Thyroid-Associated Orbitopathy

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ABSTRACT

Thyroid-associated orbitopathy (TAO) is usually diagnosed clinically. Early presentation of TAO such as ocular irritation, lid puffiness, and mild retraction may be overlooked and misdiagnosed. Careful clinical evaluation, laboratory investigations, and orbital imaging studies are needed for diagnosing early TAO. Knowing the pathogenesis will open the door for obtaining directed and effective treatment for the inflammatory process in TAO. Most patients with mild to moderate active TAO are treated with observation alone as the available treatment modalities effective in controlling the disease have many potential side effects. Severe active TAO, compressive optic neuropathy, and severe exposure keratopathy are the main indications for treatment with immunosuppressant agents, orbital radiotherapy, or orbital decompression. Surgery remains the final rehabilitation in TAO, which should be done during cicatricial (inactive) TAO when reliable and stable results can be obtained.

KEYWORDS: Thyroid-associated orbitopathy, Graves' ophthalmopathy, proptosis, lid retraction

Thyroid-associated orbitopathy (TAO) is a common orbital disease. No exact definition exists for this condition as the etiology behind it is not well understood. TAO is described as a chronic inflammation of orbital and periorbital tissue of most likely an autoimmune origin. It occurs most frequently in women with female-to-male ratio of 5:1 and it occurs most commonly between the ages of 30 and 50 years.¹ Statistically, severe exophthalmos and compressive optic neuropathy are slightly more common in older men, and the clinical manifestations of TAO are relatively less severe in pediatric patients with infrequent need for surgical treatment.² The incidence of TAO was 16.0/100,000 population per year for women and 2.9/100,000 population per year for men in a study done in Minnesota.³ The incidence and severity of TAO appear to be higher among smokers compared with nonsmokers.^{4,5}

Ophthalmopathy was part of the initial description of Graves' disease in 1835.⁶ Approximately 40% of patients with Graves' disease have or will develop thyroid ophthalmopathy, but subclinical orbital alterations can be seen on ultrasonography or computed tomography (CT) in up to 79%.⁷ Other disorders of the thyroid gland can have similar ocular manifestations to Graves' ophthalmopathy. These include Hashimoto's thyroiditis, thyroid carcinoma, and primary hyperthyroidism.⁸

Patients with TAO are clinically hyperthyroid in 77%, hypothyroid in 3%, and euthyroid in 20%.⁹ Most patients with euthyroid have some detectable laboratory evidence of subclinical thyroid abnormalities. TAO occurred before the onset of Graves' disease in 23%, concurrent with Graves' disease in 39%, and after Graves' disease in 37%.⁹

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TAO is known to progress through an active inflammatory phase, followed by a cicatricial phase. The active inflammatory phase usually spontaneously remits after ~18 months (range from 3 to 36 months), and many serious ophthalmic complications can arise during this time and persist thereafter, such as compressive optic neuropathy and exposure keratopathy.¹⁰

CLINICAL MANIFESTATION

Presentation of TAO ranges from a mild to severe with vision-threatening potential. Lid retraction is the most common finding in TAO.⁸ In early stages of the disease, lid retraction may be secondary to a sympathomimetic response, and in the later stages, it may be associated with fibrosis of lid tissues. Many patients experience improvement of lid retraction as thyrotoxicosis is treated. Lid lag (lid retraction on down gaze) and lagophthalmos (inability to close the eye) are other eyelid features of TAO.

TAO is the most common cause of bilateral or unilateral proptosis.¹¹ Typically, the proptosis in TAO is bilateral, but it may be asymmetric. Of those patients with clinical unilateral TAO, CT will detect subclinical enlargement of the extraocular muscles on the contralateral side in 50%.¹² TAO results in an axial proptosis, and displacement of the globe in any other direction is suggestive of another diagnosis. Forward displacement of the globe occurs as the muscle and connective tissue volume behind the eye increases within the confines of the bony orbit. Rarely, subluxation of the globe anteriorly may occur when the pressure within the retrobulbar tissues exceeds the counteracting forces by orbital septum and the posterior attachment of the extraocular muscles at the apex. Unlike lid retraction, proptosis measurement tends not to change with treatment of thyrotoxicosis.¹³

TAO should be considered in all cases of adult-onset strabismus. The most common motility abnormality is limitation of elevation due to fibrosis of the inferior rectus muscle, which results in diplopia on up gaze. The second most common muscle to be involved clinically is the medial rectus, followed by the superior rectus, and finally the lateral rectus. Diplopia is caused by fibrosis of

the ocular muscles that prevents full extension when their antagonist muscles contract. Rarely, patients may present with a clinical picture mimicking superior oblique paresis.

Conjunctival chemosis, injection of the conjunctival and episcleral vessels overlying the insertions of the extraocular muscles, and corneal involvement due to exposure keratitis are part of anterior segment presentation of TAO. Exposure keratitis may result from proptosis, upper eyelid retraction, lower eyelid retraction, lagophthalmos, or a combination of these. Superior limbic keratoconjunctivitis may be associated with TAO and appears to be a prognostic marker for severe disease.¹⁴ Fundus examination may reveal choroidal folds, which develop secondary to the pressure of swollen orbital tissue on the globe.

Visual loss due to compressive optic neuropathy occurs in less than 5% of patients with TAO.¹⁵ Optic neuropathy can occur without significant proptosis in patients whose orbital septum efficiently limits anterior globe displacement despite increased retrobulbar pressure affected individuals or optic nerve changes at ophthalmoscopy. Patients with TAO may develop optic neuropathy with visual acuities in the range of 20/20 to 20/25, and an afferent pupillary defect is one of the critical signs in detecting the disease in these patients. Exposure keratitis and induced refractive error by the pressure of congested orbital tissue on the globe are other causes of decrease of vision in TAO.

Patients with TAO may initially present with nonspecific complaints such as eyelid fullness, ocular irritation, or epiphora, and the diagnosis of TAO may not be suspected (Fig. 1A, B). In these situations, a high index of suspicion is required to search for clinical evidence of thyroid disease, followed by appropriate laboratory investigations.

When TAO is suspected, clinical evaluation should be done to assess the systemic thyroid status. This includes weight loss, increased appetite, heat intolerance, difficulty sleeping, weakness of the limb girdle muscles, and mood changes. Tachycardia, fine tremor, thyroid gland enlargement, and less commonly pretibial myxedema and thyroid acropathy

Figure 1 (A) A 45-year-old man presented with eyelid fullness and ocular irritation. There was no evidence of thyroid gland disease. (B) Six months later the patient developed marked eyelid retraction and proptosis as part of thyroid-associated orbitopathy.

(characterized by clubbing and subcutaneous fibrosis of the fingers) may be found during physical examination.

Recognition of active inflammatory phase of TAO during clinical evaluation is critical for treatment, as will be discussed later. Clinical features of active disease include conjunctival injection and chemosis, periorbital edema/fullness, variability in diplopia, progressive proptosis, and fluctuating vision.

PATHOLOGY AND PATHOPHYSIOLOGY

The inflammation of TAO predominantly involves the orbital soft tissues and extraocular muscles. This immune-mediated inflammation consists mostly of lymphocytes and plasma cells, with a scattering of mast cells.¹⁶ Eosinophils and germinal centers with follicles are typically not seen in thyroid orbitopathy.

The earliest change in extraocular muscles appears to be inflammation of the endomysial connective tissues, which stimulates fibroblasts to produce first hyaluronic acid and then collagen. In the acute stage, there is inflammation, edema, and deposition of glycosaminoglycans, which strongly bind water in both orbital muscle and connective tissue. Eventually, fibrosis and fatty infiltration occur with restriction of extraocular muscle motion. The muscle cells remain to be intact.¹⁷

The lacrimal gland shows a mild cellular infiltration and interstitial edema, without fibrosis or obliteration of acinar structures. Despite mild inflammation, the amount of tear production measured with Schirmer's test was found to be normal.¹⁸ The eyelid blinking is often incomplete and reduced in rate. Inflammation and fibrosis may affect the orbital fat surrounding the muscle, but primary involvement of the fat does not occur. The tendinous insertions onto the globe and the optic nerve meninges generally show no inflammation.

The increased orbital volume is due to inflammation in the connective tissue surrounding the extraocular muscles, with accumulation of glycosaminoglycans in the connective tissues of the extraocular muscles and the orbital fat compartments. This increase in orbital volume leads to elevation of retrobulbar space pressure with subsequent impaired venous drainage, chemosis, periorbital edema, and in some cases, optic nerve compression with visual loss.

Pretilial dermatopathy seen in Graves' disease showed similar histological findings to TAO with lymphocytic infiltration and increased amount of glycosaminoglycans deposition.¹⁹

The precise nature of autoimmune process responsible for development of TAO is still poorly understood. In thyroid disease, the primary thyroid target autoantigen driving the immunological process is thought to be thyroid-stimulating hormone receptor (TSHR).²⁰ Several other targets, such as thyroglobulin

and thyroid microsomal antigen, have been suggested to play a role in the immunological process.²¹ In the orbit, TSHR is expressed in lymphocytes, fibroblasts, and adipocytes. Interleukin-6, a cytokine elevated in the circulation of Graves' patients, stimulates TSHR expression in vitro in orbital preadipocyte fibroblasts.²⁰ The significance of the presence of TSHR in the orbit and its relation with TAO is still unclear.

Serum autoantibodies reactive with eye muscle protein 64 kd and protein G2s are found in patients with TAO.²² The role of the various eye muscle antibodies in the diagnosis and management of the TAO has not been defined yet.

INVESTIGATION

With the typical clinical features, the diagnosis of TAO is made clinically. Relevant investigations are needed in atypical presentation to make the diagnosis, evaluating the presence of dysthyroidism or optic nerve compression, and before doing orbital decompression to evaluate bony orbit and adjacent sinuses.

Laboratory investigation for thyroid function starts usually with obtaining the results of thyroid-stimulating hormone levels. If these levels are normal, then the patient is said to be euthyroid. Hyperthyroidism is detected by measuring increased serum free thyroxine (T4) and serum free triiodothyronine (T3) and low/absent thyroid-stimulating hormone. Euthyroid patients who have suspected TAO may need further testing with antithyroglobulin antibodies, TSHR antibodies, and antimicrosomal antibodies. Thyroid-stimulating immunoglobulin (TSI) is one of the TSHR antibodies. TSI level appears to correlate with TAO activity.²³

Visual field testing is an important part in evaluation in patients with TAO. Central scotoma or an inferior altitudinal defect is seen in cases of compressive optic neuropathy. Other visual field defects include an enlarged blind spot, paracentral scotoma, nerve fiber bundle defect, or generalized constriction.²⁴ Visual fields may provide the first clue of compressive optic neuropathy especially in patients with normal visual acuity.

Low cost, short time of investigation, and lack of radiation characterize orbital imaging with ultrasound. Ultrasonography can be useful to detect early thyroid disease in patients with equivocal laboratory tests by showing evidence of extraocular muscle involvement. Ultrasonography can visualize the tendinous insertions onto the globe and may provide a good assessment when differentiating enlarged extraocular muscles secondary to myositis from TAO. A clear differentiation regarding disease activity and precise imaging of the orbital apex cannot be achieved with ultrasonography.

Orbital CT has the advantage of short investigation time with precise imaging of the orbital apex, moderate costs, and reliable identification of minimal

enlargement of the recti muscles. CT is not necessary in most patients who present with typical clinical features and have laboratory evidence of thyroid gland disease. It is indicated when optic neuropathy is suspected, before orbital decompression, in patients with atypical proptosis or motility disturbances, or to detect early TAO in patients with equivocal results of laboratory tests. The most characteristic CT finding in thyroid orbitopathy is enlargement of the extraocular muscles with sparing the tendinous insertions onto the globe. Severe apical crowding seen in both coronal and axial planes is a strong sign for the risk of developing compressive optic neuropathy if not developed yet (Fig. 2A, B).

Magnetic resonance imaging is characterized by precise orbital tissue differentiation and lack of ionizing radiation. It is sensitive in demonstrating interstitial edema within the rectus muscles in active disease, as well as providing a good predictive value with respect to immunosuppressive therapy.²⁵ Unfortunately, using quantitative magnetic resonance imaging is an expensive method for monitoring the effect of the treatment. It may be of help to differentiate inflammatory disease from chronic fibrosis of the orbit, which dictates the treatment modality that can be offered to the patient.

DIFFERENTIAL DIAGNOSIS

Most patients with TAO present with typical signs and symptoms that are almost pathognomonic of TAO. Clinical presentations of early TAO with ocular irritation, lacrimation, and minimal eyelid retraction are often overlooked or misdiagnosed. Besides TAO being a common cause, many different diseases are known to present with lid retraction. This long list of causes can be classified as neurogenic, myogenic, mechanistic, and miscellaneous.²⁶

Proptosis, limitation ocular motility, and eyelid malposition are common presentation for many orbital diseases. These may result from an acute orbital inflammation or a chronic process. When TAO presents as an acute orbital inflammation with conjunctival injection,

proptosis, eyelid, and periorbital edema, it must be distinguished from myositis, orbital cellulitis, or scleritis. Orbital cellulitis is potentially vision threatening and possibly life threatening. It needs abrupt recognition and treatment. Patients with orbital cellulitis usually present with pain, fever, and fatigue. CT often show sinusitis and may show subperiosteal abscess.

Idiopathic orbital inflammatory disease (IOID) is a great mimicker of active TAO. IOID usually has a unilateral involvement. The presence of pain is the main differentiating feature.

Ptosis, lacrimal gland swelling and tenderness, and single muscle involvement, usually not inferior rectus, favor a diagnosis of IOID over TAO. In myositic IOID, CT and magnetic resonance imaging usually show adjacent fat irregularities and diffuse enlargement of the involved muscle along with extension of the inflammation to involve its tendon.^{27,28} Acute IOID has a more dramatic response to systemic corticosteroid compared with active TAO.²⁹ Diplopia and strabismus may be the initial presentation of TAO and may simulate the motility disturbances seen in myasthenia gravis and superior oblique palsy.³⁰ Orbital neoplasms are rarely bilateral, but lymphoma can present with bilateral signs. Vascular abnormalities such as carotid-cavernous fistula may present with conjunctival injection, proptosis, prominent vascular channels within the orbit, and usually an enlarged superior ophthalmic vein.³¹

TREATMENT

It is important to distinguish treatment of the thyroid gland abnormality from treatment of the orbital disorder. Although these two aspects may be related as an autoimmune process, perhaps based on similar antigens or proximity of genes, the clinical course of orbital involvement may seem to proceed independently of thyroid gland dysfunction. Thyroid gland treatment affects only one of the end organs of this disease process and does not alter the fundamental autoimmune process causing ophthalmopathy. Reversal or exacerbation of

Figure 2 (A) Axial and (B) coronal orbital CT show enlarged extraocular muscles and apical compression.

hyperthyroidism may have little effect on the progress of the ophthalmopathy.³² Developing or worsening of TAO was found to be higher after treatment of hyperthyroid patients with radioiodine (I-131) therapy compared with patients treated with thyroidectomy or thionamides.³³ The clinical impression of worsening ophthalmopathy after thyroid gland ablation by radioiodine or surgery may simply represent the natural course of the orbital disease regardless of thyroid treatment. Thyroid gland destruction by radioiodine may stimulate increased antigen-antibody responses that aggravate the autoimmune disease activity. Prednisone has been found to decrease the development or worsening of ophthalmopathy after I-131 therapy, especially in patients with risk factors such as smoking and having TAO before starting I-131 therapy.^{34,35} Treatment of the thyroid gland must be simultaneous but independent of treatment for ophthalmopathy. Achievement of euthyroid status under management by an endocrinologist is generally desirable before performing definitive eye care but is not absolutely essential.

During active phase, TAO can be treated with corticosteroids, immunosuppression, and local radiation therapies. The aim of treatment during active phase is to control the inflammation by interfering with lymphocyte infiltration, fibroblast activation, cytokine release, and glycosaminoglycan synthesis and accumulation. The acute stage is followed by a cicatricial stable stage with hypertrophy and fibrosis of extraocular muscles and orbital fat and subcutaneous eyelid changes. These later-stage changes are permanent and will not regress or progress spontaneously, and they don't respond to immunosuppressive treatment. Surgical treatment for TAO is done only during cicatricial stage with exception of compressive optic neuropathy, severe exposure keratopathy, and malignant exophthalmos not responding to nonsurgical treatment during the active stage.

Do all patients with TAO need treatment? Many patients with mild TAO may continue to have mild disease during the active stage with spontaneous remission.³⁶ Observation for early detection of progression or visual impairment may be all they need. Surgical repair may be needed to improve the sequel of the second stage in some patients.

Lubricating eye drops and ointment are useful for the treatment of exposure keratitis, providing relief from mild ocular irritation and foreign sensation. Elevation of the head of the bed at night may reduce edema. Prisms may be of help for treating bothersome diplopia from restricted ocular motility. Quitting smoking is very important to consider in management plan.

Medical Treatment of TAO

Corticosteroids are the mainstay of medical therapy for TAO. They may be used alone or in combination with

other drugs for immunosuppression, radiation, or surgery. Corticosteroids act by suppression of orbital inflammation and eventually decreasing the edema. Soft tissue changes may improve rapidly with corticosteroids, although high doses are initially required to obtain significant clinical effects.

Steroid therapy is useful for patients with acute inflammatory optic neuropathy, for patients with continued disease progression despite radiation or surgical therapy, and for patients undergoing orbital decompression to limit the inflammatory response to surgical trauma. Although optic neuropathy may improve with corticosteroid therapy, optic neuropathy is likely to reoccur with early tapering of the steroid.³⁷ Corticosteroids can be given by oral and intravenous routes, or as retrobulbar injections. Prednisone can be given, 60 to 100 mg orally daily for several days and then tapered over several weeks. Steroid administration once daily or on alternate days is not sufficiently effective in suppressing this disease process. High dose of intravenous steroid has been found to be effective for acute, severe proptosis and optic nerve involvement.^{38,39} The effect of corticosteroids is only temporary and is effective only while the drug is being given. The disease process rebounds promptly with cessation of therapy unless therapy is extended over many months or years with gradual tapering. A long course of therapy is difficult to administer because of side effects. Radiation or surgical treatment should be considered to provide long-term treatment.

Corticosteroid therapy has many contraindications and complications to be considered. Common side effect include gastrointestinal ulceration and hemorrhage, aggravation of diabetes and hypertension, generalized myopathy, osteoporosis, weight gain and Cushing features, sleeplessness, depression, infection, cataract, and glaucoma. Retrobulbar injection may be used to reduce the systemic side effects of corticosteroids.⁴⁰ The response with local injection is lower in comparison with systemic administration of corticosteroids and lacks the advantage of suppression of the systemic autoimmune process causing TAO. Local injection of corticosteroids may be helpful when systemic therapy is contraindicated and other therapies are not immediately effective.

Other immunosuppressive medications such as cyclosporine may be used for active TAO. Reports using cyclosporine have shown some favorable results.^{41,42} Because corticosteroids are more effective, monotherapy with cyclosporine may be indicated only when other therapies cannot be utilized. Cyclosporine may be useful in combination with corticosteroids for long-term maintenance therapy or to reduce disease relapse after steroid taper and cessation. Cyclosporine has several side effects such as nephrotoxicity and hypertension.

Figure 3 (A) Bilateral severe proptosis and eyelid retraction in a patient with thyroid-associated orbitopathy. (B) The patient underwent bilateral orbital bony decompression. Bilateral upper eyelid recessions were performed later. The left upper eyelid was positioned slightly lower to help manage continued corneal exposure despite normal exophthalmometry measurements. (C) Hard palate graft was used to manage the lower eyelids retraction.

Orbital Radiotherapy for TAO

The exact mechanism of radiation therapy in TAO is not well understood. It appears to suppress orbital radiosensitive lymphocyte and fibroblast activity.⁴³ It works on the active phase of TAO only. Effects of radiation are often less dramatic but appear to last for a longer period compared with steroids. Combination of orbital radiotherapy with corticosteroids has been reported to provide better results than either therapy alone.⁴⁴ Different protocols and varying doses have been used. A total dose of 20 Gy delivered in 10 fractions over 2 weeks is one of the popular methods for treating TAO. The use of higher doses does not appear to improve the effects of the therapy.⁴⁵ Radiation therapy has been found to be effective on soft tissue inflammation and improvement of ocular motility. Some studies questioned the effect of radiotherapy and attributed the effect noticed with radiation to natural history of spontaneous remission of TAO or placebo effect experienced by some patients after receiving high-technology therapy.^{46,47} Several authors still believe that radiotherapy is effective especially in severe TAO with optic neuropathy.⁴⁸ Side effects like cataract and radiation retinopathy are rare with the low dose that is usually used.⁴⁹

Surgical Treatment for TAO

The main aims of surgery in TAO are to manage compressive optic neuropathy, severe corneal exposure,

and diplopia and provide a good cosmesis. During active phase of TAO, eyelid malposition, extraocular involvement, and soft tissue swelling are variable. Surgery should be done during cicatricial (stable) phase with the exception of vision-threatening conditions such as compressive optic neuropathy and severe corneal exposure, which mandate urgent surgical intervention. If multiple surgeries are needed, orbital decompression should be done first, followed by muscle surgery, and finally eyelid adjustments. Orbital decompression may change the pattern of diplopia and muscle surgery has some effect on eye lid position.

The idea of bony orbital decompression is to provide more room for the orbital tissues. Several surgical techniques have been reported for orbital wall removal. The air-filled spaces of the ethmoidal and maxillary sinuses provide greatest volume prolapse, followed by temporal fossa space, and removing the orbital roof provides the least room. Removal of medial and lateral walls (so-called "balanced" decompression) can provide reposition of generally 5 to 6 mm posteriorly,^{50,51} and more achievement can be gained with removing the floor⁵² (Fig. 3A, B). Postoperative diplopia and hypoglobus is frequently seen postoperatively in one third of patients who have had a significant portion of orbital floor removal.⁵³ Different surgical approaches for orbit decompression procedures can be utilized including eyelid approaches through the skin or conjunctiva, the

transcaruncular approach to the medial wall, and transnasal endoscopic approach. The choice is a reflection of surgeon preference and which walls are to be removed. Our current approach is a lateral canthotomy and transcaruncular approach to perform the balanced decompression. Orbital wall decompression is rarely associated with serious complication such as retrobulbar hemorrhage, infection, cerebrospinal fluid leak, subarachnoid hemorrhage, and damage to the optic nerve at the orbital apex, causing loss of vision. Orbital fat removal helps in reduction of proptosis either with or without orbital wall decompression.⁵⁴

Muscle surgery should be done during cicatricial phase and after 6 months of stable deviation measurement for treating the diplopia. Muscle recession with adjustable suture is the preferred surgery. Operating on horizontal and vertical muscle can be done at the same time. Inferior rectus recession may induce lower lid retraction, and simultaneous detachment of the fascia of the capsulopalpebral head during the surgery helps to minimize this possibility.⁵⁵

Lid surgery during active phase of TAO leads to unpredictable results as the ongoing inflammatory process of the eye lids with subsequent fibrosis will change the picture of lid retraction over time. Steroids and radiation have minimal effects on lid retraction. Mild upper lid retraction (≤ 2 mm) can be treated by Müller's muscle excision and a small lateral tarsorrhaphy. Müllerectomy and modest levator recession are needed for more severe retraction. Recently a full-thickness blepharotomy has been described for improving eyelid retraction.⁵⁶ This technique is fast and relatively consistent in improving eyelid retraction. In any technique, lateral flare is generally addressed with lateral dissection of Müller's muscle and release of the lateral horn of the levator aponeurosis between the two lobes of the lacrimal gland. Blepharoplasty is of help to excise some of prolapsing orbital fat with conservative skin removal. Lower eyelid retraction is managed with recession of lower lid retractor muscles and capsulopalpebral fascia. For severe lower eyelid retraction, spacer material (usually hard palate graft or an alloplastic material such as Alloderm) can be inserted to get adequate correction⁵⁷ (Fig. 3C). Ear cartilage as a spacer provides excellent lift but creates a firm and relatively immobile lower eyelid. Multiple lid surgeries may be needed to achieve symmetrical appearance between both eyes. Topical guanethidine can be used to block the adrenergic action of norepinephrine on Müller's muscle and results in temporal lowering of the upper lid for 1 to 2 mm; this is a useful temporizing measure in selected patients looking for rapid improvement.⁵⁸

SUMMARY

TAO is a common orbital condition, presenting most frequently in women of the age that may be seeking one

or more cosmetic eyelid procedures. Severe cases showing signs of proptosis and lid retraction are obviously to be avoided as cosmetic surgical candidates in the early phases of the disease. Perhaps of more importance is for the blepharoplasty surgeon to recognize the early signs of mild TAO that may cause the patient to present for consideration of a cosmetic periocular procedure. This is most likely the middle-aged woman who presents with mild eyelid swelling, often worse in the morning. A previous history of thyroid gland abnormalities is a warning sign but is not always present. Should the clinical examination demonstrate any eyelid retraction, a consideration of TAO should be made. Other signs including lagophthalmos, lid lag on down gaze (von Graefe's sign), conjunctiva injection, or any proptosis should alert the surgeon to obtain an eyelid consultation prior to proceeding with periocular surgery. If a diagnosis of TAO is made, the principles outlined in this chapter should be applied. Likely the patient will preserve normal vision, have comfortable eyes, and eventually have an appearance near the preophthalmopathy condition.

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