BMJ Open Ophthalmology

OCT and OCTA in dysthyroid optic neuropathy: a systematic review and meta-analysis

Nan Yang ,[1] Hui Zhu ,[1] Junxin Ma,[2] Qing Shao[1]

To cite: Yang N, Zhu H, Ma J, *et al*. OCT and OCTA in dysthyroid optic neuropathy: a systematic review and meta-analysis. *BMJ Open Ophthalmology* 2023;**8**:e001379. doi:10.1136/bmjophth-2023-001379

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjophth-2023-001379).

Received 3 July 2023
Accepted 3 November 2023

[1]Department of Ophthalmology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China
[2]Department of Ophthalmology, Nanjing First Hospital, Nanjing Medical University, Nanjing, Jiangsu, China

Correspondence to
Dr Qing Shao; shaoqing0502@163.com

ABSTRACT

Purpose To explore the current research about the role of optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) in dysthyroid optic neuropathy (DON).

Methods Studies in the literature that focused on OCT, OCTA and DON were retrieved by searching PubMed, EMBASE, Cochrane databases and Clinical Trial before 20 June 2023. The methodological quality was assessed using the Newcastle-Ottawa scale. The quantitative calculation was performed using Review Manager V.5.3.

Results Twelve studies met the eligibility criteria and were included. DON group presented lower macular ganglion cell complex in the overall, superior and inferior hemifields compared with the non-DON group. Furthermore, the ganglion cell layer and inner plexiform layer in DON group was thinner in contrast to the non-DON group. The optic nerve head vessel density was lower in the DON group than that in the non-DON group. A reduction of radial peripapillary capillary vessel density could be seen in the DON group than the non-DON group in overall, inside disc, peripapillary, superior-hemifield, temporal and nasal. Besides, the macular superficial retinal capillary layer of non-DON and DON is lower than the healthy control group.

Conclusions This study supported the potential value of OCT and OCTA metrics as novel biomarkers of DON. Ophthalmologists should comprehensively consider the retinal structure and microvasculature in dealing with DON.

Ethics and dissemination This systematic review included data from published literature and was exempt from ethics approval. Results would be disseminated through peer-reviewed publication and presented at academic conferences engaging clinicians.

PROSPERO registration number CRD42023414907.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Dysthyroid optic neuropathy (DON) is a vision-threatening complication of thyroid-associated ophthalmopathy (TAO). Multiple objective metrics, including NO SPECS, CAS, VISA and EUGOGO, grade the physical indications, symptoms and severity of TAO. Several papers have investigated the role of clinical examinations such as MRI, CT, colour vision examinations and so on in the diagnosis of DON. In this area, a more complete diagnostic mode is critically needed.

WHAT THIS STUDY ADDS

⇒ This study synthesised previous research on the use of optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) in DON. Results reflected changes of the retinal structure and microvasculature about DON. In addition, we also analysed clinical activity scores, duration, visual acuity, intraocular pressure, exophthalmos, visual field mean deviation and visual field pattern SD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This article provided the evidence for clinical diagnosis of DON when applying OCT and OCTA. It will help ophthalmologists grade the severity and the progression of DON in terms of retinal structure and microvasculature. This will lead to more discussion about novel diagnostic mode of DON.

INTRODUCTION

Thyroid-associated ophthalmopathy (TAO), also known as thyroid eye disease or Graves' ophthalmopathy, is a potentially sight-threatening ocular disease that affects 50% of patients with Graves' disease.[1] It is an autoimmune disorder and can cause enlargement of extraocular muscles (EOMs), swelling of lacrimal glands and expansion of orbital fat.[2] Typical orbital signs and symptoms include proptosis, lagophthalmos, eyelid retraction, ocular motility restriction, congestion of conjunctival blood vessels and orbital pain.[3] Dysthyroid optic neuropathy (DON), a severe complication of TAO, is characterised by various visual impairments including reduced visual acuity (VA), abnormal colour vision, visual field (VF) deficits, reduced contrast sensitivity function and relative afferent pupillary deficits in unilateral cases.[4 5] It has an estimated incidence of 5%–8.6%. The exact pathogenesis of DON is uncertain, but it may be related to optic nerve inflammation, compression, stretch and ischaemia.[6–12] Determining which patients presenting with impaired visual function during an initial evaluation do currently have or will later develop a more serious condition is not an

easy or straightforward task. The clinical diagnosis of DON is based mainly on orbital imaging and clinical manifestations. However, visual functional tests might make it difficult to detect early involvement of the optic nerve and retinal tissue as the responses are all variable and the results are not always consistent.[13] Therefore, discovering early objective indications of DON is critical for identifying novel therapy targets to prevent progression of the disease.

Optical coherence tomography (OCT) is a non-invasive imaging technique that uses low-coherence interferometry to acquire cross-sectional pictures of the retinal layers and optic nerve head.[14] The most common clinical application of OCT has been in the evaluation of retinal and optic nerve diseases, particularly glaucoma and afferent visual pathway abnormalities.[15] Optical coherence tomography angiography (OCTA) is a novel imaging modality that provides high-resolution pictures of the retinal microvasculature non-invasively and quickly, allowing in-depth observation of the retinal microvascular network in the distinct retinal layers.[16] It describes a map of blood flow and vascular network in distinct layers and sections of the retina and choroid by comparing recorded signals from consecutive scans conducted at the same cross-sections in the retina and choroid.[17] Due to the excellent repeatability, sensitivity and specificity of OCTA, it assists clinicians to visualise and evaluate the retinal and choroidal perfusion.[18] We hypothesised that the thickness of the peripapillary and macular nerve fibre layer measured by OCT imaging and retinal and choroidal perfusion measured by OCTA imaging would be related to DON diagnosis and therapy.

Therefore, we conducted a systematic review and meta-analysis of the available literature in this study and summarised the differences in OCT and OCTA parameters in patients with DON compared with the healthy group and TAO without DON group. In addition, we have also investigated the changes in ophthalmic examination parameters among these groups to explore its correlation with DON.

MATERIALS AND METHODS

This systematic review and meta-analysis were conducted and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[19] Details are provided in online supplemental table S5. The study protocol was developed and registered with the International Prospective Register of Systematic Reviews.

Search strategy

We searched for relevant papers within PubMed, EMBASE, Cochrane databases and Clinical Trial, considering publications up to 10 June 2023. The search strategy consisted of combinations of keywords and/or topic headings related to OCT, OCTA and DON. Two reviewers (NY and JM) screened all studies identified in the initial literature independently. Disagreements were solved by negotiation between the two authors (NY and HZ) or by consulting the senior author (QS) if necessary. No restrictions with regard to geographic location were applied. Moreover, we conducted backward citation search by manually screening the reference lists of included studies for additional relevant references.

Inclusion and exclusion criteria

We incorporated all published research that applied OCT and OCTA to record the retinal structure and microvasculature in patients with DON. The eligible study needs to satisfy the following inclusion criteria: (a) original peer-review journal publication; (b) written in English; (c) included a clearly defined control group and (d) TAO diagnosis made based on established criteria such as the European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines and Bartley criteria.[20–22] The exclusion criteria were: (a) non-human research; (b) non-original research; (c) written in a non-English language and (d) non-comparative studies. Two reviewers (NY and JM) screened literature independently, the steps included checking for duplicates, screening the titles and abstracts to remove irrelevant studies and reading the full text of potential studies according to inclusion criteria. Disagreements were resolved by consulting with a third author (HZ).

Data extraction and quality assessment

Information of included articles included the following: first author's name, year of publication, country, study type, diagnosis criteria, image modality, arms, number of samples, age, gender ratio, clinical activity score (CAS), duration, VA, intraocular pressure (IOP), exophthalmos, visual field mean deviation (VF-MD) and visual field pattern SD (VF-PSD). Furthermore, data on OCT and OCTA such as device, objects of examination, scan area, overall parameters and section parameters were also collected. If included literature contained extreme values such as very small or large data, researchers would eliminate the unusual data.

The methodological quality and the risk of bias of the included studies were assessed using the Newcastle-Ottawa Scale.[23] Studies with a score of less than five demonstrated a significant risk of bias, whereas studies with a score of more than six might be deemed to be 'good' studies. The author (NY) independently reviewed and graded the eligible articles obtained from the literature search to assess their quality.

Statistical analysis

We applied Review Manager V.5.3 (Nordic Cochran Centre, Copenhagen, Denmark) to perform meta-analyses. We reported mean and SD of OCT and OCTA parameters in DON with a 95% CI, p value <0.05 was considered statistically significant. Heterogeneity was assessed by the χ^2-based Q test and Higgins I^2 test among studies. If the I^2 index was less than 40%, the heterogeneity was considered not important. Therefore, a

fixed-effects model was used for meta-analysis. In the event of a heterogeneity level over 40%, a random-effects model was applied. Subgroup analysis was conducted to examine sources of study heterogeneity and the influence of potential residual confounding factors.

RESULTS

A total of 75 potentially relevant articles were identified from the four databases, and 67 studies remained after duplicates were excluded. Fifty-one articles were excluded since reading the title and abstract. After reading the full text, four studies were excluded for non-comparative studies, non-English studies and improper comparison. Finally, 12 observational studies met the inclusion criteria described here. Figure 1 presents the flowchart of the study selection procedure.

Features of the studies included

Online supplemental table S1 presents a summary of the key characteristics of the included studies. All included studies were observational studies.[5 13 24–33] Eight studies were described as a prospective design[5 13 24 26–28 30 33] and three studies were retrospective studies.[25 29 32] TAO was diagnosed according to EUGOGO clinical practice guidelines and Bartley criteria. However, no single protocol completely characterised DON at present, clinicals

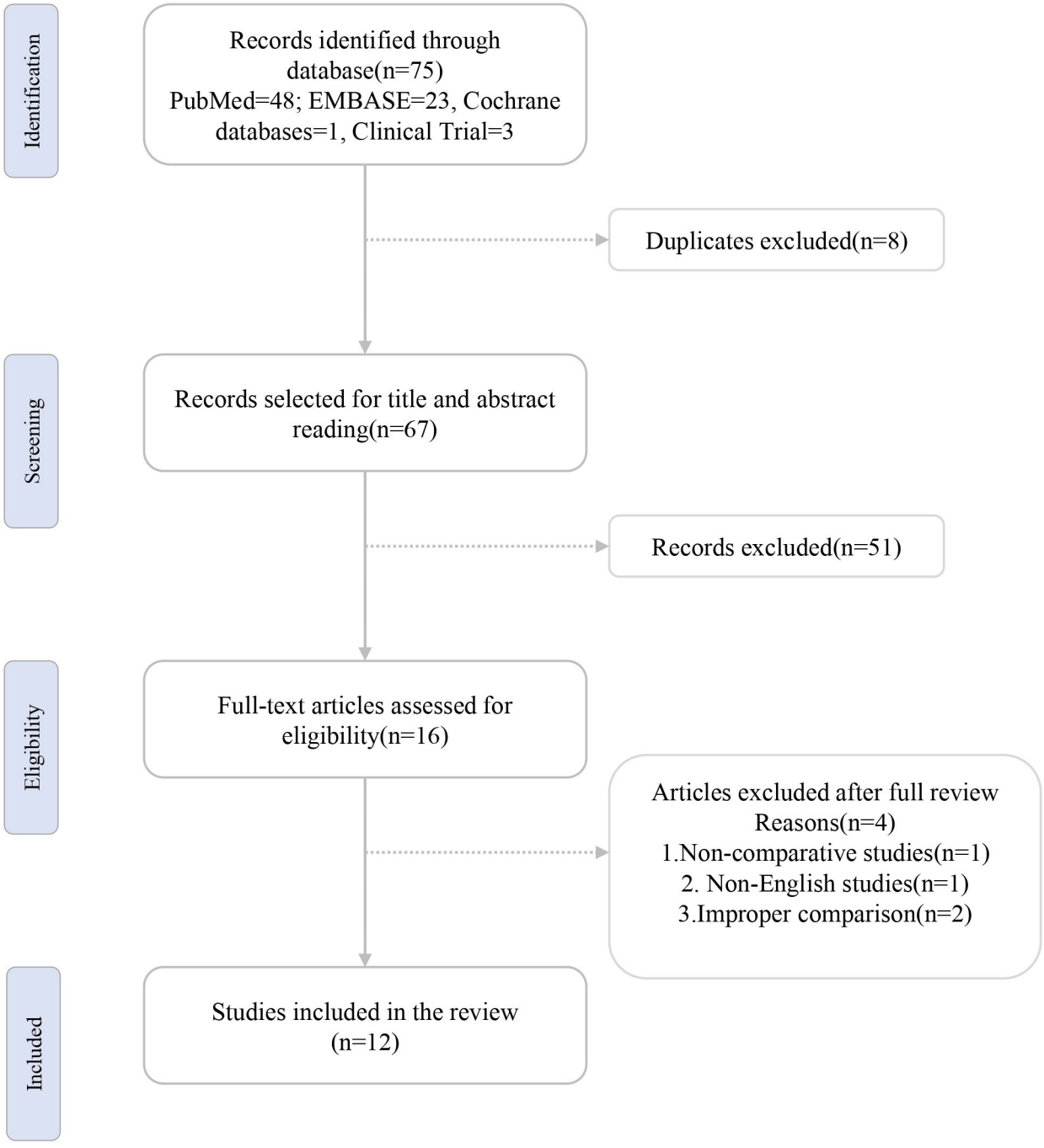

Figure 1 Flowchart of study selection.

diagnosed DON according to clinical manifestations and orbital images such as CT or MRI. The 12 included studies covered healthy control participants and TAO patients which were further divided into the non-DON group and the DON group. All studies applied OCT examinations and seven of which used OCTA examinations. Demographic parameters such as country, number of samples, age, gender ratio and ophthalmic examination parameters such as CAS, VA, IOP, exophthalmos, VF-MD and VF-PSD were collected if available. Eight studies were conducted in China, two were in Korea and the remaining two were in Iran and Poland separately. Six studies got a total score of 8, five received a score of 7 and one received a score of 6. None of them suggested a significant risk of bias.

Online supplemental tables S2 and S3 desperately summarised the main results of OCT and OCTA, which included devices, objects, scan area, overall parameters and section parameters. Regarding devices, eight studies used the Optovue RTVue XR Avanti (Optovue, Fremont, California, USA), three studies used the Zeiss Cirrus (Carl Zeiss Meditec, Dublin, California, USA) and one study used the Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany). There was no consistent nomenclature used across investigations for the section and layers of retina. For simplicity in this review, we applied the peripapillary retinal nerve fibre layer (PRNFL), macular ganglion cell complex layer (MGCCL) and ganglion cell layer and inner plexiform layer (GCL+IPL) in OCT parameters and radial peripapillary capillaries vessel density (RPC-VD), optic nerve head vessel density (ONH-VD), macular superficial retinal capillary layer (M-SRCL) and macular deep retinal capillary layer (M-DRCL) in OCTA. We recorded the scan area including size and location. In addition to the overall parameters, data from different sections such as superior-hemifield, inferior-hemifield, superior, temporal, inferior, nasal, inside disc and peripapillary were collected.

Meta-analysis of ophthalmic examination parameters in the healthy control, non-DON and DON group

As shown in table 1, the DON group demonstrated increased CAS and exophthalmos than the non-DON group (CAS: 95% CI: 1.28 (0.65 to 1.90), p<0.001; Exophthalmos: 95% CI: 1.23 (0.69 to 1.77), p<0.001). The non-DON group had higher IOP than the healthy control group (95% CI: 2.92 (2.05 to 3.80), p<0.001), whereas the DON group had higher IOP than the non-DON group (95% CI: 2.46 (0.63 to 4.29), p=0.008). The patient's vision deteriorated as the severity of the disease worsened. In VF-MD and VF-PSD, DON had a larger VF loss than the non-DON group (VF-MD: 95% CI: −7.69 (−9.50 to −5.88), p<0.001; VF-PSD: 95% CI: 3.80 (2.25 to 5.34), p<0.001). Also, the VF-MD of the DON group is larger than the healthy control group (95% CI: −5.17 (−6.46 to −3.87), p<0.001) (online supplemental figures S1–S12).

Table 1 Results of meta-analysis in main characteristics

		Overall effect		Heterogeneity	
Parameter	**Comparison**	**Mean difference (95% CI)**	**P value**	**I² test, %**	**Q test (P)**
CAS	HC versus non-DON	NA	NA	NA	NA
	HC versus DON	NA	NA	NA	NA
	non-DON versus DON	1.28 (0.65 to 1.90)	0.00	92	0.00
VA	HC versus non-DON	0.02 (−0.00 to 0.04)	0.00	90	0.05
	HC versus DON	0.39 (0.11 to 0.66)	0.00	94	0.00
	non-DON versus DON	0.32 (0.18 to 0.45)	0.00	90	0.00
Exophthalmos	HC versus non-DON	NA	NA	NA	NA
	HC versus DON	NA	NA	NA	NA
	non-DON versus DON	1.23 (0.69 to 1.77)	0.00	0	0.44
IOP	HC versus non-DON	2.92 (2.05 to 3.80)	0.00	62	0.02
	HC versus DON	6.20 (3.43 to 8.96)	0.00	87	0.00
	non-DON versus DON	2.46 (0.63 to 4.29)	0.008	79	0.00
VF-MD(dB)	HC versus non-DON	0.42 (−0.63 to 1.47)	0.43	92	0.00
	HC versus DON	−5.17 (−6.46 to −3.87)	0.00	70	0.07
	non-DON versus DON	−7.69 (−9.50 to −5.88)	0.00	91	0.00
VF-PSD(dB)	HC versus non-DON	NA	NA	NA	NA
	HC versus DON	NA	NA	NA	NA
	non-DON versus DON	3.80 (2.25 to 5.34)	0.00	95	0.00

CAS, clinical activity score; DON, dysthyroid optic neuropathy; HC, healthy control; IOP, intraocular pressure; non-DON, thyroid-associated ophthalmopathy without DON; VA, visual acuity; VF-MD, visual field mean deviation; VF-PSD, visual field pattern SD.

Table 2 Results of meta-analysis in OCT

Area	Parameter	Comparison	Overall effect		Heterogeneity	
			Mean difference (95% CI)	P value	I^2 test (%)	Q test (P)
PRNFL	Overall	HC versus non-DON	−1.51 (−4.30 to 1.28)	0.29	73	0.005
		HC versus DON	−3.90 (−13.22 to 5.43)	0.41	96	0.00
		non-DON versus DON	−7.06 (−20.52 to 6.41)	0.30	97	0.00
	Superior-hemi	HC versus non-DON	−0.62 (−5.28 to 4.03)	0.79	72	0.06
		HC versus DON	7.66 (−7.23 to 22.55)	0.31	83	0.02
		non-DON versus DON	3.84 (−9.14 to 16.81)	0.56	80	0.006
	Inferior-hemi	HC versus non-DON	−4.03 (−11.25 to 3.19)	0.27	89	0.002
		HC versus DON	2.64 (−12.20 to 17.48)	0.73	87	0.006
		non-DON versus DON	1.93 (−9.93 to 13.79)	0.75	85	0.001
	S	HC versus non-DON	−3.21 (−11.79 to 5.36)	0.46	84	0.007
		HC versus DON	−11.78 (−31.11 to 7.55)	0.23	94	0.00
		non-DON versus DON	−21.96 (−63.83 to 19.90)	0.30	97	0.00
	T	HC versus non-DON	−2.72 (−7.30 to 1.86)	0.24	55	0.11
		HC versus DON	−0.42 (−6.35 to 5.51)	0.89	77	0.002
		non-DON versus DON	−1.83 (−11.83 to 8.16)	0.72	70	0.03
	I	HC versus non-DON	−4.27 (−11.21 to 2.67)	0.23	62	0.07
		HC versus DON	−11.73 (−30.35 to 6.90)	0.22	94	0.00
		non-DON versus DON	−21.48 (−65.23 to 22.26)	0.34	97	0.00
	N	HC versus non-DON	−1.57 (−11.18 to 8.03)	0.75	88	0.00
		HC versus DON	−8.04 (−22.15 to 6.08)	0.26	96	0.00
		non-DON versus DON	−13.71 (−48.21 to 20.79)	0.44	98	0.39
MGCCL	Overall	HC versus non-DON	0.29 (−0.39 to 0.97)	0.41	69	0.01
		HC versus DON	−3.15 (−3.74 to −2.56)	0.00	87	0.00
		non-DON versus DON	−7.27 (−10.80 to −3.74)	0.00	76	0.00
	Superior-hemi	HC versus non-DON	0.02 (−0.75 to 0.80)	0.95	70	0.07
		HC versus DON	−3.38 (−4.09 to −2.66)	0.00	92	0.00
		non-DON versus DON	−7.30 (−12.84 to −1.76)	0.01	79	0.00
	Inferior-hemi	HC versus non-DON	1.07 (0.26 to 1.87)	0.009	73	0.06
		HC versus DON	−2.22 (−2.77 to −1.68)	0.00	95	0.00
		non-DON versus DON	−9.07 (−16.56 to −1.59)	0.02	88	0.00
GCL+IPL	Overall	HC versus non-DON	−4.42 (−5.81 to −3.03)	0.00	0	057
		HC versus DON	−9.41 (−11.76 to −7.06)	0.00	0	0.70
		non-DON versus DON	−4.95 (−7.42 to −2.48)	0.00	0	0.46

DON, dysthyroid optic neuropathy; GCL+IPL, ganglion cell layer and inner plexiform layer; HC, healthy control; I, inferior; Inferior-hemi, inferior hemifield; MGCCL, macular ganglion cell complex layer; N, nasal; non-DON, thyroid-associated ophthalmopathy without DON; OCT, optical coherence tomography; PRNFL, peripapillary retinal nerve fibre layer; S, superior; Superior-hemi, superior hemifield; T, temporal.

Meta-analysis of OCT parameters in the healthy control, non-DON and DON group

Table 2 shows that there was no difference in overall, superior hemifield, inferior hemifield, superior, temporal, inferior and nasal PRNFL between the healthy control, non-DON and DON group (p>0.05). DON group, on the other hand, had lower MGCCL in the overall, superior and inferior hemifields compared with the non-DON group (Overall: 95% CI: −7.27 (−10.80 to −3.74), p<0.001; Superior hemifield: 95% CI: −7.30 (−12.84 to −1.76), p=0.01; Inferior hemifield: 95% CI: −9.07 (−16.56 to −1.59), p=0.02). As for inferior hemifield, the MGCCL of the non-DON group was thicker than the healthy control group (95% CI: 1.07 (0.26 to 1.87), p=0.009). Besides, the GCL+IPL in the non-DON group is thinner than the healthy control group (95% CI: −4.42 (−5.81 to −3.03), p<0.001). Furthermore, the DON group was thinner than the non-DON group in GCL+IPL (95% CI: −4.95 (−7.42 to −2.48), p<0.001) (online supplemental figures S13–S21).

Meta-analysis of OCTA parameters in the healthy control, non-DON and DON group

Based on table 3, the ONH-VD of the DON group was lower than that of the non-DON group (Overall: 95% CI: −3.10 (−4.32 to −1.88), p<0.001; Inside disc: 95% CI: −2.70 (−4.54 to −0.87), p=0.004; Peripapillary: 95% CI: −3.15 (−4.59 to −1.71), p<0.001). The non-DON group had lower overall ONH-VD than the healthy control group (Overall: 95% CI: −1.94 (−3.56 to −0.32), p=0.02). In terms of RPC-VD, the DON group was less than the non-DON group in overall, peripapillary, superior-hemifield, temporal and nasal (p<0.05). The non-DON group had decreased RPC-VD compared with the healthy control group in the following areas: overall, inside disc, peripapillary, superior-hemifield, inferior-hemifield, temporal and nasal (p<0.05). Besides, the M-SRCL of non-DON and DON is lower than the healthy control group (non-DON 95% CI: −2.51 (−4.57 to −0.45), p=0.02; DON: 95% CI: −4.47 (−5.63 to −3.31), p<0.001) (online supplemental figures S22–S30).

Subgroup analysis of OCT and OCTA parameters in the healthy control, non-DON and DON group

We conducted subgroup analysis according to the device, region and diagnostic criteria. Results were presented in online supplemental table S4. In terms of device, the heterogeneity of overall, superior-hemifield and inferior-hemifield PRNFL and MGCCL was still obvious in the Optovue subgroup. However, superior and temporal PRNFL between HC and DON attained a huge decrease in heterogeneity to some extent and displayed no heterogeneity in the Carl Zeiss subgroup (Superior: I^2=0%, p=0.50; Temporal: I^2=0%, p=0.58) (online supplemental figures S31–S37). As for region, overall, superior-hemi and inferior-hemi MGCCL between non-DON and DON presented no heterogeneity in non-Southeast Asian subgroup (Overall: I^2=0%, p=0.34; Superior-hemi: I^2=0%, p=0.77; Inferior-hemi: I^2=0%, p=0.91) (online supplemental figures S38–S57). In diagnostic criteria of TAO, we found low heterogeneity in MGCCL between non-DON and DON based on EUGOGO criteria (Overall: I^2=37%, p=0.19; Superior-hemi: I^2=0%, p=0.77; Inferior-hemi: I^2=0%, p=0.91). In addition, overall and peripapillary ONH-VD showed no heterogeneity across three groups (online supplemental figures S58–S72).

DISCUSSION

DON is an optic nerve dysfunction that is one of the most severe complications of TAO, characterised by thyroid-related impairment of visual function, leading to permanent sight loss.[4] Multiple criteria grade the symptoms of TAO, including EUGOGO consensus, Bartley criteria and so on, however, no single protocol completely characterises DON.[34] It might be especially difficult to detect whether DON has recently formed in newly presented patients, which implies that considerable efforts should be made to improve DON diagnosis and treatment.[35] Several mechanisms including optic nerve inflammation, compression, stretch and ischaemia contributed to the development of DON.[6–11] OCT and OCTA, novel non-invasive imaging modalities, can monitor changes in structure and microvascular network in the different retinal layers.[36 37] It could be crucial in the clinical process of DON.

This systematic review and meta-analysis investigated the changes in OCT and OCTA parameters between healthy control, non-DON and DON. In terms of ophthalmic examination results, the CAS and exophthalmos of the DON group were higher than the non-DON group. During the progression of TAO, the patient's VA decreased and IOP increased gradually. Besides, the DON group presented a larger VF loss than the non-DON group. These clinical manifestations might help ophthalmologists distinguish between DON and TAO without DON in the initial diagnosis.

Intriguingly, five articles[24 25 27 28 30] reported that the PRNFL of the DON group decreased while Wu *et al*[32] and Guo *et al*[26] recorded an increasing tendency of PRNFL in the DON group than the healthy control group and non-DON group. Meta-analysis showed no difference in these three groups in terms of PRNFL overall or by region. In addition to the comparison of non-DON and DON, two articles[26 28] recorded PRNFL based on the severity of TAO from moderate to severe. A decrease of PRNFL could be seen from mild TAO to moderate-to-severe TAO (online supplemental figures S73–S75). Several factors could explain this phenomenon. The EOMs and fatty connective tissue of the orbit induce volume expansion and compression of the optic nerve at the orbital apex, resulting in optic nerve ischaemia and inhibition of the axonal nerve flow, which is the significant cause of increased PRNFL thickness.[26 34] The thinning of PRNFL can be attributed to demyelination and axonal injury that arise from compression over time.[38 39] The optic disc may be edematous in the early stages of the disease with normal vision, and later on, optic nerve dysfunction can manifest with a normal, swollen or pale disc.[4] Furthermore, the DON group witnessed a decrease in overall GCL+IPL in Wu *et al*[33] and Guo *et al*'s[26] articles through analysis. A previous study demonstrated that there was a significant correlation between visual functions and GCL/IPL thickness in chiasmal compression optic neuropathy.[40] The thinning of GCL/IPL might be a strong suggestion for closer vision follow-up and earlier decompression surgery.[26] In terms of MGCCL, five studies[5 28 30 32 33] recording MGCCL changes presented a similar result that DON group had lower MGCCL compared with the non-DON group. Previous studies have proved that GCC loss is closely correlated with the VFs and could detect changes before the appearance of abnormal VF.[41 42] It was of great significance to the diagnosis of DON at the initial stage. GCL+IPL and MGCCL have the potential to be an early indicator of optic neuropathy. There are a few articles recording them in the progression of TAO. More researches are needed in the future to prove the role of GCL+IPL and MGCCL in following up patients.

Table 3 Results of meta-analysis in OCTA

Area	Parameter	Comparison	Overall effect		Heterogeneity	
			Mean difference (95% CI)	P value	I^2 test (%)	Q test (P)
ONH-VD	Overall	HC versus non-DON	−1.94 (−3.56 to −0.32)	0.02	73	0.03
		HC versus DON	−5.01 (−6.85 to −3.17)	0.00	57	0.10
		non-DON versus DON	−3.10 (−4.32 to −1.88)	0.00	0	0.81
	Inside disc	HC versus non-DON	−1.22 (−4.61 to 2.16)	0.48	84	0.002
		HC versus DON	−3.97 (−7.70 to −0.24)	0.04	76	0.01
		non-DON versus DON	−2.70 (−4.54 to −0.87)	0.004	0	0.92
	Peripapillary	HC versus non-DON	−3.01 (−6.34 to 0.33)	0.08	91	0.00
		HC versus DON	−4.97 (−6.91 to −3.03)	0.00	43	0.17
		non-DON versus DON	−3.15 (−4.59 to −1.71)	0.00	0	0.91
RPC-VD	Overall	HC versus non-DON	−1.23 (−1.92 to −0.54)	0.00	56	0.08
		HC versus DON	−10.07 (−18.08 to −2.07)	0.01	97	0.00
		non-DON versus DON	−6.17 (−10.65 to −1.70)	0.007	96	0.00
	Inside disc	HC versus non-DON	−2.50 (−4.29 to −0.71)	0.006	49	0.14
		HC versus DON	−6.91 (−11.27 to −2.54)	0.002	64	0.09
		non-DON versus DON	−1.13 (−2.73 to 0.46)	0.08	30	0.24
	Peripapillary	HC versus non-DON	−1.16 (−2.24 to −0.08)	0.04	65	0.06
		HC versus DON	−4.64 (−7.85 to −1.43)	0.005	73	0.05
		non-DON versus DON	−2.07 (−3.97 to −0.16)	0.03	76	0.02
	Superior-hemi	HC versus non-DON	−0.78 (−1.02 to −0.54)	0.00	0	0.38
		HC versus DON	−4.21 (−6.80 to −1.61)	0.001	50	0.16
		non-DON versus DON	−1.82 (−3.30 to −0.34)	0.02	48	0.15
	Inferior-hemi	HC versus non-DON	−1.52 (−2.92 to −0.12)	0.03	74	0.02
		HC versus DON	−4.84 (−8.66 to −1.02)	0.01	74	0.05
		non-DON versus DON	−1.26 (−2.81 to 0.28)	0.11	48	0.15
	S	HC versus non-DON	−0.79 (−1.64 to 0.07)	0.00	14	0.28
		HC versus DON	−11.13 (−22.02 to −0.25)	0.05	96	0.00
		non-DON versus DON	−9.92 (−21.12 to 1.29)	0.08	96	0.00
	T	HC versus non-DON	−4.59 (−10.21 to 1.03)	0.11	89	0.003
		HC versus DON	−9.50 (−15.16 to −3.85)	0.001	96	0.00
		non-DON versus DON	−5.76 (−10.89 to −0.64)	0.03	94	0.00
	I	HC versus non-DON	−2.27 (−6.58 to 2.03)	0.30	87	0.006
		HC versus DON	−10.75 (−22.53 to 1.04)	0.07	97	0.00
		non-DON versus DON	−9.03 (−21.56 to 3.49)	0.16	97	0.00
	N	HC versus non-DON	−0.45 (−0.78 to −0.11)	0.01	0	0.82
		HC versus DON	−6.13 (−10.97 to −1.30)	0.01	93	0.00
		non-DON versus DON	−5.40 (−9.90 to −0.90)	0.02	92	0.00
RCL	M-SRCL	HC versus non-DON	−2.51 (−4.57 to −0.45)	0.02	76	0.04
		HC versus DON	−4.47 (−5.63 to −3.31)	0.00	0	0.55
		non-DON versus DON	−1.83 (−4.66 to 1.01)	0.21	76	0.04
	M-DRCL	HC versus non-DON	−2.10 (−4.87 to 0.66)	0.14	76	0.04
		HC versus DON	−4.19 (−10.22 to 1.84)	0.17	89	0.002
		non-DON versus DON	−1.72 (−3.49 to 0.05)	0.30	62	0.11

DON, dysthyroid optic neuropathy; HC, healthy control; I, inferior; Inferior-hemi, inferior hemifield; M-DRCL, macular deep retinal capillary layer; M-SRCL, macular superficial retinal capillary layer; N, nasal; non-DON, thyroid-associated ophthalmopathy without DON; OCTA, optical coherence tomography angiography; ONH-VD, optic nerve head vessel density; RCL, retinal capillary layer; RPC-VD, radial peripapillary capillary vessel density; S, superior; Superior-hemi, superior hemifield; T, temporal.

As for OCTA results of meta-analysis, seven studies[5 13 24 28 30 32 33] reported the changes of ONH-VD, RPC-VD or RCL. We found that ONH-VD in the DON group were less than the other two groups. In addition, a similar trend could also be seen in the RPC-VD of the DON group. Except for inferior and inferior hemifield, RPC-VD saw a decrease in DON groups compared with the non-DON group. Two studies[5 33] also collected data on RCL including M-SRCL and M-DRCL, results of the meta-analysis showed that the M-SRCL of the non-DON group and DON group was less than the healthy group. Both macroscopic and microscopic mechanisms could explain this phenomenon. Symptoms become severe when the disease involves the orbital apex, where the bony orbit narrows. The extraocular muscle encircles the optic nerve becoming the annulus of Zinn.[43] The optic nerve and its vasculature are then compressed, including the ophthalmic veins, central retinal veins, central retinal arteries and posterior ciliary arteries, which are the main areas of ocular perfusion, which caused the reduced vessel density.[6] Ocular endothelin-1 (ET-1) is an important peptide that modulates retinal blood flow and neuronal functions.[44] It exerts vasoactive and neuroactive functions through its G-protein-coupled receptors, endothelin receptor A (ET-A) and endothelin receptor B (ET-B), respectively, which are abundantly present in many ocular tissues.[45] It was higher than normal in thyroid hormone disorders caused by Graves' disease, which might be another reason for the lower vessel density.[46] Together, these results suggested that parameters of OCTA such as ONH-VD and RPC-VD gradually decreased with the progression of TAO from healthy condition to DON. Besides, the thickness of the retinal nerve fiber layer is paralleled to the ONH-VD and RPC-VD.[47 48] OCT has better sensitivity in monitoring early visual compromise at present. OCTA can be used as a supplementary examination to OCT.

In addition to the literature we included, there were several studies reporting the OCT or OCTA parameters before and after orbital decompression in dealing with DON. A significant decrease in PRNFL thickness could be detected after orbital decompression surgery in patients with DON. Noteworthily, greater preoperative superior, inferior and nasal PRNFL thickness was associated with better visual outcomes.[25 49 50] However, the reduction of RPC-VD could not be reversed immediately by medical and surgical decompression when vision and VF were improved.[32] After decompression, eyes with DON had a much greater reduction in ONH-VD than eyes without DON. The mechanism of ONH-VD reduction after orbital decompression is still unclear, we speculated that the body protectively lowered vascular density to avoid damage to the retina caused by reperfusion after long-term ischaemia under the condition of rapid recovery of blood supply after orbital decompression. One patient had worsening of the DON eye despite orbital decompression, and in this case, the vessel density was noted to have increased rather than decreased. This suggested that a reduction in ONH-VD correlated with improvement in DON while worsening DON may manifest as an increase in vessel density in the same area.[51] Because this conclusion was reached through only one case report. Therefore, the validity of this result needs to be verified by future comparative studies. We hypothesised that increasing vessel density meant more need of blood perfusion, combined with factors such as oedema of the vascular endothelium, which could lead to relatively lower blood perfusion after orbital decompression surgery, which affects prognosis. It proved that OCT and OCTA acted an essential part in diagnosing and treating DON. Ophthalmologists should undertake a comprehensive consideration of the retinal structure and microvasculature in estimating and treating patients with DON.

Despite the findings we achieved, the present meta-analysis had several limitations. First, heterogeneity in our meta-analysis may limit the generalisation of the pooled result and the source of heterogeneity could not be discerned by a subgroup analysis. Second, the number of studies in this meta-analysis is relatively small. Third, no single protocol completely characterises DON at present and diagnostic criteria were inconsistent across studies. Finally, all samples included in our analysis were all from Asia, and lack of coherence from other continents.

In conclusion, this systematic review and meta-analysis provided evidence on the associations of PRNFL, MGCCL and GCL+IPL in OCT and RPC-VD, ONH-VD, M-SRCL and M-DRCL in OCTA with DON. These results have important clinical implications since OCT and OCTA metrics may have the potential to be used as biomarkers of DON, which help ophthalmologists diagnose and treat patients with DON. Due to several limitations, future longitudinal studies with larger sample sizes and more potential confounders controlled are warranted to confirm our results.

Contributors NY and JM conducted the literature searches and extracted the data from published papers. NY and HZ drafted the paper and carried out a statistical analysis. QS and HZ contributed substantially to the conception and design of this paper. NY took responsibility for the drafting of the manuscript. QS provided a critical revision of the manuscript and was responsible for the overall content as the guarantor. All authors read and approved the final manuscript.

Funding This study was supported by National Natural Science Foundation of China (NSFC, grant number: 81672673). The funder has provided only financial support for the study.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iDs
Nan Yang http://orcid.org/0000-0002-1230-770X
Hui Zhu http://orcid.org/0000-0003-1326-3996

REFERENCES

1 Douglas RS, Kahaly GJ, Patel A, *et al*. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med* 2020;382:341–52.
2 Dolman PJ. Dysthyroid optic neuropathy: evaluation and management. *J Endocrinol Invest* 2021;44:421–9.
3 Taylor PN, Zhang L, Lee RWJ, *et al*. New insights into the pathogenesis and nonsurgical management of graves orbitopathy. *Nat Rev Endocrinol* 2020;16:104–16.
4 McKeag D, Lane C, Lazarus JH, *et al*. Clinical features of dysthyroid optic neuropathy: a European group on graves' orbitopathy (EUGOGO) survey. *Br J Ophthalmol* 2007;91:455–8.
5 Tu Y, Jin H, Xu M, *et al*. Reduced contrast sensitivity function correlated with superficial retinal capillary plexus impairment in early stage of dysthyroid optic neuropathy. *Eye Vis (Lond)* 2023;10:11.
6 Thyparampil P, Yen MT. Compressive optic neuropathy in thyroid eye disease. *Int Ophthalmol Clin* 2016;56:51–67.
7 Yanik B, Conkbayir I, Acaroglu G, *et al*. Graves' ophthalmopathy: comparison of the doppler sonography parameters with the clinical activity score. *J Clin Ultrasound* 2005;33:375–80.
8 Pérez-López M, Sales-Sanz M, Rebolleda G, *et al*. Retrobulbar ocular blood flow changes after orbital decompression in graves' ophthalmopathy measured by color doppler imaging. *Invest Ophthalmol Vis Sci* 2011;52:5612–7.
9 Jou IM, Lai KA, Shen CL, *et al*. Changes in conduction, blood flow, histology, and neurological status following acute nerve-stretch injury induced by femoral lengthening. *J Orthop Res* 2000;18:149–55.
10 Trobe JD, Glaser JS, Laflamme P. Dysthyroid optic neuropathy. Clinical profile and rationale for management. *Arch Ophthalmol* 1978;96:1199–209.
11 Regensburg NI, Wiersinga WM, Berendschot TTJM, *et al*. Do subtypes of graves' orbitopathy exist *Ophthalmology* 2011;118:191–6.
12 Saeed P, Tavakoli Rad S, Bisschop P. Dysthyroid optic neuropathy. *Ophthalmic Plast Reconstr Surg* 2018;34:S60–7.
13 Wu Y, Yang Q, Ding L, *et al*. Peripapillary structural and microvascular alterations in early dysthyroid optic neuropathy. *Eye Vis (Lond)* 2022;9:30.
14 Xie JS, Donaldson L, Margolin E. The use of optical coherence tomography in neurology: a review. *Brain* 2022;145:4160–77.
15 Geevarghese A, Wollstein G, Ishikawa H, *et al*. Optical coherence tomography and glaucoma. *Annu Rev Vis Sci* 2021;7:693–726.
16 Kim AY, Chu Z, Shahidzadeh A, *et al*. Quantifying microvascular density and morphology in diabetic retinopathy using spectral-domain optical coherence tomography angiography. *Invest Ophthalmol Vis Sci* 2016;57:OCT362–70.
17 Spaide RF, Fujimoto JG, Waheed NK, *et al*. Optical coherence tomography angiography. *Prog Retin Eye Res* 2018;64:1–55.
18 Wang X, Jiang C, Ko T, *et al*. Correlation between optic disc perfusion and glaucomatous severity in patients with open-angle glaucoma: an optical coherence tomography angiography study. *Graefes Arch Clin Exp Ophthalmol* 2015;253:1557–64.
19 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
20 Bartalena L, Kahaly GJ, Baldeschi L, *et al*. The 2021 European group on graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of graves' orbitopathy. *Eur J Endocrinol* 2021;185:G43–67.
21 Bartalena L, Baldeschi L, Dickinson A, *et al*. Consensus statement of the European group on graves' orbitopathy (EUGOGO) on management of GO. *Eur J Endocrinol* 2008;158:273–85.
22 Bartley GB, Gorman CA. Diagnostic criteria for graves' ophthalmopathy. *Am J Ophthalmol* 1995;119:792–5.
23 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
24 Jian H, Wang Y, Ou L, *et al*. Altered peripapillary vessel density and nerve fiber layer thickness in thyroid-associated ophthalmopathy using optical coherence tomography angiography. *Int Ophthalmol* 2022;42:855–62.
25 Park KA, Kim YD, Woo KI. Changes in optical coherence tomography measurements after orbital wall decompression in dysthyroid optic neuropathy. *Eye (Lond)* 2018;32:1123–9.
26 Guo J, Li X, Ma R, *et al*. The changes of retinal nerve fibre layer and ganglion cell layer with different severity of thyroid eye disease. *Eye (Lond)* 2022;36:129–34.
27 Jagiełło-Korzeniowska A, Bałdys-Waligórska A, Hubalewska-Dydejczyk A, *et al*. Functional and morphological changes in the visual pathway in patients with graves' orbitopathy. *J Clin Med* 2022;11:4095.
28 Abdolalizadeh P, Kashkouli MB, Moradpasandi F, *et al*. Optic nerve head vessel density changes from graves' disease without TED to TED dysthyroid optic neuropathy: does optic nerve head ischemia play a role? *Ophthalmic Plast Reconstr Surg* 2022;38:250–7.
29 Park K-A, Kim Y-D, In Woo K, *et al*. Optical coherence tomography measurements in compressive optic neuropathy associated with dysthyroid orbitopathy. *Graefes Arch Clin Exp Ophthalmol* 2016;254:1617–24.
30 Zhang T, Xiao W, Ye H, *et al*. Peripapillary and macular vessel density in dysthyroid optic neuropathy: an optical coherence tomography angiography study. *Invest Ophthalmol Vis Sci* 2019;60:1863–9.
31 Liu P, Luo B, Chen L, *et al*. Preliminary diffusion-tensor imaging evidence for trans-synaptic axonal degeneration in dysthyroid optic neuropathy due to thyroid-associated ophthalmopathy. *J Magn Reson Imaging* 2023;57:834–44.
32 Wu J-H, Luo L-Y, Zhou H, *et al*. Reduced choroidal peripapillary capillaries in thyroid-associated ophthalmopathy with early stage of dysthyroid optic neuropathy. *Int J Ophthalmol* 2022;15:1135–41.
33 Wu Y, Tu Y, Wu C, *et al*. Reduced macular inner retinal thickness and microvascular density in the early stage of patients with dysthyroid optic neuropathy. *Eye and Vis* 2020;7.
34 Blandford AD, Zhang D, Chundury RV, *et al*. Dysthyroid optic neuropathy: update on pathogenesis, diagnosis, and management. *Expert Rev Ophthalmol* 2017;12:111–21.
35 Wiersinga WM, Bartalena L. Epidemiology and prevention of graves' ophthalmopathy. *Thyroid* 2002;12:855–60.
36 Gabriele ML, Wollstein G, Ishikawa H, *et al*. Optical coherence tomography: history, current status, and laboratory work. *Invest Ophthalmol Vis Sci* 2011;52:2425.
37 Pujari A, Bhaskaran K, Sharma P, *et al*. Optical coherence tomography angiography in neuro-ophthalmology: current clinical role and future perspectives. *Surv Ophthalmol* 2021;66:471–81.
38 Setälä K, Raitta C, Välimäki M, *et al*. The value of visual evoked potentials in optic neuropathy of graves' disease. *J Endocrinol Invest* 1992;15:821–6.
39 Tsaloumas MD, Good PA, Burdon MA, *et al*. Flash and pattern visual evoked potentials in the diagnosis and monitoring of dysthyroid optic neuropathy. *Eye (Lond)* 1994;8:638–45.
40 Moura FC, Costa-Cunha LVF, Malta RFS, *et al*. Relationship between visual field sensitivity loss and quadrantic macular thickness measured with stratus-optical coherence tomography in patients with chiasmal syndrome. *Arq Bras Oftalmol* 2010;73:409–13.
41 Hwang HS, Lee EJ, Kim H, *et al*. Relationships of macular functional impairment with structural and vascular changes according to glaucoma severity. *Invest Ophthalmol Vis Sci* 2023;64:5.
42 Mahmoudinezhad G, Moghimi S, Nishida T, *et al*. Association between rate of ganglion cell complex thinning and rate of central visual field loss. *JAMA Ophthalmol* 2023;141:33.
43 Alford EL, Soparkar CNS. Management of the 'tight orbit' and associated visual loss. *Curr Opin Otolaryngol Head Neck Surg* 2013;21:417–22.
44 Shoshani YZ, Harris A, Shoja MM, *et al*. Endothelin and its suspected role in the pathogenesis and possible treatment of glaucoma. *Curr Eye Res* 2012;37:1–11.
45 Fernández-Durango R, Rollín R, Mediero A, *et al*. Localization of endothelin-1 mRNA expression and immunoreactivity in the anterior segment of human eye: expression of ETA and ETB receptors. *Mol Vis* 2003;9:103–9.
46 Chu C-H, Lee J-K, Keng H-M, *et al*. Hyperthyroidism is associated with higher plasma endothelin-1 concentrations. *Exp Biol Med (Maywood)* 2006;231:1040–3.
47 Jamshidian Tehrani M, Mahdizad Z, Kasaei A, *et al*. Early macular and peripapillary vasculature dropout in active thyroid eye disease. *Graefes Arch Clin Exp Ophthalmol* 2019;257:2533–40.
48 Wang YH, Ma J, Li H, *et al*. Peripapillary and macular vessel density in eyes with different phases of thyroid-associated ophthalmopathy. *Zhonghua Yan Ke Za Zhi* 2020;56:824–31.

49 Cheng S, Yu Y, You Y, *et al*. Retinal nerve fiber layer thickness measured by optical coherence tomography predicts visual recovery after orbital decompression for dysthyroid optic neuropathy. *Int Ophthalmol* 2021;41:3121–33.
50 Rajabi MT, Ojani M, Riazi Esfahani H, *et al*. Correlation of peripapillary nerve fiber layer thickness with visual outcomes after decompression surgery in subclinical and clinical thyroid-related compressive optic neuropathy. *J Curr Ophthalmol* 2019;31:86–91.
51 Lewis KT, Bullock JR, Drumright RT, *et al*. Changes in peripapillary blood vessel density in graves' orbitopathy after orbital decompression surgery as measured by optical coherence tomography angiography. *Orbit* 2019;38:87–94.