Investigation of the choroidal thickness in patients with hypothyroidism

Fatih Ulaş, Ümit Doğan, Oğuz Dikbaş, Serdal Çelebi¹, Asena Keleş

Purpose: The effect of hypothyroidism on the choroidal thickness (CT) was investigated in patients with subclinical hypothyroidism and overt hypothyroidism, and biochemically and clinically euthyroid patients receiving levothyroxine treatment. The patients were compared with healthy subjects.

Materials and Methods: One eye of 71 hypothyroid and 22 healthy subjects between 20 and 40 years of age were included in this study. CT measurements were taken at the fovea and at 2 points that were 1500 µm nasal and temporal to the fovea using spectral-domain optical coherence tomography. Independent sample t-test’s and was used for statistical analysis of the data. Results: The CT was significantly thicker in hypothyroid patients compared to healthy subjects (P values were 0.013 for subfoveal, 0.015 for temporal and 0.020 for nasal segments). The intraocular pressure (IOP) and body mass index (BMI) levels were also significantly higher in hypothyroid patients (P values were 0.021 and 0.003, respectively). There was not a statistically significant difference in the BMI and IOP measurements between healthy subjects and euthyroid patients (P > 0.05). However, there was a statistically significant difference in the subfoveal, temporal and nasal CT measurements between healthy subjects and euthyroid patients (P values were 0.006, 0.031 and 0.013, respectively). Conclusions: All subgroups of hypothyroid patients had thicker CT compared to healthy subjects. Euthyroid patients receiving levothyroxine treatment had lower IOP, BMI levels, and serum lipid levels than patients with subclinical hypothyroidism and overt hypothyroidism.

Key words: Choroidal thickness, enhanced depth imaging, hypothyroidism, intraocular pressure, optical coherence tomography

Hypothyroidism is characterized by a decrease in thyroid hormone production by the thyroid gland. It ranges in severity from mild subclinical to overt hypothyroidism. Subclinical hypothyroidism is characterized by serum thyroid hormone concentrations (free tetraiodothyronine [FT4] and free triiodothyronine [FT3]) within the laboratory reference range and an increase in serum thyroid-stimulating hormone (TSH) levels, which simply reflects the pituitary adaptation to maintain thyroid hormone levels.

Hypothyroid subjects may present with chemosis, periorbital edema and/or blepharoptosis, all of which are attributed to the accumulation of hydrophilic mucopolysaccharides in the ground substance of the dermis and other tissues, which causes thickening known as myxedema.¹ A higher prevalence of primary open angle glaucoma among hypothyroid subjects was reported; however, other studies have failed to confirm this association.²⁻⁵ Spontaneous choroidoretinal detachment was reported in a hypothyroid patient.⁶ Ozturk et al. reported neither hypothyroidism nor thyroid hormone replacement gave rise to any change of retinal thickness and retinal nerve fiber layer (RNFL) thickness using time-domain optical coherence tomography (OCT).⁷

Hypothyroidism impairs serum lipid regulation and is known to contribute to the progression of atherosclerotic vascular diseases.⁸ The cardiovascular system is one of the major targets for thyroid hormone action and is vulnerable to the effects of thyroid hormone deficiency even in individuals with mild thyroid failure.⁹ Given the vascular nature of the choroid, it is expected that the choroidal thickness (CT) undergoes changes as a result of hypothyroidism.

Spectral-domain OCT (SDOCT) is a technique used to acquire high-resolution cross-sectional scans of the retina, choroid, and RNFL and is an important tool in the diagnosis and management of chorioretinal diseases. The technique of enhanced depth imaging (EDI) for in vivo choroidal imaging has been described.¹⁰ This technique uses multiple scans obtained from the same retinal location to visualize the choroid, and the images are subsequently averaged by OCT software. CT measurements obtained using OCT have been shown to be repeatable and reproducible.¹¹ Further, CT is known to vary with age, refractive status, axial length and also vary in diabetic patients and in subjects with hypercholesterolemia.¹²⁻¹⁵

Further investigation of CT under the influence of different systemic conditions like hypothyroidism is needed. The current study was designed to investigate the effects of the hypothyroidism on the CT.

Materials and Methods

This cross-sectional study was conducted in one eye of healthy and hypothyroid age-matched women: 22 healthy subjects, 24 subclinical hypothyroid (SCH) patients, 23 overt hypothyroid (OVH) patients and 24 euthyroid hypothyroid patients receiving levothyroxine treatment were examined between December 2012 and June 2014. This study was performed in adherence with the tenets of the Declaration of Helsinki and was approved by the University review board (Number: 2012/132). Informed consent was obtained from all of the study participants.
The inclusion criteria were as follows: 20–40 years of age; <5-dimensional of spherical and <3-dimensional of cylindrical refractive error; best-corrected visual acuity of 20/20 or better; no history of chronic ocular disease, such as glaucoma and uveitis; no systemic disease in the healthy subjects; and no systemic disease other than hypothyroidism in the hypothyroid patients. The exclusion criteria were as follows: The presence of an ocular disease that would prevent the examination of the corneal and retinal states, prior application of laser or any ocular surgery; a history of smoking or alcohol consumption; a history of any medication use within the previous 3 months, including hormonal therapy (except for levothyroxine treatment) or systemic vasoactive drugs. We included a subject’s left eye, only if their right eye did not meet the inclusion criteria.

Serum levels of free T3 (FT3), FT4, TSH, anti-thyroid peroxidase antibody and thyroglobulin antibody levels were determined using an electrochemiluminescence immunoassay method with a fully automated immunoanalyzer according to the manufacturer’s instructions (Cobas e 601, Roche Diagnostics, Mannheim, Germany). Serum triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels were quantified using an autoanalyzer according to the manufacturer’s instructions (Architect C8000, Abbott Laboratories, Illinois, USA).

A detailed ophthalmologic examination, including best-corrected visual acuity, intraocular pressure (IOP), central corneal thickness (CCT) and retinal and CTs, was performed. IOP and CCT were measured using Goldmann applanation tonometry and an ultrasonic pachymeter (Nidek UP-1000[Nidek Co., Ltd., Aichi, Japan]), respectively. We also calculated the CCT adjusted IOP value.[16] The axial length was measured using an ultrasonic biometer (Nidek Echo Scan-3300 [Nidek Co., Ltd., Aichi, Japan]). Following the other ophthalmologic examinations, the retinal and CTs were measured using a Spectralis SDOCT system (Heidelberg Engineering, Heidelberg, Germany). The ophthalmologic examinations were performed during the morning hours (between 10:00 am and 12:00 am).

All of the SDOCT scans and measurements were acquired by the same experienced operator (FU) with the Spectralis SDOCT system (software version 5.3) using the horizontal 30° line scan EDI mode through the fovea. Using an automatic real-time (ART) imaging value of 100 and the active eye-tracking feature, the line scan images were saved for analysis after 100 frames were averaged. The retinal thickness was measured using the automatic segmentation values provided by the Spectralis SDOCT system. The CT was measured manually from the outer portion of the hyperreflective line, corresponding to the retinal pigment epithelium, to the inner surface of the sclera [Fig. 1]. Using the manual calipers provided by the SDOCT software, two experienced operators (FU and ÜD) measured the CT at 100% magnification and fine corrections were performed at 200% magnification. The EDI images for each subject was opened by another operator (AK), and CT measurements were performed by masked readers (FU and ÜD) on different sessions. For intraobserver reproducibility, FU performed 2 CT measurements and for interobserver reproducibility, ÜD performed 1 CT measurement. SDOCT scans were acquired without pupil dilation. Only images with an imaging quality score of >20 were studied. The retinal and CTs were measured at the central fovea and at 1500 μm nasal and 1500 μm temporal from the center of the fovea. The default RNFL optic disc protocol was used to measure RNFL thickness, which consisted of a 3.6 mm diameter circle scan for RNFL analysis, an ART imaging value of 100 and the active eye-tracking feature. RNFL thickness was measured using the automatic segmentation values provided by the Spectralis SDOCT system.

All data were analyzed using the SPSS statistical software package, version 21.0 (SPSS Inc., Chicago, IL, USA). For general statistical reporting, the mean values from each data set were calculated with standard deviations (SDs). A level of \( P < 0.05 \) was accepted as statistically significant. The mean of 2 CT measurements performed by FU was used for statistical analysis. The Kolmogorov–Smirnov test was used to check the normality of the sample distribution. For all of the studied continuous parameters, the \( P \) value for the Kolmogorov–Smirnov test was >0.05 (the actual values ranged from 0.101 to 0.941). Independent sample \( t \)-test’s was used for statistical analysis of the data. The coefficient of repeatability (CR), as defined by Bland and Altman, was also calculated for the CT measurements performed by the two operators to determine intraobserver and interobserver reproducibility.10

Results

The demographic and clinical characteristics of the study sample and their statistical significances are shown in Table 1. Thyroid hormone levels and serum lipid levels are presented in Table 2. SCH patients were newly diagnosed patients who had no previous history of any systemic disease. Euthyroid patients were biochemically and clinically euthyroid for at
Table 1: Demographical and clinical characteristics of the healthy subjects and hypothyroid patients including patients with subclinical hypothyroidism and overt hypothyroidism and euthyroid patients receiving levothyroxine treatment (mean±SD)

| Parameter      | Healthy subjects (n=22) | SCH patients (n=24) | OVH patients (n=23) | Euthyroid patients (n=24) | P   |
|----------------|-------------------------|---------------------|---------------------|---------------------------|-----|
| Age (years)    | 28.64±5.21              | 28.0±6.47           | 29.74±6.33          | 30.83±5.76                 | 0.547|
| BMI (kg/m²)    | 22.47±3.27              | 25.62±2.92          | 25.37±3.19          | 24.27±4.28                 | 0.003|
| AXL (mm)       | 23.15±0.64              | 23.27±0.66          | 23.19±0.52          | 23.10±0.53                 | 0.813|
| SE (diopter)   | −0.76±0.75              | −0.52±0.88          | −0.22±0.85          | −0.44±0.77                 | 0.069|
| CCT (µm)       | 546.86±36.93            | 536.88±32.55        | 549.09±35.14        | 554.67±29.25               | 0.998|
| IOP (mmHg)     | 14.73±2.71              | 16.58±3.11          | 16.91±3.57          | 16.17±2.63                 | 0.021|
| AIOP (mmHg)    | 14.73±2.71              | 16.99±3.00          | 16.71±3.35          | 15.68±2.38                 | 0.016|
| Central RT (µm)| 215.59±12.19            | 213.79±13.92        | 208.39±8.21         | 212.04±13.54               | 0.169|
| Temporal RT (µm)| 328.27±14.31          | 321.92±15.33        | 320.22±13.76        | 322.17±17.19               | 0.067|
| Nasal RT (µm)  | 354.05±15.08            | 352.50±15.52        | 351.00±18.34        | 346.83±14.69               | 0.313|
| RNFL (µm)      | 107.36±9.00             | 103.54±9.31         | 104.43±8.13         | 105.50±7.06                | 0.162|
| Subfoveal CT (µm)| 370.14±71.52        | 411.75±88.48        | 410.39±79.50        | 435.81±80.25               | 0.013|
| Temporal CT (µm)| 332.09±66.02          | 378.29±78.08        | 371.30±72.60        | 379.04±75.78               | 0.015|
| Nasal CT (µm)  | 304.09±70.15            | 345.06±82.96        | 341.72±82.33        | 353.15±83.43               | 0.020|

*Independent samples t-test analyzing the difference between healthy subjects and all subgroups of hypothyroid patients. AIOP: Central corneal thickness adjusted intraocular pressure, AXL: Ocular axial length, BMI: Body mass index, CCT: Central corneal thickness, CT: Choroidal thickness, IOP: Central corneal thickness non-adjusted intraocular pressure, RNFL: Retinal nerve fiber layer, OVH: overt hypothyroid, SCH: Subclinical hypothyroid

Table 2: Serum lipids and thyroid hormone levels of the groups (mean±SD)

| Parameter      | Healthy subjects | SCH patients | OVH patients | Euthyroid patients | Normal range |
|----------------|------------------|--------------|--------------|--------------------|--------------|
| FT3 (pg/ml)    | 2.86±0.49        | 3.17±0.44    | 2.47±0.72    | 3.18±0.50          | 2.7±4.2      |
| FT4 (ng/dl)    | 1.13±0.15        | 1.19±0.18    | 0.81±0.34    | 1.30±0.21          | 0.93±1.7     |
| TSH (µIU/ml)   | 1.96±0.73        | 6.24±1.26    | 31.67±32.25  | 2.49±0.88          | 0.27±4.2     |
| TG (mg/dl)     | 92.14±28.29      | 124.71±47.11 | 144.52±77.28 | 95.25±23.85        | 0-150        |
| TC (mg/dl)     | 184.00±23.56     | 191.13±39.77 | 199.13±46.82 | 178.33±28.50       | 50-200       |
| LDL (mg/dl)    | 113.22±17.57     | 123.00±36.47 | 129.82±39.41 | 116.44±23.35       | 80-160       |
| HDL (mg/dl)    | 50.54±6.18       | 46.05±9.15   | 45.37±9.57   | 49.27±8.04         | 35-55        |

FT3: Free triiodothyronine, FT4: Free tetraiodothyronine, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, OVH: Overt hypothyroid, SCH: Subclinical hypothyroid, SD: Standard deviation, TC: Total cholesterol, TG: Triglyceride, TSH: Thyroid-stimulating hormone

least 1-year, and they had 4.0 ± 2.81 years of hypothyroidism diagnosis (range: 2–12 years). In the OVH group, 9 patients were newly diagnosed and 14 patients had a history of levothyroxine treatment and discontinued treatment for at least 6 months (mean duration 3.58 ± 1.83 years, range: 1–8 years). The etiology of hypothyroidism was Hashimoto’s thyroiditis (49 patients, 69.01%) and idiopathic (22 patients, 30.99%). None of the hypothyroidism patients had thyroid orbitopathy. This study included 86 right and 7 left eyes of 23 patients (the right eyes of five subjects were excluded due to high myopic astigmatism and the right eye of two subjects were excluded due to high myopia).

Independent sample t-tests revealed a statistically significant difference in the body mass index (BMI), CCT adjusted IOP, CCT nonadjusted IOP, serum TG level and subfoveal, temporal and nasal CT measurements between healthy subjects and all groups of hypothyroid patients (P values were 0.003, 0.016, 0.021, 0.023, 0.013, 0.015 and 0.020, respectively) [Table 1]. However, there was not a significant difference in age, spherical equivalent, CCT, ocular axial length, retinal thickness, RNFL, serum TC, LDL and HDL levels between healthy subjects and all groups of hypothyroid patients (P values ranged between 0.069 and 0.813) [Table 1].

There was not a statistically significant difference in the BMI, CCT adjusted IOP, CCT nonadjusted IOP and serum TG levels between healthy subjects and euthyroid patients (P values were 0.117, 0.208, 0.099 and 0.688, respectively). However, there was a statistically significant difference in the subfoveal, temporal and nasal CT measurements between healthy subjects and euthyroid patients (P values were 0.006, 0.031 and 0.013, respectively).

Independent sample t-tests did not reveal a statistically significant difference in the BMI, CCT adjusted IOP, CCT nonadjusted IOP measurements and subfoveal, temporal and nasal CT measurements of the euthyroid patients and the group of overt and SCH patients (P values were 0.165, 0.114, 0.460, 0.235, 0.625 and 0.343, respectively). Serum TG levels were significantly lower in euthyroid patients (P = 0.005). Serum TC and LDL levels were also lower in euthyroid patients, but it was not statistically significant (P values were 0.091 and 0.244, respectively).
There was a statistically significant difference in BMI, CCT adjusted IOP measurements, CCT nonadjusted IOP measurements, subfoveal, temporal and nasal CT measurements between healthy subjects and the group of overt and SCH patients (P values were <0.001, 0.006, 0.015, 0.041, 0.020 and 0.045, respectively). Serum TG and HDL levels were significantly different (P values were <0.001 and 0.013, respectively), but the difference in serum TC and LDL levels was not significantly different (P values were 0.175 and 0.053, respectively).

The choroid in SCH patients, OVH patients and euthyroid patients demonstrated a wider range of thicknesses and higher SDs (range of subfoveal CT and SDs, 261.0–546.0 and 88.48; 275.5–520.0 and 79.50; and 243.0–570.0 and 80.25 µm, respectively) than healthy subjects (235.0–478.0 and 71.52 µm) [Table 1]. The study revealed that CT can be measured using SDOCT and that thicker CT exists in all subgroups of hypothyroid patients than healthy subjects [Fig.1].

Intraobserver and interobserver differences in subfoveal CT measurements are summarized in Table 3. No statistically significant difference was found between the measurements taken by the two operators (FU and ÜD). The CR ranged between 19.86 and 20.52 µm for intraobserver measurements and 22.03 and 27.29 µm for interobserver measurements [Table 3].

Discussion

In the current study, we found that spherical equivalent, CCT, retinal thickness and RNFL thickness did not significantly differ between healthy subjects and hypothyroid patients. However, CT, IOP, BMI and serum lipids were increased in hypothyroid patients. CT was thicker in all subgroups of hypothyroid patients including patients, who were euthyroid for at least 1-year. To the best of our knowledge, this is the first study to demonstrate the effects of hypothyroidism on CT.

There have been conflicting reports on the relationship between subfoveal CT and age. Fujiwara et al. reported that the CT in subjects younger than 10 years old was significantly thicker compared to other age groups, remained unchanged from 10 to 20 years of age, but then decreased gradually after age 30. However, in another study, it was reported that the subfoveal CT had no correlation with age in subjects younger than 10 years old. These studies support our results that report increased CT in all subgroups of hypothyroid patients including euthyroid patients. In the current study, despite euthyroid patients and healthy subjects having similar levels of IOP, BMI and serum lipid levels, the CT was still significantly thicker in this subgroup.

The thyroid hormones regulate cholesterol and lipoprotein metabolism, and hypothyroidism is known to alter the lipid profile. Wong et al. reported that the subfoveal CT was found to be significantly higher in subjects with hypercholesterolemia. Diabetic and hypertensive patients

| Table 3: Comparison of the CT measurements taken by operators in different sessions |
|---------------------------------|----------|----------|----------|----------|
| Scan pairs | Location | MD (µm) | P* | CR (µm) | 95% CI (µm) |
| O11 versus O12 | Subfoveal | −1.77 | 0.081 | 19.86 | −3.83:0.29 |
| | Temporal | −1.12 | 0.306 | 20.52 | −3.28:1.04 |
| | Nasal | −1.43 | 0.182 | 20.40 | −3.58:0.72 |
| O11 versus O2 | Subfoveal | 0.29 | 0.741 | 27.29 | −2.54:3.12 |
| | Temporal | 0.51 | 0.605 | 25.83 | −2.21:3.22 |
| | Nasal | 0.74 | 0.289 | 22.34 | −1.58:3.06 |
| O12 versus O2 | Subfoveal | 2.06 | 0.082 | 24.00 | −0.43:5.55 |
| | Temporal | 1.62 | 0.241 | 24.21 | −0.92:4.17 |
| | Nasal | 1.17 | 0.213 | 22.03 | −1.12:3.46 |

*P of the paired samples t-test. CI: Confidence interval, CR: Coefficient of repeatability, MD: Mean difference of the measurements, O11: First measurement of operator 1, O12: Second measurement of operator 1, O2: Measurement of operator 2, CT: Choroidal thickness.
were excluded in this study, but the thyroid hormone levels of included subjects were not reported. Salazar et al. \[30\] reported that the choroid thickness increased in hypercholesterolemic rabbits, and the change was not completely reversible upon normalization of the serum cholesterol. The current study is the first to report that hypothyroidism may result in choroidal thickening due to probable changes in the interstitial connective tissue matrix, increased capillary density and/or increased serum lipid levels. Thickening of the choroid was not reversed with thyroid replacement therapy, even after at least 1-year of maintenance of the euthyroid state, despite the decreased levels of TG, TC, and LDL in the euthyroid patients. A study comparing the CT of hyperlipidemic subjects with and without hypothyroidism is needed to interpret the effect of hyperlipidemia and hypothyroidism on the choroid.

A correlation between primary open angle glaucoma and hypothyroidism has been reported in some studies, and thyroid replacement therapy may have a protective role by decreasing IOP. \[3-4\] Despite being within normal limits, this study revealed that hypothyroid patients had a significantly higher IOP compared to healthy subjects. We found that the IOP levels were significantly higher in the subclinical and OVH patients compared to euthyroid patients and healthy subjects.

There were some limitations to this study, such as the cross-sectional study design. Our sample size was limited; however, a significant change was observed in the CT between hypothyroid patients and healthy subjects. We included young Turkish women who did not have prior use of any systemic medication other than levothyroxine. We obtained CT measurements manually because no software algorithm is currently available for choroidal segmentation. We set the calipers at 100% magnification because caliper placement can vary depending on the magnification of the scan; for instance, low magnification (below 100%) can result in improper caliper placement and very high magnification (above 200%) can decrease the image resolution, leading to indistinct borders.

In summary, this study demonstrated that hypothyroidism caused an increase in the CT, IOP, BMI and impaired serum lipid levels. Euthyroid patients receiving levothyroxine treatment had lower IOP, BMI levels, and serum lipid levels than patients with subclinical hypothyroidism and overt hypothyroidism, but the CT was thicker in all subgroups of hypothyroid patients compared to the healthy subjects. Further prospective studies with larger sample sizes are needed to determine the possible effects of hypothyroidism on the choroid. These data highlight the importance of thyroid hormone status and increase the relevance of the interpretation of the SDOCT results.

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