

Optical Coherence Tomography Angiography in Patients of Thyroid-Associated Ophthalmopathy

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ABSTRACT

Purpose: To identify the potential diagnostic abilities of optical coherence tomography angiography (OCTA) in early detection of retinal neurovascular changes in patients of thyroid-associated ophthalmopathy (TAO).

Subjects and Methods: The study included 2 groups; study group included 20 TAO patients (40 eyes), and control group included 20 healthy subjects (40 eyes) from patients attending Mansoura Ophthalmic center. The study group included recently diagnosed TAO. patients., Aged (20-60) years old. Both male and female were included. All subjects in both groups underwent OCTA.

Results: There were a statistically significant difference between TAO case group and control group regarding perfusion density values of superficial capillary plexus (40.3 ± 3.2 vs 44.8 ± 1.9), deep capillary plexus (38.2 ± 4.5 vs 43.7 ± 2.4), optic nerve head (48.4 ± 5.0 vs 53.7 ± 2.6), and peripapillary capillary plexus (48.3 ± 4.6 vs 53.7 ± 2.1) respectively, with lower levels in TAO case group. However; the study reported no statistically significant difference between active and inactive TAO regarding all the previous perfusion density values. There was a significant reduction in retinal blood flow in TAO patients compared with healthy controls. However, no change was found in perfusion density values between active and inactive TAO cases.

Conclusion: The current study revealed a reduction in retinal microvascular perfusion in superficial and deep retinal layers as well as optic nerve head and peripapillary region in TAO patients using OCTA. Reduced peripapillary perfusion density is considered a promising prognostic indicator of optic neuropathy in TAO, which can also identify early subclinical dysthyroid optic neuropathy (DON). The study revealed no changes in perfusion density values between active and inactive TAO patients. TAO Patients who have high IOP are at risk for reduced retinal vascular perfusion and nerve fiber layer thickness.

Vol No: 11, Issue: 01

Received Date: August 07, 2026

Published Date: October 12, 2026

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Citation: Abdelkader M, et al. (2026). Iontophoretic Co-delivery of NAD⁺ and KPV Rapidly Suppresses Systemic hs-CRP in Humans. Mathews J Dermatol. 11(1):40

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INTRODUCTION

Thyroid-associated Ophthalmopathy (TAO) is a systemic autoimmune condition affecting the orbital tissues. The primary pathological alterations observed in the orbital tissue consist of interstitial edema, hyperplasia of orbital fat, and significant swelling of the extraocular muscles, which may result in symptoms of orbital compression [1].

About 20% of cases with thyroid autoimmune disorders develop TAO, and between 25% to 50% of TAO individuals are strongly linked to hyperthyroidism, which is referred as Graves' ophthalmopathy and has a higher prevalence in women [2].

The precise pathogenesis of Thyroid-Associated Ophthalmopathy (TAO) remains unclear; however, the clinical symptoms can be attributed to the increase in orbital volume resulting from autoimmune inflammatory infiltration. TAO is categorized into two distinct phases including an active phase which is characterized by rapid progression in addition to an inactive phase where symptoms stabilize [3].

Dysthyroid optic neuropathy occurs in 4% to 8% of individuals with thyroid-associated ophthalmopathy. The underlying cause of optic neuropathy is likely linked to mechanical compression from excessive soft tissue and enlarged extraocular muscles [4,5].

Optical coherence tomography angiography (OCTA) is a non-invasive imaging modality that provides detailed visualization of the retinal and choroidal structures and reported that individuals with TAO exhibited a reduced thickness in the lower retinal nerve fiber layer (RNFL) with a decrease in the macular thickness. Moreover, an increase in choroidal thickness (CT) was observed in TAO patients [6].

Recent technological advancements have led to the development of OCT angiography (OCTA), a promising imaging technique that allows for non-invasive visualization of the retinal and choroidal vascular systems [6].

Early management of TAO has been shown to avert vision-threatening complications and enhance the quality of life for patients. Those in the early active phase of the disease are more likely to benefit from anti-inflammatory and immunosuppressive treatments, while individuals in the later stages may necessitate more complex interventions, including rehabilitative surgery [7].

Our objective is to study the early changes in RNFL thickness and retinal vasculature by OCTA in patients of thyroid ophthalmopathy.

SUBJECTS AND METHODS

This study is prospective, observational, cross sectional, case-control study. This Study has been conducted in Mansoura Ophthalmic Center on a sample of 20 TAO patients (40 eyes), and 20 healthy controls (40 eyes). The study was conducted over a one-year duration from (February 2025 to February 2026). TAO patients were recruited from outpatient clinics in Mansoura Ophthalmic Center following referral from the Endocrinology Department, Internal Medicine Hospital, Mansoura University.

Inclusion Criteria

Thyroid group included recently diagnosed TAO patients. Both male and female were included. Age group (20-60) years old. Both eyes were eligible for the study. Healthy group included matched-age Normal healthy individuals who had no systemic or ocular diseases were recruited in the study during their routine eye care checkup at Mansoura Ophthalmic Center.

Exclusion Criteria

Previous thyroid surgery or radioactive iodine therapy, glaucoma, diabetic retinopathy, vein occlusion or high myopia, previous retinal surgery.

TAO patients were sub-classified into two groups (active & inactive) according to Clinical Activity Score (CAS) system; (1) spontaneous orbital pain, (2) gaze-evoked orbital pain, (3) eyelid swelling, (4) eyelid erythema, (5) conjunctival redness, (6) chemosis, and (7) caruncle or plica inflammation. One point was given for each parameter. Patients with CAS score equal to or more than three were considered active group, while patients with score less than three were considered among the inactive group.

An informed written consent was obtained from each participant shared in the study prior to their participation. The whole study design was approved by Mansoura University Institutional Research Board (IRB Code MS.22.03.1931). Confidentiality and personal privacy were respected in all levels of the study. Collected data was not and will not be used for any other purposes.

Each subject in both groups was assessed as follow: Full general and ocular history have been reported for all patients included in the study. Personal history including name, age, gender, occupation and history of smoking. Medical history including symptoms of disease activity like; redness, eye lid swelling and pain. Duration of the disease, associated current or previous diseases, certain medications and prior history of radioactive iodine therapy were also documented. Surgical history including history of previous ocular surgery or thyroidectomy.

Examination

Full ophthalmic examination has been performed; Best Corrected Visual Acuity (BCVA) using Landolt broken ring chart. Anterior segment examination using slit lamp biomicroscopy (Haag Streit BP900) (Haag Streit, Koeniz, Switzerland) to detect signs of disease activity like (conjunctival injection, chemosis, swelling of the caruncle, eye lid edema and erythema). Posterior segment examination using slit lamp biomicroscopy and a Volk 90D lens, after dilatation of the pupil by mydriatic eye drops to properly assess the retina and optic nerve head. IOP measurement using Goldmann applanation tonometer. Proptosis degree was measured by Hertel exophthalmometer.

Ocular Imaging using Swept-Source OCTA: All subjects were examined with Swept-Source optical coherence tomography and optical coherence tomography angiography systems using Swept Source Topcon DRI OCT Triton (Japan, version 2015).

Technique

Pupillary dilatation was done before OCTA examination. Each step was explained to the patient before doing it. The chair height, chin rest, and the machine were adjusted to the proper position. The patient was asked to put his chin on chin rest. The patient was asked to fixate on a target inside the instrument). OCTA scanning was performed and at least two good quality images were taken. Average total thickness of the peripapillary RNFL and quadratic thickness (Superior, Inferior, Nasal and temporal) were examined.

Optical Coherence Tomography Angiography (OCTA): Imaging procedure was then started by selecting angiography mode from the main menu. First, Images were obtained from an area of 3x3 mm² centered on the fovea. Then, superficial and deep FAZ areas were measured manually *via* drawing a

continuous line along their boundaries and the area of FAZ was automated and directly written on the screen. Other scans were obtained from an area of 4.5x4.5 mm² centered on the disc. The same technique was repeated, and we chose good quality images with high resolution and no or less artifacts that would not affect the results. Macula and optic nerve perfusion density ratios were quantitatively analyzed using GNU Image Manipulation Program (GIMP) V.2.10.32 software. Macular perfusion density was measured at two angiographic levels; superficial capillary plexus (SCP) and deep capillary plexus (DCP). Optic nerve perfusion density was also analyzed at two angiographic levels; optic nerve head (ONH) and radial peripapillary capillaries (RPC) (Figure 1). From colors, we chose a threshold to reduce colors into two colors and the image was adjusted in order to visualize vascular structures. Perfusion density ratio is then measured in percentiles which represent the ratio of the area occupied by blood vessels (Whitish in color) divided by the selected area (Blackish in color). The percentage of white pixels to black pixels was calculated, assuming that this percentage indirectly represents the perfusion density (Figure 1).

From colors, we chose a threshold to reduce colors into two colors and the image was adjusted in order to visualize vascular structures. Data were coded, computed then analyzed using IBM SPSS (Statistical package for social science) version 25.

- Qualitative data: were presented by frequency tables (Number and percentages).
- Quantitative variables: the normality of data was first tested with Shapiro-Wilk test and presented data by central indices and dispersion:
 - Mean $\pm$ Standard deviation (SD) for normally distributed variables.
 - Median (minimum – maximum) for non-normally distributed
- Quantitative variables: the normality of data was first tested with Shapiro-Wilk test and presented data by central indices and dispersion:
 - Mean $\pm$ Standard deviation (SD) for normally distributed variables.
- ★ Analytical statistics: Chi-square test is used to test association between categorical variables. Association

between normally distributed continuous variables was tested using independent sample t-test (t) in 2 independent groups, while Mann-Whitney U test (z) was used to compare 2 independent non- normally distributed continuous variables.

The one-way analysis of variance (ANOVA) is used to determine whether there are any statistically significant differences between the means of two or more independent (unrelated) groups. Post hoc ("after this" in Latin) tests

are used to uncover specific differences between three or more group means when an analysis of variance (ANOVA) F test is significant. Pearson correlation is used to correlate normally distributed data, while Spearman correlation is used to correlate non- normally distributed data. Level of significance: For all above mentioned statistical tests, the results were considered significant when the probability of error is less than or equal. 5% ($p \leq 0.05$).

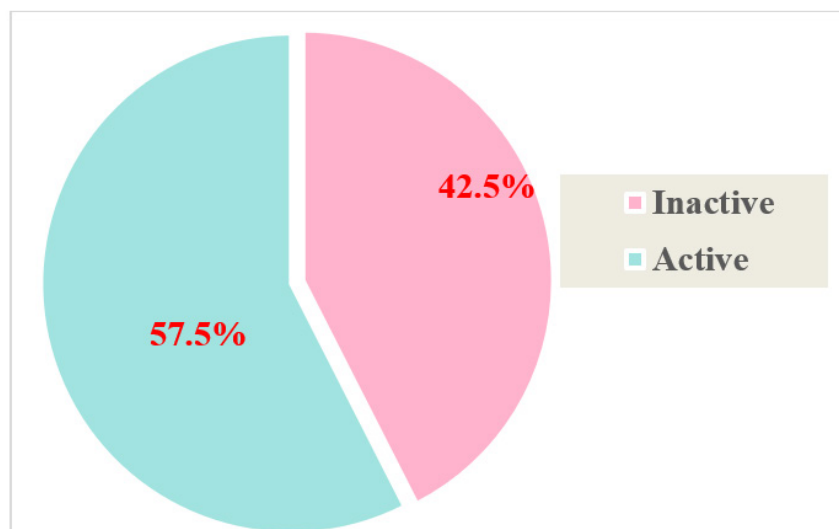


Figure 1: TAO patients' classification according to Clinical Activity Score (CAS).

RESULTS

In this study, twenty patients (40 eyes) with TAO divided into 12 females (24 eyes), 8 males (16 eyes) were compared with normal twenty individuals (40 eyes) divided into 11 females (22 eyes) and 9 males (18 eyes). Age of TAO patients ranged between 20 to 60 years with average 38.5 with no statistical difference to control group regarding age.

Best Corrected Visual Acuity was significantly reduced ($p \leq 0.001$) in TAO cases compared to control eyes (Table 1,2). There is also statistically significant difference between both groups regarding IOP with a higher level in TAO case group (18.9 ± 2.5 vs 15 ± 2.2).

Table 1. BCVA and IOP among thyroid-associated ophthalmopathy cases and control groups (n=80 eyes).

Items	TAO case group N=40	Control group N=40	Test of significance (P)
BCVA log MAR Median (min – max)	0.5 (0.16 – 1)	1 (0.5 – 1)	$\leq 0.001^*$
Intra Ocular Pressure (IOP) (mmHg) (mean $\pm$ sd) (min – max)	18.9 $\pm$ 2.5 (16 – 24)	15 $\pm$ 2.2 (10 – 18)	$P \leq 0.001^*$

TAO: Thyroid Associated- Ophthalmology. BCVA: Best Corrected Visual Acuity.
Data expressed as mean $\pm$ SD or median (minimum – maximum)

Table 2. Classification of thyroid-associated ophthalmopathy cases according to Clinical Activity Score and Hertel exophthalmometric readings (n=40 eyes).

Items	TAO Case Group N=40
Clinical Activity Score (CAS)	
1	6 (15%)
2	11 (27.5%)
3	15 (37.5%)
4	8 (20%)
Median (Min – Max) of CAS	3 (1 – 4)
TAO patients’ classification according to CAS	
Inactive (CAS ≤ 2/7)	17 (42.5%)
Active (CAS ≥ 3/7)	23 (57.5%)
Hertel exophthalmometric readings	
Mean ± SD	20.9 ± 2.0
Median (Min – Max)	(16 – 23)

According to TAO eyes, Twenty-three eyes (57.5%) had active TAO (CAS ≥ 3), whereas 17 eyes (42.5%) had inactive TAO (CAS < 3). Hertel exophthalmometric readings in TAO group ranged between 16 to 23 with a mean 20.9 (Figure 1).

No statistically significant results were encountered when FAZ of superficial (p = 0.08) and deep retinal layers (p = 0.64) were compared between both groups (Figure 2, Table 3).

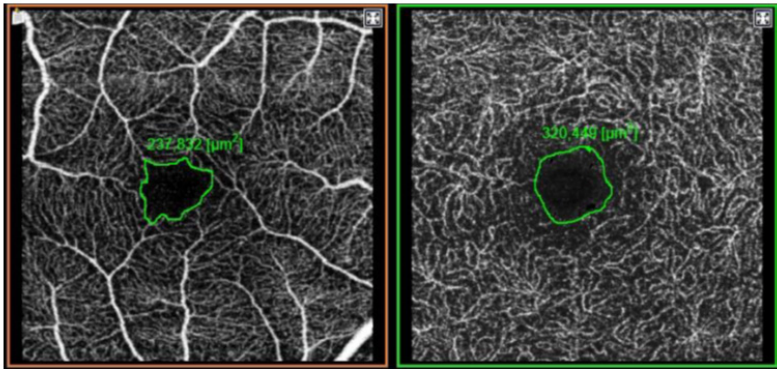


Figure 2A: FAZ area calculation in TAO study case

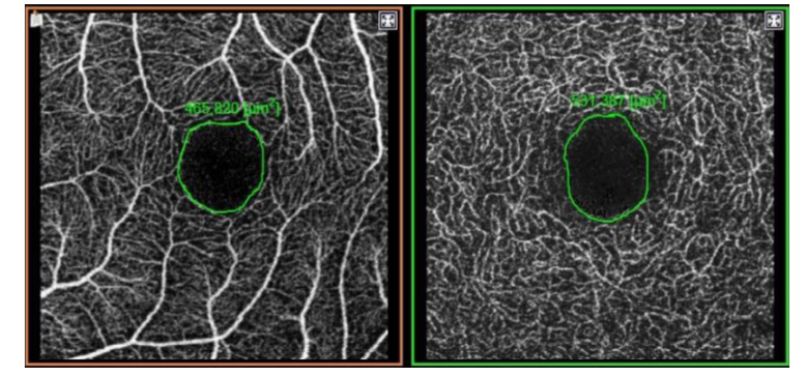


Figure 2B: FAZ area calculation in healthy control

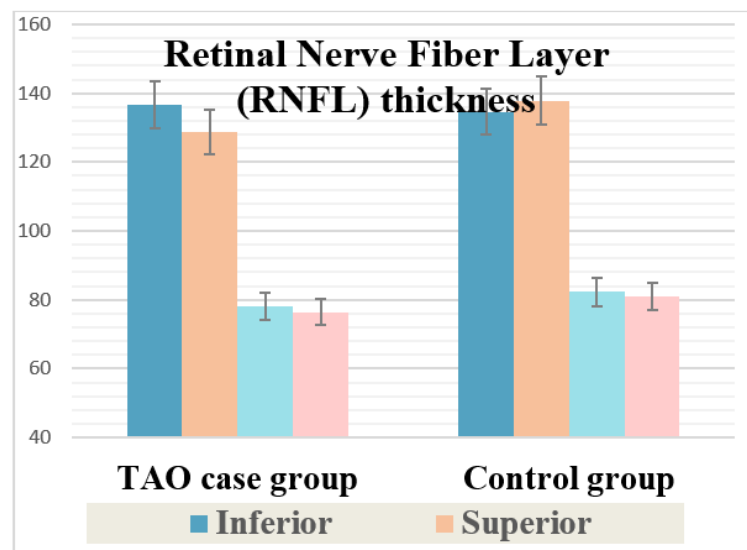
Figure 2 Shows insignificant differences between groups according FAZ

Table 3. Area of Foveal Avascular Zone. FAZ of superficial and deep retinal layers in thyroid-associated ophthalmopathy cases and control groups (n=80 eyes).

Items	TAO case group N=40	Control group N=40	Test of significance (P)
FAZ-Superficial retinal layers			
(mean $\pm$ sd)			
(min – max)	340.9 $\pm$ 106.64 206.1 – 614.8	381.2 $\pm$ 93.7 (250.3 – 566.3)	t= 1.8 P= 0.08
FAZ-Deep retinal layers			
(mean $\pm$ sd)	497.3 $\pm$ 135.3	484.8 $\pm$ 105.5	t= 0.46
(min – max) (°)	320.5 – 938.7	283.7 – 681	P= 0.64

A statistically significant difference regarding total peripapillary thickness between both groups was exhibited, with lower level in TAO case group (105.03 ± 9.4). There is also a statistically significant difference between both groups regarding RNFL thickness-Superior, with lower level in TAO case group (128.9 ± 15.6). There was also significant

difference between both groups regarding RNFL thickness-Nasal, with lower level in TAO case group (78.1 ± 10). There is no statistically significant difference between TAO case and control groups regarding RNFL thickness inferior or temporal, (Figure 3, Table 4).

**Figure 3:** Retinal Nerve Fiber Layer Thickness among thyroid-associated ophthalmopathy cases and control groups.**Table 4:** Retinal Nerve Fiber Layer thickness among thyroid-associated ophthalmopathy cases and control groups (n=80 eyes).

Items	TAO case group N=40	Control group N=40	Test of significance (P)
Total peripapillary thickness			
(mean $\pm$ sd)	105.03 $\pm$ 9.4	109.2 $\pm$ 8.2	t= 2.1
(min – max)	(84 – 123)	(96 – 129)	P= 0.04*
RNFL thickness-Inferior			
(mean $\pm$ sd)	136.7 $\pm$ 18.9	134.6 $\pm$ 14.5	t= 0.55
(min – max)	(100 – 186)	(107 – 171)	P= 0.59

RNFL thickness-Superior			
(mean ± sd)	128.9 ± 15.6	137.9 ± 17.6	t= 2.4
(min – max)	(99 – 156)	(112 – 175)	P= 0.02*
RNFL thickness-Nasal			
(mean ± sd)	78.1 ± 10	82.3 ± 9.9	t= 2.3
(min – max)	(45 – 96)	(61 – 104)	P= 0.02*
RNFL thickness-Temporal			
(mean ± sd)	76.4 ± 13.1	81.0 ± 13.3	t= 1.5
(min – max)	(20 – 99)	(55 – 110)	P= 0.13

TAO: xophthalmome.

RNFL: Retinal Nerve Fiber Layer Thickness

Data expressed as mean ± SD.

t: independent samples -t- test.

*: significant $p \leq 0.05$.

There was statistically significant difference between active and inactive TAO patients as determined by one-way ANOVA regarding IOP (active vs inactive: 20.1 ± 2.4 vs 17.2 ± 1.4 ; $p < 0.001$) and Hertel exophthalmometric readings (active vs inactive: 21.8 ± 1.7 vs 19.5 ± 1.5 ; $p < 0.001$), with higher values in active group. While there is no statistical correlation observed between both groups regarding RNFL thickness, FAZ area, superficial and deep capillary plexus PD, optic nerve head and peripapillary PD values.

There is statistically significant difference between active, inactive and normal control groups regarding IOP with the highest level (20.1 ± 2.4) in active TAO group. There is also statistically significant difference between the groups regarding superficial capillary plexus, deep capillary plexus, optic nerve head and peripapillary perfusion density values with the highest level of perfusion among normal control group (44.8 ± 1.9 , 43.7 ± 2.4 , 53.7 ± 2.6 , 53.7 ± 2.1) respectively (Table 5,6).

Table 5: Superficial and deep capillary plexus perfusion density among thyroid-associated ophthalmopathy cases and control groups (n=80 eyes).

Items	TAO case group N=40	Control group N=40	Test of significance (P)
Superficial Capillary Plexus- PD			
(mean ± sd)	40.3 ± 3.2	44.8 ± 1.9	t= 7.8
(min – max)	(34.3 – 46.7)	(39 – 47.7)	P ≤ 0.001*
Deep Capillary Plexus-PD			
(mean ± sd)	38.2 ± 4.5	43.7 ± 2.4	t= 6.9
(min – max)	(33 – 47.9)	(38.7 – 49.2)	P ≤ 0.001*

TAO: Thyroid Associated- Ophthalmology.

PD: Perfusion Density

Data expressed as mean ± SD or number (%).

Optic Nerve Head and

Table 6: Peripapillary perfusion density among thyroid-associated ophthalmopathy cases and control groups (n=80).

Items	TAO case group N=40	Control group N=40	Test of significance (P)
Optic Nerve Head-PD			
(mean ± sd)	48.4 ± 5.0	53.7 ± 2.6	t= 5.9
(min – max)	(42 – 61)	(48.5 – 59.6)	P ≤ 0.001*
Peripapillary- PD			
(mean ± sd)	48.3 ± 4.6	53.7 ± 2.1	t= 6.7
(min – max)	(44 – 62.8)	(48.2 – 57.3)	P ≤ 0.001*

TAO: Thyroid Associated- Ophthalmology.

PD: Perfusion Density

Data expressed as mean ± SD or number (%).

t: independent samples -t- test.

*: significant $p \leq 0.05$.

A significant positive moderate correlation was encountered between Hertel exophthalmometric readings and IOP ($r = 0.64$) (Table 9, Figure 4). There is also a significant positive strong correlation between Hertel exophthalmometric readings and Clinical Activity Score ($r = 0.76$). While a negative exophthalmometric readings and total peripapillary thickness ($r = -0.35$), and there is significant negative weak correlation between Hertel exophthalmometric readings and RNFL thickness-Superior ($r = -0.39$). Regarding FAZ-Superficial retinal layers, a positive moderate correlation ($r = 0.33$) was displayed with exophthalmometric readings.

While there is no statistically significant correlation between Hertel exophthalmometric readings and other parameters.

Statistical correlations have been explored between BCVA log MAR and other parameters. There is a negative weak correlation between BCVA log MAR and RNFL thickness -Nasal ($r = -0.32$). No statistical correlations were maintained between BCVA log MAR and superficial capillary plexus, deep capillary plexus, optic nerve head or peripapillary perfusion density values. Additionally; No statistical correlations were encountered between BCVA log MAR and CAS, Hertel exophthalmometric values or IOP (Table 7-9, Figure 4,5).

Table 7: Association between active and inactive TAO cases and other parameters in TAO case group (n=40 eyes).

Items	TAO patients according to CAS		Test of significance (P)
	Inactive TAO N= 17	Active TAO N=23	
Age (per year)			t=1.5
(mean $\pm$ sd)	36 $\pm$ 6.9	40.3 $\pm$ 9.8	P= 0.13
Gender			
□ Male	7 (41.2%)	9 (39.1%)	$\chi^2 = 0.02$
□ Female	10 (58.8%)	14 (60.9%)	P = 0.89
Intra Ocular Pressure (IOP)			t= 4.4
(mean $\pm$ sd)	17.2 $\pm$ 1.4	20.1 $\pm$ 2.4	P< 0.001*
Hertel exophthalmometric readings			t= 4.3
(mean $\pm$ sd)	19.5 $\pm$ 1.5	21.8 $\pm$ 1.7	P< 0.001*
FAZ-Superficial retinal layers (mean $\pm$ sd)			t= 1.6
	309.9 $\pm$ 102.5	363.9 $\pm$ 105.5	P= 0.11
FAZ-Deep retinal layers			t= 0.54
(mean $\pm$ sd)	483.8 $\pm$ 110.2	507.3 $\pm$ 152.8	P= 0.59
Total peripapillary thickness			t= 0.39
(mean $\pm$ sd)	104.4 $\pm$ 8.5	105.5 $\pm$ 10.2	P= 0.70
RFNL thickness-Inferior			t= 0.02
(mean $\pm$ sd)	136.8 $\pm$ 20.8	136.7 $\pm$ 17.8	P= 0.99
RFNL thickness-Superior			t= 0.42
(mean $\pm$ sd)	130.1 $\pm$ 14.4	128 $\pm$ 16.7	P= 0.68
RFNL thickness-Nasal			t= 0.10
(mean $\pm$ sd)	78.3 $\pm$ 9.1	78 $\pm$ 10.8	P= 0.92
RFNL thickness-Temporal			t= 1.9
(mean $\pm$ sd)	72.1 $\pm$ 15.7	79.7 $\pm$ 10	P= 0.07

Superficial Capillary Plexus- PD (<i>mean ± sd</i>)			t= 0.73
	40.7 ± 2.9	40 ± 3.4	P= 0.47
Deep Capillary Plexus-PD			t= 0.63
(<i>mean ± sd</i>)	38.7 ± 4.6	37.8 ± 4.5	P= 0.53
Optic Nerve Head-PD			t= 0.28
(<i>mean ± sd</i>)	48.6 ± 5.2	48.1 ± 5	P= 0.78
Peripapillary- PD			t= 0.09
(<i>mean ± sd</i>)	48.2 ± 4.5	48.4 ± 4.8	P= 0.93

TAO: Thyroid Associated- Ophthalmology.

RNFL: Retinal Nerve Fiber Layer Thickness

BCVA: Best Corrected Visual Acuity.

FAZ: Foveal Avascular Zone.

PD: Perfusion Density

t: independent samples -t- test.

²: chi-square test.

*: significant p ≤ 0.05.

Table 8. Comparison between active, inactive TAO cases and control groups regarding all parameters (n=80 eyes).

Items	TAO patients according to CAS		Control group N=40	Test of significance(P)
	Inactive TAO N= 17	Active TAO N=23		
Age (per year) (<i>mean ± sd</i>)	36 ± 6.9	40.3 ± 9.8	37.4 ± 9.3	F= 1.2 P= 0.29
Gender				
□ Male	7 (41.2%)	9 (39.1%)	18 (45%)	χ^2 = 0.22
□ Female	10 (58.8%)	14 (60.9%)	22 (55%)	P = 0.85
Intra Ocular Pressure (IOP) (<i>mean ± sd</i>)	17.2 ± 1.4 ^{a1}	20.1 ± 2.4 ^{a2}	15 ± 2.2 ^b	F= 43.1 P < 0.001*
FAZ-Superficial retinal layers (<i>mean ± sd</i>)	309.9 ± 102.5	363.9 ± 105.5	381.2 ± 93.7	F= 3.1 P= 0.051
FAZ-Deep retinal layers (<i>mean ± sd</i>)	483.8 ± 110.2	507.3 ± 152.8	484.8 ± 105.5	F= 0.29 P= 0.75
Total peripapillary thickness (<i>mean ± sd</i>)	104.4 ± 8.5	105.5 ± 10.2	109.2 ± 8.2	F= 2.3 P= 0.11
RFNL thickness-Inferior (<i>mean ± sd</i>)	136.8 ± 20.8	136.7 ± 17.8	134.6 ± 14.8	F= 0.15 P= 0.86
RFNL thickness-Superior (<i>mean ± sd</i>)	130.1 ± 14.4	128 ± 16.7	137.9 ± 17.6	F= 2.9 P= 0.06
RFNL thickness-Nasal (<i>mean ± sd</i>)	78.3 ± 9.1	78 ± 10.8	83.3 ± 9.9	F= 2.7 P= 0.08
RFNL thickness-Temporal (<i>mean ± sd</i>)	72.1 ± 15.7	79.7 ± 10	80.9 ± 13.3	F= 2.9 P= 0.06
Superficial Capillary Plexus- PD (<i>mean ± sd</i>)	40.7 ± 2.9 ^{a1}	40 ± 3.4 ^{a2}	44.8 ± 1.9 ^b	F= 30.5 P < 0.001*
Deep Capillary Plexus-PD (<i>mean ± sd</i>)	38.7 ± 4.6 ^{a1}	37.8 ± 4.5 ^{a2}	43.7 ± 2.4 ^b	F= 23.7 P < 0.001*
Optic Nerve Head-PD (<i>mean ± sd</i>)	48.6 ± 5.2 ^{a1}	48.1 ± 5 ^{a2}	53.7 ± 2.6 ^b	F= 17.5 P < 0.001*
Peripapillary- PD (<i>mean ± sd</i>)	48.2 ± 4.5 ^{a1}	48.4 ± 4.8 ^{a2}	53.7 ± 2.1 ^b	F= 22.5 P < 0.001*

Table 9: Spearman's Correlation between BCVA and other parameters in TAO case group (n=40 eyes).

Parameters	BCVA	
	R	P
Superficial Capillary Plexus- PD	0.15	0.35
Deep Capillary Plexus-PD	0.14	0.39
Optic Nerve Head-PD	0.13	0.43
Peripapillary- PD	0.08	0.62
Age (<i>per year</i>)	- 0.29	0.08
Intra Ocular Pressure (IOP)	- 0.2	0.22
Hertel exophthalmometric readings	- 0.22	0.17
Clinical Activity Score (CAS)	- 0.24	0.13
FAZ-Superficial retinal layers	- 0.31	0.06
FAZ-Deep retinal layers	- 0.15	0.35
Total peripapillary thickness	- 0.05	0.75
RNFL thickness-Inferior	0.02	0.93
RNFL thickness-Superior	- 0.001	0.99
RNFL thickness-Nasal	- 0.32	0.04*
RNFL thickness-Temporal	0.09	0.56

Not significant: $p > 0.05$.

r: correlation coefficient.

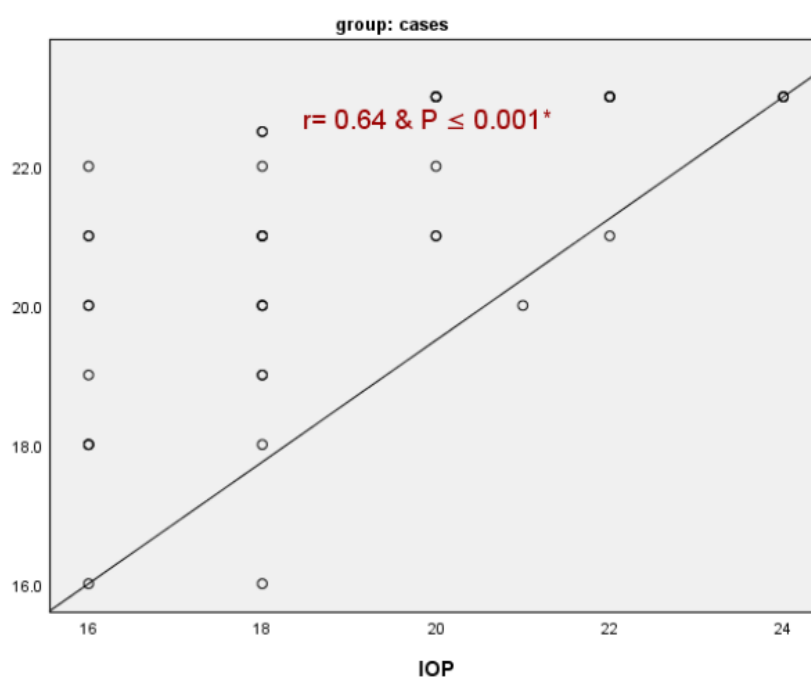
TAO: Thyroid Associated- Ophthalmology.

RNFL: Retinal Nerve Fiber Layer Thickness

BCVA: Best Corrected Visual Acuity.

FAZ: Foveal Avascular Zone.

PD: Perfusion Density

**Figure 4:** Correlation between Hertel exophthalmometric readings and IOP in TAO case group.

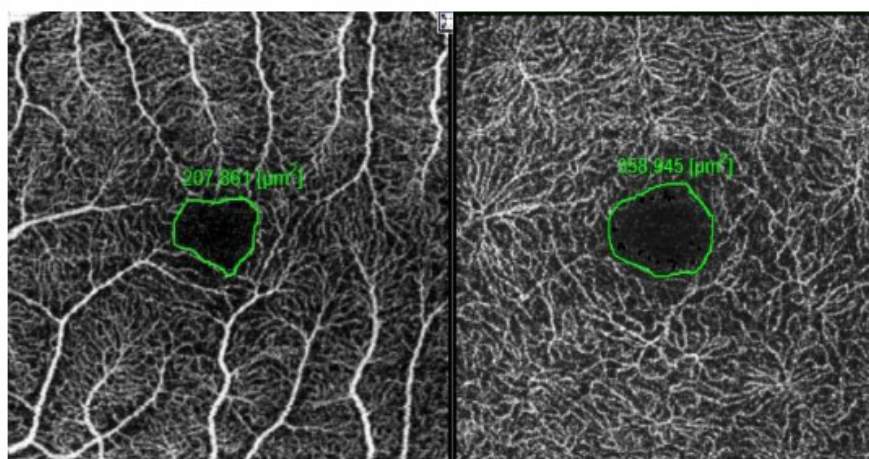
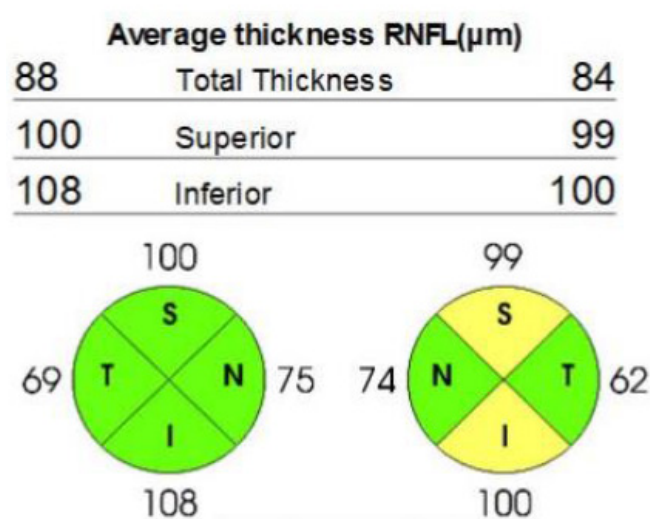
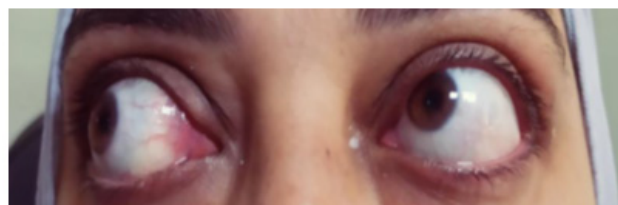
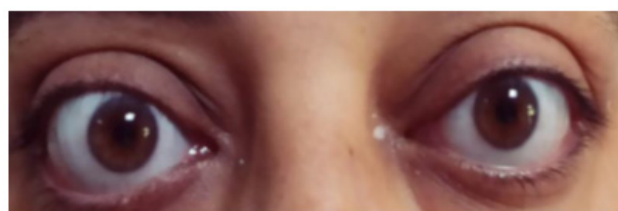


Figure 5A: Female patient aged 36 years, with thyroid-associated ophthalmopathy with Bilateral Eye lid edema, upper and lower lid retraction, conjunctival injection, inflammation of the caruncle and dryness. OCTA images of; superficial capillary plexus and FAZ area. Deep capillary plexus and FAZ area (image below)

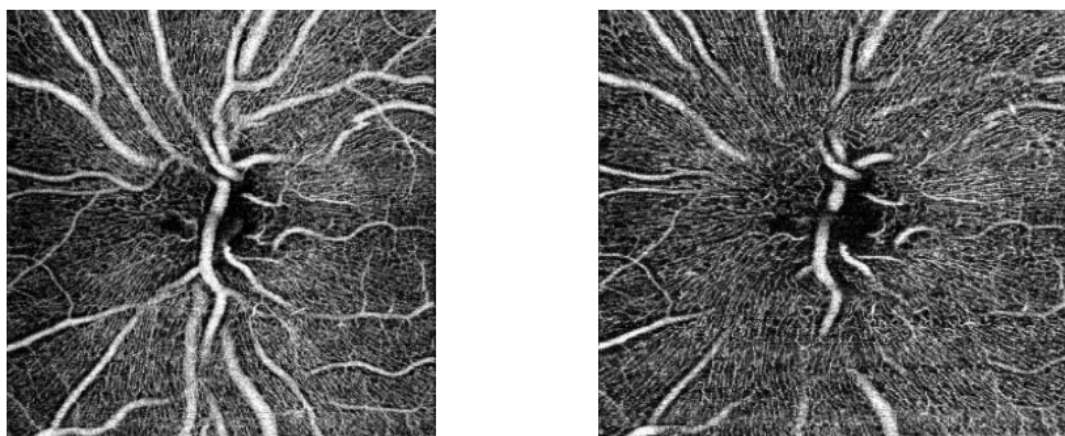
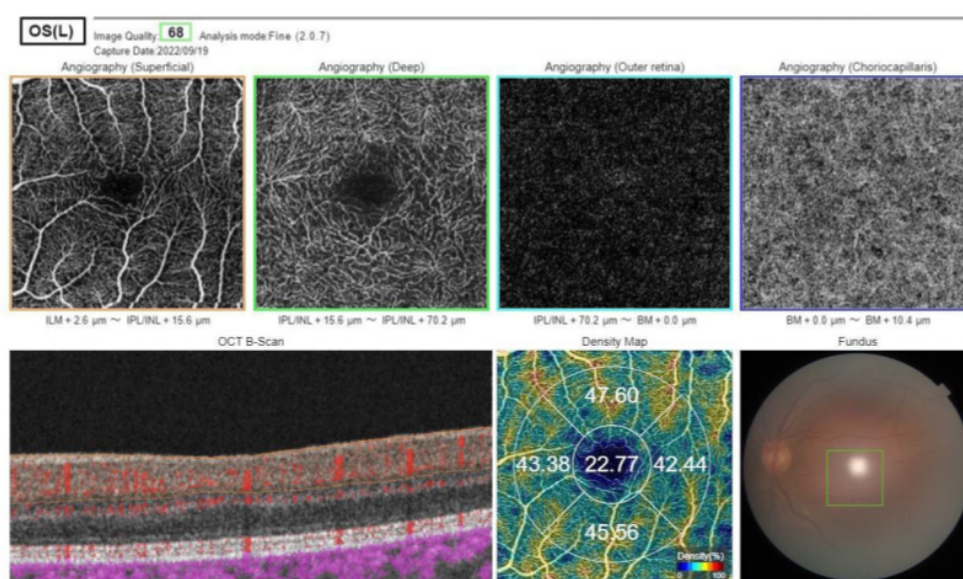
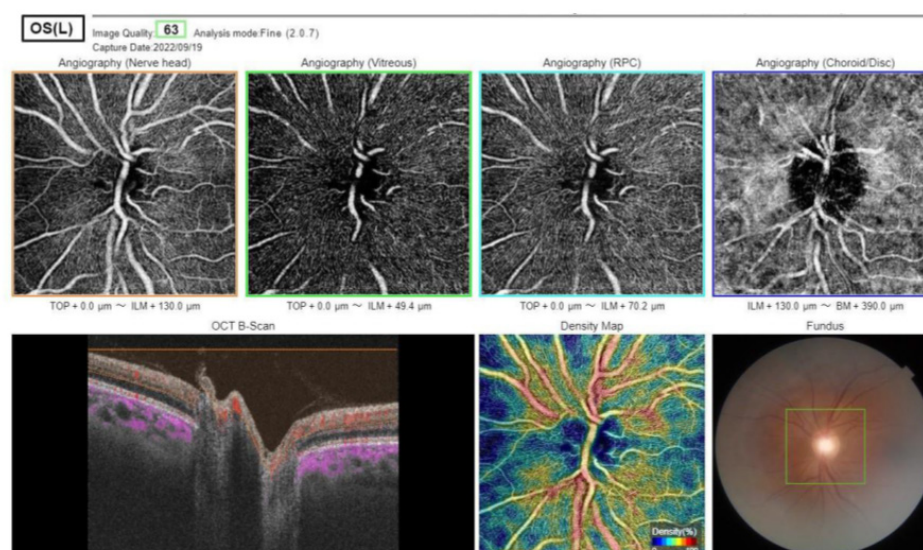


Figure 5B: OCTA images of; (A) optic nerve head. (B) Radial capillary peripapillary plexus (Left eye).



A



B

Figure 5C. OCTA Printout (A. Left macula & B. left optic Discs)

DISCUSSION

OCTA is a novel imaging modality that offers noninvasive fundus angiographs. It works without a contrast medium, so it protects against dye allergies and possible adverse reactions. OCTA relies on the intrinsic motion of blood in the retinal vessels as it separates stationary structures to identify the blood flow. OCTA can also provide 3D images compared to 2D images provided by fundus fluorescein angiography and indocyanine green angiography. It is reported that early changes in TAO could be well investigated and monitored with the objective parameters of OCT and OCTA [8,9].

In the current study, we investigated the structural and hemodynamic changes in twenty thyroid-associated ophthalmopathy patients (40 eyes) using OCT and OCTA. The patients were recently diagnosed and free from any associated comorbidities or other ocular diseases. They were subclassified according to clinical activity score (CAS) into two groups. Active group (n=23 eyes) with score equal to or more than 3, and inactive group (n=17 eyes) with score less than 3. Twenty healthy individuals (40 eyes) with nearly matched age were recruited and have been investigated with the same OCT and OCTA parameters.

Regarding OCT parameters, it is known that retinal nerve fiber layer (RNFL) thickness shows variations according to age and ethnicity [10]. That's why we used our own reference range from the healthy, age matched control group. As a result, we found a statistically significant difference in the average total peripapillary thickness in case group compared to healthy controls ($P=0.04$) with lower levels in case group (105.03 ± 9.4). The superior and nasal quadrants showed decreased levels in TAO case group ($P=0.02$) in both parameters. However, no statistically significant difference in RNFL thickness has been noted in our study between active and inactive TAO cases. Previous studies suggested that the enlarged extraocular muscles and increased orbital tissue volume might be the cause of direct compression on the optic nerve and thinning of the RNFL. Additionally, peripapillary RNFL thinning would be an early sign of optic nerve involvement [8,9]. Other causes of RNFL thinning in TAO patients have been documented in previous studies including; hypoxic ischemia from increased intraocular pressure and associated decrease in retinal vascular perfusion [11].

In our current study, we documented that, there is no statistical significant difference between case and healthy control groups regarding FAZ area of superficial and deep retinal layers ($P=0.08$), ($P=0.64$) respectively. Furthermore, our study showed no statistical significant difference between active and inactive TAO cases regarding FAZ area in superficial ($P=0.11$) and deep retinal layers ($P=0.59$), respectively. In contradiction to our results, enlargement of FAZ area was documented in previous research indicating a sign of capillary non perfusion in TAO patients [8,12].

The perfusion density values of the superficial and deep retinal layers were quantitatively evaluated in our study. The perfusion density represents the total area of the perfused vessels per unit area within an OCTA measurement area [13].

Our results revealed statistically significant difference between TAO case group and healthy control group regarding superficial and deep capillary plexus perfusion density values ($P \leq 0.001$) in both parameters, with lower levels in TAO case group ($40.3\% \pm 3.2\%$), ($38.2\% \pm 4.5\%$) respectively. Whereas our results did not show any difference between active and inactive cases regarding the perfusion density of either superficial ($P=0.47$) or deep retinal layers ($P=0.53$).

The study of retinal microvascular density changes in TAO patients revealed inconsistent results. Jamshidian et al. 2019, conducted a study to compare macular and peripapillary vasculatures in active TAO, not active and not compressive TAO, and control eyes [14]. They have concluded that whole macular and parafoveal superficial vessel density values as well as average peripapillary vessel density value were significantly lower in active TAO patients compared with the other groups. Similarly, Dave et al. [15] reported that peripapillary and macular area vascularization were reduced in patients with active TAO compared to healthy controls.

Akpolat et al. [16], recruited only inactive TAO patients in their study, they noted alterations in foveal and parafoveal vessel density in patients within active TAO. They have demonstrated a decrease in retinal vessel diameter and an increase in macular vessel density in inactive TAO patients.

Furthermore, Yu L et al. [9], have used OCT-A imaging to study the retinal microvasculature in active TAO patients. They demonstrated that the macular vessel density was altered in both superficial and deep retinal layers. They observed an increase in retinal vascular density in inactive TAO cases

compared to healthy controls, along with significant changes in RNFL thickness, choroidal thickness and superficial retinal vessels [9].

The present study evaluated OCTA as a noninvasive modality in screening TAO patients for sub-clinical compressive optic neuropathy. The compression in the orbit puts pressure on the venous system, causing retro blood flow and increased episcleral venous pressure. It is a possible explanation for reduced macular and ONH perfusion in patients with TAO [12].

In our current study, we found a statistically significant difference in optic nerve head and peripapillary perfusion density in TAO patients compared to healthy subjects with decreased levels in TAO cases (48.4 ± 5.0 vs 53.7 ± 2.6), (48.3 ± 4.6 vs 53.7 ± 2.1) respectively.

Previous studies have evaluated the optic nerve vascular perfusion in TAO patients. Mihailovic et al. [7], and Jian et al. [11] reported a decrease in the ONH perfusion and peripapillary vessel density in TAO cases which is consistent with our findings.

Conversely, Sabermoghaddam et al. 2022, demonstrated no difference between TAO cases and healthy controls regarding optic nerve head and radial peripapillary vessel density. However, they found that patients with higher CAS had a significant decrease in ONH microvasculature [17].

In another study by Del Noce et al. [18], a significant decrease in the peripapillary and deep macular capillary plexus vessel density was detected in TAO patients compared to healthy age and gender-matched controls. The study demonstrated a significant relationship between higher CAS scores and lower peripapillary vessel density [18]. Furthermore, Jian et al. [11] did not detect any significant difference between active and inactive TAO patients regarding the peripapillary perfusion density which is in line with our current results.

Peripapillary VD in TAO patients is easily affected by intraocular and orbital pressure and appears earlier than visual impairment [13]. The previous literature reported that optic disc function might be affected before clinical deterioration of vision occurs, and therefore early detection of optic nerve damage could be essential in preventing significant vision loss [17].

In the current study, we demonstrated a statistically significant difference between TAO case group and normal

control group regarding BCVA log MAR with reduced values in TAO case group (0.5 vs 1) respectively. Moreover, we investigated the association between OCT and OCTA parameters and the visual outcome. The results revealed no association except for a negative weak correlation between BCVA log MAR and RNFL thickness - Nasal ($r = -0.32$, $P = 0.04$).

Consistent with our findings, Del Noce et al., 2022 observed changes in peripapillary microvasculature in TAO patients which did not interfere with visual acuity, [18] as well as Akpolat et al. [2] who didn't find any association between visual acuity and increased vessel density in their study on inactive TAO cases. Whereas, Yu et al. [8] suggested that visual acuity might be affected by altered vessel density.

High intraocular pressure is a common finding in patients with TAO. Irreversible orbital changes such as extraocular muscle fibrosis and fatty degeneration can lead to an increase in the orbital volume with restriction of the exophthalmos process. As a result of that, aqueous humor outflow resistance and secondary elevation of the IOP can occur [11].

Consistent with the previous literature, IOP elevation is noted in TAO group in our present study. IOP levels showed a statistically significant difference between TAO case group and healthy controls (18.9 ± 2.5 vs 15 ± 2.2) respectively. Additionally, the study reported higher levels of IOP among the active TAO case group compared to the inactive group (20.1 ± 2.4 vs 17.2 ± 1.4) respectively.

Proptosis is a result of the expansion of orbital fat and muscle tissue into the bone structure. In the previous literature, proptosis was reported higher in TAO patients with dysthyroid optic neuropathy (DON) than those who do not have DON (Yang et al., 2023). In the present study, Hertel exophthalmometry values were significantly higher in active TAO patients than inactive group ($21.8 \text{ mm} \pm 1.7 \text{ mm}$), ($19.5 \text{ mm} \pm 1.5 \text{ mm}$) respectively.

Moreover, a statistically significant positive moderate correlation between Hertel exophthalmometric readings and IOP ($r = 0.64$, $P \leq 0.001$) was documented in our results. As well as a statistically significant positive strong correlation between Hertel exophthalmometric readings and Clinical Activity Score ($r = 0.76$, $P \leq 0.001$). While there is significant negative moderate correlation between exophthalmometric

readings and total peripapillary thickness ($r = -0.35$, $P = 0.03$), and there is a statistical significant negative weak correlation between exophthalmometric readings and RNFL thickness– Superior ($r = -0.39$, $P = 0.01$).

Differences in sample size, age and sex, racial diversity, parameter settings of OCTA system and inclusion criteria for TAO patients may partially explain the discrepancy among previous studies. In addition, technical differences and variations in patient activity status from moderate to severe may also contribute to the inconsistent results. Future research with more meticulous design is needed to validate the predictive and diagnostic potential of OCT and OCTA in Thyroid associated orbitopathy patients.

In conclusion, the current study revealed a reduction in retinal microvascular perfusion in superficial and deep retinal layers as well as optic nerve head and peripapillary region in TAO patients using OCTA.

Reduced peripapillary perfusion density is considered a promising prognostic indicator of optic neuropathy in TAO, which can also identify early subclinical dysthyroid optic neuropathy (DON). The study revealed no changes in perfusion density values between active and inactive TAO patients. TAO Patients who have high IOP are at risk for reduced retinal vascular perfusion and nerve fiber layer thickness

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