Ocular abnormalities in multi-transfused beta-thalassemia patients

Reza Jafari, Samira Heydarian, Hosein Karami, Mohammad Momeni Shektaei, Kiumars Noruzpour Dailami, Ahmad Ahmadzadeh Amiri, Majid Reza Sheikh Rezaee, Asad Allah Farrokh Far

Aims: The aim of this study was to assess ocular changes in thalassemia patients who have received multiple transfusions and chelate binding therapy in order to avoid iron accumulation.

Settings and Design: A cross-sectional study. Subjects and Methods: A total of 54 thalassemia major patients were selected as case group, and 54 age- and sex-matched healthy subjects were regarded as a control group. Ocular examination included visual acuity, refraction testing, slit lamp examination, funduscopy, tonometry, perimeter, tear break-up time test, and color vision testing were performed for all the participants. We computed the frequency and duration of blood transfusion, the mean serum ferritin level, pretransfusion hemoglobin concentration, and type, duration, and daily dose of chelation therapy for thalassemia patients based on their records. Statistical Analysis Used: All data analysis was performed using SPSS, version 19. Results: All the thalassemic patients were asymptomatic, but abnormal ocular findings (dry eye (33.3%), cataract (10.2%), retinal pigment epithelium degeneration (16.7%), color vision deficiency (3.7%), and visual field defects (33.7%)) were seen in 68.5% of thalassemic group. The prevalence of ocular abnormalities in normal group was 19.4%, which was significantly lower than that in thalassemia patients (P = 0.000). No significant correlation was found between ocular abnormalities and mean serum ferritin level (P = 0.627) and mean hemoglobin concentration (P = 0.143). Correlation of number of blood transfusion with the presence of ocular abnormalities was found to be statistically significant (P = 0.005).

Conclusions: As life expectancy for beta-thalassemia patients extends, regular ophthalmological evaluation to detect early changes in their ocular system is recommended.

Key words: Beta-thalassemia major, blood transfusion, chelation therapy, ferritin, ocular abnormality

Beta-thalassemia is one of the most common hemoglobinopathies.[1] Blood transfusion therapy on a continuing basis represents the primary treatment for beta-thalassemia.[2] Although this treatment alleviates anemia, it leads to massive tissue deposition of iron and may eventually result in multi-organ dysfunction.[3,4] Iron-chelation therapies are frequently used to minimize iron overload in these patients.[1]

The effectiveness of deferoxamine as a therapeutic approach to iron overload has been proved in the previous studies.[5,6] However, treatment with deferoxamine is cumbersome, expensive, and unpleasant and presents some long-term toxic effects.[7] Thus, there was a great need for development of an alternative iron-chelator based on three main criteria namely oral activity, low cost, and low toxicity.[6,8] Deferiprone and deferasirox are two new iron chelation drugs that have been introduced for clinical use as an orally effective substitute for deferoxamine.[6,9]

Ophthalmologic changes might occur as a result of the disease itself or as side effects of iron chelators and include ocular surface disorders, cataract, angiod streak, retinal venous tortuosity, retinal toxicity, retinal pigment epithelium (RPE) degeneration and mottling, optic neuropathy, and decreased visual acuity.[10-17]

This study was conducted to assess the prevalence of ocular abnormalities in multi-transfused beta-thalassemia patients and to determine their relationship with serum ferritin level, hemoglobin concentration, and the type, dosage, and duration of chelation therapy.

Subjects and Methods

This study was conducted in the thalassemia research center. Thalassemia patients in Sari are all registered in this center in order to receive treatment. Patients were selected with simple random sampling method by using computerized tables. Of 66 randomly selected patients, 10 patients were excluded because of diabetes, and 2 subjects because of previous cataract surgery. Fifty-four patients with transfused dependent beta-thalassemia major, who had been receiving chelation for at least 2 years, ranging in age between 14 and 42 years, were evaluated in the study as a case group. Each patient received regular...
transfusions of packed red cells at 15–30 days intervals to maintain their hemoglobin concentration at a level above 9 g/dl.

The serum ferritin level was measured in all thalassemic patients at 6 months intervals. Hemoglobin was measured before each transfusion, and the records were kept in their records. For the purpose of the study, we computed the frequency and duration of blood transfusion, the mean serum ferritin level, pretransfusion hemoglobin concentration, and type, duration, and daily dose of chelation therapy for each patient based on their records.

To compare the results with those of a normal population, 56 age- and sex-matched healthy control subjects were recruited from the staff of Bou-Ali Sina Hospital (2 individuals were excluded because of bilateral amблиopia). Patients in the control group did not have any history of iron deficiency or any other blood disorders.

Patients with ophthalmic disease, amблиopia, aphakia, strabismus, and systemic disease which may lead to ocular abnormalities were excluded. All patients were fully informed about the nature of the study according to the codes of ethics in the Declaration of Helsinki protocol, and then written consent for participation obtained from all participants or their legal guardians.

Each patient underwent a complete eye examination. Ocular examination included visual acuity, refractive measurement, slit lamp examination, funduscopy, tonometry, perimeter, tear break-up time (TBUT) test, and color vision testing. Refractive errors were measured by autorefractometer (mean of 3 measurements by Topcon Autorefractometer model KM 8900, Japan). Uncorrected and best-corrected visual acuity was determined monocularly, at 6 m using tumbling E chart, retro illuminated with luminance of 100 cd/m². We used this chart because, in our country, people do not use the alphabet in their native language, and it is the most prevalent chart which is used. Slit lamp biomicroscopy (model BQ 900: Haag-Streit, Bern, Switzerland), ophthalmoscopy (Ophthalmoscope Heine Beta 200, Germany), and intraocular pressure examination, using Goldman tonometer were done for each eye.

TBUT test was used to diagnose dry eye syndrome. The BUT was evaluated without topical anesthetia, using a slit lamp microscope and a cobalt-blue filter. Fluorescein solutions were instilled in the conjunctival sac of the patients. The patients were told to blink several times constantly for a few seconds to ensure homogeneous distribution of fluorescein. The time interval between the last complete blink and the first tear film break-up was recorded. A TIBUT of <10 s was considered as dry eye.[18]

Ishihara test was used to diagnose red-green color vision deficiency of patients. The Humphrey Field Analyzer II (750 I Series, Carl Zeiss Meditec) was used to conduct 30-2 SITA-fast visual field (VF) test in all subjects. We used SITA-fast strategy that decreased test duration and reduced patient fatigue in order to produce more reliable and repeatable VF test results.[19] The reliability of information derived from VF tests related to the ability of the patients. However, standardized reliability criteria have been approved at the 7th VF symposium at Amsterdam.[20] The test was repeated in patients with high fixation loss (more than 20%), high false positive (more than 33%), and high false negative (more than 33%) in order to achieve accurate and valuable results.[20–22]

To interpret VF results, we consider global hemifield test, grayscale, and total and pattern deviations of each patient. Global indices were considered as a numerical quantification of VF loss.

Data were analyzed in SPSS.19 software (SPSS for Windows, SPSS Inc., Chicago, IL, USA). Chi-square tests, Mann–Whitney U-tests, ANOVA, Student’s t-tests, and Spearman correlation were used where applicable. Ocular findings in thalassemia patients were correlated with number of blood transfusion received serum ferritin level, and the type, dose, and duration of chelation therapy. The prevalence of ocular changes in the thalassemic patients was compared with that in the control group. In order to evaluate the effect of different type of chelators on the eye of case group, thalassemia patients were divided into three groups based on the type of chelators they received: Group A received blood transfusion and subcutaneous deferoxamine, Group B blood transfusion combined with subcutaneous deferoxamine and oral deferiprone, and Group C blood transfusion along with Osveral (an Iranian-made deferasirox). The level of significance was set at 0.05.

Results

Fifty-four thalassemia subjects aged 14–42 years and 54 healthy controls aged 16–42 years were evaluated for ocular abnormalities. Among thalassemia patients, 23 subjects (42.6%) were male, and 31 subjects (57.4%) were female. The mean age ± standard deviation (SD) of thalassemic patients was 25.40 ± 6.94 years. The control group included 108 eyes of 56 subjects (54.6% male and 45.4% female) with a mean age of 26.74 ± 6.5 years. There was no significant difference for sex and age between the groups (P = 0.077, P = 0.152, respectively).

The mean serum ferritin level of thalassemic patients was 1695 ± 975 mg/ml, and the mean level of hemoglobin in them was 8.42 ± 0.96 g/dl. Of 54 thalassemia patients, 15 received blood transfusion and subcutaneous deferoxamine, 26 patients received blood transfusion combined with subcutaneous deferoxamine and oral deferiprone, and 13 patients received blood transfusion along with Osveral. Table 1 shows the characteristics of thalassemia patients based on the type of chelation they received.

The mean spherical equivalent was –0.0093 ± 0.86 in thalassemia major patients and –0.22 ± 1.33 in the normal group, and no significant difference was found between spherical equivalent of subjects in two groups (P = 0.204).

The mean ± SD values for uncorrected visual acuity was 0.93 ± 0.14 in thalassemia patients, which was significantly different from that in normal group (0.84 ± 0.27, P = 0.016). However, corrective lens normalized visual acuity in all subjects of both groups.

All the thalassemic patients were asymptomatic, but abnormal ocular findings (dry eye [33.3% (95% confidence interval [CI], 24.29%, 42.36%]), cataract [10.2% (95% CI, 4.38%, 15.98%)], Retinal pigment epithelium degeneration [16.7% (95% CI, 9.52%, 23.80%)], color vision deficiency [3.7% (95% CI, 0.08%, 7.32%)], and VF defects [33.7% (95% CI, 24.57%, 42.73%)]) were seen in
68.5% (95% CI, 59.61%, 77.41%) of thalassemic group. The prevalence of ocular abnormalities in normal group was 19.4% (95% CI, 11.85%, 27.02%), which was significantly lower than that in thalassemia patients (P = 0.000). Table 2 presents the prevalence of abnormal ocular findings between two groups.

According to the table, prevalence of cataract in thalassemia group was 10.2% (95% CI, 4.38%, 15.98%), while none of normal individuals had any cataractous changes in their lens (P = 0.001).

The mean ± SD TBUT among thalassemia patients was 12.62 ± 6.06 s which was significantly lower than that in normal group (16.12 ± 5.73 second, P = 0.000).

The mean IOP in both groups was within the normal range, and we found statistically significant difference between the groups regarding intraocular pressure (P = 0.048). The mean IOP in the case group was 11.40 ± 2.174 in comparison to 10.93 ± 2.24 in the control group.

Of 108 VF results of thalassemic patients, 4 were excluded because of poor cooperation of patients and their low test reliability (in spite of repeating the test), so we consider 104 VF results in statistical analysis. The prevalence of VF abnormality among thalassemia patients was 33.7% (95% CI, 24.57%, 42.73%), including 17.3% (95% CI, 10.03%, 24.57%) general depression, 6.7% (95% CI, 1.92%, 11.54%) paracentral scotoma, 4.8% (95% CI, 0.69%, 8.91%) superior arcuate scotoma, and 4.8% (95% CI, 0.69%, 8.91%) inferior arcuate scotoma. Table 3 represents the prevalence of different type of VF defects between the two groups.

Table 4 shows ocular involvement among thalassemic patients, based on the type of chelator they received. According to the table, there was no significant difference between the prevalence of different type of ocular abnormalities, among three thalassemic groups.

Table 5 shows the correlation of ophthalmologic manifestations with serum ferritin level, mean hemoglobin concentration, number of transfusion, and the dose and duration of chelation therapy.

According to the table, no significant correlation was found between ocular abnormalities and mean serum ferritin level (P = 0.627) and mean hemoglobin concentration (P = 0.143). Correlation of number of blood transfusion with presence of ocular abnormalities was found to be statistically significant (P = 0.005). In patients who used Osveral or deferoxamine, we found no significant correlation between the presence of ocular abnormalities with dose (P = 0.828, P = 0.302, respectively) and duration (P = 0.372, P = 0.101, respectively) of chelation therapy, while in those who used deferoxamine in combination with deferiprone, there was a significant relation between ophthalmologic manifestation with duration treatment (P = 0.001, P = 0.029, respectively), but not with dose of chelators agents (P = 0.94, P = 0.063, respectively).

**Discussion**

The prevalence of ocular abnormalities in the thalassemic patients has already been studied during the past decades.[10-17] In the present study, we found no significant differences in the spherical equivalent between thalassemia and normal patients, which was similar to the previous studies.[23,24] About 21.29% of our thalassemic patients had decreased visual acuity. In those with decreased visual acuity, refractive error was found to be the case, and the vision was fully correctable with glasses. This observation was consistent with findings of previous studies.[10,11] Taneja et al. found reduced visual acuity in 33% of their subjects which was fully correctable with corrective lenses.[11] Taher et al. also found that the type of iron chelating agent used had no influence on the decrease in visual acuity.[10]

In the current study, which involve 54 thalassemic subjects with different ages (ranged 14–42), the prevalence of ocular abnormalities was 68.5% which was higher than some previous studies.[11-12,14] Different percentages of ocular abnormalities were reported in previous studies; this is because of different parameters that they evaluate in their studies or age range.

| Table 1: Characteristics of thalassemia patients based on the type of chelation they received |
|-----------------------------------------------|
| Hemoglobin concentration (g/dl) | Serum ferritin level (mg/ml) | Number of blood transfusion | Duration of chelation therapy (year) | Duration of blood transfusion (year) | Chelators dose (ml/kg/day) |
|-----------------------------------------------|
| Desferal* 8.70±1.12 (6-10.5) 1506.66±791 (200-2500) 457.17±113 (292-730) 28.40±8.47 (13-40) 27.06±8.08 (14-40) 3333±6.06 (20-40) |
| Desferal + L-one† 8.40±0.94 (7-11) 2055.76±160 (500-4000) 363.68±98.39 (160-648) 22.30±5.92 (11-34) 22.92±5.97 (11-34) 31.15±7.04 (20-40) 3.8±1.51 (1-6) 48.40±15.82 (30-80) |
| Osveral‡ 8.15±0.73 (7-10) 1190.76±685 (310-3000) 327.89±88 (175-474) 3.15±2.6 (1-5) 20.15±5.6 (12-28) 24.23±5.23 (20-40) |
| Total 8.42±0.96 (6-11) 1695±975 (200-4000) 380.89±111.42 (160-730) 18.70±10.93 (20-40) 23.40±6.97 (11-40) |

*Deferoxamine, †Deferoxiprone, ‡Iranian-made deferasirox

| Table 2: Prevalence of abnormal ocular findings among two groups |
|-----------------------------------------------|
| Anomaly | Dry eye | Cataract | Visual field defect | RPE degeneration | Color vision deficiency | Pinguecula |
|-----------------------------------------------|
| Thalassemia (%) | 68.5 (59.61-77.41) | 33.3 (24.29-42.36) | 10.2 (4.38-15.98) | 33.7 (24.57-42.73) | 16.7 (9.52-23.80) | 3.7 (0.08-7.32) |
| Normal (%) | 19.4 (11.85-27.02) | 9.3 (3.70-14.81) | | 10.2 (4.38-15.98) | 0.9 (0.16-5.07) | 3.7 (0.08-7.32) |

CI: Confidence interval, RPE: Retinal pigment epithelium
of their participants. Dewan and Gomber[11] reported ocular involvement in 36% of their subjects while Taneja et al.[11] reported figure of 58%. They do not evaluate VF defects and dry eye in their study, which were the most prevalent ocular manifestation in our study. On the other hand, an average number of blood transfusion in our study was 327.89 ± 88 which was higher than previous studies.[11,12,14,16] This is because, we evaluate thalassemia subjects aged 14–42 years, who received blood transfusion from the 1st years of their life, while most of the previous studies evaluatethalassemia children in younger age groups with lower number of transfusion.[11,12,14,16] Moreover, as we found a significant positive correlation between the number of blood transfusion and age of thalassemic patients with prevalence of ocular abnormalities, the prevalence of ophthalmic manifestations in our study was more than that in some previous studies.[11,12,14] However, considering different age range of the participants in other studies and different parameters they evaluated, it could be difficult to make an accurate comparison.

We found peripheral cortical cataract in 10.2% of thalassemic subjects (11 out of 108 eyes). None of these opacities was in the visual axis, and, therefore, none interfered with vision. Gartaganis et al.[17] and Taneja et al.[11] found lens opacities in 13.8% and 40% of their subjects, respectively. Of 11 eyes with lens opacity, seven were in Group B, who received blood transfusion combined with subcutaneous deferoxamine and oral deferiprone. A recent report of two cases of cataract after using deferiprone raised the issue of a possible association between deferiprone consumption and development of cataract.[23] In the present study, cortical cataract was found in 6.7%, 13.7%, and 7.7% of eyes of patients who consumed deferoxamine, deferoxamine combined with deferiprone, and Osveral, respectively. Although the prevalence of cataract in those who used deferiprone was more than other patients, the difference was not statistically significant. These findings were approximately similar to those that reported by Nowroozzadeh et al.[23] In their study, the prevalence of cataract was 10.7% and 18.8% in those who consumed deferoxamine and deferiprone, respectively (P = 0.36).

We found RPE degeneration in 16.7% of thalassemic patients. Taneja et al.[11] and Sathwara et al.[12] reported figures of 31% and 17.6%, respectively, in their studies. Our results

Table 3: Prevalence of different type of visual field defects among two groups

|                | Thalasemia | Normal |
|----------------|------------|--------|
| Normal (%)     | 66.3 (57.26-75.42) | 89.8 (84.11-95.51) |
| General depression (%) | 17.3 (10.03-24.57) | 10.2 (4.48-15.88) |
| Paracentral scotoma (%) | 6.7 (1.92-11.54) | - |
| Superior arcuate scotoma (%) | 4.8 (0.69-8.91) | - |
| Inferior arcuate scotoma (%) | 4.8 (0.69-8.91) | - |
| Total           | 104        | 108    |
| Poor cooperation| 4          |        |
| Total           | 108        |        |

CI: Confidence interval

Table 4: Ocular involvement among thalassemic patients, based on the type of chelators they received

|                | Group A (%) | Group B (%) | Group C (%) |
|----------------|------------|-------------|-------------|
| Anomaly       | 80 (65.27-94.72) | 59.6 (45.99-73.23) | 73.1 (55.49-90.66) |
| Cataract       | 6.7 (1.85-21.33) | 23.1 (11.38-34.77) | 7.7 (2.13-24.14) |
| Dry eye        | 40 (21.69-58.03) | 28 (11.62-34.52) | 46.2 (26.38-65.91) |
| Visual field defect | 40 (22.50-57.53) | 23.1 (11.38-34.77) | 37.5 (18.14-56.86) |
| RPE atrophy    | 13.3 (8.11-25.84) | 7.7 (0.29-15.08) | 7.7 (2.13-24.14) |
| Color vision deficiency | 0 (0.00-0.00) | 46.2 (32.31-59.99) | 0 (0.00-0.00) |
| Pinguecula     | 46.7 (28.30-65.03) | 46.2 (32.31-59.99) | 30.8 (12.47-49.06) |

*Those who received blood transfusion and subcutaneous deferoxamine, †Those who received blood transfusion combined with subcutaneous deferoxamine and oral deferiprone, ‡Those who received blood transfusion along with Osveral (an Iranian-made deferasirox). CI: Confidence interval, RPE: Retinal pigment epithelium

Table 5: Correlation of ophthalmologic manifestations with age. Serum ferritin level, mean hemoglobin concentration, number of transfusion, and dose and duration of chelation therapy

|                | P        |
|----------------|----------|
| Anomaly        | 0.627    |
| Cataract       | 0.496    |
| Visual field defect | 0.247    |
| Dry eye        | 0.016    |
| RPE degeneration | 0.651    |
| Color vision   | 0.187    |

RPE: Retinal pigment epithelium
showed that 12 out of 18 patients with RPE degeneration were used deferiprone in combination with deferoxamine. However, we found no significant difference between the prevalence of RPE degeneration among thalassemia patients based on chelator agents they used. Taneja et al. reported that patients with RPE changes had received lesser dose of deferoxamine and larger dose of deferiprone. Thus, they conclude that deferoxamine may be protective while deferiprone use may be contributory to the occurrence of RPE degeneration.[11] Furthermore, Taher et al. found that patients on deferiprone have RPE degeneration 4 times as much as those on deferoxamine.[16] This observation is consistent with our study. Sathwara et al. reported that the prevalence of RPE degeneration in those who used deferoxamine was significantly lower than those who do not receive that and conclude that the ocular abnormalities were mainly because of iron overload and not secondary to chelation therapy.[12] Iron causes oxidative damage to protein, lipids, and DNA through the generation of free radicals in the Fenton reaction, and it has been shown to disrupt the blood-retinal barrier. Therefore, iron may play a role in the pathogenesis of retinal degeneration as a source of free radical damage.[26] However, we do not found any correlation between prevalence of RPE degeneration and serum ferritin level and number of infusion.

VF examination revealed abnormalities in 33.7% of thalassemic patients, with the most common abnormality being general depression (17.3%). Simon et al.[27] reported sudden peripheral VF loss due to high dose intravenous deferoxamine for reducing systemic iron overload. Their findings were similar to those that reported by Shahriari et al.[13] who found 74% VF abnormality among their patients and a significant correlation between the presence of VF abnormality and dose of deferoxamine. All their patients who received more than 40 mg/kg/day of deferoxamine had VF defects. However, in our study, we do not found any correlation between VF defects and type, duration, and dosage of chelator agents. This can be attributed to use of lower doses of chelators comparing to other studies. In our study like Rahiminejad et al.,[28] none of our cases were symptomatic, so we can conclude that in the absence of electrodiagnostic tests, perimetry is useful for early detection of ocular problems.

We found color vision deficiency in only 2 thalassemic patients (red-green deficiency), it seems that color vision deficiency in these patients was hereditary, and we found no correlation between incidence of color vision disorders and type, dose, and duration of chelation therapy. Our findings were similar to those that reported by Rahiminejad et al.[28] and Dewan and Gomber.[14]

Our data showed a statistically significant increase in intraocular pressure in thalassemic patients compared with controls, which was similar to Nowroozzadeh et al.[23] findings. This increase might be due to iron overload in their trabecular meshwork. However, the mean IOP in both groups was within the normal range. According to previous studies, iron is potentially related to several ocular disease, including glaucoma, cataract, and age-related macular degeneration.[29-31]

The TBUT values were significantly lower in beta-thalassemia patients than in the control subjects, which was similar to those reported by Gartaganis et al. in 2003.[23] Our data also showed that there was a significant correlation between the patient's dry eye and serum ferritin level. It is known that increased iron deposition in the glands has a cytotoxic effect leading mainly to endocrine and exocrine dysfunction. The lacrimal glands are typical tubuloacinar exocrine glands, so iron overload will impair their exocrine secretion and cause tear film deficiency in these patients.[32] Our data also revealed that the prevalence of pinguecula, which is not related to using chelator agents or own thalassemia disease was significantly higher than normal patients, and we found a significant correlation between the presence of dry eye and pinguecula in these patients.

**Conclusion**

Although all of our thalassemia patients were asymptomatic, a large number of them revealed ocular abnormalities. We do not found any significant correlation between the prevalence of ocular abnormalities with serum ferritin level, hemoglobin concentration, and the type and dose of chelation therapy. Our study has some limitations; we compared the ocular side effects of three different treatment regimes, but since in our study entering into these regimes was not randomized, the differences (or lack of differences) between the groups may be a result of selection bias during planning of the treatment. In this study, those who received Osveral or deferiprone were on deferoxamine before being shifted to their current treatment, and there is a possibility that their ocular abnormalities could have occurred before changing treatment. Overall, the association between ocular abnormality and chelator type has not been established in the present study. Hence, further prospective investigation with a large sample of thalassemia patients based on the type of chelator they received is recommended.

As life expectancy for beta-thalassemia patients extends, regular ophthalmological evaluation to detect early changes in their ocular system is recommended, in order to achieve a better life quality for this patient group.

**Acknowledgment**

The authors wish to thank the staff and patients of the thalassemia research center and Bou-Ali Sina Hospital of Mazandaran University of Medical Sciences for their cooperation. We also very much appreciate the research Vice Chancellor of Mazandaran University of Medical Sciences for his sponsorship.

**Financial support and sponsorship**

This study has been granted by Mazandaran University of Medical Sciences.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Cao A, Galanello R. Beta-thalassemia. Genet Med 2010;12:61-76.
2. Propper RD, Button LN, Nathan DG. New approaches to the transfusion management of thalassemia. Blood 1980;55:55-60.
3. Olivieri NF, Nathan DG, MacMillan JH, Wayne AS, Liu PP, McGee A, et al. Survival in medically treated patients with homozygous beta-thalassemia. N Engl J Med 1994;331:574-8.
4. Kontogiorghs GJ. Ethical issues and risk/benefit assessment of iron chelation therapy: Advances with deferiprone/deferoxamine combinations and concerns about the safety, efficacy and costs of deferasirox. Hemoglobin 2008;32:1-15.
5. Bergeron RJ, Wiegand J, Brittenham GM. HBED: A potential alternative to deferoxamine for iron-chelating therapy. Blood 1998;91:1446-22.

6. Olivieri NF, Brittenham GM, Matsui D, Berkovitch M, Blendis LM, Cameron RG, et al. Iron-chelation therapy with oral deferiprone in patients with thalassemia major. N Engl J Med 1995;332:334-39.

7. Olivieri NF, Koren G, Matsui D, Liou PP, Blendis L, Cameron R, et al. Reduction of tissue iron stores and normalization of serum ferritin during treatment with the oral iron chelator L1 in thalassemia intermedia. Ann N Y Acad Sci 1990;612:319-27.

8. Kontoghiorghes GJ. Design, properties, and effective use of the oral chelator L1 and other alpha-ketohydroxypyridines in the treatment of transfusional iron overload in thalassemia. Ann N Y Acad Sci 1990;612:339-50.

9. Meerpohl JJ, Antes G, Rucker G. Deferosirox for managing iron overload in people with thalassemia. Cochrane Collab 2010;7:45-86.

10. Taher A, Wonke B, Kennedy C, Huehns E. Ocular findings among thalassemia patients. Am J Ophthalmol 2006;142:704-5.

11. Taneja R, Malik P, Sharma M, Agarwal MC. Multiple transfused thalassemia major: Ocular manifestations in a hospital-based population. Indian J Ophthalmol 2010;58:125-30.

12. Sathwara N, Marwah K, Jethani J, Patel SH, Shah B. Ocular abnormalities in patients with beta-thalassemia on transfusion and chelation therapy. AIOC; 2009. p. 434-5.

13. Shahrizat HA, Ghasemzadeh F, Eshghi P, Masoomian B. Ocular side effects of desferal in patients with β-thalassemia. Clin Exp Ophthalmol 2014;42:106-10.

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;5:11-4.

15. Gibson JM, Chaudhuri PR, Rosenthal AR. Angioid streaks in a case of beta thalassaemia major. Br J Ophthalmol 1983;67:29-31.

16. Gaba A, Souza PD, Chandra J, Narayan S, Sen S. Ocular changes in beta thalassemia. Ann Ophthalmol 1998;30:357-60.

17. Kartaganis S, Ismiridis K, Papageorgiou O, Beratis NG, Papanastasiou D. Ocular abnormalities in patients with beta thalassemia. Am J Ophthalmol 1989;108:699-703.

18. Lee JH, Kee CW. The significance of tear film break-up time in the diagnosis of dry eye syndrome. Korean J Ophthalmol 1988;2:69-71.

19. Bengtsson B, Olsson J, Heijl A, Rootzén H. A new generation of algorithms for computerized threshold perimetry, SITA. Acta Ophthalmol Scand 1997;75:368-75.

20. Heijl A, Lindgren G, Olsson J. Reliability parameters in computerized perimetry. Doc Ophthalmol Proc Ser 1987;49:593-660. Doi:10.1007/978-94-009-3325-5_75.

21. Anderson DR, Patella VM. Automated Static Perimetry. 2nd ed. St. Louis: Mosby; 1999.

22. Humphrey Instruments Inc. Humphrey Field Analyzer II User’s Guide. San Leandro, CA: Humphrey Instruments Inc.; 1994.

23. Nowroozzadeh MH, Kalantari Z, Namvar K, Meshkibaf MH. Ocular refractive and biometric characteristics in patients with thalassaemia major. Clin Exp Ophthalmol 2011;39:361-6.

24. Khalaj M, Sarokhani MR, Mahyar A, Hashemi HJ, Godsi F. Assessing refractive errors in beta-thalassemia major patients. J Guilan Univ Med Sci 2008;67:42-9.

25. Mehdiyazadeh M, Nowroozzadeh MH. Posterior subcapsular opacity in two patients with thalassaemia major following deferiprone consumption. Clin Exp Ophthalmol 2009;32:392-4.

26. Blasiak J, Sklodowska A, Ulimska M, Szaflik JP. Iron and age-related macular degeneration. Klin Oczna 2009;111:174-7.

27. Simon S, Athanasiov FA, Jain R, Raymond G, Gilhotra JS. Desferrioxamine-related ocular toxicity: A case report. Indian J Ophthalmol 2012;60:313-7.

28. Rahiminejad MS, Rahiminejad S, Rahimi M, Baghersalimi A, Inanlou S, Karimi M, et al. Ocular complication and visual evoked potential in beta-thalassemia patients on desferal therapy. Res J Biol Sci 2009;4:928-32.

29. García-Castiñeiras S. Iron, the retina and the lens: A focused review. Exp Eye Res 2010;90:664-78.

30. Wong RW, Richa DC, Hahn P, Green WR, Dunaiif JL. Iron toxicity as a potential factor in AMD. Retina 2007;27:997-1003.

31. 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;50:1895-902.

32. Kartaganis SP, Georgakopoulos CD, Exarchou A, Mela EK, Psachoulia C, Eliopoulou M, et al. Alterations in conjunctival cytology and tear film dysfunction in patients with beta-thalassemia. Cornea 2003;22:591-7.