· Meta-Analysis ·

Optical coherence tomography findings in beta-thalassemia major: a systematic review and Meta-analysis

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Abstract
● **AIM:** To describe the optical coherence tomography (OCT) findings of the retinal nerve fiber layer thickness (RNFLT) and choroidal thickness (CT) in beta-thalassemia major.

● **METHODS:** A systematic search was conducted on PubMed, Cochrane, and Embase using a combination of specific key words. The records found were screened in two phases (title/abstract, and full-text screening). All the original observational cross-sectional studies conducted on beta-thalassemia major cases and controls reporting the RNFLT and CT were included. The Meta-analysis was run for comparing the OCT measurements between beta-thalassemia cases and controls including pooled effect size, confidence intervals (CI), quality assessment, and publication bias. The measurements included were RNFLT (average, and in various quadrants), and CT.

● **RESULTS:** A total of 10 studies were included in this Meta-analysis including a total of 684 individuals, 362 cases and 322 controls. The RNFLT and CT showed a significant reduction in the values of beta-thalassemia cases as compared to controls. The heterogeneity among the included studies was found to be 92.65% for the average RNFLT and 30.13% for the CT making it obvious to use random effects model for analyzing the RNFLT values while fixed effects model for the CT. The Egger's test showed significant publication bias among all the parameters except for nasal RNFLT (P=0.507), and CT (P=0.281). The estimated average effect size for the average RNFLT was 1.04 (95%CI: 0.35 to 1.72, Z=2.961, P=0.003) and for CT was 0.74 (95%CI: 0.51 to 0.96, Z=6.523, P<0.001).

● **CONCLUSION:** This Meta-analysis concludes that the RNFLT and CT are significantly thinner in beta-thalassemia cases in comparison to healthy individuals. Therefore, the RNFLT and CT must be evaluated in routine clinical practice in order to avoid irreversible vision loss particularly in beta-thalassemia individuals.

● **KEYWORDS:** beta-thalassemia; retinal nerve fiber layer thickness; choroidal thickness; optical coherence tomography

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INTRODUCTION

Beta-thalassemia is a genetic disorder[1-3] that causes anemia due to defective hemoglobin production[4-7]. It affects about 15 million people globally and is most severe in its transfusion-dependent form[8-9], which leads to iron overload and organ damage[4,10-15]. Iron chelation therapy is used to manage excess iron, but it has side effects[16-19] and can create psychological and financial burdens, often resulting in poor treatment adherence and a lower quality of life for patients[15,20-25]. A number of studies have been conducted on thalassemia individuals that reported abnormality in the visual functions like reduced vision, reduced contrast sensitivity, diminished visual fields, defective color vision as well as ocular structures including ocular surface, corneal structural changes, intraocular lenticular opacities, retinal pigment epithelium degeneration, optic disc changes and other fundus abnormalities[16-19,26-28].

The literature presents variable information regarding the changes in the retinal nerve fiber layer thickness (RNFLT) and choroidal thickness (CT) of the eye due to thalassemia major[4,29-37]. A few of the studies from the literature showed a significant difference in the findings of RNFLT (average and in all four quadrants) between thalassemia major cases and healthy controls, with the cases showing reduced RNFLT[29-31]. However, other studies reveal no difference between both the groups[32-35,37]. A total of five studies reported the CT, and their findings show a significant difference in the thickness values between cases and controls. The cases, however, exhibit reduced CT values in comparison to controls[32-36].

The purpose of this systematic review and Meta-analysis is to highlight the changes in the RNFLT and CT on optical coherence tomography (OCT) due to beta-thalassemia major presented in the literature compared to healthy age-matched individuals.

MATERIALS AND METHODS

Study Design A systematic review and Meta-analysis was conducted to compare the OCT findings including RNFLT and CT between beta-thalassemia individuals and healthy controls according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[38]. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the code of CRD42024526145.

This Meta-analysis was conducted after getting approval from the supervisory committee at Lincoln University. The study was carried out as a part of partial fulfilment of the degree of Doctor of Philosophy in Health Sciences (Vision Sciences-Optometry).

Eligibility Criteria All the studies with the following features were included in this Meta-analysis: 1) Original observational cross-sectional studies conducted on human population; 2) Studies possessing two comparison groups: one group having beta-thalassemia major, and the other healthy control group to make comparison between the two; 3) Beta-thalassemia cases having regular blood transfusions and taking iron chelating therapy; 4) Studies reporting the values of RNFLT (average and/ or in various quadrants) and CT (sub-foveal) as mean and standard deviation, measured using OCT (any model).

Those studies that were irrelevant to the aim of this study, clinical trials, case controls studies, cohort studies, abstracts, conference papers, case reports, case series, review articles, Meta-analysis, animal studies, and those lacking a control group were considered ineligible and were excluded.

Information Sources This systematic review of the literature regarding OCT findings including RNFLT and CT in beta-thalassemic individuals was based upon the extensive literature search. The literature search was conducted in research databases PubMed, Cochrane, and Embase to find out any relevant published data in English articles till February 2024.

Search Terms An extensive search was conducted using online databases including PubMed, Cochrane, and Embase. The following search terms were used: 1) [β-thalassemia] OR [β-thalassemia major] OR [Beta thalassemia major] OR [Beta thalassemia]; 2) [Optical coherence tomography] OR [OCT]; 3) [Retinal nerve fiber layer thickness] OR [RNFL]; 4) [Choroidal thickness]; 5) [1] AND [2] AND [3] AND [4].

Search Strategy A total of 1189 publications were retrieved including 577 from PubMed, 340 from Cochrane, and 237 from Embase, while 35 records were identified from the reference lists of the included studies. In the PubMed database, the advanced search mode was used to build the search. All the retrieved data was exported in to EndNote Library and was then subjected to the removal of duplicates followed by primary and secondary screening. Out of a total of 1189 records, 464 were found to be duplicates and were removed with a remaining number of 725 which then undergone screening. Primary screening of these 725 articles was done by reading the article titles and excluding the irrelevant data. At the end of primary screening, 686 articles were excluded and for the remaining 39 articles, available full texts were read by the researcher (secondary screening). For those abstracts whose full-texts were not found or unavailable were excluded. After reading the full text articles, only 10 were found to be included in the study based on the eligibility criteria. Only English papers were included. The authors of the articles were also contacted to recover the missing data where allowed by resources.

Data Extraction Two reviewers independently reviewed all the included studies after screening of the duplicates and irrelevant studies. Any disagreements were resolved by discussion and mutual consensus. The summarized data from the included studies was entered in an excel sheet including the author information, year of publication, study design, study location, characteristics of participants (mean age, gender distribution), sample size, OCT modality, and the mean and standard deviation pertaining to the RNFLT and CT for both the cases and controls.

Data Analysis The data extracted from different studies was gathered in an excel spreadsheet including sample size, mean, and standard deviation of the cases and control group to undergo Meta-analysis. The effect size was measured using online tools as Cohen's *d* for equal sample sizes and Hedges' *g* for unequal sample size of the two groups. The standard error of the effect size was determined in the excel spreadsheet using a specifically designed formula.

$$SEd = \sqrt{\frac{n1 + n2}{n1 \times n2} + \frac{d^2}{2(n1 + n2)}}$$

Where; *SEd* is the standard error of effect size, *n1* is the sample size of cases, *n2* is the sample size of controls, d^2 is the square of effect size.

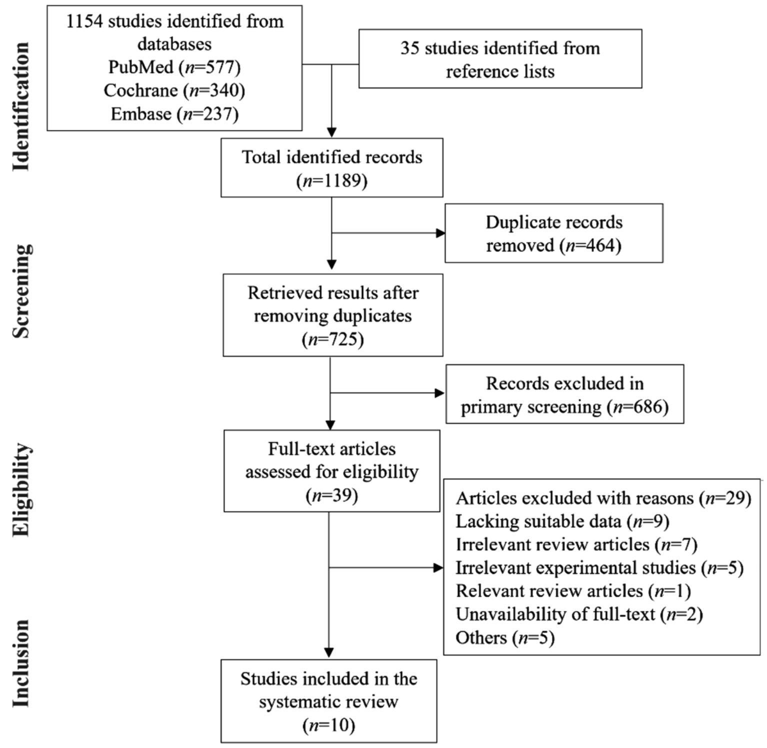

Figure 1 PRISMA flowchart representing the process of identification, screening, and inclusion of studies based on eligibility criteria.

The data was analyzed using JASP (Jeffreys's Amazing Statistics Program) software considering *P*-value of <0.05 as significant. The heterogeneity in the studies was measured using Higgins I^2 test, and the variables with heterogeneity above 40% were analyzed using random-effect models (DerSimonian-Laird model) while others were analyzed using fixed-effect model.

Egger's test and funnel plots were used to assess the potential publication bias for each of the variables. The *Z*-value of the test statistic represent the publication bias, the larger the values, the stronger the indication of publication bias. A *P*-value of less than 0.05 shows the evidence of significant publication bias.

The sensitivity analysis was also performed by omitting the studies having larger effect size and using restricted maximum likelihood random effects model instead of DerSimonian-Laird model.

Quality Assessment The quality of the included studies was assessed and the potential sources of bias in the individual studies were identified using Newcastle-Ottawa scale (NOS) for case-control studies[31-36]. NOS considers three main domains of selection, comparability, and exposure. All the statements of these domains were read and the most suitable one was selected and given a star based on the eligibility of each study (the questions were answered after carefully reading the methodology section of each study). The total number of stars were then calculated and mentioned in the form of a table against each study. A total of 8 score is the highest, the lesser the score the higher the bias and reduced the quality of the study.

RESULTS

Study Selection A PRISMA flow chart identifying all the relevant studies was shown in Figure 1. A total of 1189 records were identified including 1154 from online databases (577 from PubMed, 340 from Cochrane, and 237 from Embase), and 35 from the reference lists. A total of 725 articles were included in the screening process after the removal of duplicates (464). Out of those 725 articles that undergone primary screening (review of article title and abstract), 686 were excluded while 39 full-text articles were evaluated for eligibility. From those 39 full-text articles, 10 studies were included in this systematic review and Meta-analysis after excluding 29 articles (due to irrelevant data, experimental study design, unavailability of full-text articles, irrelevant review articles and other reasons).

Study Characteristics In this review, a total of 10 observational studies were included (all cross-sectional). Of these 10 studies included in this Meta-analysis, 9 measured RNFLT[4,29-35,37] and 5 measured CT[32-36]. Of these 9 studies, 8 reported average RNFLT[29-35,37], 7 studies reported RNFLT in the nasal, and temporal quadrant[4,29-32,35,37] while 6 studies reported the values in the superior and inferior quadrant[29-32,35,37]. All the included studies reported their data as mean and standard deviation[30]. The total number of participants reached 684, of which 362 individuals were identified as beta-thalassemia major cases and 322 were healthy controls. The publication year of all the studies ranged from 2014 to 2023. The detailed characteristics of all the included studies compromising the number of participants, gender distribution, OCT modality along with the

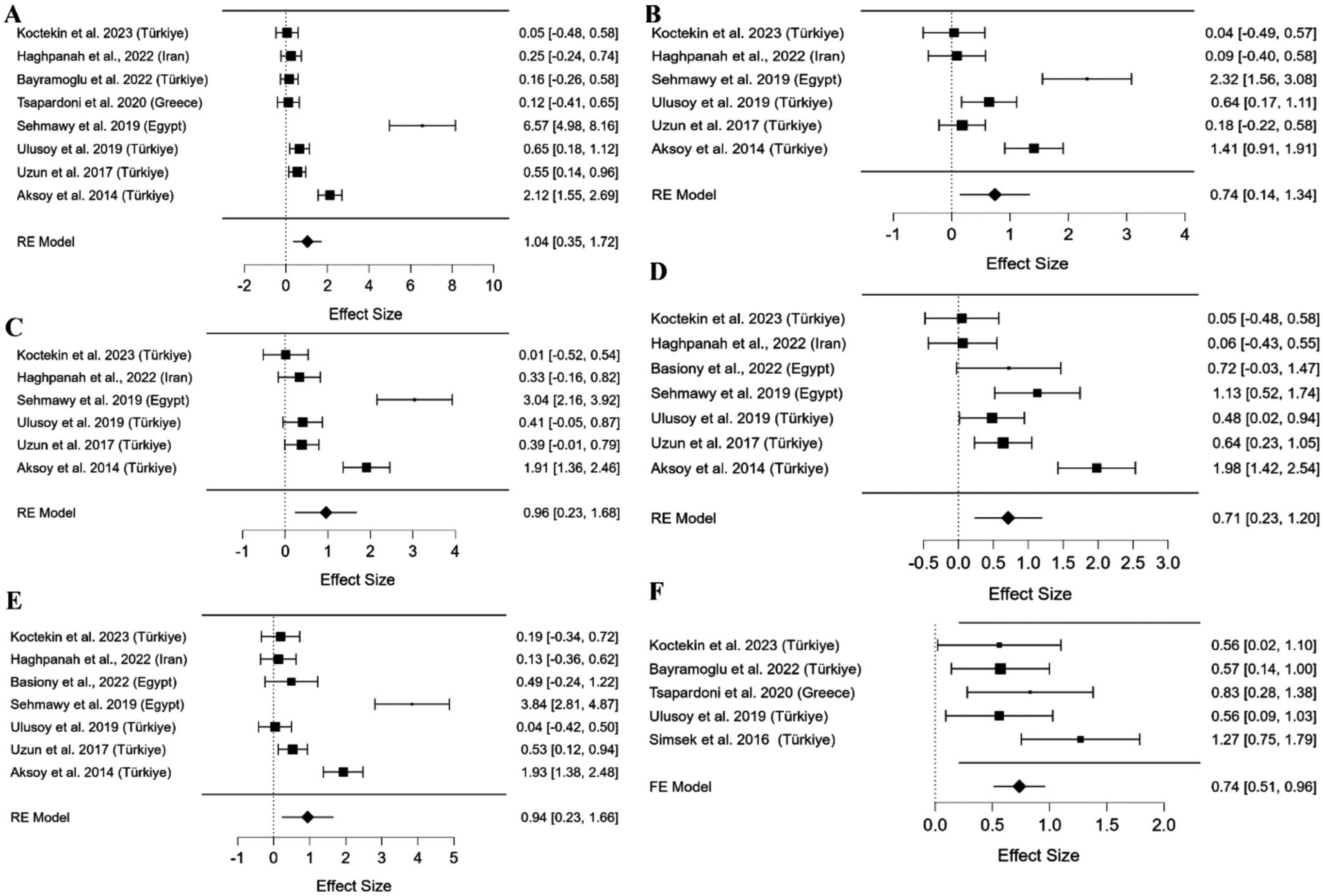

Figure 2 Forest plot of comparison of RNFLT and choroidal thickness between beta-thalassemia cases and controls A: Average RNFLT; B: Superior RNFLT; C: Inferior RNFLT; D: Nasal RNFLT; E: Temporal RNFLT; F: Choroidal thickness. RNFLT: Retinal nerve fiber layer thickness; RE model: Random effects model; FE model: Fixed effects model.

mean and standard deviations of each study were presented in Table 1.

Quality Assessment Majority of studies scored acceptable to good scores when assessed for quality using Newcastle-Ottawa scale (mean: 5.5, range: 3–6, out of 8). The studies were assessed based on selection, comparability, and exposure criteria. The least favorable component was exposure, followed by selection of the participants. It means, most of the studies showed increased bias in ascertainment of exposure and non-response rate. However, most of the studies showed good scores in comparability between two selected groups in terms of age and gender. The details of the quality score of each study were given in Table 2.

Retinal Nerve Fiber Layer Thickness The RNFLT was reported in 9 studies including 327 cases and 284 controls[4,29-35,37], from which 8 studies measured average RNFLT[29-35,37]. The estimated average effect size for average RNFLT was 1.04 [95% confidence interval (CI): 0.35 to 1.72]. Therefore, the average RNFLT differed significantly between both groups (Z=2.961, P=0.003). According to the Higgin's I^2 test of heterogeneity, substantial variability due to heterogeneity among included studies was found (I^2=92.65%), and this variability was accounted for in the random effects model. The details were shown in Table 3 and Figure 2A.

Out of 9 studies that reported RNFLT[4,29-35,37], 7 studies including 245 cases and 218 controls reported RNFLT in the nasal, and temporal quadrant[4,29-32,35,37]; while 6 studies reported the values in the superior and inferior quadrant, with a total of 230 cases and 203 controls[29-32,35,37]. The estimated average effect size for superior RNFLT was 0.74 (95%CI: 0.14 to 1.34; Figure 2B), for inferior RNFLT was 0.96 (95%CI: 0.23 to 1.68; Figure 2C), for nasal RNFLT was 0.71 (95%CI: 0.23 to 1.20; Figure 2D), and for temporal RNFLT was 0.94 (95%CI: 0.23 to 1.66; Figure 2E). The Meta-analysis of RNFLT in all the four quadrants (superior, inferior, nasal, and temporal) represent significant difference between the two groups. The intercept coefficient was found to be statistically significant in all the four quadrants; Z=2.417 (P=0.016) for the superior quadrant, Z=2.592 (P=0.010) for the inferior quadrant, Z=2.880 (P=0.004) for nasal quadrant, Z=2.575 (P=0.010) for the temporal quadrant as shown in Table 3.

The Higgin's I^2 test of heterogeneity revealed high percentage of heterogeneity among the included studies for RNFLT in all the four quadrants. I^2 value for superior RNFLT was 88.18%,

Table 1 Study characteristics

Study, y (country)	Study design	Participants (M/F)	Mean age	Matched for	OCT model	RNFLT	Superior RNFLT	Inferior RNFLT	Nasal RNFLT	Temporal RNFLT	CT
Koctekin *et al*, 2023 (Türkiye)	Cross-sectional	40 cases (15/25)	30.34±6.94	Age	Swept source OCT (DRI-OCT, Triton)	109.88±11.05	135.69±16.18	138.82±19.67	83.55±12.34	80.92±11.93	284.34±63.55
		21 controls (9/12)	32.26±6.43			109.33±10.68	134.98±16.33	139±20.23	84.14±11.86	78.79±10.23	324.98±88.05
Haghpanah *et al*, 2022 (Iran)	Cross-sectional	39 cases (12/27)	28.6±6.2	Age and gender	Spectral domain OCT	101.87±11.02	122.38±24.01	137.84±20.94	74.94±15.55	72.35±12.64	N/A
		27 controls (13/14)	27.1±6.0			99.22±9.95	120.51±14.56	131.29±18.56	74.11±12.59	70.88±9.20	N/A
Basiony *et al*, 2022 (Egypt)	Cross-sectional	15 cases (6/9)	11.8±3.17	Age and gender	Spectralis Heidelberg OCT	N/A	N/A	N/A	67.07±13.52	82.93±9.95	N/A
		15 controls (9/6)	10.2±2.96			N/A	N/A	N/A	74.33±4.25	87.67±9.35	N/A
Bayramoglu *et al*, 2022 (Türkiye)	Cross-sectional	44 cases (N/A)	15.2±6.20	Age and gender	Spectral domain OCT	96.43±11.01	N/A	N/A	N/A	N/A	287.73±47.04
		44 controls (N/A)	14.2±4.90			97.88±7.12	N/A	N/A	N/A	N/A	312.66±39.95
Tsapardoni *et al*, 2020 (Greece)	Cross-sectional	38 cases (15/23)	42±10.70	Age and gender	Enhanced depth imaging OCT	102.1±10.9	N/A	N/A	N/A	N/A	297.4±74.5
		22 controls (12/10)	40.3±10.20			100.9±8.7	N/A	N/A	N/A	N/A	358.4±71.4
El Wakeel Ibrahim El Sehmawy *et al*, 2019 (Egypt)	Cross-sectional	25 cases (11/14)	15.16±2.10	Age and gender	NIDEK RS-3000 retinal scan (NIDEK, Japan)	99.88±8.25	113.72±10.41	124.28±9.66	79.12±6.53	61±6.09	N/A
		25 controls (12/13)	14.6±1.98			139.88±2.45	134.44±7.15	153.6±9.65	85.92±5.42	80.48±3.79	N/A
Ulusoy *et al*, 2019 (Türkiye)	Cross-sectional	32 cases (14/18)	24.45±9.25	Age and gender	Spectral domain OCT	116.14±14.36	150.32±15.53	146.68±22.09	87.73±21.86	75.82±17.86	317.41±53.44
		44 controls (20/24)	25.42±8.84			123.88±9.77	162.63±21.52	153.08±8.29	99.58±26.89	76.5±19.71	353.79±71.93
Uzun *et al*, 2017 (Türkiye)	Cross-sectional	47 cases (21/26)	13.7±2.10	Age and gender	Cirrus HD Spectral domain OCT	91±11	120±16	119±26	66±15	73±9	N/A
		51 controls (20/31)	14.3±2.20			98±14	124±26	129±25	79±24	79±13	N/A
Simsek *et al*, 2016 (Türkiye)	Cross-sectional	35 cases (19/16)	8.2±2.7	N/A	Spectral domain OCT (RTVue-100 OCT)	N/A	N/A	N/A	N/A	N/A	286±33
		38 controls (22/16)	7.9±2.4			N/A	N/A	N/A	N/A	N/A	335±43
Aksoy *et al*, 2014 (Türkiye)	Cross-sectional	47 cases (N/A)	9.65 ± 4.13	Age	Spectral domain OCT	119.38±35.49	142.27±31.93	132.64±38.52	99.47±46.18	103.13±45.52	N/A
		35 controls (N/A)	9.13 ± 3.29			187.73±27.36	181.77±21.91	198.74±28.44	185.68±39.46	184.74±37.73	N/A

OCT: Optical coherence tomography; RNFLT: Retinal nerve fiber layer thickness; CT: Choroidal thickness; N/A: Not available.

Table 2 Quality assessment using Newcastle-Ottawa scale

Study, y (country)	Selection					Comparability			Exposure				Total score
	Case definition adequacy	Representative of cases	Selection of controls	Definition of controls	Subtotal	Age	Sex	Subtotal	Ascertainment of exposure	Method of ascertainment	Non-response rate	Subtotal	
Koctekin *et al*, 2023 (Türkiye)	*	*		*	3	*		1		*		1	5
Haghpanah *et al*, 2022 (Iran)	*	*		*	3	*	*	2		*		1	6
Basiony *et al*, 2022 (Egypt)	*	*		*	3	*	*	2		*		1	6
Bayramoglu *et al*, 2022 (Türkiye)				*	2	*	*	2		*		1	5
Tsapardoni *et al*, 2020 (Greece)	*	*		*	3	*	*	2		*		1	6
El Wakeel Ibrahim El Sehmawy *et al*, 2019 (Egypt)	*	*		*	3	*	*	2		*		1	6
Ulusoy *et al*, 2019 (Türkiye)	*	*		*	3	*	*	2		*		1	6
Uzun *et al*, 2017 (Türkiye)	*	*		*	3	*	*	2		*		1	6
Simsek *et al*, 2016 (Türkiye)				*	2					*		1	3
Aksoy *et al*, 2014 (Türkiye)	*	*	*	*	4	*		1		*		1	6

Table 3 Comparison of the OCT measurement values between beta-thalassemia cases and healthy individuals

OCT measurement	Overall effect				Heterogeneity	
	Effect size (95%CI)	Estimated standard error	Z	P	I^2	Q (P)
RNFL thickness						
Average	1.04 (0.35-1.72)	0.350	2.961	0.003	92.65%	<0.001
Superior	0.74 (0.14-1.34)	0.307	2.417	0.016	88.18%	<0.001
Inferior	0.96 (0.23-1.68)	0.370	2.592	0.010	91.40%	<0.001
Nasal	0.71 (0.23-1.20)	0.247	2.880	0.004	83.08%	<0.001
Temporal	0.94 (0.23-1.66)	0.366	2.575	0.010	91.68%	<0.001
Choroidal thickness	0.74 (0.51-0.96)	0.113	6.523	<0.001	30.13%	0.22

OCT: Optical coherence tomography; RNFLT: Retinal nerve fiber layer thickness; CI: Confidence interval.

for inferior RNFLT was 91.40%, for nasal RNFLT was 83.08%, and for temporal RNFLT was 91.68% respectively. This substantial variability due to heterogeneity among included studies was accounted for in the random effects model as shown in Table 3.

Choroidal Thickness The average subfoveal CT was reported in 5 studies including 189 cases and 169 controls[24-30]. The estimated average effect size for average subfoveal CT was 0.74 (95%CI: 0.51 to 0.96; Figure 2F). Therefore, the average subfoveal CT differed significantly between both groups (Z=6.523, P<0.001). According to the Higgin's I^2 test of heterogeneity, small variability due to heterogeneity among included studies was found (I^2=30.13%), and this variability was accounted for in the fixed effects model as shown in Table 3.

Publication Bias To evaluate the publication bias, Egger's test was performed and funnel plots were generated for all the analyses. The results of Egger's test revealed potential publication bias with significant asymmetry in the funnel plots in all the parameters except for nasal RNFLT (P=0.507), and CT (P=0.281) as shown in Table 4.

Table 4 Egger's test-Funnel plot asymmetry

Variable	Z-value	P-value
Average RNFLT	6.163	<0.001
Superior RNFLT	2.541	0.011
Inferior RNFLT	3.272	0.001
Nasal RNFLT	0.663	0.507
Temporal RNFLT	3.255	0.001
Choroidal thickness	1.078	0.281

RNFLT: Retinal nerve fiber layer thickness.

The sensitivity analysis was performed for all the variables using two methods: 1) By omitting the studies that showed larger effect size; 2) By using restricted maximum likelihood random effects model instead of DerSimonian-Laird model of random effects for RNFLT (average and all quadrants), except for CT which was analyzed using fixed effects model due to less heterogeneity in the included studies.

The overall heterogeneity, as estimated by Higgin's I test, was reduced by a small amount and the pooled effect size was reduced by excluding the study with larger effect size. However, the change in the overall results was not statistically significant.

DISCUSSION

This systematic review and Meta-analysis included a total of 10 observational studies, from which 7 studies were conducted in Europe, 2 in Africa and 1 in West Asia. Majority of the studies were carried out in Türkiye (n=6), whereas 2 studies were carried out in Egypt, and 1 in Greece and Iran each. In the included studies, 362 individuals were identified as beta-thalassemia cases and 322 controls. The publication year of all the studies ranged from 2014 to 2023. Out of 10 included studies, 9 studies reported RNFLT while 5 studies reported the CT.

The results of this Meta-analysis showed a significant difference in the values of RNFLT and CT between beta-thalassemia major cases and controls. The values in beta-thalassemia major cases were found to be reduced in comparison to controls (P<0.05).

The results of present Meta-analysis were supported by some of the included studies that reported a significant difference in the mean values of RNFLT between thalassemia cases and healthy subjects. Basiony *et al*[4] in 2022, reported a significant difference in the values of nasal RNFLT between cases and controls (mean RNFLT in cases was 67.07±13.52 μm while in controls was 74.33±4.25 μm, P=0.029). The results were found to be in accordance with those reported by El Wakeel Ibrahim El Sehmawy *et al*[29] 2019 in a cross-sectional study. The mean RNFLT was observed to be 99.88±8.25 μm in right eye (OD) and 98.96±6.53 μm in left eye (OS) among cases while the controls had significantly higher RNFLT than cases (OD: 139.88±2.45 μm and OS: 142.2±4.05 μm; P=0.000). All the other retinal quadrants showed significant differences among the cases and controls in terms of RNFLT (P=0.000). Uzun *et al*[30], 2017, also concluded similar findings. The mean RNFLT in both eyes was found to be significantly lower in cases (OD: 94±10 μm, OS: 91±11 μm) than in controls (OD: 100±17 μm, OS: 98±14 μm), with P-value of 0.003 and 0.005 in right and left eye respectively. The RNFLT reported in all the quadrants also showed similar results in the right eye (P<0.001) with exception in the superior quadrant (both eyes; P>0.05). Aksoy *et al*[31] (2014), also reported similar results. The mean RNFLT was reported as 119.38±35.49 μm and 187.73±27.36 μm in the cases and controls respectively (P<0.01). The values in all the other quadrants were significantly lower in cases than in controls with P<0.01 (superior quadrant cases: 142.27±31.93 μm controls: 181.77±21.91 μm, inferior quadrant cases: 132.64±38.52 μm controls: 198.74±28.44 μm, nasal quadrant cases: 99.47±46.18 μm controls: 185.68±39.46, temporal quadrant cases: 103.13±45.52 μm controls: 184.74±37.73 μm).

The abnormality in RNFLT has been reported in various ocular as well as systemic diseases along with normal age-related thinning[39]. The ocular association mainly include glaucoma[40] and to a lesser extent axial myopia[41-42]. The systemic problems that cause generalized thinning in the RNFLT includes obesity[43], multiple sclerosis, Alzheimer's disease[44], Parkinson's disease[45], and familial hypercholesterolemia[46]. In patients with beta-thalassemia, chronic anemia, tissue hypoxia, iron overload as a result of repeated blood transfusions, oxidative stress induced by iron overload, and iron chelating therapy toxicity present as the possible factors for causing retinal and choroidal damage[37]. The patients with beta-thalassemia are at increased risk of vascular complications due to hemodynamic changes they undergo. The hemodynamic changes are related to chronic anemia that causes tissue hypoxia and endothelial dysfunction. Iron is an important element of many cellular reactions occurring in the neural tissue; however, excessive iron can cause cellular toxicity leading to cell death[30-31,37]. The chronic iron overload due to repeated blood transfusions results in increased production of reactive oxygen species due to reduced bioavailability of nitric oxide that causes structural and functional changes in arteries. The microvascular damage can also occur as a result of frequent blood transfusions using stored red blood cells (RBCs), that alters the endothelial function *via* a proinflammatory pathway[34].

The results of a few studies did not support the results of this Meta-analysis. Koctekin *et al*[32], 2023, reported the mean RNFLT as 109.88±11.05 μm in cases and 109.33±10.68 μm in controls (P=0.802). All the four retinal quadrants showed insignificant difference in the values of RNFLT between cases and controls (P>0.05). Similar results were reported in a study conducted by Haghpanah *et al*[37], 2022. The results showed no significant difference between the values of cases and controls. The average RNFLT in cases was 101.87±11.02 μm, whereas in controls was 99.22±9.95 μm (P=0.322). In all the other quadrants, the difference in the values of both groups was found to be statistically insignificant (P>0.05). Basiony *et al*[4], 2022 also reported similar results regarding temporal RNFLT, which showed no significant difference between the values of both groups. The mean RNFLT in cases was 82.93±9.95 μm, while in controls the value was 87.67±9.35 μm with P=0.890. Bayramoglu *et al*[33], 2022 also found similar results. A statistically insignificant difference was reported between cases and controls (cases: 96.43±11.01 μm, controls: 97.88±7.12 μm; P=0.474). Similar results were found by Tsapardoni *et al*[34], 2020. The values of mean RNFLT were insignificantly different among cases and controls (cases: 102.1±10.9 μm, controls: 100.9±8.7 μm, P=0.658). Ulusoy *et al*[35], 2019, reported the mean values of RNFLT to be insignificantly different between both groups (cases: 116.14±14.36 μm, controls: 123.88±9.77 μm, P=0.073). The values of RNFLT in all the other quadrants showed similar pattern in terms of statistical significance (P=0.067, 0.39, 0.18, and 0.99 for the superior, inferior, nasal, and temporal quadrants respectively).

The CT was reported in five out of eight included studies.

All the studies showed a significant difference in the mean values of choroidal thickness. Koctekin *et al*[32], 2023, conducted a cross-sectional study on a sample of 40 cases and 21 controls with their mean age to be 30.34±6.94y and 32.26±6.43y respectively. The mean subfoveal CT was reported to be 284.34±63.55 μm in the cases and 324.98±88.05 μm in the controls which was significantly different among both groups with *P*-value to be 0.043. Similar results were observed by Bayramoglu *et al*[33], in a study conducted in 2022. The mean subfoveal CT was 287.73±47.04 μm in the cases and 312.66±39.95 μm in the controls (*P*=0.014), in the nasal quadrant (1 mm nasal to fovea) the values were cases: 256.47±49.74 μm and controls: 279.17±41.52 μm (*P*=0.033), in the temporal quadrant (1 mm temporal to fovea) the values were 299.55±51.42 μm and 317.53±51.21 μm among the cases and controls respectively (*P*=0.128).

Similar results were found by Tsapardoni *et al*[34], 2020, who took a sample of 38 cases with mean age 42±10.7y and 40.3±10.2y respectively. The mean subfoveal CT was observed to be 297.4±74.5 μm in cases and 358.4±71.4 μm in control group (*P*=0.03). The nasal CT (1500 μm nasally to the fovea) was found to be 252.2±82.6 μm and 291.5±68.4 μm among the cases and controls respectively (*P*=0.093), however, the temporal CT (1500 μm temporal to the fovea) was found to be significantly higher among the controls than cases (cases: 261.8±67.1 μm, controls: 327.5±65.3 μm, *P*<0.001). Similar results were found by Ulusoy *et al*[35] (2019) and Simsek *et al*[36] (2016) who reported the choroidal thickness to be significantly different between cases and controls. The subfoveal CT was measured to be 317.41±53.44 μm in the cases and 353.79±71.93 μm in the controls (*P*=0.013). In the nasal 1500 μm from the fovea, the values were 239.09±68.25 μm among the cases and 314.04±73.79 μm among the controls, while in the temporal 1500 μm from the fovea the values were 241.00±82.48 μm among the cases and 343.38±78.57 μm among the controls with *P*<0.05. According to the results of study conducted by Simsek *et al*[36], the mean CT was significantly different between the cases and controls (cases: 286±33, controls: 335±43 μm, *P*<0.001). In the nasal quadrant-1500 μm nasal to fovea, the values were 231±42 μm in the cases and 293±41 μm in the controls, while in the temporal quadrant-1500 μm temporal to fovea the values were 259±33 μm among the cases and 301±43 μm among the controls with *P*<0.001.

The choroid is the vascular and pigmented structure that requires blood supply for its proper functioning as well as to provide nourishment to the outer retina to maintain its function. The choroidal layer is thickest under the fovea which is related to increased photoreceptor activity in macular area. The choroid is responsible for providing oxygen and other nutrients to the fovea through its extensive blood supply, and this makes it necessary for choroid to have sufficient thickness in that area. As the choroid is a vascular structure, so the hemodynamic changes due to any disease can affect CT. The normal physiological factors that affect CT include age, body mass index (BMI), exercise, cigarette smoking, and use of caffeine, activity of sympathetic system, menstrual cycle, and pregnancy. However, systemic problems that can cause changes in CT include diabetes, hypertension, hypercholesterolemia, iron-deficiency anemia, heart failure, carotid artery stenosis, obesity, rheumatologic diseases, and obstructive sleep apnea syndrome. The ocular factors that induce CT changes are axial length changes, choroidal atrophy (age-related), Vogt-Koyanagi-Harada, central serous chorioretinopathy, and polypoidal choroidal vasculopathy are ocular diseases. In beta-thalassemia, the changes in the CT are reported as a result of disease itself, iron-overload due to repeated transfusions, and use of iron chelation therapy, that causes retinal and choroidal damage[33].

To the best of our knowledge, this is the first Meta-analysis investigating the changes in RNFLT and CT due to beta-thalassemia major. This Meta-analysis suggests that reduced RNFLT and CT in beta-thalassemia major patients may serve as early indicators of ocular damage, potentially allowing for early detection and intervention to prevent complications like retinopathy. These ocular parameters could also act as biomarkers for monitoring disease progression and treatment effectiveness, particularly for iron chelation therapy. However, the included studies were mostly cross-sectional, limiting causal conclusions, and small sample sizes reduced statistical power, contributing to variability in results. Measurement inconsistencies, limited geographic and ethnic diversity (primarily from Türkiye, Egypt, Greece, and Iran), and the lack of control for confounding factors such as comorbid conditions and disease severity further affect the generalizability of the findings. Future studies should account for these limitations by considering standardized measurement protocols and stratifying analyses by age, gender, and disease severity to improve the applicability of the results.

In conclusion, the Meta-analysis concludes that the RNFLT and CT are significantly thinner in beta-thalassemia cases in comparison to healthy individuals. The changes become more evident in prolonged severe disease and as a result of iron overload and iron chelation therapy. Therefore, both these parameters *i.e.*, RNFLT and CT must be evaluated in routine clinical practice in order to avoid serious vision problems in beta-thalassemia individuals. Also, there is a huge literature gap as the studies conducted in the past shows conflicting results. The studies included in this Meta-analysis reveal different results leaving more ground for the future research.

Hence, more such studies should be conducted in this area to evaluate the difference between the values of RNFLT and CT in thalassemia cases and controls.

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