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Evaluation of the optic disc, macula and retinal nerve fiber layer thickness in patients with thyroid associated ophthalmopathy

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Abstract
Background: Thyroid-associated ophthalmopathy (TAO) is an autoimmune condition with an increase in the orbital volume and raised intraocular pressure (IOP). Subclinical retinal changes may be detected even before the clinical features of compressive optic neuropathy (CON) develop. Optical coherence tomography (OCT) is a non-invasive test to evaluate these retinal changes. Not many studies have been conducted to establish these subclinical changes.
Objectives: To assess the retinal nerve fiber layer thickness (RNFL), macula and optic disc parameters of TAO patients obtained by OCT and compare it with those of age and sex- matched healthy subjects. To assess the IOP in TAO patients and compare it with the IOP of healthy controls.
Design: Observational case-control study.
Participants: 28 patients diagnosed with TAO and 28 age-sex matched healthy controls.
Methods: All the patients were subjected to detailed ophthalmic examination which includes Visual acuity, slit-lamp examination of anterior segment, IOP using Goldmann applanation tonometer, Hertel's exophthalmometer for proptosis, dilated fundoscopy using 78D/90D; optic disc, macula and retinal nerve fiber layer measurements using OCT and Clinical Activity score (CAS) for TAO activity.
Results: IOP was higher in TAO group when compared to the controls and it was statistically significant**.** Analysis of data revealed a significant RNFL and macular thinning in all the quadrants for the TAO group when compared with the control group. Cup-Disc (C/D) ratio was more in TAO group but not statistically significant.
Conclusion: Significant retinal changes were noticed in TAO patients without CON which can be detected through OCT. It is essential to evaluate these subclinical retinal changes for active intervention and to prevent severe complications associated with the disease.

Keywords: Thyroid-associated ophthalmopathy, graves ophthalmopathy, thyroid eye disease, retinal nerve fiber layer, macula, intraocular pressure, optical coherence tomography

Introduction

Thyroid Associated Ophthalmopathy (TAO), Graves Ophthalmopathy (GO), or Thyroid eye disease (TED) is an immune-mediated inflammatory disorder that leads to the expansion of the extraocular muscles and fat in the orbit [1]. Inflammatory cellular infiltration, orbital fibroblasts proliferation, accumulation of glycosaminoglycans, collagen, and adipogenesis leads to enlargement of both extraocular muscles and orbital adipose tissue [2, 3]. It is generally associated with Graves's hyperthyroidism but maybe associated with euthyroid or hypothyroid autoimmune thyroiditis [4]. 80% of the cases of TAO are associated with Grave's disease, 10% of the cases with thyroid cancers or autoimmune hypothyroidism due to Hashimoto's thyroiditis, and 10% with no thyroid disorder [5]. TAO is more common among the females, while severe TAO is associated with males. The disease occurs between 30-50 years of age and becomes severe after 50 years of age [6]. Compressive optic neuropathy is a sight-threatening complication associated with the disease. Optic nerve function is assessed clinically by testing the visual acuity, colour vision, visual fields, contrast sensitivity and pupillary reactions [3]. Altered blood flow caused by the oedema in the orbital soft tissue and raised IOP are associated with retinal changes before clinical features of optic nerve compression develop [2]. Not many studies have been conducted to establish these subclinical changes. Optical coherence tomography (OCT) is a non-invasive technique for evaluating the optic disc, peripapillary retinal nerve fiber layer thickness (RFNL) and macula [3]. A non-invasive method to study the early significant changes will help in active intervention to prevent irreversible damage to vision.

In this study, the retinal nerve fiber layer thickness, macular and optic disc measurements obtained by OCT in TAO patients are compared with those of age and sex-matched healthy subjects.

Aim and objectives of the study

(a) To assess the retinal nerve fiber layer thickness, macula, and optic disc parameters of TAO patients obtained by OCT and compare it with those of age and sex- matched healthy subjects. (b) To assess the IOP of TAO patients and compare it with those of age and sex- matched healthy subjects

Materials and Methods

The present study was conducted in VIMS & RC, Whitefield, Bangalore, on the subjects who visited the out-patient department of Ophthalmology from March 2021 to June 2022. All subjects were of Indian ethnicity and visited the centre voluntarily.

A pre-structured proforma was used to collect the baseline data and an informed written consent was obtained after explaining about the need of the study and the procedures that were to be performed for the collection of data. Detailed history was taken and ocular examination was performed as per the proforma, for those who satisfied the inclusion and exclusion criteria.

Study Design: Observational case-control study.

Study Period: 1.6 years (Between March 2021 to June 2022).

Place of Study: Department of Ophthalmology, Vydehi Hospital, Vydehi Institute of Medical Science and Research Centre, Bangalore.

Inclusion Criteria

Cases: Patients diagnosed with Thyroid associated ophthalmopathy (TAO).

Controls: Healthy subjects visiting the ophthalmology OPD.

Exclusion Criteria: In both groups.

- Those who have significant sight impairment, high myopia (<−5 D), high hypermetropia (>+3 D).
- Optic disc anomaly.
- Vitreoretinal interface disease.
- Vascular and degenerative retinal diseases.
- Cornea or lens opacity.
- Ocular surgery history, glaucoma, neurological diseases that can affect the visual field.
- History of trauma, amblyopia, diplopia, keratitis.
- History of topical or systemic steroid use.
- Presence of clinical changes of optic nerve dysfunction.

Abnormal pupillary reaction, abnormal colour vision, visual field defects.

Sample size: Was estimated by using the difference in Mean RNFL thickness between Cases (TAO) and Controls from the study Kumari Mugdha *et al*. as 92.06±12.44 and 101.28±6.64. Using these values, at 95% Confidence limit and 80% power, sample size of 25 was obtained in each group by using the below mentioned formula and Med calc sample size software. With 10% non- response, sample size of 25 + 2.5 ≈ 28 cases will be included in each group.

$$\text{Sample Size} = \frac{2SD^2 (Z_{\alpha/2} + Z_{\beta})^2}{D^2}$$

Sd-Standard Deviation = From previous studies or pilot study

$Z_{\alpha/2} = Z_{0.05/2} = Z_{0.025} = 1.96$ (From Z table) at type 1 error of 5%

$Z_{\beta} = Z_{0.20} = 0.842$ (From Z table) at 80% power

D = Effect size = difference between mean values

So, now formula will be

$$\text{Sample Size} = \frac{2SD^2 (1.96 + 0.84)^2}{D^2}$$

Method of Collection of Data

1. Study was started after obtaining clearance from the institutional ethics committee. Purpose of the study was explained to the study participants and informed consent was obtained from those who agreed to participate.
2. Study was conducted free of cost.
3. Data was obtained from the study participants using a pre-structured proforma.
4. The proforma included the following.

- Demographic details.
- Details of the disease.
- Details regarding other concurrent illnesses.
- Family history.
- Best corrected Visual Acuity, colour vision.
- Extent of proptosis.
- Assessment of field of vision.
- Anterior Segment Examination.
- Dilated fundoscopy.
- Intraocular pressure.
- Retinal nerve fiber layer thickness, macula and optic disc parameters.

Assessment tools

1. Snellen's chart, Ishihara chart.
2. Slit lamp and 78D/90D lens.
3. Goldmann Applanation Tonometer.
4. Hertel's exophthalmometer.
5. Cirrus 4000 Model spectral domain Optical coherence tomography.

Cirrus HD-OCT software version 6.5.0.772 (Carl Zeiss Meditec. Inc.) was used to acquire optic disc and macular thickness measurements. Images were rejected if there were artifacts, segmentation error, poor centration or poor signal strength (<6). The Macular Cube 512 ×128 protocol was used for the macular thickness measurement. The Optic Disc Cube 200 ×200 protocol was used for obtaining RNFL and optic nerve head parameters.

Statistical Analysis: Data was entered into Microsoft excel data sheet and analysed using SPSS 22 version software. Continuous data will be represented as mean and standard deviation. Independent t test will be the test of significance to identify the mean difference between two groups. p value <0.05 will be considered as statistically significant.

Outcome Measures

1. The retinal nerve fiber thickness, macula and optic disc parameters of TAO patients obtained by OCT and

compared with healthy controls
2. The intraocular pressure (IOP) in TAO patients and compared with the IOP of healthy controls

4. Results

This is an observational case-control study analysing 28 patients with TAO and 28 controls.

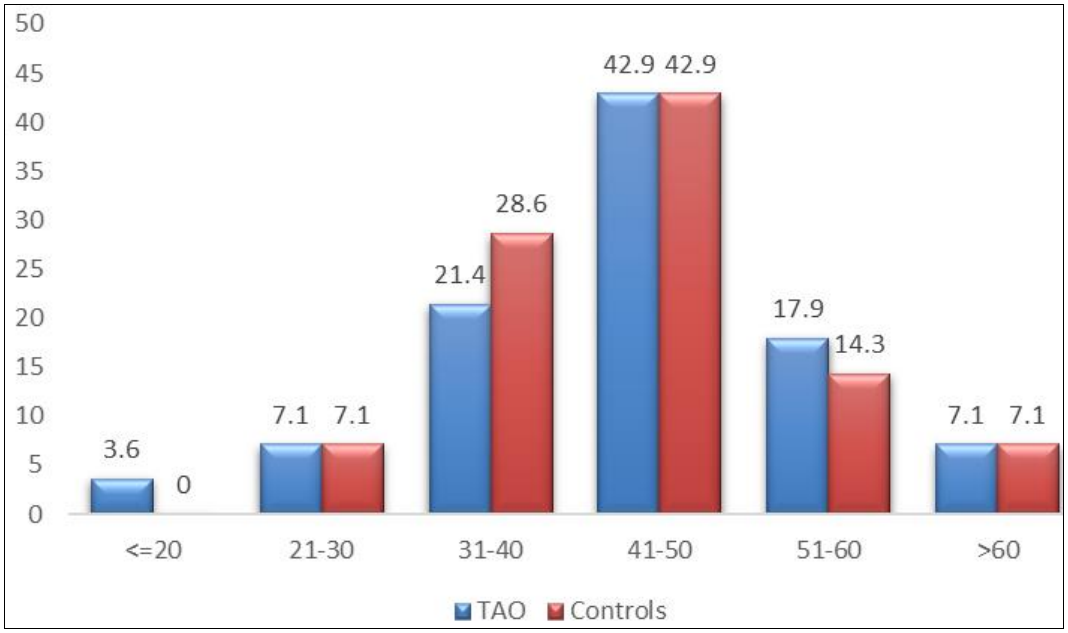

Fig 1: Age Distribution in Cases and Controls

The mean ages were 44.79±10.51 years and 44.73±10.07 years for TAO and control groups respectively, while no significant difference was found between the two groups (p value = 0.9).

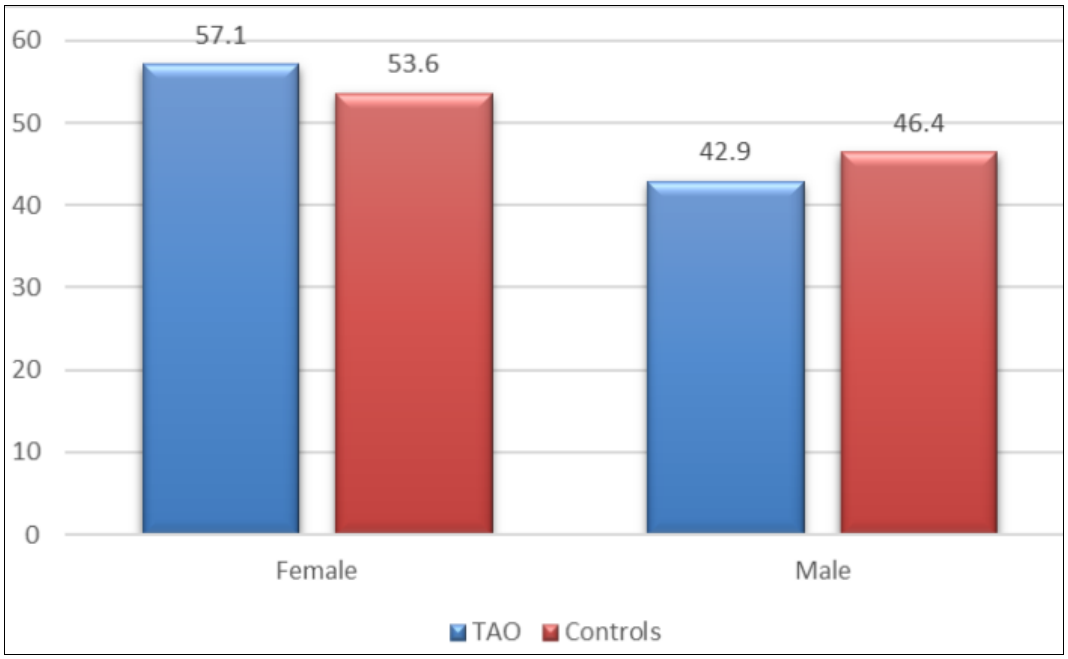

Fig 2: Gender Distribution in Cases and Controls

Sixteen (57.1%) of the TAO group were females while twelve (53.6%) were males. Among the controls, fifteen (42.9%) were females and thirteen (46.4%) were males. No statistically significant differences were found between the two groups in terms of gender distribution (p value=1).

Table 1: IOP in Cases and Controls

IOP	Mean	SD	t value	P value
Cases	15.14	3.69	5.36	0.0004 Significant
Controls	12.14	1.98		

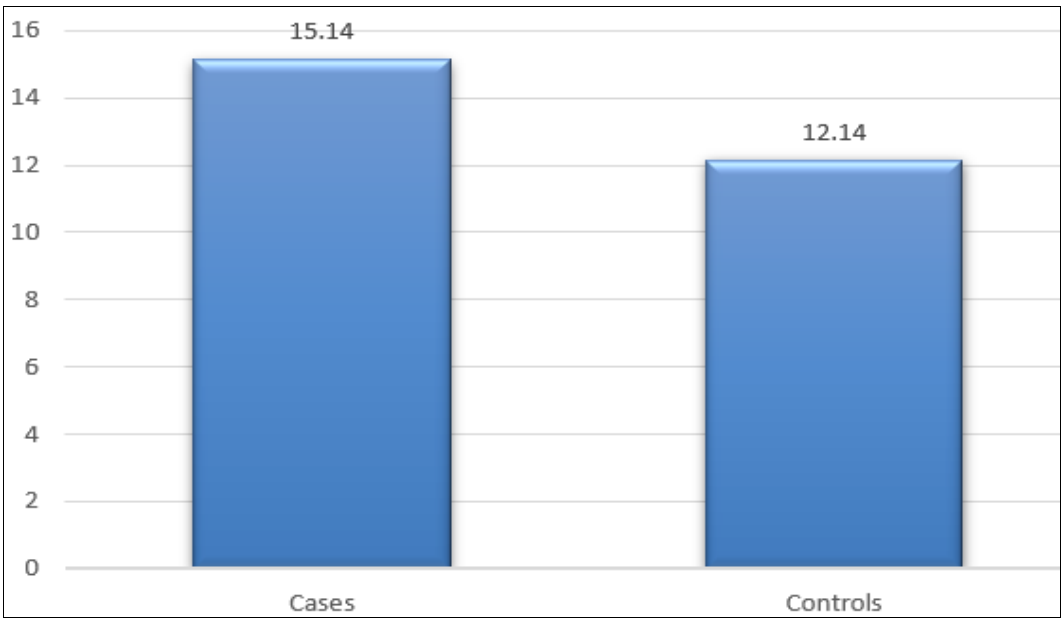

Fig 3: IOP in Cases and Controls

The mean intra-ocular pressure was 15.14±3.69 mmHg for the TAO patients and 12.14±1.98 mmHg for the control group. On comparison, the difference between the mean IOP values was statistically significant.

Table 2: C/D Ratio in Cases and Controls

C/D Ratio	Mean	SD	t value	P value
Cases	0.51	0.11	0.95	0.34 Not Significant
Controls	0.43	0.43		

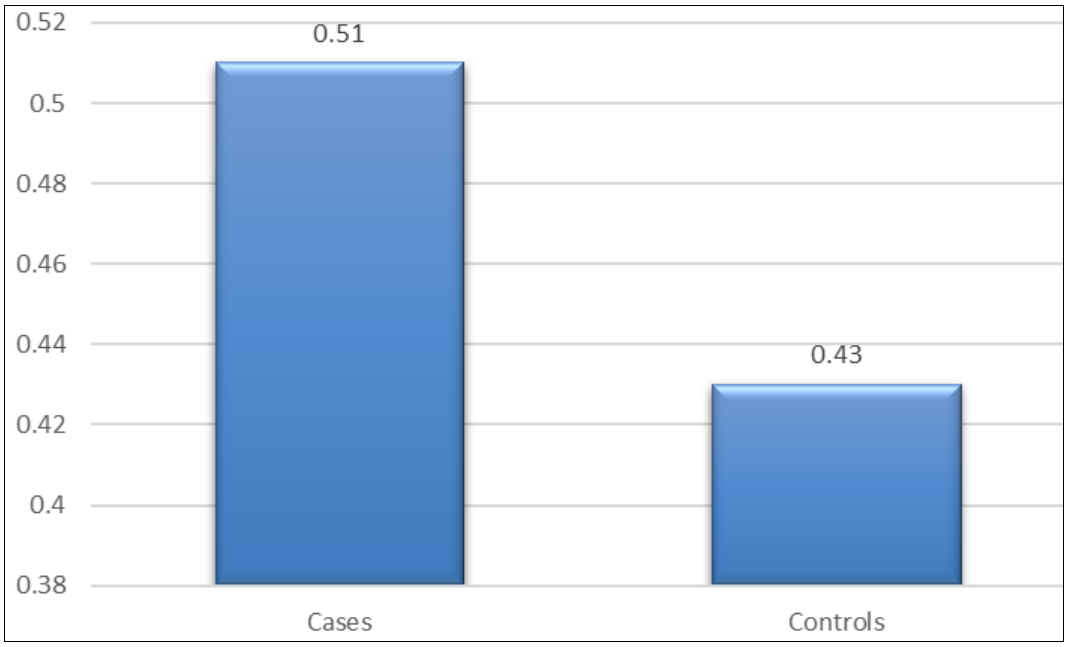

Fig 4: C/D Ratio in Cases and Controls

The mean C/D ratio among the cases (0.51±0.11) was more when compared to the controls (0.43±0.43). When assessed together, the difference was not significant statistically (p value=0.34).

Table 3: RNFL Thickness in Cases and Controls

	Cases	Controls	t-value	P value
RNFL-S	105.75±15.89	118.23±12.51	-4.62	0.0019*
RNFL-N	61.71±11.3	68.16±8.97	2.36	0.02*
RNFL-I	98.48±21.52	116.79±14.69	3.71	0.0005*
RNFL-T	55.61±9.41	65.27±10.55	3.61	0.0007*
Average RNFL	80.43±9.2	92.13±7.41	-5.24	<0.0001*

*Statistical significance

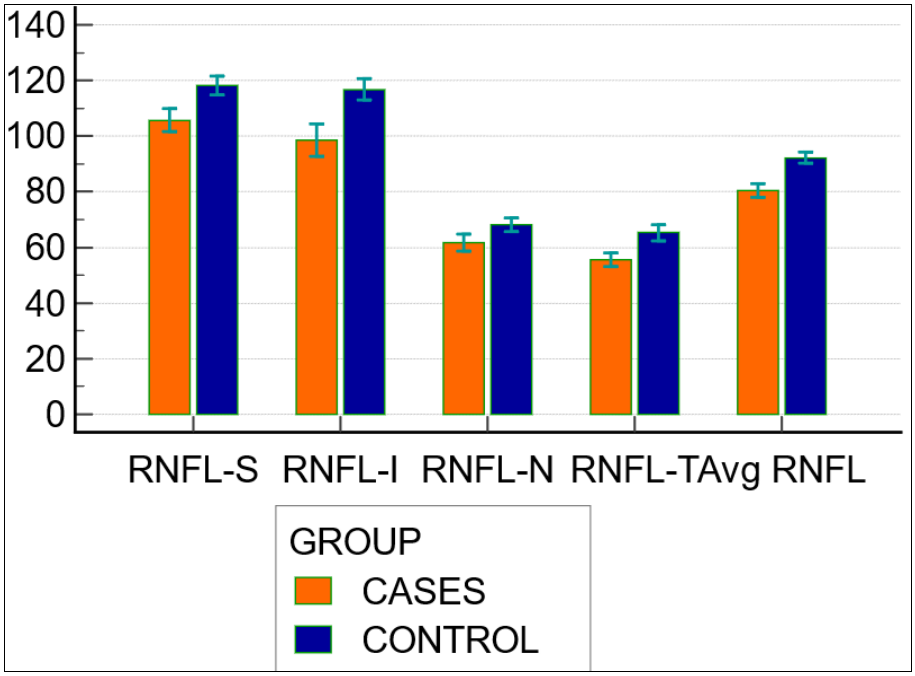

Fig 5: RNFL Thickness in Cases and Controls

Analysis of data revealed a significant RNFL thinning in all the quadrants for the TAO group when compared with the control group. The average RNFL thickness was 80.43±9.2 µm and 92.13±7.41 µm in the TAO and control group respectively and it was statistically significant.

Table 4: Central and Inner Macular Thickness in Cases and Controls

	Cases	Controls	t-value	P value
CMT	231.7±25.41	254.79±30.15	-4.38	0.003*
IMT-S	297.63±27.39	323.39±26.06	3.09	0.0031*
IMT-N	300.84±23.87	321.27±29.58	2.84	0.0063*
IMT-I	299.23±23.41	318.39±20.47	-4.61	0.0019*
IMT-T	291.18±27.57	314.5±34.56	2.79	0.0072*

*Statistical significance

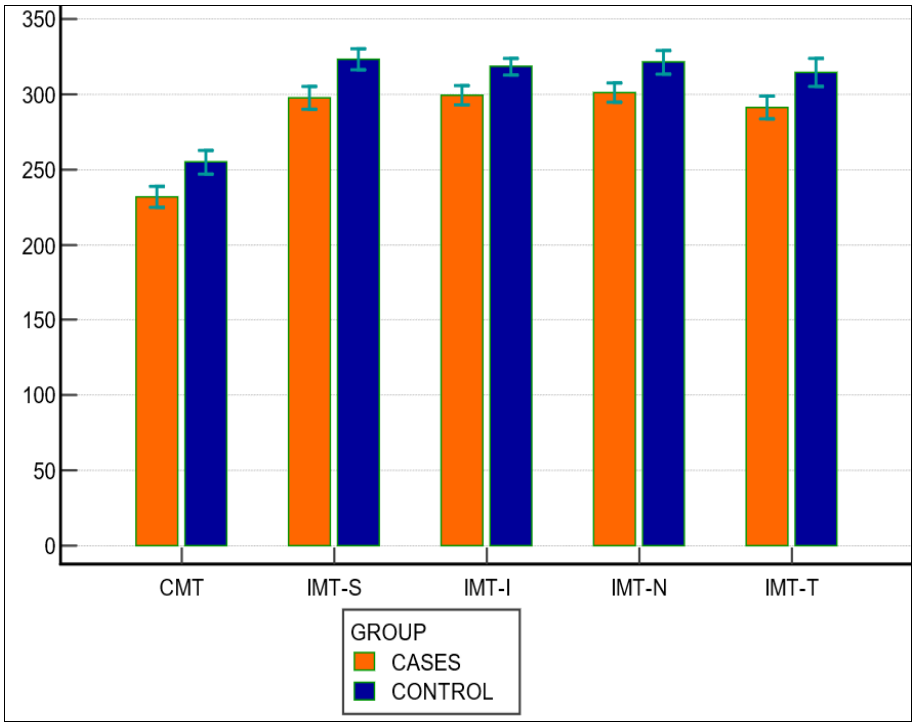

Fig 6: Central and Inner Macular Thickness in Cases and Controls

The central and inner macular thickness in all the quadrants of the patient group were found to have significant thinning when compared to the control group.

Table 5: Outer Macular Thickness in Cases and Control

	Cases	Controls	t-value	P value
OMT-S	269.79±18.06	293.14±34.47	3.17	0.0025*
OMT-N	288.57±15.22	299.63±18.67	-3.43	0.018*
OMT-I	258.96±16.12	274.55±27.22	-3.69	0.011*
OMT-T	255.71±20.14	279.25±45.76	-3.52	0.01*

*Statistical significance

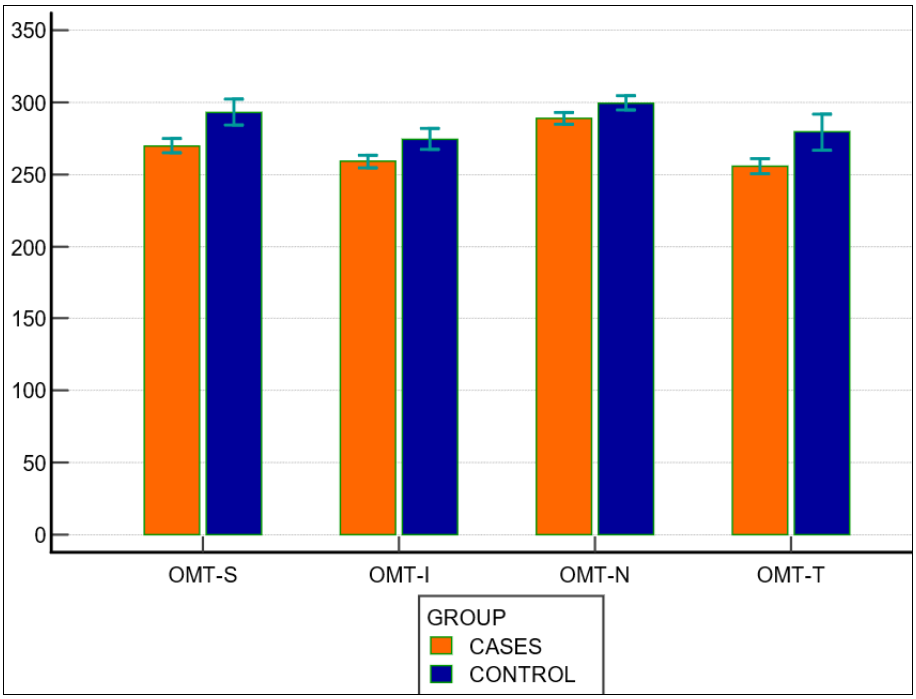

Fig 7: Outer Macular Thickness in Cases and Controls

When both the groups were assessed together, thinning was observed in all the quadrants of outer macular thickness of TAO group.

Table 6: Average Macular Thickness in Cases and Controls

Average MT	Mean	SD	t value	P value
Cases	276.02	13.75	-5.73	0.0002* Significant
Controls	296.34	22.7		

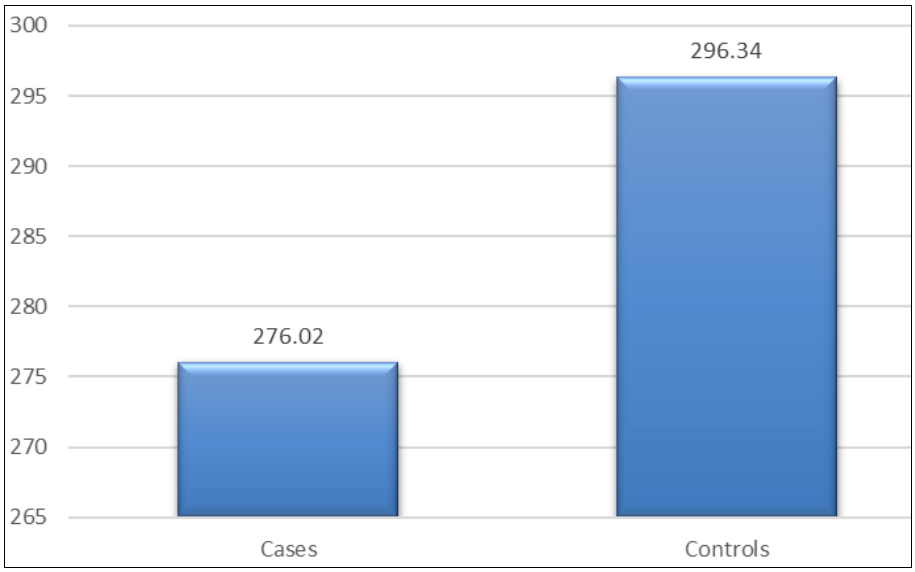

Fig 8: Average Macular Thickness in Cases and Controls

The average macular thickness in TAO and control groups were 276.02±13.75 µm and 296.34±22.7 µm respectively, and the difference between the groups was statistically significant.

Discussion

Thyroid-associated ophthalmopathy (TAO) is an autoimmune inflammation of orbital tissues characterized by an increase in the volume of the orbital contents[1]. Compressive optic neuropathy develops in TAO patients as a result of increased intra-orbital volume and pressure which leads to stretching of nerve [7].

According to Maldonado *et al*.'s study, RNFL thinning is noticed in compressive optic neuropathy, intracranial tumours causing optic chiasmal compression and also in cases of orbital and optic nerve tumours [8]. Danesh-Meyer *et al*. reported thinning of RNFL in patients with chiasmal compression detected on OCT [3]. Park *et al*. reported temporal RNFL thinning in CON patients [9]. These studies establish that RNFL is involved in CON. Bartelena *et al*. reported that subclinical neuropathy develops even in patients with mild TAO [3]. These subclinical changes may reflect on RNFL of the patients. Sen *et al*. reported that IOP was higher and mean RNFL was thinner in TAO patients when compared to the controls [10]. Forte *et al*. reported RNFL thinning in patients with TAO and ocular hypertension in comparison with control group [11]. Chu *et al*. reported increased Endothelin-1 levels in patients with Grave's disease which can alter blood flow to optic nerve head by its vasoconstrictor effect [12]. Zhang *et al*. reported that there was decreased peripapillary vessel density in CON patients[13].Based on these studies, peripapillary RNFL thinning in TAO patients can be attributed to altered microvascular blood flow and raised IOP. In our study, the mean IOP was more in the TAO group when compared to the control group along with significant thinning in all the quadrants of the RNFL when compared to healthy controls in the absence of clinical signs of optic nerve damage.

In contradiction, Meirovitch *et al*. reported RNFL thickening in TAO patients which was attributed to disc swelling as a result of edema and inflammation [1].

Poostchi *et al*. reported increase in disc area with transient increase in IOP irrespective of the glaucoma status of the patient [14]. Saym *et al*. reported that C/D ratio, IOP and disc area were more in TAO patients when compared with healthy controls [2]. In our study, C/D ratio was more in TAO patients when compared to the control group but it was not statistically significant. Similarly, in Sen *et al*.'s study, optic disc parameters between TAO and control group were not statistically significant [10].

Studies have suggested that macular thickness can be affected by the change in IOP. Sesar *et al*.'s study suggested that an increase in macular thickness was a result of decrease in IOP following glaucoma filtration surgery [15]. In Tan *et al*.'s study, macular thickness was reduced in perimetric glaucoma patients [16]. Macular thinning can be attributed to ganglion cell damage that occurred as a result of mechanical stress caused by an increase in IOP. Fernandez-Buenaga *et al*. reported macular thinning in the eyes of patients with Non-arteritic anterior ischaemic optic neuropathy (NAION) which they suggested is due to ischaemic damage to the macula-papillary bundle [17]. Hirscheider *et al*. reported that retinal perfusion was altered in TAO patients [18]. Meirovitch *et al*. and Saym *et al*. reported macular thinning in TAO patients [1, 2]. Wu *et al*. reported retinal thinning along with reduced microvascular density around the macula in TAO patients when compared with healthy controls [19]. Macular thinning in TAO patients can be attributed to altered blood supply as a result of increased intra-orbital volume and raised IOP. In our study, there was a significant thinning in all the segments of macula of the TAO group when compared with the control group.

These significant retinal changes, detected on OCT, imply that morphological changes precede visual dysfunction. However, it also important to attribute these changes to the progression and severity of the disease.

Conclusion

In our study, it was observed that there was significant peripapillary RNFL and macular thinning along with raised IOP in patients diagnosed with TAO when compared with the control group. These findings establish that RNFL damage continues to occur in TAO even before the clinical features of CON develop. This is also associated with macular thinning secondary to ganglion cell damage. These retinal changes can also be associated with reduced blood supply, caused by edema of the orbital contents and raised IOP. OCT is a non-invasive and appropriate technique for detecting these retinal changes. Hence, all TAO patients must be subjected to OCT examination of RNFL, macula and optic disc parameters. Early diagnosis of significant changes is required for active intervention and to prevent irreversible damage associated with the disease.

Conflict of Interest

Not available.

Financial Support

Not available.

References

1. Meirovitch SB, Leibovitch I, Kesler A, Varssano D, Rosenblatt A. Retina and nerve fiber layer thickness in eyes with thyroid-associated ophthalmopathy. Isr. Med. Assoc. J. 2017; 19(5):277-281.
2. Sayın O, Yeter V, Arıtürk N. Optic Disc, Macula, and Retinal Nerve Fiber Layer Measurements Obtained by OCT in Thyroid-Associated Ophthalmopathy. J Ophthalmol. 2016;2016(8):1-7.
3. Mugdha K, Kaur A, Sinha N, Saxena S. Evaluation of retinal nerve fiber layer thickness profile in thyroid ophthalmopathy without optic nerve dysfunction. Int. J Ophthalmol. 2016;9(11):1634-1637.
4. Barrio JB, Sabater AL, Farriol EB, Villoria AV, Galofre JC. Graves' Ophthalmopathy: VISA versus EUGOGO Classification, Assessment, and Management. Journal of ophthalmology. 2015 Aug 17;2015:249125.
5. Gopinath B, Musselman R, Beard N, El-Kaissi S, Tani J, Adams CL, *et al*. Antibodies targeting the calcium binding skeletal muscle protein calsequestrin are specific markers of ophthalmopathy and sensitive indicators of ocular myopathy in patients with Graves' disease. Clin. Exp. Immunol. 2006 Jul;145(1):56-62.
6. Marcocci C, Bartalena L, Bogazzi F, Panicucci M, Pinchera A. Studies on the occurrence of ophthalmopathy in Graves' disease. Acta. Endocrinol. (Copenh). 1989 Apr;120(4):473-478.
7. Maheshwari R, Weis E. Thyroid associated orbitopathy. Indian J Ophthalmol. 2012 Mar-Apr;60(2):87-93.
8. Maldonado RS, Mettu P, El-Dairi M, Bhatti MT. The application of optical coherence tomography in neurologic diseases. Neurol. Clin. Pract. 2015 Oct;5(5):460-469.

9. Park KA, Kim YD, Woo KI, Kee C, Han JC. Optical coherence tomography measurements in Compressive optic neuropathy associated with Dysthyroid orbitopathy. Graefes Arch Clin. Exp. Ophthalmol. 2016 Aug;254(8):1617-1624.
10. Sen E, Berker D, Elgin U, Tutuncu Y, Ozturk F, Guler S, *et al*. Comparison of optic disc topography in the cases with Graves disease and healthy controls. Journal of Glaucoma. 2012;21(9):586-589.
11. Forte R, Bonavolontà P, Vassallo P. Evaluation of retinal nerve fiber layer with optic nerve tracking optical coherence tomography in thyroid-associated orbitopathy. Ophthalmologica. 2010;224(2):116-121.
12. Chu CH, Lee JK, Keng HM. Hyperthyroidism is associated with Higher Plasma Endothelin-1 concentrations. Experimental Biology ad Medicine. 2006;231(6):1040-1043.
13. Zhang T, Xia OW, Ye H, Chen R, Mao Y, Yang H, *et al*. Peripapillary and Macular vessel density in Dysthyroid optic neuropathy: An Optical coherence tomography Angiography study. Invest Ophthalmol Vis Sci. 2019 May;60(6):1863-1869.
14. Insull E, Nicholas S, Ang GS, Poostchi A, Chan K, Wells A, *et al*. Optic disc area and correlation with central corneal thickness, corneal hysteresis and ocular pulse amplitude in glaucoma patients and controls. Clin Exp. Ophthalmol. 2010 Dec;38(9):839-844.
15. Sesar A, Cavar I, Sesar AP, Geber MZ, Sesar I, Laus KN, *et al*. Macular thickness after glaucoma filtration surgery. Coll. Antropol. 2013 Sep;37(3):841-845.
16. Tan O, Chopra V, Lu AT, Schuman JS, Ishikawa H, Wollstein G, *et al*. Detection of macular ganglion cell loss in glaucoma by Fourier-domain optical coherence tomography. Ophthalmology. 2009 Dec;116(12):2305-2314.
17. Buenaga RF, Rebolleda G, Muonz-Negrete FJ, Contreras I, Llera PC. Macular thickness. Ophthalmology. 2009 Aug;116(8):1587.
18. Hirscheider M, Termuhlen J, Heiduschka P, Grenzebach U, Eter N, Alnawaiseh M, *et al*. Altered retinal perfusion in Patients with Inactive Graves Ophthalmopathy using Optical coherence tomography Angiography. Endocr. Pract. 2020 Mar;26(3):312-317.
19. Wu Y, Tu Y, Wu C, Bao L, Wang J, Lu F, *et al*. Peripapillary structural and microvascular alterations in early Dysthyroid optic neuropathy. Eye Vis. 2022 Aug;9(1):30.

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