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Thyroid eye disease: From pathogenesis to targeted therapies

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Abstract:

Thyroid eye disease (TED) is the most common extrathyroidal manifestation of autoimmune Graves' hyperthyroidism. TED is a debilitating and potentially blinding disease with unclear pathogenesis. Autoreactive inflammatory reactions targeting orbital fibroblasts (OFs) lead to the expansion of orbital adipose tissues and extraocular muscle swelling within the fixed bony orbit. There are many recent advances in the understating of molecular pathogenesis of TED. The production of autoantibodies to cross-linked thyroid-stimulating hormone receptor and insulin-like growth factor-1 receptor (IGF-1R) activates OFs to produce significant cytokines and chemokines and hyaluronan production and to induce adipocyte differentiation. In moderately severe active TED patients, multicenter clinical trials showed that inhibition of IGF-1R with teprotumumab was unprecedentedly effective with minimal side effects. The emergence of novel biologics resulted in a paradigm shift in the treatment of TED. We here review the literature on advances of pathogenesis of TED and promising therapeutic targets and drugs.

Keywords:

Autoimmune, insulin growth factor-1 receptor, orbital fibroblast, pathogenesis, thyroid eye disease, thyroid-stimulating hormone receptor

Introduction

Thyroid eye disease (TED, synonyms: Graves' ophthalmopathy, Graves' orbitopathy, and thyroid-associated ophthalmopathy) is the most frequent extrathyroidal feature of Graves' disease (GD) but can also be associated with euthyroidism and Hashimoto's thyroiditis.[1,2] This is an orbital inflammatory autoimmune disorder, and the incidence of new cases is estimated at 20–50 per 100,000 people per year.[1] It is reported that 40%–50% of GD patients develop TED with heterogeneous clinical phenotypes. TED is a multifactorial autoimmune disease affected by genetics, environmental factors such as smoking and stress, and immune status. Most common symptoms of TED include eyelid retraction, exophthalmos, restrictive strabismus with diplopia, exposure-related dry eye, and dysthyroid optic neuropathy.

Thus far, high-dose glucocorticoid and orbital radiation have been a mainstay of treatment focusing on reducing orbital inflammation. These treatments mainly improve clinical activity score (CAS) and diplopia in patients with early, active inflammation. Therapy for chronic inactive TED is primarily surgical for exophthalmos, strabismus, and eyelid retraction. It is difficult to assess and manage TED patients, owing to its heterogeneity and also to predict which patients will progress into severe ophthalmopathy.

Various treatments targeting specific receptors, cytokines, and immune cells have been introduced with promising results. Recent remarkable advances in understanding pathogenesis of TED led to the emergence of a new biologic inhibitor of insulin-like growth factor-1 receptor (IGF-1R), teprotumumab, which gained approval by the US Food and Drug Administration (FDA) in early 2020.[3] This paper will review accumulated knowledge regarding the

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immunopathogenesis of TED by both clinicians and scientists and suggest promising specific drugs, as well as recently approved novel treatment for TED. A systematic search of PubMed was undertaken for studies related to pathogenesis of TED and therapeutic targets.

Orbital Fibroblast and Fibrocyte

Human orbital fibroblasts (OFs) are considered as the key target and effector cells in TED pathogenesis [Figure 1]. Studies have characterized why extrathyroidal manifestations of GD occur in the orbit, and it may be because the orbital tissues display a novel phenotype including peculiar sensitivity to cytokines and undergo characteristic remodeling. More robust production of interleukin (IL)-6, IL-8, and monocyte chemoattractant protein-1 in response to IL-1β[4,5] and a substantial induction of IL-16 and regulated on activation, normal T-cell expressed and secreted responding to GD-immunoglobulin G (IgG) was noticed in Graves' OFs but not in OFs from controls without GD.[6] Graves' OFs also showed enhanced proliferative capacity at baseline and in response to proinflammatory cytokines.[7] A subpopulation of OFs, based on the expression of the surface Thy-1 antigen, was observed with a different molecular response, which explains the heterogeneous clinical course of TED.[8] Perimysial fibroblasts express Thy-1 uniformly and do not undergo adipogenesis, whereas adipose tissue-derived fibroblasts express less Thy-1, undergo adipocyte differentiation, and express high level of peroxisome proliferator-activated receptor γ. Thy-1+ OFs produce higher levels of prostaglandin endoperoxide H synthase-2 and prostaglandin E2 than Thy-1-OFs, whereas Thy-1-OFs produced more IL-8 than Thy-1+ OFs.[8] Khoo *et al*. reported that Thy-1 mRNA and protein expression was higher in orbital tissue and OFs from TED donors compared to those from controls.[9]

Fibrocytes, bone marrow-derived fibroblast-like progenitor cells expressing CD34, CXC chemokine receptor 4, and collagen I phenotype, participate in the inflammatory process.[10,11] A significant increase of circulating CD34+ fibrocytes is observed in TED patients.[12] These fibrocytes express thyroid-stimulating hormone receptor (TSHR) and CD40 in substantially higher amounts than in OFs, producing high levels of cytokines and chemokines[12,13] and carrying plasticity to differentiate into adipocytes or myofibroblasts.[14] An assumption has been proposed that circulating CD34+ fibrocytes infiltrate orbital tissues, where they convert into CD34+ OFs mixing with CD34-OFs, all expressing both IGF-1R and TSHR.[11] Evidence shows CD34+/CD34-OFs exhibit distinct molecular functions associated with TED pathogenesis. Dramatic elevation of autoimmune regulator proteins necessary for the expression of thyroid proteins,[15] augmented TSH-induced IL-6 production by CXCL-12 (C-X-C Motif Chemokine Ligand 12),[16] and enhanced expression of tumor necrosis factor-α (TNF-α) by TSH[17] were all shown in CD34+ OFs but not in CD34-OFs. These findings suggest a modulatory role of CD34-OFs by releasing a determining factor that downregulates pathological TSHR signaling. It was recently reported that Slit2 has a distinct role in hyaluronan and cytokine productions in CD34+ fibrocytes and OFs but not in CD34-subsets.[18]

CD40-CD40 L Interaction

CD40 plays a pathogenic role in various autoimmune diseases. CD40 is active in regulating B-cell responses

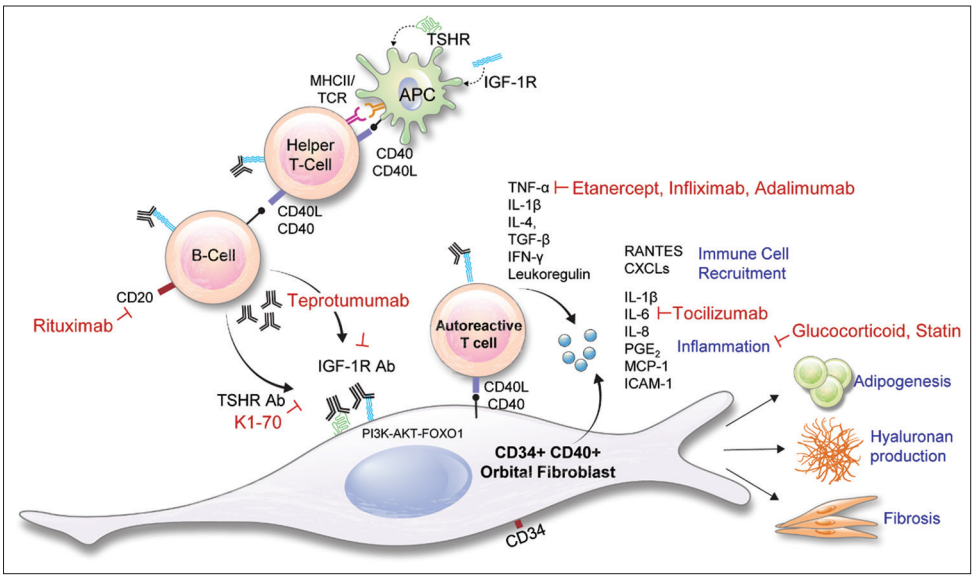

Figure 1: A schematic presentation of the complex cellular and humoral immune responses against autoantigens, thyroid-stimulating hormone receptor (TSH-R), and insulin-like growth factor-1 receptor (IGF-1R) in orbital fibroblasts and the targeted therapy

of the GD susceptibility genes identified.[19] CD40 is characterized as a molecule to active B lymphocytes through the engagement of CD40, by its ligand CD154, presented by activated CD4+ T helper (Th) cells.[20] Like B cells, CD40 is overexpressed in OFs in TED, especially in Thy-1+ OFs,[4] and CD40 L upregulates proinflammatory cytokine and chemokine production and hyaluronan synthesis.[4,21,22] High levels of CD40 are also displayed by fibrocytes,[23] and TSHR-CD40 L protein interaction and co-localization are discovered in fibrocytes.[13] Iscalimab (CFZ533), an Fc-silenced blocking anti-CD40 monoclonal antibody, was proven safe and well tolerated without depletion of leukocytes in a first-in-human randomized controlled study.[24] In an open-label multicenter phase 2 study in GD patients, iscalimab induced euthyroidism in 47%, with a decline of TSHR antibody in all patients with minimal side effects.[25] In a recent pilot study, haplotypes B and C of CD40 single nucleotide polymorphisms (SNPs) were associated with higher CD40 mRNA and clinical response to iscalimab, suggesting a pretreatment screening of SNP genotype.[26] CD40 targeting biologics have not yet been investigated in TED, which could represent a novel therapeutic approach in the disease where CD40-CD40 L interaction has a major role in the immunopathogenesis.

Thyroid-Stimulating Hormone Receptor and Insulin-Like Growth Factor-1 Receptor Crosstalk

TSHR is a glycoprotein hormone receptor with a large extracellular domain for binding to the ligand, a seven transmembrane domain, and an intracellular domain bound to G-protein subunits.[27] Several studies have exhibited that TSHR is an autoantigen shared by the orbit and the thyroid gland,[28,29] and significantly higher levels of TSHR transcript and immunoreactivity are demonstrable in Graves' orbital tissues and early passage of OFs.[30] Adipose tissues from active TED patients express higher levels of TSHR along with proinflammatory cytokines than tissues obtained from inactive patients.[31] Clinical observations demonstrate that persisting high TSHR antibody levels is associated not only with low remission rates of hyperthyroidism but also with a more severe course of ophthalmopathy, independent from smoking and age.[32] A novel TSHR luciferase reporter bioassay with Mc4-CHO cells revealed a strong positive correlation with the clinical activity and severity of TED.[33,34]

Several treatments targeting TSHR have been proposed. Isolation of human monoclonal autoantibody with blocking activity (K1-70) with high affinity resulted in a dose-dependent reduction of fT4 levels and suppressed the stimulating effect of M22 in rats.[35,36] A phase 1 open-label trial is currently obtaining safety and tolerability data in GD patients (ClinicalTrials.gov identifier: NCT02904330). Thyroid-stimulating antibody activity in serum decreased with the improvement of proptosis and inflammation of orbit following administration of K1-70 therapy in a case with follicular thyroid cancer, GD, and orbitopathy.[37] Some of the low-molecular-weight antagonists for TSHR (NIDDK/CEB-52,[38] NCGC00229600[39]) were identified to inhibit the activation of TSHR. NCGC00229600 inhibited TSH and M22 stimulated cAMP, Akt phosphorylation, and hyaluronan production in Graves' OFs.[40] Nanomolar concentrations of Org 274179-0 eliminated TSH-mediated TSHR activation with little effect on the potency of TSH by an allosteric-binding mechanism.[41] S37a, a highly selective TSHR inhibitor, was discovered to repress TSHR activation with no toxicity and high oral bioavailability in mice.[42] These TSHR antagonists possess the potential to treat TED; however, efficacy and safety have not yet been demonstrated through clinical studies.

A functional crosstalk between G-protein coupled TSHR and a tyrosine kinase receptor, IGF-1R, has been discovered, suggesting the signaling platform containing two receptors leads to synergistic stimulation of cellular responses.[43,44] Co-localization of two receptors in OFs and thyrocytes was demonstrated by immunofluorescence staining for IGF-1Rβ and TSHR.[44] IGF-1R is composed of the ligand binding, extracellular domain, IGF-1Rα, and membrane-spanning β subunit-containing tyrosine phosphorylation site for canonical signaling.[45] IGF-1R levels are considerably higher on Graves' OFs, and the IGF-1R+T cells are increased in both peripheral blood and orbital connective tissue infiltrates in patients with GD.[44,46] IGF-1R was also upregulated in B cells from GD patients, and IGF-1 synergistically adds to the IgG production by B cells from GD but not from control donors.[47] IGF-1R on OFs, when stimulated with GD-Igs or IGF-1, leads to the expression of T-cell chemoattractants[48] and enhanced synthesis of hyaluronan in Graves' OFs, which is absent in control OFs.[49] IGF-1 blocking antibody (IH7) attenuated the actions of both TSH and IGF-1 in fibrocytes with the suppression of proinflammatory cytokine production.[50] Two different IGF-1R blocking antibodies, IH7 and AF305, blocked binding of IGF-1 to IGF-1R in Graves' OFs but only 1H7 partially blocked hyaluronan production by M22, a stimulating TSHR antibody similar to the effect of linsitinib, an IGF-1R kinase inhibitor, indicating IGF-1R is activated through TSHR/IGF-1R crosstalk.[51] In a recent study, the crosstalk occurs proximal to the receptors and the distance between is within 40 nm of each other by Proximity Ligation Assay.[52] In this study, the presence of β-arrestin 1 protein was necessary for the TSHR/IGF-1R signaling complex, as knock-down of β-arrestin 1 decreased the receptor co-localization.

Teprotumumab, a fully human IgG1 monoclonal blocking antibody that binds to extracellular α-subunit domain of IGF-1R, was first developed for solid tumors and lymphomas but became the first approved drug for TED based on recent advances in the understanding the TSH/IGF1R crosstalk as an effective target. Teprotumumab has been shown to decrease TSHR and IGF-1R display and reduce TSH/M22 stimulated cytokines and Akt phosphorylation in Graves' OFs and fibrocytes.[50,53] In two randomized, multicenter, double-masked, placebo-controlled, phase 2 and 3 clinical trials, published in 2017 and 2020, teprotumumab demonstrated a significant improvement in proptosis beginning at 6 weeks of treatment and over the course of 24 weeks compared to controls, with similar effects to surgical decompression in active moderate-to-severe TED patients.[3,54] At week 24, 83% in teprotumumab group had a reduction of proptosis ≥2 mm compared to 10% in the placebo group, and all secondary outcomes including overall response, CAS, diplopia, and quality of life score were significantly better in the teprotumumab group with minimal side effects.[3] Fifty-five percent in Teprotumumab-treated group achieved proptosis reduction ≥3 mm compared to 8.9% of placebo-treated group.[55] Of the most commonly reported adverse events with teprotumumab, muscle spasm (18%), hearing loss (10%), and hyperglycemia (8%) had the greatest risk difference from placebo. Based on the evidence, FDA approved Teprotumumab in early 2020, as the first drug for TED treatment. Orbital imaging showed decreased extraocular muscle and orbital fat volume and reduced MRI signal intensity ratio of extraocular muscles in post-teprotumumab patients.[56] Some reports demonstrate that teprotumumab is effective in the resolution of optic neuropathy in the early course of teprotumumab[57,58] and significantly reduces the proptosis even in chronic TED patients with low CAS.[59,60]

T Cells Trafficking to Orbit and Their Cytokines

T cells have a significant role in the pathogenesis of TED. T cells activate B cells to stimulate the production of autoantibody and OFs through CD40/CD40 L binding. Sensitized T lymphocytes recognizing autologous orbital antigens are demonstrated in the peripheral blood and orbit from TED.[61] OFs secrete chemokines and adhesion molecules which recruit lymphocytes into orbital tissues,[61,62] and further interaction between OFs and T cells occurs. The clinical activity of TED was reported to correlate with T and B lymphocytes infiltration in orbital tissues[63] and with the TH1/Th2 cell ratio in peripheral blood.[64] Th17 cells are newly identified to contribute to the TED pathogenesis. Higher levels of IL-17A and IL-17A producing T cells were detected in the peripheral blood from TED patients,[65,66] and IL-17A enhances more robust production of cytokines in TED fibrocytes than in normal.[67] Furthermore, a positive correlation between the number of Th17 cells and CAS was found.[67]

Activated T cells, primarily CD4+T cells, produce cytokines, aggravating the inflammatory response, adipocyte differentiation, proliferation, and glycosaminoglycan accumulation in OFs.[68,69] A Th1 immune response predominates in the active early phase, leading to the production of interferon (IFN)-γ, TNF-α, IL-1β, and IL-2 that enhance fibroblast proliferation and glycosaminoglycan synthesis, whereas Th2 cytokines are more abundant later.[70] Orbital muscle tissue from TED patients was dominated by Th1 cytokines, while cytokine types varied in orbital adipose tissues, meaning clinical manifestation of TED may be dependent on types of cytokines.[71] Cytokines have been discussed as novel targets for TED. Several case and pilot studies have demonstrated that monoclonal antibody against TNF-α such as infliximab and etanercept is effective in steroid resistant, active TED patients reducing inflammation and visual function.[72,73] Adalimumab, another anti-TNF-α agents, was effective in anti-inflammatory and steroid-sparing effect in TED patients.[74] Tocilizumab, a humanized monoclonal antibody against IL-6, was effective in reducing proptosis and motility restriction with no relapse of TED in a prospective, nonrandomized study.[75] A follow-up double-masked, placebo-controlled trial demonstrated a reduction of at least 2 CAS in 93% of tocilizumab group compared to 59% receiving placebo.[76]

B Cells and Targeting CD20

B cells migrate to the orbit and recognize autoantigens expressed on OFs through B cell receptors after immune tolerance. Besides the production of antibodies, B cells have multiple other actions based on B-T cell interactions. B cells produce cytokines, mainly IL-4, IL-6, IL-10, IFN-γ, and TGF-β, and also function as antigen-presenting cells in the early phase of the autoimmune process.[77] In peripheral blood from patients with recent-onset autoimmune thyroid disease, thyroid antigen-reactive B cells are activated expressing CD86, leading to the production of autoantibodies.[78]

Rituximab (RTX) is a chimeric murine/human monoclonal antibody against CD20 antigen located on B cells. It is FDA approved in rheumatoid arthritis, granulomatosis with polyangiitis, chronic lymphocytic leukemia, and non-Hodgkin's lymphoma. It has also been used in different autoimmune disease as off-label drug.[70] RTX was proposed as a promising drug to treat TED based on reducing autoantibody. Stimulating TSHR Ab was significantly reduced when RTX was combined with antithyroid drugs in hyperthyroid

patients, compared to those administered antithyroid drugs alone.[79] Salvi *et al*. reported CAS decreased more after RTX than with IV methylprednisolone (7.5 g), and there was no reactivation in RTX group compared to five patients of IV methylprednisolone treated patients.[80] However, RTX was not effective in another randomized, placebo-controlled trial.[81] A *post hoc* analysis of the two trial results has found that the disease duration differed patients between groups and might have been responsible for inconsistent data.[82] A meta-analysis and systemic review of four randomized trials found a significant reduction of CAS but not proptosis reduction in the RTX group, compared to controls.[83] Recently, early use of low-dose RTX was reported to be effective to ameliorate inflammatory activity in active, steroid-resistant TED leading to a reduced systemic steroid administration.[84,85]

The neonatal fragment crystallizable (Fc) receptor (FcRN) has a role to prevent degradation and prolong the half-life of IgG during recycling process of IgG.[86,87] Multiple FcRN inhibitors have emerged as a potential treatment in antibody-mediated autoimmune disease and currently are in clinical trials for antibody-mediated autoimmune diseases such as myasthenia gravis and immune thrombocytopenia.[86] IMVT-1401/RVT-1401, a fully human monoclonal antibody against FcRN, developed as a subcutaneous injection, has been studied in a phase 2, multicenter, open-label trial (ASCEND GO-1) and double-blinded, placebo-controlled trial (ASCEND GO-2) for active, moderate-to-severe TED (ClinicalTrial.gov Identifier: NCT03922321, NCT03938545, retrospectively), however, unfortunately, ASCEND GO-2 was terminated due to unexpected elevation of serum cholesterol level.

Statins and Other Hypolipidemic Drugs with Pleotropic Effects

Statins are a class of hypolipidemic drug that is traditionally used to lower cholesterol by inhibiting hydroxymethylglutaryl-coenzyme A reductase. In the past recent years, extensive studies have shown that statins also have a pleiotropic anti-inflammatory, antifibrotic, and anti-immune modulatory effect.[88] Statins can shift proinflammatory Th17/Th1 cells toward regulatory T-cells resulting in decreased T-cell activation and inflammatory cytokine production.[89] In a longitudinal cohort study of 740 patients with newly diagnosed GD, statin use for ≥60 days was related to a 40% decreased hazard (adjusted hazard ratio [HR], 0.6) but not with nonstatin cholesterol-lowering agents.[2] A recent epidemiologic report showed statin users were less likely to develop TED with full adjusted HR 0.78 for men and 0.91 for women.[90] Laboratory evidence regarding therapeutic effect of statin in OFs was studied. Simvastatin inhibited TGF-β induced fibrosis markers in Graves' OFs through RhoA-mediated Erk and p38 signaling pathways.[91] Cysteine-rich protein 61, a product of an immediate early gene, is known to act as a proinflammatory factor in many inflammatory diseases and was found overexpressed in OFs and in serum from active TED patients,[92] and its induction by TNF-α was suppressed by simvastatin through the mediation of FoxO3a signaling.[93] Simvastatin also downregulated the early and late adipogenic gene and adipogenesis in OFs.[94] A hypothesis is proposed that statins reduce orbitopathy risk by modulation of both apoptosis and autophagy,[95] which are found to be involved in the pathogenesis of TED.[96] In a recent randomized controlled study, addition of oral atorvastatin to an IV glucocorticoid improved TED outcomes at 24 weeks of treatment in patients with moderate-to-severe, active eye disease and hypercholesterolemia (ClinicalTrial.govIdentifier: NCT03110848, protocol ID: STAGO).[97]

Metformin is a biguanide hypoglycemic drug for Type 2 diabetes and also has been shown to have anti-inflammatory action by blunting secretion of proinflammatory cytokines and inhibition of nuclear factor kappa β signaling.[98] In a meta-analysis of six randomized placebo-controlled studies, both total and low-density lipoprotein (LDL)-cholesterol levels decreased in metformin-treated patients.[99] In Graves' OFs, metformin and phenformin suppressed adipogenesis, proinflammatory cytokine production, and hyaluronan release, providing some evidence of the potential use of biguanide for the treatment of TED.[100]

Recently, proprotein convertase subtilisin-kexin type 9 (PCSK9) is identified to play a major role in hypercholesterolemia and atherosclerosis through promoting lysosomal degradation of LDL receptors, and the FDA approved two novel antibodies against PCSK, evolocumab and alirocumab, for lowering LDL-cholesterol.[101] PCSK9 inhibitors have also shown to have pleotropic effects of anti-inflammation beyond the LDL-lowering effect.[102] Orbital adipose tissue from TED patients had higher PCSK9 transcript levels than controls and knock-down of PCSK9 blocked proinflammatory cytokine production and adipogenesis in Graves' OFs, suggesting PCSK9 as a potential promising therapeutic target.[103]

Selenium

While the management of moderate-to-severe and active TED includes high dose intravenous glucocorticoids, orbital radiotherapy, surgery, and other biologics of specific immunologic target, an anti-oxidant trace mineral, selenium, is recommended in patients with mild TED. Selenium has been reported to show more improved quality of life, less eye involvement, and

more improvement of CAS, compared to placebo in a randomized, double-masked, placebo-controlled trial.[104] In several *in vitro* studies, selenium reduces H_2O_2-induced oxidative stress, proliferation, hyaluronan synthesis,[105] and proinflammatory cytokine production in OFs.[106,107] Controversy exists regarding the association of selenium levels with the severity or activity of TED.[108,109] The value of supplemental selenium on antithyroid drug medication in GD is still debatable in some randomized, controlled trials, especially in a selenium-sufficient cohort of GD.[110,111]

Conclusion

Over the last decades, substantial progress has been made in understanding the pathogenesis of TED, and several potential therapeutic targets have been discovered. Despite the lack of specific animal model for TED, *in vitro* studies in OFs and fibrocytes from patients with GD (recognizing the importance of IGF1-1R/THSR crosstalk) have been vital to the development of a new drug targeting IGF-1R with a remarkable treatment effect in moderate-to-severe, active TED patients, even replacing surgery in many cases. However, the high cost of the drug is a barrier to noninsured patients' treatment access and may lead to obstacles in approval in other countries. More results from multicenter, prospective longitudinal studies are needed to understand the long-term effects of teprotumumab compared to the combination of glucocorticoid and radiotherapy, which has still shows some efficacy with lower costs.

With advances in monoclonal antibody technology, there are a number of approaches targeting TSHR, B cells, T cells, and multiple cytokines, especially in the field of GD, which still need to be investigated in TED to provide a proof of efficacy. The efficacy of statins and other hypolipidemic drugs with pleotropic effects also needs verification in clinical trials. Many questions remain to be answered regarding aspects of TED including the unknown molecular pathogenesis associated with heterogeneous clinical phenotypes.

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Conflicts of interest

The authors declare that there are no conflicts of interest of this paper.

References

1. Smith TJ, Hegedüs L. Graves' disease. N Engl J Med 2016;375:1552-65.
2. Stein JD, Childers D, Gupta S, Talwar N, Nan B, Lee BJ, *et al.* Risk factors for developing thyroid-associated ophthalmopathy among individuals with Graves disease. JAMA Ophthalmol 2015;133:290-6.
3. Douglas RS, Kahaly GJ, Patel A, Sile S, Thompson EH, Perdok R, *et al.* Teprotumumab for the treatment of active thyroid eye disease. N Engl J Med 2020;382:341-52.
4. Hwang CJ, Afifiyan N, Sand D, Naik V, Said J, Pollock SJ, *et al.* Orbital fibroblasts from patients with thyroid-associated ophthalmopathy overexpress CD40: CD154 hyperinduces IL-6, IL-8, and MCP-1. Invest Ophthalmol Vis Sci 2009;50:2262-8.
5. Chen B, Tsui S, Smith TJ. IL-1 beta induces IL-6 expression in human orbital fibroblasts: Identification of an anatomic-site specific phenotypic attribute relevant to thyroid-associated ophthalmopathy. J Immunol 2005;175:1310-9.
6. Pritchard J, Horst N, Cruikshank W, Smith TJ. Igs from patients with Graves' disease induce the expression of T cell chemoattractants in their fibroblasts. J Immunol 2002;168:942-50.
7. Heufelder AE, Bahn RS. Modulation of Graves' orbital fibroblast proliferation by cytokines and glucocorticoid receptor agonists. Invest Ophthalmol Vis Sci 1994;35:120-7.
8. Koumas L, Smith TJ, Phipps RP. Fibroblast subsets in the human orbit: Thy-1+and Thy-1- subpopulations exhibit distinct phenotypes. Eur J Immunol 2002;32:477-85.
9. Khoo TK, Coenen MJ, Schiefer AR, Kumar S, Bahn RS. Evidence for enhanced Thy-1 (CD90) expression in orbital fibroblasts of patients with Graves' ophthalmopathy. Thyroid 2008;18:1291-6.
10. Smith TJ. TSH-receptor-expressing fibrocytes and thyroid-associated ophthalmopathy. Nat Rev Endocrinol 2015;11:171-81.
11. Smith TJ. Potential roles of CD34+ fibrocytes masquerading as orbital fibroblasts in thyroid-associated ophthalmopathy. J Clin Endocrinol Metab 2019;104:581-94.
12. Gillespie EF, Papageorgiou KI, Fernando R, Raychaudhuri N, Cockerham KP, Charara LK, *et al.* Increased expression of TSH receptor by fibrocytes in thyroid-associated ophthalmopathy leads to chemokine production. J Clin Endocrinol Metab 2012;97:E740-6.
13. Mester T, Raychaudhuri N, Gillespie EF, Chen H, Smith TJ, Douglas RS. CD40 expression in fibrocytes is induced by TSH: Potential synergistic immune activation. PLoS One 2016;11:e0162994.
14. Hong KM, Belperio JA, Keane MP, Burdick MD, Strieter RM. Differentiation of human circulating fibrocytes as mediated by transforming growth factor-beta and peroxisome proliferator-activated receptor gamma. J Biol Chem 2007;282:22910-20.
15. Fernando R, Lu Y, Atkins SJ, Mester T, Branham K, Smith TJ. Expression of thyrotropin receptor, thyroglobulin, sodium-iodide symporter, and thyroperoxidase by fibrocytes depends on AIRE. J Clin Endocrinol Metab 2014;99:E1236-44.
16. Fernando R, Atkins SJ, Smith TJ. Intersection of chemokine and TSH receptor pathways in human fibrocytes: Emergence of CXCL-12/CXCR4 cross talk potentially relevant to thyroid-associated ophthalmopathy. Endocrinology 2016;157:3779-87.
17. Lu Y, Atkins SJ, Fernando R, Trierweiler A, Mester T, Grisolia AB, *et al.* CD34- orbital fibroblasts from patients with thyroid-associated ophthalmopathy modulate TNF-α expression in CD34+ fibroblasts and fibrocytes. Invest Ophthalmol Vis Sci 2018;59:2615-22.
18. Fernando R, Smith TJ. Slit2 regulates hyaluronan & cytokine synthesis in fibrocytes: Potential relevance to thyroid-associated ophthalmopathy. J Clin Endocrinol Metab 2021;106:e20-33.

19. Li M, Sun H, Liu S, Yu J, Li Q, Liu P, *et al.* CD40 C/T-1 polymorphism plays different roles in Graves' disease and Hashimoto's thyroiditis: A meta-analysis. Endocr J 2012;59:1041-50.
20. Armitage RJ, Fanslow WC, Strockbine L, Sato TA, Clifford KN, Macduff BM, *et al.* Molecular and biological characterization of a murine ligand for CD40. Nature 1992;357:80-2.
21. Sempowski GD, Rozenblit J, Smith TJ, Phipps RP. Human orbital fibroblasts are activated through CD40 to induce proinflammatory cytokine production. Am J Physiol 1998;274:C707-14.
22. Cao HJ, Wang HS, Zhang Y, Lin HY, Phipps RP, Smith TJ. Activation of human orbital fibroblasts through CD40 engagement results in a dramatic induction of hyaluronan synthesis and prostaglandin endoperoxide H synthase-2 expression. Insights into potential pathogenic mechanisms of thyroid-associated ophthalmopathy. J Biol Chem 1998;273:29615-25.
23. Gillespie EF, Raychaudhuri N, Papageorgiou KI, Atkins SJ, Lu Y, Charara LK, *et al.* Interleukin-6 production in CD40-engaged fibrocytes in thyroid-associated ophthalmopathy: Involvement of Akt and NF-κB. Invest Ophthalmol Vis Sci 2012;53:7746-53.
24. Espié P, He Y, Koo P, Sickert D, Dupuy C, Chokoté E, *et al.* First-in-human clinical trial to assess pharmacokinetics, pharmacodynamics, safety, and tolerability of iscalimab, an anti-CD40 monoclonal antibody. Am J Transplant 2020;20:463-73.
25. Kahaly GJ, Stan MN, Frommer L, Gergely P, Colin L, Amer A, *et al*. A novel anti-CD40 monoclonal antibody, iscalimab, for control of graves hyperthyroidism – A proof-of-concept trial. J Clin Endocrinol Metab 2020;105:dgz013.
26. Faustino LC, Kahaly GJ, Frommer L, Concepcion E, Stefan-Lifshitz M, Tomer Y. Precision medicine in Graves' disease: CD40 gene variants predict clinical response to an anti-CD40 monoclonal antibody. Front Endocrinol (Lausanne) 2021;12:691781.
27. Rapoport B, Chazenbalk GD, Jaume JC, McLachlan SM. The thyrotropin (TSH) receptor: Interaction with TSH and autoantibodies. Endocr Rev 1998;19:673-716.
28. Bahn RS. TSH receptor expression in orbital tissue and its role in the pathogenesis of Graves' ophthalmopathy. J Endocrinol Invest 2004;27:216-20.
29. Heufelder AE, Dutton CM, Sarkar G, Donovan KA, Bahn RS. Detection of TSH receptor RNA in cultured fibroblasts from patients with Graves' ophthalmopathy and pretibial dermopathy. Thyroid 1993;3:297-300.
30. Bahn RS, Dutton CM, Natt N, Joba W, Spitzweg C, Heufelder AE. Thyrotropin receptor expression in Graves' orbital adipose/connective tissues: Potential autoantigen in Graves' ophthalmopathy. J Clin Endocrinol Metab 1998;83:998-1002.
31. Wakelkamp IM, Bakker O, Baldeschi L, Wiersinga WM, Prummel MF. TSH-R expression and cytokine profile in orbital tissue of active vs. inactive Graves' ophthalmopathy patients. Clin Endocrinol (Oxf) 2003;58:280-7.
32. Eckstein AK, Plicht M, Lax H, Neuhäuser M, Mann K, Lederbogen S, *et al.* Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease. J Clin Endocrinol Metab 2006;91:3464-70.
33. Lytton SD, Ponto KA, Kanitz M, Matheis N, Kohn LD, Kahaly GJ. A novel thyroid stimulating immunoglobulin bioassay is a functional indicator of activity and severity of Graves' orbitopathy. J Clin Endocrinol Metab 2010;95:2123-31.
34. Jang SY, Shin DY, Lee EJ, Lee SY, Yoon JS. Relevance of TSH-receptor antibody levels in predicting disease course in Graves' orbitopathy: Comparison of the third-generation TBII assay and Mc4-TSI bioassay. Eye (Lond) 2013;27:964-71.
35. Evans M, Sanders J, Tagami T, Sanders P, Young S, Roberts E, *et al.* Monoclonal autoantibodies to the TSH receptor, one with stimulating activity and one with blocking activity, obtained from the same blood sample. Clin Endocrinol (Oxf) 2010;73:404-12.
36. Furmaniak J, Sanders J, Rees Smith B. Blocking type TSH receptor antibodies. Auto Immun Highlights 2013;4:11-26.
37. Ryder M, Wentworth M, Algeciras-Schimnich A, Morris JC, Garrity J, Sanders J, *et al.* Blocking the thyrotropin receptor with K1-70 in a patient with follicular thyroid cancer, Graves' disease, and Graves' ophthalmopathy. Thyroid 2021;31:1597-602.
38. Neumann S, Kleinau G, Costanzi S, Moore S, Jiang JK, Raaka BM, *et al*. A low-molecular-weight antagonist for the human thyrotropin receptor with therapeutic potential for hyperthyroidism. Endocrinology 2008;149:5945-50.
39. Neumann S, Eliseeva E, McCoy JG, Napolitano G, Giuliani C, Monaco F, *et al*. A new small-molecule antagonist inhibits Graves' disease antibody activation of the TSH receptor. J Clin Endocrinol Metab 2011;96:548-54.
40. Turcu AF, Kumar S, Neumann S, Coenen M, Iyer S, Chiriboga P, *et al*. A small molecule antagonist inhibits thyrotropin receptor antibody-induced orbital fibroblast functions involved in the pathogenesis of Graves ophthalmopathy. J Clin Endocrinol Metab 2013;98:2153-9.
41. van Koppen CJ, de Gooyer ME, Karstens WJ, Plate R, Conti PG, van Achterberg TA, *et al.* Mechanism of action of a nanomolar potent, allosteric antagonist of the thyroid-stimulating hormone receptor. Br J Pharmacol 2012;165:2314-24.
42. Marcinkowski P, Hoyer I, Specker E, Furkert J, Rutz C, Neuenschwander M, *et al*. A new highly thyrotropin receptor-selective small-molecule antagonist with potential for the treatment of Graves' orbitopathy. Thyroid 2019;29:111-23.
43. Krieger CC, Neumann S, Gershengorn MC. TSH/IGF1 receptor crosstalk: Mechanism and clinical implications. Pharmacol Ther 2020;209:107502.
44. Tsui S, Naik V, Hoa N, Hwang CJ, Afifiyan NF, Sinha Hikim A, *et al.* Evidence for an association between thyroid-stimulating hormone and insulin-like growth factor 1 receptors: A tale of two antigens implicated in Graves' disease. J Immunol 2008;181:4397-405.
45. Adams TE, Epa VC, Garrett TP, Ward CW. Structure and function of the type 1 insulin-like growth factor receptor. Cell Mol Life Sci 2000;57:1050-93.
46. Douglas RS, Gianoukakis AG, Kamat S, Smith TJ. Aberrant expression of the insulin-like growth factor-1 receptor by T cells from patients with Graves' disease may carry functional consequences for disease pathogenesis. J Immunol 2007;178:3281-7.
47. Douglas RS, Naik V, Hwang CJ, Afifiyan NF, Gianoukakis AG, Sand D, *et al*. B cells from patients with Graves' disease aberrantly express the IGF-1 receptor: Implications for disease pathogenesis. J Immunol 2008;181:5768-74.
48. Pritchard J, Han R, Horst N, Cruikshank WW, Smith TJ. Immunoglobulin activation of T cell chemoattractant expression in fibroblasts from patients with Graves' disease is mediated through the insulin-like growth factor I receptor pathway. J Immunol 2003;170:6348-54.
49. Smith TJ, Hoa N. Immunoglobulins from patients with Graves' disease induce hyaluronan synthesis in their orbital fibroblasts through the self-antigen, insulin-like growth factor-I receptor. J Clin Endocrinol Metab 2004;89:5076-80.
50. Chen H, Mester T, Raychaudhuri N, Kauh CY, Gupta S, Smith TJ, *et al.* Teprotumumab, an IGF-1R blocking monoclonal antibody inhibits TSH and IGF-1 action in fibrocytes. J Clin Endocrinol Metab 2014;99:E1635-40.
51. Krieger CC, Place RF, Bevilacqua C, Marcus-Samuels B, Abel BS, Skarulis MC, *et al.* TSH/IGF-1 receptor cross talk in Graves' ophthalmopathy pathog enesis. J Clin Endocrinol Metab 2016;101:2340-7.
52. Krieger CC, Boutin A, Jang D, Morgan SJ, Banga JP, Kahaly GJ, *et al.* Arrestin-β-1 physically scaffolds TSH and IGF1 receptors to enable crosstalk. Endocrinology 2019;160:1468-79.

53. Chen H, Shan SJ, Mester T, Wei YH, Douglas RS. TSH-mediated TNFα production in human fibrocytes is inhibited by teprotumumab, an IGF-1R antagonist. PLoS One 2015;10:e0130322.
54. Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, *et al.* Teprotumumab for thyroid-associated ophthalmopathy. N Engl J Med 2017;376:1748-61.
55. Douglas RS. Teprotumumab, an insulin-like growth factor-1 receptor antagonist antibody, in the treatment of active thyroid eye disease: A focus on proptosis. Eye (Lond) 2019;33:183-90.
56. Jain AP, Gellada N, Ugradar S, Kumar A, Kahaly G, Douglas R. Teprotumumab reduces extraocular muscle and orbital fat volume in thyroid eye disease. Br J Ophthalmol 2020 Nov 10;bjophthalmol-2020-317806. doi: 10.1136/bjophthalmol-2020-317806.
57. Slentz DH, Smith TJ, Kim DS, Joseph SS. Teprotumumab for optic neuropathy in thyroid eye disease. JAMA Ophthalmol 2021;139:244-7.
58. Chiou CA, Reshef ER, Freitag SK. Teprotumumab for the treatment of mild compressive optic neuropathy in thyroid eye disease: A report of two cases. Am J Ophthalmol Case Rep 2021;22:101075.
59. Ugradar S, Shi L, Wang Y, Mester T, Yang H, Douglas RS. Teprotumumab for non-inflammatory thyroid eye disease (TED): Evidence for increased IGF-1R expression. Eye (Lond) 2021;35:2607-12.
60. Ozzello DJ, Dallalzadeh LO, Liu CY. Teprotumumab for chronic thyroid eye disease. Orbit 2021 Jun 1:1-8. doi: 10.1080/01676830.2021.1933081.
61. Otto EA, Ochs K, Hansen C, Wall JR, Kahaly GJ. Orbital tissue-derived T lymphocytes from patients with Graves' ophthalmopathy recognize autologous orbital antigens. J Clin Endocrinol Metab 1996;81:3045-50.
62. Grubeck-Loebenstein B, Trieb K, Sztankay A, Holter W, Anderl H, Wick G. Retrobulbar T cells from patients with Graves' ophthalmopathy are CD8+ and specifically recognize autologous fibroblasts. J Clin Invest 1994;93:2738-43.
63. Rotondo Dottore G, Torregrossa L, Caturegli P, Ionni I, Sframeli A, Sabini E, *et al.* Association of T and B cells infiltrating orbital tissues with clinical features of Graves orbitopathy. JAMA Ophthalmol 2018;136:613-9.
64. Xia N, Zhou S, Liang Y, Xiao C, Shen H, Pan H, *et al.* CD4+T cells and the Th1/Th2 imbalance are implicated in the pathogenesis of Graves' ophthalmopathy. Int J Mol Med 2006;17:911-6.
65. Kim SE, Yoon JS, Kim KH, Lee SY. Increased serum interleukin-17 in Graves' ophthalmopathy. Graefes Arch Clin Exp Ophthalmol 2012;250:1521-6.
66. Shen J, Li Z, Li W, Ge Y, Xie M, Lv M, *et al.* Th1, Th2, and Th17 cytokine involvement in thyroid associated ophthalmopathy. Dis Markers 2015;2015:609593.
67. Fang S, Huang Y, Liu X, Zhong S, Wang N, Zhao B, *et al.* Interaction between CCR6+Th17 cells and CD34+fibrocytes promotes inflammation: Implications in Graves' orbitopathy in Chinese population. Invest Ophthalmol Vis Sci 2018;59:2604-14.
68. Huang Y, Fang S, Li D, Zhou H, Li B, Fan X. The involvement of T cell pathogenesis in thyroid-associated ophthalmopathy. Eye (Lond) 2019;33:176-82.
69. Gianoukakis AG, Khadavi N, Smith TJ. Cytokines, Graves' disease, and thyroid-associated ophthalmopathy. Thyroid 2008;18:953-8.
70. Fallahi P, Ferrari SM, Elia G, Ragusa F, Paparo SR, Patrizio A, *et al*. Cytokines as targets of novel therapies for Graves' ophthalmopathy. Front Endocrinol (Lausanne) 2021;12:654473.
71. Hiromatsu Y, Yang D, Bednarczuk T, Miyake I, Nonaka K, Inoue Y. Cytokine profiles in eye muscle tissue and orbital fat tissue from patients with thyroid-associated ophthalmopathy. J Clin Endocrinol Metab 2000;85:1194-9.
72. Paridaens D, van den Bosch WA, van der Loos TL, Krenning EP, van Hagen PM. The effect of etanercept on Graves' ophthalmopathy: A pilot study. Eye (Lond) 2005;19:1286-9.
73. Durrani OM, Reuser TQ, Murray PI. Infliximab: A novel treatment for sight-threatening thyroid associated ophthalmopathy. Orbit 2005;24:117-9.
74. Ayabe R, Rootman DB, Hwang CJ, Ben-Artzi A, Goldberg R. Adalimumab as steroid-sparing treatment of inflammatory-stage thyroid eye disease. Ophthalmic Plast Reconstr Surg 2014;30:415-9.
75. Pérez-Moreiras JV, Alvarez-López A, Gómez EC. Treatment of active corticosteroid-resistant Graves' orbitopathy. Ophthalmic Plast Reconstr Surg 2014;30:162-7.
76. Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, Perez-Pampin E, Romo Lopez A, Rodríguez Alvarez FM, *et al.* Efficacy of tocilizumab in patients with moderate-to-severe corticosteroid-resistant graves orbitopathy: A randomized clinical trial. Am J Ophthalmol 2018;195:181-90.
77. Yanaba K, Bouaziz JD, Matsushita T, Magro CM, St. Clair EW, Tedder TF. B-lymphocyte contributions to human autoimmune disease. Immunol Rev 2008;223:284-99.
78. Smith MJ, Rihanek M, Coleman BM, Gottlieb PA, Sarapura VD, Cambier JC. Activation of thyroid antigen-reactive B cells in recent onset autoimmune thyroid disease patients. J Autoimmun 2018;89:82-9.
79. El Fassi D, Banga JP, Gilbert JA, Padoa C, Hegedüs L, Nielsen CH. Treatment of Graves' disease with rituximab specifically reduces the production of thyroid stimulating autoantibodies. Clin Immunol 2009;130:252-8.
80. Salvi M, Vannucchi G, Currò N, Campi I, Covelli D, Dazzi D, *et al.* Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: A randomized controlled study. J Clin Endocrinol Metab 2015;100:422-31.
81. Stan MN, Garrity JA, Carranza Leon BG, Prabin T, Bradley EA, Bahn RS. Randomized controlled trial of rituximab in patients with Graves' orbitopathy. J Clin Endocrinol Metab 2015;100:432-41.
82. Stan MN, Salvi M. Management of endocrine disease: Rituximab therapy for Graves' orbitopathy – Lessons from randomized control trials. Eur J Endocrinol 2017;176:R101-9.
83. Shen WC, Lee CH, Loh EW, Hsieh AT, Chen L, Tam KW. Efficacy and safety of rituximab for the treatment of Graves' orbitopathy: A meta-analysis of randomized controlled trials. Pharmacotherapy 2018;38:503-10.
84. Du Pasquier-Fediaevsky L, Andrei S, Berche M, Leenhardt L, Héron E, Rivière S. Low-dose rituximab for active moderate to severe Graves' orbitopathy resistant to conventional treatment. Ocul Immunol Inflamm 2019;27:844-50.
85. Insull EA, Sipkova Z, David J, Turner HE, Norris JH. Early low-dose rituximab for active thyroid eye disease: An effective and well-tolerated treatment. Clin Endocrinol (Oxf) 2019;91:179-86.
86. Peter HH, Ochs HD, Cunningham-Rundles C, Vinh DC, Kiessling P, Greve B, *et al.* Targeting FcRn for immunomodulation: Benefits, risks, and practical considerations. J Allergy Clin Immunol 2020;146:479-91.e5.
87. Patel DD, Bussel JB. Neonatal Fc receptor in human immunity: Function and role in therapeutic intervention. J Allergy Clin Immunol 2020;146:467-78.
88. Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: From protein prenylation to immunomodulation. Nat Rev Immunol 2006;6:358-70.
89. Koch CA, Krabbe S, Hehmke B. Statins, metformin, proprotein-convertase-subtilisin-kexin type-9 (PCSK9) inhibitors and sex hormones: Immunomodulatory properties? Rev Endocr Metab Disord 2018;19:363-95.
90. Nilsson A, Tsoumani K, Planck T. Statins decrease the risk of orbitopathy in newly diagnosed patients with Graves disease. J Clin Endocrinol Metab 2021;106:1325-32.
91. Wei YH, Liao SL, Wang SH, Wang CC, Yang CH. Simvastatin and ROCK inhibitor Y-27632 inhibit myofibroblast differentiation of Graves' ophthalmopathy-derived orbital fibroblasts via

RhoA-mediated ERK and p38 signaling pathways. Front Endocrinol (Lausanne) 2020;11:607968.
92. Woo YJ, Seo Y, Kim JJ, Kim JW, Park Y, Yoon JS. Serum CYR61 is associated with disease activity in Graves' orbitopathy. Ocul Immunol Inflamm 2018;26:1094-100.
93. Wei YH, Liao SL, Wang CC, Wang SH, Tang WC, Yang CH. Simvastatin inhibits CYR61 expression in orbital fibroblasts in Graves' ophthalmopathy through the regulation of FoxO3a signaling. Mediators Inflamm 2021;2021:8888913.
94. Shahida B, Johnson PS, Jain R, Brorson H, Åsman P, Lantz M, *et al.* Simvastatin downregulates adipogenesis in 3T3-L1 preadipocytes and orbital fibroblasts from Graves' ophthalmopathy patients. Endocr Connect 2019;8:1230-9.
95. Bifulco M, Ciaglia E. Statin reduces orbitopathy risk in patients with Graves' disease by modulating apoptosis and autophagy activities. Endocrine 2016;53:649-50.
96. Yoon JS, Lee HJ, Chae MK, Lee EJ. Autophagy is involved in the initiation and progression of Graves' orbitopathy. Thyroid 2015;25:445-54.
97. Lanzolla G, Sabini E, Leo M, Menconi F, Rocchi R, Sframeli A, *et al.* Statins for Graves' Orbitopathy (STAGO): A phase 2, open-label, adaptive, single centre, randomised clinical trial. Lancet Diabetes Endocrinol 2021;9:733-42.
98. Cameron AR, Morrison VL, Levin D, Mohan M, Forteath C, Beall C, *et al.* Anti-inflammatory effects of metformin irrespective of diabetes status. Circ Res 2016;119:652-65.
99. Solymár M, Ivic I, Pótó L, Hegyi P, Garami A, Hartmann P, *et al.* Metformin induces significant reduction of body weight, total cholesterol and LDL levels in the elderly – A meta-analysis. PLoS One 2018;13:e0207947.
100. Han YE, Hwang S, Kim JH, Byun JW, Yoon JS, Lee EJ. Biguanides metformin and phenformin generate therapeutic effects via AMP-activated protein kinase/extracellular-regulated kinase pathways in an *in vitro* model of Graves' orbitopathy. Thyroid 2018;28:528-36.
101. Chaudhary R, Garg J, Shah N, Sumner A. PCSK9 inhibitors: A new era of lipid lowering therapy. World J Cardiol 2017;9:76-91.
102. Momtazi-Borojeni AA, Sabouri-Rad S, Gotto AM, Pirro M, Banach M, Awan Z, *et al.* PCSK9 and inflammation: A review of experimental and clinical evidence. Eur Heart J Cardiovasc Pharmacother 2019;5:237-45.
103. Lee GE, Kim J, Lee JS, Ko J, Lee EJ, Yoon JS. Role of proprotein convertase subtilisin/kexin type 9 in the pathogenesis of Graves' orbitopathy in orbital fibroblasts. Front Endocrinol (Lausanne) 2020;11:607144.
104. Marcocci C, Kahaly GJ, Krassas GE, Bartalena L, Prummel M, Stahl M, *et al.* Selenium and the course of mild Graves' orbitopathy. N Engl J Med 2011;364:1920-31.
105. Rotondo Dottore G, Leo M, Casini G, Latrofa F, Cestari L, Sellari-Franceschini S, *et al.* Antioxidant actions of selenium in orbital fibroblasts: A basis for the effects of selenium in Graves' orbitopathy. Thyroid 2017;27:271-8.
106. Tsai CC, Wu SB, Kao SC, Kau HC, Lee FL, Wei YH. The protective effect of antioxidants on orbital fibroblasts from patients with Graves' ophthalmopathy in response to oxidative stress. Mol Vis 2013;19:927-34.
107. Kim BY, Jang SY, Choi DH, Jung CH, Mok JO, Kim CH. Anti-inflammatory and antioxidant effects of selenium on orbital fibroblasts of patients with Graves ophthalmopathy. Ophthalmic Plast Reconstr Surg 2021;37:476-81.
108. Khong JJ, Goldstein RF, Sanders KM, Schneider H, Pope J, Burdon KP, *et al.* Serum selenium status in Graves' disease with and without orbitopathy: A case-control study. Clin Endocrinol (Oxf) 2014;80:905-10.
109. Dehina N, Hofmann PJ, Behrends T, Eckstein A, Schomburg L. Lack of association between selenium status and disease severity and activity in patients with Graves' ophthalmopathy. Eur Thyroid J 2016;5:57-64.
110. Kahaly GJ, Riedl M, König J, Diana T, Schomburg L. Double-blind, placebo-controlled, randomized trial of selenium in graves hyperthyroidism. J Clin Endocrinol Metab 2017;102:4333-41.
111. Leo M, Bartalena L, Rotondo Dottore G, Piantanida E, Premoli P, Ionni I, *et al.* Effects of selenium on short-term control of hyperthyroidism due to Graves' disease treated with methimazole: Results of a randomized clinical trial. J Endocrinol Invest 2017;40:281-7.