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Comparison of the Serum and Salivary Levels of NT-proBNP in Systemically Healthy Subjects with Mild, Moderate and Severe Chronic Periodontitis

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Original Article

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ABSTRACT

Background: To assess and compare the serum and salivary levels of NT-pro BNP in otherwise systemically healthy subjects with mild, moderate, and severe chronic periodontitis.
Methods: The subjects for this study were selected from the Out-patient Department of Periodontology, Meenakshi Ammal Dental College and Hospital, Chennai. A total of 24 subjects were selected and divided into three groups which included Group I with6periodontally and systemically healthy subjects, Group II with 6

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systemically healthy subjects with mild chronic periodontitis, Group III with 6 systemically healthy subjects with moderate chronic periodontitis, and group IV with 6 systemically healthy subjects with severe chronic periodontitis. After measuring the periodontal parameters, blood and saliva samples were collected and the levels of NT-proBNP were estimated using an ELISA kit (Abbkine).

Results: The mean value of plaque index, modified gingival index, probing pocket depth and clinical attachment level were higher in Group II, Group III, and Group IV compared to Group I. The mean value of NT-proBNP increased with the increasing severity of the periodontal disease. Intergroup comparison of the mean difference of serum and salivary NT-proBNP levels was found to be statistically significant. Karl Pearson correlation analysis between salivary and serum NT-proBNP and other parameters like plaque index, modified gingival index, probing pocket depth, and clinical attachment level showed a very strong positive correlation ($P<0.001$).

Conclusion: Our findings suggest that serum and salivary NT-pro-BNP could serve as a potential biomarker for periodontitis. Further studies are required to explore the mechanism and to understand the cause-effect relationship between NT-proBNP and periodontitis.

Keywords: Biomarkers, Natriuretic Peptides, Periodontal Disease; NT-proBNP.

Introduction

The multispecies bacterial community established in the subgingival environment leads to periodontitis, which is a chronic tissue-destructive inflammatory disease. These microorganisms induce the release of pro-inflammatory mediators, which can act at the local or systemic level. The strong association of cardiovascular disease (CVD) and ischemic stroke with periodontitis is due to the low-grade chronic systemic inflammation posed by periodontitis. Patients with periodontitis show elevated levels of known CVD-associated biomarkers, such as fibrinogen, C reactive protein (CRP), interleukin-6, and pentraxin-3 in their serum.[1]

The biomarker implicated in the pathophysiology of CVD, with diagnostic and prognostic significance is the natriuretic peptides, which are also found in increased concentrations in the plasma of patients with congestive heart failure.[2] The hormones secreted from the heart with important blood-pressure-lowering properties, that is, natriuretic, diuretic, and/or kaliuretic properties are the natriuretic peptides. They comprise at least eight amino acid peptides structurally related and stored as prohormones in three different forms: atrial natriuretic peptide (ANP) prohormone (126 amino acid), B-type natriuretic peptide (BNP) prohormone (108 amino acid), and C-type natriuretic peptide (CNP) prohormone (126 amino acid).[3]

ANP, BNP, and CNP are the three biologically active peptides derived from these prohormones. The first identified member of the natriuretic peptide family was ANP. This peptide hormone was discovered in 1983–1984. The BNP and CNP were then isolated several years later from porcine brain tissues.[4]

ANP and BNP were primarily produced in the cardiac tissue. Within target tissues, they bind preferentially to the natriuretic peptide receptor-A (NPR-A) or guanylyl cyclase-A and exert similar effects by increasing the intracellular levels of cyclic guanosine monophosphate (cGMP). Not only do several factors trigger the production and secretion of ANP and BNP, but they are also regulated via multiple signalling pathways.[5]

BNP is released mainly from the cardiomyocytes in the heart ventricles in response to an increase in myocardial wall stress which in turn is caused due to increased ventricular blood volume. BNP is a prohormone that is cleaved into 2 peptides: the active hormone, BNP, and N-terminal-pro-BNP (NT-proBNP),

which is biologically inactive. The serum NT-proBNP could be a viable biomarker of CVD due to its longer half-life compared to the active form. Among the natriuretic peptides, it is the concentration of the NT-proBNP in the plasma that helps in the diagnosis and treatment monitoring of patients with congestive heart failure.[6]

The levels of NT-proBNP could help to diagnose heart failure and correlate with the functional status in patients with congestive heart failure. In addition, this peptide is related to an increased risk of cardiovascular events, cerebral ischemia, and all these cause mortalities.[7]

It is also noted that serum NT-proBNP levels are often elevated in response to inflammatory and infectious stimuli, such as lipopolysaccharide. Owing to this, the expression of BNP could be regulated by systemic inflammatory mediators. Cardiocyte BNP expression therefore might be stimulated by several proinflammatory cytokines, like interleukin-1β, interleukin-6, and TNF-α. NT-proBNP has also been related to disease activity in rheumatoid arthritis patients. Serum NT-proBNP levels also appear to be increased because of systemic inflammation in patients without cardiac dysfunction.[8]

Research in the past has demonstrated the association between periodontitis and CVD. However, there exists only a little knowledge of the relationship between this peptide, disease of the periodontium, and CVD9. Hence, the aim of this study was to evaluate if the serum and salivary levels of NT-proBNP are increased in otherwise systemically healthy subjects with periodontal disease and to correlate it with periodontal disease severity.

Materials and Methods

Study Design

The subjects for this study were recruited from the outpatient Department of Periodontology, Meenakshi Ammal Dental College and Hospital, Chennai. A total of 24 systemically healthy subjects were selected, out of which 6 were periodontally healthy. Among the remaining, 6 each had mild, moderate, and severe chronic periodontitis. The study was approved by the "Institutional Review Board", MAHER - Deemed to be University, Chennai. The subjects were explained about the study and written informed consent was obtained from those volunteers who agreed to participate in this study.

Study population

The patients included in this study were those who were willing to participate in the study and subjects in the age range of 35 - 55 years, having at least 10 teeth. The Control group included subjects who were systemically and periodontally healthy (Group I), mild chronic periodontitis group included subjects who were systemically healthy, with signs of clinical inflammation in more than two sites in different quadrants and clinical attachment loss (AL) 1-2 mm, and radiographic evidence of bone loss (Group II), moderate chronic periodontitis group included subjects who were systemically healthy with signs of clinical inflammation in more than two sites in different quadrants and clinical attachment loss (AL) 3-4 mm, and bone loss evident on a radiograph (Group III) and severe chronic periodontitis group included subjects who were systemically healthy with signs of clinical inflammation in more than two sites in different quadrants and clinical attachment loss (AL) ≥ 5 mm, and bone loss evident on a radiograph (Group IV).

Subjects were excluded if they were pregnant or lactating, had a smoking habit, those who had taken any medication which can affect the periodontal status during the past 1 month, and those who were treated for periodontal disease during the past 6 months.

University of North Carolina -15 (UNC-15) probe was used for measuring the parameters and the values were recorded to the nearest millimetre. The following periodontal parameters assessed werePlaque Index (Silness and Loe, 1964)10, Modified gingival index (Lobene et al.,1986)11, Probing Pocket Depth (PPD), and Clinical Attachment Level (CAL).

Sample Collection

After the periodontal parameters were measured saliva and serum samples were collected from all the subjects. 2mL of blood was collected from the antecubital fossa by venepuncture using a 20-gauge needle and a 5mL syringe. The test tube containing blood was centrifuged at 3000 rpm for 15 minutes at 4oC to separate the serum. The separated serum was stored at − 800C in an Eppendorf tube until the time of assay.

To standardize the collection of saliva according to the circadian rhythm, 5ml of unstimulated whole saliva was collected in the morning, two hours after the last meal. The subjects were advised to rinse thoroughly with distilled water before sample collection. They were instructed to let the saliva pool on the floor of the mouth and then expectorate into the collecting vessel till the desired quantity of saliva was collected. The saliva was then transferred to Eppendorf tubes, centrifuged at 1000 rpm for 1 minute, and stored at – 800 C until the time of assay.

NT-proBNP analysis

Saliva and serum samples were analysed for NT-proBNP using the HumanNT-proBNP enzyme-linked immunosorbent assay (ELISA) kit (Abbkine) according to the manufacturer's instructions. All standard solutions and samples were prepared and brought to room temperature before starting the assay procedure. 40 µL of the sample diluent was added to the testing sample well. Then 10 µL of the sample was added to the testing sample well. This was covered with a plate cover and incubated for 45 minutes at 37˚C. Each well was washed four times, 1-3 minutes per time using 250 µL of wash buffer. 50 µL of HRP-Conjugated detection antibody was then added. This was covered with a plate cover and incubated for 30 minutes at 37˚C. The wash process was repeated.50 µL of Chromogen solution A and 50 µL chromogen solution B was added to each well, gently mixed, and incubated for 15 minutes at 37˚C.50 µL of Stop Solution was added to each well after which the colour in the wells changed from blue to yellow. The Optical Density was measured using an ELISA plate reader (LABSERV) at 450 nm.

Statistical Analysis

Statistical analysis was done using SPSS software (IBM SPSS Statistics for Windows, Version 26.0, Armonk, NY: IBM Corp. Released 2019). The Normality test Kolmogorov-Smirnov and Shapiro-Wilks test results revealed that all variables followed a normal distribution. Therefore, to analyse the data parametric methods were applied. To compare the mean values between groups, one-way ANOVA was applied followed by Tukey's HSD post hoc tests for multiple pairwise comparisons. Karl Pearson correlations were calculated to assess the linear relationship between clinical variables. Significance level was fixed as 5% ($\alpha = 0.05$).

Results

In this study, a total of 24 patients within the age group of 35-55 years were assessed. The mean and standard deviation values of all the clinical parameters in all groups are listed in **Table 1**. The mean value of all the clinical parameters was higher in groups II, III, and IV when compared to group I.

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Variable	Groups	N	Mean ± Std. Dev
Plaque Index	Group -I	6	0.35 ± 0.08
	Group -II	6	1.37 ± 0.15
	Group -III	6	2.24 ± 0.19
	Group -IV	6	2.78 ± 0.23
Modified Gingival Index	Group -I	6	0.08 ± 0.07
	Group -II	6	0.61 ± 0.10
	Group -III	6	2.53 ± 0.22
	Group -IV	6	3.48 ± 0.14
Probing pocket Depth (mm)	Group -I	6	2.06 ± 0.09
	Group -II	6	4.12 ± 0.19
	Group -III	6	5.16 ± 0.35
	Group -IV	6	6.85 ± 0.56
Clinical Attachment Level (mm)	Group - I	6	2.06 ± 0.09
	Group -II	6	4.33 ± 0.26
	Group -III	6	5.47 ± 0.42
	Group -IV	6	8.03 ± 0.67

Table 1: Mean and Standard Deviation of periodontal parameters in Group I, II, III and IV.

The mean salivary and serum NT-proBNP levels are shown in **Table 2**. Comparison of all 4 groups showed that group I had significantly lower levels of NT-proBNP levels when compared to groups II, III, and IV. The value of NT-proBNP in serum and saliva increases as the severity of the periodontal disease increases.

Variable	Groups		Mean Difference	p-value
Salivary NT-proBNP levels (pg/mL)	Group I	Group II	-5.45	0.033*
		Group III	-25.03	0.002*
		Group IV	-38.72	<0.001*
	Group II	Group III	-19.58	<0.001*
		Group IV	-33.27	<0.001*
	Group III	Group IV	-13.68	<0.001*
Serum NT-proBNP levels (pg/mL)	Group I	Group II	-27.37	<0.001*
		Group III	-45.10	<0.001*
		Group IV	-74.37	<0.001*
	Group II	Group III	-17.73	0.001*
		Group IV	-47.00	<0.001*
	Group III	Group IV	-29.27	<0.001

Table 2: Intergroup Comparisons of mean differences between salivary and serum NT-pro BNP among Group I, II, III and IV.

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The value of correlation between salivary NT-proBNP and serum NT-proBNP for plaque index, modified gingival index, probing pocket depth and clinical attachment level showed a very strong positive correlation. Similarly, the value of correlation between the salivary and serum NT-proBNP levels was 0.948(p <0.001) which was statistically significant. This indicates a very strong positive correlation between the salivary and serum NT-proBNP levels (**Table 3**).

Variable		Salivary NT-proBNP levels (pg/mL)	Serum NT-proBNP levels (pg/mL)
Plaque Index	Correlation	0.922	0.937
	P-value	<0.001[a)]	<0.001[a)]
Modified Gingival Index	Correlation	0.981	0.931
	P-value	<0.001[a)]	<0.001[a)]
Probing Pocket Depth (mm)	Correlation	0.9507	0.9970
	P-value	<0.001[a)]	<0.001[a)]
Clinical Attachment Level (mm)	Correlation	0.9565	0.9988
	P-value	<0.001[a)]	<0.001[a)]
Salivary NT-proBNP levels (pg/mL)	Correlation		0.948
	P-value		<0.001[a)]

[a)]statistically significant

Table 3: Karl Pearson Correlation analysis between salivary and serum NT-proBNP levels and all variables.

Discussion

Periodontitis produces a biological burden due to the release of endotoxin and inflammatory cytokines into the blood stream which initiates inflammatory, atherogenic and thromboembolic events. Inflammatory activation has been recognized in congestive heart failure (CHF) patients regardless of its underlying cause, indicating a probable association between periodontitis and CHF. Smoking, diabetes mellitus, alcohol consumption, hypertension, and low socioeconomic status are some of the common risk factors for periodontitis and CHF.[12]

The regulation of cardiovascular homeostasis and extracellular fluid volume is an important role of the natriuretic peptide family. The natriuretic peptide system consists of at least three structurally homologous peptides, including ANP, BNP, and CNP.[13] The primary effect of these hormones is to maintain cardiovascular homeostasis by affecting central and peripheral hemodynamics. The intravascular volume is influenced by vasodilatory, diuretic and natriuretic effects of the three natriuretic peptides. The levels of NT-proBNP (76 AA) or BNP (32 AA) in serum can be used to diagnose heart failure (HF).[14]

Inflammation has been previously linked to high NT-proBNP and BNP levels have also been linked to patients with sepsis, patients with endocarditis, and in longitudinal studies in patients with rheumatoid arthritis. The relationship between inflammation and NT-pro BNP, in sepsis and septic shock, can be due to the hemodynamic stress experienced by these patients. In patients admitted in critical care units, hemodynamic stress due to inflammation may lead to increased NT-proBNP levels, and there exists a relationship between NT-proBNP levels and unfavorable consequences. Therefore, inflammation through its effect on hemodynamic load results in a correlation between the levels of CRP and BNP or NT-proBNP. However, in the

case of rheumatoid arthritis, the increased level of NT-proBNP is due to the stimulation of various cytokines like IL-1β or TNF-α.[15]

Periodontal microorganisms evoke the local and systemic release of mediators such as IL-6, TNF-α, and IL-1β. Increased levels of chronic inflammatory markers can be observed in chronic periodontitis subjects. Known biomarkers of cardiovascular disease risk, such as CRP, fibrinogen, IL-6, and pentraxin-3 are elevated in the serum of patients with periodontitis. Cardiocyte expression of BNP might be stimulated by proinflammatory cytokines like IL-1β, IL-6, and TNF-α. Increased serum levels of NT-proBNP in rheumatoid arthritis patients suggest that inflammation plays an important role in the release of these natriuretic peptides.[16,17]

The composition of saliva reflects our body's well-being. The diagnostic potential of saliva lies in the fact that it contains 20% similar proteins as blood. Saliva collection is noninvasive, and it does not clot like blood. Saliva samples can be easily handled and processed, and the risk of contracting blood-borne infectious diseases is also less. The half-life of BNP and NT-proBNP is approximately 20 minutes and 60–90 minutes respectively. So, the slow rate of clearance of NT-proBNP from blood allows it to flow into the saliva via GCF. In our study, unstimulated saliva was collected from all 24 subjects to estimate the levels of NT-proBNP.[16]

The intergroup comparison of mean difference of salivary NT-proBNP of Group I, II, III, and IV was found to be statistically significant. And similarly, the intergroup comparison of mean difference of serum NT-proBNP of Group I, II, III, and IV were found to be statistically significant. This study is in accordance with the study conducted by Leira Y et al who performed a case-control study, in which serum samples were collected from subjects with periodontitis and non-periodontitis individuals. Their results showed that the levels of NT-proBNP in serum were significantly higher in subjects with periodontitis compared to controls.[9]

Periodontal pathogens, such as Porphyromonas gingivalis, synthesize lipopolysaccharide that is able to spread into the bloodstream through the periodontal epithelium, binding to endothelial cells, monocytes, and macrophages. As a result of this process, an increase in the number of adhesion molecules could be observed, leading to the release of pro-inflammatory cytokines. It could be speculated that periodontal inflammation may contribute to increased levels of NT-proBNP in serum as the result of systemic inflammation.[9]

In some diseases (i.e, acute myocardial infarction or Wilson's disease), NT-proBNP is directly correlated with the production of matrix metalloproteinase-9, a key enzyme in the periodontal breakdown. Epidemiologic evidence and several other studies have shown that patients with periodontal disease are at a higher risk for atherosclerotic vascular disease (i.e, CVD and ischemic stroke). Elevated levels of this peptide could act as a biomarker, not only of ventricular dysfunction but also of CVD risk through promoting atherosclerosis. Numerous studies have proved that salivary and serum NT-proBNP could possibly serve as a biomarker for certain other systemic diseases.[9]

Periodontitis can lead to systemic events like atherogenesis and thrombogenesis due to the release of endotoxin and inflammatory cytokines into the blood. Inflammatory activation has been recognized in CHF patients regardless of the underlying cause, indicating a probable association between periodontitis and CHF.[12] Hence, there are several studies that could show the correlation between periodontitis and other systemic diseases also portraying the elevated levels of serum and salivary natriuretic peptides.

Wolfowitz M et alexamined the effect of periodontal disease on selected cardiac parameters and correlated the clinical periodontal parameters with cardiac parameters. They also examined the correlation between

periodontitis and concentration of BNP, which is a known prognostic marker for acute coronary syndrome patients. They concluded that periodontitis can constitute an independent risk factor in cardiovascular diseases.[18]

Cardiomyocyte and fibroblast augmentation are inhibited by BNP which leads to impaired synthesis of collagen in both cardiac muscle and periodontal tissues. Moreover, it inhibits the synthesis and activity of MMP's, limits neutrophil granulocytes activity, and decreases the activity of platelets. BNP level can be increased by factors such as smoking, diabetes, and age. These factors are also risk factors for periodontal diseases.

Karl Pearson correlation analysis between salivary and serum NT-proBNP and other parameters like plaque index, modified gingival index, probing pocket depth, and clinical attachment level showed a very strong positive correlation ($P<0.001$). Leira Y et al (2018) conducted a similar study where they demonstrated increased serum levels of NT-proBNP with an increase in severity of the periodontal disease. In our study, salivary levels of NT-proBNP in mild, moderate, and severe chronic periodontitis were also examined and the levels also increased with the degree of periodontal destruction.[9]

Periodontitis, an inflammatory condition of the periodontium is characterized by an increase in the levels of pro-inflammatory mediators like IL-1β, IL-6, and TNF-α. As periodontitis disease severity increases, the levels of these inflammatory mediators increase. This in turn can lead to elevated levels of NT-proBNP due to stimulation of cardiocytes by these inflammatory mediators.

Significantly higher serum and salivary NT-proBNP levels were seen in subjects with periodontitis compared to subjects without periodontitis. As periodontal destruction progressed, serum and salivary NT-proBNP concentrations increased. These results provide an insight into the potential role of NT-proBNP in the progression of periodontal disease.

Further studies with a larger sample size are needed to confirm these results. In addition, the effect of periodontal therapy on the serum and salivary levels of NT-proBNP should also be evaluated.

Conclusion

This study provides an understanding and awareness about the potential role of NT-proBNP in the periodontal disease progression. The future of saliva-based techniques for diagnosing periodontitis is a promising field, wherein BNP testing might prove to be a significant determinant. Substantiation of periodontal diagnostics will need to be benchmarked with prevailing measures of disease, including alveolar bone height and clinical attachment levels. However, further large-scale studies are desirable to substantiate these results.

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