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Evaluation of Intraocular Pressure in Thyroid-associated Orbitopathy

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ABSTRACT

Background: Elevated intraocular pressure in thyroid associated orbitopathy may lead to development of secondary glaucoma in them. This study evaluated IOP in primary gaze correlation with clinical activity score in them.

Methods: A cross-sectional study was conducted from November 2020 to October 2021.Information on age, gender, thyroid function test, intraocular pressure, cup-disc ratio and clinical activity score were recorded. Purposive sampling was done. Statistical analysis was done using Statistical Package for Social Sciences version 21.

Results: Total of 74 thyroid dysfunction patients was included in the study. There were14.86% patients with raised intraocular pressure. The mean intraocular pressure in hyperthyroidism was 15.4 ± 1.92 mm Hg and 15.48 ± 2.11mm Hg on right and left eyes respectively and in hypothyroidism, it was 15.08 ± 2.7mmHg and 15.12 ± 3.02 mmHg on right and left eyes respectively. The mean clinical activity score was 1.06 ± 1.23 mmHg. The mean intraocular pressure in eyes in active stage (n=9) was 16.3 ± 3.4 mm Hg, which was not significantly different from the mean intraocular pressure of 15 ± 2.4 mm Hg in inactive eyes (64), p= 0.1. Clinical activity score showed a significant correlation (p=0.03) with intraocular pressure in right eyes whereas it showed no significant correlation with intraocular pressure in left eyes (p=0.37).

Conclusions: In this study elevated intraocular pressure occurred in about 1 in 7 thyroid associated orbitopathy. It also had positive correlation with clinically activity score in right eyes. Regular intraocular pressure measurement should be done in thyroid associated orbitopathy to prevent intraocular morbidity.

Keywords: Clinical activity score; intraocular pressure; orbitopathy; thyroid dysfunction.

INTRODUCTION

Thyroid-associated orbitopathy (TAO) is an autoimmune, inflammatory disease of the orbital tissue.[1] It is caused by autoantibodies against the thyrotropin receptor on endothelial cells of the thyroid follicles and a subpopulation of orbital fibroblasts.[2] In Graves' disease, intraocular pressure (IOP) may be raised as a result of contraction of the increased volume of extraocular muscles against the eyeball while in the case of hypothyroidism, excessive mucopolysaccharide accumulation within the trabecular meshwork increasing aqueous resistance may be responsible for increased IOP.[3-7] The prevalence of ocular hypertension (elevated IOP in primary position) in patients with TAO has been previously studied however, it is not well characterized. This was a hospital-based cross-sectional study that was done among Thyroid associated orbitopathy aimed at evaluating IOP in primary gaze in patients of TAO. Furthermore, correlation of IOP to clinical activity score of TAO was also done.

METHODS

A hospital-based cross-sectional study, was conducted on patients' ≥18 years of age with thyroid dysfunction, presenting to the outpatient department in BP Koirala Lions center for ophthalmic studies and or referred from the Endocrine clinic, Department of Internal Medicine, TUTH. An approval from Institutional Review Committee [Reference no. 419(6) E[2] 077-078] of Institute of Medicine was obtained for this study and the research was conducted according to the principles of the Declaration of Helsinki.

Sample size was calculated from a study previous study on in Thyroid Eye Disorder in Nepal done by Palike et

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al[8] where prevalence of thyroid eye disorder (TED) was found to be 71.79% with the following formula. N = $(z^2pq)/e^2$ Where, N = sample size, Z = 1.96 for 95%, Confidence Interval P = population proportion of POAG, Q = P-1 E = error with 10% tolerance. N = 76.

Though we have included 76 patients however, 74 patients' data were complete. So, only 74 were taken for analysis in our study.

Sociodemographic features, clinical history, duration of thyroid disease, any other systemic complaints, and treatment history were taken. Detailed ophthalmic examinations included best-corrected visual acuity, soft-tissue changes, periorbital changes, measurement of proptosis by Hertel's exophthalmometer, extraocular movements, lid signs, and anterior segment evaluation for the involvement of cornea, pupil reaction, and funduscopic examination. Anterior segment examination was done by Haag Streit 900 slit-lamp biomicroscopy. Fundus examination was done using Volk +90 dioptre lens after dilatation with 1% Tropicamide and the cup-disc ratio was documented. Intraocular pressure (IOP) was measured with a Goldmann applanation tonometer. Obtained IOP was then adjusted for central corneal thickness (CCT) using Ehlers's formula.[9] A clinical activity score (CAS) was given out of a total of 7 as per CAS by Mourits.[10] Glaucoma was labeled, if the patient has IOP of >21 mm Hg in the primary gaze with typical glaucomatous optic neuropathy and/or visual field changes. The criteria for inclusion in the ocular hypertension group was with intraocular pressure above 21 mm Hg without other parameters indicative of glaucoma. The term glaucoma suspect was used when a cup-to-disc ratio of >0.3 was present. Proptosis was defined as the measurement of protrusion of the globe >20 mm from the lateral orbital rim in either eye or any discrepancy in the degree of protrusion of the two eyes by >2 mm. CT/MRI orbit was done in selected cases when required. Thyroid function status was also noted. Smoking status was also noted. Data of the patient was collected in a preformed proforma. Statistical analyses were performed using SPSS (Statistical Package for Social Sciences; SPSS Inc. IBM) version 21.0. Data are expressed as the means ± standard deviation.

The significance of differences in the mean IOP according to gender, eye, and disease activity of the eye was assessed by t-tests. The correlation was assessed with the Pearson correlation test.

RESULTS

There were 74 thyroid dysfunction patients included in the study. Ten of them were current smokers. The mean age of the patients was 42.2 ± 9.3 years (range 25-66). There were 25 males and 49 females. While 10 females had hyperthyroidism, 17 males had hyperthyroidism. Thirty-nine females had hypothyroidism and 8 males had hypothyroidism. Out of 74 patients, twenty-seven patients (36.5%) had hyperthyroidism and 47 patients (63.5%) had hypothyroidism. The majority of the patient (42) complained of grittiness in their eyes followed by prominent eyes in 25 and forward bulging of eyes in 7 patients. The average duration of thyroid dysfunction was 3.3 ± 2.5 years. All of the patients included in the study were on treatment. Among hyperthyroid patients, nine patients had history of radio ablation therapy and are currently on levothyroxine. Eighteen of the patients were on antithyroid therapy. Neither of the patients had systemic corticosteroid or orbital radiotherapy before the ocular examination. Table:1

Table 1. Demographic characteristics of patients (N=74).	
Mean age of patients	42.2 ± 9.3 years
F:M ratio	1.96:1
Hypothyroidism/Hyperthyroidism	1.74:1
Mean duration of disease	3.3 ± 2.5 years
Current smoker	13.5%
Levothyroxine treatment	75.6%

The mean CCT was 524.5 ± 21.4 µm and 525.9 ± 21.5 µm in the right eyes (RE) and left eyes (LE) respectively. No significant difference in corrected IOP was observed between genders (p=0.36) and eyes (p=0.93). Mean IOP (in mm Hg) in RE was 15.2 ± 2.4 and in LE was 15.2 ± 2.7. The mean IOP (in mm Hg) among male was 15.04 ± 2.47 in RE and 14.68 ± 3.09 in LE, and among females in RE was 15.30 ± 2.49 and in LE was 15.55 ± 2.49 (t=0.426, p=0.67; t=1.30, p=0.2). There were 11(14.86%) patients with raised IOP. Of the 11 patients, 7 were females and 4 were males. This sex difference was not statistically significant (chi-square = 0.038, p=0.85). Eight of the patients with elevated IOP had hypothyroidism and three had hyperthyroidism, and thyroid dysfunction status was not significantly associated with an increase in IOP (chi-square =0.483, p=0.49). The mean IOP in hyperthyroidism patients was 15.4 ± 1.92 in RE and 15.48 ± 2.11 in LE. Similarly, the mean IOP was 15.08

± 2.7 in RE and 15.12 ± 3.02 in LE in hypothyroidism patients. (t=0.535, p=0.59; t=0.54, p=0.58) which were not statistically significant. Seven of the patients also had proptosis. The mean IOP also was not significantly different between proptosis patients and non-proptosis patients (t=1.13, p=0.26). There was no evidence of glaucomatous optic nerve damage in any of the patients. Table:2

Table 2. Characteristics of Intraocular Pressure(IOP).

Mean IOP (mm Hg)	RE	LE	p-value
	15.2 ± 2.4	15.2 ± 2.7	
among males (mm Hg)	15.04 ± 2.47	14.68 ± 3.09	t=0.426, p=0.67
among females (mm Hg)	15.30 ± 2.49	15.55 ± 2.49	t=1.30, p=0.2
Elevated IOP (Patients=11; Eyes=13)	6 RE	7 LE	
	Gender		
	7 females	4 males	chi square test = 0.038, p=0.85
	Thyroid dysfunction		
	8 hypothyroidism	3 hyperthyroidism	chi square test =0.483, p=0.49
	Mean IOP (mm Hg)		
	Hyperthyroidism	15.4 ± 1.92 in RE and 15.48 ± 2.11in LE	t=0.535, p=0.59
	Hypothyroidism	15.08 ± 2.7 in RE and 15.12 ± 3.02 in LE	t=0.54, p=0.58

Nine patients were in active stage with CAS score of ≥ 3 whereas 64 patients were inactive with CAS score <3. The mean CAS was 1.06 ± 1.23. The mean IOP in the active stage eyes was 16.3 ± 3.4 mm Hg. This was not significantly different from the mean IOP which was 15 ± 2.4 in inactive eyes (t=1,73,p= 0.1). The mean CAS score among hyperthyroidism was 1.59 ± 0.88 and among hypothyroidism it was 0.76 ± 1.30. (t=2.95, p=0.004) which was statistically significant among the disease group. IOP in LE had a significant correlation with CAS in hyperthyroidism (Pearson correlation=-0.42; p=0.02) where as IOP in RE had a significant correlation with CAS in hypothyroidism (r=0.33;p=0.02). The CAS score showed a significant correlation (Pearson correlation, r=0.24;p=0.03) with IOP in RE whereas it showed no significant correlation with IOP in LE (Pearson correlation=0.10 p=0.37). Table.3

Table 3. Characteristics of IOP and Clinical activity score (CAS).

Mean CAS (out of 7)		
Hypothyroidism	Hyperthyroidism	P value
0.76 ± 1.30.	1.59 ± 0.88	p=0.004
Males	Females	
1.64 ± 0.99	0.77 ± 1.24	p=0.003
Mean IOP (mm Hg)		
Active 16.3 ± 3.4	Inactive 15 ± 2.4	p=0.1
Correlation of IOP to CAS		
Between eyes	RE	p=0.03
	LE	p=0.37
Correlation of IOP to CAS between thyroid dysfunction		
Hypothyroidism(n=47)	RE	p = 0.02
	LE	p=0.12
Hyperthyroidism (n=27)	RE	p=0.64
	LE	p=0.02

DISCUSSION

The relationship between thyroid dysfunction and glaucoma has been controversial.[11] Glaucoma is a chronic progressive optic neuropathy. Elevated intraocular pressure is the most important risk factor associated with its progression. However, glaucomatous progression can occur despite IOP-lowering therapy.[12] Therefore, many studies have been done to investigate other risk factors besides IOP. [12] Hormones might affect the development of glaucoma. Some studies have reported a significant relationship, while others have not.[11]

Even though thyroid-associated orbitopathy can develop in the euthyroid state [3,13] in our study we had included patients with thyroid dysfunction either in hyperthyroidism or hypothyroidism

In our study there were 11(14.86%) patients with elevated IOP with no signs of disc changes related to glaucoma and none of them were on steroid use. Elevated IOP in Graves' disease has been reported in many studies.[4,6,14] Conversely, increased IOP was also reported in association with hypothyroidism. [1-3] The prevalence of open-angle glaucoma in patients with TAO varied from 0.8 to 13.5% in different studies. However, it is still unclear whether this observation is truly due to ocular hypertension (OHT), glaucoma, or caused by less insidious causes such as chronic steroid administration or a spurious rise in intraocular pressure from differential intraocular pressure measurements. [14,15]

The mean age of the patient was 42.2 ± 9.3 years in this study, similar to that reported in a Southeast Asian population (40.2 ± 15.5 years).[16] It is estimated that the prevalence of OHT in the general population ranges from 4.5% to 9.4% for those aged >40 years.[17]In our study there were14.86% of OHT in TAO. Thus, patients with TAO may have a higher risk of OHT compared to the

general population, considering most patients with TAO are younger than 40 years.

The majority of patients in our study were female (F/M ratio=1.96:1). A study by Lim S.L et al. in a multi-ethnic Malaysian population found the female to male ratio as 1.5.[18] A similar value of 1.76 was reported by Lim C.S. et al in a Southeast Asian population in their study in TAO.[15] However, in other studies by Sara et al and Fan et al, there were more male patients than female patients.[19,20]

In a study done in Graves ophthalmopathy by Borzouei S et al, the mean IOP in males was significantly higher than that in females.[21] The IOP was increased in 15.5% of patients in a study done by Abdolreza et al.[22] In a study done by Sara et al, elevated IOP was seen in 15 (25.4%) patients [9 (37.5%) males and 6 (17%) females], however, the sex difference was not found to be significant (P=0.07).[19] In our study of the 11 patients with elevated IOP, 7 were females and 4 were males and sex differences were not statistically significant(P=0.85).

Although controversial, many studies have found IOP to be on the higher side when measured in upgaze in thyroid eye disease. Since, the elevation of lOP in upgaze has also been described in healthy volunteers, to a lesser degree.[23] We have evaluated IOP in primary gaze in this study similar to study by Fan SX et al .[20] In patients with TAO, treatment can be considered in those who have an increased IOP in their primary-gaze position rather than the gaze-dependent increase in IOP as suggested by one study.[24] A study done by Spierer et al concluded that an increase in IOP on upgaze is a normal finding augmented by Graves infiltrative ophthalmopathy.[25] In a study done on measuring IOP in primary gaze on Graves ophthalmopathy patients, 9.6% of patients had an IOP greater than or equal to 21 mm Hg, with a mean IOP of 16.61 ±3.42 mm Hg among study participants.[26] In our study we found it to be elevated in 14.8% of patients with mean IOP (in mm Hg) of 15.2 ± 2.4 in RE and 15.2 ±2.7 in LE. None of the participants had a restriction in primary position. Ocular hypertension in primary gaze if chronically elevated, may lead to progression to glaucoma.[23]

McLenachan and Davies reported that high IOP was associated with hypothyroidism.[27] Cheng and Perkins did not find a statistically significant difference in the distribution of IOP between hypothyroidism and normal control groups.[7] In our study too, the mean IOP between hypothyroidism and hyperthyroidism patients was not statistically significant.

During the course of TAO, the disease passes through several phases, assessment of which is difficult. The Clinical Activity Score (CAS) was described by Mourits and is used widely to grade the severity of activity which is based on signs of inflammation.[10] Patients with a CAS ¤3/7 should be considered as having active TAO. Behrouzi et al. and Cockerham et al. showed that active TED may result in ocular hypertension and/or progression of glaucoma.[20,27] The duration of active orbital involvement was statistically associated with progression to glaucoma in a study done by Cockerham et al.[28] In our study, as per the CAS, most patients were clinically inactive. The mean clinical activity score of TED was statistically significantly different between the hypothyroidism and hyperthyroidism groups(t=2.95, p=0.004) with hyperthyroism patients more associated with increased CAS .Similarly, Eckstein et concluded that eyes with hypothyroidism developed significantly less severe and less active TED than Hyperthyroidism.[29] However, no significant difference in CAS was observed between hyperthyroidism and hypothyroidism by Kashkouli MB et al.[30] In a study done by Savku et al mean CAS was 2.21±1.36.[31] Which was higher than we observed with the mean CAS being 1.06 ± 1.23 in our study. This may be related to having more cases of inactive TAO in our study.

There are some limitations in the present study. This study was not a population-based study. Our study was a cross-sectional study; however, because glaucoma is a progressive disease, a longitudinal approach would have provided more valuable data. Furthermore, we have recruited participants from a single hospital. Larger longitudinal and multicentric studies might validate the association of ocular hypertension as well as glaucoma in TAO.

CONCLUSIONS

In this study elevated intraocular pressure occurred in about 1 in 7 TAO. Intraocular pressure also had positive correlation with clinically activity score in right eyes. Intraocular pressure should be carefully monitored in patients with thyroid eye disease especially eyes with prolonged active TAO, as glaucoma is a progressive disease. Ocular hypertension or increase in intraocular pressure is not preventable in TAO, but regular ophthalmic examinations and follow-up can prevent its progression to glaucoma.

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