hormone may hold a value as an inflammatory mediator, associated with insulin resistance and periodontitis. The aim of the study was to determine the resistin levels in diabetic patients with and without chronic periodontitis. M**aterials and Methods:** A total of 80 patients (both Male and Female) participated in the study. Subjects were categorized into four groups (20 each); the 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). The clinical parameters, which included plaque index (PI), gingival index (GI), probing pocket depth (PPD) and clinical attachment level (CAL), random blood sugar level (RBS), glycated haemoglobin (HbA1c) were recorded. All the assessments were performed at baseline. GCF samples were collected. Resistin was examined by utilizing a monetarily accessible ELISA unit. Contrasts among groups were statistically analysed. **Results:** The expression of resisting was significantly increased between the diseased subjects when compared to healthy subjects and was statistically significant ($p< 0.001$). When all the samples were analyzed together, a significant positive correlation ($p <0.001$) was observed between GCF resistin expression, clinical parameters (GI, PI, PPD, CAL) & biochemical parameters (RBS and HbA1c). **Conclusion**: Resisting levels are increased in CP and T2DM. Hence, GCF resistin levels may be considered as a potential inflammatory marker for periodontitis with T2DM

Key words: Resisting, chronic Periodontitis, diabetes mellitus, gingival crevicular fluid, biomarker

Introduction

Periodontitis is an inflammatory disease of oral cavity with multi factorial etiology. The initiation and progression of periodontitis is mainly governed by the microbial onslaught and the host response in the form of an inflammatory reaction that ensues to combat it (Kornman 2008). Although, numerous mechanisms have been elucidated to explain the impact of diabetes mellitus on periodontium, inflammation plays an obvious role in periodontal diseases. Furthermore, evidence in the medical literature also supports the role of inflammation in the pathogenesis of diabetes and its complications Periodontitis, being described as the sixth complication of diabetes mellitus has been directly correlated with glycemic control (Loe 1993).

Resistin is a newly discovered adipocyte hormone, named after its proposed function of resisting insulin. Initially resistin was thought to be produced by adipocytes alone; however, emerging evidence suggests that it is also produced in abundance by various cells of the immunoinflammatory system, indicating its role in various chronic inflammatory diseases, thereby acting as a pro-inflammatory cytokine (Steppan, Lazar 2002).

Resistin was initially postulated to contribute to insulin resistance, more and more evidence indicated that it may also be involved in inflammatory process. Elevated levels of resistin found in diabetes mellitus highlights its impact on the glycemic status of an individual. Resistin was initially postulated to contribute to insulin resistance, more and more evidence indicated that it may also be involved in inflammatory process. It, acts as a pro-inflammatory factor and enhances the secretion of pro-inflammatory cytokines, TNF- α and IL-12, and induced the nuclear translocation of NF-kappa B transcription factor. In addition, it potentiated TNF-α, IL-6 and monocyte chemoattractant protein-1 (MCP-1) production (Silswal et al., 2005).

Resistin may hold a value as an inflammatory mediator because it has been associated with insulin resistance and periodontitis (Fu et al., 2006). This may advance the biologic link between DM and Periodontal disease. Considering the dual involvement of Resistin in periodontal diseases and diabetes mellitus, the present study is an attempt to monitor the gingival crevicular fluid Resistin levels in healthy periodontium, in subjects diagnosed with chronic periodontitis and Diabetes Mellitus (Silness, Loe et al., 1964).

Materials and Methods

The investigation was directed from the outpatient clinics of the Department of Periodontics, Thai Moogambigai dental college, Chennai, India. The examination included 80 individuals

and the patients were partitioned into four groups (20 each) as group I, group II and group III and group IV. The Inclusion criteria for the healthy periodontium were subjects having good oral hygiene, no bleeding on probing, no visual signs of gingival inflammation, the plaque index score of "0", the gingival Index score of "0", probing pocket depth and clinical attachment level of ≤3 mm. The inclusion criteria for generalized chronic PERIODONTITIS were subjects showing the presence of inflammatory changes in periodontal tissues, PI (plaque index) score ≥1, GI (gingival index) ≥1, PPD (probing pocket depth) ≥ 5mm (30 %of the sites), CAL (clinical attachment level) ≥ 4mm (30 %of the sites), Positive for BOP and Radiographic evidence of bone loss. The inclusion criteria for TYPE 2 Diabetes mellitus were previously diagnosed with T2DM as obtained from their medical history, duration of diabetes for more than 6 months, RBS(random blood sugar level) levels ≥ 200 mg/dl, Good or fair glycaemic control (confirmed with HbA1c) Patients having aggressive forms of periodontal disease, history of periodontal treatment received in the past six months, underlying systemic diseases, patients on high dose steroid therapy, pregnancy, lactation and smokers were excluded.

The investigation convention was done according to moral principles and was endorsed by the Institutional Review Board (Dr.MGRDU/TMDCH/RES/2016/2582). The purpose and type of the study was verbally explained to the subjects, educated assent was acquired from the patients.

The clinical periodontal parameters including, plaque index (PI), gingival index (GI), probing pocket depth (PPD) and clinical attachment level (CAL) were evaluated for the subjects. Midbuccal, distobuccally, mesiobuccally and palatal sites in each tooth were recorded for PI (6). The buccal, mesial, distal and lingual gingival areas were examined for GI (7). PPD and CAL were measured in millimeters and were assessed in all the teeth at six sites and CAL was calculated from cement-enamel junction to periodontal pocket base (8&9). Radiographic bone loss was recorded for each patient by intra oral periapical radiographs utilizing long cone method or orthopantomogram (OPG) to differentiate chronic periodontitis patients from healthy groups. Radiographic bone loss was recorded dichotomously (presence or absence) to differentiate chronic periodontitis patients from other groups. No further depiction was endeavoured within the chronic periodontitis group dependent on the degree of alveolar bone loss.

GCF Resistin analysis

Supra gingival scaling was done one day before collection of GCF. Using volumetric microcapillary pipettes, a volume of 1 (microlitre) was procured from each test site by an

extracrevicular approach. The collected GCF was transferred immediately to Eppendorf tubes. The GCF were stored at - 20°C until the time of assay. According to the manufacturer's protocol, the Resistin levels were estimated using Enzyme- Linked Immunosorbent Assay (ELISA). The resitin levels were expressed in ng/ml.

Statistical analysis

The outcomes acquired were recorded for the case sheets and later entered in MICROSOFT EXCEL in independent sheets for each groups. SPSS (IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp. Released 2015) was utilized to analyze the data. Significance level was fixed as 5% ($\alpha = 0.05$).

To check for the normal distribution of the data, the normality tests, Kolmogorov–Smirnov and Shapiro Wilks tests were performed. The test uncovered that, all the clinical parameters indicated normal distribution aside from GI. Along these lines, both parametric and non parametric tests were applied for the examination. For inter-group comparison, one-way ANOVA was applied after turkey's HSD post hoc tests for multiple pairwise comparisons. For the data that didn't follow the normal distribution, Kruskal – Wallis analysis was done trailed by Bonferroni adjusted Mann Whitney test for multiple pairwise- comparison.

Results

The mean and standard deviation (S. D) of the clinical parameters, RBS, HbA1C, and resistin are depicted in Table 1. The mean values of plaque index in Group- I was 0.31±0.27, Group II was 1.99± 0.26, Group III was 0.52±0.23 and Group IV was 2.76± 0.241 as depicted in table 2. The difference was statistically significant ($p<0.0001$). Tukey's HSD post hoc test was applied to compare Plaque index, gingival index, PPD and CAL between the 4 groups. A statistically significant difference ($p< 0.001$) was observed between (Group I and Group II), (Group I and Group IV), (Group II and Group III) (Group II and Group IV) (Group III and Group IV) for plaque index.

Tukey's HSD post hoc test was applied to compare all the clinical parameters between the 4 groups as shown in Table 2. A statistically significant difference ($p< 0.001$) was observed between (Group I and Group II), (Group I and Group IV), (Group II and Group III) (Group II and Group IV) & (Group III and Group IV) for plaque index. However, no statistically significant difference between (Group I and III) for the plaque index was observed. The probing

pocket depth values showed a statistically significant difference (p< 0.001) when compared between (Group I and Group II), (Group I and Group IV), (Group II and Group III) & (Group II I and Group IV) whereas statistically significant difference was not seen between (Group I and III) & (Group II and Group IV). A statistically significant difference (p< 0.001) was observed for CAL on comparing (Group I and Group II), (Group I and Group IV), (Group II and Group II I) (Group III and Group IV) while there was no statistically significant difference observed on comparing (Group I and Group III) & (Group II and Group IV).

However, a comparison of Group I and Group III did not reveal any significant difference. Multiple comparisons of the biochemical parameters is shown in Table 3**.** A statistically significant difference (p < 0.001) was observed between (Group I and Group II), (Group I and Group IV), (Group II and Group III) (Group II and Group IV) (Group III and Group IV). For RBS. However, the Comparison of Group I and Group II did not reveal any statistically significant difference. The HbA1C values showed a statistically significant difference (p< 0.001) when compared between (Group I and Group III), (Group I and Group IV), (Group II and Group III), (Group II and Group IV) and (Group II I and Group IV) except for (Group I and Group II) whose comparison did not reveal any statistically significant difference. Multiple comparisons of Resistin values with all the four groups showed a statistically significant difference (p< 0.001).

HbA1c and all clinical parameters (PI, GI, PPD, CAL, RBS, Resistin) were correlated using Pearson correlation test as shown in Table 4**.** A very strong positive correlation was observed between HbA1C and RBS (0.951) which was statistically significant (p <0.001).A strong positive correlation was observed between HbA1C and Resist in (0.675) and it was also found to be statistically significant (p <0.001). There was a Mild correlation was observed between HbA1C and Plaque index (0.373), Gingival Index (0.367) and was also statistically significant (PI - 0.003), (GI- 0.004). Mild correlation was observed between HbA1C and PPD (0.245), and CAL (0.231) however, it was not statistically significant.

Table 5, shows the correlation of all clinical parameters with resistin using Pearson correlation test. Very strong Positive correlation and a statistically significant difference (p <0.001) was observed between Resistin and RBS (0.758). A Strong Positive correlation and a statistically significant difference (p <0.001) was observed between Resistin and HbA1C (0.675). Moderate positive correlation was observed between Resistin and Plaque index (0.583) , Gingival Index

Journal of Angiotherpay
Pre-print published on 18 December 2021

(0.578), PPD (0.454) and CAL(0.462) & it was also found to be statistically significant(p <0.001).

Discussion

Oral cavity and systemic diseases are two entities that can affect each other. Golub et al proposed a “two -hit” model for chronic periodontitis and systemic diseases like diabetes mellitus. They said that the periodontopathic bacteria provided one "hit", where as systemic inflammations elevating levels of pro inflammatory biomarkers like CRP, IL- 6, TNF α etc in serum or plasma acted as a second “hit ”. Similarly, both Diabetes and peridontitis are both chronic inflammatory diseases where they have some commonalities of immune inflammatory response throughout the course of the disease. Diabetes mellitus is one of the risk factors that intensifies the extent and severity of periodontitis up to ten fold, frequently spurring rampant destruct ion of the periodontium (Loe , Silness et al., 1963).

According to Gokhale et al (Hassel et al., 1973), Gingival index (Sivertson ,Burgett 1976) was selected as a method for assessing the severity of gingival inflammation. The clinical parameters indicated the presence of active periodontal disease. (Golub et al., 2006) The relationship between T2DM and periodontal disease is based on the fact that periodontal diseases, in account of the react ion to the pathogenic biofilm stimulates a chronic inflammation systemically and contributes to inflammatory burden in the host (Gokhale et al., 2014)

Both type 1 and type 2 diabetes mellitus are associated with elevated levels of systemic markers of inflammation (Lang et al., 1986)**.** The level of glycemic control is of key importance in determining increased risk. The glycemic parameters RBS and HbA1C values were higher in group IV (T2DM with CP) followed by Group III (T2DM). The mean values of RBS is significantly high in Group IV (249.4 ± 41.6) and III (217.6 ± 16.89) than in Group II (91.6±13.93) and Group I (87.8±12.8) as shown in table 6. HbA1c is considered as a beneficial indicator of long–term homeostasis, reflecting an average blood glucose concentration for the past 2-3 months (Preshaw, Taylor, 2011). In the present study, mean HbA1C values were higher in Group IV (9.74 ± 2.17) & Group III (8.1 ± 1.36) than in Group II (5.1±0.54) and Group I (5 ± 0.49). Both RBS and HbA1C values were found to be statistically significant (p < 0.001). The elevated inflammatory state and hyperglycemia induce the activation of pathways that increase inflammation, oxidative stress, apoptosis, etc to accelerate the dysfunction in periodontal tissues that is already present because of insulin resistance. The

other specific adverse effect of hyperglycemia is its inhibitory effect on the neutrophils to resolve the infection. This increases the susceptibility to infection that could accelerate the destruction of the periodontal tissues (Dandona et al., 2004). On Multiple comparisons a statistically significant difference ($p< 0.001$) was observed between (Group I and Group II) , (Group I and Group IV) , (Group II and Group III) (Group II and Group IV) (Group III and Group IV) for RBS. However, Comparison of Group I and Group II did not reveal any statistically significant difference (table 11). In contrast, the HbA1C values on multiple comparisons showed a statistically significant difference ($p< 0.001$) when compared between (Group I and Group II I) , (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) , whose comparison did not reveal any statistically significant difference. This was in concurrence to a study by Gokhale (Gokhale et al., 2014) . A very strong positive correlation and a statistically significant difference was observed between HbA1C and RBS levels (0.951). But there was only a mi ld positive correlation between HbA1C and clinical parameters which reflected the inflammatory state of the periodontium among the four groups (table 12). However, no statistically significant difference was noted in PPD (0.245) and CAL (0.231). (Rohlfing et al., 2007 , Brownlee 2005, Losche et al., 2000, Demmer et al., 2008) who reported that there was a statistically significant difference observed between HbA1C with CAL. Another study done by Saurabh Wahi et al., 2008 who reported that the HbA1C levels were more significant in individuals with greater PPD at base line. They concluded that a possible association does exist between the levels of HbA1c and the risk of development of periodontal pathologies.

Resistin is involved in insulin resistance, inflammation, and immunity. This increase in resistin levels in patients with periodontitis could be attributed to the fact that resistin is mainly expressed from polymorphonuclear leukocytes and macrophages in inflammatory conditions. (Patel et al., 2003). Human resistin acts as a proinflammatory molecule and stimulates the synthesis and secretion of TNF- α an d IL-12, thus inducing its own production in a positive feedback cycle. (Bokarewa et al., 2005) Second, with lipopolysaccharide stimulation, resistin is released from neutrophils by putative periodontal pathogens such as Porphyromonas gingivalis (Furugen et al., 2013). Resistin displays potent proinflammatory properties by itself as it upregulated the expression and secret ion of several proinflammatory mediators such as TNF-α , IL- 1 β , IL-6, MIP-1α etc exacerbating inflammation in periodontal tissues and

this process could contribute to the shared susceptibility between periodontal disease and T2DM.

In the present study clinical and biochemical parameters for periodontitis and resistin levels were evaluated and compared in all groups of patients using Pearson correlation (table 13). On analysis, it was found that a very strong positive correlation and a statistically significant difference ($p < 0.001$) was observed between resistin and RBS (0.758). Association of resistin with a hyperglycemic state could be due to an impaired insulin mediated glucose transport , inhibitor of insulin signaling or reduced insulin sensitivity. A strong positive **correlation** (0.675) and a statistically significant difference ($p < 0.001$) was observed between HbA1C and GCF Resist in levels . This was consistent with the study by Rytter et al 2009 .This significant disparity in the resist in levels could be a result of the presence of hyper inflammatory state owing to heightened oxidative stress . In the present study, moderate positive correlation was observed between Resistin and Plaque index (0.583) , Gingival Index (0.578) , PPD (0.454) ,and CAL(0.462) and was also found to be statistically significant($p < 0.001$). This indicates that the resistin levels may be associated with inflammatory variables rather than periodontal destruction. Resistin is derived from immune cells that respond to periodontopathic microorganisms, and then this resist in seeps from GCF into the oral fluid (Sabiret al., 2015). Therefore, it is stated that resistin levels in GCF showed an overall positive correlation to PI, GI, PPD, RBS, and HbA1c. This finding was in agreement with an earlier study done by Steppan et al 2007, Tsai, et al 2002. The currently available literature suggested that resistin levels are increased in patients with chronic periodontitis compared to the clinically healthy controls. Thus, periodontitis might lead to the development of type II diabetes or diabetes, which might influence the occurrence or progression of periodontitis.

Conclusion

The observations of the present study could be significant in understanding their role in the changing dynamics of periodontal disease progression, thereby enhancing its capacity as a diagnostic and prognostic marker of disease activity. It can be observed that resistin can serve as one of the potential markers for periodontitis with Diabetes. Therefore further research can throw light on the effect of periodontal therapy and glycemic control on the levels of resistin in GCF and thus establish its possible potential as a biomarker of periodontal inflammation. Resistin levels increased with periodontal inflammation indicating its possible inflammatory role in periodontitis. Our study being an observational study proves the association of GCF

resistin levels with periodontal disease and type 2 diabetes mellitus In this manner, GCF resistin levels may be considered as a potential combustible marker for periodontitis with T2DM. However, further long-term and interventional studies with larger sample sizes are warranted, to give a direct cause-effect relationship between resistin and chronic periodontitis and to determine the exact molecular mechanism involved in increased insulin resistance.

Author contribution

Keerthidaa Govindaraj, Jayamathi Govindaraj conceived of the presented idea. S.Bhuminathan , Vidyarekha U , Kesavaram Padmavathy, Gowtham S and Nivetha V encouraged and supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

Acknowledgment

Conflict of interest

Study significance . The study represents the evaluation of resistin levels in gingival crevicular fluid in diabetic patients with and without chronic periodontitis.

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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***

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Pre-print published on 18 December 2021

	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

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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***

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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

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