European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 07, Issue 05, 2020

C-Reactive Protein and Periodontal Disease – A Review

Mohana Kondapally[1], Ramesh KSV[2], Sruthima NVS[3], Gautami S Penmetsa[4], P. Mohan kumar[5], Meghana Gangolu [6]

[1,6]Post graduate, Department of Periodontics, Vishnu Dental College
[2]Associate professor, Department of Periodontics, Vishnu Dental College
[3]Professor, Department of Periodontics, Vishnu Dental College
[4]Head and professor, Department of Periodontics, Vishnu Dental College
[5]Reader, Department of Periodontics, Vishnu Dental College

***Abstract**: C- reactive protein [CRP] is an acute phase protein observed in increased quantities in plasma during the infections and presence of any inflammation, which could be a further possible risk factor in systemic inflammatory diseases such as arthritis, diabetes mellitus, and obesity. CRP molecules help as a biological marker for the determination of the inflammatory process when obtained from the gingival crevicular fluid and there is association between periodontitis and CRP levels. These levels are found to be reduced after the non-surgical and surgical periodontal treatment. Therefore, the levels of CRP would play a major role in determination of the inflammatory process.*
Keywords: C- reactive protein, inflammatory marker, periodontitis, periodontal disease.

1. Introduction

Among the inflammatory diseases, periodontitis is a chronic inflammatory condition affecting the tooth-supporting structures [i.e. Periodontal ligament, cementum and alveolar bone] due to periodontal pathogens [gram-negative bacteria] thus affecting local and systemic immune and inflammatory responses [1]. Formation of dental biofilm at the gingival margin helps the bacteria to colonize around the tooth. Low levels of bacteremia, endotoxins derived from gram-negative microorganisms and other bacterial components may provide a stimulus for systemic inflammatory responses [2]. These bacterial bye products along with inflammatory cells, trigger a cell-mediated inflammatory response and produces lipopolysaccharides [LPS] and proinflammatory cytokines which includes tumour necrosis factor [TNF], interleukin [IL-1] and [IL-8]. Release of LPS into the periphery activates both inflammatory cells, and endothelial cells and cytokines are carried to the liver where they induce the production of acute-phase proteins such as C-reactive protein (CRP) [3].

CRP is a plasma protein, derived its name due to its ability to react with C polysaccharide isolated from pneumococcal cell walls is synthesized by hepatocytes. Increase of this acute-phase protein in plasma concentrations during infection and inflammation is considered as a golden marker of inflammation [4]. In 1983, Pepys and Baltz suggested that liver synthesizes CRP in response to diverse inflammatory stimuli, including heat, trauma, infection, and hypoxia [5].

2. Structure of CPR

C-reactive protein is from a pentraxin family of proteins which belong to the lectin fold superfamily and is non-glycosylated circulating plasma protein. The human CRP molecule is composed of five identical non-glycosylated polypeptide subunits, each containing 206 amino acid residues. The protomers are non-covalently associated in an annular configuration with cyclic pentameric symmetry. Each protomer is composed of a two-layered β sheet with flattened jellyroll topology and has the characteristic "lectin fold". The ligand-binding site is composed of loops with two calcium ions bound 4 Å apart by protein side-chains and is located on the concave face, and a single α helix is present on the other face. It is named as pentraxin family because of its electron micrographic appearance, derived from the Greek Penta (five) ragos [6].

Serum amyloid A is also one of the proteins, which are structurally same as the CRP, and they both are included in the pentraxin family where CRP is an acute-phase reactant produced by the liver, which is nonspecific and produced in response to various stimuli. CRP possesses the ability to reveal inflammation at an early stage as it rises in serum within 48 h [7]. Its long plasma half-life of 12-18 hours is the sole determinant of circulating CRP which is directly linked to the intensity of the pathological process stimulating CRP production. This property is useful for early detection of patients who are at risk for inflammatory disease [8]. Moreover, it can up regulate pro-inflammatory mediator production and has a pattern recognition molecule that binds to specific molecules that are produced during cell death or found on the surfaces of diverse bacterial pathogens. During the host defense such as innate inflammatory response, there is a rapid increase in the CRP synthesis within hours after infection [9].

CRP is produced in response to many forms of injury other than periodontitis, such as other infections, trauma and hypoxia, and it is regulated by diverse cytokines and also the levels of CRP have an association with smoking, obesity, triglycerides, diabetes, and periodontal disease [10].

3. Measurement of CRP

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 system [11]. Normal CRP levels are less than 3.0 mg/L. [12]

In two systemic reviews [13, 14], where a few articles did not show any increase in serum inflammatory markers in periodontitis patients and the mean CRP value has been above 2.1mg/l and 1.0 mg/L in only periodontitis patients [15]. Similarly; in a study by Amir, Ahmed and others, patients had normal CRP level although they had chronic periodontitis [mean CRP level=0.53 mg/l]. [16] CRP level is considered to be a reflection of inflammatory state and does not necessarily show dose effect or causal relationship with periodontal status.

The results of Salberz et al., have confirmed that Aggressive periodontitis is significantly related to elevated CRP levels as the generalised aggressive periodontitis [3.72 mg/l] group had significantly elevated levels of CRP compared to the localised aggressive periodontitis [2.57 mg/l] and non-periodontitis [1.54 mg/l] groups. Their result is consistent with the

interpretation that the surface area or volume of the periodontal lesion is the most important determinant of serum CRP levels in aggressive periodontitis patients [17].

4. Functions of CRP

CRP is a component of the innate immune system with an ability to recognize the foreign pathogens, phospholipids of damaged cells and also binds to the phosphocholine. It activates the complement system by bounding to one of its ligands, and it can also bind to phagocytic cells. An observational study suggests that it can initiate the elimination of targeted cells by its interaction with both humoral and cellular effector systems of inflammation [5]. Despite the many well-characterized activities of CRP, there has been a great deal of controversy as to whether CRP is a proinflammatory or an anti-inflammatory molecule overall. Experiments in vitro suggest that CRP stimulates the release of IL-1 and tumour necrosis factor [TNF] [18]. Similar results were obtained in human alveolar macrophages where IL-lα, IL-1β and TNF-α were stimulated by CRP [19].

CRP plays an important role in inflammatory processes and host responses to infection which includes the complement pathway, apoptosis, phagocytosis, nitric oxide [NO] release, and the production of cytokines, like interleukin-6 and tumour necrosis factor-α [20]. As IL-6 is predominantly a proinflammatory cytokine, in some cells, through the activation of membrane-bound IL-6 receptor signalling, IL-6 can have regenerative and anti-inflammatory effects. In the initial stages of inflammation, Interleukin-6 is synthesized and induces a number of acute-phase proteins, including CRP [21, 22].

CRP interacts with Fc receptors on monocytes as IgG and produces a similar stimulation of proinflammatory cytokines. The mode of presentation of CRP to the Fc receptor is essential to the type and magnitude of the response of the cell. Thus, CRP presented on a repeating polymer, such as poly-L-lysine, is likely to engage and crosslink multiple Fc receptors leading to an enhanced response [22]. CRP has a pro-coagulant effect and stimulates the tissue factor production by human peripheral blood monocytes and recruits monocytes by receptor-mediated chemotaxis into the arterial wall, which localizes with foam cells in atherosclerotic lesions [21].

5. CRP in Periodontal Disease

Long-standing periodontal disease and raised CRP levels enhances the risk of cardiovascular disease, cerebrovascular accidents and preterm low birth weight infants. Periodontitis with all its clinical symptoms and consequences can also pose a potential risk of systemic exposure to inflammatory stress with increased values of the markers of inflammation [leukocytes and neutrophils, CRP, and fibrinogen], and thus create a close connection with the systemic status of the patients [24, 25]. Literature states there is a strong association between periodontitis and cardiovascular disease with CRP and IL-6 as risk factors. A number of studies have reported elevated serum CRP levels in periodontitis subjects [2].

Sub gingival biofilm bacteria activates the acute phase hepatic response, which further increases the total count of leukocytes and other inflammatory markers and thus predispose the patient to systemic diseases and inflammation of the tissues[26, 27]. Inflamed periodontal

tissue plays a vital role in determining the extent of inflammation and the periodontal tissue destruction with a significant increase in the CRP levels in periodontitis when compared to gingivitis [28].

Studies have reported higher levels of serum CRP in chronic periodontitis than in healthy individuals [4,29,30]. Beck et al., has demonstrated the individual association of attachment loss, probing pocket depth (PPD), and bleeding on probing (BOP) with serum soluble intercellular adhesion molecule and CRP with a direct association of increased CRP levels and pocket depth. They have concluded that estimation of CRP levels plays an important role in determining the degree of systemic inflammation than traditional classifications of mild, moderate, and severe periodontitis or other measures of disease severity such as attachment loss [31]. Another study conducted by Vijayalakshmi et al. has shown increased levels of CRP in chronic periodontitis patients than in the aggressive periodontitis patients [32].

Likewise, several studies showed a significant correlation between elevated CRP and severity of periodontal disease [33, 34].

6. Effect of Periodontal Therapy on Serum CRP Level

Dental biofilm is relatively insensitive to the systemic antibiotics and its treatment requires the removal by professional mechanical instrumentation. Following successful treatment, the bacterial load is significantly reduced, while antibody titers and avidity to the specific pathogens are improved. As a result, there is a significant decrease in local inflammation in terms of decrease in the infection burden with improvement in periodontal clinical parameters (PPD, BOP) [34, 35].

Leite et al have concluded there is significant decrease in serum high sensitive CRP (hs-CRP) levels associated with severe periodontitis with a significant increase in high density lipoprotein (HDL) cholesterol therefore reducing the inflammatory risk for cardiovascular disease (CVD) after NSPT [36]. Similarly, direct correlation has been observed in circulating levels of hs-CRP and Homocysteine levels [37].

NSPT was effective in reducing the plasma levels of IL-6, CRP, and fibrinogen in patients with severe periodontitis [38, 39]. This positive association reinforces the theory, that periodontitis has a significant influence on the levels of inflammatory biomarkers, suggesting that periodontal infection can lead to a systemic impact, favoring the development and aggravation of other pathologies [40]. CRP in gingival crevicular fluid are potential candidate biomarkers in detecting the degree of inflammation, collagen degradation and bone turnover and has a positive correlation with the clinical features of periodontal disease [41]. In a multivariate model, serum CRP levels were significantly associated with the outcome of periodontal treatment after correcting for potential covariates [age, body mass index, gender, and smoking] and polymorphisms in the IL-6 (174 C/G) and IL-1A (889) genes [42].

Destructive periodontal diseases in the general population have been associated with both an increased prevalence of atherosclerotic complications and an elevation in serum CRP values. Several short-term intervention studies reported that treatment of periodontitis reduces the serum concentrations of inflammatory markers, which are thought to be initiating factors for cardiovascular disease.

Moeintaghavi et al reported periodontal treatment might significantly lower lipid profile serum levels and some inflammatory factors like CRP [16]. Immuno-turbidimetric and serum assay have further concluded there is association between the healthy and periodontitis after periodontal flap surgery with CRP levels [43, 44].

7. Conclusion

Periodontal disease elicits a mild acute-phase response with an elevation of CRP levels, which could be a further possible risk factor in systemic inflammatory diseases such as arthritis, diabetes mellitus, and obesity. This review emphasizes the importance of periodontal treatment especially the non-surgical periodontal therapy. Further insight to determine the association of CRP and periodontal disease for the overall wellbeing are needed.

8. References

[1] Smitha CN, SwetaSoni, Basu SK. Role of C-Reactive protein and periodontal disease in systemic health: A review. *J. Adv. Dent*. Res2011;[1-5] 9
[2] Williams RC, Offenbacher S. Periodontal medicine. *Periodontol 2000*; 23:9-156.
[3] Jayaprakash D, Aghanashini S, Vijayendra RR, Chatterjee A, Rosh RM, Bharwani A. Effect of periodontal therapy on C-reactive protein levels in gingival crevicular fluid of patients with gingivitis and chronic periodontitis: A clinical and biochemical study. *J Indian Soc Periodontol* 2014;18:456-60.
[4] Podzimek S, Mysak J, Janatova T, Duskova J. C-Reactive Protein in Peripheral Blood of Patients with Chronic and Aggressive Periodontitis, Gingivitis, and Gingival Recessions. *Mediators of Inflammation* 2015: 1-7
[5] Renuka D R, Vijaykumar N, Raghavendra R et al. A review of C-reactive protein: A diagnostic indicator in periodontal medicine. *J Pharm Bio allied Sci* 2012; 4[2]: S422–S426
[6] Pepys MB, Baltz ML. Acute phase proteins with special reference to C-reactive protein and related proteins [pentaxins] and serum amyloid-A protein. *Adv Immunol* 1983; 34:141– 212.
[7] S. Black, I. Kushner, and D. Samols, "C-reactive protein," *J Biol Chem*, 2004; 279[47]: 48487–48490
[8] Lata G, Afshan B, N. D. Gupta, and Vivek K S. Comparative evaluation of serum C-reactive protein levels in chronic and aggressive periodontitis patients and association with periodontal disease severity. *Contemp Clin Dent*. 2014 Oct-Dec; 5[4]: 484–488.
[9] Gomes-Filho IS, Coelho JMF, Cruz SS, Passos JS, Freitas COT, Farias NSA, et al. Chronic periodontitis and C-reactive protein levels. *J Periodontol* 2011;82:969-978.
[10] Mary Ellen Ellis. Rheumatoid Arthritis: *What CRP Levels Say About You* 2018.
[11] Gani DK, Lakshmi D, Krishnan R, Emmadi P. Evaluation of C-reactive protein and interleukin-6 in the peripheral blood of patients with chronic periodontitis. *J Ind Soc Periodontol*. 2009;13[2]:69–74.
[12] Ballou SP, Lozanski G. Induction of inflammatory cytokine release from human monocytes by C-reactive protein. Cytokine 1992; 4: 361-8
[13] Paraskevas S, Huizinga JD, Loos BG. A systematic review and metaanalyses on C-reactive protein in relation to periodontitis. *J Clin Periodontol* 2008; 35[4]: 277-90.

[14] Demmer RT, Trinquart L, Zuk A, et al. The influence of anti-infective periodontal treatment on C-reactive protein: A systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2013; 8[10]: e77441.
[15] Yamazaki K, Honda T, Oda T, et al. Effect of periodontal treatment on the C-reactive protein and proinflammatory cytokine levels in Japanese periodontitis patients. *J Periodontal Res* 2005; 40[1]: 53-8.
[16] A Moeintaghavi, Arab HR, Moghaddam MA, Shahmohammadi R, Bardan BY and SoroushZ. Evaluation of Effect of Surgical and Nonsurgical Periodontal Therapy on Serum C-Reactive Protein, Triglyceride, Cholesterol, Serum Lipoproteins and Fasting Blood Sugar in Patients with Severe Chronic Periodontitis. *Open Dent. J.* 2019;13:15-21
[17] Salzberg TN, Overstreet BT, Rogers JD, Califano JV, Best AM, Schenkein HA. C reactive protein levels in patients with aggressive periodontitis. *J Periodontol* 2006;77:933–9.
[18] Galve-de Rochemonteix B, Wiktorowicz K, Kushner I, Dayer JM. C-reactive protein increases production of IL-1 alpha, IL-1 beta, and TNF-alpha, and expression of mRNA by human alveolar macrophages. *J Leu&Biol* 1993; 53: 43945.
[19] Sproston NR and Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. *Front. Immunol.* 2018; 9:754.
[20] Zhang JM, An J. Cytokines, inflammation and pain. *IntAnesthesiolClin* 2007; 45[2]:27–37.
[21] Tanaka T, Kishimoto T. The biology and medical implications of interleu-kin-6. *Cancer Immunol Res* 2014; 2[4]:288–94.
[22] Terry W Du Clos. Function of C-reactive protein. *Ann Med* 2000; 32: 274-278.
[23] Slade GD, Ghezzi EM, Heiss G, Beck JD, Riche E, Offenbacher S. Relationship Between Periodontal Disease and C-Reactive Protein Among Adults in the Atherosclerosis Risk in Communities Study. *Arch Intern Med.* 2003;163:1172–9.
[24] American Academy of Periodontology. Parameter on chronic periodontitis. *J Periodontol*, 2000; 71: 853-855.
[25] Beck DJ, Offenbacher S. Relationships among clinical measures of periodontal disease and their association with systemic markers. *Ann Periodontol* 2002; 7[1]: 79-89.
[26] Rudin SR. Laboratory tests and their significance in Walter Hall. *Critical decisions in Periodontology* 2003; 4-6.
[27] Lopez R, Oyarzun M, Naranjo C, Cumsille F, Ortiz M, Baelum V. Coronary heart disease and periodontitis-a case control study in Chilean adults. *J ClinPeriodontol* 2002; 29: 468-473.
[28] Dhruva K G, Deepa L, Rama K, and Pamela E. Evaluation of C-reactive protein and interleukin-6 in the peripheral blood of patients with chronic periodontitis. *J Indian Soc Periodontol* 2009; 13[2]: 69–74.
[29] Paraskevas S, Huizinga JD, Loss BG. A systematic review and meta-analyses on C-reative protein in relation to periodontitis. *J Clin Periodontol* 2008; 35, 277-90.
[30] Moghadam SA, ZadFattah S, Fakour SR, Moghaddam AA, Naebi M. Comparison of C-reactive protein levels in chronic periodontitis patients with normal subjects. *J Dent Mater Tech* 2017; 6: 181-5.
[31] J. D. Beck and S. Offenbacher, "Relationships among clinicalmeasures of periodontal disease and their associations withsystemic markers," *Ann Periodontol* 2002; 7:79–89.
[32] Vijayalakshmi B, P Santha K, Surendra R M, et al. Evaluation of Serum C-reactive Protein Levels in Subjects with Aggressive and Chronic Periodontitis in Comparison with Healthy Controls: A Clinico-biochemical Study. *Int J Appl Basic Med Res* 2017; 7[2]: 121–124

[33] Slade GD, Offenbacher S, Beck JD, Heiss G, Pankow JS. Acute-phase inflammatory response to periodontal disease in the US population. *J Dent Res* 2000;79:49–57.
[34] Wu T, Trevisan M, Genco RJ, Falkner KL, Dorn JP, Sempos CT. Examination of the relation between periodontal health status and cardiovascular risk factors: Serum total and high density lipoprotein cholesterol, C-reactive protein, and plasma fibrinogen. *Am J Epidemiol* 2000;151:273–82.
[35] Ioannidou E, Malekzadeh T, Dongari-Bagtzoglou A. Effect of periodontal treatment on serum C-reactive protein levels: A systematic review and meta-analysis. *J Periodontol* 2006; 77:1635-42.
[36] Leite, A. C. E., Carneiro, V. M. de A., &Guimarães, M. do C. M. Effects of periodontal therapy on C-reactive protein and HDL in serum of subjects with periodontitis. *Revista Brasileira de Cirurgia Cardiovascular* 2014; 29[1], 69–77.
[37] Mallapragada S, Kasana J, Agrawal P. Effect of nonsurgical periodontal therapy on serum highly sensitive capsule reactive protein and homocysteine levels in chronic periodontitis: A pilot study. *Contemp Clin Dent* 2017;8:279-85
[38] Vidal F, Figueredo CM, Cordovil I, Fischer RG. Periodontal therapy reduces plasma levels of interleukin-6, C-reactive protein, and fibrinogen in patients with severe periodontitis and refractory arterial hypertension. *J Periodontol* 2009;80[5]:786-91.
[39] Marcaccini AM, Meschiari CA, Sorgi CA, Saraiva MC, de Souza AM, Faccioli LH, Tanus-Santos JE, Novaes AB, Gerlach RF. Circulating interleukin-6 and high-sensitivity C-reactive protein decrease after periodontal therapy in otherwise healthy subjects. J Periodontol 2009;80[4]:594-602.
[40] Esteves-Lima RP, Reis CS, Santirocchi-Júnior F, Abreu LG, Costa FO. Association between periodontitis and serum c-reactive protein levels. *J Clin Exp Dent* 2020;12[9]:e838-e843.
[41] Kumar S, Shah S, Budhiraja S, Desai K, Shah C, Mehta D. The effect of periodontal treatment on C-reactive protein: A clinical study. *J Nat Sc Biol Med* 2013;4:379–82.
[42] D'Aiuto F, Parkar M, Andreaou G, Brett PM, Ready D, Tonetti MS. Periodontitis and atherogenesis: causal association or simple coincidence? *J Clin Periodontol* 2004; 31:402-411.
[43] Gupta B, Sawhney A, Patil N, yadav M, Tripathi S, Sinha S, Sharma S, Gupta S. Effect of Surgical Periodontal Therapy on Serum C-reactive Protein Levels Using ELISA in Both Chronic and Aggressive Periodontitis Patient. *J. clin. diagn. res.* 2015;9[10]: ZC01-ZC05
[44] V. Radha, M. Sankari.Effect of periodontal treatment on C-reactive protein levels in periodontitis patients: A pilot study. *Drug Invent. Today* 2018;10[2]: 3097-3099