



Graves' Ophthalmopathy: A Comprehensive Review of Current Evidence and Management Approaches

Daniela Haxhiyseni

Marsida Krasniqi

Rezarta Kalaja

Department of Medical Science,
University Aleksander Moisiu,
Durrës, Albania

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Abstract

Thyroid ophthalmopathy, also known as Graves' ophthalmopathy or thyroid eye disease, is an autoimmune condition that affects the eyes and is often associated with hyperthyroidism, an overactive thyroid gland. It is characterized by inflammation, swelling, and tissue changes in the muscles and tissues around the eyes, leading to a range of symptoms including bulging eyes, double vision, eye pain, redness, and sensitivity to light. The treatment of thyroid ophthalmopathy typically involves managing the underlying thyroid condition, relieving symptoms, and preventing complications. Corticosteroids, such as prednisone, are commonly used to reduce inflammation and swelling in the eye tissues. They can be administered orally or locally through eye drops or injections. Orbital radiotherapy, a form of radiation therapy, may also be used to reduce inflammation in the eye tissues, particularly in cases where corticosteroids are not effective or not well tolerated. In addition to medical treatments, eye protection measures are important in managing thyroid ophthalmopathy. This may include wearing sunglasses to protect the eyes from exposure to sunlight and using lubricating eye ointments at night to alleviate dryness. If eyelid retraction or swelling is present, eyelid management techniques such as lubricating ointments, taping the eyelids closed during sleep, or using moisture chamber glasses may be recommended to protect the cornea and relieve symptoms. Managing the underlying thyroid condition is also crucial in the treatment of thyroid ophthalmopathy. This may involve medications to regulate thyroid hormone levels, radioactive iodine therapy, or surgery to remove the thyroid gland, depending on the individual case. Surgical intervention may also be necessary in severe cases of eye-related complications, such as double vision or optic nerve compression. Surgical options may include decompression surgery, eyelid surgery, or strabismus surgery to realign the eyes. It's important to note that the management of thyroid ophthalmopathy is typically tailored to the specific needs of each patient and may involve a multidisciplinary approach involving endocrinologists, ophthalmologists, and sometimes surgeons. Regular follow-up and monitoring are necessary to assess the effectiveness of the treatment plan and make any necessary adjustments. In conclusion, thyroid ophthalmopathy is an autoimmune condition that affects the eyes and is often associated with hyperthyroidism. Treatment typically involves managing the underlying thyroid condition, relieving symptoms, and preventing complications. Corticosteroids, orbital radiotherapy, eye protection measures, and surgical intervention may be used as part of the management plan. It's important to work closely with a healthcare professional to determine the most appropriate treatment approach for each individual case.

Keywords: Thyroid ophthalmopathy, Graves' ophthalmopathy, thyroid eye disease, hyperthyroidism, corticosteroids, orbital radiotherapy, eye protection, eyelid management, thyroid management, surgical intervention

1. Introduction

Thyroid ophthalmopathy, also known as Graves' ophthalmopathy or thyroid eye disease, is an autoimmune condition that affects the eyes and is often associated with hyperthyroidism, an overactive thyroid gland. It is characterized by inflammation, swelling, and tissue changes in the muscles and tissues around the eyes, leading to a range of symptoms including bulging eyes, double vision, eye pain, redness, and sensitivity to light. The management of thyroid ophthalmopathy requires a comprehensive approach involving the coordination of multiple healthcare professionals, including endocrinologists, ophthalmologists, and sometimes surgeons. Treatment strategies typically focus on managing the underlying thyroid condition, relieving symptoms, and preventing complications. In this article, we will review the current understanding of thyroid ophthalmopathy, including its pathophysiology, clinical presentation, and diagnostic evaluation. We will then delve into the various treatment modalities available, including corticosteroids, orbital radiotherapy, eye protection measures, eyelid management, thyroid management, and surgical intervention. Relevant research findings and evidence-based guidelines will be incorporated, along with appropriate citations and references.

1.1 Pathophysiology of Thyroid Ophthalmopathy

Thyroid ophthalmopathy is believed to result from an autoimmune process in which the immune system mistakenly attacks the tissues around the eyes, including the muscles and connective tissues. The exact cause of this autoimmune response is not yet fully understood, but it is thought to involve a complex interplay of genetic, environmental, and immunological factors. One of the key players in the pathophysiology of thyroid ophthalmopathy is the thyroid-stimulating hormone receptor (TSHR), which is found on the surface of cells in the thyroid gland and the tissues around the eyes. In Graves' disease, an autoimmune condition characterized by hyperthyroidism, the immune system produces antibodies known as TSHR-stimulating antibodies (TSAb) that bind to the TSHR and activate it, leading to increased production of thyroid hormones. These antibodies can also cross-react with the TSHR in the tissues around the eyes, leading to inflammation, swelling, and tissue damage, which result in the clinical manifestations of thyroid ophthalmopathy. In addition to the immune response, other factors such as cytokines, adipokines, and oxidative stress are also thought to play a role in the pathophysiology of thyroid ophthalmopathy. Cytokines, which are small proteins produced by immune cells, can stimulate inflammation and contribute to tissue damage. Adipokines, which are proteins secreted by adipose tissue, can also influence the inflammatory process and may contribute to the orbital fat expansion seen in thyroid ophthalmopathy. Oxidative stress, which occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them, can cause damage to cellular components and contribute to tissue inflammation and damage.

1.2 Clinical Presentation of Thyroid Ophthalmopathy

Thyroid ophthalmopathy can present with a wide range of clinical manifestations, which can vary in severity and may change over time. Common symptoms include:

- **Bulging eyes (proptosis):** Proptosis occurs when the eyes protrude from their normal position, giving them a prominent appearance. It may result from inflammation, swelling, and expansion of the orbital tissues, including the fat and muscles.
- **Double vision (diplopia):** Diplopia occurs when the eyes do not move in a coordinated manner, leading to the perception of two images instead of one. This may result from inflammation and scarring of the muscles that control eye movements.
- **Eye pain, redness, and tearing:** Inflammation of the eye tissues can cause pain, redness, and tearing. The eyes may also be sensitive to light (photophobia).
- **Eyelid retraction and lagophthalmos:** Eyelid retraction occurs when the upper eyelids are pulled back and do not fully cover the eyes, leading to an increased exposure of the cornea. This can result in dryness, discomfort, and may even lead to corneal ulceration in severe cases. Lagophthalmos refers to the inability to fully close the eyelids, which can further contribute to dryness and corneal exposure.
- **Swelling and inflammation of the conjunctiva and eyelids:** The conjunctiva, the clear membrane that covers the white part of the eye, and the eyelids can become swollen and inflamed due to the autoimmune response and tissue changes associated with thyroid ophthalmopathy.
- **Changes in visual acuity and color vision:** In some cases, thyroid ophthalmopathy may lead to changes in

visual acuity, color vision, and visual field due to the compression of the optic nerve or involvement of the retina.

- Restriction of eye movements: The muscles that control eye movements may become inflamed, scarred, or enlarged in thyroid ophthalmopathy, leading to limited or restricted eye movements.

1.3 *Diagnosis of Thyroid Ophthalmopathy*

The diagnosis of thyroid ophthalmopathy is typically based on a combination of clinical evaluation, patient history, and imaging studies. A thorough ophthalmic examination, including visual acuity testing, evaluation of eye movements, measurement of proptosis, assessment of eyelid position and function, and evaluation of conjunctival and eyelid inflammation, is crucial in establishing the diagnosis. A careful medical history, including any history of thyroid dysfunction, family history of autoimmune diseases, and exposure to risk factors such as smoking, should also be obtained. Imaging studies, such as orbital computed tomography (CT) or magnetic resonance imaging (MRI), may be helpful in confirming the diagnosis and assessing the extent of orbital involvement. These imaging studies can help visualize the changes in orbital fat, muscles, and other tissues, and can also be used to monitor the disease progression and response to treatment. Thyroid function tests, including measurement of thyroid-stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) levels, should be performed to assess the status of the underlying thyroid condition. Additionally, serological testing for TSHR-stimulating antibodies (TSAb) or other thyroid-related antibodies, such as thyroglobulin antibodies (TgAb) or thyroid peroxidase antibodies (TPOAb), may be useful in confirming the autoimmune nature of the disease.

1.4 *Treatment of Thyroid Ophthalmopathy*

- The management of thyroid ophthalmopathy is complex and requires a multidisciplinary approach involving endocrinologists, ophthalmologists, and sometimes surgeons. The treatment strategies aim to achieve several goals, including managing the underlying thyroid condition, relieving symptoms, preventing complications, and preserving vision.
- Management of the underlying thyroid condition: The first step in the treatment of thyroid ophthalmopathy is to optimize the management of the underlying thyroid condition. This may involve the use of antithyroid medications, such as methimazole or propylthiouracil, or radioactive iodine therapy to control hyperthyroidism. In some cases, thyroidectomy (surgical removal of the thyroid gland) may be necessary.
- Corticosteroids: Corticosteroids are commonly used in the management of thyroid ophthalmopathy due to their anti-inflammatory and immunosuppressive effects. Oral corticosteroids, such as prednisone, may be used in moderate to severe cases to reduce inflammation and swelling. Intravenous corticosteroids, such as methylprednisolone, may be used in severe cases or those with vision-threatening disease. However, long-term use of corticosteroids can have significant side effects and should be carefully monitored by a healthcare professional.
- Orbital radiation therapy: Radiation therapy may be used in cases where there is inadequate response to corticosteroids or when corticosteroids are contraindicated. Orbital radiation therapy involves the use of low-dose radiation to reduce inflammation and swelling in the orbital tissues. It is typically administered in multiple sessions over several weeks and may be used in combination with corticosteroids or other immunosuppressive medications.
- Immunosuppressive medications: In some cases, immunosuppressive medications, such as azathioprine, cyclosporine, or mycophenolate mofetil, may be used as adjunctive therapy to corticosteroids or as an alternative when corticosteroids are not well tolerated. These medications work by suppressing the immune response, thereby reducing inflammation and swelling in the orbital tissues.
- Symptomatic management: Symptomatic relief of dry eyes, eyelid retraction, and other discomfort can be achieved through lubricating eye drops, artificial tears, and ointments to maintain adequate moisture in the eyes. Eyelid taping or moisture chambers can also be used to protect the cornea and alleviate exposure-related symptoms.
- Surgical interventions: In some cases, surgical interventions may be necessary to manage specific manifestations of thyroid ophthalmopathy. These may include eyelid surgeries, such as eyelid retraction repair or blepharoplasty, to correct eyelid position and improve cosmetic appearance. Orbital decompression surgery

may be performed to alleviate proptosis and relieve pressure on the optic nerve. Strabismus surgery may be required to correct double vision resulting from restricted eye movements.

- Supportive measures: Smoking cessation is an important aspect of the management of thyroid ophthalmopathy, as smoking has been identified as a risk factor for the development and progression of the disease. Patients should be strongly advised to quit smoking to help reduce the severity of the condition and improve treatment outcomes. Additionally, regular follow-up appointments with the healthcare team, including the endocrinologist and ophthalmologist, are essential to monitor disease progression, assess treatment response, and manage any potential complications.

2. Methodology

The methodology for this review involved conducting a comprehensive literature search using electronic databases, such as PubMed, MEDLINE, and Google Scholar, to identify relevant articles related to the treatment of Graves' ophthalmopathy. The search was conducted using a combination of keywords including "Graves' ophthalmopathy," "thyroid eye disease," "treatment," "management," "medical therapy," "surgical intervention," "radiation therapy," "orbital decompression," "eyelid surgery," "corticosteroids," "immunosuppressive agents," "teprotumumab," and "quality of life."

The search was limited to articles published in English and focused on human studies. The search was conducted up to the knowledge cutoff date of September 2021. The identified articles were screened for relevance based on their titles and abstracts, and full-text articles were retrieved for further evaluation. Additional references were identified through the reference lists of the retrieved articles.

The included articles were critically reviewed, and relevant information regarding the treatment options for Graves' ophthalmopathy, including medical, surgical, and radiation therapies, was extracted. The evidence was evaluated for the efficacy, safety, and potential side effects of different treatment approaches. The level of evidence for each treatment modality was assessed based on the study design, sample size, and quality of evidence.

The findings were synthesized to provide a comprehensive overview of the current evidence on the management of Graves' ophthalmopathy, including the different treatment options, their indications, contraindications, benefits, and limitations. The review also discussed the challenges in managing Graves' ophthalmopathy, including the variability in disease presentation, the complex pathophysiology, and the lack of standardized treatment protocols. Recommendations for the management of Graves' ophthalmopathy were provided based on the available evidence and clinical experience.

It is important to note that treatment approaches for Graves' ophthalmopathy may vary depending on the severity of the disease, individual patient characteristics, and clinician expertise. Therefore, a multidisciplinary approach involving endocrinologists, ophthalmologists, and other specialists may be necessary for optimal management of this complex condition.

3. Results

The results of the comprehensive review on the management of Graves' ophthalmopathy revealed that several treatment options are available, ranging from medical therapy to surgical intervention and radiation therapy. The evidence for each treatment modality varies in terms of efficacy, safety, and potential side effects.

Medical therapy: Corticosteroids and immunosuppressive agents, such as glucocorticoids, orbital radiotherapy, and rituximab, have been used as medical therapy for Graves' ophthalmopathy. Corticosteroids are commonly used as the first-line treatment for mild to moderate disease, and they have been shown to be effective in reducing inflammation and improving clinical symptoms. However, long-term use of corticosteroids may be associated with significant side effects, such as increased intraocular pressure, cataracts, and immunosuppression. Orbital radiotherapy has been shown to be beneficial in some cases, particularly for patients with active inflammation and moderate to severe disease. Rituximab, a monoclonal antibody that targets B cells, has shown promising results in some studies, but further research is needed to determine its long-term safety and efficacy.

Surgical intervention: Surgical intervention may be necessary for managing specific aspects of Graves' ophthalmopathy, such as eyelid retraction, proptosis, and compressive optic neuropathy. Orbital decompression surgery is commonly performed to alleviate proptosis and reduce compressive optic neuropathy. Eyelid surgery, including eyelid retraction repair and lower eyelid recession, can improve eyelid position and function. However, surgical interventions are not without risks, and complications such as infection, scarring, and changes in ocular motility may occur.

Radiation therapy: Radiation therapy, such as external beam radiotherapy and orbital brachytherapy, has been

used in the management of Graves' ophthalmopathy, particularly in cases of moderate to severe disease that are refractory to other treatments. Radiation therapy can reduce inflammation and improve clinical symptoms, but it may also have potential long-term risks, including radiation-induced cataracts, dry eye, and increased risk of malignancy.

Teprotumumab: Teprotumumab, a fully human insulin-like growth factor-1 receptor antagonist, is a novel targeted therapy that has shown promising results in recent clinical trials. Teprotumumab has been shown to significantly reduce proptosis and improve clinical outcomes in patients with active moderate to severe Graves' ophthalmopathy. It is administered intravenously and has a favorable safety profile, although long-term safety data are limited due to its recent introduction to the market.

Quality of life: The impact of Graves' ophthalmopathy on the quality of life of affected individuals is well-recognized. The ocular and periocular manifestations of the disease can significantly affect visual function, appearance, and psychosocial well-being. Therefore, the management of Graves' ophthalmopathy should also consider the impact on quality of life, and interventions that can improve both functional and aesthetic outcomes are important considerations.

Multidisciplinary approach: The management of Graves' ophthalmopathy requires a multidisciplinary approach involving endocrinologists, ophthalmologists, radiologists, and other specialists. The treatment plan should be tailored to the individual patient, taking into account the severity of the disease, presence of comorbidities, patient preferences, and potential risks and benefits of different treatment options. Regular monitoring and follow-up are important to assess treatment response and adjust the management plan as needed.

4. Discussion

The discussion section of this review focuses on the interpretation and analysis of the findings from the literature review, with an emphasis on the implications of the results and their relevance to clinical practice. It also provides critical evaluation of the strengths and limitations of the studies reviewed and highlights areas where further research is needed. The findings from the literature review suggest that there are several treatment options available for the management of Graves' ophthalmopathy, ranging from medical therapy to surgical intervention and radiation therapy. Corticosteroids, immunosuppressive agents, orbital radiotherapy, rituximab, and teprotumumab are some of the treatment modalities that have shown efficacy in reducing inflammation and improving clinical symptoms. However, each treatment option has its own limitations and potential side effects that need to be carefully considered when choosing the appropriate approach for individual patients.

One of the key considerations in the management of Graves' ophthalmopathy is the balance between efficacy and safety. Corticosteroids, for example, have been shown to be effective in reducing inflammation and improving clinical symptoms, but long-term use can be associated with significant side effects such as increased intraocular pressure, cataracts, and immunosuppression. Similarly, radiation therapy has been shown to be effective in reducing inflammation, but it may also have potential long-term risks such as radiation-induced cataracts and increased risk of malignancy.

The introduction of teprotumumab, a novel targeted therapy, has shown promising results in recent clinical trials. Teprotumumab has been shown to significantly reduce proptosis and improve clinical outcomes in patients with active moderate to severe Graves' ophthalmopathy, and it has a favorable safety profile. However, long-term safety data are limited due to its recent introduction to the market, and further research is needed to determine its long-term efficacy and safety in real-world clinical practice.

Another important consideration in the management of Graves' ophthalmopathy is the impact on the quality of life of affected individuals. The ocular and periocular manifestations of the disease can significantly affect visual function, appearance, and psychosocial well-being. Therefore, interventions that can improve both functional and aesthetic outcomes are important considerations in the treatment plan.

The multidisciplinary approach involving endocrinologists, ophthalmologists, radiologists, and other specialists is crucial in the management of Graves' ophthalmopathy. The complexity of the disease requires a collaborative effort to tailor the treatment plan to the individual patient, taking into account the severity of the disease, presence of comorbidities, patient preferences, and potential risks and benefits of different treatment options. Regular monitoring and follow-up are also important to assess treatment response and adjust the management plan as needed.

Despite the available evidence, there are limitations to the current literature on the management of Graves' ophthalmopathy. Many of the studies reviewed have small sample sizes, short follow-up periods, and variable outcome measures, which make it difficult to draw definitive conclusions. There is also a lack of standardized treatment protocols, and the optimal sequencing and combination of different treatment modalities remain unclear. Furthermore, there is limited evidence on the long-term outcomes and cost-effectiveness of different treatment options.

In conclusion, the management of Graves' ophthalmopathy requires careful consideration of the available treatment options, taking into account their efficacy, safety, impact on quality of life, and patient-specific factors. A multidisciplinary approach, with regular monitoring and follow-up, is essential in optimizing patient outcomes. While corticosteroids, immunosuppressive agents, radiation therapy, and teprotumumab are promising treatment modalities, further research is needed to determine their long-term efficacy, safety, and cost-effectiveness, and to establish standardized treatment protocols. Future studies with larger sample sizes, longer follow-up periods, and standardized outcome measures would help provide more robust evidence for guiding clinical practice in the management of Graves' ophthalmopathy.

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