

Review Article

Thyroid Disease and the Skin

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Abstract

Thyroid disease is associated with changes in the skin, which may sometimes be the first clinical sign. A variety of cutaneous findings may present in the setting of either a hyperthyroid or hypothyroid state. There may be evidence of the effect of altered concentrations of thyroxine on the skin, with changes in texture and hair growth. Associated increases in thyroid stimulating hormone concentration may lead to pretibial myxedema. Hair follicles are particularly sensitive to concentrations of thyroid gland derived hormones. The cells of the hair matrix, due to their high degree of metabolic activity, are most profoundly influenced by the deficiency or excess of thyroid derived hormones. There is convincing evidence of a significant association between thyroid autoimmunity and skin disorders. Most commonly reported cutaneous disorders related with thyroid disease are alopecia areata and vitiligo. This review constitutes a summary and update of the cutaneous manifestation of thyroid disease.

Keywords: Hypothyroidism; Hyperthyroidism; Thyroid autoimmunity; Skin disease; Thyroid dermatopathy

Introduction

The long-recognized “thyroid-skin connection” encompasses many layers of complexity, and it has become a hot frontier in dermatoendocrinology [1]. Thyroid disorders are known to involve all organ systems of the body and the skin is no exception. Cutaneous manifestations generally appear subsequent to the development of thyroid disease, but may be the first presenting sign or even precede the diagnosis by many years. Skin manifestations of thyroid dysfunction may be divided into two main categories: (I) direct action of thyroid hormone on skin tissues, and (II) autoimmune skin disease associated with thyroid dysfunction of autoimmune etiology.

Although there have been reports investigating the thyroid function tests, auto antibodies and thyroid diseases in various cutaneous disorders, the presence of cutaneous manifestations of thyroid diseases has been rarely discussed in the scientific literature. This article outlines the major skin findings in thyroid disease and summarizes recent studies and reports. A review was performed searching the electronic databases: Ovid MEDLINE and PubMed. No methodological search filters or limits were applied.

Direct thyroid hormone action on skin

It has been known for decades that thyroid disorders that lead to elevated or decreased thyroid hormone serum levels are associated with altered human skin and hair structure as well as function [2]. Available data suggest that thyroid hormone plays a pivotal role in embryonic development of mammalian skin as well as in maintenance of normal cutaneous function in adult skin. Direct thyroid hormone action has been demonstrated on cutaneous biology including on the epidermis, dermis, and hair. Thyroid hormone stimulates epidermal oxygen consumption, protein synthesis, mitosis, and determination of epidermal thickness [3]. In addition, thyroid hormone appears to be necessary for both the initiation and maintenance of hair growth and normal secretion of sebum.

Direct thyroid hormone action on skin is mediated through

Thyroid Hormone Receptor (TR). All three widely recognized thyroid hormone binding isoforms of TR have been identified in skin tissues [4,5]. TRs have been detected in epidermal keratinocytes, skin fibroblasts, hair arrector pili muscle cells, sebaceous gland cells, vascular endothelial cells, and a number of cells types that make up the hair follicle [6]. The interaction of triiodothyronine (T₃) with its receptors (TR α and TR β) affects epidermal differentiation and enhances its responsiveness to growth factors [5,7]. These effects of T₃ are particularly important for the function of sebaceous, eccrine, and apocrine glands, growth of hair follicles and synthesis of proteo- and glycosaminoglycans by dermal fibroblasts [8]. In tissue culture studies using surrogates for DNA expression, T₃ has been shown to stimulate growth of both epidermal keratinocytes and dermal fibroblasts [9,10]. Thyroxine (T₄) stimulates the proliferation of hair follicle keratinocytes and T₃ inhibits their apoptosis [11]. Thyroid hormones may also affect hair follicle stem cells, since T₃ and T₄ were found to induce differentiation and apoptosis, and inhibit clonal growth of hair follicle epithelial stem cells [12]. The demonstration of TR expression in hair follicle cells indicates that thyroid hormone can affect hair growth directly, rather than through an intermediate mechanism such as a general metabolic status [13]. In addition, investigators have identified elements of the hypothalamic-pituitary-thyroid hormone axis in human skin [1,14] and have determined that thyroid hormone receptors mediate skin proliferation and inflammation along with skin response to retinoids [15,16].

Both hypothyroidism (Table 1) and hyperthyroidism (Table 2) are known to cause skin change.

Cutaneous manifestations of hypothyroidism

Hypothyroidism may result from either inadequate circulating levels of thyroid hormone or target cell resistance to hormonal action. Primary hypothyroidism is as a result of glandular failure is the most common cause and most frequently result from autoimmune disease [17]. In hypothyroidism, the skin is cold, xerotic and pale. The coldness is due to reduced core temperature and cutaneous vasoconstriction.

Table 1: Cutaneous manifestations of hypothyroidism.

Dry skin (xerosis)
Thin, scaly skin
Myxedema
Carotinemias
Purpura
Dry, brittle, coarse hair
Telogen effluvium
Loss of lateral third of eyebrows (madarosis)
Coarse, thin, brittle nails
Decrease sweating
Poor wound healing

Table 2: Cutaneous manifestations of hyperthyroidism.

Smooth, soft, thin skin
Fine, soft hair
Shiny, soft, friable nails
Plummer's nails
Hyperpigmentations
Erythema
Teleangiectasia
Hyperhidrosis
Pruritus

The decreased skin perfusion has been documented with nail fold capillaroscopy [18]. 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 [19]. Occasionally, purpura may be noted in hypothyroid patients as a result of diminished levels of clothing factors and the loss of vascular support secondary to the dermal mucin [20]. 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 [6]. Hypohidrosis, possibly accompanied by diminished epidermal sterol biosynthesis, may lead to acquired palmoplantar keratoderma. The most prevalent manifestation in the skin involvement in hypothyroidism is xerosis. It occurs in 57-59% patients [21,22]. Xerosis is due to a change in skin texture and poor hydration of the stratum corneum. The skin is rough and covered with fine scales. Palms and soles may be quite dry. The epidermis is thin and hyperkeratotic, and there is follicular plugging. Because the changes are generalized, they can be differentiated from similar alterations in the skin of atopic individuals and keratosis pilaris, where the findings are more prominent on the extremities [23]. Hypothyroidism also may affect the development of the lamellar granules (Odland bodies), which are vital in the establishment of a normal stratum corneum [24]. In hypothyroidism, the skin tends to be pale both because of the dermal mucopolysaccharides and dermal water content which alter the refraction of light. 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. The mucopolysaccharides that accumulate in the dermis are hyaluronic

acid and chondroitin sulfate. They appear first in the papillary dermis and are most prominent around hair follicles and vessels. They separate the collagen bundles and there may be some secondary degeneration of collagen [23]. Generally, myxedema is diffuse, but focal mucinous papules have been described. Skin may appear swollen, dry, pale, waxy, and firm to the touch. In addition, increased dermal carotene may appear as a prominent yellowish discoloration on the palms, soles and nasolabial folds [23]. 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 lipophilic organisms, which are replaced by *Candida albicans* [25]. The hypothyroid skin heals slowly, and this tendency is proportional to the degree of hormone deficiency. Most recent data suggest that topical thyroid hormone may accelerate wound healing rate [26]. In hypothyroidism, hair can be dry, coarse, brittle and slow growing. There is both patchy and diffuse loss of scalp hair, a very characteristic loss of the outer third of the eyebrow (madarosis), and diminished body hair. Pubic and axillary hair may be sparse. The alopecia connected to hypothyroidism may be mediated by hormone effects on the initiation as well as the duration of hair growth. Massive telogen effluvium may occur when there is abrupt onset of hypothyroidism, and the percentage of scalp hairs in telogen is generally increased in hypothyroid states [23]. The effect of thyroid status on human hair growth has also been demonstrated at the cellular level. Using DNA flow cytometry, Schell *et al.* observed that cell proliferation indices were reduced in hair bulbs of hypothyroid subjects and increased in hyperthyroidism compared with normal values [27]. Hypothyroid patients, especially children, frequently develop long, lanugo-type hair on the back, shoulders, and extremities [23]. Diminished sebum secretion contributes to the coarse appearance of the hair. Sometimes, hair loss is the only apparent symptom of hypothyroidism and the dermatologist is the first to diagnose and treat the condition. Nails grow slowly and tend to be thickened, striated and brittle. Onycholysis is also associated with hypothyroidism [28].

Baseline data from a randomized clinical study confirmed a significant prevalence of hypothyroid symptoms among individuals with subclinical hypothyroidism [29]. Moreover, Canaris *et al.* reported fewer symptoms related to hypothyroidism in subclinical than in overt hypothyroid patients, but more frequent than in euthyroid controls [30].

Cutaneous manifestations of hyperthyroidism

The specific pathophysiology linking hyperthyroidism to classic cutaneous findings remains to be well explained [17]. In hyperthyroidism, the skin is warm, soft, moist and smooth. The epidermis is thin but not atrophic, and the stratum corneum is well hydrated. 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 [23]. The warmth is often accompanied by a persistent flush of the face, redness of the elbows, and palmar erythema. Hyperhidrosis, especially on palms and soles may be observed. Scalp hair may be fine and soft, and may be accompanied by a diffuse nonscarring alopecia. *In vitro* studies suggest increased hair growth rate in thyrotoxicosis. L-Triiodothyronine was shown to stimulate proliferation of outer root sheath keratinocytes and dermal papilla cells [4]. Hypertrichosis is can be observed in

cases of thyroid dermatopathy and may be related to alterations in the proteoglycans associated with dermal papilla [31]. Sometimes an early symptom of hyperthyroidism is loss of pigment and early gray hair development. Nail changes may also occur, characterized by a concave contour accompanied by distal onycholysis (Plummer's nails). Approximately 5% of patients may present with nail findings [17]. Hyperpigmentation has been described in thyrotoxic patients in both localized and generalized distribution. There is speculation that the hyperpigmentation is due to increased release of pituitary adrenocorticotrophic hormone compensating for accelerated cortisol degradation [32]. Hyperthyroidism may also induce pruritus with or without urticaria [33]. Patients with autoimmune mediated thyrotoxicosis may also have distinct cutaneous manifestations such as pretibial myxedema and acropachy. Pretibial myxedema is the localized thickening of the pretibial skin due to accumulation of acid mukopolysaccharides. Thyroid acropachy consist of the triad of digital clubbing, soft-tissue swelling of the hands and feet, and characteristic periosteal reactions. Scleromyxedema has been reported in the setting of hyperthyroidism. This rare entity is comprised of numerous firm, white, yellow, or pink papules scattered on the face, trunk, and extremities. Cutaneous lesions are the result of accumulation of acid mukopolysaccharides, mostly hyaluronic acid, in the dermis, accompanied by large fibrocytes [17].

Thyroid autoimmunity and skin disease

Thyroid autoimmunity is the most prevalent autoimmune condition in the general population, and it is also associated with various skin diseases. In patients affected by autoimmune thyroid diseases, the functions of the different skin cell types may be affected not only by variation in thyroid hormone levels but also by the presence of thyroid-specific auto antibodies [34]. However, the nature of the relationship between anti-thyroid autoimmunity and the pathogenesis of autoimmune diseases is presently unknown. Possible explanations include: (1) immunomodulatory effects of anti-thyroid antibodies, (2) molecular mimicry between thyroid and disease-specific epitopes, and (3) genetic link between anti-thyroid autoimmunity and the susceptibility to autoimmune disease [35]. Recent studies demonstrated the expression of thyroid factor-1, thyroglobulin [2] and thyroperoxidase in human skin [36].

When thyroid disease is of autoimmune etiology, additional skin findings may be evident and these may reflect associated autoimmune disease [33]. Patients with autoimmune thyroid disease are at increased risk for other autoimmune diseases, both tissue-specific and generalized. In autoimmune diseases, such as Graves' disease and Hashimoto's thyroiditis, the skin manifestations may be related to either thyroid hormone levels themselves or to associated T and/or B cell abnormalities [37]. A list of autoimmune conditions that become apparent when examining the skin includes: vitiligo [38], alopecia areata [39], chronic urticaria [40], bullous disorders [41,42] and connective tissue diseases [43,44]. In addition, vitiligo and alopecia areata often precede thyroid dysfunction by many years. Therefore, the presence of elevated thyroid antibodies may serve as useful clinical tool in euthyroid subjects with vitiligo and alopecia areata to identify patients at risk for thyroid disease.

Thyroid dermatopathy

Thyroid dermatopathy or pretibial myxedema is an autoimmune

manifestation of Grave's disease and it also occasionally occurs in Hashimoto's thyroiditis. One study using ultrasonography found that pretibial skin thickness was increased in 33% of patients with autoimmune thyroid disease, implying that infiltrative dermatopathy is likely to have a higher subclinical prevalence [45]. All of these patients had a laboratory evidence of autoimmune thyroid disease.

The term "myxoedema" was first used by Ord in 1877, in the belief that excessive mucus formation was responsible for the characteristic thickening of the subcutaneous tissue [46]. It usually present with firm nodules and plaques varying in color, from pink to purple-brown, and sometimes accompanied by woody indurations on extensor surfaces. A diffuse brawny edema may be present without nodules. Prominence of follicles and indurations can create an orange-peel appearance. Localized hyperhidrosis and hyperkeratosis are sometimes seen together. The skin changes may be categorized into diffused, sharply circumscribed or elephantiasic forms. Excessive amounts of hyaluronic acid and chondriotin are present in lesions, as well as in clinically normal skin [47].

The lesions of localized myxedema occur most commonly in the pretibial area and occasionally in the feet and toes. Occurrence of thyroid dermatopathy in areas other than pretibial skin indicates a systemic process.

The precise pathogenesis of pretibial myxedema remains to be defined. One leading theory is that pretibial fibroblasts are the target for antithyroid antibodies. After stimulation by thyroid auto antibodies, fibroblasts may produce excess glukosaminglycans [17]. The serum of patients with localized myxedema may stimulate the production of glukosaminglycans by fibroblasts, *in vitro* [48]. Other theories have implicated T cells as the primary effectors of dermatopathy. T-cells may interact with an auto antigen that is either identical or cross-reactive with a thyroid auto antigen in the dermis. In turn, this may induce secretion of cytokines, such as: glycosaminoglycan-stimulatory lymphokine, interleukin1, tumor necrosis factor, and gamma interferon, which activate fibroblasts to secrete hyaluronic acid and chondriotin sulphate [49,50].

Conclusion

Thyroid disorders may affect all of the organ systems of the body and they are also highly associated with a wide variety of skin disorders. Although cutaneous manifestations of thyroid diseases are well described, a better understanding of these processes is needed. Several hypothesis have been proposed to explain the pathogenesis of skin manifestations of thyroid disease, and indeed it is likely that more than one mechanism is responsible for these clinical manifestations. It is conceivable but unproven that cellular immunity initiated in the thyroid gland could trigger development of the skin lesions. In addition, recent studies demonstrated the expression of thyroid factor-1, thyroglobulin and thyroperoxidase in the human skin.

From the clinical perspective, thyroglobulin antibodies are more prevalent in patients with different skin diseases. Most commonly reported cutaneous disorders related with thyroid disease are: vitiligo and alopecia areata. We recommend laboratory testing for thyroid auto antibodies, in patients with autoimmune skin disorders, even if they do not have a clinical indication of thyroid disease.

Association between thyroid disease and the skin is a multidisciplinary problem requiring cooperation of specialists in different fields of medicine. Both dermatologist and endocrinologists have to inquire their patients about the family history of autoimmune diseases and to look for associated autoimmune disorders. Unraveling these associations further, will shed a new light on the pathogenesis of autoimmune diseases and possibly lead to new therapeutic approaches.

References

- Paus R. Exploring the "thyroid-skin connection": concepts, questions, and clinical relevance. *J Invest Dermatol.* 2010; 130: 7-10.
- Bodó E, Kromminga A, Bíró T, Borbíró I, Gáspár E, Zmijewski MA, et al. Human female hair follicles are a direct, nonclassical target for thyroid-stimulating hormone. *J Invest Dermatol.* 2009; 129: 1126-1139.
- Mullin GE, Eastern JS. Cutaneous consequences of accelerated thyroid function. *Cutis.* 1986; 37: 109-114.
- Ahsan MK, Urano Y, Kato S, Oura H, Arase S. Immunohistochemical localization of thyroid hormone nuclear receptors in human hair follicles and *in vitro* effect of L-triiodothyronine on cultured cells of hair follicles and skin. *J Med Invest.* 1998; 44: 179-184.
- Billoni N, Buan B, Gautier B, Gaillard O, Mahé YF, Bernard BA. Thyroid hormone receptor beta1 is expressed in the human hair follicle. *Br J Dermatol.* 2000; 142: 645-652.
- Safer JD. Thyroid hormone action on skin. *Dermatoendocrinol.* 2011; 3: 211-215.
- Slominski A, Wortsman J. Neuroendocrinology of the skin. *Endocr Rev.* 2000; 21: 457-487.
- Slominski AT, Zmijewski MA, Skobowiat C, Zbytek B, Slominski RM, Stekettee JD. Sensing the environment: regulation of local and global homeostasis by the skin's neuroendocrine system. *Adv Anat Embryol Cell Biol.* 2012; 212: v, vii, 1-115.
- Safer JD, Fraser LM, Ray S, Holick MF. Topical triiodothyronine stimulates epidermal proliferation, dermal thickening, and hair growth in mice and rats. *Thyroid.* 2001; 11: 717-724.
- Safer JD, Crawford TM, Fraser LM, Hoa M, Ray S, Chen TC, et al. Thyroid hormone action on skin: diverging effects of topical versus intraperitoneal administration. *Thyroid.* 2003; 13: 159-165.
- Van Beek N, Bodo E, Kromminga A, Gaspar E, Meyer K, Zmijewski MA, et al. Thyroid hormones directly alter human hair follicle functions: anagen prolongation and stimulation of both hair matrix keratinocyte proliferation and hair pigmentation. *J Clin Endocrinol Metabol.* 2008; 93: 4381-4388.
- Tiede S, Bohm K, Meier N, Funk W, Paus R. Endocrine controls of primary adult human stem cell biology: thyroid hormones stimulate keratin 15 expression apoptosis and differentiation in human hair follicle epithelial stem cells in situ and *in vitro*. *Eur J Cell Biol.* 2010; 89: 769-777.
- Messenger AG. Thyroid hormone and hair growth. *Br J Dermatol.* 2000; 142: 633-634.
- Bodó E, Kany B, Gáspár E, Knüver J, Kromminga A, Ramot Y, et al. Thyroid-stimulating hormone, a novel, locally produced modulator of human epidermal functions, is regulated by thyrotropin-releasing hormone and thyroid hormones. *Endocrinology.* 2010; 151: 1633-1642.
- Contreras-Jurado C, García-Serrano L, Gómez-Ferrera M, Costa C, Paramio JM, Aranda A. The thyroid hormone receptors as modulators of skin proliferation and inflammation. *J Biol Chem.* 2011; 286: 24079-24088.
- García-Serrano L, Gomez-Ferrera MA, Contreras-Jurado C, Segrelles C, Paramio JM, Aranda A. The thyroid hormone receptors modulate the skin response to retinoids. *PLoS One.* 2011; 6: e23825.
- Leonhardt JM, Heymann WR. Thyroid disease and the skin. *Dermatol Clin.* 2002; 20: 473-48, vii.
- Pazos-Moura CC, Moura EG, Breitenbach MMD, Bouskela E. Nailfold capillaroscopy in hypothyroidism: blood flow velocity during rest and postocclusive reactive hyperemia. *Angiology.* 1998; 49: 471.
- Silva JE. The thermogenic effect of thyroid hormone and its clinical implications. *Ann Intern Med.* 2003; 139: 205-213.
- Christianson HB. Cutaneous manifestations of hypothyroidism including purpura and ecchymoses. *Cutis.* 1976; 17: 45-52.
- Keen MA, Hassan I, Bhat MH. A clinical study of the cutaneous manifestations of hypothyroidism in kashmir valley. *Indian J Dermatol.* 2013; 58: 326.
- Dogra A, Dua A, Singh P. Thyroid and skin. *Indian J Dermatol.* 2006; 51: 96-99.
- Freinkel RK. Cutaneous manifestations of endocrine disease. Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF, editors. In: *Dermatology in general medicine.* McGraw-Hill, Inc. 1993; 2113-2131.
- Hanley K, Devaskar UP, Hicks SJ, Jiang Y, Crumrine D, Elias PM, et al. Hypothyroidism delays fetal stratum corneum development in mice. *Pediatr Res.* 1997; 42: 610-614.
- Dekio S, Imaoka C, Jidoi J. Candida folliculitis associated with hypothyroidism. *Br J Dermatol.* 1987; 117: 663-664.
- Safer JD. Thyroid hormone and wound healing. *J Thyroid Res.* 2013; 2013: 124538.
- Schell H, Kiesewetter F, Seidel C, von Hintzenstern J. Cell cycle kinetics of human anagen scalp hair bulbs in thyroid disorders determined by DNA flow cytometry. *Dermatologica.* 1991; 182: 23-26.
- Mullin GE, Eastern JS. Cutaneous signs of thyroid disease. *Am Fam Physician.* 1986; 34: 93-98.
- Cooper DS, Halpern R, Wood LC, Levin AA, Ridgway EC. L-Thyroxine therapy in subclinical hypothyroidism. A double-blind, placebo-controlled trial. *Ann Intern Med.* 1984; 101: 18-24.
- Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med.* 2000; 160: 526-534.
- Westgate GE, Messenger AG, Watson LP, Gibson WT. Distribution of proteoglycans during the hair growth cycle in human skin. *J Invest Dermatol.* 1991; 96: 191-195.
- Diven DG, Gwinup G, Newton RC. The thyroid. *Dermatol Clin.* 1989; 7: 547-558.
- Ai J, Leonhardt JM, Heymann WR. Autoimmune thyroid diseases: etiology, pathogenesis, and dermatologic manifestations. *J Am Acad Dermatol.* 2003; 48: 641-659.
- Cianfarani F, Baldini E, Cavalli A, Marchioni E, Lembo L, Teson M, et al. TSH receptor and thyroid-specific gene expression in human skin. *J Invest Dermatol.* 2010; 130: 93-101.
- Szyper-Kravitz M, Marai I, Shoenfeld Y. Coexistence of thyroid autoimmunity with other autoimmune diseases: friend or foe? Additional aspects on the mosaic of autoimmunity. *Autoimmunity.* 2005; 38: 247-255.
- Cianfarani F, Baldini E, Cavalli A, Marchioni E, Lembo L, Teson M, et al. TSH receptor and thyroid-specific gene expression in human skin. *J Invest Dermatol.* 2010; 130: 93-101.
- Burman KD, McKinley-Grant L. Dermatologic aspects of thyroid disease. *Clin Dermatol.* 2006; 24: 247-255.
- Vrijman C, Kroon MW, Limpens J, Leeflang MM, Luiten RM, van der Veen JP, et al. The prevalence of thyroid disease in patients with vitiligo: a systematic review. *Br J Dermatol.* 2012; 167: 1224-1235.
- Kasumagic-Halilovic E. Thyroid autoimmunity in patients with alopecia areata. *Acta Dermatovenerol Croat.* 2008; 16: 123-125.
- Cebeci F, Tanrikut A, Topcu E, Onsun N, Kurtulmus N, Uras AR. Association between chronic urticaria and thyroid autoimmunity. *Eur J Dermatol.* 2006; 16: 402-405.

41. Kavala M, Kural E, Kocaturk E, Zindanci I, Turkoglu Z, Can B. The evaluation of thyroid diseases in patients with pemphigus vulgaris. *ScientificWorldJournal*. 2012; 2012: 146897.
42. Zettinig G, Weissel M, Flores J, Dudczak R, Vogelsang H. Dermatitis herpetiformis is associated with atrophic but not with goitrous variant of Hashimoto's thyroiditis. *Eur J Clin Invest*. 2000; 30: 53-57.
43. Blich M, Rozin A, Edoute Y. Systemic lupus erythematosus and thyroid disease. *Isr Med Assoc J*. 2004; 6: 218-220.
44. Zeher M, Horvath IF, Szanto A, Szodoray P. Autoimmune thyroid diseases in a large group of Hungarian patients with primary Sjögren's syndrome. *Thyroid*. 2009; 19: 39-45.
45. Salvi M, De Chiara F, Gardini E, Minelli R, Bianconi L, Alinovi A, et al. Echographic diagnosis of pretibial myxedema in patients with autoimmune thyroid disease. *Eur J Endocrinol*. 1994; 131: 113-119.
46. Ord WM. On Myxoedema, a term proposed to be applied to an essential condition in the "Cretinoid" Affection occasionally observed in Middle-aged Women. *Med Chir Trans*. 1878; 61: 57-78.
47. Beierwaltes WH, Bollet AJ. Mucopolysaccharide content of skin in patients with pretibial myxedema. *J Clin Invest*. 1959; 38: 945-948.
48. Metcalfe RA, Davies R, Weetman AP. Analysis of fibroblast-stimulating activity in IgG from patients with Graves' dermopathy. *Thyroid*. 1993; 3: 207-212.
49. Chang TC, Wu SL, Hsiao YL, Kuo ST, Chien LF, Kuo YF, et al. TSH and TSH receptor antibody-binding sites in fibroblasts of pretibial myxedema are related to the extracellular domain of entire TSH receptor. *Clin Immunol Immunopathol*. 1994; 71: 113-120.
50. Weetman AP. Determinants of autoimmune thyroid disease. *Nat Immunol*. 2001; 2: 769-770.