Resistin in serum and gingival crevicular fluid as a marker of periodontal inflammation and its correlation with single-nucleotide polymorphism in human resistin gene at −420

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Abstract

Aims: Resistin is an adipocytokine, which have been studied for its role in insulin resistance and recently in inflammation. The aim of the present study is to assess the concentration of resistin in serum and gingival crevicular fluid (GCF) and to compare the levels between subjects with and without periodontitis and type 2 diabetes mellitus (T2DM) and to further correlate the resistin levels with the single-nucleotide polymorphism (SNP) at −420. Setting and Designs: A total of 96 subjects (48 males and 48 females) were divided on the basis of gingival index (GI), probing pocket depth (PD), clinical attachment level (CAL) and hemoglobin A1c levels into healthy (group 1, n = 24), uncontrolled-diabetes related periodontitis (group 2, n = 24), controlled-diabetes related periodontitis (group 3, n = 24) and chronic periodontitis without T2DM (group 4, n = 24). Materials and Methods: The GCF and serum levels of resistin were quantified using the enzyme-linked immunosorbent assay and compared among the study groups. Further, the association of the resistin levels with periodontal inflammation and SNP at −420 was studied. Results and Conclusion: The resistin levels in GCF and serum from patients with periodontitis or diabetes mellitus related periodontitis (controlled or uncontrolled) were higher than that of healthy subjects and correlated positively with GI. Further, subjects with GG genotype at −420 showed significantly higher GI, PD, CAL as compared with genotype group CC. Resistin was detected in all serum and GCF samples and was significantly higher in periodontitis. Further, GG genotype at −420 was associated significantly with periodontal inflammation and resistin levels.

Keywords: Biomarker, diabetes mellitus, periodontitis, resistin

Introduction

Periodontitis and type 2 diabetes mellitus (T2DM) are chronic diseases for which bidirectional relationship have been suggested by numerous evidences.[3] It has been reported in several studies that patients with T2DM have an increased risk of periodontitis[3-4] and periodontitis has been considered as the sixth complication of the T2DM.[3] A meta-analysis provided evidence to support an association between diabetes and periodontal diseases.[11] Highlighting the bidirectional nature of this association, Cochrane systematic review reported on the reversible relationship (i.e., improvement in glycemic control with periodontal therapy) as indicated by measurements of hemoglobin A1c (HbA1c), an important marker of glucose metabolism.[6] Taken together, the available evidences support the existence of a relationship between periodontitis and T2DM, but the mechanism behind this association is still a matter of controversial discussion.

It has been hypothesized that inflammation, lipids and adipokines may mediate this relationship between periodontitis and T2DM.[3] Resistin is an adipocytokine that has gained recent attention for its involvement in insulin resistance and diabetes mellitus.[7] Resistin is a member of a secretory protein family, known as resistin-like molecules. The family is characterized by a highly conserved, cysteine-rich C terminus in which the spacing of the cysteines is invariant.[7] The term “resistin” was originally proposed for its role in insulin resistance.[7] Although, resistin was firstly postulated to contribute to insulin resistance, more and more evidences indicate that it may also be involved in the inflammatory process. Resistin is expressed at very low levels, if at all, in human adipose cells, whereas high levels are expressed in mononuclear leukocytes, macrophages, spleen and bone marrow cells.[8-10] Proinflammatory cytokines (interleukin [IL]-1, IL-6 and tumor necrosis factor (TNF)-α) increase the expression of resistin in human peripheral blood mononuclear cells.[11] Therefore, in humans resistin may have a major role in inflammation. Resistin levels have been found to be increased in chronic inflammatory conditions such as inflammatory bowel disease[12] and
Further highlighting its role in chronic inflammation, increased level of resistin in gingival crevicular fluid (GCF) samples from chronic periodontitis (CP) patients has been recently reported. Serum resistin concentration of elderly Japanese people was reported to be significantly higher than that of healthy subjects and was found to be associated with bleeding on probing, an important clinical marker of periodontal inflammation.

In addition, several single-nucleotide polymorphisms (SNPs) have been identified in the human resistin gene (RETN), one of these (a C to G substitution at position −420 in the 5’ flanking region of the gene) has been associated with prevalence of type 2 diabetes and is linked with increased resistin messenger ribonucleic acid levels in abdominal fat and elevated serum resistin levels. Thus, in humans resistin mainly plays a role in modulating the inflammation and its role in periodontal inflammation needs further probing.

In the light of the above facts, current study was designed with an aim to study the levels of resistin in serum and GCF in subjects with and without periodontitis and diabetes mellitus related periodontitis and further investigate the promoter SNP at −420 and its association with resistin levels and periodontal inflammation in the Indian population.

**Materials and Methods**

**Study samples**
The study was carried out from August 2010 to January 2011. The study group consisted of 96 subjects (26-59 years; gender: 48 males and 48 females) attending the out-patient section, Department of Periodontics, Government Dental College and Research Institute, Bangalore. Written informed consent was obtained from those who agreed to participate voluntarily. Patients with aggressive periodontitis, hypertension, a smoking habit, gross oral pathology, heart diseases, rheumatoid arthritis, tumors or any other systemic disease other than T2DM that can alter the course of periodontal disease or those who had any course of medication affecting periodontal status or had received periodontal therapy in the preceding 6 months were excluded from the study. The Ethical Clearance was approved by Institutional Ethical Committee and Review Board.

Each subject underwent a full-mouth periodontal probing and charting, body mass index (BMI) charting as per World Health Organization guidelines and periapical radiographs were taken using the long-cone technique. Radiographic bone loss was recorded dichotomously (presence or absence) to differentiate patients with CP from other groups. Subjects were categorized into four groups based on the gingival index (GI), pocket depth (PD), clinical attachment level (CAL), radiographic evidence of bone loss and HbA1c levels. Group 1 (healthy) consisted of 24 subjects with clinically healthy periodontium, GI = 0 (absence of clinical inflammation), PD ≤ 3 mm and CAL = 0, with no evidence of bone loss on radiographs. Group 2 (uncontrolled-diabetes related periodontitis) consisted of 24 subjects who had signs of clinical inflammation, GI > 1, PD ≥ 5 mm and CAL ≥ 3 mm, with radiographic evidence of bone loss and HbA1c > 7%. Group 3 (controlled-diabetes related periodontitis) consisted of 24 subjects who had signs of clinical inflammation, GI > 1, PD ≥ 5 mm and CAL ≥ 3 mm, with radiographic evidence of bone loss and HbA1c < 7%. Group 4 (CP) consisted of 24 subjects who had signs of clinical inflammation, GI > 1, PD ≥ 5 mm and CAL ≥ 3 mm, with radiographic evidence of bone loss.

**Site selection and GCF collection**
GCF was collected according to our previous method. Briefly, all clinical assessments using a periodontal probe (UNC-15, Hu-Freidy, Chicago, IL, USA), radiographs, group allocations and sampling-site selections were performed by one examiner (ARP) to ensure adequate intra-examiner reproducibility. Samples were collected on the subsequent day by a second examiner (SPP). This was to prevent contamination of GCF with blood associated with the probing of inflamed sites. Only one site per patient was selected on day-1 as a sampling site in the periodontitis groups (groups 2, 3 and 4), whereas in the healthy group, multiple sites (3-5 sites per patient) with an absence of inflammation were sampled to ensure the collection of an adequate amount of GCF. In patients with CP, the site showing the greatest CAL and signs of inflammation was selected for sampling. On the subsequent day, after gently drying the area, supragingival plaque was removed without touching the marginal gingiva and the area was isolated with cotton rolls to avoid saliva contamination. GCF was collected by placing the microcapillary pipette at the entrance of the gingival sulcus and gently touching the gingival margin. A standardized volume was collected using the calibration on white color-coded 1 to 5-μl calibrated volumetric micro-capillary pipettes (Sigma-Aldrich, St. Louis, MO, USA). Each sample collection was allotted a maximum of 10 min and sites that did not express any GCF within the allotted time were excluded. This was carried out to ensure atraumatism and micropipettes that were suspected to be contaminated with blood and saliva were excluded from the study. Collected GCF samples were immediately transferred to airtight plastic vials and stored at −70°C until assayed.

**Blood collection**
A total of 4 ml of blood was collected from the antecubital fossa by venipuncture using a 20-gauge needle. Blood was immediately transferred to the laboratory. 2 ml blood sample was allowed to clot at room temperature and after 1 h, serum
was separated from blood by centrifuging at 3000 g for 5 min. The extracted serum was immediately transferred to a plastic vial and stored at −70°C until the time of assay and the remaining 2 ml whole blood was used for isolation of deoxyribonucleic acid for genetic polymorphism.

**Resistin estimation**

Samples were assayed for resistin levels using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Quantikine Human Resistin Immunoassay, R and D Systems, Inc., USA). Samples were analyzed according to the instruction manual at the Department of Microbiology, Kempegowda Institute of Medical Sciences, Bangalore, India. Briefly, the GCF and serum samples were diluted with the dilution buffer in the kit and the amount of resistin determined. All the samples and standards were run in duplication.

**SNP typing**

SNP −420 was typed by TaqMan analysis (Chromous biotech). The probes used were VIC 5’-CATGAAGACGGAGGC-3’ for −420C and FAM 5’-ATGAAGAGGGAGGCC-3’ for −420G. Forward and reverse primers were 5’-CCACCTCCTGACCAGTCTCT-3’ and 5’-AGCCTTCCCACTTCCAACAG-3’, respectively.

**Statistical analyses**

A Kruskal-Wallis analysis and Bonferroni test were carried out for a comparison of resistin levels among groups. With the use of the Spearman rank correlation coefficient, the relationship between the resistin concentration and clinical parameters were analyzed with a software program (SPSS version 17.1, IBM, Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

**Results**

Descriptive statistics of study groups and the mean resistin concentrations in GCF and serum obtained from the sampling sites are presented in Table 1. The highest mean resistin concentrations in was obtained in group 2 in GCF and in group 4 in serum. The least mean resistin concentrations in serum and GCF was found in group 1. The analysis of variance showed that the differences in the levels of resistin concentrations among all the groups for GCF and serum samples were statistically significant at $P < 0.05$. Table 2 shows multiple comparisons using least square difference method for post-hoc analysis, which was carried out to find out which pair or pairs differed significantly at the 5% level of significance. Statistically significant difference in means was found between groups 1 and 2, 1 and 3 and 1 and 4 in serum resistin concentrations. GCF resistin concentrations were found to be statistically different among groups 1 and 2 and groups 1 and 4 [Table 2].

Table 3 shows the Spearman rank correlation between GCF and serum resistin levels with clinical parameters. Serum and GCF resistin levels showed a positive correlation with GI in all the groups and this correlation was significant in group 3. Serum and GCF resistin concentration did not show any significant correlation with PD and CAL. Both serum and GCF resistin levels showed a positive correlation with BMI in all the groups, which was significant in groups 1 and 3.

| Table 1: Descriptive statistics of the study population |
|--------------------------------------------------------|
| **Group 1**                                             | **Group 2**                                             | **Group 3**                                             | **Group 4**                                             |
| Age (years)                                            | 29.92±2.81 (35, 26)                                     | 49.75±5.49 (59, 43)                                     | 50.33±4.9 (58, 43)                                     | 39.88±4.68 (47, 29)                                     |
| BMI                                                    | 21.41±1.78 (24, 19)                                     | 29.83±4.8 (40, 24)                                     | 28.50±4.07 (35, 23)                                     | 26.66±5.03 (35, 20)                                     |
| GI                                                     | 0                                                      | 2.25±0.62 (3, 1)                                        | 2.33±0.49 (3, 2)                                        | 2.08±0.51 (3, 1)                                        |
| PPD (mm)                                               | 2.0±0.73 (3, 1)                                         | 7.0±1.53 (10, 5)                                        | 8.5±1.44 (11, 6)                                        | 6.67±1.37 (9, 5)                                        |
| CAL (mm)                                               | 0                                                      | 5.0±1.75 (8, 2)                                         | 7.08±1.44 (9, 5)                                        | 5.08±1.24 (7, 3)                                        |
| Serum resistin conc. (ng/ml)                           | 8.0±2.04 (11, 5)                                        | 15.83±6.8 (24, 0)                                       | 14.67±4.8 (24, 8)                                       | 16.66±4.4 (22, 8)                                       |
| GCF resistin conc. (ng/µl)                             | 4.75±1.81 (7, 2)                                        | 10.75±4.45 (18, 2)                                      | 7.58±2.96 (13, 3)                                      | 9.25±3.3 (16, 4)                                        |
| Genetic polymorphism distribution (%)                 | CC=16 (66.67)                                           | CC=6 (25)                                               | CC=4 (16.66)                                            | CC=4 (16.66)                                            |
|                                                        | CG=6 (25.00)                                            | CG=4 (16.66)                                            | CG=10 (41.66)                                           | CG=12 (50)                                              |
|                                                        | GG=2 (8.33)                                             | GG=14 (58.33)                                           | GG=10 (41.66)                                           | GG=8 (33.33)                                            |

BMI: Body mass index; GI: Gingival index; PPD: Probing pocket depth; CAL: Clinical attachment level; GCF: Gingival crevicular fluid
Correlation of serum resistin concentration with the GCF resistin concentration was positive among all the groups and reached statistical significance in group 2.

Table 4 shows the comparison of different variables for the study population based on genetic polymorphism grouping. Subjects with GG genotype showed significantly higher GI, PD and CAL as compared with genotype group CC. The values for GI, PD and CAL for genotype CG fall between the genotypes CC and GG. The concentration of serum and GCF resistin was found to be highest in genotype group GG and least in genotype group CC while these levels in group CG fall between the other two groups. None of these differences in the levels of serum and GCF resistin could reach the statistical significance [Table 4].

**Discussion**

Obesity has now been associated with chronic inflammatory response. The potential role of adipocytes in inflammation is explained by their similarity to immune cells in many properties, like activating the complement system and production of the pro-inflammatory cytokines. Resistin is an adipokine and is an important factor linking obesity to T2DM and has received recent attention owing to its role in inflammatory diseases. Although was firstly postulated to contribute to insulin resistance, more and more evidence indicated that resistin may also be involved in inflammatory processes. Further, adding to the previous evidences that linked resistin to inflammatory diseases, resistin has been recently studied in CP.

Intending to further probe into the inflammatory role of resistin, in the present study we estimated the GCF and serum levels of resistin in individuals with healthy gingiva, uncontrolled-diabetes related periodontitis and controlled-diabetes related periodontitis and CP subjects without T2DM. We further correlated the clinical parameters and resistin levels with genetic polymorphism at −420.

We employed, the extracrevicular (unstimulated) method of GCF collection using micro-capillary pipettes to ensure atraumatism, to obtain an undiluted sample of native GCF, the volume of which could be accurately assessed and to avoid non-specific attachment of the analyte to filter-paper fibers.

We found that GCF resistin level was highest in group 2 (uncontrolled-diabetes related periodontitis) and serum resistin levels were highest in group 4 (CP without T2DM). Both serum and GCF resistin levels were least in

| Study variables | Group 1 | Group 2 | Group 3 | Group 4 |
|-----------------|---------|---------|---------|---------|
| Serum resistin |  -      | 0.329   | 0.718*  | 0.490   |
| PPD            | -0.294  | 0.1     | 0.348   | 0.069   |
| CAL            | -       | 0.443   | 0.256   | -0.243  |
| BMI            | 0.646*  | 0.149   | 0.716*  | 0.339   |

| GCF resistin | Group 1 | Group 2 | Group 3 | Group 4 |
|--------------|---------|---------|---------|---------|
| GI           | -       | 0.317   | 0.749*  | 0.336   |
| PPD         | -0.104  | -0.148  | 0.415   | 0.396   |
| CAL         | -       | -0.571  | 0.666   | 0.303   |
| BMI         | 0.605*  | 0.261   | 0.286   | 0.588   |
| Serum resistin |       |         |         |         |
| GCF resistin | 0.277   | 0.892*  | 0.518   | 0.588   |

*Significant at P<0.05; BMI: Body mass index; GI: Gingival index; PPD: Probing pocket depth; CAL: Clinical attachment level; GCF: Gingival crevicular fluid

| Genetic | CC Mean | SD | Median | CG Mean | SD | Median | GG Mean | SD | Median |
|---------|---------|----|--------|---------|----|--------|---------|----|--------|
| GI      | 1.00    | 1.20| 0.00   | 1.88    | 1.02| 2.00   | 2.06    | 0.75| 2.00   |
| PPD     | 4.33    | 2.87| 3.00   | 6.19    | 2.66| 6.50   | 5.29    | 2.39| 5.00   |
| CAL     | 2.47    | 2.88| 0.00   | 4.94    | 2.84| 5.50   | 4.17    | 1.97| 8.00   |
| Serum resistin (ng/ml) | 16.10 | 9.57| 9.00   | 14.69 | 4.88| 14.00 | 15.06 | 6.18| 17.00 |
| GCF resistin (ng/µl)   | 6.33   | 2.87| 6.00  | 9.00   | 3.29| 8.00  | 8.76   | 4.78| 9.00  |

Note: Values in the same row not sharing the same subscript (a and b) are significantly different at P<0.05 in the two-sided test of equality for column means; Cells with no subscript are not included in the test; Tests assume equal variances; Tests are adjusted for all pair-wise comparisons using the Bonferroni correction; SD: Standard deviation; GI: Gingival index; PPD: Probing pocket depth; CAL: Clinical attachment level; GCF: Gingival crevicular fluid
group 1 (subjects with healthy periodontium). Our findings are in accordance with the findings of a recent study on Japanese population, where the resistin level in GCF from patients with periodontitis or diabetes mellitus-related periodontitis was reported to be significantly higher than that of healthy subjects. The levels of GCF and serum resistin correlated positively with GI, PD and CAL and this correlation was significant with GI, highlighting the inflammatory role of resistin. The rise in GCF resistin level concomitant with the serum level can be explained by the fact that resistin in GCF may be spilled from the serum resistin levels. In addition, the release of resistin from human neutrophils on stimulation with Porphyromonas gingivalis lipopolysaccharide has been demonstrated, which would be an alternate explanation for its presence in GCF.

Resistin has been studied for its role in insulin resistance and inflammation. Although resistin has been previously implied in insulin resistance, the evidence supporting its role in insulin resistance has been inconsistent. However, resistin levels in human serum were significantly associated with inflammatory disease markers. These reports suggest that resistin may play a significant role in the inflammatory process, but its role in insulin resistance is not consistently demonstrated. In the present study, the GCF and serum resistin levels were higher in CP (groups 2, 3 and 4) as compared with the healthy subjects and correlated positively with inflammatory sign (GI). However, the difference in the resistin levels between CP (group 4) and diabetes associated CP (groups 2 and 3) was not significant. These findings were consistent with those reported earlier in the Japanese study. Thus, our findings further suggest that resistin plays a significant role in inflammation of the periodontal tissues. The resistin levels in GCF was found to be remarkably higher than those in serum, these findings were similar to those reported before in Japanese population and is in accordance to various other inflammatory mediators in periodontal diseases.

When resistin levels were compared among the different genotype groups, we found that carriers of the G allele at position −420C > G had higher serum and GCF resistin levels. This finding was similar to previously reported findings in Japanese, Korean and Caucasian population. Further, carriers of G allele at position −420C > G also showed significantly higher PD, CAL and GI. Thus, GG genotype at −420 can be associated with significantly higher periodontal inflammation and destruction. These findings highlight the association of resistin gene variation with periodontal inflammation and are in accordance with previously reported association of resistin gene variation with inflammatory cytokines.

In summary, our study highlights the role of resistin in periodontal inflammation in T2DM. Considering the previously reported role of resistin in insulin resistance, increased GCF and serum resistin may be responsible for poor control of T2DM in periodontitis subjects. However, the findings of increased periodontal inflammation in carriers of G allele at position −420C > G point toward the possible genetic nature of this association. Thus, within its limitations, our study further highlights the complex and important role of resistin in linking CP to T2DM. Future prospective studies are advocated in further clarifying this association.

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