

Original Research

Association between Periodontitis and Serum C - Reactive protein Levels

¹Abhiroop Singh, ²Romesh Singh, ³Gaurav Gautam

¹MDS, Registrar, Dept of Oral and Maxillofacial Surgery, Indira Gandhi Government Dental College, Jammu, India;

²MDS, Professor and HOD, Dept of Periodontology, Institute of Dental Sciences, Jammu, India;

³Consultant Maxillofacial Surgeon, Jaipur, Rasjasthan, India

ABSTRACT:

Aim: The aim of this study to evaluate the association between periodontitis and serum C - reactive protein levels. **Methods:** The cross-sectional study was conducted among 100 Individuals who were 18 years or older and those presenting a minimum of 12 teeth were included. Sociodemographic and behavioral characteristics Participants' data on sociodemographic and behavioral characteristics were collected by means of an interview during which a structured questionnaire was used. Data on sex, age, family income (number of wages of all members of the family who were economically active), schooling (number of years of studying) and smoking (smokers, non-smokers) were collected. Clinical examination was carried out in four sites (mesial, buccal, distal and lingual) of all teeth for analysis of the following periodontal parameters for periodontal diagnosis: probing depth (PD), bleeding on probing (BOP) and clinical attachment level (CAL). During clinical examination, a manual periodontal probe. A blood test of each participant was ordered for quanti- fication of CRP. **Results:** Comparisons between the groups with normal and altered CRP levels regarding the sociodemographic variables (sex, age, family income and schooling) as well as smoking, BMI and periodontitis are presented in Table1. No significant difference between groups regarding sex, age, family income, schooling and smoking was observed. Individuals with altered CRP presented a mean BMI of 33.0, while individuals with normal CRP presented a mean BMI of 25.7. A significant difference between groups was observed ($P<0.001$). The prevalence of periodontitis among individuals with altered CRP (70%) was significantly higher than among individuals with normal CRP (70%) ($P=0.007$). The regression analyzis demonstrated that the levels of CRP among individuals with periodontitis were 1.82 times higher than the levels of CRP among individuals without periodontitis (confidence interval=1.12 – 2.93; $P=0.039$), regardless of the influence of the cofounding variables age, smoking and BMI. The analyzis also showed that the levels of CRP among obese individuals were 3.58 times higher than the levels of CRP among underweight individuals/individuals with normal weight (confidence interval=1.66 – 7.85; $P=0.003$). **Conclusions:** The alteration of the C-reactive protein levels among individuals with a higher prevalence of perio- dontitis corroborates clinical evidence that periodontal infection has a systemic impact.[5].

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Corresponding author: Abhiroop Singh, MDS, Registrar, Dept of Oral and Maxillofacial Surgery, Indira Gandhi Government Dental College, Jammu, India

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INTRODUCTION

CRP is a pentameric plasma protein with homologs in vertebrates and many invertebrates that participate in the systemic response to inflammation. It is a pattern recognition molecule, that is extremely sensitive and non-specific acute-phase marker for inflammation, produced in response to many forms of injury other than binding to specific molecular configurations that are typically exposed during cell death or found on the surfaces of pathogens [1]. It is regulated by cytokines like interleukin-6 (IL- 6), interleukin-1 α

(IL-1 α) and tumour necrosis factor- α (TNF- α) [2,3]. These in turn cause systemic changes including hepatic release of a range of plasma proteins, activation of complement proteins and various metabolic changes [4]. CRP levels have an association with smoking, obesity, triglycerides, diabetes and periodontal disease. It is proposed that changes in cellular and molecular components of peripheral blood can be found in subjects with periodontitis because of inflammatory changes of the periodontal tissues [6]. According to Panichi et al [7].

CRP is currently considered a key biomarker of systemic inflammation, and although it is mainly synthesised by hepatocytes in the liver in response to inflammation and tissue damage, it can also be produced locally by arterial tissue. CRP and other acute phase molecules are usually present at relatively low levels in plasma, but may be raised dramatically within 72hrs of tissue injury or with infection. CRP opsonizes bacteria for complement-binding and activates complement when complexed [8]. The normal CRP levels vary between populations, with mean values between 1.0 to 3.0 mg/l. However, using ultrasensitive methods, it is possible to detect CRP levels as low as <1.0 mg/l. The acute-phase reaction represents an early and highly complex reaction of the organism to a variety of injuries such as bacterial, viral or parasitic infection, mechanical or thermal trauma, ischaemic necrosis or malignant growth [2]. This induces a complex series of non-specific, systemic, physiological and metabolic responses leading to increased synthesis and secretion of plasma proteins. This phenomenon is termed as 'acute phase response' [9]. These changes are called 'acute' because most are observed within hours or days following the onset of infection or injury, although some acute phase changes also indicate chronic disease [3]. The presence of certain acute phase changes in an otherwise healthy individual can alert the physician to hidden diseases.

MATERIAL AND METHODS

The cross-sectional study was conducted in Dept. of Periodontology after taking the approval of the protocol review committee and institutional ethics committee. 100 Individuals who were 18 years or older and those presenting a minimum of 12 teeth were included. Individuals living with the human immunodeficiency virus, pregnant women, individuals who had undergone periodontal treatment within the last three months, individuals who had undergone anti-inflammatory or antimicrobial therapy within the last three months, those with diabetes, individuals with any contraindication to clinical periodontal examination and individuals reporting any systemic health condition were excluded. Sociodemographic and behavioral characteristics Participants' data on sociodemographic and behavioral characteristics were collected by means of

an interview during which a structured questionnaire was used. Data on sex, age, family income (number of wages of all members of the family who were economically active), schooling (number of years of studying) and smoking (smokers, non-smokers) were collected.

PERIODONTAL CLINICAL EXAMINATION

Clinical examination was carried out in four sites (mesial, buccal, distal and lingual) of all teeth for analysis of the following periodontal parameters for periodontal diagnosis: probing depth (PD), bleeding on probing (BOP) and clinical attachment level (CAL). During clinical examination, a manual periodontal probe

DEFINITION OF PERIODONTITIS AND ASSESSMENT OF THE PREVALENCE

The criteria for periodontitis definition was the presence of ≥ 4 teeth having ≥ 1 sites with PD ≥ 4 mm and CAL ≥ 3 mm associated with BOP [10]. A blood test of each participant was ordered for quantification of CRP. The collection of blood samples and the analysis of the samples of all individuals were carried out providing a period of eight hours of fasting. CRP values less than 3 mg/L were considered normal. Values greater than or equal to 3 mg/L were considered altered [11]. Thus, participants were divided into two groups, according to the serum levels of CRP: individuals with normal CRP and individuals with altered CRP. Weight and height were measured for body mass index (BMI) calculation. Participants could be assigned to the following subgroups according to their BMI: underweight (BMI below 18.5), normal weight (BMI between 18.5 and 24.9), overweight (BMI between 25 and 29.9) and obese (BMI above 29.9).

STATISTICAL ANALYSES

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS 21.0, Armonk, USA), a regression analysis evaluating the association between periodontitis and CRP alterations controlling for confounding variables (age, smoking and BMI) was carried out. In all analysis results with a probability lower than 5% were considered significant ($P < 0.05$).

RESULTS

Comparisons between the groups with normal and altered CRP levels regarding the sociodemographic variables (sex, age, family income and schooling) as well as smoking, BMI and periodontitis are presented in Table 1.

Table 1: Comparisons between individuals with normal and altered CRP with respect to independent variables.

Variable	Total sample	Normal CRP ^{a)}	Altered CRP ^{a)}	P-value
N	100	60	40	
Age (yr.)	38.4 (± 10.2)	38.1 (± 10.6)	38.9 (± 9.8)	0.88
Sex (%)				0.155
Male	21(21%)	15(25%)	6(15%)	
Female	79(79%)	45(75%)	34(85%)	

Family income				0.41
≤5 salary	87(87%)	51(85%)	36(90%)	
> 5 salary	13(13%)	9(15%)	4(10%)	
Schooling (yr.)				0.087
≤8	38(38%)	18(30%)	20(50%)	
9-12	46(46%)	30(50%)	16(40%)	
> 12	16(18%)	12(20%)	4(10%)	
Smoking	12(12%)	6(10%)	6(15%)	0.69
BMI (Kg/m ²)	29.8 (±4.7)	27.0 (±3.3)	34.0 (±5.2)	<0.001
CRP (mg/L)	4.9 (±5.8)	1.6 (±0.6)	9.7 (±7.7)	<0.001
Periodontitis	52(52%)	24(40%)	28(70%)	0.007

No significant difference between groups regarding sex, age, family income, schooling and smoking was observed. Individuals with altered CRP presented a mean BMI of 33.0, while individuals with normal CRP presented a mean BMI of 25.7. A significant difference between groups was observed ($P<0.001$). The prevalence of periodontitis among individuals with altered CRP (70%) was significantly higher than among individuals with normal CRP (70%) ($P=0.007$). The regression analysis demonstrated that the levels of CRP among individuals with periodontitis were 1.82 times higher than the levels of CRP among individuals without periodontitis (confidence interval=1.12 – 2.93; $P=0.039$), regardless of the influence of the confounding variables age, smoking and BMI (Table 2).

Table2: Regression analysis evaluating the association of periodontitis and CRP alteration, controlling for confounding variables (age, smoking and body mass index).

	Ratio (95% CI) Non-adjusted	P-value	Ratio (95% CI) Adjusted	P-value
Periodontitis				
No	1	0.006	1	0.039
Yes	2.12 (1.40 – 3.52)		1.82 (1.12 – 2.93)	
Age (yr.)				
≤35	1		1	
>35 to <42	0.86 (0.58– 1.86)	0.74	1.11 (0.69 – 1.81)	0.87
>43	0.95 (0.42 – 1.56)	0.52	0.60 (0.36 – 0.98)	0.05
Smoking				
No	1	0.51	1	0.45
Yes	1.41 (0.82 – 2.47)		1.34 (0.77 – 2.39)	
BMI				
Underweight/normal weight	1		1	
Overweight	1.56 (0.95 – 2.19)	0.154	1.26 (0.83 – 1.94)	0.55
Obese	4.20 (1.93 – 8.79)	<0.001	3.58 (1.66 – 7.85)	0.003

The analysis also showed that the levels of CRP among obese individuals were 3.58 times higher than the levels of CRP among underweight individuals/individuals with normal weight (confidence interval=1.66 – 7.85; $P=0.003$).

DISCUSSION

CRP, a marker for acute inflammation, is produced by the liver as a result of various types of injuries, including infectious illnesses. Inflammatory mediators arising from periodontitis may stimulate hepatocytes to produce CRP. Among these mediators, interleukin-1, interleukin-6 and tumor necrosis factor alpha are particularly involved in this process [10]. In this sense, periodontal infection may lead to systemic inflammation with a significant increase in CRP levels. The results of the present study showed that individuals with periodontitis presented a significantly higher level of CRP in comparison with individuals without periodontitis. These results allow one to accept the hypothesis that periodontitis is associated with a higher production of this nonspecific inflammatory marker with far-reaching effects on the individual affected by periodontitis. In

one previous study [12], the authors evaluated how systemic inflammation mediated the association between periodontitis and glycemic status. The results of their study showed that CRP sense of Porphyromonas gingivalis increases CRP levels in nearly 22%. It should be emphasized that almost all studies analyzing the association between periodontitis and serum CRP levels have evaluated individuals with any systemic changes, such as cardiovascular disease, diabetes or rheumatoid arthritis. The presence of systemic changes can be a confounding factor in assessing the impact of periodontitis on CRP levels. In our study, only individuals without any systemic alteration participated. The exclusion of individuals who had reported the presence of any systemic alteration during an interview strengthens the present study. However, it is possible that some unknown systemic

changes may be present in some individuals in the sample, which is a limitation. Additionally, the severity of periodontitis may have a direct impact on the levels of CRP. One study demonstrated that CRP levels increase with the severity of periodontitis. Cases of very progressive and extensive periodontitis are associated with higher CRP levels [13-22]. As regards periodontal therapy, however, intervention studies show discrepancies whether periodontal treatment has an impact on the reduction of serum CRP levels [15,16,22-24]. In addition to the periodontal infection, other factors may be associated with the increased production of CRP. This fact may explain why some individuals without periodontitis presented significant changes in CRP levels. Factors such as age, smoking and obesity have been associated with alterations of the levels of CRP [25]. Older individuals, smokers and individuals with obesity may have increased levels of this marker. This is the reason why regression analysis assessing the relationship between periodontitis and CRP levels, controlling for these confounders has been conducted herein.

In this study, individuals with normal CRP and altered CRP were roughly equal in age, and the mean age of the sample was not high. CRP concentration increases with age, probably due to the increased incidence of subclinical pathological conditions. Age is a highly relevant factor that should be taken into account when CRP is assessed. This result diverges from the fact that a higher age is associated with increased levels of CRP.²⁵ On the other hand, the prevalence and severity of periodontitis may also increase with age [26]. Therefore, age is a confounding factor that should be evaluated in studies in which the association between periodontitis and serum CRP levels is assessed. The similarity between groups of individuals with normal and altered CRP serum levels regarding age is a strong point of the present study, favoring the analysis of the relationship between periodontitis and CRP.

Here in, the regression analysis demonstrated that obese individuals presented significantly higher levels of CRP in comparison with underweight individuals/normal weight individuals. The scientific literature has shown that obesity is associated with high levels of CRP because the secretion of inflammatory cytokines is increased in individuals affected by obesity [27]. Obesity has also been associated with periodontitis. The secretion of cytokines by the adipose tissue leads to a more exacerbated inflammatory response with a strong impact on the pathogenesis of periodontitis [28]. Smoking has been associated with high levels of CRP [25]. Smoking is also a risk factor for periodontitis. Tobacco use plays an important role in the pathogenesis of inflammatory periodontal disease. Smokers present greater prevalence and severity of periodontitis [10]. Here in, no significant difference between groups regarding the number of smokers was

observed. Moreover, the regression analysis also demonstrated that the levels of CRP among smokers were not significantly different in comparison with the levels of the non-smokers. The low number of individuals who were smokers and participated in this study may explain the similarity between groups regarding the smoking habit. In addition, CRP levels appear to be higher in women and in individuals with low socioeconomic status [29,30]. Importantly, in this study, the groups of individuals with normal and altered levels of CRP were similar in relation to sex, family income and schooling.

The definition of the criteria for periodontitis diagnosis is an important methodological step in studies in which the association between periodontal disease and levels of inflammatory markers is evaluated. The criteria used for the diagnosis of periodontitis may have a great impact on the prevalence of the disease [31]. The definition of periodontitis should not underestimate or overestimate the disease. The characteristics of the periodontal condition of the sample should also be considered. Individuals with differences in the extension and severity of the periodontal disease may present different systemic behaviors. This fact should be considered when interpreting the results and conclusions of the different studies. Additionally, a thorough periodontal examination is necessary to establish an appropriate diagnosis. In the present study, a complete periodontal clinical examination was performed to evaluate the periodontal parameters and a robust diagnostic criterion was used to assess the systemic impact of periodontitis.

CONCLUSIONS

The alteration of the C-reactive protein levels among individuals with a higher prevalence of periodontitis corroborates clinical evidence that periodontal infection has a systemic impact.

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