ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/ophthal.2022-93829

The Cross-Sectional Case-Control Integrated Analysis of Vitreous Chamber Length, Corneal Volume, and Globe Biometry in Pediatric Beta-Thalassemia Major

Pediatrik Beta-Talasemi Majörde Vitreus Kamara Uzunluğu, Korneal Hacim ve Glob Biyometrisinin Kesitsel Vaka Kontrollü Entegre Analizi

Hamidu Hamisi GOBEKA[a], Zeki BAYSAL[b]

[a]Department of Ophthalmology, Afyonkarahisar Health Sciences University Faculty of Medicine, Afyonkarahisar, Türkiye
[b]Clinic of Ophthalmology, Batman Training and Research Hospital, Batman, Türkiye

ABSTRACT Objective: To determine ocular changes, particularly in vitreous chamber length (VCL) and corneal volume (CV), analyze globe biometric features in emmetrope pediatric beta-thalassemia major (β-TM) patients using Cirrus topography and IOLMaster devices, and compare the results to age- and gender-matched healthy individuals. **Material and Methods:** This cross-sectional case-control study included 36 multi-transfused β-TM patients (Group 1, 72 eyes) with a mean age of 9.18±3.14 years and no other hemoglobinopathies or anemias unrelated to β-TM. A control group (Group 2, 72 eyes) included 36 healthy children who had routine ophthalmology exams. A comprehensive ophthalmologic exam was performed, including auto-refraction, best-corrected visual acuity, and intraocular pressure (IOP), followed by dilated slit-lamp biomicroscopy. The corneal topography and globe biometric evaluation were followed by a pair-wise data comparison. **Results:** The axial length (AL) (22.58±0.64 vs 23.06±0.71 mm), VCL (15.48±0.68 vs 15.92±0.69 mm), CV (55.47±2.95 vs 57.65±2.83 mm3), IOP (12.68±2.34 vs 11.08±1.68 mmHg), keratometry values (K1, K2, Kmean, Kapex), as well as central corneal thickness (523.00±28.41 vs 547.29±26.45 μm), were all significantly different between groups 1 and 2, respectively ($p<0.05$). There were no significant differences in anterior chamber depth and volume, iridocorneal angle, horizontal visible iris diameter, horizontal anterior chamber diameter, and crystalline lens thickness ($p>0.05$). **Conclusion:** β-TM patients appear to have significant ocular growth retardation than relatively age-matched healthy children, as demonstrated by shorter AL and VCL, as well as lower CV. This circumstance could have prompted compensatory biometric modifications, as evidenced by a relatively steeper cornea and thicker crystalline lens, to accomplish emmetropization.

Keywords: Beta-thalassemia major; corneal topography; corneal volume; globe biometry; vitreous chamber length

ÖZET Amaç: Emetrop pediatrik beta-talasemi majör (β-TM) hastalarında vitreus kamara uzunluğu (VKU) ve korneal hacim (KH) başta olmak üzere oküler değişikliklerin Cirrus topografisi ve IOLMaster cihazlarıyla belirlenmesi, glob biyometrik özelliklerinin analiz edilmesi, sonuçlarının yaş ve cinsiyet uyumlu sağlıklı bireylerle karşılaştırılması. **Gereç ve Yöntemler:** Bu kesitsel vaka-kontrol çalışmasına, ortalama yaşı 9,18±3,14 olan ve β-TM ile ilişkili başka hemoglobinopati veya anemi olmayan 36 çoklu transfüze β-TM hastası (Grup 1, 72 göz) dâhil edildi. Kontrol grubu (Grup 2, 72 göz) rutin oftalmoloji muayenesi olan 36 sağlıklı çocuğu içeriyordu. Oto-refraksiyon, en iyi düzeltilmiş görme keskinliği ve göz içi basıncı (GİB) dâhil olmak üzere kapsamlı bir oftalmolojik muayene ve ardından dilate yarık lamba biyomikroskopisi yapıldı. Korneal topografi ve glob biyometrik değerlendirmesini ikili veri karşılaştırması takip etti. **Bulgular:** Aksiyel uzunluk (AU) (22,58±0,64 vs 23,06±0,71 mm), VKU (15,48±0,68 vs 15,92±0,69 mm), KH (55,47±2,95 vs 57,65±2,83 mm3), GİB (12,68±2,34 vs 11,08±1,68 mmHg), keratometri değerleri (K1, K2, Kmean, Kapex) ve santral korneal kalınlık (523,00±28,41 vs 547,29±26,45 μm), sırasıyla Grup 1 ve 2 arasında anlamlı olarak farklıydı ($p<0,05$). Ön kamara derinliği ve hacmi, iridokorneal açı, horizontal görülebilir iris çapı, horizontal ön kamara çapı ve lens kalınlığında anlamlı fark bulunmadı ($p>0,05$). **Sonuç:** β-TM hastaları, daha kısa AU ve VKU ve ayrıca daha düşük KH ile gösterildiği gibi nispeten aynı yaştaki sağlıklı çocuklara göre önemli oküler büyüme geriliğine sahip görünmektedir. Bu durum, emetropizasyonu gerçekleştirmek için nispeten daha dik bir kornea ve daha kalın lens ile kanıtlandığı gibi telafi edici biyometrik modifikasyonlarıyla ilişkili olabilir.

Anahtar Kelimeler: Beta-talasemi majör; korneal topografi; korneal hacim; glob biyometrisi; vitreus kamara uzunluğu

Correspondence: Hamidu Hamisi GOBEKA
Department of Ophthalmology, Afyonkarahisar Health Sciences University Faculty of Medicine, Afyonkarahisar, Türkiye
E-mail: hgobeka@gmail.com

Peer review under responsibility of Turkiye Klinikleri Journal of Ophthalmology.

Received: 11 Oct 2022 ***Received in revised form:*** 12 Nov 2022 ***Accepted:*** 14 Nov 2022 ***Available online:*** 18 Nov 2022

Beta-thalassemia major (β-TM) is a common hereditary chronic hemolytic anemia in the Mediterranean, Middle East, Central Asia, Transcaucasus, Indian subcontinent, and the Far East regions, with a high prevalence in consanguineous marriages. It affects over 42,000 newborns globally each year.[1] This autosomal recessive hemoglobinopathy is caused by a decrease or lack of synthesis of a beta chain of adult hemoglobin necessary for normal oxygen delivery to tissues. It destroys erythrocytes and necessitates life-long monitoring, blood transfusions, and iron chelation therapy (ICT), all of which cause social and economic issues.[2,3] Typically, the disease is not diagnosed until the 4th to 6th month of life, when fetal hemoglobin (HbF) is replaced by adult forms. This is thought to be due to the resistance of HbF-containing erythrocytes to hemolysis; therefore, β-TM is suspected once distinct clinical manifestations (lethargy, pallor, etc.) appear.[4]

Aside from systemic complications, various factors contribute to β-TM-related ocular complications. This includes erythrocyte destruction-related tissue iron accumulation, chelating agents in frequent blood transfusions, and orbital bone marrow expansion-related distinctive skeletal changes.[5] Typical craniofacial structural changes commonly include bossing of the skull, a depressed nasal bridge, and a prominent malar eminence, as well as a mongoloid eye slant and maxillary hypertrophy. Moreover, an abnormal bony orbit may develop as a result of craniofacial structural changes in β-TM patients, potentially leading to distinctive ocular biometrical modifications.[6]

The current study aimed to determine potential ocular changes, particularly in vitreous chamber length (VCL) and corneal volume (CV), analyze globe biometric features in pediatric β-TM patients using both Cirrus topography (Costruzione Strumenti Oftalmici, Florence, Italy) and IOLMaster (Zeiss Humphrey Systems, Dublin, California) devices, and compare the results to age- and gender-matched healthy individuals.

MATERIAL AND METHODS

STUDY DESIGN AND PARTICIPANTS

This non-interventional, cross-sectional case-control study included 36 multi-transfused β-TM emmetrope pediatric patients (Group 1, 72 eyes) who were followed-up at Batman Training and Research Hospital's Pediatric Hematology Department and consulted for periodic ocular exams between January and April 2022. A simple random sampling method and computerized tables were used for patient selection. A control group consisted of 36 age- and gender-matched emmetrope healthy children (Group 2, 72 eyes) with no history of iron deficiency and/or other blood disorders who visited the ophthalmology clinic for routine exams.

All participants, or their parents or legal guardians, provided written consent after being fully informed of the research's objectives in accordance with the Helsinki Declaration protocol's ethical standards. This study was approved by the Batman Training and Research Hospital Non-Interventional Clinical Research Ethics Committee, with May 30, 2022 approval date and 307 number.

ELIGIBILITY OF PARTICIPATION

Patients with (a) prior ocular or refractive surgery/trauma, (b) history of dry eye, contact lens wear, or any topical medications, and (c) history of any congenital or acquired ocular diseases, including lenticulo-corneal diseases, strabismus, aphakia, amblyopia, and/or systemic diseases with the potential to cause ocular abnormalities, were not eligible. Further, all patients in the study were medically examined and found to be free of other hemoglobinopathies or anemias unrelated to β-TM.

OPHTHALMOLOGIC ASSESSMENT

All participants were subjected to a comprehensive ophthalmologic exam, which included measuring auto-refraction (average of three values, Topcon Auto-refractometer model KM 8900, Japan), uncorrected visual acuity plus with cycloplegic refraction (with 0.5% cyclopentolate HCl) in logarithm of the Minimum Angle of Resolution (logMAR), and intraocular pressure (IOP) in millimeters of mercury (mmHg, Goldmann applanation tonometer). Also slit-lamp biomicroscopy (HaagStreit, Bern, Switzerland) was performed, concentrating on potential corneal scarring and/or lenticular opacities, including posterior subcapsular cataract. To define refractive errors in the current study, the manifest refraction

spherical equivalent was used, which was calculated mathematically by adding the sphere power and half of the cylinder power. As a result, emmetropia with astigmatism was defined as having an absolute cylindrical error of ≥0.50 diopter cylinder but having emmetropia when the spherical equivalent was taken into account (manifest refraction spherical equivalent; >-0.5 to <+0.5 Diopter).

SIRIUS CORNEAL TOPOGRAPHY (COMBINED SCHEIMPFLUG-PLACIDO DISC SYSTEM)

The anterior segment was analyzed using Sirius topography (Costruzione Strumenti Oftalmici, Florence, Italy), which is a system for analyzing the anterior segment that incorporates a monochromatic 360° -rotating Scheimpflug camera and 22-ring Placido disc technology. This system involves taking 25 corneal and anterior chamber radial sections, calculating the tangential and axial curvature of the anterior and posterior corneal surfaces (using 475 nm blue LED light), mapping the corneal global refractive power and pachymetry, as well as performing wave-front analysis. Measurements of the anterior corneal surface are acquired by accurately combining the Placido and Scheimpflug images; however, measurements of other interior structural elements are obtained through Scheimpflug imaging. This Scheimpflug topographic device measures the following parameters: central corneal thickness (CCT), CV, aqueous depth (AD), anterior chamber depth (ACD=CCT+AD), crystalline lens thickness (CLT), keratometry [K_1, K_2, K_{mean} (mean corneal anterior surface keratometry (K_m), and K_{apex}], horizontal visible iris diameter (HVID) (white-to-white), pupillography (topographic pupil diameter), anterior and posterior corneal topography, and so on.[7]

All Sirius measurement procedures, which were always performed prior to IOLMaster measurements, were carried out by a single experienced physician (HHG). The device was calibrated prior to each measurement session, and three measurements were taken in a row and averaged, as recommended by the manufacturer. All measurements were taken between 01:00 and 05:00 P.M. to reduce the influence of diurnal corneal hydration.[8]

ZEISS IOLMASTER

After approximately 5-10 minutes of topography, another experienced physician (ZB) performed globe biometric evaluation with ZEISS IOLMaster 700 (Zeiss Humphrey Systems, Dublin, California). This is a non-invasive device for measuring the axial length (AL) and other ocular components. It uses partial coherence interferometry to determine the AL, which is defined as the distance from the anterior corneal vertex to the internal limiting membrane along the line of fixation. The ACD, defined as the distance from the endothelial surface of the cornea to the anterior capsule of the lens, is measured using lateral slit illumination of the crystalline lens and cornea. The protocol was the same for both groups, and an average of three measurements were taken from both eyes prior to cycloplegia, as explained elsewhere.[9] A difference between AL and CCT+AD+CLT was used to calculate VCL.

The data was gathered and statistically analyzed using the Mann-Whitney test and the Independent t-test. If the p value was less than 0.05, the difference was considered statistically significant.

RESULTS

DEMOGRAPHICS

In Group 1, 72 eyes of 36 children aged 4 to 15 who had been diagnosed with β-TM between the ages of 6 and 12 months were studied. Blood transfusions were administered every 3-4 weeks to these patients who were being monitored regularly. They were also given Deferasirox after they turned two. Male-to-female ratios were 15:21 and 17:19 in groups 1 and 2, respectively. The mean uncorrected visual acuity plus with cycloplegic refraction was 0.00±0.00 logMAR in both groups. Group 1 had a mean age of 9.18±3.14 years, while Group 2 had a mean age of 9.11±2.75 years (p=0.946, Mann-Whitney U Test). The IOP in Group 1 (12.68±2.34 mmHg) was significantly higher than in Group 2 (11.08±1.68 mmHg) (p=0.000, Mann-Whitney U Test).

CORNEAL TOPOGRAPHIC ANALYSIS

A pairwise comparison of ocular parameters measured by the Sirius corneal topographer is summa-

TABLE 1: A pair-wise comparison of the ocular parameters measured by Sirius corneal topographer (n=36 for each group).

Parameters	Group 1 (eyes=72)	Group 2 (eyes=72)	p value
K1 (mm)	43.48±1.12	42.77±1.45	0.001†
K2 (mm)	44.20±1.22	43.49±1.48	0.002†
Kmean (mm)	43.84±1.15	43.10±1.44	0.001†
Kapex (mm)	45.22±1.56	44.16±1.58	0.000†
Topographic pupil diameter (mm)	4.32±0.76	4.37±0.67	0.668†
CV (mm^3)	55.47±2.95	57.65±2.83	0.000†
CCT (μm)	523.00±28.41	547.29±26.45	0.000†
ACD (CCT+AD) (mm)	3.69±0.18	3.67±0.26	0.730†
ACV (mm^3)	165.74±22.18	168.60±24.65	0.465†
ICA (degree)	45.39±4.48	45.25±5.64	0.870†
HVID (white-to-white) (mm)	1.226±0.46	12.17±0.50	0.278†
HACD (mm)	12.31±0.93	12.37±1.04	0.594*

*Mann-Whitney U Test; †Independent t-test; CV: Corneal volume; CCT: Central corneal thickness; ACD: Anterior chamber depth; AD: Aqueous depth; ACV: Anterior chamber volume; ICA: Iridocorneal angle; HVID: Horizontal visible iris diameter; HACD: Horizontal anterior chamber diameter; Group 1: β-TM patients; Group 2: Healthy children.

rized in Table 1. All mean keratometry values, including K_1, K_2, K_{mean}, and K_{apex}, were significantly higher in Group 1 compared to Group 2 ($p<0.05$, for all). The ACD (p=0.730), iridocorneal angle (ICA) (p=0.870), and HVID (p=0.278) were also higher in Group 1 compared to Group 2, but the differences were not statistically significant. The CCT and CV, on the other hand, were significantly lower in Group 1 compared to Group 2 ($p<0.05$, for both). Furthermore, despite non-significant differences, Group 1 had smaller topographic pupil (p=0.668) and horizontal anterior chamber (p=0.594) diameters, as well as lower anterior chamber volume (ACV) (p=0.465) than Group 2.

BIOMETRIC ANALYSIS

While VCL ($p<0.001$) and AL ($p<0.001$) were significantly lower in Group 1 than in Group 2, CLT (p=0.218) was non-significantly higher in the former (Table 2).

DISCUSSION

Despite previous research evaluating ocular biometric measurements in β-TM patients, this could be the first study to use both the Cirrus topography and the IOLMaster devices in emmetrope pediatric β-TM patients with no visual problems. Genetically, β-TM, a severe hematological condition, is caused by mutations in the β-globin gene, and thus defective β-chain manufacturing, set off a chain reaction that results in an imbalance in α/β-globin chain synthesis, inefficient erythropoiesis, decreased erythrocyte survival, and anemia.[3,10] A lack of blood transfusions is associated with death in pediatric β-TM patients under the age of three.[11]

Chronic blood transfusions can, in fact, prevent death and reduce mortality. Since humans are unable to actively excrete iron, iron-rich blood transfusions result in toxic iron accumulation in viscera organs

TABLE 2: A pair-wise comparison of the ocular parameters measured by ZEISS IOLMaster.

Parameters	Group 1 (n=36, eyes=72)	Group 2 (n=36, eyes=72)	p value
AL (mm)	22.58±0.64	23.06±0.71	0.000†
CLT (mm)	3.60±0.22	3.55±0.21	0.218†
VCL (mm)	15.48±0.68	15.92±0.69	0.000†

†Independent t-test; AL: Axial length; CLT: Crystalline lens thickness; VCL: Vitreous chamber length; Group 1: β-TM patients; Group 2: Healthy children.

such as liver, spleen, endocrine organs, myocardium, and presumably the eye, culminating in organ failure.[2] After all, iron overload is treatable with human-approved chelating agents that bind iron and facilitate its excretion [Desferrioxamine (subcutaneous or intravenous infusion), Deferiprone, and Deferasirox (oral iron chelators)].[12] Due to this fundamental fact, ICT is regarded as an essential adjuvant therapy for reducing iron stores in the body and optimizing the long-term survivability of β-TM patients. ICT is usually begun before the age of six, and to avoid complications such as heart failure, endocrine dysfunction such as pancreatic failure, and infertility, patients who receive ICT must be closely monitored. Besides, mouse model research of the retinal iron overload have shown that this therapy could slow the overall progress of retinal damage.[13] Likewise, in the current study, β-TM patients received blood transfusions every 3-4 weeks and were regularly monitored; they were also given Deferasirox after the age of two. Deferasirox, unlike Desferrioxamine and Deferiprone, provides effective systemic iron chelation, but no evidence of retinal penetration has been documented.

β-TM patients may exhibit a variety of structural and functional ocular manifestations.[1] The prevalence of β-TM-induced ocular manifestations varies across studies.[2,3] The environment and socioeconomic background are key indicators of life expectancy and the likelihood of developing systemic symptoms.[3] As a consequence, variations in manifestations may be credited to regional differences. Hence, researching the impact of thalassemia in various countries is absolutely essential. Patients who receive regular blood transfusions and ICT could experience disease course that influences not only the entire spectrum of systemic symptoms but also ocular manifestations.[2] β-TM-induced ocular manifestations can be caused by different mechanisms, including, microvasculature disease, chronic anemia, iron overload and ICT toxicity, or abnormal orbit growth as a result of abnormal craniofacial growth.[14-16] Aside from ocular surface disorders, these manifestations frequently include changes in color blindness and visual acuity, cataract and lens opacity, obliteration of iris pattern, shortened AL, thickened CLT, steepened corneal curvature, as well as various retinal vasculo-structural abnormalities.[16-19] Despite being reported to be within normal ranges in some studies, IOP in β-TM patients has been shown to be higher than in healthy individuals.[6,20,21] This is consistent with the current study, which found the same IOP trend between β-TM patients and healthy individuals, with a statistically significant difference. This condition, as previously proposed, appears to be secondary to accumulation of iron in the trabecular meshwork. Matter of fact, aside from several ocular diseases such as glaucoma and senile macular degeneration, iron has been associated with cataract formation.[22]

Further, the vast majority of β-TM-induced anterior segment abnormalities are caused by crystalline lens opacities.[5,16,21,23] These opacities are one of the most significant aspects in pediatric β-TM patients' visual acuity decline, and their proximity to the visual axis may be associated with visual impairment.[5,16] The number of blood transfusions has been strongly linked to crystalline lens opacities.[16] There is a potential link between cataract or lens opacity and various types of chelating agents as well, but the significance of this link has not been documented in other studies.[6,16,21,23] In the current study, emmetrope pediatric β-TM patients with an average age of 9.18±3.14 years and no visual impairment were investigated. These patients, who had blood transfusions every 3-4 weeks and were also given Deferasirox after the age of two, underwent a thorough dilated biomicroscopy, which revealed no crystalline lens opacities affecting the optic axis or the periphery. Despite this, β-TM patients had thicker CLT than healthy individuals, though the difference was not statistically significant. Aside from crystalline lens opacities, it seems that oxidative stress and free radical damage to the lens caused by iron overload or disruption of the oxidant/antioxidant balance is associated with an increased CLT caused by β-TM.[16]

Overall, a number of factors contribute to growth failure in β-TM patients. Chronic hypoxia secondary to chronic anemia, ICT toxicity, low serum zinc levels, hepatic iron overload with hepatic dysfunction, and iron-associated endocrinopathies such as hypogonadism, hypothyroidism, and growth hormone deficiency have all been related with it.[24] Also,

growth hormone deficiency caused by β-TM has been linked to variations in ocular biometric parameters such as shorter AL, thicker CLT, and steeper corneal curvatures.[6,25,26] A pair-wise comparison of ocular biometric data in the current study revealed the same trend of β-TM patients having significantly shorter AL and, while not statistically significant, thicker CLT.

Additionally, increased corneal topographic changes including steeper K readings, shorter VCL have also been associated with β-TM.[25] The current study also discovered, perhaps for the first time in the literature, significantly shorter VCL in β-TM patients, which was accompanied by significantly lower CV and CCT. Again, β-TM patients had significantly higher mean keratometry values, including K_1, K_2, K_{mean}, and K_{apex}, relative to healthy individuals. Despite the lack of statistical significance, higher ACD, ICA, and HVID were observed, which were accompanied by smaller topographic pupil diameter and horizontal anterior chamber diameter, as well as lower ACV. Overall, these findings appear to be the consequent compensatory mechanism of ongoing abnormal skeletal changes caused by bone marrow expansion, which could result in an abnormal bony orbit and, consequently, decreased ocular biometry.[14,27] The most widely accepted underlying causes of abnormal bony orbit are craniofacial changes such as nasal bridge depression, a propensity to ocular mongoloid slant, and maxillary hypertrophy.[28] The current study's findings primarily indicate that, in addition to changes in previously studied topographic and ocular biometric parameters, VCL, CV, and CCT exhibit a similar variation trend, which could be attributed to β-TM-induced abnormal physical growth.

There are some limitations to the current study. The current study sought to identify any potential changes in otherwise healthy emmetropic β-TM eyes with no visual problems, as extensive outcomes involving refractive errors had previously been documented.[29] The analysis of both eyes of the same patient could be viewed as a limitation. Analyzing only one eye per patient, however, may result in "waste" of information and, consequently, less than optimal estimates of effect and power. Also, if the eye is not selected randomly for analysis, the study may be biased.[30] Since this was a cross-sectional study, finding prospective β-TM-induced implications on the anterior ocular segment as a whole was impossible. There was no race-based assessment because only the Turkish pediatric population was studied. As previously stated, the environment and socio-economic background play an important role in predicting life expectancy and the likelihood of developing systemic and ocular symptoms.[3] Further, the current study would have positively affected from an assessment of bony orbital dimensions to identify any variations in relation to corneal topography and ocular biometry, particularly because β-TM-induced craniofacial variations could lead to significant variations in an abnormal bony orbit and, consequently, in the aforementioned parameters.[6] Unfortunately, exploring this essence was rendered impossible due to ethical concerns about exposing pediatric β-TM patients to potentially hazardous doses of irradiation for a computed tomography scanning. In the future, this may be conceivable by enrolling patients who are currently having computed tomography scans for other β-TM-related systemic factors. Besides, exophthalmometry-assisted orbit analysis, which has previously been studied in healthy children, appears to be another promising area for future research.[31] Large-scale multiracial longitudinal studies would also be beneficial, principally in this pediatric population where growth-related ocular structural changes are occurring.

CONCLUSION

Topographic and ocular biometric changes were observed in pediatric β-TM patients. Despite the non-significant age difference, these patients' IOP and keratometric readings were significantly higher than healthy individuals. The CLT, ACD, ICA, and HVID all increased non-significantly. All of these modifications were accompanied by a compensatory mechanism, as evidenced by significantly lower VCL, AL, CV as well as CCT. In this context, it may be worthwhile to investigate eyeball growth and its impact on ocular biometry and/or corneal topography in pediatric β-TM.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Hamidu Hamisi Gobeka, Zeki Baysal;* ***Design:*** *Hamidu Hamisi Gobeka, Zeki Baysal;* ***Control/Supervision:*** *Hamidu Hamisi Gobeka;* ***Data Collection and/or Processing:*** *Hamidu Hamisi Gobeka, Zeki Baysal;* ***Analysis and/or Interpretation:*** *Hamidu Hamisi Gobeka, Zeki Baysal;* ***Literature Review:*** *Hamidu Hamisi Gobeka, Zeki Baysal;* ***Writing the Article:*** *Hamidu Hamisi Gobeka, Zeki Baysal;* ***Critical Review:*** *Hamidu Hamisi Gobeka;* ***Materials:*** *Zeki Baysal.*

REFERENCES

1. Liaska A, Petrou P, Georgakopoulos CD, Diamanti R, Papaconstantinou D, Kanakis MG, et al. β-Thalassemia and ocular implications: a systematic review. BMC Ophthalmol. 2016;16:102. [Crossref] [PubMed] [PMC]
2. Cao A, Galanello R. Beta-thalassemia. Genet Med. 2010;12(2):61-76. [Crossref] [PubMed]
3. Rund D, Rachmilewitz E. Beta-thalassemia. N Engl J Med. 2005;353 (11):1135-46. [Crossref] [PubMed]
4. Kesse-Adu R, Howard J. Inherited anaemias: sickle cell and thalassaemia. Medicine. 2013;41(4):219-24. [Crossref]
5. Aksoy A, Aslankurt M, Aslan L, Gül O, Garipardıç M, Celik O, et al. Ocular findings in children with thalassemia major in Eastern Mediterranean. Int J Ophthalmol. 2014;7(1):118-21. [PubMed] [PMC]
6. Nowroozzadeh MH, Kalantari Z, Namvar K, Meshkibaf MH. Ocular refractive and biometric characteristics in patients with thalassaemia major. Clin Exp Optom. 2011;94(4):361-6. [Crossref] [PubMed]
7. Savini G, Barboni P, Carbonelli M, Hoffer KJ. Repeatability of automatic measurements by a new Scheimpflug camera combined with Placido topography. J Cataract Refract Surg. 2011;37(10):1809-16. [Crossref] [PubMed]
8. du Toit R, Vega JA, Fonn D, Simpson T. Diurnal variation of corneal sensitivity and thickness. Cornea. 2003;22(3):205-9. [Crossref] [PubMed]
9. Santodomingo-Rubido J, Mallen EA, Gilmartin B, Wolffsohn JS. A new non-contact optical device for ocular biometry. Br J Ophthalmol. 2002;86(4):458-62. [Crossref] [PubMed] [PMC]
10. Vichinsky EP. Changing patterns of thalassemia worldwide. Ann N Y Acad Sci. 2005;1054:18-24. [Crossref] [PubMed]
11. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ. 2008;86(6):480-7. [Crossref] [PubMed] [PMC]
12. Daar S, Pathare AV. Combined therapy with desferrioxamine and deferiprone in beta thalassemia major patients with transfusional iron overload. Ann Hematol. 2006;85(5):315-9. [Crossref] [PubMed]
13. Mehta S, Dunaief JL. The role of iron in retinal diseases. In: Mehta S, ed. Studies on Retinal and Choroidal Disorders. 1st ed. New York, NY: Humana Press; 2012. p.259e75. [Crossref]
14. Dewan P, Gomber S. Ocular changes in multi transfused children with β-thalassemia receiving deferoxamine: a case control study. SA J Child Health. 2011;5(10):11-4. [Link]
15. Heydarian S, Jafari R, Dailami KN, Hashemi H, Jafarzadehpour E, Heirani M, et al. Ocular abnormalities in beta thalassemia patients: prevalence, impact, and management strategies. Int Ophthalmol. 2020;40(2): 511-27. [Crossref] [PubMed]
16. Taneja R, Malik P, Sharma M, Agarwal MC. Multiple transfused thalassemia major: ocular manifestations in a hospital-based population. Indian J Ophthalmol. 2010;58(2):125-30. [Crossref] [PubMed] [PMC]
17. Gartaganis SP, Georgakopoulos CD, Exarchou A, Mela EK, Psachoulia C, Eliopoulou MI, et al. Alterations in conjunctival cytology and tear film dysfunction in patients with beta-thalassemia. Cornea. 2003;22(7):591-7. [Crossref] [PubMed]
18. Aksoy A, Aslan L, Aslankurt M, Eser O, Garipardic M, Okumus S, et al. Retinal fiber layer thickness in children with thalessemia major and iron deficiency anemia. Semin Ophthalmol. 2014;29(1):22-6. [Crossref] [PubMed]
19. Taher A, Bashshur Z, Shamseddeen WA, Abdulnour RE, Aoun E, Koussa S, et al. Ocular findings among thalassemia patients. Am J Ophthalmol. 2006;142(4):704-5. [Crossref] [PubMed]
20. Haghpanah S, Zekavat OR, Bordbar M, Karimi M, Zareifar S, Safaei S, et al. Ocular findings in patients with transfusion-dependent β-thalassemia in southern Iran. BMC Ophthalmol. 2020;20(1):376. [Crossref] [PubMed] [PMC]
21. Jafari R, Heydarian S, Karami H, Shektaei MM, Dailami KN, Amiri AA, et al. Ocular abnormalities in multi-transfused beta-thalassemia patients. Indian J Ophthalmol. 2015;63(9):710-5. [Crossref] [PubMed] [PMC]
22. Chen H, Lukas TJ, Du N, Suyeoka G, Neufeld AH. Dysfunction of the retinal pigment epithelium with age: increased iron decreases phagocytosis and lysosomal activity. Invest Ophthalmol Vis Sci. 2009;50(4):1895-902. [Crossref] [PubMed]
23. Abdel-Malak DSM, Dabbous OAE, Saif MYS, Saif ATS. Ocular manifestations in children with β thalassemia major and visual toxicity of iron chelating agents. J Am Sci. 2012;8(7):633-8. [Link]
24. Vogiatzi MG, Macklin EA, Trachtenberg FL, Fung EB, Cheung AM, Vichinsky E, et al; Thalassemia Clinical Research Network. Differences in the prevalence of growth, endocrine and vitamin D abnormalities among the various thalassaemia syndromes in North America. Br J Haematol. 2009;146(5):546-56. [Crossref] [PubMed] [PMC]

25. Elkitkat RS, El-Shazly AA, Ebeid WM, Deghedy MR. Relation of anthropometric measurements to ocular biometric changes and refractive error in children with thalassemia. Eur J Ophthalmol. 2018;28(2):139-43. [Crossref] [PubMed]

26. Bourla DH, Laron Z, Snir M, Lilos P, Weinberger D, Axer-Siegel R. Insulinlike growth factor I affects ocular development: a study of untreated and treated patients with Laron syndrome. Ophthalmology. 2006;113(7):1197.e1-5. [Crossref] [PubMed]

27. Voskaridou E, Terpos E. New insights into the pathophysiology and management of osteoporosis in patients with beta thalassaemia. Br J Haematol. 2004;127(2):127-39. [Crossref] [PubMed]

28. Wheatherall DJ, Glegg JB. The Thalassemia Syndromes. 4th ed. Oxford: Blackwell Science Ltd; 2001.

29. Hashemi H, Khabazkhoob M, Jafarzadehpur E, Yekta AA, Emamian MH, Shariati M, et al. High prevalence of myopia in an adult population, Shahroud, Iran. Optom Vis Sci. 2012;89(7):993-9. [Crossref] [PubMed]

30. Murdoch IE, Morris SS, Cousens SN. People and eyes: statistical approaches in ophthalmology. Br J Ophthalmol. 1998;82(8):971-3. [Crossref] [PubMed] [PMC]

31. Kashkouli MB, Nojomi M, Parvaresh MM, Sanjari MS, Modarres M, Noorani MM. Normal values of hertel exophthalmometry in children, teenagers, and adults from Tehran, Iran. Optom Vis Sci. 2008;85(10):1012-7. [Crossref] [PubMed]