

Original Research Article

Effect of non-surgical periodontal therapy on the clinical periodontal inflammatory parameters in β -thalassemia major (TM- β) patients with gingivitis

ABSTRACT

BACKGROUND: Increased prevalence of gingival diseases in thalassemia patients has been consistently reported. In diseases with neutrophil dysfunctions, periodontal tissue is lost very rapidly. β -thalassemia major (TM- β) patients exhibit defective neutrophils and macrophages. Therefore, supplementary gingival inflammation is detrimental to periodontal tissues in these patients. This warrants attention to specialized oral health care intervention in these patients.

This is the pioneer pre and post study that evaluates the effect of non-surgical periodontal therapy (NSPT) in β -thalassemia major (TM- β) patients with gingivitis. And also reports the prevalence and distribution of disease severity in TM- β patients.

METHODS: 31 patients (15 females, 16 males) fulfilling the inclusion criteria were provided with protocol guided NSPT including scaling, polishing and chemical mouthrinse (0.2% CHX). Gingival index (GI), plaque score, Papillary bleeding index (PI) and periodontal pocket depth (PPD) were recorded with a periodontal probe (UNC-15) at baseline and evaluated after 6 weeks of intervention. Paired T-test was applied for GI, PBI and plaque and Wilcoxon signed rank test for PPD at the P -value of <0.05

RESULTS: 86% of the assessed individuals had gingivitis (6% -mild, 44%-moderate and 36% - severe). NSPT showed highly significant (P - <0.000) improvement from baseline to 6 weeks after intervention for all the clinical parameters, GI, PBI, plaque score and PPD.

CONCLUSION: Within the limitations of the study, the results show that with proper protocol, multidisciplinary approach and careful screening of the patient's systemic status, TM- β patients with gingivitis respond positively to local measures of plaque control.

Keywords: { β -Thalassemia major, Gingivitis, periodontal health, Non-surgical periodontal therapy}

1. INTRODUCTION

Thalassemia is, globally, the most common commonly prevalent, yet preventable genetic disorder [1]. In β -thalassemia, the mutation of the gene located on chromosome 11, results in defective and non-functional β chains of human hemoglobin. This mutation results in life threatening anemia associated with β thalassemia patients who depend on lifelong blood transfusion for survival. It mainly occurs in Mediterranean countries [1] however, along with gene drifts and founder effects, consanguineous marriages are cited as one of the reasons for increased prevalence of thalassemia in, North and Central Africa, the Middle east, South Asia and the Sub-continent (India and Pakistan) [2]. [2]. World Health Organization (WHO) has proposed priority in the control of blood disorders, particularly β -thalassemia, in the third world countries [3]. Pakistan represents one of the highest thalassemia burdened countries in the world [4]. Despite the overwhelming disease burden there is unfortunately no baseline registry available, although, a figure of 100,000 transfusion dependent thalassemia patients is a commonly quoted number [4]. The estimated carrier rate for thalassemia is 5-7%, with approximately 9.8m carriers, reported in the total population [5]

β Thalassemia major (TM- β) exhibits distinctive oral and facial features along with its systemic manifestations. Protruded maxilla, severe crowding, open bite, protruded upper lip, flattened nose bridge, increased dental decay, and atrophic glossitis are some of the observed oral features in these patients [6,7,8,9]. Available studies have consistently reported increased prevalence of periodontal problems in thalassemia patients compared to healthy controls [7,10,11,12]. Periodontal diseases are a group of infectious inflammatory diseases - affecting the supporting structures of the teeth -gingiva, alveolar bone, cementum [13]. Periodontal diseases begin with gingivitis – localized inflammation of the gingiva initiated by bacterial plaque – a biofilm that forms on teeth and gingiva [14]. Higher prevalence of gingivitis in these patients is explained by the following mechanisms. In addition to the systemic effects of TM- β , the condition also affects the local defense mechanism where neutrophils and B lymphocytes fail to respond effectively against gingival microbial attack in patients with gingivitis [15]. The incidence of gingivitis in thalassemic patients is further favored by xerostomia due to patient's inability to close the mouth over proclined teeth, resulting in inability of TM- β patients to benefit from the salivary local immune defense against gingivitis [16]. Compromised oral hygiene, malocclusion and Chronic anoxemia in some cases also predisposes such patients to gingival disorders [10]. Due to regular transfusions, iron overload and its accumulation in systemic tissues of the thalassemia patients is well documented [17]. Iron deposits have also been found in the gingival tissues of TM- β patients, resulting in dark colored gingival margins and its accumulation leads to fibrotic degeneration of the periodontal tissues in TM- β patients [18]. Accumulation of iron deposits also causes painful inflammation of salivary glands [9]. Breakdown of haemoglobin leads to accumulation of bilirubin in the dentinal tubules of these patients leading to characteristic yellow discoloration of their teeth [19] [figure 1].



Figure 1 Intra oral picture of a thalassemia patient showing Pre (A) and post (B) scaling appearance. The blue arrows point at the characteristic yellow discoloration of the teeth

Neutrophils represent the principal leukocyte (>95%), which are recruited as the first line defence against the bacterial biofilm [20]. Their absence leads to periodontal tissue damage, whereas the excess also causes periodontal destruction. Hence, both the quantity as well as the distribution of the neutrophils is necessary for periodontal health [14]. In diseases with neutrophil dysfunctions, periodontal tissue is lost very rapidly [21]. TM- β patients exhibit defective neutrophils and macrophages with compromised ability of phagocytosis [22]. When there is supplementary gingival inflammation, that may in turn, alter the clinical signs of both the chronic diseases [23]. This suggests that patients with TM- β and gingival inflammation have two chronic inflammatory conditions, each of which may affect the other.

The reported high prevalence of periodontal diseases in TM- β patients and the effect of TM- β and periodontal diseases on each other warrant strategies and dental treatment plans tailored specially for this cohort. Due to reduced haemoglobin, compromised immune activity and subsequent higher susceptibility to infection, special considerations are warranted for dental treatment in these patients [24,25].

This is the first study that reports the effect of non-surgical periodontal therapy (NSPT), following the guidelines of dental treatment in TM- β patients with gingivitis. It also reports the prevalence of gingivitis in these patients according to disease severity which has not been reported earlier with the aim to prompt attention to the neglected oral care in these individuals and warrant a need for nationwide registry that reports baseline data for gingival diseases in these patients.

2. MATERIAL AND METHODS

This study was a joint collaboration of *Ziauddin College of Dentistry, Karachi* and *Afzaal Memorial Thalassemia Foundation (AMTF), Karachi*. A total of 137 patients, via consecutive sampling technique were screened, out of which 36 patients (18 males, 18 females) between the age range of 10y and 20y, fulfilled the selection criteria and were assessed. All patients with any systemic comorbidities, history of antibiotic use during the past 3 months, history of dental prophylaxis during the past 6 months, history of active infection with HIV, HepB and HepC, history of splenectomy, history of cognitive challenges, were excluded. All patients

diagnosed with TM- β , age >10years, patients who received or are receiving iron chelation therapy with deferasirox, calcium, vitamin D, regular erythrocyte transfusion, regular physician's follow-up, were selected.

The study follows the strengthening the reporting of observational studies in epidemiology **(STROBE)** [26] guidelines. All study participants received appropriate non-surgical periodontal therapy (NSPT). Scaling was performed for patients having calculus deposits. Using Gracey Curettes (*Hu-Friedy no. 1 to 14*) and Piezoelectric Ultra sonic scaler (*Woodpecker U-6 LED*). Followed by polishing with the polishing paste (Henry Schein Acclean prophylaxis paste) and a disposable polishing brush. All patients were instructed to use 15 ml of 0.2% chlorhexidine gluconate mouth rinse (*Protect mouthwash, Roomi Enterprises, Karachi, Pakistan*) twice daily for 60 seconds. Lastly, all the participants were taught Fone's technique of tooth brushing. All of the procedures were performed by the principal investigator (AH). All dental treatment was performed at the dental clinic setup at AMTF. All NSPT interventions for the participants of this study was scheduled in the week of the planned transfusion so that the recipient has adequate blood count [25]. The oral intervention was never scheduled on the day of transfusion as the patient is often fatigued after transfusion [24].

The primary clinical parameter to assess the prevalence and severity of gingivitis is bleeding on probing (BoP) and was recorded with the Gingival Index Score (GI) by Silness and L e [27] and papillary bleeding index (PBI) by Muhlemann [28]. The plaque score was calculated using Quigley Hein Index (QHI) [29]. Periodontal Pocket Depth (PPD) was noted on 6 surfaces (mesio-buccal, buccal, disto-buccal, mesio-lingual, lingual, disto-lingual) of all non-restored teeth , excluding hypermobile, partially erupted, third molars, using periodontal probe (UNC-15, Hu-Freidy, Chicago, USA). All the readings were noted on the specially designed periodontal chart at baseline (day 1) and 6 weeks after the intervention with NSPT. After 3 weeks of NSPT, the patients were recalled for follow-up. Clinical evaluation was carried out and oral hygiene instructions were reinforced.

Analysis were done using SPSS version 21 for windows. To check for the intra-examiner reliability, kappa statistical analysis was performed on 5 readings with KK being the rater and AH being the examiner. kappa agreement value of 1.000, for GI, 0.90 for PBI, plaque score and PPD were achieved.

The results are expressed in percentages and frequencies for all the categorical data. Mean, standard deviation (SD) and margin of error at 95% confidence interval (CI), $P < 0.05$ is computed for numerical data (Age, GI score, PBI, Plaque Score and PPD). The comparison from the baseline to 6-weeks follow-up for GI score, Plaque score and PBI was done using the paired T-test and Wilcoxon Signed rank test for PPD.

3. RESULTS AND DISCUSSION

The demographics of the study participants are shown in [Table 1]. Mean age with standard deviation (SD) for the study participants was 13.36 ± 2.84 years, with age range 10years – 20 years.

Table 1 Age and gender distribution of the study participants

Total patients	Male	Female	Age in years
			(Mean ± SD)
36	18	18	13.36 ± 2.84
			(14.36 – 12.36)*

*Values in parenthesis show confidence interval

The overall prevalence of the gingival diseases in the assessed individuals was 86% (n=31) with 14% (n=5) healthy individuals. Of the 86%, 6% (n=2) cases had mild gingivitis, 44% (n=16) had moderate gingivitis and 36% (n=13) had severe gingivitis. The prevalent severity of gingivitis in the study population and disease distribution according to the gender, as measured by GI score is shown in Table 2 and illustrated in Figure 2. No gender predilection was observed for the distribution of disease severity.

Table 2 Gingival condition status of the study participants based on GI score interpretation

Gingival condition	Healthy	Mild	Moderate	Severe
No. of patients (n)	n=5	gingivitis n=2	gingivitis n=16	gingivitis n=13
GI score (Mean ± SD)	0	0.85 ± 1.47	± 2.33	±
(male:female)	(3:2)	0.21 (1:1)	0.31 (7:9)	0.29 (7:6)
Confidence interval	--	(1.15- 0.55)	(1.63- 1.32)	(2.49- 2.16)

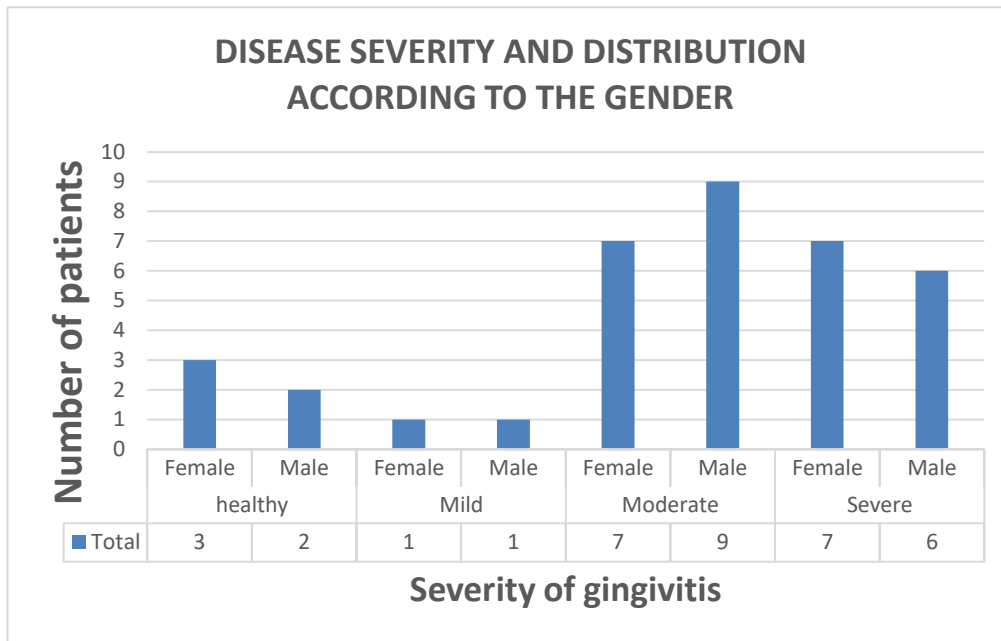


Figure 2 Distribution and severity of gingival disease according to the gender

Following the inclusion criteria of the participants for the study, medical data of the patients was collected. Of the 36 participants, 31 patients who had gingivitis and were subjected to NSPT, 2 reported allergic reaction to transfusion in 2017, 1 presented with hydronephrosis, and 1 presented with renal fullness. Further medical data is reported in [Table 3].

Table 3 Medical data of the study participants

Total patients	Mean no. of transfusions	No. of patients taking DFX*	No. of patients taking DFP**	No. of patients with hepatosplenomegaly
31	168 ± 87	28	03	28

*Deferasirox

** Deferiprone

The result of the intervention (NSPT) shows highly significant ($P < .05$) improvement for all the clinical parameters (GI score, Plaque score, PBI and PPD) from the baseline to evaluation after 6 weeks of intervention with NSPT [table 4]

Table 4 Comparison of Clinical periodontal inflammatory parameters after intervention

Parameters	Baseline	6 weeks	P-value
	Mean \pm SD	Mean \pm SD	
GI score	1.84 \pm 0.63	1.08 \pm 0.71	.001
Plaque score	3.33 \pm 0.79	1.58 \pm 1.03	.000
PBI	1.76 \pm 0.86	0.99 \pm 0.83	.001
PPD*	2.21 \pm 0.55	1.55 \pm 0.41	.000

*Wilcoxon signed rank test based on improved values observed in positive ranks

The graphical representation of the improvement in the severity and distribution of the gingivitis is shown in Figure 3. At baseline, out of the 31 patients, 3% (n=2) of the participants had mild gingivitis, 52% (n=16) had moderate gingivitis and 42% (n=13) had severe gingivitis. There were no gingivally healthy recruits. Following NSPT, at 6 weeks follow-up, the severe cases went down to 10% (n=3) from 42% (n=13), moderate cases went down to 32% (n=10) from 52% (n=16) and there were 16% (n=5) of the cases which showed healthy gingival parameters.

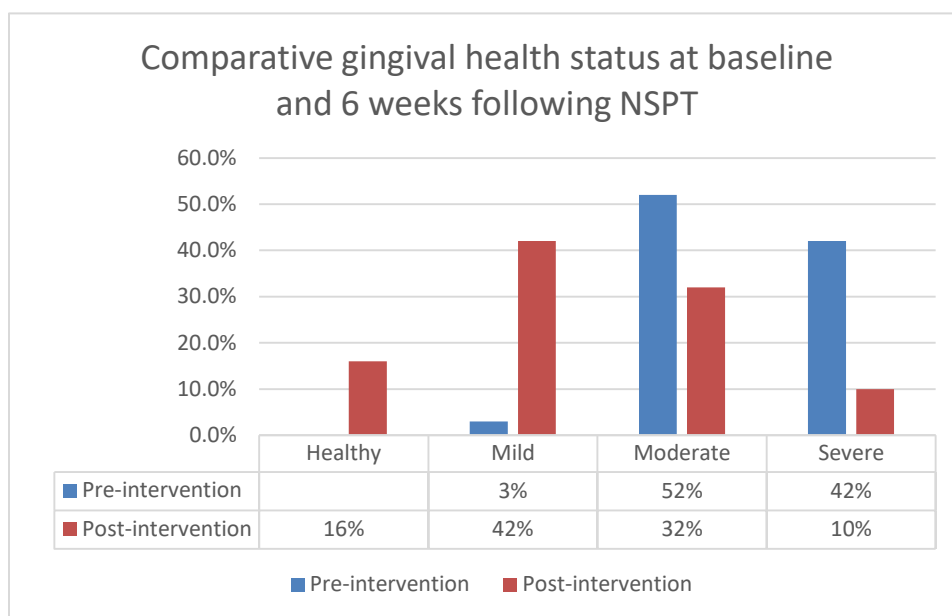


Figure 3 Distribution of severity of disease pre and post NSPT

DISCUSSION:

To the best of the author knowledge, no study has evaluated the effect of nspt on the clinical periodontal inflammatory markers in $\text{tm-}\beta$ patients with gingivitis and hence this is the pioneer study. Highly significant ($p < .05$) improvement in all clinical periodontal inflammatory parameters, evades the doubts on the systemic ability of $\text{tm-}\beta$ patients to respond to nspt – given the treatment regimen strictly follows the guidelines of dental treatment for thalassemia patients [24,25]. At baseline, there were no periodontally healthy recruits. At 6 weeks follow-up after the intervention, the severity of gingivitis was markedly reduced in all the strata and 16% of the participants presented with healthy gingival parameters [figure 3]. The present study also demonstrates highly significant ($p < .05$) reduction in plaque scores and bleeding scores, with plaque scores of 3.33 ± 0.79 at baseline reducing to 1.58 ± 1.03 and bleeding scores of 1.76 ± 0.86 at baseline reducing to 0.99 ± 0.83 at 6 weeks after nspt. Nspt has consistently demonstrated positive therapeutic effect on periodontal conditions and the results of the present study corroborate the same. In a study by wong et al., [30], nspt demonstrated reductions in plaque percentage from 72.8% to 25.4% ($p < .005$) and bleeding on probing from 86.3% to 32.0% ($p < .005$), in a group of chinese adults with periodontal inflammatory diseases. Nspt is also effective in patients who have periodontal conditions in addition to systemic diseases/conditions. Nspt in a group of pregnant women demonstrated a marked decrease in gingival inflammation ($p < .05$) in a study by yarkac, gokturk and demir [31]. Nspt in type 2 diabetes mellitus also shows improved post intervention scores. In a study by tsobgny-tsague et al., [32] in type 2 diabetic individuals, the plaque index reduced from 80.5% to 18.1% and gingival bleeding score reduced from 39.5% to 4.2% ($p < .001$). Furthermore, the same study reports significant reduction in average pocket depth (pd) where, after nspt, pd decreased from 3mm to 1.9mm ($p < .001$). Similar marked reduction in pd was observed in the present study as well where average pd at baseline was $2.21 \pm 0.55\text{mm}$ which reduced to 1.55 ± 0.41 ($p < .000$) at 6 weeks after nspt for $\text{tm-}\beta$ patients with gingivitis.

There has been consistent reporting of increased prevalence of gingival and periodontal diseases in $\text{tm-}\beta$ patients [6,10,11,12], however, the severity of disease distribution has not been reported. This study reports the overall prevalence of gingivitis in $\text{tm-}\beta$ patients in a pakistani population and also stratifies the severity of gingivitis according to gender. It was

interesting to note that severity of gingivitis in α -thalassemia patients shows no gender predilection [figure 2]. With the majority of the study participants presenting with moderate (44%) and severe (36%) forms of gingivitis, it is pertinent that attention should be directed to oral health care protocols in this group.

4. CONCLUSION

α -thalassemia patients present with higher prevalence of gingivitis. The results of the study show that with proper protocol, multidisciplinary approach and careful screening of the patient's systemic status, α -thalassemia patients with gingivitis respond positively to local measures of plaque control without additional systemic antibiotic coverage. There are more than 40 thalassemia centers currently operating across the Pakistan [33]. The present study findings will be encouraging for both the dentists and the thalassemia patients to seek appropriate oral care from the designated centers. As much as the results are promising, the authors still propose robust studies in a bigger sample with longitudinal follow-ups to authentically propose the efficiency of NSPT in patients with both periodontal conditions and α -thalassemia.

CONSENT

All authors declare that 'A signed informed consent and minor assent form was filled by all study participants and their guardians for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the Ethical Research Committee (ERC) at the Ziauddin University, bearing the reference code (0780119AHOM) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

1. Bellis G, Parant A. Beta-thalassemia in Mediterranean countries. Findings and outlook. *Investigaciones Geográficas*. 2022;(77):129.
2. Weatherall D, Williams T, Allen S, O'Donnell A. The Population Genetics and Dynamics of the Thalassemias. *Hematology/Oncology Clinics of North America*. 2010;24(6):1021-1031.

3. Modell B. Global epidemiology of haemoglobin disorders and derived service indicators. *Bulletin of the World Health Organization*. 2008;2008(6):480-487.
4. Zaheer H, Waheed U, Abdella Y, Konings F. Thalassemia in Pakistan: A forward-looking solution to a serious health issue. *Global Journal of Transfusion Medicine*. 2020;5(1):108.
5. Ahmed S, Saleem M, Modell B, Petrou M. Screening Extended Families for Genetic Hemoglobin Disorders in Pakistan. *New England Journal of Medicine*. 2002;347(15):1162-1168.
6. FN H. Periodontal Condition and Orofacial Changes in Patients with Thalassemia Major. *Journal of Clinical Pediatric Dentistry*. 2012;36(3):301-308.
7. Alhajja E. Cephalometric measurements and facial deformities in subjects with -thalassaemia major. *The European Journal of Orthodontics*. 2002;24(1):9-19.
8. Wang Y, Yu-Fong Chang J, Wu Y, Cheng S, Chen H, Sun A. Oral manifestations and blood profile in patients with thalassemia trait. *Journal of the Formosan Medical Association*. 2013;112(12):761-765.
9. Helmi N, Bashir M, Shireen A, Mirza AI. Thalassemia review: features, dental considerations and management. *Electronic physician*. 2017;9(3):4003-4008.
10. Singh J, Singh N, Kumar A, Kedia NB, Agarwal A. Dental and periodontal health status of beta thalassemia major and sickle cell anemic patients: A comparative study. *Journal of International Oral Health*. 2013;5(5):53-58.
11. Tamaddoni A, Fereidooni M, Khafri S, Faghani M. The relationship between gingivitis and periodontitis with β -thalassemia disease. *Journal of Babol University of Medical Sciences*. 2014;16(11):22-27.
12. Eugenio P. Dental and Periodontal Condition in Patients affected by β -Thalassemia Major and β -Thalassemia Intermedia: A Study among Adults in Sicily, Italy. *Journal of Dental Health, Oral Disorders & Therapy*. 2015;3(1).
13. Cortés-Vieyra R, Rosales C, Uribe-Querol E. Neutrophil Functions in Periodontal Homeostasis. *Journal of Immunology Research*. 2016;2016:1-9.
14. Kinane D, Stathopoulou P, Papapanou P. Periodontal diseases. *Nature Reviews Disease Primers*. 2017;3(1).
15. Arabsolghar M, Mohammadi M, Kaheh A, Norouzifard A, Ahmadzade S. Different type of periodontitis and gingivitis in patients with major thalassemia comparing to healthy people. *Journal of Oral Health and Oral Epidemiology*. 2015;4(1): 24-9.
16. Siamopoulou-mavridou A, Mavridis A, Galanakis E, Vasakos S, Fatourou H, Lapatsanis P. Flow rate and chemistry of parotid saliva related to dental caries and gingivitis in patients with thalassaemia major. *International Journal of Paediatric Dentistry*. 2009;2(2):93-97.
17. Taher A, Saliba A. Iron overload in thalassemia: different organs at different rates. *Hematology*. 2017;2017(1):265-271.
18. Calışkan U, Tonguç MO, Ciriş M, et al. The investigation of gingival iron accumulation in thalassemia major patients. *Pediatric Hematology and Oncology*. 2011;33:98-102.
19. Hattab FN, Qudeimat MA, Al-Rimawi HS. Dental discoloration: an overview. *Journal of Esthetic Dentistry*. 1999;11:291-310.
20. Hajishengallis E, Hajishengallis G. Neutrophil homeostasis and periodontal health in children and adults. *Journal of Dental Research*. 2014;93(3):231-237.
21. Moutsopoulos N, Konkel J, Sarmadi M, Eskan M, Wild T, Dutzan N et al. Defective Neutrophil Recruitment in Leukocyte Adhesion Deficiency Type I Disease Causes Local IL-17-Driven Inflammatory Bone Loss. *Science Translational Medicine*. 2014;6(229).

22. Consolini R, Calleri A, Legitimo A, Massei F. Immunological Evaluation of Patients with Beta-Thalassemia major. *Acta Haematologica*. 2001;105(1):7-12.
23. Akcalı A, Kahraman Çeneli S, Gümüş P, Buduneli N, Lappin D, Özçaka Ö. The Association Between Thalassemia Major and Periodontal Health. *Journal of Periodontology*. 2015;86(9):1047-1057.
24. Kumar N, Hattab FN. Dental care. In: Cappellini MD, Cohen A, Porter J, et al., editors. *Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT)* [Internet]. 3rd edition. Nicosia (CY): Thalassaemia International Federation; 2014. Chapter 11. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK269385/>
25. Cdh.org. 2016. *Thalassemia factsheet*. [online] Available at: <https://www.cdh.org/Advisories/CDHO_Factsheet_Thalassemia.pdf> [Accessed 20 January 2022].
26. Cuschieri S. The STROBE guidelines. *Saudi Journal of Anaesthesiology*. 2019;13(5):31.
27. Harald Loe. Gingival index. *Journal of Periodontology*. 1967;38:610-616.
28. Mühlemann HR. Psychological and chemical mediators of gingival health. *Journal of Preventive Dentistry*. 1977;4(4):6-17.
29. Turesky, S, Gilmore ND, Glickman I. Reduced plaque formation by the chloromethyl analogue of vitamin C. *Journal of Periodontology*. 1970;41;41–43.
30. Wong R, Ng S, Corbet E, Keung Leung W. Non-surgical periodontal therapy improves oral health-related quality of life. *Journal of Clinical Periodontology*. 2011;39(1);53-61.
31. Yarkac F, Gokturk O, Demir O. Effect of non-surgical periodontal therapy on the degree of gingival inflammation and stress markers related to pregnancy. *Journal of Applied Oral Science*. 2018;26(0).
32. Tsobgny-Tsague N, Lontchi-Yimagou E, Nana A, Tankeu A, Katte J, Dehayem M et al. Effects of nonsurgical periodontal treatment on glycated haemoglobin on type 2 diabetes patients (PARODIA 1 study): a randomized controlled trial in a sub-Saharan Africa population. *BMC Oral Health*. 2018;18(1).
33. Naghmi A, Khalid H. Management of Thalassemia in Pakistan. *Journal of Islamabad Medical and Dental College*. 2016;5(4);152-153.

DEFINITIONS, ACRONYMS, ABBREVIATIONS

UNC-15 – University of North Carolina 15

GI – Gingival Index

(TM- β) - β -thalassemia major

WHO – World Health Organisation

AMTF – Afzaal Memorial Thalassemia Foundation

ERC – Ethical Research Committee

HIV – Human Immunodeficiency Virus

STROBE - Strengthening the Reporting of Observational studies in Epidemiology

NSPT – Non-surgical periodontal therapy

BoP – Bleeding on Probing