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CLINICAL STUDY

## Effect of Nonsurgical Periodontal Treatment on C-Reactive Protein Levels in Maintenance Hemodialysis Patients

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### Abstract

**Objective:** C-reactive protein (CRP) has been implicated as a possible mediator of the association between periodontitis and several systemic diseases. This study evaluated the impact of nonsurgical periodontal treatment on the serum levels of CRP in chronic kidney disease (CKD) patients on hemodialysis. **Methods:** A total of 77 CKD patients on hemodialysis were included in this study. At baseline, periodontal examination was assessed for all the patients, and chronic periodontitis was defined through clinical attachment level and probing pocket depth, according to the American Association of Periodontology. Nonsurgical periodontal treatment was performed and serum levels of CRP were evaluated at baseline and 8 weeks after periodontal treatment. **Results:** Periodontal treatment resulted in significant reductions in CRP levels ( $p < 0.001$ ). The difference between pre- and posttreatment CRP concentrations did not show any significant relationship with the severity of periodontitis. **Conclusions:** Periodontitis is an important source of systemic inflammation in CKD patients. Nonsurgical periodontal treatment can effectively reduce the serum level of CRP in these patients.

**Keywords:** C-reactive protein, chronic kidney disease, hemodialysis, periodontal treatment

### INTRODUCTION

Periodontitis is a chronic inflammatory disease of infectious origin contributing to the destruction of the supporting structures of the teeth, including the periodontal ligament, as its consequences.<sup>1</sup> It includes local inflammation and is associated with systemic inflammatory response.<sup>2</sup> Ultimately, it may lead to tooth loss.<sup>1</sup> In this infectious disease, Gram-negative bacteria are recognized as the main pathogens.<sup>3</sup> Periodontal diseases are estimated to affect more than 70% of the general population.<sup>4</sup> Different researches have shown that about 10% of the adult population and about 30% of the persons over the age of 50 years suffer from severe periodontitis.<sup>5</sup>

Chronic kidney disease (CKD) is a major public health problem that its rising prevalence and consequences have made it a worldwide challenge. Studies revealed that approximately 25 million people in the United States may have CKD.<sup>6</sup> Its prevalence is on the increase in the industrialized countries.<sup>7</sup>

CKD is characterized by a progressive and irreversible failure in renal function which is associated with a reduced glomerular filtration rate.<sup>8</sup> It has high morbidity and mortality. For example, the mortality rate of chronic dialysis patients in the United States is reported to be 24% per year.<sup>9</sup> The increasing rate of morbidity and mortality is mostly because of atherosclerotic complications, especially among younger patients. The conditions that contribute to these complications include myocardial infarction, cardiac arrest, and cardiac arrhythmia that may lead to sudden death and cerebrovascular accidents.<sup>7</sup> The treatments of CKD include diet modification, recognition and treatment of systemic complications, dialysis, and finally, kidney transplantation.<sup>2,8</sup>

Nowadays renal replacement therapies have improved the survival rate of end-stage renal disease (ESRD) patients, so the number of the patients seeking renal replacement therapy as well as dental treatments has increased. Both chronic renal disease and renal

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replacement therapy that includes hemodialysis, peritoneal dialysis, or renal transplantation can affect periodontal tissue.<sup>7</sup> That is, these patients usually show increased levels of plaque, calculus, and gingival inflammation. Also, gingival hyperplasia and possible increased prevalence and severity of destructive periodontal diseases are reported in ESRD patients.<sup>5</sup> A positive correlation between the periodontal index and the age and time of dialysis has been obtained in different studies.<sup>10</sup>

Several studies have been conducted, assessing the presence of dental plaque, calculus, gingival bleeding, and probing pocket depth (PD) in these patients.<sup>11</sup> Also, dental management of renal patients is greatly affected by their chronic disease and renal replacement therapies.<sup>7</sup>

Furthermore, CKD and periodontitis can have significant reciprocal effects.<sup>7</sup> This means that chronic periodontitis by its overall systemic inflammatory effects can influence the management of CKD patients on hemodialysis maintenance therapy.<sup>7</sup> It is not yet fully understood whether periodontitis plays a role as a risk factor for CKD. However, in many cases, the common etiology of kidney diseases such as diabetes mellitus, hypertension, pyelonephritis, glomerulonephritis, nephrosclerosis, polycystic kidney disease, and collagen vascular diseases cannot explain the onset of CKD. So other unknown etiologic factors may be suspected.<sup>12</sup>

The production of cytokines, prostaglandins and, in some cases, acute-phase reagents play an important role in the pathogenesis of periodontitis.<sup>13</sup> This means that in spite of the chronic nature of periodontitis, acute-phase elements also take part in its immunopathogenesis.<sup>14</sup> This explains that how periodontitis as an unrecognized infection can sometimes induce an acute-phase response, enhance a systemic inflammatory process, and elevate levels of acute inflammatory mediators.<sup>14</sup> By this way systemic levels of inflammatory mediators maybe affected by persistent localized infections such as periodontitis.<sup>14</sup> Among the acute-phase elements in inflammatory process, C-reactive protein (CRP) is one of the most interested mediators.<sup>15</sup>

CRP is one of the nonspecific mediators that can be produced in various inflammatory situations. Its concentration increases rapidly following inflammation and raised serum levels may be detected within 6 h. The potential stimuli that provoke its production include trauma, (unknown) infection and/or inflammation, smoking, obesity, and hypoxia.<sup>14</sup> Due to its various provoking situations, CRP can be used as a reliable biomarker for clinical purposes in asymptomatic individuals.<sup>16</sup> It is primarily synthesized in the liver.<sup>17</sup> Hepatic CRP synthesis is upregulated by proinflammatory cytokines that are released locally at the site of infection or inflammation.<sup>18</sup> Some studies have shown that human gingiva is also able to produce CRP *in situ*.<sup>17</sup>

CRP is useful in making decisions regarding diagnosis, monitoring, and treatment of inflammatory processes and accompanying diseases.<sup>14</sup> Numerous studies have suggested that CRP maybe a more powerful indicator for

cardiovascular diseases (CVDs) than traditional risk factors such as low-density lipoprotein (LDL) in the general population as well as in the CKD patients.<sup>19</sup> Many studies have shown a strong relationship between CRP levels and cardiovascular problems; i.e., CRP is considered as a key marker of atherosclerosis, and elevated levels of CRP (e.g., >2.1 mg/L) is a risk factor for CVDs.<sup>20</sup> This association has led to the hypothesis that controlling of inflammation and thus reducing the CRP levels may be beneficial in attenuating atherothrombotic process.<sup>20</sup> The mechanism of CRP involvement in the pathogenesis of CVDs is not obvious; however, CRP may activate the complement system and participate in atheroma formation.<sup>21</sup>

Due to the fact that periodontitis is associated with CVDs and several studies have shown the association between periodontitis and the risk of atherosclerosis, myocardial infarction and stroke,<sup>22</sup> there is also interest in studying the relationship between periodontitis and CRP. A positive association between chronic periodontal infections and elevated CRP levels has been established in numerous studies.<sup>23,24</sup>

Based on different studies, it is proposed that elevated levels of CRP in periodontitis can partly explain the association between periodontitis and CVDs.<sup>14</sup>

There is sustained interest in the field of periodontology that if progression and treatment of periodontitis can affect serious systemic diseases.<sup>25</sup> Despite the fact that poor periodontal health has been linked to higher systemic CRP levels, at present, the question that whether successful periodontal treatment can reduce CRP levels remains to be answered. It is expected that due to significant rise in CRP levels in the presence of periodontal disease, the potential for reduction with treatment is greater in periodontal patients.<sup>4</sup>

Upon the hypothesis that part of the inflammatory response seen in the CKD patients originates from the chronic periodontitis and act through an increase in the expression of inflammatory markers such as CRP, the researchers of this study were motivated to design this study. Therefore, the purpose of this study was to investigate the impact of initial periodontal treatment on the serum levels of CRP in patients with chronic periodontitis and CKD and also to determine whether there is a causal association between chronic periodontitis activity and high serum levels of CRP. Recently, a high-sensitivity assay (<3–5 mg/L CRP concentrations) has been developed to detect CRP below what was previously considered the normal range.<sup>4,26</sup> This recent development has made the detection of even mild elevations of CRP possible.<sup>27</sup> As this high-sensitivity test was applied in this study, the results of this study are expected to be comparable to that of other studies.

## MATERIALS AND METHODS

The present study was an interventional, uncontrolled clinical trial. The study population included 77 CKD

patients, on hemodialysis, who were recruited from the hemodialysis centers of Shahid Faghihi, Namazi and Haj Ebrahimi hospitals in Shiraz. All the subjects included in the study were informed about the aim of the study, risks, and benefits and signed an informed consent form. The Ethics Committee of Shiraz University of Medical Sciences reviewed and approved this study. Also, all the medical and dental procedures were in accordance with the ethical standards for human experimentation established by the Declaration of Helsinki.<sup>28</sup> The inclusion criteria for the volunteers to take part in the study consisted of diagnosed as ESRD patients according to clinical practice guidelines in the National Kidney Foundation, being on regular maintenance hemodialysis (since 6 months ago) and at least two times per week and the presence of at least 15 teeth. The exclusion criteria for the study were known systemic diseases that interfere with kidney replacement therapies (such as HIV-positivity, lupus erythematosus, rheumatoid arthritis, and diabetes), the history and/or the presence of other infections, treatment with any medication known to affect serum levels of CRP, pregnancy or lactation in females, the need for antibiotic prophylaxis, systemic antibiotic prescription, or any periodontal treatment in the preceding 6 months and smoking.

At the baseline visit, a questionnaire including the following information was completed: age, sex, occupation, complete medical history, medications used, and dialysis status. All the volunteers received a full-mouth periodontal examination, except for the third molars, performed at six sites per teeth (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, and distolingual) by one trained examiner. The periodontal examinations included the following parameters: the number of teeth, probing PD, gingival recession, and clinical attachment level (CAL). These examinations were conducted by Williams probe and the measurements were approximated to the nearest millimeter.

Also, plaque index (PI) for assessing supra gingival plaque and bleeding index (BI) for detecting the marginal gingival bleeding were performed for all teeth.

According to the American Academy of Periodontology classification<sup>29</sup> and considering CAL, participants were classified as gingivitis, mild, moderate, and severe periodontitis. Also generalized chronic periodontitis was diagnosed by the presence of >30% periodontal involvement and localized clinical periodontitis by the involvement of <30% of the sites. Gingivitis was defined as no presence of CAL, no site with PD  $\geq$  5 mm and apparent clinical signs of gingival inflammation.

After baseline examinations, all the subjects received conservative nonsurgical periodontal treatment. This phase was initiated with oral hygiene instructions including proper brushing and flossing and introducing other interproximal cleansing aids, when needed, and continued as scaling and root planning with ultrasound devices and manual instruments (Gracey curettes), polishing, and subgingival curettage. The treatment procedure

was performed by a periodontist in 1-h sessions and repeated according to the need of each patient. Local anesthesia was used when necessary. All other necessary dental treatments including extraction of hopeless teeth and restoration of carious lesions were carried out in order to decrease the accumulation of microbial plaque. Upon completing the periodontal treatment, based on the need of the patients, a follow-up program was carried out, for the additional oral hygiene instructions and supragingival prophylaxis.

Nonfasting blood samples were collected from the participants at two periods: at the baseline visit before periodontal treatment and 8 weeks after initial treatment. The samples were immediately stored at  $-80^{\circ}\text{C}$  and processed blindly by staff. The serum CRP concentration (high sensitivity) was quantified in milligram per liter by nephelometric method, using MININEPH<sup>TM</sup> human CRP kit (The Binding Site Ltd., Birmingham, UK). The test was performed according to the instructions of the manufacturer. The approximate measuring range was 3.5–112 mg/L at a sample dilution of 1/40. The sensitivity limit was 0.44 mg/L when using a 1/5 sample dilution.

### Statistical Analyses

Paired-sample *t*-test was used for comparing the means of CRP levels before and after the treatment. For detecting the relation between pre- and posttreatment CRP levels difference and sex of the patients, Mann–Whitney test was used. Also, Kruskal–Wallis test was used for detecting this relation between pre- and posttreatment difference of CRP levels and the severity of periodontitis. The relation between the severity of periodontitis and pretreatment levels of CRP was also determined by Kruskal–Wallis test. The strength of linear relationship between pretreatment CRP levels and age, PI, and BI was assessed by Pearson's correlation coefficient. Data were expressed as frequencies and means ( $\pm$ SD).  $P < 0.05$  were considered statistically significant. All statistical analyses were carried out with IBM spss19.0 for windows software (SPSS Inc., Chicago, IL., USA).

### RESULTS

A total of 77 stable maintenance hemodialysis patients consisting of 52 (67.5%) males and 25 (32.5%) females with mean age of  $44.35 \pm 17.2$  years (range 14–88 years) were included in this study. Periodontal examination revealed that gingivitis was present in 15.6%, mild periodontitis in 7.8%, moderate periodontitis in 46.8%, and severe periodontitis in 29.9% of the cases (Table 1). The mean CAL of mild periodontitis group was in the range of 1–2 mm, that of moderate periodontitis was in the range of 3–4 mm, and that of severe periodontitis was  $\geq$  5 mm. Mean PI and BI were  $72.36 \pm 20.98$  and  $72.09 \pm 21.76$ , respectively. At baseline, the mean of CRP was  $9.369 \pm 11.25$  mg/L, but its concentration

Table 1. Distribution of different periodontal problems ( $N = 77$ ).

Periodontal problem	Frequency	%
Gingivitis	12	15.6
Mild periodontitis	6	7.8
Moderate periodontitis	36	46.8
Severe periodontitis	23	29.9
Total	77	100

did not show any significant relation neither to the severity of the periodontitis ( $p = 0.823$ ) (Table 2) nor to the BI ( $p = 0.899$ ). Eight weeks after periodontal treatment, the mean CRP concentration was  $5.628 \pm 4.79$  mg/L. Comparison of CRP data before and after treatment showed significant reduction ( $p < 0.001$ ) (Table 3 and Figure 1). However, no significant relation was found between this difference and the severity of periodontitis (Table 4).

## DISCUSSION

Over the last 50 years, dentists and physicians used to believe that periodontal infections were localized only to the marginal periodontium and that there was rarely systemic adverse effects.<sup>30</sup> But nowadays, the concept that progression and treatment of periodontitis can affect systemic diseases is the focus of sustained interest in the field of periodontology.<sup>12</sup>

CKD patients suffer from undesired systemic outcomes such as cardiovascular problems that are associated with systemic inflammation.<sup>31</sup> Nevertheless, the origin and nature of this inflammation are not always identifiable.<sup>32</sup> There are many potential sources of inflammation in CKD patients who are on maintenance hemodialysis treatment. These include vascular access infection, urinary tract infection, dialysis water contamination, bio-incompatible membrane, sinusitis, otitis, and periodontal disease.<sup>33</sup>

Local tissue destruction that occurs in periodontitis favors the systemic dissemination of periodontal

Table 2. Relation of pretreatment CRP levels and periodontal problem.

Periodontal problem	Mean $\pm$ SD	Median	$p$ -Value
Gingivitis	$9.61 \pm 9.22$	6.23	0.823
Mild periodontitis	$6.58 \pm 2.48$	5.76	
Moderate periodontitis	$9.12 \pm 11.99$	5.48	
Severe periodontitis	$10.35 \pm 12.69$	5.14	

Table 3. Comparison of CRP levels before and after periodontal therapy.

CRP level	Mean $\pm$ SD	$p$ -Value
CRP1	$9.369 \pm 11.251$	0.001
CRP2	$5.628 \pm 4.792$	

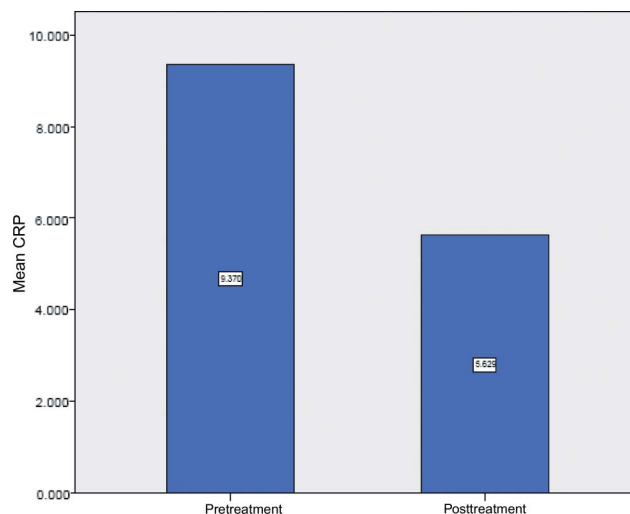


Figure 1. The means of CRP levels before and after periodontal treatment.

Table 4. Relation of difference of pre- and posttreatment CRP levels and periodontal problem.

Problem	Mean $\pm$ SD	Median	$p$ -Value
Gingivitis	$-4.21 \pm 6.85$	-1.68	0.693
Mild periodontitis	$-1.12 \pm 2.75$	-1.14	
Moderate periodontitis	$-4.07 \pm 8.57$	-1.56	
Severe periodontitis	$-3.66 \pm 12.58$	-0.59	

pathogens and their products (e.g., lipopolysaccharides). This leads to the local production of inflammatory mediators, such as CRP, IL-6, IL-1, TNF- $\alpha$ , and PGE-2.<sup>34</sup> CRP represents as an accurate and reliable marker of the acute-phase response to infectious burdens and/or inflammation and it is also effectively used for the early detection of individuals at risk for future cardiovascular accidents.<sup>14,35</sup> It has been shown that the acute-phase inflammatory response initiated by periodontitis can be measured by the serum level of CRP.<sup>36</sup>

Although multiple mechanisms can explain elevated values of CRP in the ESRD patients, many of them experience high levels of CRP in the absence of apparent infection or inflammation.<sup>18</sup>

Considering that periodontitis is a risk factor for atherosclerotic changes in CKD patients, the researchers have found it an important preventive measure to make an early diagnosis of periodontitis followed by periodontal treatment in the treatment course of CKD patients.<sup>37</sup>

There are different studies that reveal the association between high serum levels of CRP and the severity of periodontitis in ESRD who are on hemodialysis.<sup>7,38,39</sup>

Although there are numerous studies that have examined the effect of different periodontal treatment modalities on serum CRP levels in chronic periodontitis patients, this is scarcely performed on patients suffering from both periodontitis and CKD.

From the first category, many treatment studies show an effect on CRP levels in favor of periodontal treatment. Teixeira de Freitas et al.<sup>40</sup> have concluded from a meta-analysis that nonsurgical periodontal treatment can exert a reductive effect on the serum levels of CRP. These authors propose that the time of measuring CRP and the type and the extent of periodontal treatment can influence the results of the studies dramatically. Also, D'Aiuto et al.,<sup>30,35</sup> Paraskevas et al.<sup>36</sup> reported that initial periodontal treatment can lead to a reduction in serum CRP levels.

On the contrary, some other studies failed to show this positive result. For example, in a meta-analysis performed by Loannidou et al.,<sup>4</sup> the information from randomized clinical trials and small single-cohort studies did not support the hypothesis that periodontal treatment can reduce systemic CRP levels. These reviewers concluded that the mean pretreatment level of CRP is an important determinant in the evaluation of research results. This means that not very high pretreatment levels of CRP, which was shown in most of the investigated studies (mean 2.6 mg/L), were not conducive to a large improvement after treatment.<sup>25</sup> This relatively low CRP level before treatment is in agreement with some other reports in the literature for chronic periodontitis patients with no known history of systemic diseases such as cardiovascular or cerebrovascular accidents. It is noteworthy to mention that some of the studies have shown that periodontal disease significantly affects CRP levels only in the patients with an apparent history of thromboembolic accidents.<sup>41</sup>

Also, Loannidou et al.<sup>4</sup> have concluded that whether complete or inadequate periodontal treatment is performed for the patients has a detrimental effect on the systemic levels of CRP. This means that those patients with moderate and severe periodontitis who need more advanced periodontal treatment may not benefit much from nonsurgical periodontal treatment.<sup>25</sup>

Yamazaki et al.<sup>42</sup> failed to demonstrate the positive effect of initial periodontal treatment on serum levels of CRP in Japanese population, although there was a tendency for CRP to decrease following successful periodontal treatment. These authors related their obtained results to the relatively small number of patients. The findings of their study were consistent with those of Idle et al.<sup>43</sup>

Siribamrungwong et al.<sup>39</sup> found significant decrease in the serum levels of CRP 8 weeks after the completion of periodontal treatment in 30 maintenance hemodialysis patients. Vilela et al.<sup>37</sup> also reported the reduction of CRP, IL-6, and prohepcidin levels in both CKD and control patients 12 weeks following periodontal treatment. The reduction of inflammatory burden, as well as serum levels of CRP, was shown in the study. This indicates that periodontal treatment may constitute an important intervention therapy during the therapeutic course of CKD patients.<sup>37</sup>

The present study showed that initial periodontal treatment was associated with a significant decrease in serum levels of CRP in CKD patients on hemodialysis. This finding was in agreement with the results of some other publications.<sup>37,39</sup> During the study, patients were under observation and no important changes in the life-style, habits, medical health, or medications were noticed. So it can be proposed that different degrees of periodontal inflammation that were present in these patients and controlled by treatment, have contributed to their inflammatory burden.

According to the Centers for Disease Control and Prevention (CDC) recommendations, serum CRP levels less than 1 mg/L are considered low risk, 1 to 3 mg/L average risk and more than 3 mg/L high risk for the development of coronary heart disease.<sup>20</sup> On the other hand, some other investigators have proposed that CRP values less than 10 mg/mL, in the general population, can be considered as normal. However, the more accepted CRP values are that, the range of 5–10 mg/L is 420 regarded as “high normal”. In fact, this range can be predictive of atherosclerotic complications with underlying inflammatory process.<sup>44</sup>

The participants of this study had mean baseline CRP concentrations about  $9.369 \pm 11.25$  that was in the range of high risk for developing CVDs. Although periodontal treatment significantly reduced the mean levels of CRP, it was still in the high risk limit after treatment ( $5.628 \pm 4.79$  mg/L). It can be proposed that given the needs of each patient, maybe more definitive periodontal treatment, could lower the serum level of CRP more efficiently. Recent studies have proposed that even a modest increase in CRP levels, such as those seen in periodontal patients, may predict a risky situation for atherosclerosis and CVDs.<sup>45–48</sup> In the present study the patients who present situations favoring the production of CRP were excluded from the study design. So the authors speculated that the relatively high pretreatment level of CRP that yields itself to the periodontal treatment, could be related to the presence of periodontal infection. Also, it is proposed that if this increased level of acute-phase response, left unchanged, in part may contribute to a higher risk for CVDs.

Also, based on the periodontal examination and classification, none of the subjects participated in this study were periodontally normal. The majority of the patients (84.4%) had periodontitis and the minority had different degrees of gingivitis (15.6%). This means that there were different levels of local periodontal inflammation in all subjects that may have contributed to the relatively mean high level of CRP in this population in comparison with other studies.

Regarding the prevalence of destructive periodontal diseases in the general population, and since periodontal examinations are not normally performed as a part of the routine medical assessment of ESRD patients on hemodialysis therapy, periodontitis can be introduced as an overlooked source of inflammation in these patients. The

authors of this article would like to alert the physicians to the possible role of destructive periodontal diseases in the management of CKD and ESRD patients. So preventive measures such as regular visits to a dental professional and improvement of oral hygiene procedures as well as definitive periodontal treatment modalities and maintenance of patients in a health situation, after treatment, are highly recommended to be considered as a part of medical treatment of CKD patients.

In conclusion, chronic destructive periodontitis is an important source of systemic inflammation in the maintenance of hemodialysis patients. It can induce an acute-phase response, including elevation in CRP values, which in turn is associated with atherosclerotic complications. Effective management of periodontitis can improve systemic inflammation in this population and may lower the risk of associated systemic complications. The results of this investigation can be used in the design and implementation of other longitudinal follow-up studies with a larger sample size, in order to evaluate the effect of periodontal therapy on the CRP serum levels as well as on the other systemic inflammatory markers and also on the kidney performance criteria. In studies with extended samples, the effect of severity of periodontal destruction on baseline CRP levels and on its changes after treatment could be better evaluated.

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