SEEING THROUGH GRAVES’ OPHTHALMOPATHY: TREATMENT EFFICACY AND QUALITY OF LIFE ENHANCEMENT

Layssa Paiva de Castro
http://lattes.cnpq.br/1988588036521998

Lícia Wênia Santos Pimenta Torres
http://lattes.cnpq.br/6329306989275649

Jéssica Leiko Okumura Tioda
http://lattes.cnpq.br/7860230569333582

Rodrigo Zamignan Carpi
http://lattes.cnpq.br/6600348584962076

Eder Felipe Rosado Malheiros
http://lattes.cnpq.br/2979326287415579

Vinícius de Oliveira Santos
https://lattes.cnpq.br/3251085561317685

Eduarda Mandio
http://lattes.cnpq.br/4791743372358340

Letícia Beatriz Freire Quintino
http://lattes.cnpq.br/5912857070361347

Felipe Silva Teixeira
http://lattes.cnpq.br/7530552868233205

Lucas Rodgher de lírio
http://lattes.cnpq.br/6180592222308189

Francesco Enrico Aloise
http://lattes.cnpq.br/8265204949797248

Mauricio Lopes da Silva Netto
http://lattes.cnpq.br/4791743372358340
Abstract: INTRODUCTION Graves’ ophthalmopathy, associated with Graves’ disease, leads to eye problems like bulging and redness, significantly impacting life quality. It’s linked to systemic issues like hyperthyroidism, with varied prevalence globally, affecting both physical and psychological well-being. Effective management is key to improving patients’ overall quality of life.

OBJETIVE Analyze and describe the main aspects treatment efficacy and quality of life enhancement in patients with graves’ ophthalmopathy of the last years.

METHODS This is a narrative review, included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases, using the following descriptors: “Orbitopathy” AND “Graves’ disease” AND “Quality of life” AND “Treatment”.

RESULTS AND DISCUSSION: Graves’ orbitopathy is a complex condition primarily driven by the unique responses of orbital fibroblasts to immune stimuli, leading to varied symptoms due to their potential to become different cell types. Key in diagnosis and management is the Clinical Activity Score and treatments range from traditional corticosteroids to innovative biologic agents like rituximab, emphasizing the importance of personalized, patient-centered approaches. Despite advancements, the disconnection between thyroid function and orbitopathy progression highlights the need for ongoing research and comprehensive treatment strategies. This calls for a multidisciplinary approach to address both the physical symptoms and the overall quality of life for patients, underscoring the necessity for continuous exploration of therapeutic options and patient care practices to better manage this challenging ophthalmic condition.

CONCLUSION Graves’ orbitopathy is a multifaceted condition requiring personalized, multidisciplinary management approaches that extend beyond traditional treatments like corticosteroids. Advancements in biologic therapies offer new hope, yet the separation between thyroid management and ocular symptoms remains a significant challenge. Future strategies should emphasize a holistic approach, focusing on both physical health and quality of life, while continuous research is crucial for addressing unresolved clinical issues and refining treatment methodologies. The ultimate goal is to enhance patient care through tailored treatments, integrating both medical and psychosocial support for comprehensive patient well-being.

INTRODUCTION

Graves’ ophthalmopathy, also known as thyroid eye disease, is an autoimmune inflammatory disorder affecting the orbit around the eye, leading to severe eye symptoms such as exophthalmos (protrusion of the eyeball), redness and swelling.¹ This condition is closely related to Graves’ disease, an autoimmune disorder that leads to overactivity of the thyroid gland (hyperthyroidism). Severe ophthalmopathy can significantly impair visual function and aesthetics, causing substantial morbidity and negatively impacting the quality of life².

The epidemiology of Graves’ disease shows variability across different geographical regions and populations³. Globally, Graves’ disease affects approximately 0.5% to 2% of the population⁴. However, the prevalence and incidence can vary significantly; for instance, in Brazil, the prevalence of Graves’ disease has been reported to be higher compared to global averages, suggesting genetic and environmental influences on disease manifestation⁵.
Systemic signs and symptoms of Graves’ disease are predominantly due to hyperthyroidism and include weight loss, heat intolerance, palpitations, and increased bowel movements. Additionally, patients may experience muscle weakness, tremors, and significant fatigue, which collectively impact daily functioning and well-being.

Ocular changes in Graves’ disease encompass a spectrum from mild to severe. Besides the characteristic exophthalmos, patients may suffer from diplopia (double vision), eye pain, and pressure sensation. In severe cases, corneal ulceration and compressive optic neuropathy can occur, potentially leading to vision loss. These symptoms substantially affect patients’ ability to perform daily activities and can lead to social withdrawal.

Psychiatric symptoms are also prevalent in patients with Graves’ disease, particularly those with ophthalmopathy. The visible ocular changes can lead to psychological distress, significantly impacting self-esteem and increasing levels of anxiety and depression. The interplay between physical appearance changes and psychological well-being can create a vicious cycle, exacerbating the overall disease burden. Studies have shown that effective management of ophthalmopathy can lead to significant improvements in anxiety, depression, and overall quality of life.

OBJECTIVES
Analyze and describe the main aspects of treatment efficacy and quality of life enhancement in patients with Graves’ ophthalmopathy of the last years.

SECONDARY OBJECTIVES
1. Spectrum of Treatment Modalities;
2. Treatment Efficacy;
3. Quality of Life Impacts;
4. Treatment Side Effects and Risk;
5. Patient-Centered Care Approaches;
6. Gaps in Research and Clinical Practice;

METHODS
This is a narrative review, in which the main aspects of treatment efficacy and quality of life enhancement in patients with Graves’ ophthalmopathy in recent years were analyzed. The beginning of the study was carried out with theoretical training using the following databases: PubMed, sciELO and Medline, using as descriptors: “Orbitopathy” AND “Graves’ disease” AND “Quality of life” AND “Treatment” in the last years. As it is a narrative review, this study does not have any risks.

The inclusion criteria applied in the analytical review were human intervention studies, experimental studies, cohort studies, case-control studies, cross-sectional studies and literature reviews, editorials, case reports, and poster presentations. Also, only studies writing in English and Portuguese were included.

RESULTS AND DISCUSSION
The development of Graves’ orbitopathy is intricately linked with the unique properties of orbital fibroblasts, which diverge in their response to stimuli compared to standard fibroblasts. These cells exhibit aberrant behavior, including unusual hyaluronan production and insensitivity to typical regulatory signals. Significantly, they express the thyrotropin receptors (TSHr), implicating their direct involvement in the pathology of Graves’ orbitopathy, particularly as this expression escalates during adipogenesis.
suggesting a crucial role in the manifestation of the disease\textsuperscript{17}.

Graves’ orbitopathy presents a range of symptoms stemming from both myogenic and lipogenic alterations, primarily due to the diverse potentialities of orbital fibroblasts to transdifferentiate into myofibroblasts and adipocytes\textsuperscript{18}. This ability significantly contributes to the varied clinical presentations observed in patients\textsuperscript{19}. The process is modulated by factors including the activation of peroxisome proliferator-activated receptor-\(\gamma\) (PPAR-\(\gamma\)), which plays a pivotal role in the differentiation and remodeling processes of orbital tissues\textsuperscript{20}.

The diagnosis of this ophthalmopathy primarily leverages the Clinical Activity Score (CAS), a critical tool in assessing the activity level of the disease and informing subsequent treatment pathways\textsuperscript{21}. This systematic approach assists in the accurate monitoring and decision-making processes essential for disease management\textsuperscript{22,23,24}.

Among the treatments, corticosteroids represent a cornerstone, administered in forms ranging from oral to pulse therapies, aiming to mitigate inflammation\textsuperscript{25}. However, they carry potential risks for systemic and ocular side effects, which necessitates careful consideration and monitoring\textsuperscript{26}. On another front, anti-inflammatory radiotherapy, while effective, is generally reserved for particular scenarios due to its side effects\textsuperscript{27,28}.

Noteworthy is the advent of novel therapies such as rituximab, tocilizumab, and teprotumumab, each targeting specific elements of the immune response and demonstrating potential in the management of severe cases of orbitopathy\textsuperscript{27,29}. This represents a significant shift towards more targeted therapeutic interventions\textsuperscript{29}.

The intricate relationship between thyroid management and the progression of orbitopathy underscores the necessity for specialized ocular treatments, revealing the complexity of the disease and the multifaceted approach required for effective management\textsuperscript{30}. In instances where pharmacological interventions fall short, surgical options such as orbital decompression, eyelid adjustments, or strabismus corrections are considered to enhance both functionality and cosmetic appearance, tailored according to individual patient needs and disease severity\textsuperscript{29,30}.

Moreover, the overarching impact of these treatments on the quality of life for patients cannot be overstated, necessitating a holistic approach that goes beyond mere symptom control to address the comprehensive needs of the patients\textsuperscript{31}. The exploration into patient-centered care practices underlines the significance of tailored treatment plans and the benefits of a multidisciplinary approach, emphasizing the importance of incorporating patient preferences and values into the decision-making process, thereby enhancing adherence and satisfaction\textsuperscript{32}.

Lastly, the identification of existing gaps in research and clinical practice draws attention to the necessity for ongoing investigations into unresolved clinical challenges and novel therapeutic strategies, emphasizing the importance of addressing long-term safety, efficacy, and quality of life concerns for those affected by Graves’ orbitopathy\textsuperscript{33}.

**CONCLUSION**

In conclusion, Graves’ orbitopathy presents a complex clinical challenge characterized by its multifactorial pathogenesis, notably involving the aberrant behavior of orbital fibroblasts and their response to immune system interactions. The therapeutic landscape for this condition has evolved significantly, moving beyond traditional corticosteroid treatments to include novel biologic agents targeting specific pathways implicated in the disease process. Despite
these advancements, the dissociation between thyroid function control and orbitopathy progression underscores the necessity for a tailored, patient-centric approach in treatment planning.

Management strategies must not only address the physical manifestations of the disease but also consider the significant impact on patients’ quality of life. This holistic approach necessitates the integration of multidisciplinary care teams to ensure comprehensive patient support, from clinical management to psychosocial interventions. Furthermore, ongoing research is essential to fill existing knowledge gaps, particularly in understanding the long-term efficacy and safety of emerging treatments and in developing strategies for refractory cases.

Future efforts should continue to focus on the refinement of diagnostic criteria, the exploration of novel therapeutic agents, and the establishment of personalized care plans that prioritize both the physical and emotional well-being of patients. As our understanding of Graves’ orbitopathy continues to evolve, so too will our ability to provide effective, compassionate care for those affected by this challenging condition.

REFERENCES


