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# Anemia of Chronic Disease and Chronic Periodontitis: Estimation of Hematological Status and its Correlation with Clinical Parameters

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## Abstract

Periodontitis is an inflammatory disease of the supporting tissues of the tooth caused by specific bacteria in a susceptible host. Lainson stated that anemia is a systemic cause of periodontitis. While leukocytosis is a common feature of severe periodontitis, a smaller amount of evidence has been produced on erythrocyte counts in periodontitis, suggesting a possible tendency to develop anemia. The present study was carried out with a view to investigate the associations and estimation of the hematological status and its correlation with the clinical parameters between periodontitis and the Hematocrit, Hb, MCV, MCH, MCHC, TLC, Differential WBC count, Platelet count, BT and CT.

### Aim

To evaluate levels of hematological parameters in healthy and chronic periodontitis patients.

### Methodology

The parameters assessed were the hematocrit, hemoglobin (Hb), MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Hemoglobin), MCHC (Mean Corpuscular Hemoglobin Concentration), Total Leucocyte count (TLC), Differential WBC count, Platelet count, Bleeding time (BT) and Clotting time (CT) will be measured.

### Result

The decrease in the hematocrit and Hb with mean gingival index, mean plaque index, leukocytosis, thrombocytosis was significantly higher in periodontitis patients than in the healthy group and were statistically significant. Differential WBC Count showed a MCV was slightly lower in the periodontitis group while MCH, MCHC, BT and CT were also known to affect but were not statistically significant. There is no significant correlation between GI, CAL, BOP, MCHC. No statistically significant correlation exists between PPD changes and hematological factors associated with anemia.

### Conclusion

The authors conclude that the patients suffering from untreated chronic periodontitis often suffer from anemia of chronic disease with marked leucocytosis and reactive thrombocytosis.



## Keywords

Anemia of chronic disease; bacteremia; hematology; chronic periodontitis


## Introduction

The inter-relationship between oral and systemic health, has been a matter of debate since the controversial theory of focal infection by Dr. Miller. The focal infection theory states that the oral pathogens show inherent capability to either directly enter or release their toxic products into the systemic circulation. Since oral health has a significant influence over the final prognosis of a number of systemic disorders, understanding of the underlying pathophysiology linking oral to systemic health is essential [1].

Anemia of chronic disease (ACD) is the second most prevalent type of anemia after iron deficiency anemia. It is also commonly known as Anemia of Inflammation. Weiss and Goodnough in 2005 estimated prevalence of 23-50% of ACD amongst the periodontitis patients [2]. While Seigel in 1945 stated marked erythropenia secondary to the periodontitis. The three pathologic processes involved in the ACD as postulated by Cartwright in 1966 are : 1) shortened erythrocyte survival, 2) failure of the bone marrow to increase RBC production to compensate for the increased demand, and 3) impaired release of iron from the reticuloendothelial system [3].

One of the earliest changes associated with the transition from periodontal health to gingivitis is increase in GCF level of the neutrophil chemoattractant IL-8, in which the pocket epithelium forms epithelial pegs into the connective tissue, and the epithelial surface towards the connective tissue increases. The inflammatory cell infiltrate of early gingivitis mainly consists of neutrophils. During the established gingivitis the infiltrate is characterised mainly by increase in plasma cells (10-30% of inflammatory cell infiltration), while plasma cells become the dominant cell (> 50%) in periodontitis, when alveolar bone is lost and JE is migrating in an apical direction. During early gingivitis, collagen fibres in the gingiva are dilapidated which creates space for extravasation of inflammatory cells into the gingival connective tissue. In the later stages, JE migrates more apically as the alevolar bone is adrifted [4].

An inflammatory disease of the supporting tissues of the tooth more commonly caused by specific micro-organisms in a susceptible host is often termed as Periodontitis. The pathognomonic features of periodontitis are the breakdown of periodontal connective tissue with infiltration of the sub-epithelial area adjacent to the deepened pathological sulcus (periodontal pocket) by an inflammatory infiltrate [5]. The loss of connective tissue coupled with the apical migration of the epithelial attachment and marginal alveolar bone loss leads to clinical attachment loss that can culminate in tooth morbidity and ultimately tooth loss. The bacteria and their products evoke an immuno-inflammatory reaction in the host tissue. Though this process is intended to eliminate the microbial challenge, it often results in damage to the host tissue. The pro-inflammatory cytokines released in periodontitis interact with hepcidin (the iron regulating hormone) that further leads to downregulation of erythropoiesis. Furthermore, a marked decline in erythropoiesis reflects a relative deficit of erythropoiesis due to an increased demand to produce neutrophil and other granulocytes with few immune-competent cells in response to periodontitis [6,7].

ACD is anemia occurring in chronic inflammatory conditions, infections, or neoplastic disorders that are not due to marrow deficiencies or other diseases, and occur despite the presence of adequate iron stores and vitamins. The current concept states that the pro-inflammatory cytokines released in the bloodstream in any chronic systemic disease tend to downregulate the process of erythropoiesis. The processes involved in the progression of ACD could be attributed to the cytokines and interferons that lead to shortened red cell survival, blunted erythropoietin response to anemia, impaired erythroid colony formation in response to erythropoietin and abnormal mobilization of reticulo-endothelial iron stores [8,9].

A plethora of studies have been carried out till date to elucidate the inter-relationship between ACD and

periodontitis, there is still a lacunae in exploration of data amongst the Maharashtrian population. As a result, the present study was envisaged with a view to investigate the associations between periodontitis and the hematological parameters amongst the Maharashtrian population.

## Material and Methodology

A total of 400 male patients of from the age group 30-60 years participated in the present study. The study population included 200 patients who were referred to the Department of Periodontology and Oral Implantology, M A Rangoonwala College of Dental Sciences and Research Centre, Pune for diagnosis and treatment of periodontitis. Of which the first 200 patients were periodontally healthy and visited hospital for regular dental check-up.

The present study was a cross-sectional study. Prior to the initiation, the design and purpose of the study was explained to the patients, a detailed proforma was prepared, and informed consent was obtained from all patients. The study was approved by the Institutional Ethics Committee and was conducted in accordance with the Helsinky's Declaration. The study included patients diagnosed with severe chronic periodontitis, as manifested by generalized probing pocket depth (PPD) ≥5 mm (test group) and periodontally healthy subjects with PPD ≤3 mm (control group). All the patients were selected based on the inclusion and exclusion criteria.

### Inclusion Criteria

a. Patients with PPD of ≥5mm in >30% of sites and bone loss >50% as seen in radiographs.
b. The control group included patients with clinically healthy gingiva with probing depth of ≤3mm.

### Exclusion Criteria

a. All Female patients
b. Patients with any systemic disorder
c. Patients with previous history of any periodontal therapy in past 6 months
d. Patients with a current or past habit of tobacco smoking or chewing
**e.** Patients with a history of hospitalization or intake of medications in the last 6 months**,** Patients receiving nutritional supplements**,** Pregnant and lactating mothers
f. All the clinical parameters were assessed through Modified gingival index given by Lobene et al 1986, Modified plaque index given by Turesky Gilmore and which is modification of Quigley Hein Plaque Index, Bleeding on probing, PPD, and level of clinical attachment.
g. PPD and loss of clinical attachment were assessed using a UNC 15 probe to the nearest 1 mm marking.

## Hematological Analysis

Under aseptic conditions, venous blood samples were collected from the antecubital fossa of each patient by venous puncture. The blood was carried in vacuum tubes containing ethylenediaminetetraacetic acid

(EDTA) and transported to Oral Pathology laboratory. The standardized and automated procedure was followed for assessing all the hematological parameters.

## Statistical Analysis

The data was obtained and entered in Microsoft Excel version 13. The data was subjected to Statistical Analysis using IBM SPSS Version 21. For continuous variables Mean and Standard Deviation was obtained. For comparison between Groups unpaired t test was applied. All the statistical tests were applied keeping confidence interval at 95% and ($p<0.05$) was considered to be statistically significant.

## Results

### Comparison of the Clinical Parameters between test and Healthy Participants

| | N | Test (Mean ± SD) | Healthy (Mean ± SD) | Mean Difference | T | P Value |
|---|---|---|---|---|---|---|
| Gingival Index | 430 | 3.56 ± 0.51 | 2.86 ± 0.76 | 0.7 | 16.02 | 0.00* |
| Plaque Index | 430 | 2.4 ± 0.56 | 1.61 ± 0.82 | 0.78 | 15.68 | 0.00* |
| PPD | 430 | 6.68 ± 1.16 | 3.51 ± 0.62 | 3.17 | 49.81 | 0.00* |
| CAL | 430 | 7.03 ± 0.97 | 2.49 ± 0.5 | 4.54 | 85.16 | 0.00* |
| BOP | 430 | 3.21 ± 1.2 | 0.78 ± 0.71 | 2.43 | 35.96 | 0.00* |

**Table 1: SD –** Standard Deviation, (*= $p<0.05$, comparison done using unpaired t test).

| | **N** | **Test (Mean ± SD)** | **Healthy (Mean ± SD)** | **Mean Difference** | **t** | **P value** |
|---|---|---|---|---|---|---|
| Hematocrit | 430 | 34.85 ± 3.3 | 44.33 ± 2.79 | -9.49 | -44.32 | 0.00* |
| Hemoglobin | 430 | 9.58 ± 1.43 | 13.94 ± 0.98 | -4.36 | -55.61 | 0.00* |
| MCV | 430 | 65.11 ± 5.61 | 108.23 ± 8.01 | -43.12 | -88.73 | 0.00* |
| MCH | 430 | 30.7 ± 3.13 | 33.68 ± 2.1 | -2.98 | -15.92 | 0.00* |
| MCHC | 430 | 33.35 ± 2.11 | 34.52 ± 2.45 | -1.17 | -7.35 | 0.00* |
| Time (Bt) | 430 | 3.42 ± 1.11 | 3.46 ± 1.08 | -0.03 | -0.45 | 0.65 |
| Clotting Time (Ct) | 430 | 3.57 ± 0.82 | 3.43 ± 0.85 | 0.14 | 2.65 | 0.01* |
| Platelets | 430 | 447604.65 ± 95324.65 | 312372.09 ± 52919 | 135232.56 | 25.54 | 0.00* |
| Total Leucocyte Count | 430 | 9393.02 ± 3743.08 | 6223.26 ± 1685.37 | 3169.77 | 16.03 | 0.00* |
| Neutrophil | 430 | 75.09 ± 6.55 | 64.31 ± 10.47 | 10.78 | 18.94 | 0.00* |
| Eosinophil | 430 | 3.71 ± 1.63 | 3.59 ± 1.31 | 0.13 | 1.32 | 0.19 |
| Basophil | 430 | 2.8 ± 1.08 | 2.72 ± 1.09 | 0.08 | 1.03 | 0.3 |
| Lymphocyte | 430 | 38.89 ± 8.84 | 38.73 ± 4.12 | 0.16 | 0.34 | 0.74 |
| Monocyte | 430 | 3.75 ± 1.58 | 3.85 ± 1.56 | -0.11 | -1.03 | 0.31 |

**Table 2:** SD – Standard Deviation, (*= $p<0.05$, comparison done using unpaired t test).

## Interpretation

The comparison of the clinical parameters between Test and Healthy Individuals depicted a statistically significant difference in mean for GI, PI, PPD, CAL and BOP ($p<0.05$). The Mean values observed were significantly higher in the Test Group as compared to the Healthy individuals.

When comparison of the hematological parameters between test and healthy groups; statistically significanr difference was seen and it was observed that the mean values were significantly higher in Healthy individuals with respect to Haematocrit, Hemoglobin, MCV, MCH, MCHC ($p<0.05$), Whereas the other parameters depicted a statistically significant difference in Mean ($p<0.05$).

## Discussion

In the present study, a total of 400 male patients were enrolled. Female patients were excluded due to higher tendency to develop anemia. Since smokers show greater tendency to develop anemia as well as periodontitis, they were excluded too. Similarly, patients receiving nutritional supplements and other medications could alter the results and hence refrained from the present study.

In the present study, a decrease in the total erythrocyte count, Hb and leucocytosis was found to be statistically significant and in accordance with the study carried out by Hutter in 2001. The anemic status of patients in our study was thought to be caused by periodontal tissue inflammation upregulating the pro-inflammatory cytokines. It has been proposed that hepcidin, a primary factor in the pathogenesis of ACD, which causes cytokine-mediated anemia commonly encountered in clinical practice is characterized by hypoferremia with adequate reticulo-endothelial iron stores. Faquin reported that IL-1 (a or b), TNF-a, and TGF-b inhibits production of erythropoietin from the hepatoma cell line Hep3B.8 The distinctive feature of ACD is low serum iron in the presence of adequate reticulo-endothelial iron stores. The hypoferremia was associated with abnormalities of iron release from the reticulo-endothelial system and incorporation into RBCs. The results of the present study were in accordance with the study carried out by Gokhale.4 Similarly, study carried out by Kamma highlighted significance of IL-6–hepcidin axis in the development of hypoferremia during inflammation.10 Contradictory results were found on comparison of Hb levels with periodontitis [11].

The decline in MCV values suggest micro-cytosis and occur as a result of iron deficiency, while elevated levels of MCV suggest macro-cytosis caused due to vitamin deficiency. MCV was found lower in both the groups. Therefore, decline in haematocrit, significantly lowers the erythrocytes. Similarly, the mean Hb was found significantly lower in the test group, although the MCH and MCHC values were within the normal range. Bleeding time and Clotting time were also known to be affected but not statistically significant [12].

Neutrophil, lymphocyte, and eosinophil counts were increased in the periodontitis group while the increase in TLC was statistically significant. Similar results were found [13, 14]. In reported leucocytosis in periodontitis patients. The higher numbers of leukocytes more is the viscosity, and more cells may adhere to endothelial cells lining the blood vessels, thereby decreasing blood flow. Reduced blood flow could play a role in relation to cardiovascular diseases, especially in narrow or partly blocked arteries due to atherosclerotic plaque formation [15].

Agnihotram studied various blood markers in chronic periodontitis patients and found lower number of

erythrocytes and increased WBC and neutrophil count, as compared to healthy subjects [16]. These findings were in accordance with the present study. PMNs have a dose response relationship with periodontitis and are part of the innate immune system; it is possible that these cells are recruited at higher levels during episodes of bacteremia in periodontitis or LPS leakage into the systemic circulation. Bacteria through inflammatory and infectious processes activate thrombocytes in granulation tissue where thrombocytes actually internalize bacteria or bacterial antigens and, as a result, produce AMPs and cytokines. The activated thrombocytes also lead to micro-aggregation, which subsequently results in activation and obstruction of blood vessels thereby formation of micro-thrombo emboli. In general, inflammatory and infectious processes can result in an increase in the number of active thrombocytes; in this respect, one refers to the phenomenon of ‘‘reactive thrombocytosis.’’ Therefore, slight increase in circulating thrombocytes could occur in periodontitis patients and that was statistically significant in the present study [17].

The clinical parameters assessed in the present study, the plaque and gingival indices showed significant increase in the periodontitis group, that indicates inflamed sulcular epithelium due to effects of bacterial plaque. Moreover, Siegel (1945) reported that periodontal therapy resulted in resolution of anemia. In essence, comparison of post therapeutic blood parameters in patients suffering from chronic periodontitis would add to our understanding with regard to the changes in blood parameters in chronic periodontitis [18].

Hence, the authors confirm a positive association between anemia of chronic disease and chronic periodontitis based on clinical and hematological assessments supported by statistical analysis. Furthermore, these results were in accordance with the results of the studies conducted by Lainson et al, Hutter et al, Gokhale et al, Naik et al, Aljohani et al, Wakai et al and Nibali et al. However, it would be prudent to suggest that longitudinal studies with greater sample size and determining the effect of periodontal interventional therapeutics on the hematological parameters will be desired to arrive at a definitive conclusion. Certain limitations of the present study were the blood parameters of chronic periodontitis patients were not available in their healthy state, and so, it became difficult to ascertain whether the changes in blood parameters had occurred due to the diseased condition.

## Conclusion

In the light of this evidence, it is crystal clear that anemia and periodontitis are inter-related and there is confirm relationship between ACD and periodontitis. Since in the present study the authors did not intervene the periodontal conditions by way of treatment and measurements later on, it was not possible to comment whether anemia was a factor that caused periodontitis or a consequence. Nevertheless, the authors conclude that long-term clinical trials with appropriate intervention should be carried out in order to co-relate hematologic parameters in individuals susceptible with periodontitis and individuals suffering from periodontitis.

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