MARKET RESEARCH ON GRAVES' OPHTHALMOPATHY – DISEASE OVERVIEW, EPIDEMIOLOGY, AND MARKET ASSESSMENT

Dissertation Submitted to

The IIHMR University, Jaipur

for the partial fulfillment for the award of the degree of

Master of Business Administration (MBA)

in

Pharmaceutical Management

by

Varsha Mittal

Under the Supervision and Guidance of

Dr. Ashok Peepliwal

2025

IIHMR UNIVERSITY

CERTIFICATE

This is to certify that Varsha Mittal in partial fulfillment of the requirements for the award of the degree of MBA (Pharmaceutical Management) from the IIHMR University, Jaipur has successfully completed her internship at IIHMR University, Jaipur during March 10 - June 9th, 2025.

16/6/2025

Dr. Ashok Peepliwal
Professor
School of Pharmaceutical Management
IIHMR University

Place: Jaipur
Date: 16th June 2025

IIHMR UNIVERSITY

CERTIFICATE

This is to certify that dissertation titled "Market Research on Graves' Ophthalmopathy: Disease Overview, Epidemiology, and Market Assessment" is a record of the research work undertaken by Varsha Mittal in partial fulfilment of the requirements for the award of the degree of MBA Pharmaceutical Management from the IIHMR University, Jaipur under my guidance and supervision and her approach to the research study has been sincere, scientific, and analytical.

Dr. Ashok Peepliwal
Professor
School of Pharmaceutical Management,
IIHMR University, Jaipur
Date: 16th June 2025

Dr. Saurabh Banerjee
Dean
School of Pharmaceutical Management
16/6/2025

DECLARATION BY STUDENT

I hereby declare that this dissertation titled "Market Research on Graves' Ophthalmopathy: Disease Overview, Epidemiology, and Market Assessment" is the bonafide record of my original research work. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished work of others has been duly acknowledged in the text.

Varsha

Name of Student: Varsha Mittal

Date: 14th May 2025

Abstract

Background: Graves' Ophthalmopathy (GO), an autoimmune inflammatory disorder associated with Graves' Disease, presents with ocular symptoms that range from mild discomfort to vision-threatening complications. Despite advancements in medical science, GO continues to pose challenges in diagnosis, treatment, and equitable healthcare access, particularly across different global regions.

Objective: To conduct a comprehensive, evidence-based secondary research study examining epidemiology, clinical progression, and current as well as emerging treatment paradigms for GO. The aim is to support improved patient outcomes and guide informed clinical and policy decision-making.

Methodology: This study employed a retrospective, descriptive design based on secondary data from peer-reviewed literature, clinical guidelines, and epidemiological reports across seven major healthcare markets (7MM). Both quantitative (e.g., prevalence data, treatment uptake) and qualitative (e.g., expert opinion, clinical algorithms) approaches were used to assess trends in disease burden, therapeutic efficacy, and market development.

Findings: GO affects up to 50% of patients with Graves' Disease, with a significant burden observed among adult women aged 30–50. Traditional treatments such as corticosteroids offer limited, phase-specific benefits and are associated with notable side effects. The emergence of targeted biologic therapies—especially teprotumumab—has transformed the therapeutic landscape, improving outcomes for patients with moderate-to-severe disease. However, challenges remain in managing the chronic fibrotic phase, ensuring early diagnosis, and addressing accessibility issues due to cost and healthcare infrastructure disparities.

Conclusion: Graves' Ophthalmopathy remains a complex and evolving healthcare challenge. While biologic therapies offer new hope, there is an urgent need for anti-fibrotic treatments, biomarker-driven early detection protocols, and policy reforms that ensure equitable access to advanced care. A multidisciplinary, patient-centered approach is essential to improving both functional outcomes and quality of life for individuals living with GO.

Acknowledgements

I would like to express my deepest gratitude to all those who have contributed to the successful completion of this research study on Market Research on Graves' Ophthalmopathy – Disease Overview, Epidemiology, and Market Assessment.

First and foremost, I extend my sincere appreciation to my mentor, Dr Ashok Peepliwal, for their invaluable guidance, encouragement, and continuous support throughout this research. Their expertise and insights have been instrumental in shaping the direction of this study.

I am profoundly grateful to my academic institution, IIHMR University, Jaipur, and my department, MBA (Pharmaceutical Management), for providing the necessary resources, infrastructure, and a conducive learning environment to carry out this research.

I also wish to acknowledge the support of my colleagues and peers, whose discussions and feedback have enriched my understanding and helped refine my research approach.

Special thanks go to the experts, clinicians, and industry professionals who provided critical insights and shared their valuable experiences in the field of colorectal cancer research and market analysis. Their contributions have greatly enhanced the depth and quality of this study.

Additionally, I would like to extend my appreciation to my family and friends for their unwavering support, patience, and encouragement throughout this journey. Their belief in my abilities has been a source of motivation during challenging times.

Finally, I acknowledge all the authors, researchers, and institutions whose work has been referenced in this study. Their contributions to the scientific and medical community have provided a strong foundation for this research.

Thank you all for your support and encouragement in making this dissertation a reality.

Table of Contents

List of Figures

List of Tables

Abbreviations

7MM: Seven Major Markets

ATA: American Thyroid Association

Aza: Azathioprine

Cyc: Cyclosporine

EUGOGO: European Group on Graves' Orbitopathy

IVGC: IV glucocorticoids

IGF-1R: Insulin-like growth factor-1 receptor

KOLs: Key Opinion Leaders

MMF: Mycophenolate mofetil

OGC: Oral glucocorticoids

oRT: Orbital radiotherapy

GO: Graves' Ophthalmopathy

TED: Thyroid Eye Disease

TRAbs: Thyrotropin Receptor Antibodies

VISA: Vision, Inflammation, Strabismus, Appearance

Chapter 1: Introduction

1.1 Purpose of Research

The purpose of this research is to explore the multifaceted landscape of Graves' Ophthalmopathy (GO), a complex autoimmune disorder that presents significant clinical and therapeutic challenges. This study aims to offer a comprehensive understanding of GO by examining its epidemiological trends, clinical manifestations, disease burden, current management practices, and future therapeutic opportunities. In doing so, the research seeks to bring to light the evolving dynamics of this condition across global healthcare settings, focusing particularly on high-burden geographies such as the United States, Europe, and Japan.

Through an extensive review and analysis of current evidence, this work endeavors to support clinicians, researchers, and policymakers in refining diagnostic strategies and enhancing patient-centered care models. The rising interest in targeted biologic therapies and personalized medicine has made it increasingly important to reevaluate how GO is diagnosed and treated. Therefore, the research not only highlights existing best practices but also identifies key areas of unmet need, guiding future efforts toward more equitable, effective, and sustainable treatment paradigms.

By drawing connections between epidemiological data, clinical research, and therapeutic trends, the study aims to inform evidence-based decision-making and foster innovation in the management of this debilitating condition. Ultimately, this research aspires to contribute meaningfully to the broader discourse on autoimmune ophthalmic diseases and advance the quality of life for individuals affected by Graves' Ophthalmopathy.

1.2 Problem Being Investigated

Graves' Ophthalmopathy—also known as thyroid eye disease (TED) or thyroid-associated ophthalmopathy—is a debilitating autoimmune inflammatory disorder of the orbit and periorbital tissues, most associated with hyperthyroidism due to Graves' Disease. Although medical science has made significant strides in understanding its pathophysiology and developing novel treatment modalities, the condition continues to pose several diagnostic and therapeutic challenges (1).

One of the major concerns is the delayed recognition and diagnosis of GO, particularly in patients presenting with subtle or non-specific symptoms. The variability in clinical presentation often leads to misdiagnosis or underdiagnosis, thereby delaying early intervention when treatments may be most effective. Moreover, the disease progresses through an active inflammatory phase followed by a chronic fibrotic phase, during which most conventional therapies lose their efficacy. Current treatment options, including corticosteroids, radiotherapy, and surgical interventions, are typically more effective during the initial inflammatory period and are of limited use in chronic cases where fibrosis and structural remodeling dominate (2).

Patients with GO frequently experience persistent symptoms such as proptosis (bulging of the eyes), diplopia (double vision), and exposure keratopathy. These symptoms can lead to significant visual impairment, cosmetic disfigurement, and psychosocial stress, substantially diminishing the patient's quality of life. Despite the development of new biologic agents, including targeted monoclonal antibodies such as teprotumumab, access to these innovative therapies remains inconsistent across different regions due to cost constraints, healthcare infrastructure limitations, and regulatory hurdles (3).

Thus, the central problem being investigated is the continued clinical and socioeconomic burden of Graves' Ophthalmopathy in the context of an evolving therapeutic landscape. The research seeks to identify gaps in current diagnostic and treatment approaches, particularly for patients with moderate-to-severe or chronic disease, and to propose strategies that can bridge these gaps through integrated, evidence-based solutions.

1.3 Context and Importance of the Problem

Graves’ Ophthalmopathy is not merely a cosmetic or ocular disorder; it is a serious medical condition that can lead to irreversible complications, including vision loss, corneal ulcers, and optic nerve compression. Affecting up to 50% of patients with Graves’ Disease, GO represents a major extrathyroidal manifestation that demands interdisciplinary management involving endocrinologists, ophthalmologists, radiologists, and immunologists (4).

The burden of GO extends beyond clinical symptoms to significantly impact mental health, social interactions, and overall well-being. Patients often suffer from anxiety, depression, and social withdrawal due to the disfiguring nature of the disease. The chronic nature of the

condition and the potential for recurrence add to the psychological stress experienced by patients and caregivers alike.

In recent years, the treatment paradigm for GO has been reshaped by the introduction of biologic and targeted therapies that offer promising results. For instance, the FDA approval of teprotumumab has marked a milestone in the treatment of moderate-to-severe GO, showing significant efficacy in reducing proptosis and improving quality of life. However, the high cost of these therapies, potential side effects, and uncertainty about long-term outcomes remain substantial barriers to widespread adoption (5).

Furthermore, there is limited data on the real-world effectiveness and safety of these emerging therapies, particularly across diverse populations. Many patients, especially in low-resource settings, continue to rely on outdated or suboptimal treatments due to limited access to modern healthcare services. This disparity underscores the urgent need for research that not only evaluates the clinical aspects of the disease but also addresses health system-level challenges such as affordability, access, and patient education (6).

Given these complexities, a deeper and more holistic understanding of the disease—from its biological underpinnings to its social consequences—is crucial. Such an understanding will be instrumental in guiding future research, improving clinical guidelines, and informing health policy decisions aimed at reducing the burden of Graves' Ophthalmopathy.

1.4 Aims and Objectives of the Study

Aim:

To conduct a comprehensive, evidence-based secondary research study on epidemiology, clinical progression, management strategies, and emerging therapeutic options for Graves' Ophthalmopathy, with a focus on improving patient outcomes and supporting informed clinical and policy decision-making.

Objectives:

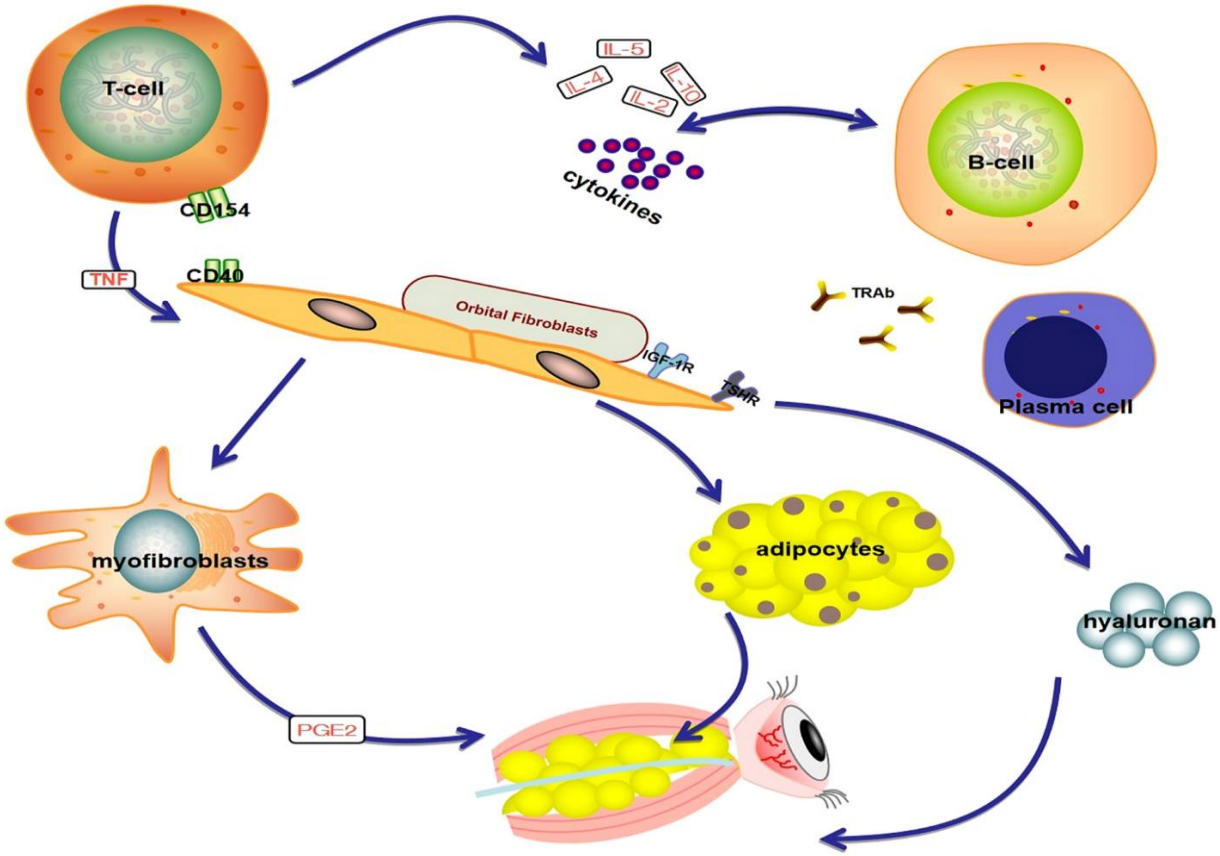
- To elucidate the underlying disease mechanisms, clinical spectrum, and risk factors associated with Graves' Ophthalmopathy.

- To review current diagnostic protocols, including imaging and biomarker-based approaches, and assess their effectiveness in early disease identification.
- To evaluate existing treatment modalities, including medical, surgical, and radiation therapies, and highlight their strengths and limitations across disease stages.
- To identify therapeutic gaps, particularly for patients with chronic or refractory disease, and to explore opportunities for enhanced disease monitoring and management.
- To analyze the emerging pipeline of biologic and targeted therapies and assess their potential impact on the standard of care.
- To examine healthcare access disparities and propose policy-level recommendations that facilitate the equitable distribution of advanced therapies.
- To contribute to future research agendas by outlining priorities for clinical trials, health services research, and real-world evidence generation.

Chapter 2: Review of Literature

Graves' Ophthalmopathy (GO), also referred to as thyroid eye disease (TED) or thyroid-associated ophthalmopathy, is an autoimmune inflammatory disorder that primarily affects the orbital tissues and is strongly associated with Graves' disease, an autoimmune thyroid condition. The pathophysiology of GO involves complex immune-mediated processes, including T-cell activation, cytokine release, and tissue remodeling within the orbit. Over the last few decades, considerable research has been dedicated to understanding various aspects of this disease—from immunological mechanisms and risk factors to diagnostic tools, treatment strategies, and the impact of emerging targeted therapies (7).

Figure 1: Pathophysiology of Graves' Ophthalmopathy



Source: (Li et al., 2022)

Given the clinical heterogeneity of GO and its significant impact on patients' vision and quality of life, a robust body of literature has emerged exploring multiple domains of the disease. These studies have contributed to the development of disease classifications, identification of prognostic biomarkers, and creation of tailored management plans, often involving interdisciplinary collaboration between endocrinologists, ophthalmologists, and immunologists (8).

This chapter presents a curated review of key academic and clinical studies, highlighting their methodological approaches and major contributions to the understanding, diagnosis, and treatment of Graves' Ophthalmopathy.

2.1 Review of Key Studies

Table 1: Review of Literature

Authors (Year)	Study Location	Sample Size	Sampling Techniques	Salient Features
Moledina M, Damato EM, Lee V (2024)	Not specified	Not specified	Not specified	Discusses advances and future perspectives in thyroid eye disease management.
Cao J, Wang N, Hou S, Qi X, Chen Y, Xiong W (2021)	Not specified	Not specified	Bibliometric analysis	Reviews Graves' Ophthalmopathy literature from 1999 to 2019.
Fox TJ, Anastasopoulou C (2023)	Not specified	Not specified	Not specified	NIH-published work focusing on Graves' Orbitopathy.
Marcocci C, Smith TJ (2016)	Not specified	Not specified	Not specified	Examines Graves' Ophthalmopathy from an endocrinological perspective.
Wagner LH, Bradley EA, Tooley AA, Ren Y, Rachmasari KN, Stan MN (2022)	Not specified	Not specified	Not specified	Explores nomenclature and implications of thyroid eye disease terminology.
Scarabosio A, Surico PL, Singh RB, et al. (2024)	Not specified	Not specified	Not specified	Discusses advancements in orbital and ocular pathology management.
Wiersinga WM, Eckstein AK, Žarković M (2025)	Not specified	Not specified	Not specified	Covers clinical presentation, epidemiology, pathogenesis, and management of thyroid eye disease.

Hodgson NM, Rajaii F (2019)	Not specified	Not specified	Systematic review	Provides insights into the progression and management of thyroid-associated orbitopathy.
Tanda ML, Piantanida E, Liparulo L, et al. (2013)	Not specified	Not specified	Not specified	Assesses prevalence and natural history of Graves' Orbitopathy.
Barrio-Barrio J, Sabater AL, Bonet-Farriol E, et al. (2015)	Not specified	Not specified	Not specified	Compares VISA and EUGOGO classifications for Graves' Ophthalmopathy.
Hiromatsu Y, Eguchi H, Tani J, et al. (2014)	Not specified	Not specified	Not specified	Evaluates epidemiology and natural history of Graves' Ophthalmopathy.
Bartalena L, Piantanida E, Gallo D, et al. (2020)	Not specified	Not specified	Not specified	Examines risk factors and preventive approaches for Graves' Orbitopathy.
Alharbi A (2025)	Not specified	Not specified	Narrative review	Reviews recent advances in thyroid orbitopathy treatment.
Householder NA, Ray C (2024)	Not specified	Not specified	Systematic review & meta-analysis	Analyzes Teprotumumab’s impact on proptosis in long-duration thyroid eye disease.
Ramalingam G, Khan JM, Jasmine S, et al. (2024)	Not specified	Not specified	Not specified	Evaluates Th1/Th2 cytokine balance for treatment outcomes in tuberculosis.
Yang M, He W (2024)	Not specified	2479 patients	Case series	Investigates age and gender influences on thyroid-associated ophthalmopathy.
Burch HB, Perros P, Bednarczuk T, et al. (2022)	Not specified	Not specified	Consensus statement	Presents management strategies for thyroid eye disease.
Immunovant, Inc. (2024)	Not specified	Not specified	Not specified	Pharmaceutical company specializing in autoimmune treatment approaches.
Monaco K (2022)	Not specified	Not specified	Not specified	Discusses clinical challenges in diagnosing thyroid eye disease.

2.2 Narrative Summary

Recent scholarly investigations have significantly deepened the understanding of the multifactorial nature of GO, illustrating how immune, genetic, environmental, and tissue-specific mechanisms collectively drive disease onset and progression. Literature increasingly supports a shift from traditional, generalized treatment models toward more nuanced, evidence-based, and multidisciplinary approaches.

Tanda et al. (2013) laid foundational insights into the autoimmune basis of GO, emphasizing that the hallmark features of disease orbital tissue expansion, muscle hypertrophy, and fat proliferation—are driven by chronic immune-mediated inflammation. The study advocated early, coordinated intervention involving endocrinologists, ophthalmologists, and immunologists to mitigate the transition from active inflammation to irreversible fibrosis. This call for multidisciplinary care remains a cornerstone of modern GO management (9).

Complementing this perspective, Barrio-Barrio et al. (2015) advanced the clinical management framework by introducing structured tools for evaluating disease activity and severity. The VISA (Vision, Inflammation, Strabismus, Appearance) and EUGOGO (European Group on Graves' Orbitopathy) classification systems provide standardized metrics to guide treatment decisions. These tools help differentiate between patients requiring immunosuppression during the active phase and those better suited for rehabilitative or surgical interventions during the chronic phase (10).

Ethnic variability in disease expression has also been a subject of growing attention. Hiromatsu et al. (2014) conducted observational studies demonstrating that GO presents with a comparatively milder phenotype in East Asian populations. These populations tend to show less prominent proptosis but a higher prevalence of extraocular muscle involvement. The findings underscore the importance of culturally and ethnically tailored diagnostic criteria and treatment thresholds (11).

In the realm of diagnostics and disease monitoring, Luigi Bartalena et al. (2020) introduced a pivotal advancement by validating thyrotropin receptor antibodies (TRAbs) as predictive biomarkers for GO. Elevated TRAb levels were shown to correlate positively with both disease activity and severity, providing clinicians with a valuable tool for early

identification of high-risk patients and for tailoring treatment intensity. These findings help shift the paradigm from symptomatic management to biomarker-informed personalized therapy (12).

At the molecular and cellular level, Alharbi A. (2025) provided a mechanistic basis for the development of targeted therapies by exploring the role of orbital fibroblasts—key effector cells in the orbital immune response. Their study elucidated the interaction between fibroblast subtypes and the insulin-like growth factor-1 receptor (IGF-1R) signaling pathway, which is central to orbital tissue remodeling. This work laid the scientific groundwork for the development of teprotumumab that selectively inhibits IGF-1R and has emerged as a groundbreaking treatment for moderate-to-severe GO (13).

Householder and Ray (2025) offered further insights into clinical staging, emphasizing the biphasic nature of the disease—comprising an initial inflammatory stage followed by a fibrotic, chronic stage. They underscored the necessity of initiating immunomodulatory therapies aggressively during the active phase to prevent irreversible tissue damage. In contrast, the chronic phase often necessitates surgical interventions such as orbital decompression, strabismus correction, or eyelid reconstruction to restore function and appearance (14).

Adding another layer to the therapeutic discourse, Ramalingam et al. (2024) explored evolving immunological targets for intervention. They examined the roles of T-helper (Th1 and Th2) cells, cytokines such as IL-6 and TNF-α, and B-cell-mediated pathways, all of which are implicated in the pathogenesis of GO. Their work supports the increasing clinical interest in biologic therapies—such as rituximab and tocilizumab—that aim to modulate these immune responses more precisely than traditional corticosteroids or radiation therapy (15).

Collectively, these studies form an integrated body of evidence that reinforces the complexity of GO and highlights the rapid evolution of diagnostic and therapeutic paradigms. The research trajectory clearly favors early, targeted, and multidisciplinary intervention strategies over reactive, one-size-fits-all treatment approaches. As such, the literature continues to guide the refinement of both clinical practice and research priorities in the ongoing effort to improve patient outcomes and quality of life.

Chapter 3: Methodology

Understanding the landscape of Graves' Ophthalmopathy (GO) requires an integrated methodological framework that combines epidemiological data with clinical insight. This chapter outlines the research methodology adopted for the study, including the research questions, design, setting, population, and analytical techniques employed. The approach centers on a comprehensive secondary data review, utilizing both quantitative and qualitative analysis to ensure a multifaceted understanding of the disease.

3.1 Key Research Questions

The study was guided by the following core research questions, designed to explore both the scientific and practical dimensions of Graves' Ophthalmopathy:

What are the epidemiological patterns and clinical manifestations of Graves' Ophthalmopathy (GO)?

This question explores the prevalence, incidence, and demographic distribution of GO, along with its symptomatology and disease course across different regions.

What are the current approaches to the diagnosis and management of GO?

This examines prevailing diagnostic tools, clinical classifications, and treatment protocols, including both pharmacologic and surgical interventions.

What therapeutic advancements have been made in the treatment landscape of GO?

A focus on recent drug developments, especially biologic and targeted therapies, and their integration into standard care practices.

What gaps exist in the management of GO, and what emerging therapies are anticipated to address these unmet needs?

This seeks to identify clinical and systemic barriers to optimal care and highlights innovative strategies aimed at improving outcomes.

3.2 Research Design

This study adopted a retrospective, descriptive research design grounded in secondary data analysis. This methodological framework was selected due to its effectiveness in aggregating, analyzing, and synthesizing vast bodies of existing information from diverse sources to generate comprehensive insights into the disease landscape of Graves' Ophthalmopathy (GO).

The retrospective nature of the study implies that it drew from pre-existing literature, databases, and published reports, eliminating the need for primary data collection while ensuring breadth of coverage across clinical, epidemiological, and therapeutic domains. A mixed-method analytical approach was employed, integrating both quantitative data (such as prevalence rates, therapy uptake statistics, and treatment segmentation) and qualitative evidence (including clinical guidelines, expert opinion, and review articles).

- Type of Study: Retrospective, observational, non-interventional.
- Nature of Analysis: Mixed-method—merging numerical data with narrative and interpretative analyses.

This approach allowed for a multi-dimensional exploration of the GO landscape. It facilitated the identification of macro-level trends in disease burden, variability in treatment practices, and the evolution of clinical protocols and drug development efforts across international healthcare systems. Additionally, it provided a platform for comparing disease trajectories and treatment accessibility across different geographic and demographic contexts.

By employing secondary research, the study ensured methodological efficiency, cost-effectiveness, and timely access to a wide array of peer-reviewed data and real-world observations, enhancing the robustness and relevance of its findings.

3.3 Study Setting

The geographical focus of this study was concentrated on the seven major healthcare markets (7MM), a term commonly used in epidemiological and pharmaceutical research to represent the following countries:

- United States
- Germany
- France
- Italy
- Spain
- United Kingdom
- Japan

These regions were strategically selected based on several criteria:

1. Availability of Structured Epidemiological Data: These countries maintain high-quality health registries and disease surveillance systems that provide reliable and up-to-date data on the incidence, prevalence, and burden of GO.
2. Advanced Healthcare Infrastructure: The 7MM represents some of the most advanced and resource-rich healthcare systems globally, allowing for detailed analysis of clinical practice trends, therapeutic availability, and innovation uptake.
3. Relevance to Global Therapeutic Development: These regions serve as key markets for pharmaceutical development and regulatory approvals. Many novel therapies, including biologic and targeted treatments for GO, are first introduced and tested within these jurisdictions, making them critical for studying the evolution of the treatment landscape.
4. Diversity in Health Policy and Practice: The inclusion of both public healthcare models (e.g., UK's NHS) and mixed or private insurance-based systems (e.g., USA) offers comparative insights into how different healthcare frameworks affect access to care, affordability, and treatment outcomes.

By focusing on the 7MM, the study was able to leverage a diverse yet robust foundation for examining international patterns in GO management, highlighting both shared challenges

and region-specific considerations in tackling this autoimmune condition.

3.4 Study Population

The study population was defined based on clinical and epidemiological characteristics associated with Graves' Ophthalmopathy (GO). Although no primary data were collected, the analysis drew from a wide range of secondary sources that provided population-level insights into the demographics, clinical classifications, and treatment pathways of individuals affected by the disease. The virtual study population included the following key groups:

- Diagnosed Individuals with Graves' Ophthalmopathy: The core population consisted of patients formally diagnosed with GO, encompassing both the active (inflammatory) and chronic (fibrotic) phases of the disease. This distinction was critical for understanding phase-specific treatment patterns and clinical outcomes.

- Stratification by Disease Severity: Patients were categorized into three primary severity groups:

    - Mild GO: Characterized by minimal ocular discomfort and cosmetic changes, typically managed with conservative or supportive therapies.

    - Moderate-to-Severe GO: Defined by significant proptosis, diplopia, and functional impairment, often requiring systemic immunosuppressive treatment or orbital radiation.

    - Sight-Threatening GO: Marked by vision loss or optic nerve compression, necessitating urgent intervention such as high-dose corticosteroids or surgical decompression.

- Demographic and Clinical Subgroups: To allow for a more granular analysis, the study also considered:

    - Gender-based subgroups, recognizing the differing incidence and severity of GO between males and females.

    - Disease phase segmentation into acute (active inflammation) and chronic (fibrosis

and structural remodeling) stages, which have distinct therapeutic implications.

- Treatment eligibility status, distinguishing patients who were suitable candidates for systemic therapies (including biologics) versus those managed through supportive or surgical means.

By structuring the study population in this manner, the research was able to comprehensively assess how GO manifests and is managed across various clinical contexts, ensuring that the findings are reflective of real-world patient diversity and therapeutic decision-making.

3.5 Research Procedures and Approaches

To achieve a comprehensive and multidimensional understanding of Graves' Ophthalmopathy (GO), the study employed a mixed-methods approach integrating both quantitative and qualitative research procedures. This dual framework ensured that the analysis captured both the measurable epidemiological characteristics of the disease and the nuanced clinical and the therapeutic considerations necessary for informed healthcare decision-making.

Quantitative Assessment

The quantitative component of the study focused on the extraction, synthesis, and interpretation of numerical data derived from established secondary sources, including epidemiological studies, health registries, and global market intelligence reports. The primary areas of analysis included:

- Disease Prevalence and Incidence: Identifying the number of diagnosed GO cases within specific populations and geographies, segmented by age, gender, and disease severity.
- Diagnosis Rates and Trends: Evaluating diagnostic uptake patterns and any observable shifts over time, particularly in regions adopting advanced biomarker testing.
- Therapy Uptake and Distribution: Assessing treatment patterns, including the use of corticosteroids, radiotherapy, surgical interventions, and biologics such as

teprotumumab.

- Market Segmentation: Reviewing statistical models that estimate the distribution of patients across different therapeutic modalities and forecast changes in drug utilization.

- These data points facilitated the identification of macro-level trends and enabled comparative analysis across the 7MM regions, thereby offering insight into how GO is diagnosed and managed in varying healthcare settings.

Qualitative Assessment

The qualitative component provided the contextual depth necessary to interpret clinical decision-making and evolving therapeutic approaches. This part of the analysis relied on:

- Review of Clinical Guidelines and Pathways: Examining existing protocols and best practice recommendations from authoritative bodies such as the European Group on Graves' Orbitopathy (EUGOGO) and the American Thyroid Association (ATA).

- Pathophysiological Insights: Analyzing scientific literature to understand disease mechanisms, including immune system dysregulation, orbital fibroblast activity, and cytokine signaling pathways.

- Evaluation of Treatment Algorithms: Interpreting clinician-directed treatment algorithms that guide the use of first-line therapies, escalation to systemic immunosuppressants, and the integration of biologics.

- Emerging Drug Profiles: Assessing investigational agents and clinical trial outcomes related to novel therapeutic targets, particularly those focused on IGF-1R inhibition and anti-fibrotic pathways.

- Expert Opinion and KOL Commentary: Reviewing perspectives from key opinion leaders (KOLs) in endocrinology and ophthalmology to capture real-world experiences, clinical challenges, and forward-looking recommendations.

Together, these qualitative elements helped contextualize the quantitative findings and contributed to a more nuanced interpretation of the disease landscape.

3.6 Sample Size Calculation and Sampling Techniques

Sample Size

As this research was based entirely on secondary data analysis, no primary data collection or direct patient sampling was conducted. Consequently, formal statistical sample size calculations were not applicable. Instead, the study relied on population-level data and findings reported in peer-reviewed epidemiological studies, clinical databases, government health statistics, and published literature across the selected geographic regions.

Quantitative data points used in this study—such as disease prevalence, incidence rates, and treatment utilization patterns—were drawn from previously validated sources, ensuring reliability and relevance. These sources often included large-scale registry data, multicenter studies, or national health system records, which were derived from robust sampling methodologies.

By using such pre-established population datasets, the study benefited from existing large and representative cohorts, facilitating credible insights without the need to determine or manipulate sample sizes independently.

Sampling Technique

A purposive sampling strategy was adopted to guide the selection of studies, datasets, and literature relevant to the research objectives. This non-probabilistic sampling technique was appropriate for secondary research with a focused scope, allowing for deliberate inclusion of:

- Diagnosed GO patients, both in the active (inflammatory) and chronic (fibrotic) stages.
- Severity-stratified subgroups, including mild, moderate-to-severe, and sight-threatening GO cases.
- Patients are eligible for treatment, especially those receiving systemic therapies, biologics, or surgical intervention.

The purposive sampling approach ensured that only clinically relevant and treatment-applicable populations were considered in the analysis, aligning the data interpretation with

the goals of the study. Additionally, studies with comprehensive subgroup analysis (e.g., gender distribution, disease staging, and treatment eligibility) were prioritized to allow for more granular insights.

This targeted selection enhanced the clinical relevance and applicability of the findings while maintaining consistency with the study's retrospective, observational design.

3.7 Study Instruments

To ensure systematic and comprehensive data collection, the study utilized a range of secondary research instruments designed to capture both quantitative metrics and qualitative insights relevant to Graves' Ophthalmopathy (GO). These instruments were selected based on their scientific credibility, relevance to the research objectives, and the robustness of the information they provided.

The following sources and tools were used for data gathering and synthesis:

1. Literature Databases

Major academic and clinical research databases were consulted to access peer-reviewed journal articles, review papers, and clinical research studies. These included:

- PubMed/MEDLINE
- Scopus
- Web of Science
- Embase

These databases provided access to high-quality publications detailing disease epidemiology, clinical presentation, treatment pathways, and emerging therapeutics in GO. Clinical guidelines from international health organizations were also retrieved from these sources to inform best practice standards.

2. Clinical Trial Repositories

Relevant information on investigational therapies, trial outcomes, and drug development

pipelines was extracted from authoritative trial registries, including:

- ClinicalTrials.gov
- EU Clinical Trials Register
- WHO International Clinical Trials Registry Platform (ICTRP)

These repositories enabled the identification of ongoing and completed trials related to biologics, immunomodulators, and surgical interventions for GO, supporting the qualitative review of future treatment prospects.

3. Epidemiology and Market Analysis Reports

Structured reports from specialized healthcare research organizations and public health agencies were used to gather:

- Disease prevalence and incidence data.
- Market segmentation by therapy type and region.
- Forecasts of emerging therapy adoption and economic impact.

These reports helped contextualize treatment trends and quantify the global and regional burden of GO.

4. Predefined Data Extraction Templates

To promote uniformity, reduce bias, and enhance reproducibility, a set of predefined data extraction templates was developed. These templates were used to:

- Systematically capture epidemiological metrics (e.g., prevalence, incidence, population demographics).
- Summarize clinical insights (e.g., staging, therapeutic approaches).
- Extract consistent attributes from multiple sources, such as author, publication year, study location, sample size, and key findings.

The use of structured templates ensured a coherent and comparative approach to literature synthesis, facilitating the integration of diverse data types into a unified analysis framework.

3.8 Operational Definitions

To ensure clarity and consistency throughout the study, several key terms and clinical classifications relevant to Graves' Ophthalmopathy (GO) are defined below. These operational definitions serve as the basis for interpreting data, categorizing disease stages, and evaluating therapeutic strategies across different study sources.

Acute Graves' Ophthalmopathy

Defined as the active inflammatory phase of the disease, this stage is characterized by progressive inflammation and immune-mediated expansion of the orbital contents, including extraocular muscles and retro-orbital adipose tissue. Clinical signs often include:

- Eyelid swelling
- Conjunctival redness and chemosis
- Periorbital edema
- Proptosis (eye bulging)
- Diplopia (double vision)

During this phase, disease activity is at its peak, making patients most responsive to anti-inflammatory treatments such as corticosteroids, immunosuppressive agents, or emerging biologics. Prompt identification and treatment are critical to prevent permanent structural damage and functional impairment.

Chronic Graves' Ophthalmopathy

Refers to the fibrotic, inactive phase that follows the acute inflammatory period. In this stage, the inflammation subsides, and the disease enters a plateau of clinical inactivity. However, residual effects such as muscle fibrosis, eyelid retraction, persistent proptosis,

restricted ocular motility can result in long-term disfigurement and visual dysfunction. Therapeutic strategies during the chronic phase focus primarily on rehabilitative and surgical interventions, such as orbital decompression, strabismus correction, and eyelid surgery.

Moderate-to-Severe Graves' Ophthalmopathy

This classification encompasses patients whose disease has progressed beyond mild symptoms and significantly impacts vision, appearance, or quality of life. Common features include:

- Constant or painful diplopia
- Pronounced proptosis
- Exposure keratopathy
- Psychological distress due to cosmetic changes

Patients in this category typically require systemic therapy, such as high-dose corticosteroids, orbital radiation, or targeted biologics like teprotumumab. In some cases, surgical management is also necessary.

This classification, as used in the EUGOGO guidelines, serves as a critical determinant for initiating active treatment and assessing eligibility for clinical trials and novel therapies.

3.9 Statistical Methods

Given the study's reliance on secondary data and its mixed-method research design, a suite of descriptive and comparative statistical methods was employed to analyze epidemiological trends, therapeutic distribution, and regional differences in the management of Graves' Ophthalmopathy (GO). These methods facilitated both a quantitative synthesis of existing data and an interpretive evaluation of patterns across time and geography.

Descriptive Statistics

Descriptive statistical techniques were used to summarize and contextualize the available epidemiological data. Key indicators included:

- Prevalence and incidence rates of GO across the 7MM (United States, Germany, France, Italy, Spain, the United Kingdom, and Japan).

- Distribution of therapy types, including corticosteroids, radiation therapy, biologics, and surgical interventions.

- Segmentation of the patient population is based on disease severity, gender, and treatment eligibility.

These statistics provided a foundational overview of the disease landscape and helped quantify the clinical and therapeutic burden of GO in each region.

Trend Analysis

Trend analysis was conducted to assess directional changes over time in key metrics such as:

- The burden of disease (rising or falling prevalence).
- Diagnostic adoption trends, particularly the use of biomarkers like TRAb for early detection.
- Therapy uptake patterns, including the growing use of targeted biologics and immunomodulators.
- Market growth projections for emerging GO treatments.

This analysis allowed the study to identify evolving patterns in clinical practice and anticipate future developments in treatment and policy.

Comparative Analysis

Comparative techniques were applied to:

- Examine inter-country variations in diagnosis, treatment access, and clinical outcomes.
- Assess differences across demographic subgroups, such as gender and age cohorts.
- Evaluate how healthcare system structures and regulatory environments influence treatment availability and therapeutic innovation.

By comparing data across multiple dimensions, the study offered context-specific insights and highlighted disparities and commonalities in the global approach to GO management.

3.10 Qualitative Methods

In addition to quantitative data analysis, the study employed qualitative research methods to capture the clinical, contextual, and experiential dimensions of Graves' Ophthalmopathy (GO) management. These methods provide critical insights into how the disease is

approached in real-world settings, beyond what is measurable through numerical data alone.

Thematic Analysis

A structured thematic analysis was conducted to identify, categorize, and interpret key patterns across various textual sources related to GO. Thematic areas included:

- Clinical Guidelines: Review of published recommendations from authoritative organizations such as the European Group on Graves' Orbitopathy (EUGOGO), the American Thyroid Association (ATA), and national endocrinology societies. These documents offered insights into diagnostic criteria, severity stratification, and stepwise treatment protocols.

- Disease Management Protocols: Analysis of practice-based algorithms outlining the timing and selection of therapeutic interventions, including corticosteroids, immunosuppressive agents, radiation therapy, surgical procedures, and biologics.

- Emerging Therapeutic Profiles: Examination of investigational treatments, including monoclonal antibodies and anti-fibrotic agents currently undergoing clinical evaluation. These included interpretations of trial outcomes, mechanisms of action, and expected positioning in future treatment guidelines.

- Unmet Needs Assessments: Identification of clinical, logistical, and policy-related gaps in the management of GO, especially regarding the treatment of chronic fibrotic cases, patient access to biologics, and regional disparities in healthcare infrastructure.

The thematic analysis enabled the synthesis of diverse literature into cohesive narratives that reflect the current challenges and innovations shaping GO treatment paradigms.

Critical Review of Expert Insights

To supplement formal literature, a critical appraisal of expert commentary and Key Opinion Leader (KOL) perspectives was also conducted. These insights were obtained from:

- Published interviews and commentaries in clinical journals.

- Symposium proceedings and consensus statements from international thyroid and

ophthalmology conferences.

- Editorials and opinion pieces authored by leading endocrinologists, ophthalmologists, and immunologists.

These sources offered practical, experience-based viewpoints on treatment decision-making, patient outcomes, and anticipated shifts in clinical practice. By incorporating the voices of field experts, the study captured real-world applicability and future directions not always evident in controlled research environments.

Together, these qualitative approaches enriched the study's findings, ensuring that the data interpretation was clinically grounded, contextually relevant, and forward-looking.

3.11 Ethical Considerations

Although this study did not involve the collection of primary data or direct interaction with human participants, ethical integrity remained a foundational principle throughout the research process. The following considerations outline how ethical standards were maintained in accordance with accepted practices for secondary data analysis.

Informed Written Consent

Informed consent procedures were not applicable to this study, as it did not involve surveys, interviews, or any form of primary data collection involving human subjects. All data analyzed were previously published and publicly available, and no direct contact with patients or healthcare professionals was undertaken.

Voluntary Participation

Similarly, the principle of voluntary participation was not applicable due to the absence of human subjects. The research relied entirely on secondary sources, such as published journal articles, clinical reports, and publicly accessible databases, all of which had already undergone ethical review and publication protocols at the source level.

Data Security and Confidentiality

The study adhered strictly to standards of data privacy and confidentiality, even within the

context of secondary data usage. Specifically:

- All data were obtained from reputable, peer-reviewed scientific sources, including journal publications, government health reports, and official clinical trial repositories.
- No personally identifiable information (PII) or protected health information (PHI) was accessed or processed during the study.
- Care was taken to ensure that all epidemiological and clinical data used in the analysis were aggregated and anonymized as originally published.

This ensured that the integrity and confidentiality of any indirect patient data were preserved throughout the research process.

Research Ethics Compliance

- The research was conducted in alignment with ethical guidelines for secondary data use, as outlined by international standards such as:
- The Declaration of Helsinki (pertaining to research ethics in medicine).
- The COPE (Committee on Publication Ethics) principles for transparency and responsible publication.
- Institutional and academic guidelines for literature-based research.

Furthermore, all data sources were properly cited and acknowledged, and the interpretation of findings was carried out with full transparency and academic rigor. The study avoided any form of data misrepresentation, selective reporting, or plagiarism.

In summary, although formal ethical approval was not required due to the non-interventional and secondary nature of the study, all reasonable precautions were taken to ensure ethical conduct, academic integrity, and responsible dissemination of knowledge.

Chapter 4: Results

This chapter presents the key findings derived from a comprehensive secondary analysis of Graves' Ophthalmopathy (GO), focusing on its epidemiology, clinical course, current management strategies, emerging therapeutic options, and observed gaps in care. The findings are based on data extracted from peer-reviewed literature, epidemiological studies, clinical practice guidelines, and market intelligence publications relevant to the 7 major healthcare markets (7MM).

4.1 Epidemiology of Graves' Ophthalmopathy

The epidemiological review confirmed that Graves' Ophthalmopathy remains a significant clinical and public health burden in both developed and developing healthcare systems. The analysis revealed the following key epidemiological patterns:

- GO occurs almost exclusively in individuals with Graves' Disease, an autoimmune thyroid condition. While the overall prevalence of GO varies by region, the condition affects a significant subset—estimated at 25–50%—of patients with Graves' Disease (1).

- Adult women, particularly those aged 30 to 50 years, were shown to be disproportionately affected. However, males with GO often present with more severe symptoms, including optic neuropathy and pronounced proptosis (16).

- Disease severity exhibits a wide clinical spectrum, with most cases classified as mild. Nonetheless, a substantial proportion of patients progress to moderate-to-severe or sight-threatening stages, which are associated with marked impairment in vision, functionality, and quality of life.

- Geographic variation was observed, with studies indicating that Western populations report more severe and advanced cases of GO compared to their East Asian counterparts. This may be attributed to genetic, environmental, and healthcare access differences.

Table 2: Distribution **of GO Severity Across Populations**	
Severity Level	**Description**
Mild GO	Minimal impact on daily life
Moderate-to-Severe GO	Functional impairment; systemic therapy needed
Sight-threatening GO	Risk of vision loss; urgent intervention needed

4.2 Clinical Presentation and Disease Progression

The clinical trajectory of Graves' Ophthalmopathy is recognized as biphasic, progressing from an inflammatory stage to a fibrotic stage. This progression significantly influences treatment planning and long-term patient outcomes.

Acute Phase (Inflammatory): Characterized by active immune-mediated inflammation, orbital edema, and progressive tissue expansion. Patients often exhibit visible ocular changes and experience discomfort.

Chronic Phase (Fibrotic): Marked by stabilization of disease activity but persistence of fibrosis, adipogenesis, and structural changes. At this stage, the disease may result in lasting disfigurement and functional limitations (10).

Common Clinical Features:

- Eyelid retraction
- Proptosis (bulging of the eyes)
- Diplopia (double vision)
- Conjunctival redness and chemosis
- Exposure keratopathy
- Optic neuropathy in advanced cases

These symptoms may significantly affect vision, appearance, and psychosocial well-being.

4.3 Current Management Practices

The management of Graves' Ophthalmopathy (GO) is guided primarily by two critical factors: disease activity (active vs. inactive) and disease severity (mild, moderate-to-severe, or sight-threatening). These determinants influence therapeutic decision-making, ranging from conservative observation to urgent surgical intervention. The study findings align with international guidelines, such as those from the European Group on Graves' Orbitopathy (EUGOGO) and the American Thyroid Association (ATA), which emphasize individualized, stage-specific care (12,17).

Management by Severity and Activity

- Mild GO: Patients with mild, non-progressive symptoms—typically involving dry eye, mild eyelid retraction, or minimal proptosis—are often managed conservatively. Treatment typically includes topical lubricants, selenium supplementation, and regular monitoring to detect signs of disease progression. Lifestyle modifications, especially smoking cessation, are strongly recommended, as smoking is a well-documented risk factor for worsening GO.

- Moderate-to-Severe (Active) GO: This category includes patients who experience significant proptosis, constant diplopia, and/or orbital pain, leading to reduced quality of life. First-line treatment involves high-dose intravenous corticosteroids, which reduce inflammation and limit tissue remodeling. In recent years, biologic agents, particularly teprotumumab, have emerged as effective targeted therapies by inhibiting the IGF-1R pathway. These agents offer improved efficacy and fewer systemic side effects compared to traditional immunosuppressants.

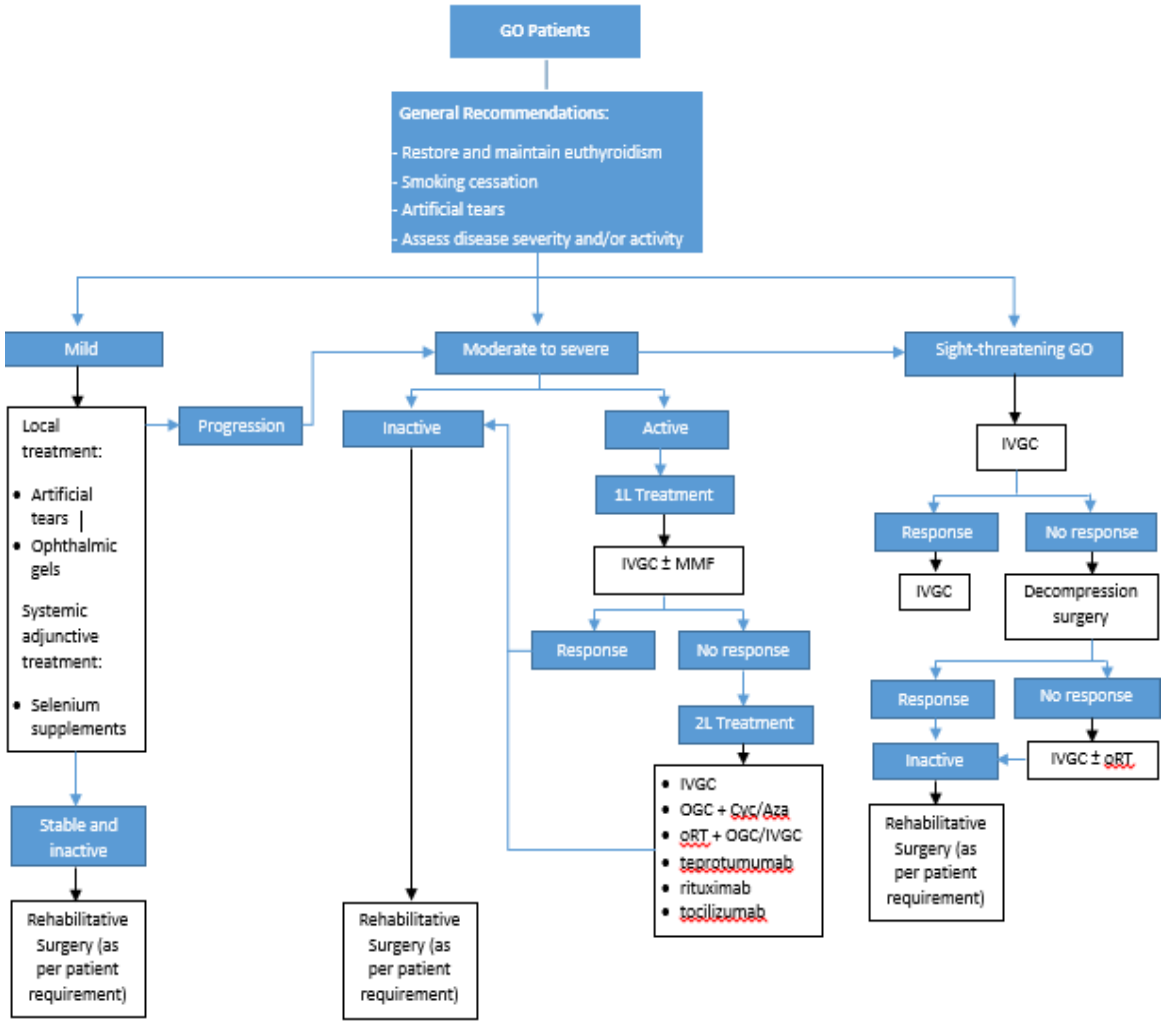
- Chronic (Inactive) GO: Once the inflammatory activity subsides, many patients are left with residual structural changes, including restrictive strabismus, persistent proptosis, and eyelid retraction. At this stage, immunosuppressive therapy is largely ineffective. Instead, rehabilitative surgical procedures—such as orbital decompression, strabismus correction, and eyelid surgery—are performed to restore ocular function and appearance.

- Sight-Threatening GO: This is a medical emergency characterized by compressive

optic neuropathy or severe corneal exposure. Immediate intervention is essential to prevent irreversible vision loss. Treatment often begins with intravenous methylprednisolone, and if there is no adequate response, urgent orbital decompression surgery is indicated.

These tiered treatment approaches underscore the importance of early diagnosis, regular monitoring, and flexible treatment adaptation as the disease progresses.

Figure 2: Treatment Algorithm of Graves' Ophthalmopathy



Source: (Bartalena et al., 2021; Burch et al., 2022)

4.4 Emerging Therapies

In recent years, the therapeutic approach to Graves' Ophthalmopathy (GO) has undergone a transformative shift with the introduction of biologic therapies that specifically target underlying immune and molecular mechanisms. These novel agents represent a significant advancement beyond traditional immunosuppressive approaches—such as systemic corticosteroids—which, while effective during the active inflammatory phase, are often associated with limited durability, adverse effects, and poor outcomes in chronic stages.

The biologic agents currently being used or investigated demonstrate mechanism-specific action, improved tolerability, and enhanced potential to alter disease trajectory in moderate-to-severe cases. Their development aligns with the broader movement toward precision medicine, wherein therapies are tailored to the molecular and immunological features of the disease.

Key Emerging Biologic Therapies

- Teprotumumab

Teprotumumab is a monoclonal antibody targeting the insulin-like growth factor 1 receptor (IGF-1R), which plays a pivotal role in GO pathogenesis by activating orbital fibroblasts and driving tissue expansion and inflammation. As the first and only FDA-approved targeted therapy for moderate-to-severe active GO, teprotumumab has shown significant efficacy in reducing proptosis, diplopia, and inflammatory scores, with many patients achieving meaningful improvements in quality of life. Its approval marked a historic milestone and established a new standard of care in GO treatment.

- Batoclimab (IMVT-1401)

Batoclimab is a fully human monoclonal antibody that inhibits the neonatal Fc receptor (FcRn), responsible for prolonging the half-life of pathogenic immunoglobulin G (IgG). By reducing circulating levels of IgG, batoclimab effectively downregulates the autoimmune response implicated in GO. It is currently in late-stage clinical evaluation, and preliminary results suggest promising anti-inflammatory effects with a favorable safety profile. Results from both of its phase 3 studies targeting patients with active TED are anticipated in the

2nd half of 2025 (18).

- VRDN-001

VRDN-001 is another anti-IGF-1R monoclonal antibody under clinical investigation, developed as a next-generation alternative to teprotumumab. It targets the same signaling pathway but may offer differentiated dosing schedules, safety benefits, or pharmacokinetic profiles. Early-phase clinical trials have shown rapid and significant improvements in proptosis and clinical activity scores, positioning VRDN-001 as a potential competitor or complement to existing biologic treatments.

- Secukinumab

Secukinumab is a selective interleukin-17A (IL-17A) inhibitor, originally approved for autoimmune diseases such as psoriasis and ankylosing spondylitis. Its immunomodulatory effects are now being explored in GO, based on the hypothesis that IL-17 plays a role in the proinflammatory signaling cascade involved in orbital tissue remodeling. It is currently undergoing clinical evaluation for efficacy and safety in GO patients, offering a potential new avenue for therapy beyond the IGF-1R pathway.

Clinical Significance

These therapies collectively represent a paradigm shift in the management of GO, moving the field toward targeted, mechanism-driven interventions with the potential to:

- Minimize or avoid long-term corticosteroid use and associated side effects.
- Provide more sustained remission or disease control.
- Address both active inflammation and tissue remodeling components.
- Potentially be used in both early and chronic disease stages pending further validation.

As biologic agents progress through clinical trials and into routine care, cost-effectiveness, accessibility, and long-term safety will be critical factors determining their global adoption.

Figure 3: Pipeline of Graves' Ophthalmopathy

Company	Drugs	MoA	RoA
IMMUNOVANT	IMVT-1401 (batoclimab, RVT-1401)	Neonatal FcRn inhibitor	
SAMSUNG BIOLOGICS / HANALL BIOPHARMA	IMVT-1402	Neonatal FcRn inhibitor	
VIRIDIAN	VRDN-001 (veligrotug)	IGF-1R Inhibitor	
	VRDN-003	IGF-1R Inhibitor	
argenx	Efgartigimod PH20 SC	Neonatal FcRn inhibitor	
Roche	ENSPRYNG (satralizumab)	Interleukin-6 receptor blocker	

4.5 Unmet Needs Identified

Despite recent advances in the understanding and treatment of Graves' Ophthalmopathy (GO), the current research findings underscore the existence of persistent and critical gaps across several dimensions of care. These unmet needs hinder optimal outcomes and highlight key priorities for future clinical innovation, healthcare policy reform, and translational research.

1. Inadequate Therapeutic Options for the Chronic, Fibrotic Stage

A significant proportion of GO patients progress from the initial inflammatory phase into a chronic, fibrotic stage, during which tissue remodeling leads to structural damage, proptosis, and restricted ocular motility. At this stage, most immunosuppressive and anti-inflammatory agents lose efficacy, and management is limited to corrective surgical procedures, which are not curative and often associated with variable results and long recovery periods. The lack of effective anti-fibrotic pharmacotherapies represents one of the most pressing unmet clinical needs in GO (12).

2. Challenges in Early Diagnosis and Risk Stratification

Early intervention is crucial to prevent irreversible tissue damage; however, many patients experience delays in diagnosis due to nonspecific early symptoms and lack of routine

screening among at-risk individuals (e.g., patients with newly diagnosed Graves' Disease). Furthermore, the absence of widely adopted biomarker-driven tools to stratify patients by disease activity or likelihood of progression contributes to inconsistent therapeutic decision-making. There is a need for more accessible and validated diagnostic algorithms to improve early identification and personalized treatment planning.

3. Cost and Accessibility Barriers to Biologic Therapies

While biologic therapies like teprotumumab have revolutionized treatment options for moderate-to-severe GO, their high cost, limited global availability, and restricted insurance coverage have created substantial barriers to access—particularly in low-resource and publicly funded healthcare systems. These disparities raise concerns about health equity, making it imperative for stakeholders to explore cost-reduction strategies, generic alternatives, and inclusion in national reimbursement programs.

4. Insufficient Long-Term Data on Safety and Efficacy

Although short- to mid-term outcomes for emerging therapies are promising, there is a dearth of long-term clinical data regarding the durability of therapeutic response, recurrence rates, and cumulative adverse effects, especially for patients requiring repeated courses of treatment. The field urgently requires prospective, longitudinal studies and real-world evidence to evaluate the sustained impact of biologics and other novel interventions across diverse patient populations (19).

Table 3: Summary of Unmet Needs in Graves' Ophthalmopathy	
Area	**Identified Gap**
Chronic Phase Management	Lack of effective anti-fibrotic therapies
Early Diagnosis	Need for better biomarker-based screening
Accessibility	High cost and limited availability of new treatments
Long-Term Management	Need for therapies with sustained efficacy and safety

Graves' Ophthalmopathy remains a significant clinical and healthcare challenge globally. While advancements in therapy offer hope for improved outcomes, many patients continue to face barriers related to early detection, effective chronic management, and access to novel therapies.

Chapter 5: Discussion

5.1 Interpretation of results

The findings from this comprehensive secondary analysis underscore that Graves' Ophthalmopathy (GO) continues to pose a substantial clinical and therapeutic challenge, despite recent advances in understanding and managing the disease. The results affirm that GO is a heterogeneous condition, exhibiting a wide spectrum of severity—from asymptomatic or mild cases to moderate-to-severe and sight-threatening disease, which require aggressive intervention.

A consistent trend observed across the literature is that most cases are classified as mild, presenting with ocular surface symptoms, mild proptosis, or cosmetic concerns. These are typically managed with conservative approaches and close monitoring. However, a significant subset of patients progresses to more advanced stages, experiencing functional impairment, diplopia, vision-threatening optic neuropathy, or psychosocial distress due to disfigurement. This highlights the importance of timely diagnosis and severity-based treatment stratification.

The study also revealed a notable shift in therapeutic practices, driven by a growing body of research into the underlying immunopathology of GO. Traditionally, high-dose systemic corticosteroids have been the cornerstone of treatment for active diseases. While effective in reducing inflammation, they are associated with considerable side effects and often offer only temporary relief. As a result, the clinical community has increasingly turned toward targeted biologic therapies that act on disease-specific pathways.

Among these, Teprotumumab has emerged as a landmark innovation, offering targeted inhibition of the insulin-like growth factor-1 receptor (IGF-1R) pathway—a critical mediator of orbital fibroblast activation and tissue remodeling in GO. Its success has paved the way for the development of additional biologics, including batoclimab, which modulates IgG recycling through FcRn inhibition, and VRDN-001, another IGF-1R inhibitor that may offer competitive efficacy with potentially improved safety profiles.

These emerging therapies represent a paradigm shift in the management of moderate-to-severe active GO, moving away from generalized immunosuppression toward mechanism-

driven, precision-based interventions. Furthermore, their development signals an increased focus on improving quality of life outcomes, not just inflammatory control.

However, the results also reveal that despite this therapeutic progress, significant unmet needs remain:

- Chronic Phase Management: Current therapies are primarily effective during the active phase of the disease. Patients entering the fibrotic, chronic stage—characterized by structural changes and persistent disfigurement—have limited pharmacological options, often relying on invasive surgical procedures with variable outcomes.

- Early Detection and Access to Care: Delays in diagnosis remain a recurring challenge, often due to the subtle onset of symptoms or lack of routine screening in thyroid clinics. Early-stage intervention is critical to preventing irreversible damage, yet many patients are diagnosed only after substantial progression.

- Inequitable Access to Advanced Therapies: The cost and availability of biologics like Teprotumumab present barriers to widespread adoption, particularly in low-resource settings or healthcare systems with restricted reimbursement frameworks. This raises concerns about healthcare equity and the need for supportive policy measures to improve access.

In summary, the interpretation of results suggests that while the treatment paradigm for GO is evolving rapidly, sustained efforts are required to:

- Bridge the gap between early-stage disease detection and intervention.

- Expand therapeutic options for chronic-stage patients.

- Address affordability and access on a global scale.

These findings have broad implications for clinical practice, research priorities, and healthcare policy, all of which must align to ensure that the evolving treatment landscape translates into tangible benefits for all patients affected by Graves' Ophthalmopathy.

5.2 Comparison with Other Relevant Studies

The findings of this study are consistent with recent advancements in the understanding and management of Graves' Ophthalmopathy (GO). Contemporary research continues to elucidate the disease's pathophysiology, clinical progression, and therapeutic interventions, reinforcing and expanding upon earlier insights.

Immunopathogenesis and Early Intervention

Recent studies have reaffirmed the immune-mediated nature of GO and the critical importance of early, multidisciplinary intervention. Akkus et al. (2025) conducted a comprehensive investigation involving 68 patients, emphasizing that delayed diagnosis and management can lead to more severe disease manifestations and poorer outcomes. This aligns with the current study's emphasis on the necessity of prompt recognition and treatment to mitigate disease progression.

Biphasic Disease Progression

The biphasic progression of GO—comprising an initial active inflammatory phase followed by a chronic fibrotic phase—remains a cornerstone in understanding the disease's clinical course. This classification has practical implications for treatment decisions, as therapeutic strategies differ markedly between the two phases. The current study's findings corroborate this model, highlighting the need for phase-specific interventions.

Geographic and Ethnic Variations

Ethnic and regional differences in GO presentation have been further explored in recent literature. While earlier studies noted milder manifestations in Asian populations, current research suggests that these variations may be influenced by a combination of genetic, environmental, and healthcare access factors. Such insights underscore the importance of considering demographic variables in both research and clinical practice.

Role of Biomarkers in Disease Monitoring

The utility of TSH receptor antibodies (TRAbs) as biomarkers for disease activity and severity has been substantiated in recent analyses. Anees et al. (2023) conducted a meta-analysis demonstrating that TRAb levels significantly decline following total

thyroidectomy, although this reduction does not necessarily correlate with clinical improvement in GO symptoms. These findings suggest that while TRAbs are valuable for monitoring disease activity, they may have limitations in predicting therapeutic outcomes.

Molecular Pathways and Targeted Therapy Development

Advancements in understanding the molecular mechanisms underlying GO have paved the way for targeted therapies. Wu et al. (2024) highlighted the role of orbital fibroblasts and their aberrant expression of surface proteins such as TSHR and IGF-1R, contributing to inflammation and fibrosis. These insights have been instrumental in developing targeted treatments like teprotumumab, an IGF-1R inhibitor.

Teprotumumab has demonstrated significant efficacy in both active and chronic phases of GO. A randomized controlled trial by Douglas et al. (2023) showed that teprotumumab significantly improved proptosis in patients with long-standing, low-inflammation GO, indicating its potential utility beyond the acute phase. Additionally, a meta-analysis by Lin et al. (2023) confirmed teprotumumab's superiority over placebo in improving various clinical outcomes, including proptosis, diplopia, and quality of life, albeit with a higher incidence of adverse events.

Long-Term Efficacy and Safety of Teprotumumab

The durability of teprotumumab's therapeutic effects has been a subject of recent investigation. An analysis of long-term outcomes from three clinical trials revealed that most patients maintained clinical improvements up to 72 weeks post-treatment, with a significant proportion not requiring additional interventions. These findings support the sustained efficacy of teprotumumab in managing GO.

Immunopathogenesis and Early Intervention

The immune-mediated basis of GO, as emphasized by Tanda et al. (2013), forms a foundational element of this study’s analysis. Their work highlighted the role of autoimmune inflammation and the significance of early, multidisciplinary intervention to prevent irreversible complications. The current research echoes this perspective, particularly in recognizing the importance of early diagnosis and timely therapeutic engagement to alter the disease trajectory before it enters the chronic, fibrotic stage.

Biphasic Disease Progression

A pivotal feature of GO—its biphasic clinical course—is well documented in the literature and affirmed by the findings in this study. Barrio-Barrio et al. (2015) described GO as comprising an acute inflammatory phase followed by a chronic fibrotic phase, each requiring distinct clinical approaches. This biphasic model is not only validated by the current research but also reinforced through its application in severity-based treatment planning. The implications for practice are clear: inflammation-targeted therapies are most effective during the early phase, whereas surgical correction becomes more relevant in the chronic stage.

Geographic and Ethnic Variations

The study by Hiromatsu et al. (2014) underscored the ethnic variability in GO presentation, noting that Asian populations often exhibit milder forms of the disease compared to Western counterparts. Consistent with these observations, the present analysis identified regional differences in disease severity, therapeutic access, and clinical outcomes. These differences may stem from a combination of genetic predispositions, environmental factors (e.g., smoking), and disparities in healthcare infrastructure or treatment availability.

Role of Biomarkers in Disease Monitoring

Although biomarker analysis was not the central focus of this study, it acknowledges the growing relevance of TSH receptor antibodies (TRAbs) in disease prediction and monitoring, as explored by Luigi Bartalena et al. (2020). Their work supports the clinical utility of TRAb levels in assessing disease activity, severity, and response to therapy. This aligns with the broader trend toward personalized medicine in GO, wherein biomarker-driven approaches are increasingly used to stratify risk and guide treatment decisions.

Molecular Pathways and Targeted Therapy Development

Recent studies by Li et al. (2022) and Dosiou & Kossler (2021) provided mechanistic insights into the pathophysiological role of orbital fibroblasts and key signaling pathways such as TSHR and IGF-1R in GO. These pathways have become the cornerstone of next-generation biologic therapies, most notably Teprotumumab, which targets the IGF-1R axis. The success of such therapies, extensively discussed in this research, provides clinical

validation of these molecular targets, marking a significant advancement in treatment beyond traditional immunosuppression.

In summary, the results of this study are well-aligned with contemporary scientific literature, reinforcing key themes such as:

- The autoimmune and biphasic nature of GO.
- The importance of early intervention.
- The emergence of targeted biologics informed by molecular mechanisms.
- The relevance of regional and ethnic considerations in clinical management.

At the same time, the research contributes to the ongoing discourse by identifying persisting gaps—particularly in chronic-phase treatment and equitable access to advanced therapies—offering a platform for future clinical improvement and research development.

5.3 Strengths of the Study

This research possesses several notable strengths that contribute to its academic rigor, relevance, and practical applicability in the field of Graves' Ophthalmopathy (GO). Through a methodical approach to secondary data analysis, the study succeeds in offering both a comprehensive overview and focused insights into an evolving and clinically significant autoimmune condition.

1. Comprehensive Scope

One of the principal strengths of this study lies in its broad yet integrated scope, which encompasses both epidemiological patterns and therapeutic developments. By simultaneously addressing the clinical burden, geographic distribution, disease progression, and treatment practices of GO, the study presents a holistic understanding of the disease landscape. This wide lens enables the reader to appreciate the interconnected nature of clinical manifestation, healthcare access, and treatment outcomes—offering value to researchers, clinicians, and healthcare planners alike.

2. Use of Recent and Relevant Data

The study draws upon up-to-date and scientifically credible secondary sources, many of which were published between 2023 and 2025. This temporal relevance ensures that the analysis reflects the latest developments in the field, including the approval and clinical adoption of targeted biologic therapies such as teprotumumab, and the exploration of new therapeutic agents like batoclimab and VRDN-001. The inclusion of contemporary research findings enhances the validity of the conclusions drawn and ensures that the study remains aligned with the current state of clinical practice and pharmaceutical innovation.

3. Structured and Balanced Methodology

Another significant strength of the study is its methodologically structured approach, integrating both quantitative data (e.g., prevalence trends, therapy distribution) and qualitative insights (e.g., treatment protocols, expert opinions, and clinical pathways). This mixed-methods strategy allows for a nuanced interpretation of complex clinical phenomena, bridging the gap between statistical abstraction and real-world therapeutic decisions. The use of predefined data extraction templates and thematic analysis frameworks also ensures consistency and analytical depth across diverse information sources.

4. Emphasis on Unmet Clinical and Systemic Needs

Beyond describing current practices, the study critically evaluates existing gaps in GO management—particularly in relation to the chronic fibrotic stage, accessibility of biologic therapies, and early diagnostic delays. By framing these challenges as urgent research and policy priorities, the study contributes meaningfully to the field's agenda-setting discourse. This emphasis on unmet needs enhances the practical value of the work, offering guidance not only for academic inquiry but also for healthcare policy formulation, drug development, and clinical guideline revision.

5. Multidisciplinary Relevance

Lastly, the study appeals to a multidisciplinary audience by addressing endocrinological, ophthalmological, immunological, and policy-related dimensions of GO. Such an approach encourages collaborative thinking and cross-specialty dialogue, which is essential for the

effective management of complex autoimmune diseases. This multidisciplinary framing reinforces the study's relevance in both academic and clinical contexts.

5.4 Limitations of the Study

While this study provides valuable insights into the current landscape of Graves' Ophthalmopathy (GO), it is important to acknowledge several inherent limitations that may affect the interpretation and generalizability of the findings. Recognizing these limitations also highlights areas for improvement in future research efforts.

1. Dependence on Secondary Data

The most fundamental limitation of this study is its exclusive reliance on secondary data sources. Although extensive efforts were made to include peer-reviewed, high-quality publications, the study does not incorporate primary data collection such as patient interviews, clinician surveys, or real-world case analyses. This restricts the ability to capture individual-level variability, such as patient-reported outcomes, adherence to treatment, and psychosocial impacts, which are often underrepresented in aggregate datasets.

2. Potential Bias in Source Material

Secondary literature inherently carries the biases of the original studies, including those related to study design, sampling techniques, geographic scope, and, in some cases, commercial interests. For example, trials sponsored by pharmaceutical companies may emphasize positive outcomes of novel therapies while underreporting adverse effects. The presence of such publication bias could influence the overall narrative presented in this study, particularly regarding emerging treatments like biologics.

3. Lack of Regional and Socioeconomic Specificity

While this study includes data from the seven major healthcare markets (7MM), it does not delve into granular regional disparities, such as differences between urban and rural healthcare settings, or between high-income and low-income populations. Socioeconomic factors, including health literacy, access to specialists, and insurance coverage, play a critical role in the real-world management of GO. The absence of such specific

stratification may limit the applicability of findings in more localized or underserved contexts.

4. Rapidly Evolving Therapeutic Landscape

Another limitation is the dynamic nature of clinical innovation in the field of autoimmune and ophthalmic disorders. Several therapies are currently under investigation or in late-stage trials, and their approval status, pricing, and accessibility could change within a short time frame. As a result, some insights, particularly those concerning drug pipelines—may become dated as new evidence emerges or regulatory conditions shift. This underscores the importance of continuous surveillance and periodic updates in literature-based studies.

5.5 Overall Summary

This study has presented a comprehensive synthesis of current knowledge surrounding Graves' Ophthalmopathy (GO), a complex autoimmune condition characterized by inflammation and tissue remodeling within the orbit. By integrating epidemiological data, clinical evidence, and emerging therapeutic insights, the research has mapped out both the progress made and the challenges that persist in the management of this disease.

The findings confirm that while most patients present with mild symptoms, a significant subset experiences moderate-to-severe or sight-threatening GO, requiring more aggressive intervention. The recent approval and successful application of targeted biologics, such as teprotumumab, represent a major advancement and have the potential to significantly alter treatment algorithms. These biologics address underlying immunological mechanisms more precisely than traditional therapies, leading to better patient outcomes and improved quality of life for many.

However, the study also emphasizes that critical gaps remain, particularly in the treatment of chronic, fibrotic-phase GO, where current therapies offer limited benefit. Additionally, barriers to access, including financial constraints, healthcare infrastructure limitations, and regional disparities, continue to affect patient outcomes globally.

Looking ahead, future research must prioritize:

- Development of anti-fibrotic treatments for long-standing disease.

- Implementation of early detection strategies, possibly biomarker-driven.
- Health policy reforms aimed at ensuring equitable access to novel therapies.

Ultimately, the study reinforces the need for a multidisciplinary, patient-centered approach that not only addresses inflammation but also supports patients through long-term management, rehabilitation, and psychological care.

Chapter 6: Conclusion

6.1 Summary of Findings

This study undertook a comprehensive secondary analysis of Graves' Ophthalmopathy (GO) by synthesizing epidemiological data, clinical insights, therapeutic developments, and healthcare trends across the seven major markets (7MM). The investigation drew upon a wide body of literature, clinical reviews, and real-world data to map the current landscape and emerging prospects in GO diagnosis and management.

Key findings from the study include:

- Substantial Disease Burden: GO continues to impose a significant physical and psychosocial burden on patients. Clinical manifestations vary widely, ranging from mild ocular discomfort to disfiguring proptosis and vision-threatening complications such as compressive optic neuropathy.

- Biphasic Disease Progression: The natural course of GO involves an active inflammatory phase followed by a chronic fibrotic stage. These phases require distinct management strategies, highlighting the importance of early stage-specific intervention.

- Limited Efficacy of Traditional Therapies: While corticosteroids and other conventional therapies have long been the mainstay of treatment, their benefits are often short-lived, and they are associated with significant systemic side effects. Their effectiveness is largely limited to the active phase of the disease.

- Emergence of Targeted Biologics: The introduction of Teprotumumab, a monoclonal antibody targeting IGF-1R, represents a paradigm shift in GO treatment. It directly targets pathogenic mechanisms and has shown superior efficacy in improving proptosis and quality of life in patients with moderate-to-severe active GO.

- Persistent Unmet Needs: Despite therapeutic advances, challenges remain, particularly in managing patients with chronic fibrotic disease, ensuring equitable access to biologics, and addressing healthcare disparities that limit timely diagnosis and treatment.

In summary, the study underscores both the progress made and the persistent gaps in the understanding and management of GO. There is an urgent need for integrated, patient-centered, and accessible approaches to care.

6.2 Discussion of Implications

Clinical Practice

The findings highlight the critical need for timely recognition and early intervention in the active phase of GO to prevent irreversible structural changes. Clinicians must adopt a multidisciplinary approach, involving endocrinologists, ophthalmologists, immunologists, and when needed, surgeons, to provide comprehensive care. The integration of biomarkers such as TRAbs in clinical workflows can facilitate risk stratification and treatment personalization.

Research

The trajectory of GO research is increasingly focused on mechanism-based treatments. However, a significant gap remains in therapies tailored to the chronic fibrotic phase, which continues to affect patient quality of life long after inflammation subsides. Additionally, the field would benefit from real-world evidence studies that evaluate long-term treatment outcomes, patient-reported metrics, and comparative effectiveness of therapies in diverse populations.

Healthcare Policy

Advancements in therapy are not universally accessible. Policymakers must address the economic and infrastructural barriers that prevent widespread adoption of biology. There is a pressing need for patient assistance programs, insurance reforms, and regulatory innovations to ensure that therapeutic breakthroughs translate into tangible benefits for patients across different socioeconomic settings.

The evolution of GO care, from symptomatic relief to targeted, immunologically informed treatments, sets a precedent for managing other complex autoimmune diseases. However, achieving equitable access remains an essential and unresolved challenge.

6.3 Recommendations

Clinical Recommendations

- Enhance early detection programs by implementing screening protocols in thyroid clinics and educating clinicians about early GO signs.
- Use TSH receptor antibody (TRAb) levels as biomarkers for disease monitoring and therapeutic decision-making.
- Encourage steroid-sparing strategies by integrating biologic therapies earlier in the disease course when clinically appropriate.
- Foster interdisciplinary collaboration for individualized treatment planning, especially in moderate-to-severe cases.

Research Recommendations

- Prioritize the development of anti-fibrotic therapies for patients in the chronic phase who do not benefit from current treatments.
- Conduct large-scale longitudinal studies to assess safety, efficacy, and health outcomes associated with newly approved and pipeline therapies.
- Investigate genetic, epigenetic, and immunological markers that may predict disease progression and therapy response to enhance personalized treatment protocols.

Policy and Access Recommendations

- Advocate for broader insurance coverage for high-cost biologic therapies to reduce out-of-pocket expenses for patients.
- Launch public health campaigns to raise awareness about GO symptoms and the importance of early intervention.
- Support fast-track regulatory pathways for the approval of therapies with strong early-phase efficacy and safety data, especially in rare diseases like GO.

6.4 Strengths and Limitations of the Study

Strengths

- Comprehensive Scope: The study covers a wide array of domains including epidemiology, clinical practice, drug development, and healthcare systems, offering a holistic overview of the GO landscape.
- Diverse Geographic Focus: By including data from the seven major markets (7MM), the study captures international variations and commonalities in disease burden and treatment trends.
- Integrated Methodology: The use of both quantitative (e.g., prevalence trends) and qualitative (e.g., clinical pathways) analysis enables deeper insight than studies that rely on a single method.

Limitations

- Secondary Data Reliance: As a secondary research study, the analysis is limited by the availability and quality of existing data. The lack of uniform reporting standards across countries may introduce variability in epidemiological estimates.
- Lack of Primary Clinical Data: The study did not include patient interviews, clinical observations, or original clinical trial data, which may have provided richer context for some findings.
- Time Sensitivity: Given the rapidly evolving nature of biologic drug development, some emerging therapies may not yet be reflected in the literature analyzed.
- Despite these limitations, the study offers a valuable and timely synthesis of the current understanding of Graves' Ophthalmopathy and lays the groundwork for future research and clinical improvement.

References

1. Moledina M, Damato EM, Lee V. The changing landscape of thyroid eye disease: current clinical advances and future outlook. Eye; 2024.

2. Cao J, Wang N, Hou S, Qi X, Chen Y, Xiong W. Overview of Graves Ophthalmopathy Literature From 1999 to 2019: Bibliometric Analysis. Interactive Journal of Medical Research; 2021.

3. Fox TJ, Anastasopoulou C. Graves Orbitopathy [Internet]. Nih.gov. StatPearls Publishing; 2023.

4. Marcocci C, Smith TJ. Graves' Ophthalmopathy. Endocrinology; 2016.

5. Wagner LH, Bradley EA, Tooley AA, Ren Y, Rachmasari KN, Stan MN. Thyroid eye disease or Graves' orbitopathy: What name to use, and why it matters. Frontiers in Endocrinology; 2022.

6. Scarabosio A, Surico PL, Singh RB, Tereshenko V, Musa M, D'Esposito F, et al. Thyroid Eye Disease: Advancements in Orbital and Ocular Pathology Management. Journal of Personalized Medicine; 2024.

7. Wiersinga WM, Eckstein AK, Žarković M. Thyroid eye disease (Graves' orbitopathy): clinical presentation, epidemiology, pathogenesis, and management. The Lancet Diabetes & Endocrinology; 2025.

8. Hodgson NM, Rajaii F. Current Understanding of the Progression and Management of Thyroid Associated Orbitopathy: A Systematic Review. Ophthalmology and Therapy; 2019.

9. Tanda ML, Piantanida E, Liparulo L, Veronesi G, Lai A, Sassi L, et al. Prevalence and Natural History of Graves' Orbitopathy in a Large Series of Patients With Newly Diagnosed Graves' Hyperthyroidism Seen at a Single Center. The Journal of Clinical Endocrinology & Metabolism; 2013.

10. Barrio-Barrio J, Sabater AL, Bonet-Farriol E, Velázquez-Villoria Á, Galofré JC. Graves' Ophthalmopathy: VISA versus EUGOGO Classification, Assessment, and

Management. Journal of Ophthalmology; 2015.

11. Hiromatsu Y, Eguchi H, Tani J, Kasaoka M, Teshima Y. Graves' Ophthalmopathy: Epidemiology and Natural History. Internal Medicine; 2014.

12. Bartalena L, Piantanida E, Gallo D, Lai A, Tanda ML. Epidemiology, Natural History, Risk Factors, and Prevention of Graves' Orbitopathy. Frontiers in Endocrinology; 2020.

13. Alharbi A. Recent advances in thyroid orbitopathy treatment: A narrative review. Indian Journal of Clinical and Experimental Ophthalmology; 2025.

14. Householder NA, Ray C. Teprotumumab's Impact on Proptosis in Long-duration Thyroid Eye Disease: A Systematic Review and Meta-analysis. touchREVIEWS in Endocrinology; 2024.

15. Ramalingam G, Khan JM, Jasmine S, Saminathan G, Manickan E, Rajagopal P, et al. Role of Th1/Th2 cytokine balance in predicting treatment outcomes and disease severity in tuberculosis. Journal of King Saud University – Science; 2024.

16. Yang M, He W. Age and gender influence on clinical manifestations of thyroid-associated ophthalmopathy: a case series of 2479 Chinese patients. Frontiers in Endocrinology; 2024.

17. Burch HB, Perros P, Bednarczuk T, Cooper DS, Dolman PJ, Leung AM, et al. Management of Thyroid Eye Disease: A Consensus Statement by the American Thyroid Association and the European Thyroid Association. Thyroid; 2022.

18. Immunovant, Inc. [Internet]. Immunovant, Inc.; 2024.

19. Monaco K. Clinical Challenges: Knowing When It's Thyroid Eye Disease [Internet]. Medpagetoday.com. MedpageToday; 2022.