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CEPHALOMETRIC AND ANTHROPOMETRIC ASSESSMENT OF CRANIOFACIAL MANIFESTATIONS IN PATIENTS WITH TRANSFUSION-DEPENDENT B-THALASSEMIA MAJOR

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Craniofacial changes in adults with transfusion-dependent beta-thalassemia major remain important for orthodontic diagnosis and treatment planning. This exploratory observational study included 34 adult patients, 16 men and 18 women, who underwent combined anthropometric and cephalometric assessment. Anthropometric analysis included proportional indices of the head, face, mandibular region, lips, and mouth and was performed separately by sex. Cephalometric analysis was performed in the same patient cohort and compared with 35 healthy individuals with neutral occlusion. Data distribution was assessed before statistical testing, and parametric or nonparametric methods were applied as appropriate. Patients demonstrated altered craniofacial proportions, especially in the mandibular region, together with cephalometric features suggesting skeletal Class II tendency, vertical growth direction, posterior mandibular rotation, altered incisor inclination, and a more protrusive lip profile. The findings should be interpreted cautiously because of the exploratory design.

Key words: beta-thalassemia major, cephalometry, facial anthropometry, craniofacial morphology, mandibular region, orthodontic diagnosis.

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ЦЕФАЛОМЕТРИЧНА ТА АНТРОПОМЕТРИЧНА ОЦІНКА ЧЕРЕПНО-ЛИЦЕВИХ ПРОЯВІВ У ПАЦІЄНТІВ ІЗ ТРАНСФУЗІЙНО-ЗАЛЕЖНОЮ ВЕЛИКОЮ В-ТАЛАСЕМІЄЮ

Краніофасціальні зміни у дорослих пацієнтів із трансфузійно-залежною β-таласемією великої форми залишаються важливими для ортодонтичної діагностики та планування лікування. Це розвідувальне обсерваційне дослідження включало 34 дорослих пацієнтів (16 чоловіків та 18 жінок), яким було проведено комбіновану антропометричну та цефалометричну оцінку. Антропометричний аналіз охоплював пропорційні індекси голови, обличчя, нижньої щелепи, губ та ротової ділянки й виконувався окремо за статтю. Цефалометричний аналіз проводився у тій самій когорті пацієнтів та порівнювався з 35 здоровими особами з нейтральним прикусом. Перед статистичним тестуванням оцінювали розподіл даних, після чого застосовували параметричні або непараметричні методи залежно від ситуації. У пацієнтів виявлено змінені краніофасціальні пропорції, особливо в ділянці нижньої щелепи, а також цефалометричні ознаки, що свідчать про тенденцію до скелетного класу II, вертикальний напрямок росту, задню ротацію нижньої щелепи, змінену інклинацію різців та більш виступаючий профіль губ. Отримані результати слід інтерпретувати з обережністю через розвідувальний дизайн дослідження.

Ключові слова: β-таласемія велика, цефалометрія, антропометрія обличчя, краніофасціальна морфологія, нижня щелепа, ортодонтична діагностика.

β-thalassemia major is a severe inherited blood disorder caused by impaired synthesis of the β-globin chains of hemoglobin. Mutations in the β-globin gene lead to an imbalance between α- and β-globin chains, excessive accumulation of free α-chains, damage to erythroid cells, and the development of chronic hemolytic anemia [4, 7].

Chronic anemia and increased erythropoietic activity result in expansion of the bone marrow spaces, disruption of bone remodeling, and systemic changes, including growth retardation, skeletal deformities, and abnormalities of craniofacial development [6, 9]. The craniofacial manifestations of β-thalassemia may involve skeletal, dentoalveolar, and soft-tissue components. These changes are generally associated with altered bone remodeling, chronic stimulation of erythropoiesis, and specific patterns of facial skeletal growth. Modern transfusion protocols and iron-chelation therapy have significantly improved prognosis and quality of life in these patients. However, they do not fully prevent craniofacial alterations that remain clinically relevant for dentistry and orthodontics.

Orthodontic treatment contributes to the improvement of oral function and quality of life in patients with beta-thalassemia major. When planning orthodontic treatment, it is necessary to consider the severity of craniofacial deformity, the patient's age, sagittal jaw relationship, degree of dental arch narrowing, and presence of incisor protrusion. Depending on age and clinical indications, removable, fixed, mechanical, and functional orthodontic appliances may be used.

Although craniofacial features of β-thalassemia major have been described in previous studies, most investigations have analyzed either cephalometric parameters of the facial skeleton or anthropometric characteristics of the facial soft tissues separately [5, 13, 15].

Previous observations in patients without systemic diseases and in patients with beta-thalassemia major showed forward displacement of the mandible after functional orthodontic treatment, indicating the potential relevance of growth-modifying approaches in this group [15].

From an orthodontic diagnostic perspective, it is important to assess not only the presence of skeletal changes, but also the extent to which these changes are reflected in the external facial proportions and soft-tissue profile. Therefore, an unresolved clinically relevant question remains: to what extent do facial anthropometric parameters reflect underlying cephalometric skeletal changes in β -thalassemia major.

The purpose of the study was to assess the correspondence between facial anthropometric parameters and cephalometric skeletal changes in adult patients with β -thalassemia major.

Materials and methods. Anthropometric and cephalometric examinations were conducted from 2018 to 2025 at the Republican Thalassemia Center of Azerbaijan in Baku and at the clinical base of Azerbaijan Medical University. The study was designed as an exploratory observational study of adults with transfusion-dependent beta-thalassemia major. The study group included 34 patients: 16 men aged 18–29 years and 18 women aged 17–34 years. Anthropometric and cephalometric examinations were performed in the same patient cohort. Cephalometric parameters were compared with those of 35 clinically healthy individuals with neutral occlusion.

The study protocol was approved by the Ethics Committee of Azerbaijan Medical University at its meeting held on May 11, 2018 (Protocol No. 2). All procedures were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Anthropometric measurements were obtained using a digital absolute caliper, digital spreading caliper, and large sliding caliper with levels.

Anthropometric examination was performed according to the method described by Farkas [8]. Proportional indices of the head, face, mandibular region, lips, and mouth were calculated. Because soft-tissue anthropometric parameters are sex-dependent, anthropometric indices were analyzed separately in men and women and compared with corresponding reference values for healthy individuals matched by sex, age, and ethnic origin.

Cephalometric analysis was based on lateral cephalometric radiographs obtained using the Morita Veraview system (Japan). Measurements were performed using Dolphin Imaging software, version 11.9. The evaluated parameters included cranial base morphology, sagittal jaw relationships, vertical growth pattern, mandibular dimensions, incisor position, and lip profile. Before pooling the cephalometric data, male and female patients were compared separately. No statistically significant sex-related differences were found in the main cephalometric parameters; therefore, cephalometric data were analyzed in a combined patient group.

To assess measurement reliability, anthropometric and cephalometric measurements were repeated after a two-week interval. Intra-observer reliability was evaluated using intraclass correlation coefficients.

Results of the study. The anthropometric analysis demonstrated differences in craniofacial proportions between patients with β -thalassemia major and healthy controls. The most notable differences involved indices characterizing head and facial proportions, including lip and mouth dimensions, in both male and female subgroups (Table 1).

Table 1

Head, facial, lip, and mouth proportion indices in patients with β -thalassemia major and control group

Indices	Male patients	Male controls	P-	Indices	Male patients	Male controls
Head proportion indices						
$(eu-eu) \times 100 / g-op$	68.6 $\pm$ 0.9	78.3 $\pm$ 0.8	<0.001	69.0 $\pm$ 1.1	78.2 $\pm$ 0.9	<0.001
$(ft-ft) \times 100 / eu-eu$	92.8 $\pm$ 0.7	77.9 $\pm$ 0.8	<0.001	92.5 $\pm$ 1.3	78.7 $\pm$ 0.6	<0.001
$(t-t) \times 100 / eu-eu$	108.1 $\pm$ 1.3	95.7 $\pm$ 0.9	<0.001	106.9 $\pm$ 1.4	94.2 $\pm$ 0.8	<0.001
$(eu-eu) \times 100 / v-gn$	62.3 $\pm$ 0.9	64.5 $\pm$ 0.9	0.090	64.4 $\pm$ 0.9	67.0 $\pm$ 1.0	0.058
$(v-n) \times 100 / v-gn$	43.8 $\pm$ 0.2	50.1 $\pm$ 0.8	<0.001	43.3 $\pm$ 0.9	51.1 $\pm$ 0.5	<0.001
$(tr-n) \times 100 / v-n$	82.2 $\pm$ 0.3	60.1 $\pm$ 1.7	<0.001	87.8 $\pm$ 2.9	56.41 $\pm$ 0.9	<0.001
Facial proportion indices						
$(n-gn) \times 100 / zy-zy$	91.3 $\pm$ 1.0	88.5 $\pm$ 1.1	0.082	88.3 $\pm$ 1.7	86.2 $\pm$ 1.0	0.282
$(go-go) \times 100 / zy-zy$	80.7 $\pm$ 1.3	70.8 $\pm$ 0.8	<0.001	85.6 $\pm$ 1.2	70.1 $\pm$ 0.9	<0.001
$(go-go) \times 100 / n-gn$	88.6 $\pm$ 1.5	80.3 $\pm$ 1.5	0.001	97.2 $\pm$ 1.3	81.7 $\pm$ 1.3	<0.001
$(sto-gn) \times 100 / go-go$	44.3 $\pm$ 1.6	51.8 $\pm$ 1.4	0.001	41.7 $\pm$ 0.8	49.8 $\pm$ 1.1	<0.001
$(go-go) \times 100 / gn-t,l$	75.3 $\pm$ 1.3	70.2 $\pm$ 1.0	0.004	80.2 $\pm$ 0.7	70.6 $\pm$ 1.2	<0.001
$(n-gn) \times 100 / tr-gn$	63.0 $\pm$ 0.7	64.7 $\pm$ 0.5	0.059	60.8 $\pm$ 0.6	64.9 $\pm$ 0.5	<0.001
$(go-go) \times 100 / tr-gn$	55.8 $\pm$ 1.1	51.9 $\pm$ 0.9	0.008	59.1 $\pm$ 0.8	53.0 $\pm$ 0.9	<0.001
Lip and mouth proportion indices						
$(sn-sto) \times 100 / ch-ch$	46.4 $\pm$ 1.0	41.1 $\pm$ 1.2	0.002	43.9 $\pm$ 1.9	39.5 $\pm$ 1.1	0.052
$(sn-ls) \times 100 / sn-sto$	68.9 $\pm$ 1.6	66.4 $\pm$ 1.5	0.258	67.0 $\pm$ 2.5	68.9 $\pm$ 1.5	0.517
$(sn-sto) \times 100 / sn-ls + ls-st$	95.9 $\pm$ 1.1	92.2 $\pm$ 1.4	0.045	92.7 $\pm$ 2.3	85.7 $\pm$ 1.1	0.008
$(ls-sto) \times 100 / sto-li$	72.4 $\pm$ 3.9	87.8 $\pm$ 4.1	0.012	78.4 $\pm$ 2.7	87.4 $\pm$ 3.5	0.055

The cephalic index was lower in patients with β -thalassemia major than in controls in both male and female subgroups. In contrast, the forehead-to-head width index was higher in patients of both sexes. The head height-to-craniofacial height index showed a tendency toward lower values in patients, whereas the forehead height-to-head height index was increased, with this difference being more pronounced in female patients.

Among facial proportion indices, the most pronounced differences were found in the mandibular region. The mandibular width-to-facial width index and mandibular width-to-facial height index were higher in both male and female patients with β -thalassemia major compared with controls. In contrast, the mandibular index was lower in both sexes. This pattern suggests disproportion of the mandibular region, characterized by a relatively increased transverse component and reduced vertical expression. The facial height index was lower mainly in female patients, supporting the relevance of sex-specific analysis in the evaluation of anthropometric craniofacial indices.

In the lip and oral region, male patients showed higher values of the upper lip height-to-mouth width index and lower values of the upper lip height proper index compared with controls. In female patients, these parameters showed less pronounced differences. The upper lip vertical contour index was higher in both sexes, with a more evident difference in females. Overall, lip and oral proportion indices demonstrated sex-related patterns: in males, changes were more evident in the relative height of the upper lip proper, whereas in females, changes were more prominent in the vertical contour of the upper lip.

Cephalometric analysis revealed characteristic craniofacial features in patients with β -thalassemia major compared with healthy individuals with neutral occlusion (Table 2).

Before the main intergroup comparison, a preliminary sex-based analysis was performed among patients with β -thalassemia major. This analysis did not reveal statistically significant differences in the main cephalometric parameters between male and female patients; therefore, subsequent cephalometric comparisons were performed using the combined patient group.

Table 2

Cephalometric parameters of patients with β -thalassemia major and the control group

Parameters	Control group, n = 35	Study group, n = 34	Difference	P-value
NSBa	128.0 $\pm$ 6.8	133.5 $\pm$ 5.0	+5.5	0.041
SNA	80.3 $\pm$ 3.6	82.9 $\pm$ 3.3	+2.6	0.099
SNB	78.1 $\pm$ 3.5	75.9 $\pm$ 4.6	-2.2	0.174
GoGn	76.1 $\pm$ 6.0	71.7 $\pm$ 7.1	-4.4	0.166
ANB	2.15 $\pm$ 1.04	7.04 $\pm$ 2.47	+4.89	0.001
NSL-ML	33.7 $\pm$ 3.8	39.4 $\pm$ 6.1	+5.7	0.005
NSL-NL	11.7 $\pm$ 4.2	8.1 $\pm$ 3.7	-3.6	0.039
ML-NL	21.9 $\pm$ 4.7	31.2 $\pm$ 6.5	+9.3	0.001
Björk's sum angle	393.7 $\pm$ 3.8	399.4 $\pm$ 6.1	+5.7	0.005
SGo/NMe	66.3 $\pm$ 3.1	63.5 $\pm$ 3.4	-2.8	0.020
U1-L1	127.4 $\pm$ 12.0	130.5 $\pm$ 11.9	+3.1	0.697
U1-NL	27.9 $\pm$ 2.6	31.1 $\pm$ 3.4	+3.2	0.010
L1-ML	39.4 $\pm$ 2.3	43.0 $\pm$ 3.4	+3.6	0.007
UL-E line	-6.1 $\pm$ 0.02	-0.2 $\pm$ 0.01	+5.9	0.001
LL-E line	-2.5 $\pm$ 0.01	3.8 $\pm$ 0.02	+6.3	0.001
STC	130.3 $\pm$ 4.8	133.5 $\pm$ 6.5	+3.2	0.206
CI-Sn-UL	103.0 $\pm$ 8.5	95.7 $\pm$ 28.0	-7.3	0.884

Compared with the control group, patients with β -thalassemia major demonstrated differences in several skeletal, dentoalveolar, and soft-tissue parameters. The ANB angle was higher in the study group, indicating a sagittal jaw discrepancy consistent with a skeletal Class II tendency. The NSBa angle was also increased, suggesting changes in cranial base morphology. Parameters reflecting mandibular position, including SNB and SNPog, showed a tendency toward a more posterior mandibular position.

Vertical skeletal parameters demonstrated a tendency toward a vertical growth pattern. Increased NSL-ML, ML-NL, and Björk's sum angles, together with a reduced SGo/NMe index, indicated mandibular plane divergence, reduced posterior facial

height proportion, and a tendency toward posterior mandibular rotation.

Dentoalveolar parameters also differed between groups. Increased U1-NL and L1-ML values suggested altered inclination of the upper and lower incisors, which may reflect dentoalveolar compensation for the underlying skeletal discrepancy.

Soft-tissue cephalometric parameters showed a more anterior position of the lips in patients with β -thalassemia major. Increased UL-E line and LL-E line values reflected a more protrusive lip profile relative to the esthetic line.

Discussion. The present findings indicate that the craniofacial phenotype of patients with β -thalassemia major is formed by a combination of

skeletal, dentoalveolar, and soft-tissue changes [1, 5, 13, 15]. The mandibular region appears to be the most clinically relevant area for orthodontic evaluation, as it demonstrates a clear relationship between cephalometric features of skeletal Class II pattern and anthropometric alterations in facial proportions.

Our cephalometric findings showed an increased ANB angle, which represents the anteroposterior relationship between the maxilla and mandible. The higher ANB value in patients with β -thalassemia major indicates a sagittal jaw discrepancy and a tendency toward mandibular retrognathia.

The vertical cephalometric parameters in the present study indicate a clear tendency toward vertical facial growth in patients with β -thalassemia major. Increased NSL-ML and ML-NL angles reflect a steeper mandibular plane and a greater divergence between the maxillary and mandibular bases. The increased Björk's sum angle further supports a vertical growth pattern, while the reduced SGo/NMe index indicates a lower proportion of posterior facial height relative to total anterior facial height. Together, these findings suggest posterior mandibular rotation and a hyperdivergent craniofacial pattern. This vertical component may contribute to the skeletal Class II tendency and should be considered during orthodontic diagnosis and treatment planning.

The mandibular component represents a clinically significant aspect of orthodontic assessment, as mandibular disproportions may contribute to the skeletal Class II tendency, vertical growth pattern, and altered soft-tissue profile observed in patients with β -thalassemia major [11]. In the present study, anthropometric indices related to mandibular width relative to facial width and facial height were increased, while the mandibular index was reduced. This combination suggests a disproportion of the mandibular region, with a relatively increased transverse component and reduced vertical expression. These findings are in line with current research trends. Movahhedian et al. specifically analyzed mandibular features in patients with β -thalassemia major and compared them with unaffected individuals, emphasizing the need for separate assessment of the mandible as an important element of craniofacial deformity [12].

The study by Roussos et al. further supports this interpretation. Using geometric morphometric analysis of lateral cephalograms, the authors demonstrated that in patients with β -thalassemia, not only individual angular and linear measurements, but also the overall shape of the craniofacial complex should be considered [14]. This supports the main concept of the present study: isolated evaluation of separate parameters may be less informative than a combined assessment of skeletal and soft-tissue characteristics.

In a comparative observational study, Amjad et al. divided 90 participants into a control group, a

group of patients with β -thalassemia major receiving transfusions, and a group receiving fetal hemoglobin induction therapy in addition to transfusions. This design reflects a shift in current research from simple morphological description toward evaluation of how treatment modalities may influence cephalometric parameters [2]. This is relevant to the present study, as differences between published data and our findings may be related not only to ethnic characteristics, but also to transfusion regimens, chelation therapy, and early clinical management.

Attention should also be given to the study by Genç et al., who examined craniofacial anthropometry in children with β -thalassemia major using a case-control design. Their work confirms that anthropometric analysis remains a useful method for evaluating craniofacial characteristics in β -thalassemia. At the same time, it highlights the importance of age, since morphological patterns in children and adults may differ due to growth, disease duration, and cumulative treatment effects [10].

In the present study, perioral soft tissues demonstrated more selective changes. Cephalometric analysis showed increased U1-NL and L1-ML angles, indicating a more proclined position of the upper and lower incisors. Increased UL-E line and LL-E line values reflected a more anterior position of the lips relative to the esthetic line, suggesting a more protrusive soft-tissue profile. Proportional indices of the upper lip were generally close to control values, whereas mouth width and certain lip-oral indices showed significant differences. These findings are consistent with the results of Al-Taei et al., who also reported that the most pronounced anthropometric differences in the perioral region of thalassemia patients were related to mouth width [1].

Recent radiological studies also support the need for comprehensive diagnostic evaluation in patients with β -thalassemia major. Bayati et al. investigated radiographic features of maxillofacial anomalies in patients with β -thalassemia major and analyzed their relationship with hemoglobin and ferritin levels. The inclusion of 72 patients with β -thalassemia and 70 healthy controls allowed the authors to demonstrate the clinical relevance of the association between hematological status and the severity of maxillofacial changes [3].

Taking together, the present results indicate that in patients with β -thalassemia major, facial soft-tissue parameters only partially reflect underlying skeletal changes. The strongest correspondence between soft- and hard-tissue characteristics was observed in the mandibular region. At the same time, vertical facial proportions did not fully correspond to cephalometric indicators of vertical growth pattern. Therefore, in patients with β -thalassemia major, anthropometric assessment of facial soft tissues should be complemented by cephalometric analysis.

Conclusions

1. Adults with transfusion-dependent beta-thalassemia major demonstrated measurable changes in craniofacial proportions. The cephalic index was lower in both male patients, 68.6 ± 0.9 compared with 78.3 ± 0.8 in controls, and female patients, 69.0 ± 1.1 compared with 78.2 ± 0.9 in controls, indicating altered head proportions.
2. The most pronounced anthropometric differences were observed in the mandibular region. The mandibular width-to-facial width index was increased in men, 80.7 ± 1.3 compared with 70.8 ± 0.8 , and in women, 85.6 ± 1.2 compared with 70.1 ± 0.9 . At the same time, the mandibular index was reduced in both sexes, suggesting disproportion between transverse and vertical mandibular components.
3. Cephalometric analysis showed skeletal differences in patients with beta-thalassemia major compared with healthy controls with neutral occlusion. The ANB angle was increased, 7.04 ± 2.47 compared with 2.15 ± 1.04 , indicating a skeletal Class II tendency. Increased NSL-ML, ML-NL, and Björk's sum angles, together with reduced SGo/NMe values, reflected a vertical growth pattern and posterior mandibular rotation.
4. Dentoalveolar and soft-tissue changes were also identified. Increased U1-NL, 31.1 ± 3.4 compared with 27.9 ± 2.6 , and L1-ML, 43.0 ± 3.4 compared with 39.4 ± 2.3 , indicated altered upper and lower incisor inclination. Changes in UL-E line, -0.2 compared with -6.1 , and LL-E line, 3.8 compared with -2.5 , reflected a more anterior lip position relative to the esthetic line.
5. Anthropometric proportional indices provided additional information about the soft-tissue expression of skeletal changes, but they did not fully reflect the direction or severity of underlying cephalometric alterations. The mandibular region showed the clearest hard- and soft-tissue correspondence, whereas vertical facial parameters showed only partial agreement with cephalometric indicators of vertical growth.
6. Combined anthropometric and cephalometric assessment may improve orthodontic evaluation of patients with transfusion-dependent beta-thalassemia major. The results may be useful for early detection of craniofacial disproportions and individualized orthodontic treatment planning; however, they should be interpreted cautiously because of the exploratory design and limited sample size.

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