Effect of Nonsurgical Periodontal Therapy on Serum Highly Sensitive Capsule Reactive Protein and Homocysteine Levels in Chronic Periodontitis: A Pilot Study

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Abstract

Introduction: The aim of the present study was to assess the effect of nonsurgical periodontal therapy on circulating serum high-sensitivity capsule reactive protein (hs-CRP) and homocysteine (Hcy) levels in patients with chronic periodontitis. Materials and Methods: The study involved fifty participants. The test group included 25 systemically healthy controls (mean age 38.44 ± 3.27 years) with severe chronic periodontitis and the control group (n = 25) included age- and sex-matched systemically and periodontally healthy controls. Clinical parameters were recorded, intraoral periapical radiographs were taken, hematological tests and assessment of serum hs-CRP levels and Hcy levels were performed at baseline and 3 months after completion of nonsurgical periodontal therapy. Results: Mean serum hs-CRP and Hcy concentration in patients with chronic periodontitis were 3.37 ± 0.54 mg/L and 21.47 ± 7.93 µmol/L, respectively, and was significantly higher than the controls (1.68 ± 0.71 mg/L and 13.93 ± 8.30 µmol/L, respectively) (P < 0.05). Posttreatment, the mean serum hs-CRP and Hcy concentration reduced significantly in both test and control groups (P < 0.05). Conclusion: Chronic periodontitis leads to an increase in circulating levels of hs-CRP and Hcy in plasma and nonsurgical periodontal therapy decreases periodontal inflammation, which in turn reduces systemic inflammation and consequently decreases serum levels of hs-CRP and Hcy.

Keywords: Cardiovascular diseases, chronic periodontitis, highly sensitive capsule reactive protein, homocysteine, nonsurgical periodontal therapy

Introduction

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels including coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic and congenital heart disease, deep vein thrombosis, and pulmonary embolism. According to the World Health Organization, CVDs are the number one cause of death globally, representing 31% of all global deaths in 2015.[3]

Periodontal diseases are chronic inflammatory progressive diseases of the supporting tissues of the teeth implicated in the onset and development of CVDs as well as other systemic conditions such as diabetes mellitus, occlusive respiratory diseases, and preterm low birth weight.[2] Mounting evidence points to an association of periodontal diseases with CVDs; however, it is yet unknown whether this is coincidental or causal. Periodontitis and CVDs share common risk factors such as diabetes mellitus, hyperlipidemia, smoking, and aging.[3] The prevalence of CVDs seems to be highest in individuals with periodontitis coexisting with increased serum capsule reactive protein (CRP) levels. This may signify that periodontitis is a CVD risk factor in individuals who react to the infection with a systemic inflammatory response.[4]

Thus, the conceivable etiologic mechanism linking periodontal disease and CVDs are the presence of chronic low-grade inflammation.[2] Inflammation and CVD both are associated with elevated serum levels of CRP and homocysteine (Hcy).

CRP is a pentameric plasma protein synthesized in liver. It is considered as a key acute-phase nonspecific marker of systemic inflammation. Studies have found a positive association between the presence of chronic periodontitis and high-serum CRP levels in patients with CVDs.[3] The presence of CVDs is significantly associated with increased serum CRP levels in patients with periodontitis. This study aims to assess the effect of nonsurgical periodontal therapy on circulating serum high-sensitivity capsule reactive protein (hs-CRP) and homocysteine (Hcy) levels in patients with chronic periodontitis.

Access this article online
Website: www.contempclindent.org
DOI: 10.4103/ccd.ccd_140_17

How to cite this article: 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.
levels. The plausible suggested mechanism is stimulation of hepatocytes to produce CRP, by the inflammatory mediators (interleukin [IL]-1, IL-6, and tumor necrosis factor [TNF]-α) released in chronic periodontitis. The development of high sensitivity CRP (hs-CRP) assays has enabled more accurate detection of lower concentrations of this protein (0.5–10 mg/L) in various biological fluids.

Hcy is a sulfur-containing amino acid that is a product of the methionine metabolic pathway and can get accumulated as a result of deficiency or systemic over utilization of folate, Vitamin B12, or Vitamin B6. Elevated levels of plasma Hcy has been detected in patients with chronic periodontitis. Possible mechanisms include the sustained production of pro-inflammatory cytokines such as ILs and TNF-α from inflamed periodontal tissues. These mediators can initiate an inflammatory cascade that has the potential to disturb the Hcy homeostasis, thereby elevating plasma Hcy concentrations.

A positive correlation has also been shown to exist between the concentration of Hcy and circulating levels of CRP. Inflammation and chronic infections such as periodontal disease are becoming the targets of interest as potential novel risk factors for CVDs. Evidence also indicates that rise of plasma CRP and Hcy is risk factor for CVDs. Thus, it would be beneficial to attempt to reduce their circulating levels. Treatment of chronic periodontitis may form a link in decreasing the possible systemic inflammatory effects and reducing circulating levels of CRP and Hcy, subsequently reducing the risk of CVDs.

To the best of our knowledge, no authoritative studies have been conducted analyzing the link between periodontal treatment and plasma hs-CRP and Hcy levels together. Thus, the aim of this study was to study the effect of nonsurgical periodontal treatment on circulating hs-CRP and Hcy levels in otherwise healthy controls.

Materials and Methods

The study involved fifty participants and was conducted over a span of around 1 year. The Institutional Ethics Committee, Sharda University, Greater Noida, India, approved the study and a written informed consent was obtained from all participants. The study was conducted in full accordance with ethical principles for research involving human subjects outlined in the World Medical Association Declaration of Helsinki (version 2008).

Test group included 25 systemically healthy controls with clinical indicators of severe chronic periodontitis with radiographic evidence of alveolar bone loss, selected from outpatient section of the Department of Periodontology, School of Dental Sciences, Sharda University, Greater Noida, Uttar Pradesh, India. The participants were within age range 35–55 years and consented to follow oral hygiene instructions and come for follow-up visits. According to the case definition by the Centers for Disease Control and Prevention criteria, American Academy of Periodontology, severe periodontitis was defined as ≥1 interproximal site with probing depth ≥5 mm and ≥2 interproximal sites with clinical attachment loss ≥6 mm not on the same tooth.

The control group (25 participants) was selected from age- and sex-matched systemically and periodontally healthy controls who had no clinical signs of gingival inflammation.

Participants with <20 permanent teeth remaining, with a history of periodontal therapy (surgical or nonsurgical) within 6 months, or who had received antibiotics, anti-inflammatory drugs, steroids, immunosuppressant, statins, anticoagulants, lipid-lowering drugs, or vitamin supplementation therapy within 6 months and smokers were excluded from the study.

Participants with systemic diseases and conditions such as hypertension, CVDs, renal disease, rheumatoid arthritis, diabetes mellitus, gastrointestinal disorders, bronchitis or other obstructive pulmonary diseases, nutritional deficiencies, and pregnant and lactating females were also excluded from the study.

A detailed questionnaire was used to evaluate the participants. Demographic characteristics, such as age, gender, diet, body mass index (BMI), and medical history, were recorded.

Assessment of oral hygiene and gingival status was done using Turesky–Gilmore–Glickman modification of the Quigley-Hein plaque index (PI) (1970), calculus component of simplified oral hygiene index (Greene and Vermillion 1964), and modified gingival index (MGI) (Lobene et al. 1986).

Full-mouth periodontal probing depth and clinical attachment level (CAL) were measured on six sites (mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, and distolingual) per tooth using a graduated University of North Carolina-15 probe. A single trained examiner made all measurements. A set of full mouth intraoral periapical radiographs was taken to assess alveolar bone loss.

The parameters were assessed at the baseline and 3 months after completion of nonsurgical periodontal treatment.

Nonsurgical periodontal treatment

Both test and control groups underwent instruction on oral hygiene techniques, demonstration of a manual tooth brushing, interproximal brushing, the use of dental floss as well as supragingival prophylaxis.

Participants with chronic periodontitis received nonsurgical periodontal therapy including two 1 h sessions of scaling and root planing using Gracey curettes and ultrasonic scaler over a maximum of 4 weeks. Participants were followed up every 15 days for 3 months.
(oral hygiene instructions + supragingival prophylaxis was carried out).

**Sample collection and biochemical analysis**

Five milliliter of fasting (minimum 12 h) venous blood samples were collected in plain vials from the median cubital vein at baseline and 3 months after the periodontal therapy. The samples were immediately sent to the laboratory for biochemical analysis. The hematological tests performed included complete blood count (hemoglobin, total leukocytes count, differential leukocyte count, and platelet count), fasting blood sugar (FBS), total cholesterol (TCHO), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL).

Serum hs-CRP levels were assessed by nephelometric method (Behring Nephelometer Analyzer). The serum Hcy levels were assessed using enzyme-linked immunoassay (Axis® Homocysteine EIA, Axis-Shield Diagnostics Ltd., Scotland, UK). Since the Hcy concentration tends to increase over time due to synthesis and release by red blood cells, the samples were immediately centrifuged and plasma was separated and stored at 2°C–8°C till assayed.

**Statistical analysis**

Statistical Package for Social Sciences (SPSS) version 21 (IBM®, Armonk, NY: IBM Corp) was used for data analysis. All the variables were summarized as mean and standard deviation. Normality of the data was checked by Shapiro–Wilk test. The data failed to satisfy the condition of normal distribution; hence, inferential statistics were performed using nonparametric tests of significance. Wilcoxon signed-ranks test was used for intragroup comparison of the parameters at baseline and 3 months posttreatment. Mann–Whitney U-test was used to perform intergroup comparison of the assessed parameters. *P* < 0.05 was considered statistically significant.

**Results**

A total of fifty participants participated in the study and there were no dropouts during the study. Twenty-five participants with chronic periodontitis (males = 14, females = 11) with mean age of 38.44 ± 3.27 years received nonsurgical periodontal therapy (test group) and 25 periodontally healthy controls (males = 13, females = 12) with mean age of 37.48 ± 2.79 years were considered as controls.

There was no statistically significant difference between the test and control groups at baseline and 3 months posttreatment for the mean value of age, BMI, FBS, TCHO, TG, HDL, LDL, and VLDL (*P* > 0.05) [Table 1].

However, significant differences in mean PI, MGI, Calculus index-Simplified Oral Hygiene Index (OHIS), pocket depth (PD), CAL between the participants with periodontitis and the controls (*P* < 0.05) as well as between the participants with periodontitis pre- and post-treatment were observed (*P* < 0.05) [Table 2].

Mean serum hs-CRP and Hcy concentration in participants with chronic periodontitis were 3.37 ± 0.54 mg/L and 21.47 ± 7.93 µmol/L, respectively, and were significantly higher than the controls (1.68 ± 0.71 mg/L and 13.93 ± 8.30 µmol/L, respectively) (*P* < 0.05). Posttreatment, the mean serum hs-CRP and Hcy concentration in participants with chronic periodontitis were 1.77 ± 0.64 mg/L and 11.87 ± 2.89 µmol/L, respectively, and were 1.32 ± 0.54 mg/L and 10.09 ± 3.67 µmol/L, respectively, in the control group. The differences were statistically significant (*P* < 0.05) [Table 2, Graphs 1 and 2].

**Discussion**

A role for inflammation has become a well-established phenomenon in the pathogenesis of atherosclerotic disease.
Inflammation also functions in all stages of periodontitis from initiation through progression including the atherosclerotic complications, emerging as an integrative cardiovascular factor. CRP is an acute-phase protein, which is produced in response to inflammatory, infectious, and/or traumatic stimulation. It is considered as a key biomarker of systemic inflammation. Although synthesized primarily by hepatocytes in response to pro-inflammatory cytokines, extrahepatic synthesis of CRP by arterial tissues has been reported. CRP has also been found in gingival biopsies, saliva, and gingival crevicular fluid. It has been implicated as an active contributor to atherosclerosis and inflammation. The suggested role of CRP in cardiovascular pathogenesis is by direct damage of blood vessels through activation of the complement cascade, by enhancing the formation of atherosclerotic lesions, and by endothelial dysfunction.

Writing Group of Centers for Disease Control and Prevention and the American Heart Association 2003 had concluded that hs-CRP levels seem to have predictive abilities for CVD events (hs-CRP >3 mg/L - high relative risk category) and can also be measured as an adjunct to the major risk factors to further assess absolute risk for primary prevention of CVDs.

Hcy, a sulfur amino acid, is an intermediate product of methionine metabolism. Hcy metabolism involves intersection of two mechanisms: remethylation, which requires folic acid and Vitamin B-12 coenzymes, and transsulfuration, which requires Vitamin B-6 coenzyme. Elevated plasma Hcy levels are suggestive of increased risk for occlusive vascular disease, increased CVD mortality, increased incidence of stroke, increased incidence of dementia and Alzheimer’s disease, and higher prevalence of chronic heart failure.

It is hypothesized that methionine metabolism can be affected by the periodontal inflammatory cascade thus leading to increased plasma Hcy levels. Hence, the present study was conducted to evaluate the serum levels of two systemic markers: hs-CRP and Hcy before and 3 months after nonsurgical periodontal therapy in age- and gender-matched healthy and chronic periodontitis participants in Indian population.

A total of fifty participants within age group 35–55 years were enrolled in the study using strict inclusion criteria to diminish the influence of potential confounders. Test group comprised 25 systemically healthy controls with untreated chronic periodontitis with a mean age of 38.44 years and control group comprised 25 systemically and periodontally healthy controls with a mean age of 37.48 years. Systemic conditions such as diabetes mellitus, obesity, and higher CVD risk are potential confounders of serum CRP and Hcy levels; hence, serum FBS, lipid profile, and BMI analysis were conducted to exclude systemically compromised individuals.

Venous blood samples were collected at baseline and 3 months post nonsurgical periodontal therapy, after 12 h...
of fasting to prevent any influence of diet on plasma CRP and Hcy concentrations.\(^\text{[7,19]}\)

The results revealed that hs-CRP and Hcy levels were significantly elevated in participants with chronic periodontitis compared to healthy controls \((P < 0.01)\).

As early as 1967, Boucher et al. reported an association between CRP and periodontitis.\(^\text{[20]}\) Thereafter, a relationship of chronic periodontitis with elevated plasma hs-CRP levels has been reported by various authors.\(^\text{[21-23]}\)

CRP is a strong acute-phase protein, which responds rapidly to inflammatory stimuli and serve phagocytic and microbicidal function to restore tissue homeostasis. CRP is generally present in ng/ml quantities and may show a dramatic 100–1000-fold increase within hours following tissue injury or inflammation.\(^\text{[24,25]}\)

As periodontitis ensues, there is elevation of the local pro-inflammatory cytokines and mediators, the initiation of a localized specific host response, and subsequently a serum antibody response to the microorganisms and their by-products. During periods of active tissue destruction, the locally produced cytokines that are primarily responsible for the clinical signs and symptoms and tissue destruction associated with progressing periodontitis may gain access to systemic circulation and stimulate synthesis of CRP by liver eventually leading to increase serum CRP levels. Consequently, the localized inflammation may manifest itself systemically within the affected host. Various studies have revealed the role of cytokines in eliciting the systemic acute-phase response in diverse chronic inflammatory diseases.\(^\text{[26,27]}\)

Similar to the our study, Agnihotram et al. 2010 and Joseph et al. 2011 demonstrated higher plasma Hcy concentrations in chronic periodontitis participants over the controls.\(^\text{[6,28]}\) As recognized in the preceding studies and the present study, there could be a biologically conceivable association between chronic periodontitis and serum Hcy levels with several possible underlying mechanisms explaining this link.

Periodontal bacteria may induce the production of pro-inflammatory cytokines such as IL-6 from inflamed periodontal pockets which in turn may interact systemically with Vitamin B6 metabolism, stimulate the activity of pyridoxal phosphatase in hepatocytes, thereby reducing pyridoxal phosphate levels, compromising cystathionine beta-synthase activity, and increasing plasma Hcy.\(^\text{[29]}\)

Heightened immune activation in periodontitis is associated with production of reactive oxygen species by macrophages and monocytes. The developing oxidative stress leads to overloading of the detoxifying system and reduction of blood concentrations of oxidation-sensitive tetrahydrofolate and Vitamin B12 (which are required for the metabolism of Hcy) leading to raised Hcy concentrations.\(^\text{[30]}\)

Similar to conditions such as stroke or myocardial infarction, periodontal tissue damage may also accelerate specific remethylation reactions of DNA, RNA, and various proteins during tissue repair, consequently generating S-adenosyl Hcy and release of Hcy.\(^\text{[31]}\)

Since rise in the serum CRP and Hcy levels was associated with periodontal inflammation, decrease in their serum levels could be anticipated following periodontal therapy, subsequently leading to a decline in systemic inflammatory load. Thus, in the present study, the effect of nonsurgical periodontal therapy on serum hs-CRP and Hcy concentrations in patients with chronic periodontitis were also evaluated.

Serum hs-CRP and Hcy levels were found to significantly decrease 3 months after nonsurgical periodontal therapy in both test and control groups \((P < 0.05)\). There was also a significant reduction in probing PD and gain in CAL in participants with chronic periodontitis \((P < 0.05)\). Further the scores of PI, gingival index, and bleeding index decreased significantly posttherapy in the participants with chronic periodontitis. Therefore, the results of the present study highlights that there is a decrease in the levels of systemic inflammatory markers, following therapy in periodontal patients, and subsequently there is also an improvement in the periodontal parameters.

Similar to the findings in our study, meta-analysis conducted by Freitas et al. 2009 and Paraskevas et al. 2008 indicated that nonsurgical periodontal treatment has a positive effect on significantly reducing the serum levels of CRP.\(^\text{[32,23]}\) Several studies have indicated that periodontal therapy is successful in reducing serum CRP most in patients with high CRP levels or inflammatory burden at baseline.\(^\text{[33,34]}\)

As demonstrated in our study, Bhardwaj et al. 2015 also have demonstrated a significant reduction of plasma Hcy levels to 11.34 ± 1.87 \(\mu\)mol/L from 17.87 ± 1.21 \(\mu\)mol/L after 12 weeks of nonsurgical periodontal therapy in patients with chronic periodontitis.\(^\text{[17]}\)

Thus, our study demonstrates an association between periodontal disease and serum CRP and Hcy levels. Periodontitis has been marked as a “low-grade systemic disease.”\(^\text{[35]}\) Moreover, the elevated serum CRP and Hcy levels in chronic periodontitis patients in our study denote the influence of persistent localized infection on the systemic continuum.

Periodontal bacteria can act through various mechanisms to cause systemic effects including invasion of adjacent tissue, bacterial seeding through circulation, aspiration, endotoxemia, systemic dissemination of virulence factor, induction of systemic immune response, and production of pro-inflammatory mediators.\(^\text{[36]}\)

Park et al. 2010 in the 3rd National Health and Nutrition Examination Survey demonstrated elevated circulating CRP
levels and hyper-Hcy in participants with high 10-year risk for CVDs.[37] Yan et al. 2010 have reported a linear association between Hcy and hs-CRP and stated that combination of increased Hcy (≥18 μmol/L) with increased hs-CRP levels (>3 mg/L) has a stronger predictive value and is a more precise risk factor for new vascular events than increased hs-CRP or increased total Hcy levels alone.[38]

**Conclusion**

Thus, within the confines of our study, it can be concluded that chronic periodontitis leads to an increase in the circulating levels of hs-CRP and Hcy in serum. Nonsurgical periodontal therapy decreases periodontal inflammation, which in turn reduces systemic inflammation and serum levels of hs-CRP and Hcy thus contributing to reduction of risk of developing cardiovascular events.

Further longitudinal randomized clinical trials should be conducted with larger sample size to verify the role of periodontal therapy in lowering the risk of developing CVDs.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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