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Research article

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Evaluation of macular perfusion in patients with treatment-naive overt hypothyroidism using optical coherence tomography angiography

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Ethics approval for this study was obtained from Uludag University, Faculty of Medicine, Ethics Committee (2021-4/6, 24.02.2021).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Thyroid hormones play an essential role in retinal development and physiological functions. Although the effects of hyperthyroidism on ocular circulation are well-defined, no studies report the effects of clinical hypothyroidism on retinal and choroidal circulation. We aimed to compare the macular vessel density and flow indexes of patients with treatment-naive hypothyroidism and healthy controls using optical coherence tomography angiography (OCTA).

Methods: This case-control study included 104 eyes of 52 participants. Group 1 (n=24) consisted of patients with treatment-naive overt hypothyroidism, while Group 2 (n=28) consisted of age and sex-matched healthy controls. Images were obtained using AngioVue software 2.0 of the OCTA device in a 6 × 6 mm area centered on the macula. Foveal avascular zone (FAZ) area, macular retinal thickness, FAZ perimeter (PERIM), choroidal flow index (CF), outer retinal flow index (ORF) and macular vessel density (VD) in the superficial (SCP) and deep retinal capillary plexus (DCP) were recorded for all patients.

Results: The whole [Group 1: 49.9 (7.0)%; Group 2: 54.6 (5.9)%], parafoveal [Group 1: 54.7 (4.8)%; Group 2: 58.6 (3.9)%] and perifoveal [Group 1: 51.5 (7.2)%; Group 2: 55.9 (6.8)%] VD in DCP were significantly lower in Group 1 compared to Group 2 (P=0.012; P=0.002 and P=0.028 respectively). However, parafoveal VD in SCP was significantly higher in Group 1 [52.4 (2.26)] than in Group 2 [49.9 (6.87)] (P=0.032). The mean VD in DCP was significantly positively correlated with the choroidal (P=0.021) and outer retinal flow indexes (P=0.033). The mean foveal VD in DCP was significantly positively correlated with the mean foveal (P<0.001), parafoveal (P=0.001) and perifoveal retinal thicknesses (P<0.001).

Conclusion: Our study has provided, for the first time, a quantitative assessment of macular perfusion in patients with overt hypothyroidism using OCTA. The reduction in VD in the DCP might be attributed to the lack of angiogenic effects of T4 or neural hypometabolism secondary to hypothyroidism.

Keywords: Choroidal flow, Hypothyroidism, Macular perfusion, Optic coherence tomography angiography, Vessel density

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Introduction

Hypothyroidism, which is most often caused by autoimmune thyroiditis (Hashimoto), is a relatively common disorder affecting approximately 5% of the population [1]. Females are eight times more likely to be affected than males and the incidence increases with age in both sexes [2]. Overt hypothyroidism is characterized by an increased thyroid-stimulating hormone (TSH) and a reduced thyroxine (T4) level, while subclinical hypothyroidism refers to slightly increased serum TSH level in the presence of normal serum T4 level [3].

Symptoms of hypothyroidism include fatigue, weight gain with poor appetite, constipation, poor memory and concentration, shortness of breath, hair loss, dry skin, and menstrual irregularities [4, 5]. Typical findings on physical examination include dry, coarse skin, bradycardia, increases in the level of cholesterol and triglycerides, sleep apnea, cognitive impairment, periorbital and pedal edema. Common ocular manifestations including periorbital edema and blepharoptosis' are generally attributed to the deposition of glycosaminoglycans in the dermis, which results in swelling of the affected area [6].

Thyroid hormones are essential for the development and proper functioning of the central nervous system through their role in gene expression, myelin production, axonal transportation, and neurotransmission [7]. Although less investigated, hypothyroidism may also cause a reduction in flow and vessel density of the central nervous system [8, 9]. Since the retina and optic nerves represent an extension of the central nervous system, one can suggest that hypothyroidism may cause alterations in retinal microstructure and perfusion. Accordingly, changes in peripapillary and macular vessel density values were recently shown in patients with established thyroid eye disease [10].

In the present study, we aimed to assess alterations in microvascular structure and perfusion of the macula in patients with treatment-naive, overt hypothyroidism using optic coherence tomography angiography (OCTA). There are many reports on retinal and choroidal changes related to Graves' Ophthalmopathy in the literature [11, 12]. However, to the best of our knowledge, this is the first study assessing the macular perfusion changes in patients with hypothyroidism using OCTA.

Materials and methods

This retrospective study included 48 eyes of 24 patients with treatment-naive overt hypothyroidism (Group 1) and 56 eyes of 28 age-matched euthyroid, healthy individuals (Group 2) examined between March 2017 and November 2019. A post hoc power analysis revealed that based on the mean, an n of approximately 34 would be needed to obtain statistical power of the recommended 0.80 level. The alpha was set at 0.05. The patients with hypothyroidism were referred to the ophthalmology clinic for suspected glaucoma, dry eye or thyroid-associated ophthalmopathy by an internist. The data recorded included clinical and endocrinologic analysis in addition to ocular examination. Informed consent was obtained from all participants included in the study. The study was conducted in accordance with the Declaration of Helsinki Ethical Principles and Good Clinical Practices and was approved by the Ethics Committee of Uludağ University Faculty of Medicine, Bursa, Turkey (2021-4/6).

Patient eligibility

Included were cases aged 20-60 years with spherical or cylindrical refractive error < 6.0 diopters, visual acuity ≥ 20/20, and no systemic diseases in Group 2, and no systemic disease other than hypothyroidism in Group 1. Excluded were patients with diabetic retinopathy or any other choroidal/retinal pathologies, history of any intraocular surgery or laser treatment, history of regular smoking or medication use, including levothyroxine and OCTA images with motion artifacts or signal strength index < 60.

All participants were tested for thyroid function, including free T3, free T4 and thyroid-stimulating hormone (TSH). Overt hypothyroidism was diagnosed in the presence of serum TSH > 4.5 mIU/L and low serum free T4 concentration by an internist. All patients underwent comprehensive ophthalmologic examination, including visual acuity, biomicroscopic anterior and posterior examination, intraocular pressure (IOP, mmHg) assessment and OCTA.

Prior to OCTA measurements, the patients were asked to rest in the sitting position at least for 10 minutes and systemic blood pressure and pulse rate were measured. OCTA measurements were obtained at 3 p.m to avoid normal diurnal variations in flow density [13].

OCTA measurement system

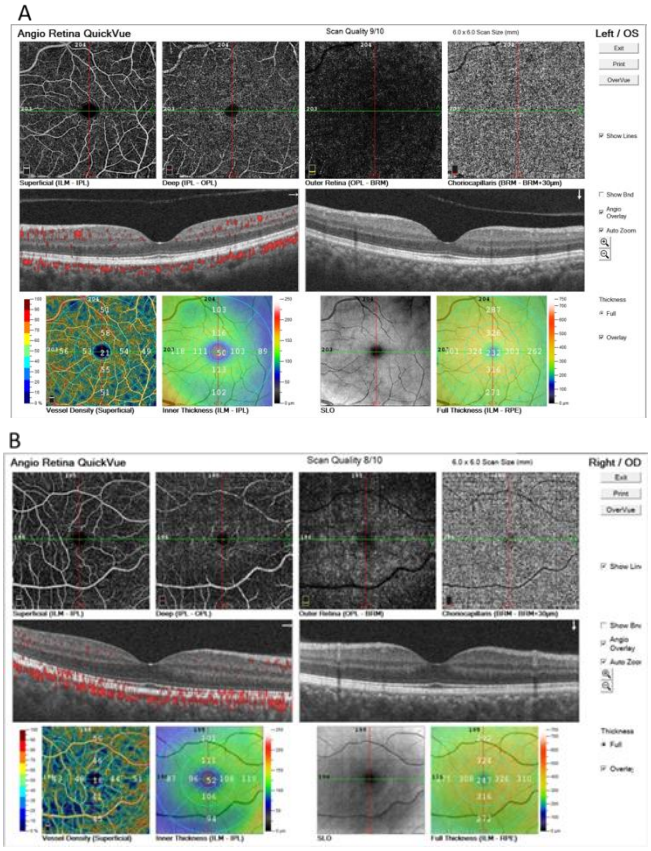
OCTA images were obtained using AngioVue OCTA device (v. 2015.0.1.7, Optovue, Inc., Freemont, CA, USA). This system used a split-spectrum amplitude-decorrelation angiography (SSADA) software algorithm and acquired 70,000 A-scans per second to compose OCTA volumes consisting of 304 × 304 A-scans [14]. The macula was imaged using a 6 mm × 6 mm scan. Quantitative analysis was performed on the OCTA using the AngioAnalytics Phase 7 software. Pupils of all the participants were dilated with 2.5% phenylephrine and 1.0% tropicamide prior to OCTA assessment. The OCTA images of the superficial and deep capillary networks were generated separately using the Optovue software. Based on these default settings, the superficial network comprised between 3 μm below the internal limiting membrane to 15 μm below the inner plexiform layer (IPL), while deep capillary plexus comprised between 15 to 70 μm below the IPL.

The measurements of foveal avascular zone (FAZ) area, FAZ perimeter (PERIM), choroidal flow index (CF) and outer retinal flow index (ORF), whole superficial capillary vessel density (wsVD), foveal superficial vessel density (fsVD), parafoveal superficial vessel density (pasVD), perifoveal superficial vessel density (pesVD), whole deep vessel density (wdVD), foveal deep vessel density (fdVD), parafoveal deep vessel density (padVD), perifoveal deep vessel density (pedVD) in addition to whole, foveal (FT), parafoveal (PaT) and perifoveal (PeT) retinal thicknesses were recorded for Group 1 (Figure 1 A) and Group 2 (Figure 1 B).

The automated FAZ boundary detection, provided by AngioVue, was used. Foveal thickness was expressed as the mean retinal thickness within the center of 1 mm diameter ring, whereas parafovea and perifovea were defined as rings centered on the fovea with inner and outer diameters of 1-3 mm and 3-6

mm, respectively. Vessel density is defined as the percentage area occupied by the blood vessels, while flow index is calculated as the average flow signal in the area of interest, providing information on both vessel area and blood velocity.

Figure 1: The quantitative analysis of macula on the OCTA in a patient with overt-hypothyroidism (A) and control subject (B) using a 6 mm × 6 mm scan



Statistical analysis

All statistical analyses were performed using SPSS 21.0 (Statistical Package for Social Science 21.0). The Kolmogorov–Smirnov test was used to analyze the normality of the data and an independent t test was used to compare the numerical variables between groups. The Chi-square test was used to compare categorical data. Pearson correlation coefficient was used to measure the linear correlation between two variables. A *P*-value less than 0.05 was considered statistically significant.

Results

The mean age of Groups 1 and 2 were 42.83 (11.07) (26-58) years and 41.0 (9.57) (28-57) years, respectively (P=0.53). Sixteen patients (66.6%) in Group 1 were female and the remaining 8 (33.3%) were male. Eighteen patients (64.2%) were female and 10 (35.8%) were male in Group 2 (P=0.89). All patients in Group 1 were newly diagnosed with overt hypothroidism and no thyroid replacement therapy was initiated yet. The mean free T4 and TSH concentrations were 0.430 (0.43) ng/dl and 60.96 (16.68) mIU/L, respectively, in Group 1 and 1.030 (0.347) ng/dl and 2.68 (0.32) mIU/, respectively, in Group 2 (P=0.004, P=0.001). The body mass index (BMI) in Group 1 [28.87 (1.79) kg/m^2] was significantly higher compared with Group 2 [21.83 (1.87) kg/m^2] (P<0.001). The IOP measurements were similar between the groups [Group 1:18.8 (2.24) mmHg, Group 2: 18.2 (1.84) mmHg] (P=0.46).

The mean OCTA features of two groups are shown and compared in Table 1. The parafoveal superficial vessel density was significantly higher in Group 1 compared to Group 2 (P=0.032); whole (P=0.012), parafoveal (P=0.002) and perifoveal (P=0.028) deep vessel density values were significantly lower in Group 1 than Group 2. No statistically significant difference was detected in terms of age, gender, fT4, TSH concentrations, BMI and OCTA parameters (P>0.05 for all).

Table 1: Comparison of the mean OCTA values of the eyes in Group 1(n=48 eyes) and Group 2 (n=56 eyes)

Measurements	Group 1 n=48 eyes	Group 2 n=56 eyes	*P*-value**
FAZ area (mm^2)	0.263 (0.09)	0.269 (0.77)	0.805
PERIM (mm)	1.96 (0.42)	1.98 (0.29)	0.857
CF (mm^2)	2.08 (0.14)	2.13 (0.15)	0.251
ORF (mm^2)	0.60 (0.47)	1.19 (0.60)	0.660
wsVD (%)	49.2 (3.52)	50.3 (2.90)	0.199
fsVD (%)	19.9 (5.08)	24.07 (9.36)	0.714
pasVD (%)	52.4 (2.26)	49.9 (6.87)	0.032*
pesVD (%)	49.9 (3.59)	50.9 (2.97)	0.283
wdVD (%)	49.9 (7.05)	54.6 (5.96)	0.012*
fdVD (%)	37.9 (8.31)	40.4 (6.78)	0.228
padVD (%)	54.7 (4.83)	58.6 (3.99)	0.002*
pedVD (%)	51.5 (7.29)	55.9 (6.81)	0.028*
Whole rT (µm)	285.6 (12.40)	286.5 (15.47)	0.833
FT (µm)	250.2 (25.34)	250.7 (16.13)	0.944
PaT (µm)	315.6 (12.15)	328.0 (16.50)	0.898
PeT (µm)	284.5 (11.17)	283.8 (17.04)	0.866

** Statistical analysis was performed by independent samples t-test, * statistically significant. Bold values represent the variables which show statistical significance, FAZ area: foveal avascular zone area, PERIM: FAZ perimeter, CF: choroidal flow index, ORF: outer retinal flow index, wsVD: whole superficial capillary vessel density, fsVD: foveal superficial vessel density, pasVD: parafoveal superficial vessel density, pesVD: perifoveal superficial vessel density, wdVD: whole deep vessel density, fdVD: foveal deep vessel density, padVD: parafoveal deep vessel density, pedVD: perifoveal deep vessel density, rT: retinal thickness, FT: foveal thickness, paT: parafoveal thickness and peT: perifoveal thickness, SCP: superficial capillary plexus, DCP: deep capillary plexus

The mean wdVD was significantly positively correlated with the mean outer flow and choroid flow (P=0.033, r=0.62; P=0.021, r=0.66, respectively). However, the relationship between the wsVD and outer retinal flow, choroidal flow did not reach statistical significance (P=0.205, P=0.081 respectively). The mean fdVD was significantly positively correlated with mean FT (P<0.001), PaT (P=0.001) and PeT (P<0.001). No significant correlation was observed between any other parameters (P>0.05 for all).

Discussion

The prevalence of overt hypothyroidism in relatively iodine-sufficient populations ranges between 0.3–0.5%, increases in incidence with age and is more common in females than in males at a ratio of 10:1 [15]. The clinical manifestations of hypothyroidism include a wide variety of symptoms that result from hypometabolism of different systems or over-accumulation of glucosaminoglycans in the connective tissues [16, 17]. Ocular findings of hypothyroidism include glaucoma, chemosis, periorbital edema and blepharoptosis due to the accumulation of mucopolysaccharides in the extracellular matrix [6, 18].

Significant associations between hypothyroidism and primary open-angle glaucoma have been reported in the literature [19, 20]. The possible mechanisms that could result in susceptibility to glaucoma include the accumulation of glycosaminoglycans in the meshwork pores, leading to an increase in outflow resistance and reduction in optic nerve head perfusion [21, 22].

The OCTA is a new imaging modality, which allows non-invasive qualitative and quantitative assessment of the retinal and choroidal microvasculature [23-25]. It relies on repeated B-scan OCT images from the same location of the

retina, which provides flow maps of retinal circulation. In addition, cross-sectional images of different retinal layers provide multi-depth assessment of retinal microvasculature. OCTA can measure retinal vessel density, which is defined as the percentage of vessel area with blood flow over the total area measured. Various studies investigated the applicability of OCTA for patients with glaucoma [26], diabetes [27], age-related macular degeneration [28], and Graves' ophthalmopathy [11]. However, no previous research investigated the macular microvascular alterations in hypothyroid patients. This is the first study investigating macular perfusion in hypothyroid patients using swept-source OCTA technology.

In the current study, superficial and deep foveal, parafoveal and perifoveal vessel density, FAZ area and choroidal, outer retinal flow indexes of the patients with treatment-naive overt hypothyroidism were evaluated using OCTA. We found that the whole, parafoveal and perifoveal VD values in DCP were significantly lower in the hypothyroidism group compared with the healthy subjects. The VD is a proportional measurement defining the percentage of the vessel area to the total measurement area. Therefore, the reduction in VD might be attributed to reduced vessel volume or increased total retinal extracellular volume. The glial cell over-stimulation by TSH results in increased production of glycosaminoglycan and connective tissue matrix in hypothyroidism. Accordingly, the mean choroidal thickness is higher in patients with hypothyroidism than in healthy subjects [29].

There are also studies that emphasize the vasomotor effects of thyroid hormones on microcirculation [30-32]. Hypothyroidism is characterized by a reduction in cardiac output and heart rate, and an increase in peripheral vascular resistance [33]. As a result, hypoperfusion of all the major organ systems of the body occurs. Tang et al. [34] reported a significant reduction in the myocardial blood flow and arteriolar vessel density in the drug-induced hypothyroidism animal model. Accordingly, Savinova et al. [35] reported a study investigating the capillary remodeling effect of T3 treatment in hypothyroid rats. The study demonstrated that T3 replacement therapy provides restoration of the arteriolar density to control levels as early as 72 hours. Furthermore, T3 treatment resulted in the simultaneous upregulation of Angiopoietin 1 and 2 expressions, consistent with vessel density improvement.

Another well-known mediator associated with angiogenesis is vascular endothelial growth factor (VEGF). Dedecjus et al. [36] detected significantly reduced plasma VEGF levels in hypothyroid patients. They also noted that the plasma VEGF level returned to a normal value following treatment with T4. Schlenker et al. [37] reported that the forebrain vessel density was reduced in adult thyroidectomized rats compared with healthy controls. They also observed a significant improvement in forebrain VD following 3.5-diiothyroprionic acid (DITPA) or T4 treatments comparable with levels noted in euthyroid rats.

In the current study we found a significant reduction in deep vessel density, which was correlated with outer retinal and choroidal flow indexes, and an increase in superficial parafoveal vessel density in the hypothyroid group. These results can be attributed to the unique circulatory system of the posterior segment. The outer retinal layers are perfused by choroidal vessels via diffusion [38]. However, the inner two thirds of the retina is perfused by the central retinal artery, which is the first branch of the ophthalmic artery. While inner retinal perfusion is mostly regulated by local angiogenic factors, deep retinal perfusion is associated with the systemic perfusion pressure reflecting the cardiac output [39]. Therefore, the cardiac output and, accordingly the outer retinal perfusion decreases in hypothyroidism [33].

This hypoperfusion could induce a compensatory vasodilator mechanism in the inner retina resulting in an increase in superficial retinal perfusion. On the other hand, thyroid hormones play an important role in embryonic development and physiology of the central nervous system throughout life. T3 is essential for myelination, and synaptogenesis, neuronal migration and differentiation [40]. In our study, the mean foveal deep vessel density was positively correlated with macular thickness, indicating a parallelism between macular perfusion and neurosensory retina vitality.

Limitations

There were some limitations to this study, such as the lack of post-treatment microvascular assessment, retrospective study design and a limited number of patients. Further longitudinal studies with a large population, including the comparison of pre-treatment and post-levothyroxine treatment values, are needed to determine whether hormone replacement would provide improvement in macular perfusion.

Conclusions

To the best of our knowledge, this is the first study that provides a quantitative assessment of macular perfusion in patients with treatment-naive overt hypothyroidism. The results of our study demonstrated a significantly reduced whole, parafoveal and perifoveal deep vessel density in the treatment-naive overt hypothyroid patients. Furthermore, the vessel density in the deep capillary plexus is correlated with the choroidal and outer retinal flow indexes and, accordingly, central retinal thickness. We postulate that these changes could reflect early microvascular disruption that precedes permanent thinning of the neurosensory retina.

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