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"INCREASED PLASMA HOMOCYSTEINE LEVELS IN CHRONIC PERIODONTITIS: A CASE- CONTROL STUDY"

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Background:

Elevated plasma Hcy has been linked to cardiovascular diseases and is found in higher levels in inflammatory conditions like rheumatoid arthritis.The research aims to determine if chronic periodontitis is associated with changes in plasma Hcy levels.

Material and methods:

The study included 85 individuals with chronic periodontitis and 91 healthy controls, matched by age and gender. Participants were categorized into moderate or severe periodontitis groups.Various health parameters, including plaque index, components of oral hygiene, BMI, fasting blood sugar, lipid profile (cholesterol, triglycerides, lipoproteins), and plasma Hcy levels, were measured.

Results:

There were no significant differences in fasting blood sugar, lipid profile, or BMI between the case and control groups.The average plasma Hcy level was significantly higher in the periodontitis group (19.23 ± 8.28 mmol/L) compared to the controls (10.28 ± 2.51 mmol/L), with a statistically significant difference ($P < 0.05$).No significant variation in plasma Hcy levels was observed between moderate and severe periodontitis cases ($P = 0.723$).

Conclusions:

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Plasma Hcy levels were notably higher in patients with chronic periodontitis than in healthy controls.Further studies should investigate the effect of periodontal treatments on plasma Hcylevels.This suggests that chronic periodontitis might be linked to increased plasma Hcy levels, potentially raising cardiovascular risk. Additional research is needed to understand how periodontal treatment might influence these levels.

Introduction

Homocysteine (Hcy) is a sulfur-containing amino acid that forms from methionine during its metabolism. Increased plasma Hcy levels, or hyperhomocysteinemia (HHcy), have been associated with oxidative damage to the vascular endothelium, growth of vascular smooth muscle cells, and lipid peroxidation, which can contribute to atherosclerosis and peripheral arterial disease.[1-5] According to World Health Organization statistics,[6] cardiovascular disease (CVD) is the leading cause of illness and death worldwide.[7,8]Moreover, more than 50% of patients with atherosclerosis have no identifiable risk factors, suggesting the presence of unknown risk factors. These may include chronic infections and inflammation, along with biomarkers such as C-reactive protein and elevated Hcy levels. However, there is ongoing debate in the literature about the strength of the relationship between Hcy and the risk of CVD and peripheral arterial disease.[9-14]

Plasma homocysteine (Hcy) is involved in the systemic inflammatory response. It has mainly been studied as an inflammation biomarker in individuals with rheumatoid arthritis (RA). Studies have shown a positive association between Hcy levels and various inflammatory markers, such as soluble cytokine receptors (e.g., interleukin [IL]-2sRa, Stnfr75), adhesion molecules (e.g., sICAM-1),[15] and C-reactive protein.[16-18] Periodontitis, a chronic inflammatory disease that leads to the destruction of the teeth-supporting structures, shares an immunoinflammatory profile similar to that of RA. Moreover, periodontal pathogens like *Porphyromonasgingivalis* can invade gingival tissues and enter the bloodstream.[19] Current evidence-based research suggests that periodontitis can impact overall systemic health, contributing to conditions such as cardiovascular disease (CVD),[20,21] diabetes, and preterm low-birth-weight births.[22,24]This connection between periodontal disease and systemic health is thought to be mediated through inflammatory molecules, such as acute-phase proteins and immune effectors.[25,26]

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Since periodontitis shares a similar immunoinflammatory profile with rheumatoid arthritis (RA), a similar connection may exist between chronic periodontitis and plasma Hcy in otherwise healthy individuals. However, this link has not been clearly explored in existing research. No definitive studies have established the relationship between chronic periodontitis and hyperhomocysteinemia (HHcy). Therefore, we hypothesize that plasma Hcy levels may be elevated in individuals with chronic periodontitis. This study aims to evaluate plasma Hcy levels in individuals with chronic periodontitis and explore the relationship between the severity of periodontitis and plasma Hcy levels.

Materials and method:

This case-control study included 176 participants and was conducted between March 2023 and April 2024. The case group consisted of 85 individuals diagnosed with chronic periodontitis, recruited from patients attending the outpatient clinic at the Department of Periodontology, Rama Dental College, Hospital and Research Centre,Kanpur . The control group consisted of 91 clinically healthy individuals matched by age and sex. The case group had 28 males and 57 females, while the control group had 35 males and 56 females. The study was approved by the Institutional Ethics Committee of Rama Dental College, Hospital and Research Centre, Kanpur, and written informed consent was obtained from all participants.

The case group was identified based on the Centres for Disease Control and Prevention criteria established by the American Academy of Periodontology. Subjects with moderate or severe chronic periodontitis were included. Moderate periodontitis was defined as having at least two interproximal sites with a clinical attachment loss (AL) of 4 mm or more (not on the same tooth), or at least two interproximal sites with a probing depth (PD) of 5 mm or more (not on the same tooth). Severe periodontitis was defined as having at least two interproximal sites with an AL of 6 mm or more (not on the same tooth), and at least one interproximal site with a PD of 5 mm or more.

The control group consisted of age- and sex-matched individuals who were systemically and periodontally healthy. These subjects were selected from healthy volunteers accompanying patients, as well as students and staff from the Rama Dental College, Hospital and Research Centre, Kanpur, India. Patients younger than 15 years or older than 45 years, those with fewer than 10 permanent teeth, individuals who had undergone periodontal therapy within the past

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six months, those who had taken antibiotics in the past three weeks, and smokers were excluded from the study. Additionally, individuals with known systemic diseases or conditions such as cardiovascular disease (CVD), renal diseases, rheumatoid arthritis (RA), diabetes mellitus, nutritional deficiencies, or pregnant and lactating women were also excluded.

Participants were assessed through a comprehensive questionnaire, which recorded demographic information such as age, sex, diet, and medical history. Oral hygiene and gingival status were evaluated using the Turesky-Gilmore-Glickman modification of the Quigley-Hein plaque index, the calculus component of the simplified oral hygiene index, and the modified gingival index. Probing depth (PD), gingival recession, and clinical attachment loss (AL) were measured at six sites (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, and disto-lingual) per tooth using a graduated periodontal probe with Williams markings. All measurements were performed by a single trained examiner (SGN).

Patients were classified into moderate and severe periodontitis groups according to the Centers for Disease Control and Prevention criteria. Systemic parameters, including body mass index (BMI), fasting blood sugar (FBS), total cholesterol (TCHO), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), and plasma homocysteine (Hcy) levels, were measured. LDL cholesterol was calculated based on TCHO, HDL cholesterol, and TG.

Biomarker Analysis (Plasma Hcy) by Enzyme Immunoassay

An enzyme immunoassay was used to measure homocysteine (Hcy) levels in plasma. This method is based on the principle that protein-bound Hcy is reduced to free Hcy and then enzymatically converted to S-adenosyl-L-homocysteine. The enzyme used is specific for the L form of Hcy, which is the only form found in the blood. Since Hcy synthesis continues in red blood cells after blood is drawn, the samples were centrifuged, and plasma was separated and stored at 2°C to 8°C. A four-parameter logistic curve was used to create the calibration curve and calculate the values for unknown samples.

Statistical Analyses

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All data were analyzed using statistical software. The Mann-Whitney U test and Student t-test were employed to determine the significance between the cases and controls. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 176 participants took part in this case-control study. There was no statistically significant difference in age between the groups (P = 0.63) (Table 1). BMI was categorized according to the World Health Organization (2000) classification: normal weight (BMI 18.5 to 24.9 kg/m²), overweight (BMI 25 to 29.9 kg/m²), and obese (BMI ≥30 kg/m²). The mean values for BMI (P = 0.484), fasting blood sugar (FBS) (P = 0.918), total cholesterol (TCHO) (P = 0.526), high-density lipoprotein (HDL) (P = 0.55), low-density lipoprotein (LDL) (P = 0.78), triglycerides (TG) (P = 0.18), and very-low-density lipoprotein (VLDL) (P = 0.274) did not show statistically significant differences between the case and control groups (Table 1).

Table 1: Demographic and Systemic Parameters in Cases and Controls

Parameter	**Cases(85) Mean ± SD**	**Controls(91) Mean ± SD**	**P Value**
Age (years)	34.08±7.901	33.41±5.523	0.64
Body mass index (kg/m^2)	23.77±2.66	23.35±2.03	0.484
Fasting blood sugar (mg%)	87.50±11.16	87.36±8.744	0.918
Triglycerides (mg/dl)	41.96±23.32	41.96±23.32	0.18
High-density lipoprotein (mg/dl)	41.55±7.94	41.55±7.96	0.55
Low-density lipoprotein (mg/dl)	104.03±26.26	104.03±26.24	0.78
Total cholesterol (mg/dl)	163.94±27.60	163.92±27.60	0.526

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Very-low-density lipoprotein (mg/dl)	18.47±5.17	18.47±5.17	0.274

Significant differences were observed in the mean gingival index (P = 0.00), plaque index (P = 0.00), and mean simplified oral hygiene index (P = 0.00) between the cases and controls (Table 2). The mean plasma Hcy levels were 19.23 ± 8.28 mmol/L for the cases and 10.28 ± 2.51 mmol/L for the controls, with a statistically significant difference (P = 0.00). This indicates an association between chronic periodontitis and elevated plasma Hcy (Table 2).

Table 2: Periodontal Parameters and Plasma Homocysteine in Cases and Controls

Parameter	**Case(85) Mean ± SD**	**Controls(91) Mean ± SD**	**P Value**	**95% Confidence interval Lower**	**95% Confidence interval Upper**
Gingival index	2.37 ± 0.365	0.0006 ± 0.002	0.00	2.26	2.46
Plaque index	2.22±0.34	0.06±0.18	0.00	2.03	2.25
Oral hygiene index	1.86±0.25	0.06±0.11	0.00	1.686	1.858
Plasma homocysteine (mmol/L)	19.23 ±8.28	10.28 ±2.51	0.00	5.96	11.12

P<0.05

Of the 85 patients with chronic periodontitis, 24 had moderate periodontitis and 61 had severe periodontitis. However, there was no statistically significant difference in plasma Hcy levels between the moderate and severe periodontitis groups (P = 0.723) (Table 3).

Table 3:Comparison of Plasma Homocysteine Among Cases With Moderate and Severe Chronic Periodontitis

Group	**Number**	**Mean ± SD**	**P Value**
Moderate	24	19.93 ± 8.25	0.723

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periodontitis			
Severe periodontitis	61	18.93± 8.41	-

Discussion

Homocysteine (Hcy) is a sulfur-containing amino acid that is produced from methionine during its metabolism.Methionine is the only known source of Hcy in the human body. On average, about 2 grams of methionine are consumed daily. Free methionine released from dietary proteins is transported through the bloodstream to body organs, where it is taken up by cells. Normal Hcy levels range from 5 to 15 mmol/L, while Hcy levels between 16 and 30, 31 and 100, and above 100 mmol/L are classified as mild, moderate, and severe hyperhomocysteinemia (HHcy), respectively. Under normal conditions, most of the Hcy produced during transmethylation reactions is remethylated into methionine or converted into cysteine through transsulfuration reactions. The B-complex vitamins are essential for these transformations and the excretion of Hcy.

This case-control study included 176 participants, aged 15 to 45 years, who were matched for age and sex. A review based on the Framingham Heart Study cohorts has shown that total Hcy levels tend to be higher in men and postmenopausal women. Chronic periodontitis is also associated with age. By focusing on individuals aged 15 to 45 years, the study helps eliminate age-related and female sex-related (due to menopause) confounding factors, which can be difficult to control. Diabetes mellitus and obesity are potential confounders for plasma Hcy levels. In our study, subjects with diabetes were excluded.[27-30] Previous reports suggest that obesity, as measured by BMI, is linked to periodontitis. However, the definition of periodontitis and sample sizes in previous epidemiological studies vary considerably. In our study, the BMI of both cases and controls fell within the normal range (>25 kg/m²). The small sample size and the criteria used for defining periodontitis may explain the observed variations.

The lipid profiles of both cases and controls in our study were within the normal range, aligning with findings from Machado et al.[31] and Saxlin et al.[32] However, contrary to our results, Katz et al.[33] and Cutler et al.[34] reported higher lipid profiles in patients with periodontitis. The conflict in results may be due to the small sample size or the study design.

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In this study, patients with chronic periodontitis showed elevated plasma homocysteine (Hcy) levels, indicating an association between periodontal disease and plasma Hcy. However, no correlation was found between the severity of chronic periodontitis and increased plasma Hcy levels upon statistical analysis. All other systemic parameters measured were within the normal range, except for plasma Hcy. The elevated plasma Hcy in the case group could be a result of persistent immunoinflammatory activation caused by periodontal pathogens.

There are several potential mechanisms that may explain the connection between chronic periodontitis and elevated plasma Hcy. Proinflammatory cytokines, such as interleukin-6 (IL-6), may be released from inflamed periodontal pockets, triggering the production of acute-phase reactants in the systemic circulation. McCarty has suggested that IL-6 could interact with vitamin B6 metabolism and impair cystathionine β-synthase activity, leading to an increase in plasma Hcy concentrations. This indicates that hyperhomocysteinemia (HHcy) could be linked to the release of IL-6 from the inflamed periodontal tissues.

Interleukin-6 (IL-6) also triggers the Th1 immune response, causing the release of large amounts of interferon-gamma, which strongly promotes the production of reactive oxygen species (ROS) by monocytes and macrophages. ROS are responsible for cellular damage, but the body usually counters them with specific antioxidant agents. However, in the case of chronic immune activation, these detoxifying systems may become overloaded, causing oxidative-sensitive molecules like tetrahydrofolate and vitamin B12—which are crucial for homocysteine (Hcy) metabolism—to be targeted by ROS. As a result, the inflammatory processes associated with chronic periodontitis may lead to a significant buildup of Hcy.

Additionally, it can be hypothesized that damage to periodontal tissue may accelerate specific remethylation reactions of DNA, RNA, and proteins during tissue repair, which would lead to the production of S-adenosylhomocysteine and the release of plasma Hcy. This mechanism is similar to what is observed in autoimmune conditions such as rheumatoid arthritis (RA). These processes provide insight into how inflammation in chronic periodontitis can affect plasma Hcy levels.

In the inflammatory response, leukocytes first adhere and then migrate through the endothelial wall, a process driven by chemotactic factors. RANTES (regulated on activation, normal T cells expressed and secreted) is a chemokine that plays an important role in this process. It is mainly produced by T lymphocytes but can also be secreted by monocytes and macrophages. RANTES-induced migration of leukocytes through the endothelium is

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involved in the early stages of inflammation in atherosclerosis. Increased secretion of RANTES in monocytes has been observed in patients with hyperhomocysteinemia (HHcy). Further research is necessary to examine the impact of HHcy on the immune-inflammatory mechanisms in chronic periodontitis.

To the best of our knowledge, very limited studies have explored the relationship between plasma homocysteine (Hcy) levels and chronic periodontitis. However, significant associations have been observed between plasma Hcy and other chronic inflammatory diseases, such as rheumatoid arthritis (RA), Behçet's disease, and systemic lupus erythematosus. This study clearly shows that inflammatory conditions like chronic periodontitis are associated with elevated plasma Hcy levels. Pro-inflammatory cytokines and acute-phase reactants released from inflamed periodontal pockets could contribute to the increase in plasma Hcy levels. However, no significant difference in plasma Hcy levels was found between moderate and severe chronic periodontitis. The elevated plasma Hcy levels in patients with chronic periodontitis might serve as an indicator of systemic inflammation.

This study has certain limitations. Being hospital-based, it may not accurately represent the broader population. The enzyme-linked immunosorbent assay (ELISA) was used to estimate plasma Hcy levels, whereas high-performance liquid chromatography (HPLC) would be a more accurate method. Additionally, the cross-sectional design of the study does not rule out the possibility of reverse causality, where plasma Hcy may directly stimulate pro-inflammatory signaling molecules and chemoattractants in the periodontium. The novel association between periodontal disease and plasma Hcy may offer a potential mechanistic link between periodontal disease and cardiovascular disease (CVD). Given that elevated plasma Hcy is a known risk factor for CVD, interventions to reduce plasma Hcy levels could be beneficial. However, there is conflicting evidence in the literature regarding the effectiveness of B-complex vitamins in lowering plasma Hcy levels. The 2009 Cochrane Review concluded that there was no conclusive evidence to support the use of Hcy-lowering interventions for preventing cardiovascular events.[35]

Conclusions: This study highlights the elevated plasma Hcy levels in patients with chronic periodontitis. Further interventional studies are needed to explore how periodontal therapy may impact plasma Hcy levels. Future research should focus on microbiological assessments of periodontal pathogens, particularly *Porphyromonasgingivalis*, and the levels of pro-inflammatory cytokines, such as IL-6, in otherwise healthy individuals with chronic

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periodontitis and how these relate to changes in plasma Hcy levels. Large-scale, prospective multicenter clinical trials examining the effects of periodontal therapy on plasma Hcy levels could provide clearer insights into the association observed in this study.

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