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Optic Coherence Tomography Findings in Hyperthyroid Patients without Ophthalmopathy

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ABSTRACT

Aim The aim of this study is to compare the choroidal, retinal, and peripapillary nerve fiber layer thickness of the patients diagnosed with hyperthyroidism but did not develop ophthalmopathy with the euthyroid patients.

Material and Methods: Thyroid stimulating hormone (TSH), freeT3 (fT3) and freeT4 (fT4) tests of the patients were analyzed. Cases who came in with symptoms of hyperthyroidism and had a TSH lower than 0.5 mu/L were included to the study. Retinal thickness (RT), retinal nerve fiber layer (RNFL) thickness, and choroidal thickness (CT) were calculated by means of spectral domain optical coherence tomography.

Results: A total of 82 participants, covering 40 (49%) hyperthyroid patients and 42 (51%) euthyroid healthy individuals, were examined. In terms of RT measurements, T500,T1000,T1500 and N1500 values were found to be lower in the HT group compared to the control group, and they were statistically significant ($p<0.001$; $p<0.001$; $p<0.001$; $p=0.011$;respectively). In terms of CT measurements, Central, N500,N1000 and N1500,T500,T1000,T1500 values were found to be lower in the HT group and they were statistically significant ($p=0.003$; $p=0.002$; $p=0.005$; $p=0.005$; $p=0.002$; $p=0.002$; $p=0.028$; respectively). In terms of RNFL measurements, T, TS, TI segments were found to be lower and NI segment was found to be higher in the HT group compared to the control group, and this difference was statistically significant ($p=0.008$; $p=0.001$; $p=0.002$ and $p=0.009$; respectively).

Conclusion: As a result, it is advised to regularly perform eye controls of patients with hyperthyroidism, not only the ones with ophthalmopathy but also those without ophthalmopathy, after the diagnosis.

Keywords: Hyperthyroidism; retinal thickness; choroidal thickness; retinal nerve fiber thickness.

Oftalmopatisiz Hipertiroidik Hastalarda Optik Cohorens Tomografi Bulguları

ÖZ

Amaç: Bu çalışmada, hipertiroidi tanısı olan ve oftalmopati gelişmemiş hastalardaki koroid, retina ve peripapiller sinir lifi tabakasının kalınlığını ötiroid hasta grubuyla karşılaştırmak amaçlanmıştır.

Gereç ve Yöntemler: Hastaların serum tiroid stimülan hormon (TSH), serbest T3 (fT3), serbest T4 (fT4) değerleri incelendi. Hipertiroidi semptomları ile başvuran ve tetkiklerinde TSH; 0,5 mu/L'nin altında saptanan olgular çalışmaya dahil edildi. Spektral domain optik koherens tomografi ile retina kalınlığı (RT), retina sinir lifi tabakası (RSLT) kalınlığı ve koroid kalınlığı (CT) hesaplandı.

Bulgular: Çalışmaya 40'ı (%49) hipertiroidi hastası (HT), 42'si (%51) ötiroidik sağlıklı bireyler olmak üzere toplamda 82 kişi dahil edildi. RT ölçümleri açısından T500, T1000, T1500 ve N1500 değerlerinin HT grupta kontrol grubuna göre daha düşük olduğu olduğu ve bunların istatistiksel olarak anlamlı olduğu görüldü (sırasıyla $p<0,001$; $p<0,001$; $p<0,001$; $p=0,011$). CT ölçümleri açısından Central, N500, N1000 ve N1500, T500, T1000, T1500, HT grupta daha düşük olduğu ve bunların istatistiksel olarak anlamlı olduğu görüldü (sırasıyla $p=0,003$; $p=0,002$; $p=0,005$; $p=0,005$; $p=0,002$; $p=0,002$; $p=0,028$). RSLT ölçümleri açısından HT grubunda kontrol grubuna göre T, TS, TI segmentlerinde düşük, NI segmentinde yüksek olduğu ve bu farkın istatistiksel olarak anlamlı olduğu görüldü (sırasıyla $p=0,008$; $p=0,001$; $p=0,002$ ve $p=0,009$).

Sonuç: Hipertiroidi tespit edilen hastalara, sadece oftalmopatisi olanlara değil oftalmopatisi olmayanlara da tanı konulduktan sonra düzenli göz kontrolleri yapılması gerektiği düşünülmüştür.

Anahtar Kelimeler: Hipertiroidi; retina kalınlığı; koroid kalınlığı; retina sinir lifi kalınlığı.

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INTRODUCTION

Thyrotoxicosis is a clinical syndrome characterized by increase in the metabolic effects as a result of the exposure of tissues to the high level of thyroid hormone. Thyrotoxicosis may also be affiliated with rare thyroid hormone intake of the thyroid gland to the increase in the activation of the activation of the thyroid globe (1,2). The most common causes of hyperthyroidism are Graves disease, toxic multinodular goiter and toxic adenoma. Graves disease is of autoimmune origin and depends on the TSH receptor stimulus antibody stimulating the thyroid gland. Toxic adenoma develops depending on producing excess thyroid hormone as a result of a single thyroid adenoma to gain autonomous features with a mechanism that is not yet clearly explained (2,3,4).

In cases of hyperthyroidism, as a result of proliferation of inflammatory cells in the orbit, there is an increase in the volume of the orbit, and exophthalmos can be seen in advanced stages. In addition, dry eye, exposure keratopathy, diplopia and vision loss can be seen due to optic disc compression in the last stage (5,6). There are several studies in the literature on the ocular findings of hyperthyroid patients with ophthalmopathy (7-11). However, current literature lacks studies on patients without ophthalmopathy.

Before the development of ophthalmopathy in the disease, it is necessary to examine important ocular parameters in to prevent the development of ocular findings and to monitor their effects on eyes. In this study, we aimed to examine the retinal, retinal nerve fiber layer, and choroidal thickness parameters in hyperthyroid patients without ophthalmopathy.

MATERIAL AND METHODS

In our study, hyperthyroidism cases without ophthalmopathy were prospectively analyzed between January 2019 and January 2021. The study was planned by adhering to the principles of Helsinki and obtaining the approval of the Düzce Ethics Committee (Ethics committee number: 2018-05). The participants in our study were informed about the study, and informed consent was obtained from each of them.

Our study consisted of 82 people in total, 40 of who were hyperthyroid patients and 42 of who were euthyroid healthy individuals. Thyroid Stimulating Hormone (TSH), free T3 (fT3) and free T4 (fT4) blood tests of the subjects were analyzed. Cases who presented with symptoms of hyperthyroidism and had a TSH below 0.5 mu/L in the examinations (hyperthyroidic and subclinical hyperthyroid cases) were included in the study, taking into account that they had not received medical (steroid, antithyroid drug) or ablative treatment (surgery, radioactive iodine) before.

Exclusion criteria are undergone refractive surgery, those who have any disease affecting the cornea, those who have a history of smoking and alcohol use, systemic diseases such as diabetes or blood pressure, those who have undergone eye surgery for any reason, amblyopia, strabismus, cataract, spherical and cylindrical refractive error more than 1, those with restrictive myopathy or compressive optic neuropathy, those who are pregnant or breastfeeding, those with a history of intraocular trauma, a history of ocular surgery, a history of previous corticosteroid use (within the last two months), those with a diagnosis of dry eye, those using contact lenses, ocular infection and intraocular. Those with corneal anomalies that could affect pressure measurement were excluded from the study.

The right eye was subjected to analysis for all participants. Detailed eye examinations involving best corrected visual acuity, pupillary reflexes, slit-lamp biomicroscopy, dilated-pupil fundus examination with a 90-diopter lens, and Goldman applanation tonometry were performed on all participants. Ultrasonic pachymetry device Echoscan US 500 system (Nidek Co. Ltd., Aichi, Japan) was used for all central corneal thickness(CCT), axial length(AXL), anterior chamber depth(ACD) measurements. Retinal thickness (RT), retinal nerve fiber layer (RNFL) thickness, and choroidal thickness (CT) were calculated using spectral domain optical coherence tomography (SD-OCT, Heidelberg Engineering, Heidelberg, Germany). CT scans were performed with an enhanced SD-OCT depth-imaging method. Eye scans were carried out by a trained ophthalmologist between 08:00 and 11:00 am for the purpose of minimizing diurnal variability. The disc margin contour line was drawn at the inner border of the scleral ring with the identification of seven distinct points. RNFL thicknesses were calculated both globally and also for the temporal, superotemporal, superonasal, nasal, inferotemporal, and inferonasal sectors. CT was defined as the perpendicular distance from the hyper-reflective outer border of the retinal pigment epithelial layer (detected automatically by the device) as far as the manually drawn choroidal scleral interface. RT and CT measurements (one subfoveal, three temporal, and three nasal) were taken using the caliper system at 500-mm intervals up to 1,500 mm.(12) Dilated fundus examinations were conducted following the extractions in order that OCT measurements should not be affected by dilatation. Once the measurements had been taken, dilated fundus examinations were conducted using tropicamide. All examinations were carried out by a single ophthalmologist blinded to the clinical data. Measurements were performed in triplicate, the average of these being calculated to avoid bias.

Statistical Analyses

The data obtained in the research were analyzed with the SPSS 25.0 (Statistical Package for the Social Sciences) version package program. Descriptive statistics for numerical variables mean±standard deviation; descriptive statistics for categorical variables are given as numbers and %. Whether the data fit the normal distribution or not was analyzed with the Kolmogorov-Smirnov test. In the comparison of two independent groups, the Independent Sample t-Test was used because the data showed normal distribution. The comparison of categorical data was made with the Chi-Square Test.

RESULTS

Demographic characteristics of the participants in the control group and the participants who have hyperthyroid (HT) and the information of TSH, fT4, fT3, IOP, CCT, ACD and AXL are shown in table (Table-1). The gender distribution was similar between the two groups, with 21 males and 19 females in the HT group, and 22 males and 20 females in the control group (p= 0.991). Similarly, the

mean ages of the two groups were close to each other. The mean age was 47.6 ± 15.0 years in those with HT, and 48.3 ± 12.7 years in the control group and there is no significant difference between the mean age (p= 0.300). TSH value was statistically significantly lower in the HT group compared to the control group, and fT3 and fT4 values were statistically significantly higher (p<0.001; p=0.001; p<0.001, respectively). While IOP and ACD values were 15.9 ± 2.1 mmHg and 3.0 ± 0.6mm in the HT group, they were 13.3 ± 2.6 mmHg and 3.3 ± 0.5 mm in the control group and this difference was found to be statistically significant.(p<0.001 and p=0.036, respectively).

Table 1. Demographic data and clinical features in hyperthyroid patients and healthy control subjects

Parameters	Hyperthyroid Group (mean± SD)	Control Group (mean± SD)	Statis-tics	*P value*
Age (Years)	47.6 ± 15.0	48.3 ± 12.7	t=3.022	0.300
Female/Male(n)	21(52%)/19(48%)	22(52%)/20(48%)	X^2=0.000	0.991
TSH	0.014 ± 0.021	3.628 ± 0.998	t=-23.472	**<0.001**
Free T4	1.8 ± 0.9	1.0 ± 0.3	t=5.433	**<0.001**
Free T3	4.2 ± 1.5	3.5 ± 0.6	t=2.682	**0.010**
IOP	15.9 ± 2.1	13.3 ± 2.6	t=4.951	**<0.001**
CCT	553.3 ± 38.6	560.6 ± 26.2	t=-1.020	0.311
ACD	3.0 ± 0.6	3.3 ± 0.5	t=-2.134	**0.036**
AXL	22.8 ± 0.8	22.5 ± 1.0	t=1.681	0.097

TSH:Thyroid Stimulating Hormone , IOP: intraocular pressure, CCT:central corneal thickness, ACD: anteior chamber depth, AXL: axial length, SD:Standart deviation

RT between HT and the control group was examined. In terms of RT measurements, T500, T1000 and T1500 were found to be lower and N1500 was found to be higher in the compared to HT group and they were statistically significant (p<0.001; p<0.001; p<0.001; p=0.011; respectively). No statistically significant differences were observed in Central, N500 and N1000 (p=0.230; p=0.256; p=0.675; respectively) (Table-2).

Table 2. Statistics of the retinal thickness at different locations.

Retinal Thickness, µm	Hyperthyroid Group (mean± SD)	Control Group (mean± SD)	Statis-tics	*P value*
Central	227.7 ± 32.0	220.7 ± 18.1	t=1.213	0.230
Nasal-500	287.1 ± 34.7	294.4 ± 22.3	t=-1.143	0.256
Nasal-1000	336.2 ± 27.7	333.8 ± 22.5	t=0.421	0.675
Nasal-1500	342.0 ± 23.1	330.4 ± 17.1	t=2.606	**0.011**
Temporal-500	279.8 ± 24.2	301.5 ± 24.8	t=-3.998	**<0.001**
Temporal-1000	323.1 ± 24.2	344.5 ± 26.8	t=-3.807	**<0.001**
Temporal-1500	321.2 ± 24.1	352.5 ± 17.2	t=-6.793	**<0.001**

SD:Standart deviation

CT measurement differences between HT and control groups are given in Table 3. In terms of CT measurements, Central, N500, N1000 and N1500, T500, T1000 and T1500 were found to be lower in the compared to the control group and they were statistically significant. (p=0.003; p=0.002; p=0.005; p=0.005; p=0.002; p=0.002; p=0.028; respectively) (Table-3)

Table 3. Statistics of the mean choroidal thickness at different locations.

Choroidal thickness, µm	Hyperthyroid Group (mean± SD)	Control Group (mean± SD)	Statis-tics	*P value*
Central	304.4 ± 90.3	373.6 ± 110.0	t=-3.104	**0.003**
Nasal-500	298.8 ± 99.4	370.2 ± 104.8	t=-3.159	**0.002**
Nasal-1000	288.7 ± 104.9	356.1 ± 106.5	t=-2.884	**0.005**
Nasal-1500	278.3 ± 102.1	344.9 ± 107.6	t=-2.871	**0.005**
Temporal-500	298.1 ± 88.1	368.8 ± 114.4	t=-3.146	**0.002**
Temporal-1000	291.7 ± 85.8	361.2 ± 110.7	t=-3.170	**0.002**
Temporal-1500	290.7 ± 86.8	340.7 ± 112.9	t=-2.242	**0.028**

SD:Standart deviation

RNFL measurement differences between HT and control groups are given in Table 4. In terms of RNFL measurements, it was observed that the HT group was lower in the T, TS, TI segments, and higher in the NI segment compared to the control group, and this difference was statistically significant (p=0.008; p=0.001; p=0.002 and p=0.009, respectively). There were no statistically significant differences in NS, N and G segments (respectively p=0.610; p=0.094; p=0.473) (Table-4).

Table 4. Statistics of the mean RNFL thickness at different quadrants in Hyperthyroid patients and healthy subjects

RNLF Thickness, µm	Hyperthyroid Group (mean± SD)	Control Group (mean± SD)	Statis-tics	*P value*
T	60.1 ± 10.5	77.9 ± 17.8	t=-2.733	**0.008**
TS	122.7 ± 31.1	143.1 ± 22.5	t=-3.409	**0.001**
NS	113.5 ± 29.0	110.9 ± 14.6	t=0.513	0.610
N	81.8 ± 19.9	75.1 ± 15.7	t=1.696	0.094
NI	115.2 ± 25.1	101.5 ± 21.0	t=2.696	**0.009**
TI	127.1 ± 30.4	145.6 ± 22.7	t=-3.135	**0.002**
G	99.0 ± 13.0	100.8 ± 8.8	t=-0.721	0.473

G:global, T: Temporal, TS: superotemporal, NS: superonasal, N: nasal, TI: inferotemporal, and NI:inferonasal, SD:Standart deviation

DISCUSSION

Hyperthyroidism is the high level of thyroid hormones in the body due to excessive thyroid hormone synthesis by the thyroid gland(13). In the present study, we found significantly lower values in many segments of RT, CT and RNLF in the HT group compared to those of the control group.

The ocular effects and pathophysiology of hyperthyroidism have not been fully elucidated. Graves' ophthalmopathy (GO) is the most common and most important extrathyroid finding of GO and is an autoimmune inflammatory disease of the orbit. In the light of the information obtained so far, TSH receptor antibodies bind to TSH receptors in the retro orbital regions and stimulate T cells, which causes fibroblasts to be stimulated by cytokine and leads to the production and accumulation of glycosaminoglycans by fibroblasts. GO is characterized by extraocular muscle edema and inflammation, accompanied by an increase in soft tissue volume due to orbital inflammation. While GO is generally mild, it can cause serious total vision loss in a small group of patients. Hyperthyroidism and hypothyroidism have been shown to exacerbate ophthalmopathy (3,5,6,13). In addition, the findings of various layers of the eye such as retina, RNLF and choroid, which differ in eye diseases, have been detected thanks to the latest developments in swept-source (SS) OCT in technology (14). In addition, there is limited information about them in patients with hyperthyroidism.

In our study, the IOP value was found to be statistically and significantly higher in the HT group than in the control group. Yu et al.(16) in their study on thyroid ophthalmopathy in 82 individuals and Forte et al.(17) found the IOP value to be higher in patients with HT, similar to our study (16,17).

There are theories on the formation mechanisms of the causes of increased IOP. One of them is the restriction and pressure caused by the fibrotic and enlarged eye muscles around the eyeball. Another one is the increased episcleral venous pressure caused by the pressure behind the globe that rises above the normal venous pressure. Yet another main theory is the increased resistance to trabecular outflow with mucopolysaccharide accumulation in the trabecular meshwork (18,19). In our study, we found a statistically significant increase in the HT group. No study has been found in the related literature. The difference may be related to the relatively low number of patients or other unknown factors.

Kurt et al (8) found no statistically significant difference in the ganglion cell layer compared to the control group in their study on 58 patients with GO on RT. Meirovitch et al.(20) found a statistically significant decrease in the retinal layer in their study on 21 patients with Thyroid-associated ophthalmopathy (TAO), similar to our study, and similarly, Casini et al. (7) found a statistically significant decrease in central retinal thickness in their study on 40 patients with GO. In our study, it was observed that RT measurements were lower in the T500, T1000, T1500 and HT groups, and these were statistically significant.

When the studies in the CT related literature were evaluated, it was seen that the studies were in different patient groups and stages of thyroid disease, so there was no complete consensus. Lai et al. (21) found an increase in choroidal thickness in patients with TAO in their study. Caliskan et al (11) investigated the patients with GO and found that there was an increase in choroidal thickness in patients with active GO. Noce et al. (22) found that choroidal thickness was lower in patients with thyroid ophthalmopathy than in patients with mild TAO compared to severe TAO. In addition, Casini et al. (7) found that there was no significant difference in CT in their study of patients with GO. Gül et al. (23) found that the CT was lower in the subfoveal and temporal regions in the study they conducted between two groups with stable and active thyroid disease. Similarly, in our study, a decrease in choroidal thickness was observed in all segments in the hyperthyroidic patient group without ophthalmopathy. We think that this difference is due to the accumulation of cells starting with thyroid hormones.

In terms of RNLF, Yu et al. (16) found that in the study they conducted between patients consisting of inactive TAO, active TAO and control groups, although they did not find a statistically significant difference in terms of RNLF between inactive TAO and the control group, they found that the average RNLF was lower in patients with inactive TAO. Luo et al. (24) found that there was no statistically significant difference in the mild thyroid-associated ophthalmopathy group compared to the control group. Kurt et al. (8) found a statistically significant decrease in the RNLF superior segment compared to the control group in their study on patients with GO. In our study, it was observed that the HT group was lower in the T, TS, TI segments, and higher in the NI segment compared to the control group, and this difference was statistically significant.

Because of their proximity to RT, CT, and RNLF, all three of them may be affected due to changes in blood flow due to their feeding from the central retinal artery. Hormonal changes in the body primarily affect the choroid and then the retina. Chu et al. (25) reported that plasma endothelin-1(ET1) concentrations were higher in patients with hyperthyroidism. High ET-1 levels can affect the vascular structures in the choroid, retina and optic disc head, causing decreased perfusion and malnutrition in all vessels, especially the retinal artery. As a result, we think that high ongoing thyroid hormone levels may cause a decrease in the thickness of the retina and the head of the choroidal optic disc. In addition, we have seen in terms of choroidal thinning similar results in patients with FMF. While there was an increase in RT and CT during the active FMF attack period, there was a decrease in CT and RT in the post-attack periods. In the post-attack period choroidal thickening may be triggered by the influx of inflammatory cells into the uveal tissue-choroid and dilatation of the choriocapillaris. Inflammation can often reduce the choroid's vascular support and function (26,27). We consider that there may be a decrease in CT, RT and RNFL due to these two phenomena. We also believe that the differences between the segments of these three parameters may be related to the relatively low number of patients. In addition, our study group, unlike similar publications in the literature, consists of patients who have not been treated for thyroid and who have been diagnosed for the first time. It should also be kept in mind that the findings may change after

the start of treatment or in the advanced stages of thyroid-related diseases.

The limitation of our study was the relatively low number of patients in the study group (the study group consisted of only first-diagnosis patients since patients who had previously been diagnosed with surgery or medical treatment were excluded from the study). The strength of our study was that it was the first clinical study in the literature of subclinical hyperthyroid patients without ophthalmopathy.

CONCLUSION

Hyperthyroidism is a common disease that can cause ocular problems, particulary in its advanced stages. Although there are many studies on ophthalmopathy due to hyperthyroidism, no study was found in patients who did not develop ophthalmopathy. In our results, we found statistically significant differences in some segments of RT, CT, and RNLF measurements compared to the control group. In conclusion, we think that regular eye check-ups should be made after the diagnosis of hyperthyroidism in patients with thyroid disease, not only in those with ophthalmopathy but also in those without ophthalmopathy.

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