

Thyroid-Associated Ophthalmopathy in Iranian Patients

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Abstract- We determined the frequency of clinical thyroid ophthalmopathy in Iranian patients. This cross-sectional study was performed at the Endocrinology Institute of Tehran University of Medical Sciences. All patients with documented thyroid disorders from September 2003 to July 2005 were recruited. Eye examinations included evaluation of soft tissue changes, measurement of proptosis, lid width, lagophthalmos, evaluation of eye muscle function, and determination of visual acuity. The activity of ophthalmopathy was scored according to the NOSPECS scale. Among 851 visited patients, 303 cases had thyroid eye disease (TED). The nature of the ophthalmopathy breaks down as follows: 53.4% were hypothyroid (9.3% Hashimoto disease), 5.5% euthyroid and 41.1% had Graves' disease. The prevalence of TED in males was 60% which was nearly 2 times the prevalence of TED in females. There was a significant relationship between presentation of TED and active smoking of the patients ($P<0.0001$) while no significant relationship with passive smoking was obtained ($P=0.181$). The most common clinical sign of TED in descending order respectively were proptosis with 63.4%, soft tissue involvement (40.9%), extraocular muscle involvement (22.1%), corneal involvement (12.9%) and optic nerve dysfunction (6.3%). Myasthenia gravis occurred in only 2 patients. In the logistic regression, occurrence of TED was influenced by cardiovascular disease (OR=5.346), Graves' disease (OR=47.507), radioiodine therapy (OR=2.590), and anti-thyroid medications (OR=0.650). Thyroid ophthalmopathy (orbitopathy) is a matter of important health concern among patients with thyroid disorder. Since TED occurred with a high prevalence in all thyroid states, a close collaboration between endocrinologists and ophthalmologists along with timely referrals of patients with any eye complaint is deemed necessary. Also smoking was the most important risk factor for developing TED. Therefore, it is advisable to raise awareness and to strongly encourage smokers with thyroid disorders to quit smoking.

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Introduction

Thyroid eye disease (TED) is an extremely unpleasant, painful, cosmetically distressing and occasionally sight threatening condition. Thyroid eye disease is also known as Graves' ophthalmopathy, thyroid associated ophthalmopathy (TAO) and is usually associated with autoimmune hyperthyroidism (Graves' disease) (1).

Several theories have been postulated to explain the disorder's unusual association with thyroid autoimmunity. Most of them favor the role of autoimmunity against a thyroid-stimulating hormone receptor (TSH-r)-like protein in the orbital pre-adipocyte and possibly the extraocular muscle fibers (2). The

symptoms of TED depend on the degree of disease activity (intensity of acute inflammatory reactions) and its severity (extent of anatomical, functional, and cosmetic features) (1). Its typical ocular manifestations are recognized by a variety of clinical features including pain, gritty eyes, photophobia, chemosis, diplopia, and exophthalmos (1,3). Compression of the optic nerve can in extreme cases lead to blindness. The accompanying signs include edema of the conjunctiva and eyelid, proptosis and diplopia owing to the involvement of extraocular muscles. Even though the acute inflammation recedes with disease progression, signs and symptoms improve only partially because of residual fibrosis and scarring of the orbital contents

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(1,3). In the U.S, the incidence of TED is approximately 16/100,000 in females and 2.9/100,000 in males annually and although it is most prevalent in fourth and fifth decades, a wide age range exists (4,5).

Many clinicians find thyroid orbitopathy difficult to manage, largely because of uncertainty regarding the natural history and spectrum of the disorder. In order to manage the individual patients, it is important to understand the key factors that help to predict their probable course. Attention should be paid to age, sex, race, association with smoking, acuity of onset, and type of thyroid disorder. The clinical features, such as symptoms and character of onset of soft tissue signs and motility problems, degree of early physical distortion (proptosis), lid retraction and rapidly of progression also should be considered. These factors govern management and prognostication of the individual patients (3,6).

Considering the high rate of TED among patients with thyroid disorders and its significant contribution to a patient's morbidity and mortality, TED has become an important health concern (3). However, there are few published data comprehensively exploring TED and its relationship with all thyroid states among Iranian individuals with thyroid disease. We therefore performed this study to determine the frequency of thyroid ophthalmopathy in patients with thyroid disease in Iran and to evaluate the severity of ophthalmopathy in patients with TED.

Materials and Methods

The study was a prospective cross-sectional analysis reporting the frequency of thyroid-associated ophthalmopathy in Iranian individuals. The study was conducted in the Endocrinology Institute of Tehran University of Medical Sciences. From September 2003 to July 2005, a total of 851 patients with thyroid disorders were recruited. The study protocol was reviewed and approved by the institutional review board of Endocrinology Institute of Tehran University of Medical Sciences. All patients gave their informed written consent.

The patients were examined by general practitioners who were trained to evaluate thyroid disease and physically assess the thyroid. Data were then recorded on research forms. Demographic data along with information on past medical history and history of thyroid disorder (such as thyroid function, family history of thyroid disorders, treatment history, present treatment and any other endocrinopathy) were recorded. In addition, eye history (eye complaint, glaucoma, systemic

and topical medication usage, and eye surgery) were collected for all participants. Eye signs and symptoms included pain on motion or behind the eye, dryness, burning and watery eyes. Any patient who had at least one of the above mentioned signs and symptoms was referred to oculoplastic clinic in Rassoul Akram Hospital (a main referral center for eye disease in Tehran) for further examination.

The eye examinations included the evaluation of soft tissue changes, measurement of proptosis (by Hertel exophthalmometer), lid width, lagophthalmos, evaluation of eye muscle function with the Hess chart and determination of visual acuity. The activity of ophthalmopathy was scored by the method of Mourits *et al.* (5), which takes into considerations seven manifestations of disease (spontaneous retrobulbar pain, pain with eye movement, eyelid erythema, eyelid edema, conjunctival injection, chemosis and swelling of the caruncle). Eye examinations were assessed with the recording of the corrected visual acuity and by fundoscopy, by a slit lamp to inspect for corneal exposure keratitis, and the NOSPECS classification was graded. The statistical analysis was performed using SPSS, version 13 (SPSS Inc., Chicago, IL, USA). We used One Way ANOVA and Post Hoc tests for comparing means between groups if the distributions were normal. Also Chi-square test for independent proportions or Fisher's exact test was used. Multiple logistic regression analysis was used to analyze the joint effect of the independent variables on thyroid eye disease.

Results

Among 851 participants, 303 (35.6%) patients had TED. Among all the recruited patients, 681 were female of which 29.5% (201 cases) had TED. Prevalence of TED in males was 60% which was nearly 2 times the prevalence of TED in females ($P<0.0001$). The mean age of the patients was 37.1 ± 14.4 years (range 6 to 80 years). There was no significant relationship between presentation of TED and age of the patients ($P=0.893$).

Table 1 indicates patients' characteristics based on thyroid diseases. Forty-one percent of the patients had Graves' (77.1% had TED) and 9.3% Hashimoto (7.6% had TED). Forty-four percent of the patients were primary hypothyroid (5.9% had TED), and 5.5% euthyroid (10.6% had TED). The prevalence of TED in patients with Graves' disease was statistically higher than other patients ($P<0.0001$). The mean duration of thyroid dysfunction was 61.4 months (median 36 months) which includes the mean duration of thyroid

Table 1. Patients' characteristics based on their thyroid disease

	Primary Hypothyroidism (n=375)	Grave's disease (n=350)	Hashimoto disease (n=79)	Euthyroid (n=47)	Total (n=851)
Female, n (%)	352 (93.9%)	231 (66%)	58 (73.4%)	40 (85.1%)	681 (80%)
Age, mean year \pm SD	34.8 \pm 13.4	39 \pm 15.1	41.3 \pm 16	34.5 \pm 10.7	37.1 \pm 14.4
BMI, mean kg/m ² \pm SD	27.1 \pm 16.2	25 \pm 4.4	27.7 \pm 12.1	27.1 \pm 4.8	26.6 \pm 12.7
Smoker, n (%)					
Active	15 (4%)	61 (17.4%)	11 (13.9%)	4 (8.5%)	91 (10.7%)
Passive	93 (24.8%)	74 (21.1%)	18 (22.8%)	20 (42.6%)	205 (24.1)
Diabetes mellitus, n (%)	15 (4%)	18 (5.2%)	9 (11.4%)	-	42 (4.9%)
Cardiovascular disorders, n (%)	28 (7.5%)	35 (10%)	10 (12.7%)	1 (2.1%)	74 (8.7%)
Myasthenia gravis, n (%)	-	2 (0.6%)	-	-	2 (0.2%)
Autoimmune disorders, n (%)	9 (2.4%)	9 (2.6%)	2 (2.5%)	1 (2.1%)	21 (2.5%)
duration of thyroid involvement mean months \pm SD	67.9 \pm 82	53.8 \pm 69.3	68.7 \pm 79.3	54.3 \pm 66	61.4 \pm 76.1
Eye complaint, n (%)	83 (22.1%)	247 (70.6%)	34 (43%)	7 (14.9%)	371 (43.6%)
Duration of eye complaint median (range)	0 (0-60)	3 (0-324)	0 (0-84)	0 (0-12)	0 (0-324)
Hx. eye surgery, n (%)	9 (2.4%)	25 (7.2%)	7 (8.9%)	3 (6.4%)	44 (5.2%)
Hx. lacrimal drainage, n (%)	2 (0.5%)	-	-	-	2 (0.2%)
Hx. eyelid surgery, n (%)	1 (0.3%)	8 (2.3%)	-	-	9 (1.1%)
Hx. orbital decompression, n (%)	-	4 (1.1%)	1 (1.3%)	-	5 (0.6%)
Systemic steroid, n (%)	13 (3.5%)	85 (24.4%)	9 (11.4%)	2 (4.3%)	109 (12.8%)
Glaucoma, n (%)	-	11 (3.2%)	-	-	11 (1.3%)

dysfunction in patients without TED (67.8 months, median 36) and that of patients with TED (mean 49.8 months, median 24). There was a significant correlation between TED and duration of occurrence of thyroid dysfunction ($P=0.001$).

There was a significant relationship between presence of TED and family history of hyperthyroidism ($P<0.0001$), number of hyperthyroid relatives ($P<0.0001$), and number of the hypothyroid relatives ($P=0.053$).

Also a significant relationship was detected between presence of TED and history of previous eye surgery ($P=0.004$), history of previous eyelid surgery ($P=0.003$), history of glaucoma ($P=0.014$), while there was no significant relationship between presence of TED and previous history of lacrimal drainage ($P=0.233$).

Presence of TED was influenced by the duration of eye complaint ($P<0.0001$), duration of thyroid involvement ($P=0.001$) and pack year ($P<0.0001$).

In our patient population, 10.7% were active smokers while 24.1% were passive smokers. Among the TED patients, 18.2% were active smokers whereas in patients without TED, 6.6% were active smokers ($P<0.0001$). There was no significant relationship between presentation of TED and passive smoking ($P=0.181$).

Among TED patients, 3.6% (11 cases) had diabetes mellitus, 10.6% (32 cases) had cardiovascular disease, 3% (9 cases) had autoimmune disease and 0.7% (2 cases) had myasthenia gravis. There was no considerable relationship between presentations of TED and comorbid conditions.

In all the participants, 50.2% of cases had not received any previous treatment, while 40.1% were taking anti-thyroid medication, 16.3% had received radioactive iodine and 5.9% were taking levothyroxine. We found a significant difference between the prevalence of patients with a history of radioactive iodine with TED and others [(29% vs. 9.3%), ($P<0.0001$)]. Also, there was a significant difference in prevalence of anti-thyroid medications in patients with TED compared to others [(80.8% vs. 32.6%), ($P<0.0001$)]. According to Table 1, 371 patients (43.6%) had an eye complaint of which bilateral proptosis (9.9%), burning sensation (5.4%), pain behind the eye (5.3%) and puffiness (4.7%) were the most common eye signs and symptoms. Grades within NOSPECS classes and the activity score of TED in patients with thyroid disease is shown in Table 2. The approximate frequency of soft tissue involvement was 40.9%, proptosis 63.4%, extraocular muscle involvement 22.1%, corneal involvement 12.9% and optic nerve dysfunction 6.3%.

Table 2. Grades within NOSPECS classes in patients with thyroid eye disease

	Primary Hypothyroidism (n=22)	Graves' disease (n=270)	Hashimoto disease (n=6)	Euthyroid (n=5)	Total (n=303)
Soft tissue involvement with symptoms and signs					
absent	18	155	2	4	179
minimal	0	95	4	1	100
moderate	4	18	0	0	22
marked	0	2	0	0	2
Proptosis					
Absent	10	96	3	2	111
1-3 mm	12	130	2	3	147
4-7 mm	0	36	1	0	37
> 7 mm	0	8	0	0	8
Extraocular muscle involvement					
absent	18	208	5	5	236
limitation of motion at extremes of gaze	2	44	1	0	47
evident restriction of motion	2	17	0	0	19
fixation of a globe or globes	0	1	0	0	1
Corneal involvement					
absent	22	231	6	5	264
erosion (SPK)	0	39	0	0	39
Optic nerve dysfunction					
normal	18	255	6	5	284
20/20 -20/60 or VF or RAPD or color	2	10	0	0	12
20/70 -20/200 or VF or RAPD or color	0	3	0	0	3
<20/200 or VF or RAPD or color	2	2	0	0	4
Activity score, mean \pm SD	1.4 \pm 1.5	1.7 \pm 1.6	1.3 \pm 0.8	1.2 \pm 1.1	1.6 \pm 1.5
Rundle					
A	7	53	3	1	64
B	9	149	2	4	164
C	2	53	1	0	56
D	4	15	0	0	19
General State					
Active	4	66	0	1	71
Inactive	18	204	6	4	232
Activity Score					
0	6	67	1	1	75
1	10	83	2	3	98
2	2	51	3	0	56
3	1	26	0	1	28
4	2	29	0	0	31
5	0	6	0	0	6
6	1	5	0	0	6
7	0	3	0	0	3

Table 3 shows results of the multiple logistic regression analysis from the effect of independent variables on thyroid eye disease. According to this Table, occurrence of TED is influenced by age

(OR=0.963), cardiovascular disease (OR=5.346), Graves' disease (OR=47.507), radioiodine therapy (OR=2.590), and anti-thyroid medications (OR=0.650).

Table 3. Results of multiple logistic regression analysis of the effect of independent variables on thyroid eye disease

	Odds ratio for TED (CI 95%)	P-value
Gender, Male	1.872 (0.957-3.658)	0.067
Age, per year	0.963 (0.942-0.984)	0.001
BMI, per kg/m ²	1.001 (0.960-1.043)	0.968
Smoker		
active	0.824 (0.332-2.043)	0.675
passive	1.157 (0.619-2.162)	0.647
Diabetes mellitus	0.296 (0.079-1.119)	0.073
Cardiovascular disorders	5.346 (1.930-14.807)	0.001
Autoimmune disorders	2.790 (0.462-16.844)	0.263
Duration of thyroid involvement per months	0.999 (0.995-1.003)	0.687
Primary Hypothyroidism	0.464 (0.122-1.770)	0.261
Graves' disease	47.507 (11.860-190.296)	0.000
Hashimoto disease	1.579 (0.315-7.920)	0.579
Radioactive iodine	2.590 (1.264-5.308)	0.009
Anti-thyroid medications	0.650 (0.433-0.977)	0.038
Hx. Levothyroxine	2.848 (0.890-9.1130)	0.078

Discussion

Thyroid eye disease (TED) can be manifested in all thyroid states and is the most frequent extra-thyroidal manifestation of Graves' disease. In most instances it is mild and non-progressive but in 3-5% of cases it may lead to severe complications. Non-severe TED requires only supportive measures, such as eye ointments, sunglasses and prisms. In contrast, severe TED requires aggressive treatment, either medical (high-dose glucocorticoids, orbital radiotherapy) or surgical (orbital decompression) (6, 7).

The focus of the present study was to determine the clinical manifestations of thyroid ophthalmopathy in patients with thyroid disease in a prospective study. The literature showed that among patients with clinical ophthalmopathy, 90% had Graves' hyperthyroidism, 1% had primary hypothyroidism, and 6% were euthyroid and 3% had Hashimoto thyroiditis (8). However, our study showed that 44.1% of the patients were hypothyroid and 5.5% euthyroid. Among all the participants 41.1% had Graves' disease while 9.3% Hashimoto disease. Thyroid eye disease is clinically evident in 25-50% of patients with Graves' disease and 3-5% of cases develop severe eye disease (9-11). This study concurs with the literature as the occurrence of TED was influenced by Graves' disease (OR=42.857), ($P<0.0001$), where 77.1% of our patients with Graves' disease had TED.

According to our data, occurrence of TED was also influenced by age. Bartley *et al.* (7) indicated that the incidence rate for Graves' ophthalmopathy had an apparent bimodal peak for men and women, noting that the peak for men occurred approximately five years after that of women. The study states that peak incidence rates occur in the age group 40-44 yr and 60-64 yr in women, and 45-49 yr and 65-69 yr in men.

Women are five times more likely to be affected by thyroid eye disease than men, but this largely reflects the increased incidence of Graves' disease in women (9-11). This study showed that prevalence of TED in men was 60% which was nearly 2 times higher than the prevalence of TED in women. Bartalena *et al.* (12) however state the female/male ratio of TED as a ratio of 2:1. Manji *et al.* in a large study on 2805 Caucasian subjects didn't show predisposing risk factors of female sex similar to our finding in this context (13). They also found a significant relationship between presence of Graves' disease and family history of hyperthyroidism as well as Hashimoto disease and history of hypothyroidism. In our study there was a significant relationship between presence of TED and family history of hyperthyroidism.

Patients with thyroid eye disease are four times more likely to be smokers or former smokers than nonsmokers. The greater the number of cigarettes smoked per day, the greater the risk of developing thyroid eye disease, although quitting smoking seems to reduce this risk. Smoking also increases the risk for

progression of ophthalmopathy after radioiodine therapy (7,12,14). In the study by Stamato *et al.*, smokers had a more severe ophthalmopathy than the nonsmokers (15). Smoking can decrease immunosuppression, allowing greater expression of the autoimmune process (16,17). Tellez *et al.* (18) indicated that smokers had a risk of 2.41 of developing eye signs relative to non-smokers ($P=0.02$). Salvi *et al.* (19) also indicated the prevalence of smokers among patients without TED was significantly lower than that among those with TED ($P<0.03$). A significant association ($P<0.001$) between the presence of ophthalmopathy and current smoking is also obtained from Manji *et al.*, study (13). In agreement with these studies, we found a significant difference between prevalence of TED in active smokers and others ($P<0.0001$). Eckstein *et al.* (20) determined that smoking also influences the course of TED during treatment. They showed clinical activity score decreased ($P<0.05$) and motility improved ($P<0.02$) significantly faster and to a greater extent in non-smokers than smokers.

Strong evidence shows that radioiodine, which is used to treat hyperthyroidism, can cause a flare in thyroid eye disease, although some controversy remains as to what degree radioiodine worsens thyroid eye disease (21,22). The development or progression of ophthalmopathy after radioiodine therapy might be related to the release of thyroid antigens as a result of radiation injury and to subsequent enhancement of the autoimmune response directed toward antigens shared by the thyroid and the orbit (23). In this study, we found that the development or the progression of ophthalmopathy in patients with TED was affected by radioiodine therapy.

Common symptoms of TED are pain and discomfort followed by gritty sensation in the eye, double vision and photophobia (24). Bartley *et al.* (7) indicated that eyelid retraction was the most common sign of Graves' ophthalmopathy and being present at diagnosis in 75% of patients. In our study, bilateral proptosis (9.9%), burning sensation (5.4%), pain behind eye (5.3%) and puffiness (4.7%) were the most common signs and symptoms, respectively.

Frequency of extraocular muscle involvement was 62% in Bartley *et al.* study (7) and 22.1% in our study. Soft tissue involvement was observed in 90% in Wiersinga study (17), which was 40.9% in our study.

Sight loss due to optic neuropathy in previous study ranged from 6% to 34% (8); we assessed in 6.3% of patients with thyroid orbitopathy.

It is known from our research that smoking and female sex is a risk factor for thyroid eye disease. To minimize the risk of thyroid ophthalmopathy as far as possible, patients should therefore be advised not to smoke, and be followed closely to manage any ocular changes. The ocular prognosis depends on the amplitude and the duration of the ocular changes, the functional state and the presence of complications.

It is recommended from this study that general practitioners and endocrinologists to refer any patient with preliminary symptoms of TED to an ophthalmologist considering that TED contributes significantly to the morbidity, cosmetic and economic burden.

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