ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 06 | June - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A REVIEW ON THYROID EYE DISEASE

Neurology

Dr Arushee Bhatnagar Neurology Resident, Indraprastha Apollo Hospital, New Delhi.

Dr Dinesh Mohan Chaudhari Associate Consultant, Institute of Neurosciences, Indraprastha Apollo Hospitals, Delhi – 110076.

Dr Pushpendra N Renjen* Sr. Consultant Neurologist & Academic Coordinator, Institute of Neurosciences, Indraprastha Apollo Hospitals, Delhi. *Corresponding Author

Dr Urusa Hasan Neurology Resident, Indraprastha Apollo Hospital, New Delhi.

KEYWORDS

INTRODUCTION:

Graves orbitopathy (GO) is associated with thyroid autoimmunity (AITD) and is highly complex. It is defined by the expansion and remodelling of the orbital tissue due to inflammation of retrobulbar tissues, increased adipogenesis, and glycosaminoglycans (GAGs) accumulation in the extraocular muscles. GO is an extrathyroidal manifestation of Graves' disease (GD) and can also be seen with Hashimoto's thyroiditis or Euthyroid Graves' Orbitopathy. (1) GO results from a complex interaction of endogenous (unmodifiable) and exogenous/environmental (modifiable) risk factors. The former include age, gender, and genetic factors. As described in a previous section of this manuscript, GO tends to be more severe in men, in whom it occurs at an older age than in women. Several modifiable risk factors for the occurrence/progression have been identified. The modifiable risk factors may include smoking, hyperthyroidism/ hypothyroidism, radioiodine treatment, oxidative Stress, TSH-Receptor Antibody Levels and hypercholesterolemia (2). The GO is usually mild and rarely progresses to the severe course can be managed by restoring the euthyroid state.

Pathophysiology:

The pathophysiology of TED is complex and incompletely understood. It is believed that there is a loss of self-tolerance to thyrotropin receptor (TSHR) and insulin-like growth factor-1 receptor (IGF-1R). These receptors are internalized by APCs and presented to helper T cells, causing B cells' activation and induction to produce autoantibodies (GD-IgGs) or may become autoreactive T cells. These autoantibodies interact with TSHR on thyroid follicular epithelial cells, causing follicular hyperplasia /hypertrophy. The T-cell chemoattractants cause autoreactive CD4 T cells to travel orbital tissue and interact with orbital fibroblasts (OFs), leading to mutual activation of both cell types. T cells, B cells, and OFs overexpress IGF-1R, which interacts with GD-IgGs, resulting in cellular activation.

On the surface of OFs, a physical and functional complex is formed with IGF-1R and TSHR interacting with GD-IgGs. Activated OFs can increase hyaluronan synthesis by differentiating into either adipocytes or myofibroblasts, causing expansion of orbital soft tissues in TED.OFs are classified based on Thy1/CD90 (3,4,5,6) surface marker expression. Thy1+ OFs are expressed in the perimysium of the extraocular muscles and can differentiate into myofibroblasts upon activation (6). on the other hand, Thy1− OFs are present in preadipocytes found throughout the orbit and can differentiate into mature adipocytes (3,6,).

Fibrocytes are another type of cell said to have a role in the pathogenesis of TED. They are bone marrow-derived, fibroblast-like progenitor cells that circulate in the peripheral blood that expresses CD34 a, the hematopoietic stem cell marker, CD45 a leukocyte common antigen, and other fibroblast proteins like alpha-smooth muscle actin, collagen I and III, fibronectin, and vimentin. They migrate to injury sites and differentiate into fibroblasts or adipocytes, leading to tissue remodelling and T-cell proliferation (7,8). They are known to infiltrate both the orbital and thyroid tissues in GD patients (9).

Titers of the two subtypes of TSHR antibodies, thyroid-stimulating immunoglobulins (TSI), which directly activate TSHR, and TSHR binding inhibitory immunoglobulins (TBII), which prevent TSH from binding TSHR, are both positively correlated with the clinical activity and severity of TED (10).

Clinical Features:

Detailed patient history is essential to elicit if the patient has any symptoms. Patients with proptosis can be asymptomatic and may present as a foreign body sensation in the eyes with tearing, swelling, redness, pain or pressure behind the eyes or any movement. In rare cases, they may have diplopia, blurring, desaturation of colour vision, or complete loss of vision. Some patients may notice an inability to close their eyes completely lagophthalmos. The first step in the physical examination is to inspect the eyes for proptosis and look for symmetry. An exophthalmometer should be available to measure the degree of proptosis. Other signs of inflammation like conjunctival injection, chemosis, and periorbital oedema should also be evaluated. Upper eyelid retraction is not specific for GO but is often present. After inspection, a full closure of the eyes must be measured to identify at-risk corneal damage due to exposure to keratopathy. Following this, extraocular muscles must be tested in all quadrants to look for signs of pain or muscle entrapment. Finally, visual acuity and colour vision should be checked as part of the comprehensive examination. There is a multitude of signs observed in the physical examination, which may include Jellinek's sign- hyperpigmentation of the superior fold of the eyelid, Tella's sign- hyperpigmentation of the inferior eyelid and Rosenbach's sign of fine tremors of the eyelids when closed, Moebius' sign lack of convergence with gaze fixed; fundoscopy may show Beck's sign that is pulsating retinal arteries, and on auscultation, Snellen-Rieseman's sign systolic murmur with placed over the closed eyelid (11).

Diagnosis:

The initial confirmatory test used is thyroid function tests(TFTs) which include serum TSH and free T4 levels along with TSH receptor antibody levels is essential to measure severity and treatment response (12). Many scoring systems are used to classify GO. The NO SPECS criteria help assess the severity and have four grades; 0- no signs or symptoms, I- limited signs (i.e., lid retraction/lag), II soft tissue involvement, III- proptosis stage, and IV- extraocular muscle involvement (13). Another scoring tool used is the EUGOGO (European Group on Graves Orbitopathy) classification used to classify GO as mild, moderate-to-severe, and sight-threatening (14). The VISA classification assesses vision changes, evidence of inflammation/congestion such as chemosis, conjunctival redness, strabismus/restricted motility of the eye and appearance (proptosis, lid retraction) or exposure (those symptoms and signs related to exposure keratopathy) (15). The scoring system CAS (clinical activity score) should be used to evaluate the clinical activity of GO. A score more than or equal to 3 indicates a clinically active GO (15), or a score of 4 or more on follow-up visits is considered clinically active. Clinically active cases of GO should undergo immediate ophthalmology and immediate initiation of treatment. Imaging techniques are also used to identify clinically active diseases and can help to decide if

immunomodulatory therapy shall be effective. MRI is a valuable modality if orbital nerve compression or asymmetry is present to rule out other differential pathologies. The CT scan does not help to determine clinical activity but may help in the planning stages of orbital decompression surgery (16).

Management:

The mainstay of treatment for graves orbitopathy targets a euthyroid state as early as possible. Moreover, it can be achieved with antithyroid drugs (ATD), followed by other definitive treatment modalities, including surgery or radioiodine therapy (RAI). The choice of treatment depends on the patient's age, the thyroid volume, the presence of GO and its degree of activity and severity. Progression of GO can be prevented with the administration of oral low dose steroid (0.2 mg/kg BW of prednisone for six weeks) prophylaxis when treating RAI patients with GD. A higher dose may be necessary for patients with moderate GO [17].

Mild Orbitopathy

The literature indicates that most patients with GD have mild to no GO at presentation and that the progression of mild GO to severe forms is infrequent, while partial or complete remission is frequent. Therefore, a wait and watch strategy should be adopted along with supportive measures and patient reassurance. As per the data available, 35–65% of patients have shown improvement, disease stabilization in 20–45% and worsening in 4–25%. Symptomatic local measures should be taken, including lubricants during the daytime and ointments at night for dryness, redness, itching, light sensitivity, excessive tearing or feeling of a foreign body. Lagophthalmos may need taping of the eyelids during the night. The addition of 0.05% cyclosporine A as a local immunosuppressive agent to the artificial tear drops has shown no improvement (18). for Photophobia, the use of sunglasses and for morning periorbital congestive swelling can be reduced by increasing the elevation of the head at night. However, mild GO does not affect the patients' quality of life, but when there is a significant deterioration or in refractory cases, radiotherapy can be used [19]. Prisms for diplopia and Botulinum toxin type A injections may reduce upper lid retraction. *Smoking cessation* is crucial to decreasing the chance of proptosis/diplopia and halting GO progression. Other supportive measures may include antioxidant supplementation, especially in deficient populations. Selenium has antioxidant, anti-inflammatory, and immunomodulatory actions [20]. A recent multicenter randomized, 6month placebo-controlled trial showed that selenium (sodium selenite 100 µg twice daily) could effectively ameliorate the quality of life in GO without adverse events [21]. However, the population was from selenium-deficient areas, so the evidence of its effectiveness is still relatively weak.

Moderate to Severe Orbitopathy

The natural course of GO is self-limited and includes an active phase of inflammation of the orbital tissues, where disease severity progresses, followed by stabilization and partial remission of disease signs, as per the "Rundle curve" [22]. Immunosuppressive therapies, namely glucocorticoids (GCs), are only effective in the active phase of moderate-severe GO as an anti-inflammatory; at higher doses, has an immunosuppressive effect. It helps to reduce the degree of compression around the optic nerve by eye muscles and consequently reduces the need for subsequent rehabilitative surgery. GCs act by decreasing the synthesis and secretion of glycosaminoglycans by orbital fibroblasts, downregulating some adhesion molecules, inhibiting cytokines and antibodies secretion, interfering with T and B lymphocytes functions, and decreasing the recruitment of neutrophils and macrophages at the inflammation sites [23].

Administration of GCs (subconjunctival or peribulbar) is not recommended. Administration of local triamcinolone injections has been associated with complications such as intractable intraocular hypertension, globe perforation, conjunctival or corneoscleral melting, vascular occlusion or pressure-induced optic nerve compression, fat atrophy, depigmentation, and granulomas due to the vehicle of the depot injections. However, oral therapy is more often associated with long-term side effects, including hepatotoxicity, Cushing's syndrome, osteoporosis, glaucoma, and diabetes mellitus. Intravenous methylprednisolone (ivMP) is 70–80% effective with a better safety profile than oral prednisone [24].

Targeted Immunomodulation Therapy:

TSH Receptor Therapy: With recent medical advancements a, low molecular weighted TSHR ligands are synthesized to treat GD/GO acting by 1) TSHR agonists (ligands that activate receptors), 2) neutral antagonists (ligands that inhibit receptor activation by agonists), and 3) inverse agonists (ligands that inhibit receptor activation by agonists and also basal or constitutive signalling).

IGF-1 receptor therapy: This receptor is co-expressed on orbital fibroblasts with the TSH-R. Teprotumumab (RV 001, R1507) is a specific fully human monoclonal antibody binding to the extracellular-subunit domain of the IGF-1 receptor (IGF-1R). although it helps to decrease the expression of TSHR and IGF-1R on fibrocytes or weakens TSH-dependent IL-6, IL-8 expression and Akt phosphorylation with weak evidence. (25)

B Cells and Rituximab: Rituximab (RTX) is an off label drug for GO treatment, although it is widely used in rheumatoid arthritis and antineutrophil cytoplasmic antibody-associated (ANCA) vasculitis. It is a chimeric mouse-human monoclonal antibody that targets CD20, a human B lymphocyte-specific antigen expressed on B cells from the stages of immature to mature B cells, but not on antibody-producing plasma cells due to it is not able to remove long-lived plasma cells from the peripheral blood and antibody production is maintained, despite peripheral B cell depletion [26]. RTX use in GO blocks pathogenic autoantibody generation and production of inflammatory cytokines or the depletion of B cells as antigen-presenting cells. It may affect specific B cell clones from the germinal centres or even extrafollicular lymphoid structures without interfering with B and T cell interaction, therefore having a little therapeutic impact on pathogenic specific autoantibodies [27]. It has been noted that it can also help in the depletion of T cells, mainly CD4+ cells and is an excellent alternative to refractory steroid cases. Combination therapy is a good option with orbital radiotherapy associated with either oral steroids or ivMP, or cyclosporin.

Monoclonal Antibodies:

The production of pro-inflammatory and Th1-derived cytokines such as IL-6 and IL-1 and IFN-gamma-induced chemokines(CXCL10) is a predominant inactive phase of GO. Immunoglobulins binding TSH receptors may increase the IL-1 receptor expression on orbital fibroblasts [28]. Anakinra, an interleukin-1 (IL-1) receptor antagonist, is hypothesized to play a role in the therapeutic management of GO. TNF inhibitors (etanercept, infliximab, adalimumab) used in autoimmune rheumatic diseases have shown efficacy in GO cases. *Etanercept* is a recombinant dimeric fusion protein that binds TNF and prevents TNF-mediated inflammatory responses. Tocilizumab- a recombinant, humanized monoclonal antibody is an IL-6 receptor antagonist. Intravenous tocilizumab has improved disease activity in steroid-refractory patients with GO [29].

Orbital Radiotherapy:

Orbital radiotherapy has better effects than irradiation and oral prednisone, especially in eye motility and reducing GO severity. There is also strong evidence that radiotherapy synergistically potentiates oral GC effects and the effectiveness of RT with oral GC as a combination therapy over IV GC monotherapy (30). A cumulative dose of 20 Gray (Gy) per orbit fractionated in ten daily doses over 2-weeks is administered (31). A concomitant low-dose oral prednisone is given to treat mild exacerbation of ocular symptoms during RT. It is relatively safe but (32) should be avoided in patients with hypertension or diabetic retinopathy.

Treatment of sight-threatening Ophthalmopathy:

Rehabilitative Surgery:

Approximately 3–5% of patients have severe GO, accounting for dysthyroid optic neuropathy (DON) or severe corneal damage. The standard gold treatment adopted for DON is urgent orbital decompression, following which 40% of patients may respond to high dose ivMP course within 1–2 weeks [30]. Rehabilitative surgery rectifies orbital decompression, squint, lid lengthening and blepharoplasty. In emergencies, many techniques allow a graded reduction of proptosis and optic nerve decompression. To treat diplopia, extraocular muscle recessions are performed. Only large or complex squint angles are difficult to treat, and step by step procedures are recommended for these patients. Under LA, lid lengthening procedures are commonly performed in GO patients with rare adverse events and a good prognosis (33). The diagnosis of DON is sometimes challenging, and the distinction between subclinical and overt forms is not always straightforward. It is recommended to use high dose ivMP

(500 mg or 1 000 mg) as the first line of treatment consecutively for three days, with a follow-up dose in one week. In responsive patients, oral prednisone may be used later and tapered over the next few weeks or by weekly pulses of ivMP, up to a cumulative dose of 8 g [30,31]. Urgent orbital decompression is performed in ivMP resistant or when contraindicated. A total or subtotal thyroidectomy does not affect ophthalmopathy. However, total thyroid ablation with surgery and RAI may help achieve thyroid antigen disappearance. This has now gained importance in the treatment of GO, especially the ones undergoing thyroid surgery or severe resistant un ophthalmopathy (34).

CONCLUSION:

GO is an extrathyroidal manifestation of Graves' disease but is rarely seen in euthyroid/hypothyroid patients with chronic autoimmune thyroiditis. GO tends to improve and eventually inactivates (inactive or burnt-out phase). Mild GO tends spontaneously to remit spontaneously with no recurrence. Many risk factors contribute to GO, and cigarette smoking is the most. Early diagnosis, control and removal of modifiable risk factors, early treatment of mild forms, and stable control of thyroid dysfunction may effectively limit the risk of progression to more severe forms of GO, which have a profound and dramatic impact on the quality of life of affected individuals, and remain a therapeutic challenge, often requiring long-lasting and multiple medical and surgical therapies.

REFERENCES:

1. M. Salvi, I. Campi Medical Treatment of Graves' Orbitopathy Horm Metab Res 2015; 47(10): 779-788 DOI: 10.1055/s 0035-1554721 Bartalena Luigi, Piantanida Eliana, Gallo Daniela, Lai Adriana, Tanda Maria Laura Epidemiology, Natural History, Risk Factors, and Prevention of Graves' Orbitopathy Frontiers in Endocrinology VOL11 2020
2. https://www.frontiersin.org/article/10.3389/fendo.2020.615993 DOI=10.3389/fendo.2020.615993 ISSN=1664-2392
3. Smith TJ, Koumas L, Gagnon A, Bell A, Sempowski GD, Phipps RP, Sorisky A. Orbital fibroblast heterogeneity may determine the clinical presentation of thyroid-associated ophthalmopathy. J Clin Endocrinol Metab. 2002;87:385–392.
4. Wiersinga WM. Autoimmunity in Graves' ophthalmopathy: an unfortunate marriage between TSH receptors and IGF-1 receptors? J Clin Endocrinol Metab. 2011;96:2386–2394.
5. Smith TJ, Tsai CC, Shih MJ, Tsui S, Chen B, Han R, Naik V, King CS, Press C, Kamat S, Goldberg RA, Phipps RP, Douglas RS, Gianoukakis AG. Unique attributes of orbital fibroblasts and global alterations in IGF-1 receptor signalling could explain thyroid-associated ophthalmopathy. Thyroid. 2008;18:983–988.
6. Koumas L, Smith TJ, Feldon S, Blumberg N, Phipps RP. Thy-1 expression in human fibroblast subsets defines myofibroblastic or lipofibroblastic phenotypes. Am J Pathol. 2003;163:1291–1300.
7. Chesney J, Bacher M, Bender A, Bucala R. The peripheral blood fibrocyte is a potent antigen-presenting cell capable of priming naive T cells in situ. Proc Natl Acad Sci U S A. 1997;94:6307–6312.
8. 37. Quan TE, Cowper S, Wu SP, Bockenstedt LK, Bucala R. Circulating fibrocytes: collagen-secreting cells of the peripheral blood. Int J Biochem Cell Biol. 2004;36:598–606.
9. Smith TJ, Padovani-Claudio DA, Lu Y, Raychaudhuri N, Fernando R, Atkins S, Gillespie EF, Gianoukakis AG, Miller BS, Gauger PG, Doherty GM, Douglas RS. Fibroblasts expressing the thyrotropin receptor overarch thyroid and orbit in Graves' disease. J Clin Endocrinol Metab. 2011;96:3827–3837.
10. Eckstein AK, Plicht M, Lax H, Hirche H, Quadbeck B, Mann K, Steuhl KP, Esser J, Morganthaler NG. Clinical results of anti-inflammatoryanti-inflammatory therapy in Graves' ophthalmopathy and association with thyroidal autoantibodies. Clin Endocrinol (Oxf). 2004;61:612–618.
11. Saraci G, Treta A. Ocular changes and approaches of ophthalmopathy in Basedow - graves- parry- flajani disease. Medica (Bucur). 2011 Apr;6(2):146-52
12. Eckstein AK, Plicht M, Lax H, Neuhäuser M, Mann K, Lederbogen S, Heckmann C, Esser J, Morgenthaler NG. Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease. J Clin Endocrinol Metab. 2006 Sep;91(9):3464-70.
13. Werner SC. Modification of the classification of the eye changes of Graves' disease. Am J Ophthalmol. 1977 May;83(5):725-7.
14. Barrio-Barrio J, Sabater AL, Bonet-Farriol E, Velázquez-Villoria Á, Galofré JC. Graves' Ophthalmopathy: VISA versus EUGOGO Classification, Assessment, and Management. J Ophthalmol. 2015;2015:249125.
15. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clin Endocrinol (Oxf). 1997 Jul;47(1):9-14
16. Kirsch E, von Arx G, Hammer B. Imaging in Graves' orbitopathy. Orbit. 2009;28(4):219-25.
17. Shiber S, Stiebel-Kalish H, Shimon I, Grossman A, Robenshtok E. Glucocorticoid regimens for prevention of Graves' ophthalmopathy progression following radioiodine treatment: systematic review and meta-analysis. Thyroid 2014; 24: 1515-1523
18. Gürdal C, Genç I, Saraç O, Gönül I, Takmaz T, Can I. Topical cyclosporine in thyroid orbitopathy-related dry eye: clinical findings, conjunctival epithelial apoptosis, and MMP-9 expression. Curr Eye Res 2010; 35: 771-777
19. Wiersinga WM, Prummel MF, Terwee CB. Effects of Graves' ophthalmopathy on quality of life. J Endocrinol Invest 2004; 27: 259-264
20. Marcocci C, Bartalena L. Role of oxidative stress and selenium in Graves' hyperthyroidism and orbitopathy. J Endocrinol Invest 2013; 36: 15-20
21. Marcocci C, Kahaly GJ, Krassas GE, Bartalena L, Prummel M, Stahl M, Altea MA, Nardi M, Pitz S, Boboridis K, Savelli P, von Arx G, Mourits MP, Baldeschi L, Bencivelli W, Wiersinga W. European Group on Graves Orbitopathy . Selenium and the course of mild Graves' orbitopathy. N Engl J Med 2011; 364: 1920-1931
22. Bahn RS, Heufelder AE. Pathogenesis of Graves ophthalmopathy. Engl J Med 1993; 329: 1468-1475
23. Heufelder AE, Wenzel BE, Bahn RS. Glucocorticoids modulate the synthesis and expression of a 72 kDa heat shock protein in cultured Graves' retroocular fibroblasts. Acta Endocrinol 1993; 128: 41-50
24. Kahaly GJ, Pitz S, Hommel G, Dittmar M. Randomized, single-blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. J Clin Endocrinol Metab 2005; 90: 5234-5240
25. Chen H, Mester T, Raychaudhuri N, Kauh CY, Gupta S, Smith TJ, Douglas RS. Teprotumumab, an IGF-1R blocking monoclonal antibody inhibits TSH and IGF-1 action in fibrocytes. J Clin Endocrinol Metab 2014; 99: E1635-E1640
26. Kurtz J-E, Ray-Coquard I. PI3 kinase inhibitors in the clinic: an update. Anticancer Res 2012; 32: 2463-2470
27. 85 Gong Q, Ou Q, Ye S, Lee WP, Cornelius J, Diehl L, Lin WY, Hu Z, Lu Y, Chen Y, Wu Y, Meng YG, Gribling P, Lin Z, Nguyen K, Tran T, Zhang Y, Rosen H, Martin F, Chan AC. Importance of cellular microenvironment and circulatory dynamics in B cell immunotherapy. J Immunol 2005; 174: 817-826
28. Li B, Smith TJ. Regulation of IL-1 receptor antagonist by TSH in fibrocytes and orbital fibroblasts. J Clin Endocrinol Metab 2014; 99: E625-E633
29. Pérez-Moreiras JV, Alvarez-López A, Gómez EC. Treatment of active corticosteroid-resistant Graves' orbitopathy. Ophthal Plast Reconstr Surg 2014; 30: 162-167
30. Wakelkamp IM, Baldeschi L, Saeed P, Mourits MP, Prummel MF, Wiersinga WM. Surgical or medical decompression as a first-line treatment of optic neuropathy in Graves' ophthalmopathy? A randomized controlled trial. Clin Endocrinol 2005; 63: 323-328
31. Currò N, Covelli D, Vannucchi G, Campi I, Pirola G, Simonetta S, Dazzi D, Guastella C, Pignataro L, Beck-Peccoz P, Ratiglia R, Salvi M. Therapeutic outcomes of high-dose intravenous steroids in the treatment of dysthyroid optic neuropathy. Thyroid 2014; 24: 897-905
32. McKeag D, Lane C, Lazarus JH, Baldeschi L, Boboridis K, Dickinson AJ, Hullo AI, Kahaly G, Krassas G, Marcocci C, Marinò M, Mourits MP, Nardi M, Neoh C, Orgiazzi J, Perros P, Pinchera A, Pitz S, Prummel MF, Sartini MS, Wiersinga WM. European Group on Graves Orbitopathy (EUGOGO) Clinical features of dysthyroid optic neuropathy: a European Group on Graves Orbitopathy (EUGOGO) survey. Br J Ophthalmol 2007; 91: 455-458
33. Anja Eckstein, Michael Schittkowski, Joachim Esser, Surgical treatment of Graves' ophthalmopathy,Best Practice & Research Clinical Endocrinology & Metabolism, Vol 26, Issue 3,2012, 339-358,ISSN 1521-690X, https://doi.org/10.1016/j.beem.2011.11.002.
34. Azzam I, Tordjman K. Clinical update: treatment of hyperthyroidism in Graves' ophthalmopathy. Pediatric Endocrinology Reviews : PER. 2010 Mar;7 Suppl 2:193-197. PMID: 20467362.