Archives of Orofacial Sciences
The Journal of the School of Dental Sciences
Universiti Sains Malaysia

Arch Orofac Sci (2015), **10**(2): 57-64.

Original Article

Chronic periodontitis and anaemia of chronic disease: an observational study

HN Santosh [a]*, Chaya M David [b], Hanoch Kumar [c], CJ Sanjay[d], Aditi Bose[e]

[a] Department of Oral Medicine and Radiology, Sri Rajiv Gandhi Dental College and Hospital, Cholanagar, Bangalore 560032, Karnataka, India.
[b] Department of Oral Medicine and Radiology, Dayananda Sagar College of Dental Sciences, Bangalore 560078, Karnataka, India.
[c] Department of Oral Medicine and Radiology, Dr Shyamala Reddy Dental College Hospital and Research Centre, Bangalore 560037,Karnataka,India.
[d] JSS Dental College and Hospital, Bannimantap, Mysore 570015, Karnataka, India.
[e] Department of Periodontology, Sri Rajiv Gandhi Dental College and Hospital, Cholanagar, Bangalore 560032, Karnataka, India.

* Corresponding author: drhnsantosh29@yahoo.co.in

Submitted: 09/07/2015. Accepted: 28/12/2015. Published online: 28/12/2015.

Abstract Anaemia of chronic disease (ACD) is caused due to an underlying chronic inflammatory process. It is not due to marrow deficiency of iron. Chronic periodontitis is a chronic inflammatory condition which has been associated with anaemia of chronic disease. The aim of this study is to estimate various hematologic parameters suggestive of ACD in patients with chronic periodontitis and in the process to establish a relation between the two. Forty patients were selected and were categorized, based on the presence and absence of chronic periodontitis, into case and control groups, with 20 subjects in each group. Hematologic evaluation was done. Complete haemogram, haematocrit, erythrocyte sedimentation rate (ESR) and estimation of serum ferritin were done. An independent t-test was calculated. Statistically significant values (p<0.05) were obtained for neutrophil count, ESR, red blood cells (RBC), mean corpuscular haemoglobin concentration (MCHC) and serum ferritin. ESR, RBC and serum ferritin levels were significantly increased in subjects with chronic periodontitis. There were significant differences in neutrophil, ESR, RBC and serum ferritin in subjects having severe form of generalized chronic periodontitis. Thus, it was concluded that chronic generalized periodontitis, by means of an inflammatory process, influences various hematologic parameters are suggestive of anaemia of chronic disease.

Keywords: anaemia of chronic disease, chronic generalized periodontitis, chronic inflammation.

Introduction

Anaemia of chronic disease (ACD) is defined as the anaemia that occurs in chronic infections, inflammatory conditions or neoplastic disorders that is not due to marrow deficiencies and occurs despite the presence of adequate iron stores and vitamins. The most frequent conditions associated with anaemia of chronic diseases are acute and chronic infections, cancer, autoimmune disorders, chronic kidney diseases and chronic inflammation. Due to the close association of ACD with chronic inflammation, the condition has been termed anaemia of inflammation. The estimated prevalence of ACD caused due to chronic inflammation accounts to 23-50% (Weiss and Goodnough, 2005). A number of different pathways contribute to the pathogenesis of ACD such as diversion of iron traffic, a diminished erythropoiesis, impaired response to erythropoietin, erythro phagocytosis and bone marrow invasion by tumour cells and pathogens. ACD is a widely prevalent but poorly understood condition that afflicts patients with a wide variety of diseases, including infections, malignancies and rheumatologic disorders. It is the second most prevalent form of anaemia after nutritional and iron deficiency anaemia and can co-exist, causing

additional anaemic burden (Weiss, 2002; Weiss and Goodnough 2005). ACD is a cytokine-mediated anaemia characterized by hypoferremia, with adequate reticulo endothelial iron stores and normal-to-elevated ferritin concentrations.

Rheumatoid arthritis demonstrates a pattern of hard and soft tissue destruction caused by an inflammatory process (Mercado *et al.*, 2000). This process is similar to the inflammatory process seen in chronic periodontitis. Chronic periodontitis is an infectious disease resulting in inflammation within the supporting tissues of the teeth and progressive attachment and bone loss. It is recognized as the most frequently occurring form of periodontitis. Long-standing chronic inflammation can lead to anaemia. Additionally, hepcidin (Haurani, 2006), an iron binding protein, plays an important role in the pathogenesis of ACD. This protein is upregulated by interleukin-56 (IL-56). This subsequently reduces iron uptake for erythropoeisis. Cytokines also reduce erythropoietin, a hormone that regulates erythropoeisis, leading to anaemia. It is well established that periodontitis, being a chronic inflammatory disease, causes an elevation in numerous systemic inflammatory markers like IL-6, IL-1 and can have systemic effects. Elevated levels of various systemic markers of inflammation have been noted in moderate-to-severe periodontal disease. Considering the relatively high prevalence of anaemia, as well as periodontal disease in Indians, determining the etiological contribution of periodontitis to the presence of an anaemic status assumes clinical significance.

Periodontitis is a chronic inflammatory disease mainly due to bacterial infection. It is one of the most common oral diseases of humans. Prevalence of periodontal diseases varies among different countries and increases concomitantly with age (Mealey and Rose, 2008). Epidemiologic studies have suggested that chronic periodontitis increases the risk of systemic problems such as cardiovascular diseases, atherosclerosis, diabetes mellitus and pre-term low birth weight of infants. In addition, some studies had found that periodontal infection even elicits systemic hematologic changes (Wakai *et al.*, 1999). Chronic periodontitis is a chronic inflammatory disease which leads to the production of cytokines, most characteristically tumour necrosis factor- alpha, IL-1 and IL-6 (Wakai *et al.*, 1999). Such inflammatory cytokines decrease the erythropoietin production leading to the development of anaemia (Naik *et al.*, 2010). A tendency towards anaemia in patients with chronic periodontitis was also reported in the same study, whereas a reverse relationship was presented in data obtained during the third National Health And Nutrition Examination Survey (NHANES III), which suggested that individuals with anaemia may be more likely to have periodontal disease (Naik *et al.*, 2010).

Chawla *et al*. (1971) suggested that anaemia is an important factor in the aetiology or pathogenesis of periodontal disease. Until then, Lainson *et al*. (1968) implicated anaemia as a cause of periodontitis. Seigel (1945) reported a depression in the number of erythrocytes apparently secondary to the presence of periodontal disease. Hutter *et al.* (2001) evaluated the blood parameters in patients with chronic periodontitis and concluded that these patients showed signs of anaemia. In a landmark study (Pradeep and Anuj, 2011), it was concluded that chronic periodontitis may tend towards anaemia and provides evidence that non-surgical periodontal therapy can improve the anaemic status of patients with chronic periodontitis, and that improvement in hematologic parameters was greater in female subjects.

Anaemic status in patients with chronic periodontitis with no history of systemic disease indicates that chronic periodontitis may lead to anaemia. It can also be hypothesized that chronic periodontitis should be considered as a possible cause of ACD. With this background, the present study aims to evaluate the levels of systemic hematologic markers indicative of anaemia in patients with generalized chronic periodontitis and to explore a link between severe periodontal disease and anaemia of chronic disease (ACD).

Materials and methods

This is a cross sectional observational study and was approved by the ethical board of Dayananda Sagar College of Dental Sciences. Forty systemically healthy male subjects in the age group of 30-70 years were included for the study. The study period was from July 2013 to January 2014. Female patients were opted out of the study; subjects with habit of smoking, chewing or snuffing tobacco were excluded. Subjects with an intake of iron or vitamin supplements within the previous 3 months were excluded as it would have improved the iron stores. The nature and purpose of the study was explained to the patients and written consent was obtained. Oral health status examination was carried out for all the patients. Periodontal status was assessed by the following parameters:

a) Gingival Bleeding Index (Ainamo and Bay, 1975),
b) Mean probing pocket depth,
c) Mean clinical attachment level.

After the screening process, 40 patients were segregated into case group and control group consisting of 20 patients in each group. Case group consisted of generalized severe periodontitis patients with 10% or greater number of sites with probing depth ≥ 6mm and 30% of sites with clinical attachment loss ≥ 5mm. Control group consisted of periodontally healthy individuals with probing depth less than or equal to 3mm with no clinical attachment loss.

Collection and analysis of blood sample

Under aseptic measures, venous blood samples were drawn by venipuncture in antecubital fossa using 5ml syringe and collected in an ethylene diamine tetra acetic acid (EDTA) coated vacuutainer tubes (3ml) for haemogram and non-coated vacuutainers (2ml) for serum ferritin and transported to clinical laboratory and processed within 4 hours of collection in an automated haematology analyser (Sysmex Cell Counter, Trans Asia Co., India) for haemogram i.e. Hb% (haemoglobin), MCV (mean corpuscular volume), PCV (packed cell volume), MCH (mean corpuscular haemoglobin), MCHC (mean corpuscular haemoglobin concentration), TC (total count), DC (differential count), ESR (erythrocyte sedimentation rate). The samples were evaluated for serum ferritin (Roche- Elecsys 2010™ Chemiluminesence Analyser, Germany) by electro chemiluminescence immunoassay. Statistical analysis of the data was performed using the SPSS software (IBM, 2013). Independent t-test was carried out to study the difference in blood parameters between the groups.

Results

Statistically significant values were obtained for neutrophil, ESR, RBC, MCHC and serum ferritin levels with $p< 0.05$ (Table 1). Mean count of polymorphonuclear neutrophils (PMNs) in the case group (59.9±7.65%) was significantly higher than the control group (53.10±9.19%). This difference is statistically significant ($p<0.05$). The mean erythrocyte sedimentation rate (ESR) in the case group was 41.9±9.65 mm/hr which was found to be significantly higher than the control group, which was 16.95±8.24 mm/hr. Mean count of red blood cells (RBCs) in the case group (4.74±0.365 cells/mm^3) was significantly lower than the control group (5.07±.421 cells/mm^3). Both these values were statistically significant as the *p* value was less than 0.05. Mean corpuscular haemoglobin concentration (MCHC) in the case group (35.15±2.69%) was found to be significantly higher than the control group (33.58±1.05%). Ferritin is an acute phase protein which is usually increased in anaemia of chronic disease. Mean levels of serum ferritin in the case group was found to be significantly higher (126.9±42.47 mcg/ltr) than the control group (50.79±11.07 mcg/ltr), with a *p* value of 0.000 ($p<0.05$), showing statistical significance on intergroup comparison.

Discussion

The association between anaemia and periodontitis has been studied since a long time but with varying results. In the earlier studies, it was reported that anaemia plays a direct role in the aetiology of periodontal disease (Chawla *et al.*, 1971). On the

contrary, Seigel (1945) demonstrated that anaemia occurred as a result of destructive periodontal disease.

In the present study, female patients were excluded from the study population, as the prevalence of anaemia is known to be much higher in females of reproductive age in India especially iron deficiency anaemia, because of poor nutrition, increased menstrual loss, high incidence of tropical and intestinal infections, and other miscellaneous factors (Gokhale *et al*., 2010). Females are also prone to hormonal imbalance during puberty, reproductive phase, and towards menopausal age (Takami *et al.*, 2003). The microbial flora and host immune response are altered leading to exaggerated response of the periodontal tissues to local factors (Wakai *et al.*, 1999). Therefore, to eliminate bias, only male patients were included in the study.

Further, both past and current smokers were not included in the present study, because there is evidence suggesting that smoking is a co-factor for development of periodontitis. Smoking affects the immune system and microflora of the patient leading to deeper probing depth and greater clinical attachment and bone loss (Bergström, 2003). Neutrophil functions, such as phagocytosis, superoxide production and protease inhibitor production, are hampered by exposure to nicotine. In addition, tobacco products may modify the production of cytokines. Smoking has a greater effect on the release of cytokines from neutrophils than periodontal disease. Smoking also affects erythrocytes and other blood parameters (Erdemir *et al.*, 2008).

According to a study by Erdemir *et al.* (2008), smokers with chronic periodontitis had a lower number of erythrocytes, a lower value of haemoglobin, and lower haematocrit and iron compared to non-smokers with chronic periodontitis. Thus only non-smokers and those not consuming any smokeless forms of tobacco were included in our study. Betel quid chewing has been independently associated with an increased risk of periodontal disease, gingival bleeding and systemic conditions, such as cardiovascular disease, metabolic syndrome and diabetes, thus betel quid chewers were excluded from the study (Gokhale *et al.*, 2010).

The results of the present study showed that haemoglobin levels were not significantly different between the case group and the control group. This is in accordance with a study done by Aljohani (2010) of which, they compared the mean haemoglobin levels with varying severity of periodontitis and reported that mean haemoglobin level was not associated with severity of periodontitis. On the contrary, Pradeep and Anuj (2011) reported that patients with severe periodontitis had a tendency towards anaemia compared to mild or moderate periodontitis, although in their study, there was no reported data to support this finding. Further in their study, it was not clear as to what criteria was adapted to define the severity of periodontitis. Hutter *et al.* (2001) has reported that male patients with severe periodontitis, as evidenced by ≥7 teeth with >50% bone loss, had lower mean haemoglobin levels compared to moderate periodontitis and control group. These results could be influenced by the presence of confounding factors such as underlying nutritional deficiency or presence of any chronic inflammation.

In the present study, the total cell count, mean number of eosinophils, basophils, monocytes, lymphocytes were found to be almost similar in both groups with no significant statistical difference. These findings are similar to the study done by Nibali *et al*. (2007). Mean count of neutrophils (PMNs) in the case group was found to be higher than the control group and the difference was statistically significant ($p<0.05$). This data can be attributed to the fact that exaggerated neutrophils of host response are a very important component in the pathogenesis of periodontal disease.

The RBC count in case group were marginally lower than the reference range, while those in control group were within normal limits, and the intergroup difference was found to be statistically significant, correlating with the suggestion that depressed erythropoiesis and decreased RBC survival act as a mechanism in ACD. This finding was similar to a study done by Hutter *et al.* (2001) which showed that periodontitis patients had lower haematocrit levels, lower RBC counts and lower Hb levels.

Further, a more recent study by Gokhale *et al*. (2010) also reported similar findings in 30 male chronic periodontitis patients in an Indian population. They found decreased hematocrit values in patients with chronic peridontitis. Nevertheless, earlier studies by Wakai *et al.* (1999) did not observe any relationship between increasing CPITN scores and Hb levels, which was in accordance with our study results.

ESR is a measure of the rate at which erythrocytes sediment in anticoagulated whole blood under a given set of conditions. Accelerated erythrocyte aggregation is caused by large, asymmetrical plasma proteins (fibrinogen, immunoglobulins, lipoproteins and α-2 macroglobulin) and inflammation related proteins (cytokines and chemokines) inhibiting the negative electrical forces which, normally keep the erythrocytes apart. In the present study, ESR was significantly higher in the case group as compared to the control. These results were similar to an earlier study by Hutter *et al.* (2001) who found higher ESR values in patients with moderate and severe periodontitis than in the control subjects. For this observation, it could be reasoned that the elevation of ESR is caused by the inflammatory process.

Mean packed cell volume (PCV), mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) in the case group was almost similar to the control group and the difference was therefore, found to be statistically insignificant. The minimal change in MCV suggested that the anaemia related to periodontitis is normocytic and hence not due to iron or vitamin deficiency (Medappa, 2000). Again the small increment in MCH values compared to increase in haemoglobin levels implies that anaemia associated with periodontitis is of normochromic type (Johnson, 1990). Mean corpuscular haemoglobin concentration (MCHC) in the case group was found to be significantly higher than the mean value in the control group.

Our findings are similar to those reported previously, although we evaluated a smaller sample comprising of only male non-smokers in order to eliminate possible confounders. A previous study, which did not find a significant association, considered a broader spectrum of periodontal disease severity (Erdemir *et al.*, 2008). In the present study, as we included only generalized, severe periodontal disease, the variation in results could be attributed to this fact.

Ferritin is an acute-phase reactant and is thus elevated in inflammation, autoimmune disorders, chronic infection and liver disease. The acute phase refers to a series of events that occur in response to infection or tissue damage (Lipschitz *et al.*, 1974). The local reaction is termed inflammation and the systemic response is referred to as the acute phase response. The acute phase response may be induced by toxic chemicals, physical trauma, infection, inflammation, malignancy, tissue necrosis (e.g. myocardial infarction) and immunisation (Mast *et al.*, 1998). The clinical and metabolic features of the acute phase response include fever, leucocytosis, thrombocytosis and metabolic alterations, as well as changes in the concentration of a number of plasma proteins. There are changes in several plasma proteins including ferritin during infection.

Beyond its role as an acute phase protein, ferritin plays an important role in iron storage and recycling. Ferritin stores iron in a non-toxic and soluble form and releases it in a controlled fashion.

In addition to iron storage, another important function of ferritin in humans is its role in macrophages where it recycles iron from old red blood cells (RBCs) and transfers it to apo-ferritin. The iron in transferring is delivered to immature red blood cells in the bone marrow, thus completing the cycle.

Ferritin also plays an important role in host immune response as is evident from its increased concentration during infection in order to counter infective agents that attempt to bind iron from the host tissue. An 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 (Lipschitz *et al.*, 1974).

Ferritin is used as a marker of iron storage, and a level of 15 ng per millilitre is generally taken as indicating absent iron stores. However, a ferritin level of 30 ng per millilitre provides better positive predictive values for iron-deficiency anaemia (92 to 98 percent) when studied in several populations. For patients with anaemia of chronic disease, however, ferritin levels are normal or increased, reflecting increased storage and retention of iron within the reticuloendothelial system, along with increased ferritin levels due to immune activation (Weiss and Goodnough, 2005).

In the present study, mean levels of serum ferritin in the case group were found to be significantly higher than the control group. This could be attributed to the fact that chronic periodontitis is an inflammatory disease and the primary pathogenesis for anaemia of chronic disease is presence of inflammation or chronic infection. However, whether the rise in levels of serum ferritin is concomitant with the degree of inflammation or chronicity of inflammation remains questionable. Consequently our results were contradictory to those obtained by Prakash *et al.* (2012) who found lower levels of serum ferritin in periodontitis subjects. On the contrary, the results obtained by Chakraborty *et al*. (2014) reflected a different opinion. They found an increase in the levels of serum ferritin in patients with chronic periodontitis and decreased after non-surgical periodontal therapy thus establishing the fact that chronic periodontitis could lead to anaemia of chronic disease.

The findings of our study indicate possibility of anaemia of chronic disease in periodontitis affected individuals but there is a lack of literature to correlate serum ferritin values and periodontal disease. So, further research is required to validate this association between serum ferritin levels and chronic periodontitis.

The limitations of the present study could be the small sample size of patients. Although the RBC indices and serum ferritin levels noted in our study are suggestive of ACD, an analysis of the soluble serum transferrin receptor concentration, or a bone marrow examination, would be necessary to quantify iron stores and definitively distinguish between ACD and iron-deficiency anaemia in patients with periodontal disease.

Conclusion

In this study, a compendious evaluation of the various hematologic parameters indicative of anaemia was made. There were significant differences in some of the parameters like neutrophil, ESR, RBC and serum ferritin in subjects having severe form of generalized chronic periodontitis compared to patients not having periodontitis. On the contrary other parameters like Hb, TC, lymphocyte, monocyte, eosinophil, basophil, PCV, MCV and MCH did not show any statistically significant variations.

Thus it can be concluded that severe form of chronic generalized periodontitis, by means of an inflammatory process may result in the presence of anaemia of chronic disease. However, the question remains whether degree of anaemia varies with degree of inflammation and whether mere reduction of inflammation would treat the ACD is still elusive. Further interventional studies using larger sample size should be carried out to establish this relationship.

Clinical significance

The relation between anaemia of chronic disease and chronic periodontitis is bitemporal. It could be a cause and effect relation. Thus, identification and rectification of the cause i.e. chronic inflammatory process like periodontitis may resolve the anaemic status of the patient.

Table 1 Independent t-test used to analyze the difference between cases and controls among various variables

Variables	Groups	N	Mean	Std. Deviation	Std. Error Mean	t - value	df	*p*- value
Hb	case	20	15.180000	0.6932760	0.1550212	-1.432	38	0.160
	control	20	15.580000	1.0390279	0.2323337			
TC	case	20	8430.00	1149.416	257.017	-0.091	38	0.928
	control	20	8462.50	1121.662	250.811			
Neutrophil	case	20	59.90	7.656	1.712	2.541	38	0.015*
	control	20	53.10	9.199	2.057			
Lymphocyte	case	20	36.30	6.806	1.522	0.153	38	0.880
	control	20	35.95	7.681	1.718			
Monocyte	case	20	1.00	1.298	0.290	-0.335	38	0.739
	control	20	1.10	0.308	0.069			
Eosinophil	case	20	3.15	0.875	0.196	1.740	38	0.090
	control	20	2.45	1.572	0.352			
Basophil	case	20	0.05	0.224	0.050	1.000	38	0.324
	control	20	0.00	0.000	0.000			
ESR	case	20	41.90	9.651	2.158	8.791	38	0.000*
	control	20	16.95	8.243	1.843			
RBC	case	20	4.742500	0.3651946	0.0816600	-2.652	38	0.012*
	control	20	5.073000	0.4211151	0.0941642			
PCV	case	20	42.845000	2.9351724	0.6563245	0.576	38	0.568
	control	20	42.240000	3.6629583	0.8190624			
MCV	case	20	86.990000	6.3481369	1.4194866	0.320	38	0.751
	control	20	86.450000	4.0766989	0.9115776			
MCH	case	20	33.775000	6.1878382	1.3836427	1.984	38	0.054
	control	20	30.860000	2.2058296	0.4932385			
MCHC	case	20	35.155000	2.6976549	0.6032140	2.425	38	0.020*
	control	20	33.585000	1.0504510	0.2348880			
Serum Ferritin	case	20	126.9190	42.47691	9.49813	7.755	38	0.000*
	control	20	50.7985	11.07132	2.47562			

Values indicated with * are statistically significant.

Independent t-test was done to ascertain the *p* value.

References

Ainamo J, Bay I (1975). Problems and proposals for recording gingivitis and plaque. *Int Dent J*, **25**(4): 229-235.

Aljohani HA (2010). Association between hemoglobin level and severity of chronic periodontitis. *JKAU Med Sci*, **17**(1): 53-64.

Bergström, J (2003). Tobacco smoking and risk for periodontal disease. *J Clin Periodontol*, 30(2): 107-113.

Chakraborty S, Tewari S, Sharma RK, Narula SC (2014). Effect of non-surgical periodontal therapy on serum ferritin levels: an interventional study. *J Periodontol*, **85**(5): 688-696.

Chawla TN, Kapoor KK, Teotia SP, Singh NK (1971). Anaemia and periodontal disease: a correlative study. *J Indian Dent Assoc*, **43**(4): 67-78.

Erdemir EO, Nalcaci R, Caglayan O (2008). Evaluation of systemic markers related to anemia of chronic disease in the peripheral blood of smokers and non-smokers with chronic periodontitis. *Eur J Dent*, **2**(2): 102-109.

Gokhale SR, Sumanth S, Padhye AM (2010). Evaluation of blood parameters in patients with chronic periodontitis for signs of anemia. *J Periodontol*, **81**(8): 1202-1206.

Haurani FI (2006). Hepcidin and the anemia of chronic disease. *Ann Clin Lab Sci*, **36**(1): 3-6.

Hutter JW, Van der Velden U, Varoufaki A, Huffels RAM, Hoek FJ, Loos BG (2001). Lower number of erythrocytes and lower levels of hemoglobin in periodontitis patients compared to control subjects. *J Clin Periodontol*, **28**(10): 930-936.

IBM (2013). *IBM SPSS Statistics for Windows, version 22.0*. Armonk, NY: IBM Corp.

Johnson MA (1990). Iron: nutrition monitoring and nutrition status assessment. *J Nutr*, **120**(Suppl 11): 1486-1491.

Lainson PA, Brady PP, Fraleigh CM (1968). Anemia, a systemic cause of periodontal disease? *J Periodontol*, **39**(1): 35-38.

Lipschitz DA, Cook JD, Finch CA (1974). A clinical evaluation of serum ferritin as an index of iron stores. *N Engl J Med*, **290**(22): 1213-1216.

Mast AE, Blinder MA, Gronowski AM, Chumley C, Scott MG (1998). Clinical utility of the soluble transferrin receptor and comparison with serum ferritin in several populations. *Clin Chem*, **44**(1): 45-51.

Mealey BL, Rose LF (2008). Diabetes mellitus and inflammatory periodontal diseases. *Compend Contin Educ Dent*, **29**(7): 402-408, 410, 412-413.

Medappa N (2000). Iron absorption and its implications on strategies to control iron deficiency anaemia. *Indian Coun Med Res Bull*, **30**: 1-7.

Mercado F, Marshall RI, Klestov AC, Bartold PM (2000). Is there a relationship between rheumatoid arthritis and periodontal disease? *J Clin Periodontol*, **27**(4): 267-272.

Naik V, Acharya A, Deshmukh VL, Shetty S, Shirhatti R (2010). Generalized, severe, chronic periodontitis is associated with anemia of chronic disease: a pilot study in urban, Indian males. *J Investig Clin Dent*, **1**(2): 139-143.

Nibali L, D'Aiuto F, Griffiths G, Patel K, Suvan J, Tonetti MS (2007). Severe periodontitis is associated with systemic inflammation and a dysmetabolic status: a case-control study. *J Clin Periodontol*, **34**(11): 931-937.

Pradeep AR, Anuj S (2011). Anemia of chronic disease and chronic periodontitis: does periodontal therapy have an effect on anemic status? *J Periodontol*, **82**(3): 388-394.

Prakash S, Dhingra K, Priya S (2012). Similar hematological and biochemical parametres among periodontits and control subjects. *Eur J Dent*, **6**(3): 287-294.

Seigel EH (1945). Total erythrocyte, leucocyte and differential white cell counts of blood in chronic periodontal disease. *J Dent Res*, **24**: 270-271.

Takami Y, Nakagaki H, Morita I, Tsuboi S, Takami S, Suzuki N *et al*. (2003). Blood test values and Community Periodontal Index scores in medical health checkup recipients. *J Periodontol*, **74**(12): 1778-1784.

Wakai K, Kawamura T, Umemura O, Hara Y, Machida J, Anno T *et al*. (1999). Associations of medical status and physical fitness with periodontal disease. *J Clin Periodontol*, **26**(10): 664-672.

Weiss G (2002). Pathogenesis and treatment of anaemia of chronic disease. *Blood Rev*, **16**(2): 87-96.

Weiss G, Goodnough LT (2005). Anemia of chronic disease. *N Engl J Med*, **352**(10): 1011-1023.