PERIODONTAL HEALTH IN SICKLE CELL DISEASE - A CASE CONTROL STUDY

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Abstract

Patients with Indian haplotype of SCD although exhibit milder symptoms of disease, this factor may be contributory to our finding of no significant higher periodontal breakdown in SCD,SCT as compared to healthy group. Yet the basic pathophysiology of SCD raise questions on our understanding of periodontitis, which require further research.

Keywords

Sickle Cell Disease, Periodontitis,

Introduction

The term Sickle cell disease (SCD) includes a group of conditions in which a pathological process results due to presence of HBS (Sickle Cell Heamoglobin).It is an inherited autosomal recessive disease [2].

There are six genotype variations of sickle cell disease the major being –

- Homozygous sickle cell disease –SS
- Sickle cell- hemoglobin C disease-SC

HbS is an example of single point mutation in which the codon determining the amino acid chain at position β6 has changed from GAG coding to GTG. It also occurs from inheritance of HbS with a wide variety of genes of beta thalassaemia1. In this disease due to low oxygen tension in the blood the red blood cells assume sickle shape and a similar relationship is seen with erythrocytes in sickle cell trait although greater degree of hypoxia is required in the latter3.Sickle cell disease is a homozygous condition and sickle cell trait is the heterozygous form.

It is pertinent to mention that Dr James Henrick of Chicago in November 1910 described the first case of sickle cell disease in the case of an African student who was undergoing training in dentistry at the Chicago College of Dental Surgery 1904-1907[5].

In India sickle haemoglobin was first reported by Catbush in tribal population of Nilgiri Hills of South India in 1957[20]. Later, it was reported from the tribal population of Central India i.e. Madhya Pradesh and Chhattisgarh and its surrounding areas falling in the States of Rajasthan, Gujarat, Maharashtra, Andhra Pradesh and Orissa[21, 22]. The highest frequency of sickle cell trait is found among tribal groups like 24% in Abujhmaria tribal of Bastar region followed by kondhs of Orissa 20 percent [21, 22].

It has often been stated that sickle cell anemia (SCA) in Indians being linked to the Arab-Indian haplotype has a mild clinical presentation which goes unnoticed, sometimes throughout life. This has been attributed to the high fetal haemoglobin and associated α−thalassemia commonly seen among these patients. Thus the clinical severity of sickle cell disease in India is comparatively milder than those seen in sickle cell disease patients in Africa, but highly variable within the country. [19]

Periodontitis is often described as eco genetic disease meaning that in the presence of environmental and behavioral factors along with predisposing genetic and epigenetic factors there is dys-biosis with increase in number of pathogenic organisms. The response of host leads to disproportionate response to the microbial insult which leads to destruction of connective tissue of the periodontium. This vicious process of unresolved inflammation leads to further

destruction of supporting tissues of teeth.

The periodontal apparatus supporting the tooth is a highly vascularized tissue with abundance of micro vascular channels. In Sickle cell disease the alteration of red blood cells to sickle shape is reversible through exposure to increased oxygen levels but repeated episode of sickling leads to rigidity of cell walls of red blood cells making them irreversibly sickle cells [ISC][4]. In our study Sickle cell anaemic group patients had minimum 2 sickle crisis during their life time with a maximum of 32 hospital admissions in a 24 year old female, who had also received 80 units of blood transfusions.The passage of these cells through microvasculature leads to clogging causing circulatory disturbances, along with reduced oxygen capacity.

This feature of sickle cell disease may adversely affect the delicate, vascularized tissue compartments of supporting structure of tooth namely the periodontal ligament, the gingival components specially the junctional epithelium which is the terminal end of gingival epithelium which is in direct contact with tooth surface as it has close proximity to vascular plexus namely gingival plexus[6]. The Junctional epithelium is considered to be highly metabolically active region because of the continuous detachment of daughter cells which replace the degenerating cells on tooth surface by mitotic activity. Thus reduced oxygen supply in sickle cell disease to this critical component of dentogingival unit might induce damage at this level.

Another important area where the vasoocclusive feature of the disease might play a role is the capability of periodontal ligament to withstand various forces exerted on tooth surface is also believed to be linked to the ability of vascular channels to undergo stenosis and through arterial back pressure and ballooning of vessels according to viscoelsatic theory[7]. But in sickle cell disease vaso-occlusion of microcirculation is caused by abnormal adherence of HBS containing red cells probably due to expression of CD36 marker by micro vascular endothelium, as the endothelial cells of larger vessels do not express this marker .Along with reduced flexibility and abnormal endothelial adherence of HBS containing red blood cells tissue ischemia and infarction occurs[5].

Thus in principle these two features of disease namely vaso occlusion in microvasculature and

reduced oxygen carrying capacity might adversely affect the periodontal ligament and the junctional epithelium.

Sickle cell anaemia can lead to many systemic complications especially in areas that are most likely to have reduced oxygen level and microvascular occlusion leading to infarction.

Sickle cell anaemia affects the bone marrow due to diminished lifespan of the red blood cells to approximately 8 to 25 days leading to compensatory erythropoietic activity[4]. There is sustained erythropoietic expansion with intermittent episodes of acute necrosis in painful crisis.
Erythropoietic expansion may deepen the maxilla leading to protrusion of the anterior part of maxillary bone and proclination of upper incisors. Similar changes with protrusion of mandible and anterior angulation of teeth in the lower arch facial deformity and malocclusion may become more marked with increasing age[10]. Above mentioned features of the disease may also contribute to malocclusion which might act as a local factor predisposing the patient to increased plaque accumulation and other contributory factors like trauma from occlusion which might play a role as a predisposing factor for initiation and progression of localized periodontitis

The lamina dura although normal is rendered more prominent by deficiency of compact bone, histological abnormalities in dental pulp have been reported and periodontal infection may precipitate painful crisis[12, 13].

Infarction of the mandible may occur during painful crisis, mental nerve neuropathy associated with molar peri apical inflammation. Numbness or parasthesia along mental nerve course may occur during painful crisis[19]. Osteomyelitis of mandible has been reported with varied bacteriology although it differs from other bones[17]. Osteonecrosis of jaw bones due to other reasons may be exacerbated by Ischemia and or avascularity. Osteonecrosis of tempromandibular joint has been reported[16]. Bone density is lost in patients with sickle cell anemia and along with poor blood flow (avascularity) within the bone. Patients with a history of sickle cell anemia should have their peri apical radiographs evaluated thoroughly for an increase in trabeculation[14].

Spleen in early life is enlarged due to congestion of reticular spaces with sickle red cells and later in life there is intense congestion and haemorrhage in terminal arterioles finally it is reduced to small, wrinkled remnant[8].

Immune system is compromised because of early loss of function of spleen which brings circulating antigen onto close contact with reticulo-endothelial system, also there are abnormalities in complement, immunoglobulin's, leucocyte function and cell mediated immunity. Defects in opsonisation affect the process of phagocytosis of encapsulated bacteria. Another important feature is the abnormality in the alternative pathway of complement fixation[9].

The abnormality in the alternative pathway should affect the periodontal tissues because both gingivitis and chronic periodontitis have been characterized primarily as activators of the alternative pathway of complement activation. In chronic periodontitis even though pathogen specific antibodies are formed but the activation of complement system is still via the alternative pathway[10].

As mentioned previously the vaso occlusion in microvasculature ,presence of irreversibly sickled cells and the compromised status of immune response of host with compromise in major immunological events such as opsonisation, defects in alternative pathway of complement system coupled with abnormalities in immunoglobulin might compromise the basic inflammatory and immune pathways in the gingival, periodontal compartment .Thus an individual suffering from Sickle cell disease might be more prone to a multi factorial complex disease such as periodontitis. This biological plausibility is the main rationale behind this study.
The aim of our study was to find whether patients with sickle cell disease have higher prevalence of periodontitis as compared to sickle cell trait patients and healthy controls.

Material and Methods

The duration of study was three months. Patients for the study were selected from the outpatient department of the Institute of Sickle Cell Disease under Government Medical College, Raipur. To maintain homogeneity in the study groups the subjects of healthy group were either the

relatives or friends of sickle cell group and those of sickle cell trait group were relatives of sickle cell disease group.The Sickle Cell Institute Raipur is the tertiary referral institute in the state so we had sickle cell patients coming from distant places and all corners of the state of Chhattisgarh. Haemoglobin variant of patients was detected by high performance liquid chromatography.

Inclusion criteria:

(1) Patients between the age group of 18 to 45 years.
(2) Patients attending regular follow up in the institute for the past six months.
(3) Patients with at least one relative having sickle trait.
(4) Patients who had no periodontal treatment in the past six months.

Exclusion criteria:

(1) Smoking and tobacco use in any form.
(2) Pregnant and lactating females.
(3) Patients unwilling to participate in study.
(4) Subjects with systemic illness such as diabetes mellitus, cardiac diseases.
(5) Subjects taking medications, such as corticosteroids, calcium channel blockers or immunosuppressive drugs.

Each patient was informed about the study and written consent was obtained. Detailed medical histories including number of admissions, blood transfusion were also recorded for patients of sickle cell disease group. Out of total 150 subjects selected for study there were 43% females and 57% males. The mean age of control group patients was 30 years, that of SCT group was 33 years and that of SCD group was 26 years.

The patients were divided into three groups:

(1) Group 1- Healthy patients

(2) Group 2-Sickle cell trait group=SCT

(3) Group 3-Sickle cell disease group=SCD

The screening and diagnosis of patients with chronic periodontitis was made based on the clinical criteria proposed by the 1999 International World Workshop for Classification of Periodontal Diseases and Conditions.

Clinical Indices

(1) Complete medical history was taken and missing teeth were charted
(2) Plaque index of *Silness J and* L*oe* H[23] and the Gingival index of L*oe* H and *Silness J* [24] were determined.
(3) Probing depths and probing attachment levels were measured for all teeth, with the exception of the third molars, at the mesial and distal line angles and mid facial and lingual aspects of each tooth.
(4) Probing attachment levels were measured by reference to the Cemento enamel Junction (CEJ) [27].
(5) When the surface of tooth was covered by supra and/or sub gingival calculus and detection of the CEJ was not possible, the teeth were excluded from probing attachment level measurements and sometimes from probing depth measurement.
(6) Modified sulcular bleeding index[26] was used to measure bleeding by gently moving the UNC[15] probe circumferentially around the tooth.
(7) All patients from the three groups were examined by same examiner (JC) in the same dental chair under consistent light conditions.
(8) UNC[15] periodontal probes which had been carefully examined for comparability of markings were used throughout the study.

Observation

Table–1: It gives the results of the Chi Square Test. The table gives the mean, standard deviation of GI, PI, PPD, CAL and Msbi among the three groups. For assessing any association or relationship in mean GI among the three groups chi square test was applied. In the sickle cell trait group Mean & SD values of GI, PI and PPD values are higher than other groups but after chi square test p value is not significant. In control group and sickle cell trait group Mean & SD values were higher than sickle cell anemia group after CHI square test P=0.018 denotes significantly higher sulcular bleeding in healthy group followed by sickle cell trait in comparison to sickle cell disease group.

Table–1

INDICES	GROUPS	MEAN ± SD	CHI SQUARE VALUE	P VALUE
GI	Healthy	1.53 ± 0.43	84.80	0.28
	Sickle Cell Trait	1.55 ± 0.42		
	Sickle Cell disease	1.40 ± 0.44		
PI	Healthy	1.53 ± 0.43	72.52	0.33
	Sickle Cell Trait	1.54 ± 0.43		
	Sickle Cell disease	1.38 ± 0.45		
PPD	Healthy	2.04 ± 0.68	100.21	0.26
	Sickle Cell Trait	2.17 ± 0.72		
	Sickle Cell disease	1.91 ± 0.47		
CAL	Healthy	1.44±2.97	86.60	0.36
	Sickle Cell Trait	1.82±2.98		
	Sickle Cell disease	1.52±3.28		
MSBI	Healthy	1.68 ± 0.97	15.26	0.018
	Sickle Cell Trait	1.38 ± 0.96		
	Sickle Cell disease	0.94 ± 0.89		
HB	Healthy	11.24 ±2.10	25.68	0.00
	Sickle Cell Trait	9.96 ±1.34		
	Sickle Cell disease	8.82 ±1.30		

Chart -1: Shows variations in mean values of GI.PI, PPD AND CAL among all the three groups - Healthy, SCD and SCT. In SCT group mean value of all parameters is higher than other two groups. Although the p value is non significant but mean of these parameters in sickle cell trait group is even higher than healthy group.

CHART NUMBER -1 SHOWING COMPARISION OF MEAN VALUE AMONG THE GROUPS

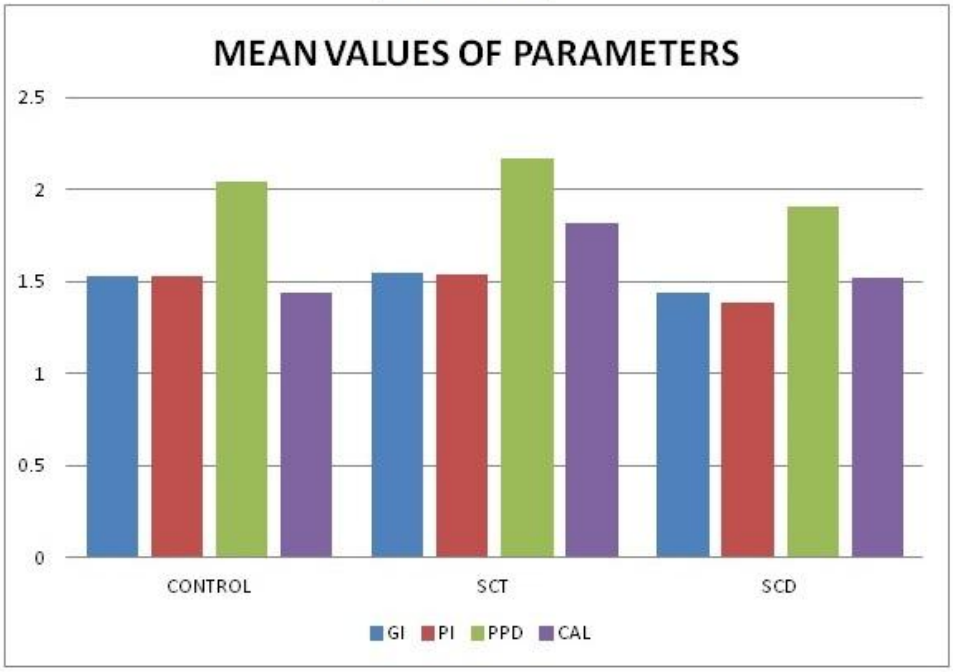

CHART-2 SHOWING VARIATIONS IN HB TOTAL AMONG GROUPS

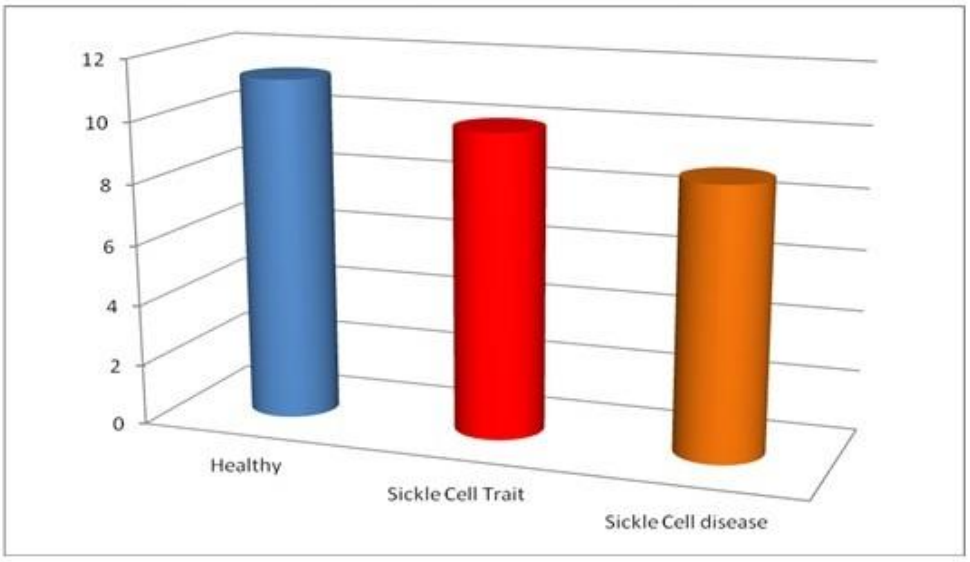

CHART-3 SHOWING MEAN AGE OF SUBJECTS AMONG THE THREE GROUPS

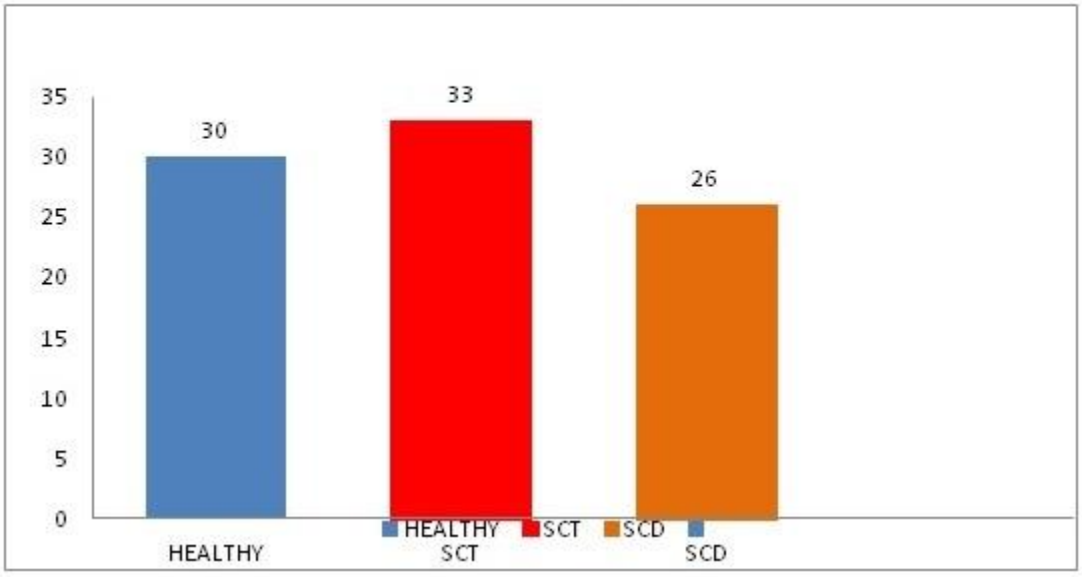

Table -2:

POST HOC ANOVA FOR HEAMOGLOBIN TOTAL

Further evaluate the intra group variation in haemoglobin total levels among the 3 study groups post hoc Anova test was applied. The mean difference was statistically significant among healthy and SCD group and SCD and ST group.

Table:2 - COMPARISON OF Hb total AMONG THREE GROUPS

VARIABLE	GROUP		MEAN DIFFERENCE	P VALUE
HAEMOGLOBIN	Healthy	Sickle Trait	1.26400*	0.001
		Sickle Disease	2.40400*	0.001
	Sickle Trait	Sickle Disease	1.14000*	0.001

Table -3:

POST HOC ANOVA FOR Msbi

To further evaluate the intra group variation in Msbi among the 3 study groups post hoc Anova test was applied .The mean difference was statistically significant among healthy and SCD group and SCD and ST group.

Table:3 - COMPARISON OF MSBI AMONG THREE GROUPS

VARIABLE	GROUP		MEAN DIFFERENCE	P VALUE
MSBI	Healthy	Sickle Trait	.30000	0.115
MEAN SULCULAR		Sickle Disease	.74000*	0.001
BLEEDING INDEX	Sickle Trait	Sickle Disease	.44000*	.021

Results

Although in SCD patients due to systemic involvements, hospital admission, poor socioeconomic background and limited educational background of patients one expects general neglect of oral hygiene yet surprisingly in our study almost all the patients maintained reasonable good oral hygiene with majority of patients reported brushing at least once daily with only 1% reported Datun use. Similar findings were found in the ST group and control group. 2% of patients from ST group reported sickle related crisis at least once in their life time. In the SCD group average number of times of hospital admissions due to sickle related events was 8.1 times. The average number of blood transfusions in SCD group was 9.7 units. With respect to clinical indices like GI, PI, PPD, CAL no significant difference was found among all the three groups that is SCD group, ST group and healthy group.

Although with respect to SCT group mean and standard deviation of PI -1.55±0.42, GI 1.54±0.43, PPD- 2.17± 0.72 was higher than the SCD and control group, but after chi square test it was found to be non significant [TABLE 1].

With respect to Msbi mean and standard deviation in healthy group was 1.68±0.97 and SCT 1.38±0.96 have significantly higher sulcular bleeding as compared to individuals of sickle cell group P=0.018.[TABLE 1]

Anova test results also revealed between groups significance only with respect to Msbi p=0.001 and haemoglobin levels p=0.000[TABLE 3] .

Post hoc Anova results revealed higher Msbi in healthy as compared to SCT and SCD P=0.001 in comparison of SCT to SCD p= 0.021.

Similar results were seen with respect to haemoglobin levels healthy compared to SCT and SCD p=0.001 and with respect to SCT compared to SCD p=0.01.[TABLE 2 & 3].

Discussion

Systemic effects of sickle cell disease have been studied extensively and are well documented. Going through dental literature one finds that there are few publications about the periodontal aspect of sickle cell disease. Periodontal implications of sickle cell disease were first reported by Crawford JM 1988, Arowojolu 1999, Famili.et al 2004, Guzeldemir et al 2011.

Most of the previously mentioned studies about periodontal implications have been carried out in African continent or in patients of African origin. Studies in India have focused mainly on the oral hygiene aspect of SCD patients by taking into account parameters like GI, PI & DMFT, OHIS-S,PD,CAL. They include studies by Singh J, Singh N, Kumar A, Kedia NB, Agarwal A. 2015, Rathod S, Brahmankar R 2013, Bhat N et al 2015. To the best of our knowledge and as per available data base, ours is probably the first study in India which focused on the specific question of association between sickle cell anemia and periodontitis by comparative evaluation of accepted periodontal parameters between sickle cell anaemic, sickle cell trait and healthy patients using standardized probe in a completely homogenous group having same educational, dietary and socio economic back ground.

Crawford in 1987[28] conducted a study on patients with sickle cell anaemia (SS), haemoglobin

SC disease (SC) or S Thalassemia and compared with an appropriate control population using clinical and radiographic indices of periodontal disease severity. He concluded that although no relationship between sickle cell disease and periodontal disease has been demonstrated in this study, it is possible that in some sickle cell disease subjects, periodontal disease is a sufficient inflammatory stimulus to precipitate a crisis. Our results concur with Crawford as they also concluded that the populations of sickle cell disease subjects examined do not have mean levels of destructive periodontal diseases that are clinically more severe than a group of non sickle subjects matched for age, general dental care.

Guzeldemir et al in 2011[29] in their study on Sickle cell disease patients and healthy individuals evaluated periodontal status by [plaque index (Pl), gingival index (GI), probing depth (PD), bleeding on probing (BOP)], alveolar bone level (ABL), mandibular cortex index, and bone quality index. They found that the P1, GI, and BOP were higher in sickle cell diseases patients than in the healthy individuals ($P < 0.0001$) but no significant differences regarding PD was found among the two groups. However the P1 and GI were significantly higher in patients with SCD, which according to them reflected an as yet undefined variable response to microbes.. Therefore they were unable to confirm any significant relationship between SCD and periodontal diseases. They did not find any attachment loss or periodontal disease in their study group, we did find attachment loss in all the three groups but subsequently on analysis of data there was no significant higher prevalence of attachment loss in both sickle cell disease or trait group as compared to healthy group.

Our results concur with Arowojolu 1999[30] who in their study on young sickle cell anaemic Nigerians checked the probing depth in both SCA group and healthy control group. The mean and standard deviation of PD was reported to be 2.68±0.44 which was slightly higher than the healthy group, since they did not find PD greater than 5mm so they concluded that there is no clinical periodontal disease or attachment loss in patients with Sickle Cell Disease. The age group in their study was 11 to 19 years and since it was carried out on African natives so no comparison can be drawn between their study and our study as the age group and haplotype of SCD patients both differ yet in our study PPD mean and SD in SCA group was 1.91±0.47. Another important finding in our study was that mean and SD of PPD in SCT group was 2.17 ±

0.72 which is higher than both healthy and SCA group

Famili et al 2008 in their study concluded that Afro American sickle cell disease patients exhibited higher periodontal involvement but we cannot compare our results with their results, may be because of the haplotype variant of haemoglobin or other factors. Jaideep et al in 2013[31] in their study divided subjects into three groups beta thalassemic group, sickle cell anaemic and control group found that, prevalence of dental caries and periodontal diseases was significantly more in beta thalassemic patients followed by sickle cell anaemic patients than control group.

However, when group I (beta thalassemia) was compared with group II (sickle cell anemia), results were found to be highly significant ($P<0.001$) only for decayed missing filled tooth. The clinical indices used in this study were Decayed-Missing-Filled Teeth Index (DMFT Index), Plaque index (PI) and Gingival index (GI).On the basis of these indices they have concluded higher prevalence of periodontitis.

Our results are also contradictory to this study although thalassemic patients were not included in our study but we incorporated PPD, CAL and Msbi and found no significant mean difference in our study groups. Rathod and Brahmankar 2013[32] in their study on sickle cell disease patients concluded that although oral health is not a priority in sickle cell disease patients they should be encouraged to maintain strict oral hygiene. The age group in their study was 18 to 40 and parameters examined were simplified oral hygiene index, probing depth, CAL, GI, modified PI and DMFT. Their study had only one group that is sickle cell anaemic patients so no comparative inference can be deduced. Oral hygiene was found fair in 53% of patients, 21% patients had poor oral hygiene and only 2.5% patients had good oral hygiene. Probing depth, GI, modified PI and CAL has also been reported .The interpretation of the results of this study show significantly high GI, CAL and PD as compared to the results of these parameters in our sickle cell study group. Regarding CAL they have reported 4-6mm in 44.5% and greater than 6mm in 26% of patients where as in our study only 10% patients of SCA group had CAL 4-6mm and 8% patients had CAL greater than 6mm and with respect to our SCT group in 18% of patients we found CAL greater than 6mm.

Regarding oral hygiene our results are contradictory to findings of Bhat et al 2015[33] who in their study on subjects of Dhamtari district of Chhattisgarh concluded that patients with Sickle cell disease had poor oral hygiene because of preoccupation with multiple hospital visits. They used oral hygiene index simplified as a clinical index. In our study we had a wider base as our patients came from all the major districts of Chhattisgarh. Although in our study mean & standard difference with respect to PI & GI was higher but after chi-square test these results were non significant, thus our results with respect to oral hygiene are not in agreement with their study.

The basic limitation of our study is the number of subjects, because the life expectancy of sickle cell anaemic patients is low thus getting large number of subjects is a challenge. Although the Institute of Sickle Cell Disease provided us with a reasonable number of patients but getting subjects of higher age group that is above 45 years was not possible.

The sickle cell disease adversely affects the life of an individual with painful sickle crisis which in addition to other general precipitating events, with respect to dental pathologies such as periapical infection, periodontitis or interventional treatment procedure like extraction may lead to sickle cell crisis. With increasing awareness due to government initiatives the life span of sickle cell patients is increasing .Thus in practice of dentistry increasing number of patients are being encountered in day to day practice.

Ability to elicit proper history from patients and knowledge of ethnic /caste groups who are more prone to the disease along recognizing clinical features will help in preventing intra operative or post operative complications. A standard protocol for management of sickle cell patients is the need of hour because of increased urbanization and development because the earlier scenario of presence of patients in a particular belt is no longer valid. That is why a thorough understanding of dental and systemic features of sickle cell disease is of prime importance. This can be achieved by performing detailed histological study of the gingival vasculature with emphasis on the vascularity of junctional epithelium and if the presence of irreversibly sickled cells leads to compromised functioning of periodontal apparatus in response to various occlusal forces in sickle cell patients sickle cell disease patients is required to shed

further light on this aspect of the disease.

Another important aspect of SCD is the compromised immune system, although it is true that compromised immune system is a feature common in other anaemic conditions also, but the specific defects in the activation of alternative pathway of complement fixation is of importance because in both gingivitis and periodontitis alternative pathway of complement fixation plays an important role. Thus further studies in sickle cell disease patient with emphasis on junctional epithelium, periodontal ligament and immune pathways may present a new model in understanding of periodontitis.

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