Original Article

Thyroid eye disease survey: An anonymous web-based survey in the Indian subcontinent

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Purpose: To evaluate the current practice patterns in the treatment of thyroid eye disease (TED) in Indian subcontinent through a web-based survey of members of Oculoplastics Association of India (OPAI). **Methods:** This was an online web-based questionnaire survey disseminated via monkeysurvey.com to all ratified active members of OPAI between May 1, 2016 and June 30, 2016. Questions encompassed the background, training, region, and experience of oculoplastic surgeons along with the management protocol of TED. **Results:** Of the 435 emails sent to OPAI members, 9 bounced and 180 (42.3%) responded within the study period. A large majority (96%) of respondents were oculoplastic surgeons practicing in India and the remaining practiced within South-East Asia. Two-thirds of respondents were oculoplastic surgeons with less than 10 years of clinical experience; 82% were fellowship trained in Oculoplasty. Almost all (99%) favored a multidisciplinary management of TED. A large majority routinely grade the severity (89%) and activity (87%) of disease before management. While corticosteroid remained the treatment of choice, 54% preferred immune-modulators as the second-line of therapy for recalcitrant TED. Three-quarters did not use orbital radiotherapy as a management modality in active TED owing to concerns over its efficacy and/or safety. **Conclusion:** The survey gives useful insights to the practice patterns of TED management in Indian subcontinent. Multidisciplinary approach and grading of disease severity and activity were the rule rather than exception among OPAI members. Immune modulation was the preferred steroid-sparing agent in recalcitrant disease. Orbital radiotherapy was an uncommon treatment choice.

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Thyroid eye disease is an autoimmune disease. It involves the deposition of hydrophilic glycosaminoglycans, proliferation of orbital adipose tissue, and/or fibrosis of the extraocular muscles.[1,2] Characteristic clinical features include upper lid retraction, proptosis, periorbital edema, conjunctival injection, diplopia, and strabismus.[3] In severe cases, muscle swelling may result in apical crowding and dysthyroid optic neuropathy (DON).[4] The management involves different modalities and recommendations for treatment.[5-9] Corticosteroid is the first-line of treatment.[10] Other options include immune-modulators, biologics, surgical decompression, and orbital radiation.[11]

Several questionnaires to gain insights into the practice trends in TED among practitioners have been conducted in Europe, Latin America, Asia-Pacific, and North America.[12-16] The TED survey was conducted in Europe by Weetman and Wiersingha in 1998.[12] This seminal survey used an index TED case and multiple variants of the same and respondents gave their choice of therapy.[12] The survey concluded that marked geographical variation was present in the treatment of TED across Europe.[12] A subsequent TED survey by Perros *et al*. was conducted among endocrinologists and ophthalmologists in Europe in 2006.[13] Ramos *et al*. reported the results of an identical TED survey among members of the Latin American Thyroid Association in 2008.[14] Both the above surveys by Perros *et al*. and Ramos *et al*. found deficiencies in the management of TED and recommended training of specialists and development of multidisciplinary centers for optimal TED management.[13,14] This eventually helped formulate the European Group On Grave's Orbitopathy (EUGOGO) guidelines.[13,14] In 2013, Perumal and Meyer conducted a similar survey in the United States among members of the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS) for the treatment of severe TED.[15] This survey reported that oral corticosteroids were preferred over intravenous corticosteroids (43% versus 40%) in severe TED by the members of the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASPORS).[15] Orbital decompression and orbital radiation also play significant roles in the management of severe TED.[15]

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Sundar *et al*. conducted a TED survey in 2014 among members of the Asia Pacific Society for Ophthalmic Plastic and Reconstructive Surgery (APSOPRS).[16] This survey had a few respondents from India. This study showed that CAS grading system was most commonly used and in active TED, intravenous methylprednisolone (1000 mg/day) for 3 days for 1–4 cycles was the most common management approach.[16] Orbital decompression was not common among APSOPRS members.[16] We conducted an online web-based survey among active ratified members of the Oculoplastics Association of India (OPAI) to gain insights into the practice patterns involved in the management of TED in India.

Methods

An online survey on current practice patterns of TED management was created using the online program Survey Monkey (SurveyMonkey.com, Portland, OR, USA). The questionnaire was designed after an extensive review of the previous TED surveys.[12-16] Efforts to include inputs from several active OPAI members (AG, AGN, MN, SD) were made. The survey contained 22 questions, most (19) of which had multiple choices and a few (3) allowed open-ended answers. Emails were sent to all 435 ratified members of the OPAI. In addition to evaluating the background, training, and experience of respondents, the survey encompassed the use of different modalities including intravenous/oral/orbital corticosteroids, immune-modulators, orbital radiotherapy, orbital decompression, and biologics in the Indian subcontinent.

The first invitations were sent out via email on May 1, 2016 to a total of 435 email addresses and responses were collected for the next 4 weeks. Subsequently, reminders were sent to encourage participation from nonresponders. The collection of responses ended on June 30, 2016. Responses were anonymous. Unanswered questions were excluded from further analysis. This study adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee.

Results

A total of 435 invitations were sent out in the study period. Nine e-mails were returned ("bounced"), resulting in a total of 426 e-mails successfully delivered. In all, a total of 180 responses were received with a response rate of 42.3%.

What is the profile of surgeons managing TED?

Those responding to the survey were primarily from India (96%) with the remaining from outside India. Within India, the regional distribution was 33.5% from the South, 24.3% from North, 21.4% from the West, and 16.8% from eastern India [Fig. 1a] including North-eastern states. When respondents were asked to choose the number of years they had spent practicing in the field of oculoplasty, the largest group (42%) belonged to those who had between 1 and 5 years of experience [Fig. 1b] followed by 22% between 6 and 10 years, 19% between 11 and 15 years, 10% between 16 and 20 years, and 7% with more than 20 years in practice. A large majority (82.4%) of respondents were fellowship trained in oculoplasty (long-term fellowship 65.9% and short-term fellowship 16.5%) and 17.6% had no formal training in oculoplasty.

What Investigations were most commonly requested?

A large number of respondents (61%) saw between 1 and 10 TED patients [Fig. 2a] in a month. A third of the respondents felt euthyroid TED constituted 10% of their TED patients. TSH receptor antibody titre (39%) was the most commonly performed investigation when faced with a case of euthyroid TED [Fig. 2b] followed by imaging (CT orbit; 21.3%) and a repeat thyroid function test (16.5%). Almost all oculoplastic surgeons managed TED as part of a team which almost always had endocrinologists and internists (99.4%). The opinion of specialists in radiation oncology (12%) and rheumatology (11.5%) was also sought by a few members. A small minority routinely sought the help of psychiatrists (3%) while managing TED patients.

How common is Sight threatening TED?

Most oculoplastic surgeons felt that dysthyroid optic neuropathy (DON; 53.9%) was the most common cause of visual loss in TED patients followed by exposure keratopathy (25.8%). One surgeon thought that corticosteroid-induced glaucoma was the cause of visual loss. Interestingly, 20% of oculoplastic surgeons had not encountered sight-threatening TED.

What Grading is followed for TED?

Grading the severity of TED was done by 89% and the activity of TED by 87% of members. VISA score (45%) was the most commonly used system to grade the severity of TED [Fig. 3a] followed by EUGOGO severity scale (27%) and Werner's NOSPECS score (17%). A small fraction (<10%) of oculoplastic surgeons did not grade the severity of disease. To grade the activity of TED, the clinical activity score (CAS) proposed by Mourits was most popular (60%) followed by VISA (27%) system [Fig. 3b].

How is TED managed medically?

Corticosteroid remains the first-line of treatment for active TED. A large majority (90%) of oculoplastic surgeons followed recommendation of EUGOGO (2016) and restricted the cumulative dose of intravenous methylprednisolone therapy within 8 g over one course of therapy.[17] In response to a question, a little over half of oculoplastic surgeons (54%) shared that they gave oral corticosteroids between pulse doses of intravenous methylprednisolone. When asked about the preferred second-line of therapy for recalcitrant active TED, 54% of oculoplastic surgeons chose immune-modulators followed by orbital decompression (20%), orbital radiotherapy (17%), and biologics (8%). Orbital radiotherapy as a management modality in early, progressive TED was acceptable to a quarter (26%) of oculoplastic surgeons [Fig. 4a] with three-fourths (74%) giving a negative response. Among those who used orbital radiotherapy (XRT) in TED, half (44%) preferred standard protocol (20 Gray over 2 weeks), followed by 26% who preferred reduced dose protocol (10 Gray over 2 weeks) and 15% who preferred low dose protocol (20 Gray over 20 weeks). Among those who did not use XRT in TED, 64% cited concerns about the safety and/or efficacy of XRT in TED as the primary reason. Prohibitive cost was cited as a reason for not using XRT by 7% of members. Three members thought that poor access to radiotherapy was the reason [Fig. 4b] for not using XRT in TED.

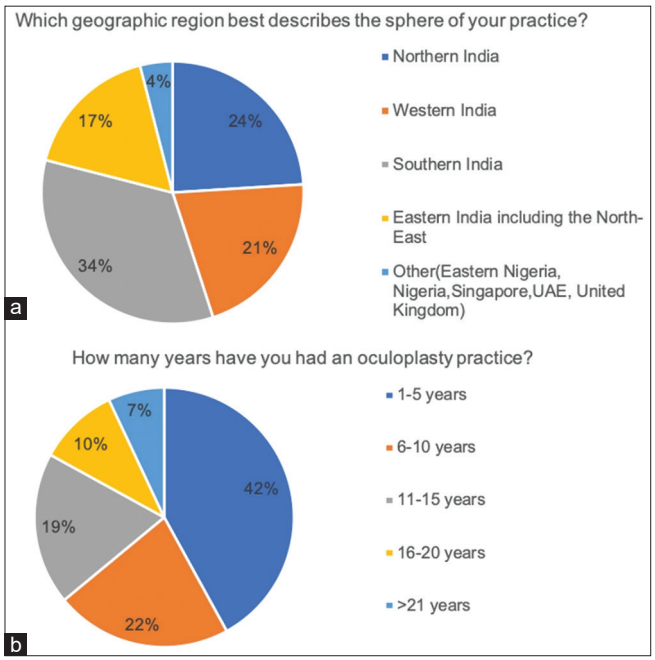

Figure 1: (a) Pictorial representation showing percentage of participants from different parts of India and other countries. (b) Years of Oculoplasty practice

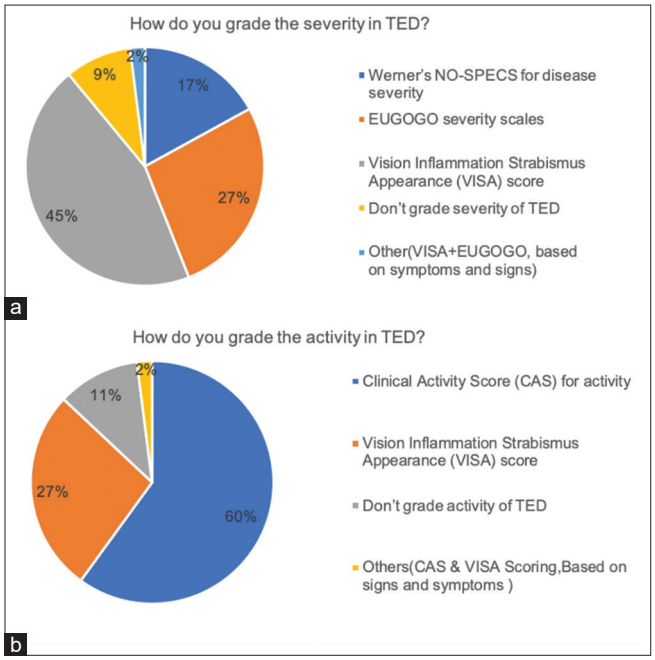

Figure 3: (a) Pictorial representation showing percentage of respondents using different systems to grade severity of TED; (b) Different systems to grade activity of TED

How is TED managed surgically?

Three-fourths of oculoplastic surgeons routinely performed orbital decompression for TED. Of these, a small number (6%) performed at least one orbital decompression in a month. Remaining performed orbital decompressions at frequencies of less than one per month. Almost a quarter (24%) respondents had never performed orbital decompression for TED. Bone

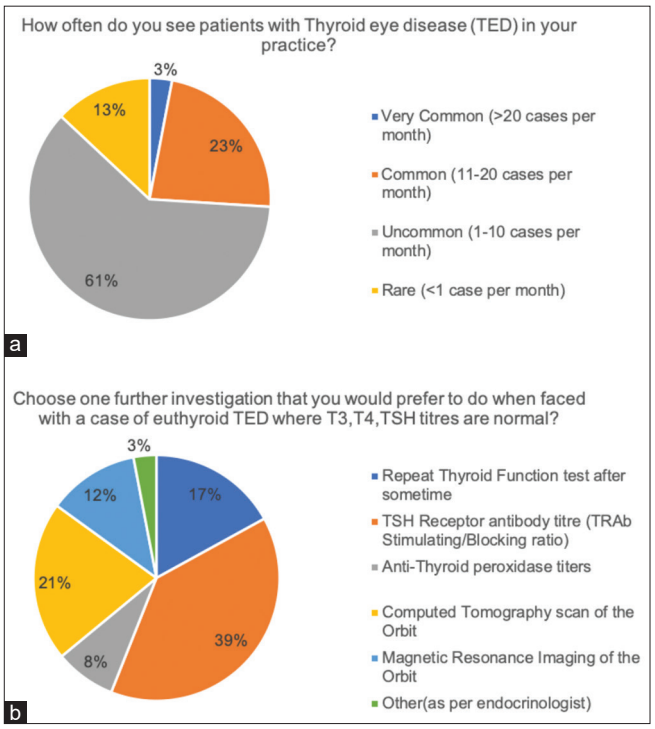

Figure 2: (a) Pictorial representation showing percentage of patients seen per month by the respondents; (b) Preferred investigation of choice in Euthyroid TED patients

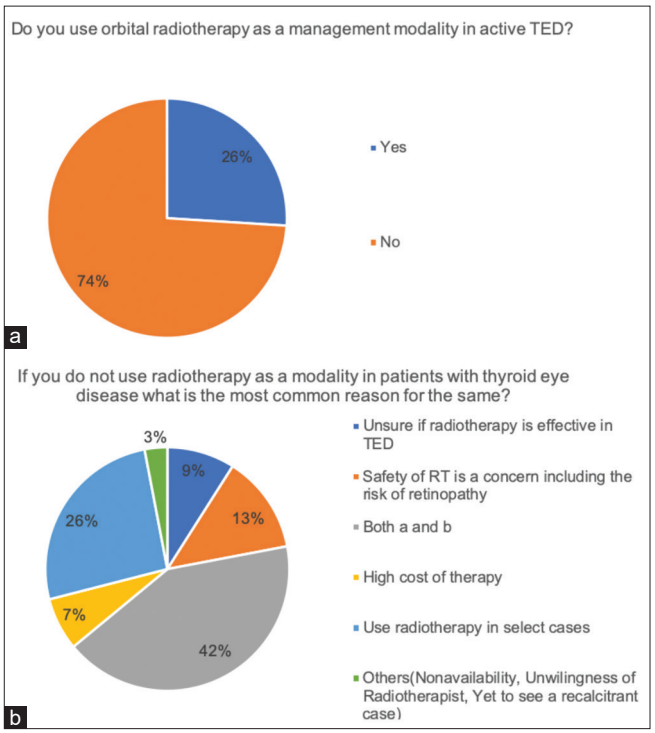

Figure 4: (a) Pictorial representation showing percentage of respondents using orbital radiotherapy for management of TED; (b) Reasons for not using orbital radiotherapy

and fat decompression was preferred by 58.4% and 6.7% performed only bone, followed by endoscopic (6%) and only fat decompression (3.4%).

Discussion

TED surveys have provided useful insights about practice patterns from Europe, Latin America, Asia-Pacific, and North America.[12-16] Serial TED surveys in Europe brought to the fore geographic variations in treatment and the need for training and development of multidisciplinary centers for TED management.[12,13] Some of these surveys helped formulate the EUGOGO practice guidelines in 2009.[12-14] Our TED survey had members of OPAI of which 2/3 were oculoplastic surgeons with <10 years of clinical practice, 82% were fellowship trained in oculoplasty, 99% favored a multidisciplinary management approach in TED, and 87%–89% routinely graded the severity and activity of disease. More than half preferred immune-modulators as the second-line of therapy for recalcitrant TED, one quarter used XRT, and three quarters routinely performed an orbital decompression in TED.

Overall, we received a good response (42.3%) to our online survey. Response rates of prior TED surveys were 34% for a survey by Ramos *et al*. in Latin America, 23% for Perros *et al*. in Europe, 25% for Sundar *et al*. in Asia-Pacific, 28% for EUGOGO survey and 38% for ASOPRS survey.[12-16] Surveys done by Perros *et al*. and Ramos *et al*. in Europe and Latin America, respectively, included endocrinologists, orbital surgeons, specialists in nuclear medicine, and physicians.[13,14] In contrast, ASOPRS and APSOPRS surveys were sent to members who were primarily oculoplastic surgeons.[15,16] Our TED survey was sent to all active members of OPAI who practiced in India and South-East Asia. We chose to do this survey among OPAI members assuming this was the group who were most likely to be involved in the management of TED patients in India.

Several grading systems are available for TED. In the APSOPRS survey, 70.5% used the CAS, 18.2% NOSPECS grading system, and 11.4% VISA-ITEDS system to grade TED.[16] In our survey, VISA-ITEDS system (45%) was the most commonly used system to grade the severity of the disease. To grade the activity of TED, CAS system was the most commonly used (60.2%) followed by VISA (26.7%). While there may have been overlap in regions covered by APSOPRS and our survey, it is heartening to note that a large majority of oculoplastic surgeons believed in grading the severity and activity of TED in the subcontinent. This is likely to be useful in collaborative studies done in the region. It is pertinent to keep in mind that two-thirds of our responses came from oculoplastic surgeons with <10 years clinical practice and 82% were fellowship trained. This may have skewed our results in favor of grading the severity and activity of disease and multidisciplinary approach to management. EUGOGO recommended that Grave's ophthalmopathy should be managed by an interdisciplinary team involving endocrinologists, ophthalmologists, and orbital surgeons for better outcome.[13]

Across surveys done in Europe, Latin America, North America, and Far-East Asia, corticosteroids were shown to be the mainstay disease-modifying agent for the treatment of TED.[12-15] In Asia-pacific study, intravenous pulsed methylprednisolone was the first therapeutic choice (79.5%) followed by oral corticosteroids (56.4%).[16] Other second-line management approaches included orbital radiotherapy (12.8%), immuno-suppressants (10.3%), and watchful waiting (7.7%).[16] ASOPRS study showed oral corticosteroid was preferred over intravenous corticosteroid though this difference was marginal.[15] Our TED survey threw valuable insights on the preferred management approach of OPAI members. A large majority of respondents in our survey (90%) restricted the cumulative dose of intravenous methylprednisolone to less than 8 g over one course of therapy. This aligned with EUGOGO recommendation and with the largely held belief that cumulative dose of IVMP >8 g is associated with higher systemic morbidity.[17-19]

While corticosteroids were found to be the most preferred (56%) disease-modifying agents in the index case in European survey reported by Weetman and Wiersingha, variants of TED like those with DON and diabetes mellitus showed appreciable shifts in preferences toward corticosteroid sparing agents like orbital radiotherapy, decompression, and immune-modulators.[12] However, geographic differences were noted between nations across Europe.[12] A similar shift in preferences toward immune-modulators was again seen by Perros *et al*. and Ramos *et al*. in subsequent surveys conducted in Europe and Latin America.[13,14] In our TED survey, immuno-modulators were the preferred (54%) second-line agents for recalcitrant TED followed by orbital decompression (20%) and orbital radiotherapy (17%). We believe that this is an interesting finding of our survey in sharp contrast to the European, Latin American, and even the ASOPRS surveys.[12-14,16] Preference of immune-modulators as the second-line agent in recalcitrant TED may be driven by several factors in South-East Asian region. In our survey, orbital radiotherapy was an uncommon choice among members. We also found almost all members favored a multidisciplinary approach and 11.5% closely managed TED patients with their rheumatology colleagues. These factors may have driven toward immune-modulation as the preferred steroid-sparing agent. India has high prevalence of diabetes with an overall nationwide prevalence of 7.3% in the population.[20] Association of diabetes with TED may have been responsible for an increased preference for immune-modulators among members. We realize that this is hypothetical and our questionnaire unfortunately did not probe the association of TED with diabetes as a possible variant.

Orbital radiotherapy was preferred by only a quarter [Fig. 4a] of the OPAI members. Concerns about efficacy and/or safety of orbital therapy were cited by members as reasons (64%) for not using XRT [Fig. 4b]. Cumulative evidence tend to suggest that ocular and systemic complications can be minimal with judicious use of XRT in active TED.[21,22] Retrospective studies by Marcocci *et al*. and Wakelkamp *et al*. demonstrated the risk of cataract formation after XRT was comparable to control and age-matched populations.[22,23] Marcocci *et al*. found evidence of radiation retinopathy in only 2 of 204 patients (1%) treated with XRT using a linear accelerator.[22] Theoretical estimates of lifetime risk of secondary tumor formation after bilateral orbital irradiation range between 0.6% and 1.4% of which 0.3%–0.5% are malignant.[24-26] Schaefer *et al*. in their study of 250 patients with a median follow-up of 31 years demonstrated no tumors within the radiation field.[27] An increased awareness of the efficacy and safety of XRT in early progressive TED may help in a wider acceptance of XRT as disease-modifying therapy for TED in the subcontinent.

Orbital decompression is commonly performed as rehabilitative surgery in inactive TED. It may also be performed, albeit rarely, in sight-threatening DON that is recalcitrant to corticosteroid therapy.[28] In the European survey by Weetman and Wiersingha, orbital decompression was the preferred treatment in variants of TED with optic nerve compromise and diabetes.[12] In ASOPRS survey, orbital decompression was first-line treatment in 10% respondents but this increased to 39% when respondents were asked about their preferred second-line treatment.[15] The APSOPRS survey showed that orbital decompression was not common procedure.[16] Our survey showed that orbital decompression was done by 76% of respondents. Out of it, 69% respondents do less than one case per month, rest 6% do 1–4 cases of decompression every month. One quarter (24%) of respondents had never performed an orbital decompression. Therefore, oculoplastic training programs and hands-on surgical skill development workshops may go a long way in making orbital decompression surgery a more common modality in armamentarium of every OPAI member.

Preferred practice patterns for TED may be governed by several factors—evidence showing efficacy and safety of available treatment modalities including their cost, surgical skills, availability of radiation facilities, and fellowship training as well as bias of physicians' and surgeons' and patient's preferences.[12] The major strength of our study is the good response received to our anonymous web-based survey and equitable representation from various parts of the country. Clinical practices may vary across geographical locations and our TED survey gives an Indian perspective to the existing literature. Our study did have its share of limitations. First, recall bias is inherent to all questionnaire-based surveys and is likely to have influenced responses. Our survey was sent to members of OPAI and thus responses may vary from a spectrum of physicians, endocrinologists, and general ophthalmologists who may be treating patients with TED. We acknowledge this as a shortcoming of our survey and agree that such a survey among physicians, endocrinologists, and general ophthalmologists may help formulating uniform practice patterns on TED in the region. Our questionnaire failed to address all aspects of TED management like eyelid and strabismus problems.

Conclusion

In conclusion, our TED survey provided useful insights to clinical practice patterns of TED management among members of OPAI in India. Almost all favored a multidisciplinary approach. Grading severity and activity of TED was the rule rather than exception in TED management. While corticosteroids remained modalities of first choice, more than half preferred immune-modulators as the steroid-sparing agent for recalcitrant TED. Orbital radiotherapy was relatively an uncommon treatment choice. An increased awareness toward evidence-based disease-modifying treatment modalities may help in the development of multiple nation-wide centers for TED management.

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Conflicts of interest

There are no conflicts of interest.

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