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REVIEW

# The Relevance and Potential Role of Orbital Fat in Inflammatory Orbital Diseases: Implications for Diagnosis and Treatment

Prince Dadson · Peter Ngum · Luis Eduardo Juarez-Orozco · Michael Ntodie · Piotr Loba

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## ABSTRACT

The orbit is an important structure within the skull that houses the eye, optic nerve, and extraocular muscles. It also contains adipose/fat tissue, which provides a protective cushion for these components. Inflammatory orbital disease can affect any or all components of the orbit, often arising from various underlying pathologic conditions, including autoimmune, infectious, and vascular diseases. Typical signs and symptoms of orbital inflammation include swelling, redness, pain, discomfort, and potential loss of function. The role of orbital fat in the pathogenesis of inflammatory orbital diseases has not been fully explored. This review aims to provide a comprehensive description of orbital fat, its relevance and the potential role in inflammatory diseases of the orbit, and the use of radiologic imaging studies for evaluating this fat depot in cases of as inflammatory orbital diseases. Additionally, this review discusses the various procedures available for the treatment and management of these conditions. A range of interventions, including pharmacotherapy and surgical procedures, will be evaluated as promising therapeutic options. This review also explores the characteristics and potential applications of orbital fat-derived stem cells, with an emphasis on their regenerative abilities and anti-inflammatory effects. Understanding the role of

Prince Dadson and Piotr Loba have shared corresponding authorship.

P. Dadson (✉) · L. E. Juarez-Orozco
Turku PET Centre, University of Turku, Kiinamyllynkatu 4-8, 20520 Turku, Finland
e-mail: pryada@utu.fi

P. Dadson · L. E. Juarez-Orozco
Turku PET Centre, Turku University Hospital, Kiinamyllynkatu 4-8, 20520 Turku, Finland

P. Ngum
Turku Brain Injury Center, Turku University Hospital and University of Turku, Turku, Finland

L. E. Juarez-Orozco
Division Heart and Lungs, Department of Cardiology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

M. Ntodie
Centre for Optometry and Vision Science, Biomedical Sciences Research Institute, Ulster University, Coleraine, UK

P. Loba (✉)
Department of Binocular Vision Pathophysiology and Strabismus, Medical University of Lodz, University Barlicki Hospital No.1, Kopcinskiego Street 22, 90-153 Lodz, Poland
e-mail: piotr.loba@umed.lodz.pl

orbital fat and its contribution to inflammatory orbital diseases is essential for optimizing diagnostic and treatment strategies.

**Keywords:** Orbital fat; Inflammatory orbital disease; Diagnostic; Treatment; Radiologic imaging studies

| Key Summary Points |
| --- |
| Inflammatory orbital diseases (IOD) are a group of inflammatory conditions affecting the orbit, potentially leading to vision problems. |
| The relevance and the contribution of orbital fat, a protective tissue within the orbit, to IOD is not fully understood. |
| Orbital fat's unique structure and metabolic profile compared to other fat tissues likely contribute to its susceptibility and involvement in IOD. |
| This narrative review explores the importance and the potential role of orbital fat in IOD pathogenesis. |
| Imaging techniques like CT and MRI are crucial for diagnosis involving orbital fat, while PET scans hold promise for earlier detection and identification of underlying systemic disorders. The study also highlights the potential of orbital fat biopsies for investigating infiltrative lesions associated with IOD. |
| Orbital fat-derived stem cells possess significant regenerative potential, making them promising candidates for tissue repair, ocular surface injuries, and inflammatory diseases. |
| Understanding the role of orbital fat in IOD pathogenesis is essential for optimizing diagnostic, treatment, and management strategies. |

## INTRODUCTION

The orbits are symmetrical bony cavities in the skull that house the eyeballs. These structures also contain the extraocular muscles, nerves, blood vessels, the lacrimal apparatus, and adipose tissue (fat) [1]. Orbital fat is a highly specialized type of white adipose tissue (WAT) that differs significantly from subcutaneous fat in development, structure, and function [2]. It functions as a protective cushion for the eye, providing pathways for essential vessels, nerves, and extraocular muscles [3]. Moreover, this soft cushion facilitates the smooth movement of the extraocular muscles, enabling efficient eye motility [1].

Inflammatory orbital disease (IOD) is a collective term for various medical conditions characterized by inflammation in the tissues within the orbit [4]. IOD accounts for up to 6% of orbital diseases, affecting patients across all age groups, and is one of the most frequent indications for orbital biopsy acquisition [5]. Common signs and symptoms of IOD include eye pain or discomfort, swelling and redness around the eye, limited eye movement, double vision, proptosis, changes in vision, and a general sense of discomfort or headaches [6]. The evaluation of a patient with suspected IOD must include a thorough history, physical examination, and appropriate laboratory and radiologic studies [5].

Inflammatory orbital disease is believed to result from an abnormal immune system response, infection, or other underlying medical conditions [4]. Orbital fat is increasingly recognized for its crucial role in the pathogenesis of several IOD, particularly due to its characteristics, such as immunologic activity and anatomical positioning [7]. This review aims to provide a comprehensive understanding of the anatomy and physiologic functions of orbital fat, explore its role in the pathogenesis of various inflammatory diseases affecting the orbit, and assess current diagnostic tools, particularly the use of radiologic imaging techniques in evaluating orbital fat in orbital inflammation. Additionally, the review offers an in-depth analysis of

the different procedures available for managing orbital fat in the context of IOD, including surgery, pharmacotherapy, and other proven interventions. This narrative review also discusses the characteristics and potential applications of orbital fat-derived stem cells, highlighting their significant regenerative and anti-inflammatory properties. Ultimately, this review is intended to guide current clinical practice and provide a structured framework for future research, with the goal of improving patient outcomes in a more targeted manner.

## Methodology

### *Literature Search*

A comprehensive search was conducted using various electronic databases, primarily PubMed, to identify relevant articles pertaining to orbital fat and inflammatory diseases of the orbit. The search was conducted without time limitations, utilizing a combination of keywords and Medical Subject Headings (MeSH) terms: ("orbital fat" OR "orbital adipose tissue") AND ("orbital inflammation" OR "inflammatory orbital diseases") AND ("Orbital fat" OR "orbital adipose tissue"). Additionally, the MeSH terms ("orbital fat" OR "orbital adipose tissue" AND "stem cells") were used to retrieve studies focused on orbital fat-derived stem cells and their potential applications. Orbital inflammation caused by neoplastic lesions was excluded from the review to ensure a focused investigation into non-neoplastic inflammatory processes that involve orbital fat. The literature search was restricted to articles published in English and appeared in peer-reviewed journals. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

### *Study Selection and Data Extraction*

Studies were selected based on their relevance to the review's objectives, prioritizing articles that provide insights into the anatomy and physiology of orbital fat, discuss its role in various inflammatory conditions affecting the orbit, focus on diagnostic approaches, particularly radiologic imaging techniques, and evaluate conservative and surgical therapeutic interventions. Both original research articles and other reviews were included, along with case studies, clinical trials, retrospective studies, and expert opinions if they contributed valuable information relevant to the review's scope. Relevant information, such as the type of study, main findings, methodologies used, and conclusions, were extracted from the selected articles. Where possible, we also evaluated the quality and rigor of the studies to ensure reliability and validity. This data extraction laid the groundwork for our review, enabling us to summarize and interpret the current body of knowledge on orbital fat and its role in inflammatory diseases of the orbit.

## Orbital Fat in the Bony Cavity

The orbital cavity is divided into several distinct spaces: the subperiorbital (or subperiosteal) space, situated between the periosteum and the bony orbit; the two main compartments of intraconal and extraconal spaces; and the lacrimal space. The intraconal compartment is bordered on either side by the musculofascial cone and contains fat, nerves (including the optic nerve, which is surrounded by meninges), and blood vessels. The conal compartment is comprised of the rectus muscles and their associated fasciae. The four rectus muscles—superior, inferior, medial, and lateral rectus—insert into the globe at various positions posterior to the limbus, with the base of the intraconal space corresponding to the posterior aspect of the globe [8]. The extraconal compartment is bounded anteriorly by the orbital septum, laterally by the orbital wall and its periosteum, and medially by the rectus muscles. It contains fat, nerves, blood vessels, non-rectus extraocular muscles (including the superior oblique, inferior oblique, and levator palpebrae superioris), and the lacrimal gland. The intra- and extraconal orbital fat is situated inside and around the myofascial cone of the eye, giving structural support and protection to the vascular and neural structures that reach the eye from the intracranial space [8–10]. Central orbital fat, located deep within the intraconal

space, provides critical structural support to the optic nerve and surrounding neurovascular elements. In contrast, medial orbital fat is typically situated in the extraconal space, adjacent to the medial orbital wall, where it plays a significant role in facilitating the movement and function of the medial rectus muscle [10].

Orbital fat, which primarily consists of WAT, is composed of adipocytes, fibroblasts, macrophages, leukocytes, stem cells, and endothelial cells [11]. It is abundant both within the orbital cavity and around the outer orbital area, occupying all spaces not filled by the periorbita, connective tissue septa, globe, muscles, neurovascular structures, and lacrimal and glandular tissues. This fat constitutes nearly half of the total orbital volume. The shape and distribution of fat within the anterior and posterior compartments of the orbit show clear differences depending on their location. In the anterior peripheral orbital regions, fat lobules are smaller, are densely packed, and have more fibrous septa. On the other hand, the retrobulbar central zone, extending toward the orbital apex, has larger, ovoid-shaped lobules with fewer and thinner fibrous septa mixed within the fat tissue [10, 12–14]. The connective tissue of the orbit, primarily composed of type I collagen and elastin, forms the structural framework supporting fat cells and orbital fat tissue [15].

Facial subcutaneous WAT plays a crucial role in shaping facial features. It comprises deep and superficial depots, including sub-orbital, intraorbital, buccal, nasolabial, cheek, temporal, forehead, orbital, and jowl adipose [16]. Aging leads to significant reduction in facial WAT, contributing to facial aging and wrinkling [2]. In mice, facial adipocytes, similar to adjacent skeletal structures, develop from neural crest during development [17]. Recognizing the parallels between facial and orbital fat can provide insights into the distinctive properties of orbital fat in inflammatory diseases, while also shedding light on the potential implications of fat distribution for both facial aesthetics and the pathogenesis of orbital inflammatory conditions.

## Pathophysiologic Particularities of the Orbital Fat Depot

The development of orbital fat usually occurs during the gestation period between weeks 14 and 32 [18]. Ocular and orbital structures arise from a combination of both mesoderm and neural crest cells [19]. Additionally, the central pad of the upper eyelid, along with the central and temporal pads of the lower eyelid, are mesoderm-derived [20]. Conversely, the medial fat pads in both the upper and lower eyelids originate from the neural crest [20]. Owing to its different embryologic origin, there are biochemical and structural differences compared with corporal fat [15]. Adipocytes from the orbit are significantly smaller in terms of area, maximum diameter, and perimeter compared to adipocytes from omental and subcutaneous adipose tissues, especially in non-obese individuals [body mass index (BMI) < 25 kg/m$^2$] [21]. Furthermore, orbital fat significantly differs from subcutaneous fat in terms of the relative volume of collagen, endothelial cell content, and quantitative density of mast cells [22]. The mean diameter of adipocytes and their volume density (VD) in orbital fat are significantly lower than in subcutaneous fat [22]. However, the VD of vessels and elements of the connective tissue in orbital fat is higher than in subcutaneous fat. Analysis of the macro- and microscopic structure of orbital and subcutaneous fat reveals additional differences in VD of blood vessels, adipocytes, and elements of the connective tissue [22]. Additionally, the mobility of the eye bulb and the oculomotor system is facilitated by the presence of small lobes and a high content of connective tissue elements in orbital fat [22]. The higher VD observed in the vessels within orbital fat highlights the dense network of branching vessels involved in the formation of orbital fat in human embryos [22].

The presence of lymphatics within the orbit was previously debated. However, emerging evidence suggests lymphatics may reside in the orbital fat, lacrimal gland, and optic nerve sheath [25]. Some investigations have not identified lymphatics in healthy orbital fat, while others report them in the bulbar conjunctiva

extending towards the ciliary body [23]. This discrepancy suggests a possible link between inflammatory conditions and lymphatic vessel formation in tissues that typically lack them [23]. Interestingly, most well-vascularized adipose tissues, like those in the subcutaneous and abdominal regions, possess lymphatic vessels, unlike the apparent absence observed in healthy orbital fat [24].

Adipocytes from each of the various depots differ in their metabolic capacities and their responses to environmental stimuli [25]. Orbital fat, subcutaneous fat, and omental fat express the glucocorticoid receptor. The modulation of autocrine and paracrine interactions between orbital fat and inflammatory cells, such as lymphocytes and macrophages, by exogenous glucocorticoids leads to the secretion of chemokines and cytokines [21]. Other fat depots, including those found in the orbits, palms, soles, and periarticular regions, serve a more mechanical or protective function [25].

The composition of fatty acids in orbital fat differs from that found in other body regions, such as the abdomen [15]. The predominant fatty acids include oleic, palmitic acid, and linoleic acid [15]. Orbital fat also contains less palmitic acid but more oleic and linoleic acid, making it more unsaturated than fat elsewhere in the body [15]. This higher unsaturation may facilitate ease of movement in the orbital region because of the decreased viscosity of unsaturated fatty acids, promoting frictionless movement [15].

A distinctive characteristic of orbital tissue is the storage of carotenoids in orbital fat [26], likely a result of retinoic acid (RA)'s involvement in visual transduction and orbital biology [27]. The retinoids present in orbital fat naturally possess the capacity to influence orbital fibroblasts, prompting the expression of genes associated with inflammation [28]. Retinoic acid is the biologically active form of vitamin A. RA depends on nuclear receptors RA receptor (RAR) and retinoid X receptor (RXR) [29]. RARα is the most frequently expressed RAR in cells [30]. A previous study compared all-trans retinoic acid (ATRA)-induced monocyte chemoattractant protein 1 (MCP-1) induction in normal versus TED-derived orbital fibroblasts and found that TED-derived orbital fibroblasts displayed significantly higher secretion of MCP-1, a proinflammatory protein, compared to normal orbital fibroblasts [28]. Additionally, ATRA treatment induced the expression of retinoic acid receptors RARβ and RARγ, but not RARα, and inhibited the expression of thyroid hormone receptors TRα and TRβ [28].

### *Structural and Degenerative Conditions Associated with Orbital Fat*

A study by Lee et al. [31] demonstrated that the volume of orbital fat decreases after the age of 70 years in both men and women. This decline may be attributed to soft tissue atrophy, including intraorbital fat atrophy [31]. The clinical manifestation of "sunken upper eyelids" or "sunken globe," characterized by the age-related decrease in orbital fat, is associated with ocular surface morbidity that may extend to corneal epithelial erosion, posing a potential threat to vision [32]. Previously, it has been reported that lagophthalmos and enophthalmos are present in patients experiencing senile loss of orbital fat, contributing to an increase in the morbidity associated with these conditions [33]. Additionally, deficiencies in orbital soft tissue volume can stem from a loss of orbital fat or an enlarged bony orbital cavity [32]. This deficiency in orbital soft tissue may manifest as a sunken appearance of the eyelids and a deepening of the upper eyelid sulcus/sunken upper eyelids [32]. Additionally, orbital fat has a tendency to migrate under the influence of gravity and pressure. Any disruption to the surrounding connective tissue, whether caused by aging, surgery, trauma, or disease, can lead to the displacement of orbital fat into either the intraconal or extraconal fat depots [34].

## THE ROLE OF ORBITAL FAT IN INFLAMMATORY ORBITAL DISEASE

Orbital inflammation includes a range of inflammatory conditions affecting various structures within the orbit, including the anterior aspect (up to the posterior aspect of the globe), diffuse

disease (intra- and/or extra-conal fat), apical (posterior orbit), myositis (extraocular muscles), and dacryoadenitis (lacrimal gland). Infectious agents and various pathogens have been linked to increased orbital inflammation [35]. Orbital inflammation can be classified into specific and idiopathic types. Specific orbital inflammation is secondary to a systemic or autoimmune disease, while idiopathic orbital inflammation disease (IOID) occurs with no identifiable systemic disease and has an unknown etiology [36].

## Specific Inflammatory Orbital Diseases

### *Graves' Ophthalmopathy*

***Orbital Tissue Expansion, Adipogenesis, and Clinical Implications in GO Pathogenesis*** Graves' orbitopathy ophthalmopathy (GO), also known as thyroid eye disease or thyroid-associated orbitopathy, is an autoimmune inflammatory disorder affecting retro-ocular tissues [37], causing the expansion of the orbital muscles and fat from edema and deposition of glycosaminoglycans and collagen [37]. It is a potentially sight-threatening ocular disease that generally occurs in patients with hyperthyroidism or a history of hyperthyroidism due to Graves' disease, and can sometimes sporadically occur in patients who are euthyroid or even hypothyroid as a result of chronic thyroiditis [37]. The key pathologic features of GO include the expansion of orbital tissue due to excess accumulation of glycosaminoglycans and adipogenesis of orbital fibroblasts [38], as well as increased volume of extraocular muscles, particularly the inferior and medial recti, along with expanded orbital fat tissue due to hyaluronic acid accumulation in muscles [37].

***Immunologic Insights and Signaling Pathways into Orbital Fat Activities in GO*** Thyroid-associated orbitopathy is far more common in Graves' disease, accounting for the vast majority of patients with this condition, and may also occur in Hashimoto's thyroiditis [39]. The pathophysiology of this condition is based on the TSH receptor (TSHR) antigen, which is shared by both the thyroid follicular cells and orbital fibroblasts [40, 41]. The association of GO with Graves' disease suggests that TSHR is the autoantigen responsible for hyperthyroidism in Graves' disease [42]. Additionally, other thyroidal antigens, such as thyroglobulin [43] found in orbital tissue, have also been implicated in this disease.

In Graves' disease, the immune system generates thyroid-stimulating immunoglobulin antibodies that bind to the thyrotropin receptor (TSH-R) [44]. This binding stimulates thyroid gland cells to overproduce thyroid hormones, causing hyperthyroidism [44]. TSH-receptor antibodies (TRAb) are the hallmark of Graves disease, and TRAb production is likely the initiating event and a prerequisite for the development of GO [45]. Following binding to the TSH-R on orbital fibroblasts, TRAb activates the immune cascade, leading to infiltration of activated B and T cells, as well as bone marrow-derived CD34 + fibrocytes, which differentiate into myofibroblasts or adipocytes [46]. The phosphoinositide 3-kinase/protein kinase B (PI3K/pAkt) signaling partly facilitates TRAb and TSH-induced adipogenesis in these cells [47]. Fang et al. found that the GO orbital microenvironment contains various immune cells, particularly CD34 + orbital fibroblasts, with few B cells. They observed enhanced Th17 and Th2 responses, marked by increased IL-17A, IL-13, and associated transcription factors. The Th17 pathway, involving IL-17A, IFN-γ, RORγt, IL-23R, and IL-1R, was strongly linked to GO and correlated with disease severity. CD34 + fibroblasts promoted Th17 activity through the PGE2-EP2/EP4-cAMP-CREB signaling pathway, increasing IL-23R and IL-1R expression and contributing to the inflammatory environment in GO [48].

During the inflammatory phase of the disease, preadipocytes and fibroblasts located within the perimysium of rectus and oblique muscles, as well as in orbital fat, secrete abundant amounts of glycosaminoglycans [49]. Cytokines, oxygen-free radicals, and fibrogenic growth factors, released by both infiltrating inflammatory cells and resident cells, act on orbital fat, stimulating adipogenesis, fibroblast proliferation, glycosaminoglycan synthesis, and the expression

of immunomodulatory molecules [50]. Furthermore, circulating lymphocytes and humoral agents infiltrate the orbital soft tissues, inducing orbital fibroblasts to initiate characteristic pathologic changes of GO, such as expansion of orbital fat, muscle fibrosis, and deposition of glycosaminoglycans within the extraocular muscles [51]. Fibrosis of orbital fat in GO is driven by cytokines such as TGF-β, which promotes myofibroblast differentiation and ECM accumulation. Activation of receptors like the TSHR and insulin-like growth factor 1 (IGF-1) receptor on orbital fat contributes to this fibrotic response, leading to symptoms such as proptosis and reduced ocular motility [52]. Elevated cytokines, including IL-17A, exacerbate this fibrosis by further stimulating ECM production and inflammation [52].

A previous study observed significantly higher levels of IL-6 and TNF-α in orbital fibroblasts obtained from the orbital fat of patients with GO compared to those from control patients [53]. Differences in fibroblast growth factor 10 expression were observed in orbital adipose tissues between GO and non-GO control samples, indicating its role in GO [54]. Additionally, higher levels of 4-hydroxynonenal, a marker of oxidative stress, were found in GO orbital fat tissues compared to control tissues [55]. A previous study found increased ATP production via mitochondrial oxidative phosphorylation (OXPHOS) during adipogenesis in preadipocytes from orbital fat but not from WAT. Mitochondrial dysfunction in preadipocytes from GO was characterized by disrupted OXPHOS-ATP and glycolysis-ATP ratios compared to healthy orbital fat. The study also found that fatty acid supplementation stimulated adipogenesis in both healthy and GO preadipocytes, which was facilitated by guanosine diphosphate and inhibited by a mitochondrial inhibitor. The increased adipogenesis was positively correlated with the OXPHOS-ATP/glycolysis-ATP ratio, highlighting the role of mitochondrial OXPHOS-ATP production and guanosine diphosphate in adipogenesis, particularly in the context of GO [56].

***Genetic and Proteomic Insights and Orbital Fat in GO Pathogenesis*** Pathway analysis of the genes enriched in GO orbital fat revealed several significantly enriched signaling pathways compared to controls without GO [57]. These pathways include PI3K/pAkt signaling, cyclic adenosine monophosphate signaling, advanced glycation end products (AGE)-receptor for advanced glycation end products (RAGE) signaling, regulation of lipolysis in adipocytes, and the thyroid hormone signaling pathway [57]. Notably, genes such as thyroid hormone receptor alpha and IGF-1 were found to be enriched in GO orbital fat [57].

A previous study investigated differential gene expression in orbital fat in GO and identified WNT and IGF-1 signaling genes as potentially implicated in pathogenesis [58]. Furthermore, the mRNA expression levels of sphingosine-1-phosphate receptors (S1P1, S1P2, and S1P3) were significantly higher in GO orbital fat than in non-GO orbital tissues [59]. Cysteine-rich angiogenic inducer 61 (CYR61) may play a role in both orbital inflammation and adipogenesis, serving as a marker of disease activity [60]. The level of microRNA 146a (miR-146a) expression was found to be significantly higher in GO orbital fat tissue than in non-GO, indicating a negative regulation of immune responses and inflammation [61].

In subjects with active GO, an overexpression of collagen XIII was observed in extraocular fat, while burned-out GO-affected fat or normal adult extraocular fat showed no expression of collagen XIII [62]. Collagen XIII, encoded by the COL13A1 gene and known for its association with uncontrolled growth in tumors, presents a plausible link to the observed uncontrolled growth in fat cells affected by GO [63]. Previous research examining serum calprotectin, S100A8, and S100A9 mRNA expression in orbital fat or connective tissue from patients with GO and healthy controls found significantly elevated S100A8 mRNA expression in GO orbital tissues [64]. Furthermore, MCP-1 mRNA exhibited high expression in the orbital fat of patients with GO compared to that of healthy donors [65]. MCP-1's role in attracting leukocytes suggests its involvement in the development of GO [65]. Transcriptomic analysis of adipocytes from WAT, healthy orbital fat, and orbital fat from GO showed reduced leptin and mitofusin 2 (a BAT marker) in healthy orbital fat compared to WAT,

with increased UCP1 and mitofusin 2 in GO [66]. RNA sequencing indicated lower expression of lipid metabolic genes and higher levels of the fatty acid transporter SLC27A6 in healthy orbital fat. Additionally, healthy orbital fat demonstrated reduced lipid metabolism and signaling pathway activity, with increased activation of Wnt/Ca2+, fibroblast growth factor, and sirtuin signaling pathways [66]. In vitro studies on orbital adipose-derived stem cells harvested from patients with GO have shown a downregulation of early neural crest markers and ectopic expression of homeobox genes [67].

Proteomic analysis of orbital fat from individuals with GO revealed increased expression of proteins associated with lipid metabolism, inflammation, and tissue remodeling [68]. For instance, the increased expression of the LDL receptor could facilitate elevated cellular uptake of cholesterol and fatty acids, which are essential for lipid storage, cell division, and the synthesis of cholesterol-derived steroid hormones [69].

***Regulating Orbital Adipogenesis in GO: PPAR-γ Pathway and Thy-1 Heterogeneity*** A previous study suggests that de novo adipogenesis may be enhanced in GO via the peroxisome proliferator-activated receptor-γ (PPAR-γ) pathway [70]. PPAR-γ antagonists have been shown to reduce adipogenesis in untreated preadipocytes isolated from patients with GO [71]. Furthermore, orbital preadipocytes exhibit heterogeneity in their expression of Thy-1 or CD90 (Cluster of Differentiation 90), a surface protein [72]. Previous research suggests that the balance between Thy-1-negative and Thy-1-positive preadipocyte populations within the orbit might be critical for the development and progression of inflammation associated with GO [72].

***Clinical Manifestations, Influencing Factors, and Orbital Fat in GO*** A strong positive association between orbital fat volume and proptosis has been demonstrated in patients with obesity without endocrinopathy [73]. Additionally, a previous report described the development of exophthalmos in patients with type 2 diabetes mellitus (T2DM) receiving thiazolidinedione treatment [74]. However, as these studies involved patients with GO and T2DM, the observed increase in exophthalmos might be a consequence of a pre-existing hyperinsulinemic state specific to this population [74]. A separate study identified obesity, Graves' disease, and Cushing syndrome as the most common underlying conditions in patients with proptosis and excess orbital fat [75].

### *Orbital Lipogranulomatous Inflammation*

Orbital lipogranulomatous inflammation (OLGI) is a condition affecting the orbital region, including the eyes, adjacent tissues, and eye socket bones. OLGI is characterized by the buildup of lipids (fats) and immune cells like macrophages and lymphocytes in the affected area [76]. The symptoms of OLGI can differ depending on the location and magnitude of the inflammation [76]. In a case of orbital lipogranulomatous lesions secondary to local disorders such as mycobacterial infections, a detailed histologic examination of an iatrogenic *Mycobacterium abscessus* orbital infection highlights orbital fat as a potential source of lipid material, which may serve as a reservoir that allows the organisms to evade host immunosurveillance. In a patient presenting with a rare case of idiopathic orbital OLGI, an imaging study revealed an enhancing infiltrative mass within the left intraconal space. A biopsy of the anterior orbital fat showed extensive lipogranulomatous inflammation, with no abnormalities detected in flow cytometry, culture, or special stains [76]. Previous literature indicates that the development of upper eyelid swelling and ptosis in patients may be linked to lipogranulomatous inflammation affecting the eyelid skin and preaponeurotic orbital fat [77]. Additionally, histology of the skin, orbicularis muscle, and preaponeurotic fat revealed aggregations of histiocytic cells with foamy cytoplasm and vacuoles, strongly suggestive for a histiocytic reaction to silicone oil in all three tissue types [77]. Silicone oil, commonly used intraocularly in vitreoretinal surgery, can leak into the eyelid tissues, causing an inflammatory reaction that results in eyelid swelling and ptosis [77]. In a study of pediatric patients

with orbital pseudotumor, biopsies consistently showed mild lymphocytic inflammation. Additionally, some biopsies revealed lipogranulomatous responses to damaged fat cells, along with fibrosis and tissue eosinophilia [78].

### *Sarcoidosis*

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology. The disease can affect various organs, including the lungs, hilar lymph nodes, eyes, and skin [79].While ocular manifestations of sarcoidosis primarily include uveitis and conjunctival granulomas, involvement of orbital tissues is less commonly reported [80]. Orbital fat tissue can be infiltrated in cases of orbital sarcoidosis, presenting with a granulomatous inflammatory process characterized by noncaseating granulomas [81]. These granulomas are composed of tightly clustered epithelioid histiocytes and multinucleated giant cells surrounded by lymphocytes and plasma cells. The inflammatory infiltrate may include calcification, fibrous stroma, or high cellular density, contributing to the histopathologic appearance and immune response observed in sarcoidosis [81]. Histopathologic examination confirms the granulomatous inflammation without necrosis or vasculitis, and immunohistochemical analysis shows a predominance of T-lymphocytes, particularly CD3 + cells, with a paucity of B-lymphocytes [81]. Diffuse, painless swelling of the left lower eyelid in a 70-year-old woman led to a diagnosis of orbital sarcoidosis [82]. While initial CT imaging showed no mass or soft tissue infiltration, surgical exploration uncovered stiff, coarse orbital fat. Histopathologic examination revealed non-caseating granulomas with epithelioid histiocytes and lymphocytic infiltration, confirming sarcoidosis [82]. Transcript for lysozyme levels along with marked elevation of levels of angiotensin-converting enzyme were found in the orbital fat of subjects with sarcoidosis [83]. In most patients, there is an additional involvement of lacrimal gland and orbital fat [84]. The pathologic activation of PPAR-$\gamma$ in sarcoidosis suggests the potential involvement of adipocytes in the pathogenesis of the disease [85].

### *IgG4-Related Disease*

Immunoglobulin G4-related diseases (IgG4-RD) include a range of systemic inflammatory conditions with an unclear cause. These disorders are characterized by the infiltration of affected tissues by IgG4-positive plasma cells and the presence of fibrosis with a sclerosing nature [86]. Ocular structures, including the lacrimal gland, extraocular muscles, trigeminal nerve, and orbital fat, are frequently compromised in IgG4-RD [87]. A patient with a long-standing history of orbital pseudotumor was ultimately diagnosed with IgG4-related disease following a biopsy. The disease involved multiple orbital structures, including the lacrimal gland, extraocular muscles, intraconal fat, and trigeminal nerve. Imaging studies revealed significant edema and inflammation within the intraconal fat, which extended to adjacent structures [88]. A patient with well-controlled T2DM presented with bilateral exophthalmos, progressive visual impairment, and significant weight loss. Imaging revealed homogeneously enhancing soft-tissue masses within the orbits, causing optic nerve compression, especially on the right side. Elevated serum IgG4 levels and increased glucose metabolic rate in the orbital masses suggested a diagnosis of IgG4-RD.

In another study of patients with IgG4-RD and systemic fibrosis, uveitis was frequently observed, typically bilateral, and predominantly affected the anterior segment. It often presented as an initial symptom or in conjunction with other IgG4-related manifestations [89]. Uveitis was associated with involvement of multiple organs, elevated serum IgG4 and C-reactive protein levels, and variable autoantibody profiles. Ocular tissue pathology was crucial for diagnosis in several cases, while brain MRI abnormalities were infrequently noted [89]. IgG4-RD patients with orbital symptoms, proptosis, and periorbital swelling were predominant. Imaging frequently revealed extraocular muscle and lacrimal gland enlargement, with the lateral rectus muscle most commonly affected. Orbital fat infiltration and infraorbital nerve enlargement were also noted along with occasional intracranial involvement. Serum IgG4 levels were often elevated, typically recorded after

diagnosis. Extracranial IgG4-related lesions and paranasal sinus mucosal thickening were commonly observed [90]. In hyper-IgG4 syndrome, orbital fat infiltration is a key feature, often leading to bilateral proptosis. Imaging finding typically reveals this infiltrative process affecting orbital fat, extraocular muscles, and lacrimal glands. Diagnosis is confirmed through biopsy showing IgG4-rich lymphoplasmocytic infiltrate and fibrosis. Elevated serum IgG4 levels are not definitive for diagnosis [91].

Optic perineuritis (OPN) often involves orbital fat infiltration and is frequently linked to autoimmune diseases, particularly IgG4-RD. OPN cases typically show patterns such as orbital fat infiltration and trigeminal nerve branch involvement, notably in IgG4-RD. This association, along with older age and bilateral involvement, helps distinguish OPN from idiopathic demyelinating optic neuritis. Recognizing changes in orbital fat and the presence of IgG4-RD is crucial for diagnosing underlying autoimmune conditions in patients with ocular symptoms [92]. In a previous study, orbital fat infiltration was a significant characteristic in IgG4-related ophthalmic disease (IgG4-ROD), often accompanied by extraocular muscle involvement. Bilateral orbital involvement was frequently observed in patients, marked by smaller tumor volumes and the involvement of infraorbital and supraorbital nerves. The presence of orbital fat infiltration in some cases highlights the complexity of IgG4-ROD, emphasizing the crucial role of imaging in diagnosis, although imaging features alone may not suffice for a definitive diagnosis [93].

In a case of progressive bilateral proptosis and eyelid swelling unresponsive to steroids, imaging revealed significant involvement of orbital fat, with diffuse enlargement of the lacrimal glands and extraocular muscles. Biopsy confirmed IgG4-ROD with a prominent lymphoplasmacytic infiltrate and elevated IgG4-positive plasma cells. The patient's elevated serum IgG4 levels and histopathology supported the diagnosis [94].

### *Orbital Myositis*

Orbital myositis is the inflammation of the extraocular muscles (EOMs) [95]. It often results in the unilateral thickening of one or more EOMs. Orbital myositis accounts for < 1% of all cases of orbital inflammation [95]. In orbital Graves' disease, the primary pathology is the swelling of the extraocular muscles, particularly within their bellies, with tendon sparing—distinct from the tendon-involved myositis seen in IOID. While orbital fat changes are secondary and relatively insignificant, the enlarged extraocular muscles can lead to proptosis, venous stasis, and optic nerve compression, ultimately impairing vision. Lymphocytic and plasmacytic infiltration in the muscles triggers fibroblast activation, resulting in fibrosis [96]. Additionally, IOID, including orbital myositis, predominantly affects middle-aged women and typically presents with unilateral periorbital pain and edema [97]. Dacryoadenitis and myositis are common, with the medial rectus muscle most frequently involved, followed by the superior and lateral rectus muscles [97]. Orbital fat changes are secondary to the primary inflammation in the extraocular muscles and are relatively minor. Significant tissue restriction and damage occur infrequently, usually in cases with extensive sclerosis and poor treatment outcomes [97]. An unusual case of orbital pseudotumor presenting as subacute orbital myositis was reported in an infant, characterized by unilateral lateral rectus muscle enlargement and imaging findings consistent with the condition. The case was atypical because of the absence of orbital pain and chemosis, along with a poor response to steroid therapy. Unlike typical orbital myositis, which often presents with pain, chemosis, and proptosis, this patient exhibited less common symptoms and an unclear paretic phase [98]. Orbital inflammation, particularly monomyositis, can be triggered by pregnancy or appear for the first time postpartum [99]. Pregnancy may also provoke nonorbital myositis or worsen preexisting systemic conditions, such as dermatomyositis and polymyositis [100]. In a previous study, lymphoid masses predominantly located within the EOM led to clinical manifestations such as exophthalmos, ptosis, and restricted upgaze—symptoms commonly observed in Graves' myopathy and idiopathic orbital myositis. Importantly, these lymphoid infiltrates extended into the orbital fat in all cases [101].

### *Churg-Strauss Syndrome (CSS)*

Churg-Strauss syndrome (CSS) is a systemic vasculitis characterized by necrotizing granulomatous inflammation, hypereosinophilia, asthma, and allergic rhinitis [102]. While CSS rarely presents with orbital manifestations, these can include an inflammatory mass, periscleritis, perineuritis, dacryoadenitis, and myositis [103]. Orbital imaging in CSS typically reveals diffuse inflammation of orbital fat and extraocular muscles, with MRI often showing enlargement of these structures and infiltration of orbital fat [104]. Histopathologic analysis commonly demonstrates granulomatous inflammation with eosinophils, sometimes accompanied by necrotic areas [104]. In previous case reports, imaging revealed bilateral proptosis and periocular edema, with MRI and CT scans showing soft-tissue infiltration and muscle enlargement. Biopsies from affected tissues confirmed eosinophil-rich granulomatous inflammation. Systemic tests, including ANCA and eosinophil counts, supported the diagnosis of CSS [104].

### *Systemic Lupus Erythematosus*

Systemic lupus erythematosus (SLE) is a persistent autoimmune disorder where the immune system erroneously targets healthy tissues and organs, affecting various tissue and organ in the body [105]. Ocular manifestations can occur in at least one-third of SLE cases, and in instances of orbital myositis within patients with SLE, imaging studies of the orbits revealed features such as thickening of periorbital soft tissues and stranding of adjacent fat [106]. In a case of IOIO secondary to SLE, orbital MRI without contrast revealed extensive bilateral preseptal soft tissue swelling, predominantly on the right side, and pronounced congestion of intraorbital fat, including both intraconal and extraconal compartments [107]. Fat stranding around the optic nerves and increased T2 signal in the extraocular muscles, indicative of edema, were noted. B-scan ocular ultrasound showed normal results [107]. In a case of lupus erythematosus profundus, a rare subtype of lupus erythematosus, orbital imaging and histopathology revealed distinct characteristics. Orbital MRI demonstrated diffuse loss of fat signal and enhancement of orbital fat and extraocular muscles, reflecting significant inflammation. This was supported by histologic findings from biopsies of the eyelid skin, orbital fat, and extraocular muscles, which showed perivascular lymphoplasmacytic infiltrates and fat hyalinization. The fat within the orbit exhibited marked inflammatory and fibrous infiltrates, leading to pronounced fat loss visible on MRI [108]. CT and MRI imaging finding of orbital inflammatory disease associated with SLE revealed opacification and diffuse sclerosis of the left ethmoid sinus and orbit, with MRI showing a loss of fat signal. Histopathologic analysis of biopsies indicated a predominance of lymphocytes, plasma cells, and histiocytes, consistent with a sclerosing pseudotumor [109].

### *Scleroderma*

Scleroderma is a chronic inflammatory condition affecting connective tissue, characterized by both functional and structural changes in small blood vessels, such as capillaries and arterioles, and an excess accumulation of collagen in various tissues [110]. The disease can be categorized into several subtypes based on clinical characteristics, including localized scleroderma, systemic sclerosis, overlap syndrome, and scleroderma-like conditions resulting from exposure to toxic substances or pharmaceutical agents [111]. Orbital fat atrophy has been observed as a complication in localized scleroderma, though it is not commonly seen in systemic sclerosis [112]. A patient with hypertension presented with progressive diplopia and a hyperpigmented, atrophic scar extending from the forehead to the upper eyelid, suggestive of localized scleroderma. Clinical examination showed normal visual acuity and pupil responses, but exophthalmometry revealed asymmetry [113]. Orbital MRI demonstrated significant atrophy of retrobulbar fat, enophthalmos, and scalloping of subcutaneous fat in the right frontal region [113]. Additional imaging showed fat atrophy in the right eyebrow, upper eyelid, anterior orbit, preaponeurotic fat pads, and the area between the levator palpebrae superioris and superior rectus muscles. These findings indicate localized scleroderma, characterized by localized fat

atrophy and sclerotic changes, without brain involvement [113].

### *Erdheim-Chester Disease*

Erdheim-Chester disease (ECD) is a rare form of non-Langerhans cell histiocytosis characterized by the presence of lipid-laden histiocytes, leading to xanthogranulomatous infiltration across various bodily systems [114]. ECD tends to affect individuals in their 50s to 70s, with an almost equal occurrence in both male and female individuals [115]. Orbital involvement is observed in 27% of ECD cases and is typically present on both sides. In a previous study, orbital fat infiltration was observed in 88% of cases, with the intraconal fat surrounding the optic nerve sheath involved in 84% of cases [116]. A previous examination of the orbital biopsy revealed extensive replacement of orbital fat with fibrous tissue containing a diffuse mixed inflammatory infiltrate that included eosinophils and neutrophils [117]. A study of patients with ECD revealed key details about orbital abnormalities. Imaging frequently showed fat infiltration and enophthalmos, with notable atrophy of intraconal fat, scalloping of subcutaneous fat, and optic nerve sheath involvement. MRI scans revealed a predominantly fibrous lesion component [115]. An evaluation of a patient with suspected ECD revealed notable orbital and systemic abnormalities. CT of the paranasal sinuses showed an extraconal soft tissue mass in the left orbit, causing scalloping of the orbital roof and erosion of surrounding structures. Histopathologic analysis of an ultrasound-guided biopsy identified sheets of histiocytes positive for S100 and CD68 but negative for CD1a, consistent with non-Langerhans cell histiocytosis [118]. A patient with exophthalmos, itching, and facial pain was diagnosed with ECD following imaging and biopsy. Orbital MRI revealed intraconal fat infiltration causing severe proptosis and retroocular pressure. Additional MRI findings included thickening of the sphenoid and maxillary sinuses and a small sella turcica with an absent posterior pituitary lobe, consistent with diabetes insipidus. Histopathology of pericardial tissue showed fibrotic inflammation with foamy CD68-positive, CD1a-negative histiocytes. Imaging also indicated diffuse increased metabolism in the extrinsic ocular muscles and retroocular soft tissues [119].

### *Cholesterol Granuloma*

Cholesterol granulomas (CG), characterized by the accumulation of organized blood byproducts, may develop in the orbit because of events causing orbital hemorrhage, such as minor trauma or spontaneous hemorrhage, in patients receiving anticoagulation therapy [120]. Orbital CGs are uncommon growths mostly situated in the upper outer part of the eye socket. In a previous study, it was observed that the periosteum adhered to the pitted orbital bone, and the adjacent orbital fat seemed to be infiltrated [121]. An investigation into lytic Paget disease as a potential cause of orbital CG showed that the periorbita underlying the area was thinned in some places and absent in others, revealing normal orbital fat [122]. Investigation of cases of orbital CG presenting with ptosis and proptosis revealed that imaging studies, including CT and MRI, identified well-demarcated cystic lesions with varying degrees of bony expansion and globe pressure. Histopathologic examination consistently showed cholesterol clefts surrounded by granulomatous inflammation, foreign body giant cells, hemosiderin deposition, and blood-derived debris, with no epithelial components or endothelial lining present. In the first case, a cystic mass in the lacrimal fossa was associated with bone pitting and infiltration of adjacent orbital fat. In the second case, a cystic mass exerted posterior pressure on the globe [123].

### *Orbital Vasculitis*

Orbital vasculitis is a rare condition that damages blood vessels in the eye and orbit, leading to inflammation and potential vision loss. Several types of vasculitis can affect part of the eye and orbit including orbital nerves, and orbital fat [124].

***Polyarteritis Nodosa*** Polyarteritis nodosa (PAN) is a form of vasculitis that primarily targets medium-sized blood vessels, with the

potential to cause damage to both the eyes and the central nervous system [125]. Roughly 10% of cases involve the skin, eyes, and orbit [126]. It has previously been shown that the ophthalmic presentations of patients with PAN include scleritis, peripheral ulcerative keratitis, non-granulomatous uveitis, retinal vasculitis, orbital pseudotumor, and central retinal artery occlusion associated with temporal arteritis [127]. Diffused inflammation in the orbit caused by PAN can affect both intra- and extraconal fat in the orbit [124]. In a case of orbital pseudotumor with a confirmed case of PAN, review of the biopsies from the orbit and ethmoidal sinuses found the presence of granuloma that tightly surrounded the optic nerve and replaced much of the orbital fat [128].

***Giant Cell Arteritis*** Giant cell arteritis (GCA) is a systemic, inflammatory vasculitis that affects small- to medium-sized arteries and tends to affect individuals ≥ 50 years [129]. A review of the literature found previous cases of giant cell arteritis presenting with bilateral orbital inflammation [130]. Imaging studies showed bilateral enhancement of the temporal arteries with intraconal fat stranding but with no extraocular muscle enlargement or orbital mass [130]. In a case study of a patient with bilateral visual loss, MRI of the orbits revealed significant orbital inflammation, characterized by bilateral enhancement of the optic nerve sheaths, suggesting active inflammatory processes involving the orbital fat and surrounding structures. Histopathologic analysis of the optic nerve sheath biopsy further confirmed the presence of giant cells, a hallmark of GCA [131].

***Granulomatosis with Polyangiitis (GPA) or Wegener Granulomatosis*** Granulomatosis with polyangiitis (GPA) is a form of vasculitis characterized by inflammation in small to medium-sized blood vessels [132]. It is belongs to the anti-neutrophil cytoplasmic antibody-associated vasculitides [132]. Orbital involvement is observed in approximately 60% of patients with GPA [133]. Clinical manifestations of ocular GPA result from inflammation affecting various eye structures, including the globe, orbital fat, orbital nerves, extraocular muscles, lacrimal glands, and the optic nerve [133]. In a study examining the clinical and pathologic characteristics of orbital WG, the authors identified key aspects of the disease's presentation and progression. Orbital masses were commonly observed alongside necrotizing scleritis, proptosis, and significant visual loss. CT imaging frequently revealed diffuse orbital involvement with masses that displaced the globe and infiltrated surrounding fat planes. Histopathologic analysis consistently demonstrated fat disruption, necrosis with lipid-laden macrophages, granulomatous inflammation, and occasional necrotizing vasculitis, while immunohistochemistry indicated endothelial activation [134].

## Non-specific Inflammatory Orbital Diseases

### *Idiopathic Orbital Inflammatory Disease/ Orbital Pseudotumor*

Idiopathic orbital inflammatory disease, also known as or orbital pseudotumor or nonspecific orbital inflammation, is a benign, non-infectious, and non-neoplastic inflammatory condition affecting the orbit and surrounding tissues. IOID ranks as the third most common disease of the orbit, with only Graves' disease and lymphoproliferative diseases being more common [135]. There is no racial or gender predominance, but it primarily affects adults, with children representing only 6–17% of cases [136]. The etiology of IOID remains unknown, with no identifiable local or systemic causes [137]. However, autoimmune markers are frequently used to explore potential underlying causes of orbital inflammatory diseases [138].

IOID comprises a heterogeneous group of disorders and is a diagnosis of exclusion. In the classification of IOID in adult and pediatric populations, patients were divided into nine categories based on the site of involvement and histopathologic features [139]. These categories included anterior (affecting the lid, conjunctiva, Tenon's capsule, or sclera), dacryoadenitis (involving the lacrimal gland), myositis (one or more extraocular muscles),

perineural involvement, acute fat involvement, focal mass (with well-defined margins), orbital apex involvement, diffuse sclerosing form (a fibrosing mass with indistinct margins), and multiple tissue involvement [139]. The disease was further categorized by its course as acute (< 1 week), subacute (1 week to 1 month), or chronic (> 1 month), with histopathologic findings playing a key role in this classification [139].

Infectious agents, including various microbiologic agents such as viruses, bacteria, and atypical species, have been suggested as potential triggers of IOID and linked to increased orbital inflammation [140, 141]. Previous research indicates a possible connection between the onset of IOID and certain viral infections, including herpesviruses (HSV) [142], SARS-CoV-2 [143], and Epstein-Barr virus (EBV) [144]. In at-risk patients, HIV has been associated with orbital myositis, leading to a T-cell-mediated proinflammatory response [145]. Additionally, upper respiratory tract infections, sinusitis, and dacryoadenitis have been linked to IOID [146, 147]. The presence of streptococcal pharyngitis or viral upper respiratory infections has been reported to correlate with the occurrence of IOID. Molecular mimicry between foreign antigens and self-antigens is one proposed mechanism underlying IOID following infection [141]. The classical clinical presentation is the acute or subacute onset of proptosis, periorbital swelling and erythema, pain, diplopia, visual disturbance, and response to treatment with oral corticosteroids [148]. However, there are numerous individual variations.

Various classification systems have been proposed, but due to the highly variable clinical and pathologic features of IOID, none are universally accepted and used [149–151]. IOID can be classified into three main types based on histopathology: lymphoid, granulomatous, and sclerosing. The lymphoid and granulomatous types can progress to the sclerosing type as the disease advances. The lymphoid type typically responds well to radiation therapy but shows only limited or temporary improvement with anti-inflammatory medications. In contrast, the granulomatous type often responds effectively to anti-inflammatory drugs but poorly to radiation. The sclerosing type is generally resistant to both anti-inflammatory and radiation treatments. Given these variations in treatment response and the potential for progression to the more challenging sclerosing type, early intervention in orbital IOID is crucial [151].

In a previous study assessing biopsy-confirmed IOID in a patient cohort, the lacrimal gland and extraocular muscles were commonly affected, with significant involvement of orbital fat. The study also noted occasional involvement of the sclera, optic nerve, and other orbital structures [152]. Orbital fat involvement in IOID is characterized by diffuse infiltration surrounding the globe, often extending to the optic nerve sheath complex [45]. This infiltration typically results in blurred margins of adjacent tissues, reflecting its significant role in the inflammatory process. These infiltrates are predominantly composed of T lymphocytes and macrophages [45], and the presence of excessive amounts of glycosaminoglycans [46]. In cases of IOID involving orbital fat, the tissue shows a mixed inflammatory infiltrate with an increase in supportive fibrous tissue. The normally delicate interlobular septa become thickened, more prominent, and may merge together. Lipogranuloma formation can occur as a reaction to injury in fat cells, and this fat injury is likely due to the severity of the inflammation [149]. The release of intracellular lipids into the surrounding space triggers a granulomatous inflammatory response, involving macrophages, lipophages, and both mononuclear and multinuclear histiocytes [149]. IOID has highly variable clinical features, ranging from a diffuse to very focal process targeting specific orbital tissues, such as the lacrimal gland, extraocular muscles, and orbital fat [97]. In a comprehensive study of IOID, orbital fat involvement was identified as a significant and recurrent feature across multiple subtypes [43]. These subtypes included inflammation of the lacrimal gland, extraocular muscles, preseptal tissues, sclera, episclera, Tenon's capsule, uvea, and optic nerve sheath. Orbital fat typically exhibited diffuse infiltration, often extending to surrounding structures such as the optic nerve sheath, reflecting the extent and severity of the inflammatory process [43].

The diffuse involvement of orbital fat not only contributed to clinical symptoms like pain and periorbital edema but also played a crucial role in disease progression. The inflammation frequently obscured the margins of adjacent structures, complicating both diagnosis and management. Moreover, orbital fat involvement often indicated a more widespread or severe inflammatory process, potentially leading to complex clinical scenarios, including the optic nerve [43].

### *Orbital Cellulitis*

Orbital cellulitis is an infection causing inflammation of the orbital content posterior to the orbital septum often caused by sinus infections, facial trauma, or surgery [156]. Preseptal cellulitis, on the other hand, affects the anterior portion of the eyelid and is less severe [156]. The spread of infection into the orbit is most frequently from the ethmoid sinuses [157]. Patients may present with eye pain, especially with eye movements due to irritation of inflamed extraocular muscles [158].

The most common causative organisms are *Staphylococcus* and *Streptococcus* species, specifically *Staphylococcus aureus* and group A Streptococcus, with increasing incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) being of great concern [158]. *Haemophilus influenzae* and *Streptococcus pneumoniae* are historically considered important contenders in these types of infections. The causes of these bacterial orbital cellulitises are mostly through sinus infections, infections of adjacent facial structures, penetrating trauma, and surgery [159]. The lower intraorbital fat is supplied by a branch of the infraorbital artery. A compromised blood supply to the intraorbital fat may cause anaerobic cellulitis or enophthalmos [160].

One study suggested that orbital fat is a source of lipid material that can harbor low-virulence organisms such as *Mycobacterium abscessus*, allowing them to escape the host's immunosurveillance [161]. It is possible that the lipid protects the organisms from enzymes and/or ingestion by macrophages. In such cases, the lipid probably originated from orbital adipose tissue [161].

### *Viral and Fungal Infection and Orbital Fat*

Fungal infections of the orbit are relatively uncommon and are usually secondary to spread from an adjacent paranasal sinus [162]. The two most common infections are mucormycosis and aspergillosis [162]. Periorbital mucormycosis may involve not only the cutaneous and subcutaneous tissues but also the fat, muscle, and fascial layers beneath [162].

In acute invasive fungal rhinosinusitis (AIFRS), patients showed either histopathologic evidence of fungal hyphae invasion into vessels or acute tissue necrosis [163]. Orbital involvement in AIFRS was defined as orbital fat stranding, subperiosteal abscess, or extraocular muscle swelling, or if the patient presented with symptoms of orbital cellulitis, including proptosis, conjunctival chemosis, and ophthalmoplegia [163]. In patients with AIFRS, type 2 diabetes other than hematologic malignancy was the main risk factor for orbital-involved disease [163].

Orbital apex syndrome (OAS) due to invasive aspergillosis in an immunocompetent patient, soft tissue thickening and indistinctness of fat in the region of the right optic canal and right orbital apex were observed in the patients, possibly representing extension of paranasal inflammatory disease [164]. However, in OAS caused by invasive aspergillosis in patient with post-coronavirus disease 2019 (COVID-19) infection, no inflammatory changes were seen in the orbital fat [165].

Coronavirus disease 2019 has rarely been associated with inflammatory orbital diseases. A prior study demonstrated marked enlargement of the rectus muscle and lacrimal gland, along with mild stranding of the surrounding intraorbital fat, leading to proptosis [166]. In the case of visual loss in COVID-associated rhino-orbito-cerebral mucormycosis, histopathologil examination showed orbital fat necrosis, fungal hyphae, acute inflammation, granuloma formation, and ischemic thrombosis of the ophthalmic artery [167]. In the examination of COVID-19-associated acute invasive fungal rhinosinusitis, it was observed that pre-antral and retroantral fat involvement was mostly in the form of fat stranding, followed by obliteration

of the fat with inflammatory and/or necrotic tissue [168]. Retroantral fat involvement was often associated with extension into the pterygopalatine fossa [168]. In a study of increased invasive fungal rhinosinusitis in patients with COVID-19, fat stranding was found outside the sinus perimeter in the intraorbital and periantral fat depot [169].

Aspergillosis of the brain and paranasal sinuses in immunocompromised patients, abnormal enhancement of the optic nerve and sheath with infiltrating enhancing soft tissue within the intraorbital fat was observed in the patient population [170]. An initial presentation of acquired immunodeficiency syndrome (AIDS) manifested as optic nerve toxoplasmosis and orbital inflammation; inflammatory changes were observed in the right optic nerve, extraocular muscles, and orbital fat [171].

In a case of herpes zoster involving the right trigeminal nerve, histologic examination revealed fat necrosis vasculitis in the capsule, without perineuritis [172]. Additionally, a severe case of right-sided herpes zoster ophthalmicus showed that orbital inflammation or abscesses might result from sterile ischemic fat necrosis due to zoster vasculitis [172].

## IMAGING CONSIDERATIONS REGARDING ORBITAL FAT AND ORBITAL INFLAMMATION

The orbit is the site of many pathologies of diverse etiologies, and imaging has to be tailored to the symptoms and clinical findings. The contrast of the soft tissue, the fluid-filled globe, retrobulbar contents within the fat and bony walls of the orbits provide clear delineation of the orbital anatomy [173]. The most frequent clinical reasons for orbital imaging include proptosis, vision loss, enophthalmos, diplopia, leukocoria, pain, tumors, and trauma [173].

Ultrasonography (US) techniques are widely used in orbital inflammation cases [174]. It is a commonly used diagnostic tool for ocular abnormalities as it is cost-effective, widely available, and portable and does not expose the lens to ionizing radiation [175], facilitating its use in various clinical settings. US provides real-time imaging, allowing dynamic assessment and immediate evaluation of pathologic changes [176]. Additionally, US provides good contrast for soft tissues, can guide needle placements for biopsies or injections, and can assess blood flow using Doppler techniques [177]. Bright (B)-scan US can be used for the diagnosis of posterior scleritis, a condition that may present with nonspecific clinical symptoms, such as pain, redness, and photophobia [178, 179]. The presence of diffuse scleral thickening with fluid in the Tenon space results in a low reflective area between the outer sclera and orbital fat, particularly in the peripapillary region [178, 179]. In thyroid orbitopathy, B-scans of orbital fat typically show uniformity, except for dilated blood vessels or masses [180]. B-scan ultrasonography can frequently reveal inflammatory changes occurring in orbital fat and extraocular muscles during active eye changes associated with Graves' disease, allowing differentiation from expanding orbital neoplastic lesions and eliminating the need for orbital biopsy [181]. Despite its usefulness, USG is limited by its ability to image the bony architecture and provide detailed visualization of the orbital apex and intracranial extension of pathologies.

Magnetic resonance imaging (MRI) and computed tomography (CT) are established tools for evaluating orbital inflammation, each offering unique strengths and limitations [173]. Compared to CT, MRI excels in visualizing the anatomy of the orbit, including the extraocular muscles, orbital fat, and optic nerve [182]. This detailed depiction allows for quantitative analysis of various parameters relevant to inflammatory processes, such as the degree of exophthalmos, thickness or volume of extraocular muscles, and orbital fat volume [182]. Furthermore, MRI with contrast enhancement and fat suppression techniques is widely considered the gold standard for detecting subtle inflammatory changes within the orbit [150]. Its capability for real-time dynamic imaging has also led some to favor it over CT for soft-tissue disease evaluation [183]. Orbital imaging in patients with sarcoid-like granulomatous orbitopathy revealed notable characteristics related to orbital fat tissue [84]. Imaging often showed diffuse muscular swelling

or enlarged muscles adjacent to an orbital mass, with the superior rectus/levator complex being the most frequently affected. Orbital fat involvement was prevalent, and histopathologic examination commonly revealed non-caseating granulomas indicative of sarcoidosis. Although initial CT scans might not always detect soft tissue infiltration, surgical debulking frequently exposed stiff, coarse orbital fat with granulomatous inflammation. Imaging findings such as hilar lymphadenopathy were common, while histologic analysis confirmed granulomatous inflammation in the orbital fat [84].

Calculated T2 relaxation times of eye muscles differed significantly between control subjects and patients with stage III and IV of GO [184]. Quantitation of MRI indicates total fat expansion in the orbit without distinguishing between WAT and brown (BAT) adipose tissue [185]. WAT adipocytes store excess energy as triglycerides in large unilocular lipid droplets. In contrast, brown adipocytes are distinguished by a multilocular morphology, high mitochondrial density, and elevated expression of uncoupling protein 1 (UCP-1), essential for heat dissipation through non-shivering thermogenesis [186]. Beige adipocytes, predominantly located in WAT, can transition to a thermogenic phenotype resembling BAT when activated. Consequently, beige adipocytes exhibit a versatile phenotype and can potentially engage in either energy storage or dissipation based on environmental or physiologic conditions [187].

A multimodal $^{1}H/^{19}F$ MRI can be used to comprehensively assess orbital immune cell infiltration, the development of edema, and alterations in the extracellular matrix and can also be used for the quantification of fat and muscle dimensions [188]. Measurement of these data revealed elevated levels of macrophages, increased collagen deposition, and enlargement of BAT or beige fat depots in orbits mouse models [188].

A previous study found that $^{19}F$-MRI showed inflammation to be confined to orbital muscle and optic nerve, but orbital fat showed no difference in inflammatory signs in comparison to control β-Gal-immunized animals [185]. Schmidt and colleagues used MRI to demonstrate the positive correlation between adiposity index such as BMI or waist circumference and the exophthalmometric values such as the degree of proptosis [189]. Darcy et al. [190] used high-resolution orbital MRI images to study lower eyelid prominence, in a quasi-sagittal plane parallel to the long axis of the orbit passing through the globe center for measurement of orbital fat. They found that with aging, there was a significant increase in anterior inferior periocular soft-tissue volume, primarily due to fat expansion [190].

In a previous study by Brown et al. [191], the researchers investigated the use of manual and automatic segmentation techniques to quantify orbital fat tissue on T1-weighted MRI scans acquired at both 3- and 1.5-T field strengths for image calibration. This approach leverages the distinct signal properties of different tissues in T1-weighted images, where muscles typically demonstrate increased signal intensity compared to fat. While T2-weighted MRI can be valuable for assessing inflammatory edema, a hallmark of the active phase of orbitopathy, it is less effective for evaluating water content within adipose tissue [192].

Computed tomography is the imaging method of choice because of its good contrast of orbital fat, muscle, bony structures, and air in the adjacent paranasal sinuses [193]. Increased water content of the orbital fat accounted for a barely detectable rise in the attenuation coefficient of the orbital fat [194]. Ramieri et al. [195] previously utilized CT images to investigate orbital fat volume in post-traumatic enophthalmos. In the delineation and measurement of orbital soft tissues, CT numbers are set at − 200 to 100 Hounsfield units (HU) for bony orbital volume, − 200 to − 30 HU for fat tissue, and − 30 to 100 HU for muscle tissue [196]. Normal fat in the orbit and in other anatomical sites ha homogeneous low attenuation in CT images, whereas diseased fat has increased attenuation (e.g., − 60 to − 40 HU) [197]. Using CT scans, it is thus plausible to measure the volume and density (HU) of intraorbital and extraorbital fat, extraocular muscle, and the lacrimal gland to assess the inflammatory activities in the orbit [198]. Using CT radiodensity measurements, the mean volume of extraorbital and intraorbital fat was significantly higher in patients with GO than in controls [198]. The mean density of

extraorbital fat and the lacrimal gland was also found to be significantly different among active GO, inactive GO, and control groups [198]. For inflammatory orbital disease presenting as anterior uveitis in an adult [199], CT of the orbits showed a thickened left optic nerve with perineural enhancement and an ill-defined mass-like soft tissue within the intraconal fat posterior to the left globe [199].

Orbital cellulitis due to sinusitis can be detected by CT scans, either as a diffuse infiltration of the orbital fat or as a detachment of the periorbita (subperiosteal abscess) or a true orbital abscess [200]. When the cellulitis is the result of recent trauma, there is a significant increase in the attenuation coefficient of orbital fat, presumably the result of contusion [201]. Reported CT signs of orbital cellulitis include rostral displacement of the globe, obscuration of the orbital fat, swelling of orbital tissues and adjacent masticatory muscles, increased contrast uptake by orbital soft tissues, focal lack of contrast uptake as a result of abscess, foreign body identification, periodontal osteolysis, or thickening of orbital bones [202]. CT performed in cases of orbital cellulitis typically shows diffuse orbital infiltrate with decreased signal of orbital fat and may show sinus involvement, bony erosions, or venous thrombosis [135]. CT imaging of the orbits with contrast showed soft tissue fat stranding within the superior temporal aspect of the right orbit adjacent to the superior rectus muscle, consistent with orbital inflammation [203]. Surface-coil MR appears to add specificity to the CT appearance of orbital pseudotumor [204].

Fludeoxyglucose F-18 (FDG) is a positron-emitting radiotracer used in combination with positron emission tomography (PET) to diagnose and monitor various conditions and pathologies [205]. Because of its high sensitivity, FDG-PET/CT can be a useful diagnostic tool for detecting underlying systemic diseases in the course of OID [206]. FDG-PET/CT may be useful in distinguishing inflammatory disorders of the orbit from other conditions [207]. Additionally, FDG-PET/CT may also offer superior capabilities compared to other imaging modalities in detecting inflammation in GO [207]. It was previously shown that inflammation in GO may be clinically detectable in PET/CT-negative cases, and cases with negative clinical findings may exhibit inflammation on PET/CT [208]. The basis of using 68 Ga-DOTANOC (gallium-68 DOTA-1-NaI3-octreotide) PET/CT in IgG4 orbital disease is the known expression of somatostatin receptors in chronic inflammatory cells [209] and also avidity shown previously in other IgG4-related diseases [210]. Additionally, 99mTc-DTPA SPECT (Technetium-99 m Diethylenetriaminepentaacetic Acid Single Photon Emission Computed Tomography) has been used in evaluating retrobulbar inflammation in patients with GO [211]. Tc-99 m-HMPAO (hexamethylpropyleneamine oxime)-labeled WBC scintigraphy is one of the technetium radiopharmaceuticals used in white blood cell imaging provides information on the extent and the limits of the infectious process in the orbit [212].

## MANAGEMENT OF ORBITAL INFLAMMATION

### Surgical Approach

Orbital decompression is commonly used to treat patients with proptosis caused by GO [213]. This procedure involves various techniques aimed at increasing the orbital volume and/or reducing the volume of orbital fat by enlarging the bony confines of the orbital skeleton, often extending into the adjacent ethmoid sinus, with or without thinning of the lateral wall [214]. The removal of selected orbital walls can be combined with orbital fat removal for proptosis reduction tailored to the individual patient [215]. Prolapse of orbital fat into the nasal cavity provides sufficient proptosis reduction in many patients with GO without the need for excising the orbital fat, as described in the original endoscopic medial wall decompression [216].

During the non-active phase of GO, procedures such as bone and fat removal orbital decompression are performed to improve the cosmetic appearance and functional well-being of individuals exhibiting symptoms such as exophthalmos,

diplopia, orbital pain, orbital congestion, and ocular hypertension [217]. Retrobulbar fat excision is associated with a reduced incidence of motility complications compared to bony decompression [218]. During retrobulbar fat excision, fat is typically removed from the inferolateral, inferomedial, and/or superomedial regions [218]. It is generally possible to remove between 3 and 8 ml of fat per orbit, with the removal of 1 ml of fat resulting in a 1-mm reduction in proptosis. A previous study demonstrated that the removal of orbital fat led to a reduction in exophthalmos of approximately 3–4 mm [214]. In specific cases, the average reduction in exophthalmos following fat decompression can be as much as 5.3 mm [214]. However, surgical resection or transposition of orbital fat can potentially induce inflammation within the fat tissue, leading to the vertical descent of the lower eyelid [219].

In a prior investigation, concerns were raised regarding the occurrence of post-operative diplopia in cases where lateral orbital wall decompression was not appropriately balanced [220]. The removal of orbital fat during surgery and the potential reduction of inciting factors in the operated eye are associated with a decrease in inflammatory factors [221]. Despite the potential risks of orbital decompression surgery, such as damage to blood vessels and nerves increasing the risk of strabismus, it remains the principal treatment option for the removal of hyperplastic adipose tissue [222]. Owing to the complications associated with the procedure, there are new modifications to the surgical approach, such as preserving the most anterosuperior portion of the lamina papyracea to prevent fat prolapse and scar formation in the region of the frontal recess [223].

When clinical and radiologic findings are inconclusive, indeterminate, or atypical, consideration should be given to biopsy of an orbital inflammatory mass [224]. Open surgical biopsy is preferred over fine-needle aspiration biopsy, as the latter may fail to demonstrate diagnostic features or retrieve adequate tissue, particularly in cases of firm masses [225]. In a previous study involving 24 patients with biopsy-proven nonspecific orbital inflammation, the findings revealed the following involvement rates: lacrimal gland in 54.2% of cases, extraocular muscles in 50.0%, orbital fat in 75.0%, sclera in 4.2%, optic nerve in 20.8%, and other (eyelid and medial canthal mass) areas in 8.3% [226].

## Pharmacotherapy

### *Management of Inflammation with Corticosteroids*

Corticosteroids have anti-inflammatory and immunosuppressive effects by inhibiting enzymes in the arachidonic acid pathway, reducing the production of various inflammatory mediators and suppressing immune responses [227]. However, as a result of these actions, they can also have secondary effects on orbital fat. Local ophthalmic corticosteroid administration may carry risks, including epithelial toxicity, reduced wound strength, orbital fat atrophy, ptosis, limited ocular movement, and decreased endogenous cortisol levels [227], and following periocular steroid injections [228]. Orbital rim fat atrophy has been observed in cases of recurrent iritis and headaches treated with periocular corticosteroids [229].

In a previously reported study, patients with active, moderate-to-severe GO receiving methylprednisolone were divided into responsive and unresponsive groups. Compared to the unresponsive group, the responsive group exhibited a thicker inferior rectus muscle and thinner orbital fat [182]. In GO treatment, appropriate RAR expression, modulated by glucocorticoid therapy, helps reduce adipocyte proliferation and inflammation [230]. Additionally, orbital fibroblasts from a patient with GO expressed the RARα gene decreased with lower glucocorticoid doses [230]. Treatment of parabulbar triamcinolone in patients with active and moderate GO caused a significant decrease in signal intensity ratio of the fat suggesting reduces orbital inflammation [231]. In patients with giant cell arteritis presenting with MRI enhancement of retrobulbar fat indicative of orbital inflammation, resolution of the inflammation was observed following corticosteroid treatment. One patient received an IV bolus of solumedrol followed by an oral prednisone taper [232], while another patient was treated with oral prednisone [130].

### *Monoclonal Antibodies in the Management of Orbital Inflammation*

Teprotumumab, a novel human monoclonal inhibitor of the IGF-1 receptor, binds specifically to IGF-1R, leading to the internalization and degradation of the antibody-receptor complex [233]. This inhibition of IGF-1R subsequently reduces downstream signaling, resulting in decreased hyaluronan and cytokine production, ultimately leading to a reduction in inflammation and orbital soft tissue expansion [233]. Teprotumumab blocks pathologic immune responses in active GO and mediates the reduction in orbital fat, contributing to associated decreases in proptosis [217]. Following teprotumumab treatment, there is a a marked reduction in total extraocular muscle volume within each orbit, along with a reduction in total orbital fat volume [234]. Moreover, teprotumumab has been shown to reverse fat and muscle volume enlargement in GO [235], potentially contributing to the decrease in proptosis [236]. In a study investigating the predictive value of orbital fat-to-muscle ratio (FMR) for proptosis reduction in GO with surgical decompression or teprotumumab, it was observed that individuals with low FMR achieved comparable proptosis reduction with either teprotumumab or surgery [237]. Conversely, high FMR correlated with a more significant proptosis reduction after surgery compared to teprotumumab [237].

In evaluating the therapeutic outcomes of tocilizumab (TCZ) in patients who did not respond to first-line treatments with corticosteroids, all individuals with moderate to severe GO showed a 2-point improvement in their clinical activity score 6 weeks after receiving TCZ [238]. This improvement is attributed to a reduction in the volume of retrobulbar fat [238].

Rituximab, a monoclonal antibody recognizing CD20, a surface transmembrane protein on mature B-lymphocytes [239], helps reduce inflammation by decreasing B cell activity as antigen-presenting cells, lowering production of inflammatory cytokines, and potentially inhibiting pathogenic autoantibody generation [240, 241]. Examination of orbital fat and peripheral blood samples demonstrated complete depletion of CD20 + B-lymphocytes after rituximab treatment for GO compared to a control GO patient who was not treated with rituximab [242]. A previous study found that the $^{131}$I plus rituximab (RTX)-treated group had a decrease of retrobulbar muscle and fat volumes [243]. Additionally, $^{131}$I plus RTX showed the most significant effects on proptosis and an improvement in ophthalmic parameters such as clinical activity score [243]. In a case report of presumed idiopathic intractable orbital disease, treatment with rituximab improved proptosis, normalized serum IgG4 levels, and rendered the orbital disease dormant [88, 244]. However, in a study utilizing a small dose of rituximab for the treatment of GO, no significant changes were observed in the exophthalmos of the left eye and the thickness of orbital fat following the rituximab treatment [245].

### *Integrated Approaches and Experimental Therapies for the Management of Orbital Inflammation*

In GO, treatment with astragaloside IV has demonstrated a significant reduction in IL-1β-induced production of inflammatory cytokines in orbital fibroblasts in vitro [246]. It has also shown the ability to mitigate orbital inflammation, fat accumulation, collagen deposition, and macrophage infiltration in vivo [246]. A previous study reported a 50% decrease in mature adipocytes when using diclofenac, an inhibitor of cyclooxygenases with antagonistic effects on PPAR-γ [247].

Methotrexate, a folic acid antagonist, inhibits dihydrofolate reductase, an essential enzyme for DNA and RNA synthesis [248]. This action suppresses rapidly proliferating cells, including B- and T-cells. Methotrexate has been identified as a potential therapeutic option for the rare and persistent disease of adult-onset xanthogranuloma, which commonly involves the preseptal fat [248].

In vivo, exposure of rat orbital adipocytes to retrobulbar depot injections of topical prostaglandin analogs (PGA), such as bimatoprost, resulted in the atrophy of intraconal adipocytes [249]. While bimatoprost was effective for orbital fat atrophy in rat models, further

research is needed to generalize these results to humans [249].

Treatment with alpha-lipoic acid (ALA) for GO has due inhibitory effects on ROS production, proinflammatory cytokines, and chemokines, ultimately aimed preventing adipose tissue expansion [250]. ALA significantly inhibits TNFα-induced P65 phosphorylation and intracellular accumulation of lipid droplets induced by $H_2O_2$ [250].

Research on the effects of quercetin has uncovered its ability to inhibit fibrotic markers in primary cell and orbital fat tissue cultures obtained from GO subjects, even at non-toxic concentrations [251]. This finding suggests that quercetin could be a promising candidate for treating active inflammation and preventing chronic fibrosis in GO. Additionally, treatment with quercetin inhibits the accumulation of intracytoplasmic lipid droplets [252]. It has also been shown that quercetin effectively mitigates the dose- and time-dependent increase in hyaluronan production triggered by IL-1β or TNF-α [253].

Treating human macrophages with triacsin C, an inhibitor of acyl-CoA synthetase in de novo ceramide synthesis, results in a reduction of palmitate-induced secretion of TNF-α, IL-8, and IL-1β [254]. Conversely, pretreatment with triacsin C enhances palmitate-induced IL-6 secretion in adipocytes [255]. In a controlled animal study, the injection of hyaluronic acid gel and human orbital adipose-derived stem cells (hoADSCs) increased the exophthalmometric value [256]. This outcome suggests that the transplantation of hoADSCs with HAG is a safe and effective technique for expanding orbital fat volume [256].

## Alternative Strategies for Managing Orbital Fat in Inflammatory Ophthalmopathies

Radiotherapy (RT) could play a role in the management IOD because its effectiveness in suppressing the inflammatory process [257]. It can therefore be used in the treatment of ophthalmopathies, potentially enhancing the outcomes of orbital decompression procedures, and it could be used in adjunct to corticosteroids to facilitate its tapering [258]. External beam radiation can intervene in the process of thickening extraocular muscles and increasing orbital fat volume by arresting fibroblast proliferation, leading to the permanent resolution of orbital inflammation [259].

Even in patients who did not have decompression surgery, there was a slight non-significant, clinically inconsequential decrease in total volume of retrobulbar fat and muscle after orbital radiotherapy [260]. In the combined orbital RT and steroid pulse therapy group, significant reductions in orbital, extraocular muscles, and fat volume were observed, whereas in the steroid pulse therapy-only (ST) group [196], only fat volume decreased. Orbital RT is slower to show a therapeutic effect than glucocorticoid therapy but can be effective for a longer period [261]. In response to orbital RT, volumes of the superior rectus, inferior rectus, medial rectus, lateral rectus, and orbital fat significantly decreased post-RT [262].

Mesotherapy, the injection of various substances to dissolve fat without surgical incision, has previously been used as an alternative to liposuction for cosmetic purposes [263]. In a previous study, acute orbital inflammation in the inferior orbital fat compartments was greatly reduced after receiving cosmetic mesotherapy [264].

It has previously been reported that orbital shaking of fat tissue enhances its anti-inflammatory properties, and the derived mesenchymal stem cells maintain such enhanced activity [265]. The application of an orbital mechanical force to fat inhibits the expression of TNF-α and stimulates the expression of TNF-stimulated gene-6, which has protective and anti-inflammatory effects when applied to animal models of rheumatic diseases [265]. Examination of biopsy, lipoaspirate, and mechanically activated fat showed that, in addition to the increased TSG-6, SOX2, NANOG, and OCT4 were also strongly enhanced by mechanical activation, suggesting an effect on stromal cell stemness [265].

## ORBITAL FAT-DERIVED STEM CELLS AND THEIR POTENTIAL APPLICATIONS

Orbital fat tissue is a source of adipose tissue-derived stem cells (ADSCs) developed from embryonic mesenchyme [266]. The morphology, growth kinetics, and surface immuno-phenotype of orbital fat-derived stem cells (OFSCs) are similar, although not identical, to mesenchymal stem cells from other tissue types, e.g., bone marrow [266]. OFSCs are plastic-adherent, spindle-shaped cells with significant expansion potential and tri-lineage differentiation capabilities, including osteogenic, chondrogenic, and adipogenic pathways [266]. Phenotypically, OFSCs are negative for hematopoietic (both lymphoid and myeloid) and endothelial markers, but positive for CD29, CD44, CD90, and CD105, indicating their mesenchymal stem cell nature [267]. OFSCs are known to suppress inflammation mediated by macrophages and induce cell cycle arrest in macrophages through a paracrine effect [268]. OFSCs can differentiate into epithelial cells when co-cultured with corneal epithelial cells (HCE-T), displaying markers CK (cytokeratin)19 and CK3. This epithelial differentiation is enhanced by direct cell contact with HCE-T cells, a feature not observed in ADSCs [266]. OFSCs have been shown to exhibit low immunogenicity, as indicated by their lack of significant impact on pro-inflammatory cytokines TNF-α and IFN-γ in xenotransplantation models, and they effectively ameliorate inflammation in lung injury models by inhibiting macrophage activation and reducing inflammatory cytokine levels [267]. These properties suggest that OFSCs could be valuable for therapeutic applications, particularly in reducing inflammation and promoting tissue repair in various disease contexts [267].

Regenerative cells isolated from nasal and central orbital fat have high viability (over 94%) and exhibit similar yields of colony-forming cells, although these yields are lower than those from other fat depots [20]. Morphologically, fat-derived stem cells from both nasal and central depots exhibit cellular processes similar to those of oligodendrocytes. In differentiation assays, OFSCs demonstrate adipogenic potential, with lipid accumulation similar to that of abdominal fat-derived stem cells, and show limited smooth muscle differentiation. Importantly, fat-derived stem cells from the central depot have greater neurogenic and glial differentiation potential compared to nasal stem cells, suggesting that OFSCs could be valuable for tissue regeneration and repair in various clinical applications [20].

In coculture, OFSCs preserved hepatocyte viability and functionality, particularly through the secretion of IL-6, which played a critical role in immunomodulation. These protective effects occurred independently of OFSC differentiation into hepatocyte-like cells, suggesting that OFSCs could be a valuable therapeutic tool for managing liver injury through their anti-inflammatory and supportive properties [269]. OFSCs have shown potential in promoting corneal wound healing in mice, particularly after alkali-induced corneal injuries. In models with both limbal-sparing and limbal-involved injuries, topical application of OFSCs significantly accelerated corneal re-epithelialization, reduced inflammation, and minimized corneal edema [270]. OFSCs localized to the corneal epithelium and stroma, where they contributed to tissue repair without inducing excessive scarring or teratoma formation. While OFSCs did not fully differentiate into corneal epithelial cells within the initial days post-transplant, their presence improved corneal transparency and reduced macrophage infiltration, demonstrating their therapeutic potential for ocular surface injuries [270].

Orbital fat-derived stem cells demonstrate distinct advantages in regenerative medicine due to their enhanced adipogenic and myofibrogenic potentials. Compared to adipose-derived stem cells from other anatomical sites, OFSCs show superior adipogenesis, as evidenced by increased lipid droplet accumulation and higher expression of adipogenic markers such as adiponectin and hyaluronan synthase (HAS)–2. Furthermore, orbital OFSCs have pronounced myofibrogenic capability, producing a higher percentage of α-smooth muscle actin (α-SMA)-positive myofibroblasts upon stimulation with transforming growth factor-beta 1 (TGF-β1), in contrast to subcutaneous adipose-derived stem cells. These features highlight the potential of OFSCs in

applications requiring significant adipogenic and fibrogenic activities [271].

Human OFSCs demonstrate significant potential in treating GO due to their effects on adipogenesis and inflammation. In animal models, human OFSCs and their engineered variant effectively reduced pathologic expansion of orbital fat and optic nerve thickening, both common in GO [272]. These cells also suppressed adipogenic gene expression and decreased lipid accumulation in GO-derived orbital fibroblasts. Furthermore, both human OFSCs and the engineered variant modulated key signaling pathways, such as TSHR-SREBP2-HMGCR, involved in adipogenesis. Importantly, both the OFSCs and the engineered variant exhibited superior anti-inflammatory and anti-adipogenic effects compared to standard steroid treatments, highlighting their potential for managing GO-related tissue remodeling and inflammation [272].

In GO, OFSCs, specifically those targeting TSG-6 (tumor necrosis factor-stimulated gene-6), demonstrate significant therapeutic potential. TSG-6 expression is notably markedly in GO orbital tissues, correlating with elevated IL-6 levels and inflammation [273]. In a GO mouse model, TSG-6 treatment effectively reduced lipogenesis, inflammation, and fibrosis compared to untreated controls, showing improved histopathologic outcomes and decreased macrophage infiltration. TSG-6 not only alleviated orbital fat expansion and optic nerve compression but also outperformed dexamethasone in reducing collagen deposition and mucin accumulation, highlighting its superior efficacy in managing GO-related orbital inflammation and fibrosis [273].

## CONCLUSIONS

These findings highlight a distinct role for orbital fat in the pathogenesis of inflammatory orbital disease (IOD). The unique structural and metabolic characteristics of orbital fat, compared to other adipose tissues, likely contribute to its increased susceptibility and involvement in IOD. This condition manifests as inflammation within the orbit, which may arise from either primary or secondary causes. A key feature of IOD is the diffuse infiltration of inflammatory cells within the orbital fat compartment. Radiologic imaging, including CT and MRI, is crucial for diagnosing IOD. These techniques provide detailed tissue characterization and help assess the extent, location, and severity of the disease. Additionally, nuclear imaging, such as PET scans, shows promise for the earlier diagnosis of IOD and for identifying underlying systemic disorders. Orbital fat biopsies may be required to investigate infiltrative lesions associated with IOD. The primary treatment for managing IOD involves orbital decompression to remove portions of orbital fat. The management of IOD focuses on controlling inflammation, with corticosteroids being the first-line therapy. However, their long-term use and potential side effects necessitate exploration of alternative treatment options. Immunomodulatory medications offer a potential treatment pathway for IOD. Additionally, strategies such as mesotherapy and orbital shaking show potential benefits for managing IOD affecting the orbital fat compartment. Orbital fat-derived stem cells also hold potential in regenerative medicine due to their ability to repair tissue, reduce inflammation, and differentiate into various cell types, which could be beneficial for treating ocular and inflammatory conditions. Further research is needed to understand the specific mechanisms by which orbital fat contributes to IOD and to optimize treatment strategies for improved patient outcomes.

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### *Declarations*

***Conflict of Interest.*** The authors (Prince Dadson, Peter Ngum, Luis Eduardo Juarez-Orozco, Michael Ntodie, Piotr Loba) declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

***Ethical Approval.*** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.



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