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Research Article

Assessment of Salivary Neutrophil Gelatinase-Associated Lipocalin Levels in Diseased and Healthy Periodontium

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ABSTRACT

Background: periodontal disease is one of the most frequent human diseases. Depending on the severity of the inflammation, the destructive process may affect both the gingiva (gingivitis) and/or the periodontal ligament and alveolar bone that surround and support the teeth (periodontitis).

Objective: The study aimed to determine and compare the level of salivary Neutrophil gelatinase-associated lipocalin in periodontal health and disease (gingivitis and periodontitis stage I-III).

Subjects and Methods: A total of 90 individuals participated in the research separated into five groups, clinically healthy (n=10), gingivitis (n=20), stage I periodontitis (n=20), stage II periodontitis (n=20) and stage III periodontitis (n=20), periodontal parameters were recorded, and the level of salivary Neutrophil gelatinase-associated lipocalin was assessed by using the enzyme-linked immunosorbent assay.

Results: Neutrophil gelatinase-associated lipocalin salivary level was significantly higher ($p<0.05$) in periodontal disease groups compared to healthy controls. A statistically significant difference was also found between gingivitis and advanced periodontitis (stageII-III) ($p<0.05$). No significant difference ($p>0.05$) was found between different stages of periodontitis.

Conclusions: Neutrophil gelatinase-associated lipocalin is associated with periodontal diseases and my play a role in its pathogenesis

Introduction

Periodontal disease is the most common health issue(1), caused by the microorganisms that adhere to teeth as dental plaque. Bacteria interact with each other and with the host. With time, dysbiotic microbiota and dysregulated host inflammation promote the development of certain microorganisms inside the biofilm, generating elements that increase inflammation, resulting in tissue degradation and tooth loss (2, 3).

Periodontal disease is a collection of inflammatory disorders that damage the teeth's attachment apparatus (4). Unlike gingivitis, in periodontitis, tooth-supporting structures are destroyed, and the junctional epithelium migrates apically. Its main characteristics include impairment of supporting periodontal tissue, as evidenced by clinical attachment loss (CAL), periodontal pockets, gingival bleeding, and radiographic evidence of alveolar bone loss. Early diagnosis of periodontal diseases is important because periodontitis

may result in tooth dysfunction and loss, eventually leading to occlusal and aesthetic problems (5, 6).

One of the important inflammatory modifiers during the onset and development of periodontal disease is the proinflammatory cytokines. Neutrophil gelatinase-associated lipocalin (NGAL) is a novel amino acid adipocytokine, that is predominantly expressed by neutrophils and oral epithelial cells that engage in a range of physiological and pathophysiological processes, including metabolic homeostasis, apoptosis, inflammation, infection, and immune response (7, 8).

Neutrophil gelatinase-associated lipocalin (NGAL) is a member of the lipocalin family and was originally identified as a glycoprotein in complex with matrix metalloproteinase-9 (MMP-9) in human neutrophils. NGAL is thought to play a role in regulating inflammation and antimicrobial defense (9, 10), having the capability to bind iron, fatty acids, prostaglandins, steroids, and matrix metalloproteinases. By sequestering iron-loaded siderophores, NGAL plays an important role in mediating the innate immune response to bacterial infections; it is a neutrophil chemoattractant that promotes their maturation, adhesion, extravasation, and phagocyte capability. In addition to activating regulatory T cells (11, 12).

Among the first leukocytes to aggregate at the site of inflammation are polymorphonuclear neutrophils. Due to their phagocytotic and microbicidal capabilities, these cells are essential as the first line of defense of the innate immune system. Insufficient resolution and incapacity to restore tissue to equilibrium result in neutrophil-mediated damage and persistent inflammation (13, 14).

In vivo experiments revealed that neutrophils exerted from NGAL-deficient mice were incapable of phagocytosing and killing bacteria, incapable of extravasation to sites of infection, and exhibited poor chemotaxis and adhesion (15, 16).

Both gingival crevicular fluid (GCF) and saliva have been found to contain NGAL (17). NGAL has reportedly been identified as a biomarker for patient monitoring and regulating disease activity (18). However, there hasn't been enough research done on the association between this biomarker and periodontal disease.

Saliva is a very effective biological fluid that contain several interesting salivary biomarkers that correlate with the periodontitis clinical parameters. Saliva collection is a quick, painless, and safe procedure (19, 20).

Since the 1999 workshop, researchers have generated significant new findings that spurred the 2017 workshop to propose a new classification system that included periodontitis which mainly depends on staging and grading. Both the severity of the condition upon assessment and the degree of complexity for management are crucial for determining the stage of periodontitis (21).

This study aimed to evaluate and compare salivary NGAL levels in in periodontal health and disease (gingivitis and periodontitis stage I-III).

Subjects and Methods

The ethical committee of the College of Dentistry/University of Baghdad approved this research, project number 448/448606.

Ninety Iraqi participants with age range 22-58, who were systemically healthy with at least 20 teeth participated voluntarily in this analytical observational case control study after a thorough explanation of the study's objectives and were given informed consent in accordance with the Collage of Dentistry in University of Baghdad to sign. The subjects in this study attended the College of Dentistry University of Kufa and the specialized dental center in Al Najaf city from February 2022 to June 2022.

The sample size were based on a recent study (17), With 80% power and a 5% alpha error of probability, The study subjects were divided into five groups following the "2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions"(21): Control group: clinically healthy periodontium (n=10).

Experimental groups: generalized gingivitis group (n=20), stage I periodontitis group (n=20), stage II periodontitis group(n=20) and stage III periodontitis group (n=20).

The periodontally healthy group is characterized by “no clinical attachment loss (Probing pocket depth ≤3 mm, Bleeding on probing <10%, no Radiological bone loss).” Gingivitis group is characterized by “intact periodontium (no clinical attachment loss), probing pocket depths ≤3 mm, and bleeding on probing >30% (generalized).” Stage I periodontitis is characterized by “Interproximal bone loss <15% or 1-2 mm.” Stage II periodontitis is characterized by “Interproximal bone loss involving coronal third of the root.” Stage III periodontitis is characterized by “Interproximal bone loss extending to the mid-third of the root.”

All Periodontitis groups were determined as "generalized (more than 30% of teeth) with unstable condition PPD ≥ 5mm or PPD at ≥ 4mm and BOP" (22).

The inclusion criteria include systemically healthy participant with healthy periodontium, generalized gingivitis, stage I,II and III periodontitis, while Patients with systemic disease, smokers, alcoholics, patients taking any medication affecting values of periodontal parameters, receiving periodontal or antibiotic treatment within the three months prior to the study, receiving orthodontic treatment, and females who are pregnant or taking contraceptive medication were excluded from the study.

Unstimulated whole saliva samples were collected by passive drooling from all participants into plastic containers (CNWTC, Jangsu,China) between 9 and 11 am, according to Navazesh and Kumar (23). Before sample collection, participants were asked to refrain from eating, drinking, chewing gum, and oral hygiene practices for at least one hour. The samples were immediately put in an ice box (Wanmei, Foshan, China), then centrifuged (80-1 Electric Centrifuge, Shanghai, China), and the clear supernatants were kept in eppendrof tubes (CNWTC/OEM, Jiangsu, China) in a deep freezer at -80 degrees Celsius (Angelantoni Life Science, Perugia, Italy) until further examination (24, 25).

All clinical periodontal parameters for all individuals were assessed by a single calibrated examiner.

The following clinical periodontal parameters were assessed: 1) Bleeding on Probing (BOP), which was noted within 30 seconds of probing . 2) Probing Pocket Depth (PPD) which was assessed "from the gingival margin to the base of the pocket." 3) Clinical Attachment Level (CAL), which was assessed "from the cementoenamel junction to the base of the pocket". These measurements were evaluated using a periodontal probe (UNC 15 probe, Premium Instruments, New

York, USA) at six sites for each tooth (26). Plaque index (PI) was determined using a disclosing agent (Co., Ltd., Etoy, Switzerland) at four sites for each tooth (27).

For the biochemical analysis, Human Specific Enzyme-Linked Immunosorbent Assay (ELISA) kits from (bioassay technology laboratory Zhejiang, china) were utilized to determine salivary NGAL levels per the manufacturer's instructions. Salivary samples were thawed and labeled prior to the procedure. Kit's sensitivity values were 2.01ng/ml, with a detection range of 5-600ng/ml. The optical density was measured at 450 nm.

Shapiro–Wilk test was used for the assessment of normality using SPSS version 26.0 (Statistical Package for Social Science), all data revealed normal distribution ($p>0.05$). Data analyses were performed by one-way analysis of variance (ANOVA) followed by Games-Howell post hoc test, and Pearson correlation coefficient was utilized to determine the correlation between variables. P value is significant at level 0.05.

Results

The demographic data of the study groups are shown in table (1). Ninety participants were included in this study with an age range of 22-58, with 54 males (60%) and 36 females (44%).

The mean age for the study groups increases progressively from to the control group stage III periodontitis group.

As for sex, male percentages were higher in all the studied groups (60%, 75%, 65%, 70%) except for stage I periodontitis group (30%).

Analysis of levels of NGAL using one way ANOVA test showed a statically significant difference ($p<0.05$) amongst study groups; further multiple group comparison revealed a statistically significant difference ($P<0.05$) when comparing the experimental groups with Control and when comparing gingivitis with stage II and III groups (Figure 1).

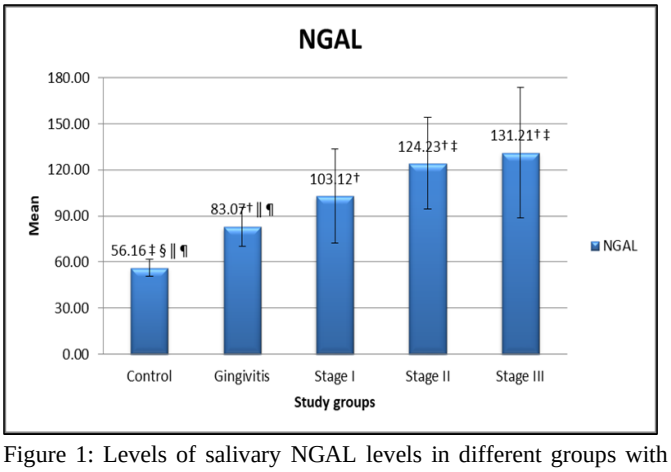

Figure 1: Levels of salivary NGAL levels in different groups with comparison. †: significantly different than Control, ‡: significantly different than Gingivitis, §: significantly different than Stage I, ‖: significantly different than Stage II, ¶ significantly different than Stage III ($p<0.05$).

Regarding the clinical periodontal parameters PI, PPD, BOP and CAL, descriptive statistics are illustrated in table (2).

As for the correlations of periodontal parameter with NGAL, a statistically significant difference was found with a positive correlation between NGAL and CAL in all periodontitis groups($p<0.05$), stage III group also showed a statistically significant difference with a positive correlation between NGAL and PPD($p<0.05$). Control group showed a statistically significant positive correlation between NGAL and BOP (Table 3).

Discussion

NGAL is an acute-phase protein that has gained attention as a possible clinical biomarker for inflammatory diseases. The potential use of NGAL as a biomarker for the onset and monitoring of disease progression is supported by the fact that its levels are typically low in biological fluids and yet are elevated in an inflammatory state (28).

In this case-control study, the level of salivary NGAL in healthy and diseased periodontium were evaluated to investigate the association between this marker and periodontal health and disease. The current study demonstrated a significant increase in salivary NGAL levels in gingivitis and periodontitis in comparison to control group, which is confirmed by its positive association with clinical periodontal parameters (CAL and PPD). NGAL was statistically positively correlated with CAL in all experimental groups. Stage III also showed a statistically positive correlation with PPD, which agrees with Nakajima et al., (29).

NGAL may play a role in the pathogenesis of periodontitis. It stabilizes matrix metalloproteinase 9 (a catabolic enzyme that degrades gelatine, fibronectin, elastin, and type IV, V, VII, and X and the denatured type I collagen) (30) by complexing with it, prolong its activity by preventing its autodegradation and enhancing the collagenolytic activity that is a hallmark of periodontitis (29, 31), which might explain the results of the study. Also, NGAL is produced by extravasated neutrophils, participates in a positive inflammatory feedback loop by promoting chemotaxis, migration of neutrophil, and extravasation to inflammation sites (32).

Regarding the differentiation between healthy controls and periodontitis, NGAL revealed a progressive increase from health to periodontitis groups and showed the capacity to differentiate between healthy controls and periodontitis, in addition to differentiating between gingivitis and periodontitis (stage II and III) with a statistically significant difference, which agrees with Morelli et al., (33) Pradeep et al.,(34) ,Tan et al.,(17) and Ceylan et al.,(32).

Regarding the differentiation between gingivitis and stage I periodontitis, the study results disagreed with Tan et al., (17). As for differentiation between gingivitis and stage III periodontitis, the study results were consistent with Tan et al., (17), while disagreeing with Ceylan et al., (32).

Regarding periodontitis stages, the level of NGAL increases from stage I to stage III but with no statistically significant difference among them, which agrees with Nakajima et al., (29) and disagrees with Tan et al., (17).

Table 1: Demographic parameters of the study population

Parameters	Categorization	Control	Gingivitis	Stage I	Stage II	Stage III
Age	Min.-Max.	26-31	22-55	24-52	23-57	22-58
	Mean±SD	28.7±1.42	33.1±7.9	36.2±8.13	39.3±9.44	43.00±10.22
Sex	Male	6 (60%)	15(75%)	6 (30%)	13 (65%)	14 (70%)
	Female	4 (40%)	5(25%)	14 (70%)	7 (35%)	6 (60%)

Table 2: Descriptive statistics of clinical parameters

Parameters	Categorization	Control	Gingivitis	Stage I	Stage II	Stage III
PI	Mean ± SD	38.7 ±15.52‡§ǁ¶	71.65 ±12.31†	70.03 ±9.56†	74.42 ±10.18†	73.89 ±9.24†
BOP	Mean ± SD	4.06 ±2.59‡§ǁ¶	42.74 ±10.13†	47.33 ±13.57†	49.46 ±13.65†	52.36 ±14.08†
PPD (mm)	Mean ± SD	-	-	3.65 ±0.25ǁ,¶	4.24 ±0.32§,¶	4.71 ±0.45§,ǁ
CAL (mm)	Mean ± SD	-	-	1.56 ±0.25ǁ,¶	2.62 ±0.45§,¶	3.30 ±0.60§,ǁ

†: significantly different than Control, ‡: significantly different than Gingivitis, §: significantly different than Stage I, ǁ: significantly different than Stage II, ¶ significantly different than Stage III ($p<0.05$). PI: Plaque Index, BOP: Bleeding on Probing, PPD: Probing Pocket Depth, CAL: Clinical Attachment Loss.

Table 3: Correlations of periodontal parameters with NGAL

Groups	Markers	PI		BOP		PPD		CAL	
		r	p-value	r	p-value	r	p-value	r	p-value
Control	NGAL	0.541	0.439	0.709*	0.022	-	-	-	-
Gingivitis	NGAL	0.232	0.324	0.073	0.759	-	-	-	-
Stage I	NGAL	-0.280	0.232	-0.117	0.623	0.047	0.845	0.448*	0.048
Stage II	NGAL	-0.061	0.800	0.044	0.853	0.329	0.157	0.470*	0.037
Stage III	NGAL	0.148	0.534	0.359	0.120	0.552*	0.012	0.471*	0.036

* statistically significant difference ($p<0.05$)

Saliva is an optimal biological fluid, which can be used to evaluate and diagnose in periodontal disease. There are many benefits to using saliva as a biological fluid. In addition, saliva as a "mirror of the human body" can reflect the physiological and pathological condition of the body. Saliva may be utilized to detect biomarkers specific to the physiological characteristics of periodontal disease because saliva collection is quick, cheap, safe, and non-invasive. (35, 36).

Biomarkers serve a key role in light of the fact that biomarkers are reliable indicators of a variety of diseases (1). The identification of biomarkers is useful for the prevention, diagnosis and prognosis of diseases, as well as for monitoring the progression of pathological disorders (20).

ELISA is reliable, sensitive and specific. Compared to other immunoassays, ELISA provides highly reproducible, quantitative data that makes it an advantageous biotechnological tool in scientific research and clinical diagnosis (37).

Staging comprises four groups (stages I-IV) which depend on several factors like the amount of attachment loss, bone loss percentage, existence and degree of angular bony defects, mobility of teeth, and tooth loss caused by periodontitis (38). The main objectives of staging a patient with periodontitis are to categorize their condition's severity and extent based on the extent of destroyed and damaged tissue that can currently be attributed to the disease, and to evaluate a number of factors that may influence the level of complexity of controlling existing illness and managing both the patient's long-term function and aesthetics of their dentition (22).

The study's findings revealed significant variations in the age distribution between the periodontitis group and the control group, The length of time periodontal tissues have been exposed to bacterial plaque is likely connected to the severity of periodontal disease and bone loss as people age, and is thought to indicate a person's overall oral history (39).

As for sex distribution, the results showed that male percentage was highest in all the experimental groups except stage I periodontitis, This may be related to the oral hygiene ignorance, and poorer oral hygiene habits which is usually observed among males (40).

Further future studies needed to evaluate the cut-off values of salivary NGAL levels in periodontally healthy and diseased patients and using interventional methods (comparing NGAL levels prior to and following non-surgical periodontal treatment) to evaluate its clinical significance in the diagnosis of periodontal disease.

Limitations of the study

The study excluded patients with periodontal diseases associated with risk factors. The study did not include localized gingivitis and stage 4 periodontitis. The usage of saliva does not reflect the specific site of active disease.

Conclusion

Study results suggest that NGAL can be used to differentiate between periodontally healthy and diseased patients, and between gingivitis and moderate to severe periodontitis but failed to distinguish between gingivitis and early state of periodontitis (stage I). CAL was positively correlated with NGAL in all periodontitis groups emphasizing the importance of NGAL's role in the pathogenesis of periodontitis.

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Conflict of Interest

Authors declare no conflict of interest.

Data availability

Data are available upon reasonable request.

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