

## Coronary Artery Disease and Periodontitis: A Prospective Study.

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**Abstract:** The present study was conducted on the patients visiting the out-patient department of ITSCDSR, Ghaziabad with the objective of strengthening the association between periodontal disease and coronary artery disease. Sixty (60) patients, aged 40 to 60 years, were divided into 2 groups, of 30 patients each, based on their periodontal status in to periodontally healthy and periodontally diseased groups. The two groups were compared for periodontal parameters and hs-CRP levels. The periodontally diseased group of patients showed significantly higher levels of hs-CRP.

**Conclusion:** The present study demonstrated that the patients with more advanced periodontal disease displayed higher CRP levels than those at a higher risk for coronary artery disease.

### INTRODUCTION

An association between oral infection and systemic diseases has been suspected for centuries. The effect of oral health on the rest of body was proposed by Assyrians as early as the 7<sup>th</sup> century B.C.<sup>1</sup> The focal infection theory, given by William Hunter in 1911, was discarded due to lack of scientific evidence.<sup>2</sup> As we tread on the part of a new century, we marvel at the profound changes that have taken place in the practice and science of medicine and dentistry, which have led us to revisit this theory.

Periodontal disease is an encompassing term relating to the destructive inflammatory disorders of the hard and soft tissues surrounding teeth. Long term plaque accumulation induces chronic inflammation of the periodontal tissues, which may lead to destruction of the attachment of the periodontal ligament and bone.<sup>2</sup> This could occur via the host's immuno-inflammatory mediators that are elicited in response to bacteria, bacterial toxins or localized tissue response. These locally produced inflammatory mediators can spill over into the systemic circulation along with micro-organisms and this immune-inflammatory response of periodontal tissues and systemic vascular response can offer an explanation for shift in causality and directionality of oral and systemic diseases.

C-reactive protein (CRP) is an acute phase reactant that has long been considered a classic marker for inflammation. Although normally circulating at low levels, acute inflammation, infection, or tissue injury induces a marked increase in hepatic synthesis of CRP, which can raise the serum level a hundredfold or more. It is now known that atherosclerosis, the process underlying CVD, which includes coronary heart disease (CHD), myocardial infarction (MI), and ischemic stroke, as well as peripheral vascular disease (PVD), is due at least in part to a chronic, low-level inflammation of the vascular endothelium<sup>3</sup>.

Several prospective clinical case-controlled studies in the US on middle-aged men (Physicians Health Study,<sup>4,7</sup> Multiple Risk Factor Intervention Trial<sup>8</sup>), postmenopausal women (Women's Health Study<sup>9,10</sup>) and elderly men and women (Cardiovascular Health Study, Rural Health Promotion Project<sup>11</sup>) have identified CRP as a strong, independent risk factor for CVD. This finding receives additional support from studies in Germany (Monitoring Trends and Determinants in Cardiovascular Disease<sup>12</sup> Finland Helsinki Heart Study<sup>13</sup>), and the UK<sup>14</sup>, all conducted on middle-aged men.

Although ischemic heart disease is of multi-factorial origin, one of

the chief causes is atherosclerosis which has been defined as "progressive inflammatory process that involves the large to medium size muscular and the large elastic arteries".<sup>15</sup>

The possible linking mechanisms between periodontal disease and ischemic heart disease are shared risk factors, role of monocytes in periodontal disease and atherosclerosis, increased fibrinogen and WBC counts, effect of bacterial lipopolysaccharides and inflammatory mediators, role of CRP and role of oral bacteria. Periodontitis is shown to raise inflammatory markers such as CRP in the blood<sup>16, 17, 18</sup> which is an acute phase reactant protein considered to be a risk indicator for both periodontitis as well as cardiovascular disease.<sup>19, 20, 21, 22</sup> It increases during the states of acute inflammation and is largely produced in the liver and to a certain extent in fat of the abdominal cavity, smooth muscle cells and macrophages in atheromatous plaque. It is believed that high sensitivity CRP (hs-CRP) can amplify the inflammatory response through complement activation, tissue damage and activation of endothelial cells by following mechanisms<sup>23</sup>: Upregulation of endothelial cell surface adhesion molecules (VCAM-1, E-selectin, MCP-1), decreased fibrinolytic capacity, increase proliferation and migration of smooth muscle cells, expression of Angiotensin type-1 receptor, increased endothelin-1 production, enhanced T-cell mediated endothelial cell destruction and modulation of oxidation of LDL.

### MATERIALS AND METHODS

The study was designed and conducted in the Department of Periodontology and Oral Implantology, ITS CDSR, Muradnagar, Ghaziabad, U.P. India. 60 patients, aged 40 to 60 years, who visited the out-patient Department of Periodontology & Oral Implantology, ITS CDSR Ghaziabad, were divided into 2 groups, of 30 patients each, based on their periodontal status. **Group A** consisted of patients suffering from chronic generalized Periodontitis, diagnosed as having more than 30% of sites with periodontal pocket depth greater than or equal to 4 mm. **Group B** consisted of patients without any evidence of chronic generalized periodontitis. Patients suffering from any other systemic disease, patients who had undergone any cardiac surgery prior to the study and patients with a history of smoking were excluded from the study. A full mouth periodontal examination was performed consisting of Plaque index, Gingival index and full mouth pocket depth assessment. Plaque index utilized was the Tureskey-Glickman- Gilmore modification of the Quigley Hein Plaque Index.<sup>24</sup> Gingival Index used for this study was the one proposed by Loe and

Silness.<sup>25</sup> Pocket depth was measured at six sites per tooth (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual and disto-lingual) and the average of all the sites was considered as the average pocket depth of the individual.

A non fasting venous blood sample was collected for each patient in a plain vacutainer and allowed to clot. The vacutainer was centrifuged at 1000 rpm for 3-5 minutes to obtain clear straw coloured serum, which was stored at -20°C. This serum was then brought to room temperature before lab investigation for CRP. hs-CRP was analyzed using the BS 300 CRP analyser.

The data was tabulated and subjected to statistical analysis using the two-sample t-test to compare the variables between the two groups. Pearsons correlation coefficient was used to calculate the correlation between the hs-CRP and the periodontal variables.

## RESULTS

There were obvious differences in the two groups on statistical comparison of the three parameters analysed in the study (Table 1). The statistical analysis demonstrated significant differences between the levels of hs-CRP between the two groups (Table 2, V.H.S.).

The Pearson's correlation coefficient showed significant association between the levels of hs-CRP and Gingival index scores (Table 3) and hs-CRP, Probing pocket depth (Table 4). And hs-CRP and plaque Index (Table 5).

**Table 1:** Paired t-test for comparison of periodontal parameters between the two groups

Parameter	Plaque Index scores (n=30)		Gingival Index scores (n=30)		Probing pocket depth in mm (n=30)	
	Group A	Group B	Group A	Group B	Group A	Group B
Mean	2.1790	1.7470	2.4157	0.8353	3.6843	1.6867
S.D.	0.5491	0.3594	0.3999	0.4123	0.5043	0.5413
S.E. mean	0.1003	0.0656	0.0730	0.0753	0.0921	0.0988
p- value	0.0027		<0.0001		<0.0001	
t- value	3.2836		12.8616		14.7889	
Significance	V.H.S		V.H.S		V.H.S	
Df	29		29		58	

**Table 2:** Paired t-test for comparison of CRP values between the two groups

CRP values	Group A (n=30)	Group B (n=30)
Mean	4.573	1.460
S.D.	1.795	0.813
S.E. mean	0.328	0.148
p- value	<0.0001	
t- value	8.6520	
Significance	V.H.S	
Df	58	

**Table 3:** Pearson's correlation between hs-CRP and Gingival Index

		hsCRP	PPD
hsCRP	Pearson Correlation	1	.754**
	Sig. (2-tailed)		.000
	N	60	60
PPD	Pearson Correlation	.754**	1
	Sig. (2-tailed)	.000	
	N	60	60

\*\*Correlation is significant at the 0.01 level (2-tailed).

**Table 4:** Pearson's correlation between hs-CRP and PPD

		hsCRP	GI
hsCRP	Pearson Correlation	1	.653**
	Sig. (2-tailed)		.000
	N	60	60
GI	Pearson Correlation	.653**	1
	Sig. (2-tailed)	.000	
	N	60	60

\*\*Correlation is significant at the 0.01 level (2-tailed).

**Table 5:** Pearson's correlation between hs-CRP and Plaque Index

		hsCRP	PI
hsCRP	Pearson Correlation	1	.222
	Sig. (2-tailed)		.088
	N	60	60
PI	Pearson Correlation	.222	1
	Sig. (2-tailed)	.088	
	N	60	60

In the present study, Group A individuals demonstrated higher mean Plaque Index, and Gingival Index scores, along with higher probing pocket depth, than Group B individuals.

The hs-C reactive protein levels in Group A patients were significantly higher than Group B patients.

The hs-CRP levels showed significant association with the Probing pocket depth levels and Gingival Index scores. The association between hs-CRP levels and Plaque levels was show to be non-significant.

## DISCUSSION

An elevated level of C-reactive protein, a non-specific marker of inflammation, has been associated with an increased risk of cardiovascular disease. It has since been shown that C-reactive protein is normally present in ng/ml quantities but may increase dramatically to hundreds of mg/ml within 72 h following tissue injury. This represents a 100- to 1000-fold increase within hours of tissue damage.<sup>26</sup> The effect of periodontal disease progression on the risk of having higher levels of CRP appears to predict cardiovascular disease and has been well documented in the current literature<sup>27-31</sup>. Setting optimal cut-off levels to predict cardiovascular disease risk remains problematic, as does the possible role of CRP in cardiovascular disease. hsCRP is an independent predictor of increased cardiovascular risk. The risk prediction based on CRP as proposed by AHA/CDC categorizes patients with 1 to 3 mg/L as being at moderate risk. Ridker *et al*<sup>32</sup> recommended a cut-off level of CRP >2 mg/L as a level that predicts cardiovascular risk. In their study, Craig *et al*<sup>31</sup> reported this value to be associated with more advanced periodontitis. An increased risk of cardiovascular disease in a Japanese population has been reported with CRP levels above 1.3 mg/L. Since minor changes in CRP levels are critical for such predictions, it seems that there is still lack of consensus and a precise numerical value is not yet agreed<sup>33, 34</sup>.

That periodontal disorder which can result in increased CRP level elevations could be explained by the inflammatory/infective nature of the disease. The presence of periodontal pathogens could stimulate the inflammatory response sharing a common pathogenic pathway to that in atherosclerosis. This might result in elevated levels of inflammatory markers like tumor necrosis factor- $\alpha$ , IL-6, IL-1, which trigger the inflammatory cascade. These proinflammatory effects have been found to have profound effects on endothelial cells, causing upregulation of vascular adhesion molecule 1, intracellular adhesion molecule 2, and E-selectin. All of these modulate monocyte recruitment in the presence of fatty streaks form foam cells, which results in atheroma<sup>36</sup>. In their study, Haraszthy *et al*<sup>36</sup> found that periodontal pathogens like *P. gingivalis* have also been isolated in the atheroma of patients with atherosclerosis, which points to a possible infective nature of this disease. Elevated levels of pathogens,

either individually or as a cumulative “pathogen burden” have correlated with elevated C-reactive protein levels.<sup>37</sup>

Since both periodontitis and cardiovascular events may share a common pathogenic pathway and common risk factors, it is difficult to confirm a cause-and-effect relationship. Interventional studies are therefore needed. Glurich *et al*<sup>38</sup> found elevated levels of CRP in patients with periodontal and cardiovascular diseases. However, the levels increased 3-fold when both conditions were present, suggesting that inflammation-associated molecules may contribute to an additional burden in the infectious and inflammatory processes in both conditions.

We must recognize that there do appear to be statistical associations between periodontitis and cardiovascular disease. But when these associations are looked at more closely, they do not appear to be as robust as we might have thought. Indeed, concepts have come to light suggesting that the apparent correlations between periodontitis and cardiovascular disease may be related to the possibility that patients who are at risk for one disease may be genetically at risk for the other. This may be particularly so if such patients are exposed to the same epigenetic risk factors known to play a role in both disorder groups, e.g. smoking.

For every 20% increase in bone loss, the incidence of total cardiovascular disease increased by 40%<sup>15</sup> After completing a case control study with 303 patients examined within seven days after acute ischemic stroke or transient ischemic attack<sup>39</sup>, it was further concluded that periodontitis is an independent risk factor for stroke. Subjects with severe periodontitis had 4.3 times higher risk for cerebral ischaemia than subjects with mild or without periodontal disease<sup>40</sup>. The weight of epidemiological evidence, then, seems to support the concept that periodontitis and cardiovascular disease co-presence and may predict one another’s presence. The studies still do not indicate, however, that there are causal associations between the two diseases; or even if there are causal associations, whether they are bidirectional as has been demonstrated with diabetes.

Risk factors, such as smoking, genetics, stress and increasing age, could independently lead to periodontal disease and to cardiovascular disease in a group of patients, possibly leading to the incorrect assumption that the two diseases are linked<sup>41</sup>. In studies where adjustment for smoking dose (cigarettes per day) was included in the analysis, the relationship between periodontitis and cardiovascular disease was shown to be insignificant. None of the studies to-date demonstrated a link between periodontitis and cardiovascular disease in non-smokers<sup>41</sup>.

While the compelling evidence regarding the clinical importance of hsCRP in cardiovascular risk assessment is widely accepted, not all experts in the cardiovascular community share this view. The causal role of CRP in the development of cardiovascular disease therefore needs further validation.

In summary, the present study demonstrated that the patients with more advanced periodontal disease displayed higher CRP levels.

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