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Original Article

Assessment of mandibular characteristics in patients affected with β-thalassaemia major: A retrospective case-control study

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Summary

Objective > Thalassemia is the most common hereditary blood disorder across the world. This study aimed to identify some mandibular features of thalassaemic patients and compare them with unaffected counterparts.

Material and methods > This retrospective case-control study was carried out on lateral cephalograms of 60 subjects (26 males, 34 females) with class II malocclusion and age range of 11 to 15 years. The control group consisted of 60 non-thalassaemic subjects with class II malocclusion and similar chronological age, gender and vertical facial dimension. Based on the Jarabak index, the case and control subjects were classified into hyperdivergent, normodivergent and hypodivergent growth patterns. Four linear (ramus height, ramus width, mandibular depth, and antegonial notch depth) and 3 angular (symphyseal angle, gonial angle, and mandibular arc angle) cephalometric parameters were measured to represent mandibular morphology. The data were analysed using Chi-square test and Student's t-test.

Results > No significant difference was found in linear measurements between thalassaemic patients and controls. The symphysis angle was significantly greater and the mandibular arc angle was significantly smaller in the total thalassaemic sample than the control individuals ($P < 0.001$ and $P = 0.004$, respectively). The difference in symphysis angle was significant in both hyperdivergent and normodivergent subjects ($P = 0.004$ and $P = 0.002$, respectively), whereas the difference in mandibular arc angle was only significant in the normodivergent subgroup $P = 0.001$).

Conclusions > The smaller mandibular arc angle in the thalassaemic sample suggests a more superior than posterior growth direction of condyles compared with healthy individuals. The difference in symphyseal angle represents inherent differences in chin morphology between thalassaemic subjects and controls.

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Introduction

Thalassemia is the most common hereditary blood disorder across the world [1]. It affects the growth of the maxillofacial complex and causes great aesthetic concerns for affected subjects. The disease has a high prevalence in a broad area including the Mediterranean region, parts of Africa, the Middle East, the Indian subcontinent, Southeast Asia, and Melanesia [2–4]. The carrier frequency for β-thalassemia has been estimated to be between 1 to 20% in these areas [2].

Patients with β-thalassemia present systemic manifestations due to the chronic anaemia and the resultant hypoxia. Iron accumulation as a result of frequent blood transfusions can lead to organ failure in many patients [5]. The involvement of endocrine glands results in skeletal retardation and developmental defects [4,6,7]. Bone marrow expansion is the characteristic feature of individuals with β-thalassemia major [3] that creates an expanded skull together with an overgrown and protruded maxilla; rendering a facial appearance that has been termed as "chipmunk facies" or described as a "rodent face" [8–11]. Other common facial malformations in thalassaemic subjects are nasal bridge depression, malar bone prominence, partial obliteration of maxillary sinuses, and thinning of mandibular cortices [3,4,2–15].

Previous studies demonstrated that thalassaemic subjects usually present skeletal class II malocclusion with vertical growth tendency [3,4,16–20]. Increased anterior facial height (AFH) and decreased posterior facial height (PFH), anterior dental open bite, increased overjet, and generalized dental spacing are among other frequent orthodontic complaints of thalassaemic patients [3,4,16,18]. However, there is controversial information regarding mandibular features of patients with β-thalassemia major. Some studies attributed the class II discrepancy mainly to maxillary protrusion [6,8,14]; whereas others reported that the mandible of thalassaemic patients was smaller in size and more retruded in the face as compared to unaffected individuals [3,4,16].

Until the recent advances in the field of medical management, thalassaemic subjects rarely survived beyond their twenties due to the complications caused by iron overload in multiple organs [18]. Along with the extended life expectancy, there is a strong willingness towards orthodontic treatment to alleviate facial abnormalities associated with the disease and promote dental and smile aesthetics [21]. It is clear that the biomechanics of orthodontic treatment is in close relation to the amount/direction of the maxillofacial growth. In other words, different responses are expected following orthodontic treatment in patients with different vertical skeletal patterns [22]. Noticeable vertical growth direction of the face is a frequent finding in thalassaemic patients, however normal and reduced vertical growth may also be found in affected subjects; though not usually mentioned in the literature. There is limited research concerning condylar growth direction and mandibular manifestations of the disease in β-thalassemia patients. Therefore, the present study was undertaken to identify some mandibular features of β-thalassaemic patients with different skeletal growth patterns and compare them with unaffected counterparts.

Material and methods

Subjects

This retrospective case-control study was carried out on lateral cephalograms of 60 subjects with β-thalassemia major referring to the Department of Orthodontics, School of Dentistry, Shiraz University of Medical sciences, Shiraz, Iran. The selected patients had Angle class II malocclusion and were in the age range of 11 to 15 years. The sample size was determined according to the available records present in the Department of Orthodontics of Dental School. The control group consisted of 60 non-thalassaemic subjects with class II malocclusion and similar chronological age, sex and vertical facial pattern, and their pre-treatment records were recruited from the Department of Orthodontics of the same centre. The exclusion criteria were the poor quality and clarity of cephalograms, a positive history of trauma to the mandible, the presence of asymmetry, and the background of previous orthodontic treatment. Considering the inclusion and exclusion criteria, the final sample consisted of 34 females and 26 males in the thalassaemic group with the mean age of 13.0 $\pm$ 1.66 years. In the non-thalassaemic control group, there were 32 females and 28 males with the mean age of 13.1 $\pm$ 1.70 years. The protocol of the study was reviewed and approved by the Ethics committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1394.9504).

Cephalometric analysis

Lateral cephalograms were taken by Planmeca X-ray unit (Planmeca ProMax® Helsinki, Finland) under standard conditions using 60–84 kV anode voltage, 1-16 mA anode current, and 0.2-5 s exposure time. Each patient was asked to hold the head in natural head position (NHP) with lips in a relaxed position and teeth in centric occlusion. The cephalograms were then digitized by a table scanner (Microtech 800; Microtek International Inc., Carson, CA, USA) in 300 Dpi and imported to the AutoCAD 2007 software (Autodesk Inc., CA, USA) for analysis. The landmarks were identified by two oral and maxillofacial radiologists and the linear and angular measurements were recorded to the nearest 0.5 mm and 0.5°, respectively. One week after the data collection, 20% of the cephalometric radiographs were randomly selected and measured again by both radiologists to calculate the intra- and inter-examiner reliability by intraclass correlation coefficient (ICC).

Classification of vertical facial pattern

The anterior facial height (AFH) was determined by measuring the distance between points Nasion (N) and Menton (Me) and the posterior facial height (PFH) by measuring the distance between points Sella (S) and Gonion (Go). Based on the Jarabak index (the ratio of PFH to AFH), the case and control subjects were classified into the following growth patterns [22]:

- hyperdivergent growth pattern: Jarabak index < 62%;
- normodivergent growth pattern: Jarabak index = 62–65%;
- hypodivergent growth pattern: Jarabak index > 65%.

Identification of cephalometric landmarks

The following landmarks were identified and marked on the cephalograms (*figure 1*a). If bilateral landmarks were not overlapped, the middle points between the right and left images were assumed.

Articular (Ar): a point of intersection between the posterior border of the ramus and the inferior border of the posterior cranial base (occipital bone).

Basion (Ba): the lowest point on the anterior margin of the foramen magnum.

Nasion (N): the most anterior point on the frontonasal suture in the midsagittal plane.

Sella (S): The centre of the Sella turcica.

Porion (Po): the most superiorly positioned point of the external auditory meatus located by using the ear rods of the cephalostat (mechanical Po).

Orbitale (Or): the lowest point on the inferior rim of the orbit.

Point A (A): the most posterior midline point in the concavity between the anterior nasal spine (ANS) and the prosthion.

Pterygomaxillare (PTM): the contour of the pterygomaxillary fissure formed anteriorly by the retromolar tuberosity of the maxilla and posteriorly by the anterior curve of the pterygoid process of the sphenoid bone. The lowest point of the opening is used.

Point B (B): the deepest point in the concavity of the anterior border of the mandible between the alveolar crest and the chin.

Pogonion (Pog): the most anterior point of the symphysis.

Menton (Me): the most inferior point of the symphysis.

Gnathion (Gn): the midpoint of the symphysis outline between Pogonion and Menton.

Suprapogonion or Protuberance menti (Pm): a point at which symphysis mentalis changes from convex to concave.

Gonion (Go): the most posterior, inferior point on the angle of the mandible.

Dc point (Dc): the centre of the condylar neck along the Ba-N line.

Xi: A point located at the geometric centre of the ramus. The location of the Xi point is keyed geometrically to the Frankfort horizontal (FH) and the pterygoid vertical planes (PtV). To define the Xi point, first draw FH and then draw PtV plane perpendicular to the FH. Construct four planes tangent to points R1, R2, R3, and R4 on the borders of the ramus. These planes are parallel to FH and PtV. The constructed planes form a rectangle enclosing the ramus. Xi point is located at the intersection of the diagonals.

R1-mandible: the deepest point on the anterior border of the ramus.

R2-mandible: a point located on the posterior border of the ramus of the mandible, opposite to R-1.

R3-mandible: the deepest point and the centre of the sigmoid notch of the mandibular ramus.

R4-mandible: a point on the inferior border of the mandible, opposite to R3.

Determination of mandibular linear parameters

Four linear cephalometric parameters were selected to represent mandibular morphology. The linear measurements included in the study have been presented in *figure 1*b and were as follows:

- ramus height: the distance between points Articular (Ar) and Gonion (Go);

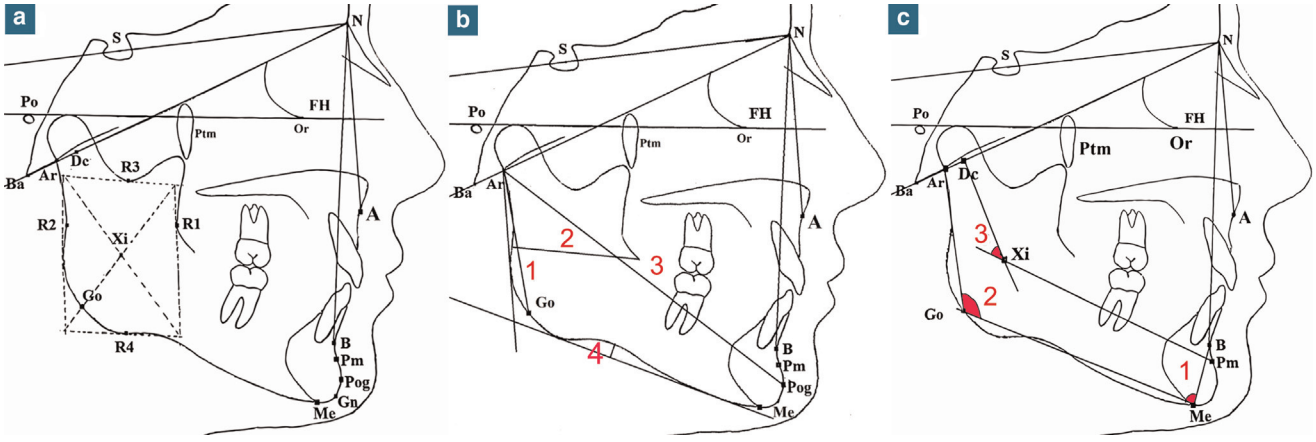

FIGURE 1

The cephalometric tracing of a 12-year-old boy with beta-thalassemia major. a: reference points; b: skeletal linear measurements used 1. Ramus height; 2. Ramus width; 3. Mandibular depth; 4. Antegonial notch depth; c: angular parameters in the present study: 1. Symphysis angle; 2. Gonial angle; 3. Mandibular arc angle

- ramus width: the distance between anterior and posterior borders of the ramus at the height of the occlusal plane;
- mandibular depth: the distance between points Articular (Ar) and Pogonion (Pog);
- antegonial notch depth: the perpendicular distance between the most concave part of the notch and a tangent through the two points of greatest convexity on the inferior border of the mandible, at either side of the notch.

Determination of mandibular angular parameters

Three angular cephalometric parameters were selected to represent mandibular morphology. The angular measurements included in the study have been presented in *figure 1*c and were as follows:

- symphyseal angle: posterosuperior angle between the mandibular plane (Go-Me) and the plane formed by Menton (Me) and point B;
- gonial angle: the angle formed between Articular (Ar)-Gonion (Go) and mandibular (Go-Me) planes;
- mandibular arc angle: the posterosuperior angle formed by the points Dc, Xi, Pm at Xi.

Statistical analysis

The normality of the data was confirmed by the Kolmogorov-Smirnov test ($P > 0.05$). The Chi-square test and Student's t-test were applied to compare the sex ratio and mean age between the patients with β-thalassemia major and unaffected controls, respectively. The student's t-test was also employed to compare the mandibular indices between the two study groups and different subgroups. The data obtained were analysed using the statistical package for the social sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA) and the significance level was set at $\alpha = 0.05$. The Bonferroni correction was implemented to control for the inflation of type I error due to multiple t-tests usage, and alpha of 0.05 was divided by the total number of t-tests used. This resulted in a modified alpha of 0.0031 for linear measurement, since 16 t-tests were employed. For the angular measurements, the adjusted alpha was 0.0041 considering 12 comparisons.

The Cohen's effect size (EF) was computed for all variables, and in cases that the effect size was moderate to large, the power value was calculated. It was revealed that the power was ≥ 0.80 in these cases, indicating sufficient sample size.

TABLE I

The mean, standard deviation (SD) and significance of the mandibular linear measurements between β-thalassemic patients and controls according to the vertical skeletal pattern.

		Thalassemia group	Control group	*P*-value*
Linear measurements mm	Vertical pattern	Mean ± SD	Mean ± SD	
Ramus height	Hyperdivergent	3.83mm ± 0.4	3.82 mm ± 0.62	0.881
	Normodivergent	3.98 mm ± 0.43	3.93 mm ± 0.2	0.705
	Hypodivergent	4.41 mm ± 0.46	4.3 mm ± 0.56	0.580
	Total	4 mm ± 0.47	3.95 mm ± 0.56	0.611
Ramus width	Hyperdivergent	2.76 mm ± 0.32	2.71mm ± 0.32	0.485
	Normodivergent	2.9 mm ± 0.32	2.8 mm ± 0.16	0.292
	Hypodivergent	2.93 mm ± 0.16	2.95 mm ± 0.21	0.782
	Total	2.83 mm ± 0.30	2.78 mm ± 0.28	0.333
Mandibular depth	Hyperdivergent	8.88 mm ± 0.97	8.82 mm ± 1.3	0.834
	Normodivergent	8.87 mm ± 0.43	9.14 mm ± 0.58	0.170
	Hypodivergent	9.31 mm ± 0.57	9.34 mm ± 0.71	0.890
	Total	8.97 mm ± 8.0	9.01 mm ± 1.07	0.831
Antegonial notch depth	Hyperdivergent	0.19 mm ± 0.07	0.17 mm ± 0.07	0.191
	Normodivergent	0.21 mm ± 0.06	0.21 mm ± 0.21	0.331
	Hypodivergent	0.23 mm ± 0.2	0.2 mm ± 0.23	0.774
	Total	0.20 mm ± 0.11	0.18 mm ± 0.15	0.450

The level of type I error was adjusted regarding the number of comparisons.
*$P < 0.0031$ indicates a statistically significant difference.

Table II

Means, standard deviations (SD) and significance of the mandibular angular measurements between β-thalassemic patients and controls according to the vertical skeletal pattern.

		Thalassemia group	Control group	*P*-value
Angular measurements	Vertical pattern	Mean ± SD	Mean ± SD	
Symphysis angle	Hyperdivergent	81.1° ± 4.67	77.48 ± 4.97	0.004*
	Normodivergent	83.87° ± 5.59	75.27 ± 7.5	0.002*
	Hypodivergent	80.57° ± 5.58	80.6 ± 5.7	0.981
	Total	81.68° ± 5.18	77.64 ± 5.97	< 0.001*
Gonial angle	Hyperdivergent	135.7° ± 4.61	134.5 ± 4.91	0.315
	Normodivergent	132° ± 4.95	131.3 ± 4.5	0.672
	Hypodivergent	127.6° ± 6.11	124.6 ± 6.05	0.211
	Total	133° ± 5.93	131.6 ± 6.36	0.203
Mandibular arc angle	Hyperdivergent	24.6° ± 3.86	26.46 ± 6.37	0.157
	Normodivergent	23.7° ± 4.97	30.53 ± 4.65	0.001*
	Hypodivergent	30.68° ± 4.61	33.42 ± 7.6	0.286
	Total	25.6° ± 5.01	28.92 ± 6.85	0.004*

*$P < 0.0041$ indicates a statistically significant difference. The level of type I error rate was adjusted regarding the number of comparisons.

Results

There was a meaningful correlation between the data obtained at two measurements ($P < 0.05$). The correlation coefficients ranged from 0.81 to 0.98, indicating excellent intra- and inter-rater reliability. The narrowest 95% confidence interval belonged to intra-rater agreement for the ramus height (0.89–0.98) and the widest belonged to inter-rater agreement for the mandibular arc angle (0.81–0.97).

From the 60 thalassaemic adolescents, 32 were hyperdivergent, 15 were normodivergent, and 13 were hypodivergent, with the mean Jarabak indices of 57.97 ± 0.03, 62.80 ± 0.01, and 67.30 ± 0.02 percent, respectively. In the control group, there were 33 hyperdivergent, 14 normodivergent, and 13 hypodivergent subjects, and the corresponding Jarabak indices were 58.43 ± 0.04, 63.47 ± 0.00 and 69.70 ± 0.04 percent, respectively. There was a similar distribution of the three growth patterns in both groups. No significant differences were found in the mean age ($P = 0.580$) and sex ratio ($P = 0.714$) between the two groups. *Tables I and II* present the mean, standard deviation (SD) and significance of the linear and angular mandibular parameters in β-thalassaemic patients and controls in the total sample as well as the three vertical growth pattern subgroups. No significant difference was found in the linear measurements including ramus height, ramus width, mandibular depth and antegonial notch depth between the thalassaemic patients and controls ($P > 0.0031$; *table I*).

Concerning the angular measurements (*table II*), the gonial angle was statistically comparable between the two groups ($P > 0.0041$). The symphysis angle was significantly greater in adolescents with β-thalassemia major when compared to controls ($P < 0.001$), whereas the mean value of mandibular arc angle was significantly smaller in thalassaemic than the control individuals ($P = 0.004$). When the differences in symphysis and mandibular arc angles between the two groups were analysed according to the vertical growth pattern, it was revealed that the difference in symphysis angle was significant in both hyperdivergent and normodivergent subjects ($P = 0.004$ and $P = 0.002$, respectively) whereas the difference in mandibular arc angle was only significant in normodivergent subgroup ($P = 0.001$).

Discussion

In the present study, some mandibular parameters of individuals affected with β-thalassemia major and different facial types were compared with non-affected counterparts. The patients fell in the age range of 11 to 15 years as this is the most common time period that patients refer for orthodontic treatment. The study groups were matched regarding sex ratio to compensate for differences in skeletal development between genders. The thalassaemic subjects were classified into three subgroups including hypodivergnt, normodivergent and hyperdivergent according to the Jarabak index. The control group of this study

was selected in a way to ensure comparable vertical skeletal patterns to the thalassaemic patients in order to investigate whether any observed difference between the groups is due to the disease itself or to the accompanying facial growth direction. The percentage of subjects who showed hyperdivergent pattern was greater in the sample. This is in agreement with the outcomes of previous authors who found that subjects with β-thalassemia major predominantly show a vertical growth tendency in the maxillomandibular region and an increase of lower anterior facial height [3,4,19].

The outcomes of this study revealed no significant difference in mandibular linear parameters between subjects with β-thalassemia major and unaffected controls. The ramal height, ramal width, and antegonial notch depth were comparable between the groups as well as the mandibular depth (Ar-Pog), which was considered representative for corpus size. Using panoramic radiography, Hazza'a and Al-Jamal [12] reported that thalassemia was not associated with the occurrence of prominent antegonial notch. It has been demonstrated that the most prevalent craniofacial pattern among thalassaemic patients is class II skeletal relationship with strong vertical growth direction [3,4,16–20]. However, there is a controversy regarding maxillary versus mandibular contribution to class II malocclusion. The outcomes of this study revealed that ramus height and width as well as the size of the mandibular corpus were not significantly different between thalassaemic subjects and healthy controls. The outcomes of this study contradict the results of some previous investigators who reported that the mandible of thalassaemic patients tended to be more retruded in the face and the chin was in a posterior position [3,4]. Toman et al. [16] reported that the class II malocclusion in thalassaemic subjects is caused by a smaller mandibular body and is further complicated by a short ramus. Abu Alhaija et al. [18] displayed that the mandibular base length (Ar-Gn) was significantly smaller in thalassaemic subjects. Hattab [23] indicated that the ramus length and width were significantly smaller in patients with β-thalassemia major compared to controls. It should be noted that this study is comprised of subjects with class II malocclusion and similar vertical skeletal patterns in the case and control groups, whereas other authors did not match thalassaemic subjects with the control group in the sagittal and vertical plans [3,4,16,18]. Therefore, these findings should be interpreted within the context of the inclusion criteria of the study.

Comparison of mandibular angular parameters between thalassaemic patients and controls revealed no significant difference in gonial angle, but mandibular arc angle and symphysis angle were significantly different between the two groups. Numerous studies exhibited that the most important factor that affects the gonial angle is the vertical growth pattern [22,24–26]. Since we matched the groups with respect to the facial type, the lack of difference in gonial angle between the groups would be expected.

The mandibular arc angle has been suggested as a representative of condylar growth direction [27]. Ricketts established the normal value of 26° for mandibular arc angle. Owen employed mandibular arc angle for diagnosis and treatment planning in the vertical plane and reported that values < 21° indicate clockwise rotation and values > 31° show counter-clockwise mandibular growth. In the present study, the mandibular arc angle was smaller in thalassaemic subjects than controls, indicating a more superior than posterior growth direction of the condyles. According to the authors' knowledge, this is the first study that assessed condylar growth direction in β-thalassemia subjects. Although this measurement was smaller in all subgroups of the thalassaemic subjects, significant between-group differences were only observed in normodivergent individuals as well as the total thalassaemic sample. The condylar growth tendency could have potential diagnostic and therapeutic values, especially in class II individuals where favourable condylar growth in a posterior rather than superior direction is required for the correction of mandibular deficiency. Therefore, the success of treatment with functional appliances would be compromised in class II thalassaemic subjects compared to unaffected counterparts. Previous studies presented various explanations concerning the strong vertical growth pattern in subjects with β-thalassemia major such as muscle weakness, mouth breathing, downward positioning of posterior maxilla due to enlargement of marrow spaces, short ramus and reduced condylar growth [3,19]. According to the outcomes of this study, vertical growth direction of condyles may be another aetiologic factor for long face trend in individuals with β-thalassemia major.

The outcomes of this study revealed that patients affected with β-thalassemia major have greater symphyseal angle compared with healthy individuals. Although all of the subgroups demonstrated this property, the statistical differences were found in total thalassaemic sample as well as the hyperdivergent and normodivergent subgroups. The morphology of mandibular symphysis is important in orthodontic and surgical treatment planning as it plays a great role in facial and profile aesthetics. The dense cortical structure of symphysis also provides limitations for orthodontic tooth movement [28]. Since the groups of this study were matched in the anteroposterior as well as the vertical dimension, it can be concluded that the differences observed in the symphysis angle is due to the inherent differences in chin morphology between thalassaemic subjects and unaffected counterparts. This may be due to the bone marrow expansion, which is a part of the pathological process in thalassaemic patients. There is little information on the symphysis angle of adolescents suffering from β-thalassemia major as compared to normal individuals. Therefore, comparison of the results of this study with other investigations is limited.

In the present study, there was no significant difference in mandibular parameters between hypodivergent thalassaemic individuals and their corresponding controls. This means that the

hypodivergent growth pattern alleviates any difference in mandibular morphology between subjects with thalassemia and healthy controls. The lack of significant difference between the hypodivergent subgroups may also be related to the small sample size, as this facial growth pattern is rarely found in patients with β-thalassemia major. There is limited information on the craniofacial parameters of hypodivergent thalassaemic patients in the literature.

The present study revealed some differences in mandibular growth direction and chin morphology between thalassaemic subjects and unaffected counterparts. These data can help the clinician concerning orthodontic diagnosis and treatment planning. Among the limitations of the present study was the small sample size especially in the hypodivergent subgroup. Furthermore, the assessment of condylar growth direction may not be accurate enough as cephalograms provide a two-dimensional image from a three-dimensional structure. Another limitation was the age range of the cases enrolled (11–15 years), considering that these patients may experience growth in the coming years. Whether the differences observed between the groups will accentuate or diminish with growth is not known and could be considered an interesting subject for future research. Further studies, with larger sample sizes are warranted to compare craniofacial characteristics of thalassaemic patients with different growth patterns and different genders using more precise data obtained from three-dimensional (3D) cone-beam computed tomography (CBCT) images.

Conclusion

Based on the results of the present study the following conclusions can be drawn:

- there were no significant differences in mandibular linear measurements including ramus height, ramus width, mandibular depth and antegonial notch depth between subjects with β-thalassemia major and controls;
- the symphysis angle was significantly greater in adolescents with β-thalassemia major when compared to controls. The difference in symphyseal angle implies inherent differences in chin morphology between thalassaemic subjects and unaffected counterparts;
- the mean value of mandibular arc angle was significantly smaller in total thalassaemic sample than the control individuals. The smaller mandibular arc angle in the thalassaemic sample suggests a more superior than posterior growth direction of condyles compared with healthy individuals;
- the hpodivergent growth pattern was not associated with any significant difference in mandibular linear and angular parameters between thalassaemic patients and controls.

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