Tikrit Journal for Dental Sciences 11(1) (2023) 93-104
ISSN:2073-1213
https://doi.org/10.25130/tjds.11.1.11 Tikrit Journal for Dental Sciences
https://tjds.tu.edu.iq

Prevalence of Oral Manifestation of Thalassemic Patients in Sulaymaniyah Thalassemia Center

Dastan Rahim Abdulkarim [1] *
Shanaz M. Gaphor [2]

[1,2] Department of Oral Medicine, Sulaymaniyah, Iraq.

Article Info:
-Article History:
-Received: 16/8/2022
-Accepted: 1/9/2022
-Available Online: **Jun**, 2023

Keywords:
Orofacial features, mucosal pallor, halitosis, xerostomia

***Corresponding Author:**
Email:

Department of Oral Medicine, Sulaymaniyah, Iraq.

Abstract

Thalassemia is a genetic blood disorder characterized by abnormal hemoglobin formation, leading to chronic anemia. The objective of this study was to evaluate orofacial complications in thalassemia patients and to detect the blood profile among these patients. Patients and method included a total of 100 thalassemic patients who were enrolled in this study. Oral examination and dental status of each patient was carried out using OHI-simplified. In addition, each patient took a blood investigation (Hb, RBC, MCV, RDW, and ferritin). Result of this study showed that the majority of the patients were female (68%) of which 50 of them had major Thalassemia, with the most frequent age range was between 21-39 years. Patients had statistically higher frequencies of all oral manifestations ($p < 0.001$ for all). Of which pale mucosa accounted for most frequency, 79%, followed by halitosis 39%, ulceration, brown pigmentation 33%, atrophic glossitis and actinic cheilitis 11%, hypomineralisation 8%, candidiasis and burning sensation 7%, geographic tongue and fissured tongue 6%, angular cheilitis 5%. Besides poor oral hygiene measure was 42%. Also, there was a significant positive correlation between most oral manifestations and blood transfusion. As a conclusion, thalassemia disease is associated with orofacial manifestation, which can adversely affect the oral health status of the patient. Therefore, dentists should understand the complications and management of the disease.

Introduction:

Thalassemia is a group of disorders that are inherited and characterized by the presence of abnormal hemoglobin production. Since the defect is in the synthesis of either α- or β-polypeptide chains of hemoglobin, the condition is referred to as α- or β-thalassemia (1). The main problem in a patient with Thalassemia is a lack of healthy hemoglobin that the body needs to become properly oxygenated (2-4). Due to its genetic heterogeneity and clinical and hematologic variability, Thalassemia is commonly classified as homozygous, heterozygous, or compound heterozygous. The homozygous β-thalassemia has a wide-ranging spectrum from thalassemia

minor, which consists of mild hypochromic microcytic anemia without apparent clinical manifestations, to β-thalassemia major, characterized by severe anemia during the first few years of life and is transfusion dependent. Moreover, Thalassemia is β- Thalassemia intermedia, which is neither that severe to be classified as β-thalassemia major, nor that mild to be considered thalassemia minor. Thalassemia intermedia belongs to the group of non-transfusion-dependent Thalassemia (5). Homozygous β-thalassemia major (Cooley anemia, or Mediterranean anemia) causes the most severe signs and symptoms (6). Thalassemia major is a life-threatening condition that commonly manifests during early infancy. The main complications in children are feeding problems, recurrent fever, infection liability, pathological fractures of long bones and vertebrae, Osteoporosis, endocrine abnormalities, and growth retardation, in addition to pronounced orofacial abnormalities (1, 7). Furthermore, the less severe form of Thalassemia refers to thalassemia minor or thalassemia trait, in which an individual carries a thalassemia gene but is still considered a healthy person since the hemoglobin production is enough in their body. Patients with the minor form of α-or β-thalassemia often have hypochromic and microcytic anemia but usually have no obvious systemic symptoms (2, 8, 9). Regarding the clinical manifestation of thalassemia major, severe anemia may develop during the first few years after birth. Other symptoms and signs include facial bone deformities, fatigue, growth failure, shortness of breath, and yellow skin (jaundice) (9). Furthermore, since Thalassemia is treated with blood transfusions, this causes excess iron to accumulate in an individual's bloodstream gradually. Thus, several heart problems, such as irregular heartbeats, heart attacks, and even death by heart failure, can result from this iron buildup (8, 10). In addition, Osteoporosis is another very common problem in patients with Thalassemia, which causes the bones to become brittle and break easily (11-13). Concerning oral and maxillofacial manifestation, skeletal and craniofacial deformities are the common manifestation of Thalassemia Major. The most noticeable orofacial changes in Thalassemia Major are chipmunk face features, which are craniofacial deformities characterized by prominent frontal bossing and cheekbones, overgrowth of the maxilla, flaring of the anterior maxillary teeth, and malocclusion (14-18). There is an increased chance of the migration and spacing of upper anterior teeth, and there may also be malocclusion of varying degrees in such patients (19). Other than that, the teeth may be more prone to decay, discolored, and have short crowns and roots (15). Patients with Thalassemia might also complain of a sore or burning tongue due to folate deficiency (10, 20). Moreover, thalassaemic patients also experience painful swelling of salivary glands and a dry mouth which leads to reduced salivary protection (20). Regarding management of Thalassemia, the central management of patients with thalassemia major include regular blood transfusion therapy to keep hemoglobin levels of at least 9 to 10 g per deciliter to allow improved growth and development and to reduce hepatosplenomegaly and bone deformities (21). The main problem with blood transfusion is the iron overload that causes most of the mortality and morbidity associated with Thalassemia (22). Hence, patients receiving regular transfusions need to be on chelation therapy to help excrete excess iron (23). The most effective iron chelating agent currently available is deferoxamine. Calcium with vitamin D must also be received, since Osteoporosis is common in Thalassemia (6, 24). Regarding dental considerations for thalassemic patients, a Multidisciplinary approach involving dental surgeon, haematologist, and orthodontist should be practiced. Any invasive procedure should be done under antibiotic cover and immediately after transfusion. Before dental procedures are carried out, Liver function and coagulation tests should be done. Caution should be exercised in thalassemia patients due to complications related to compromised immunity, liver function, splenectomy, and cardiovascular issues (23).

Aim of the study

This study aimed to highlight the most prominent oral manifestation among minor and major thalassemic patients and to determine the particular blood profile of the two groups.

Patient and method:

This cross-sectional study was designed to determine the oral manifestations of patients with major and minor Thalassemia from the thalassemia center in Sulaimaniyah city. The sample comprised 100 thalassemic patients. Eighty cases of major Thalassemia and twenty cases of minor Thalassemia. Data collection was carried out from December 2021 to May 2022. The study was reviewed and approved by the Ethics Committee of the Kurdistan Board of Medical specialties. Permission was taken from the thalassemic center to examine the patients. Patients who have autoimmune diseases or any other systemic diseases and patients under twelve years of age were all excluded.

Demographic data (age, sex), history, and intraoral examination for signs and symptoms (candida, ulcer, pigmentation, burning sensation, taste alteration, etc.) were all carried out using dental examination instruments (dental mirror, prob, tweezer, cotton rolls, and portable headlight).

Following WHO criteria, the dental status of each subject was determined using the oral hygiene index-simplified (OHI-S). In order to assess xerostomia in relation to oral functions, the patients were asked four questions (a possible sum score of 0-4 positive answers) predictive of salivary gland hypofunction as proposed by (Fox et al., 1987): (I) Do you sip liquids to aid in swallowing dry foods; (II) Does your mouth feel dry when eating a meal; (III) Do you have difficulties swallowing any foods; and (IV) Does the amount of saliva in your mouth seem to be too little, too much, or you do not notice it.

Furthermore, blood investigations (Hb, RBC, MCV, RDW, and ferritin) were also carried out after receiving formal consent from each patient.

Statistical analysis:

The data were tabulated in excel sheets. The statistical study was performed using the SPSS software package (version 16). Tables accurately illustrated the frequency distribution, percentages, and relations of studied parameters. The Chi-square test was used to see the association between the categorical variables. Also, the Mann-Whitney and independent-Samples Kruskal-Wallis tests were used to associate different blood investigations with gender and age groups. P value > 0.05 was considered as the statistical significance for the variables.

Results:

1-Patients' demographic features of the studied sample:

A total of 100 thalassemic patients were examined in this study. Most patients were female (68%), of which 50 had major Thalassemia. Moreover, the most frequent age range for Thalassemia was between 21-39 years old, as shown in Table (1). and Figure (1).

2-Correlation of Thalassemia with both gender and family history

The Pearson Chi-square test revealed an association of Thalassemia with gender that is statistically counted as significant, although not highly significant (P value is on border 0.05). Conversely, it revealed a highly significant correlation of Thalassemia with family history (P value < 0.02). Details are shown in Table (2).

3. The correlation of gender with the different blood investigations (Hb, RBC, MCV, RDW, Ferritin)

According to the Mann-Whitney test, the result shows that except for the ferritin blood test, which is significantly correlated with gender and the level has essentially decreased among female patients; all the other blood tests were not significantly correlated with gender. As shown in Table 3.

4-Association between different blood investigations across the age group of thalassemic patients

The independent-Samples Kruskal-Wallis test was used to test the association of different blood investigations across age groups by comparing two samples of age groups (>=20 and 21-39), (21-39 and 40-60), and (40-60 and >=20). The test revealed a statistically significant association between blood investigations and the samples of age group (>=20 and 21-39), and the highest significant association was found for the ferritin blood test (P value=0.019). Details are shown in Table 4

5. Association of oral manifestations with Thalassemia:

Regarding oral manifestations, the Chi-square test revealed a highly significant association between Thalassemia and oral manifestations (p value< 0.05). The result shows that the most prominent oral feature among the patients was pale mucosa, in which 79 out of 100 thalassemic patients had this feature. Further illustrations are shown in Table 5.

6-The association of oral manifestation with both male and female gender:

Considering the oral manifestations between male and female thalassemic patients, results showed that most of the oral manifestations were equally found between both genders, except for features like ulcerations, brown pigmentations, halitosis, and pale mucosa which were more frequently found in female patients and the result was a statistically significant correlation between these features and female thalassemic patients. As illustrated in Table 6.

- **7- Correlation of oral manifestations and blood transfusion among thalassemic patients:**

Regarding the oral manifestations among thalassemic patients who had undergone blood transfusion within the one-month duration, the Chi-square test revealed that some oral manifestations such as (ulceration, atrophic glossitis, brown pigmentation, dry mouth, and halitosis) are significantly correlated with blood transfusion amongst thalassemic patients. Details are shown in Table 7.

8-Association between oral manifestations and age group among thalassemic patients:

Again, the Chi-square test shows that although not all of the oral manifestations are correlated statistically with the age group among thalassemic patients, some of the oral findings have been found to be significantly correlated with the group of (>20 years of age) among these patients. Moreover, these findings are (ulceration, halitosis, and pale mucosa). As shown in Table 8.

Discussion:

Thalassemia is the most familiar genetic blood disorder characterized by a defect in globin genes synthesis resulting in a decrease or absence of either α_ or β_ globulin protein chains, resulting in anemia of varying degrees referred to as α_or β_ thalassemia (25).

In the present study, the result shows that the majority of the patients were female (68%). This finding supports the previous study by Husna et al. (26). Since Thalassemia is inherited as an autosomal recessive disorder, thus, it is not affected by gender (27). Therefore, this finding could be related to the fact that more female participants were enrolled in the study than males. Hence, the probability of Thalassemia in females was higher than in males. Regarding age distribution, the result shows that the most common age group of the participants was <=20. This is concomitant with the previous study by Adly and Ebeid (28), who revealed that 39 % of the participants were between 10-19 years old.

Furthermore, in the current study, family history shows a highly significant correlation with Thalassemia, and (33%) of the patients reported positive family history. This data concords with Adly and Ebeid's previous study (28). This could be attributed to a strong cultural preference for consanguineous marriage and a high birth rate (28).

The current study shows that the blood investigations (RBC, Hb, MCV, RDW) were not statistically correlated with gender, except ferritin level was significantly correlated with gender. This result supports the finding of the previous study by Ali and Jahan (29), who concluded that female thalassemic patients had a significant positive correlation with serum ferritin levels.

Moreover, one parameter of the present study claims that all the blood investigations performed in this study (RBC, Hb, MCV, RDW, and ferritin) were significantly correlated across age groups. This finding agrees with a form study by Bandyopadhyay et al. (30). In another study by Mishra and Tiwari (31), serum ferritin levels increased as the age of the patients increased. This finding also agrees with the study conducted by Ali and Jahan (29), who concluded that hemoglobin and ferritin levels are significantly correlated with the patient's age.

Furthermore, the present study shows significantly higher frequencies of all oral manifestations considered in this study. This finding supports the study by Wang et al. (32), who concluded that oral manifestations like ulcers, oral candidosis, atrophic glossitis, dry mouth, oral burning sensation, and oral numbness were significantly higher among thalassemic patients. This could be explained by the fact that these patients have anemia of varying degrees resulting in atrophic glossitis and atrophy of oral mucosa, which in turn causes a burning sensation (32). Also, in this study, the percentage of the participants with pale oral mucosa is 79%, which concord with the result reported by Hattab F. (33), in which 38.9% of his thalassemic patients had pale oral mucosa due to anemia. Regarding oral hygiene, the data of the present study shows that 42 patients had poor oral hygiene, which is in accordance with a previous study by Shadlinskaya R. (34). Oral bad odor (halitosis) is also significantly increased in thalassemic patients in the present study which supports the result of the study by Malath and Al-Aswad (35). This finding is attributed to the foul-smelling produced by oral bacteria in thalassemia patients, which causes halitosis in addition to the poor gingival and periodontal health resulting from neglected oral health (35). This result also agrees with the study by Hamid et al. (36), who stated that thalassemic patients have specific oral manifestations compared to normal people.

However, the distribution of the oral manifestation in relation to gender in this study shows no significant correlation for most of the oral findings, except for ulceration, brown pigmentation, halitosis, and mucosal pallor which were found to be more in female patients, which could again be explained by the certainty that more female patients enrolled in this study. This is in line with a previous study by Hazza'a et al. (37), who reported no significant association between oral candidiasis and gender in thalassemic patients.

The standard treatment of major Thalassemia is regular transfusion for a lifelong; however, this continuous transfusion causes iron overload, negatively impacting oral health. In the current study, the correlation of oral manifestation with blood transfusion among thalassemic patients was statistically significant regarding oral ulceration, atrophic glossitis, brown pigmentation, dry mouth, oral hygiene measure, halitosis, and pale mucosa. This finding is concomitant with a previous study by Ibraheem M. and Salman B. (38), who concluded that a significant correlation was reported between transfusion and the oral health status of the study group. It also agrees with Girinath et al. (39), who revealed that the prevalence of oral and maxillofacial complications decreases when patients receive blood transfusion at younger ages and that the severity of oral manifestation increases when the blood picture deteriorates.

The final parameter in this study is the correlation of the oral manifestation with age group among thalassemic patients. The result shows that only (ulceration, halitosis, and pale mucosa) were statistically significant with age groups and found to be more among the young age group (=<20 years old). This finding can be considered as nearly concomitant with that of Salehi et al. (40), who also

found a statistically significant correlation of mucosal discoloration with age and attributed the presence of this tint of lemon color in oral mucosa to the existing bilirubin produced by the decomposition of red cells.

Conclusion:

In conclusion, a dentist should be aware of thalassemia-related oral manifestations such as ulceration, oral candidiasis, atrophic glossitis, actinic cheilitis, brown pigmentation, oral mucosal pallor, xerostomia, and halitosis. These oral findings are associated with the patient's blood profile, especially ferritin level. The lack of dental awareness, education and care, and poor oral hygiene play significant roles in the prevalence of oral complications amongst thalassemic patients. Therefore, providing preventive and curative oral care to such patients is crucial.

Table 1: The demographic features of the participants

Frequency Table											
Gender		Male					Female				
Family History		No		Yes		**Total**	No		Yes		**Total**
Blood Transfusion		No	Yes	No	Yes		No	Yes	No	Yes	
Age Group	**<= 20**	1	13	0	6	**20**	0	17	1	9	**27**
	21-39	0	4	0	6	**10**	10	13	0	10	**33**
	40-60	2	0	0	0	**2**	7	0	0	1	**8**
		3	**17**	**0**	**12**	**32**	**17**	**30**	**1**	**20**	**68**
Total		**20**		**12**			**47**		**21**		
		32					**68**				

Table 2: Correlation of Thalassemia with gender and family history

		Thalassemia		**Total**	
		Minor	**major**		
Gender	**Male**	3	29	32	0.050
	female	18	50	68	
Total		21	79	100	
Family history	**No**	20	47	67	0.002
	Yes	1	32	33	
Total		21	79	100	

Table 3. Correlation of gender and different blood investigations (Hb, RBC, MCV, RDW, Ferritin)

	Hb	RBC	MCV	RDW	Ferritin
Mann-Whitney U	918.500	944.000	951.500	952.000	677.500
Wilcoxon W	1446.500	1472.000	3297.500	3298.000	3023.500
Z	-1.253	-1.064	-1.009	-1.005	-3.033
P-value	0.210	0.287	0.313	0.315	0.002

Table 4. Association of different blood tests across age groups

Test	Sample 1	Sample 2	Std, Error	P value
HB	40-60	<= 20	10.095	0.738
	40-60	21-39	10.177	0.020
	<=20	21-39	6.117	0.001
RBC	40-60	<= 20	10.102	0.777
	40-60	21-39	10.184	0.079
	<=20	21-39	6.122	0.001
MCV	40-60	<= 20	10.102	0.810
	40-60	21-39	10.184	0.070
	<=20	21-39	6.122	0.001
RDW	40-60	<= 20	10.101	0.723
	40-60	21-39	10.183	0.228
	<=20	21-39	6.121	0.010
Ferritin	40-60	<= 20	10.103	0.777
	40-60	21-39	10.185	0.066
	<=20	21-39	6.122	0.009

Table 5: Association of oral manifestations with Thalassemia

Oral manifestations		Answer	Chi-square	p-value
ulceration	No	67	57.6	< 0.000 *
	RAS	27		
	Herpes labialis	6		
	Total	100		
Candidiasis	No	93	74.0	< 0.000 *
	Yes	7		
	Total	100		
atrophic glossitis	No	89	60.8	< 0.000 *
	Yes	11		
	Total	100		
angular cheilitis	No	95	81.0	< 0.000 *
	yes	5		
	Total	100		
geographic tongue	No	94	77.4	< 0.000 *
	yes	6		
	Total	100		
brown pigmentation	No	67	55.3	< 0.000 *
	localized	25		
	generalized	8		
	Total	100		
fissured tongue	No	94	77.4	< 0.000 *
	Yes	6		

	Total	100		
actinic cheilitis	No	89	60.8	< 0.000 *
	Yes	11		
	Total	100		
hypo mineralization	No	92	70.6	< 0.000 *
	Yes	8		
	Total	100		
burning sensation	No	93	74.0	< 0.000 *
	yes	7		
	Total	100		
Dry Mouth	No	78	31.4	< 0.000 *
	Yes	22		
	Total	100		
oral hygiene	fair	42	3.9	< 0.000 *
	poor	26		
	good	32		
	Total	100		
halitosis	No	61	4.8	< 0.000 *
	Yes	39		
	Total	100		
pale mucosa	No	21	33.6	< 0.000 *
	Yes	79		
	Total	100		

Table 6. Association between oral manifestation and gender among thalassemic patients

oral manifestations	Gender	Frequency	chi-square	p-value
ulceration	Male	9	6.81	< 0.009 *
	Female	24		
Candidiasis	Male	4	0.143	0.705
	Female	3		
atrophic glossitis	Male	4	0.818	0.36
	Female	7		
angular cheilitis	Male	3	0.2	0.65
	Female	2		
geographic tongue	Male	1	2.66	0.1
	Female	5		
brown pigmentation	Male	10	5.12	< 0.02 *
	Female	23		
fissured tongue	Male	4	0.687	0.46
	Female	2		
actinic cheilitis	Male	5	0.09	0.76
	Female	6		
hypo mineralization	Male	2	0.28	0.21
	Female	6		
burning sensation	Male	2	0.45	0.32
	Female	5		
Dry Mouth	Male	7	2.9	0.08
	Female	15		

oral hygiene	Male	Poor	16	3.79	0.15
		Fair	10		
		good	6		
	Female	Poor	26		
		Fair	16		
		good	26		
halitosis	Male		12	5.76	< 0.01 *
	Female		27		
pale mucosa	Male		25	10.64	< 0.001 *
	Female		54		

Table 7. Correlation of oral manifestations and blood transfusion among thalassemic patients

Oral manifestations		Blood Transfusion	Frequency	Chi-square	p-value
ulceration		No	6	13.36	< 0.000 *
		Yes	27		
Candidiasis		No	0		
		Yes	7		
atrophic glossitis		No	2	4.45	< 0.04 *
		Yes	9		
angular cheilitis		No	1	0.37	0.31
		Yes	4		
geographic tongue		No	1	0.21	0.18
		Yes	5		
brown pigmentation		No	1	29.10	< 0.000 *
		Yes	32		
fissured tongue		No	3		
		Yes	3		
actinic cheilitis		No	3	2.27	0.1
		Yes	8		
hypo mineralization		No	0		
		Yes	8		
burning sensation		No	0		
		Yes	7		
Dry Mouth		No	1	18.18	< 0.000 *
		Yes	21		
oral hygiene	Poor	No	7	33.64	< 0.000 *
	Fair		4		
	good		10		
	Poor	Yes	35		
	Fair		22		
	good		22		
halitosis		No	6	18.69	< 0.000 *
		Yes	33		

Table 8. Association between oral manifestation and the age group among thalassemic patients

Oral Manifestations	Age group		Frequency	chi-square	p-value
ulceration	<= 20		19	10.36	< 0.006 *
	21-39		10		
	40-60		4		
Candidiasis	<= 20		3	0.71	0.192
	21-39		3		
	40-60		1		
atrophic glossitis	<= 20		6	0.21	0.078
	21-39		4		
	40-60		1		
angular cheilitis	<= 20		3	0.630	0.247
	21-39		1		
	40-60		1		
geographic tongue	<= 20		2	0.687	0.469
	21-39		4		
	40-60		0		
brown pigmentation	<= 20		20	1.5	0.223
	21-39		13		
	40-60		0		
fissured tongue	<= 20		1	0.219	0.188
	21-39		5		
	40-60		0		
actinic cheilitis	<= 20		4	3.45	0.178
	21-39		6		
	40-60		1		
hypo mineralization	<= 20		4	1.0	0.3
	21-39		4		
	40-60		0		
burning sensation	<= 20		4	1.0	0.5
	21-39		3		
	40-60		0		
Dry Mouth	<= 20		12	0.182	0.670
	21-39		10		
	40-60		0		
oral hygiene	fair	<= 20	18	3.0	0.56
	poor		14		
	good		15		
	fair	21 - 39	21		
	poor		8		
	good		14		
	fair	40 - 60	3		
	poor		4		
	good		3		
halitosis	<= 20		20	8.76	< 0.012 *
	21-39		14		
	40-60		5		
pale mucosa	<= 20		44	36.03	< 0.000 *
	21-39		33		
	40-60		2		

References

Vij R, Machado RFJC. Pulmonary complications of hemoglobinopathies. Chest. 2010;138(4):973-83.

2. Joly P, Pondarre C, Badens C, editors. Beta-thalassemias: molecular, epidemiological, diagnostical and clinical aspects. Ann Biol Clin . 2014; 72(6):639-68.
3. Bernaudin F, Verlhac S, Chevret S, Torres M, Coic L, Arnaud C, et al. G6PD deficiency, absence of α-thalassemia, and hemolytic rate at baseline are significant independent risk factors for abnormally high cerebral velocities in patients with sickle cell anemia. Blood. 2008;112(10):4314-7.
4. Rund D, Rachmilewitz E. β-Thalassemia. NEJM. 2005;353(11):1135-46.
5. Lukens JN. Wintrobe's clinical hematology. The thalassemias and related disorders: quantitative disorders of hemoglobin synthesis. 1993;1103.
6. Olivieri NF. Medical progress: the beta thalassaemia. 1999; 99-109
7. Chaliasos N, Challa A, Hatzimichael E, Koutsouka F, Bourantas DK, Vlahos AP, Siamopoulou A, Bourantas KL, Makis A. Serum adipocytokine and vascular inflammation marker levels in beta-thalassaemia major patients. Acta Haematologica. 2010;124(4):191-6.
8. Habibian N, Alipour A, Rezaianzadeh A. Association between iron deficiency anemia and febrile convulsion in 3-to 60-month-old children: a systematic review and meta-analysis. Iran J Med Sci. 2014;39(6):496.
9. Muncie Jr HL, Campbell JS. Alpha and beta thalassemia. Am Fam Physician. 2009;80(4):339-44.
10. Harteveld CL, Higgs DR. α-thalassaemia. Orphanet J Rare Dis. 2010;5(1):1-21.
11. Baldini M, Marcon A, Cassin R, Ulivieri F, Spinelli D, Cappellini M, et al. Beta-thalassaemia intermedia: evaluation of endocrine and bone complications. Biomed Res Int. 2014;2014.
12. Rossi F, Perrotta S, Bellini G, Luongo L, Tortora C, Siniscalco D, et al. Iron overload causes Osteoporosis in thalassemia major patients through interaction with transient receptor potential vanilloid type 1 (TRPV1) channels. Haematol. 2014;99(12):1876.
13. De Sanctis V, Soliman AT, Elsedfy H, Yassin M, Canatan D, Kilinc Y, et al. Osteoporosis in thalassemia major: an update and the I-CET 2013 recommendations for surveillance and treatment. Pediatr Endocrinol Rev. 2013;11(2):167-80.
14. Singh J, Singh N, Kumar A, Kedia NB, Agarwal AJ. Dental and periodontal health status of Beta thalassemia major and sickle cell anemic patients: a comparative study. Int Oral Health. 2013;5(5):53-58.
15. Hattab FN, dentistry e. Mesiodistal crown diameters and tooth size discrepancy of permanent dentition in thalassemic patients. J Clin Exp Dent. 2013;5(5):e239-44.
16. Van Dis ML, Langlais RP. The thalassemias: oral manifestations and complications. Oral Surg Oral Med Oral Pathol. 1986;62(2):229-33.
17. Alhaija ESA, Hattab FN, Al-Omari MA. Cephalometric measurements and facial deformities in subjects with β-thalassaemia major. Eur J Orthod. 2002;24(1):9-19.
18. Hattab FJ. Periodontal condition and orofacial changes in patients with thalassemia major: a clinical and radiographic overview. J Clin Pediatr Dent. 2012;36(3).
19. Hattab FN. Patterns of physical growth and dental development in Jordanian children and adolescents with thalassemia major. J Oral Sci. 2013;55(1):71-7.
20. Luglie P, Campus G, Deiola C, Mela M, Gallisai D. Oral condition, chemistry of saliva, and salivary levels of Streptococcus mutans in thalassemic patients. Clin Oral Investig. 2002;6(4):223-6.
21. Cunningham MJ, Macklin EA, Neufeld EJ, Cohen AR, Blood TC. Complications of β-thalassemia major in North America. Blood. 2004;104(1):34-9.
22. Modell B, Khan M, Darlison MJTL. Survival in β-thalassaemia major in the UK: data from the UK Thalassaemia Register. 2000;355(9220):2051-2.
23. Helmi N, Bashir M, Shireen A, Ahmed I. Thalassemia review: features, dental considerations and management. Electron Physician. 2017;9(3):4003.
24. Olivieri NF. The β-thalassemias. N Engl J Med. 1999;341(2):99-109.
25. Duggal M, Bedi R, Kinsey S, Williams S. The dental management of children with sickle cell disease and β-thalassaemia: a review. Int J Paediatr Dent. 1996;6(4):227-34.
26. Husna N, Sanka I, Arif AA, Putri C, Leonard E, Nur Handayani N. Prevalence and distribution of thalassemia trait screening. J Med Sci. 2017;49(3):106-13.
27. Vichinsky EP. Clinical manifestations of α-thalassemia. Cold Spring Harb Perspect Med. 2013;3(5):a011742.
28. Adly AA, Ebeid FSES. Cultural preferences and limited public resources influence the spectrum of Thalassemia in Egypt. J Pediatr Hematol Oncol. 2015;37(4):281-4.
29. Ali S, Jahan S. Growth failure in β-thalassemia major patients undergoing repeated transfusions. J Islamic Int Med Coll. 2016;11(3):120-5.
30. Bandyopadhyay U, Kundu D, Sinha A, Banerjee K, Bandyopadhyay R, Mandal T, et al. Conservative management of Beta-thalassemia major cases in the sub-division level hospital of rural West Bengal, India. J Nat Sci Biol Med. 2013;4(1):108.
31. Mishra AK, Tiwari A. Iron overload in beta thalassaemia major and intermedia patients. Maedica. 2013;8(4):328.
32. Wang Y-P, Chang JY-F, Wu Y-C, Cheng S-J, Chen H-M, Sun A. Oral manifestations and

blood profile in patients with thalassemia trait. J Formos Med Assoc. 2013;112(12):761-5.
33. Hattab F. Periodontal condition and orofacial changes in patients with thalassemia major: a clinical and radiographic overview. J Clin Pediatr Dent. 2012;36(3):301-7
34. Shadlinskaya R. Evaluation of oral hygiene and dental caries status in patients with beta thalassemia. Мир медицины и биологии. 2020;16(1 (71)):141-5.
35. Malath N, Al-Aswad FD. Oro-facial manifestations, microbial study and salivary enzyme analysis in patients with β-Thalassemia Major. Scientific Journal Published by the College of Dentistry–University of Baghdad. 2012:52.
36. Hamid RN, Mudher SH, Jabber WF. Oral Manifestations for Thalassemia Patients at the Thalassemia Center Located at Ramadi Women and Children Hospital. Systematic Reviews in Pharmacy. 2020;11(3).
37. Hazza'a A, Darwazeh AM, Museedi OS. Oral Candida flora in a group of Jordanian patients with β-thalassemia major. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;109(2):252-6.
38. Ibraheem M, Salman B. Comparative Evaluation of Oral Health Status in Children With β-Thalassemia Major In Lattakia City-Syria. Int J Dentistry Oral Sci. 2021;8(03):1746-50.
39. Girinath P, Vahanwala SP, Krishnamurthy V, Pagare SS. Evaluation of orofacial manifestations in 50 thalassemic patients: A Clinical Study. J Indian Acad Oral Med Radiol. 2010;22(3):126.
40. Salehi M, Farhoud D, Tohidast EZ, Saheb JM. Prevalence of orofacial complications in Iranian patients with b-thalassemia major. Iranian J Publ Health. 2007; (36) 2:43-46.