

Verification of CRP Levels in Peripheral Blood Samples for Localized Aggressive Periodontitis (LAP)

Hussein Mohammed Shoga Al-Deen¹, Khaled A AL-Haddad¹, Amani Abdulhakeem Al-Sharani², Abdulwahab Ismail Mohamed Al-Kholani³, Mohammed Mohammed Ali Al-Najhi^{1,4}, Ameen Abdullah Yahya Al-Akwa¹, Hassan Abdulwahab Al-Shamahy^{5,6*} and Azhar Azher Mohammed Al-Ankoshy⁷

¹Department of Faculty of Dentistry, Orthodontics, Pedodontics and Prevention Sana'a University, Yemen

²Department of Oral Medicines and Periodontology College of Dentistry, University of Sciences and Technology, Yemen

³Department of conservative dentistry, Faculty of Dentistry, Sana'a University, Republic of Yemen

⁴Department Faculty of Dentistry, Orthodontics, Pedodontics and Prevention Genius University for Sciences & Technology, Dhamar city, Republic of Yemen

⁵Departement of Basic Sciences, Faculty of Dentistry, Sana'a University, Republic of Yemen

⁶Medical Microbiology department, Faculty of Medicine, Genius University for Sciences & Technology, Dhamar city, Republic of Yemen

⁷Department of Physiology Jabir ibnHayyan Medical University, Faculty of Medicine, Iraq.

Received December 10, 2022; Revised December 31, 2022; Accepted January 03, 2023

ABSTRACT

Background and aims: Circulating C-reactive protein (CRP) provides a window to investigate periodontal status such as levels of inflammatory mediators, the consequences of which due to increased local destruction of connective tissue structural elements are ideal markers of disease activity that can be estimated in CRP in circulation. This study aimed to investigate CRP levels in peripheral blood samples of locally aggressive periodontitis (LAP), patients devoid of any other systemic disease compared to healthy subjects as controls; and the influence of host factors such as age and sex on the CRP inflammation biomarker.

Methods: This study included 33 patients with clinically and radiologically confirmed localized aggressive periodontitis, who were admitted to the dental clinic of Al-Jumhuri University Hospital and private dental clinic (Al-Morada Dental Clinic) in Sana'a. It also included 33 healthy control groups. CRP levels (mg/L) in the circulation were measured by photometry and turbidimetry. Samples were processed immediately and set values were recorded. All patients were informed in detail about and consented to the determination of this marker. Differences in mean CRP concentrations (mg/L) from the blood sample were determined for each individual with variables including age and sex.

Results: The patient group consisted of 24.4% males and 57.6 females, with an age range of 16-47 years, with a mean of 26.3 years. With regard to the control group, 24.4% were males and 57.6% were females, between the ages of 16-44 years, with an average age of 29.1 years. In total patients, the mean $\pm$ SD of circulating C-reactive protein was 4.67 ± 0.841 mg/L, and ranged from 2.8 to 6.1 mg/L, for males 4.42 ± 0.57 mg/L versus 4.85 ± 0.968 mg/L for females. For healthy controls, C-reactive protein concentrations (mg/L) were lower than those for patients (2.067 ± 0.387 mg/L). Considering the effect of age groups and gender on CRP concentrations (mg/L) of aggressive periodontitis patients, levels were approximately equal in both sexes and all age groups.

Conclusion: CRP levels increase with aggressive periodontitis patients, and there was no significant effect of sex or ages in CRP level differences. More studies are needed to clarify this relationship and the confounding factors associated with it. Further research is needed as other systemic markers that may be more specific to periodontal disease such as fibrinogen, leptin, white blood cell count and interleukin-6 should be considered.

Keywords: C-reactive protein (CRP), Host factors, Inflammatory biomarker, Localized aggressive periodontitis (LAP), Peripheral blood

Abbreviations: BOP: Bleeding on Probing Examination; CRP: C-Reactive Protein; CVD: Cardiovascular Disease; IPT: Intensive Periodontal Treatment; IQR: Interquartile Range; LAP: Localized Aggressive Periodontitis; LPS: Lipopolysaccharides; NSPT: Standard Non-Intensive Periodontal Treatment; PD: Pocket Depth

Corresponding author: Hassan Abdulwahab Al-Shamahy, Faculty of Medicine and Health Sciences, Sana'a University, Republic of Yemen, Tel: +967-1-239551, Mobile: +967-770299847; E-mail: shmahe@yemen.net.ye, al-shamahy@gust.edu.ye

Citation: Al-Deen HMS, AL-Haddad KA, Al-Sharani AA, Al-Kholani AIM, Al-Najhi MMA, et al. (2023) Verification of CRP Levels in Peripheral Blood Samples for Localized Aggressive Periodontitis (LAP). J Oral Health Dent, 6(2): 498-504.

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INTRODUCTION

One of the major diseases affecting the periodontal tissues is periodontitis [1]. This condition occurs in response to a predominantly Gram-negative bacterial infection arising from dental plaque [2]. Subgingival biofilms present a continuous replenishing reservoir of lipopolysaccharides (LPS) and Gram-negative bacteria with easy access to the periodontal tissue. Gram-negative microorganisms and the LPS they secrete act as systemic challenges by inducing key vascular responses, including infiltration of inflammatory cells into vessel walls, vascular fatty degeneration, vascular smooth muscle proliferation, and intravascular coagulation [3]. Periodontitis is a chronic inflammatory disease initiated by a biofilm dysplasia of the teeth [4] and followed by a progressive destruction of the periodontal tissue [5]. Bacteria and their products progressively affect periodontal integrity, which can trigger a local inflammatory response but also a systemic response [5]. Elevated levels of pro-inflammatory mediators have been reported in patients with periodontitis [6] who also show distinct hematologic changes [7] including elevated levels of C-reactive protein (CRP) [8]. CRP is an acute-phase protein principally formed by the liver in response to tissue damage or infections [9]. At the same time as CRP is a more traditional marker of inflammation with lower resolution (in the range of 10 to 1000 mg/L), high-sensitivity CRP (hs-CRP) is a highly accurate and accurate marker (in the range of 0.5 to 10 mg/L) [10]. The association between CRP and periodontitis has received considerable attention in part due to the association between periodontitis and cardiovascular disease (CVD) [8]. In spite of this, CRP has been recognized as a marker of the association of periodontitis with other systemic diseases [7]. Preceding systematic reviews have intimated raised CRP levels in patients with periodontitis [8-12]. However, there are inconsistent evidence-based findings on the effect of two different approaches to periodontal treatment [13]. Standard non-intensive periodontal treatment (NSPT) consists of conventional mechanical scaling and root planning with quarter-by-quarter polishing under local anesthesia. While, intensive periodontal treatment (IPT) includes an intensive session of complete sub gingival root debridement over a 24 h period under local anesthesia (gum surgery, tooth removal, or topical antibiotics can be administered). Prearranged the clinical significance of chronic inflammation and prospect systemic health outcomes, comprising in patients with periodontitis, the newly available amount of evidence, and an updated and robust assessment of data relating to the association of periodontitis and its treatment with CRP levels were thought to be of benefit [8-13].

Although previous research has been conducted on dental caries, oral and facial abscesses of odontogenic origin, localized aggressive gingivitis (LAP), periodontitis, bacterial and fungal oral infections, interleukin-1 levels in human gingival sulcus, etc. in Yemen [14-32], there is no

information or research regarding systemic CRP levels in periodontitis in Yemen. Therefore, this study aimed to investigate the levels of C-reactive protein in blood samples in patients with localized aggressive periodontitis (LAP), who are free from any other systemic disease and their results were compared to healthy subjects as controls; and the influence of host factors such as age and gender on the levels of the CRP inflammatory biomarker.

MATERIALS AND METHODS

Control group: Regarding control group, they were healthy individual selected from community, matched the cases in sex and age groups. They are 24.4% males and 57.6% females, ranging in age from 16-44 years, with a mean equal to 29.1 years old.

Patients group: This study included 33 patients clinically and radio logically confirmed with localized aggressive periodontitis (LAP), who were admitted to the dental clinic at the Republican University Hospital and private dental clinic (Al-Mortadda dental clinic) in Sana'a. CRP levels (mg/L) were measured in circulating blood by photometry and turbidimetry. The samples were immediately processed and the established values were recorded. All patients were informed in detail about and consented to this marker determination. Differences in mean CRP concentrations (mg/l) of the blood sample collection for each individual with variables that included age and sex were determined.

Periodontal Evaluation: Patients with aggressive periodontitis should have at least one tooth with positive bleeding on probing examination (BOP) and a pocket depth (PD) greater than 5 mm in all quadrants (except third molars). Pocket depth was assessed with a WHO periodontal probe with a cut of 11.5 mm from six locations in each present tooth. Bleeding on examination is a sign of inflammation and indicates some type of destruction and erosion of the lining of the sulcus [33] or ulceration of the sulcular epithelium. Blood comes from the lamina propria after ulceration of the lining.

Inclusion criteria: Inclusion criteria were good general health, no medication, and diagnosis of aggressive periodontitis recession according to the AAP Classification [34], and patient's agreement with CRP level determination from venous blood.

Exclusion criteria: Exclusion criteria for cases and controls: included history of any systemic disease or any other disease manifested locally in oral cavity, current pregnancy or lactation, high blood pressure, sleep disturbances, depression, excessive smoking recently or in past 10 years. All patients and controls were of Yemeni origin.

Statistical analysis: For calculations descriptive statistics were used: mean standard deviation, frequencies, and standard error. CRP and other indices present in groups. With a mode, the median, the range, the 75% interquartile

range (IQR) and the variance in all individual values tested by t-test and p value. Significance level of 0.05 was used in all tests. Epi-Info version 7 was used.

Ethical Consideration: Ethical approval for this study, No: 375 dated January 23, 2021 were obtained from the Medical Ethics and Research Committee of the Faculty of Medicine and Health Sciences, Sana'a University. All procedures were according to the ethical guidelines of the review committee.

RESULTS

The study included 33 aggressive periodontitis patients and 33 healthy individuals. Patient group included 24.4% male and 57.6 female, ranging in age from 16-47 years, with a mean equal to 26.3 years old. Regarding control group 24.4% were males and 57.6% were females, ranging in age from 16-44 years, with a mean equal to 29.1 years old (**Table 1**). In total, the mean $\pm$ SD of circular C-reactive protein was 4.67 ± 0.841 mg/l, with a mode equal to 4.9 mg/L, the median was 4.9 mg/L, and ranged from 2.8 to 6.1 mg/l with the 75% interquartile range (IQR) equal to 5.1 mg/l; the variance in all individual values was significantly distributed on the normal curve with t-test of 31.8 and $p < 0.0001$. For males the mean $\pm$ SD of circular C-reactive protein was 4.42 ± 0.57 mg/l, with a mode equal to 3.9 mg/L, the median was 4.33 mg/L, and ranged from 3.7 to 5.7 mg/l with the 75% interquartile range (IQR) equal to 4.9 mg/l; the variance in all individual values was significantly distributed on the normal curve with t-test of 28 and $p < 0.0001$. For females the mean $\pm$ SD of circular C-reactive protein was 4.85 ± 0.968 mg/l, with a mode equal to 5.1 mg/L, the median was 5.1 mg/L, and ranged from 2.8 to 6.1 mg/l with the 75% interquartile range (IQR) equal to 5.4 mg/l; the variance in all individual values was significantly distributed on the normal curve with t-test of 21.8 and $p < 0.0001$ (**Table 2**).

Table 1. Characteristics of patients and healthy controls, tested for C-reactive protein concentrations (mg/l) in the blood circulation.

Characteristics	Patients n (%)	Controls n (%)
	Mean age =26.3 years; Range =16-47 years	Mean age =29.1 years; Range =16-44 years
Age group (years)		
<20	10 (30.3)	5 (15.2)
20-29	12 (36.4)	12 (36.4)
30-39	7 (21.8)	11 (33.3)
≥ 40	4 (12.1)	5 (15.2)
Total	33 (100)	33 (100)
Gender		
Male	14 (42.4)	14 (42.4)
Female	19 (57.6)	19 (57.6)

Table 2. C-reactive protein concentrations (mg/l) for aggressive periodontitis total patients and a comparison of males and females, in a research testing of circulating CRP Levels in human blood.

Statistic	C-reactive protein concentrations (mg/l)		
	Total n=33	Males n=14	Females n=19
Mean	4.67	4.42	4.85
SD	0.841	0.57	0.968
SE	0.146	0.153	0.22
Mode	4.9	3.9	5.1
Median	4.9	4.33	5.1
Min	2.8	3.7	2.8
Max	6.1	5.7	6.1
25% ile	4.1	3.9	4.7
75% ile	5.1	4.9	5.4
T-test	31.8	28	21.8
df	32	13	18
P	<0.0001	<0.0001	<0.0001

The mean: the average value; The median: the middle value (it's a robust alternative to mean), and the mode: the most frequent value and the interquartile range (IQR) (25 and 75%): it gives the full spread of the data in 25% and 75% of the values.

C-reactive protein concentrations (mg/l) for aggressive periodontitis total patients was as follow: the mean $\pm$ SD of circular C-reactive protein was 4.67 ± 0.841 mg/l, with a mode equal to 4.9 mg/L, the median was 4.9 mg/L, and ranged from 2.8 to 6.1 mg/l with the 75% interquartile range (IQR) equal to 5.1 mg/l; the variance in all individual values was significantly distributed on the normal curve with t-test of 31.8 and $p < 0.0001$.

While for healthy controls the C-reactive protein concentrations (mg/l) were lower than that of the patients in which the mean $\pm$ SD of circular C-reactive protein was 2.067 ± 0.387 mg/l, with a mode equal to 2.1 mg/L, the median was 2.1 mg/L, and ranged from 1.2 to 3.1 mg/l with the 75% interquartile range (IQR) equal to 2.2 mg/l; the variance in all individual values was significantly distributed on the normal curve with t-test of 30.6 and $p < 0.0001$ (**Table 3**). Considering age groups effects on the C-reactive protein concentrations (mg/l) for aggressive periodontitis patients, roughly equal levels values were occurred in all age groups (**Table 4**).

Table 3. C-reactive protein concentrations (mg/l) for aggressive periodontitis total patients and a comparison with healthy controls, in a research testing of circulating CRP Levels in human blood.

Statistic	C-reactive protein concentrations (mg/l)	
	Cases n=33	Controls n=33
Mean	4.67	2.06
SD	0.841	0.387
SE	0.146	0.067
Mode	4.9	2.1
Median	4.9	2.1
Min	2.8	1.2
Max	6.1	3.1
25% ile	4.1	1.9
75% ile	5.1	2.2
T-test	31.8	30.6
df	32	32
P	<0.0001	<0.0001

The mean: the average value. The median: the middle value (it's a robust alternative to mean), and the mode: the most frequent value and the interquartile range (IQR) (25 and 75%): it gives the full spread of the data in 25% and 75% of the values.

Table 4. C-reactive protein concentrations (mg/l) for aggressive periodontitis of different age groups, in a research testing of circulating CRP Levels in human blood.

Statistic	C-reactive protein concentrations (mg/l)			
	<20 years group n=10	20-29 years n=12	30-39 years n=7	≥40 years n=4
Mean	4.67	4.567	4.60	5.1
SD	0.668	1.006	0.945	0.638
SE	0.211	0.29	0.357	0.319
Mode	3.9	2.9	5.1	4.5
Median	4.8	4.85	5.1	4.95
Min	3.9	2.9	2.8	4.5
Max	5.6	6.1	5.4	6
25% ile	3.9	3.9	3.90	4.7
75% ile	5.1	5.15	5.3	5.5
T-test	22	15.7	12.8	15.9
df	9	11	6	3
P	<0.0001	<0.0001	<0.0001	0.0005

The mean: the average value. The median: the middle value (it's a robust alternative to mean), and the mode: the most frequent value and the interquartile range (IQR) (25 and 75%): it gives the full spread of the data in 25% and 75% of the values.

DISCUSSION

CRP represents a dependable marker of acute phase response to infectious burden and/or inflammation [35]. As a result of its kinetic possessions, C-reactive protein best illustrates the inflammatory state of the human [36]. Recent evidence indicated that patients with acute periodontitis had

increased serum C-reactive protein levels compared to an unaffected control group [37]. We compared and evaluated systemic levels of CRP in peripheral blood samples of patients with aggressive periodontitis and healthy controls. CRP levels may fluctuate with various factors such as hypertension, alcohol use, smoking, diabetes, sleep disorders, chronic fatigue, depression, several other systemic diseases, and pregnancy or lactation [38]. Therefore, we established robust exclusion criteria (see Methods) for patients to be included in this study.

In the current study, the C-reactive protein (mg/L) concentrations of periodontitis patients were approximately 2.5 volumes higher than that of healthy controls (patients' mean $\pm$ SD = 4.67 ± 0.841 mg/L vs. 2.067 ± 0.387 mg/L of control). This underscores the fact that CRP levels correlate with severity of periodontal affection and aggressive periodontitis shows a stronger systemic inflammatory burden than the control group similar to that reported by Wohlfeil [39]. Also, our finding is similar to that study of Goyal [40] showed the highest CRP levels in patients with aggressive periodontitis and the lowest values in the group of healthy patients [40]. Other studies showed increased CRP levels in patients with chronic periodontitis compared to patients with gingivitis [41,42]. In a study by Podzimek [43] aggressive periodontitis patients had an average CRP of 2.8 mg/L below or levels of the same patient group (4.67 ± 0.841 mg/L). This difference may be explained by that, race has been found to influence CRP levels [44] and data in diverse populations are not comparable. A study from the USA reported C-reactive protein (CRP) levels of 2.05 mg/L in aggressive periodontitis patients with the generalized form and C-reactive protein (CRP) levels of 1.1 mg/L in patients with the localized form [45]. However, our result (4.67 ± 0.841 mg/L) is similar to another study from the USA that showed C-reactive protein (CRP) levels of 4.06 mg/L in subjects with high levels of clinical attachment loss mean [46].

While lower values were reported in a Swedish study showing an average CRP of 2 mg/L in periodontitis patients [47]. In the Netherlands, a study reported lower CRP levels than (1.45 mg/L) in patients with a generalized form of periodontitis and CRP levels of 1.30 mg/L in patients with the localized form [48]. Another study from India showed a higher level than our study where CRP levels of 7.49mg/L in aggressive periodontitis patients and CRP levels of 4.88mg/L in chronic periodontitis patients were found [49]. Therefore, in our study, only patients of Yemeni origin were included.

Regarding the statistical associations between male and female indices as well as ages with CRP levels determined in periodontitis patient groups, there were no significant differences with C-reactive protein concentrations (mg/L) for the comparison of aggressive periodontitis for males and females or for age groups (Tables 2 & 3). These results are

similar to those previously reported in which no significant differences were found between sexes or between ages [43]. Thus, CRP increases with periodontal impairments. The CRP indicator is a very important issue. The observed association between periodontal conditions and systemic CRP demonstrated that periodontal affections may be a contributing factor to systemic inflammation. In the study by Beck [50]. CRP as a clinical parameter was more difficult to estimate the degree of systemic inflammation than traditional classifications of mild, moderate, and severe periodontitis or other measures of disease severity such as attachment loss [50]. The novelty of the results obtained was based on comparing one type of periodontal disease with healthy controls, as two or three types are usually compared, and on comparing various periodontal indices with subsequently determined CRP levels in the patient's peripheral blood.

CONCLUSION

Our study results show that CRP levels increase subsequently with the aggressive periodontitis patients, and there was no significant effect of sex or ages in the level. Further studies are needed to clarify this association and the associated confounding factors. In further research, other systemic markers that might be more specific to periodontal disease such as fibrinogen, leptin, white blood cell count, and interleukin-6 should be considered. Changes in their values during the treatment of periodontal disease could lead to improved monitoring of periodontal tissue status during therapy. Elevated levels of such markers of systemic inflammation are connected to both systemic diseases and periodontal diseases. Studying these markers would certainly be beneficial for monitoring periodontal disease therapy.

ACKNOWLEDGMENTS

The authors thank the Faculty of Dentistry, Sana'a University, Sana'a, and Yemen for their generous support.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

AUTHOR'S CONTRIBUTIONS

This article is part of a research supervised by Professor Hassan Al-Shamahy who conceived the subject, wrote a draft of the manuscript and analyzed the data. Other co-authors helped in the clinical parts of the study.

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