Periodontal Condition and Orofacial Changes in Patients with Thalassemia Major: A Clinical and Radiographic Overview

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Objective: *To assess the prevalence of periodontal disease, orofacial changes and craniofacial abnormalities in patients with thalassemia major (TM). Dental management is discussed.* ***Study design:*** *The sample consisted of 54 patients with TM, 31 males and 23 females aged 5.5 to 18.3 years, with the mean age (± SD) of 11.6 ± 3.2 years. The sample was divided into two subgroups according to age. A similar number of unaffected control group matched by age and sex served as a control. Clinical and radiographic examinations were carried out to assess the prevalence of changes caused by this disorder. Student's t-test was used to compare the means between thalassemic group and the control group. The Chi-square test was employed to determine statistical differences in frequencies between the two groups.* ***Results:*** *Poor oral hygiene and gingivitis were observed in 61.1% and 43.0% of the thalassemic patients, respectively. The overall mean plaque score was 1.66 ± 0.51 and gingival score 1.43 ± 0.59. In all tested periodontal parameters, a higher frequency and severity were noted in the thalassemic patients compared with controls. More than half of the patients exhibited frontal bossing, saddle nose and to less extent maxillary protrusion; giving in severe cases (16.7%) a "chipmunk" like appearance. Dental discoloration and pallor oral mucosa were noted in 44.4% and 38.9%, respectively. Dental / jaw pain was reported by 40.0% and headache by 29.6% of the patients. Increased overjet was evident in 25.9% of the patients. The majority of the patients had thickened frontal bone (66.7%), and thinned inferior border of the mandible (64.6%). Widened dipolic spaces and spiky roots and were observed in one-third of the patients. The ramus length and width in the patients were significantly smaller than in controls (P < 0.001).* ***Conclusion:*** *TM may particularly diagnose through orofacial abnormalities. Dentists required understanding the complications and management of the disease.*

Keywords: *periodontal status, orofacial features, thalassemia major, children*
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INTRODUCTION

Thalassemia is considered the most common genetic disorder worldwide; presenting a major public health and social problems in the high incidence areas. The disease is characterized by reduced synthesis of either alpha- or beta-globin chains, leading to decreased hemoglobin production and hypochromic microcytic anemia. Thereby, thalassemia is classified into alpha or beta type, with several subtypes manifested in diverse clinical pictures. Based on genetic heterogeneity, clinical and hematological variability, thalassemia is classified as homozygous, heterozygous, or compound heterozygous. The heterozygous form of the disease (beta-thalassemia minor) is the most common with minimal clinical expression. The homozygous type of beta-thalassemia (also known as thalassemia major, Cooley's anemia or Mediterranean anemia) exhibits the most severe clinical symptoms.

Beta-thalassemia major (TM) is life threating commonly manifested during early infancy. Thereafter, affected children become progressively pallor, severely anemic and fail to thrive. They suffer from feeding problems, diarrhea, recurrent fever, bleeding tendencies especially toward epistaxis, susceptibility to infection, pathological fractures of long bones and vertebrae, osteoporosis, endocrine abnormalities, splenomegaly, lack of sexual maturation, and retardation of growth.[1,2] Patients with TM usually require blood transfusion to keep their hemoglobin level near normal in order to abate the symptoms of hypoxia.

Some of the most striking changes in TM are seen in orofacial expressions and craniofacial deformities. Skeletal abnormalities result primarily from hypertrophy and expansion of the erythroid marrow consequent to ineffective erythropoiesis. The typical facial appearance include frontal bossing, prominent malar bones, depression of the bridge of the nose, overgrowth of the maxilla and malocclusion.[3-5] Patients with TM being at high risk of dental caries,[6,7] oral infection and bacteremia.[8-10] They exhibit yellow dental dis-

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coloration due to chronic jaundice[11] and smaller tooth size than in healthy control group.[12]

About 3% of the world's population carry beta-thalassemia gene.[2] These genes are particularly prevalent in inhabitants of southern Italy, Greece and Cyprus with prevalence 10 to 15%. The condition is also described in Arab countries, Turkey, Iran, southeast Asia and Africa with frequency ranged between 1.5 to 5%.[1,2] In North America, thalassemia is noted primarily in persons of Italian, Greek, Asian decent and in Blacks.

Studies on certain groups of people with genetic defects, immunological anomalies or inborn error of metabolism such as diabetes, Down's syndrome, Papillon-Lefèvre syndrome, or acquired immunodeficiency syndrome demonstrated a high susceptibility to periodontal diseases.[13-15] Very few prevalence reports on the periodontal condition and orofacial abnormalities in thalassemic patients are available. The aim of the present study was to evaluate the periodontal condition, orofacial features, and craniofacial morphology in Jordanian patients with TM and to compare the results with unaffected (thalassemia-free) control group when appropriate. Management modalities are described.

METHOD

The sample comprised of 54 patients with thalassemia major, 31 males and 23 females aged 5.5 to 18.3 years, with the mean age (± SD) of 11.6 ± 3.2 years. The sample was divided into two subgroups according to age; 6-11 years and 12-18 years. A similar number of unaffected control group matched by age and sex to the study group were tested. Patients were examined clinically for assessment of periodontal status and orofacial expressions supplemented with photographs. Information regarding social profile and family history were collected from both hospital records and face-to-face interview. The rates of consanguineous marriage in affected families were 41% for first-cousins marriage, 32% of second cousins, and 27% of distally related or not related. The average number of children per family was 6.1; with 30.9% of the siblings were affected. Medical history revealed that 56% of the patients had undergone splenectomy.

Oral hygiene and periodontal indices

The oral hygiene and periodontal status was assessed using plane mouth mirror, sickle explorer, and periodontal probe with William's marking. The index teeth examined were maxillary right first molar, maxillary right central incisor, maxillary left first molar, mandibular left first molar , mandibular left central incisor, and the mandibular right first molar. Plaque deposits were evaluated at four surfaces of each indexed teeth. The amount of accumulated plaque was graded according to the criteria of plaque index (P1.I) of Silness and Löe.[16] Calculus deposits were scored by placing a dental explorer into the distal gingival crevice and drawing it subgingivally to the mesial contact area. Both supra- and subgingival calculus was recorded. Gingivitis was assessed for the six index teeth using the criteria of gingival index (GI) of Löe and Silness.[17] The numerical scores of the GI used were as follows: 0.1-1.0 mild gingivitis, 1.1-2.0 moderate gingivitis, 2.1-3.0 severe gingivitis. Periodontal condition was assessed by measuring the distance from the free gingival margin to the bottom of the gingival crevice (gingival sulcus depth) or periodontal pocket (probing pocket depth, PPD).

Radiographic examination

Panoramic and lateral cephalometric radiographs were taken for 48 and 33 thalassemic patients, with mean age = 11.2 ± 3.1 years and 10.9 ± 2.8 years, respectively. Similar number of radiographs for unaffected control subjects matched by age and sex to the thalassemic group were taken. The panoramic radiographs were taken for evaluation of dentoalveolar features and mandibular dimensions. Cephalometric radiographs were analyzed for craniofacial abnormalities. Linear and angular measurements of the mandible were obtained from tracing the panoramic radiographs on overlying acetate paper.[18] The measurements were carried out as follows (Fig. 1):

- Ramus length (height): the distance between the highest point of the condylar head and the lowest point on the posterior border of mandible.
- Ramus width: the distance between the deepest point on the anterior and posterior borders of the ramus.
- Intercondylar distance: the distance between the highest point of the head of the right and left condyles.
- Gonial angle: the angle formed between one line tangent to the lower border of the mandible and another line tangent to the distal border of the ascending ramus and the condyle.

The statistical significance of differences in mean values between the thalassemic group and control group were assessed employing Student's t-test. The Chi-square test was used to determine statistical differences in frequencies between the two groups. The level of significance was chosen as $P < 0.05$.

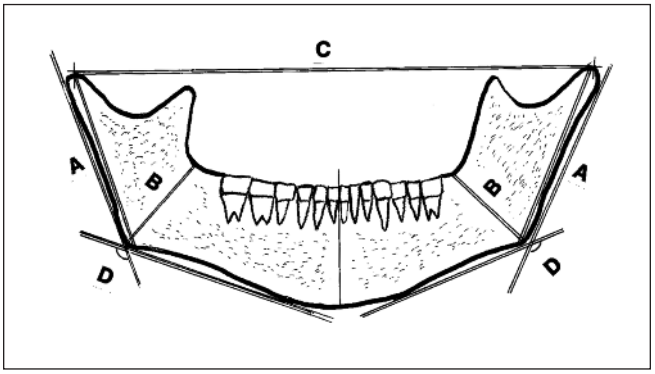

Figure 1. Schematic drawing of panoramic film shows measurements recorded: A, ramus length; B, ramus width; C, intercondylar distance; D, gonial angle.

RESULTS

The mean P1.I and GI scores in the thalassemic and control groups are presented in Table 1. In thalassemic subgroups, the mean P1.I in the 6-11 years olds was 1.57 ± 0.44 and 1.74 ± 0.57 in the 12-18 years olds. The corresponding mean GI in the subgroups was 1.30 ± 0.49 and 1.56 ± 0.69, respectively. The overall mean P1.I and GI scores in thalassemia group were 1.66 ± 0.51 and 1.43 ±0.59, respectively. The corresponding data in the control group was 1.55 ± 0.65 and 1.36 ± 0.51. The differences in P1.I and GI between thalassemic and control groups were statistically not significant. In both thalassemic and control groups, GI was significantly higher in older ages than the younger ones ($P < 0.025$). Of the total 54 patients examined, 61.1% had poor oral hygiene (plaque score ≥ 2.0); that is moderate to accumulation of soft deposits within the gingival pocket. Thin plaque film (score 1) was found in 33.4% of the patients. Only 5.5% of the patients showed no visible plaque deposits. Supra- and subgingival calculus was found in 32.5 thalassemic patients and 21.8% in the controls ($P > 0.05$).

The GI showed that 49.2% of the thalassemic patients had mild gingivitis (no bleeding on probing; score 0.1-1.0), 34.7% moderate gingivitis (bleeding on probing; score 1.1-2.0), 8.3% severe gingivitis (spontaneous bleeding; score 2.1-3.0). Only 7.8% showed no sign of gingivitis versus 25.2% in the controls. Of the thalassemic patients, 16.7% had gingival sulcus depth of 3 mm, 6.1% had pocket depth of 4-5 mm, and 1.9% exhibited pocket depth of ≥ 6 mm. The mean PPD in thalassemic patients was 2.7 ± 1.4 mm versus 2.3 ± 1.2 mm in the controls. The tendency toward higher frequencies and means of periodontal disease in thalassemic group compared with control group did not, however, reached the significant level of $P < 0.05$.

The frequency of changes in the orofacial expressions of thalassemic patients were evaluated clinically and photographically (Table 2). Of the 54 patients, 61.1% exhibited frontal bossing with prominence of cheek bones and 59.2% had saddle nose. These changes with the maxillary protrusion (24.1%), giving in severe cases (16.7%) a distinctive "chipmunk" like appearance (Fig. 2). Yellow dental discoloration and pallor oral mucosa were noted in 44.4% and 38.9%, respectively (Fig. 3), with the majority of the patients showed icteric yellow skin. Increased overjet, measured on study casts, was evident in 25.9% of the patients (Figs. 4 and 5). Dental pain was reported by 30.2% and jaw pain by 10.5% of the patients. Transitory headache and nasal airway problem was described by 29.6% and 16.7% of the patients, respectively. Lower lip paresthesia was recorded in 13.0% of the patients. Only three cases (5.6%) had parotid gland enlargement and tenderness in this region.

Table 1. Oral hygiene status and periodontal condition of patients with thalassemia major and unaffected control group measured by plaqvue index (P1.I) and gingival index (GI).

Age group	Thalassemic group (mean ± SD)		Control group (mean ± SD)	
(years)	P1.I	GI	P1.I	GI
6 – 11 (n = 23)	1.54 ± 0.44	1.30 ± 0.49	1.43 ± 0.63	1.24 ± 0.40
12 – 18 (n = 31)	1.74 ± 0.57	1.56 ± 0.69	1.67 ± 0.68	1.48 ± 0.61

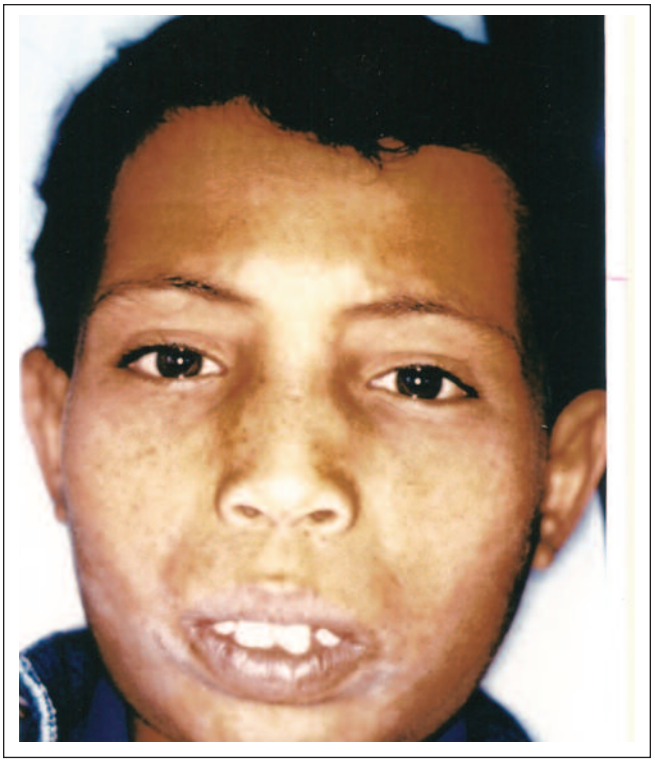

Figure 2. Profile view of a 13-year-old boy showing typical facial deformities in TM; characterized by frontal bossing, bulging cheek bone, saddle nose, and maxillary protrusion (chipmunk facies).

The prevalence of radiographic orofacial abnormalities in thalassemic group are presented in table 3 and depicted in figures 5 and 6.The majority of patients exhibited thickened frontal bone (66.7%) and thinned inferior border (cortex) of the mandible (64.6%) as measured in the region of the first molar. The thickness of mandibular cortex showed that 63.9% measured between 3 to 4 mm and 27.7% measured less than 3 mm in thickness. Only in four cases (8.3%) the thickness exceeded 4 mm. Enlarged marrow spaces, faint lamina dura, and small maxillary sinus were noted in 37.5 to 42.4% of the patients. Widened dipolic spaces, spiky short

Table 2. Prevalence of clinical orofacial complications in 54 thalassemic patients aged between 5.5 and 18.3 years.

Manifestations	Number	Percentage
Frontal bossing	33	61.1
Saddle nose	32	59.2
Lip incompetence	28	51.8
Discolored teeth	24	44.4
Dental and jaw pain	22	40.7
Pallor oral mucosa	21	38.9
Headache	16	29.6
Increased overjet	14	25.9
Maxillary protrusion	13	24.1
"Chipmunk" facies	9	16.7
Nasal airway problem	9	16.7
Lower lip paresthesia	7	13.0
Parotid gland enlargement	3	5.6

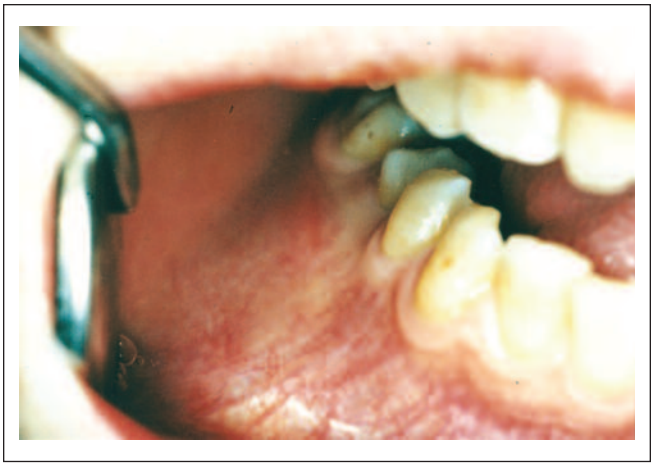

Figure 3. Yellow dental discoloration an dpallor oral mucosa in TM.

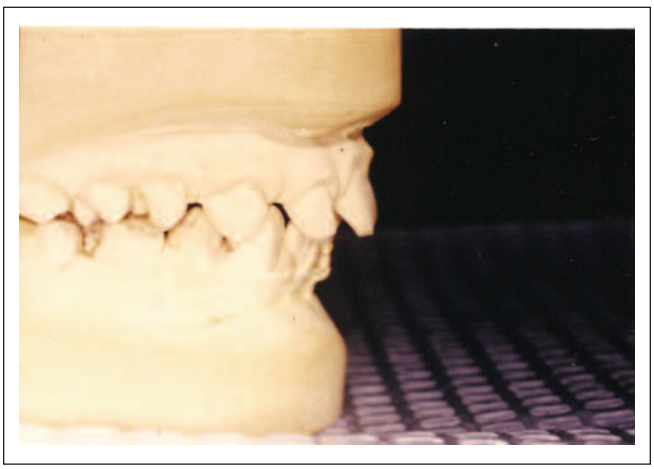

Figure 4. Dental cast showing increased overjet, faring of the maxillary incisors, spacing of teeth, and varying degrees of malocclusion.

roots, and thin borders of the mandibular canal were observed in one-third of the patients. Bony spicules may be seen as" hair-on-end" appearance at calvarium was uncommon finding. Orofacial changes became more pronounced with increasing age.

The linear and angular measurements of the mandible in the thalassemic and control groups are presented in Table 4 and depicted in Figure 1. The mean ramus length and width in thalassemic patients were reduced by 3.2 and 1.8 mm; respectively, compared with the control group. The differences were statistically significant ($P < 0.001$). The mean intercondylar distance in thalassemic group was reduced by 6.9 mm, with differences between the groups were not significant. Interestingly, the gonial angle was significantly larger in thalassemic than that in controls ($P < 0.001$).

DISCUSSION

Thalassemias are among the most common genetic disorders in the world. The course of illness in thalassemia major depends whether adequate blood-transfusion and other therapeutic facilities are available. If so, many patients survive to the fifth decade of life in developed countries.[19,20] The

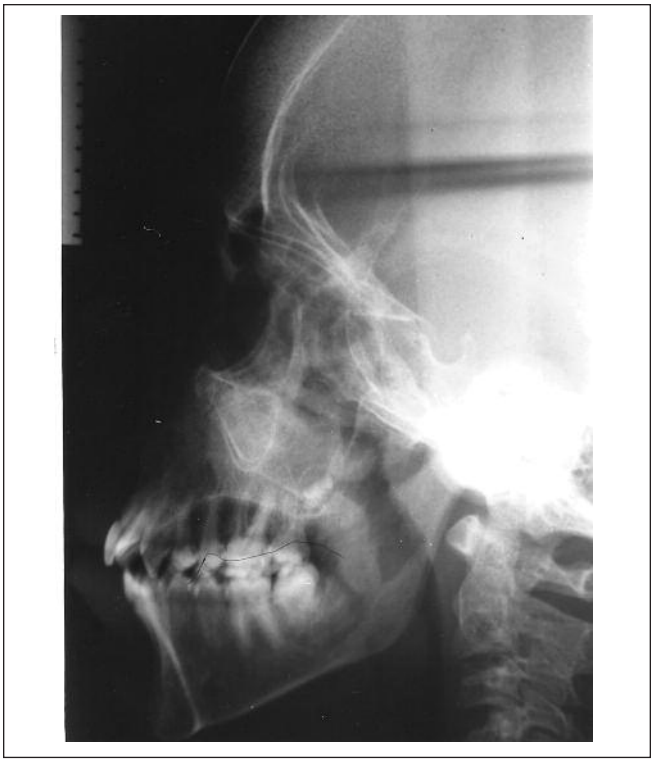

Figure 5. Cephalometric radiograph of a 15-year-old boy with thalassemia major disclosing thickened frontal bone thinned inferior border of the mandible, and prominent premaxilla. Note partially obliterated maxillary sinus and widened dipolic spaces in the frontal bone.

main causes of death are cardiac failure due to iron overload as a result of blood transfusional hemosidrosis. Infections constitute the second most common cause of mortality and a main cause of morbidity in thalassemic patients.

The present study showed that all periodontal parameters in thalassemic patients were higher than those in the controls. Only 7.8% of thalassemic patients showed no signs of gingivitis versus 25.2% in the controls. A study published in 1964. Kaplan *et al*[21] reported that 32% of thalassemic patients had gingivitis and 10% had periodontal pockets. As no indices were used in their study, direct comparison with the present findings is difficult. The means P1.I (1.57 ± 0.44) and GI (1.30 ± 0.49) in thalassemic subgroup aged 6-11

Table 3. Panoramic (n = 48) and lateral cephalometric (n = 33) radiographs showing the prevalence of oro-maxillofacial abnormalities in thalassemic groups.

Manifestations	Number	Percentage
Thickened frontal bone *	22	66.7
Thinned mandibular cortex **	31	64.6
Maxillary sinus hypoplasia*	14	42.4
Faint lamina dura**	19	39.6
Enlarged marrow spaces **	18	37.5
Widened dipolic spaces*	12	36.4
Spiky short roots **	16	33.3
"Hair-on-end" calvarium*	2	6.1

*Lateral radiographs, **Panoramic radiographs

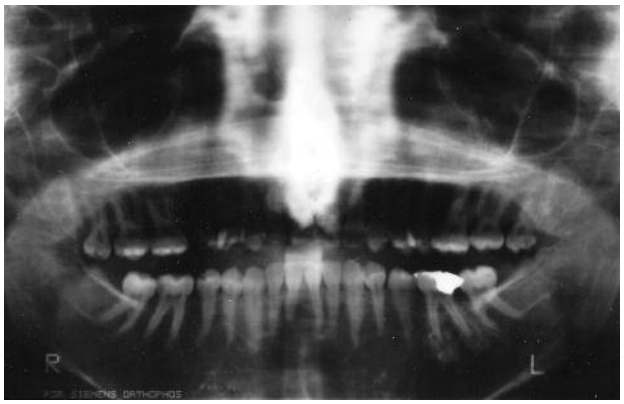

Figure 6. Panoramic radiograph of an 18-year-old thalassemic girl revealing spiky short roots, faint lamina dura and borders of the mandibular canal, and enlarged marrow spaces.

years (Table 1) are comparable with those reported in Iranian thalassemic sample, which showed mean P1.I and GI scores of 1.51 ± 0.62 and 1.36 ± 0.58, respectively.[22] Both studies did not found significant differences in P1.I, GI, and PPD scores between the thalassemic patients and the controls. The relatively high incidence of periodontal disease in thalassemic patients could primarily be related to local factors such as poor oral hygiene, malocclusion, drying of the gingival tissues due to lip incompetence. Systemic factors including lowered resistance to infection, nutritional deficiencies, and chronic anemia contributes to the complexity of etiology.

This study showed that two-third of the patients had frontal bossing, prominent malar bones, and saddle nose. Maxillary protrusion was evident in 24% of the patients. These changes cause in severe cases the typical thalassemic "chipmunk" facies appearance (Fig. 2). The orofacial disfigurements presented in this study are comparable to those reported in Greek TM patients who showed that 32% had normal appearance, 23% had mild maxillary overgrowth, and 14% displayed "rodent like facies".[3] In this study, discolored teeth and pallor oral mucosa were noted in 44.4% and 38.9% of the patients (Table 2, Fig. 3). Frequent occurrence of pallor oral mucosa was reported by Kaplan *et al*,[21] while de Mattia *et al* [23] found only three cases of the 60 thalassemic had pale atrophic mucosa. Half of the present cases exhibited lip retraction because of drifting of upper incisors due to enlargement of the premaxilla. A review of the literature reveals inconsistency regarding the degree and type of malocclusion in TM patients determined in clinical appearance or radiographic measurement. However, the high incidence of Class II malocclusion with increased overjet was reported in some studies.[5, 23-25] One of the explanation for these inconsistency could be derived from Scutellari *et al* [24] who demonstrated that all TM patients being treated with low transfusion regimes had dental and / or skeletal Class II malocclusion versus 40.7% of the adequately transfused patients had malocclusion. Piras *et al* [26] have shown that hypogonadism play an important role in determining the type of malocclusion in male thalassemic patients. To my knowledge no reports regarding the incidence of dental and jaw pain, headache, lower lip paresthesia, pain and swelling of the parotid gland are available to compare with the present findings. In a study on 25 patients with sickle cell anemia, Cox[27] found 36% of these patients experienced transitory pain in the oral-maxillofacial complex.

Craniofacial and skeletal changes in TM are characterized by widening of the marrow spaces and thinning of the cortices with consequent osteopenia or osteoporosis as a result of increased bone resorption, decreased mineralization, and decreased bone-forming sites.[1,28] The present radiographic analysis showed that the majority of the patients had thickened frontal bone and thinned inferior border (cortex) of the mandible. Enlarged marrow spaces, small maxillary sinus, thin lamina dura and faint inferior alveolar canal were found in more than one-third of the patients (Table 3). In a study on 16 thalassemic cases, Poyton and Darvey [29] reported that 88% of the cases had thickening of calvarium, faint lamina dura, and thin mandibular cortex. A high frequency of widened dipolic spaces (74%) and spiky roots (56%) was noted in their study. In a more recent study on 60 Thai thalassemic patients, Wisetsin [30] showed that 63.3% had thickening of frontal bone, 73.3% had thin mandibular cortex, 8.3% had " hair-on-end" calvarium, and 5% showed absence of maxillary sinus. It has been suggested that thinning of the inferior border of the mandible occur when the mandibular cortex measured 4 mm or less in contrast to a normal thickness of about 6 mm.[31] The differences in the frequency of manifestations associated with thalassemia major must be interpreted in the light of severity of anemia, the patient's age, sample size, the duration of clinical symptoms, the timing and frequency of blood transfusion and iron chelation therapy, bone marrow transplantation, and splenectomy. Basically, thalassemia is a disease in which

Table 4. Radiographic features of the mandible in 48 thalassemic patients and unaffected control group.

Variables	Thalassemia Mean ± SD	Control Mean ± SD	Difference between means	P-value
Linear measurements (mm)				
Ramus length	62.5 ± 4.8	65.7 ± 4.3	- 3.2	< 0.001
Ramus width	32.8 ± 2.6	34.6 ± 3.1	- 1.8	< 0.001
Intercondylar distance	195.4 ± 11.7	202.3 ± 10.9	- 6.9	NS
Angular measurements (°)				
Gonial angle	127.3 ± 7.4	121.5 ± 6.6	5.8	< 0.001

abnormalities are modulated by several genetic and environmental factors.

Radiographic measurements of mandibular dimensions (Table 4) revealed significant reduction in the ramus length and width of thalassemic patients compared with the controls. On contrary, the mean gonial angle in thalassemic patients was significantly greater than in controls (127.3 ± 7.4º versus 121.5 ± 6.7º). A previous study on healthy Jordanian sample showed a mean gonial angle measured 122.1 degrees.[18] Because the lack of studies on mandibular dimensional changes in thalassemia major, no comparison with the present findings could be made. However, cephalometric measurements of sicklic patients revealed a reduced ramus length of 1.8 mm and increased gonial angle of 4.5 mm compared with the unaffected control group.[32]

Primary management of patients with thalassemia major can be considered under four headings: transfusion therapy, iron chelation agents, splenectomy, and bone marrow transplantation. The goals of transfusion include correction of anemia, suppression of erythropoiesis, retard the development of splenomegaly, and inhibition of increased gut absorption of iron.[2,28] The most effective iron chelating agent currently available is deferoxamine (Desferal®). Regular folic acid supplements should be given to suppress erythropoiesis. Thalassemic patients should avoid foods that contain iron such as infant cereal, liver, oysters, pork, beef, beans, peas, and spinach. Foods that inhibit iron absorption are coffee, tea, chocolate, and soy products. Because osteoporosis is common in thalassemia, patients must obtain plenty of calcium with vitamin D. Dairy products are a good sources of calcium and they reduce iron absorption.

The evidence presented indicates that patients with thalassemia major are at risk for dental caries and periodontal disease. Therefore, patients should be maintained on a preventive program with regular follow-up. Oral hygiene instructions, diet counseling, and preventive measures including prophylaxis, fluoride application, and fissure sealant should be emphasized to minimize the need for extensive dental procedures. Correction of drifted maxillary anterior teeth and increased overjet should be undertaken to improve esthetics, reduce susceptibility to trauma, avoid gingival inflammation, and improve functional ability. It is recommended that orthodontic treatment be initiated as early as possible concentrating on preventive and interceptive approaches.

A patient who has had a splenectomy is at high risk of massive infection following bacteremia.[10,19] In such cases antibiotic prophylaxis similar to that used for the prevention of bacterial endocarditis should be used prior to invasive procedure. All splenectomized children under five years of age should be treated with prophylaxis antibiotics; oral penicillin 125 mg twice daily for children under two years, and 250 mg twice daily for children two years and over.[33] Children should receive immunization with pneumococcal vaccine and influenza vaccination after six months of age, and meningococcal vaccination after 2 years of age. Because thalassemic patients are at increased risk of viral hepatitis, appropriate precautions should be taken by the dental team when these patients are to be treated. Most patients with thalassemia major can be treated normally, using local anesthetic supplemented if necessary with inhalation sedation. Because of the possibility of impairing local circulation, short procedure can be performed using anesthetic without vasoconstrictor. However, if the procedure requires long, profound anesthesia, 2% Lidocaine with 1/100,000 epinephrine is the anesthetic of choice. Nitrous oxide can be safely used as far as the concentration of oxygen is greater than 50%, the flow rate is high, and the patient is able to ventilate adequately. General anesthesia is hazardous in this group of patients because of anemia hypoxia. Psychological adjustment should be considered to improve the quality of life, enabling patients to live normal life.[34] It is hoped that the present study will alert dental practitioners, especially working in multiracial communities to understand the nature of this disorder, its implication on the oral health and dental care.

CONCLUSSIONS

Thalassemia major produces a variety of signs, symptoms, and complications. Based on the present data, the following conclusions can be drawn:

1. All P1.I, GI, and PPD scores were higher in thalassemic group than in the control group. Only few thalassemic cases showed no signs of periodontal disease.
2. The most frequent orofacial complications in thalassemia major are frontal bossing and saddle nose, followed by dental and jaw pain, discolored teeth, pallor oral mucosa, headache, and maxillary protrusion. Nasal airway problem and lower lip paresthesia was reported by some patients.
3. Radiographic analysis revealed that most of the patients exhibited thickened frontal bone, thinned mandibular cortex and reduced ramus dimensions. Enlarged marrow spaces, faint lamina dura and small maxillary sinus were noted in 37.5% to 42.4%.
4. Manifestations of thalassemia major increased with age. Early diagnosis and management allow more favorable prognosis and minimize complication.

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