

Original

Patterns of physical growth and dental development in Jordanian children and adolescents with thalassemia major

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Abstract: Dental development and physical growth are of particular interest in pediatric dentistry and orthodontics. This study evaluated these variables in patients with thalassemia major (TM). Physical growth was assessed in 54 patients (31 males and 23 females) aged 5.5 to 18.3 years and dental development was analyzed using panoramic radiographs from 39 of the 54 patients. The Demirjian system was used to characterize dental development of the seven left mandibular permanent teeth. Chronologic age (CA) and dental age (DA) were compared using the paired t-test, and the correlation between CA and extent of delay in dental development (DA minus CA) was assessed using Pearson's correlation coefficients. Growth retardation (< 10th percentile for height and weight) was present in 75.9% of TM patients. Height less than the third percentile was noted in 41.9% (13/31) of males and 34.8% (8/23) of females. Mean (SD) body mass index was 16.5 ± 2.2 kg/m². The extent of growth retardation increased with advancing age. Patient radiographs revealed a delay in dental development in 31 of 39 (79.5%) of participants (mean delay, 1.12 years in males and 0.81 years in females; range, 0.1 to 2.7 years). The mean difference between CA and DA was 0.97 years ($P < 0.001$). CA was significantly correlated with extent of dental developmental delay ($r = 0.64$, $P < 0.01$). The results show that, among children and adolescents with TM, the proportions of those who had short stature, were underweight, and had a low growth rate increased with age. In addition, participants had significant delays in dental development. (J Oral Sci 55, 71-77, 2013)

Keywords: physical growth; dental development; thalassemia major.

Introduction

Thalassemia refers to a group of hemolytic anemia disorders that involve defects in the synthesis of hemoglobin α - or β -polypeptide chains (α - and β -thalassemia, respectively). It leads to decreased hemoglobin production and hypochromic microcytic anemia associated with erythrocyte dysplasia and destruction. The several subtypes of thalassemia present with diverse clinical characteristics. Due to its genetic heterogeneity and clinical and hematologic variability, thalassemia is classified as homozygous, heterozygous, or compound heterozygous. Homozygous β -thalassemia (also known as thalassemia major, Cooley anemia, or Mediterranean anemia) is associated with the most severe signs and symptoms, including marked orofacial abnormalities.

Thalassemia is one of the most common genetic disorders worldwide and presents major public health and social challenges in areas of high incidence. About 3% of the world's population carry the thalassemia gene (1,2). The disorder is most common among individuals of Mediterranean descent, particularly those living in southern Italy, Greece, and Cyprus, where prevalence is 10% to 15%. The disorder has also been described in Arab countries, Turkey, Iran, Southeast Asia, and Africa, with frequency in those regions ranges from 1.5% to 5% (1,2). In North America, thalassemia occurs primarily in people of Italian and Greek descent and in Blacks.

Thalassemia major (TM) is a life-threatening condition that commonly manifests during early infancy, after which progressive pallor, severe anemia, and failure to thrive are common. Children with TM often develop feeding problems, recurrent fever, bleeding tendencies



Fig. 1 Profile view shows typical facial features of thalassemia major, namely frontal and cheek bossing, saddle nose, and maxillary protrusion (chipmunk face).



Fig. 2 Cephalometric radiograph of patient with thalassemia major shows prominent premaxilla, causing drifting of incisors and excessive overjet with Class II malocclusion.

(especially epistaxis), susceptibility to infection, pathologic fractures of long bones and vertebrae, endocrine abnormalities, splenomegaly, lack of sexual maturation, and growth retardation (1-3). Hemoglobin level may be as low as 3 to 5 g/dL when a child with TM becomes symptomatic. To treat hypoxia symptoms, people with TM usually require blood transfusion in order to normalize hemoglobin level.

Skeletal and craniofacial deformities are the common manifestation of TM. They result primarily from hypertrophy and expansion of the erythroid marrow due to ineffective erythropoiesis (formation of erythrocytes). Orofacial changes in TM have described in earlier reports (4-8). TM patients are at high risk of dental caries (9,10) periodontal diseases (8,11) and oral infection (5,12). They also have smaller tooth crown (13), reduced dental arches dimensions (14), and dental discoloration due to chronic jaundice (15). The prevalence of orofacial changes in TM has been previously described (8,16).

Growth assessment is the best way to measure the health and nutritional status of children. Variations in growth patterns arise from a complex interaction of genetic, racial, and environmental variables. Dentition development is an integral aspect of craniofacial growth, even though it is only marginally related to other maturation processes and is less susceptible to environmental influences (17-19).

Dental maturity, expressed as dental age (DA), is a method for estimating age. In both pediatric dentistry and orthodontics, a child's growth and development status are especially important in diagnosis and treatment. In addition, assessment of dental development is one of the most reliable indicators of chronologic age (CA) and the most widely used in forensic and legal dentistry. Several methods of estimating dental maturity measure

the degree of calcification in radiographs of permanent teeth. The most widely used method was developed by Demirjian et al. (20), based on observation of the seven left mandibular teeth in children of French-Canadian descent and has been subsequently used in a number of different populations.

There are no published studies of physical growth and dental development in a single group of patients with thalassemia. This study examined the interrelationships among physical growth patterns, DA, and CA in Jordanian children and adolescents with TM.

Materials and Methods

The typical orofacial changes in TM patients include prominent frontal bossing and cheek bones, depression of the bridge of the nose, overgrowth of the maxilla, flaring of the maxillary anterior teeth, lip retraction, and malocclusion (Figs. 1 and 2).

Physical growth was assessed in 54 children and adolescents with TM (31 males and 23 females; age range, 5.5 to 18.3 years). Mean (\pm SD) age was 11.4 ± 3.1 for males and 12.1 ± 3.4 years for females (overall mean age, 11.6 ± 3.2 years). Patients were referred to a university clinic for dental examination by the regional thalassemia center. Ethical approval for the study was obtained from the Research Committee of Jordan University of Science and Technology (31/97, 1999), and consent was obtained from the parents of all participants. Family histories revealed that 41% of the patients were offspring of first-cousin marriage, 32% were offspring of second-cousin marriages, and 27% were offspring of distantly related or unrelated parents. The average number of siblings per family was 6.1, and 31% of siblings had TM. Panoramic radiographs were taken by an orthopantomograph (Orthophos-5, Siemens, Munich,

Table 1 Example of determining dental age using the Demirjian method (see Fig. 3).

a. Determining the developmental stage of 7 left mandibular permanent teeth, from A to H. The stages represent development from first appearance of calcified points (stage A) to apex closure (stage H)

Tooth	Stage
M2	D
M1	G
P2	D
P1	E
C	F
I2	G
I1	H

b. Conversion of developmental stages to maturity scores for boys

Tooth	A	B	C	D	E	F	G	H
M2	2.1	3.5	5.9	10.1	12.5	13.2	13.6	15.4
M1				8	9.6	12.3	17.0	19.3
P2	1.7	3.1	5.4	9.7	12	12.8	13.2	14.4
P1			3.4	7	11	12.3	12.7	13.5
C				3.5	7.9	10	11	11.9
I2				3.2	5.2	7.8	11.7	13.7
I1				0	1.9	4.1	8.2	11.8

c. Total dental maturity score = $10.1 + 17.0 + 9.7 + 11.0 + 10.0 + 11.7 + 11.8 = 81.3$

d. A total dental maturity score of 81.3 is equivalent to a DA of 8.7 years (according to the Demirjian method), which is then compared to CA. In this example, a delay in dental development of 1.1 years was estimated in a boy aged 9.8 years with thalassemia.

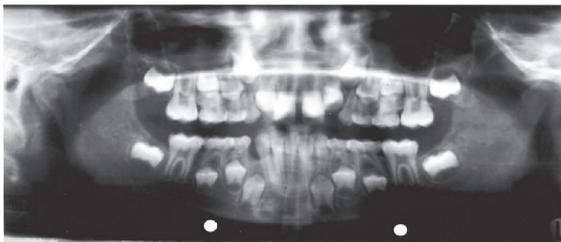


Fig. 3 Panoramic radiograph of boy with thalassemia aged 9.8 years used in the example of determining dental age in Table 1.

Germany), at a magnification factor of 1.3. The criteria for selecting patient radiographs were high quality and sharpness and no extraction or agenesis of a tooth in the mandible. Of the 54 patient radiographs, 39 (22 males, 17 females; mean age, 10.5 years; age range, 5.5–16.4 years) were used in the analysis of dental development.

Height was measured using a wall-mounted stadiometer with the patient standing erect with shoes off and feet together and heels, buttocks, and upper back pressed against a wall. After removal of shoes and heavy clothing, body weight was measured on a digital scale to the nearest 0.1 kg. Body mass index (BMI) was estimated as body weight in kilograms divided by the square of the height in meters (kg/m^2). The physical growth patterns of

the participants were compared with the standard growth chart for Jordanian schoolchildren.

Dental development, defined from first appearance of calcified points to apex closure, was assessed according to the method of Demirjian et al. (20). The seven left mandibular permanent teeth (second molar to central incisor) of each participant were rated on an eight-stage scale of dental maturity (A to H, Table 1a). The stages describe dental development from first appearance of calcified points (stage A) to apex closure (stage H). The sum of the scores for all seven teeth was used to describe dental maturity, which was converted to DA by using a conversion table and/or percentile curve (Table 1b-d). An example of determining dental age using the Demirjian method is shown in Fig. 3 and Table 1 a-d. CA was calculated by subtracting the date of the panoramic radiograph from the date of birth. Decimal ages were estimated on yearly basis; e.g., 9 years and 8 months was expressed as 9.7 years.

Statistical analysis

The difference between mean DA and CA among the 39 sample pairs was analyzed using the paired *t*-test. In addition, Pearson's correlation coefficients (*r*) were calculated to describe correlations between the extent of the delay in dental development and CA.

Table 2 Mean (\pm SD) growth measurements, number (n) of patients with thalassemia major (TM) in each age group, and corresponding values on the Jordanian standard chart (sexes pooled)

Age (Years)	n	Weight (kg)		Height (cm)		BMI (kg/m ²)	
		TM	standard	TM	standard	TM	standard
6-7	9	18.2 \pm 2.1	20.4	113 \pm 7.7	118	14.1 \pm 2.1	14.7
8-9	12	21.9 \pm 3.0	25.6	122 \pm 6.9	128	14.7 \pm 2.3	15.6
10-11	14	25.6 \pm 2.4	31.1	127 \pm 6.6	136	15.5 \pm 1.9	16.8
12-13	10	29.7 \pm 3.2	40.2	133 \pm 7.5	148	16.7 \pm 2.4	18.2
14-15	6	34.5 \pm 2.1	51.0	139 \pm 7.7	160	17.8 \pm 2.7	19.7
16-18	3	38.6 \pm 3.5	61.8	143 \pm 8.1	168	18.7 \pm 3.5	21.9

Table 3 Growth measurements of patients with thalassemia major, by sex and proportions of patients with values less than the third and tenth percentiles on the Jordanian standard growth chart

Variables	Males ($n = 31$)			Females ($n = 23$)		
	Mean \pm SD	3% tile	10% tile	Mean \pm SD	3% tile	10% tile
Weight	27.7 \pm 4.3	18/31	21/31	27.9 \pm 5.9	9/23	10/23
Height	128.6 \pm 10.5	13/31	20/31	126.7 \pm 11.2	8/23	12/23
BMI	16.3 \pm 1.8	12/31	–	16.9 \pm 2.3	7/23	–

Table 4 Comparison of chronologic age (CA) and dental age (DA) in patients with thalassemia major

Age Group	CA Mean \pm SD	DA Mean \pm SD	Mean differences (DA minus CA)
Male ($n = 22$)			
5.5-6.8	6.1 \pm 0.65	5.9 \pm 0.43	-0.2
7.0-7.9	7.5 \pm 0.50	7.1 \pm 0.47	-0.4
8.4-9.2	8.9 \pm 0.57	9.1 \pm 0.68	0.2
9.6-10.7	10.5 \pm 0.68	9.6 \pm 0.54	-0.9
11.5-12.4	11.8 \pm 0.61	10.0 \pm 0.63	-1.8
13.3-14.1	13.7 \pm 0.79	12.1 \pm 0.71	-1.6
15.0-16.4	15.7 \pm 0.85	13.5 \pm 0.96	-2.2
Female ($n = 17$)			
5.8-6.7	6.5 \pm 0.75	6.8 \pm 0.81	0.3
7.4-7.9	7.8 \pm 0.69	7.7 \pm 0.67	-0.1
8.8-9.6	9.3 \pm 0.61	9.1 \pm 0.96	-0.2
10.0-10.6	10.4 \pm 0.78	10.0 \pm 0.72	-0.4
11.2-12.5	11.4 \pm 0.73	10.5 \pm 0.76	-0.9
12.8-13.9	13.1 \pm 0.82	11.9 \pm 0.65	-1.2
14.7-18.3	15.3 \pm 0.94	13.3 \pm 0.86	-2.0

Results

Table 2 compares the weight, height, and BMI, by age group, of the participants with the respective values from the standard Jordanian growth chart. Growth retardation was evident in all participant age groups: the values for 75.9% (41/54) of participants were less than the 10th percentiles of weight and height. The data show that growth retardation was worse in patients older than 10 years: 45.4% of patients aged 6-10 years had heights less than the third percentile, as compared with 68.7%

of patients older than 10 years. As shown in Table 3, the mean (\pm SD) weight and height of patients with thalassemia were 27.7 \pm 4.3 kg and 128.6 \pm 10.5 cm, respectively, for males and 27.9 \pm 5.9 kg and 126.7 \pm 11.2 cm for females. Approximately 41.9% (13/31) of males and 34.8% (8/23) of females had heights-for-age less than the third percentile. The weights of 58.1% (18/31) of males and 39.1% (9/23) of females were less than the third percentiles.

The mean BMI of participants ranged from 14.1 to 18.7 (kg/m²), as compared with a range of 14.7 to 21.9 kg/m² on the standard chart (Table 2). As shown in Table 3, the mean (\pm SD) BMI was 16.3 \pm 1.8 kg/m² for males and 16.9 \pm 2.3 kg/m² for females (overall mean, 16.5 \pm 2.2 kg/m²). BMI was less than the 10th percentile in 38.7% (12/31) of males and 30.4% (7/23) of females. BMI was less than the 10th percentile in 21.6% of participants younger than 10 years versus 37.2% of those older than 10 years. No significant sex differences were found with respect to growth data.

Differences between mean CA and DA, by age subgroup, are shown in Table 4. Twelve of the 14 age subgroups showed delay in dental development. Of the 39 patients, 31 (79.5%) had delayed dentition development. The difference between CA and DA ranged from 0.1 to 2.7 years. Mean (\pm SD) delay in dental development was 1.12 \pm 0.58 years in males and 0.81 \pm 0.53 years in females. The difference of 0.31 years between sexes was statistically insignificant. The difference between mean CA and DA showed a delay in dental development of 0.97 years relative to CA ($P < 0.001$, $df = 38$). As compared

with males, females had more-advanced formation of dentition. A significant correlation was found between the extent of delay in dental development and CA ($r = 0.64$, $P < 0.01$), which indicates that the delay increased with advancing age. The association between DA and CA was stronger than that between DA and body growth ($r = 0.87$ vs. 0.58).

Discussion

Thalassemia major is a serious medical, social, and psychological problem. The course of illness depends on the availability of adequate blood transfusion and other therapeutic facilities. When such treatments are given, many patients in developed countries survive to the fifth decade of life (21). Through their effects on bones and growth, chronic anemia and gross bone marrow expansion due to ineffective erythropoiesis lead to development of most of the characteristic clinical features of TM. The cause of growth retardation in children with TM is multifactorial and includes chronic anemia and hypoxia, iron overload, low somatomedin activity, endocrinopathies, low socioeconomic status, and racial factors (1,22,23). As compared with their peers, children and adolescents with TM are less satisfied with their bodies and have more symptoms of anxiety and depression, which is reflected in their social activities and education (24).

There was a marked delay in physical growth in the present participants, which became obvious after age 10 years (Table 2). Growth less than the third percentile of height-for-age was present in 41.9% of males and 34.8% of females (Table 3). In general, the present participants were underweight, as indicated by their low BMI (average 16.5 kg/m^2 vs $18.5\text{-}25 \text{ kg/m}^2$ for healthy individuals, according to reference values from the World Health Organization/Centers for Disease Control). First- and second-cousin marriage was noted in as many as 73% of the families of participants. A previous study of consanguineous marriage in Jordan showed first- and second-cousin marriage in 39%, marriage of distant relatives in 11%, and marriage of unrelated individuals in 50% of families (25).

A review of the literature reveals some inconsistency regarding the age at which growth retardation occurs in children with TM. Some reports found that slowing of growth was more evident as puberty approached (26,27), while others noted a tendency for retarded growth at age 8-10 years (28,29). In a recent study of Indian children with TM, Saxena (23) reported marked growth retardation in height and weight after age 11 years in boys and after age 9 years in girls. She found that bone age retardation in TM increased with age and that it started much

earlier than height and weight retardation. Lapatsanis et al. (30) noted that half of children aged 5-7 years with thalassemia had bone retardation (> 6 months), whereas age retardation was found in almost two-thirds of older children.

Physical growth patterns of individuals with TM have been studied in a number of populations. Borgna-Pignatti et al. (26) reported that, among 250 Italian adolescents with TM, 62% of males and 35% of females had short stature, and 83% of males and 75% of females had delays in skeletal maturation. Kattamis et al. (27) reported that 21.7% of males and 13% of females had growth retardation among a group of 405 Greeks with TM; the highest incidence of growth retardation was among those aged 15-20 years. A study of 68 Chinese children with TM in Hong Kong showed that 75% of girls and 62% of boys older than 12 years were below the third percentile of height (31). The present study showed that BMI was less than 10th percentile in 21.6% of patients younger than 10 years versus 37.2% of those older than 10 years. A study of 565 Iranians with TM revealed that BMI was less than the 10th percentile in 12.4% of those younger than 10 years and 46.5% of those older than 10 years (32). This considerable variation in the prevalence of growth retardation among TM patients must be interpreted in the light of anemia severity, timing and frequency of blood transfusion, age at initiation of iron chelation therapy, bone marrow transplantation, and socioeconomic background. In addition, thalassemia is a disease in which manifestations are modulated by several genetic, racial, and environmental factors.

There was a significant delay in dental development among the present participants. Further, there was a significant correlation between the extent of this delay and CA, which indicates that the delay increases as the patient gets older. Studies have shown a low correlation between dental maturity and physical development, which suggests that dental development is less influenced than somatic development by environmental factors (17-19). Greater delays in skeletal maturation than in dental development were found in children with major abnormalities affecting growth such as anemia, hypothyroidism, hypopituitarism, short familial stature, and cerebral palsy (17,19,33). Garn et al. (17) found that the extent of delay in dental development was approximately one-third that of skeletal delay. Evidence indicates that dental development is more closely related to CA than to skeletal, somatic, or sexual-maturity indicators (17-19). The present results show that dental development in the participants better correlated with CA than with variables for physical growth. In parallel with the general growth

retardation and delay in the dental development found in this study, a significant reduction in tooth crown size and dimensions of dental arches was reported in patients with thalassemia (13,14). Pediatric dentists and orthodontists must be mindful of both the growth patterns associated with thalassemia and the effects that delays in dental development have on diagnosis and treatment timing.

In conclusion, most (75.9%) of the present patients with thalassemia had height and weight growth less than the 10th percentile. In addition, BMI was less than the 10th percentile in 25.8% of males and 21.7% of females, and growth retardation worsened with advancing age. There were no significant sex differences in growth parameters. Moreover, dentition development (DA) in patients with thalassemia was significantly delayed (average, 0.97 years) relative to CA, and the delay was greater in males than in females with thalassemia (difference, 0.31 years). Dental development was more advanced in females had in males. The association between DA and CA was stronger than that between DA and body growth ($r = 0.87$ vs. 0.58).

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