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Thyroid hormone action on skin

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The skin characteristics associated with thyroid hormone are classic. The name "myxedema" refers to the associated skin condition caused by increased glycosaminoglycan deposition in the skin. Generalized myxedema is still the classic cutaneous sign of hypothyroidism. It is caused by deposition of dermal acid mucopolysaccharides, notably hyaluronic acid. Despite its appearance, the skin does not pit with pressure.

Introduction

Thyrotoxicosis is also classically associated with cutaneous manifestations. In a review of thyrotoxic presentations, hyperhydrosis, was the second most common finding.[1] Although certain manifestations are specific to Graves disease, thyrotoxicosis of any etiology can include skin sequelae.

Skin manifestations of thyroid dysfunction may be divided into three categories: (1) direct action of thyroid hormone on skin tissues (**Table 1**), (2) skin manifestations of direct thyroid hormone action on non-skin tissues (**Table 2**) and (3) autoimmune skin disease associated with thyroid dysfunction of autoimmune etiology (**Table 3**).

Direct Thyroid Hormone Action on Skin Tissues

Direct thyroid hormone action on skin is mediated through the thyroid hormone receptor (TR). All three widely recognized thyroid hormone binding isoforms of TR have been identified in skin tissues.[2-5] TRs have been detected in epidermal keratinocytes, skin fibroblasts, hair arrector pili muscle cells, other smooth muscle cells, sebaceous gland cells, vascular endothelial cells, Schwann cells, and a number of cell types that make up the hair follicle. In addition, several thyroid hormone responsive genes have been identified in skin. More recently, investigators have identified elements of the hypothalamic-pituitary-thyroid hormone axis in human skin.[6-8]

Epidermal changes. Thyroid hormone is an important regulator of epidermal homeostasis. The skin in hypothyroidism is rough and covered with fine scales, notably on the extensor extremities.[9] Xerosis may resemble an acquired ichthyosis. Palms and soles may be quite dry.[10] Histologic examination reveals epidermal thinning and hyperkeratosis.[11]

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At the same time, clinical examination reveals the thyrotoxic epidermis to be thin but not atrophic. Relatively little formal study has been done to explain the clinical findings in thyrotoxic states. Clinical observations have been complicated by the fact that most thyrotoxicosis results from Graves disease which may include autoimmune mediated glycosaminoglycan deposition with resulting thickened dermis. Indeed, there is one report of thickened epidermis in biopsies of thyrotoxic humans.[12]

In tissue culture studies using surrogates for DNA expression, T_3 has been shown to stimulate growth of both epidermal keratinocytes and dermal fibroblasts.[13-15] However, thyroid hormone mediated inhibition of keratinocyte growth has been observed when the keratinocytes were co-cultured with dermal fibroblasts.[14] Thus, in vivo, skin proliferation directly stimulated by T_3 may be offset by inhibiting factors dependent on the systemic T_3. The research suggests that systemically induced inhibiting factors may be bypassed with topically administered T_3.

In addition to the thyroid hormone mediated growth noted above, in vitro keratinocyte studies have shown that depletion of T_3 results in elevated levels of transglutaminase, which is involved in the formation of the cornified envelope. Further in vitro analysis has suggested that T_3 depleted keratinocytes have diminished levels of plasminogen activator, an enzyme implicated in the corneocyte shedding process.[16]

Studies of thyroidectomized rats have suggested that sterol synthesis is altered in epidermal keratinocytes deprived of thyroid hormone.[17] Thyroid hormone accelerates barrier formation by increasing the activity of enzymes in the cholesterol sulfate cycle. Thus, hypothyroidism may hinder the epidermal barrier function.[18] Hypothyroidism also may affect the development of the lamellar granules (Odland bodies), which are vital in the establishment of a normal stratum corneum.[19]

As noted above, a number of thyroid hormone responsive genes have been identified including the following: the keratin genes, the "hairless" (*hr*) gene and ZAKI-4.[20-24] The keratin genes encode the intermediate filaments which make up about 30% of the protein of the epidermis. Thyroid hormone exerts direct control over keratin genes at the nuclear level through thyroid hormone response elements in their upstream promoters.[20,21] Although thyroid hormone stimulates expression of proliferation associated keratin genes both in vivo and in vitro,[25] only negative thyroid hormone response elements have been identified for these genes.[20] It is not known whether the above reflects thyroid hormone induction of indirect keratin gene stimulating pathways or the existence of unidentified positive thyroid hormone response elements for the keratin genes.

Table 1. Direct thyroid hormone action on skin tissues

HYPOTHYROIDISM
Epidermal Changes
Coarsened, thin, scaly skin
Dermal Changes
Non-pitting edema (myxedema)
Edema (hands, face, eyelids)
Carotenemia
Pallor
Hair and Nail Changes
Dry, brittle, coarse hair
Alopecia
Loss of lateral third of eyebrows
Coarse, dull, thin, brittle nails
Sweat Gland Changes
Dry skin (xerosis)
Decreased sweating
THYROTOXICOSIS
Epidermal Changes
Smooth, thin skin
Hair and Nail Changes
Fine hair ("loses wave")
Alopecia
Shiny, soft, friable nails (onycholysis, Plummer's nails)

Table 2. Skin manifestation of thyroid hormone action on other tissues

HYPOTHYROIDISM
Cold intolerance
Pallor
Purpura
Drooping of upper eyelids
Nerve entrapment syndromes
THYROTOXICOSIS
Warm skin
Heat intolerance
Increased sweating (hyperhydrosis)
Hyperpigmentation
Erythema
Telangiectasia

Table 3. Associated autoimmune phenomena

Dermopathy (pretibial myxedema)
Acropachy
Urticaria, pruritis
Vitiligo
Pernicious anemia
Bullous disorders
Eczema
Connective tissue diseases

Mutations in the *hr* gene are associated with atrichia/alopecia phenotypes in mice[26] and mutations in the human homolog gene are associated with similar phenotypes in humans.[27-30] Thompson[22,23] reported that *hr* is regulated by TR in brain and that the promoter region of the *hr* gene contains a thyroid hormone response element. Hypothyroid mice have reduced *hr* expression in brain relative to euthyroid mice. Addition of exogenous T_3 results in restoration of *hr* expression. In contrast, *hr* expression in skin has been reported to be the same for both hypo- and euthyroid mice. The connection among the *hr* gene, thyroid hormone and normal skin remains to be demonstrated.

Dermal changes. In thyrotoxic patients, most dermal findings derive from autoimmunity rather than direct thyroid hormone action. In hypothyroidism, the skin tends to be pale both because of the dermal mucopolysaccharides and dermal water content. In addition, increased dermal carotene may appear as a prominent yellow hue on the palms, soles and nasolabial folds.

The seminal histological evaluation of the skin of a patient with hypothyroidism was done by Reuter in 1931.[11] Reuter was able to demonstrate increased hyaluronic acid in hypothyroid dermis. Later, Gabrilove et al.[31] biopsied the skin of individuals with hypothyroidism before and after treatment. Histological changes were observed within 3–4 weeks of thyroid hormone changes.

Hyaluronic acid is the major glycosaminoglycan that accumulates in myxedema.[32] Its hygroscopic nature allows it to swell to one thousand times its dry weight when hydrated. Mucin deposition involves not only the skin but also the tongue, myocardium, kidney and most other organs of the body. Increased transcapillary escape of albumin, resulting in extravascular accumulation, may also contribute to the edema. In addition, inadequate lymphatic drainage may further explain the formation of exudates that are apparent in the myxedematous state.[33]

In tissue culture studies, thyroid hormone stimulates proliferation of dermal fibroblasts.[2,14] Additional reported thyroid hormone actions on cultured skin fibroblasts include inhibiting synthesis of hyaluronic acid, fibronectin and collagen.[34-36] The net effect of thyroid hormone on dermal thickness remains the subject of debate, however. In 1967, investigators[37] reported skin thinning in rats made thyrotoxic with intraperitoneal (IP) T_4. They used proline-^{14}C uptake as a surrogate for collagen production to demonstrate decreased collagen production in the thyrotoxic animals. However, increased collagen catabolism in thyrotoxic rats has also been reported in reference 37 and 38. More recent investigations suggest increased dermal thickness in mice treated with T_3, whether topically or intraperitoneally administered.[13,14] There is also a report of increased dermal thickness in mice treated topically with the thyroid hormone analog, triac.[39]

Topical thyroid hormone may serve as a useful means to accelerate wound healing rate. Topical application of supra-physiological doses of T_3 accelerated wound healing in normal mice[40] and a human wound healing formulation has been described that requires T_4 in addition to growth hormone and insulin.[41]

The importance of thyroid hormone in wound healing had been debated. In 1973 and 1974, Mehregan and Zamick

reported that oral T_3 accelerated the rate of wound healing in euthyroid rats and improved the quality of the wounds.[42,43] In addition, scars were smoother in the T_3 treated animals. Lennox and Johnston reported accelerated wound healing and increased tensile strength when rats were given supra-physiologic doses of T_4.[44] Although Pirk et al. reported no change in wound healing with 1.3 μg/100 mg body weight intraperitoneal T_4 in hamsters, the investigators noted increased rate of fracture repair.[45] Ashton et al. also reported increased fracture repair rate in mice given 20 μg/100 mg body weight subcutaneous T_4.[46] There are also reports of hypothyroid patients who required thyroid hormone to achieve healing of radiation induced neck fistulae.[49,50] Conversely, Cannon[49] reported that hypothyroidism did not diminish wound strength in pigs and Ladenson et al.[50] did not detect wound healing deficits in hypothyroid humans.

Hair and nail changes. Hale and Ebling documented the impact of thyroid hormone on rat hair growth cycles.[51] They demonstrated that intraperitoneal T_4 decreased both the resting phase of the hair growth cycle (telogen) and the growth phase of the hair growth cycle (anagen). Although there was enhanced turnover, the net hair length at any given time was not changed from that of untreated animals. The time to regrowth of hair following epilation was shortened by approximately 10%. The induction of hypothyroidism with the antithyroid drug, propylthiouracil (PTU), in the drinking water increased the time to the restoration of hair by approximately 20%.

Clinically, the hair in thyrotoxicosis is often fine and soft. Nail changes may also occur, characterized by a concave contour accompanied by distal onycholysis (Plummer's nails). A diffuse, nonscarring alopecia may be observed also. In vitro studies suggest increased hair growth rate in thyrotoxicosis. DNA flow cytometry studies of dissected anagen hairs from thyrotoxic patients (compared with follicles taken from euthyroid controls) demonstrated a 30% increase in the S and G_2 + M phases of the cell cycle.[52]

However, like with epidermal proliferation, hair changes with thyrotoxicosis are different than what can be effected with topically administered thyroid hormone. Mice and rats treated daily for 1–2 weeks with topical T_3 had increased hair counts but mice made thyrotoxic with daily intraperitoneal T_3 for 1–2 weeks had decreased hair counts.[13,14] Thyrotoxic goats had increased mohair length but decreased fiber diameter.[53] A topical mixture including thyroxine, insulin and growth hormone increased hair counts over a 6 month treatment period in men with androgenic alopecia.[54]

In hypothyroidism, hair can be dry, coarse, brittle and slow growing. Similarly, nails may be thickened, brittle and slow growing.[55] Diffuse or partial alopecia may be observed along with loss of the lateral third of the eyebrow (madarosis). The alopecia connected to hypothyroidism may be mediated by hormone effects on the initiation as well as the duration of hair growth.

There is one report of long, terminal hairs on the backs and extremities of hypothyroid children.[56] The hair disappeared following thyroid hormone replacement but no mechanism was determined.

Hypothyroid patients may sometimes suffer Candida folliculitis. It has been theorized that because the sebaceous glands of hypothyroid patients secrete decreased sebum relative to those of euthyroid persons, the hair follicles may develop a flora with fewer lipophilic organisms, which are replaced by *Candida albicans*.[57]

Sweat gland changes. The dryness of hypothyroid skin results from decreased eccrine gland secretion. The mechanism for decreased sweating is not clear although the hypothyroid glands are atrophic on histologic examination. A role may also be played by a periodic acid-Schiff (PAS)-positive material that can accumulate in hypothyroid patients.[58] Hypothyroidism has been reported to be a cause of increased sweat electrolytes, requiring differentiation from cystic fibrosis.[59]

Skin Manifestation of Thyroid Hormone Action on Other Tissues

Thyrotoxic skin is sometimes described as the texture of an infant's skin: warm, moist and smooth. While the smooth skin is an epidermal finding, the warmth is caused by increased cutaneous blood flow and the moisture is a reflection of the underlying metabolic state. Increased blood flow in the skin along with peripheral vasodilatation may be responsible for facial flushing and palmar erythema. The increased skin perfusion of thyrotoxicosis has been confirmed experimentally by laser Doppler techniques[60] and nailfold capillaroscopy.[61]

The thyrotoxic patient may suffer generalized hyperhydrosis, usually more prominent on the palms and soles. Sweating in thyrotoxicosis is a reflection of the underlying metabolic state. It is thought to be related to the increased sympathoadrenal activity resulting from the synergistic action between catecholamines and thyroid hormone.[62] Localized hyperhydrosis has been reported in cases of pretibial myxedema. Investigators have proposed that peripheral sympathetic nerves when stimulated by perineural infiltration of mucin.[63]

Hyperpigmentation has been described in thyrotoxic patients in both localized and generalized distribution similar to that of Addison disease (creases of the palms and soles, gingivae, buccal mucosa). There is speculation that the hyperpigmentation is due to increased release of pituitary adrenocorticotropic hormone compensating for accelerated cortisol degradation.[64] Treatment with T_4 has been shown to alter hair growth and pigmentation in cattle.[65]

Like with thyrotoxicosis, several dermatological manifestations of hypothyroidism derive from hypothyroidism in non-skin tissues. Thyroid hormone mediated changes to the basal metabolic, vascular and sympathetic nervous systems are evident when the skin is examined.

Cool pale skin may result from decreased skin perfusion in hypothyroidism. The decreased skin perfusion has been documented with both nail fold capillaroscopy[61] and laser Doppler.[60] It has been suggested that the diminished skin perfusion is reflex vasoconstriction compensatory to diminished core temperature. The diminished core temperature itself may be secondary to reduced thermogenesis.[66] Occasionally, purpura may be noted in

hypothyroid patients as a result of diminished levels of clotting factors or the loss of vascular support secondary to the dermal mucin.[67,68]

Drooping of the upper lids has been attributed to decreased sympathetic stimulation of the superior palpebral muscle. Entrapment syndromes, such as carpal tunnel syndrome and facial nerve palsy, have been reported in reference 64.

Associated Autoimmune Phenomena

When thyroid disease is of autoimmune etiology, additional skin findings may be evident which reflect associated autoimmune disease.[69] Although patients with autoimmune thyroid disease are at increased risk for other autoimmune diseases, both tissue-specific and generalized, screening hypothyroid patients for other autoimmune disease is not cost-effective. Conversely, autoimmune thyroid disease is sufficiently common that patients with other autoimmune disease deserve screening for thyroid dysfunction.

A list of autoimmune conditions apparent when examining the skin includes vitiligo, alopecia areata, pernicious anemia, bullous disorders (pemphigus, bullous pemphigoid, dermatitis herpetiformis), connective tissue diseases (lupus erythematosus, scleroderma), lichen sclerosus et atrophicus, palmoplantar pustulosis and urticaria. Some patients with autoimmune dermatological diseases may present with pitting nails[70] independent of the brittle nails associated with direct thyroid hormone action. It has been reported that a subset of patients with chronic urticaria and angioedema associated with thyroid autoimmunity may have their urticaria abate with the administration of thyroid hormone.[71] A potential mechanism for a connection has been proposed relating to the finding that anti thyroid peroxidase (TPO) IgE antibodies are greater in patients with the urticaria.[72] Thyroid hormone treatment can result in decreased TPO antibody titers which might be predicted to diminish the urticaria.

Patients with Graves disease may have distinctive cutaneous findings related to autoimmune attack on skin and other tissues. Thyroid dermopathy (formerly termed pretibial myxedema) is noted in 0.5% to 4% of patients,[73] and acropachy is observed in approximately 1% of patients with Graves disease.[74] Although pruritus is often considered a cutaneous manifestation of thyrotoxicosis, it is more likely secondary to urticaria, which may be associated with thyroid autoimmunity.[75]

Patients with autoimmune mediated thyrotoxicosis may manifest a localized skin thickening identical to that seen in hypothyroidism. The dermopathy was termed "pretibial myxedema" for many years due to its common identification in the pretibial area. Since the glycosaminoglycan accumulations occur throughout the body, the newer term "thyroid dermopathy" is more precise. The clinical presentation varies from an infiltrative process with a "peau d'orange" appearance to extreme infiltration. The infiltration is due to the accumulation of hyaluronic acid in the dermis and occasionally in the subcutis.[76] A satisfactory explanation for the presence of the hyaluronic acid remains elusive. Aside from the accumulation of hyaluronic acid in dermopathy, alterations in elastic tissue have been recognized. A decrease in elastin and irregularly shaped microfibrils has been attributed to abnormalities in fibroblast function.[77]

Thyroid dermopathy almost always associated with ophthalmopathy. As such, dermopathy usually reflects severe Graves disease. The commonest locations for thyroid dermopathy are the pretibial area (whence its original name) and the distal lower extremities. There are reports of involvement of the upper extremities, shoulders, back, ears, nose and scar tissues. The lesions are raised and waxy with coloring ranging from light to yellowish brown. Lesions are aggravated by trauma and can recur if surgically removed. Treatment is not usually indicated but local corticosteroids, applied nightly and covered with an occlusive dressing, have been used when treatment has been desired. The efficacy of local steroids long term has been debated. Although the vast majority of patients with dermopathy have Graves disease, it has been reported in Hashimoto's thyroiditis also.[78,79] Hypertrichosis is can be observed in cases of thyroid dermopathy and may be related to alterations in the proteoglycans associated with the dermal papilla.[80]

Acropachy is quite rare. Its skin manifestations may resemble myxedema. It typically occurs in the presence of both ophthalmopathy and dermopathy. Acropachy consists of the following three signs: digital clubbing, soft-tissue swelling of the hands and feet, and periosteal new bone formation. Bone manifestations can result in focal uptake of radioisotope on bone scan or characteristic frothy appearing mid-diaphysis on plain X-ray. Treatment with steroids is reported to be effective.

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