# Orbital imaging in thyroid-related orbitopathy

Christopher Lo, MD, Shoaib Ugradar, MD, and Daniel Rootman, MD, MS

SUMMARY

A broad understanding of the different imaging modalities used to assess the physiologic changes seen in Graves' orbitopathy complement clinical examination. Subtle applications of radiographic imaging techniques allow for a better understanding of the overall physiology of the orbit, quantify progression of disease, and differentiate it from orbital diseases with overlapping features. A nuanced approach to interpreting imaging features may allow us to delineate inactive from active thyroid eye disease, and advances within this field may arm clinicians with the ability to better predict and prevent dysthyroid optic neuropathy. (J AAPOS 2018;22:256.e1-256.e9)

rbital imaging plays a central role in the diagnosis and management of thyroid-related orbitopathy (TRO). Diagnostically, it is used to compliment a careful ophthalmic examination, laboratory values, and ancillary studies to confirm the presence of TRO and/or dysthyroid optic neuropathy (DON). It can also be helpful in surgical planning and understanding the progression of thyroid myopathy. Computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, and nuclear medicine all have applications in the field. In this review we present the imaging features of TRO and discuss the current utility of imaging to assess disease activity. Differential diagnoses and indications for biopsy are also described. A range of imaging features and their practical applications are presented.

# **Imaging Findings**

#### Muscles

Extraocular muscle enlargement is a hallmark of Graves' orbitopathy that has been observed intraoperatively, radiographically, and in postmortem studies.<sup>1-5</sup> In many cases the changes are obvious; however, the determination of whether a muscle is enlarged volumetrically can pose a challenge, particularly if there is symmetric mild disease (Figure 1). In the clinical setting, it is practical to determine muscle width in the midbelly region (approximately 1 cm posterior to the globe), which can be used as a proxy for muscle volume.<sup>6,7</sup> Normative data has been developed:

Author affiliation: Division of Orbital and Ophthalmic Plastic Surgery, Stein and Doheny Eye institutes, University of California, Los Angeles

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mean inferior rectus width, 4.8 mm; medial rectus width, 4.2 mm; superior rectus width, 4.6 mm; and lateral rectus width, 3.3 mm.<sup>8,9</sup> These numbers can be used as a guide; however, they represent population averages, each with significant variation. Overlap in populations exist, and both diseased and nondiseased muscles can have widths close to these values. In the end, there are no strict rules.

In terms of muscle involvement, clinical myopathy is thought to most often involve the inferior rectus muscle, followed by the medial, superior, and lateral rectus muscles.<sup>10</sup> However, any of the extraocular muscles can be involved. Multiple muscles are typically involved simultaneously, and bilateral disease is found in 76%-90% of patients, although it is often asymmetric (Figure 2).<sup>11,12</sup> Isolated muscle disease (often the superior muscle complex) is rare but seen in 5% of cases.<sup>10</sup> It is also important to consider the image to be a snapshot in time and view myopathy as a dynamic process. Serial MRI can demonstrate fluctuations and change (Figure 3).

Classically, enlargement is described to spare the anterior tendon insertion (Figure 4A). This feature may help differentiate TRO disease from other forms of myositis. However, the rectus insertion can be enlarged in some cases of TRO (Figure 4B)<sup>3,13,14</sup> and, conversely, can be spared in non-TRO-related myositis.<sup>15</sup> The precise sensitivity and specificity of this sign is not well established and therefore represents supportive evidence of disease in the context of other characteristic biochemical and clinical findings, rather than a pathognomonic sign.

#### Fat

Fat expansion is additionally a central characteristic of TRO. A spectrum of disease exists, with fat predominant at one end and muscle predominant at the other. Lipogenic, or type 1, patients tend not to exhibit significant muscle enlargement or dysfunction (Figure 5), and in these circumstances clinical and biochemical correlates are critical for diagnosis.<sup>16</sup> Further, type 1 patients are less likely to develop strabismus after decompression surgery, making

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Correspondence: Daniel Rootman, MD, MS, 100 Stein Plaza #2-267, Los Angeles, CA 90095 (email: Rootman@jsei.ucla.edu).



**FIG 1.** Axial computed tomography (CT) of the orbits with symmetric enlargement of bilateral medial and inferior rectus muscle groups.



FIG 2. Axial CT of the orbits with prominent asymmetric muscle enlargement of the inferior and medial rectus on the right side compared with the left.

the phenotype important in prognosticating. Although each end can manifest at any age, muscle predominant disease is more frequently observed in older patients and fat predominant disease in younger.<sup>17</sup>

Though hypertrophy and hyperplasia of the fatty tissue may account for expansion of this compartment, an increase in orbital fat volume as a result of venous congestion from compression of the superior ophthalmic vein has been postulated as an alternative etiology for this phenotype.<sup>3,18</sup>

Clinically, expansion of the brow, galeal, premalar region, and cheek fat have also been described.<sup>19-23</sup> Complimentary changes to the retro-orbicularis oculi fat and the premalar suborbicularis oculi fat can also be detected using multiple imaging modalities.<sup>24,25</sup> This fat expansion is often underappreciated; however, it is pathologic in terms of the histology, and is widely derided by patients with the disease (Figure 6).<sup>20</sup>

#### Exophthalmos

While extraocular muscle enlargement is a principle radiographic abnormality of TRO, exophthalmos is a common clinical measure that can be confirmed radiographically.



**FIG 3.** Serial coronal magnetic resonance imaging (MRI) T1 fat saturation sequence with contrast demonstrating progressive enlargement of the right inferior rectus and the left superior rectus muscle during the active stage of thyroid-related orbitopathy (TRO). A, Baseline exam. B, 6 months. C, Examination 5 months later.

Multiple methods have been proposed for this purpose. One involves tracing a reference line between the anterior extents of each zygomatic bone in a midorbital axial section. The distance from this line to the posterior aspect of the globe can then be measured. A normal distance is defined as being >10 mm, while smaller (or negative) distances indicate exophthalmos (Figure 7).<sup>26</sup>

#### **Bony Changes**

It is well known that the bony orbit undergoes remodeling in TRO. Bowing of the lamina papyracea of the ethmoid (Figure 8A) may represent an adaptive response to the enlargement of the adjacent medial rectus muscle and/or elevation of the intraorbital pressure.<sup>3,27,28</sup> This type of remodeling is less well described in the lateral wall because of differences in bone compliance, but it can occur (Figure 8B).<sup>29</sup> Medial wall bowing on CT or MRI is associated with diplopia and DON, both indicators of disease severity.<sup>28,30,31</sup>



**FIG 4.** Axial CT of the orbit. A, Left orbit with muscle enlargement sparing the anterior tendon insertion of the medial rectus. B, Case of TRO with medial rectus enlargement that involves the anterior tendon insertion of the medial rectus.



**FIG 5.** Coronal (A) and axial (B) CT of the orbits representing lipogenic subset of TRO with fat predominant phenotype.



**FIG 6.** Color clinical photograph of TRO patient with characteristic expansion of the brow, galeal, and premalar fat.

# Superior Ophthalmic Vein

The superior ophthalmic vein is often noted to be enlarged due to venous congestion in patients with TRO and may be more common in patients demonstrating DON.<sup>32</sup> It has been postulated that obstruction of venous drainage from enlargement of the extraocular muscles may contribute to expansion of soft tissue structures and exophthalmos.<sup>3,10,33</sup>

# Lacrimal Gland

With expansion of the orbital fat and muscle, the lacrimal gland is often anteriorly displaced.<sup>10</sup> In addition, the mean lacrimal gland volume can be increased in TRO



**FIG 7.** Axial CT of patient with bilateral exophthalmos. Red line indicates reference line between the anterior extents of the zygomatic bones.



**FIG 8.** Axial CT of the orbit in TRO with bowing of the medial wall (A) and bony remodeling of the lateral wall (B).



**FIG 9.** Axial MRI T1 fat saturation sequence of the orbit with arrow pointing to enlarged lacrimal gland on the patient's right side.

(Figure 9).<sup>34</sup> This is perhaps due to venous stasis and/or direct lymphocytic infiltration, the latter of which has been correlated pathologically.<sup>3,34,35</sup> Imaging studies have been able to differentiate active, inactive, and



**FIG 10.** Coronal CT of the posterior orbit showing apical crowding in a patient with severe TRO and dysthyroid optic neuropathy.

matched controls by comparing the density of the lacrimal gland.<sup>36</sup>

# **Clinical-Imaging Correlates**

#### **Dysthyroid Optic Neuropathy**

DON affects approximately 5% of patients with Graves' orbitopathy.<sup>5</sup> High risk groups include older, male, and/ or diabetic patients as well as those with ptosis or asymmetric restrictive motility.<sup>37,38</sup> DON is diagnosed with the typical features of optic neuropathy. Other clinical findings related to orbital apex crowding can be found in DON, such as discomfort, tearing, swelling, proptosis, diplopia, restricted motility, or increased intraocular pressure with upgaze.<sup>37,38</sup>

DON is thought to arise from compressive, inflammatory, or vascular compromise to the optic nerve in the orbital apex. Many studies have demonstrated a relationship between optic neuropathy and greater enlargement of the extraocular muscles.<sup>2,3,34,39-41</sup> Though all muscle groups increase proportionally in compressive disease, medial rectus size in particular is an important predictor of DON.<sup>31</sup> Enlargement at the apex, or crowding (Figure 10), is a classically described imaging feature in DON.<sup>38,42</sup>

Other radiographic features that reflect increases in orbital volume and apical crowding, such as dilated superior ophthalmic vein, anteriorization of the lacrimal gland and intracranial fat prolapse through the superior orbital fissure, have all additionally been found to correlate with DON and can be used as ancillary information in equivocal cases with overlapping intraocular disease.<sup>3,10,33,37,39,43,44</sup>

Severe proptosis may lead to optic nerve stretch and tenting of the posterior globe. Rarely, stretch optic neuropathy can occur.<sup>10,29,45,46</sup> In these cases, progressive narrowing of the posterior globe angle correlates with severity of visual impairment. Patients with a posterior globe angle of  $>130^{\circ}$  often have a good visual recovery, while an angle  $<120^{\circ}$  often portends a poor visual prognosis.<sup>45</sup>



**FIG 11.** Coronal (A) and Axial (B) CT highlighting muscle enlargement with patchy hypodensities in the medial and inferior recti muscle groups (arrows) in a patient with active Graves' orbitopathy.

Though imaging is a powerful tool to elicit radiographic findings of DON, many of these features are also found in 35% of patients affected by moderate-to-severe TRO without optic neuropathy.<sup>47</sup> Conversely, there are cases of clinical DON that have developed in the absence of these radiographic findings.<sup>37,48</sup> Advanced imaging modalities do not supersede a thorough clinical examination and mainly offer support for the diagnosis and potential targets for therapy.

#### **Staging of Disease**

In active Graves' orbitopathy, muscle enlargement may be accompanied by patchy hypodensities in the body of the rectus muscles suggestive of lymphocytic and mucopoly-saccharide deposition (Figure 11).<sup>27,34</sup> In this stage, the density of the fat and the lacrimal glands may also increase due to lymphocytic infiltration and vascular congestion.<sup>36,49</sup> Fat volume has not been associated with disease activity or DON.<sup>36,40</sup>

In chronic TRO, the muscles may appear atrophic. CT may demonstrate fatty replacement in the extraocular muscles, which decreases the calculated muscle density.<sup>34</sup> Fat volume may also be increased in patients with a longer duration of disease.<sup>36,50,51</sup>

While CT and MRI both demonstrate similar structural changes in TRO, MRI is likely superior in evaluating soft tissue and differentiating imaging features of active and stable disease.<sup>34,52</sup> MRI may be preferable in cases where there are overlapping orbital disease processes and imaging features. In all stages, on T1-weighted imaging, isointense enhancement of the enlarged extraocular muscles is noted. Contrast administration may demonstrate decreased or delayed muscle enhancement compared with normals due to impaired microcirculation secondary to venous stasis or intraorbital mass effect.<sup>34</sup> MRI T1-weighted imaging can also be used to detect fatty degeneration in the muscle body.<sup>34</sup>

Increased signal intensity on T2-weighted imaging with fat saturation represents elevated water content. Such a finding can be indicative of active inflammation and edema. This has been associated with active disease and is a positive predictor of response to immunosuppression or radiation therapy.<sup>27,53,54</sup> The diminished signal in chronic and

stable stage disease implies low water content, fat infiltration and fibrotic degeneration.<sup>27,34</sup>

Short-tau inversion recovery (STIR) sequences are also useful in detecting active inflammation and increased fluid content in tissue. The STIR images demonstrate a higher signal intensity ratio of muscles and fat in TRO patients compared with controls, irrespective of disease stage.<sup>51</sup> STIR sequence muscle intensity has also been positively associated with clinical activity scores and response to steroid treatment.<sup>51,55,56</sup>

In TRO without evidence of DON, there is no change in optic nerve diameter.<sup>57</sup> However, newer imaging sequences can elucidate a nuanced approach to the staging of disease by nerve appearance. Diffusion-tensor imaging (DTI) is a MRI technique commonly used for early detection of brain infarcts. By investigating the various components of this signal sequence, it may be possible to detect early signs of disease activity in the optic nerve that could reflect risk of DON.<sup>58</sup> Additionally, the medial rectus body may demonstrate signal features (radial diffusivity) that are specific to active disease.<sup>59</sup> This area of research is still evolving and may provide new clues in the future.

The portability of ultrasound makes it ideal for bedside screening and diagnosis. Ultrasound has been found to yield measurements that correlate with CT measurements of muscles on B-scan.<sup>60</sup> It can also be used to identify periorbital changes including expansion of the eyebrow tissue and the retro-orbicularis oculi fat.<sup>24</sup> Color Doppler examination can be used to document dilation of the superior ophthalmic vein and increased arterial flow in the extraocular muscles, which may be more pronounced during active disease.<sup>61</sup>

In TRO, A-scan will reveal irregularity with medium to high reflectivity. During active disease, the internal reflectivity may be lower due to edema and inflammation.<sup>27</sup> Higher internal reflectivity can be seen in inactive disease with fibrotic changes to the muscle belly. However, variability in A-scan data may limit its practical use.

Nuclear Medicine imaging techniques may also play a role in determining disease activity, particularly if MRI is unavailable. Numerous radiopharmaceuticals, including radiolabeled octreotide, have been shown to localize to the orbit and lacrimal gland in active TRO representing high metabolic activity and activated lymphocytes. Radio-nucleotide uptake has been shown to correlate well with clinical activity score and recti muscle volume<sup>62,63</sup> Additionally, level of uptake corresponds with response to immunosuppressive and radiation treatments.<sup>63-68</sup>

#### Strabismus

Cross sectional areas of recti muscles on CT have been found to correlate with the degree of angle deviation.<sup>69</sup> Increase in thickness of the superior rectus complex and thickness of superior oblique have also been found to be associated with higher rates of postoperative intorsion following strabismus surgery. These findings may be helpful in both anticipating strabismus and in surgical planning.<sup>70</sup> US findings are a less reliable predictor of strabismus measurements.<sup>27</sup>

### **Postsurgical Imaging**

Postsurgical imaging can be useful in confirming the extent of orbital decompression. In addition to bony removal and less apical crowding, there may be displacement of the orbital fat with bowing of the rectus muscles in the expanded orbit. The lateral rectus muscle, compared with the medial rectus, has been observed to expand more on postoperative imaging (Figure 12).<sup>71</sup> Such expansion may limit the degree of proptosis reduction relative to volume of bone removed.

# **Differential Diagnosis**

### Nonspecific Orbital Inflammation

Nonspecific orbital inflammation may share both clinical and radiographic features with TRO. Classically, unilateral, single-muscle inflammation with tendon involvement is the most easily differentiating finding on imaging. However, bilateral and multifocal inflammation sparing the tendon can obfuscate accurate diagnosis.<sup>72</sup>

### Specific Orbital Inflammation

Specific orbital inflammation, including systemic lupus erythematosus, sarcoidosis and HLA B27-associated inflammatory disease, can present with unilateral or bilateral involvement of the muscles and lacrimal gland and can be difficult to differentiate on imaging. Giant cell myocarditis is a generalized inflammatory skeletal muscle disorder that can also present with bilateral myositis.<sup>73,74</sup> Skeletal muscle weakness and cardiac failure or arrhythmia may follow. Thus, timely tissue diagnosis with cardiac workup may be a life-preserving intervention.

#### Vascular

Arteriovenous malformations and carotid cavernous fistulas can lead to enlargement of the extraocular muscles due to an increase in orbital venous pressure. Unilateral uniform muscle enlargement with an engorged superior ophthalmic vein may be an indicator of a vascular process.<sup>15</sup> MR angiogram, CT angiogram, or a dynamic arterial and valsalva-augmented venous phase protocol can be used for demonstrating characteristic changes in the cavernous sinus, or expansile fistula elements in the orbit.<sup>75,76</sup>

# Neoplasia

Orbital lymphoma is the most commonly diagnosed primary orbital tumor. Up to 11% of ocular adnexal lymphomas present with extraocular muscle involvement preferentially of the superior muscle complex.<sup>72,77-81</sup> Although typically affecting the lacrimal gland, uniform,



FIG 12. Preoperative coronal (A) and axial (C) CT scans. Coronal (B) and axial (D) CT scans following bony decompression demonstrating postoperative expansion of the lateral recti.



FIG 13. A, Coronal MRI showing enlargement of the left superior oblique in a patient with orbital lymphoma. B, Axial MRI with a well circumscribed right medial rectus lesion from a metastatic carcinoid tumor. C, Metastatic breast cancer to the left recti muscles. (D) Bilateral xanthogranulomatous inflammation in Erdheim Chester disease.

isolated muscle enlargement can also be characteristic (Figure 13A).

Neoplasms may invade extraocular muscles or compress their venous drainage causing secondary muscle enlargement. Metastatic disease to the muscles most commonly arise from carcinoid tumor (Figure 13B) and cutaneous melanoma but can also come from breast (Figure 13C), renal, thyroid, or other gastrointestinal primary sources.<sup>72,82</sup> The frequency of muscles involved (in decreasing order) are medial, lateral, superior and inferior. Bilateral involvement is seen in approximately 15% of patients.<sup>72</sup>

#### **Infiltrative Disease**

Primary orbital amyloidosis can infiltrate unilateral or bilateral extraocular muscles and involve the adjacent fat in a reticular pattern.<sup>72,83-85</sup> Presenting features include ptosis, proptosis, swelling, ophthalmoplegia, and skin deposition.

Erdheim Chester disease is a known clinical and radiological masquerader that can present with bilateral exophthalmos (Figure 13D).<sup>86</sup> Other symptoms include knee and leg bone pain, diabetes insipidus, ataxia, and pulmonary fibrosis. Long bone survey can be useful for diagnosis.

Acromegaly can cause moderate enlargement of all recti and can be seen as a part of generalized organomegaly.<sup>15,72</sup> These muscle changes present in isolation of significant exophthalmos and serum assessment can be useful in making this diagnosis.

#### **Indications for Biopsy**

Primary or locally invasive muscle neoplasms may lead to a greater degree of muscular enlargement (size >11 mm) or could show atrophic changes atypical in active TRO. A well-defined intramuscular lesion would also be cause for intervention.

Infectious or inflammatory etiologies may exhibit muscle enlargement with blurred or feathered margins, which would be atypical for myopathy associated with TRO. Although unilateral muscle involvement may be present in TRO, it is uncommon and such a presentation may be more indicative of an inflammatory cause.<sup>72</sup>

Infiltration of the orbital fat, though seen in cases of active TRO, may be an indication of an inflammatory, infectious, or a malignant process. Bone may remodel in TRO cases, however sharp excavation or erosion of bone spaces should alert suspicion for other aggressive pathology.<sup>15,72</sup>

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