Assessment of disease activity of Graves' using Orbital Ultrasonography

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***Abstract*: Orbital ultrasound also has a wide range of clinical indications. For example, following examination of a patient with ocular discomfort or pain, clinicians can use ultrasonography to help confirm a diagnosis of scleritis, orbital myositis, or dacryoadenitis. Clinicians can use ultrasonography to evaluate retrobulbar tissue, including the extraocular muscles, in a patient with exophthalmos and suspected soft tissue expansion secondary to Graves' disease.**

Although imaging can help narrow the range of diagnoses to consider, images are only useful in that they reveal patterns and locations of tissue involvement which may statistically be more common in certain disease entities.

I. INTRODUCTION

The concept of disease activity originates from observations of the natural course of the eye signs in patients left untreated for the ophthalmopathy, and from a small number of histologic studies performed on orbital tissues from patients with variable duration of the eye disease.

Nevertheless, Kessel *et al* noted that there was a tendency towards spontaneous regression of the eye signs over time, though without reaching the pre-morbid state. He found that the eye disease begins with a dynamic phase, characterized by ingravescence and remissions, followed by a static phase: depicted as Rundle's curve (Fig. 1). A similar curve was made by Dobyns. Both authors agreed that despite some remission, the eye disease often is still severe when the static phase is reached.

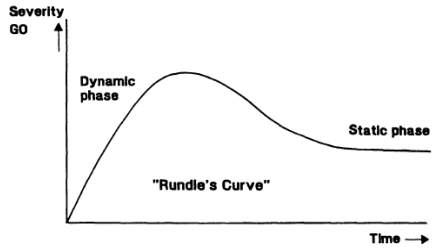

Figure 1. Rundle's curve, describing the natural course of the eye disease over a variable period of several months to a few years. (Contributed by M.F. Prummel)

II. DISCUSSION

Thyroid Associated Orbitopathy (TAO), also referred to as Graves' ophthalmopathy, Graves' orbitopathy, and thyroid eye disease, is a constellation of signs and symptoms resulting from chronic autoimmune-related orbital inflammation.

This disorder is characterized by inflammation, congestion, hypertrophy, and fibrosis of the extra-ocular muscles Because patients with TAO must be followed and treated on the basis of disease activity, several different classification systems based on the clinical assessment have been developed. The evaluation of Graves' orbitopathy activity is important for predicting medical treatment results because treatment is more effective in the active phase. Different scores have been developed to detect activity of the disease, such as the clinical activity score (CAS), the European Group on Graves' Orbitopathy (EUGOGO) classifications and the vision, inflammation, strabismus, and appearance (VISA) classification. The CAS is based on four classical signs of inflammation (pain, redness, swelling, and impaired function), and consists of 10 equally-weighted items. The total CAS may range from 0–10. The higher the CAS, the greater the response to immunosuppression. The CAS in Graves' orbitopathy is correlated with immunosuppressant treatment response and laboratory tests such as thyroid-stimulating hormone. (Table 1) (1-24)

Table 1. GO assessment criteria.

Criteria	Category
Clinical Activity Score	1.Spontaneous retrobulbar pain; 2. Pain on attempted upward or downward gaze; 3. Redness of eyelids; 4. Redness of conjunctiva; 5. Swelling of caruncle or plica; 6. Swelling of eyelids; 7. Swelling of conjunctiva (chemosis); 8. Increase proptosis 2 mm or more in 1-3 mths; 9. Decrease eye movement 8 Degree or more in 1-3 mths; 10. Decrease visual activity 2 line or more in 1-3 mths
NOSPECS	0 No physical signs or symptoms 1 Only signs, no symptoms (lid retraction, stare, lid lag) 2 Soft-tissue involvements (symptoms and signs) 3 Proptosis 4 Extraocular muscle involvement 5 Corneal involvements 6 Sight loss (optic nerve involvement)
VISA classification	Vision (visual blurring, color desaturation); Inflammation (orbital aching at rest or with movement, eyelid or conjunctival swelling or redness); Strabismus (diplopia, with horizontal or vertical gaze, intermittent in primary gaze, constant in primary gaze);

	Appearance changes (distress about bulging eyes, eyelid retraction, and/ or fat pockets, dry eye symptoms).
EUGOGO	Mild GO: GO have a minor impact on daily life. One or more of the following: Minor lid retraction (<2mm); mild soft-tissue involvement; exophthalmos; <3mm above normal for race and gender; no or intermittent diplopia, and corneal exposure responsive to lubricants; Moderate-to-severe GO: GO has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). Two or more of the following: lid retraction ≥ 2mm; moderate or severe soft-tissue involvement; exophthalmos ≥ 3mm above normal for race and gender; inconstant or constant diplopia; Sight-threatening GO: Patients with dysthyroid optic neuropathy (DON) and/ or corneal breakdown.

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Studies investigating ultrasonography in TAO demonstrated that extraocular muscle thickness increases with increasing disease severity as measured via A and B-scans. (9) There is also a high degree of correlation between the right and left eyes, the symmetry of which is invaluable in differentiating TAO from other similar but often unilateral diagnostic entities, such as idiopathic orbital inflammatory syndrome and lymphoma.(8,9) Extraocular muscle thickness demonstrated on ultrasonography has also been shown to correlate with the degree of proptosis (10) In fact, Werner et al. demonstrated that extraocular muscle enlargement is detected more accurately with ultrasonography than by clinical exam.(8) Other sonographic studies of TAO also advocate that a significant association exists between proptosis and the volume of extraocular muscle and orbital fat (11)

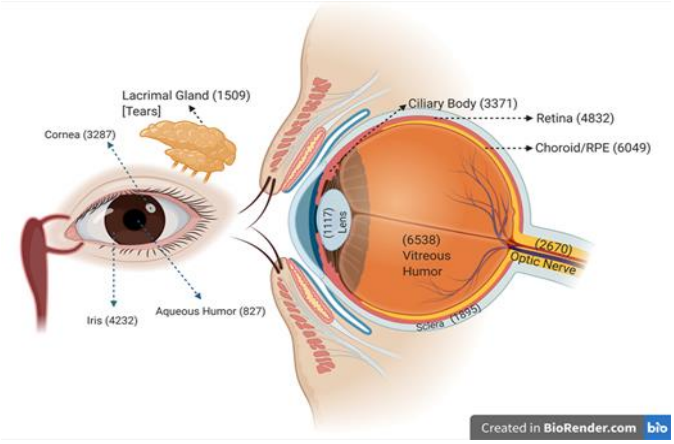


Table 2. GO Ultrasound activity scoring criteria. (khazaei@ohsu.edu)

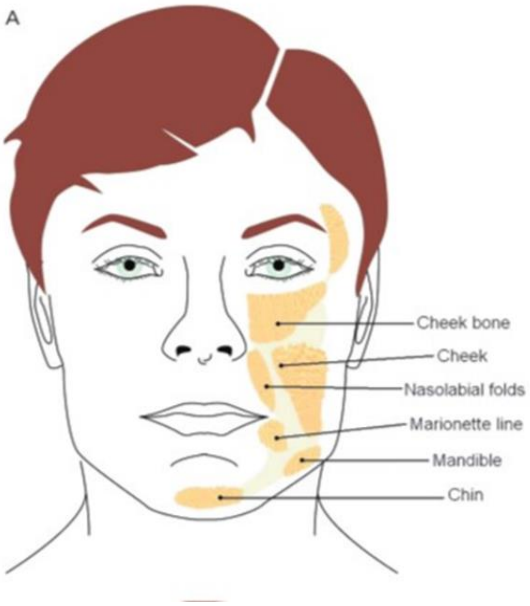
Criteria	Category
Ultrasound Active scoring	1. Peri- Orbital oedema; Paucity or complete absence of fat in the confined subdermal layer, with inflammatory signs. 2. Lacrimal Gland enlargement/Mass with inflammatory response. (Volumetric measurement- small organ study) 3. Optic nerve oedema with fluid accumulation. (Nerve study)
	4. Crowding of orbital apex including vasculature. (Doppler study) 5. Crowding of Intra-conal space (Fat attenuation -TGC) 6. Crowding of Extra-conal space (Muscle attenuation - TGC) 7. Muscle enlargement (3D Orbital Ultrasonography)

Assessment of orbital inflammation can be achieved by the analysis of orbital volume and density of orbital soft tissues which could improve our ability to diagnose active TAO. The aim of this study was to evaluate the quality of both volume and density measurements of orbital soft tissues to assess the inflammatory activity of TAO, using clinical activity score (CAS) as the basis for clinical classification of TAO patients. The endpoints of this study were:

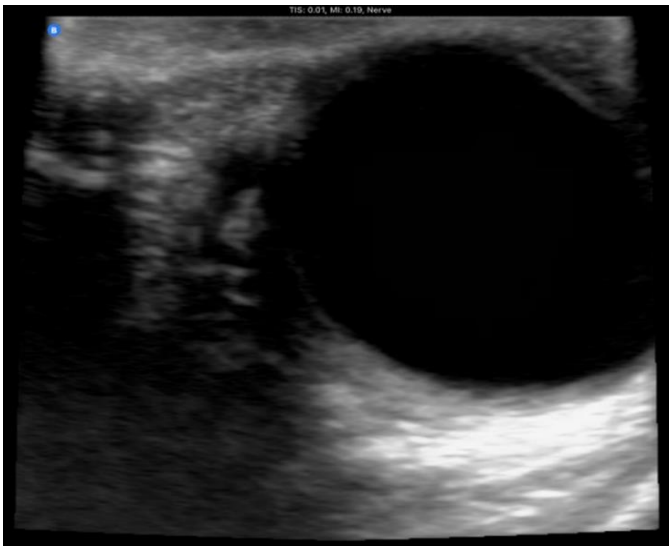
1. To evaluate Orbital Ultrasonography findings in patients with Grave's Orbitopathy.
2. 2.To evaluate the clinically meaningful inflammatory responses in patients with Grave's Orbitopathy as the primary endpoint.
3. Comparing primary endpoint results with Clinical Active scoring system in patients with Grave's Orbitopathy to find any correlations as secondary endpoint. (Table 2)

Facial Nerve and Parotid gland

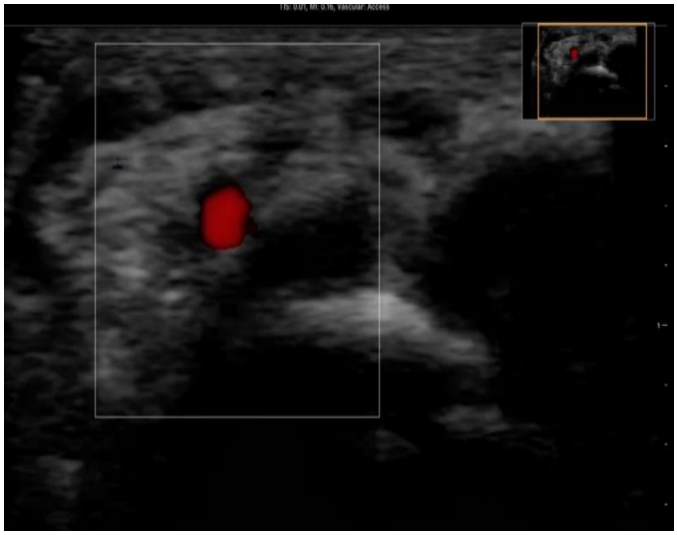
Skin and Ocular Adnexal Ultrasonography

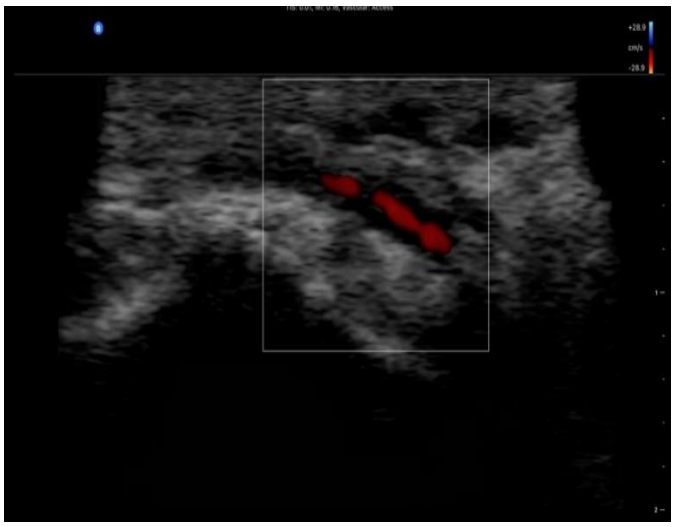


Lacrimal Gland Ultrasonography

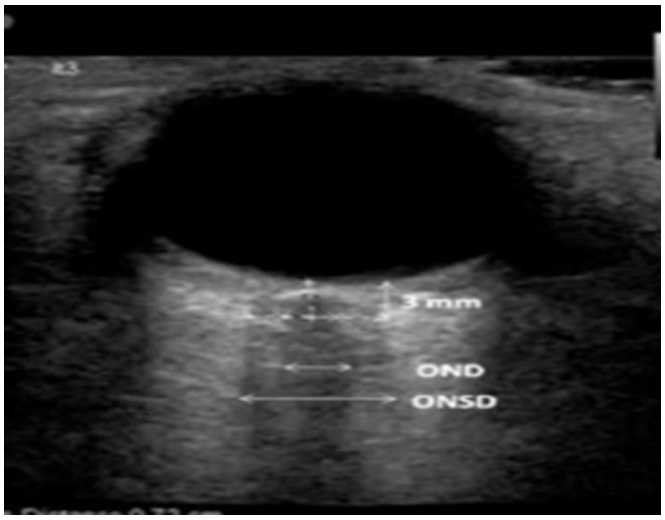


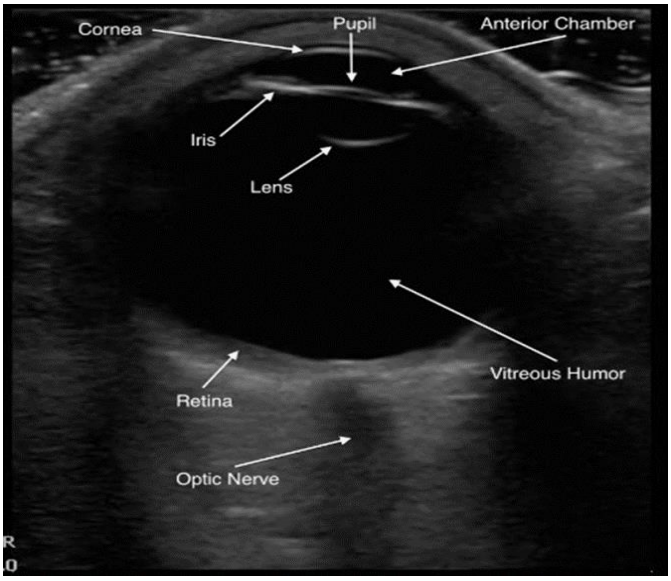
Orbital Doppler Ultrasonography



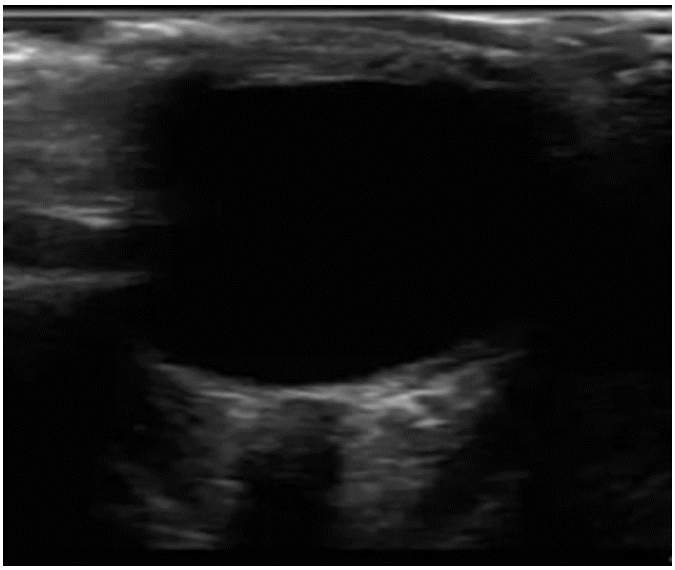


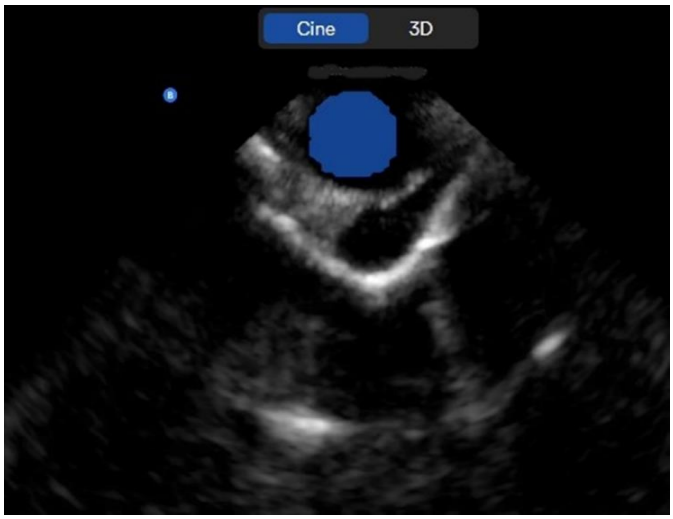
Optic Nerve Ultrasonography





Extra ocular Muscle Ultrasonography





III. METHODOLOGY

All Patients have undergone orbital imaging and measure of clinical disease activity by an orbital specialist. The standard eye examination was included Snellen's visual acuity with and without correction, color vision by Ishihara plates, testing for an afferent pupillary defect, intraocular pressure by Tonopen tonometer, Hertel exophthalmometry, assessment of extraocular motility, assessment for chemosis and redness, corneal staining for epithelial loss and examination of the optic nerve using slit lamp and direct retinoscopy to look for changes such as pallor or edema.

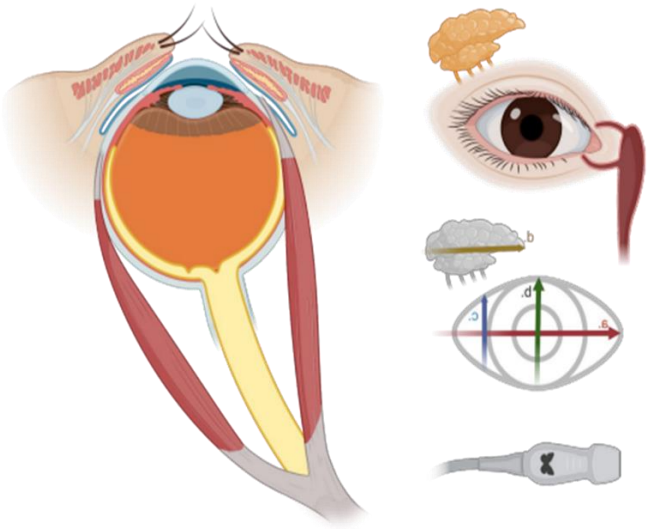
We did assign all patients with diagnosed Graves' Orbitopathy to undergo orbital ultrasonography every 3 months for 12 months; the last trial visit for this analysis were at the end of one year. During each visit the orbital tissue attenuation (extra ocular muscles thickness, Optic nerve oedema, orbital fat density and lacrimal gland enlargement) were examined. Time gain compensation (TGC) were applied in diagnostic ultrasound imaging to account for tissue attenuation following standard operation procedure for orbital ultrasonography. (Figure 2)

- Modifications - At each visit proptosis were measured by the same observer using the same Hertel instrument. Inflammation was quantified according to the Clinical Activity Score, which was based on seven components: spontaneous retrobulbar pain, pain on attempted eye movements (upward, side to-side, and downward gazes), conjunctival redness, redness of the eyelids, chemosis, swelling of the caruncle or plica, and swelling of the eyelids. Each component was scored as present or absent (score of 1 or 0, respectively), and the Clinical Activity Score was given as the sum of the scores (range, 0 to 7, with higher scores indicating greater level of inflammation). A change of at least 2 points was considered clinically meaningful.
- Methods – All patients did have at least one postbaseline value, and were completed the follow-up period. After 12 months data were included in the analyses, regardless of premature discontinuation of the follow-up period. In the

primary outcome analysis, we did assess the between-group differences. Cochran–Mantel–Hansel weighting were used to estimate the percentage-point differences between groups and the standard error of the point difference.

Figure 2: Standard operating procedure for orbital ultrasonography:

1) Obtain approved consent and authorization form
2) Clean and prepare the site of interest and ultrasound probe
3) Apply sterile coupling agents on ultrasound probe headpiece
4) Connect the probe to mobile device and launch the app
5) Select the appropriate preset to start scanning
   a. Horizontal linear scan (medial orientation) - adjust depth and ΔTGC
   b. Vertical linear scan (superior orientation) - adjust depth and ΔTGC
   c. Lateral vertical oblique scan (Ossining technique + doppler) - optic nerve assessment
   d. Horizontal linear (Lacrimal gland) scan - volumetric and ΔTGC
6) 3D scan/Cine recording of orbit



IV. CONCLUSION

Orbital ultrasound (US)can demonstrate extraocular muscle reflectivity changes, orbital fat attenuation, lacrimal gland enlargements and optic nerve oedema in the inflammatory phase of GO, suggesting that US is a reliable tool for the determination of disease activity. In the active phase, the extraocular muscles have a lower internal reflectivity, presumably due to edema, whereas in end-stage disease, the muscles tend to show irregular high reflectivity from the echogenic fibrotic scar tissue. Similarly, the orbital fat, lacrimal gland and optic nerve demonstrate inflammatory changes in active phase of disease which may not correlate with clinical active scoring (CAS). IN the current trial, we have investigated the efficacy and safety of orbital ultrasonography in patients with Grave's Orbitopathy. The use of US has also been proposed for evaluating disease activity. (25-30)

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