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Thyroid Related Opthalmopathy and Dermopathy and Their Treatment

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Abstract: **Background: Thyroid-associated ophthalmopathy ansd dermopathy are dynamic eye disorders issues described by immune-mediated inflammation of the extraocular muscles and orbital connective tissue.**
Objective: to discuss the thyroid related opthalmopathy and dermopathy and their management to evaluate and demonstrate different evidence based concerning different population, and make this evidence easy to understand and all summarized in one article.
Methodology: We performed a systemic review study up to July 2016; all our reference articles were obtained from Pubmed. The key words for search were thyroid ophthalmopathy, thyroid orbitopathy, thyroid associated ophthalmopathy, ocular and skin manifestations of thyroid, ocular features of Graves' disease, thyroid eye disease, and Graves' ophthalmopathy and dermopathy.
Conclusion: Opthalmopathy and dermopathy related to thyroid is a self-limiting autoimmune disease associated mainly with hyperthyroidism, but also with hypothyroid and euthyroid states. Almost all cases of thyroid dermopathy are associated with relatively severe ophthalmopathy. Usually ophthalmopathy appears first and dermopathy much later.

Keywords: **Opthalmopathy, Dermopathy, Thyroid.**

1. INTRODUCTION

Thyroid hormones are critical and have different diverse functions. They follow up on for all intents cell in the body to alter gene transcription: under- or over-production of these hormones has strong impacts. Most of functional disorders connected with changed thyroid hormone secretion are common and affect about 5% women and 0.5% men [(1)]. Thyroid-associated ophthalmopathy is a dynamic eye disorders issues described by immune-mediated inflammation of the extraocular muscles and orbital connective tissue. The impacts of inflammation, interceded through cytokine release, incorporate expansion of fibroblasts, expanded affidavit of extracellular grid, and adipocyte separation and multiplication. Accordingly, edema, augmentation of the extraocular muscles, and expanded volume of the orbital delicate tissues happen with resulting exophthalmos and, in a few patients compression of the optic nerve [(1)].

Thyroid associated ophthalmopathy correlates with Graves' hyperthyroidism in about 80% of all cases [(18)]. Graves' disease is an autoimmune condition commonly associated with thyroid dysfunction and with anti-thyroid antibodies, more often than not TSH receptor animating antibodies. Thyroid autoimmunity also may be associated with extra thyroidal manifestations. Most regular additional thyroidal sign is ophthalmopathy. Less common is thyroid dermopathy [(2,3)]. The close clinical and temporal relationships between hyperthyroidism, Graves' ophthalmopathy, and thyroid dermopathy suggest that these conditions evolve from a single underlying systemic process with variable expression in the thyroid, eyes, and skin [(4)]. Bilateral ocular symptoms and hyperthyroidism most often occur simultaneously or within 18 months of each other, although occasionally Graves' ophthalmopathy precedes or follows the onset of hyperthyroidism by many years [(5)]. Thyrotoxicosis is also classically associated with cutaneous manifestations. In a review of thyrotoxic presentations, hyperhydrosis, was the second most common finding. Although certain manifestations are specific to Graves disease, thyrotoxicosis of any etiology can include skin sequelae [(6)].

Moreover Hashimoto's thyroiditis as certified by high thyroid affiliation opthalmopathy neutralizer titre in our patient proposes that continuous immune system devastation was in charge of his hypothyroid state. Immune system thyroprivic

hypothyroidism is normally not connected with thyroid related ophthalmopathy or dermopathy, in spite of expanded groupings of TSH which may follow up on TSH receptors present on visual or dermal fibroblasts like thyroid fortifying immunoglobulins (TSI). The probable reasons are that autoimmunity in Hashimoto's thyroiditis is confined to thyroid gland only and/or thyroid stimulating immunoglobulins possibly act on some other orbital or dermal antigens other than TSH receptors [7].

Finally Pretibial myxedema or localized myxedema or thyroid dermopathy is an autoimmune manifestation of Graves' disease. It also occasionally occurs in Hashimoto's thyroiditis. Lesions of thyroid dermopathy are usually asymptomatic and have only cosmetic importance. Advanced forms of dermopathy are associated with elephantiasis or thyroid acropachy. Almost all cases of thyroid dermopathy are associated with relatively severe ophthalmopathy [8].

2. OBJECTIVES

Current evidence demonstrates the efficacy of treatment of thyroid associated opthalmopathy and dermopathy and this has to be insured after understanding the background of these disorders and their complication. Therefore we performed this study which aimed to discuss the thyroid related opthalmopathy and dermopathy and their management to evaluate and demonstrate different evidence based concerning different population, and make this evidence easy to understand and all summarized in one article.

3. METHODOLOGY

We performed a systemic review study up to July 2016, all our reference articles were obtained from Pubmed. The key words for search were thyroid ophthalmopathy, thyroid orbitopathy, thyroid associated ophthalmopathy, ocular and skin manifestations of thyroid, ocular features of Graves' disease, thyroid eye disease, and Graves' ophthalmopathy and dermopathy. We included trials regardless of publication status and language. We did include studies evaluating treatments for Graves' disease in which ophthalmopathy was a secondary outcome and did not include studies evaluating modalities aimed at alleviating selective complications of Graves' ophthalmopathy such as diplopia or exophthalmos.

4. RESULTS AND DISCUSSION

Most common cause of thyroid Opthalmopathy and their pathogenesis:

Current evidence points to orbital fibroblasts as the target cells in Graves' ophthalmopathy and suggests that their normal functions are dysregulated through autoimmune mechanisms [9,10]. The concept that fibroblast proteins are autoantigens in Graves' ophthalmopathy derives in part from the finding that orbital T cells obtained from patients with Graves' ophthalmopathy proliferate when exposed in vitro to autologous orbital fibroblast proteins [11].

The clinical features of thyroid ophthalmopathy depend on the stage of the disease. The initial acute stage of the disease is characterized by active inflammation in which the eyes are red and painful and the disease later progresses to a stable or a quiescent stage in which the eyes are white and unchanging with a painless motility defect [12].

Mechanisms of inflammation involved in thyroid ophthalmopathy:

Studies on the inflammatory activation of orbital fibroblasts in thyroid ophthalmopathy have shown an involvement of immune cell derived mediators and fibroblast surface gangliosides [13, 14), (15]. Importantly, orbital fibroblasts also express the costimulatory transmembrane molecule CD40 [16] which is normally absent from these cells [17]. As CD40 interacts with the stimulating T helper (Th) cell molecule CD154, it has been hypothesised that orbital fibroblasts may be activated by Th cells. Yet the structure of CD40 implies further unidentified ligands, [17] so that the actual process currently remains elusive.

pproximately 80% of cases of thyroid ophthalmopathy occur in association with hyperthyroidism, yet the onset may not coincide with the onset of the hyperthyroid state. In relation to hyperthyroidism, thyroid ophthalmopathy may present well before the onset of thyroid dysfunction, during thyroid dysfunction, or when the patient is euthyroid following therapy [18]. Five to ten percent of patients with thyroid ophthalmopathy do not develop hyperthyroidism and are called euthyroid thyroid ophthalmopathy, [19] and 10% of thyroid ophthalmopathy patients have primary autoimmune hypothyroidism [20].

Clinical Features In Thyroid Ophthalmopathy:

The most frequent sign in thyroid ophthalmopathy is eyelid retraction, which affects 90–98% of patients [21,22] and frequently varies with attentive gaze [23] (Kocher's sign). Contour of the retracted upper eyelid often shows lateral flare, an appearance that is almost pathognomic for thyroid ophthalmopathy [24]. Lid retraction is multifactorial and is due to increased sympathetic stimulation of Muller's muscle, contraction of the levator muscle, and scarring between the lacrimal gland fascia and levator, which specifically gives rise to the lateral flare [25,26] as it seen in (figure1).

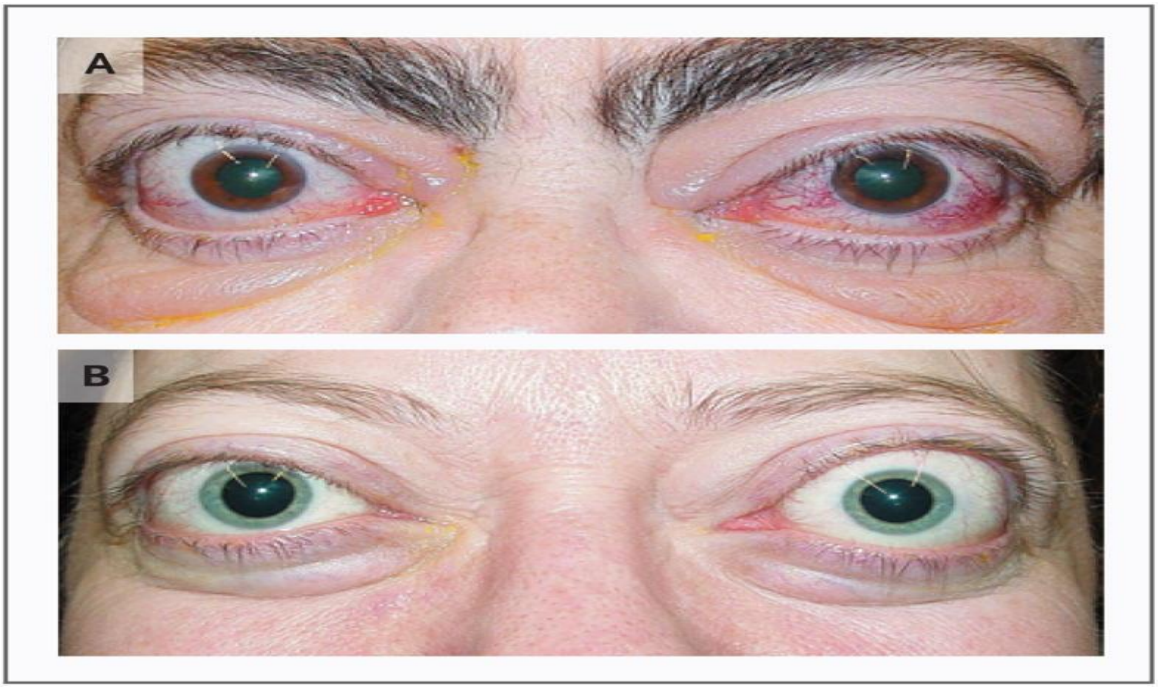

Figure1: Patients with Graves' Ophthalmopathy

Panel **A** shows excess proptosis, moderate eyelid edema, and erythema with moderate eyelid retraction affecting all four eyelids. Conjunctival chemosis (edema) and erythema with bilateral edema of the caruncles, with prolapse of the right caruncle, are evident. Panel **B** shows excess proptosis, minimal bilateral injection, and chemosis with slight erythema of the eyelids. She also had evidence, on slit-lamp examination, of moderate superior limbic keratoconjunctivitis. Frueh et al, [25]

Histologic studies of Graves' ophthalmopathy have focused on extraocular muscles, owing to their obvious enlargement in patients with the disease. However, electron microscopy reveals intact extraocular muscle fibers in such patients [27]. The extraocular muscles are widely separated by an amorphous accumulation of granular material consisting primarily of collagen fibrils and glycosaminoglycans, among which hyaluronan predominates (Figure.2) [28]

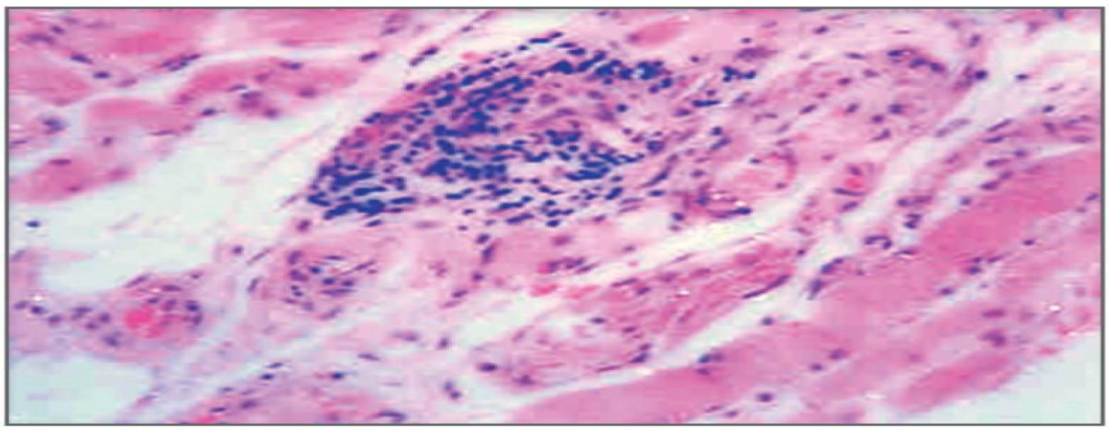

Figure2: Histologic Appearance of Extraocular Muscle in Graves' Ophthalmopathy (Hematoxylin and Eosin) [28]

Dermopathy related to Thyroid disorders:

Study by Tapan et al, 2014,[29] was discussing dermopathy related to thyroid disorder stated that Thyroid dermopathy is an infrequent manifestation of autoimmune thyroid disease characterized by localized thickening of the skin commonly seen in the pretibial area. It is almost always associated with ophthalmopathy (96%) and sign and symptoms of hyperthyroidism [29]. Almost 97% of dermopathy patients have coexisting ophthalmopathy and features of hyperthyroidism [30]. Generally, thyrotoxicosis develops first, followed by ophthalmopathy and finally dermopathy in patients who have all of these manifestations [31,32]. Cutaneous myxedema in the absence of, or preceding ophthalmopathy, or as the initial manifestation of hyperthyroidism, is rare.

Treatment of thyroid related opthalmopathy and dermopathy:

General considerations about Graves treatment:

From the endocrine perspective, the goal of treatment for patients with Graves' disease is the achievement of a euthyroid state. Patients should be counseled regarding the risks of smoking and the benefits of smoking cessation.

According to evidence based study in India performed by Rajat et al, 2012 [33] the decision on whether ophthalmopathy must be treated and requires what type of treatment relies on activity and severity of the disease [Table 1]. The sequence of the sections (V-I-S-A) described earlier reflects the order in which the problems should be managed [33].

Table 1: Suggested treatment for Graves Ophthalmopathy as function of disease severity and activity[33]

Ocular involvement	Activity	Treatment
Nonsevere	Active	Supportive measures
Nonsevere	Inactive	Supportive measures
Severe	Active	Glucocorticoids
		Orbital radiotherapy
		Orbital decompression*
Severe	Inactive	Orbital decompression
		Strabismus surgery
		Eyelid retraction surgery

*Only in the setting of compressive optic neuropathy that has not resolved with maximal medical management. (Bartalena L, Pinchera A, Marcocci C. Management of Graves' ophthalmopathy: reality and perspectives. Endocr Rev 2000;21(2):168-99)

Some studies have disscussed the agents that neutralize cytokine-induced inflammation or production of hyaluronan by orbital fibroblasts, such as anti-TNF agents and agents targeting the interleukin-1 receptor [40] or the interleukin-6 receptor [41] (Table 2), are attractive potential treatments for Graves' ophthalmopathy. Targeting TNF in patients with Graves' ophthalmopathy might affect the production by preadipocytes of chemoattractant protein 1, a macrophage-attracting protein [43]. The findings of a case report [42] and a small, open study [44] should encourage the performance of randomized trials of anti-TNF therapy in patients with Graves' ophthalmopathy. Antioxidants such as selenium may be useful, since they have a beneficial effect on autoimmunity in Graves' disease [45].Neutralizing the profibrotic effects of TGF-β may also be of benefit, especially in patients with inactive Graves' ophthalmopathy, in whom countering the antiinflammatory and antiadipogenic effects of this cytokine may be less detrimental than in those with the active disease [46].

Table2: Potential Therapeutic Targets in Graves' Ophthalmopathy and dermopathy [40,41,42,43,44,45,46]

Target	Current Agent	Description	Potential Benefit
TNF	Infliximab, adalimumab	TNF-specific monoclonal antibodies	Reduction in inflammation, leukocyte recruitment, and hyaluronan production
TNF receptor	Etanercept	TNF receptor–IgG Fc fusion molecule	Reduction in inflammation, leukocyte recruitment, and hyaluronan production
Interleukin-1 receptor	Anakinra	Interleukin-1–receptor antagonist	Reduction in inflammation, leukocyte recruitment, and hyaluronan production

Interleukin-6 receptor	Tocilizumab	Interleukin-6 receptor–specific mono-clonal antibody	Reduction in inflammation, leukocyte recruitment, and hyaluronan production
TGF-β	Lerdelimumab, GC1008	TGF-β–specific monoclonal antibodies	Reduction in fibrosis
Oxygen free radicals	Selenium	Essential trace element	Antiinflammatory activity
CD20	Rituximab, ocrelizumab, ofatumumab	Partially or fully humanized CD20-specific monoclonal antibodies	Decreased antigen presentation and T-cell activation; possible modulation of anti–thyrotropin-receptor antibody production
CD3	ChAglyCD3	Fc-mutated CD3-specific monoclonal antibody	Induction of tolerance
CD28	Abatacept	CTLA-4–immunoglobulin recombinant protein	Modulation of costimulatory pathways
CD154	IDEC-131	Humanized CD154-specific monoclonal antibody	Modulation of costimulatory pathways
PPAR-γ	Selective PPAR modulators	Novel selective PPAR-γantagonists	Reduction in inflammation and orbital adipogenesis
Somatostatin receptor	SOM230	Synthetic high-affinity somatostatin analogue	Inhibition of orbital preadipocyte proliferation
Thyrotropin receptor	NIDDK/CEB-52	Low-molecular-weight thyrotropin-receptor antagonist	Inhibition of orbital adipogenesis and hyaluronan production

Applying Radiation Therapy:

Evidence regarding the efficacy of radiation therapy in the management of thyroid related opthalmopathy is limited, owing to methodologic weaknesses of available studies. The rationale for the use of radiotherapy for thyroid related opthalmopathy resides both in its nonspecific anti-inflammatory effect and in the high radiosensitivity of lymphocytes infiltrating the orbit [(34)]. Orbital radiotherapy is effective in patients who have active eye disease with recent progression. Patients with inactive graves opthalmopathy do not respond to irradiation [(35)]. The most common delivered dose is 20 Gy per eye; this cumulative dose is fractionated over a 2-week period. Orbital radiotherapy may be associated with transient exacerbations of inflammation, but this can typically be avoided with co-coverage with glucocorticoids. With modern techniques, there seems to be no increased risk of cataract, or secondary malignancies, and only a remote risk of retinopathy [(36)]. In patients with diabetes mellitus, irradiation should be considered as a relative contraindication. Even though the efficacy of radiation therapy has been recently questioned, it remains widely used [(37)].

Steroid-Sparing Immunosuppressive Drugs:

The autoimmune nature of TAO prompted the attempt to use steroid-sparing immunosuppressive drugs for this disease. Cyclosporine has been thoroughly evaluated in the management of Opthalmopathy and dermopathy related to Graves's disease. It affects both cell-mediated and humoral immune reactions. But the effect of cyclosporine given as monotherapy was inferior to prednisone. A few controlled studies have proven that the use of cyclosporine in combination with prednisone is more effective than monotherapy with prednisone alone. Regular monitoring for side effects during the course of cyclosporine is required while a patient is on treatment [(38,39)].

5. CONCLUSION

Opthalmopathy and dermopathy related to thyroid is a self-limiting autoimmune disease associated mainly with hyperthyroidism, but also with hypothyroid and euthyroid states.Almost all cases of thyroid dermopathy are associated with relatively severe ophthalmopathy. Usually ophthalmopathy appears first and dermopathy much later.

Decompression may be needed in either phase. Although appropriate treatment can restore near normal function and appearance in most cases, the management of TAO is difficult, controversial, and far from optimal. Disease severity is the key determinant of the indication for therapy. Current therapeutic options include local supportive measures,

corticosteroids, external beam radiation and steroid-sparing immunosuppressive agents for reducing the inflammation during active disease, and surgery for correcting the residual abnormalities secondary to fibrosis in the inactive state of the disease.

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