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Research Article

A Clinical and Hematological Study to Evaluate the Association Between Chronic Periodontitis and Hemoglobin Level in Patients with and without Chronic Periodontitis - A Case Control Study

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Received: December 21, 2022; **Published:** January 30, 2023

Abstract

Background: Periodontitis is one of the most common chronic infectious diseases, multifactorial in origin, affecting the supporting structures of teeth. The plethora of bacterial challenge that is typical of chronic periodontitis poses a threat to the integrity of sulcular epithelium, which acts as a protective barrier. The extent of resulting bacteremia is directly related to severity of inflammation of periodontal tissues therefore, it has been speculated that periodontitis results in low grade systemic inflammation. Scientific evidence supports, that there may be a direct or indirect association between periodontitis and increase in the risk of systemic diseases. The bacteria and their products evoke an immune inflammatory reaction in the host tissue leading to one of the causes of 'Anemia of Chronic Disease' (ACD). The present study was aimed to study the association between chronic periodontitis and hemoglobin level in subjects with and without chronic periodontitis.

Material and Methods: In this study, a total of 10 subjects were selected and divided into groups of 5 each:

- Group I: 5 systemically healthy subjects, without chronic generalized periodontitis.
- Group II: 5 systemically healthy subjects, with chronic generalized periodontitis.

Clinical and hematological parameters were recorded of all the subjects and then tabulated and put to statistical analysis.

Results: The intergroup comparison of clinical parameters like PPD and CAL were significantly higher in the experimental group as compared to the control group ($p = 0.001$). The results showed that periodontitis like other inflammatory conditions could lead to anemia as stated by the low hemoglobin and RBC levels in experimental group.

Conclusion: The present study suggested that chronic periodontitis may cause reduction of hemoglobin concentration and RBC count which may be attributed due to increase in pro-inflammatory cytokines which are thought to act as mediators in suppressing erythropoiesis from the bone marrow leading to anemia.

Keywords: *Chronic Periodontitis; Anemia; Hemoglobin; Red Blood Cells; ESR*

Introduction

Periodontitis is one of the most common chronic infectious diseases with multifactorial etiology affecting the supporting structures of teeth. The release of bacterial endotoxins in chronic periodontitis gives rise to a threat to the integrity of sulcular epithelium which provides a protective barrier [1]. Sulcular epithelium acts a as gateway to the bacterial irritants to enter the connective tissue and thus into the systemic circulation which may lead to bacteremia. The extent of resulting bacteremia is directly related to the severity of inflammation of periodontal tissues. Therefore, it has been hypothesized that periodontitis may result in low grade systemic inflammation [2]. This is further supported by scientific evidence in the literature that there is an association between periodontitis and increased risk for systemic diseases. These observations may indicate that periodontitis patients may have a sub clinical inflammatory reaction [3]. Blood has been considered as a diagnostic body fluid for assessing the status of various infections and systemic diseases. The scientific evidence suggests that plaque induced chronic periodontitis has been linked to a number of systemic infections and this association is based on the alteration of cellular and molecular components which are present in the blood [4].

Anemia of chronic disease (ACD) is defined as anemia occurring in chronic infections, inflammatory conditions or neoplastic disorders that are not due to marrow deficiencies or other diseases and occurred despite presence of adequate iron stores and vitamins [3]. Anemia of chronic disease is the second only to iron deficiency anemia in terms of prevalence. Its etiology is most likely multifactorial. The hallmark of ACD is the development of disturbance of iron homeostasis with increased uptake and retention within cells of reticuloendothelial system. This may lead to the limited availability of iron for erythroid progenitor cells. Further the proliferation and differentiation of erythroid precursors is impaired due to blunt response to erythropoietin. The erythropoietin deficiency is responsible for the lack of compensatory proliferation of erythrocytes as seen in patients with anemia of chronic disease.

ACD is normochromic, normocytic anemia characterized by mild (Hb level 9.5 g/dl) to moderate (Hb level 8 g/dl) and decreased serum iron and total iron binding capacity with increased or normal iron stores. A definitive diagnosis may be hampered by coexisting blood loss, effect of medications or in borne errors of hemoglobin synthesis.

ACD patients have a very different pattern regarding the iron distribution in the tissues. This change is due to Hepcidin hormone that regulates iron. It is produced by liver in response to inflammatory cytokines such as IL-6. Hepcidin expression is induced by lipopolysaccharide and IL-6 and is inhibited by TNF-α [5].

Three mechanisms have been proposed which can cause decrease in hemoglobin during inflammation:

1. Pro-inflammatory cytokines such as IL- 1,6 and TNF-α causing suppression of erythroid proliferation and change in iron homeostasis in bone marrow.
2. Inflammatory cytokines alter the release of erythropoietin from kidney.
3. Reduction in the life cycle of red blood cells.

Therefore, pro-inflammatory cytokines such as IL-1 and TNF-α play a central role in the pathogenesis of periodontal disease and might be a plausible pathogenic relationship between ACD and periodontal disease. When these pro- inflammatory cytokines (IL-1, 6 and TNF-α) are released into the blood, there are changes at the systemic level. As a result, there is an alteration in the host immune response leading to increased periodontal inflammation. The synergistic effect of prostaglandin E_2, IL-1β and inflammatory cytokines under the influence of TNF-α may lead to increase the incidence of periodontal disease [6].

The concept of anemia leading to periodontitis and periodontitis as a causative factor of anemia, have been put forward by various authors. Most of the authors were of the opinion that perhaps anemia was one of the causes that led to the development of periodontitis [7]. Recently with a resurgence of interest on systemic impact on periodontal inflammation various studies are exploring role of periodontitis as a causative factor leading to anemia. Hutter., *et al*. [3] concluded that periodontitis, like other chronic conditions, lead to anemia due to a decrease in number of erythrocytes and level of hemoglobin. The third national health and nutrition examination survey (NHANES III) conducted nationwide from 1988 - 1994 and comprising of 33,994 persons analysis revealed that a positive diagnosis if anemia carried with it a 1.445 odds ratio of having periodontitis [8]. A recently published interventional study concluded that periodontal treatment results in significant in red blood cells (RBC) counts [9].

Aim of the Study

The present study was conducted with an aim to assess the association between chronic periodontitis and hemoglobin level and to compare the level of hemoglobin in subjects with and without chronic periodontitis.

Materials and Methods

Study population

This was a pilot study conducted in out-patient department of National Dental College and Hospital, Dera Bassi, Punjab. An ethical approval for the study was obtained from the Institutional Ethical Board Committee at National Dental College and Hospital, Derabassi, Punjab. Each subject was given a detailed verbal and written description of study and all the selected subjects signed an informed consent form prior to commencement of the study.

Study design

The patients were examined for Oral Health Status and categorized into Chronic Periodontitis and Non- Chronic Periodontitis. The selected subjects were divided into two groups:

- **Group I (Control group):** 5 systemically healthy subjects without chronic generalized periodontitis.
- **Group II (Experimental group):** 5 systemically healthy subjects with chronic generalized periodontitis.

Inclusion criteria

- Male subjects aged between 35 - 65 years
- Subjects without chronic periodontitis
- Subjects with chronic periodontitis, with probing depth > 4 mm and clinical attachment loss > 2 mm.

Exclusion criteria

- Female subjects
- Subjects with acute or chronic medical conditions diabetics, viral, fungal or bacterial infection
- Subjects with history of periodontal treatment performed in the past six months

- Use of vitamins, antibiotics, iron supplements, steroids for past six months
- Smokers
- Subjects who had malaria or jaundice in last one year
- Subjects with recent trauma or tooth extraction
- Subjects with hematological disorders.

Assessment of clinical parameters

Periodontal examination was done at baseline through recording of clinical parameters such as oral hygiene index -simplified (OHI-S), gingival index (GI) (Loe and Silness), probing pocket depth (PPD) and clinical attachment level (CAL) to the nearest mm using William's graduated periodontal probe at six sites (mesio-buccal/labial, mid-buccal/labial, disto-buccal/labial, mesio-lingual/palatal, mid-lingual/palatal, disto-lingual/palatal) per tooth, in all the teeth.

Radiographic parameters, such as orthopantomograph was also taken for the assessment of bone level and categorisation of systemically healthy subjects without chronic generalized periodontitis and systemically healthy subjects with chronic generalized periodontitis.

Assessment of hematological parameters

Assessment of hematological parameters included Hb, RBC, MCV, MCH, MCHC, PCV, TLC, DC, ESR levels were evaluated at baseline.

Methodology

10 male subjects, within the age group of 35 - 65 years were selected for the study. The selected subjects were divided into two groups:

- **Group I (Control group)**: 5 systemically healthy subjects without chronic generalized periodontitis were selected. All the clinical parameters OHI-S, GI, PPD, CAL and OPG (for the assessment of bone levels) were recorded at baseline using William's graduated periodontal probe at six sites (mesio-buccal/labial, mid-buccal/labial, disto-buccal/labial, mesio-lingual/palatal, mid-lingual/palatal, disto-lingual/palatal) in all the teeth. Blood samples were also collected for the assessment of hematological parameters.
- **Group II (Experimental group)**: 5 systemically healthy subjects with chronic generalized periodontitis with probing pocket depth more than 4 mm and clinical attachment loss more than 2 mm were randomly selected. All the clinical parameters OHI-S, GI, PPD, CAL and OPG (for the assessment of bone levels) were recorded using William's graduated periodontal probe at six sites (mesio-buccal/labial, mid-buccal/labial, disto-buccal/labial, mesio-lingual/palatal, mid-lingual/palatal, disto-lingual/palatal) in all the teeth. Blood samples were also collected for the assessment of hematological parameters that included Hb, RBC, MCV, MCH, MCHC, PCV, TLC, DC, ESR levels.

Assessment of hematological parameters (Hb, RBC, MCV, MCH, MCHC, PCV, TLC, DC, ESR): Subjects were seated comfortably with the arm supported. Aseptic measures were taken and tourniquet was applied 2 inches above the elbow of upper arm. Site of puncture was cleaned using sterile gauze dipped in 100% alcohol. Using vaccute and needle, 2 ml of blood was drawn from ante- cubital vein in the violet vacutainer with EDTA. All the samples were collected and analysed at the general pathology lab (Life care foundation labs) for the assessment of complete hematological parameters (Hb, RBC, MCV, MCH, MCHC, PCV, TLC, DC, ESR).

Results

Statistical analysis

The data for the present study was entered in the Microsoft Excel 2007 and analyzed using the SPSS statistical software 23.0 Version. The descriptive statistics included mean, standard deviation. The level of the significance for the present study was fixed at 5%.

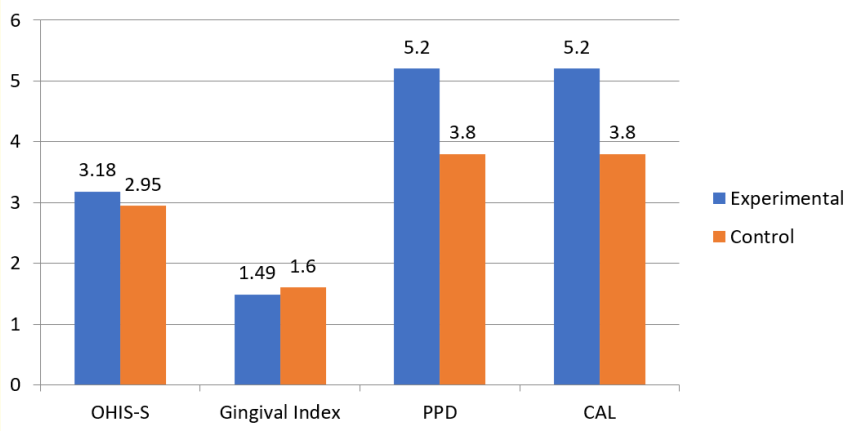
The intergroup comparison for the difference of mean scores between two independent groups was done using the unpaired/independent t test.

The Shapiro-Wilk test was used to investigate the distribution of the data and Levene's test to explore the homogeneity of the variables. The data were found to be homogeneous and normally distributed. Mean and standard deviation (SD) were computed for each variable.

Clinical parameters	Experimental group	Control group	P value
OHIS-S	3.18 ± 0.177	2.95 ± 0.24	0.124*
Gingival Index	1.49 ± 0.12	1.60 ± 0.08	0.143*
PPD	5.20 ± 0.45	3.80 ± 0.44	0.001**
CAL	5.20 ± 0.44	3.80 ± 0,44	0.001**

Table 1: *Intergroup comparison of clinical parameters (periodontal) between experimental and control group.*

**Statistically non-significant, **Statistically significant.*



Graph 1: *Intergroup comparison of clinical parameters (periodontal) between experimental and control group.*

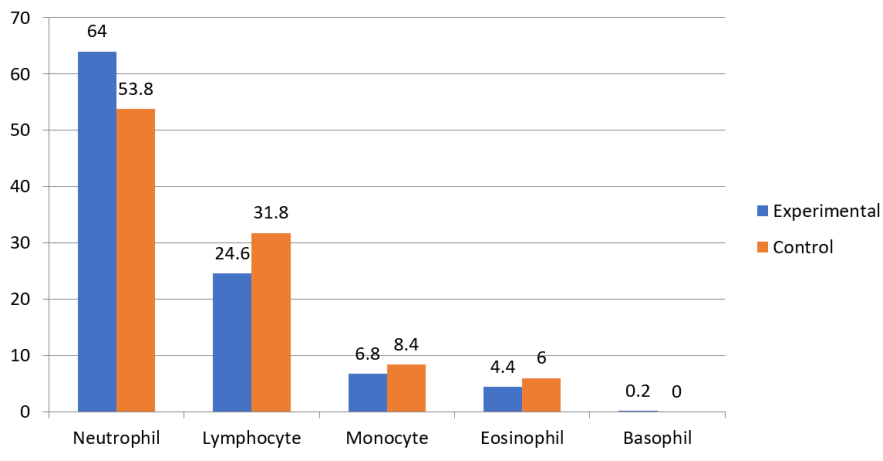
Table 1, graph 1 showed the intergroup comparison of clinical parameters between experimental and control group. The mean OHI-S score in the experimental group was 3.18 ± 0.177 and in the control group was 2.95 ± 0.24. The intergroup comparison done using independent t test was statistically non-significant (p = 0.124). The mean gingival index score in the experimental group was 1.49 ± 0.12 and 1.60 ± 0.08 in the control group. The intergroup comparison done using independent t test was statistically non-significant (p = 0.143). The probing pocket depth in the experimental group (5.20 ± 0.45) was significantly higher (p = 0.001) as compared to the control group

(3.80 ± 0.44). The CAL in experimental group was 5.20 ± 0.44 and 3.80 ± 0.44 in the control group. The intergroup comparison done using independent t test was found to be statistically significant (p = 0.001).

Hematological parameters	Experimental group	Control group	P value
TLC	7022.03 ± 1190.38	6920.03 ± 742.96	0.875*
DLC			
Neutrophil	64.00 ± 9.92	53.80 ± 1.78	0.049**
Lymphocyte	24.60 ± 7.86	31.80 ± 1.30	0.078*
Monocyte	6.80 ± 1.09	8.40 ± 0.54	0.019**
Eosinophil	4.40 ± 2.30	6.00 ± 2.73	0.347*
Basophil	0.20 ± 0.44	0.00 ± 0.00	0.347*

Table 2: *Intergroup comparison of TLC and DLC between experimental and control group.*

**Statistically non-significant, **Statistically significant.*



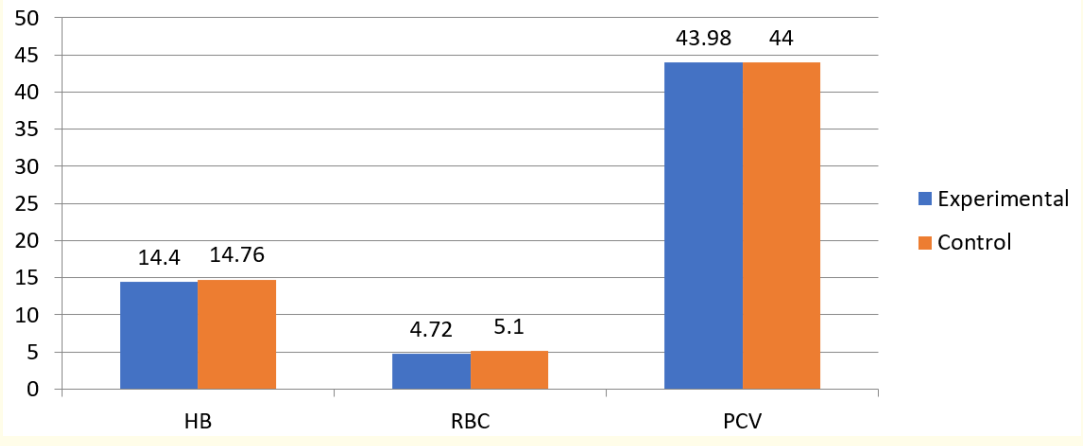
Graph 2: *Intergroup comparison of DLC between experimental and control group.*

Table 2 showed intergroup comparison of TLC and DLC between experimental and control group. The mean TLC count in the case group was 7022.03 ± 1190.38 and 6920.03 ± 742.96 in the control group. The difference between the groups was statistically non-significant (p = 0.875). Table 2, graph 2 showed intergroup comparison of DLC between experimental and control group. The mean neutrophil count in the experimental group was 64.00 ± 9.92 and 53.80 ± 1.78 in the controls. The difference between the groups was found to be statistically significant (p = 0.049). The mean lymphocyte count in the cases was found to be 24.60 ± 7.86 and 31.80 ± 1.30 in the controls. The difference between the groups was found to be statistically non-significant (p = 0.078). The mean monocyte count was 6.80 ± 1.09 in the experimental group and 8.40 ± 0.54 in the control group. The difference between the groups was found to be statistically significant when analyzed using independent t test (p = 0.019). The mean eosinophil and basophil count between the experimental and control group was statistically non-significant (p = 0.34).

Hematological parameters	Experimental group	Control group	P value
Hb	14.40 ± 1.35	14.76 ± 1.49	0.700*
RBC	4.72 ± 0.48	5.10 ± 0.36	0.201*
PCV	43.98 ± 3.30	44.00 ± 4.41	0.994*

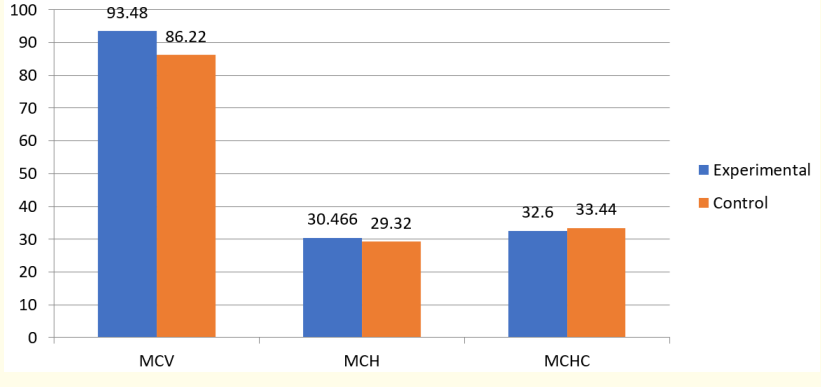
Table 3: *Intergroup comparison of hematological parameters (Hb, RBC, PCV) between experimental and control group.*

**Statistically non-significant.*



Graph 3: *Intergroup comparison of hematological parameters (Hb, RBC, PCV) between experimental and control group.*

Table 3, graph 3 showed intergroup comparison of hematological parameters (Hb, RBC, PCV) between experimental and control group. The mean hemoglobin count between experimental group (14.40 ± 1.35) and control group (14.76 ± 1.49) and it found to be statistically non-significant between the groups (p = 0.700). The mean RBC count between the experimental (4.72 ± 0.48) and control group (5.10 ± 0.36) was found to be statistically non-significant when compared by using independent t test (p = 0.201). The intergroup comparison of mean PCV between experimental and control group was found to be statistically non-significant (p = 0.994).



Graph 4: *Intergroup comparison of hematological parameters (MCV, MCH, MCHC) between experimental and control group.*

Hematological parameters	Experimental group	Control group	P value
MCV	93.48 ± 5.16	86.22 ± 4.24	0.041**
MCH	30.46 ± 1.15	29.32 ± 0.99	0.133*
MCHC	32.60 ± 1.00	33.44 ± 0.80	0.181*

Table 4: *Intergroup comparison of hematological parameters (MCV, MCH, MCHC) between experimental and control group.*

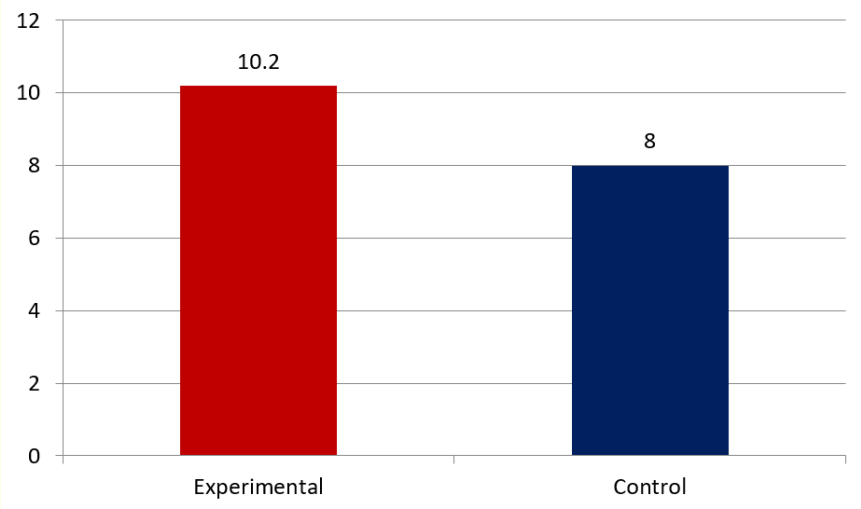
**Statistically non-significant, **Statistically significant.*

Table 4, graph 4 showed intergroup comparison of hematological parameters (MCV, MCH, MCHC) between experimental and control group. The mean MCV count was 93.48 ± 5.16 in the experimental group and 86.22 ± 4.24 in the control group. The intergroup comparison between the experimental and control group was done using the independent t -test and found to be statistically significant (p = 0.041). The mean MCH and MCHC count was found to be statistically non-significant between the experimental and control group.

Hematological parameters	Experimental group	Control group	P value
ESR	10.20 ± 7.19	8.00 ± 3.67	0.559*

Table 5: *Intergroup comparison of hematological parameter (ESR) between experimental and control group.*

**Statistically non-significant.*



Graph 5: *Intergroup comparison of hematological parameter (ESR) between experimental and control group.*

Table 5, graph 5 showed intergroup comparison of hematological parameters (ESR) between experimental and control group. The mean ESR in the cases was 10.20 ± 7.19 and 8.00 ± 3.67 in the controls. The intergroup comparison between experimental and control group was found to be statistically non-significant (p = 0.559).

Discussion

Recent years have seen a growing interest in periodontal medicine which focuses on relationship between periodontal and systemic health [1]. This means a two-way relationship exists, in which the periodontal diseases in an individual may have an effect on his/her systemic health and vice versa. The initiation, progression of gingivitis and periodontitis may be affected by certain systemic conditions. This is manifested by an early onset or a rapid rate of destruction clinically. The converse side of the relationship, be it systemic and oral health has also been demonstrated. This means that there may be a potential effect of periodontal disease on a wide range of organ system.

Periodontitis has been associated with an increased risk for systemic diseases like atherosclerosis, cardiovascular disease, pre mature low birth weight babies and pulmonary diseases. The hematological parameters have been used to establish a relationship between periodontitis and systemic diseases. Therefore, hematocrit and related blood parameters can be used to explore a relationship between periodontitis and anemia [1,10].

Chronic periodontitis is an inflammatory disease of the supporting structures of the teeth and bacterial challenge in chronic periodontitis may pose a threat to the integrity of sulcular epithelium which acts as protective barrier. The bacterial endotoxins enter into connective tissue through this gateway and host response becomes active by releasing interleukins and TNF-α which may further decrease erythropoietin production and lead to development of anemia.

Earlier reports have suggested that anemia is to be a cause and not a consequence of destructive periodontitis. Lainson., *et al*. [11] was one of the first authors to implicate anemia as a systemic cause of periodontitis. Siegel., *et al*. [12] evaluated blood parameters in patients with chronic periodontitis and concluded that these patients have anemia.

The purpose of the present study was to compare and find out the association between levels of hemoglobin in patients with and without chronic periodontitis. Only male subjects between 35 - 65 years of age were included in the study. Smokers were excluded because smoking is considered as a co factor for development of periodontitis and anemia [13-15]. The use of tobacco may affect the local microflora as well as the host response of the individual especially altering the effect of neutrophils, cytokines, phagocytosis and protease inhibitor production [16]. Therefore, to prevent the confounding effect of tobacco smokers were excluded from the study.

Females were also excluded due to inability to adjust to menopausal status and blood loss due to menstrual cycle. Females are commonly affected by anemia than males because of increased menstrual loss, poor nutrition, high incidence of tropical and intestinal; infection and hormonal imbalance. All these factors may act as exaggerated response of periodontal tissue towards local factors may be found [17]. This may have led to bias in the present study. To overcome this limitation, the present study only included male subjects.

Various studies have tried to evaluate the relation between periodontitis and anemia. These studies present conflicting results. Hutter., *et al*. [3], Thomas., *et al*. [18], Kolte., *et al*. [19] showed that periodontitis patients have lower hematocrit, lower number of erythrocytes, lower-level of hemoglobin, and higher ESR rates. However studies conducted by Wakai., *et al*. [20], Shoba., *et al*. [21] and Havemose-poulsen., *et al*. [22] failed to show any association between level of hemoglobin and periodontal status.

The results of the present study indicate that there were statistical differences between experimental and control group wrt clinical parameters that included PPD and CAL. However, the results were found to be statistically non-significant, in terms of clinical parameters such as OHI-S and gingival index. The results are in accordance with the results obtained in various other studies. Probing pocket depth and clinical attachment loss was found to be more in experimental group as compared to control group which showed a statistically significant difference with a p value < 0.005. The results were consistent with the study conducted by Aggrawal., *et al*. [23], who concluded that periodontitis like other inflammatory conditions could lead to anemia, with a positive significant correlation between clinical attachment loss and red cell parameters.

In the present study, lower mean hematocrit value was 14.40 ± 1.35 in experimental group as compared to control group with mean hemoglobin value of 14.76 ± 1.49 and it was found to be statistically non-significant. Lower mean hematocrit value was 43.98 ± 3.30 in experimental group as compared to control group with mean hematocrit value of 44.00 ± 4.41 and also it was found to be statistically non-significant. Lower mean erythrocyte value was 4.72 ± 0.48 in experimental group as compared to control group with mean erythrocyte value of 5.10 ± 0.36 and it as found to be statistically non-significant. Higher mean ESR value was 10.20 ± 7.19 in experimental group as compared to control group with mean ESR value of 8.00 ± 3.67 and it was also found to be statistically non-significant.

These findings are in agreement with the finding of Hutter JW [3], Sneha R Gokhale [24], V. Naik [25], where lower hemoglobin, hematocrit, erthrocytes and higher ESR values was seen in experimental group. On the contrary, this is in variance with findings of Wakai., *et al*. [20] who failed to show any association between hemoglobin levels and periodontal status. Mean values for MCV, MCH and MCHC are nearly equal in both the group and are statistically non-significant for MCH and MCHC but statistically significant for MCV in between the study groups.

Cartwright [26] postulated pathologic processes are involved in anemia of chronic disease:

1) Shortened erythrocyte survival

2) Failure of the bone marrow to increase RBC production to compensate for this increased demand

3) Impaired release of iron from the reticuloendothelial system.

ESR is considered a valuable parameter for any inflammatory process. Elevated values of ESR suggested that chronic periodontitis has an inflammatory component in it. Although elevation of ESR can occur in iron-deficiency anemia also, the ESR value can be utilized to distinguish coexisting iron deficiency in patients with ACD. Our data analysis, showed that periodontitis patients have a lower hematocrit value. Depressed MCV values suggest microcytosis most commonly caused by iron deficiency [20] and elevated levels of MCV suggest macrocytosis caused by vitamin deficiency. MCV was higher in experimental groups, thereby suggesting that the anemic status can be attributed to iron or vitamin deficiency. Therefore, the lower value of hematocrit can be attributed to the significantly lower number of erythrocytes.

Similarly, the mean hemoglobin value was significantly lower in experimental group, although the MCH and MCHC values were within the normal range. Therefore, decrease in hemoglobin value with increase in ESR value and increase in MCV, MCH, MCHC value denote anaemic status due to inflammatory component as well as due to iron or vitamin deficiency, as seen in our study. These results suggest that periodontitis and the progression of periodontal disease is associated with anemia and further decrease in hemoglobin values is seen with increase in severity of periodontitis.

The strength of the study was that the present study was conducted only among the male subjects and female subjects were not included in the study. This was because of increased prevalence of anemia in Indian females thus removing any bias in the study. Smokers were excluded since smoking tends to act as a cofactor in periodontitis. However, there were certain limitations such as sample size of the study was small; hence to apply it to a general population study with larger sample sizes would be needed. Due to the exclusion of females, the influence of gender on periodontitis could not be evaluated.

Conclusion

Chronic systemic conditions have a direct effect on the general health and well-being of an individual. The present study suggests that chronic periodontitis may cause reduction of hemoglobin concentration and RBC count which may be attributed to increased pro-

inflammatory cytokines which are thought to act as mediators in suppressing erythropoiesis from the bone marrow leading to anemia. The present study also strengthens the evidence that periodontitis does have various systemic effects. However, considering the limited sample size and lack of evaluation of the relationship between severity of periodontitis and anemia in the present study, future studies must be conducted which will further reduce the bias occurring due to other confounding factors and provide a better and more thorough view of the real situation.

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