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Soluble FcγRIIIb (CD16b) and Alpha Defensin as Markers of Neutrophils Activation in Periodontal Disease

Fatima Sabah Jasim[1*] and Batool Hassan Al-Ghurabi[2]
[1,2] Department of Basic Science, College of Dentistry, University of Baghdad. Baghdad, Iraq.

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Abstract

Neutrophils in saliva cause tissue death in inflammatory disorders, including periodontal disease. Identifying biomarkers for neutrophil mediators is crucial for accurate diagnosis in periodontics research. This study is to investigate the salivary levels of soluble cluster of differentiation 16b (sCD16b) and alpha defensin, which are biomarkers of neutrophil activation in patients with periodontal diseases, and to examine the correlation between these levels and clinical periodontal parameters. In this particular case-control study, a total of sixty subjects who were diagnosed with periodontal disease, including 30 with periodontitis and 30 with gingivitis, were recruited. These subjects ranged in age from 17 to 65 years. The study also included 25 healthy volunteers, matching their ages and genders with those of the patients. The periodontal parameters utilized in this study included plaque index, bleeding on probing, probing pocket depth, and clinical attachment loss. We collected saliva samples from all participants, including both patients and controls. In order to estimate the salivary levels of sCD16b and alpha defensin, ELISA was performed. The present findings revealed a significant increase ($P \leq 0.05$) in the salivary levels of sCD16b and alpha defensin in periodontitis and gingivitis patients as compared to the control group. Moreover, there was a significant increase ($P \leq 0.05$) in the level of sCD16b among periodontitis patients when compared to gingivitis patients, while for the alpha-defensin level, there was no significant difference ($P > 0.05$) between the two groups. On the other hand, this study found a significantly positive correlation for two biomarkers with CAL in the periodontics group. This study indicated that an increase in salivary levels of sCD16b and alpha defensin could be associated with enhanced innate response in periodontics disease, and might serve as biomarkers of neutrophil activation in periodontal disease.

Keywords: Periodontitis disease, neutrophils, cluster of differentiation 16b and alpha defensin.

1.Introduction

The second most prevalent oral illness in the world is periodontal disease, which is still a serious and ongoing public health issue (1, 2). Periodontal disease develops when an upset in bacterial homeostasis occurs. This increases the colonization of periopathogenic microorganisms

and triggers an inflammatory response in the host, which may result in tissue loss (3, 4, 5). The release of inflammatory mediators and cytokines into the periodontal tissues caused by periodontal bacteria induces periodontal deterioration (6, 7, 8). These host mediators participate either directly or indirectly in bone resorption and periodontal tissue injury (9, 10, 11). Despite being a minor and curable type of periodontic disease, gingivitis often progresses to periodontics (12). Periodontics is an infectious illness that causes tooth loss and immune-mediated destruction of the supporting tissues of the periodontium (13, 14). Numerous variables affect the etiology and pathogenesis of periodontal disease; its pathogenesis is not fully understood. It is believed that host genetic, microbial, and environmental variables influence the illness's progression (15, 16, 17). The most prevalent leukocytes, neutrophils (also known as polymorphonuclear leukocytes), are professional phagocytes with the main function of eradicating extracellular infections. In addition to working to connect the innate and adaptive arms of the immune response, neutrophils and macrophages are phagocytic cell types that aid in inflammation resolution and tissue repair. The gingival crevice and epithelium widely distribute neutrophils, which are considered the primary protective cell type in the periodontal tissues. According to the histopathology of periodontal diseases, the neutrophil "wall" that forms between the junctional epithelium and the pathogen-rich tooth plaque acts as a powerful barrier against microbes and a unified system for phagocytosis. However, neutrophil defense comes with a cost, as excessive neutrophil activity can cause tissue damage and prolong the occurrence and severity of inflammatory periodontal disorders. Human antimicrobial peptides (AMPs), a non-oxidative antibacterial mechanism, are released by neutrophils as a means of eradicating microorganisms by acting as a defense against the inflammatory mediator generated by the microbes (18). The azurophilic granule of neutrophils, one of the three major granules, includes alpha-defensin, an antibacterial defense substance released in saliva from gingival crevicular fluid (19). By regulating the creation of biofilms, alpha-defensins effectively guard the tooth structure from oral pathogen microorganisms and inhibit the development of oral infections [20]. As a result of neutrophil activation, which results in the degranulation of azurophilic granules that can be seen in the cluster of differentiation 63 (CD63) marker on the surface of neutrophils, alpha-defensins are secreted. Additionally, the surface expression of CD16 [Fc gamma receptor (FcR)], which is a marker for degranulation, adhesion, and antigen recognition processes, reveals an activated state in oral neutrophils. No matter the cell's location, amount of activity, or periodontics disease, neutrophils continuously display the marker CD16 (21). This research was designed to look at the salivary levels of sCD16b and alpha defensin, two biomarkers of neutrophil activation in individuals with periodontal disorders, and to compare those levels to clinical periodontal characteristics.

2. Materials and Methods

2.1. Subjects

This case-control research included 85 participants, 37 men and 48 women, ranging in age from 17 to 65. Special remarks on participants were noted on a questionnaire. From November 2022 to January 2023, all participants were clinic visitors at the Department of Periodontics, College of Dentistry, and University of Baghdad. Clinical periodontics parameters were measured by a specialist dentist in the Periodontics Department. The subjects were divided into two groups: a study group (30 patients with periodontics and 30 patients with gingivitis) and 25 individuals as

a control group with clinically healthy periodontium, their age and gender matched with the patients' group.

2.2. Sample size

The sample size was determined with the help of the program G Power 3.1.9.7, which was developed by Franz-Faul at the University of Kiel in Germany. The parameters used in the calculation were as follows: The power of the study was set to 95%, the alpha error of probability was set to 0.05 two-sided, the statistical test used was a two-sample independent T test, and it was assumed that the effect size between the two groups was large. Under these circumstances, the sample size is 84; thus, 85 participants are adequate and more precise than G Power (22).

2.3. Eligibility criteria

2.3.1. Inclusion criteria

Participants needed to qualify for inclusion in the research by being in excellent overall health, not being regular users of any drugs, not having had any periodontics treatment in the preceding six months, not being heavy smokers or drinkers, and having at least 20 or more natural teeth. Regarding the gingivitis case, it must be generalized with intact periodontium, exhibit more than thirty percent of sites affected by BOP, have no PPD more than three millimeters, and have no CAL (23). For periodontics cases: Interdental CAL > 2 mm for non-adjacent teeth or buccal/oral CAL ≥ 3 mm with a pocket > 3 mm at ≥ 2 teeth. Generalized Periodontics—> bone loss exceeds 30% of teeth, unstable (PPD > 5 mm or PPD > 4 mm with BOP). For the control case: healthy, intact periodontium, BOP ≤ 10%, PPD ≤ 3 mm, no CAL.

2.3.2. Exclusion criteria

The population of the research did not include women who were pregnant, patients who were currently undergoing orthodontic treatment, or patients who had previously had periodontics therapy.

2.4. Clinical Finding

Oral examination was performed by a specialist dentist for every subject who is under the study. The periodontics status of all teeth was assessed using a periodontics probe of William's graduation. The periodontics parameters include PLI, BOP, PPD, and CAL.

2.5. Sample collection

Saliva that had not been stimulated was taken from all of the individuals. Before collecting the samples, we instructed the participants to thoroughly clean their mouths with water to remove any debris or contaminated material. We instructed the participant to sit in a comfortable posture during the sample collection process. The patient received a clear instruction not to move their tongue, jaw, lips, or cheeks in any way. We only slightly cracked the subject's lips open, allowing their saliva to passively drip into the test tube over their bottom lip. It is important to remember not to spit into the test tube. Additionally, during the treatment, the individual should not consume any liquids or food [24]. We threw away the samples tainted with blood. We wrote the subject's number on the tube label, matching the number on the previous case sheet. We centrifuged the samples for twenty minutes at a speed of 2500 revolutions per minute to extract the clear supernatant, then aspirated it with a micropipette into Eppendorf tubes and frozen it at a temperature of -80 degrees Celsius until the day of analysis.

Measurement of salivary CD16 and alpha defensin: Salivary levels of biomarkers (mybiosoures, USA) were determined by ELISA.

2.6. Statistical analysis:

The Statistical Package for the Social Sciences, version 21, was used for all of the data-related tasks, including description, analysis, and presentation. We carried out the Shapiro–Wilk test to determine whether or not quantitative variables fall into a normal distribution across groups. We employed the Dunn-Bonferroni technique and the Kruskal-Wallis test to investigate whether there was a significant difference in the mean ranks of several independent groups. When the anticipated cell counts were less than 5, we used the Chi-square test to investigate whether a relationship existed between the distributions of two qualitative variables. We used the Spearman correlation test to establish a monotonic connection between two non-normally distributed variables. We conducted additional comparisons between the groups using the Bonferroni post-hoc test if the results were significantly different. If the p-value was less than 0.05, we determined it to have statistical significance.

3. Results

Table (1) and **Figure (1)** demonstrate the values of clinical periodontics parameters obtained from patients and controls, respectively. The research findings indicate that the mean rank of sCD16b levels was significantly higher in the periodontics group (667.83 pg/ml) compared to the gingivitis group (43.17 pg/ml) and the control group (13.00 pg/ml), as illustrated in **Table (2)** and **Figure (2)**. This finding was statistically significant at the $P \leq 0.05$ level. In addition, statistically significant differences were found between the periodontics group and each of the gingivitis and control groups, as well as between the periodontics and gingivitis groups ($P \leq 0.05$) when comparing the groups. This research demonstrates that there was a significant association between sCD16 and CAL ($r= -0.415$; $p = 0.022$) in the group of patients diagnosed with periodontics; however, there was no significant correlation found between sCD16 and periodontics parameters in the group of patients diagnosed with gingivitis, as shown in **Table (3)**.

Table 1. Median values of PPD, CAL in patients and control groups.

	Groups	Median	Mean Rank	Kruskal-Wallis	P value
PPD	P	4.40		-	
CAL	P	4.00		-	

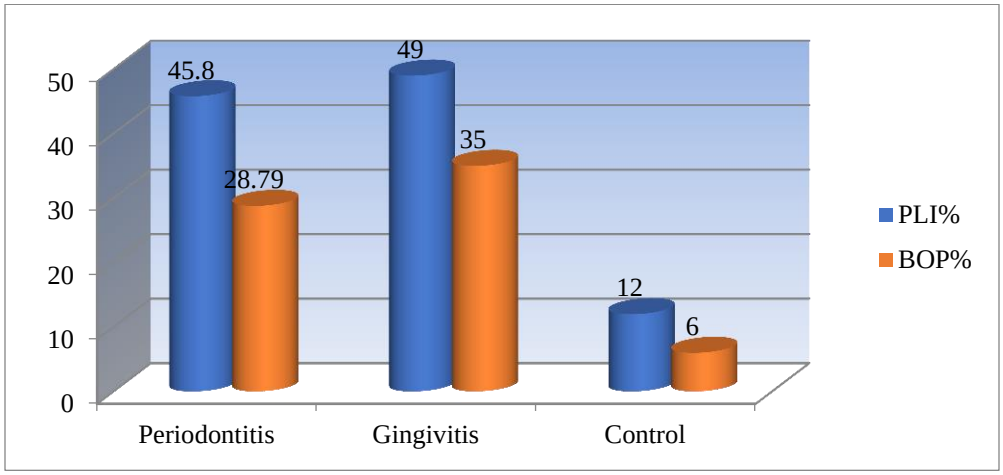

Figure 1. Median percentage of PLI and BOP in patients and control groups.

Table 2. Salivary levels of sCD16 (pg/ml) in patients and control groups.

Groups	Median	Mean rank	Kruskal-Wallis	P value	Dunn-Bonferroni MPC	
Periodontics	162.8095	67.83			Periodontics –Gingivitis	0.000
Gingivitis	118.8615	43.17	67.308	0.000	Periodontics –control	0.000
Control	49.2780	13.00			Gingivitis – Control	0.000

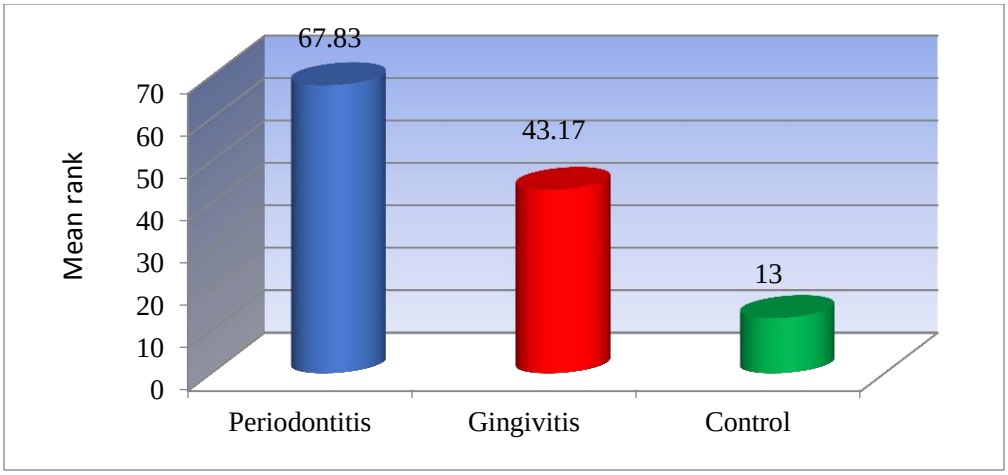

Figure 2. Salivary levels of sCD16 (pg/ml) in patients and control groups.

Table 3. CD 16 and periodontitis markers have been shown to have a correlation in patient groups.

Groups		PLI		BOP		PPD		CAL	
		R	P	R	P	R	P	r	p
Periodontitis	CD16	-0.003	0.988	-0.286	0.125	0.099	0.604	-0.415	0.022
Gingivitis		0.046	0.811	0.011	0.952				

Table (4) and **Figure (3)** showed a significant increase (P≤0.05) in terms of the mean rank value of alpha-defensins among patients with periodontics and gingivitis (53.93 and 55.77 ng/ml), in contrast to the value of 14.56 ng/ml seen in the control group. When the groups were examined, it was shown that the levels of alpha-defensins are not statistically different (P>0.05) between gingivitis and periodontics; nevertheless, there is a substantial difference (P>0.05) between periodontics and the control group. In addition, as can be seen in **Table (5)**, the findings revealed that there was not a statistically positive connection between alpha-defensins and periodontics measures in the periodontics group; nevertheless, there was a significantly positive correlation between CAL and periodontics parameters (r=0.389, p=0.033).

Table 4. Salivary level of alpha-defensins (ng/ml) in patients and control groups.

Groups	Median	Mean rank	Kruskal-Wallis	P value	Dunn-Bonferroni MPC	
Periodontics	18.0375	53.93			Periodontics –Gingivitis	0.999
Gingivitis	20.4255	55.77	47.108	0.000	Periodontics –Control	0.000
Control	7.9650	14.56			Gingivitis – Control	0.000

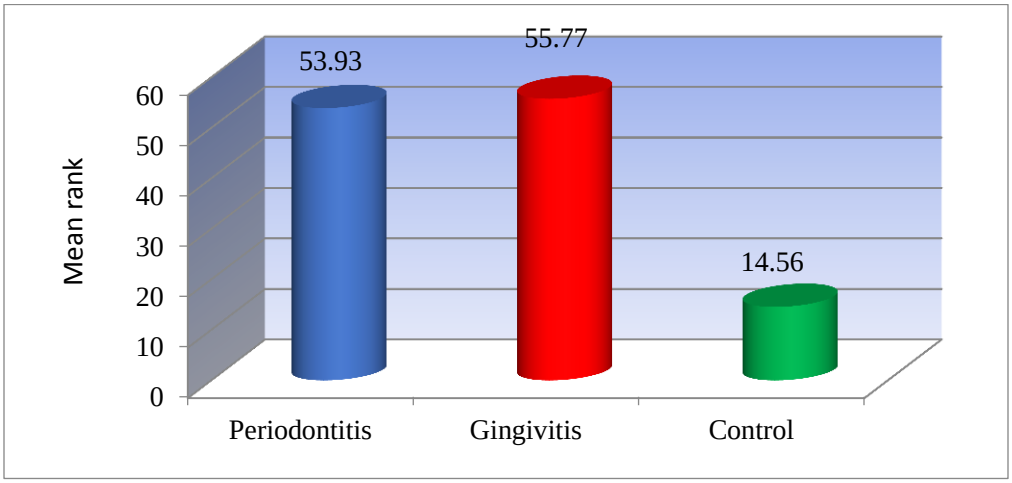

Figure 3. Salivary level of alpha-defensins (ng/ml) in patients and control groups.

Table 5. Correlation between alpha-defensins periodontics parameters in patients groups.

Groups	PLI		BOP		PPD		CAL	
	R	p	R	P	R	P	r	p
Periodontics	0.291	0.118	-0.037	0.846	0.192	0.309	0.389	**0.033**
Gingivitis	-0.157	0.407	0.046	0.810				

4. Discussion

It is becoming clear that neutrophils play a significant role in the aetiology of periodontal disease. They are able to react nearly rapidly to a wide variety of inflammatory stimuli and danger signals because the surface expression of cellular markers makes this possible. After activation by a variety of stimuli, the CD16b surface marker is lost from the human neutrophil surface in a manner that is both highly quick and very efficient (25).

According to the findings of the present research, people with periodontics and gingivitis have much higher amounts of sCD16b in their saliva than healthy persons do. This is in contrast to the levels seen in healthy individuals. In addition, the level of sCD16b is much higher in instances of periodontics than in cases of gingivitis. This is a significant difference. Because the presence of this marker suggested processes of degranulation, adhesion, and antigen recognition, a higher level of sCD16b might be linked to the activation state of oral neutrophils. To the best of our knowledge, there were no previously recorded investigations on the salivary level of sCD16b in individuals suffering from periodontal disease that could be used as a comparison to this study. However, the findings that were reported in this work may be supported by a previous study that was conducted on CD16. That study identified it as a marker that is consistently expressed on neutrophils regardless of the cell location, level of activation, or state of periodontics disease, and it did so by using high-throughput flow cytometry against a panel of 374 known CD antibodies (26). This study may lend support to the findings that were reported in this work. On the other hand, a study done in 2007 found that CD16+ CD14+ monocytes, which exhibit both surface markers, are notably implicated and elevated in periodontics (27).

These monocytes also release greater levels of proinflammatory cytokines in response to a microbial challenge. This research also demonstrated that a positive connection existed between sCD16 and CAL in the periodontics group; however, there were no other studies on this association in periodontics that could be used to draw comparisons with this study. On the other hand, Reeves and colleagues found a correlation between the levels of sCD16b and the

inflammatory condition of the patients (28). In addition to this, research from the year 2009 [29], revealed that the treatment of periodontics considerably affects different neutrophil phenotypes in peripheral blood, and that suppressive neutrophils may play a role in the pathogenesis of periodontics. The most prevalent type of AMPs is called alpha defensin, and it is kept in the azurophilic granules of neutrophils. During an illness, the quantities of alpha-defensins found in saliva and other bodily fluids have been shown to increase (30). The results of this investigation demonstrated that the levels of alpha-defensins in patients with periodontal disease were significantly greater than those in the healthy control group. On the other hand, there is an increase in the gingivitis group compared to the periodontics group, although the difference is not statistically significant. It is possible that factors other than neutrophils are involved in the formation of defensins in inflamed periodontics and gingival tissue. This would explain the high level of alpha-defensins that are present in periodontics and gingivitis. It has been found that alpha-defensins are also expressed in lymphocytes and monocytes, both of which are numerous in periodontal locations (31, 32). This is consistent with previous findings. In addition, there is some speculation that an increase in the amounts of alpha-defensins that occurs during gingivitis may have a protective impact on alveolar bone during the early stages of periodontics. Researchers (33, 34) found this conclusion to be in line with their earlier research. Patients with periodontics showed higher levels of HNP1-3 compared to controls. In a similar vein, the research conducted in 35 showed that individuals suffering from oral inflammation had increased levels of alpha-defensins in their saliva compared to healthy people. Furthermore, research (36) revealed that elevated levels of GCF suggest the impact of these AMPs on the microbiota within the gingival crevice. The hypothesis was based on the discovery of high levels in the GCF. In contrast, the findings of another study (33), which reported no significant difference between healthy and diseased sites despite the presence of alpha-defensins in a higher percentage of healthy sites, indicated the presence of alpha-defensins in both periodontics and periodontics-ly healthy sites. This result, however, was not consistent with those findings. Regarding the relationship between the salivary level of alpha-defensins and periodontics parameters, this research found no significant correlation between alpha-defensins and clinical periodontics parameters, with the exception of CAL, which showed a significant result. This stands in stark contrast to the discovery of a significant correlation between CAL and clinical periodontics parameters. The results of another investigation (37), substantiated this discovery. The results of (38, 39), showed that there wasn't a strong link between alpha-defensins and CAL (38), but they did show that there was a strong link between the level of alpha-defensins and the CAL parameter in the periodontics group. It's plausible that an elevated level of salivary alpha-defensins in periodontics, coupled with a positive correlation with CAL, could potentially establish a connection between alpha-defensins and inflammation in periodontics.

5. Conclusion

This study indicated that an increase in salivary levels of sCD16b and alpha defensin could be associated with enhanced innate response in periodontal disease and might serve as biomarkers of neutrophil activation in periodontal disease.

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Conflicts of interest

The authors declare that they have no conflicts of interest

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Ethical Clearance

The study advanced after receiving institutional ethical committee (IEC) approval. The College of Dentistry Ethics committee approves the research proposal to be conducted in the presented form. None of the investigators and co-investigators participating in this study took part in the decision-making and voting procedure for this study.

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