

Epidemiological Status of Thyroid Eye Disease in Central Iran

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Abstract

Purpose: To focus on clinical manifestations and epidemiology of thyroid eye disease (TED) in Central Iran's population.

Methods: In this retrospective case study, we analyzed all patients with TED who were referred to our oculoplastic clinic from 2015 to 2019. The patients' epidemiological characteristics and clinical presentation were compared between different thyroid disease groups and genders.

Results: Overall, 383 patients (155 male; 40.5% and 228 female; 59.5%) were included. The mean age was 39.55 years (standard deviation \pm 13.45, range 10–72). Most patients (89%) were hyperthyroid with the highest duration of ocular involvement among all categories (25.6 months). The most common signs on ophthalmic examinations were proptosis (80.4%), followed by eyelid retraction (72.3.0%). TED was classified as mild in 24.5%, moderate to severe in 67.6%, and sight-threatening in 7.9%. Thirty patients (7.8%) had active TED.

Conclusions: This series with a relatively more significant number of TED cases in Central Iran found similar epidemiological and clinical characteristics of TED compared to other studies from Iran. Most of our patients were hyperthyroid, with more females compared to males. Proptosis and eyelid retraction were the most common manifestations. Most TED patients were classified as moderate to severe.

Keywords: Graves' disease, Proptosis, Thyroid eye disease, Thyroid orbitopathy, Thyroid-associated ophthalmopathy

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INTRODUCTION

Thyroid eye disease (TED), also known as thyroid-associated orbitopathy (TAO), is an autoimmune inflammatory disorder that causes deterioration of the patient's appearance, threatens vision, and severely loses the quality of life.¹ Symptom depends on two factors: intensity of acute inflammatory reactions and the severity of TED, including proptosis, lid retraction, diplopia due to restrictive extraocular muscles, and inflammatory ocular surface disorders.^{2,3} TED may also lead to optic neuropathy in severe cases, resulting in loss of visual acuity and visual field constriction.⁴

Every relative afferent pupillary defect (RAPD) year, 16 women and 3 men out of every hundred thousand people are diagnosed with TED, usually in their middle ages (between 30 and 50).^{5,6} Although 80% of TED patients have Graves' disease, 10% have autoimmune hypothyroidism due to Hashimoto's

thyroiditis, with the rest having no thyroid disease.⁷ Most TED patients develop eye symptoms within the initial 18 months of autoimmune thyroid disease; 13% become symptomatic beyond 2 years; and 3% are diagnosed more than 12 months before Graves' disease.⁸

Ethnic diversity and different disease manifestations make the treatment complicated for each patient.⁹ A few studies have analyzed the characteristics of TED in the Iranian population which have been mostly conducted more than a decade ago.^{10,11}

Considering the importance of early diagnosis of patients in the prognosis of thyroid ophthalmopathy and the fact that no new epidemiological study has been performed in Central Iran, this study was designed to focus on the frequency of thyroid ophthalmopathy in patients with thyroid disease and evaluation of the severity of ophthalmopathy in patients with TED.

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METHODS

Patients included those diagnosed as TED by the senior author (see the below criteria) and were referred to a private oculoplastic clinic and the Feiz Hospital in Isfahan from 2015 to 2019. Feiz Hospital is the referral center of ophthalmology in Isfahan province in Central Iran, located almost 400 km south of the capital of Iran. It covers a population of approximately 3 million people. We obtained written consent from all patients and ethical approval from the Department of Ophthalmology, Isfahan University of Medical Sciences (Ethics code of IR.MUI.MED.REC.1399.1001). The same ophthalmologist filled all patients' research forms.

TED was diagnosed according to the criteria by Bartley and Gorman.¹² In patients with eyelid retraction, any of the following conditions led to the diagnosis of TED: objective evidence of thyroid dysfunction or abnormal regulation,¹² exophthalmos, optic nerve dysfunction, or extraocular muscle involvement. If eyelid retraction was absent, TED was diagnosed only in the presence of exophthalmos, optic nerve involvement, or restrictive extraocular myopathy, associated with thyroid dysfunction or abnormal regulation and if no other cause for the ophthalmic feature was apparent. We excluded patients with a previous history of orbital decompression, strabismus operation, or eyelid surgery related to TED complications. In addition, those who had received systemic steroids or immunomodulators for active TED were excluded because these medications can affect the measures used to evaluate clinical activity scores (CAS).

The following variables were recorded for all patients: age, gender, thyroid history data such as type of thyroid dysfunction (hypo, hyper, or euthyroid), duration of thyroid disease (time interval between diagnosis of hyper/hypothyroidism and referral for TED), when TED started (before, after or at the same time with thyroid dysfunction), duration of eye involvement (time interval between first relevant ocular signs/symptoms and referral for TED), and laterality of TED. Ocular symptoms and signs including tearing, photophobia, redness, foreign-body sensation, pain at rest or during eye movement, diplopia, and RAPD were examined.

Other ophthalmic parameters such as visual acuity (determined by Snellen chart), color vision (Ishihara color vision testing plate set), upper eyelid retraction (defined as the position of upper lid margin located at or above the superior limbus in the primary position of gaze), and proptosis (defined as Hertel exophthalmometry reading ≥ 20 mm) were assessed.

Patients were defined as active and inactive according to the CAS (chemosis, conjunctival injection, lid edema, lid erythema, pain in rest, pain in movement, and caruncle inflammation).¹³ CAS ≥ 3 was considered active TED. For those with active TED, medical treatment was used, including oral or parenteral corticosteroids, mycophenolate mofetil, or rituximab. Disease severity was assessed according to the European Group of Graves' Orbitopathy criteria.¹⁴

The visual field test was performed using Goldmann perimeter for patients suspected to have dysthyroid optic neuropathy. Orbital computerized tomography scan without contrast was also performed for the former patients and those with extraocular muscles involvement (defined as diplopia and restriction of extraocular muscle movement).

Data analysis was conducted using SPSS software (version 21, SPSS Inc., Chicago, IL, USA). Chi-square, analysis of variance, and *t*-tests were used for analyses, and $P < 0.05$ indicated statistical significance.

RESULTS

In this study, 383 patients (155 males [40.5%] and 228 females [59.5%]) with a mean age of 39.55 ± 13.45 years were enrolled. Table 1 summarizes the patients' characteristics based on the status of thyroid diseases.

Most patients (341 of 383; 89%) had hyperthyroidism, and only 2.4% were euthyroid. The duration of eye involvement was highest for hyperthyroid patients (25.6 ± 41.69 months), followed by hypothyroid (19.23 ± 33.60 months) and euthyroid groups (16.60 ± 24.57 months). No significant difference was present between the duration of eye involvement among these subcategories ($P = 0.937$). The mean duration of thyroid disease in all patients with TED was 42.8 ± 55.1 months, with a significantly longer mean period among the hypothyroid patients (61.33 ± 47.31 months), compared to hyperthyroid cases (39.92 ± 55.75 months, $P = 0.008$). Eye involvement appeared most after the systemic thyroid disease (in 80% of hypothyroid vs. 48.1% of hyperthyroid cases, $P = 0.001$).

In clinical examinations, the most common sign was proptosis (80.4%), followed by eyelid retraction (72.3%). Frequencies of extraocular muscle involvement (22.4%), optic nerve dysfunction (6.3%), and corneal involvement (1%) are shown in different categories in Table 2. There were 28 patients with sight-threatening involvement. There was no statistically significant relation between thyroid disease type and severity of TED ($P = 0.114$). Thirty patients (7.8%) were determined to have active TED based on CAS scores. Only 3.4% of patients had bilaterally active disease.

We compared men and women with regard to activity and severity of TED. Active TED was observed in 22/135 males (16.3%) versus 8/228 females (3.51%), which was statistically significant ($P < 0.001$). Similarly, men had a higher incidence of sight-threatening TED, while women had more mild involvement, as shown in Table 3.

The data analysis did not show any statistically significant relationship between the type of thyroid disease and ophthalmic features except in the case of proptosis [Table 2].

DISCUSSION

This study focused on thyroid ophthalmopathy in central Iran's population. Heretofore, eight studies have discussed

Table 1: Patients' characteristics based on their thyroid disease

Variable	Euthyroid (n=9), n (%)	Hyperthyroid (n=341), n (%)	Hypothyroid (n=33), n (%)	Total, n (%)	P
Sex					
Male	2 (22.2)	147 (43.1)	6 (18.2)	155 (40.5)	0.289 ^o
Female	7 (77.8)	194 (56.9)	27 (81.8)	228 (59.5)	
Age (years)					
Mean±SD	38.0±11.86	39.45±13.80	40.93±9.94	39.55±13.45	0.768 ^f
Median (minimum-maximum)	34 (21-56)	38 (10-72)	37.5 (21-65)	38 (10-72)	
Duration of eye involvement (months)					
Mean months±SD	16.60±24.57	25.65±41.69	19.23±33.60	23.71±40.73	0.937 ^f
Median (minimum-maximum)	6 (2-60)	9 (1-288)	12 (1-180)	9 (1-288)	
Time of thyroid disease (months)					
Mean months±SD	-	39.92±55.75	61.33±47.31	42.81±55.13	0.008 ^f
Median (minimum-maximum)	-	18 (1-300)	62 (2-180)	24.0 (1-300)	
Difference time (thyroid-eye)	-				
Mean months±SD	-	15.06±41.75	46.03±40.78	18.0±42.50	0.001 ^f
Median (minimum-maximum)	-	2 (-280-239)	48 (-3-114)	3 (-280-239)	
Point of eye involvement	-				
After thyroid	-	153 (48.1)	24 (80.0)	178 (50.9)	0.001 ^o
With thyroid	-	114 (35.8)	5 (16.7)	119 (34.2)	
Before thyroid	-	51 (16.0)	1 (3.3)	52 (14.9)	

^fResulted from one-way ANOVA, ^oResulted from Fisher exact test. SD: Standard deviation, ANOVA: Analysis of variance

Table 2: Patients' characteristics based on their thyroid disease

Variable	Euthyroid (n=9), n (%)	Hyperthyroid (n=341), n (%)	Hypothyroid (n=33), n (%)	Total (n=383), n (%)	P
Proptosis					
Bilateral	3 (33.3)	237 (69.5)	20 (60.6)	260 (67.9)	0.036 ^o
Unilateral	3 (33.3)	38 (11.1)	8 (24.2)	49 (12.8)	
Eyelid retraction					
Bilateral	2 (22.2)	142 (44.7)	8 (27.6)	152 (42.7)	0.086 ^o
Unilateral	6 (66.7)	108 (34.0)	11 (37.9)	125 (35.1)	
Sight threatening					
Optic nerve dysfunction	0	19 (5.6)	5.0 (15.2)	24.0 (6.3)	0.114 ^o
Corneal involvement	0	4.0 (1.2)	0	4.0 (1.0)	
Severity					
Mild	4 (50.0)	74 (23.4)	9.0 (29.0)	87.0 (24.5)	0.114 ^o
Moderate to severe	4 (50.0)	219 (69.3)	17 (54.8)	240 (67.6)	
Sight threatening	0	23 (7.3)	5 (16.1)	28.0 (7.9)	
General state					
Active	0	25 (7.3)	5 (15.2)	30 (7.8)	0.179 ^o
Bilaterally active	0	10/25 (40.0)	3/5 (60.0)	13/30 (43.3)	
Inactive	9 (100.0)	316 (92.7)	28 (84.8)	353 (92.2)	

^oResulted from Fisher exact test

Table 3: Comparison of severity of thyroid eye disease between men and women

Sex/severity	Mild, n/total (%)	Moderate to severe, n/total (%)	Sight-threatening, n/total (%)	P
Male	22/144 (15.2)	98/144 (68.1)	24/144 (16.7)	<0.001
Female	65/211 (30.8)	142/211 (67.3)	4/211 (1.9)	

the epidemiology of TED in different regions of Iran.^{10,11,15-19} Table 4 summarizes the main findings of these previous studies compared with our results. The present study has included the highest number of TED cases among other Iranian studies.

The majority (89%) of our patients were hyperthyroid, with more occurrence in females than males, as observed in Table 1. Similar associations between TED and hyperthyroidism in other population-based studies were

Table 4: Comparison of previous studies on epidemiology of thyroid eye disease (TED) in Iran, in order of number of TED cases included

Study location (city)	Time (author [reference number])	Number of TED cases included	Thyroid disease type	Male (%)/female (%) Mean age (years)	Main clinical TED hallmarks (retraction and proptosis)	Mean duration of eye involvement and thyroid disease and sequence of ophthalmopathy in relation to thyroid dis
Central Iran (Isfahan)	2015-2019 (Eshraghi <i>et al.</i> ^{This study})	383	89% Hyper 8.6% Hypo 2.3% Eu	40.5/59.5 39.5	Retraction 77% (of which 54% bilateral) Proptosis 80% (of which 84% bilateral)	Duration of ophthalmopathy: 23.7 months; Duration of systemic thyroid dis: 42.8 months; Sequence: 50.9% after, 14.9% before, 34.2% simultaneous
Capital of Iran (Tehran)	2003-2005 (Kashkouli <i>et al.</i> ¹⁰)	303	41.1% Hyper 53.4% Hypo 5.5% Eu	33.7/66.3 37.1	Proptosis 63.4%	Duration of systemic thyroid dis: 49.8 months
North of Iran (Rasht)	2012-2014 (Medghalchi <i>et al.</i> ¹⁷)	103	81% Hyper 18% Hypo 0.9% Eu	47.6/52.4 42	Retraction 88% (of which 35% bilateral) Proptosis 55% (of which 59% bilateral)	Duration of ophthalmopathy: 36.5 months; Duration of systemic thyroid dis: 69 months; Interval between diagnosis of thyroid disease and TED was <18 months in 66%, 19-60 months in <20%, and >60 months in 14%
Capital of Iran (Tehran)	2003-2005 (Tari <i>et al.</i> ¹⁹)	103	92.2% Hyper 2.9% Hypo 4.8% Eu	46.6/53.4 45	Retraction 87% (of which 88.9% bilateral) Proptosis 77.6% (of which 87.5% bilateral)	Duration of ophthalmopathy: 13.2 months Duration of systemic thyroid dis: 39.4 months
North-West of Iran (Hamadan)	2016-2017 (Eslami <i>et al.</i> ¹⁵)	93	All had Graves' disease	27.9/72.1	Retraction 62.4% Proptosis 46.2%	No data presented
North of Iran (Babol)	2011-2012 (Gharib <i>et al.</i> ¹⁶)	70	Among 105 Graves' disease patients	37.1/62.9 35	Proptosis 63% (of which 68% bilateral) Retraction 53% (of which 78% bilateral)	Sequence: In 65% TED was simultaneous with or occurred within 6 months of diagnosis of thyroid disease, in 20%: Within 7-24 months and in 15% >24 months
North-East of Iran (Mashhad)	2002-2005 (Razavi <i>et al.</i> ¹⁸)	68	86.2% Hyper 3% Hypo 10.8% Eu	35.3/64.7 38	Retraction 64% (of which 95% bilateral) Proptosis 53% (of which 85% bilateral)	Duration of systemic thyroid dis: 29.5 months
Central Iran (Yazd)	2001-2002 (Besharati and Rastegar ¹¹)	95	Among 95 Graves' disease patients	37.9/62.1 36.5	Proptosis 49.5% (of which 70% bilateral) Retraction 48.4%	43.8% showed TED 18 months after diagnosis of Graves' disease

TED: Thyroid eye disease, Hypo: Hypothyroid, Hyper: Hyperthyroid, Eu: Euthyroid

seen. For example, in one study in the capital of Iran, similar proportions were found.¹⁰ Yet in a recent study in China, the hyperthyroid population was 81.5%.⁹ Caucasian ethnicity statistics are similar to the values of our study, with regard to the hyperthyroid patients comprising almost 90% of TED cases and a preponderance of the females.^{20,21} In all thyroid disease subcategories, the mean age was similar and found to be around 39.55 ± 13.45 years, which is comparable to many other Asian studies but younger compared to reports from Europe and North America.²²

A significant difference was observed among different subcategories of thyroid disease in the interval between thyroid disease and its first orbitopathy manifestations. For hyperthyroid patients, the first ocular manifestation appeared on average 15.06 ± 41.75 months after the thyroid disease, while this duration was 46.03 ± 40.78 months for the hypothyroid subgroup.

The mean duration of thyroid disease and TED in our patients in all subcategories were 42.81 ± 55.13 and 23.71 ± 40.73 months, respectively, which were similar to the other report on the Chinese population, though much longer than European patients.^{9,23}

Another significant difference observed between hypo and hyperthyroid patients was the sequence of occurrence of TED compared to the thyroid disease. In hypothyroid patients, it was almost twice as likely to see the eye involvement after thyroid disease manifestation compared to hyperthyroid patients (80% vs. 48.1%). However, the proportion of those having TED (ocular manifestations) before the diagnosis of thyroid disease was 16% in hyperthyroid subjects compared to 3.3% in hypothyroid patients.

Proptosis and eyelid retraction were the most common manifestations, with 80.42% and 72.3% of the affected population, respectively. In another study on the northern

population of Iran, proptosis was only manifested in 55.3%, while eyelid retraction prevalence was as high as 88.3%.¹⁷ Gharib also studied the same demographic region with 63.8% proptosis and 52.8% eyelid retraction.¹⁶ Kashkouli reported proptosis as the most common clinical manifestation with 63.4%.¹⁰ Bartley reported upper eyelid retraction with 90% and proptosis with 62% as the most common symptoms in the North American population.²⁴ Eyelid retraction was observed among 62% of the studied population in East Asia, which indicates that the affected populations vary based on the demographic regions. A smaller margin reflex distance was suggested as the cause of this discrepancy.²⁵ We also speculate that this inconsistency in the data may originate from the fact that not all patients were referred by the endocrinologist to us, especially with mild symptoms of retraction and proptosis.

The frequency of extraocular muscle involvement was 22.4%, consistent with other Iranian studies. The involvement was 22.1% in the capital of Iran and 19.1% in another study on the northeastern population of Iran.^{10,18} For eastern Asian populations, this manifestation affected 75.5% of the population.⁹ In Europe and North America, the prevalence of eye muscle involvement was reported to be as high as 49% and 85%, respectively.^{23,26} In Africa, one study found 36.7% of the population with this symptom.²⁷

In our study, most patients were classified as moderate-to-severe TED (67.6%). Mild TED was present in 24.5%, and 7.9% of our cases had sight-threatening manifestations. Only 7.8% were considered active cases. A few other studies have focused on the activity of the Iranian population based on CAS metrics. A similar result was reported for the northern population of Iran, yet in another study, activity was reported in 28.9% of the patients in the capital of Iran.^{17,28} In one study in Africa, a similar severity rate was seen.²⁷ In an Indian study, only 3% were active, with 83% of patients categorized as mild. In Caucasians, 27.2% of the population had severe TAO and 60% were in the active state, much higher than our study (with only 7.8% active TED cases).²³ Compared to other studies in which most cases were mild, we suspect not all patients, especially with mild symptoms of retraction and proptosis, were referred to us by the endocrinologist, hence the increased prevalence of moderate-to-severe disease in our series. In our study, men were more prone to active TED than women (14.2% and 3.5%, respectively). A similar relationship was observed between gender and severity, where males with sight-threatening conditions were more likely to encounter than females (16.7% and 1.9%, respectively). This is corroborated in several other studies that have found men to suffer more severe forms of TED.^{29,30} In the study by Lat *et al.* on 163 cases, severe disease was observed in 16% of males and 7% of females ($P = 0.041$), which is similar to our results.³¹ However, in their group of patients, the association between sex and activity of TED did not reach statistical significance. Nevertheless, a recent publication on a pooled analysis of the 56 articles on TED found male sex to be a significant risk factor for active TED, which is in line with our findings.³²

Among sight-threatening patients (7.3%), the majority had optic nerve dysfunction (6.3% of all patients), and only in 4 cases (1% of all patients), corneal involvement was observed.³² In another Iranian study, similar statistics for optic nerve dysfunction was seen (6.3%), but the corneal involvement was much higher (12.9%).¹⁰ For the northern population of Iran, 19.4% of patients had corneal infiltration, but no data for optic nerve dysfunction were reported.¹⁷ In Caucasians, optic nerve dysfunction and corneal involvement were seen in 21% and 16% of patients, respectively.²³

We reported a lower percentage of corneal involvement compared to other studies. This discrepancy might be explained because we included epithelial defects that resisted treatments and neglected mild infiltration and punctate epithelial erosion.

This study has some limitations as we mainly focused on the referred patients. First, the endocrinologists might not have referred all TED patients, especially those with mild symptoms. Second, we were unable to study the incidence and prevalence rate of TED in the total population of our geographic location.

In conclusion, we studied epidemiologic aspects of TED in a population in Central Iran. Our results were comparable to other studies from the country, yet the sample size of this survey was larger. Further multicenter epidemiologic studies are required to illustrate better the characteristics of TED among different populations in regions of Iran.

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Conflicts of interest

There are no conflicts of interest.

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