Review Article

A Review on Ophthalmologic Manifestations in Beta-Thalassemia Major Patients

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Abstract

Background: Beta-thalassemia is an inherited blood disorder that leads to early apoptosis of red blood cells (RBCs), ineffective erythropoiesis, and ocular complications. The disease is classified into beta-thalassemia minor (β-TMi), beta-thalassemia intermedia (β-TI), and beta-thalassemia major (β-TM).We aim to review various functional and structural ocular manifestations of β-TM patients in different studies and present the most important findings based on the prevalence and etiologies of each ocular complication.

Materials and methods: To reach this purpose, we developed a search strategy using the keywords "eye disease," "ocular complications," "ocular manifestations," and "ocular abnormality," each with "beta-thalassemia" in the two popular search engines PubMed and Google Scholar up to December 2022. We also reviewed related references of the chosen papers.

Results: According to the literature review, the most consistent is the correlation of β-TM with dry eye disease and fundus alterations, while there are still many challenges regarding the prevalence and etiologies of other ocular complications in β-TM patients.

Conclusion: This finding warrants studies with larger sample sizes to reach more reliable results and take them into action for preventing and timely diagnosing such ocular complications.

Keywords: Beta-Thalassemia Major; Ocular Complications; Iron Chelation Therapy; Iron Overload.

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Introduction

Adult hemoglobin (HbA) is a tetramer consisting of two alpha-globin and two beta-globin chains[1]. Beta-thalassemia is an inherited blood disorder mostly inherited as an autosomal recessive disorder caused by reduced beta chain synthesis (β^+) or lack of absent beta chain synthesis (β^0), which leads to an imbalance between alpha and beta chains in RBC. Therefore, unstable alpha chains deposit as inclusion bodies in RBCs, resulting in their reduced life span, intramedullary and extramedullary hemolysis, early apoptosis of RBCs, and anemia (ineffective erythropoiesis). The more imbalance between the Hb chains, the more severe the disease presents [2, 3].

More than 40500 infants with beta-thalassemia are born annually, approximately 25500 with transfusion-dependent anemia [1]. Beta-thalassemia is highly prevalent in Mediterranean countries, Middle East Asia, South East Asia, the Indian subcontinent, and North African countries. There is a high prevalence of beta-thalassemia carrier state in the regions with a high prevalence of malaria because these patients' erythrocytes are resistant to malaria. Migration and interethnic marriage have increased the incidence rate of the disease in regions that used to have low frequencies of beta-thalassemia, such as North America and North European countries [4, 5].

Considering various inheritances of beta-thalassemia alleles and resulting clinical and hematological manifestations, beta-thalassemia is sub-classified into three main forms: β-TMi, known as carrier state, β-TI, and β-TM. Their detailed characteristics are thoroughly discussed [2, 3, 6].

β-TMi is usually asymptomatic, but some cases might present mild anemia manifestations. β-TI manifestations present 2-6 years after birth and cover a broad spectrum from asymptomatic beta-thalassemia carrier to severe transfusion-dependent beta-thalassemia (TDT). Therefore, some β-TI patients need regular blood transfusion therapy. β-TM is a chronic life-threatening transfusion-dependent anemia with severe anemia manifestations, which is usually diagnosed 6-24 months after birth. Since these patients' survival depends on regular life-long blood transfusion, iron overload is unavoidable among them, and iron chelation therapy (ICT) would be necessary. Survival and complications in patients with β-TM are affected by the on-time initiation of transfusion therapy and patients' compliance to regular blood transfusion and chelating therapy [2, 3, 6].

β-TM, as the most severe type of beta-thalassemia, causes more complications than the other two types. The first complications of β-TM stem from anemia and resultant hypoxia, such as pallor and growth retardation. Although regular blood transfusion improves anemia, it leads to iron overload-related complications. Excess iron is deposited in organs such as the heart, the liver, endocrine glands, and the retina, leading to various complications. The most common cause of mortality and morbidity in β-TM is myocardiopathy and heart failure resulting from iron overload. The complications can be prevented by efficient chelating therapy [2, 6-8] while iron-chelating agents can also be the reason for some complications. Other important complications are due to extramedullary hematopoiesis, including hepatosplenomegaly and craniofacial bone deformities. Ophthalmologic complications can be caused by all mentioned mechanisms [9, 10].

The first known iron-chelating agent is deferoxamine (DFO). Despite its significant effect on reducing iron-overload-related mortalities and morbidities, its subcutaneous

or intravenous administration makes it hard for patients to comply with this medicine. Besides common adverse effects such as infection of the injection site, serious complications of DFO are auditory toxicity, ocular problems like visual impairment and cataracts, and growth retardation, especially in high dosage. Deferiprone (DFP) is a newer iron chelation medicine administered orally, so it is more convenient to comply with and more effective in lowering myocardial iron and, therefore, more cardioprotective than DFO. Serious adverse effects of DFP are neutropenia and agranulocytosis, for which patients need to be monitored regularly. Deferasirox (DFX) is a new tridentate oral iron chelator with promising results. This medicine also has adverse effects such as gastrointestinal problems, skin rashes, and a mild increase in serum creatinine levels [2, 6-8].

The present review aims to review various functional and structural ocular abnormalities of β-TM patients in different studies and present the most important recent findings. The significant prevalence of β-TM, increased life expectancy of affected patients, and limited data related to the ocular complications of this disease led us to review the available papers about ophthalmologic complications in β-TM patients to assist in early diagnosis and better management of such complications. Although some β-TI patients depend on blood transfusion therapy, we focused on TDT patients diagnosed with β-TM. We organized our content based on the main ocular complications in the literature and revealed related prevalence and etiologies. The discussed abnormalities were given in Table 1.

Research method

We started our literature review in September 2022 and searched "ocular complications in beta-thalassemia" in the PubMed database, which gave us 42 results. By filtering data for the last 10 years, results were reduced to 24, 12 of which were excluded by paper subject; hence, 12 related papers remained. Then we searched the keywords "eye disease," "ocular complications," "ocular manifestations," and "ocular abnormality," each with "beta-thalassemia" in Google Scholar and set the publication year to "since 2012". This search strategy gave us more than 200 results. Considering the papers' subject, we chose seven papers different from those we obtained from PubMed; thus, we earned 19 original papers to review. While checking the sources, we came across other references and used them.

Biometric changes, refractive errors, and presbyopia

Studies have shown that β-TM children have general growth retardation compared to healthy individuals. Despite lower height and weight, and therefore smaller body-mass index (BMI) among the children with thalassemia, their occipitofrontal circumference was not significantly different from the healthy individuals. These patients also had lower ocular growth, indicated by shorter axial length and vitreous chamber depth, while anterior chamber depth was not significantly different from the control group. The ocular parametric changes (lower ocular growth) among β-TM patients can be caused by lower physical growth and facial bone deformity (resulting from bone marrow expansion). Mentioned ocular growth changes lead to compensatory events to overcome smaller ocular parameters in terms of emmetropization. Biometric changes such as steeper cornea (determined by keratometry reading) and thicker lenses are compensatory mechanisms [11, 12] that, if severe,

can lead to a myopic shift in patients with thalassemia.

However, the literature review showed consistent results about biometric ocular changes, and they disagree regarding refractive errors. Although Elkitkat et al. found myopia as the most prevalent refractive error among the β-TM group compared to the normal group[11], Heydarian et al. did not demonstrate significant differences in refractive errors between the two groups [12]. Merchant et al. found refractive errors in 23 % of the study population, while they did not find any significant association between these findings and different characteristics of β-TM patients or ICT [13].

Abo-Zied et al. demonstrated an 8.88 % prevalence in decreased visual acuity (VA) among a case group of 90 β-TM patients, which was completely corrected using glasses; thus, the reason for this manifestation was found to be refractive errors that were not specified[14]. These findings agree with the study done by Jafari et al [15].

Elkitkat et al. demonstrated that against-the-rule astigmatism was prevalent in both case and control groups, and the difference in this refractive error was insignificant between the two groups [11]. In another study, although there was no meaningful difference in astigmatism prevalence between the two groups, β-TM patients tended to have an against-the-rule pattern in total astigmatism more than with-the-rule astigmatism, while the healthy group showed the opposite. Of note, the examination of corneal astigmatism demonstrated that with-the-rule astigmatism was more prevalent than against-the-rule pattern in both groups; therefore, despite the patients' group, the total astigmatism follows the corneal astigmatism pattern in the healthy group [12].

Nuzzi et al. compared ocular complications among 80 β-TM patients using three chelators (DFO, DFP, or DFX). They found a significant correlation between myopia (32.5 % of the patients) and presbyopia (22.5 % of the patients), with ICT, both of which were associated with the duration of treatment with DFO while taking a higher dosage of DFP had a protective effect against premature presbyopia. This study did not show a significant relationship between ICT and other refractive errors, such as hyperopia and astigmatism [16].

Heydarian et al. studied refractive errors in 54 β-TM patients. They compared them with healthy individuals, finding an insignificant difference between the mean spherical equivalent (SE) of two groups [12], showing equivalent results in the study by Jafari et al. [14]. This results was consistent with these authors' later study in which the mean SE of β-TM group (-0.0093 ± 0.86) was not significantly different from the healthy control group [15]. Although there was a significant correlation between the SE and ocular biometric parameters (especially axial length and vitreous chamber depth) in the normal group, there was no such correlation between these parameters in the patients' group [12]. In contrast, Elkitkat et al. found a significant difference between the mean SE of the control and patient groups. They demonstrated that SE had an inverse, direct, and inverse relationship with keratometry reading, lens thickness, and anterior chamber depth, respectively [11].

As mentioned, if compensatory biometric ocular mechanisms in β-TM patients, including steeper corneas and thicker lenses, happen severely, that may lead to myopia. Literature is inconsistent with the prevalence of specific refractive errors among β-TM patients and their correlation with hematological characteristics, iron overload, and different chelators.

Corneal and anterior chamber alterations

Corneal and anterior chamber abnormalities include various changes mostly discussed in general in the literature. In the following, we consider the reports on the corneal and anterior chamber alterations except for dry eye disease. In a cross-sectional study on 50 patients with pediatric thalassemia, Ramakrishnan et al. reported no anterior chamber abnormalities by examining 50 β-TM patients [17].

Nuzzi et al. detected anterior chamber alterations in 2.5 % of 80 patients. There was no significant correlation between these alterations and dosage or duration of chelation therapy [16].

In a cross-sectional study on 52 β-TM patients as the case group and 30 anemic patients as the control group, Thakur et al. found anterior segment involvement in 17.3 % of β-TM patients, significantly more prevalent than in the control group [18].

Haghpanah et al. detected pinguecula and pterygium in 8.9 % and 3.8 % of patients, respectively, significantly more prevalent than in an age-matched normal group observed in another study. This difference can be due to iron overload and subsequent free radical damage [19]. Jafari et al. showed that the prevalence of pinguecula was significantly higher in the patients than in healthy individuals. This higher prevalence was unrelated to the type of chelator they received [15].

The reviewed studies have conflicting and ambiguous results for anterior chamber changes in β-TM patients. There is poor agreement about the relationship between the disease and chelator type on anterior chamber alterations.

Dry eye disease

As the most concerned cornea disease among patients with thalassemia, dry eye disease has been the subject of some studies about β-TM patients. Dry eye disease can be evaluated and diagnosed by tests, including the Schirmer, tear film break-up time (TBUT), and ocular surface staining (OSS) tests with fluorescein and lissamine green. Other useful methods are evaluating corneal epithelial thickness (CET) by anterior segment optical coherence tomography (AS-OCT) and using the ocular surface disease index (OSDI) questionnaire, which gives us a subjective view of dry eye disease [20].

Ebeid et al. investigated dry eye disease with the above-discussed methods in thalassemia and healthy adolescent groups. Based on their results, patients with thalassemia had more symptoms of dry eye disease (higher OSDI scores) and thinner corneal epithelium with more thickness variability. The case group showed significantly lower TBUT and higher OSS grades than the control group, while the Schirmer test results were not significantly different between the groups [20]. Similarly, two other studies showed that β-TM patients had significantly lower TBUT values than the control group, and the prevalence of dry eye disease was strongly higher among them [14, 15]. Fagehi et al. used the OSDI questionnaire, tear ferning, and phenol red thread tests to evaluate dry eye disease in β-TM patients compared to healthy individuals. All resulting scores demonstrated that dry eye disease was significantly more prevalent in the case group than in the control group [21].

A cross-sectional study in which 50 β-TM patients were examined showed a prevalence of 38 % of mild dry eye disease using the Schirmer test [17].

A significant correlation between superior and inferior CET and most dry eye disease tests demonstrates that CET evaluation can be a helpful method for diagnosing dry eye disease

and patient follow-up [20].

A strong association between liver iron overload and most features of dry eye disease (CET, TBUT, OSS, and OSDI) advocates that high serum ferritin concentration and resulting organ iron overload can be possible pathogenesis of dry eye disease [14, 20]. Iron deposition in glands can lead to cytotoxic effects and exocrine and endocrine function impairment. Hence, this mechanism can affect tear production and secretion of lacrimal glands, which are exocrine glands among transfusion-dependent thalassemia patients [22]. Jafari et al. showed that although there was no significant association between dry eye disease and chelator type and dosage, dry eye disease was significantly related to the duration of chelator therapy among β-TM patients. However, the study has not clarified whether the correlation is direct or inverse [15].

Most evidence shows that β-TM patients have more potential to get dry eye disease than normal people, which is more likely due to their iron overload status. Hence, they should be regularly evaluated regarding this ophthalmologic complication with one or a combination of previously mentioned methods. To this end, CET monitoring using AS-OCT is a helpful method for diagnosing patients and following up their improvement as a non-invasive method.

Lens opacities and cataracts

Cataract is the leading cause of blindness globally (51 %) [23]. The most recent grading system for cataracts is the lens opacities classification system III (LOCS III), based on which there are three types of cataracts, including nuclear, cortical, and posterior subcapsular cataracts [24]. Cataracts and their complications can be prevented by being detected early in the disease [25].

Abo-Zied et al. assessed ocular alterations among β-TM patients compared to a healthy group and evaluated if there is any correlation between the ocular abnormalities and different aspects of ICT. They found a strong difference between the prevalence of cataracts in the two groups. Despite high cataract prevalence in those who had taken DFP, there was an insignificant difference between different groups of patients based on their chelating agent type. The values correlated with cataracts among β-TM patients were age and duration of ICT. It is worth mentioning that there was an insignificant correlation between cataracts and the number of blood transfusions [14].

Another study showed that cataract was significantly more prevalent in the β-TM group. All patients with thalassemia had peripheral cortical cataracts, so they were asymptomatic regarding their vision. Although β-TM patients taking DFP had high cataract prevalence, this difference was not statistically significant between different β-TM groups based on various chelators [15].

Nuzzi et al. found mild sutural opacity in one patient (1.25 %) of the beta-thalassemia population who had never used DFP, and there was not any significant correlation between this anomaly and during or dosage of ICT [16].

Haghpanah et al. detected lens opacities and cataracts in four patients (5.1 %) of the study population, all over 18. All cataract patients had been taking DFO as monotherapy or combination therapy with other chelators during the past two years since the beginning of the study. Considering that patients with thalassemia usually change the type of chelators used during their lifespan, and compared to other studies, the authors cannot relate cataract and lens opacity to the type of iron chelator [19].

Akritidou et al. detected lens opacities in

21.8 % of the study population, which affected their VA. In other studies, lenticular opacity was considered as a visual impairment factor in patients with thalassemia [9, 26]. They detected that lens opacities were strongly correlated with the number of blood transfusions and serum iron and ferritin levels among β-TM patients [27].

Regarding the reviewed papers, lens opacities and cataracts among β-TM patients, besides age, can be facilitated by factors such as serum ferritin level (as an indicator of iron overload) and using DFO and/or DFP as a chelator. Of note, there is controversy over the effect of the chelator type on inducing cataracts.

Posterior chamber and fundus abnormalities

β-TM patients have the potential to develop retinal abnormalities. Most of the retinal pathologies found in these patients are the same as eye manifestations of pseudoxanthoma elasticum (PXE) syndrome; thus, retinal manifestations among patients with thalassemia are subclassified into two groups: PXE-like and non-PXE-like syndrome. PXE is a genetic disorder caused by a mutation in the ABCC6 gene on chromosome 16. This gene is responsible for producing a protein found in various organs such as kidneys, skin, and eyes. This disorder leads to the deposition of calcium and other minerals in the elastic binds of the mentioned organs. Bruch's membrane is the mineralization site in the eyes. Notably, retinal manifestations in β-TM patients are counted as acquired PXE-like syndrome [28].

PXE-like syndrome consists of retinal alterations such as angioid streaks, peau d'orange, and optic disc drusen. Retinal venous (RV) tortuosity is a non-PXE-like syndrome manifestation [19, 28].

Mechanisms that may be responsible for retinal alterations among β-TM patients are chronic anemia, iron overload, and the type of chelation therapy [9, 16, 27]. Iron overload leads to oxidative damage to the cell structure using free radicals, and this process destroys the brain-retinal barrier and other retinal abnormalities [29]. Considering this explanation, ICT can protect against retinal changes, while different chelators can have protective or helping effects on retinal alterations based on different evidence, as discussed below.

Jafari et al. found significantly more retinal abnormalities in β-TM patients than in the healthy groups, and their finding was consistent with Abo-Zied et al. [14, 15]. Saif et al. found retinal alterations among β-TM patients, including high cup-to-disc (C/D) ratio, RV tortuosity, and arterial-venous (A-V) crossing changes, which their prevalence was 15, 13.3, and 6.7, respectively [30]. Ramakrishnan et al. detected fundus alterations in 14 % of patients with thalassemia, all of whom showed A-V tortuosity, and one of them also had a tessellated fundus [17]. Akritidou et al. detected retinal pigment epithelium (RPE) changes, fundus atrophy, epiretinal membrane (ERM), angioid streaks, and macular edema in 15.6, 9.3, 7.8, 4.6, and 3.1 % of β-TM population, respectively. The RPE degeneration was the most commonly observed fundus abnormality, and angioid streaks with choroidal neovascularization (CNV) were the most severe vision-threatening finding. Angioid streaks are usually asymptomatic, but if they extend to the fovea and result in subretinal hemorrhage or CNV, they cause significant disturbances in VA. ERM may lead to vitreoretinal traction (27). Haghpanah et al. detected fundus anomalies in 8 (10.1 %) of patients with thalassemia, 6 of whom showed non-PXE-like syndrome manifestations, and the most prevalent retinal alteration was

increased C/D ratio (more than 30) with a prevalence of 3.8 % [19].

Abo-Zied et al. showed that the association between retinal changes and serum ferritin level was insignificant among the patient group (14). Haghpanah et al. findings were in the same line [19]. Although iron overload can be an important pathology for fundus abnormality in β-TM patients, finding no significant correlation between serum ferritin level and retinal changes can be due to the small size of the study sample and not using a more accurate method for showing iron overload, such as liver iron concentration or liver T2-weighted MRI imaging. These results were in contrast with other studies reviewed. Saif et al. detected a highly/strong significant correlation between various fundus alterations (increased C/D ratio, venous tortuosity, and A-V crossing changes) with serum ferritin [30]. Jafari et al. also found a significant correlation between RPE degeneration and serum ferritin levels [15].

Abo-Zied et al. showed an insignificant correlation between retinal changes of β-TM patients and the frequency of blood transfusions, which agreed with the results in the study by Saif et al. [14, 30].

Jethani et al. studied 112 β-TM children and showed that retinal alterations in patients taking DFO were significantly lower than in the patients not taking DFO and concluded that such complications are due to iron overload and not secondary iron overload due to ICT [31], while Saif et al. reported a highly significant correlation between using ICT and developing different fundus alterations among β-TM patients; the prevalence of these changes in the patients taking ICT was more than those not taking [30].

Haghpanah et al. showed that there was not any significant association between fundus abnormalities among β-TM patients based on the type of chelators they consumed [19]. Jafari et al. did not find any significant association between the prevalence of RPE degeneration and the chelator type among β-TM patients, while 12/18 % (most) of β-TM patients developed retinal changes (RPE degeneration) were taking DFO in combination with DFX [15]. In the study by Abo-Zied et al., although all β-TM patients with retinal abnormalities took DFO together with DFP, there was an insignificant correlation between retinal alterations and the type of chelating agents (14). By examining the long-term impact of ICT on ocular manifestations, Nuzzi et al. found a protective effect against retinal alterations in patients taking higher dosages of DFX (p-value: 0.006, OR: 0.93) [16]. [NO_PRINTED_FORM][NO_PRINTED_FORM] [13]

While most references are consistent with the impact of iron overload in evolving retinal changes, there is controversy over the effect of chelator type on developing fundus alterations among patients with thalassemia. Studies' results are so unequal from those that find DFO as a protective factor for RPE degeneration and DFP as a helping factor for this alteration to those which introduce DFO as a major factor for retinal abnormalities, especially in high dosage and intravenous administration route [26, 28, 32-36]. Numerous pieces of evidence show an insignificant association between the type of chelators and developing retinal abnormalities [13, 37].

Increased intraocular pressure

The normal value of increased intraocular pressure (IOP) is considered as <= 21 mmHg [16]. Increased IOP and ocular hypertension can be detected among patients with thalassemia. A possible cause is iron overload in the trabecular meshwork [14, 19].

Abo-Zied et al. found that the prevalence of ocular hypertension in the β-TM group was significantly higher than in the healthy group [14]. In the study by Jafari et al., although the mean IOP values were in the normal range in both case and control groups, the mean IOP values of β-TM patients were significantly higher than the control group [15]. On the contrary, Elkitkat et al. did not find a significant difference between the mean IOP values of the two groups, and their findings agreed with those reported by Aksoy et al. [11, 38]. Examined IOPs among β-TM patients in the study by Nuzzi et al. were within the normal range. Linear regression showed that higher IOPs were inversely correlated with the duration of DFO therapy so that for each year of treatment, there was a probability of 0.12 mmHg reduction in IOP (P-value: 0.002, association coefficient -0.12) [16]. Haghpanah et al. found that the IOP values of almost all β-TM patients were within the normal ranges except for two diabetic patients with diabetes mellitus whose IOPs were 24 and 25 mmHg. They also found that the IOP values of diabetic patients with diabetes were significantly higher than non-diabetic patients, while, as mentioned, the IOP values of only two of them were above normal limits [19].

Evidence shows that the IOP values of β-TM patients are mostly within the normal limit, and DM is a factor found with increased IOPs among these patients.

Abnormal OCT findings

Measurement of retinal nerve fiber layer (RNFL) thickness provides valuable information about structural changes in the retina and the diseases related to the optic nerve. Optical coherence tomography (OCT) is a non-invasive procedure that determines this information with high-level sensitivity [13, 39, 40].

Haghpanah et al. demonstrated that there was not any significant difference between the RNFL values of patients and controls (41). Nuzzi et al. also revealed the same results in terms of RNFL thickness [16].

Based on two studies, the mean peripapillary RNFL thickness among β-TM patients was significantly lower than the healthy individuals in all quadrants [38, 40]. Thinner RNFL thickness can be due to iron overload in the optic nerve, consequent oxidative damage, and cell apoptosis [38].

In a study, the macular thickness was compared between β-TM patients and controls, and the results showed significantly lower macular thickness in the case group [41].

According to conflicting results of RNFL measurements in β-TM patients, new studies should be done to reach more consistent results.

Visual field defects

The visual field (VF) consists of central and peripheral portions (superior, inferior, nasal, and temporal), which are examined by perimetry [42].

Nuzzi et al. examined the VF of the study population by manual and computerized methods. They found alterations in 10 eyes (7.35 %) of the β-TM study sample, 8 of which were asymptomatic and had a mild incision in the temporal VF. The remaining two eyes had upper VF narrowing, probably due to blepharochalasis. Mentioned findings had no relationship with the treatment duration or dosage of the chelator agents [16].

Jafari et al. examined the VF of the study sample and detected general depression, paracentral scotoma, and superior and inferior arcuate scotoma in 66.3, 17.3, 6.7, 4.8, and 4.8 % of the thalassemia group, respectively. These findings had no significant correlation with the type, duration, dosage of received

chelators, or serum ferritin level [15].

Some studies demonstrated correlations between the incidence of VF alterations among β-TM patients and high-dosage and IV administration routes of DFO therapy; therefore, using low dosages of DFO subcutaneously will not cause VF disturbances [28, 32, 43].

Impaired Visual acuity

Visual acuity (VA) is the ability of the visual system to distinguish details of objects (contrast)[44]. which is normally evaluated by subjective methods [45].

Nuzzi et al., by examining the effect of iron chelation therapy on 80 β-TM patients, did not find any decreased VA among the study sample [16], while Thakur et al. concluded that decreased VA was significantly more prevalent among the patients' group than the control group. There was no statistical correlation between this finding and serum ferritin level (18). In a study by Ramakrishnan et al., 20 % of the study sample had decreased VA for distant vision, while all had normal near vision [17].

Jafari et al. demonstrated that uncorrected VA in the β-TM group was significantly more prevalent than in the healthy group, and their defect was completely resolved using correcting lenses; thus, the reason for decreased VA among these cases turned out to be refractive errors [15]. This result was consistent with the study by Abo-Zied et al. [14]. In a study on 30 children with thalassemia, a decreased VA was detected in 66.7 % of the study sample, and none had retinal alterations [30], while Akritidou et al. found that 6.25 % of the study population had impaired VA due to CNV formation resulting from angioid streaks [27].

Some studies showed VA abnormalities due to DFO consumption, which were diminished after stopping DFO therapy or taking it in the form of subcutaneous administration instead of the IV route [32–34].

According to the literature, if impaired VA presents among β-TM patients, it can be due to refractive errors, developed retinal alterations, or the type of ICT (taking DFO).

A summary of what was stated earlier in this review about the relationship between the treatments of thalassemia major and the ocular complications observed in these patients can be seen in Tables 2 and 3.

Conclusion

β-TM patients are at risk of evolving ophthalmologic complications due to chronic anemia, iron overload, iron chelating therapy, and orbital bone changes. The literature review showed conflicting results regarding the impact of iron-chelating agents on ocular abnormalities; some consider these medications as ocular protective agents, while some surveys consider them as risk factors. Hence, new studies with larger sample sizes need to be conducted to reach more consistent results by using only one type of iron-chelating agent from the beginning of their therapeutic regimen. On the other hand, there are many controversies regarding the prevalence of various ocular complications and their correlation with different characteristics of β-TM, such as hematologic values, which warrants studies with larger sample sizes. As a result of the progress in the treatment and management methods of β-TM and, therefore, increased patients' life expectancy, finding more complications, including ophthalmologic complications, is unavoidable among them; therefore, a regular life-long follow-up would be necessary for timely diagnosis and treatment of such complications.

Table 1: The most important ocular abnormalities related to β-TM raised in the literature

Ocular complication	References
Biometric changes	11,12
Refractive errors	11–16
Presbyopia	13
Corneal and anterior chamber alterations	13,15,17–19
Dry eye disease	14,15,18,20,21
Lens opacities and cataracts	9,13–15,19,22,23
Posterior chamber and fundus abnormalities	9,13–16,18,19,22–33
Increased intraocular pressure (IOP)	11,13–15,19,34
Abnormal optical coherence tomography (OCT) findings	13,16,34–37
Visual field (VF) defects	13,15,24,27,38
Impaired visual acuity (VA)	13–15,17,18,23,27,28,31,32

Table 2: β-TM treatments and their significant risk associated ophthalmologic complications based on the literature

Conditions and treatments related to β-TM	Beta-thalassemia-related ophthalmologic complications
Number of RBC transfusions	Cataract [23]
Iron overload due to RBC transfusion (evaluated with serum ferritin or liver iron concentration)	- Corneal and anterior chamber alterations [19] - Dry eye disease [14,21,39] - Cataract [23] - Posterior chamber and fundus abnormalities [15,25,31]
Iron chelation therapy (ICT) without considering the chelator type	- Cataract [14] - Posterior chamber and fundus abnormalities [31]
Deferoxamine (DFO)	- Myopia, presbyopia [13] - Posterior chamber and fundus abnormalities [24,27–30,32]
Deferiprone (DFP)	Posterior chamber and fundus abnormalities [22]

Table 3: The ophthalmologic complications that their risk association with β-TM treatment was insignificant in the literature

Ophthalmologic complications	β-TM-related treatments and medications that have no risk associated with ophthalmologic complications or have no protective effects
Refractive errors	- Iron chelation therapy (ICT) [16] - Iron overload due to RBC transfusion [16]
Hyperopia and astigmatism	- ICT [13]
Presbyopia	- DFP dosage (protective effect) [13]
Corneal and anterior chamber alterations	- Dosage and duration of ICT [13] - Type of ICT [15]
Dry eye disease	- Type or dosage of ICT [15]
Cataract	- Dosage or duration of ICT [13] - Type of ICT [14,15] - Number of RBC transfusions [14]
Posterior chamber and fundus abnormalities	- Iron overload due to RBC transfusion [14,19,43] - Number of RBC transfusions [31] - ICT [13,26] - Type of ICT [14–16,19,33] - DFP [24] - DFO (protective effect) [22] - DFX (protective effect) [13]
Increased intraocular pressure	- DFO (protective effect) [13]
Visual field defects	- Iron overload due to RBC transfusion [15] - Dosage of ICT [13] - Type, dosage, or duration of ICT [15]
Impaired visual acuity	- Iron overload due to RBC transfusion [17]

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Footnotes and Financial Disclosures

Conflict of interest:

The authors have no conflict of interest with the subject matter of the present manuscript.