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Dysthyroid optic neuropathy: update on pathogenesis, diagnosis, and management

Alexander D. Blandford, MD[1], **Dalia Zhang**[2], **Rao V. Chundury, MD, MBA**[3], and **Julian D. Perry, MD**[1]

[1]Cole Eye Institute, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195

[2]Case Western Reserve University School of Medicine, 2109 Adelbert Road, Cleveland, OH 44106

[3]Eugene and Marilyn Glick Eye Institute, Indiana University, 1160 W Michigan St, Indianapolis, IN 46202

Abstract

Introduction—Dysthyroid optic neuropathy (DON) is a severe manifestation of thyroid eye disease (TED) that can result in permanent vision loss. Management is complex, multidisciplinary, and involves medical and/or surgical therapies. This review describes current concepts in the epidemiology, pathophysiology, diagnosis, and treatment of DON.

Areas covered—An extensive review of the literature was performed to detail current concepts on the diagnosis and management of DON. This includes utilization of various medical and surgical modalities for disease management.

Expert commentary—DON can result in permanent blindness and often requires the use of corticosteroids and surgical decompression. We favor the use of intravenous corticosteroids and a transcaruncular approach when surgical decompression is indicated. The use of orbital radiation for DON is often reserved for patients that are poor surgical candidates and/or patients with refractory disease.

Keywords

Graves' Ophthalmopathy; Thyroid Eye Disease; Dysthyroid Optic Neuropathy; Compressive Optic Neuropathy; Orbital Apex Syndrome; Orbital Decompression; Orbital Radiotherapy; Rituximab

1. Introduction

Thyroid eye disease (TED) represents the most common extraocular manifestation of Graves' disease (GD). While the pathophysiology behind Graves' hyperthyroidism is fairly well understood, that of Graves' orbitopathy is less so. Approximately 50% of patients with

Declaration of interest

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GD will suffer from TED before, during, or after the development of hyperthyroidism. While about 60 percent only experience mild discomfort related to eyelid retraction, some 35% will suffer from diplopia interfering with daily life activities or disfiguring proptosis, and finally 3–7 % develop vision threatening complications such as dysthyroid optic neuropathy (DON)[1]. This review provides a consolidated overview of our current understanding of DON.

2. Overview and Epidemiology

The overall prevalence of GD is 13.9 per 100,000 in the United States, with no significant ethnic predisposition[2]. Approximately 25–50% of these patients will display clinically apparent ophthalmopathy, though imaging reveals subclinical features in the majority[2,3]. The gender distribution of patients with TED shows a 5:1 predominance of females over males, yet patients with severe eye disease are more likely to be male and over age 60 years[1,2,4,5].

The natural history of TED is characterized by an active inflammatory phase lasting about 1–3 years and followed by an inactive fibrotic phase [6]. About 1% of patients experience recurrence of active disease, sometimes years following remission. While the majority of patients who develop TED exhibit mild-to-moderate symptoms that require only supportive treatments, about 3–7% experience severe inflammation resulting in sight-threatening ophthalmopathy from exposure keratopathy or DON[2]. (FIGURE 1)

3. Risk Factors

Several genes related to immune modulation, thyroid hormone metabolism and other mechanisms have been implicated in the pathogenesis of TED, however none has been found to be necessary, sufficient, or specific to the development of TED and/or DON[3]. Numerous other risk factors are associated with TED including age, gender, genetics, smoking, thyroid dysfunction, as well as treatments for hyperthyroidism. Discordant identical twin studies suggest that both genetic and environmental factors[7]. Some of these risk factors may also be associated with the development of DON.

The prevalence of smokers in patients with TED is markedly high relative to all other thyroid disorders[8]. Tobacco use is associated with a 7–8× increased risk for developing TED, increased disease severity, and a dampened response to treatment[9,10]. Smoking may represent a risk factor for DON as well, although the evidence is not as overwhelming. A recent review of 604 patients with Grave’s orbitopathy found an odds ratio (OR) of 1.5 for current smokers developing DON, but this was not statistically significant[11]. Wiersinga et al identified male sex, older age, and heavy smoking as the biggest risk factors for developing DON, however no detailed statistics were provided[12]. Another retrospective study found smoking to be the strongest predictive factor in the development of both severe TED (OR = 6.57) and DON (OR = 10.00)[13].

Diabetes mellitus (DM) has also been cited as a risk factor for TED. There exists a complex interplay between glycemic control and thyroid function. While the prevalence of diabetic patients with TED is similar to the normal population (0.22 – 0.26%), the prevalence of

patients with insulin-dependent diabetes mellitus (IDDM) is significantly higher (1.7%), and among these patients, the disease course is generally more severe and refractory [14]. The vasculopathy associated with DM leads to marginal oxygenation of the optic nerve, leaving it more susceptible to damage due to EOM expansion and optic nerve compression. In one study, while only 3.1% of patients with TED had diabetes and 3.9% developed DON, 33.3% of patients with diabetes eventually developed DON. Medical and/or surgical treatment may be less effective in improving visual outcome for patients with diabetes[15].

Thyroid dysfunction is closely related to the development and severity of TED. Dysthyroidism has long been observed to contribute to the development and progression of TED; potential risk cofactors include hypothyroidism as well as the severity, duration, and recent onset of hyperthyroidism. Establishment and maintenance of euthyroidism is essential[16]. The specific treatment of thyroid dysfunction may impact the course of TED[16]. Radioiodine (RAI) therapy may increase the risk of TED progression by 15–39% over anti-thyroid medications or thyroidectomy[3]. In the same way, RAI may increase the risk of developing DON, although no meaningful data exist to validate this extrapolation.

Age and gender also appear to influence the severity of TED, including the development of DON. Increased age correlates with greater severity of thyroid eye disease and age may represent one of the biggest risk factors for DON[2,5]. Patients with DON are significantly older than those with TED alone, with an average age of 61 years[4]. In another large retrospective study, 8.6% of patients with TED developed DON, and patients with DON were older (54 years versus 46 years)) compared to those without DON[1]. Several other studies also show a strong correlation between age and DON [17,18]. For every decade increase in age of onset of TED, the odds of developing DON may increase by 58%[11]. Age may also affect the response to DON treatment with younger age predicting a better outcome (p=0.049)[19]. Male gender also shows a strong correlation with the development of DON, especially with advancing age[1,4,5,17].

4. Pathophysiology

The pathogenesis of DON has been described as having mechanical, vascular, and inflammatory components. The most widely accepted mechanism is secondary to an apex or compartment syndrome from orbital fibroblast deposition of hyaluronic acid (HA) leading to extraocular muscle (EOM) enlargement, enlargement of orbital fat, and overall increased vascular congestion[1,20–25].

As the EOMs converge at the orbital apex, their common insertions form the annulus of Zinn. Here, the medial rectus is most proximal to the optic nerve and compression from EOM swelling can cause optic nerve ischemia or inhibit axonal flow. The medial rectus volume, which can be approximated by medial rectus axial diameter, seems to be the strongest predictor of DON[26]. Orbital computed tomography (CT) studies demonstrate significant optic nerve crowding at the orbital apex in the vast majority of patients with DON, and may also demonstrate intracranial fat prolapse or an increased superior ophthalmic vein diameter[1,23,27,28]. Also implicating direct optic nerve compression in DON is that retrobulbar pressure markedly decreases after decompression surgery[29].

Orbital fibroblasts represent the main effector cells in TED; in addition to producing HA to cause congestion and compression, fibroblasts may differentiate and proliferate[11]. The TSH receptor serves as the autoimmune target in TED and antibody levels correlate with disease activity and severity. Orbital fibroblasts in TED, as compared to normal individuals, express higher levels of TSH receptor, suggesting its potential role as an autoantigen[30]. Insulin-like growth factor-1 receptor (IGF-1R) appears to activate orbital fibroblasts to cause cell proliferation, adipogenesis, and HA synthesis[30]. A subset of fibroblasts may arise from fibrocytes, which are CD34+ mesenchymal cells derived from bone marrow. These circulate as mononuclear cells capable of infiltrating tissue to participate in inflammation, healing, and fibrosis. This leads to fibrotic, less compliant muscles in the apex, which may contribute to the development of DON[20]. (FIGURE 2)

In addition to apex compression and inflammation, changes in orbital vasculature may relate to DON. Doppler sonography shows the superior ophthalmic vein as the most susceptible to changes, exhibiting decreased flow in the active stage and reversed or absent flow in the setting of severe orbitopathy[31]. These vascular changes may contribute to DON. Rarely, short optic nerve or stretch of the optic nerve may cause DON in the absence of EOM involvement[32]. The mechanism by which this occurs may involve the optic nerve vasculature to produce ischemia.

5. Clinical presentation and diagnosis

Multiple objective measures grade the physical signs, symptoms, and severity of TED, including NO SPECS, CAS, VISA, and EUGOGO (Table 1 and 2) however, no single protocol completely characterizes DON [33–36]. Patients may be classified as Type I or Type II, with predominantly fat or EOM enlargement, respectively [37]. Type II orbitopathy may more commonly produce DON, as patients with a muscle index <50% rarely develop DON[21,23,28]. Further, retrobulbar fat volume compares similarly in TED patients with or without DON. Alternatively, Type I and Type II classifications may simply represent extremes on the sprectrum of disease presentation; results from a large tertiary referral center found that the majority of patients presenting with TED demonstrated predominantly an increase of their orbital muscle volume[38].

Most clinicians utilize a combination of clinical and radiological findings to diagnose DON. Tissue enlargement in patients with DON often results in congestion at the orbital apex rather than severe proptosis, and patients may not demonstrate external signs of overt orbital inflammation[25]. The visual acuity often lags behind other symptoms and signs of DON. Color vision, pupillary exam, contrast sensitivity, and automated visual field perimetry help characterize optic nerve function for the diagnosis and management of DON, and DON may result in some characteristic changes in these tests. (FIGURE 3)

Visual acuity decline in TED often occurs from etiologies other than DON, including tear film abnormalities, poor blink, exposure, and resultant corneal irregularities[23]. While decreased acuity is nonspecific, it is decreased more in eyes with DON compared to those with TED alone. In one study, only 53% of patients with DON had visual acuity of 20/40 or better, compared to 97% of patients having TED without DON[1].

An afferent pupillary defect in the setting of TED is highly specific for DON[1]. However, it may be absent in bilateral DON, or it may occur for reasons other than DON. Color vision changes represent an early sign of optic nerve compression. Contrast sensitivity may diminish in TED patients who do not show other signs of DON, indicating this test may detect subclinical optic nerve damage early in the disease process[39].

Visual field testing accurately detects DON[14]. Nearly all eyes with DON develop a central or paracentral scotoma, and many develop other peripheral breakout patterns as well, including inferior arcuate defects, inferior altitudinal, increased blind spot/nerve bundle defect generalized field constriction, and inferolateral defects[1,4]. Visual Evoked Potential (VEP) may also help detect and follow DON, and it may be more sensitive than kinetic perimetry[1,40,41].

Orbital imaging techniques, particularly CT imaging, help to diagnosis and follow DON. Imaging gains particular importance in patients with bilateral disease as an afferent pupillary defect and color testing are less useful in this situation[21]. It is also important when other diagnostic tests do not clearly point to DON, as almost all patients with DON demonstrate CT imaging findings.

In addition to apical crowding, the overwhelming majority of CT imaging studies in cases of DON demonstrate moderate to severe muscle enlargement[1] (FIGURE 4A/4B). The muscle index represents a way to approximate the relative EOM volume within the orbit, and is significantly greater in orbits with DON than in orbits with TED alone[21]. The muscle index is calculated viewing a posterior coronal image of the orbit halfway between the orbital apex and the posterior globe. A horizontal line is drawn to transect the optic nerve, medial, and lateral rectus muscles. A vertical line is drawn to transect the optic nerve, superior, and inferior rectus muscles. The horizontal muscle index is calculated by the percentage of the orbital width that is occupied by the medial and lateral rectus muscles. The vertical muscle index is calculated by the percentage of orbital height that is occupied by the superior and inferior rectus muscles. A muscle index of greater than 70% is seen in about 2/3 of cases of DON, and DON almost never occurs in the setting of a muscle index < 50%[21,23,28].

Orbital fat prolapse through the superior orbital fissure may predict DON, with up to 94% sensitivity, 91% specificity, a positive predict value of 69%, and a negative predictive value of 98%, however, a recent study found this feature in a lower percentage of cases of DON[22,23,47]. Enlargement of the superior ophthalmic vein may also predict DON[28]. An anteriorly displaced or enlarged lacrimal gland may also be seen in the setting of TED and possibly DON[48–50].

Magnetic resonance imaging (MRI) may reveal findings similar to CT imaging, but allows for superior soft tissue imaging[51–54]. T2-weighted and fat suppressed images using TIRM (Turbo-Inversion-Recovery-Magnitude) and STIR (Short-Tau Inversion Recovery) sequences enable detection of extraocular muscle/orbital fat interstitial edema and therefore disease activity. This makes MRI ideal for distinguishing active inflammatory TED from fibrotic end stage disease and is critical to the type and timing of treatment[51,55,56]. MRI

changes of the optic nerve may correlate with clinical activity scores, suggesting that future MR imaging studies of the optic nerve itself may help detect DON[51,55,57–59]. Although MRI is superior at imaging soft tissue, CT is better at evaluating bony orbital anatomy, which is critical for surgical planning.

6. Treatment overview

As the majority of patients with TED develop only mild-moderate symptoms that improve spontaneously, supportive and conservative treatment generally suffices[60]. For patients with moderate-severe and active TED, therapy may reduce disease duration and severity. First line treatment generally consists of oral or intravenous (IV) glucocorticoids, and possibly orbital radiotherapy (ORT). Management of hyperthyroidism should be considered carefully, as dysthyroidism may precipitate disease progression and the treatment modality may affect the course of the disease, though this still remains unclear. Other immunosuppressive and biologic agents, such as methotrexate, rapamycin, adalimumab, and rituximab, have been investigated but are generally second line therapies. Rehabilitative surgery is best performed after cessation of active disease, but may be required earlier for cases of DON refractory to medical treatment.

There exists no consensus regarding the best treatment strategy for TED or DON. American Society of Ophthalmic and Reconstructive Surgery (ASOPRS) members chose both oral (43% of members) and IV (49% of members) steroids as first line treatments for severe TED. In contrast, European and Latin American physicians favor the use of IV over oral steroids as first line therapy[61]. ASOPRS members also use orbital decompression (83%), ORT (70%), biologic agents (33%), and intraorbital steroid injections (28%). Sight-threatening TED may involve a combination of these treatments.

7. Corticosteroids

Corticosteroids are the most widely used medical treatment for DON. Locally administered peribulbar steroids, such as triamcinolone acetonide may improve CAS with fewer side effects compared to oral glucocorticoids, but their effect on DON is less clear[62].

Pulsed IV glucocorticoids (iv-GC) treat TED more effectively than oral steroids, with fewer adverse effects [16]. However, iv-GC may rarely produce severe complications, including fatal acute liver failure, as well as cardiovascular and cerebrovascular events. The majority of severe complications are associated with doses exceeding 8 grams and daily or alternate day intravenous methylprednisolone (iv-MP)[63,64]. A recent EUGOGO consensus statement advocates iv-GC as a first line treatment for moderate-severe TED[16]. A generally accepted dosing regimen for these patients is a once-per-week dose of 500 milligrams iv-MP per week for 6 weeks, followed by 250 milligrams per week for another 6 weeks[65]. Cumulative dose should remain under approximately 6–8g, and patients should be continuously monitored during treatment.

DON may necessitate more aggressive measures, such as 500–1,000 milligrams iv-MP daily for 3 consecutive days, and repeated if necessary after 1 week[64,66]. Regimens such as this may lead to complete visual recovery in approximately 43% of cases. Other iv-MP regimens

show similarly successful outcomes[67]. Some milder cases can be managed with oral steroids and careful monitoring. Because systemic glucocorticoids can effectively treat DON, they should be considered as a first line treatment in most cases.

8. Radiation Therapy

Many clinicians use ORT to treat moderate-to-severe TED. The most common dosing regimen calls for a cumulative dose of 20 Gy per eye, fractionated into ten doses over 10 days[68]. This regimen has proven very safe, and side effects are typically mild (periorbital edema, hair loss at entry ports, and conjunctival injection) and regress after treatment[69]. Severe side effects such as radiation retinopathy, optic neuropathy, and scleral necrosis are rare, and typically in the setting of prior chemotherapy treatment, diabetes mellitus, or systemic hypertension. Absolute contraindications for radiation therapy include severe hypertension and diabetic retinopathy, while diabetes mellitus without retinopathy is considered a relative contraindication. ORT should be avoided in patients under age 35 years[35,70]. (FIGURE 5) While existing data do not point to any clear and significant effect of ORT on the duration or severity of TED its role in treatment of DON are not well studied[71]. ORT does seem to play a preventative role in the development of DON, so it may also play a role in its treatment[72,73]. We typically use ORT in patients refractory to iv-MP who refuse surgery or who are poor surgical candidates.

9. Alternative Immunosuppressive Agents

A variety of steroid-sparing agents for TED and DON have been proposed and studied. Insights into new molecular pathways have exposed more specific targets for therapy. As Th-1 and macrophage type cytokines are implicated in the early stages of TED pathogenesis, agents targeting receptors for IL-1, IL-6, and TNF may be effective in treatment. These include anakinra, tocilizumab, lerdelimumab, infliximab, adalimumab, and etanercept[24]. Both TSHR and IGF-1R are potential targets for small molecule agents and monoclonal antibodies, such as M22 and teprotumumab[74,75]. Other options include modulation of co-stimulatory pathways and inhibition of T-cell migration and response through blockade of CXCR3 signaling with agents such as peroxisome proliferator-activated receptor (PPAR) γ or α agonists, and CXCR3 antagonists[76].

Publications regarding the use of these agents for treatment of DON consist mostly of case reports, and small case series. Rapamycin was reported to improve symptoms, visual acuity, color plate testing, and visual fields in a case of DON refractory to steroids and maximal surgical decompression[77]. Adalimumab, an anti-TNF-α monoclonal antibody, was found in one retrospective study to significantly improve inflammation in active TED, but only in patients with a high inflammatory index at baseline[78]. Tocilizumab, an anti-IL-6 monoclonal antibody, showed promising results in treatment of patients with corticosteroid-resistant TED in a prospective interventional study[79]. Methotrexate improves CAS but may not completely treat DON[80]. Teprotumumab, an anti-IGF-1R monoclonal antibody, is currently under investigation in a clinical trial[81].

Rituximab, an anti-CD20 monoclonal antibody, may be of some benefit in treating TED and DON[82–84]. This agent may improve both visual acuity and CAS in cases of DON refractory to steroids and surgical decompression[83]. However, in patients with moderate-severe TED it may not significantly improve CAS as compared to placebo and may cause adverse events[85].

While further studies of rituximab and alternative immunosuppressive agents for DON seem warranted, newer agents in the future may prove more useful. When medical management of DON fails, efforts are directed at surgical decompression.

10. Surgical Decompression

Surgery for DON should decrease orbital soft tissue volume and/or expand its bony volume to decompress the optic nerve at the orbital apex. (FIGURE 6) Fat can be removed from any location within the orbit and the bony expansion can occur along any orbital wall. The inferomedial wall extends deeper into the orbital apex and generally represents the first-line approach to decompress the apex, although deep lateral wall bone removal and/or fat-only removal may also decompress the orbital apex. Several approaches to the medial wall have been described, including the transantral, transcutaneous, endonasal, and transcaruncular approaches.

11. Transantral

The transantral approach allows for removal of the inferior and medial orbital walls through a mucosal incision within the buccal sulcus, and removal of the anterior face of the maxilla. The technique can successfully treat DON, with improvement in visual acuity and visual field defects in approximately 91% of patients[86]. However, approximately 2/3 of patients may develop new-onset diplopia after surgery. Other complications include lower eyelid entropion (9%), alveolar branch trigeminal nerve hypoesthesia (5%), and CSF leak (3.5%) [86].

12. Transcutaneous

A lower eyelid subciliary incision, either with or without a swinging eyelid approach, yields excellent exposure of the inferomedial orbit for treatment of DON[87,88]. The swinging eyelid approach allows for greater visualization of the inferolateral orbital fat and lateral wall[87].

Although the Lynch approach is almost obsolete, a smaller incision (1.5–2cm) transcutaneous medial approach yields adequate exposure and may result in less medial canthal webbing, telecanthus, iatrogenic diplopia, and damage to the lacrimal outflow system.[90,91].

13. Orbital fat decompression

Orbital fat can be removed during bony decompression or independently for treatment of DON. Transpalpebral extraconal and/or intraconal fat removal without bony decompression

(but with iv-GC and/or ORT) successfully treated DON in 69 patients, though the specific outcomes regarding patients with DON were not reported[92]. In patients with DON having only modest EOM enlargement and more fat compartment enlargement, fat decompression alone may reverse DON in all cases with minimal complications[93].

14. Endoscopic transnasal

The inferomedial orbit may also be decompressed via a transnasal endoscopic approach. Described in 1990 by Kennedy et al, the endonasal approach effectively treats DON, but may induce new diplopia in 60–80% of cases[94–96]. This may be due to the difficulty in maintaining an inferomedial bony strut via the endoscopic approach[95,97]. More recent attempts at selective posterior endoscopic decompression for DON may result in less post-operative diplopia[95]. Fat can also be removed during this approach to improve visual acuity and color vision with a low rate of consecutive diplopia[98].

15. Transcaruncular

The transcaruncular approach allows for quick, safe access to the orbital apex for removal of the medial and inferior walls[43,89,99]. It allows for more medial wall exposure than the transcutaneous approach, but it avoids adverse structural or functional consequences associated with a cutaneous incision. (FIGURE 7)

Several studies demonstrate significant improvement in all parameters of optic nerve function after transcaruncular approach decompression, allowing for rapid steroid taper[42,43,100,101]. This technique allows for a graded approach to removing the ethmoidal air cells and the inferior wall to preserve as much of the maxillo-ethmoidal strut as desired, lowering the risk of new-onset postoperative diplopia[43,89]. A meta-analysis of techniques for DON surgical decompression described the transcaruncular approach as easy and safe access to the orbital apex[99].

16. Lateral Wall

Lateral wall decompression can be performed through an upper eyelid or lateral canthal incision, and involves removal of the deep lateral orbital wall, typically with a high-speed drill or ultrasonic aspirator [102–105]. Lateral wall-only decompression can be performed with or without fat removal, and results in a low rate of new-onset postoperative diplopia[106]. The lateral wall does not extend as far posteriorly as the medial wall, but aggressive deep bony decompression with or without fat removal seems to decompress the orbital apex effectively for treatment of DON[107]. (FIGURE 8)

17. Treatment Outcomes and Quality of Life

Without treatment, DON may result in permanent vision loss[25]. Fortunately, regimens consisting of iv-MP, ORT, and surgical decompression effectively improve visual outcome in the vast majority of cases with complete visual recovery in approximately 70% of cases [14,19]. Positive predictive factors include younger age, shorter duration of neuropathy, and higher initial CAS, likely indicating earlier disease course[19]. Though quality of life (QoL)

comprises an essential aspect of treatment outcome, it is far less commonly assessed and studied than clinical measures, especially for DON. Several studies have shown clinical measures to correlate poorly with QoL outcomes except in extreme cases, in which patients consistently report lower QoL scores[108].

18. Expert Commentary

Despite strong evidence to support the use of iv-GC as first-line treatment for moderate-severe TED, recent survey results indicate that a large proportion of physicians still favor oral steroids, especially in the United States. This may be due to the association of iv-GC with severe, possibly fatal adverse events. However, studies consistently show that iv-GC are better tolerated, more effective, and associated with less morbidity compared to oral steroids. Creating safe treatment practices based on the available data entails awareness of safe dosing regimens, screening patients based on risk factors such as cardiovascular disease and DM, and close monitoring of liver enzymes and cardiac function throughout treatment. Also, while corticosteroids often decrease disease activity, they rarely result in proptosis reduction and surgical decompression may still be warranted.

While ORT may prevent DON in some patients, its indiscriminate use for DON would result in treatment of many patients who would not benefit from the therapy. Therefore, given the current data, we reserve ORT for patients with refractory DON who do not elect, or are poor candidates for, surgical decompression. While a variety of approaches adequately decompress the orbital apex, we typically employ a transcaruncular approach, or occasionally a transnasal endoscopic approach.

19. Five-year view

As our understanding of the environmental, genetic, and immune factors underlying Graves' disease improves, future therapies will better target cellular and molecular mechanisms to prevent and treat DON. A promising animal model provides the opportunity to study the effects of novel drugs and treatments in vivo[109–111]. Pursuing studies that distinguish between the heterogeneous types of antibodies found in patients with DON will contribute greatly to understanding the pathophysiology of the disease, as well as provide more information on targets for treatment.

Reports of new treatment options for TED and DON are numerous, but data from controlled clinical trials are lacking. Well-designed clinical trials testing the efficacy of novel agents and surgical techniques will be essential in advancing and improving current treatment regimens and reducing disease mortality. This is especially true for treatments of DON, however, the rarity of this condition and the need for urgent treatment makes Level 1 data difficult to obtain. Efforts on the part of organizations such as EUGOGO and ITEDS will hopefully make possible organized multi-center randomized controlled trials, and provide valuable evidence-based data to enhance and refine techniques for managing both DON and TED.

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20. Key Issues

- Dysthyroid Optic Neuropathy (DON) can cause permanent vision loss and results from an orbital apex syndrome.
- In addition to thyroid dysfunction, male gender and older age are strong risk factors for development of DON while the role of tobacco status is less defined.
- Careful clinical evaluation for DON is critical and visual acuity, color vision, pupillary exam, contrast sensitivity, visual field testing, and visual evoked potential can aid in diagnosis and tracking progression.
- DON management involves obtaining a euthyroid state, protecting the ocular surface, and orbital decompression via medical or surgical means.
- Medical management of DON involves corticosteroids and some centers also employ orbital radiotherapy and/or immunosuppressive agents
- Surgical orbital decompression is often necessary for DON refractory to medical management.
- Prompt treatment in DON can result in stabilization and improvement in vision.
- Further studies, including randomized controlled clinical trials are necessary to better elucidate the role of novel agents and surgical techniques to better optimize DON management.

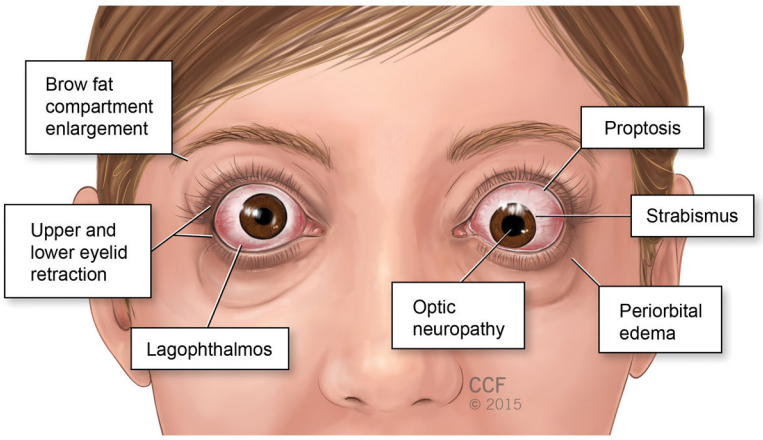

Figure 1.

Thyroid eye disease illustration. Various clinical manifestations found in moderate to severe thyroid eye disease are shown in this illustration

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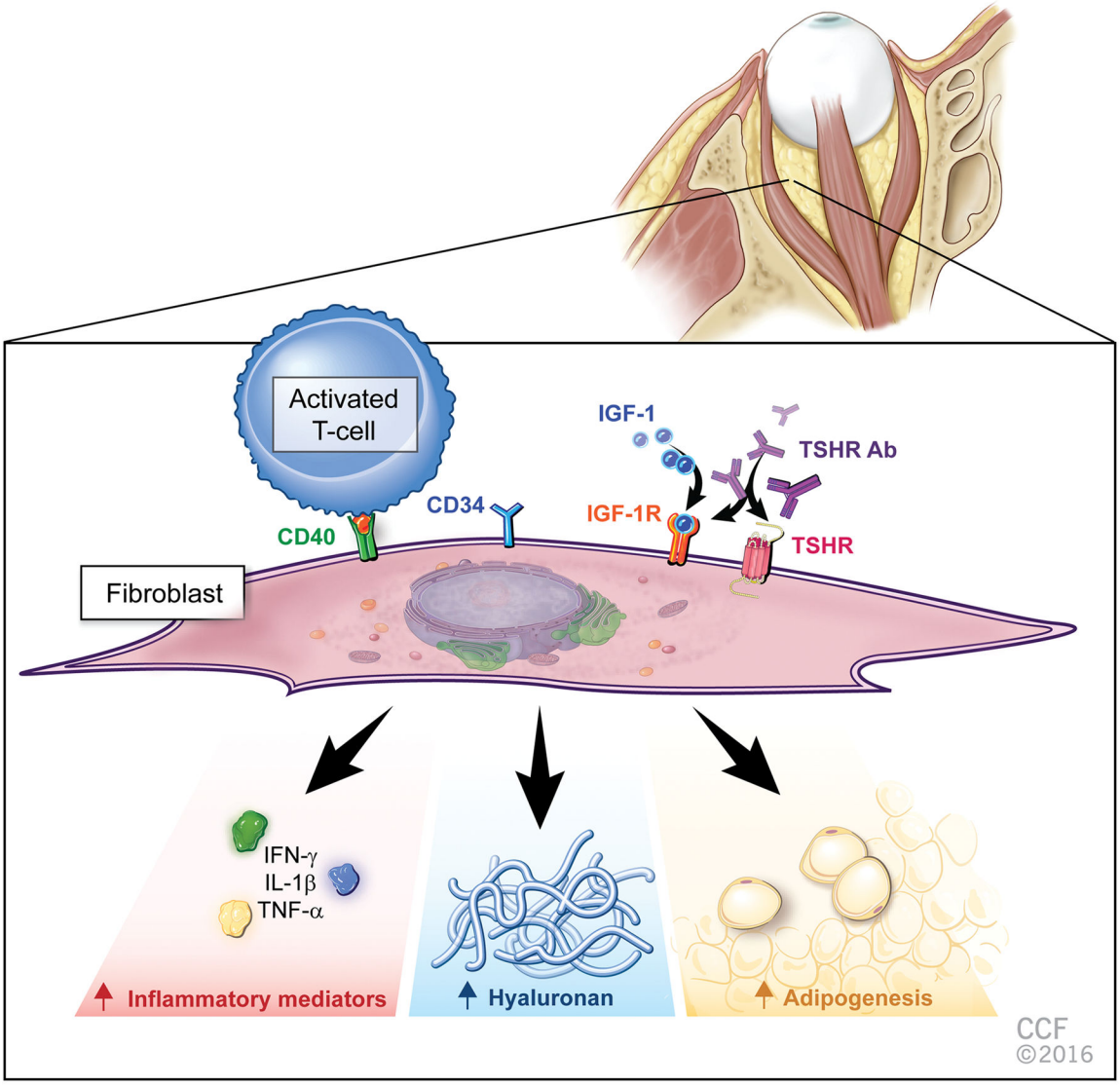

Figure 2.

Orbital Fibroblast role in Thyroid Eye Disease

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Examination/Test:	Classic Finding
Visual Acuity	Often <20/40, but may be later finding
Pupillary Exam	May have relative APD if unilateral or asymmetric
Color Vision	Often decreased
Contrast Sensitivity	Often decreased
Visual Field Testing	Central/Paracentral Scotoma with peripheral break out patterns
Visual Evoked Potential	Often decreased P2/P100 amplitude and increased P100 latency

Figure 3.
Clinical Evaluation of Optic Nerve Function in DON

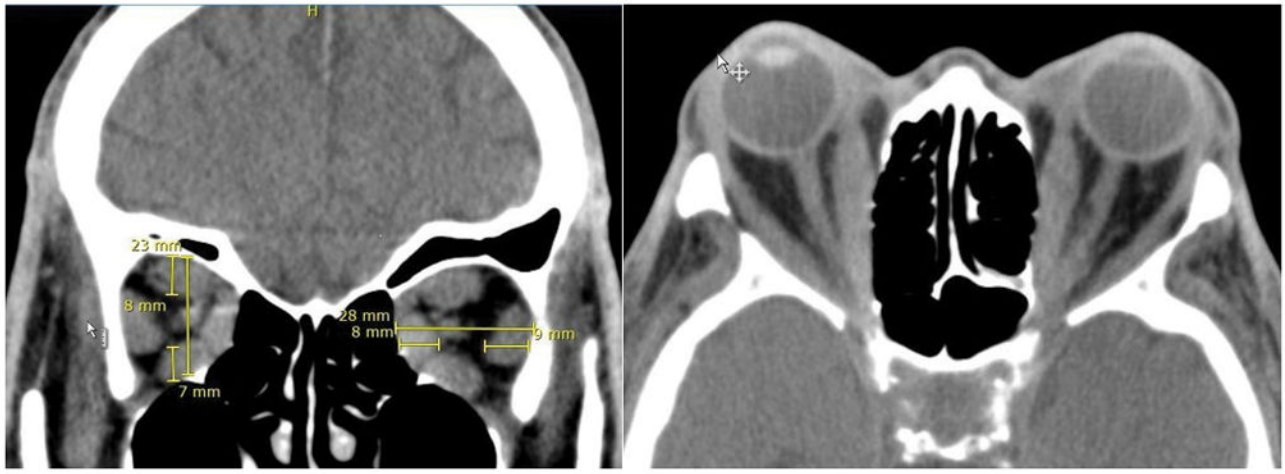

FIG. 4.

A. Muscle Index measurement. B. Apical Crowding.

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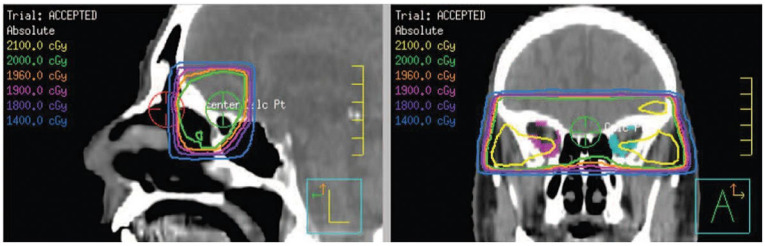

Figure 5.

ORT isodose plan. Pretreatment evaluation involves isodose planning which can target x-rays to specific anatomic locations. In this plan, the extraocular muscles are targeted along with orbital fat with attempt to minimize radiation to other important ocular structures. ORT, orbital radiation therapy.

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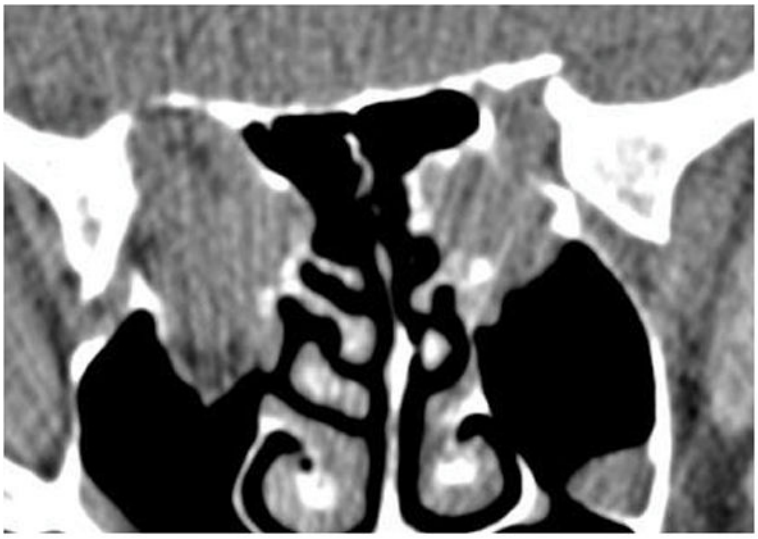

Figure 6.
Coronal CT scan post-orbital decompression for DON.
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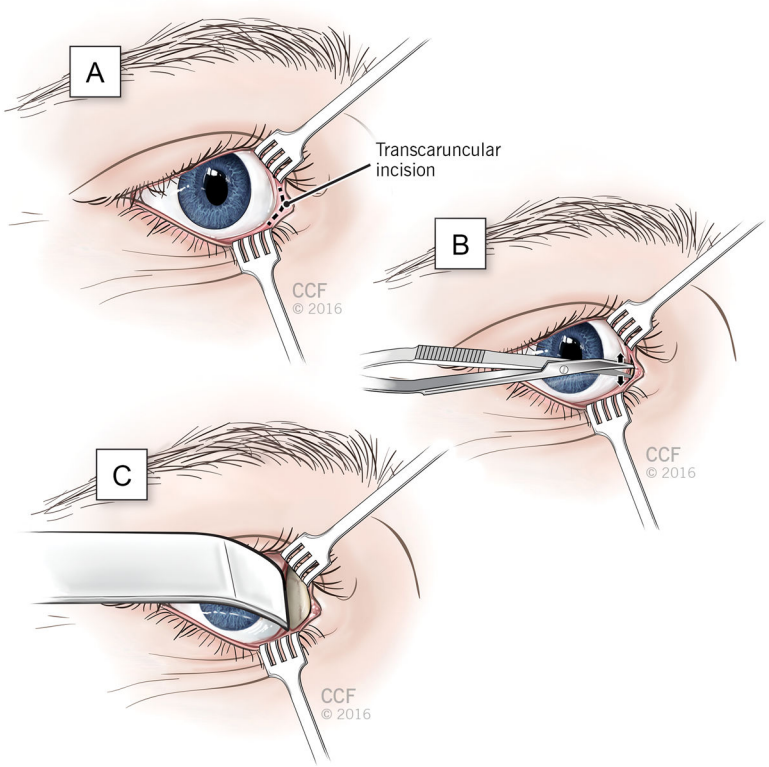

Figure 7.

Transcaruncular approach to medial orbit

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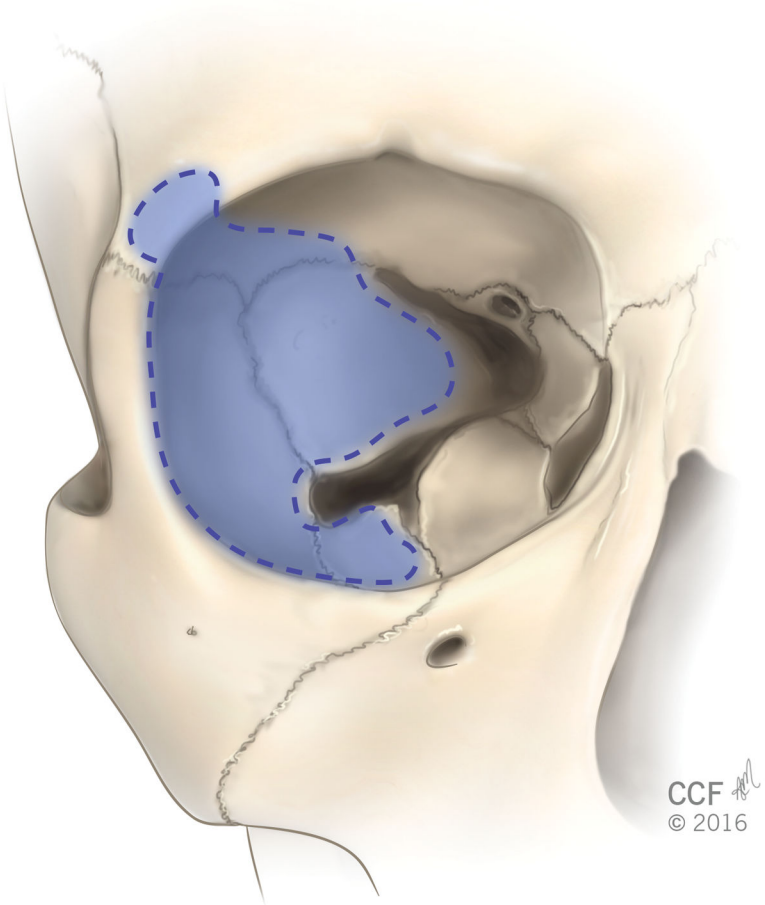

Figure 8.
Lateral orbital decompression for DON
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Table 1

Clinical Activity Score (CAS). Presence of each symptom/sign receives 1 point. A sum score greater than 3/7 at first exam or greater than 4/10 in subsequent examinations defines active ophthalmopathy (altered after Mourits et al original description)

Initial Exam (max score of 7 points)
• Ocular or retrobulbar pain
• Pain with eye movement
• Eyelid erythema
• Eyelid swelling
• Conjunctival chemosis
• Conjunctival erythema
• Swelling/erythema of caruncle
Subsequent Exam, 1–3 months later (max score of 10 points, combining pa0ameters above and below)
• ≥2mm increase in proptosis
• Impaired ductions in any one direction >8 degrees
• ≥1 line decrease in Snellen visual acuity chart

Table 2

VISA Inflammatory Score. Presence of each sign/symptom receives 1–2 points (max score of 10). Patients with sum scores <4/10 are managed conservatively while patients with scores >5/10 or with evidence of inflammatory progression are more aggressively treated (altered after Dolman and Rootman original description).

• Swelling of caruncle (1 point)
• Conjunctival chemosis that lies behind the grey line (1 point) OR extends anterior to grey line of eyelid (2 points)
• Conjunctival erythema (1 point)
• Eyelid erythema (1 point)
• Eyelid swelling without redundant tissues (1 point) OR swelling that causes bulging in the palpebral skin, including lower lid festoon (2 points)
• Retrobulbar pain at rest (1 point)
• Retrobulbar pain with eye movement (1 point)
• Diurnal variation (1 point)