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GRAVITY OF GRAVES' ORBITOPATHY: IMPACT ON VISION, OPTIC NERVE FUNCTION AND PERIPAPILLARY BLOOD FLOW

Ophthalmology

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ABSTRACT

Background: Graves' Orbitopathy (GO) is the inflammation of the orbital, ocular, and periocular tissues associated with thyroid autoimmunity and is primarily linked with hyperthyroidism. Its pathogenesis involves orbital fibroblast stimulation leading to increased adipocyte proliferation and hyaluronan synthesis, eventually compressing vital orbital structures. Despite its low risk of vision loss (4-8%), GO imposes a substantial socio-economic and psychological burden, impacting quality of life. **Objectives:** To correlate the severity of GO with the following parameters: vision, optic nerve function and peripapillary hemodynamic alterations. In addition, the study aimed to compare the above-mentioned parameters with those of healthy controls. **Methods:** Hospital-based analytical cross-sectional study recruiting 50 eyes from 25 adults diagnosed with GO and 50 eyes from appropriately matched controls between December 2023 and July 2024. Comprehensive ocular examination was performed, including best corrected visual acuity (BCVA), optic nerve function tests, and OCT-A imaging to quantify peripapillary vessel densities. Subsequent classification as per European Group on GO (EUGOGO) was done. ImageJ software was used to analyze the vessel densities across key regions of the optic disc among various GO severity groups and controls. **Results:** Among the cases, majority (80%) had mild GO and were hyperthyroid. BCVA and optic nerve function tests were similar amongst controls, mild GO and moderate-severe GO, but those with sight-threatening GO showed reduced BCVA, defective colour vision, poor contrast sensitivity and visual field defects. Detailed OCT-A analysis showed a generalized reduction of vessel densities (VDs) in cases. A statistically significant decrease in VD ($P < 0.001$) was found in two niche regions (intrapapillary small VD and peripapillary superior hemifield all VD), with the reduction becoming more pronounced as GO severity worsened and in cases of active disease. **Conclusion:** This study found significant reductions in peripapillary vessel densities using OCT-A across progressive GO stages, suggesting OCT-A as a potential prognostic tool, detecting changes overlooked by routine clinical exmination.

KEYWORDS

Graves' orbitopathy (GO), optical coherence tomography angiography (OCT-A), peripapillary vessel density (VD), European group on GO (EUGOGO).

INTRODUCTION:

Graves' Orbitopathy (GO) or Thyroid Eye Disease (TED) refers to the inflammation of the orbital, ocular and periocular tissues linked to autoimmune thyroid disease.[1] While the likelihood of permanent vision loss is relatively low (4-8%), it still presents a considerable socio-economic and psychological burden worldwide.[2] It plagues 15-20% patients with dysthyroidism and is usually associated with primary hyperthyroidism. It may also affect hypothyroid and euthyroid patients, assuming a milder and significantly asymmetric course in such patients.[3]

GO, being a multifactorial disorder, has important non-modifiable risk factors such as female gender (F:M > 4:1), older age groups, positive family history and thyroid autoantibodies.[4-7] Smoking is the strongest modifiable risk factor followed by radioactive iodine exposure and vitamin D deficiency.[8-10]Stimulation of over-expressed TSH receptors (TSHRs) and Insulin-like growth factor (IGF) -1 receptors (IGFRs) on orbital preadipocytes (subgroup of fibroblasts differentiating into adipocytes) by thyroid stimulating autoantibodies and IGF-1 kickstarts the disorder. The stimulated fibroblasts, in turn, trigger a leading to increased orbital adipocytes and hyaluronan synthesis (Figure 1). Eventual expansion of orbital fat compresses vital orbital structures leading to a plethora of clinical features[2,11-14]

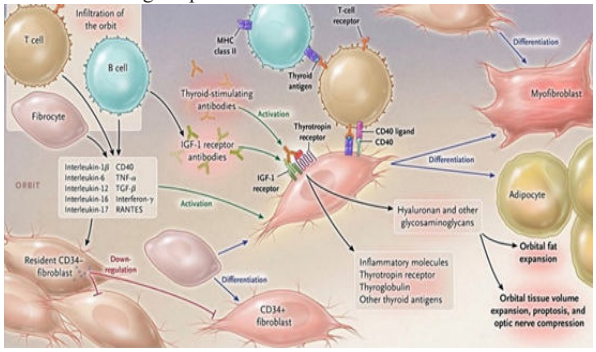

Figure 1: Pathogenesis of GO[11]

Over time, various classifications for GO have emerged as our understanding of the disease has improved. The latest European Group on GO (EUGOGO) severity classification (Figure 2), being validated through numerous clinical trials, has played a key role in shaping management guidelines. Several diagnostic methods like computed tomography (CT) and magnetic resonance imaging (MRI) of the orbits have been used in the management of the condition but they seldom offer valuable insights into disease prognostication.[15]

Classification	Features
Mild GO	Patients whose features of GO have only a minor impact on daily life that have insufficient impact to justify immunomodulation or surgical treatment. They usually have one or more of the following: • minor lid retraction (<2 mm) • mild soft-tissue involvement • exophthalmos • <3 mm above normal for race and gender • no or intermittent diplopia and corneal exposure responsive to lubricants
Moderate-to-severe GO	Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). They usually have two or more of the following: • lid retraction ≥ 2 mm • moderate or severe soft-tissue involvement • exophthalmos ≥ 3 mm above normal for race and gender • inconstant or constant diplopia
Sight-threatening (very severe) GO	Patients with dysthyroid optic neuropathy and/or corneal breakdown

Figure 2: EUGOGO Severity Classification [15]

While the correlation of increasing GO severity on vision, optic nerve function and retino-choroidal blood flow seems intuitive given the pathogenesis, the role of modern, non-invasive and non-ionizing ocular imaging techniques like optical coherence tomography angiography (OCT-A) in assessing severity progression remains relatively unexplored. Few studies have noted significant alterations of retinal blood flow in specific along different disease stages.[16] With conventional testing, sight threatening GO is unfortunately detected very late having minimal scope for improvement despite aggressive management. Through this study, we attempt to establish a relationship between worsening GO disease and vision, optic nerve function and peripapillary microvasculature changes. Furthermore, it also seeks to identify certain 'niche' areas in the retina and optic disc which may help predict disease progression. With conventional testing, sight threatening GO is unfortunately detected very late and no scope for improvement despite aggressive management. OCT-A, as a prognostic tool, can be employed to predict development of worsening GO and allow for timely mitigative interventional strategies.

MATERIALS AND METHODS:

In our study, we aim to correlate the severity of Grave's Orbitopathy (GO) with the following parameters: vision, optic nerve function and peripapillary hemodynamic alterations. We also aim to compare the above-mentioned parameters with those of healthy controls. Conducted at a tertiary eye care centre, this hospital-based analytical cross-sectional study involved examining 100 eyes from 50 patients between December 2023 and July 2024. A convenient sampling method was used, and the sample size was determined using nMaster software 2.0, ensuring a 0.05 error margin and 99% power. The research followed the ethical guidelines of the Declaration of Helsinki and written informed consent was obtained from all participants before taking part in the study.

The study involved 25 treatment-naïve adults (50 eyes) exhibiting signs of GO, along with control participants matched by age and gender. However, individuals with other systemic conditions, significant media opacities affecting fundus evaluation, existing orbital pathologies, prior retinal conditions and non-compressive optic neuropathies were excluded from participation.

After the Institutional Ethics Committee (IEC) approval, a thorough case history and comprehensive ocular assessment including best corrected visual acuity (BCVA) evaluation using Snellen's chart [which was later converted to logarithm of minimum angle of resolution (LogMAR) value], intraocular pressure (IOP) measurement (by Goldmann's applanation tonometry), slit lamp examination (using +75 dioptre lens) with indirect ophthalmoscopy (using +20 dioptre lens) and optic nerve function tests (colour vision by Ishihara chart and contrast sensitivity by Pelli-Robson chart) were performed by a single trained ophthalmologist. Subsequent segregation was done as per EUGOGO severity.

Baseline fasting serum thyroid function tests (TFTs) and thyroid autoantibodies were collected from recent records (taken < 1 month from baseline visit) or were newly performed if records unavailable. Based on TFTs, cases were categorized as hypothyroid, euthyroid or hyperthyroid. Baseline OCT-A was taken using optic disc cube 200 x 200 mode of Carl Zeiss Meditec CIRRUS® 5000 (Ver: 11.5.2.54532) to obtain AngioPlex images of various capillary levels (Figure 3A). ImageJ (a NIH software accessible free of cost) was employed to quantify vessel densities (VDs as %) within a 4.5 x 4.5 mm area centred around the optic nerve head. Images were initially made binary (Figure 3B), later skeletonized (Figure 3C) and finally, VD was calculated in various sectors after installing an appropriate software plug-in (Figure 3D). Baseline automated perimetry (visual field analysis) with the 30'-2 pattern was assessed using Carl Zeiss Humphrey Field Analyser-3® Model 830 (Ver: 1.5.3.714).

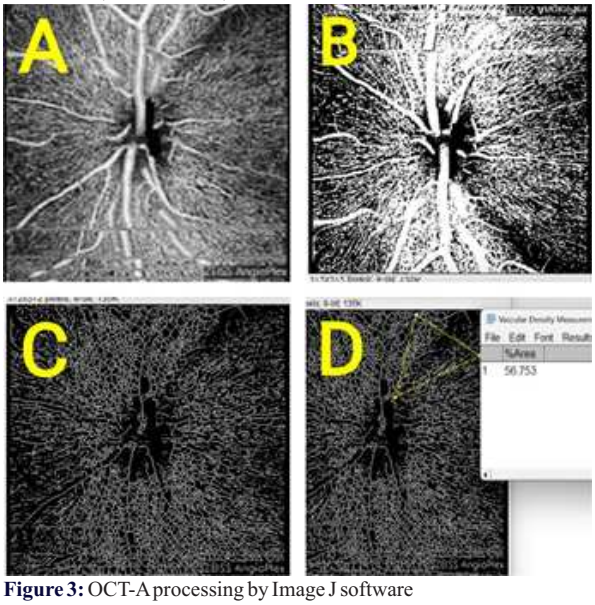

Figure 3: OCT-A processing by Image J software

Multivariate analyses were performed on retrieved data using Statistical Package for Social Sciences Version 29.0 for Windows (SPSS Inc, IBM Corp, Armonk, NY, USA). Level of statistical significance was set at $p < 0.05$ with 95% confidence interval.

RESULTS:

The study included 100 eyes from patients aged 49 to 67 years who satisfied the inclusion and exclusion criteria. Of these, 50 eyes belonged to the case group, while the remaining 50 served as age- and case-matched euthyroid controls. Age variations among controls and case groups based on GO severity were not statistically significant. The gender distribution was comparable, with females being the majority in both groups. Of the 50 GO eyes, majority were hyperthyroid. Most (80%) had mild GO, while 8 eyes had moderate-severe GO, and only 2% experienced sight-threatening GO. There was a significant increase in clinical activity score (CAS) with worsening GO grades such that all sight-threatening GO cases were active (Table 1).

Table 1: Baseline Patient Characteristics

Baseline characteristic	Controls	Mild GO	Moderate-Severe GO	Sight Threatening GO
No. of eyes (%) Male Female	50 (50%) 16 34	40 (40%) 15 25	8 (8%) 2 6	2 (2%) 1 1
Age (Mean ± SD) in years	59.42 ± 2.62	55.83 ± 6.24	57.25 ± 2.74	65.5 ± 0.5
Thyroid Status Euthyroid Hypothyroid Hyperthyroid	 50 0 0	 4 8 28	 0 2 6	 0 0 2
Proptosis (mm)	17.2 ± 1.36	21.5 ± 1.01	23.6 ± 0.97	26.5 ± 0.5
Clinical activity score (CAS)	Not applicable	1.775 ± 1.3	3.4 ± 1.6	6.5 ± 0.5
GO activity (per CAS) Active Inactive	Not applicable	 16 24	 5 3	 2 0
BCVA (Mean ± SD)	0.135 ± 0.0375	0.143 ± 0.0536	0.186 ± 0.131	1.1 ± 0.5
Colour vision	24/24	24/24	24/24	8/24 (Red-green defects)
Contrast Sensitivity (Log score)	2	2	2	1.2
Visual Fields	Unremarkable	Unremarkable	Unremarkable	Non-specific defects

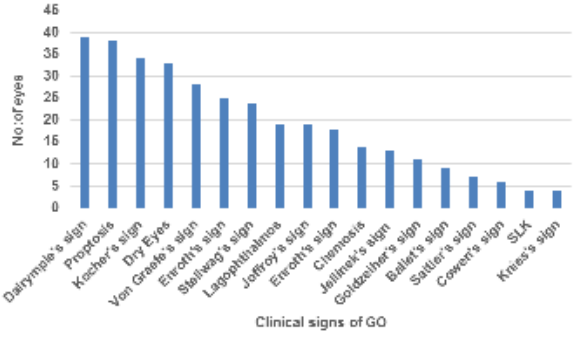

Figure 4: Bar Graph Representing Key Clinical Signs Observed In Cases

Majority (76%) of the GO patients presented with a history of ocular discomfort followed closely by foreign body (FB) sensation. Other common symptoms included swelling of eyelids, redness and protrusion of the eyeball. Diminution of near vision and diplopia were less frequent. On examination, lid signs were the most predominant with 78% of cases exhibiting lid retraction (Dalrymple's sign), 68% showing compulsive retraction on fixation (Kocher's sign), 56% showing lid lag on downgaze (Von Graefe's sign), 38% exhibited lagophthalmos while 36% had edema of lower lid (Enroth's sign). Proptosis was observed in 38 eyes, 50% of which was unilateral and 26% bilateral. Among the facial signs, infrequent blinking (Stellwag's sign) was the most observed feature (48%) followed by absent forehead creases on upgaze (Joffroy's sign) seen in 38% and

hyperpigmentation of superior eye folds (Jellinek's sign) in 26%. Conjunctival signs such as chemosis and deep conjunctival congestion at the extraocular muscle (EOM) insertions and bulbar area (Goldzeiher's sign) were observed in 28% and 22% of GO eyes respectively. Corneal signs observed were dry eyes [detected by tear film assessment using tear meniscus height, Schirmer's 1 test and tear film breakup time (TBUT)] in 66% cases and superior limbic keratitis (SLK) in 8% eyes. EOM signs were relatively uncommon, with only 18% cases showing restriction of movements (Ballet's sign). Intraocular pressure (IOP) in primary gaze was normal for all cases but 14% raised IOP on attempted upgaze (Sattler's sign). Overall, pupillary signs were the least common with a sparse 12% of cases showing jerky light reflex (Cowen's sign) and 8% showing unequal pupillary dilation in dim light (Knies's sign) [Figure 4].

The mean BCVA (LogMAR score) for controls was 0.135 ± 0.0375, while eyes with mild GO (n=40) had a mean score of 0.143 ± 0.0536. Eyes with moderate-severe GO (n=8) showed a mean score of 0.186 ± 0.131, and sight-threatening GO eyes (n=2) had a significantly higher score of 1.1 ± 0.196. No significant differences were found between the BCVA of mild and moderate-severe GO eyes (P = 0.07). However, a statistically significant deviation was observed between sight-threatening GO eyes and both controls and other GO groups (P < 0.001).

Optic nerve function was evaluated through three tests: color vision, contrast sensitivity, and automated perimetry. Both controls and cases with mild and moderate-severe GO had normal color vision (24/24), normal contrast sensitivity (score=2), and unremarkable visual fields. However, sight-threatening GO eyes showed red-green color deficiency (score= 8/24), reduced contrast sensitivity (score= 1.2), and non-specific visual field defects.

A comprehensive OCT-A analysis was conducted to assess all vessel densities (AVDs) and small vessel densities (SVDs) using ImageJ software in five key regions of interest: the whole image (WI), intrapapillary (IP), whole papillary (WP), peripapillary superior hemifield (PPSH), and peripapillary inferior hemifield (PPIH). Averages values of VDs ranged from 41-69% with higher densities observed for all vessels in PPIH area and small vessels in WP area. This analysis showed a generalized reduction in VDs in GO cases compared to controls, with the decrease becoming more pronounced as GO severity increased, as illustrated in the radar maps (Figure 5). Similarly, there was overall reduction in active GO as compared to inactive GO. Two specific regions (IP SVD, and PPSH AVD) were statistically significant, with IP SVD showing the most substantial reduction (P < 0.001) among the groups and between active and inactive disease. Furthermore, there no significant difference noted between VDs of inactive disease and controls. (Table 2)

Table 2: Specific Vessel Densities (VDs) Among Controls, Severity-based Case Groups And Activity.

Specific vessel density (VD)	Controls	Inactive GO		Active GO			P value
		Mild GO	Moderate-Severe GO	Mild GO	Moderate-Severe GO	Sight-threatening GO	
Whole image (WI) AVD	58.41 ± 2.31	58.26 ± 2.59	57.77 ± 2.02	57.82 ± 2.66	57.69 ± 1.76	54.81 ± 0.18	0.41
Whole image (WI) SVD	59.66 ± 3.73	58.85 ± 2.83	58.02 ± 1.78	57.97 ± 2.43	57.84 ± 1.67	55.30 ± 1.28	0.20
Intrapapillary (IP) AVD	60.12 ± 2.76	59.53 ± 3.84	58.47 ± 2.12	59.11 ± 2.56	57.25 ± 1.84	56.25 ± 1.29	0.21
Intrapapillary (IP) SVD	55.94 ± 2.98	53.65 ± 3.76	50.11 ± 2.65	52.79 ± 2.71	48.47 ± 2.12	44.52 ± 1.13	< 0.001
Whole peripapillary (WP) AVD	60.44 ± 4.42	60.09 ± 2.47	59.34 ± 1.54	59.67 ± 2.39	57.82 ± 1.17	57.33 ± 0.83	0.55
Whole peripapillary (WP) SVD	59.02 ± 4.67	58.34 ± 2.65	57.29 ± 1.38	57.16 ± 2.42	56.47 ± 1.48	55.35 ± 0.76	0.32
Peripapillary superior hemifield (PPSH) AVD	62.66 ± 3.51	60.73 ± 4.72	56.99 ± 3.34	59.77 ± 3.26	53.21 ± 2.64	50.29 ± 2.01	< 0.001
Peripapillary superior hemifield (PPSH) SVD	58.77 ± 3.45	57.91 ± 2.76	57.34 ± 1.53	57.41 ± 2.84	56.92 ± 1.49	56.18 ± 0.88	0.40
Peripapillary inferior hemifield (PPIH) AVD	59.79 ± 4.79	58.92 ± 3.83	57.45 ± 2.47	57.44 ± 3.47	56.19 ± 2.13	55.46 ± 1.84	0.17
Peripapillary inferior hemifield (PPIH) SVD	58.56 ± 3.56	58.01 ± 3.69	56.96 ± 2.03	57.71 ± 3.25	55.56 ± 2.11	52.79 ± 1.02	0.13

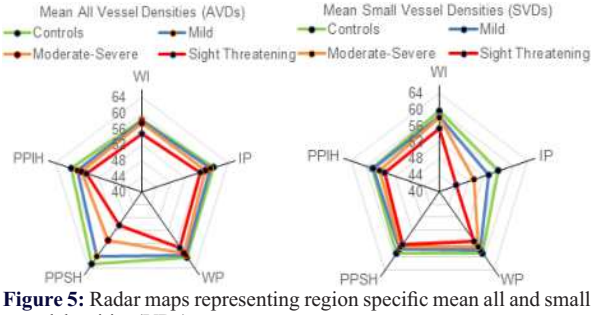

Figure 5: Radar maps representing region specific mean all and small vessel densities (VDs).

DISCUSSION:

The median age for GO onset is typically 43 years, but studies have noted a bimodal age distribution, particularly among females, who tend to develop the condition earlier. A study by Bartley in Minnesota (USA) identified the first peak in females between ages 40-44 and in males between 45-49. The second peak occurred between ages 60-64 in females and 65-69 in males. Additionally, 90% of GO cases were linked to hyperthyroidism. Overall, the prognosis worsens with advancing age, especially after 50 years[17] Our study presented similar results, with most GO cases occurring in the 55-65 age group, and about 72% of affected eyes were associated with hyperthyroidism. Patients with more severe grades of GO were found to be from older age groups. Abraham-Nordling et al. conducted a multicentre study in Sweden (2003-2005) and confirmed that Graves' disease was the leading cause of GO. They also found a significant gender disparity, with females more commonly affected in a ratio of 4.2:1.[18] While our findings showed a more modest female predominance at a 2:1 ratio, the overall trend aligns with previous research, emphasizing the age, gender and thyroid-related aspects of GO. Intraocular pressure (IOP) in primary gaze was normal in all patients.

The clinical features of GO have been extensively documented with identification of numerous eponymous signs. A cross-sectional study in Nepal examined the ocular manifestations of GO in 117 patients with dysthyroidism. Common clinical features included lid retraction, lid lag, and proptosis in 33.3% of cases, with 68% experiencing bilateral proptosis. Corneal ulcers occurred in 7.1%, optic neuropathy in 1.2%, and elevated intraocular pressure in 27.3%.[19] Dry eye was observed in 61.9% of cases. Research has consistently shown that lid signs are the most common features of GO.[20]

Diminution of visual acuity in GO has multiple causes. During the acute phase (lasting 12-18 months), transient visual obscuration usually occurs due to orbital congestion. In contrast, the chronic phase leads to more permanent vision loss, resulting from tear film abnormalities, optic neuropathy, exposure keratopathy, corneal ulceration, or, in rare cases, chorio-retinal folds. Subtle optic nerve involvement may go undetected unless specifically investigated by imaging modalities and may result in irreversible visual impairment. [21, 22] In a study by McKeag et al., 12 out of 46 eyes with dysthyroid optic neuropathy (DON) had "normal" visual acuity, indicating that normal vision does not rule out the diagnosis of DON.[23] In our study, patients with mild and moderate-severe GO had normal best-corrected visual acuity (BCVA), color vision, contrast sensitivity, and visual fields. However, in two eyes with sight-threatening GO, BCVA was reduced, optic nerve function tests were abnormal and non-specific field defects were present. Therefore, a seemingly normal routine visual acuity and optic nerve function tests may not necessarily preclude optic nerve dysfunction and progression of GO.

A diagnosis of sight-threatening GO with the onset of DON offers little hope to patients because most interventions aim to prevent further damage rather than restore vision. Vision loss in this stage is mostly irreversible, prompting the need for more objective methods to predict and detect GO progression, which is crucial for prognosis. Various imaging techniques, from non-invasive color Doppler to invasive CT angiography, have been suggested to assess blood flow from ophthalmic arteries to retinal microvasculature and venous drainage via the superior ophthalmic veins. However, incorporating these methods into routine clinical practice remains difficult due to poor feasibility and concerns about the risk-benefit ratio.

In this context, novel non-invasive and non-ionizing imaging techniques like OCT-A are increasingly used to detect subtle changes in retinal microvasculature, which could indicate the worsening of GO. A Chinese research group compared peripapillary VD in patients with GO and DON. They observed that total peripapillary VD was significantly reduced in patients with DON compared to the other groups ($P < 0.001$). However, no notable differences were found in specific VDs of controls, active and inactive non-sight-threatening GO cases. [24] Another study by Wang et al examined optic disc VDs in different phases of GO and its correlation with visual function. They found a significant reduction in optic disc VDs in both acute and chronic DON compared to controls. This reduction in VD was associated with more severe visual field defects. [25] Consistent with these findings, our study also demonstrated an overall reduction in VD in GO patients compared to controls, with further decreases across various GO severity levels. Interestingly, a significant reduction in SVDs of two niche areas (namely IP SVD, and PPSH AVD) was noted with worsening GO.

In a study by Yilmaz et al. conducted in Turkey, researchers used OCT-A to assess optic nerve head and macular VD in patients with inactive GO. They found no significant changes in VD within the optic disc area, except for the inferior peripapillary region, where VD was higher in GO patients. Despite reduced macular perfusion, retinal nerve fibre layer (RNFL) thickness remained similar between GO patients and healthy controls. [26] Similarly, Mihailovic et al. evaluated retinal and optic disc perfusion in inactive GO patients, finding significantly lower VD in the superficial retinal and optic nerve head (ONH) regions compared to healthy subjects. However, they found no significant relationship between VD and clinical function or disease severity. [27] In our study, we observed a general decline in VD across controls, inactive, and active GO patients, with the most significant reductions in VD noted in the IP SVD and the PPSH AVD.

As with any research, this study has its own limitations. The small sample size and restricted geographical scope limit the generalizability of the findings. Additionally, the study did not assess risk factors or their correlation with microvascular changes. A lack of follow-up prevented evaluation of disease progression and treatment outcomes.

CONCLUSION:

In conclusion, this study identified a significant reduction of peripapillary vessel densities in two niche areas (particularly the intrapapillary small vessel density) using OCT-A across progressive grades of GO, despite similar visual acuity and optic nerve function in mild and moderate-severe cases.

The above findings suggest that OCT-A could serve as an alternative prognostic tool for GO, as it is able to detect subtle hemodynamic changes in later stages that are often overlooked by traditional visual acuity and optic nerve function tests. The potential influence of GO on the optic nerve head vasculature may require further large-scale studies.

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