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THYROID HORMONES AND THEIR OPHTHALMIC IMPLICATIONS

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ABSTRACT

THYROID hormones are critical determinants of growth and development in infants and of metabolic activity in infants and adults. They affect the functions of virtually every organ system, and they must be constantly available to carry out these functions. It is important to keep the thyroid function stable. The treatment will depend on whether the thyroid gland is overactive (majority of cases) or underactive. . Still today, less of information exists per se the exact mechanism of action and the specific ocular processes affected by the thyroid hormone in ocular health and disease. Current understanding of thyroid hormone and their ophthalmic implications can unmask the underlying potential of thyroid hormones.

KEYWORDS: Eye, thyroid hormone, hormone action, meibomian gland, conjunctiva, AMD, intraocular pressure.

3.1 Thyroid Hormone: Synthesis and Target Tissues

The thyroid hormones are created from thyroglobulin. This is a protein within the follicular space that is originally created within the rough endoplasmic reticulum of follicular cells and then transported into the follicular space. Thyroglobulin contains 123 units of tyrosine, which reacts with iodine within the follicular space.[7]

Iodine is essential for the production of the thyroid hormones. Iodine (I^0) travels in the blood as iodide (I^-), which is taken up into the follicular cells by a sodium-iodide symporter. This is an ion channel on the cell membrane which in the same action transports two sodium ions and an iodide ion into the cell[8] Iodide then travels from within the cell into the follicular space, through the action of pendrin, an iodide-chloride antiporter. In the follicular space, the iodide is then oxidized to iodine. This makes it more reactive,[9] and the iodine is attached to the active tyrosine units in thyroglobulin by the enzyme thyroid peroxidase. This forms the precursors of thyroid hormones monoiodotyrosine (MIT), and diiodotyrosine(DIT).[2]

When the follicular cells are stimulated by thyroid-stimulating hormone, the follicular cells reabsorb thyroglobulin from the follicular space. The iodinated tyrosines are cleaved, forming the thyroid hormones T_4, T_3, DIT, MIT, and traces of reverse triiodothyronine. T_3 and T_4 are released into the blood. The hormones secreted from the gland are about 80–90% $T_4$and about 10–20% T_3.[10,11] Deiodinase enzymes in peripheral tissues remove the iodine from MIT and DIT and convert T_4 to T_3 and RT_3.[33] This is a major source of both RT_3 (95%) and T_3 (87%) in peripheral tissues.[37]

The production of thyroxine and triiodothyronine is primarily regulated by thyroid-stimulating hormone (TSH), released by the anterior pituitary gland. TSH release in turn is stimulated by thyrotropin releasing hormone (TRH), released in a pulsatile manner from the hypothalamus.[38] The thyroid hormones provide negative feedback to the thyrotropes TSH and TRH: when the thyroid hormones are high, TSH production is suppressed. This negative feedback also occurs when levels of TSH are high, causing TRH production to be suppressed.[39]

TRH is secreted at an increased rate in situations such as cold exposure in order to stimulate thermogenesis.[40] In addition to being suppressed by the presence of thyroid hormones, TSH production is blunted by dopamine, somatostatin, and glucocorticoids.[41]

3.2 Thyroid Hormone and the Meibomian Glands

Meibomian gland dysfunction (MGD) is considered to be a discrete disease entity without prominent inflammatory alterations of the lid margins and a frequent cause of wetting deficiencies of the ocular surface leading to dry eye disease.[1] MGD is grouped as obstructive and seborrheic dysfunction.[2,3] Obstructive MGD is characterized by hyperkeratinization of the ductal epithelium and increased viscosity of the meibum resulting in obstruction of the meibomian gland duct and orifice.[1,2] Obstructive MGD is reported to be much

more frequent in the general population and increases with age.[2] Seborrheic MGD is characterized by hypersecretion of meibum.[3]

Very little information exists concerning the correlation of serum levels of thyroid hormones with seborrheic MGD between 20–30 years of age. The function of TSH on sebocytes has not been reported before. Study has revealed significant increase serum levels of TSH only in female gender of the patients with seborrheic MGD with respect to the control gender[1shahin]. The correlation of serum levels of TSH with seborrheic MGD also remains to be determined in larger cohorts. No significant difference of serum levels of other hormones including bound and unbound T3 and T4 were found between patients with seborheic MGD and controls in both genders. However, the correlations of serum levels of TSH with seborrheic MGD need to be further investigated.

3.3 Thyroid Hormone and the Lacrimal Gland

Dry eye is one of the most common clinical problems with several adverse effects on the quality of life.[1,2] This disorder may be a manifestation of several systemic or autoimmune disorders including autoimmune thyroiditis and hypothyroidism.[3] Dry eye syndrome may affect visual acuity and daily activities, along with social and physical skills, resulting in significant decrease in the quality of life.[4,5] Any defect in the lacrimal gland, eyelid, and the ocular surface may lead to this syndrome.[6] Dry eye is also the most common finding of thyroid-associated ophthalmopathy (TAO)[7] in thyroid disorders such as Graves' disease and Hashimoto thyroiditis.[8] TAO is defined as an autoimmune disease of the extraocular muscle tissue and the lacrimal glands, characterized by extraocular myopathy, optic neuropathy, and ocular surface inflammation.[9] The exact etiopathogenesis has been not established currently and several factors are considered to be responsible for the development of this disorder. The most common factors are T cell-dependent ocular surface inflammation, increased tear film evaporation and hyperosmolarity due to proptosis, especially in Graves' disease. Additionally, the effect of several inflammatory cytokines such as IL1-α, IL-4, and IGF-1 may play a role in this process.[8] Recently, in addition to these factors, thyroid hormone receptors β-1 (Thrb-1), which are located on lacrimal glands, were found to be responsible for the development of dry eye.[10] These receptors are known to cause susceptibility toward hypothyroidism, by converting the lacrimal glands as a target tissue for thyroid hormones.

3.4 Thyroid Hormone and the Conjunctiva

The bulbar and palpebral conjunctiva represent the majority of the adnexal ocular surface area with lesser contributions from the upper and lower tarsal plates. The integrity of the ocular surface is dependent not only on the underlying health of the conjunctiva but also on the condition of the tear film.

Inflammatory infiltration of the lacrimal excretory system affects both volume of the tear production and tear composition. Baker and colleagues[11] collected reflex tears in smokers and patients with thryoid-related orbitopathy and analyzed the specimens with electrophoresis and mass spectrometry. Composition differences were noted with increased expression of zinc-alpha-2-glycoprotein and lactoferrin in patients with thyroid-related orbitopathy and smokers compared to nonsmokers. They were unable, however, to correlate tear TSHr activity with clinical activity score. In another study, Khalil and associates[12] studied the levels of secretory IgA and lysozyme in patients with thyroid-related orbitopathy vs controls and noted a higher ratio of IgA to lysozyme.

Histopathologically, however, the conjunctiva has not been extensively studied. Studies of the conjunctiva have focused on its involvement in superior limbic keratoconjunctivitis,[13] conjunctivochalasis,[14] and cell morphology using impression cytology.[15] Of particular interest is the clinical implication of the conjunctiva in the pathogenesis and treatment of upper eyelid retraction.[16] Surgeons have suspected clinically that the conjunctiva is involved. One study described the occurrence of fibrosis of the conjunctival substantia propria using a trichrome stain.[17] Only three specimens were examined, however, and there were no controls. We were unable to find any other studies in the literature that specifically examined the palpebral conjunctiva for fibrosis or inflammation in this disease process.

3.5 Thyroid Hormone and the Colour Vision

Studies in mice have shown that thyroid hormone also plays an important role in the development of the eye and particularly the cone visual cells. In the retina of the eye, the cones are the visual cells responsible for colour vision. Most mammals have two spectral cone types containing either of two visual pigments (opsins), one sensitive to shortwave light (UV/blue opsin), the other to middle-to-long wave light (green opsin). Cones express a thyroid hormone receptor. Its activation by the hormone suppresses the synthesis of UV/blue opsin and activates the production of green opsin.

"In addition to their importance for basic retinal research, findings may also have clinical relevance", says Martin Glösmann, who currently examines the genetic foundations of the process at the University of Veterinary Medicine, Vienna. "If this mechanism also acts in human cones, the adult-onset of thyroid hormone deficiency - e.g. as a consequence of dietary iodine deficiency or removal of the thyroid-would also affect the cone opsins and colour vision". There are no such reports in the clinical literature, presumably because the general symptoms of thyroid hormone deficiency are so severe that therapy is initiated before the cone opsin shifts would show up18.

3.6 Thyroid Hormone and the Intraocular pressure (IOP)

Hormones might affect the development of glaucoma and IOP through various mechanisms, and some studies have reported that thyroid hormone affects IOP. Thyroid hormones play a key role in metabolism and homeostasis.[19] Some studies have reported a significant relationship, while others have not. Forte et al.[20] suggested that ocular hypertension (OHT) patients with Graves' orbitopathy showed diffuse abnormalities of the VF and RNFL thinning.

Thyroid hormone affects the maintenance of homeostasis in the body and regulates the basal body metabolism[19] Hyperthyroidism might induce IOP increase through increased intraorbital pressure or contraction of enlarged extraocular muscles.[14,15] The main mechanism could be elevation of episcleral venous pressure secondary to increasing of intraorbital content and pressure. The increased IOP in hypothyroidism could be due to the excessive accumulation of mucopolysaccharides in the trabecular meshwork.[21,22] Smith et al.[21] reported that the prevalence of hypothyroidism in the primary open-angle glaucoma group was higher than those in the control subjects in their case-control study. They proposed that, in the untreated hypothyroid state, hyaluronic acid accumulates excessively in the trabecular meshwork and/or aqueous, causing an obstruction to facility of outflow. This phenomenon was thought to be due to decreased enzyme activity in the hypothyroid state and decreased degradation of hyaluronic acid. After treatment of hypothyroidism, the outflow of aqueous humor was recovered. Some studies have reported that treating hypothyroidism decreases IOP through increasing aqueous outflow. Centanni et al.[22] reported that the IOP of subjects who showed a significantly higher IOP than the control group of subclinical hypothyroidism were decreased approximately by 3 mmHg after treatment of hypothyroidism. Bahceci et al.[23] reported that hypothyroidism reversibly induced increasing IOP. On the other hand, Cheng and Perkins[24] did not find a statistically significant difference in the distribution of IOP between hypothyroidism and normal control groups. However, their study included thyroid hormone-treated patients, which could have affected the results due to the reversible effects of the treatment. McLenachan and Davies[25] reported that high IOP was associated with hypothyroidism due to changes in the quantity and quality of mucopolysaccharides in the trabecular meshwork.

3.7 Thyroid Hormone and Age Related Macular Degenration(ARMD)

Epidemiologic evidence of a relationship between thyroid dysfunction and age-related macular degeneration (AMD) is inconsistent and unclear.

Rotterdam Study reports significant positive association between FT4 values and incident AMD. Overt hyperthyroidism (low TSH and high FT4 levels) in older adults is independently associated with ~3-fold increased risk of developing any AMD.[26]

Potential underlying mechanisms for observed association with overt hyperthyroidism (i.e., an overactive thyroid and overproduction of thyroid hormones). First, elevated thyroid hormone levels can accelerate the basal metabolic rate and oxidative metabolism by induction of mitochondrial enzymes, which causes a hypermetabolic state with increased generation of reactive oxygen species.[27,28] Further, there is evidence that stimulating thyroid hormone signaling could cause degeneration of cone photoreceptors[29] and thyroid hormone itself could adversely influence retinal pigment epithelial cells,[26,30] which could also partly explain the observed association between clinical hyperthyroidism and AMD.

3.8 Thyroid Hormone and Retina

Subclinical hypothyroidism (SCH) is a common endocrine disorder and characterized as elevated serum thyroid-stimulating hormone (TSH) levels in the presence of serum free thyroxine (FT4) and triiodothyronine (T3) levels within the reference range31. In general population screening surveys, the prevalence of SCH has been reported to range from 4% to 10% 32, and the risk factors of SCH are baseline TSH level33, iodine-sufficient34,35,36, old age, female sex, and the presence of thyroid autoantibodies37,38,39,40,41.

Current data suggests prevalence of SCH in diabetes varying between 2.2% to 17 % 42,43. Further, the thyroid hormone axis has an important role in the development of the retina and contributes to retinal vascular density. Experimental studies have shown that hypothyroidism is associated with pre-retinal neovascularization and that systemic thyroxine supplementation is associated with changes in the vessel density and area 44,45.

CONCLUSIONS

This study emphasizes on the role of thyroid hormone in health and disease of various eye components. The various effects of thyroid hormones on the ocular tissues result from the modulation of ocular parameters such as tissue morphology, gene expression, protein synthesis, lipid production, mucous secretion, aqueous tear output, tear film stability, immunological activity, colour vision, aqueous humor outflow. Also, the study highlights the understanding of hormonal balance to be considered in the therapeutic approach to eye pathologies. The final goal of management should take into account all the aspects of an ocular disease, including ocular endocrinology, as the thyroid hormones have ophthalmic implications. Further studies – both experimental and clinical are required to expand our understanding of thyroid hormone in different ocular diseases, and help to draw a better clinical vignette, for a epitomized treatment of the disease.

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