Adrenomedullin, periodontitis, diabetes-unraveling the equivocal relationship: A clinicobiochemical cross-sectional study

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Abstract

Context: Antimicrobial proteins and peptides constitute a diverse class of host-defense molecules that act early to combat invasion and infection with bacteria and other microorganisms. Among the various antimicrobial peptides in the oral cavity, adrenomedullin (ADM), a cationic peptide, is found in gingival crevicular fluids (GCFs) in amounts twice as high in periodontal disease sites as healthy sites. Studies have also shown that plasma levels of ADM increased in patients with type 2 diabetes mellitus as compared with controls. **Aims:** This clinico-biochemical study was undertaken to try to decipher the probable link between ADM, diabetes and periodontitis. **Materials and Methods:** The study comprised of 90 patients who were divided into three groups based on community periodontal index scores and diabetes status. Probing pocket depth and clinical attachment level were measured in all subjects. GCF was collected from all the participants using micropipettes and blood samples were collected from subjects in Groups III, for analysis of glycated hemoglobin. ADM levels were measured in GCF samples by the enzyme-linked immunosorbent assay. **Statistical Analysis Used:** The data obtained were subjected to analysis of variance, Bonferroni test and Pearson's correlation. **Results:** An increase in GCF levels of ADM from periodontal health to disease and in periodontitis patients with type 2 diabetes was noted. **Conclusions:** Increase in GCF levels of ADM from periodontal health to disease and in periodontitis patients with type 2 diabetes reinforces the perio-systemic interlink concept.

Keywords: Adrenomedullin, gingival crevicular fluid, periodontitis, type 2 diabetes

Introduction

Antimicrobial proteins and peptides constitute a diverse class of host-defense molecules that act early to combat invasion and infection with bacteria and other microorganisms.[1] Oral epithelial cells, neutrophils and salivary glands secrete at least 45 known antimicrobial gene products that are found in saliva. A subset of these antimicrobial peptides is also found in gingival crevicular fluid (GCF). Indeed, all antimicrobial peptides found in GCF are also found in saliva. Several antimicrobial peptides are more highly concentrated in GCF than in saliva.[1] Multiple antimicrobial peptides with different minimal inhibitory concentrations act on oral microbes.[2] The various functional families of antimicrobial peptides in the oral cavity include; cationic peptides, neuropeptides, antimicrobial peptides showing bacterial agglutination and adhesion, metal ion chelators, protease inhibitors, activity against bacterial cell wall.[1]

Among the various antimicrobial peptides in the oral cavity, adrenomedullin (ADM), a cationic peptide, is found in GCF in amounts twice as high in periodontal disease sites as healthy sites.[3] This 185 amino acid protein is proteolytically processed and C-terminally amidated to produce the 52 amino acid mature ADM, a cationic amphipathic peptide with one disulfide bond.[1] It is found in GCF and glandular and whole saliva. Whole saliva contains higher concentrations of ADM than glandular saliva, suggesting that oral epithelial cells contribute to the salivary expression.[4] Epithelial cells also secrete ADM when they are exposed to various bacterial species and inflammatory cytokines.[5] In addition to the antibacterial role of ADM, it creates a feedback mechanism to activate the inflammatory response to pathogens.[6] ADM has vasodilator effects and might increase the numbers of inflammatory cells and mediators in inflamed gingival tissue.[6]

Periodontal diseases are a group of inflammatory lesions affecting the tissues surrounding and supporting the teeth in their sockets.[7] The interactions between the host defense mechanism and microbial challenge are important factors for the susceptibility of the host to periodontitis.[8] ADM, which is constitutively expressed and secreted by oral epithelial cells, is an important antimicrobial peptide having a role in the innate host defense.[3] It is found to be active against *Porphyromonas gingivalis* (Minimum Inhibitory

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Concentration MIC 7.75×10^{-4} μg/ml),[9] which is an important periodontopathogen, and *Streptococcus mutans* (MIC 12.5 μg/ml).[1] The probable protective role of ADM in periodontitis is a scant researched avenue and which, if explored, may provide with templates for design of effective antibiotics against oral microbes.

Studies have also shown that plasma levels of ADM increased in patients with type 2 diabetes mellitus as compared to controls and also its levels have been found to be increased significantly in subjects with complications of type 2 diabetes mellitus.[10]

Periodontal disease and diabetes is like a two-way street. Evidence in the literature supports the role of inflammation as a major component in the pathogenesis of diabetes and diabetic complications as well as periodontitis.[11] The elevated levels of ADM in both diabetes and periodontitis bespeak of a tenable, but ambiguous role of this antimicrobial peptide in linking the disease processes.

There is a paucity of studies evaluating and comparing the levels of ADM in healthy, periodontitis and periodontitis with type 2 diabetes patients. This clinico-biochemical study was undertaken to overcome this paucity and to try to decipher the probable link between ADM, diabetes and periodontitis.

Materials and Methods

Sources of data

Ethical clearance for the study was received from the Institutional Ethical Committee and Review Board, DAPMRV Dental College, Bengaluru, India. The data was collected over a period of 1½ years, spanning from December 2011 to May 2012, from subjects visiting the out-patient section of Department of Periodontics, DAPMRV Dental College, Bengaluru, India. Written informed consent was obtained from all patients. Patients with age range of 35-75 years were included in this study and comprised of both sexes. Exclusion criteria were patients with systemic diseases such as type 1 diabetes mellitus, cardiovascular disorder, immunologic disorders, hepatitis and human immunodeficiency virus infections, smokers, pregnant and lactating women and those taking oral contraceptive drugs or any anti-inflammatory or corticosteroids drugs. Subjects who had received antibiotics or treatment for periodontal disease in the 6 months preceding the study were also excluded.

A total of 90 subjects were divided into three groups on the basis of their glycemic control (as indicated by glycated hemoglobin level) and based on their periodontal status assessed using the community periodontal index CPI index, recorded using a community Periodontal Index for Treatment Needs-C probe.

The criteria for the CPI are as follows:
Code 0: Colored band of the probe remains completely visible in the deepest sulcus of the sextant - healthy.

Code 1: Colored band of the probe remains completely visible in the deepest sulcus of the sextant, some bleeding after gentle probing.

Code 2: Colored band of the probe still completely visible, but there is bleeding on probing, supragingival or subgingival calculus and/or defective margins are present.

Code 3: The colored band is partially submerged. Pocket 4-5 mm deep.

Code 4: The colored band completely disappears in the pocket, indicating a depth greater than 5.5 mm and a loss of attachment of 3 mm or more.

Code X: Excluded sextant.

Code 9: Not recorded.

Criteria for subject grouping

Group I (healthy): Consisted of 15 subjects with clinically healthy periodontium with no evidence of disease. CPI score 0.

Group II (periodontitis): Consisted of 30 subjects with a CPI score of 3 or more.

Group III (periodontitis with type 2 diabetes): Consisted of 45 diabetic subjects, who showed CPI score of 3 or more. The hemoglobin A1c (HbA1c) value was more than 6.

In Group I, the sample size was restricted to 15, due to resource and financial constraints and owing to the fact that ADM levels does not seem to significantly vary in the healthy subjects and thus would not significantly affect the results. Group III comprised of patients with different glycemic controls; the sample size was equivalent to the sum of Groups I and II to encompass the groups with varying glycemic levels.

Clinical evaluation of subjects

Initial clinical examination consisted of recording the demographic data, brief history of diabetes, dental and periodontal examination. The participants were then categorized to different groups based on their CPI score and HbA1c scores. In subjects with periodontitis, the site with the highest CPI score was chosen for GCF collection. In the healthy group, to standardize site selection and obtain adequate fluid volume, sampling was predetermined to be from the mesio-buccal region of the maxillary right first molar, in the absence of which the left first molar was sampled.

Procedure for sample collection

Method of collection of blood

Patients were comfortably seated and the procedure was explained once again before collection of blood. The left antecubital fossa was swabbed with an alcohol swab and a cuff was used to apply pressure above the fossa. Blood was drawn using a 5 ml syringe and immediately transferred to a vacutainer. HbA1c was estimated by the turbidimetric inhibition assay method.

Clinical examination

After the selection of patients based on CPI score, all the participants underwent a detailed periodontal examination for the measurement of probing pocket depth (PPD) and clinical attachment level (CAL) using a University of North Carolina Probe (UNC-15 probe).

Method of collection of GCF

Any loosely adherent debris or supragingival calculus at the test site, if present, was removed as the first step in GCF collection. The site was then dried and isolated with cotton rolls. Samples of GCF were obtained from the pre-determined sites by placing calibrated, volumetric, micro capillary pipettes with 0-5 µl range. The micropipettes were placed at the entrance of the gingival crevice and 2-3 µl of GCF was collected from each subject. The pipettes contaminated with blood/saliva were discarded and the process was repeated with a different pipette. The GCF was transferred into vials containing 100 µl phosphate buffer saline and the samples were frozen at −70°C until they were assayed for ADM.

Measurement of ADM levels

The colorimetric assay procedure was done at the Department of Microbiology, Maratha Mandal's Nathajirao G Halgekar Dental College, Belgaum. The ADM levels were measured using a commercially available colorimetric assay kit for human ADM enzyme-linked immunosorbent assay (ELISA kit, Bio-medical Assay, Beijing China).

Statistical analyses

All data were analyzed using a software program Statistical Package for the Social Sciences (SPSS, version 14.0, SPSS, Chicago, IL). Analysis of variance (ANOVA) was carried out to test the hypothesis of equality among the three groups for ADM. Multiple comparisons for ADM levels using Bonferroni test was carried out to find out which pair or pairs differ significantly. Pearson's correlation coefficient test was used to observe any correlation between the clinical parameters recorded i.e. PPD, CAL, HbA1c and GCF ADM levels.

Results

PPD and CAL

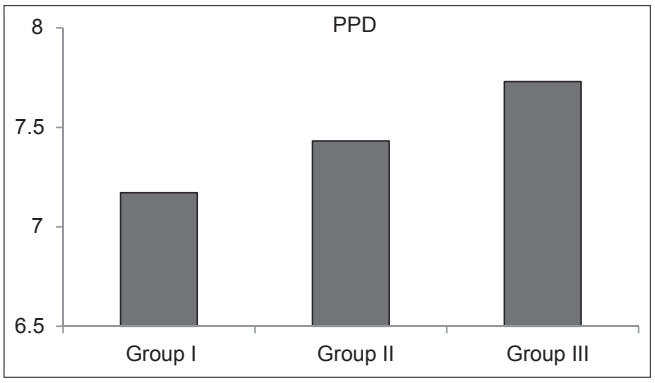
The mean PPD and CAL for Groups I, II and III were 7.172, 7.432, 7.733 and 0.4, 5.098, 6.019 respectively [Graphs 1 and 2].

ADM concentrations

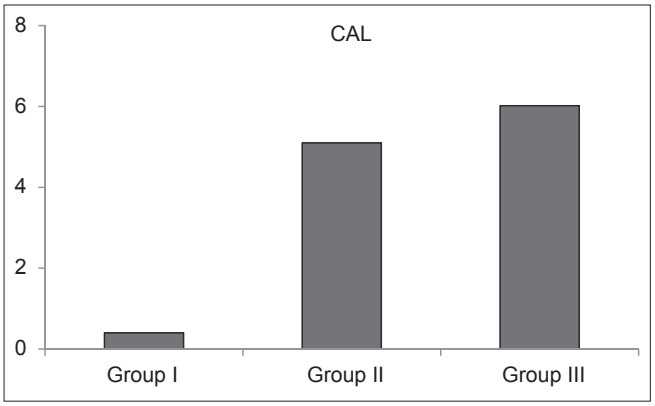
The mean ADM levels for Group I to Group III were 13.637, 25.22 and 38.667 µmol/l [Table 1 and Graph 3] respectively. ANOVA was carried out to test the hypothesis of equality among the three groups, the results of which are tabulated in Table 2. The *F* value obtained was 99.488 with $P < 0.001$. Hence the hypothesis of equality of means for levels of ADM in GCF was rejected at 5% level of significance ($P < 0.05$), indicating that the means among the various groups differ significantly.

Correlations

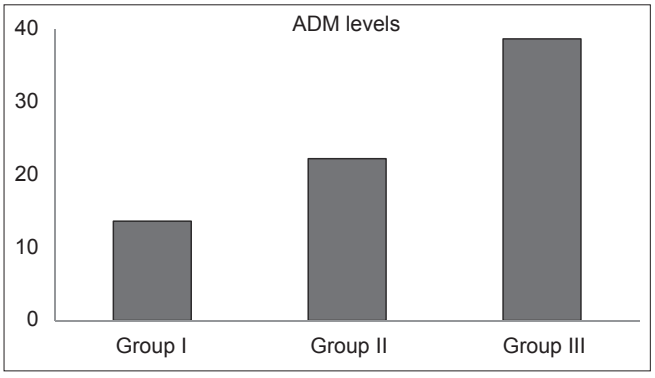
Pearson's correlation coefficient test was used to observe any correlation between the clinical parameters recorded i.e. PPD,



Graph 1: Mean probing pocket depth



Graph 2: Mean clinical attachment level



Graph 3: Mean adrenomedullin levels

CAL, HbA1c and GCF ADM levels. ADM was found to be positively correlated with PPD, CAL in Groups II and III and also with HbA1c in Group III. In Group I, a positive correlation of ADM with PPD and a negative correlation of ADM with CAL were found.

The correlations were found to be statistically significant between ADM and PPD in all groups except Group I. For ADM and CAL the correlation was found to be statistically significant for Groups II and III. A statistically significant correlation between ADM and HbA1c in Group III was found [Table 3].

Discussion

Gingivitis and periodontitis are chronic inflammatory diseases of the periodontium. The interaction of micro-organisms with the host determines the course and severity of the resulting disease. The fundamental event in the transition from gingivitis to periodontitis is the loss of soft tissue attachment of the tooth and subsequent loss of alveolar bone. Systemic diseases like diabetes mellitus often exacerbate this destructive process. Diabetes mellitus and periodontal disease are two common chronic diseases that have long been considered to be biologically linked.

Table 1: Analysis showing mean values and SD for adrenomedullin levels (µmol/l)

Groups	Mean±SD
I	13.637±2.921
II	22.225±4.899
III	38.667±7.591

SD: Standard deviation

Table 2: Results of ANOVA test comparing the mean adrenomedullin levels (µmol/l) between all the groups

Groups	*n*	ANOVA *F* value	*P* value
I	15	99.488	<0.001*
II	30		
III	45		

**n* denotes number of samples; *Significant at *P*<0.05; ANOVA: Analysis of variance

Table 3: Pearson's correlation co-efficient test comparing ADM levels (µmol/l) with PPD, CAL and HbA1c

Groups	ADM and PPD		ADM and CAL		ADM and HbA1c	
	r	*P* value	*r*	*P* value	*r*	*P* value
I	0.051	0.855	−0.083	0.769	-	-
II	0.743	<0.001*	0.745	<0.001*	-	-
III	0.865	<0.001*	0.765	<0.001*	0.694	0.005*

PPD: Probing pocket depth; CAL: Clinical attachment level; ADM: Adrenomedullin; HbA1c: Hemoglobin A1c; *Significant at *P*<0.05

It is generally accepted that much of the periodontal tissue destruction observed in periodontitis is host-mediated through release of proinflammatory cytokines by local tissues and immune cells in response to the bacterial flora and its products/metabolites, especially lipopolysaccharides. Antimicrobial peptides including defensins, cathelicidin and ADM are important contributors for maintaining the balance between the healthy and diseased conditions of the oral cavity.[8,12] These peptides are an important part of the host innate immune response in gingival tissues.[2]

Literature shows studies which have evaluated the ADM levels in GCF of periodontitis patients and serum of diabetic patients.[13-16] There are scarcely any studies reporting levels of GCF ADM levels in periodontal disease and type 2 diabetes mellitus. Thus, this study was undertaken to estimate and compare the ADM levels in GCF from subjects with clinically healthy periodontium, periodontitis patients and periodontitis patients with impaired glycemic controls.

The study consisted of 90 subjects with age ranging from 35 to 75 years. Age is a significant factor for periodontal disease as the prevalence of periodontal disease increases rapidly with age and also most people with type 2 diabetes belong to this age group.[17,18] This age range is in accordance with other studies.[19,20]

Patients were divided into three groups Group I to Group III based on their periodontal disease status and glycated hemoglobin levels. Glycated hemoglobin indicates the glucose status during at least half the life of RBC i.e. 30-90 days. Thus, HbA1c estimates the glycemic control of patients over the preceding 3 months.[20]

CPI score has been used for the screening of periodontal disease in this study as it is a practical method for routine screening and recording of periodontal disease indicators.[21]

The composition of GCF is the result of interplay between the bacterial biofilm and cells of the periodontal tissues. In the present study GCF was collected by the extra crevicular method which has an advantage of being non-invasive as compared to gingival biopsies.[22] Analysis of special constituents in the GCF provides a qualitative biochemical indicator for evaluation of local cellular metabolism that clearly reflects the existing periodontal status. Furthermore, the concentrations ADM are enriched about 30-fold in GCF as compared to saliva.[1]

Microcapillary pipettes were used for collection of GCF samples in this study to avoid non-specific attachment of the analyte to filter paper fibers, ensuing in false reduction in the detectable ADM levels that, in turn, can underestimate the correlation of ADM levels to disease severity. Microcapillary pipettes facilitated the collection of a standardized GCF

volume of 3 µl for all the subjects, as required for the biochemical analysis of GCF.

GCF was collected from the mesio-buccal region of the maxillary right first molar in healthy subjects, in the absence of which the left first molar was sampled. This site was selected as adequate fluid volume could be obtained from this site. In case of periodontitis patients, the site with deepest probing depth was selected for GCF collection.

Colorimetric ELISA assay was performed on the collected samples and the results were analyzed to estimate and to compare the levels of ADM in periodontal health and disease and periodontitis patients with type 2 diabetes.

results of the present study reported that levels of ADM in GCF increases progressively from healthy (13.637 ± 2.921 µmol/l) to periodontitis subjects (22.225 ± 4.899 µmol/l); and to an even greater value in periodontitis subjects with diabetes (38.667 ± 7.591). Studies by Lundy *et al*. and Türkoğlu *et al*.[3,13] have also reported an increase in the levels of ADM in patients with periodontitis.

More severe inflammation and periodontal destruction and an increase of bacteria-stimulated ADM production by epithelial cells to protect the host from bacterial invasion may be the reason behind the elevated ADM levels seen periodontitis.[23] However, the elevated ADM levels have been found to be inefficient in protecting the periodontal tissues against the disease induced destruction. This may be because *P. gingivalis*, which is an important periodontopathogen for chronic periodontitis, is able to defend against the antimicrobial effect of ADM.[24]

In this study, the level of ADM in GCF was found to increase from non-diabetic subjects (Groups I and II) to type 2 diabetic subjects (Groups III). Turk *et al*. examined 64 type 2 diabetic patients and 20 healthy subjects as control group and found that plasma ADM levels were significantly elevated in patients with type 2 diabetes when compared with the control group.[16]

Studies have shown that individuals with type 2 diabetes were at a higher risk for vascular injury due to the endothelial dysfunction and ADM, which is produced by the endothelium, has vasoprotective (vasodilating and anti-proliferative) properties, so the rise in ADM GCF levels in type 2 diabetic patients can be due to hyperglycemia induced increased expression of ADM.

The higher level of ADM at sites with periodontitis in subjects with impaired glycemic control raises the questions; did the diabetic process and periodontal disease process contribute to rise in ADM? Did ADM contribute to the impaired glycemic control and subsequent periodontal disease?

Perhaps, periodontal destruction and diabetes have a synergistic effect in elevating the ADM levels, though at present, this link cannot be completely confirmed. It still remains unclear whether ADM levels are influenced by or influences diabetes severity, or, the circulating ADM gets influenced by the severity of periodontitis.

The results of this study shows statistically significant relationship between ADM and PPD and CAL in all the groups except in healthy group, which is in accordance with the other studies.[13] The variability of ADM concentrations within the patients of each group may be attributed to the response of ADM to increasing severity of both periodontal disease and presence of diabetes.

The limitation of this study is its small sample size. Study on a larger population is required to arrive at a more definitive conclusion. The study did not eliminate the confounding influence of obesity. This is important as ADM is found be higher in obese individuals than in non-obese individuals. In addition, the ADM levels have not been evaluated separately in patients with different glycemic controls, which would have helped further in elucidating the role of ADM in glycemic control and duration of diabetes in the subjects has also not been taken into consideration.

Conclusion

Based on the above study, it can be concluded that ADM is present in GCF in periodontal health and disease and there is a substantial increase in the levels of ADM in GCF in periodontitis and periodontitis with type 2 diabetes mellitus. Significant correlation was seen between PPD and CAL and ADM levels in GCF in all the periodontitis patients with or without type 2 diabetes and between HbA1c and ADM levels in GCF of type 2 diabetic periodontitis patients.

The question of whether ADM level is influenced by the severity of diabetes and periodontitis and whether the increase in ADM levels is a defensive mechanism against the disease processes needs to be probed further.

The possible role of ADM in GCF as an antibacterial factor and the function it plays in the protection against microvascular disturbance in diabetic patients also has to be elucidated.

Further longitudinal studies with large sample size are needed to validate ADM as a marker in periodontal disease and diabetes progression and to clarify the ambiguity of its role in periodontal disease and type 2 diabetes mellitus.

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