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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Ophthalmology / Göz Hastalıkları

Alterations of Neuroretinal and Corneal Thickness in Hashimoto's Thyroiditis

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ABSTRACT

Purpose: To compare changes in macula, retinal nerve fiber layer (RNFL) and central corneal thickness (CCT) in patients with Hashimoto's thyroiditis (HT) with age-matched healthy control group.

Materials and Methods: This study was conducted with a prospective, observational, cross-sectional design. The individuals participating in the study were divided into 2 groups: patients with a diagnosis of HT (group 1, n:54 eyes) and age-matched healthy participants (group 2, n:70 eyes). Corneal, retinal and macular thickness measured by optical coherence tomography. Mean outcome measurements were CCT, intra-ocular pressure (IOP), central 1 mm foveal thickness (CFT), subfoveal choroidal thickness (SFCT), total macular volume (TMV), central 1 mm foveal volume (CFV), and RNFL thickness in superior, nasal, inferior and temporal quadrants.

Results: The mean IOP was 17.07±2.34µm in group 1 and 14.20±2.76µm in group 2, respectively (p<0.001). Mean CCTs were 539.44±35.27µm and 555.06±40.53µm (p=0.001), CFTs were 227.35±17.52µm and 230.38±23.52µm (p=0.57), SFCT were 210,79±20,13µm and 268,47±24,56µm (p<0.001), TMVs were 7.16±0.35mm3 and 7.02±0.26mm3(p=0.07), CFVs were 0.17±0.01mm3 and 0.19±0.07mm3 (p=0.16) in group 1and group 2, respectively. RNFL thickness values were significantly thinner in the group 1(p<0.05) in all quadrants except for the nasal quadrant (p=0.086).

Conclusion: Hypothyroidism secondary to HT may be a determining factor affecting the development of the cornea and retina. Elevated IOP and decrement of RNFL thickness in children with HT increased the risk of developing glaucoma, as well as decreased SFCT may predispose to the development of chorioretinal disorders in the future.

Keywords: Corneal thickness, Hashimoto's thyroiditis, retinal nerve fiber layer thickness, macula

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Hashimoto Tiroiditinde Nöroretinal ve Kornea Kalınlığındaki Değişiklikler

ÖZET

Amaç: Hashimoto tiroiditi (HT) olan hastalarda makula, retina sinir lifi tabakası (RSLT) ve santral kornea kalınlığındaki (SKK) değişiklikleri yaşa uygun sağlıklı kontrol grubu ile karşılaştırmak.

Hastalar ve Yöntemler: Bu çalışma prospektif, gözlemsel, kesitsel dizayn ile yapılmıştır. Çalışmaya katılan bireyler 2 gruba ayrıldı: HT tanısı olan hastalar (grup 1, n: 54 göz) ve yaşları eşleştirilmiş sağlıklı katılımcılar (grup 2, n: 70 göz). Optik koherens tomografi (OKT) ile kornea, retina ve maküler kalınlıklar ölçüldü. Ortalama sonuç ölçümleri SKK, göz içi basıncı (GİB), merkezi 1 mm foveal kalınlık (MFK), subfoveal koroid kalınlığı (SFKK), toplam maküler hacim (TMH), santral 1 mm foveal hacim (SFH) ve üst, nazal, alt ve temporal kadranlardı.

Bulgular: Ortalama GİB grup 1'de 17.07 ± 2.34µm, grup 2'de 14.20 ± 2.76µm idi (p <0.001). Ortalama SKK'lar 539.44 ± 35.27µm ve 555.06 ± 40.53µm (p = 0.001), SFK'lar 227.35 ± 17.52µm ve 230.38 ± 23.52µm (p = 0.57), SFKK 210,79 ± 20,13µm ve 268,47 ± 24,56µm idi Grup 1 ve grup 2'de sırasıyla, (p <0.001), TMH'lar 7.16 ± 0.35mm3 ve 7.02 ± 0.26mm3 (p = 0.07), CFV'ler 0.17 ± 0.01mm3 ve 0.19 ± 0.07mm3 (p = 0.16) idi. Grup 1'de RSLT kalınlık değerleri, nazal kadran hariç tüm kadranlarda anlamlı olarak daha ince bulundu (p <0.05) (p = 0.086).

Sonuç: HT'ye bağlı hipotiroidizm, kornea ve retinanın gelişimini etkileyen belirleyici bir faktör olabilir. HT'li çocuklarda yüksek GİB ve RSLT kalınlığının azalması, glokom gelişme riskini artırdığı gibi, azalmış SFKK de gelecekte korioretinal bozuklukların gelişimine yatkınlık yaratabilir.

Anahtar Kelimeler: Kornea kalınlığı, Hashimoto tiroiditi, retina sinir lifi tabakası, makula

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Hashimoto's thyroiditis (HT) was firstly described by Hakaru Hashimoto in 1912 which had explained by pathological mechanism as: the thyroid gland is attacked by antibody-mediated immune processes (1). Thyroid function varies from euthyroidism to thyrotoxicosis. With the development of hypothyroidism in patients, the enlarged thyroid gland generally undergoes atrophy (2). No information on the pathogenesis of HT was known until 1956. Rose et al. have reported thyroglobulin antibodies and thyroiditis in rabbits which immunized with thyroid extract (3). Thyroid hormone (TH) plays a critical role in eye embryogenesis, but its effect on the development of cornea and neuroretinal tissue is not fully understood. TH can cause a wide variety of effects on different neural tissues, including proliferation, differentiation, and migration (4). There are several studies in the literature with conflicting results investigating the relationship between hypothyroidism and retino-choroidal or corneal changes, as well as ocular alterations (5-7). Herein, we aimed to investigate macular thickness, subfoveal choroidal thickness (SFCT), central corneal thickness (CCT), and retinal nerve fiber layer (RNFL) thickness in the patients with the diagnosis of hypothyroidism due to HT and compare the results with healthy age-matched control group.

MATERIALS AND METHODS

This prospective, single-center clinical study was conducted in the ophthalmology clinic of a tertiary hospital in collaboration with the endocrinology clinic between January 2015 and February 2018. The study conformed to the tenets of the Declaration of Helsinki and was approved by the Research Ethics Committee. Informed written consent was obtained from each participant. Patients with any sign of orbitopathy, corneal pathology, glaucoma, and retinal vascular disease such as diabetic or hypertensive retinopathy were excluded from the study. The patients who had the diagnosis of hypothyroidism due to HT in the outpatient clinic of the endocrinology department were enrolled as study group. Healthy age-matched participants constituted as the control group. Individuals with HT are in remission and under strict monitoring. A complete ophthalmic examination including visual acuity with Snellen chart, intraocular pressure measurement (IOP) (Goldmann applanation), anterior segment and fundus examinations, measurements of corneal, macular, SFCT and RNFL thickness were performed for each patient. CCT measurements were implemented by optical coherence tomography (OCT) (Optovue Avanti®). The mean of three sequential measurements from the central cornea was utilized for the assessment. RNFL thickness were measured by spectral domain optical coherence tomography (SD-OCT) (Optovue Avanti® Inc., Fremont, CA, USA). The SD-OCT assessments were performed in a dim room after mydriasis with tropicamide 0.5% drops by one of the authors (OOO). Mean outcome measures were central foveal thickness (CFT), mean SFCT, total macular volume (TMV), central foveal volume (CFV), and the RNFL thickness in the superior, nasal, inferior and temporal quadrants calculated automatically by SD-OCT. Subfoveal choroidal thickness were measured by the enhanced depth image optical coherence tomography (EDI-OCT) imaging method described by Spaide et al (8). SFCT was characterized as the vertical distance from the basal edge of retinal pigment epithelium below the central fovea to the endpoint of the choroid-scleral junction. Figure 1 shows EDI-OCT and mapping of the macula measurements on eyes with HT. Figure 2 shows optic nerve head measurements from an healthy individual. Figure 3 demonstrates the CCT measurement of a healthy individual.

Statistical analysis

The data was analyzed by using the Statistical Package for Social Science (SPSS) programme (SPSS version 15.0 for Windows; SPSS, Chicago, IL). Levene test for equality of variances and t test for equality of means were used for the comparison of the groups. P value of < 0.05 was considered as statistically significant.

RESULTS

Twenty-seven participants with 54 eyes that female:male ratio was 12:15 in group 1 and 35 participants with 70 eyes that female:male ratio was 16:19 in group 2 were included in study. There was no statistically significant difference in demographic data between the groups ($p > 0.05$). The mean age was 12.4±1.3 years (range, 9-14 years) in group 1, and 11.9±1.4 years (range, 7-14 years) in group 2. The mean weight and height were 36.9±8.4 kg and 146.3±15.2 cm in group 1; 37.7±7.6 kg and 147.4±13.9 cm in group 2. Descriptive characteristics (age, weight, height, gender distribution) of each groups are shown in Table 1. The mean CCT was 539.44 ± 35.27 µm in group 1 and 555.06 ± 40.53 µm in group 2 ($p=0.001$). The mean IOP was 17.07 ± 2.34 µm in group 1 and 14.20 ± 2.76 µm in group 2 ($p<0.001$). The mean CFT was 227.35±17.52 µm in group 1, 230.38±23.52 µm group 2 ($p=0.001$). Mean SFCT was 210.79±20.13 µm in group 1, 268.47±24.56 µm group 2 ($p<0.001$). Mean TMVs were 7.16±0.35 mm3 and 7.02±0.26 mm3($p=0.07$), CFVs were 0.17±0.01 mm3 and 0.19±0.07 mm3 in group 1 and group 2, respectively ($p=0.16$).

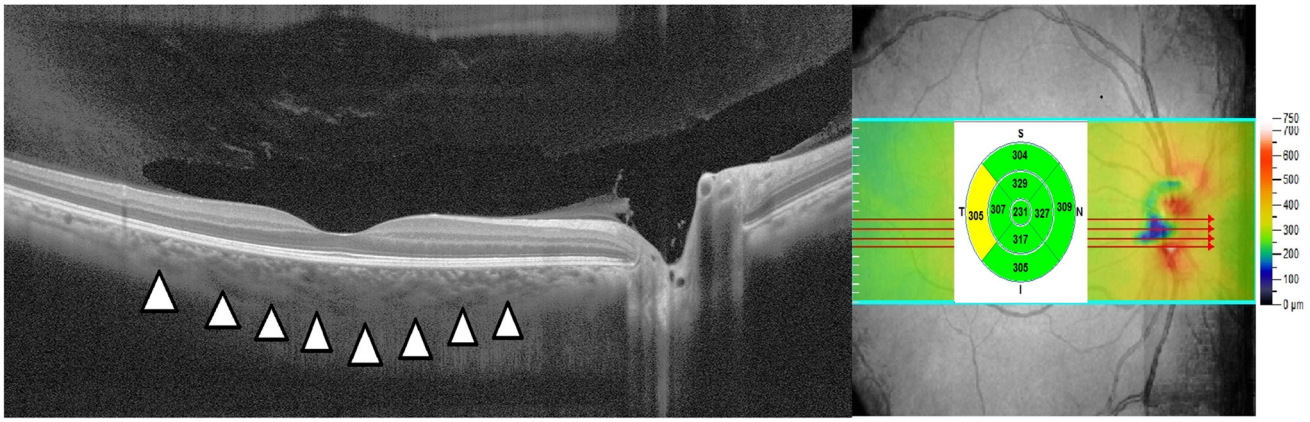

Figure 1. Enhanced optical coherence tomography (EDI-OCT) and mapping of the macula in eyes with Hashimoto's thyroiditis are shown. White arrows show the choroidal-scleral junction and its border.

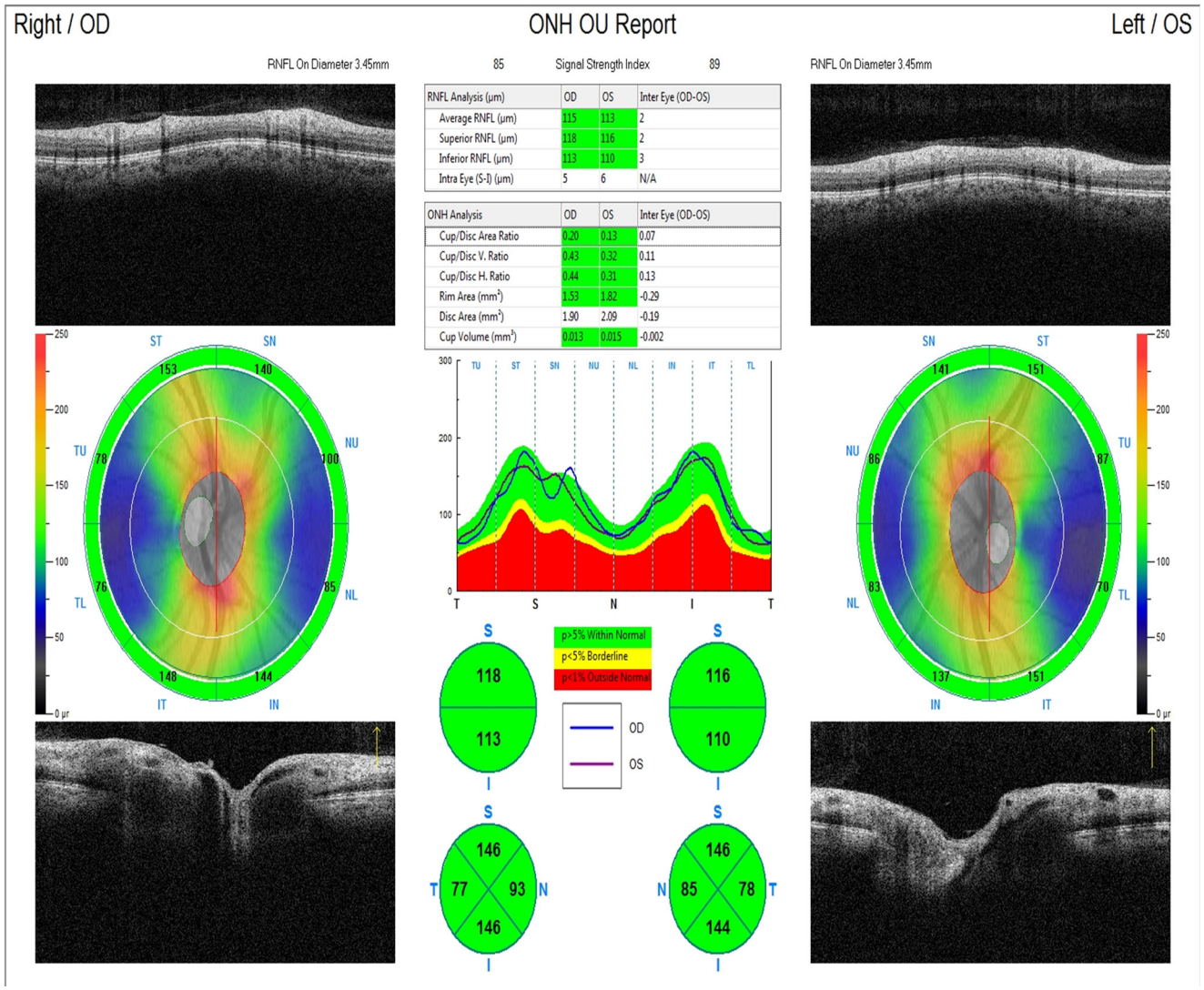

Figure 2. The optic nerve head (ONH) measurements of a healthy individual are shown.

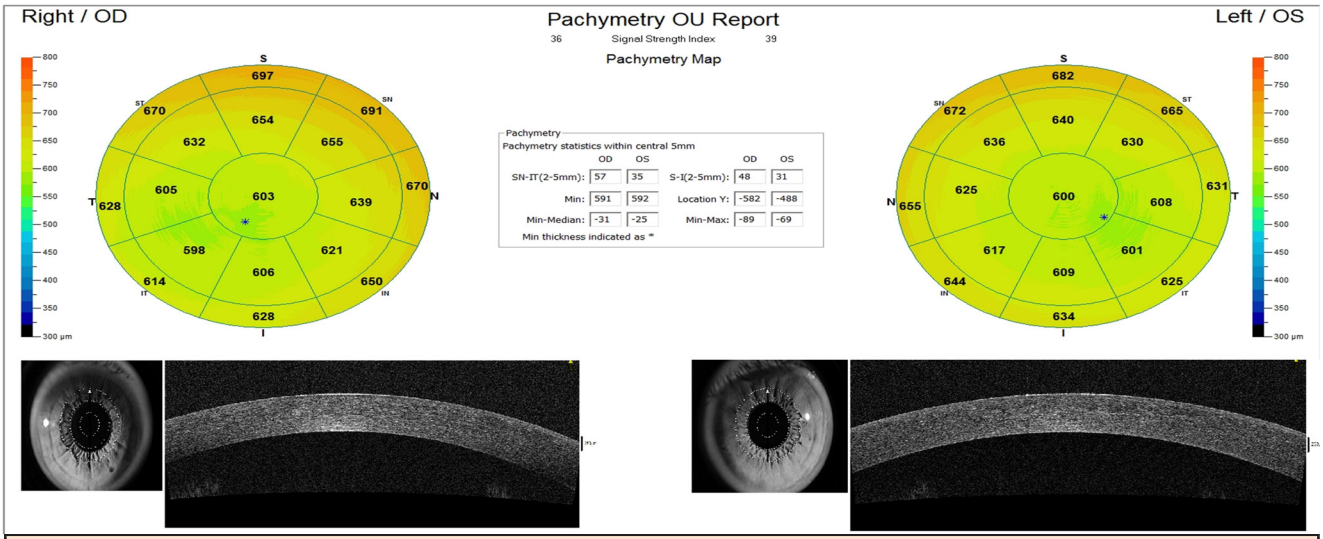

Figure 3. The image of central corneal thickness (CCT) measurement of a healthy individual was displayed.

Table 1: Demographic characteristics of groups

Mean ±SD	Group 1 Hashimoto group (n=54)	Group 2 Control Group (n=70)	*p values*
Age (years)	12.4±1.3 (9-14 years)	11.9±1.4 (7-14 years)	***0.879***
Weight (kg)	36.9±8.4	37.7±7.6	***0.745***
Height (cm)	146.3±15.2	147.4±13.9	***0.912***
Male/Female (n)	15/12	19/16	***0.749***

Student t test*
n:number; SD, standard deviation.

Table 2. Results of the study

Mean ± SD	Group 1 Hashimoto Group (n=54)	Group 2 Control Group (n=70)	*p values*
CFT, µm	227.35±17.52	230.38±23.52	***0.57***
SFCT, µm	210.79±20.13	268.47±24.56	***0.001****
TMV, mm3	7.16±0.35	7.02±0.26	***0.07***
CFV, mm3	0.17±0.01	0.19±0.07	***0.16***
IOP, mmHg	17.07 ± 2.34	14.20 ± 2.76	***0.002****
CCT, µm	539.44 ± 35.27	555.06 ± 40.53	***0.001****

Student t test*
CFT: Central 1 mm foveal thickness,
SFCT: Subfoveal choroidal thickness at the foveal pit,
IOP: Intraocular pressure, CCT: Central corneal thickness.
n: number; SD, standard deviation.

The results of the study are summarized in Table 2. As for RNFL measurements, mean RNFL thicknesses in central, superior, inferior, nasal and temporal quadrants were 109.40±12.50 µm, 130.72±16.38 µm, 139.42±17.60 µm, 81.14±9.51 µm, and 72.18±8.08 µm in group 1, and 115.41±12.80 µm, 141.65±17.48 µm, 156.25±17.96 µm, 80.67±11.84 µm, and 76.81±12.43 µm in group 2 (p=0.019, p=0.048, p=0.014, p=0.86 and p=0.028). RNFL thickness analysis of the study are given in Table 3. Figure 4 shows graphic of the results in the study.

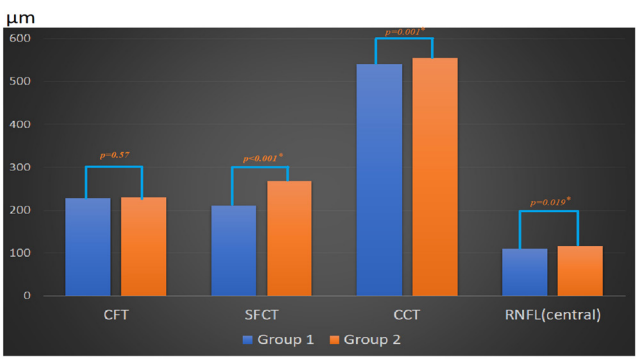

Figure 4. The graphic of the results is summarized in the study.

Table 3. Retinal nerve fiber layers analysis of the study			
Mean ± SD	**Group 1 Hashimoto Group (n=54)**	**Group 2 Control Group (n=70)**	***p values***
Mean RNFL central, µm	109.40 ± 12.50	115.41 ± 12.80	***0.019****
Mean RNFL superior, µm	130.72±16.38	141.65±17.48	***0.048****
Mean RNFL inferior, µm	139.42±17.60	156.25±17.96	***0.014****
Mean RNFL	81.14±9.51	80.67±11.84	***0.86***
nasal, µm	72.18±8.08	76.81±12.43	***0.028****
Mean temporal RNFL, µm			

DISCUSSION

Hypothyroidism is second common endocrine disorder following diabetes mellitus (9). HT is also known as chronic lymphocytic thyroiditis, chronic autoimmune thyroiditis, and lymphadenoid goiter. Most patients with HT are euthyroid or have subclinical hypothyroidism with goiter and circulating thyroid antibodies. As time passes, overt hypothyroidism will develop at a rate of about 5% per year (2). The specific factor initiating autoimmunity to thyroid antigens is a dilemma. Similar to other autoimmune diseases, HT is assumed to appear from a breakdown of self-tolerance to thyroid antigens (10). Latest studies have focused attention on many contributor to the increased risk such as; vitamin D receptor gene polymorphisms (11), interleukin 6 gene promoter polymorphism (12), polymorphism in the interferon gamma gene (13), T cell receptor restriction fragment length polymorphism (14), specific allotypes of the immunoglobulin G heavy chain (15), CT 60 polymorphism of cytotoxic T-lymphocyte-associated protein-4 maps (16), and X chromosome inactivation (17). Thyroid hormone is crucial for the normal development of the central nervous system (18). Clinical and experimental studies have focused attention on the role played by TH also in neuroretinal development. However, knowledge on TH mechanisms on the developing visual system is still uncompleted. Recently, many studies have demonstrated the implication of TH in cone differentiation during the retinal development, growth and regeneration (19). Visual system morphogenesis and functioning rely on the accurate location of specific cells and the formation of relevant intercellular connections (20,21). Pinazo-Duran et al. investigated the role of TH in the developing retina and optic nerve, in a rat model of controlled TH deficiency. They reported that a depletion in the volume of the eye ($p<0.001$) and optic nerve cross- sectional zone ($p<0.001$), attenuation of the retinal layers ($p<0.001$), and remarkably postponed glial development and myelination in the TH defiency optic nerves ($p<0.001$), as compared to controls (22). Durieux et al. investigated electroretinogram (ERG) findings in three hypothyroid adult dogs with and without levothyroxine treatment, and reported that a dose of 20 µg/kg of levothyroxine given to adult dogs was associated with a noticeable peak time shortening of both photopic and scotopic ERGs (23). Ittermann et al. used data from 3189 individuals and investigated association between serum thyrotropin (TSH) levels and retinal artery narrowing and defined by arterio-venous ratio from static vessel analysis. They reported that high serum TSH levels were accompanied by retinal arteriolar narrowing, and described potential mechanisms by long-term hypertension, atherosclerotic processes, and inflammation (24). Studies about the effects of thyroid disorders on central corneal thickness are still unsatisfactory. The implication of TH in corneal physiology is being investigated in some studies. Conrad et al. reported the presence of thyroxin receptors alpha and beta in the chicken cornea (25). Bahceci et al. demonstrated a significant increase in CCT in hypothyroid patients that could be reversed with thyroxine replacement medication. Additionally, they concluded that the prevalence of glaucoma in hypothyroidism might not be as high as they previously reported when IOP was corrected for CCT (26). In the study of Gül et al., it was aimed to compare choroidal thickness in active and stable phases of Hashimoto thyroid eye disease. Subfoveal, temporal macula, nasal macula, temporal peripapillary and nasal peripapillary choroidal thickness measurements were performed in 23 eyes of 23 patients. SFCT was significantly thicker in the group with thyroid eye disease in the active phase than in the group with stable phase disease ($p=0.04$) (6). In our study, CCT was thicker in patients with HT, and found to be statistically significant difference in CCT among the groups ($p=0.001$).

Although similar results were obtained in our study, the sample size and prospective design constituted our superior aspects compared to this study. association between hypothyroidism and open angle glaucoma but none of them evaluate The literature contains controversial results considering the d patients according to etiology. Some studies report an association, whereas others failed to find such an association (27-29). Lin et al. investigated the risk of open-angle glaucoma after a diagnosis of hypothyroidism during the 5-year follow-up period. Their study group consisted of 257 hypothyroidism patients and the comparison group involved 2056 subjects. They reported that hypothyroidism patients had 1.78-fold greater risk of developing open angle glaucoma. In our study, IOP was higher in patients with HT, and there was statistically significant difference in IOP between the groups (p=0.002) (30). In a study conducted by Kırgız et al., they compared CCT and IOP values of 48 HT and 49 control healthy eyes. Although there was no significant difference in central corneal thickness (CCT) values between the HT group and the control group (p = 0.65), IOP values were significantly higher in HT group (p = 0.001) (7). To the best of our knowledge, this study is the first of its kind where individuals with HT were examined for corneal and neuroretinal thicknesses together. Bahceci et al. measured RNFL thicknesses parameters with scanning laser polarimeter and did not find any statistically significant result formed by hypothyroidism (26). Ozturk et al. investigated RNFL thickness of 33 patients diagnosed to have primary hypothyroidism and reported statistically significant change ($p<0.05$) (31). A statistically significant change was found in mean RNFL thickness among the groups in our study ($p<0.05$). Limitations of this study are the small sample size, lack of control group and short follow-up period that might affect the statistical power. Advantages of present study are prospective design and detailed statistical parameters. In conclusion, hypothyroidism due to HT may be definitive factor affecting corneal and retinal development as presumed in some previous studies. Therefore, close follow-up and frequent examinations should be prioritized. Future prospective studies involving large subsets may provide further evidence of the susceptibility of HT to ocular disease.

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Conflict of Interest: No conflicting relationship exists for any author.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained prior to every surgical procedure from all individual participants included in the study.

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