

Clinical Study of Ocular Manifestations of Thyroid Disease in Tertiary Eye Care Center

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Abstract

Introduction: Thyroid eye disease (TED), Graves' ophthalmopathy, or Thyroid associated orbitopathy (TAO) are an immune-mediated inflammatory disorder that produces expansion of the extraocular muscles and fat in the orbit. TED is most commonly associated with Graves' hyperthyroidism but can also be noted in hypothyroid and euthyroid states.

Aim: The aim of the study is to evaluate the ocular manifestation of thyroid dysfunction (TD).

Materials and Methods: A prospective non-randomized observational study was carried out on 106 patients of TD. They were examined in detail for demography, systemic, and ocular examination and laboratory investigation. Period of study was 1 year.

Results: In this study, average age of presentation of TD was 42.54 years. Female-to-male ratio was 3.1:1. Lid retraction was the most common (82.4%) lid sign in patients of hyperthyroidism while in patients of hypothyroidism, it was lid edema (28.9%). The second most common lid sign was lid lag which was present 70.6% cases. Proptosis was present in 52.9% hyperthyroid patients. Three patients had unilateral proptosis. Corneal ulcer (due to exposure keratopathy) was present in 17.6% of hyperthyroid patients.

Conclusion: Females were more commonly affected. However, ocular manifestations were more severe in male. Hence, it is important to rule out TD in patient with other ocular symptom.

Key words: Graves' ophthalmopathy, Thyroid-associated orbitopathy, Thyroid eye disease

INTRODUCTION

TED, GO, or TAO is an immune-mediated inflammatory disorder that produces expansion of the extraocular muscles and fat in the orbit. TED is most commonly associated with Graves' hyperthyroidism but can also be noted in hypothyroid and euthyroid states.^[1]

It is part of a systemic process with variable expression in the eyes, thyroid and skin caused by autoantibodies that bind to tissues in those organs and in general, occurs with hyperthyroidism. The most common form of

hyperthyroidism is Graves' disease. About 10% of cases do not have Graves' disease but do have autoantibodies. The autoantibodies target the fibroblasts in the eye muscles, and those fibroblasts can differentiate into fat cells (adipocytes). Fat cells and muscles expand and become inflamed. Veins become compressed and are unable to drain fluid causing edema. Swelling of the fatty tissue can cause the eyes to become red. This can also cause the eyes to be pushed forward (staring eyes and proptosis). In severe cases, the damage at the back of the eye can cause swelling and stiffness of the muscles that move the eye causing double vision, especially when you look from side to side as the muscles cannot keep the eyes exactly in line with each other.^[2]

The acute progression of the disease is an ocular emergency, particularly optic nerve compression and corneal disease secondary to exposure. However, TED may occur in patients who have hypothyroidism (most commonly Hashimoto's thyroiditis) or euthyroidism. The two most serious signs are optic neuropathy and exposure

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keratopathy as both can abruptly lead to blindness, so they should be treated as ocular emergencies.^[3]

It has been established that receptors of thyroid hormones are present in all tissues and organs of the body. It is quite credible that tonicity of ciliary muscles (smooth fibers) also depends on the activity of thyroid gland. That is why hyperthyroidism can cause refractive changes, mostly those of myopia.^[4]

There are several risk factors of thyroid disease. Smoking is one of them; smoking is a risk factor for the development of TAO, an inflammatory process primarily affecting the fibroblasts in extraocular muscles.^[5]

TD and diabetes mellitus are endocrine disorders most commonly seen in clinical practice. Both mutually influence each other and reported as has been reported in literature. On the one hand, thyroid hormones effects carbohydrate metabolism, and on the other hand, diabetes influences thyroid function. Many trials have shown immunological and genetic correlation between the two types of disorders.^[6,7]

Aims and Objectives

1. To study the different types of ocular manifestation of thyroid disease
2. To assess the risk factors associated with TED
3. To find the association of thyroid disease with diabetes mellitus.

MATERIALS AND METHODS

This prospective study was carried out in the Department of Ophthalmology, S. S. Medical College and Gandhi Medical Hospital, Rewa, Madhya Pradesh, India, during the period from March 2016 to September 2017.

Case Selection

A total of 220 eyes of 110 patients attending the outpatient department, having TD, and fulfilling the following criteria were enrolled in the study.

Inclusion Criteria

- a. All patients with diagnosed thyroid disease
- b. Age >15
- c. Those who are willing to sign informed consent form.

Exclusion Criteria

- a. Congenital thyroid disease
- b. Ocular manifestation of other systemic diseases
- c. Any other ophthalmic disorder
- d. Undergone any ophthalmic surgery
- e. Those not willing to sign the consent form.

Data Collection and Method

Participants who satisfy all inclusion criteria and meet no exclusion criteria were included in the study. Informed consent was taken. The purpose of study was explained to the participants, and confidentiality was assured.

After taking a verbal consent, a detailed clinical history was taken including the chief visual complaint, history of present illness, past history, personal history, medical history, family, and professional history. General examination and systemic examination were done; all positive findings were recorded. Ocular manifestations of TED were classified according to the NOSPECS classification of TAO.

Investigations

Thyroid function test of T₃, T₄, and *thyroid-stimulating hormone* was sent all patients if not done. Color vision was performed. Visual field test was done in case of open-angle glaucoma. In cases of corneal ulcer, corneal scraping and culture were done. B scan for orbit was performed in all cases of proptosis. Computed tomography scan was ordered in cases of proptosis and with any one of the signs of vision threatening condition like exposure keratopathy, squint and optic neuropathy.

Data Analysis

Statistical analyses were performed. Pearson's Chi-square test, likelihood ratio, and Fisher's test were used for the comparison of categorical variables, and Student's *t*-test was used for the comparison of continuous variables. Finally, a $P < 0.05$ was considered as statistically significant. Mean was used as a measure of central tendency. Similarly, standard deviation (SD) and range were used as a measure of dispersion. The prevalence was calculated in percentage at 95% confidence interval.

Table 1: Number of smokers and non-smokers

Thyroid status	Frequency (%)	
	Smokers	Non-smokers
Hyperthyroid (n=19)	12 (63.2)	7 (36.9)
Hypothyroid (n=80)	13 (16.3)	67 (83.8)
Euthyroid (n=11)	-	11 (100)
Total (n=110)	25 (22.7)	85 (77.3)

Table 2: Distribution of diabetes mellitus in the study population

Thyroid status	Frequency (%)	
	Diabetic	Non-diabetic
Hyperthyroid (n=19)	12 (63.2)	7 (36.9)
Hypothyroid (n=80)	16 (20.0)	64 (80)
Euthyroid (n=11)	-	11 (100)
Total (n=110)	28 (25.5)	82 (74.5)

For risk factor, univariate as well as multivariate analysis were performed, and odds ratio was calculated. The level of significance was set at 95%.

RESULTS

According to history, clinical examination, ocular examination, and laboratory investigation, patients were divided into three group hyperthyroid, hypothyroid, and euthyroid.

The maximum number of patients was found in the age group of 41–50 year which is 39.09% of the cases, and the next highest number of patients was found in the age group 31–40 (30.90%). Mean age of patients was 42.54 years (SD-9.5). Among 110 patients studied, 24.54%

were males and 75.5% were females. In this study, ratio is F:M = 3.1:1. Among 110 patients, 19 (17.3%) were hyperthyroid, 80 (72.7%) were hypothyroid, and 11 (10%) patients were euthyroid.

Among 110 patients, 25 (22.7%) were smokers. There was a significant association of smoking with thyroid disease ($P < 0.05$) [Table 1].

Among 110 patients, 28 (25.5%) were diabetic. There was a significant association of diabetes mellitus with thyroid disease ($P < 0.05$) [Table 2].

Table 3 shows the ocular manifestation in study group. Among 110 patients, 55 patients had ocular manifestation. Out of 55 patients, 17 (30.9%) patients of hyperthyroid had ocular manifestations and 38 (69%) patients of hypothyroid had ocular manifestations.

Table 4 shows the frequency of different symptoms among the study group. Most of the patients came with complaint of foreign body sensation (38.4%). The second most common symptom was itching (36.4%). Lid swelling and proptosis were common.

Table 5 shows the different types of signs among these two groups. In hyperthyroid lid, retraction was more common (82.4%). In hypothyroid lid, edema was more common (28.9%). Frequency of dry eye syndrome in patients with TD was present; 29 (26.4%) patients had dry eye disease. In hyperthyroid patients, 9 (47.4%) had dry eye syndrome, and in hypothyroid, 20 (25%) patients had dry eye syndrome. In the study group, the mean value of exophthalmometry was 16.73 with 1.79 SD. The association was statistically significant ($P < 0.05$). Among 110 patients, proptosis was present in 9 patients in which 6 patients had bilateral proptosis and 3 patients had unilateral proptosis. Most of the patients were myopic. There was a significant association ($P = 0.006$) of refractive error in thyroid. Among 110 patients, 42 (38.2%) were myopic and 13 (11.8) were hypermetropic.

Table 3: Ocular manifestations (n=55)

Thyroid status	Frequency (%)		
	Male	Female	Total
Hyperthyroid	7 (12.7)	10 (18.2)	17 (30.9)
Hypothyroid	8 (14.5)	30 (54.5)	38 (69.0)
Total	15 (27.3)	40 (72.7)	55 (100)

Table 4: Symptoms of thyroid eye disease patients (n=110)

Symptoms	Frequency (%)
FB sensation	42 (38.2)
Itching	40 (36.4)
Dry eye	29 (26.4)
Lid swelling	16 (14.5)
Difficulty in reading	16 (14.5)
Redness	14 (12.7)
Protrusion of eye	9 (8.2)
Diminution of vision	6 (5.5)
Watering	3 (2.7)
Double vision	1 (0.9)
Others	6 (5.5)

FB: Foreign body

Table 5: Signs in thyroid eye disease

Signs	Hyperthyroid (n=17), n (%)	Hypothyroid (n=38), n (%)	P
Lid edema (Enroth's sign)	8 (47.1)	11 (28.9)	0.000
Lid retraction (Dalrymple sign)	14 (82.4)	-	0.000
Lid lag (Graefe's sign)	12 (70.6)	-	0.000
Conjunctival congestion	11 (64.7)	3 (7.8)	0.000
Corneal ulcer	3 (17.6)	1 (2.6)	0.000
Proptosis	9 (52.9)	-	0.000
Scleral show	9 (52.9)	-	0.000
Increased palpebral aperture	16 (94.1)	-	0.000
Restrictive myopathy	1 (5.9)	-	0.000
Refractive error	17 (100)	38 (100)	0.006
Increase IOP with optic disk and visual field change	1 (5.9)	-	0.000

IOP: Intraocular pressure

DISCUSSION

Thyroid disease is an autoimmune disorder, affects females more commonly, and is seen in the 4th and 5th decades of life and commonly in females as cited by many previous studies. The mean age of presentation of the TED was 42.54 years in our study. This was similar to the results of Bartley *et al.*^[8] who reported median age as of 43 years and 39.7 years by Palikhe Sabita *et al.*^[9] who documented 39.7 years as the median age.

There was female preponderance in our study. Out of 110 patients, 83 (45.46%) were female and 27 (24.54%) were male. This was similar to the results of Palikhe *et al.*^[9] who reported 80 (68.4%) patients were females and 37 (31.6%) were male. We found that there is a significant association of TD and diabetes mellitus. In hyperthyroid patients, 63.2% had diabetes mellitus, and in hypothyroid, 19.3% had diabetes mellitus which was similar to results shown by Demitrost and Ranabir^[10] and Maskey *et al.*^[11]

In our study, we observed a significant association of smoking with TD. History of smoking was positive in 22.7% similar to results shown by Tellez *et al.*^[12]

The prevalence of TED in TD in our study was 50%. Variable prevalence rates have been reported in literature. It was reported as low as 17.3% by Woo *et al.*^[13] and as high as 51.7% by Manji *et al.*^[14] and 71.7% by Palikhe *et al.*^[9] The difference in the prevalence of TED between our study and others may be attributed to the definition of TED in our study. We have defined TED as the presence of any one sign of TED (NOSPECS), while other studies have taken at least two signs. In a study done in India by Kashkouli *et al.*,^[15] the prevalence was 35.6%.

TED can occur in any form of TD either hyper, hypo, or euthyroid state. In our study, out of 55 TED patients, 17 (30.8%) were hyperthyroid and 38 (69.2%) were hypothyroid. The study by Palikhe *et al.*^[9] showed that out of 84 TED patients, 63 (75%) were hyperthyroid, 14 (16.7%) were hypothyroid, and 7 (8.3%) were euthyroid. A study reported by Bartley *et al.*^[8] at Mayo Clinic, Rochester, USA, has cited that 90% patients were hyperthyroid, 6% euthyroid, 1% had primary hyperthyroidism, and 3% had Hashimoto's thyroiditis [Figure 1].

Our study showed that eyelid retraction [Figure 2] was present in 82.4% ($n = 17$) which was similar to results of Palikhe *et al.*^[9] by 79.8% and Bartley *et al.*^[8] by 90%. Another study by Saks *et al.*^[16] reported that lid retraction was present in 98% of the patients. Similarly, lid lag [Figure 3] was present in 70.6% ($n = 17$) of cases in our study while it was

reported as 76.2% by Palikhe *et al.*^[9] and 43.33% by Bartley *et al.*^[8] This difference could be due to ethnic variation and also due to varying degree of disease severity.

Exophthalmos is the most widely known sign of TED and occurs in 20%–30% of patients with Graves' disease and up to 40%–70% of patients with thyroid-associated ophthalmopathy. It is bilateral in 80%–90% of cases. In our study, exophthalmos was present in 52.9% ($n = 17$) cases of hyperthyroid which was similar to that in study by Palikhe *et al.*,^[9] they found 33.3% cases out of which 68% and Jarusaitiene *et al.*^[17] found 65.8% cases of proptosis [Figure 4 and 5].

Restrictive extraocular myopathy was seen in only in 5.9% in patients with hyperthyroidism. This finding is similar to that found in the study by Palikhe *et al.*^[9]

In our study, corneal ulcer was seen in 17.6 % of cases of hyperthyroidism. Bartley *et al.*^[8] reported 10% of cases with corneal involvement and Palikhe *et al.*^[9] reported 7.1% cases of corneal ulcer.

We found diplopia was noted in 0.9 % cases. Bartley *et al.*^[8] reported 17% of the patients presenting with diplopia. Palikhe *et al.*^[9] reported 4.8% cases.

In our series of the patients, most common complaints of patients were foreign body sensation, itching, and painless swelling of the lid [Figure 6]; this was consistent with that noted by Palikhe *et al.*^[9] Diminution of vision was present in 5.5% of cases which was in accordance with the study of Bartley *et al.*^[8] who reported decreased vision in 5%–9% of cases while Palikhe *et al.*^[9] reported 1.2% of cases of reduced visual acuity.

TED has been found to be usually associated with glaucoma. The possible cause of increased intraocular pressure (IOP) and thus causing optic neuropathy might be increased episcleral pressure which hinders the outflow thus increasing IOP. The other mechanism of increased IOP might be compression of the globe by inflamed and fibrosed inferior rectus muscle.



Figure 1: Thyroid gland enlargement



Figure 2: Dalrymple's sign (lid retraction)



Figure 3: Von Graefe's sign

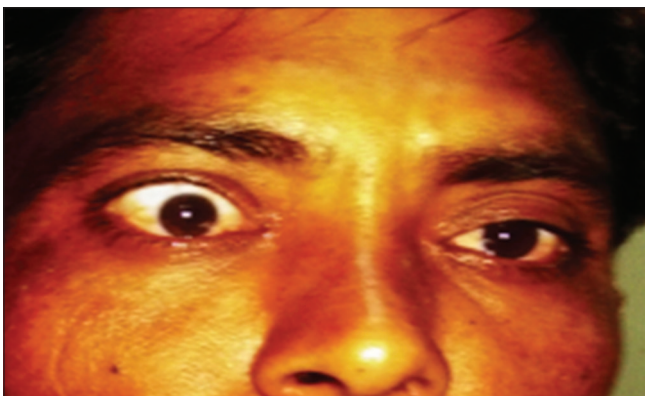


Figure 4: Unilateral proptosis

In our study of the total number of patients with TED, 55 patients, in which accounted for 17 (30.9%) cases, had hyperthyroid. Out of 17, only 1 case (5.9%) had primary open-angle glaucoma and 3 cases were glaucoma suspects. Palikhe *et al.*^[9] found 8.3% cases of primary open-angle glaucoma, Cross *et al.*^[18] found 6.5% cases of primary open angle glaucoma, and Sultana *et al.*^[19] reported 7.5% cases of primary open-angle glaucoma. Cockerham *et al.*^[20] reviewed 500 patients with TED and found 120 (24%) had increased IOP. Of this, 2% developed glaucomatous field defect over a follow-up of 48 months.

In our study, most of the patient with TED had myopic shift, with 63.2% cases having hyperthyroidism



Figure 5: Kocher's sign (staring look)



Figure 6: Enroth's sign (fullness of eyelids)



Figure 7: Lagophthalmos

and 37.5 % cases having hypothyroid. Only 21.2% of hyperthyroid patients and 11.2% of hypothyroid patients had hypermetropia. Jankauskiene *et al.*^[21] found that the excess of thyroid hormones brought about by the mutation of receptors of thyroid hormones had an influence on the development of myopia. Chandrasekaran *et al.*^[22] noted that myopic shift after decompression is consistent with mechanisms involving the posterior pole. Combination of enlarged extraocular muscles, anterior displacement of the globe, and orbital hypertension related to elevated muscle and fat volumes in endocrine ophthalmopathy flattens the posterior pole, which may produce choroidal folds.

Other ocular pathology like dry eyes was seen in 47.4% ($n = 19$) hyperthyroid and 20% ($n = 80$) hypothyroid



Figure 8: Computed tomography scan showing medial rectus muscle hypertrophy

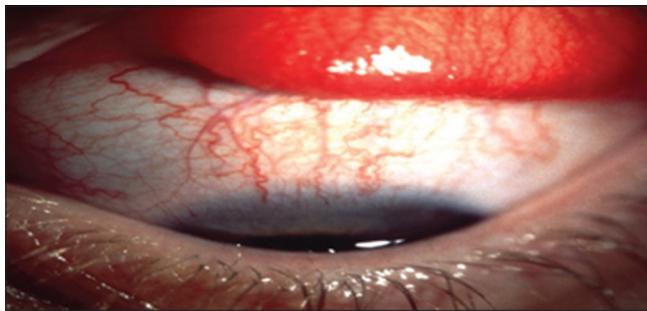


Figure 9: Superior limbic keratoconjunctivitis

patients in our study. This may be due to exposure or due to the immunological process associated with TED. It is cited in literature that five factors potentially associated with corneal exposure-palpebral fissure width, exophthalmos, lagophthalmos [Figure 7], and lid lag. All the factors were evaluated in 19 patients with Graves' disease in a study to determine which were associated with ocular surface damage. Multiple regression analysis revealed that increased palpebral fissure width and proptosis were both significant predictors of ocular surface damage. However, Schirmer test score and tear film breakup time value were not significant predictors. This finding was similar to that in study by Gürdal *et al.*^[23] but dissimilar to that in study by Eckstein *et al.*^[24] who found that Schirmer test and tear film breakup time were significant predictors [Figure 8 and 9].

CONCLUSION

- TED affects the majority of thyroid disease patients. The ocular manifestations were present 52.28% patients
- Females are affected most commonly but severity of disease more in males. The common lid manifestation was lid lag and lid retraction
- Ocular manifestations are more in hyperthyroidism than hypothyroidism.

Limitations of Study

- Since our sample size was small due to lesser number of patients attending outpatient department, this was insufficient to estimate the exact prevalence of ocular manifestations of thyroid disease
- Some patients with TD were taking systemic steroid and other immunosuppressive drug due to some other systemic disease, these drugs are known to be having anti-inflammatory effects, and this can be a confounding factor in our study
- The presence of severe degree of eye involvement in our set up may be due to late presentation and due to unawareness of their disease process at presentation. It may be due to our center being tertiary eye center, and we get majority of complicated and referred cases.

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