



The Emerging FGF21 Axis in Thyroid Eye Disease: Metabolic–Immune Crosstalk and Therapeutic Perspectives

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Abstract

Background: Thyroid eye disease (TED) is an organ-specific autoimmune disorder characterized by orbital inflammation, fibroblast activation, extracellular matrix expansion, adipogenesis, extraocular muscle enlargement, and progressive tissue remodeling. Although thyrotropin receptor and insulin-like growth factor-1 receptor signaling remain central to current models of TED pathogenesis, increasing evidence indicates that metabolic stress, oxidative injury, mitochondrial dysfunction, and altered immunometabolic signaling may contribute to disease initiation and progression. Fibroblast growth factor 21 (FGF21) is a stress-responsive endocrine factor produced predominantly by the liver that regulates glucose and lipid metabolism through fibroblast growth factor receptors and the obligate co-receptor β -Klotho. Beyond its metabolic effects, FGF21 participates in cellular stress adaptation, redox regulation, mitochondrial homeostasis, adipose tissue biology, and modulation of inflammatory pathways. These properties provide a biologically plausible connection between FGF21 signaling and several processes involved in TED. Importantly, circulating FGF21 is influenced by thyroid hormone status, and a prospective biomarker study has reported increased FGF21 in patients with Graves' disease who subsequently developed TED, creating direct clinical interest in this axis. The available evidence, however, remains insufficient to establish FGF21 as a causal mediator of orbital disease. This review integrates current understanding of TED immunopathogenesis with FGF21 biology, examines potential interactions involving orbital fibroblasts, oxidative stress, adipogenesis, inflammation, and fibrosis, and evaluates FGF21 as a candidate biomarker and therapeutic pathway. Carefully controlled longitudinal and mechanistic studies are required to determine whether FGF21 represents a compensatory stress response, a marker of disease susceptibility, or an active component of TED pathobiology.

Keywords: fibroblast growth factor 21, thyroid eye disease, orbital fibroblasts, immunometabolism

Introduction

Thyroid eye disease (TED), also termed Graves' orbitopathy or thyroid-associated orbitopathy, is the most clinically important extrathyroidal manifestation of Graves' disease. Its manifestations range from ocular surface irritation, eyelid retraction, and periorbital edema to proptosis, restrictive diplopia, corneal breakdown, and dysthyroid optic neuropathy. TED is distinguished from uncomplicated Graves' hyperthyroidism by a highly specialized orbital immune response that ultimately expands tissues within a rigid bony compartment. Contemporary evidence indicates that moderate-to-severe disease represents only a minority of TED cases, but this group accounts for substantial visual morbidity, disfigurement, functional disability, impaired quality of life, and health-care utilization. The disease therefore remains clinically important even as its epidemiological profile has changed with earlier diagnosis and improved control of Graves' disease. [1]

Clinical management is guided by two related but distinct concepts: disease **activity**, reflecting current inflammation, and disease **severity**, reflecting the functional and anatomical burden of orbital involvement. The European Group on Graves' Orbitopathy classifies TED as mild, moderate-to-severe, or sight-threatening, while inflammatory activity is commonly estimated using the Clinical Activity Score (CAS). The active phase offers the greatest opportunity for immunomodulatory treatment, whereas residual proptosis, diplopia, eyelid abnormalities, and fibrosis during inactive disease may require rehabilitative intervention. Cigarette smoking, uncontrolled thyroid dysfunction, elevated thyrotropin receptor antibody concentrations, and radioactive iodine exposure in susceptible patients are recognized modifiers of TED risk and progression. [2]



The traditional model of TED focused principally on thyroid autoimmunity and orbital expression of the thyrotropin receptor (TSHR). Current understanding is considerably broader. TSHR interacts functionally with insulin-like growth factor-1 receptor (IGF-1R), while T cells, B cells, monocyte-lineage cells, fibrocytes, cytokines, reactive oxygen species, extracellular matrix pathways, and heterogeneous orbital fibroblast populations create a self-reinforcing inflammatory and remodeling microenvironment. Clinical success with receptor-directed treatment has confirmed that TED is not simply a consequence of circulating excess thyroid hormone but a specific orbital autoimmune process with identifiable signaling vulnerabilities. [3]

Graves' disease itself arises from loss of immune tolerance to TSHR, resulting in stimulatory TSHR autoantibodies and thyroid hyperfunction. The relationship between the thyroid and orbit is therefore immunological as well as endocrine. Thyroid hormone excess changes basal metabolic rate, lipid turnover, oxidative metabolism, mitochondrial activity, and several circulating metabolic hormones. This relationship is highly relevant when investigating FGF21 because FGF21 concentrations are responsive to nutritional and metabolic stress and are directly influenced by thyroid hormone signaling. Any association between FGF21 and TED must therefore separate the effects of orbital autoimmunity from the metabolic consequences of hyperthyroidism. [4]

Interest in FGF21 offers an opportunity to connect two areas of TED biology that have often been considered separately: autoimmunity and metabolism. FGF21 is a stress-inducible endocrine regulator with established actions on energy balance, adipose tissue, glucose handling, lipid oxidation, mitochondrial biology, and cellular stress responses. The research gap is substantial: direct human evidence linking FGF21 with TED is limited, mechanisms within orbital tissue have not been adequately defined, and it is unknown whether increased FGF21 represents pathogenic signaling or a protective compensatory response. The aim of this review is therefore to integrate established TED mechanisms with current FGF21 biology and critically assess the potential diagnostic, pathogenic, and therapeutic relevance of the FGF21 axis.

Immunopathological Framework of Thyroid Eye Disease

Orbital fibroblasts as central effector cells

Orbital fibroblasts occupy a central position in TED because they convert autoimmune receptor stimulation and inflammatory signals into the characteristic anatomical changes of the disease. Compared with fibroblasts from many other anatomical sites, orbital fibroblast populations exhibit distinctive receptor profiles and considerable functional heterogeneity. Once activated, they can proliferate, synthesize inflammatory mediators, generate large quantities of glycosaminoglycans, particularly hyaluronan, and differentiate toward adipocytes or myofibroblasts. These processes explain why TED simultaneously displays features of inflammation, edema, adipose expansion, extraocular muscle enlargement, and late fibrosis. [5]

Hyaluronan is especially important because its highly hydrophilic nature permits substantial water retention. Increased synthesis and reduced clearance of extracellular matrix components enlarge orbital tissues, increasing pressure inside a confined bony compartment. Adipogenic differentiation further increases orbital volume, whereas myofibroblast differentiation and collagen deposition contribute to restrictive extraocular muscle disease. The balance between these cellular fates varies among patients and may explain phenotypic differences between predominantly fat-expanded and muscle-predominant forms of TED. [6]

Orbital fibroblasts are not a uniform population. CD34-positive fibrocyte-derived cells and resident CD34-negative fibroblasts appear to contribute differently to immune activation and matrix production. Circulating fibrocytes can migrate into orbital tissue and express thyroid-associated proteins, including TSHR, while resident fibroblasts display strong capacity for hyaluronan production and tissue remodeling. This cellular diversity suggests that systemic endocrine or metabolic factors could influence different orbital cell populations unequally. Such heterogeneity becomes important when considering FGF21 because responsiveness to FGF21 depends on receptor composition and β -Klotho expression rather than simply the presence of an FGF receptor. [7]

TSHR–IGF-1R signaling

TSHR remains the best-established disease-specific autoantigen in Graves' disease and TED. In orbital fibroblasts, activation of TSHR stimulates cyclic AMP-dependent pathways and promotes adipogenesis and hyaluronan synthesis. Evidence also supports close physical and functional relationships between TSHR and IGF-1R. Signaling through this receptor network can activate PI3K–AKT, MAPK, mTOR, and related intracellular pathways, thereby enhancing cytokine production, extracellular matrix synthesis, cell survival, and differentiation. This receptor partnership provides a mechanistic explanation for the effectiveness of IGF-1R inhibition in a disease initiated primarily by thyroid autoimmunity. [8]

The importance of receptor crosstalk also broadens the biological context in which FGF21 should be studied. FGF21 signals through receptor tyrosine kinase complexes and activates intracellular pathways that overlap partly with metabolic signaling networks relevant to fibroblast survival, glucose handling, redox regulation, and differentiation. It would therefore be premature to assume either that FGF21 acts independently of the established TSHR–IGF-1R system or that it directly modifies it. Determining whether these pathways converge within orbital fibroblasts is one of the



most important mechanistic questions for future experimental work.

Immune-cell recruitment and cytokine signaling

TED orbital tissue contains T lymphocytes, B lymphocytes, macrophages, fibrocytes, and other inflammatory populations that communicate bidirectionally with orbital fibroblasts. Activated fibroblasts produce interleukin (IL)-6, IL-8, chemokines, prostaglandins, and other mediators that recruit and sustain immune-cell activity. Immune cells in turn expose fibroblasts to cytokines and receptor ligands that amplify matrix synthesis and differentiation. This reciprocal interaction helps explain why an initially immune-mediated process becomes a fibroproliferative and remodeling disease. [9]

Th17 biology is particularly relevant to this transition. IL-17A-producing T cells have been detected in TED and can influence both inflammation and fibroblast phenotype. Experimental work indicates that pathogenic Th17 cells can regulate adipogenesis and fibrosis in orbital fibroblasts, providing a bridge between adaptive immunity and the structural manifestations of TED. This finding also supports the broader concept that metabolic programs of immune cells and fibroblasts are likely to influence disease behavior. [10]

Oxidative Stress and Immunometabolism in TED

Oxidative stress is increasingly regarded as a major contributor to TED rather than a secondary consequence of inflammation. Orbital fibroblasts from affected patients show abnormal redox responses, while reactive oxygen species can stimulate proliferation, inflammatory mediator release, adipogenic signaling, and hyaluronan synthesis. Hyperthyroidism itself increases oxygen consumption and mitochondrial activity, creating a systemic environment in which oxidative stress may be enhanced. Smoking adds a further oxidative and inflammatory burden and remains one of the strongest modifiable risk factors for clinically significant TED. [11]

Direct studies of orbital fibroblasts have demonstrated increased oxidative DNA damage, lipid peroxidation, and reactive oxygen species in TED-derived cells compared with controls. Such findings indicate that the orbital microenvironment is not simply exposed to more oxidants; the cells themselves may possess altered antioxidant defenses or increased susceptibility to oxidative stimulation. Redox-sensitive signaling can activate NF- κ B, MAPKs, and other transcriptional programs that overlap with cytokine-induced fibroblast activation. [12]

Antioxidant observations provide additional clinical support for the relevance of oxidative pathways. Selenium improved quality of life and ocular outcomes and reduced progression in a randomized trial of patients with mild Graves' orbitopathy. Selenium should not be interpreted as proof that oxidative stress is the sole driver of TED, and geographical selenium status influences its clinical use, but the trial demonstrates that modification of redox-related biology can affect the course of mild disease. [13]

The CD40–CD154 system provides another interface between immunity, fibroblast activation, and cellular metabolism. Orbital fibroblasts express functional CD40, and receptor engagement can markedly increase production of inflammatory cytokines. Interferon- γ can further enhance CD40 expression, creating a mechanism by which immune-cell signals make fibroblasts increasingly responsive to subsequent inflammatory stimulation. [14]

CD40 activation also increases hyaluronan synthesis and cyclooxygenase-related inflammatory signaling in orbital fibroblasts. These observations illustrate a central principle in TED: inflammatory pathways and tissue-expansion pathways are not separate biological processes. The same receptor stimulus can simultaneously increase immune mediators and extracellular matrix production. A candidate immunometabolic hormone such as FGF21 should therefore be assessed across multiple outputs—including cytokine production, reactive oxygen species, adipogenesis, hyaluronan, and fibrosis—rather than through a single inflammatory marker. [15]

FGF21 Biology and Signaling

FGF21 belongs to the endocrine subgroup of the fibroblast growth factor family. Unlike classical FGFs that primarily act locally, endocrine FGFs have reduced affinity for heparan sulfate and circulate to distant tissues. FGF21 is produced predominantly by the liver under many physiological conditions, although adipose tissue, skeletal muscle, pancreas, heart, and other organs can contribute in specific metabolic or cellular stress states. Its expression is strongly responsive to nutrient availability, fasting, protein restriction, carbohydrate excess, mitochondrial stress, and endoplasmic reticulum stress. [16]

FGF21 differs fundamentally from conventional growth factors in both physiology and receptor requirements. Its metabolic actions depend largely on fibroblast growth factor receptor 1c (FGFR1c) together with the transmembrane co-receptor β -Klotho. β -Klotho provides high-affinity recognition and determines tissue sensitivity to circulating FGF21. After receptor-complex engagement, signaling can involve FRS2, ERK1/2, PI3K–AKT, AMPK-associated responses, and tissue-specific downstream programs. Consequently, circulating FGF21 concentration alone does not establish biological activity; receptor abundance and β -Klotho expression are equally important. [17]

FGF21 has been described as a metabolic stress hormone because its circulating concentration often rises in states of metabolic challenge. Pharmacological FGF21 improves several metabolic abnormalities in experimental models, whereas obesity, type 2 diabetes, and fatty liver disease may display high endogenous FGF21 levels. This apparent paradox has generated the concept of impaired FGF21 responsiveness or “FGF21 resistance,” although the extent and



mechanism of true resistance in humans remain debated. Elevated FGF21 can therefore indicate an adaptive response to stress rather than excessive FGF21 bioactivity. [18]

Nutrient sensing is a major regulator of FGF21 expression. During fasting, hepatic PPAR α contributes to FGF21 induction, linking fatty-acid metabolism with endocrine adaptation. Protein restriction and amino-acid stress can induce FGF21 through integrated stress response pathways involving eIF2 α and ATF4, whereas carbohydrate availability can regulate FGF21 through carbohydrate-responsive transcriptional programs. This ability to integrate multiple forms of metabolic stress makes FGF21 biologically attractive in TED, where thyroid hormone excess, systemic metabolic change, orbital inflammation, and oxidative injury may occur concurrently. [19]

FGF21 also acts through the central nervous system and adipose tissue to coordinate systemic responses. Experimental studies demonstrate that β -Klotho-dependent neuronal pathways contribute to effects on energy expenditure, circadian behavior, sympathetic activity, and nutrient preference. These findings are important because they discourage an overly narrow interpretation of serum FGF21. A change in circulating FGF21 in TED could originate from systemic thyroid-related metabolic adaptation without implying local production or direct signaling within the orbit. [20]

The FGF21–Thyroid Hormone Relationship

The relationship between thyroid hormones and FGF21 is particularly important for TED research. Experimental data demonstrate that triiodothyronine can induce hepatic FGF21 expression through mechanisms involving thyroid hormone receptor- β and PPAR α . Thyroid hormones therefore have the capacity to alter FGF21 independent of orbital disease. Any comparison between patients with TED and euthyroid controls that does not adequately account for thyroid functional status risks attributing an endocrine effect of thyrotoxicosis to TED itself. [21]

Human data confirm this concern. In a case-control study involving patients with hyperthyroidism, serum FGF21 concentrations were significantly higher than in healthy controls and decreased substantially after antithyroid treatment restored euthyroidism. FGF21 remained associated with hyperthyroidism after adjustment for several potential confounders. These findings provide strong evidence that thyroid functional state is a determinant of circulating FGF21 in humans. [22]

The opposite thyroid state also affects FGF21. Patients with overt hypothyroidism have been reported to show reduced circulating FGF21, with concentrations increasing after levothyroxine treatment. Changes in FGF21 correlated with changes in thyroid hormone levels in that study. Taken together with hyperthyroidism data, this supports a biologically meaningful thyroid hormone–FGF21 relationship and indicates that serum FGF21 should not be interpreted in isolation from TSH, free T4, and free T3. [23]

More recent work in autoimmune thyroid disease suggests that thyroid autoimmunity may further modify this relationship. Patients with treated Hashimoto thyroiditis have been reported to show altered circulating FGF21 and loss of some of the usual relationships between FGF21 and thyroid hormone parameters. Although Hashimoto thyroiditis differs from Graves' disease and TED, the observation raises the possibility that inflammatory or autoimmune status can influence FGF21 regulation beyond hormone concentrations alone. [24]

Direct Evidence Linking FGF21 With Thyroid Eye Disease

The strongest direct human evidence for an FGF21–TED relationship comes from a biomarker study of patients with Graves' disease in which a broad panel of inflammatory proteins was assessed. Among 100 patients with Graves' disease, 36 had TED, and several inflammatory biomarkers differed according to disease phenotype. Of particular interest, FGF21 was significantly increased in individuals without clinical TED at baseline who subsequently developed TED. The study also identified IL-6, CSF1, and FLT3 ligand as potentially relevant markers, placing FGF21 within a wider inflammatory signature rather than identifying it as an isolated abnormality. [25]

This finding is important for three reasons. First, FGF21 elevation preceded clinically recognized TED in a subgroup, which makes it more interesting as a susceptibility or prediction biomarker than a molecule measured only after advanced orbital inflammation has developed. Second, the observation emerged from multiplex inflammatory profiling rather than from a study specifically designed to establish FGF21 causality. Third, the sample of patients who progressed to TED was necessarily smaller than the overall cohort. Replication in independent longitudinal populations is therefore essential before FGF21 can be considered a validated TED biomarker. [25]

The current evidence does not establish whether FGF21 contributes to orbital injury, represents a protective response, or simply reflects systemic stress associated with Graves' disease. These interpretations have very different therapeutic implications. If FGF21 is compensatory, increased levels might indicate an endogenous attempt to limit oxidative or metabolic injury. If FGF21 signaling is defective despite increased hormone concentration, elevated levels might represent inadequate compensation. A pathogenic interpretation would require evidence that FGF21 directly activates orbital disease mechanisms, which has not yet been demonstrated.

Potential Mechanisms Connecting FGF21 With TED

FGF21 and oxidative-stress adaptation

One of the strongest conceptual links between FGF21 and TED involves cellular stress. Mitochondrial and endoplasmic reticulum stress can induce FGF21 through the integrated stress response, particularly through ATF4-related



transcriptional programs. FGF21 can subsequently participate in systemic adaptations that improve metabolic efficiency and reduce cellular stress in several experimental settings. This biology creates a plausible feedback model in which increased FGF21 during Graves' disease could arise in response to heightened oxidative metabolism and inflammatory stress. [26]

The integrated stress response is relevant to orbital fibroblasts because sustained reactive oxygen species can alter proliferation, differentiation, and cytokine production. If orbital cells express an effective FGFR1c/ β -Klotho signaling complex, FGF21 could theoretically modulate AMPK-related signaling, mitochondrial function, or antioxidant defenses. At present, however, the presence and functional importance of β -Klotho in human TED orbital fibroblast subsets have not been established sufficiently to support such a conclusion. Demonstrating receptor competence should therefore precede claims regarding local FGF21 action.

Inflammation and immune regulation

FGF21 has shown anti-inflammatory effects in multiple experimental contexts, frequently in association with reduced inflammatory signaling, improved metabolic homeostasis, and changes in macrophage biology. FGF21 treatment can alter adipose-tissue immune composition, while metabolic improvement itself may reduce inflammatory signaling. Distinguishing direct immune effects from secondary metabolic effects remains difficult. In TED, this distinction is especially relevant because systemic metabolic changes and local autoimmunity occur simultaneously. [27]

IL-6 provides a useful example of potential convergence. IL-6 is produced by activated orbital fibroblasts, immune cells, and other tissues and has been associated with TED activity. FGF21 and IL-6 were both identified within the inflammatory biomarker profile associated with TED, but their coexistence does not prove a direct regulatory relationship. A rational experimental approach would examine whether FGF21 modifies IL-6 production after TSHR, IGF-1R, CD40, or oxidative stimulation of patient-derived orbital fibroblasts. [28]

Adipogenesis and orbital tissue expansion

Adipogenesis is central to many TED phenotypes and represents another potential intersection with FGF21. Systemically, FGF21 has major effects on adipose tissue, insulin sensitivity, lipid flux, thermogenic programs, and adipokine secretion. Pharmacological FGF21 can remodel adipose metabolism rather than simply suppress adipocyte formation. The orbital fat compartment, however, has specialized developmental and functional characteristics; metabolic effects observed in subcutaneous or brown adipose tissue cannot automatically be extrapolated to orbital fibroblasts. [29]

TED adipogenesis is regulated by TSHR activity, PPAR γ , IGF-1R-associated signaling, and cytokine exposure. Basic fibroblast growth factor and other growth factors can also influence orbital adipogenic differentiation. FGF21 could theoretically alter this process at several points, including insulin signaling, PPAR-related transcription, mitochondrial metabolism, and differentiation. Direct studies using TED-derived orbital fibroblasts undergoing adipogenic induction are required to determine whether physiological or pharmacological FGF21 concentrations enhance, inhibit, or have no meaningful effect on this phenotype. [30]

Fibrosis and extracellular matrix remodeling

Fibrosis determines much of the persistent morbidity of chronic TED. TGF- β -dependent myofibroblast differentiation promotes collagen production and contractile behavior, while altered hyaluronan metabolism contributes to persistent tissue expansion. Recent work demonstrates that myofibroblast differentiation changes both synthesis and turnover of hyaluronan in orbital fibroblasts, indicating that matrix biology evolves as TED progresses from inflammation to structural remodeling. [31]

FGF21 has been investigated in fibrotic disorders outside the orbit, particularly metabolic liver disease, where FGF21 analogues can improve biochemical and histological markers of steatohepatitis and fibrosis. These findings show that pharmacological FGF21 signaling can influence fibrotic disease biology at an organ level, but they cannot be translated directly to TED because the dominant cell populations, disease triggers, receptor distribution, and therapeutic exposure differ. Any proposed antifibrotic role in TED remains a testable hypothesis rather than an established mechanism. [32]

FGF21 as a Candidate Biomarker in TED

An ideal TED biomarker would identify patients with Graves' disease at risk of developing orbital involvement, distinguish active from inactive disease, predict progression, correlate with clinically meaningful outcomes, or forecast treatment response. Current clinical assessment still relies heavily on examination, CAS, severity classification, imaging when indicated, and TSHR antibody measurements. CAS is useful but does not capture the full molecular heterogeneity of TED, which explains continuing interest in circulating biomarkers. [33]

FGF21 is attractive because an elevation before TED onset has already been observed, but its biological nonspecificity is a major limitation. Circulating FGF21 is influenced by age, body composition, obesity, insulin resistance, diabetes, liver disease, renal dysfunction, nutritional state, fasting, cardiovascular disease, exercise, medications, and thyroid hormone status. A poorly controlled study could therefore detect statistically significant differences that have little specific relationship to orbital autoimmunity. [18]

This issue strongly supports restrictive phenotyping in early FGF21–TED investigations. Studies should document



BMI, waist measures, fasting status, glucose metabolism, liver enzymes and steatotic liver disease, renal function, cardiovascular disease, thyroid hormone concentrations, TSHR antibody status, smoking, and relevant medications. Drugs that modify metabolic pathways—including glucose-lowering agents and PPAR-directed therapies—may also alter FGF21 biology. Such control of confounding is particularly important when sample sizes are modest. The exclusion strategy proposed in the accompanying thesis protocol appropriately recognizes several of these major determinants.

A stronger design would include at least three clinically distinct comparator groups: Graves' disease with TED, Graves' disease without TED, and healthy controls. Restricting analysis to euthyroid or near-euthyroid participants, or statistically adjusting carefully for free T3 and free T4, would reduce confounding by thyrotoxicosis. Within TED, FGF21 should then be analyzed against CAS, EUGOGO severity, proptosis, diplopia, extraocular muscle enlargement, orbital fat volume, TSHR antibody levels, disease duration, and treatment exposure. Longitudinal measurements before and after disease activation would be more informative than a single cross-sectional value.

The distinction between activity and severity is critical. A molecule associated with systemic inflammatory stress may correlate with CAS but not structural severity; a marker related to fibroblast remodeling may correlate with proptosis or muscle volume despite low CAS. Treating all TED as a single biological phenotype could obscure clinically important relationships. Molecular biomarker reviews increasingly support multimarker rather than single-analyte approaches, because TED represents overlapping immune, fibrotic, vascular, and metabolic processes. [34]

Therapeutic Context: Lessons From Current TED Treatments

Current TED therapy demonstrates that modifying defined biological pathways can produce meaningful anatomical improvement. Intravenous glucocorticoids remain important for active moderate-to-severe disease in many treatment algorithms, often in combination with mycophenolate according to European recommendations. The MINGO trial showed that addition of mycophenolate to methylprednisolone improved some later response outcomes, although its prespecified early primary response endpoint was not significantly different. Such results illustrate the difficulty of treating a heterogeneous disease through broad immunosuppression alone. [35]

Targeting IL-6 signaling is another strategy. In a randomized trial involving corticosteroid-resistant moderate-to-severe Graves' orbitopathy, tocilizumab produced greater improvement in clinical activity than placebo. The study supports a meaningful role for cytokine-directed treatment in selected patients, while also demonstrating that inflammatory control does not necessarily address every anatomical component of TED. [36]

B-cell depletion with rituximab has produced less consistent trial results. One randomized study reported benefit in active moderate-to-severe Graves' orbitopathy, while another placebo-controlled trial did not demonstrate a significant therapeutic advantage. Differences in patient selection, disease duration, treatment regimens, and outcome definitions may partly explain the discordance. These trials serve as a caution for FGF21 research: strong biological rationale does not guarantee reproducible clinical efficacy, and treatment effects may depend strongly on disease stage. [37,38]

The development of teprotumumab marked a major shift toward receptor-directed therapy. In the phase 2 trial, inhibition of IGF-1R produced substantial improvement in combined inflammatory and proptosis outcomes compared with placebo, supporting the pathogenic importance of the TSHR–IGF-1R signaling network. [39]

The subsequent phase 3 OPTIC trial confirmed substantial reductions in proptosis and improvements in diplopia, activity, and quality of life with teprotumumab. Its efficacy demonstrates that modification of fibroblast-associated receptor signaling can reverse anatomical manifestations previously considered difficult to modify medically. At the same time, adverse effects such as hyperglycemia and hearing-related events illustrate why targeted biological efficacy must be evaluated together with systemic pathway function. [40]

More recent controlled data suggest that teprotumumab can improve proptosis even in patients with longstanding, low-activity TED. This observation challenges a strict binary distinction between inflammatory active disease and fixed inactive remodeling and suggests that receptor-dependent biology may persist after overt inflammation has diminished. For FGF21, this implies that studies should not be restricted exclusively to high-CAS disease; receptor expression and pathway activity across disease phases may be more informative. [41]

Could FGF21 Become a Therapeutic Target?

The therapeutic question must be separated into two opposing possibilities: increasing FGF21 signaling or inhibiting it. Existing metabolic literature largely supports pharmacological FGF21 agonism because FGF21 analogues can improve dyslipidemia, hepatic fat, insulin sensitivity, and selected fibrotic outcomes. Recombinant native FGF21 is unsuitable for routine therapy because of short half-life and biophysical limitations, leading to development of engineered analogues with longer duration of action. [42]

LY2405319 provided early proof that an engineered FGF21 analogue is biologically active in humans. In patients with obesity and type 2 diabetes, treatment improved lipid parameters and adiponectin and produced favorable changes in body weight, although glucose-lowering effects were less dramatic than expected from animal models. This experience is relevant because it highlights species differences and demonstrates that the most prominent human effects of FGF21 pharmacology may not match those predicted from experimental models. [43]



Long-acting FGF21 strategies have subsequently been developed for metabolic disease. PF-05231023, for example, produced metabolic effects in obese individuals with hypertriglyceridemia, while also drawing attention to the importance of systemic consequences such as effects on body weight, blood pressure, and bone-related biomarkers. Any future use of FGF21-directed therapy in TED would therefore require evaluation far beyond orbital outcomes. [44]

The current clinical frontier for FGF21 analogues is metabolic dysfunction-associated steatohepatitis rather than autoimmune orbital disease. Efruxifermin and related agents have demonstrated antifibrotic or disease-modifying signals in clinical trials of metabolic liver disease. These trials establish the feasibility of sustained pharmacological activation of the FGF21 pathway in humans, but they do not establish efficacy in autoimmune or orbital fibrosis. [45] A recent systematic review and meta-analysis of FGF21 analogues in steatohepatitis found improved histological and biochemical outcomes compared with placebo, alongside an increase in treatment-emergent adverse events. The important lesson for TED is not that these agents should currently be used, but that clinically developed FGF21 molecules already exist and provide potential translational tools if convincing orbital mechanisms are demonstrated. [46]

Conclusion

FGF21 provides a biologically compelling link between metabolic stress and the immune–fibroblast network of thyroid eye disease, but its role remains at an early stage of definition. Established TED biology centers on TSHR and IGF-1R signaling, immune-cell recruitment, orbital fibroblast activation, oxidative stress, adipogenesis, hyaluronan accumulation, and fibrosis. FGF21 intersects conceptually with several of these processes through its regulation of cellular stress responses, energy metabolism, adipose biology, and inflammatory signaling. The observation that FGF21 may increase before clinical TED develops creates a credible rationale for further investigation, while the strong dependence of FGF21 on thyroid hormone status and metabolic comorbidities demands careful control of confounding. Current evidence does not justify viewing FGF21 as either a pathogenic mediator or a therapeutic target in TED. The most productive next steps are prospective biomarker validation, receptor mapping in orbital tissue, and functional studies in patient-derived fibroblasts. These approaches can determine whether the emerging FGF21 axis represents a marker of systemic stress, an endogenous protective response, or a previously unrecognized contributor to orbital disease.

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