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PREVALENCE OF THYROID EYE DISEASE AND VARIOUS OPHTHALMIC MANIFESTATIONS, IN PATIENTS WITH THYROID DISORDERS ATTENDING A TERTIARY CARE HOSPITAL, TELANGANA, INDIA.

Dr. K Rajeshwar[1], Dr.NavneethServey[2], Dr. S Kapil Sai[3], Dr.Doddoju Veera Bhadreshwara Anusha[4*]

[1]Assistant Professor, Department of General Medicine, RVM medical college, Telangana India.

[2]Assistant Professor, Department of Ophthalmology, RVM medical college, Telangana India.

[3]Assistant Professor, Department of Ophthalmology, RVM medical college, Telangana India.

[4*]Associate Professor, Department of Community Medicine, RVM institute of medical sciences and research centre.

Corresponding Author: Dr.Doddoju Veera Bhadreshwara Anusha
Associate professor, Department of Community Medicine, RVM institute of medical sciences and research centre, H.NO: 2-51/1Laxmakkapally village, Mulugu mandal, Siddipet District, Telangana.

Abstract:

Introduction: Thyroid eye disease (TED) is the most common extra thyroidal manifestation of Graves' disease. TED is characterized by inflammatory reactions to the orbital and periocular tissues which cause discomfort and pain and also result in eyelid malposition and exophthalmos, distorting self-image and provoking psychological or social problems. The activity and severity of thyroid eye disease is diverse as well. Hence the current study was undertaken to understand the prevalence of various manifestations of Thyroid eye disease and its associated factor, which would guide further in appropriate management and patient care.
Methodology: A hospital based cross-sectional study was done in 400 adult patients with thyroid dysfunction attending tertiary care hospital, after obtaining ethical committee clearance. Patients' with-out thyroid dysfunction with other ocular manifestations, incoherent patients and those who were not willing to participate were excluded. Patients were selected by convenient sampling method during study period of February 2020 to February 2023.Detailed systemic medical and ophthalmological examination was done. Data collected using semi structured questionnaire. Statistical analysis was done in SPSS version 20, using student t test and chi-square test with $P<0.05$ considered as statistically significant.

Results: Out of the 400 patients in this study, there were 175(43.5%) males and 225(56.5%) female patients. Age ranges from 18-78 years with mean ± Standard deviation (SD) of age being 48.14 ± 15.82. TED was seen in 168(42%) of patients. CAS score ≥ 3 was seen in 62 (15.5%) patients.Foreign body sensation was the most common eye manifestation seen in 256(64%), followed by dry eye in 171(42.75%).

Conclusion: Mean TSH and CAS score was high in patients with TED when compared to patients with- out TED. Higher mean age, male gender, hypothyroid status, higher mean duration of thyroid disorder, lower free T3, lesser free T4, higher TSH, and smoking were significantly associated with patients with CAS ≥3.

Keywords: Thyroid eye disease, prevalence, ophthalmic manifestations, tertiary care, risk factors.

INTRODUCTION

Thyroid eye disease (TED) is the most common extra thyroidal manifestation of Graves' disease. TED is characterized by inflammatory reactions to the orbital and periocular tissues which cause discomfort and pain and also result in eyelid malposition and exophthalmos, distorting self-image and provoking psychological or social problems [1,2].It is associated with hyperthyroidism in 90% of cases, up to 5% of patients may be Euthyroid at the time of onset of the eye disorder and about 5% may be hypothyroid [1,3,4].

Ocular manifestations of thyroid disease range from mild symptoms of ocular irritation, lid retraction, lid lag, and ocular injection to signs of orbital infiltration such as chemosis, proptosis and restriction of ocular motility, corneal exposure, and optic nerve compression. These infiltrative orbital changes have also been characterized into two main types based on different mechanisms of pathogenesis. Type I orbitopathy is characterized as predominantly fat deposition, while type II orbitopathy involves predominantly extraocular muscle enlargement [5]. Orbital infiltration is marked by conjunctival injection, chemosis, and protusion of the globe (proptosis or exophthalmos, when bilateral).

The extraocular muscle changes lead to more serious complications, such as strabismus or visual disturbances. The activity and severity of thyroid eye disease is diverse as well. Hence the current study is undertaken to understand the prevalence of various manifestations of Thyroid eye disease and its associated factor, which would guide further in appropriate management and patient care.

METHODOLOGY

A hospital based cross-sectional study was done in adult patients with thyroid dysfunction attending tertiary care hospital, after obtaining ethical committee clearance. Patients with-out thyroid dysfunction with other ocular manifestations, incoherent patients and those who were not willing to participate were excluded. Patients were selected by convenient sampling method during study period of February 2020 to February 2023.

Sample size was calculated by using the formula,

Sample size = Z2p (1-p)/d2 Where Z (Is standard normal variate) = 1.96 at 5 % level of significance p =40% (as per study by Dahal P et al)[6] d (precision) = 5% Taking the later value, the sample size of the study would be, Sample size= 1.962×0.40 (1-0.40)/0.05 2 = 369, with 10% nonresponse rate sample size was 400.

Information obtained from participants included demographic details, smoking history, duration of thyroid dysfunction, systemic and ocular symptoms (includes foreign body sensation, Redness, Proptosis, Keratopathy, Lid swelling, Chemosis). Detailed systemic medical and ophthalmological examination was done. The diagnosis of thyroid dysfunction was based onclinical evaluation, thyroid hormone level, and classified intohyperthyroid, hypothyroid, and Euthyroid. The diagnosis ofTED was clinical and based on thyroid disorder

associated witha specific one of the thyroid eye signs [7,8,9]. Patients with TED werefurther evaluated for disease activity (Mourits Clinical activityscore [CAS])[9].

Procedure: Systemic examination included general physical examination, blood pressure and cardiovascular evaluation, and palpation of the neck. Visual acuity (unaided, with previous glass and with pinhole) was measured with self-illuminated Snellen chart at 6-meter distance at room illumination assessing subjective as well as objective refraction. Extra ocular movement and cover test were performed with the help of torch light in all the cardinal gazes and any restriction or over action was noted. Forced duction test was performed in cases with restricted extraocular motility to differentiate restrictive and paralytic. Detail examination of lid was done with the help of torchlight to see if there was any eyelid sign of thyroid eye disease.The signs that were looked for were Lid retraction (Dalrymple's sign), Lid lag, Enroth's sign (Edema especially of the upper eyelid), thin tremors when closed eyelid (Rosenbach's sign). Simple ruler scale was used for evaluation of upper lid retraction [10]. Schirmers test was used for the evaluation of dry eye disease and was considered negative if more than 10 mm of wetness of the Schirmers strip over 5 minutes.

Proptosis is measured clinically as the corneocanthal distance (horizontal distance from the lateral canthus to the apex of the cornea) taken with an exophthalmometer. In this study, a corneocanthal distance of 21 mm was defined as the limit for the diagnosis of proptosis in accordance with the guidelines of the European Group for the study of Graves' Ophthalmopathy [11]. Detail examination of conjunctiva, cornea and anterior segment was done with the help of torch light followed by Haag Streit 900 Slit lamp biomicroscopy to find out any abnormalities present. Presence of congestion at the site of insertion of extra ocular muscle, superior limbic keratoconjunctivitis, and any tear film abnormalities were noted. Pupillary light reflex both direct and consensual was noted using bright torch light. Fundus examination was done after pupillary dilatation using eye drop Tropicamide 1% with the help of direct and indirect ophthalmoscope and using + 90 lens in selected cases wherever necessary. IOP was taken with the help of Goldman applanation tonometer attached to the slit lamp in primary and up gazes.

Data analysis: All the data was entered in to MS office 2019 and analysis was done using SPSS version 20. Data represented as proportions, mean and SD and bar diagrams. Statistical analysis was done using student t test and chisquare test with $P<0.05$ considered as statistically significant.

RESULTS

Out of the 400 patients in the study, there were 175(43.5%) males and 225(56.5%) female patients. Age ranges from 18-78 years with mean ± Standard deviation (SD) of age being 48.14 ± 15.82, with majority belonging to 40-60(42%) years age group. Other comorbidities found were hypertension in 128(32%) patients, diabetes mellitus in 66(16.5%) patients, coronary heart disease in 15 (3.75%), cerebro-vascular disease in 4(1%) and other inflammatory conditions in 10 (2.5%). Addictions present were smoking in 45(11.25%) and alcohol in 62(15.5%) patients. With respect to type ofthyroid disorder, hypothyroid patients

were 192 (48%), hyperthyroid were 128 (32%) and euthyroid were 80 (20%). About 58% were suffering from Thyroid disorder for more than 5 years. (shown in table 1)

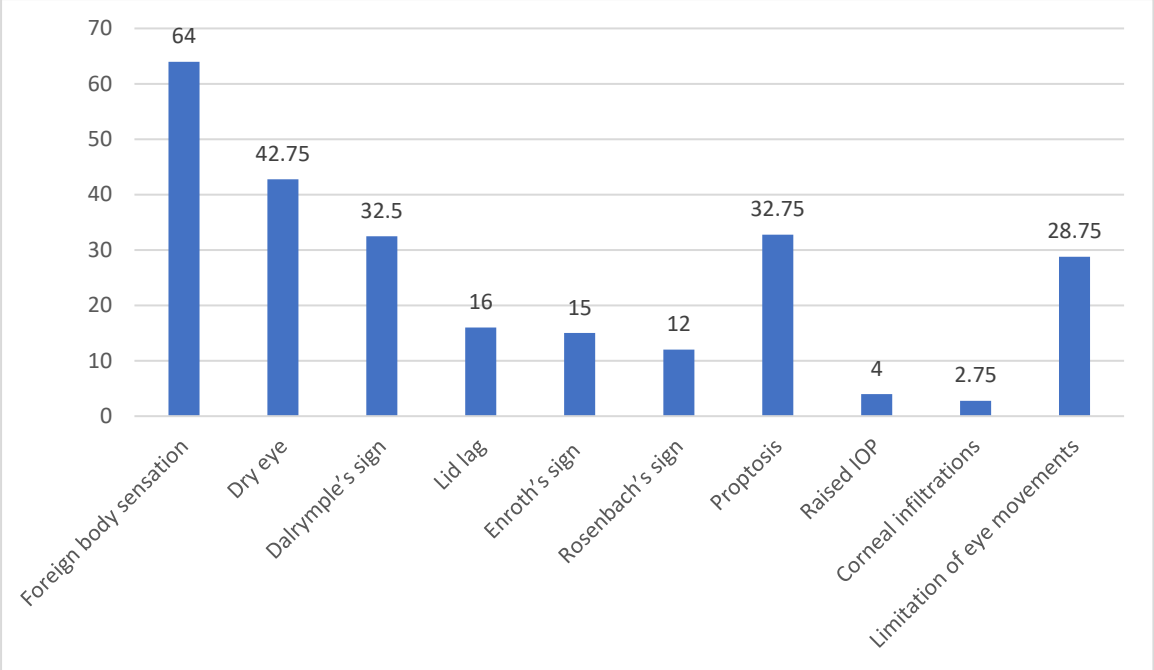
TABLE 1: PATIENTS BY AGE, SEX AND DURATION OF TYPE2 DM

Socio-demographic detail	Category	Frequency (n=400)	Percentage
Age in years	18-40	92	28%
	41-60	168	42%
	>60	120	30%
Sex	Male	175	43.5%
	Female	225	56.5%
Other comorbidities	Hypertension	128	32%
	Diabetes mellitus	66	16.5%
	Coronary heart disease	15	3.75%
	Cerebro vascular disease	4	1%
	Other inflammatory conditions	10	2.5%
Addictions present	Smoking	45	11.25%
	Alcohol	62	15.5%
Duration Of Thyroid disorder	< 5 year	232	58%
	≥ 5year	168	42%
Type of thyroid disorder	Hypothyroid	192	48%
	Hyperthyroid	128	32%
	Euthyroid	80	20%

TED was seen in 168(42%) patients. Foreign body sensation was the most common eye manifestation seenin 256(64%) patients, followed by dry eyein 171(42.75%), dalrymple's sign in 130 (32.5%), lid lag in 64(16%), enroth's sign in 60(15%), rosenbach's signin 48(12%), proptosis in 131(32.75%), raised IOPin16(4%), cornealinfiltrations in

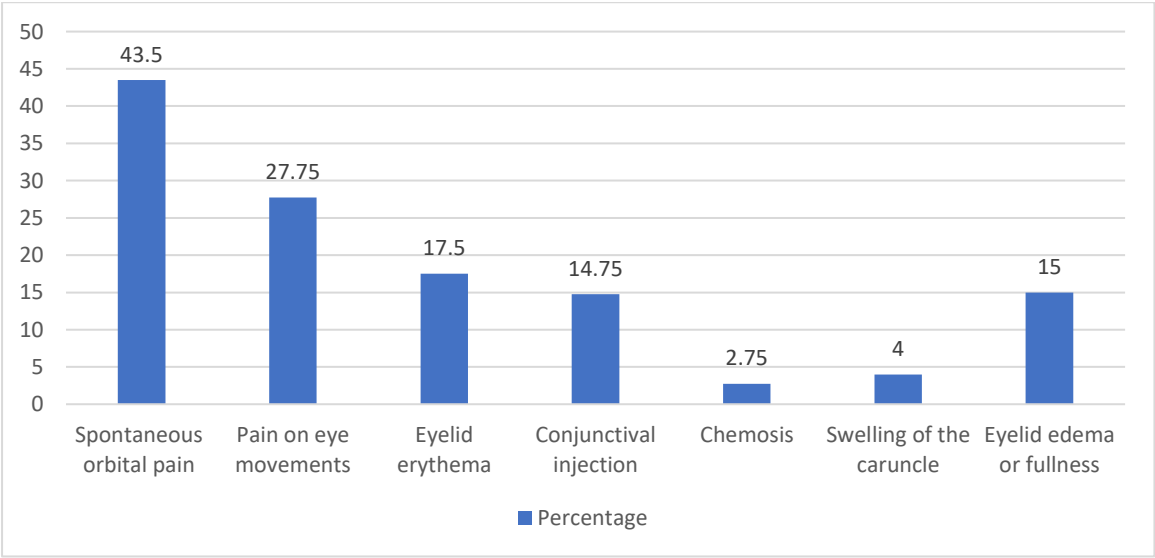
11(2.75%) and limitation of eye movements in 115(28.75%) of total study participants. (figure 1)

Figure 1: Prevalence of clinical eye symptoms and signs assessed



Spontaneous orbital pain was seen in 174(43.5%) of patients, pain on eye movements in 111(27.75%), eyelid erythema in 130 (17.5%), conjunctival injection in 59 (14.75%), chemosis in 11(2.75%), swelling of the caruncle in 16 (4%) and eyelid edema or fullness in 60(15%). CAS score ≥ 3 was seen in 62 (15.5%) patients. (figure2)

Figure 2: Prevalence of various symptoms of thyroid eye disease as per clinical activity score (CAS)



Mean TSH and CAS score was high in patients with TED when compared to patients with-out TEDwhich was statistically significant. More proportion of patients with hypothyroidism (46.3%) have TED compared to euthyroid (27.5%) and hyperthyroid (44.5%) which was significant statistically. Mean of free T3, T4in patients with TED was low compared to patients without TED alsomean TSHin patients with TED was high compared to patients without TEDwhichwas significant.There was no significant difference in mean age, gender distribution and duration of thyroid disorder in patients with TED compared to patients with-out TED. (table 2)

Table 2: Distribution of variables in patients with various type of thyroid disorder

Characteristics		TED present (168)	TED absent (232)	Chi-square or Anova test/ P value
Age in years (mean ± SD)		46.6±4.9	47.2±6.7	0.98/0.325
Gender	Male	73	102	0.01/0.918
	Female	95	130	
Duration of Thyroid disorder in years (mean ± SD)		5.7±2.9 years	4.3±4.9 years	1.36/0.17
Thyroid disorder status	Euthyroid	22 (27.5%)	58 (72.5%)	8.73/0.0127
	Hypothyroid	89 (46.3%)	103 (53.7%)	
	Hyperthyroid	57 (44.5%)	71 (55.5%)	
Free T3 (pg/ml) (mean ± SD)		3.11±2.1	3.7±1.5	3.27/0.0011
Free T4 (µg/dl) (mean ± SD)		5.6±2.7	6.7±2.1	4/0.0.0001
TSH (µg/dl) (mean ± SD)		16±2.7	5.9±2.1	6.246/0.0001
CAS score (mean ± SD)		4.9±2.1	3.2±3.9	5.135/0.0001
Addictions	Smoking	26	19	5.18/0.02283
	Alcohol	30	32	1.288/0.2679

Higher mean age, male gender, hypothyroid status, higher mean duration of thyroid disorder, lower free T3, lesser free T4, higher TSH, and smoking were significantly associated with patients with CAS ≥3. (table 3)

Table 3: Distribution of characteristics in patients versus clinical activity score

Characteristics		CAS <3 (338)	CAS ≥3 (62)	Chi-square or t test/ P value
Age in years (mean ± SD)		42.6±7.3	54.2±9.7	10.89/0.0001
Gender	Male	139(21.7%)	36(33.1%)	6.10/0.013
	Female	199(18.7%)	26 (31.1%)	
Thyroid disorder status	Euthyroid	72	8	15.667/0.00039
	Hypothyroid	148	44	

	Hyperthyroid	118	10	
Duration of Thyroid disorder in years (mean ± SD)		4.5±2.7 years	5.9±4.2 years	3.40/0.0007
Free T3 (pg/ml) (mean ± SD)		5.11±7.1	1.5±2.3	3.962/0.0001
Free T4 (µg/dl) (mean ± SD)		6.5±2.4	4.8±6.5	3.652/0.0003
TSH (µg/dl) (mean ± SD)		4.2±3.1	9.1±6.2	9.4692/0.0001
Addictions	Smoking	39	16	8.993/<0.0027
	Alcohol	50	12	0.775/0.082

DISCUSSION

Thyroid eye disease is the most common public health problem which can progress to sight threatening eye disease.

Current study was done in 400 patients, with 175(43.5%) males and 225(56.5%) female patients. Age range was from 18-78 years with mean ± Standard deviation (SD) of age being 48.14 ± 15.82, and majority belonging to 40-60(42%) years age group. Similarlyin study by Sabita P et al, A total of 117 cases, 80 female (68.4%) and 37 male (31.6%), of thyroid dysfunction were included. The mean age of presentation was 39.7 years that ranged from 17 - 65 years [12]. Also study by Choudhari P.C et al found that most common age group affected with thyroid disease was 41-50 yearsand, females were seen to be more commonly affected than men. 54 out of 72 patients were females and 18 were males [13]. In study by Nabi T et al, the mean age of the patients with thyroid disorder was 42.4 ± 10.2 [14].Like in other studies, the present study also supports that thyroid eye disease is more commonly seen in women than in men.

In this study with respect to type of thyroid disorder, Hypothyroid patients were 192 (48%), Hyperthyroid were 128 (32%) and euthyroid were 80 (20%). Similarly in study by Vijayleela et al, cohort of 201 patients with thyroid dysfunction, 42.7% (86) were hyperthyroid, 55.22% (111) were hypothyroid, and 1.99% (4) euthyroid [15].Incontrast study by Choudhari P.C et al 72 patients were studied, 36 patients were found to be of hypothyroid status, 34 patients were having hyperthyroidism.[13]

In this study prevalence of TED in patients with thyroid dysfunction was 42% and also more common in patients with hypothyroidism. Similarly in study by Dahal P et al, out of 320 patients the prevalence of Thyroid eye disease was 40%, and is more prevalent in hypothyroid patients [6]. In contrast study by Woo KI et al, thyroid eye disease prevalence was low it showed TED in 283 (17.34%; 95% CI, 15.50 to 19.18) of the 1,632 patients examined (225 females and 58 males, female-to-male [3.9 : 1]) [16].How ever in study by Lavaju P et al, among the recruited patients, the prevalence of TED was 40.8% (n = 82), of which 46 patients (56%) were hyperthyroid, 34 (41.4%) hypothyroid, and 2 (2.32%) euthyroid, TED was statistically significantly associated with hyperthyroid (P = 0.005). (n = 82), [17].

In our study CAS score ≥ 3 was seen in 62 (15.5%) of patients. Similarly in study by Nabi T et al the disease was of mild in severity in majority number of the patients (34 [65.4%]) and moderate to severe in 18 (34.6%) patients. None of the patients had any evidence of sight-threatening disease [14].

In this study, foreign body sensation was the most common complaint seen in 256(64%) patients, followed by dry eye in 171(42.75%), dalrymple's sign in 130 (32.5%), lid lag in 64(16%), enroth's sign in 60(15%), rosenbach's sign in 48(12%), proptosis in 131(32.75%), raised IOP in 16(4%), corneal infiltrations in 11(2.75%) and limitation of eye movements in 115(28.75%) of total study participants. Whereas in study by Medghalchi A et al, most common findings in clinical examinations were eye movement limitation in 101 (98%) patients, eyelid retraction in 91 patients (88.3%), and proptosis in 57 patients (55.33%), which were bilateral in 96.1%, 31.1%, and 33%, respectively. Corneal infiltrations were found on examination in only 19 (18.4%) patients in the right eye and in 15 (14.6%) patients in the left eye [18]. In study by Lavaju P et al, the most common thyroid eye sign was Dalrymple sign (eyelid retraction in primary gaze) in 80%, followed by Enroth's sign (puffiness of eyelid) in 75.6% [17].

In this study spontaneous orbital pain was seen in 174(43.5%) patients, pain on eye movements in 111(27.75%), eyelid erythema in 130 (17.5%), conjunctival injection in 59 (14.75%), chemosis in 11(2.75%), swelling of the caruncle in 16 (4%) and eyelid edema or fullness in 60(15%). In study by Lavaju P et al, foreign body sensation was the most common presenting symptoms (56%), followed by burning sensation (43.9%), bulging of eyes (39%), redness (25.6%), and watering (1.21%) [17].In study by Sabita P et al majority of patients (63%) presented with ocular symptoms, consisting mainly of tearing, foreign body sensation, ocular injection, blurring of vision, and photophobia. Diplopia was rare. Only four patients (5.3%) reported diplopia, and this was intermittent in nature. A third of patients had no ocular symptoms at all. [12]

In our study there was no significant difference in mean age, gender distribution and duration of thyroid disorder in patients with TED versus with-out TED. As per study by Woo KI et al, there was no difference in the prevalence of thyroid eye disease between genders (females, 225 / 1,301 [17.3%]; males, 58 / 331 [17.5%]; p = 0.6847) [16]. In study by Medghalchi A et al, the mean duration of thyroid disease in patients with TED was 69.04 ± 80.3 (range, 3–480) months [18]. In study by Woo KI et al, Multivariable logistic regression analyses for thyroid eye disease revealed that female gender, Graves' disease, dermopathy, anti-thyroid medication, and radioiodine treatment were strongly associated with thyroid eye disease. The risk of thyroid eye disease was shown to be lower with age.[16].Study by Nabi T et al, On multiple logistic regression analysis, which included all patients with GO, male gender, current smoking, TRAb>2 upper limit of normal (ULN), and differential IOP >6 mmHg were found to be associated with severe GO.[14].

In this study mean TSH and CAS score was high in patients with TED when compared to patients with- out TED which was statistically significant and CAS score ≥ 3 was seen in 62 (15.5%) of patients. Similarly in study by Medghalchi A et al, the mean CAS in hyperthyroid

patients was less than in hypothyroid patients (0.26 ± 0.69 vs. 0.57 ± 1.0, respectively, P = 0.04) [18].

CONCLUSION

TED was seen in 168(42%) patients. CAS score ≥ 3 was seen in 62 (15.5%) patients. Foreign body sensation was the most common eye manifestation seen in 256(64%), followed by dry eye in 171(42.75%).Mean TSH and CAS score was high in patients with TED when compared to patients with- out TED. Higher mean age, male gender, hypothyroid status, higher mean duration of thyroid disorder, lower free T3, lesser free T4, higher TSH, and smoking were significantly associated with patients with CAS ≥3.

REFERENCES

1. Neag EJ, Smith TJ. 2021 update on thyroid-associated ophthalmopathy. J Endocrinol Invest. 2022 Feb;45(2):235-259.
2. Woo KI, Kim YD, Lee SY. Prevalence and risk factors for thyroid eye disease among Korean dysthyroid patients. Korean J Ophthalmol. 2013 Dec;27(6):397-404.
3. Phelps PO, Williams K. Thyroid eye disease for the primary care physician. Dis Mon. 2014 Jun;60(6):292-8.
4. George A, Diana T, Längericht J, Kahaly GJ. Stimulatory Thyrotropin Receptor Antibodies Are a Biomarker for Graves' Orbitopathy. Front Endocrinol (Lausanne). 2021 Feb 2;11:629925.
5. Kuriyan AE, Woeller CF, O'Loughlin CW, Phipps RP, Feldon SE. Orbital fibroblasts from thyroid eye disease patients differ in proliferative and adipogenic responses depending on disease subtype. Invest Ophthalmol Vis Sci. 2013;54:7370–7.
6. Dahal P, Khatiwada S, Lamichhane K, Suvedi A, Khanal N, Adhikari R. Prevalence of thyroid eye disease in patients with thyroid dysfunction in a tertiary care hospital of central Nepal. Journal of Chitwan Medical College.2023;13(46):49-52.
7. Werner SC. Modification of the classification of the eye changes of Graves' disease: Recommendations of the Ad hoc Committee of the American Thyroid Association J Clin Endocrinol Metab. 1977;44:203–4
8. Barrio-Barrio J, Sabater AL, Bonet-Farriol E, Velázquez-Villoria Á, Galofré JC. Graves' ophthalmopathy: VISA versus EUGOGO classification, assessment, and management J Ophthalmol. 2015;2015:249125.
9. Mourits MP, Koornneef L, Wiersinga WM, Prummel MF, Berghout A, van der Gaag R, et al Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: A novel approach Br J Ophthalmol. 1989;73:639–44
10. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol. 2021; 185: G43–67.
11. European Group on Graves' Orbitopathy (EUGOGO); Wiersinga WM, Perros P, Kahaly GJ, Mourits MP, Baldeschi L, Boboridis K, et al. Clinical assessment of patients with Graves' orbitopathy: the European Group on Graves' Orbitopathy

recommendations to generalists, specialists and clinical researchers. Eur J Endocrinol. 2006 Sep;155(3):387-9. doi: 10.1530/eje.1.02230. PMID: 16914591.

12. Sabita, P, Ajit, T, Narayan, S, Kumar, S. and Niranjan, A. Ocular Manifestations in Thyroid Eye Disorder: A Cross-Sectional Study from Nepal. International Journal of Clinical Medicine, 2016;7, 814-823.
13. Choudhari P.C, Usgaonkar U, Shrivastav D. Ophthalmic manifestations of thyroid disease and the association of serum levels of T3, T4 and TSH with thyroid eye disease. Trop J Ophthalmol Otolaryngol.2019;4(8):468-477.
14. Nabi T, Rafiq N. Factors associated with severity of orbitopathy in patients with Graves' disease. Taiwan J Ophthalmol. 2020 May 4;10(3):197-202.
15. Vijayleela M, Babu B. Ophthalmic manifestations in thyroid disease. IOSR J Dent Med Sci. 2017;16(1):59-65.
16. Woo KI, Kim YD, Lee SY. Prevalence and risk factors for thyroid eye disease among Korean dysthyroid patients. Korean J Ophthalmol. 2013 Dec;27(6):397-404.
17. Lavaju, Poonam; Badhu, Badri Prasad; Maskey, Robin1. Pattern of ocular manifestations in patients with thyroid disease presenting in Eastern Nepal. Thyroid Research and Practice 2019;16(1): 20-25.
18. AbdolrezaMedghalchi, Mitra Akbari, Yousef Alizadeh, Reza Soltani Moghadam. The epidemiological characteristics of patients with thyroid eye disease in a referral center in northern Iran, Journal of Current Ophthalmology, 2018;30 (4), 353-358.