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Assessment of Retinal and Choroidal Alterations in Women With Iron-Deficiency Anemia: An Optical Coherence Tomography Study

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Abstract

Objective: To evaluate the retinal and choroidal thicknesses in women with iron-deficiency anemia (IDA) by enhanced-depth imaging optical coherence tomography (EDI-OCT) and to compare the results with healthy controls.

Methods: Forty reproductive-aged female patients who had IDA and 40 healthy female control were enrolled in the study. Laboratory data including serum hemoglobin (Hb), serum iron, ferritin, and mean corpuscular volume (MCV) were recorded. The average peripapillary retinal nerve fiber layer (pRNFL) thicknesses were measured for all study participants. The central retinal thickness (CRT) and choroidal thickness (CT) in the foveal region and 500 μm in the nasal and temporal directions were analyzed by EDI-OCT.

Results: Any significant differences between the control and the patient groups were not determined in comparisons of age, intraocular pressure, central corneal thickness, and axial length ($P > .05$). The mean CRTs were 238.4 ± 32.1 μm [201-276] and 233.9 ± 29.9 μm [203-268] in control and patient groups, respectively ($P = .259$). The mean CTs were 295.5 ± 45.9 μm [245-339] in the healthy controls and 271.9 ± 41.3 μm [230-319] in the patients with IDA ($P < 0.001$). The average pRNFL thickness was significantly lower in the patient group ($P < .001$, 128.4 ± 12.5 μm vs. 107.8 ± 13.9 μm). A positive correlation was found between serum Hgb, iron, MCV, ferritin values with the pRNFL, and CT ($P < .001$). No correlation was found between hematological outcomes and mean age, CRT, IOP, CCT, and AL measurements.

Conclusion: CT in women with IDA was significantly thinner compared to healthy controls. Choroidal thickness changes may be observed in patients with IDA before significant ocular disorders, especially ischemic changes, occurred.

Keywords: Choroidal thickness, enhanced-depth imaging optical coherence tomography, iron-deficiency anemia

Demir Eksikliği Anemili Kadınlarda Retinal ve Koroidal Değişikliklerin Değerlendirilmesi: Bir Optik Koherens Tomografi Anjiyografi Çalışması

Öz

Amaç: Demir eksikliği anemisi (DEA) olan kadınlarda retina ve koroid kalınlıklarını artmış derinlikli optik koherens tomografi (EDI-OKT) ile değerlendirmek ve sağlıklı kontrollerle karşılaştırmak amaçlanmıştır.

Yöntemler: DEA olan üreme çağındaki 40 kadın hasta ve 40 sağlıklı kadın kontrol grubu olarak çalışmaya alındı. Serum hemoglobini (Hb), serum demiri, ferritin ve ortalama korpüsküler hacmi (OKH) içeren laboratuvar verileri kaydedildi. Tüm çalışma katılımcıları için ortalama peripapiller retina sinir lifi tabakası (pRSLT) kalınlıkları, merkezi retina kalınlığı (MRK) ve EDI-OKT ile foveal bölgede, 500 μm nazal ve temporal yönlerde koroid kalınlığı (KK) analiz edildi.

Bulgular: Yaş, göz içi basıncı (GİB), santral kornea kalınlığı (SKK) ve aksiyel uzunluk (AU) açısından hasta ve kontrol grubu arasında anlamlı fark izlenmedi. ($P > ,05$) Ortalama MRK sırasıyla kontrol ve hasta gruplarında 238,4 ± 32,1 μm [201-276] ve 233,9 ± 29,9 μm idi [203-268] ($P = ,259$). Sağlıklı kontrollerde ortalama KK 295,5 ± 45,9 μm [245-339] iken DEA'li hastalarda 271.9 ± 41.3 μm [230-319] idi ($P < ,001$). Hasta grubunda ortalama pRNFL kalınlığı anlamlı olarak daha düşüktü ($P < ,001$, 128,4 ± 12,5 μm vs. 107,8 ± 13,9 μm). Serum Hgb, demir, MCV, ferritin değerleri ile pRSLT ve KK arasında pozitif korelasyon bulundu ($P < ,001$). Hematolojik sonuçlar ile ortalama yaş, MRK, GİB, SKK ve AU ölçümleri arasında korelasyon bulunmadı.

Sonuç: DEA'lı kadınlarda koroid kalınlığı sağlıklı kontrollere kıyasla önemli ölçüde daha inceydi. DEA'li hastalarda önemli oküler bozukluklar, özellikle iskemik değişiklikler meydana gelmeden önce koroid kalınlığı değişiklikleri görülebilir.

Anahtar Kelimeler: Koroid kalınlığı, artmış derinlik görüntülemeli optik koherens tomografi, demir eksikliği anemisi

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Anemia is a common public health problem, and the most prevalent cause of anemia is iron-deficiency anemia (IDA).[1] Pregnant women and women of reproductive age constitute the most affected group from IDA. In women of reproductive age, IDA may accompany risky diseases that result in morbidity and mortality.[2,3] The most important cause is menorrhagia in patients with IDA.[4,5]

Iron plays key role in neurometabolism, normal nerve myelination, neurotransmitter synthesis, and oxygen transport in the central nervous system.[6] Eye pathologies such as ischemic retinopathy, retinal vein occlusion, retinal hemorrhage, and papilledema have been previously mentioned in IDA patients in the literature.[7,8]

The choroid exists between the sclera and the retina and provides oxygen and sustenance to the outer retina, consisting of the retinal pigment epithelium as well as its photoreceptors. The posterior ciliary artery is the main source of blood supply to the choroid. Choroid provides approximately 90% of the ocular blood flow. It has been reported by previous studies that changes in choroidal circulation may be associated with choroidal thickness.[9] Functional or structural alterations in choroidal blood flow may result in disrupted function or structure of the retina.

In this study, we considered to evaluate the ophthalmological, especially retinal and choroidal alterations of reproductive-aged IDA females by comparing them with a control group.

Methods

Ethical Approval and Settings

This study was performed in Erzincan Binali Yıldırım University Faculty of Medicine Department of Ophthalmology. Informed consent was obtained from all participants, and Ethics Committee (E.2728, November 01, 2017) approved the study. Female patients of reproductive age with the diagnosis of IDA were enrolled in the patient group, while the control group included healthy adult women of reproductive age. Forty eyes of 40 patients diagnosed with IDA were included in the study. The hemoglobin (Hb), serum iron, ferritin, and mean corpuscular volume (MCV) values of the patients that were studied in the last month were recorded. Forty eyes of 40 age- and gender-matched women without anemia or any systemic disease were included in the control group. Patients with a serum hemoglobin (Hb) level of <12 g/dL, serum iron level of <60 μg/dL, and serum ferritin level of <10 ng/dL were considered IDA.

Ocular Examinations and OCT Measurements

A comprehensive medical history was obtained, and best corrected visual acuity (BCVA) determination with LogMAR using the Snellen chart, detailed biomicroscopic and fundoscopic examination, intraocular pressure measurement with Goldmann applanation tonometry was performed in all patients. Patients with the diagnosis or history of any systemic diseases (e.g., hypertension, diabetes, vascular disease, and autoimmune disease) were excluded from the study. Smokers are not included in the study. Women who were in their periods were excluded from the study. Patients with a measured axial length of >24 mm, patients with spherical equivalent <−1 diopter or >+1 diopter, history of ocular surgery or ocular disease (uveitis, retinitis, glaucoma, trauma history) were not included in the study. No ocular ischemic changes were observed in the study participants.

The central corneal thickness (CCT) and axial length (AL) of the patients were measured by the ocular biometry system (AL-Scan Optical Biometer NIDEK, Japan) and recorded. The peripapillary retinal nerve fiber layer thickness (pRNFL) and central retinal thickness (CRT) of the patients were measured by using Nidek RS-3000 Advance Optical Coherence Tomography (OCT) device (Nidek Co. Tokyo, Japan). Choroidal thickness (CT) of the patients was measured by using enhanced-depth imaging (EDI) mode of OCT device.

The right eyes of the patients were included in the study. All scans were performed in the morning between 9:00 and 11:00 AM, by the same experienced technician in a blind manner. The experienced ophthalmologists who carried out the measurement performed the measurements by manually outlining the choroid and sclera boundaries with the help of the software in the EDI-OCT device. Choroidal thickness was manually measured as the distance from the outer border of the retinal pigment epithelium to the hyperreflective line of the scleral interface behind the large choroidal vascular layers (Figure 1 and 2). The measurements were taken from three points; at the foveal center, at nasal, and temporal 500 μm distance from the foveal center. The mean of the values obtained from these three points was recorded for all patients.

Statistical Analyses

Statistical analysis was performed by using IBM Statistical Package for the Social Sciences (IBM SPSS Corp., Armonk, NY, USA) 22.0 program. The consistency of continuous variables to normal distribution was evaluated by Shapiro–Wilk test. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. The chi-square test was used to analyze the categorical variables. Variables with normal distribution among the demographic, laboratory, and ocular characteristics and pRNFL, CRT, and CT measurements between the groups were compared with the independent sample *t*-test in addition to the analysis of variation (ANOVA) in independent groups, and variables without normal distribution were compared with the Mann–Whitney *U*-test. The Friedman variance analysis test was performed to compare the variables in repeated measures, Wilcoxon's signed-rank test for the pairwise comparisons of these variables, and the Pearson's or Spearman correlation tests for the assessment of the correlations between the variables. The level of significance was set at $P < .05$.

Results

Demographic, laboratory, and ocular characteristics of the study groups are represented in Table 1. The study included 40 eyes of 40 patients with IDA and 40 eyes of 40 healthy controls without any systemic diseases. The mean age was 31 ± 13.1 [19-45] in the patient group and 30.4 ± 12.9 [19-45] years in the control group (Table 1). No significant difference was observed between the study groups in terms of mean age ($P = .744$). The mean IOP was 13.7 ± 1.5

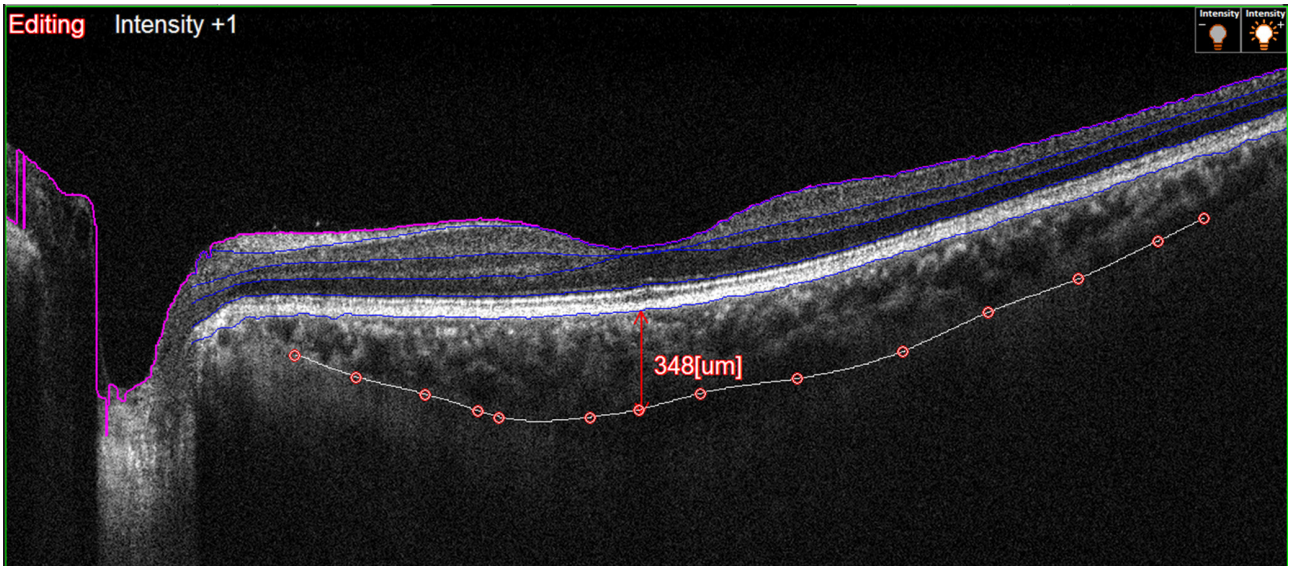

Figure 1. Choroidal boundaries were manually drawn by technician with a software asistance.

[11-18] mmHg in control group and 14.1 ± 1.3 [11-19] mmHg in the patient group (*P*= .143).

When the laboratory findings of the two groups were compared, the Hb, MCV, serum iron, and ferritin outcomes of the patient group were significantly lower compared to the control group as expected (*P*< .001). When the ophthalmologic findings were compared, there was no difference between the two groups in terms of BCVA, IOP, CCT, and AL (Table 1).

OCT measurements of the study participants are shown in Table 2.

The average pRNFL thickness was significantly lower in the patient group (*P*< .001, 128.4 ± 12.5 [109-142] µm vs. 107.8 ± 13.9 [92-125] µm). The mean CRTs were 238.4 ± 32.1 µm [201-276] in control group and 233.9 ± 29.9 µm [203-268] in patients with IDA group (*P*= .259). The mean CTs were 295.5 ± 45.9 µm [245-339] in the healthy controls and 271.9 ± 41.3 µm [230-319] in the patients with IDA (*P*< .001).

Correlations between patients' CT and pRNFL measurements and demographic, laboratory, and ocular characteristics are presented in Tables 3 and 4.

Discussion

The choroid is an eye tissue with the highest rate of blood flow per unit weight. It has an important role in the nutrition of outer layers of the retina and homeostasis of the retina.[9-11] Since the choroid has a high blood flow rate, it is the eye tissue where the first findings of damage caused by systemic vascular pathologies are observed.[12] Systemic arterial hypertension is associated with choroidal

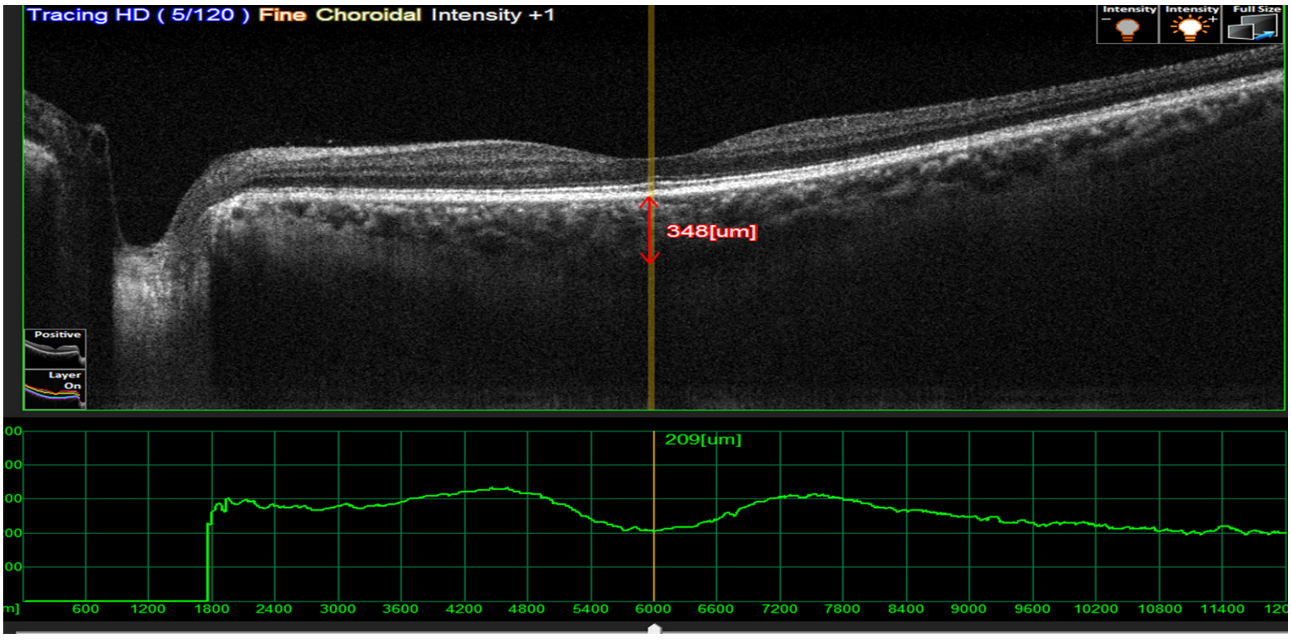

Figure 2. Choroidal thickness was measured manually with a software asistance.

Table 1. Demographic, Laboratory, and Ocular Characteristics of the Study Groups

	Control	Patient	*P*
Number of patients	40	40	-
Mean age	30.4 ± 12.9	31 ± 13.1	.744
BCVA, logMAR	0.005 ± 0.004	0.007 ± 005	.819
IOP, mmHg	13.7 ± 1.5	14.1 ± 1.3	.143
CCT, µm	523.4 ± 21.2	519.9 ± 27.5	.405
AL, mm	22.7 ± 0.7	22.9 ± 0.8	.542
Hb, g/dL	14.1 ± 1.8	10.4 ± 1.5	<.001
MCV, fL	87.9 ± 6.6	75.2 ± 7.3	<.001
Serum iron, µg/dL	84.3 ± 21.4	24.4 ± 10.6	<.001
Ferritin, ng/mL	35.3 ± 17.9	6.3 ± 2.4	<.001

BCVA, best corrected visual acuity; IOP, intraocular pressure; CCT, central corneal thickness; AL, axial length; Hb, hemoglobin; MCV, mean corpuscular volume; logMAR, logarithm of the minimum angle of resolution.

thinning, while diabetes mellitus causes choroidal thickening at an early stage before the development of diabetic retinopathy.[10,11] The choroid was used to be evaluated with techniques such as indocyanine green angiography, ultrasonography before the use of OCT devices. Choroidal vessel abnormalities and alterations in blood flow can be demonstrated by these techniques but they lack to give anatomical information about the choroid in three dimensions. The OCT device provides more penetration than the retinal pigment epithelium and allows the choroid layer to be accurately visualized in three dimensions and measured in vivo.

The choroidal studies using OCT have reported a decrease in choroidal thickness in systemic and ocular diseases such as diabetic retinopathy and rheumatoid arthritis.[13-15] Moreover, Mathew et al.[16] found that patients with sickle cell disease had thinned choroidal thickness and they reported that decreased choroid thickness may be a result of slow blood flow and ischemia. In our study, we evaluated choroidal thickness in the eyes of females with IDA and compared them with the control group. In patients with IDA, the CT was thinner than the controls.

Iron is very important for oxygen transport.[17] IDA is characterized by neurological developmental problems in patients.[6,18] Anemia is a hematologic disorder characterized by a decrease in the total number of circulating red blood cells and/or the level of hemoglobin. It has been determined that factors such as vasospasm, venous stasis, and hypoxia have an important role in the formation of anemic retinal nerve fiber and choroidal disorders.[8,18-20] Similarly, we determined the significant decreases in the pRNFL and CT measurements in patients with IDA in our study.

Retinal ganglion cell and nerve fiber layer development may be affected in patients with IDA.[18,20,21] There are many studies evaluating the effects of IDA on the retina and RNFL.[22-25] Simsek et al.[22] evaluated CT with OCT in children with IDA. They found that the CT was thinner in

Table 2. Comparison of the OCT Measurements of the Study Participants

	Control	Patient	*P*
pRNFL Ave, µm	128.4 ± 12.5	107.8 ± 13.9	<.001
pRNFL T, µm	105.3 ± 7.1	80.7 ± 6.9	<.001
pRNFL N, µm	93.6 ± 6.8	79.2 ± 5.7	<.001
pRNFL TS, µm	179.5 ± 26.8	146 ± 20.3	<.001
pRNFL, NS, µm	134.2 ± 15.1	118 ± 14.3	<.001
pRNFL, TI, µm	180.1 ± 19.8	149 ± 17.1	<.001
pRNFL, NI, µm	138.7 ± 14.2	120.2 ± 11.8	<.001
CRT, Ave, µm	238.4 ± 32.1	233.9 ± 29.9	.259
CRT, SF, µm	224.8 ± 29.3	220.8 ± 27.1	.314
CRT, 500N, µm	247.5 ± 35.8	242.6 ± 31.3	.424
CRT, 500T, µm	242.9 ± 31.2	238.7 ± 28.5	.379
CT, Ave, µm	295.5 ± 45.9	271.9 ± 41.3	<.001
CT, SF, µm	289.2 ± 39.7	265.7 ± 35.7	<.001
CT, 500N, µm	299.1 ± 49.3	276.3 ± 44.2	<.001
CT, 500T, µm	297.2 ± 46.9	273.6 ± 42.8	<.001

pRNFL, peripapillary retinal nerve fiber layer; CRT, central retinal thickness; CT, choroidal thickness; Ave, average; T, temporal; N, nasal; TS, temporal superior; NS, nasal superior; TI, temporal inferior; NI, nasal inferior; SF, subfoveal; 500N, 500 µm nasal from central foveal area; 500T, 500 µm temporal from central foveal area.

Table 3. Correlations Between Patients' CT Measurements and Demographic, Laboratory and Ocular Characteristics

Characteristics	r	*P*
Age	−0.102	.533
IOP, mmHg	0.112	.490
CCT, µm	0.023	.887
AL, mm	0.057	.725
CRT, µm	0.118	.424
Hb, g/dL	0.472	.011
MCV, fL	0.624	.004
Iron, µg/dL	0.387	.014
Ferritin, ng/mL	0.570	.008

IOP, intraocular pressure; CCT, central corneal thickness; AL, axial length; CRT, central retinal thickness; Hb, hemoglobin; MCV, mean corpuscular volume.

Table 4. Correlations Between Patients' pRNFL Measurements and Demographic, Laboratory, and Ocular Characteristics

Characteristics	r	*P*
Age	−0.254	.612
IOP, mmHg	0.179	.598
CCT, µm	0.083	.327
AL, mm	−0.187	.154
CRT, µm	0.214	.312
Hb, g/dL	0.390	.012
MCV, fL	0.424	.025
Iron, µg/dL	0.351	.021
Ferritin, ng/mL	0.599	<.001

IOP, intraocular pressure; CCT, central corneal thickness; AL, axial length; CRT, central retinal thickness; Hb, hemoglobin; MCV, mean corpuscular volume.

children with IDA than the healthy children, similar to the results of our study. They mentioned that choroidal thinning may be an early sign of impaired ocular blood circulation in childhood.[22] Yumusak et al.[23] evaluated the CRT and CT in women of reproductive age using EDI-OCT. Similar to the results of our study, they found that CT was significantly lower at all measured points in their study (temporal, nasal, and subfoveal). Cikmazkara et al.[24] evaluated the pRNFL thickness in patients with IDA and found that the pRNFL was thinner in adult women patients with IDA. They emphasized that this change could have a significant effect on the management of many disorders such as glaucoma and neuro-ophthalmological diseases.[24] Likewise, in the study by Turkyilmaz et al.[25] evaluating the effects of IDA on RNLF, they reported that the superior and inferior quadrants in IDA patients were significantly lower when compared to controls.

In previous studies, it has been determined that the thinning in CT is associated with increased axial length, progressed myopia, thick central corneal thickness (CCT), elevated intraocular pressure (IOP), and advanced age.[26,27] Our study did not reveal a significant correlation between CT and CCT, IOP, axial length, or age. This may be related to our patients being young (18-45 years). The exclusion of patients with a measured axial length >24 mm, refractive error <−1 diopter, and patients diagnosed with glaucoma can be shown as the reason for this result.

Decreasing Hb, iron, MCV, and ferritin values affect RNFL and CT measurements.[21-24] RNFL and CT values are shown to decrease in IDA.[21-24] A positive correlation was found between serum Hb, iron, MCV, and ferritin levels with the pRNFL and CT measurements in the study participants ($P < .001$). No correlation was found between hematological outcomes and mean age, CRT, IOP, CCT, and AL measurements ($P > .05$).

The major limitation of the study was that we could not appraise the patients with OCT-angiography. A detailed retinal vascular network can be evaluated in further studies with larger participants. In addition, we did not know how long the patients were followed up for IDA before they were included in our study. Therefore, we were unable to evaluate the long-term effect of anemia on retinal and choroidal structures.

The pRNFL in all quadrants and CT were thinner in patients with IDA than the healthy controls. Since IDA is a common public health problem, we concluded that it should definitely be kept in mind in the differential diagnosis of patients who are detected to have a thin choroidal thickness in ophthalmologic examination.Examination of patients who are detected to have choroidal thinning on the ophthalmologic examinations in terms of IDA will provide early diagnosis and treatment of the disease and will significantly contribute to public health by preventing morbidity and mortality associated with this disease.

Ethics Committee Approval: This study was performed in Erzincan Binali Yıldırım University Faculty of Medicine Department of Ophthalmology and Ethics Committee (E.2728, November 01, 2017) approved the study.

Informed Consent: Informed consent was obtained from all the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – A.U.; Design – A.U.; Supervision – A.U.; Resources – N.G.T.; Materials – N.G.T.; Data Collection and/or Processing – N.G.T., E.İ.; Analysis and/or Interpretation – A.U., E.İ.; Literature Search – N.G.T., E.İ.; Writing Manuscript – A.U., N.G.T.; Critical Review – A.U.

Conflict of Interest: Informed consent was obtained from all individual participants included in the study.

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Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan tüm katılımcılardan alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

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