

## Visual morbidity in thyroid eye disease in Asian Indian patients

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**Purpose:** To describe visual morbidity in thyroid orbitopathy in Asian Indians and the factors influencing its onset. **Methods:** A retrospective chart review was performed for patients with thyroid related orbitopathy seen between May 2014 and April 2019. Three hundred and one patients were included in the study. Relevant history, clinical findings, investigations, and treatment were documented. **Results:** Nineteen percent of patients had at least 1 visual morbidity feature such as compressive optic neuropathy, exposure keratopathy or diplopia, requiring intravenous glucocorticoid. Male gender, older age, and diabetes were the significant risk factors for high visual morbidity (all  $P < 0.05$ ). Systemic thyroid status, degree of proptosis, and duration of disease were not significant. Average dose of intravenous glucocorticoid needed was 3.8 g; 24 (7.9%) patients required orbital decompression, and 13 (4.3%) needed eyelid surgery. At the last follow-up, 97% of patients had vision 6/12 or better in both eyes. **Conclusion:** There is significant visual morbidity found in Indian patients with TED, even with moderate proptosis and systemic control of thyroid status. This is the first set of data on the subject.

**Key words:** Dysthyroid optic neuropathy, Indian, thyroid eye disease

Thyroid orbitopathy or thyroid eye disease (TED) is an immune related inflammatory condition of the orbit, often associated with Graves' disease. It is commonly seen in hyperthyroid patients, but may present in euthyroid or hypothyroid patients as well.<sup>[1]</sup> The overall incidence in the population is low.<sup>[2]</sup> One population-based study estimates the incidence at 16/100,000 for females and 3/100,000 for males.<sup>[2]</sup> A small proportion of the patients develop moderate to severe disease, and about 5% of patients develop a sight threatening optic neuropathy.<sup>[2,3]</sup>

In the Indian population, the TED patients are under-reported and have received attention only in the recent years. A cohort of TED patients examined at an endocrinology service give an account of severity similar to that reported in literature.<sup>[4]</sup> However, case series from orbital disease services indicate that TED in India causes significant visual morbidity (Mahesh L, Proceedings of All India Ophthalmic Conference 2015). This study aims to describe the visual morbidity, factors influencing the disease, and outcomes in TED patients in an Indian oculoplasty and orbit clinic.

### Methods

The authors performed a retrospective chart review of all patients with TED examined in the Orbit clinic of a tertiary care eye institute in south India, between May 2014 and April 2019. The study followed the principles of Declaration of Helsinki. Approval was taken from the institute Ethics Committee.

The patients were identified through a search in the electronic medical record database, and the charts were reviewed for

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all patients with the diagnosis of TED. We excluded any patient who did not meet the criteria for TED as given by Bartley.<sup>[5]</sup> The diagnostic criteria included eyelid retraction plus any one—thyroid dysfunction (including abnormal antibody), or exophthalmos, or optic nerve dysfunction, or extraocular muscle involvement (including imaging).<sup>[5]</sup> In the absence of eyelid retraction, thyroid dysfunction plus any one of the following—exophthalmos or optic nerve dysfunction or extraocular muscle involvement.<sup>[5]</sup> To maintain uniformity of assessment and management decisions, we included all consecutive patients where the senior author was the principal physician. The charts were reviewed for systemic and ocular manifestations of disease, comorbidities, visual morbidities, and outcome.

We used the EUGOGO scale and clinical activity score (CAS) for the assessment of severity and activity.<sup>[6,7]</sup> We defined visual morbidities to include any one of the following—exposure keratopathy not resolving with topical medication, compressive optic neuropathy, and diplopia in primary gaze.

Dysthyroid optic neuropathy (DON) was defined as: one or more than one factor of the following—relative afferent pupillary defect, optic disc edema [Fig. 1a], abnormal color vision, abnormal visual fields, and diminished visual acuity. All DON underwent orbital imaging—computed tomography (CT) or magnetic resonance imaging (MRI) to confirm enlarged extraocular muscles and compression of the optic nerve [Fig. 1b]. For visual fields we used Humphrey

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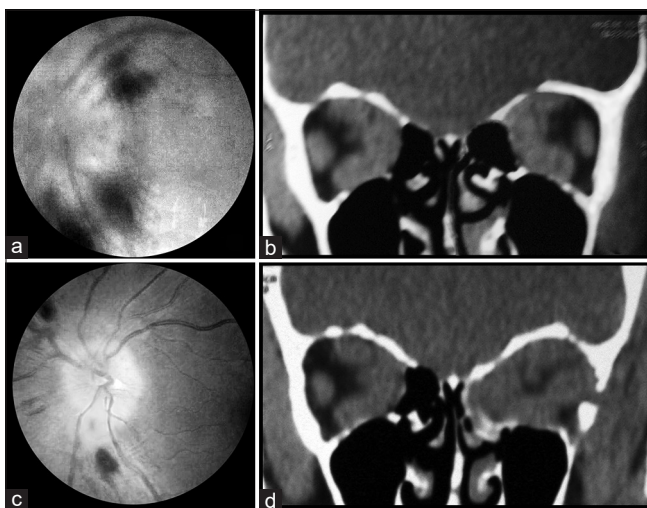
visual fields, 30-2 [Figs. 2-5b and c]. DON was diagnosed after eliminating any other etiology for the above findings.

All patients were advised thyroid function tests (TFT) at initial diagnosis (T3, T4, TSH) and to follow the advice of endocrinologist regarding systemic control of disease. Antithyroid antibodies were not routinely advised in patients with known abnormal TFT. Antithyroid antibodies (anti-TPO, TSH-R antibody) were advised in patients with clinical suspicion of TED, and normal TFT; if the antibody was positive in such patients, they were included in TED. The most recent thyroid function status was noted at every follow-up visit. The choice of the antibodies was dependent on availability in the local laboratories. For the purpose of this study, we categorized patients as “controlled systemic thyroid status” if the TFT was within normal limits at every visit, irrespective of any systemic medication the patient was on. All patients on oral medication

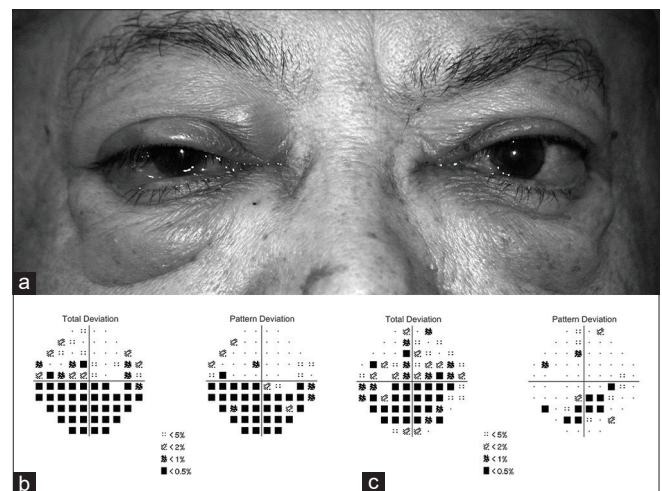
or insulin for blood sugar were categorized as diabetic. All smokers were advised to stop smoking.

The patients were treated with intravenous methyl prednisolone if the patients had any of the visual morbidities, or a clinical activity score (CAS) 4 or more [Fig. 2a, 3a and 4a].<sup>[6,7]</sup> They received methylprednisolone as per the different EUGOGO protocols for high clinical activity (CAS 4 or more) and for DON.<sup>[6,8]</sup> CAS 4 or more was treated with intravenous methylprednisolone 500 mg for 6 weeks, then 250 mg for 6 weeks.<sup>[6]</sup> DON was treated with 0.5-1 g intravenous methylprednisolone alternate days for 2 weeks, or for 3 consecutive days.<sup>[8]</sup> We monitored the patients for improvement, adverse effects or for a cumulative dose approaching 8 g.<sup>[8]</sup>

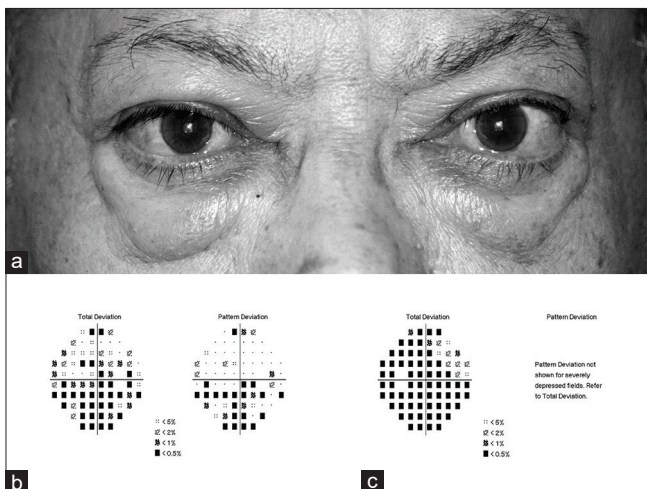
Patients with exposure keratopathy were first treated with topical lubricants. When the keratopathy did not respond to



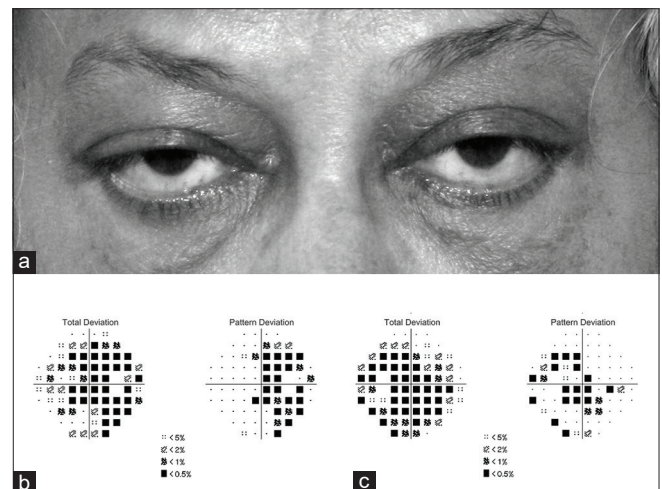
**Figure 1:** (a). Left eye disc edema in dysthyroid optic neuropathy. (b). Computed tomography showing extraocular muscles compressing the optic nerve. (c). Resolving disc edema after orbital decompression. (d). Computed tomography after left orbital decompression



**Figure 2:** (a). Clinical photograph of patient with severe inflammatory features. (b and c) Right and left eye visual fields (HVF 30-2) of the same patient showing generalised depression of sensitivity



**Figure 3:** (a). Clinical photograph of previous patient after intravenous methylprednisolone, showing apparent improvement in inflammatory features. Figure (b and c). Visual fields of right and left eye of the same patient show deteriorating optic neuropathy at the same time



**Figure 4:** (a). Clinical photograph of patient with moderate inflammatory features and moderate proptosis. Patient is on intravenous methylprednisolone. (b and c). Right and left eye visual fields of the same patient showing compressive optic neuropathy while on intravenous methylprednisolone

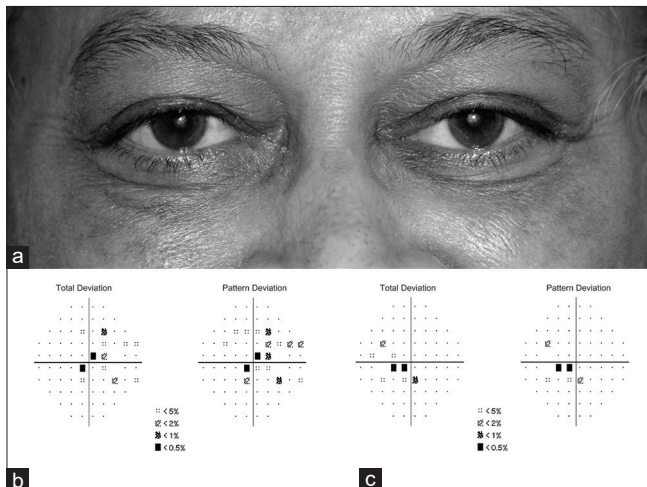


lubricants, they required tarsorrhaphy. Corneal breakdown is categorized as “Very severe disease” by EUGOGO.<sup>[8]</sup> The same consensus recommends use of intravenous glucocorticoids in “moderate to severe” and “severe” disease.<sup>[8]</sup> We based our management of corneal breakdown on these recommendations. In a patient with active TED and corneal breakdown, the proptosis, edema of the tissues, chemosis, conjunctival prolapse, lagophthalmos, limitation of movement and poor Bell’s phenomenon, incomplete blink, all contribute to the exposure keratopathy. Use of glucocorticoids mitigates these contributory factors.

Patients with compressive optic neuropathy underwent orbital decompression for any of the following—systemic intolerance to intravenous glucocorticoid, optic neuropathy non-responsive to the IVMP, or on continued progressive morbidity despite the total cumulative dose approaching 8 g [Figs. 1c, d and 5]. For compressive optic neuropathy, patients underwent balanced orbital decompression along with removal of orbital fat; the medial wall was decompressed by the trans-caruncular approach, the deep lateral wall by the lid crease approach.

Systemic immunosuppressants were added as steroid sparing agents in patients with CAS 4 or more when the cumulative intravenous glucocorticoid dose approached 8 g. This was in conjunction with a consultant rheumatologist, and azathioprine 50 mg/day was used for 3–6 months.<sup>[9]</sup> Orbital radiation was added in patients with DON, who were not improving with intravenous glucocorticoid, who were approaching 8 g cumulative dose, and were poor candidates for surgery or were showing recurrent DON after decompression.<sup>[8]</sup> Orbital radiation was administered as 20 Gy in fractionated doses.<sup>[8]</sup>

The patients with mild or inactive disease were managed conservatively, with cold compresses, topical tear substitutes, bed head elevation, and occasional non-steroidal anti-inflammatory drugs (NSAIDs). Patients with severe inactive disease were offered reconstructive surgery including eyelid correction and orbital decompression for proptosis. Patients with diplopia were advised prisms and surgery for strabismus.



**Figure 5:** (a). Clinical photograph of previous patient after bilateral orbital decompression of DON non-responsive to steroids. (b and c). Right and left eye visual fields of the same patient show recovery after orbital decompression

## Statistical analysis

Descriptive data was compiled using Microsoft Excel. Comparative statistics included Student’s *t*-test for continuous variables and Chi-square test for proportions. Logistic regression and multiple regression were used to determine the effect of known risk factors—male gender, smoking, dysthyroid status, prior use of radioiodine, diabetes mellitus. The statistics were performed on Medcalc Version v19.0.5. Level of significance was defined as  $P < 0.05$ .

## Results

The final analysis included 301 patients. The series included 53.1% female patients and 46.8% male patients, with average age 47.2 years. Table 1 shows the demographic and other characteristics of the two groups, one with visual morbidity, one without visual morbidity.

Overall, the mean duration of ocular symptoms and signs at presentation was 17.29 months (median 6 months, range 1–300 months), and the mean duration of systemic thyroid dysfunction was 5.85 years (median 5 years, range 0.5–30). Initial diagnosis at the onset of systemic disease could be determined from prescriptions available in 248 patients, 68% hyperthyroid, and 32% hypothyroid. The other patients did not have their old records. At presentation to our clinic, 129/301 (42.8%) were of controlled systemic thyroid status, initially either hyperthyroid or hypothyroid. Management for thyroid included systemic medication (carbimazole, methimazole, propylthiouracil, propranolol, or thyroxine) in 190/301 (63.1%) patients and radioiodine in 37/301 (12.2%) patients. The remaining patients were off any therapy as per advice of their endocrinologists. Two patients tested positive for anti-TPO antibody, where other TFT were normal.

The systemic comorbidities present in this cohort included diabetes mellitus, hypertension, chronic renal disease. Fifty-six (18.6%) of the patients were diabetic at presentation. Five of the patients had co-existing autoimmune conditions such as rheumatoid arthritis and myasthenia. Thirty-seven (12.3%) patients were smokers at presentation to the clinic.

The final outcome with mean 15.5 months (SD 17, range single visit to 58 months) follow-up was as follows. A total of 27.2% of patients received intravenous methyl prednisolone with a mean dose of 3,800 mg (Mean dose 4,250 mg in patients with visual morbidity, and 2,500 mg in patients treated for high CAS, but without visual morbidity). Overall, 57/301 (18.9%) showed visual morbidities requiring intravenous glucocorticoid and/or surgery, and 244/301 (81%) did not show visual morbidities. Of the patients who required intravenous glucocorticoid, 30/301 (10%) needed it for exposure keratopathy, 43/301 (14.3%) for compressive optic neuropathy, and 26/301 (8.6%) for diplopia. Some patients showed more than one feature. Overall, 19% patients were affected. Eyelid surgery was required by 13 (4.3%) patients. Twenty-four (7.9%) patients underwent orbital decompression for recalcitrant DON. Two patients developed postoperative diplopia. Five patients received systemic azathioprine for immunosuppression. Nine patients received orbital radiation. At the last follow-up, 9/301 (2.9%) had less than 6/12 vision in any eye, and 97% had vision 6/12 or better in both eyes. Table 2 shows details of the patients with less than 6/12 vision. Eleven (3.6%) showed residual corneal opacity, six patients (1.9%) had primary gaze diplopia. No

**Table 1: Comparison of patients with and without visual morbidity**

	Group A: Visual morbidity present n=57	Group B: Visual morbidity absent n=244	P
Mean age in years	55.5	45.2	P<0.0001
Male gender	68%	41.8%	P=0.0004
Systemic thyroid control	45.6%	42.2%	P=0.64
Mean proptosis	23.6 mm	22.2 mm	P=0.20
Mean duration of thyroid dysfunction	5.9 years	5.8 years	P=0.9
Mean duration of TED	12.9 months	18.4 months	P=0.3

**Table 2: Clinical course in patients with final vision 6/12 or less**

Patient number	Worst visual acuity right eye, left eye	Final visual acuity right eye, left eye	Treatment	Comment
1	HM, 6/12	1/60, 6/9	IVMP, bilateral orbital decompression	Right eye dense corneal opacity
2	6/18, 6/18	6/18, 6/18	Left follow up after first dose IVMP and tarsorrhaphy	Bilateral exposure keratopathy
3	Counting finger, 2/60	Counting finger, 3/60	Left follow up after 2 doses of IVMP and tarsorrhaphy	Right eye corneal scar, left eye exposure keratopathy
4	6/60, hand movement	6/18, hand movement	Left follow up after starting IVMP	Right eye improved, left eye cataract
6	6/60, 3/60	6/24, 3/60	Left follow up after 2 cycles IVMP	Both eyes lasered PDR, foveal thinning
7	6/6, 6/36	6/6, 6/36	TED quiescent	Diabetic retinopathy, Old CRVO
8*	6/12, PR inaccurate	6/6, 6/60	DON, not responding to IVMP for 3 weeks, bilateral orbital decompression	Disc edema resolved, temporal pallor
9	2/60, 6/12	2/60, 6/12	Quiescent eye disease	Both eyes cataract

\*Patient from Figure 1

patient included in this report has undergone corneal transplant. Strabismus surgery and use of prisms were advised for patients with diplopia after achieving quiescence; no patient in this cohort opted for surgical correction of strabismus. Orbital decompression for exophthalmos was offered for patients with proptosis with quiescent eye disease. Six patients in this cohort underwent orbital decompression in the inactive phase.

On analysis of the two groups with and without visual morbidity, it was seen that older age, male gender, and presence of systemic diabetes mellitus were associated with visual morbidity [Tables 1 and 3]. Duration of the condition, degree of proptosis and systemic control of thyroid status were not significantly different in the two groups [Table 1]. On analysis, the factors predicting visual morbidities requiring intravenous glucocorticoid included male gender ( $P = 0.04$ ) and systemic diabetes mellitus ( $P = 0.006$ ) on multiple logistic regression analysis [Table 3]. However, no factor was predictive for recalcitrant DON progressing to orbital decompression.

## Discussion

Thyroid orbitopathy is a rare entity in the general population, an estimated 0.5 per 100 population, with only 25–50% having clinical manifestation.<sup>[10]</sup> Sight threatening thyroid orbitopathy, DON is said to be rarer still.<sup>[3]</sup> However, the population-based reports are not from Indian population. As of the time of preparation of this manuscript, there is one single case series of thyroid eye disease in India, from an endocrinology practice.<sup>[4]</sup> It stands to reason, that the severe forms of the thyroid eye disease will be more commonly encountered in a

**Table 3: Analysis of risk factors for visual morbidity in orbitopathy**

Variable	Odds ratio	95% CI	P
Dysthyroid status	0.7136	0.3795-1.3419	0.2950
Diabetes	2.5881	1.3071-5.1245	<b>0.0064</b>
Male gender	1.9589	1.0273-3.7354	<b>0.0412</b>
Use of radioiodine	0.4642	0.1329-1.6214	0.2291
Smoking	1.4167	0.6824-2.9409	0.3500

P<0.05 significant

sub-specialty orbit clinic where they have been referred. This cohort of patients will tell us which patients need the closest attention. It is possible that including only the patients seen by the senior author may result in selection of cases with increased morbidity.

Racial variations are known in exophthalmometric readings, where the delimitations of normal measurements are 19 mm in Han Chinese patients, 21 mm in Caucasians, and 24 mm for black patients.<sup>[11-13]</sup> An Indian study showed the upper limit of exophthalmometric readings to be 19 mm in males and 21 mm in females.<sup>[14]</sup> The mean exophthalmometric reading in our case series was 22.4 mm. There was no significant difference in the exophthalmometry readings of the two groups, one with high visual morbidity and the other with lower morbidity. The following can explain this finding: first, Indian patients showed less proptosis than patients from several other racial backgrounds.<sup>[15]</sup> Second, proptosis can remain unchanged in quiescent TED.

In our orbit clinic, as many as 43% patients were of controlled systemic thyroid status. These patients were on systemic medication from elsewhere before consulting the orbit clinic. Having a controlled systemic thyroid status was not protective against visual morbidities. This is explained by the molecular mechanism of TED; pro-inflammatory factors act against the receptors on orbital fibroblasts, which then secrete chemokines and cytokines, leading to the cascade of TED.<sup>[16,17]</sup> Control of systemic thyroid status alone is not adequate, and a patient on medication may not show an improvement in eye disease.<sup>[18]</sup> Only a regular monitoring of the ocular features will help detect these morbidities. However, it is recommended that all patients with thyroid eye disease achieve a good systemic control.<sup>[18]</sup>

Male gender and older age group are known to have DON and severe forms of eye disease.<sup>[19,20]</sup> In our series, male gender was predictive for having visual morbidity due to TED [Tables 1 and 3]. However, on subgroup analysis, male gender was not predictive for DON non-responsive to steroids and requiring orbital decompression. In this series, the patients with greater visual morbidities and requiring intravenous glucocorticoids were seen to be significantly older than those without visual morbidity [Table 1].

Systemic immunosuppression has some effect on control on TED, when used in conjunction with glucocorticoids.<sup>[9,21]</sup> Orbital radiation has been seen to potentiate the effects of systemic steroids, and have a beneficial effect on the vision and ocular motility.<sup>[8,22]</sup> Our series had a few patients, who were advised immunosuppressant or orbital radiation along with systemic glucocorticoids. All the patients achieved quiescence of the clinical activity; we are unable to analyze further because of the small number and combined therapy with glucocorticoid.

In several studies, prior use of radioiodine has been associated with increased incidence and severity of TED.<sup>[23]</sup> Our cohort of patients did not show such a predilection. The low proportion of radio-iodine use (about 12%) may have influenced this result.

Smoking and use of tobacco have been associated with increased severity of thyroid eye disease.<sup>[23]</sup> Smoking leads to a higher risk for reactivation of thyroid orbitopathy after surgery. Passive smoking has also been implicated in severe TED.<sup>[24]</sup> However, our case series did not show a correlation between smoking and worsening of eye disease. It is our practice to enquire about tobacco usage habits at the initial visit, and very firmly insist on the patient stopping use of tobacco. This intervention may have influenced the results of our study.

Systemic comorbidities, particularly diabetes mellitus, are associated with increased severity of TED. Diabetes mellitus type two patients are more prone to developing severe orbitopathy, and DON.<sup>[25]</sup> The compromised microvascular disease increases the risk of loss of vision.<sup>[26]</sup> Diabetic patients have worse eye disease, need closer monitoring for blood sugar levels while administering intravenous glucocorticoids, and are more prone to develop radiation retinopathy on use of orbital irradiation.<sup>[27]</sup> In our study, systemic diabetes mellitus was the factor most strongly associated with worse outcome of eye disease. This is particularly relevant, since Indians have a high susceptibility to diabetes.<sup>[28]</sup>

Our patients showed a 14.3% prevalence of DON, and overall 19% patients developed visual morbidities. We

have chosen to combine the three conditions – keratopathy, neuropathy and myopathy – which are most likely to result in the patient being unable to perform his visual tasks. A case series for an endocrinology service in India put the incidence of extraocular muscle involvement at 5% and DON at 2%.<sup>[4]</sup> However, since higher morbidity from the disease is commoner in ophthalmology practices, sensitization of both patients and physicians is appropriate and necessary.

We compared our set of data with available reports from south Asia and southeast Asia. In a study from Singapore, the mix of ethnic Chinese, Malay, and Indian patients showed DON in 4.6% patients, corneal erosions in 19% and epiblepharon in 2.3%, which required surgery.<sup>[15]</sup> This study had 63% female patients. A report from Iran showed 52.4% women patients, with no optic neuropathy, and corneal infiltrates in 18.4%.<sup>[29]</sup> Our series included 53% female patients, with keratopathy in 10% and DON in 14.3%.

## Conclusion

In conclusion, visual morbidities can set in several months after the onset of either dysthyroid condition, or several months after thyroid eye disease. Older age, male gender, and presence of diabetes mellitus are associated with visual morbidity in TED. A large proportion of TED patients attain good vision after treatment for the ocular conditions. We recommend regular comprehensive ocular examination in patients with systemic thyroid dysfunction.

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## Conflicts of interest

There are no conflicts of interest.

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