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A sight into the pathogenesis and treatment of thyroid-associated ophthalmopathy

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ABSTRACT

Introduction and aim. Thyroid-associated ophthalmopathy (TAO), often referred to as thyroid eye disease or Graves' ophthalmopathy, is a syndrome characterized by autoimmune inflammation affecting the eye muscles, connective tissue, and orbital fat. The aim of this literature review is to present TAO and integrate the available data in the literature regarding the pathogenesis and treatment methods. Based on these, the authors aim to examine whether, despite the extensive knowledge already available on TAO, there are still issues to be investigated.

Material and methods. In this literature review, books and scientific publications in both Polish and English languages have been assessed. The search criteria included keywords such as TAO, Graves' disease, thyroid-associated ophthalmopathy. The evaluation covered the following databases: PubMed, Scopus, Google Scholar.

Analysis of the literature. Typically, the eyeball is not involved, but in exceptional cases, corneal ulceration may occur, or inflammation of the optic nerve may ensue. TAO most commonly occurs in the course of hyperthyroidism in Graves' disease, involving up to 25–50% of cases. The coexistence of autoantigens shared between the thyroid and orbital tissues is considered the primary cause of TAO when it occurs concurrently with hyperthyroidism, later in its course, or even preceding the manifestation of hyperthyroidism, with or without concurrent thyroid dysfunction. TAO is generally bilateral, although dominance on one side is often observed. Common symptoms include eye pain, photophobia, diplopia, varying degrees of proptosis, and impaired vision. The cornerstone of treatment lies in managing hyperthyroidism, as TAO cannot be cured without it.

Conclusion. First-line treatment involves glucocorticoids, with radiation therapy as a supplementary option, and in cases unresponsive to pharmacological treatment, surgical intervention may be necessary.
Keywords. Graves' disease, TAO, thyroid-associated ophthalmopathy, thyroid eye disease

Introduction

Thyroid-associated ophthalmopathy (TAO) constitutes a clinical syndrome associated with hyperthyroidism in Graves' disease and represents its most common extrathyroidal manifestation.[1-9] It involves autoimmune inflammation of the soft tissues within the orbit, including the extraocular muscles, connective tissue, and orbital fat.[3,8,10-12] The estimated prevalence of this condition is 16/100,000 in women and 2.9/100,000 in men, with an overall occurrence of at least around 10/10,000.[3,13-16] Inflammation of these structures leads to their swelling, ultimately resulting in the protrusion of the eyeball from the orbital cavity. TAO occurs in 30% of individuals with Graves' and Basedow's diseases, but only 10% of them experience a severe course necessitating immunosuppressive treatment.[9,17-19] The exact cause of TAO remains not fully understood; however, it predominantly occurs in patients with hyperthyroidism or a history of it. Nevertheless, 5–8% of TAO cases are associated with thyroid inflammation in euthyroidism or hypothyroidism.[1,9,20] The hyperthyroidism in Graves' and Basedow's diseases is induced by autoantibodies that bind to the thyroid follicular cell's thyrotropin receptor, stimulating excessive thyroid hormone production. The presence of these antibodies in almost all TAO patients suggests that immune reactivity against the thyrotropin receptor underlies both hyperthyroidism and TAO.[20] Autoimmune processes leading to fibroblast proliferation, increased adipogenesis, and extracellular matrix expansion are involved in the pathophysiology of TAO.[8] Risk factors for TAO include stressful life events, genetics, gender, age, ethnic origin, smoking, thyroid dysfunction, and antibodies against thyrotropin. Smoking is identified as the most potent modifiable risk factor for the disease.[3] Common TAO symptoms include bilateral and symmetric retraction of the eyelids, proptosis, and double vision. Additionally, the disease manifests with tearing, redness, photophobia, and eye pain, significantly impacting patients' daily activities such as driving and interpersonal interactions. Ophthalmopathy typically occurs bilaterally, but unilateral cases may arise, often associated with the dominant side of the disease process. However, in 5% of cases, true unilateral occurrence occurs, posing diagnostic challenges due to its atypical presentation.[1,8]

Aim

The aim of the article is to review the available literature on thyroid-associated ophthalmopathy and to closely examine its pathogenesis, clinical presentation, and treatment methods in order to better understand this complex disease process and develop more effective treatment approaches.

Material and methods

In this literature review, books and scientific publications in both Polish and English languages have been assessed. The search criteria included keywords such as TAO, Graves' disease, thyroid-associated ophthalmopathy. The evaluation covered the following databases: PubMed, Scopus, Google Scholar.

Analysis of the literature

Pathogenesis

Thyroid-associated ophthalmopathy (TAO) is most commonly associated with hyperthyroidism in Graves' disease, although in 5-8% of cases, it can coexist with autoimmune thyroid inflammation in euthyroidism or hypothyroidism.[1,9,20] The occurrence of TAO is linked to an autoimmune process. The enlargement of extraocular muscles, connective tissue, and orbital fat results from interactions among orbital fibroblasts, cytokines, autoantibodies, immune cells, environmental factors, and genetic factors.[7]

Due to the frequent coexistence of ophthalmopathy in Graves' disease, there is a presence of similar antigens in both conditions. In Graves' disease, the loss of tolerance to the thyrotropin receptor (TSHR) occurs, making TAO inducible by autoimmune reactions against TSHR.[9,12,21] Clinical and experimental evidence supports this, with immunohistochemical studies showing TSHR overexpression in orbital tissues of TAO patients, with the highest receptor expression in individuals with clinically active disease. The expansion of orbital fat tissue results from early TSHR activation, enhancing the differentiation of orbital preadipocytes into adipocytes. Therefore, a strong association exists between circulating TSHR antibodies and TAO occurrence.[9,11,20-25] Moreover, tests have demonstrated that TSHR levels are correlated with the activity and severity of ophthalmopathy.[12] Recent studies have indicated significantly elevated expression levels of insulin-like growth factor-1 (IGF-1) and the insulin-like growth factor-1 Receptor (IGF-1R), suggesting their potential involvement in TAO pathogenesis. It has also been shown that IGF-1R and TSHR can form functional complexes, synergistically promoting the accumulation of hyaluronic acid with cytokines, thus inducing inflammation and the expansion of orbital muscle and fat tissue.[3,9,26,27]

Another component of the etiopathogenesis of TAO is considered to be orbital fibroblasts. As a result of autoimmune reactions, these fibroblasts produce glycosaminoglycans, mainly hyaluronic acid. These hydrophilic molecules attract water, causing swelling of the orbital tissue and extraocular muscles. The increase in the volume of soft tissues within the orbit explains the accompanying symptoms of TAO, including proptosis, dysfunction of extraocular muscles, and compression of the optic nerve.[9]

The initial triggering factor for the immunologic reaction in TAO is the activation of auto-reactive T lymphocytes by the thyroid-stimulating hormone receptor (TSHR) on the surface of orbital fibroblasts. This process leads to the release of pro-inflammatory cytokines, including interleukins (IL). Interleukins are proteins that regulate the immune response in the body. In the pathogenesis of TAO, IL-1, IL-6, IL-10, IL-

17, and IL-18 play a significant role in the inflammatory cascade.[3,4,6,10,12,17,22] IL-1 promotes the inflammatory process and cell adhesion, while IL-6 is involved in immune responses. It promotes the development of TH17 in naïve T lymphocytes under the influence of IL-23 and TGF-β. IL-17 is responsible for the recruitment of immune cells and contributes to tissue inflammation.[3,6] IL-18 is a pro-inflammatory cytokine that modulates the innate and adaptive immune systems, stimulates the production of cytokines and chemokines. It activates the chemotaxis of neutrophils and lymphocytes and the production of interferon-γ (IFN-γ) by natural killer (NK) cells. Studies conducted by Myśliwiec et al. have shown that the levels of IL-18 in the serum of TAO patients were significantly higher than in control groups, and after glucocorticoid treatment, their levels decreased. There is limited research on the role of IL-18 in TAO, so further studies are needed to better understand its role.[3]

IL-6 is identified as a critical mediator in the etiopathogenesis of TAO. It activates fibroblasts to produce hyaluronan, leading to increased inflammation and tissue growth. The activation of fibroblasts simultaneously results in the overexpression of TSHR, thereby perpetuating the autoimmune response.[12] Studies have shown that serum IL-6 levels are elevated in patients with Graves' disease, particularly in those with TAO, and its levels correlate with disease activity.[3]

IL-17 recruits neutrophils to the orbital tissues, releasing reactive oxygen species and other inflammatory mediators. This exacerbates tissue damage and contributes to the clinical symptoms of TAO.[3,21] IL-10 is an anti-inflammatory cytokine and also plays a role in regulating the immune response.[6]

Initially, IL-38 was thought to have anti-inflammatory effects, but it seems to have such a role only at high concentrations. Therefore, the function of IL-38 is controversial. It is believed to limit inflammation in orbital fibroblasts in TAO patients.[3] IL-38 may have potential significance in the therapeutic process, but further research is needed to conclusively determine its action.

In TAO, the balance between pro-inflammatory and anti-inflammatory cytokines is disrupted, significantly contributing to increased and chronic inflammation and tissue remodeling in the orbital region. The precise identification of interleukins and understanding their roles in the inflammatory process in TAO could significantly contribute to the development of diagnostics and treatment for this complex disease.

In the pathogenesis of Graves' disease, 20–60% of patients have a positive family history of thyroid diseases. Patients with this disease also show an increased expression of certain human leukocyte antigen (HLA) genes more frequently than healthy individuals. The HLA-B8, DR3, DQA10501 haplotype may increase susceptibility to the disease. On the other hand, in patients with TAO, researchers have examined the frequency of major histocompatibility complex class II (MHC II) alleles in 81 Brazilian TAO patients and 161 healthy individuals in the control group. It was found that in TAO patients with greater involvement of extraocular muscles, the HLA-DRB116 allele is more common, while in patients with minimal involvement of extraocular muscles, the HLA-DRB1*03 allele is more frequent.[7,28] The role of genetic factors has also been demonstrated in studies conducted on twins and families.[9] In Danish population studies

of monozygotic twins, the concordance coefficient was 35%, suggesting low penetrance of the implicated genes.[7] Several genes have been identified that predispose patients with Graves' disease to the development of TAO, but the diversity of the genetic profile of patients remains uncertain.[9] Conducted studies suggest an association between genetic predisposition and the manifestation of TAO. This provides further scope for development and the conduct of additional research to more precisely determine the genes involved in the disease process.

Additional interesting studies have been initiated on differences in the composition of gut microbiota in patients with Graves' disease, with and without TAO, as well as research on animals suggesting a crucial role of gut microbiota in TSHR-induced disease.[9] This opens up another field of research and may contribute to a better understanding and identification of factors involved in the occurrence of TAO.

Clinical presentation

The clinical picture of thyroid-associated ophthalmopathy (TAO) is typically characteristic in the majority of cases. Symptoms are mostly bilateral, with the disease process dominating on one side in 9-34% of patients; however, it remains bilateral in those cases [8]. Truly unilateral TAO occurs in only about 5% of cases.[1,8] The most common symptom of TAO is eyelid retraction, present in 90-98% of patients, often changing with gaze—a phenomenon known as Kocher's sign, where the upper border of the sclera is exposed when looking upward. Another nearly pathognomonic sign for TAO is lateral widening of the retracted eyelid contour. Several factors contribute to eyelid retraction, including increased sympathetic stimulation of the Müller muscle, contraction of the levator muscle, and scarring between the fascia of the lacrimal gland and the levator. Another frequent symptom in TAO patients is incomplete eyelid closure, leading to dryness, foreign body sensation, roughness, tearing, photophobia, and, consequently, corneal ulceration. Soft tissue swelling in the orbit causes visible proptosis and redness. This results in a disturbance in the relaxation of the extraocular muscles, leading to double vision. In severe cases with pronounced edema, compression of the optic nerve may occur, causing visual impairment up to blindness, observed in only 5% of patients.[1,2,7,29-32] TAO is the most common cause of adult-onset strabismus.[14]

Treatment

Given its strong association with Graves' disease, TAO treatment should begin with managing hyperthyroidism. Effective TAO treatment is not possible without controlling hyperthyroidism. In the treatment process, the priority is visual disturbances, which, depending on the presence of inflammation, can be treated with corticosteroids, radiotherapy, or orbital decompression surgery. Another priority is controlling inflammation, which can be treated with corticosteroids, steroid-sparing immunosuppressive drugs, or radiotherapy. Strabismus and changes in appearance are often treated conservatively, waiting for

inflammation to resolve before considering surgical intervention.[1,2,7,9,10,14,25] It is crucial for patients to quit smoking as there is a strong association between TAO and cigarette smoking.[8,33,34]

Systemic treatment relies significantly on glucocorticoids (GCS), with an estimated effectiveness of 40-60%. However, relapses at the end of therapy or during treatment are common. The use of pulsatile GCS administration has been developed to harness the immunosuppressive effects of GCS while simultaneously reducing side effects. Methylprednisolone, given in pulses over 12 weeks at a cumulative dose of 4.5 to 7.5g, has proven effective, with a higher dose effectively reducing the overall severity of the disease.[1,3,11,19,25,35-37] Protocols utilizing cumulative methylprednisolone doses exceeding 8g have been associated with severe, even fatal, liver toxicity and should not be routinely applied.[11,19,25,35] Studies have shown a significant advantage of intravenous methylprednisolone over orally administered prednisone, with the former demonstrating better clinical response and fewer adverse effects.[1,11,25,38]

Immunosuppressive treatment options include mycophenolate mofetil, cyclosporine A, and azathioprine, usually employed as adjunctive therapy for inadequate response to GCS.[7,39-41] A randomized study compared the effectiveness of monotherapy with GCS (methylprednisolone) to combined treatment with GCS and mycophenolate sodium for 24 weeks, followed by a 12-week observation. While patients receiving both drugs showed greater improvement, the benefits of combining GCS with mycophenolate were not significantly higher. Monotherapy with azathioprine did not significantly alter the course of the disease in moderate and severe TAO over a 2-year period, though later studies lacked sufficient statistical power for clear conclusions.[11,42,43] Studies involving cyclosporine A demonstrated that its use as monotherapy was less effective than oral prednisone. However, when used in combination, both drugs proved more effective than prednisone alone, potentially useful for patients unresponsive to GCS therapy.[25]

The pathogenesis of TAO is likely attributed to immune cells and cytokines; hence, monoclonal antibodies disrupting cytokine signaling may have therapeutic applications. Although only a few drugs have been tested in randomized studies, the results are promising. In one study, 152 TAO patients treated with rituximab (RTX) showed a significant reduction in symptoms and recurrence frequency, although resolution of proptosis or improvement in double vision was not described compared to baseline values. RTX effectively inactivates TAO and limits disease recurrence, proving effective even in patients resistant to GCS therapy.[11,19,38,44-46] The use of Tocilizumab (TCZ) in a randomized clinical trial resulted in disease inactivation in 93% of TAO patients compared to 59% receiving a placebo after 16 weeks. While TCZ reduced proptosis, improvement in double vision was observed in only 5-6% of patients. TCZ appears effective in patients resistant to conventional GCS therapy.[19,38,47] The further development of therapy using monoclonal antibodies appears to be crucial in refining conservative treatment methods, given the strong association between autoimmune processes and the occurrence of TAO.

Radiation therapy is another method of treating TAO. Assessing its effectiveness is challenging due to the lack of controlled studies and frequent concomitant use of GCS, significantly complicating retrospective

data analysis. Orbital radiotherapy is effective only in patients with active disease and recent progression. Patients with inactive TAO do not respond to radiotherapy. Typically, a dose of 20 Gy per side is administered in 10 fractions over 2 weeks. During orbital radiotherapy, there may be a transient worsening of inflammation, which can be easily prevented by simultaneously using GCS. This method is often used as a supplementary treatment in systemic therapy. Although the effectiveness of radiotherapy in TAO has been questioned, it remains in constant use. It is a relatively safe method, with a low risk of optic neuropathy or retinopathy.[7,19,25,48,49]

Indications for surgical treatment in TAO include optic neuropathy, double vision, and corneal exposure. The goal of surgical intervention is orbital decompression, strabismus correction, and correction of eyelid abnormalities. The most appropriate sequence in surgical treatment is typically decompression of the orbit first, followed by strabismus surgery, and finally, eyelid procedures. The majority of surgeries are performed in a state of inactive TAO when the condition has been stable for at least 6-8 months. However, decompression may be necessary urgently in cases of compressive optic neuropathy or severe proptosis with corneal ulceration.[7,25,50] Orbital decompression involves removing parts of the bone building the orbit and removing fat from the orbit. Currently, the most common surgical approach includes medial wall, orbital floor, and/or lateral wall decompression. Simultaneous decompression of bones combined with fat removal is gaining importance due to its good clinical outcomes. Surgery on the extraocular muscles aims to alleviate double vision in the primary position and downward gaze. Eyelid surgery involves gradually weakening the Müller and levator palpebrae superioris muscles to better cover the cornea with the upper eyelid. In cases of significant retraction of the lower eyelid, a spacer graft may be necessary.[7,51]

Effective treatment of TAO is possible with various therapeutic methods. The choice of treatment depends on the severity of the disease, its activity, and the individual needs and preferences of the patient. Treating TAO poses a therapeutic challenge, but continuously improving methods help achieve successful treatment and limit the lasting consequences of the disease.

Quality of life of patients

TAO exerts a significant impact on the quality of life of patients. Visual disturbances such as double or blurred vision affect their daily functioning, greatly limiting both physical and professional activities. Patients report difficulties in driving and challenges in computer work. In a descriptive study conducted on patients with varying degrees of TAO, the quality of life was assessed using the short-form standardized questionnaire, the medical outcomes study (MOS-36). In the examined group of German TAO patients, low scores were observed on the MOS-36 scale, with clear differences compared to the control group noted in the areas of social functioning, mental health, health perception, and bodily pain. These results highlight the impact of common visual symptoms on health and well-being measured using the MOS-36 scale.[1,52] In other studies, it has been shown that in patients with Graves' disease who developed TAO, the quality of

life decreased regardless of the treatment applied. It is also significant that patients with TAO returned to physical health within a year, but the recovery of mental health took twice as long.[53] In the course of TAO, exophthalmos often occurs, leading to a decrease in self-acceptance among patients and a deterioration in interpersonal relationships.[1] Considering the above, paying attention to the psychological aspects of TAO patients appears to be crucial.

Conclusion

Despite significant progress in understanding TAO, certain elements are still lacking. It is essential to emphasize the need for further development in clinical research to discover new biomarkers involved in the onset of TAO. This will be crucial for a better understanding of the disease's pathogenesis and, consequently, for the development and more precise selection of treatment, particularly using monoclonal antibodies. Such an approach should help limit the occurrence of irreversible consequences of TAO and, in turn, enhance the effectiveness of the conducted therapy. Both review literature and works based on clinical research were utilized to provide a broader perspective on the presented topic.

Declarations

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Author contributions

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Conflicts of interest

The author(s) declare no competing interests.

Data availability

Not applicable.

References

1. Şahlı E, Gündüz K. Thyroid-associated Ophthalmopathy. *Turk J Ophthalmol.* 2017;47(2):94-105. doi: 10.4274/tjo.80688

2. Moledina M, Damato EM, Lee V. The changing landscape of thyroid eye disease: current clinical advances and future outlook. *Eye.* 2024. doi:10.1038/s41433-024-02967-9
3. Zhang P, Zhu H. Cytokines in Thyroid-Associated Ophthalmopathy. *J Immunol Res*. 2022;2022:2528046. doi: 10.1155/2022/2528046
4. Feldon SE, Weiner JM. Clinical significance of extraocular muscle volumes in Graves' ophthalmopathy: a quantitative computed tomography study. *Arch Ophthalmol.* 1982;100(8):1266-1269. doi: 10.1001/archopht.1982.01030040244006
5. Nunery WR, Nunery CW, Martin RT, Truong TV, Osborn DR. The risk of diplopia following orbital floor and medial wall decompression in subtypes of ophthalmic Graves' disease. *Ophthal Plast Reconstr Surg.* 1997;13:153-60. doi: 10.1097/00002341-199709000-00001
6. Smith TJ, Hoa N. Immunoglobulins from patients with Graves' disease induce hyaluronan synthesis in their orbital fibroblasts through the self-antigen, insulin-like growth factor-I receptor. *J Clin Endocrinol Metab*. 2004;89:5076-5080. doi: 10.1210/jc.2004-0716
7. Maheshwari R, Weis E. Thyroid associated orbitopathy. *Indian J Ophthalmol*. 2012;60(2):87-93. doi: 10.4103/0301-4738.94048
8. Panagiotou G, Perros P. Asymmetric Graves' Orbitopathy. *Front Endocrinol (Lausanne).* 2020;11:611845. doi: 10.3389/fendo.2020.611845.
9. Bartalena L, Tanda M. Current concepts regarding Graves' orbitopathy. *J Intern Med*. 2022; 292(5):692-716. doi: 10.1111/joim.13524
10. Taylor P, Zhang L, Lee R, et al. New insights into the pathogenesis and nonsurgical management of Graves orbitopathy. *Nat Rev Endocrinol.* 2020;16(2):104-116. doi: 10.1038/s41574-019-0305-4.
11. Neag E, Smith T. 2021 Update on Thyroid-Associated Ophthalmopathy. *J Endocrinol Invest.* 2022;45(2):235-259. doi: 10.1007/s40618-021-01663-9
12. Turck N, Eperon S, De Los Angeles Gracia M. Thyroid-Associated Orbitopathy and Biomarkers. Where We Are and What We Can Hope for the Future. *Dis Markers*. 2018;2018:7010196. doi: 10.1155/2018/7010196
13. Weiler D. Thyroid eye disease: a review. *Clin Exp Optom*. 2017;100(1):20-25. doi: 10.1111/cxo.12472
14. Hennein L, Robbins S. Thyroid-Associated Orbitopathy. Management and Treatment. *J Binocul Vis Ocul Motil.* 2022;72(1):32-46.
15. Lazarus J. H. Epidemiology of Graves' orbitopathy (GO) and relationship with thyroid disease. *Best Pract Res Clin Endocrinol Metab*. 2012;26(3):273-279. doi: 10.1016/j.beem.2011.10.005

16. Perros P, Hegedüs L, Bartalena L, et al. Graves' orbitopathy as a rare disease in Europe. a European group on Graves' orbitopathy (EUGOGO) position statement. *Orphanet Journal of Rare Diseases*. 2017;12(1):72. doi: 10.1186/s13023-017-0625-1
17. Chin YH, Ng CH, Lee MH et al. Prevalence of thyroid eye disease in Graves' disease. a meta-analysis and systematic review. *Clin Endocrinol*. 2020;93:363-374. doi: 10.1111/cen.14296
18. Ippolito S, Cusini C, Lasalvia P, et al. Change in newly diagnosed Graves' disease phenotype between the twentieth and the twenty-first centuries. meta-analysis and meta-regression. *J Endocrinol Invest.* 2021;44:1707-1718. doi: 10.1007/s40618-020-01479-z
19. Barbesino G, Salvi M, Freitag S. Future Projections in Thyroid Eye Disease. *J Clin Endocrinol Metab*. 2022;107(1):47-56. doi: 10.1210/clinem/dgac252
20. Bahn R. Graves' Ophthalmopathy. *N Engl J Med*. 2010;362(8):726-738. doi: 10.1056/NEJMra0905750
21. Burch HB, Wartofsky L. Graves' ophthalmopathy: current concepts regarding pathogenesis and management. *Endocr Rev*. 1993;14:747-793. doi: 10.1210/edrv-14-6-747
22. Boschi A, Daumerie C, Spiritus M, et al. Quantification of cells expressing the thyrotropin receptor in extraocular muscles in thyroid associated orbitopathy. *Br J Ophthalmol*. 2005;89:724-729. doi: 10.1136/bjo.2004.050807
23. Hai YP, Lee ACH, Frommer L, Diana T, Kahaly GJ. Immunohistochemical analysis of human orbital tissue in Graves' orbitopathy. *J Endocrinol Invest*. 2020;43:123-137. doi: 10.1007/s40618-019-01116-4
24. Wakelkamp IM, Bakker O, Baldeschi L, Wiersinga WM, Prummel MF. TSH-receptor expression and cytokine profile in orbital tissue of active vs. inactive Graves' ophthalmopathy patients. *Clin Endocrinol*. 2003;58:280-287. doi: 10.1046/j.1365-2265.2003.01708.x
25. Ahn E, Subramanian P. Treatment modalities of thyroid related orbitopathy. *Indian J Ophthalmol*. 2014;62(10):999-1002. doi: 10.4103/0301-4738.145994
26. Tsui S, Naik V, Hoa N, et al. Evidence for an association between thyroid-stimulating hormone and insulin-like growth factor-1 receptors. a tale of two antigens implicated in Graves' disease. *J Immunol.* 2008;181:4397-4405. doi: 10.4049/jimmunol.181.6.4397
27. Krieger CC, Sui X, Kahaly GJ, Neumann S, Gershengorn MC. Inhibition of TSH/IGF-1 receptor crosstalk by teprotumumab as a treatment modality of thyroid eye disease. *J Clin Endocrinol Metab.* 2021;107(4):1653-1660. doi: 10.1210/clinem/dgab824
28. Akaishi P, Cruz A, Silva F. The role of major histocompatibility complex alleles in the susceptibility of Brazilian patients to develop the myogenic type of Graves' orbitopathy. *Thyroid*. 2008;18(4):443-447. doi: 10.1089/thy.2007.0194

29. Wiersinga WM, Kahaly GJ. Graves orbitopathy. A multidisciplinary approach. *J Clin Endocrinol Metab.* 2001;86(2):501-503. doi: 10.1210/jcem.86.2.7338
30. Gilbard JP, Farris RL. Ocular surface drying and tear film osmolarity in thyroid eye disease. *Acta Ophthalmol (Copenh).* 1983;61:108-116. doi: 10.1111/j.1755-3768.1983.tb01401.x
31. Dickinson AJ, Perros P. Controversies in the clinical evaluation of active thyroid-associated orbitopathy. Use of a detailed protocol with comparative photographs for objective assessment. *Clin Endocrinol (Oxf)*. 2001;55:283-303. doi: 10.1046/j.1365-2265.2001.01349.x
32. Frueh BR, Musch DC, Garber FW. Lid retraction and levator aponeurosis defects in Graves' eye disease. *Ophthalmic Surg*. 1986;17:216-220.
33. Cawood TJ, Moriarty P, O'Farrelly C, O'Shea D. Smoking and thyroid-associated ophthalmopathy. A novel explanation of the biological link. *J Clin Endocrinol Metab*. 2007;92:59-64. doi: 10.1210/jc.2006-1824
34. Krassas GE, Wiersinga W. Smoking and autoimmune thyroid disease. The plot thickens. *Eur J Endocrinol.* 2006;154:777-780. doi: 10.1530/eje.1.02157
35. Marino M, Morabito E, Brunetto R. Acute and severe liver damage associated with intravenous glucocorticoid pulse therapy in patients with Graves' ophthalmopathy. *Thyroid*. 2004;14(5):403-406. doi: 10.1089/105072504774193276
36. Nagayama Y, Izumi M, Kiriyama T, et al. Treatment of Graves' ophthalmopathy with high-dose intravenous methylprednisolone pulse therapy. *Acta Endocrinol (Copenh).*1987;116(4):513-518. doi: 10.1530/acta.0.1160513
37. Dandona P, Havard CW, Mier A. Methylprednisolone and Graves' ophthalmopathy. *BMJ*. 1989;298(6676):830-830. doi: 10.1136/bmj.298.6676.830
38. González-García A, Sales-Sanz M: Treatment of Graves' ophthalmopathy. *Med Clin (Barc).* 2021;156(4):180-186. doi: 10.1016/j.medcli.2020.07.031
39. Ye X, Bo X, Hu X, et al. Efficacy and safety of mycophenolate mofetil in patients with active moderate-to-severe Graves' orbitopathy. *Clin Endocrinol (Oxf)*. 2017;86(2):247-255. doi: 10.1111/cen.13170
40. Kahaly GJ, Riedl M, Konig J, et al. European Group on Graves' Orbitopathy (EUGOGO). Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial. *Lancet Diabetes Endocrinol.* 2018;6(4):287-298. doi: 10.1016/S2213-8587(18)30020-2
41. Bartalena L, Kahaly GJ, Baldeschi L, 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(4):43-67. doi: 10.1530/EJE-21-0479

42. Kahaly G, Riedl M, König J. Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial. *Lancet Diabetes Endocrinol*. 2018;6(4):287-298. doi: 10.1016/S2213-8587(18)30020-2
43. Kelley W, Rosenbloom F, Seegmiller J. The effects of azathioprine (imuran) on purine synthesis in clinical disorders of purine metabolism: *J Clin Invest*. 1967;46(9):1518-1529. doi: 10.1172/JCI105643.
44. Salvi M, Vannucchi G, Beck-Peccoz P. Potential utility of rituximab for Graves' orbitopathy. *J Clin Endocrinol Metab.* 2013;98(11):4291-4299. doi: 10.1210/jc.2013-1804
45. Silkiss RZ, Reier A, Coleman M, Lauer SA: Rituximab for thyroid eye disease. *Ophthalmic Plast Reconstr Surg*. 2010;26(5):310-314. doi: 10.1097/IOP.0b013e3181c4dfde
46. Chen J, Chen G, Sun H. Intravenous rituximab therapy for active Graves' ophthalmopathy: a meta-analysis. *Hormones (Athens).* 2021;20(2):279-286. doi: 10.1007/s42000-021-00282-6
47. Moreiras J, Gomez-Reino J, Perez-Pampis. Efficacy of Tocilizumab in Patients with Moderate-to-Severe Corticosteroid-Resistant Graves Orbitopathy. A Randomized Clinical Trial. *Am J Ophthalmol*. 2018;195:181-190. doi: 10.1016/j.ajo.2018.07.038
48. Bartley G, Gorman C. Perspective--Part I: the Mayo Orbital Radiotherapy for Graves Ophthalmopathy (ORGO) study lessons learned. *Ophthalmic Plast Reconstr Surg*. 2002;18(3):170-172. doi: 10.1097/00002341-200205000-00002
49. Grassi P, Strianese D, Piscopo R, Pacelli R, Bonavolonta G. Radiotherapy for the treatment of thyroid eye disease-a prospective comparison is orbital radiotherapy a suitable alternative to steroids. *Ir J Med Sci.* 2017;186(3):647-652. doi: 10.1007/s11845-016-1542-3
50. Finn AP, Bleier B, Cestari DM, et al. A retrospective review of orbital decompression for thyroid orbitopathy with endoscopic preservation of the inferomedial orbital bone strut. *Ophthalmic Plast Reconstr Surg.* 2017;33(5):334-339. doi: 10.1097/IOP.0000000000000782
51. Rootman DB, Golan S, Pavlovich P, Rootman J. Postoperative changes in strabismus, ductions, exophthalmometry, and eyelid retraction after orbital decompression for thyroid orbitopathy. *Ophthalmic Plast Reconstr Surg*. 2017;33(4):289-293. doi: 10.1097/IOP.0000000000000758
52. Kahaly GJ, Hardt J, Petrak F, Engle UT. Psychosocial Factors in Subjects with Thyroid-Associated Ophthalmopathy. *Thyroid*. 2002;12(3):237-239. doi: 10.1089/105072502753600205
53. Abraham-Nordling M, Wallin G, Traisk F, et al. Thyroid-associated ophthalmopathy; quality of life follow-up of patients randomized to treatment with antithyroid drugs or radioiodine. *Eur J Endocrinol.* 2010;163(4):651-657. doi: 10.1530/EJE-10-0475