Clinical Study

Crevicular Fluid and Serum Concentrations of Progranulin and High Sensitivity CRP in Chronic Periodontitis and Type 2 Diabetes

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Introduction. This study was designed to correlate the serum and gingival crevicular fluid (GCF) levels of progranulin (PGRN) and high sensitivity C-reactive protein (hs CRP) in chronic periodontitis and type 2 diabetes mellitus (DM). *Design*. PGRN and hs CRP levels were estimated in 3 groups: healthy, chronic periodontitis, and type 2 DM with chronic periodontitis. *Results*. The mean PGRN and hs CRP concentrations in serum and GCF were the highest for group 3 followed by group 2 and the least in group 1. *Conclusion*. PGRN and hs CRP may be biomarkers of the inflammatory response in type 2 DM and chronic periodontitis.

1. Introduction

Chronic periodontitis is an infectious disease that involves a host immune inflammatory response in the periodontal tissues against the microorganisms present in dental plaque [1]. The clinical features of periodontitis include clinical attachment level (CAL), alveolar bone loss, periodontal pockets, and gingival inflammation [2]. Host immune inflammatory reactions are thought to protect the host against the infectious agents, but the persistent release of inflammatory mediators by immune cells results in the destruction of soft and mineralized periodontal tissues [3].

Periodontal inflammation has a significant impact on various systemic diseases with high prevalence, incidence, morbidity and mortality, for example, diabetes mellitus (DM) and cardiovascular diseases. Thus, preexisting periodontitis influences glycemic control and complication outcomes in diabetes patients. On the other hand, extensive epidemiological studies have shown that DM increases the risk of periodontal tissue damage [4, 5].

DM, a chronic metabolic disease characterized by hyperglycemia, is often attributed to environmental and genetic factors. The prevalence of DM has risen dramatically in recent years, resulting in a rapid increase of diabetic patients. Asia in particular has the highest prevalence of diabetes in the world. Countries exhibiting the fastest rate in diabetic population growth include India and China, among many other developing countries [6].

Progranulin (PGRN), also called as granulin/epithelin precursor, proepithelin, PC cells-derived growth factor, and acrogranin, is a glycosylated protein released by a variety of cells [7]. PGRN is a 593-amino acid, cysteine-rich protein with an estimated molecular weight of 68.5 kDa that runs at 90 kDa on standard western blots due to heavy glycosylation [8]. Proteolytic cleavage of the precursor protein by extracellular proteases, such as elastase, gives rise to smaller peptide fragments termed granulins or epithelins [9]. These fragments range in size from 6 to 25 kDa and have been implicated in a range of biological functions [9, 10]. PGRN mRNA has been demonstrated in various tissues and organs including the reproductive organs, gastrointestinal tract, endocrinal organs, and neural tissues [11, 12]. It is particularly prominent in epithelial and hematopoietic cells

and tends to be more highly expressed in tissues with high turnover rates such as gastric mucosa, lymphoid tissue, and tumor cell lines [12, 13].

PGRN has been also implicated in wound healing and inflammation [14–16]. Circulating PGRN significantly correlates with high sensitivity C-reactive protein (hs-CRP) serum concentrations, A1C values, and total cholesterol. Multivariable linear regression analyses revealed CRP levels as the strongest independent predictor of circulating PGRN [17].

CRP is an extremely sensitive and nonspecific acute-phase marker for inflammation that is produced in response to many forms of injury other than periodontitis, such as other infections, trauma, and hypoxia [18]. CRP presents associations with smoking, obesity, coffee consumption, triglycerides, diabetes, and periodontal disease [19, 20]. CRP and interleukin-6 (IL-6) are reported to be significant risk indicators for the development or progression of DM [21].

A study suggests a close coregulation between CRP and PGRN serum concentration and demonstrated that PGRN may be a novel biomarker of the chronic inflammatory response in type 2 DM and associated disturbances [17]. Hence, PGRN is an important molecule in inflammatory response and could therefore be involved in chronic subclinical inflammation associated with type 2 DM and chronic periodontitis.

However, till date, PGRN and hs-CRP concentration in serum and GCF in type 2 DM subjects with chronic periodontitis has not been explored. Hence, the aim of the present study is to assess the concentration of PGRN and hs-CRP in serum and GCF of type 2 DM subjects with chronic periodontitis to find their association, if any.

2. Materials and Methods

The study was carried out from November 2011 to February 2012. The study group consisted of 40, age and gender balanced subjects (25–45 years; gender: 20 males and 20 females) attending the outpatient section, Department of Periodontics, Government Dental College and Research Institute, Bangalore. Written informed consent was obtained from those who agreed to participate voluntarily. The Ethical Clearance was approved by the Institutional Ethical Committee and Review Board.

2.1. Inclusion Criteria. Subjects should be in the age group of 25–45 years with the presence of at least 20 natural teeth; subjects should be with a diagnosis of chronic periodontitis based on clinical parameters like probing depth (PD), clinical attachment level (CAL) [22], gingival index (GI) [23]. A body mass index should be (BMI) in range of 18.5–22.9 kg/m^2 and waist circumference <90 cm (men) and <80 cm (women) [24]; subjects should not have received periodontal therapy within preceding six months; Well-controlled type 2 diabetic patients classified based on criteria given by the American Diabetic Association (ADA) in 2010 and glycated hemoglobin levels [25].

2.2. Exclusion Criteria. Subjects with aggressive periodontitis, hypertension, a smoking habit, gross oral pathology, heart diseases rheumatoid arthritis, tumors, or any other systemic disease 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.

2.3. Grouping Criteria. Group 1 (healthy) consisted of 10 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 (chronic periodontitis subjects) consisted of 15 subjects who had signs of clinical inflammation, GI > 1, greater than 30% sites had PD ≥ 5 mm, and CAL ≥3 mm, HbA1c ≤ 7% with radiographic evidence of bone loss. Group 3 (chronic periodontitis subjects with type 2 DM) consisted of 15 subjects who had signs of clinical inflammation, GI > 1, greater than 30% sites had PD ≥ 5 mm, and CAL ≥ 3 mm, with radiographic evidence of bone loss. Only well-controlled (HbA1c ≤ 7%) type 2 DM subjects were selected based on ADA's criteria for diagnoses of diabetes.

2.4. Clinical Evaluation of Subjects. Group allocations and sample site selections were performed by the chief coordinator (ARP). A calibrated examiner (PN) did the clinical evaluation measuring the clinical parameters including PD, CAL, and GI, using a University of North Carolina-15 periodontal probe (Hu-friedy, Chicago, IL, USA). The same examiner (PN) also did the radiographic evaluation and collected the GCF samples.

2.5. Site Selection and GCF Collection. Two test sites for GCF sample collection were selected based on the highest scored sites in the oral cavity. In group 3 and group 4 subjects, the 2 sites showing the greatest CAL and signs of inflammation, along with radiographic confirmation of bone loss, were selected for sampling. One of the 2 sites selected/subject was used for hs-CRP while the other for PGRN analysis. In the healthy group, to standardize site selection and obtain adequate fluid volume, sampling was predetermined to be from the mesiobuccal region of the maxillary right first molar, in the absence of which the left first molar was sampled. First, the selected site was cleaned, isolated, and air dried using sterile cotton rolls, and the supragingival plaque was removed gently using a Universal gracey curette #4R/4L (Hu-friedy, Chicago, IL, USA) to avoid contamination of the paper strips. The paper strips (Periopaper, Ora Flow Inc., Amityville, NY USA) were placed gently at the entrance of the gingival sulcus/crevice until the light resistance was felt [26], care being taken to avoid mechanical injury, and left in place for 60 seconds. The absorbed GCF volume of each strip was determined by electronic impedance (Periotron 8000, ProFlow Inc., Amityville, NY, USA). Samples that were suspected to be contaminated with blood and saliva were excluded from the study. After collection of the gingival fluid, the two periopaper strips/site that absorbed GCF from each subject were pooled and were immediately transferred

in microcentrifuge tubes (premarked with the biomarker name) containing $400 \mu L$ of phosphate buffer saline and stored frozen at $-70°C$ for subsequent analysis. Periodontal treatment (scaling and root planning) was performed for CP subjects at the same appointment after GCF collection by the operator (NK).

2.6. Blood Collection. Two milliliters of blood was collected from the antecubital fossa by venipuncture using a 20-gauge needle with 2 mL syringe and immediately transferred to the laboratory. The blood sample was allowed to clot at room temperature, and after 1 hour serum was separated from blood by centrifuging at 3000 rpm for 5 min. The serum was immediately transferred to a plastic vial and stored at $-70°C$ until the time of assay.

2.7. PGRN Analysis. The samples were assayed for PGRN using enzyme-linked immunosorbent assay (ELISA) kit according to manufacturer's instructions (Adipogen International Inc, Incheon, South Korea). The GCF sample tubes were first homogenized for 30 seconds and centrifuged for 5 minutes at 1,500 g to elute. The elute was then used as sample for ELISA estimation from GCF samples. A polyclonal antibody specific for human PGRN had been precoated onto 96 well microplate. Standards and samples were pipetted into the wells, and any PGRN present was bound byimmobilized antibody. Bound PGRN was captured by biotinylated anti-human PGRN polyclonal antibody. HRP conjugated strep-tavidin was added. After washing, a substrate solution was added. The colors developed in proportion to the bounded PGRN quantity. Colour development was monitored using a microplate reader until an optimum optical density was reached, a stop solution was added, and the optical density was read at 450 nm. The total PGRN was determined in nanograms (ng), and the calculation of the concentration in each sample was performed by dividing the amount of PGRN by the volume of sample (ng/mL).

2.8. hs-CRP Analysis. The samples for CRP were measured immunoturbidimetrically using RANDOX analyser. The microcentrifuge tubes containing the periopaper strips and plastic vials containing serum were transferred to the lab for immunoturbidimetric analysis. Serum was used undiluted. The measuring range of CRP is 0–220 mg/L, with the normal value of CRP being <5 mg/L [27].

3. Statistical Analysis

All data were analyzed using a software program (SPSS Inc. version 17.1, Chicago, IL, USA). Test for the validity of normality assumption using standardized range statistics was carried out, and it was found that the assumption is valid. Analysis of variance (ANOVA) was carried out for a comparison of GCF and serum levels of PGRN between the groups. Using Pearson's correlation coefficient, the relationship between PGRN levels and clinical parameters was analyzed using a software program. P values < 0.05 were considered statistically significant.

TABLE 1: Descriptive Statistics of study population (mean ± S.D.).

Study group	Group 1 ($n = 10$)	Group 2 ($n = 15$)	Group 3 ($n = 15$)
Age (in years)	34.22 ± 3.43	32.11 ± 3.21	33.12 ± 3.03
Sex (M/F)	5/5	8/7	7/8
GI	—	2.21 ± 0.54	2.15 ± 0.51
PD	2.42 ± 0.32	7.33 ± 1.32	8.12 ± 1.76
CAL	2.31 ± 0.12	6.34 ± 1.22	6.55 ± 1.52
Serum PGRN (ng/mL)	76.3 ± 2.34	197.3 ± 2.55	255.4 ± 2.65
GCF PGRN (ng/mL)	72.5 ± 2.11	183.6 ± 2.35	239.2 ± 2.42
Serum hs-CRP (mg/L)	1.9 ± 0.34	3.55 ± 0.14	5.59 ± 0.25
GCF hs-CRP (mg/L)	0.61 ± 0.13	0.86 ± 0.55	1.34 ± 0.22

4. Results

The descriptive statistics along with the mean ± SD of both serum and GCF (of all groups) are tabulated in Table 1. The mean hs-CRP and PGRN concentrations both in serum and GCF were the highest for group 3 followed by group 2 and the least in group 1. To find out the equality of means between the three groups, ANOVA test was carried out (Table 2). A significant difference in the serum and GCF levels of hs-CRP and PGRN was found between the 3 groups. The serum and GCF levels of PGRN were found to be significantly correlated ($P < 0.05$) to PD in groups 2 and 3. The serum levels of hs-CRP were found to be significantly correlated ($P < 0.05$) to PD in group 3. The GCF levels of hs-CRP were found to be significantly correlated ($P < 0.05$) to PD in group 2. Pearson, correlation coefficient test was applied to evaluate the correlation between serum levels of hs-CRP and serum levels of PGRN and also for their GCF values. Table 3 shows the correlation coefficients and P values. The correlations of the GCF and serum levels of the two biomarkers with clinical parameters are presented in Tables 4 and 5.

5. Discussion

Periodontal disease has been proposed as the sixth complication of diabetes, based on the highly frequent presence of both diseases in the same patient [28, 29]. Studies [30–32] showed that the prevalence and severity of periodontal disease are high in patients with DM. The putative theory is that the accumulation of advanced glycation end products induces the formation of proinflammatory cytokines (such as IL-1b) in hyperglycemia, and the cytokine-induced low-grade inflammation plays an essential role in the development of insulin resistance, which is a hallmark of type 2 DM [33] and is involved in the destructive process of periodontitis [34]. Likewise, periodontal pathogens secrete endotoxin that may increase the amount of inflammation markers, such as CRP, tumor necrosis factor alpha, and IL-6 [35, 36]. This study evaluated the serum and GCF concentrations of PGRN and hs-CRP that can be used as a marker of periodontal disease as well as a risk indicator for DM.

CRP levels were generally high in the group 2 and 3. This was reported to represent a higher DM risk for groups

TABLE 2: Results of ANOVA comparing the mean serum and GCF PGRN concentrations. between three groups.

Study groups	PGRN				hs-CRP			
	Serum		GCF		Serum		GCF	
	F-value	P value	F-value	P value	F-value	P value	F-value	P value
Group 1								
Group 2	248.1	<0.001*	215.2	<0.001*	112.4	<0.001*	25.4	<0.001*
Group 3								

*Significant at P value < 0.001.

TABLE 3: Correlation of serum and GCF PGRN and hs-CRP in each group using Spearman's rank correlation coefficient test.

Group	Serum		GCF	
	Correlation coefficient	P value	Correlation coefficient	P value
Group 1	0.36526	NS	−0.52301	NS
Group 2	0.12322	0.000*	0.46548	NS
Group 3	−0.46878	NS	−0.23332	NS

*Significant at P value < 0.05.
NS: not significant.

TABLE 4: Relationship of PGRN to clinical parameters.

	Parameters	Group 1	Group 2	Group 3
	GI	—	0.4234	0.7652
Serum	PD	0.3212	0.0068*	0.0088*
	CAL	0.0572	0.0325*	0.0322*
	GI	—	0.5124	0.7826
GCF	PD	0.2246	0.0005*	0.0082*
	CAL	0.4235	0.0687	0.0422*

*Significant at P value < 0.05.

TABLE 5: Relationship of hs-CRP to clinical parameters.

	Parameters	Group 1	Group 2	Group 3
	GI	—	0.8484	0.8261
Serum	PD	0.7456	0.0038*	0.4261
	CAL	0.2384	0.0927	0.5231
	GI	—	0.0854	0.2235
GCF	PD	0.2667	0.2877	0.0665
	CAL	0.0000*	0.1667	0.0242*

*Significant at P value < 0.05.

with chronic periodontitis and groups without it. However, because the group with chronic periodontitis showed CRP levels greater than the levels in the group without chronic periodontitis, it is possible that a greater activity of periodontitis may have been responsible for these differences, particularly among individuals with a profile of high degrees of inflammation.

PGRN is a multifunctional protein that has gained attention in the neuroscience field, because of the discovery that frontotemporal dementia is associated with PGRN mutations in some subjects [37]. The physiological function of PGRN is complex, with the full-length form of the protein having trophic and anti-inflammatory activity, whereas proteolytic cleavage generates granulin peptides that promote inflammatory activity [38]. In the periphery, PGRN promotes wound healing by increasing the accumulation of neutrophils, macrophages, and other cells in wounds [15]. PGRN plays a role in the association between obesity, type 2 diabetes, and inflammatory response.

ELISA estimation of serum and GCF PGRN levels was done, and hs CRP concentrations were estimated by immunoturbidimetry method. PGRN and hs-CRP serum and GCF concentrations are not different in men and women and do not seem to be age dependent. PGRN and hs CRP levels correlate with PD and CAL. The results of the present study indicated that concentrations of PGRN and hs CRP in serum and GCF increased progressively from healthy to periodontitis sites, while in periodontitis sites in diabetes subjects the mean concentration of PGRN was higher than the concentrations obtained in groups 1 and 2, suggesting that these markers reflect chronic inflammation as the periodontal disease advances from health to chronic periodontitis, and their levels are much higher in chronic periodontitis subjects with DM. The results of the present study are in accordance with those of previous study in which serum PGRN levels were elevated in diabetic subjects [17]. The increase in serum and GCF concentrations of hs-CRP from health to chronic periodontitis to chronic periodontitis with DM in the present study is in accordance with a previous study [39]. We further found significant relationship between PGRN and hs-CRP concentrations. In a recently conducted cross sectional study, the levels of PGRN and hs-CRP were assessed in serum and GCF of obese and health individuals with and without periodontitis. We found that the levels of these two inflammatory markers were the highest in obese periodontitis subjects followed by nonobese chronic periodontitis individuals and the least in nonobese individuals [40]. This is the first study evaluating and correlating hs-CRP and PGRN in chronic periodontitis with and without DM, and our data therefore suggest an association between CRP and PGRN levels and demonstrate that PGRN and hs CRP may be biomarkers of the chronic inflammatory response in DM and chronic periodontitis.

6. Conclusion

Thus within the limits of the current study, PGRN and hs-CRP levels may be markers of chronic inflammatory response in chronic periodontitis and type 2 DM. Further

longitudinal prospective studies involving a larger population are needed to confirm the findings of the present study, to better understand the role of these markers in the pathogenesis, and also to address the clinical implication and pathological mechanism of the markers in periodontal disease progression.

Acknowledgment

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