Research Article

Association of salivary Interleukin-6 levels in smokers with periodontitis

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Abstract: Background: Periodontal disease is caused by a combination of factors, with a plaque being the primary causative factor. Although periodontal bacteria play a significant contribution in the onset of periodontitis, the sustained inflammatory immune reaction, which is mostly directed by the elevation of pro-inflammatory cytokines, is the primary component responsible for tissue damage associated with periodontitis. Interleukin (IL)-6 is a pleiotropic cytokine, and it is released by a variety of cell types. IL-6 is crucial in the processes that lead to periodontal disease and has also been linked to the migration of inflammatory cells. Smoking is a key potential factor for periodontal disorders and is associated with an increase in both the onset and severity of periodontitis, this studay aims to assess the association between smoking cigarettes and the salivary levels of IL-6 in patients with periodontitis in comparison to healthy controls. Materials and Methods: The sample population consisted of seventy-four males, and they were separated into four different groups: a clinically healthy periodontium non-smoker group (n=12), a clinically healthy periodontium smoker group (n=12), a periodontitis non-smoker group (n=25) and a periodontitis smoker group (n=25). All of the participants' saliva samples were taken, and then clinical periodontal parameters were looked at (plaque index, bleeding on probing, probing pocket depth and clinical attachment level). Biochemical analysis with an Enzyme-Linked Immunosorbent Assay (ELISA) was used to find out how much IL-6 was in the saliva. Results: The levels of IL-6 were found to be greater in the periodontitis groups compared to the control groups and in the smoking groups compared to the non-smoking groups. Most periodontal measures correlated significantly with IL-6 concentration in the saliva.Conclusion: This research revealed that smokers (both with and without periodontitis) have higher amounts of IL-6 in their saliva than nonsmokers (both healthy and periodontitis). This shows that smoking cigarettes had a boosting effect on the levels of IL-6 in the saliva.

Keywords: periodontitis, saliva, IL-6, cigarette smoking.

Introduction

Periodontitis (PT) is an inflammatory periodontal disease caused by a variety of pathogenic microorganisms, which results in loss of attachment and resorption of alveolar bone [(1)]. Periodontitis is a common condition that affects up to 50% of the population and is ranked 11th among chronic diseases worldwide [(2)]. An important initiating factor for gingivitis and periodontitis is dental plaque[(3)] . Furthermore, altered dynamic interactions among certain subgingival microorganisms, host immune responses, environmental and genetic variables are linked to periodontitis and likely contribute to its development [(4)].

Periodontal microorganisms must be present, but they alone are not enough to cause periodontitis to develop, factors like smoking, diabetes, and the ability to evade the immune system, for example, can change immune-inflammatory reactions that may cause tissue destruction and result in periodontitis [5, 6].
The main environmental risk factor for periodontal disorders is thought to be smoking, and Smokers are more likely to develop severe periodontitis with greater loss of periodontal tissue, gingival recession, and tooth loss risk.[7] Smoking increases the amount and appearance of harmful inflammatory cytokines in the gingival crevicular fluid (GCF), such as interleukin (IL) 1 and IL-6[8, 9]. Moreover, Patients with periodontitis who smoke have been observed to lose more bone and attachment tissue than those who do not smoke [10, 11]. Interleukin-6 (IL-6) is a cytokine with both pro-inflammatory and anti-inflammatory properties in humans[12]. Both immunological and non-immune cells, such as fibroblasts, keratinocytes, and endothelial cells, secrete IL-6 when stimulated[13]. Because it has a variety of biological functions in numerous target cells, IL-6 plays a significant role in vascular inflammation [14]. IL-6 is recognized as a key biomarker with acceptable diagnostic accuracy for periodontitis[15]. Considering IL-6 in saliva has been shown to be a reliable marker of periodontal inflammation, it seems reasonable that it might be used to detect current and past exposure to periodontal infections[16]. Additionally, evidence suggests that abnormal IL-6 levels may predict the early development of PT more reliably than other periodontal pathogens in the biofilm [17, 18].
In order to obtain locally improved gingival crevicular medication concentration with lesser systemic adverse effects, the intra pocket drug delivery system is an appealing and promising method to administer antimicrobial agents into the periodontal pocket[19]. For instance, the addition of nano-doxycycline periodontal gel as a supplement to scaling-root planing (SRP) was reliable and enhanced clinical indices as well as inflammatory indicators (such as IL-6) for up to three months [20].

Materials and Methods

Study design

The investigation was planned as a case-control study. This study was approved by the Ethics Board of the Baghdad University School of Dentistry and corresponded to the Helsinki and Tokyo standards for human research. In accordance with the inclusion and exclusion criteria of the research, the human sample consisted of seventy-four, all male volunteers ranging in age from thirty-five to fifty-five years. We began collecting samples in February 2022 and finished in May of that year. Inclusion criteria included systemically healthy patients with at least twenty teeth and cigarette smokers who have been smoking for at least a year and have an average daily consumption of five or more cigarettes[21]. Exclusion criteria included Females, Alcohol drinking, Patients who, within the last three months, have completed or are undergoing intensive periodontal treatment and who have been on a course of anti-inflammatory or antimicrobial treatment, dual smokers (water pipe and E-cig smokers) beside cigarette smoking, Clear pathology lesion in the mouth, for instance, oral malignancy. All individuals were distributed into four groups; a healthy non-smoker group (12 subjects), a healthy smoker group; (12 subjects), a periodontitis smoker (25 patients) and a periodontitis non-smoker (25 patients). Periodontal health was defined as PPD ≤ 3mm, BOP <10%, and intact periodontium (no probing attachment loss). Periodontitis groups were defined as interdental CAL equal to or greater than two in nonadjacent teeth or buccal/oral CAL ≥3 mm with pocketing >3mm detected at ≥ 2 teeth[22]. Participants were given detailed information about the study, and they were asked to complete a questionnaire detailing their background information, medical history, and dental history.

Clinical assessment: An examination of the entire mouth was achieved using the university of Michigan O probe with Williams marking at 1,2,3,5,7,8,9 and 10 mm. All teeth will be examined except the wisdom teeth. Full examinations of clinical periodontal parameters will be carried out: Assessment of soft deposits by full mouth plaque score (FMPS)[23]. Assessment of Gingival Bleeding on Probing (BOP), probing pocket depth (PPD), and clinical attachment level (CAL) were calculated at six sites per tooth for each patient.

Sample collection

All four groups' participants' unstipulated whole saliva samples will be obtained. The participant is required to abstain from eating or drinking anything other than water one hour prior to the collection of the sample. The participant will be asked to thoroughly rinse his mouth with water in order to ensure the removal of any potential debris or contaminating materials. Then he will wait for one to two minutes for the water to clear out of his mouth. After the collection, the samples will be stored in a compact cooling box in order to inhibit the growth of bacteria. The subject's number will be written on the label of the tube, which will correspond to the number that was previously written on the case sheet. After that, the samples will be centrifuged at a speed of 4000 rpm for 15 minutes, and then they will be stored in a freezer at a temperature of -20 degrees Celsius until the day of evaluation. Before any samples are analyzed, we will let each one thaw completely and let them stand at room temperature[24].

IL-6 measurement: An enzyme-linked immunosorbent assay kit (BioSource Systems, Invitrogen, NY, USA) was used to detect MT concentration in the saliva. The above-presented kit reported an assay sensitivity of < 1.0 Pg/ml. The assays were carried out as directed by the manufacturer. A total level of salivary MT was estimated based on the concentration of IL-6 measured.

Statistical analysis:

Statistical analysis was completed utilizing SPSS21 software. For nominal variables, standard deviation (SD) and mean were used. Furthermore, independent sample T-test, Levine's test, spearman correlation coefficient (r) and Shapiro-Wilk test were used. Level of significance was: Not significant P>0.05, Significant P<0.05.

Results

The healthy control group exhibited significantly lower values in all clinical periodontal measurements than the periodontitis group ($P < 0.05$). There were significant differences between the non-smoker and smoker periodontitis groups in BOP and CAL variables ($P < 0.05$) as demonstrated in Table 1. In relation to IL-6 analysis, the data indicate that the healthy non-smoking group had the lowest concentrations of salivary IL-6, whereas the smoker periodontitis group had the highest concentrations of salivary IL-6, with a notable variation between groups(table 2). In Table 3, the correlation between IL-6 and clinical periodontal variables revealed a strong positive correlation of IL-6 with most clinical parameters.

Table 1: Periodontal findings among control and case groups.

Variables	Oral Health status	Smoking status Non-Smokers Mean ±SD	Smokers Mean ±SD	T test	P value
PLI%	Healthy	21.583±8.229	22.167±9.262	0.163	**0.872
	Periodontitis	62.720±22.615	64.400±21.901	0.267	**0.791
	T test	8.052	8.230		
	P value	*0.000	*0.000		
BOP%	Healthy	4.250±2.179	2.667±2.103	1.811	**0.084
	Periodontitis	59.880±22.016	24.480±7.880	7.569	*0.000
	T test	12.507	12.916		
	P value	*0.000	*0.000		
PPD(mm)	Periodontitis	4.774±0.622	4.803±0.635	0.150	**0.882
CAL(mm)	Periodontitis	2.894±0.640	3.619±0.705	3.810	*0.000

Independent sample t test, SD: Standard deviation,*: Significant difference $p < 0.05$, **:Non-significant difference $p > 0.05$, PLI: Plaque index, BOP: Bleeding on probing, PPD: Probing pocket depth, CAL: clinical attachment level.

Table 2: IL-6 concentration (Pg/mL) among groups.

Smoking status		Oral health status Healthy	Periodontitis	T test	P value
Non-Smokers	Mean ±SD	6.304±2.456	18.724 ±8.563	4.896	*0.000
Smoker	Mean±SD	7.284±3.205	23.716±11.000	5.040	*0.000
T test		0.840	1.790		
P value		**0.410	**0.080		

SD: Standard deviation,* $p < 0.05$, ** $p > 0.05$.

Table3: Correlation of salivary IL-6 with clinical periodontal Variables in all groups.

Oral health status	Smoking status		IL-6 r	IL-6 p
Healthy	Non-Smokers	PLI%	0.670	*0.017
		BOP%	0.413	**0.182
	Smokers	PLI%	0.804	*0.002
		BOP%	0.769	*0.003
Periodontitis	Non-Smokers	PLI%	0.659	*0.000
		BOP%	0.602	*0.001
	Smokers	PLI%	0.649	*0.000
		BOP%	0.370	**0.069
Periodontitis	Non-Smokers	PPD	0.873	*0.000
		CAL	0.479	*0.015
Periodontitis	Smokers	PPD	0.762	*0.000
		CAL	0.512	*0.009

r: Pearson correlation, * $p < 0.05$, ** $p > 0.05$

Discussion

According to the study's findings, smokers (PT) had the highest mean value of plaque index (PLI), and significant differences between the disease and healthy groups were also noted.This result is consistent with other researches [25, 26], which demonstrated that smokers had a higher mean PL level while, these findings contrasted with Visvanathan etal. (2014) [27], who found lower levels of plaque in smokers. One possible reason for this is that tobacco consumption discolors teeth, which in turn makes the tooth surface rougher and promotes plaque buildup more quickly [28].

The outcomes of the current study revealed that the control groups had significantly fewer sites with bleeding on probing (BOP) than the disease groups. Additionally, there was a statistically significant difference between the smoker and non-smoker periodontitis groups, with the smokers (PT) group having fewer bleeding sites. These investigations were in conformity with Jassim, Ibrahim(2016) [29] and Chang et al.(2018)[30], who observed a significant difference between smokers and non-smokers in the number of bleeding sites. Whereas these findings did not coincide with Kubota et al. (2011)[31]and Kanmaz et al.(2019)[32], who found higher BOP positive site percentages in non-smokers than smokers. This outcome may happen from smoking, which might minimize gingival bleeding by suppressing angiogenesis or from the effect of vasoactive smoke components or metabolites on the already-existing gingival microvasculature, it is also conceivable that both processes occur concurrently [33].

Smokers' probing pocket depth (PPD) measures in the current study were higher than non-smokers' (PT), and the comparison reveals no statistically significant difference. These results were in line with Kubota et al. (2011) [31], who demonstrated a higher value of PPD measurements in smokers with non-significance difference, while disagreed with Ameer, Ali (2015)[34], who found higher PPD measurements in non- smokers than smokers.

The outcomes of this study showed that smokers (PT) had higher clinical attachment level (CAL) assessments than non-smokers (PT), and there was a highly significant difference between the groups. The results were consistent with previous findings [35, 36] In contrast, The findings were in disagreement with Ameer and Ali (2015)[34], who demonstrated that non-smoker patients had high measurements of CAL than smokers.There is a reasonable explanation for this result, Advanced glycation endproducts (AGEs) are produced in more significant quantities in Cigarette smokers, and when these AGEs interact with their receptors, it exacerbates inflammation in the periodontal tissues[37]. In the periodontium, AGEs promote bone resorption and collagen fiber degradation, resulting in periodontal support deterioration and tooth movement[38]. Moreover, Tobacco smoking increases oxidative stress in periodontal tissues, which, if unregulated, may lead to periodontitis [39,40].

The biochemical analysis of salivary IL-6 results showed that the mean value of salivary IL-6 was higher in Smokers (PT) than in other groups. There was a significant mean difference between healthy and periodontitis groups, and It was found that IL-6 levels increased in periodontitis groups when compared with healthy groups, and smoker groups showed higher IL-6 levels when compared with non-smoker groups. These results were parallel with Ebersole et al. (2013)[41], Kusuyama et al.(2019)[42] and Iso et al. (2021)[43], who found that the subjects with periodontitis had a significantly higher salivary IL-6 level than healthy subjects.Moreover,these data were consistent with several research [44, 45, 46, 36] ,which revealed that smokers had considerably higher concentrations of salivary IL-6 than non-smokers.

These findings contradict those of Ramseier et al.(2009)[47], Gursoy et al. (2009[48] and Teles et al.(2009)[49] , who discovered no difference in salivary IL-6 concentrations between those with periodontitis and healthy individuals. Furthermore, The current study results disagree with Kibayashi et al.(2007)[50] and Rathnayake et al. (2013)[51], who noted that the Salivary concentrations of IL-6 do not appear to be affected by smoking.

IL-6 is a proinflammatory cytokine, and the results of the current investigation were consistent with IL-6's role in modulating periodontitis [52]. Large quantities of gram-negative periodontopathic bacteria found

in the subgingival plaque are the most evident source for this elevation in IL-6 in individuals with periodontitis, as these microorganisms do not penetrate the periodontium in significant numbers, their solubilized substances spread into periodontal tissues, including the epithelium, therefore stimulating the generation of cytokines [53]. In addition, IL-6 is released by osteoblasts, which may influence the differentiation of monocytes into osteoclasts, osteoclasts play a crucial role in alveolar bone resorption, which is a keystone of periodontitis advancement. [54] Numerous studies have revealed that those who regularly use tobacco products, such as cigarettes or smokeless tobacco, are more probably to develop periodontitis than non-users [55,56]. Patients with periodontitis may have increased IL-6 production due to the combined effects of nicotine from cigarettes and lipopolysaccharide from bacterial infection [57]. Statistically, Pearson`s Correlation test was utilized to examine the correlativity between salivary IL-6 levels and the clinically periodontal parameters for the control and study groups. The results of this study exhibited a strong positive significant correlation between the levels of salivary IL-6 and all clinical periodontal variables except in the non-smoker(H) group and the smoker periodontitis group, the correlation was weak positive, non-significant between (BOP) and the levels of IL-6, and for(CAL) in the non-smoker periodontitis group, where there were weakly positive, significant correlations with salivary IL-6 levels.

The outcomes of this investigation were similar to previous observations [58, 59], which clarified the strong correlation between IL-6 levels in saliva and clinical variables and reported that IL-6 levels increased linearly to the severity of the periodontal disease.Whereas these results disagree with Teles et al.(2009))[49], who reported no association between the levels of salivary cytokines and clinical parameters of periodontal disease, likewise Reis etal.(2014) [60] reported a weak positive non-significant correlation between(PPDandCAL)and GCF levels of IL-6.

The positive correlation between IL-6 levels and different periodontal variables can be assigned to to the existence of biofilm and dental concrements, specifically the action of lipopolysaccharide on the tissue, which activates monocyte/T-lymphocytes, their activation increases the release of cytokines, including IL-6.[59] Furthermore, Keles et al. ,(2020) [61] reported a Significant reduction of IL-6 levels following non-surgical periodontal treatment due to reduction of plaque and gingival inflammation.

Conclusion

According to the findings of this study, the results revealed that smokers (both with and without periodontitis) have higher amounts of IL-6 in their saliva than nonsmokers (both healthy and periodontitis). This shows that smoking cigarettes had a boosting effect on the levels of IL-6 in the saliva.

Conflict of interest:

The authors state no potential conflict of interest.

Author contributions

AA and AM; study conception and design, Methodology, statistical analysis and interpretation of resultsAA; data collection,writing -review, original draft manuscript preparation. HA and HA; editing, supervision, and Both authors reviewed the results and approved the final version of the manuscript to be published.

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الترابط بين مستويات إنترلوكين 6 اللعابي في المدخنين مع المصابين بالتهاب اللثة

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المستخلص:

الخلفية :تحدث أمراض اللثة بسبب مجموعة من العوامل ، مع كون الصفيحة الجرثومية هي العامل المسبب الرئيسي, وعلى الرغم من أن بكتيريا دواعم السن تلعب دورًا مهمًا في ظهور التهاب دواعم السن ، فإن التفاعل المناعي الالتهابي المستمر، والذي يتم توجيهه في الغالب من خلال ارتفاع السيتوكينات المؤيدة للالتهابات، هو المكون الأساسي المسؤول عن تلف الأنسجة المرتبط بالتهاب دواعم السن. يعتبر الانترلوكين-6 (IL -6) سيتوكين متعدد الاتجاهات، ويتم إطلاقه بواسطة أنواع متعددة من الخلايا. و يعتبر IL-6 عاملا حاسمًا في العمليات التي تؤدي إلى أمراض اللثة وقد تم ربطه أيضًا بهجرة الخلايا الالتهابية. يعتبر التدخين عاملاً محتملاً رئيسيًا لاضطرابات ما حول الاسنان ويرتبط بزيادة في كل من ظهور وشدة التهاب اللثة ، وتهدف هذه الدراسة إلى تقييم العلاقة بين تدخين السجائر ومستويات اللعاب من IL-6 في المرضى الذين يعانون من التهاب دواعم السن مقارنة بالاصحاء, المواد والطرق: يتكون مجتمع العينة من أربعة وسبعين من الذكور ، وتم تقسيمهم إلى أربع مجاميع مختلفة: مجموعة غير المدخنين يمتلكون انسجة ما حول الأسنان سليمة سريريًا (عدد = 12)، مجموعة مدخنين يمتلكون انسجة ما حول الأسنان سليمة سريريًا (عدد = 12)، مجموعة التهاب دواعم الاسنان لغير المدخنين (عدد = 25) ومجموعة التهاب دواعم الاسنان للمدخنين (عدد = 25). تم أخذ عينات لعاب جميع المشاركين، ثم تم فحص معايير ما حول الاسنان السريرية (مؤشر الصفيحة الجرثومية ، مؤشرالنزف عند التسبير، مؤشر عمق الجيب بالاضافة الى فقدان الانسجة الرابطة سريرا) ، النتائج: وجد أن مستويات IL-6 أعلى في مجاميع التهاب دواعم السن مقارنة مع مجاميع السيطرة وفي مجاميع المدخنين مقارنة مع مجاميع غير المدخنين. ارتبطت معظم معايير ما حول الاسنان بشكل معنوي مع تركيز IL-6 في اللعاب. الاستنتاج: كشف هذا البحث أن المدخنين (سواء المصابين أو غير المصابين بالتهاب دواعم السن) لديهم كميات أعلى من IL-6 في لعابهم مقارنة بغير المدخنين (الاصحاء والتهاب دواعم الأسنان). وهذا يدل على أن تدخين السجائر كان له تأثير معزز على مستويات IL-6 في اللعاب.