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Relation Between Probing Pocket Depth and Hemoglobin and Serum Ferritin Level in Male Patients with Chronic Periodontitis

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Abstract

Background and Objective: Periodontitis is an infectious immunoinflammatory disease, triggered and aggravated by subgingival microbiota. Locally secreted cytokines and periodontal pathogens can induce low grade systemic inflammation. It may act as a common pathophysiological mechanism that links periodontal diseases and systemic conditions. Periodontitis is associated with anemia of chronic disease which is occurring in chronic infections, inflammatory conditions, etc. Cytokines associated with periodontal inflammation inhibit proliferation and differentiation of erythrocytes and affect iron metabolism leading to anaemia. The present study was undertaken to evaluate the relation between chronic periodontitis, hemoglobin level and serum ferritin.

Materials and Methods: This observational study consists of two groups. Case group comprised of 40 male patients aged between 35 - 65 with chronic periodontitis (CAL > 5 mm, PPD > 6 mm) and were consecutively selected from the Dept. of Periodontics, GDC Kozhikode. 40 healthy volunteers aged between 35 - 65 with (PPD < 3 mm, CAL < 3 mm) were selected as control group. All subject were assessed for periodontal parameters (BOP, PPD, CAL, OHI-S Index and Gingival index) and hematological parameters (Hb, MCV, MCH, MCHC, PCV, and serum ferritin).

Result and Discussion: Mean hemoglobin level in case and control group was 13.18 ± .57 and 14.04 ± .57 respectively and the difference was significant ($p < 0.001$). Serum ferritin level was significantly high in subject with chronic periodontitis ($p < 0.03$) as compared to control group. Significant difference was observed in MCHC, MCH and PCV level ($p < 0.001$, $p < 0.001$ and $p < 0.001$ respectively). A negative correlation showed between PPD and Hb level, there was a weak positive correlation exist between serum ferritin and mean PPD.

Interpretation and Conclusion: Inflammation associated with chronic periodontitis influences serum hemoglobin level, ferritin level and other hematological parameters. Chronic periodontitis may have a definite role in the occurrence of anaemia of chronic disease (ACD). Successful management of periodontal infection could improve the level of haemoglobin.

Keywords: *Anemia of Chronic Disease; Chronic Periodontitis; Hemoglobin; Ferritin*

Abbreviations

ACD: Anemia in Chronic Disease; BOP: Bleeding on Probing; CAL: Clinical Attachment Loss; CDC: Centers for Disease Control and Prevention; CEJ: Cementoenamel Junction; CI-S: Calculus Index -Simplified; DI-S: Debris Index-Simplified; EPO: Erythropoietin; GCF: Gingival Crevicular; GI: Gingival Index; Hb: Haemoglobin; MCH: Mean Corpuscular Haemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; MCV: Mean Corpuscular Volume; OHI-S: Simplified Oral Hygiene Index; OPD: Out Patient Department; PCV: Packed Cell Volume; PI: Plaque Index; PPD: Periodontal Pocket Depth; SI: Serum Iron; TIBC: Total Iron Binding Capacity

Introduction

Periodontitis is a chronic multifactorial immunoinflammatory disease associated with dysbiotic plaque biofilms. It is characterized by the presence of gingival inflammation, periodontal pocket, clinical attachment loss (CAL), and alveolar bone loss [1].

Inflammation of the gingiva begins as a response to the colonization of periodontal pathogens in the gingival sulcus. Progression of inflammation leads to the periodontal pocket formation. The pocket epithelium acts as a gateway for the bacteria and its products to enter the connective tissue and it activates the host response. Periodontal pathogens stimulate fibroblasts, keratinocytes, and macrophages to release inflammatory cytokines.

Locally secreted cytokines and periodontal pathogens can enter the bloodstream and induce low-grade systemic inflammation. The low-grade inflammatory burden may act as a common pathophysiological mechanism that links periodontal diseases and systemic conditions [2]. Periodontitis is associated with an increased risk of systemic diseases and conditions like cardiovascular diseases [3], cerebrovascular ischemia [4], atherosclerosis, and preterm low birth weight [5] and anemia of chronic disease [6].

Anemia of chronic disease (ACD) is defined as anemia occurring in chronic infections, inflammatory conditions, or a neoplastic disorder, etc. which is not caused by marrow deficiencies and occurs despite the presence of adequate iron stores and vitamins [7]. The estimated prevalence of ACD caused due to chronic inflammation accounts for 23 - 50% [6]. ACD is usually identified as normocytic or microcytic anemia [8] and have a distinctive pattern of iron distribution. The level of serum iron (SI) and total iron binding capacity (TIBC) are low to normal, while serum ferritin levels can be normal or elevated. Hepcidin hormone regulates iron metabolism. It is produced by the liver in response to inflammatory cytokines such as IL-6, IL-1, etc. and inhibits iron transport by binding to the iron export channel ferroprotein.

Low-grade inflammatory burden in periodontitis may be related to the suppression of erythroid proliferation in the bone marrow and decreased release of erythropoietin from the kidney. Subsequently, there will be a reduction in the life cycle of red blood cells, the number of erythrocytes, and the level of hemoglobin. Maturation and differentiation of erythroid are also impaired [9]. Inflammation plays a central role in the pathogenesis of both periodontitis and ACD. Even though studies [10,11] have reported a significant correlation between ACD and periodontitis, conflicting reports are also available in the literature.

Objective of the Study

This study was conducted to know the relationship between chronic periodontitis and ACD. The objectives of this study were: 1) To assess the serum hemoglobin level, and serum ferritin level in chronic periodontitis and healthy subjects, 2) To find the correlation between hemoglobin level and periodontal pocket depth, and 3) To find the correlation between serum ferritin and periodontal pocket depth.

Materials and Methods

This hospital-based observational study was conducted in the department of periodontics and it comprised of 80 male subjects (Figure 1). The sample size was calculated based on a previous study [12]. The case group consists of 40 male patients with chronic periodontitis.

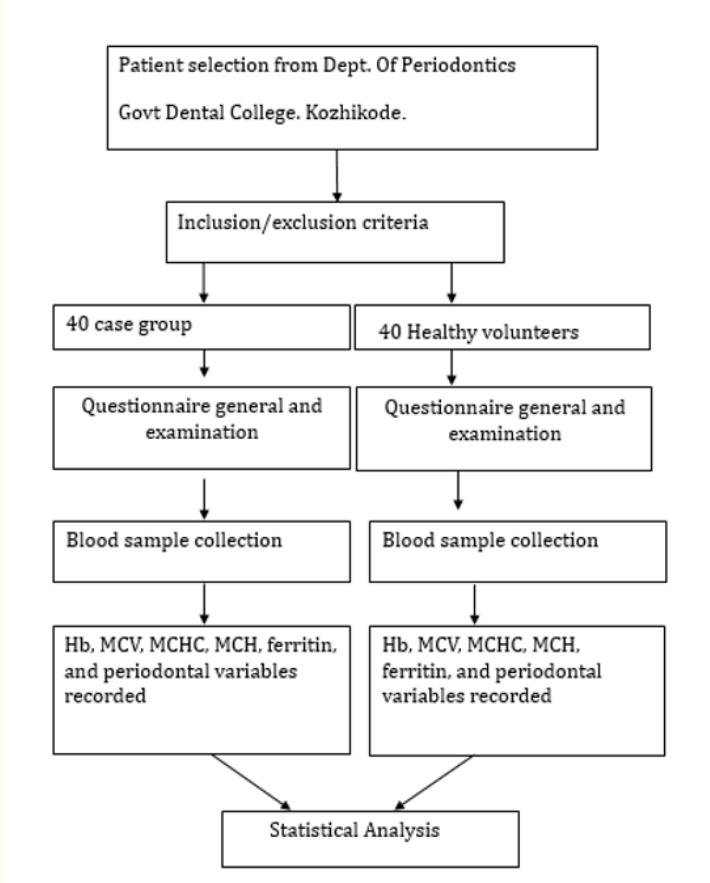


Figure 1: *Flow diagram. Hb: Hemoglobin; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration.*

The inclusion criteria for case group were male patients aged between 35 - 65 years old with moderate to severe periodontitis, i.e. CAL > 5 mm, (CDC criteria 2012 update) and the presence of a minimum of 20 teeth. The control group comprised 40 healthy volunteers aged between 35 - 65yrs with PPD < 3 mm.

The exclusion criteria were:

1. Patient with Vitamins and iron supplementation, anti-inflammatory and antimicrobial drug therapy.
2. Patients with known systemic diseases and conditions.
3. Patients with an acute condition that contraindicates periodontal examination.
4. Patients who received periodontal therapy (scaling and root planing or surgery) within the past 1 year.
5. Smokers and alcohol users.

This study was approved by the Institutional Ethics Committee (Ref no. IEC 123/2018, dated 30-10-2018). Written informed consent was obtained from all study subjects. The study was conducted in accordance with the Helsinki declaration of 1975, and 2013 revision. The study period was one year and it was conducted between February-2019 to February 2020.

The periodontal examinations were conducted by a single calibrated examiner (SHA) using a standard mouth mirror and William's graduated periodontal probe. The periodontal status was measured by probing pocket depth (PPD), gingival recession (GR), and clinical attachment level (CAL) in millimeters at four sites on each tooth. Modified gingival index [13] oral hygiene index-simplified (OHI-S index) [14] and plaque index [15] were assessed. Biochemical parameters like hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), Hematocrit, and Serum Ferritin were also assessed using a fully automated analyzer EM-360 (ERBA).

Statistical analysis

Mean (± standard deviation) was calculated for quantitative variables and frequency for qualitative variables. Independent t-tests and chi-square tests were used to compare the quantitative and qualitative variables between the groups respectively. The correlation between serum ferritin with PPD and hemoglobin with PPD was done by the Pearson correlation test. Data were analyzed by using SPSS Version18. ∞ was set at 5%.

Results

The mean age in the case group (42.53 ± 5.9) and control group (43.93 ± 5.7) showed no statistical difference (P = 0.286). A statistically significant difference was observed with regard to the occupation (P < 0.001) and socioeconomic status (P = 0.03) between the case and control groups (Table 1). There was no significant difference between groups for method and frequency of teeth cleaning (Table 2). The food habits in the case and control group showed no statistical difference (P = 0.16) (Table 3), where as statistically significant difference was found for DI-S, CI-S, OHI-S, PI index, MGI index, and BOP between the case and control group (P < 0.001) (Table 4).

Sociodemographic characteristics		Case group	Control group	P value
Age (yrs) (mean ± SD)		42.53 ± 5.9	43.93 ± 5.73	0.28
Religion Frequency (% within Group)	Hindu	23 (57.5%)	17 (42.5%)	0.19
	Muslim	17(42.5%)	21 (52.5%)	
	Christian	0	2 (5%)	
Education Frequency (% within Group)	Up to High school	23 (57.5%)	12 (30%)	0.06
	Above high school	17(42.5%)	28 (70%)	
Occupation (% within Group)	Unemployed	1 (2.5%)	0	< 0.001*
	Unskilled worker	12 (32.5%)	1 (3.25%)	
	Semiskilled worker	16 (40%)	11 (27.5%)	
	Skilled worker	10 (25%)	18 (45%)	
	Clerical/shop owner/farmer	0	7 (17.5%)	
	Professional	0	2 (6.25%)	
	Business	1 (3.25%)	1 (2.5%)	

Socioeconomic status Frequency (% within Group)	APL	21 (52.5%)	30 (75%)	0.03*
	BPL	19 (47.5%)	10 (25%)	
Income Frequency (% within Group)	2158 - 6407	7 (10%)	10 (25%)	0.02*
	6408 - 10679	6 (7.5%)	17 (42.5%)	
	10680 - 106020	9 (11.3%)	6 (15%)	
	16021 - 21360	7 (8.8%)	5 (12.5%)	
	21361 - 42720	6 (7.5%)	2 (5%)	
	> 42721	4 (5%)	0	

Table 1: *Comparison of sociodemographic characteristics in case group and control groups.*

*APL: Above Poverty Line; BPL, Below Poverty Line; *p < 0.05 significant.*

Oral hygiene practices		Case group (n = 40) Frequency (%)	Control group (n = 40) Frequency (%)	P value
Method of teeth cleaning	Finger	1 (2.5%)	0 (0%)	0.31
	Brush	39 (97.5%)	40 (100%)	
	Others	0 (0%)	0 (0%)	
Material used for teeth cleaning	Tooth paste	40 (100%)	40 (100%)	
	Tooth powder	0 (0%)	0 (0%)	
	Others	0 (0%)	0 (0%)	
Frequency of teeth cleaning	Once	17 (42.5%)	14 (35%)	0.49
	Twice	23 (57.5%)	26 (65%)	
	After every meal	0 (0%)	0 (0%)	

Table 2: *Comparison of oral hygiene practices in case group and control groups.*

Variables	Case group (n = 40) Frequency (%)	Control group (n = 40) Frequency (%)	P value
Vegetarian	1 (2.5%)	4 (10%)	0.16
Non-Vegetarian	39 (97.5%)	36 (90%)	

Table 3: *Comparison of food habits in case group and control group.*

Variables	Control Group (n = 40) (Mean ± SD)	Case Group (n = 40) (Mean ± SD)	P value	Mean Difference	95% Confidence Interval	
					Lower	Upper
DI-S	0.48 ± 0.23	2.66 ± 0.26	< 0.001*	2.17	2.06	2.28
CI-S	0.50 ± 0.24	2.68 ± 0.25	< 0.001*	2.18	2.07	2.29
OHI-S	1.13 ± .33	5.34 ± 0.43	< 0.001*	1.62	1.45	1.79
PI	1.13 ± .33	2.83 ± 0.38	< 0.001*	1.7	1.53	1.86
MGI	0.28 ± .24	2.44 ± .194	< 0.001*	2.15	2.05	2.25
BOP	0.30 ± .12	1.12 ± 0.45	< 0.001*	0.81	0.66	0.96

Table 4: *Comparison of oral hygiene status in case group and control group (OHI-S, DI-S, CI-S, PI, MGI, BOP).*
*CI-S: Calculus Index-Simplified; DI-S: Debris Index-Simplified; OHI-S: Oral Hygiene Index Simplified; PI: Plaque Index; MGI: Modified Gingival Index; BOP: Bleeding on Probing, *Significant, P < 0.05.*

A statistically significant difference was observed in mean PPD (4.01 ± 44, 2.66 ± 0.29), CAL (4.22 ± .44 and0.01 ± 0.03), and gingival recession between the case and control group (P value < 0.001) (Table 5). The mean Hb level in the case and control group was 13.18 ± .57 and 14.04 ± .57 respectively and the difference was significant (P < 0.001). There was a significant difference in mean serum ferritin level between the case (243.11 ± 117.49) and control group (194.35 ± 82.82), (P = 0.035). A significant difference was observed in MCHC, MCH, and PCV levels (P < 0.001, p < 0.001 and p < 0.001respectively). There is no significant difference observed in mean MCV (P = 0.248) between the case and control groups (Table 6).

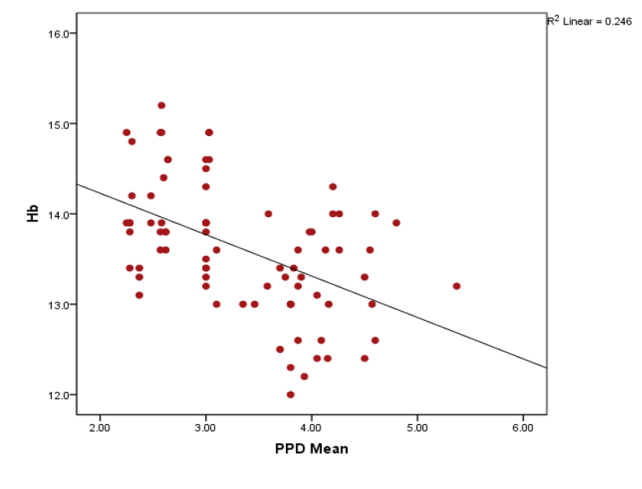
Variables	Control Group (n = 40) (Mean ± SD) % of site.	Case Group (n = 40) (Mean ± SD) % of site.	P value	Mean Difference. ±	95% Confidence Interval	
					Lower	Upper
PPD	2.66 ± 0.29	4.01 ± .44	<0.001*	1.53	1.18	1.59
CAL	0.01 ± 0.03	4.22 ± .44	<0.001*	4.23	4.07	4.35
Gingival recession	0.03 ± 0.01	0.31 ± .25	<0.001*	0.30	0.22	0.38

Table 5: *Comparison of probing pocket depth, clinical attachment level and gingival recession in case group and control group.*
*PPD: Probing Pocket Depth; CAL: Clinical Attachment Loss, *Significant, P < 0.05.*

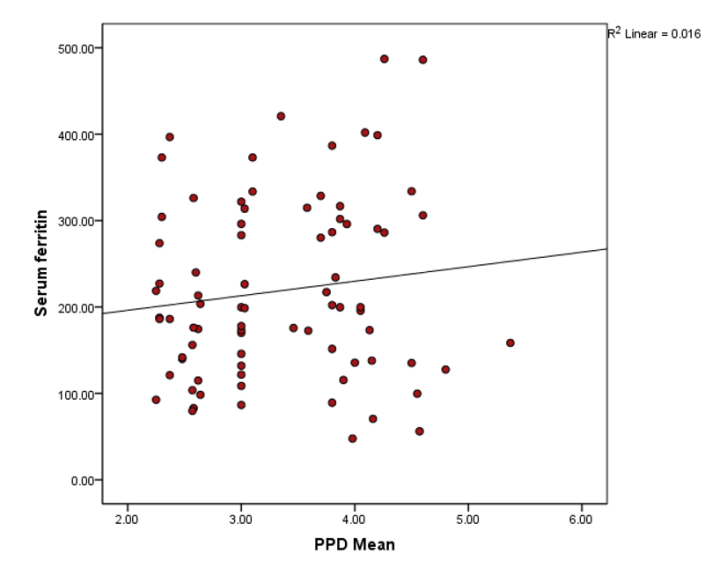
Variables	Control group (n = 40) (Mean ± SD)	Case group (n = 40) (Mean ± SD)	P value	Mean Difference	95% Confidence Interval	
					Lower	Upper
Hb	14.04 ± .57	13.18 ± .57	< 0.001*	-0.86	-1.12	-0.61
MCV	76.55 ± 8.85	78.25 ± 2.56	0.248	1.69	1.20	4.59
MCH	23.61 ± 1.11	25.20 ± 1.26	< 0.001*	1.59	1.06	2.13
MCHC	30.19 ± 1.02	31.59 ± 1.21	< 0.001*	1.40	0.90	1.90
PCV	45.02 ± 3.03	41.10 ± 2.43	< 0.001*	3.91	-5.14	-2.69
Serum Ferritin	194.35 ± 82.82	243.11 ± 117.49	0.035*	48.75	3.50	94

Table 6: *Comparison of hematological parameters between case and control group.*

A significant negative correlation was observed between hemoglobin and mean PPD (Pearson coefficient of correlation was -0.46, R^2 0.246, P < 0.001) (Graph 1). There was a weak positive correlation between serum ferritin and mean PPD and it was not significant (Pearson co-efficient of correlation 0.126, r^2 = 0.016 and P = 0.26) (Graph 2).



Graph 1: *Correlation between haemoglobin and mean probing pocket depth in case and control group.*
A significant negative correlation was observed between hemoglobin and mean. PPD: Pearson Coefficient of correlation was -0.46, R2 0.246, P < 0.001.



Graph 2: *Correlation between serum ferritin and mean probing pocket depth in case and control groups.*
Pearson co-efficient of correlation 0.126, r2 = 0.016 and P = 0.26.

Discussion

Proinflammatory cytokines like interleukin-1, interleukin-6, and TNF-α have a central role in periodontal tissue destruction. Locally secreted cytokines and periodontal pathogens can enter the bloodstream and have systemic effects. It has been observed that periodontitis like any other chronic condition may tend towards anemia as the number of erythrocytes and level of hemoglobin is lower in affected individuals despite the presence of adequate iron and vitamin sources and the absence of any other systemic chronic diseases.

This observational study evaluated the relationship between periodontal inflammation and serum hemoglobin in subject with and without periodontitis. In this study, smokers were excluded to eliminate confounding bias associated with nicotine consumption. Smokers with chronic periodontitis had a lower number of erythrocytes, a lower level of hemoglobin, and lower hematocrit value and iron level compared to non-smokers with chronic periodontitis [16]**.** Females were not included because anemia is more prevalent in females in the Indian population because of poor nutrition, increased menstrual loss, and high incidence of infections. They are also prone to hormonal fluctuations during puberty, pregnancy, and menopause [17].

In the present study no significant difference in mean age (yrs) and education level between the case and control groups. The percentage of persons above the poverty line (APL) was more in the control group as compared to the case group. Food habits were analyzed between groups and it was found that most of the study subjects were non-vegetarian.

In this study, there was no significant difference in oral hygiene practices between groups, 98% of the participants were using a toothbrush as the tooth-cleaning method and toothpaste as the cleaning material. This could be attributed to the fact that the subjects in the present study have a good awareness of oral hygiene practices. However, it was observed that the case group had a high OHI-S score and PI score as compared to the control. High OHI-S and PI scores may be due to the presence of periodontitis and difficulty in maintaining proper oral hygiene. In this study, a significant difference was observed in the modified gingival index (MGI) and bleeding on probing (BOP) between the case and control [18]. The sulcular epithelium is ulcerated and irregular in chronic periodontitis, contributing to increased bleeding sites and gingival inflammation in the case group [19].

The PPD, CAL, and GR are the most commonly used tool for assessing the severity of periodontal inflammation. There was a significant difference in PPD and clinical attachment loss between case and control groups. This is due to the presence of periodontitis and virulent subgingival microbiota which provide a significant and persistent gram-negative bacterial challenge to the host. The host response in turn activates C- reactive protein, interleukin-6 and tumor necrosis factor α (TNFα), etc. which leads to more inflammatory destruction in the periodontium.

In this observational study, the mean hemoglobin level was significantly lower in the case group (13.18 ± .57) as compared to the control (14.04 ± .57). A negative correlation between hemoglobin level and periodontal pocket depth was observed in this study. This may be due to the presence of periodontitis in the case group. Presence of pro–inflammatory cytokines such as TNF-α, IL-1β, INF–γ and PGE2 are found in high concentrations in inflamed periodontal tissues. Locally secreted cytokines and periodontal pathogens can enter the bloodstream and induce persistent subclinical inflammation. The low-grade inflammatory burden has been related to the suppression of erythropoiesis [20]. It subsequently reduces the no. of erythrocytes and the level of hemoglobin. The mechanisms leading to a decrease in Hb during inflammation are 1) Inflammatory cytokines causing suppression of erythroid proliferation in the bone marrow 2) Inflammatory cytokines preventing the release of erythropoietin from kidney 3) Reduction in the life cycle of red blood cells [21]**.** Lowe., *et al*. [22] and Patel., *et al*. [23] reported a definite correlation between anemia and chronic periodontitis.

Parihar., *et al*. [24] in a cross-sectional study concluded that a positive relationship exists between the hematological parameters and severity of chronic periodontal disease and opined that long-standing chronic periodontitis may lead to the development of signs of

anemia. Agarwal., *et al*. [20] reported that chronic periodontitis may tend towards anemia and nonsurgical periodontal treatment could improve the anemic status of patients with chronic periodontitis. From these studies, it is evident that periodontal inflammation may have an effect on the suppression of erythropoiesis and subsequently reduce the no. of erythrocytes and level of hemoglobin.

Conflicting reports are also available in the literature. Gayatri., *et al*. [25] reported there was no correlation between periodontal disease and anemia. Alijohani., *et al*. indicated increased hemoglobin levels in association with increased severity of periodontal disease. These contrasting reports may be due to differences in case selection, small sample size, and difference in the definition of periodontitis.

The hematocrit value in this study was significantly lower in patients with chronic periodontitis as compared to healthy subjects. Hutter., *et al*. [26] showed that periodontitis patients have lower hematocrit values and lower Hb levels. Agarwal., *et al*. [20] conducted an interventional study to evaluate the effect of periodontal therapy on hemoglobin and erythrocyte levels in chronic generalized periodontitis and concluded that treatment of periodontitis leads to an improvement in hematocrit and other related blood parameters in chronic generalized periodontitis patients.

Ferritin is an acute-phase reactant and is elevated in inflammation and chronic infection. It has an important role in the host immune response and increased immune response augments the migration of ferritin from the plasma to within the cells so that iron is not available to the infective agent [27]. In anemia of chronic disease, ferritin levels are normal or increased, reflecting increased storage and retention of iron within the reticuloendothelial system.

In the present study, the mean level of serum ferritin in the case group was found to be significantly higher as compared to healthy control (p value < 0.05) This could be attributed to the fact that chronic periodontitis is an infectious- immune inflammatory disease and subsequent release of various pro-inflammatory cytokines likeIL-1, TNF-α and interferon γ and bacterial lipopolysaccharide leads to periodontal destruction. Cytokines may upregulate the expression of DMT1 (divalent metal transporter), a transmembrane protein involved in the import of ferrous ions into macrophages and the subsequent retention of iron in these cells. Cytokines may also induce ferritin synthesis by hepatocytes. The increase in ferritin synthesis by hepatocytes and reticuloendothelial cells underlines the increase in iron storage in inflammation.

In accordance with our study, Chakraborty., *et al*. [28] reported that serum ferritin level was increased in patients with chronic periodontitis and decreased after nonsurgical periodontal therapy. They opined that chronic periodontitis could lead to anemia of chronic disease. Contradictory to this, Prakash., *et al*. [29] found lower levels of serum ferritin in periodontitis subjects. However, whether the rise in levels of serum ferritin is concomitant with the degree of inflammation or chronicity of inflammation remains questionable. Even though the serum ferritin level was increased in the case group but a weak positive correlation was observed between the serum ferritin and probing pocket depth (PPD) among study subjects. However, many studies are available regarding the association between periodontitis and serum Ferritin level but there is a lack of sufficient literature regarding the correlation between serum ferritin level and PPD (severity of periodontal disease). So, further research is required to confirm this correlation.

In this study; patients with chronic periodontitis showed lower hemoglobin levels, hematocrit value, and increased serum ferritin, indicating that chronic periodontitis has a definite effect on anemia of chronic disease. Further longitudinal and interventional studies with large sample sizes are needed to confirm that chronic periodontitis can lead to hematological signs of anemia.

Limitation of the Study

One of the limitations of the present study was its small sample size. An analysis of the soluble serum transferrin receptor concentration, and bone marrow examination, would be necessary to quantify iron stores and to distinguish between ACD and iron deficiency anemia in patients with periodontal disease. Inflammatory markers like IL-1, IL-6, TNF-α, CRP, and MMPs were not assessed in this study. Evaluation of these inflammatory markers is needed for the better assessment inflammatory status of periodontal disease.

Conclusion

The level of hemoglobin in a patient with chronic periodontitis was lower as compared to healthy subjects. A negative correlation of hemoglobin level with periodontal pocket depth was observed in this study. The mean level of serum ferritin in the case group was found to be significantly higher as compared to the healthy control. It could be attributed to the fact that chronic periodontitis is an infectious immunoinflammatory disease and the subsequent release of various pro-inflammatory cytokines induce changes in iron homeostasis. Successful management of periodontal infection could improve the level of hemoglobin.

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Authors Contribution

All authors have made a substantial contribution to the conception and design of the study. Sakeer Hussain Arimbra and Rosamma Joseph Vadakkekuttical have been involved in data collection and data analysis. Sakeer Hussain Arimbra, Rosamma Joseph Vadakkekuttical, Harikumar Kanakkath, and Simna Pattayil have been involved in data interpretation, drafting the manuscript and revising it critically, and have given final approval of the version to be published.

Conflict of Interest and Sources of Funding Statement

The authors declare that there are no conflicts of interest. This study was supported by the personnel funds of the authors.

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