Skin Changes in Newly Diagnosed Cases of Hypothyroidism

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Author’s Contribution
1. Conception of study
2. Experimentation/Study conduct
3. Analysis/Interpretation/Discussion
4. Manuscript Writing
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Abstract

Introduction: Thyroid disorders are frequent in our population that lead to a variety of cutaneous manifestations. Our study aimed to determine the frequencies of skin changes of hypothyroidism and their association with gender.

Materials and Methods: This observational study was conducted at RIHS Islamabad (1st Jun to 31st Dec 2019) after ethical approval. A total of 105 patients (≥18 years of age) of both genders confirmed to have hypothyroidism based on thyroid function tests were included. Secondary hypothyroidism, sick thyroid disease, pregnant women, receiving thyroxin therapy, carcinoma of the thyroid, critically ill cases, post-thyroidectomy and iatrogenic thyroid cases were excluded. After informed consent, demographic details were documented. Patients were clinically evaluated and examined in detail including dermatological examination for cutaneous manifestations. Various skin findings are studied with respect to gender. Data were analysed by SPSS version 21. The Chi-square test was applied with a significant p<0.05.

Results: Among 105 cases of hypothyroidism (62% females and 38% males), the mean age was 38.04±12.61 years. The mean TSH level was found to be 32.08±33.96 (mean TSH was 35.31±37.31 in females Vs. 26.96±27.19 in males; p=0.001). Common skin findings were dry skin in 69.5%, diffuse hair loss in 58%, coarse skin in 57%, pruritis in 51.4%, madarosis in 37%, and seborrhoeic dermatitis in 34%, coarse scalp hairs in 27% and slow nail growth in 23%. The brittle nails, alopecia areata, chronic urticaria, acanthosis nigricans, ivory yellow skin, purpura ecchymosis, ichthyosis, herpes simplex and certain other findings were found in <20% cases. Obesity was observed in 53(50.5%) cases of hypothyroidism. The dry, coarse skin, diffuse hair loss and seborrhoeic dermatitis were associated with the female gender (p>0.05). Slow nail growth, brittle nails, acne vulgaris, acrochordons, vitiligo, and xanthelasma were more common in males however the difference wasn’t statistically significant.

Conclusion: Skin acts as an important diagnostic window to diseases affecting internal organs including thyroid disorders. Dry skin was the commonest skin manifestation followed by diffuse hair loss, more in females as compared to males so hypothyroidism can be easily diagnosed by these skin changes in our patients. Authors recommended screening for thyroid functions, in patients presenting with suggestive dermatological manifestations irrespective of age and gender.

Keywords: Hypothyroidism, Thyroid Diseases, Skin Changes, Thyroid Stimulating Hormone, Thyroid Gland.
Introduction

The thyroid gland is a butterfly-shaped endocrine gland situated in the lower part of the front of the neck. It is present below the larynx, in front and sides of the trachea.\(^1\) Thyroid gland plays a major role in the metabolism, development and growth of the human body and regulates several body functions including basal metabolic rate (BMR). It stimulates somatic and psychic growth other than having important participation in calcium metabolism.\(^2,3\)

Hypothyroidism is caused by thyroid hormone deficiency either due to decreased production of hormones, defective distribution, lack of effects of thyroid hormone or consequence of drug-induced thyroid dysfunction. Central hypothyroidism may be induced by the inhibition of thyroid-stimulating hormone (TSH) by corticosteroids or immunological mechanisms (anti-CTLA4 or anti-PD-1 antibody drugs).\(^4\) The prevalence of hypothyroidism is 4-5% in developed countries, whereas 11% in India, 4.6% in the USA and 2% in the UK. It is more common in females as compared to males.\(^3\) Hypothyroidism can be easily diagnosed and managed. However, untreated cases may present with systemic complications as well as poor quality of life. This may even lead to death in severe cases.\(^5\)

Thyroid hormones play an important role in regulating healthy normal skin. Certain skin changes in hypothyroidism vary with the age group or gender.\(^6\) Actions of thyroid hormone on the skin are mediated through thyroid hormones receptor (TR) i.e., present in epidermal keratinocytes, erector pili muscle, hair follicles, sebaceous gland cells, skin fibroblasts, vascular endothelial cells and Schwann cells. The epidermal homeostasis is regulated by thyroid hormones. Skin in hypothyroidism is rough, dry, and scaly over extensor surfaces.\(^7\)

The thyroid hormone increases the activity of an enzyme in cholesterol sulphate synthesis and enhances the skin barrier formation. In hypothyroidism, there is a hindrance in the barrier formation of the epidermis.\(^8\) Dermal changes include myxoedema (due to glucose-aminoglycan deposition in the skin), oedema of hands, face, eyelid and pallor. Generalized myxoedema is a classical sign of hypothyroidism.\(^8\) Prominent yellowish hue of skin on palms, soles and nasolabial folds known as carotenemia which is secondary to increased dermal carotene deposition.\(^9\)

Hair changes in hypothyroidism include dry brittle, coarse hair, slow-growing, patchy or diffuse hair loss (alopecia), and loss of lateral 3\(^{rd}\) of eyebrows (madarosis) while nail changes are coarse dull brittle striated nails, slow nail growth, longitudinal and transverse striations and onycholysis. Dry skin (xerosis) and decreased sweating secondary to sweat gland changes are also observed. Other skin manifestations include intolerance to cold, purpura, upper eyelids drooping, nerve entrapment syndromes, puffy face, Palmo-planter keratoderma, xanthelasma palpebrum. It is also associated with livedo reticularis of extremities secondary to vasoconstriction and decreased sebaceous gland secretion. Decreased skin perfusion may lead to cold, pale skin which can be examined by nail fold capillaroscopy and laser doppler.\(^8,10,11,12\)

Clinical features of hypothyroidism and subclinical hypothyroidism range from mild symptoms to life-threatening conditions. Common symptoms in adults are fatigue, lethargy, cold intolerance, weight gain, myxedematous facies, constipation, change in voice, dry skin, poor concentration, altered mood, cognitive dysfunction, depression, menstrual irregularities, bradycardia, pericardial effusion and cardiac tamponade. These clinical features vary with age and gender.\(^5,11,13,14\)

Vitiligo, urticaria and alopecia areata may be associated with autoimmune hypothyroidism. Occasionally, dermal deposition of mucin leads to a decreased level of clotting factors and loss of vascular support leading to purpura. Hypothyroidism is associated with impaired vascular function. hypohidrosis and palmoplantar keratoderma secondary to decreased epidermal cholesterol biosynthesis. The decreased sebum production in hypothyroid patients may present with candida folliculitis. Former studies have mentioned that 40-70% of patients with melanin spots have thyroid dysfunction. Similarly, 42% of males and 62% of females with vitiligo, 50% of chronic mucocutaneous candidiasis, 34% of dermatitis herpetiformis, 8% of delayed hypersensitivity reactions and 8% of alopecia areata cases have thyroid disorders.\(^8,10,11,12\)

Certain associations of autoimmune thyroid disease are with bullous diseases like pemphigus, connective tissue disorders, Kaposi’s sarcoma, pernicious anaemia, dermatomyositis, Sjogren’s, syndrome, polymyositis, etc. Certain other associations are with acanthosis nigricans, McCune-Albright syndrome, sweet syndrome), CREST syndrome, psoriasis, Cowden’s syndrome, ANOTHER syndrome (alopecia, nail dystrophy, hypo-hydrosis and ephelides), acropachies, and atopic manifestations (urticaria, dermographism and angiodema.\(^19,20\)
Most of the skin changes of hypothyroidism are non-specific and may present with or without thyroid problems. There needs to evaluate the case presenting with cutaneous manifestations associated with thyroid disease. This research was designed to determine the frequency of skin changes in hypothyroid cases and study these changes in association with gender. This may help us study the trend and gender-wise distribution of cutaneous changes in our patients that may lead to improved outcomes dermatologically, systemically as well as the quality of life.

**Materials and Methods**

This observational study was conducted at the Department of Medicine Rawal Institute of Health Sciences Islamabad from 1st June 2019 to 31st Dec 2019. Ethical approval was obtained from the ethical review board.

**Inclusion criteria:** Adult patients (≥18 years) of both genders with a confirmed diagnosis of hypothyroidism based on thyroid function tests (TSH, T3 and T4).

**Exclusion criteria:** Patients with secondary hypothyroidism, sick thyroid disease and pregnant women were excluded. Also, the patients receiving thyroxin therapy for >1 month, cases of carcinoma of the thyroid, terminal or critically ill cases requiring intensive care, patients who had undergone thyroid surgery, or who have iatrogenic thyroid disordered i.e., post thyroidectomy or post-radioactive iodine therapy was excluded.

The sample size was calculated to be a minimum of 73 cases (5% prevalence of hypothyroidism, 5% precision and 95% confidence interval).20 Total 105 confirmed cases of hypothyroidism meeting the inclusion and exclusion criteria were included by convenience sampling. Informed consent was obtained and demographic data, height, weight and BMI were calculated. Their co-morbid conditions, a detailed history and clinical examination were performed supported by relevant labs. Complete medical, as well as dermatological examination, was done. Skin findings were documented on a specially designed proforma.

SPSS version 21 was used for data analysis. Quantitative variables (i.e., age and TSH levels) were presented as mean and standard deviation. Qualitative variables (i.e., gender, presence of co-morbid conditions and skin findings) as frequencies and percentages. The Chi-square test was used to study the association of various skin changes with gender, p-value <0.05 was considered statistically significant.

**Results**

Among 105 cases of hypothyroidism, there were 65(62%) females and 40(38%) males. The mean age was 38.04±12.61 (18-65) years. Obesity was observed in 53(50.5%) cases (Table 1). Amongst these, had dry skin was found in 73(69.5%), diffuse hair loss 61(58.1%), coarse skin 60(57%), pruritis 54(51.4%), madarosis 39(37.1%), seborrhoeic dermatitis 36(34.3%), coarse scalp hairs 28(26.7%), slow nail growth 24(22.9%), brittle nails 19(18.1%), alopecia areata 18(17.1%), chronic urticaria 18(17.1%), acanthosis nigricans 15(14.3%), ivory yellow skin 13(12.4%), purpura ecchymosis 12(11.4%), ichthyosis 11(10.5%) and herpes simplex 11(10.5%).

Certain changes were observed in <10% cases including acrochordons, vitiligo, keratoderma, onycholysis, loss of axillary hair, carotenemia, xanthelasma palpebrum, lichen planus, loss of pubic hair, seborrhoeic keratosis and ephelides. The actinic keratosis, scleroderma, granuloma annulare, polymorphic light eruption and baker’s naevoidus, Granuloma annulare, polymorphic light eruption and baker’s nevus weren’t found in these patients (Figure 1).

Regarding co-morbid conditions, 20(19%) cases had type 2 diabetes mellitus and 23(21.9%) cases had hypertension. There was dyslipidaemia in 12(11.4%) cases. Anaemia was present in 09(8.6%) cases. The mean Thyroid-stimulating hormone (TSH) level was found to be 32.08±33.96 (range 4.6-175). There were 32(49.2%) obese females and 21(52.5%) obese males (p=0.745). 14(21.5%) diabetic females and 6(15%) males (p=0.407). 19(29.2%) hypertensive females and 4(10%) hypertensive males (p=0.021). dyslipidaemia was found in 8(12.3%) females and 4(10%) males (p=0.718).

Anaemia was present in 9(13.8%) females and none of the males (p=0.014). This Means TSH in females was 35.31±37.31 and in males 26.96±27.19 (p=0.001). The frequency of various skin findings and their association with gender is presented in Table 2.
Table 1: Presenting demographic variables and co-morbid conditions observed in Hypothyroid cases (n=105)

| Demographic variables       | n(%)         | Females   | Males   | p-value |
|-----------------------------|--------------|-----------|---------|---------|
| Mean age (years)            | 38.04±12.61(18-65) | 38.35±12.65 | 37.52±12.69 | 0.230   |
| Mean TSH levels             | 32.12±33.92(4.6-175) | 35.30±37.31 | 26.96±27.19 | <0.0001 |
| Diabetes mellitus           | 20(19%)      | 14(21.5%) | 06(15%) | 0.407   |
| Dyslipidaemia               | 12(11.4%)    | 08(12.3%) | 04(10%) | 0.718   |
| Anaemia                     | 09(8.6%)     | 09(13.8%) | 00(0%)  | 0.014   |
| Hypertension                | 23(22%)      | 19(29.2%) | 04(10%) | 0.021   |
| Obesity (BMI >30)           | 33(50.5%)    | 32(49.2%) | 21(52.5%) | 0.745   |

(Test of significance Chi-square test; Significant p < 0.05)

Table 2: Skin findings in hypothyroid cases and their association with gender (n=105)

| Cutaneous finding        | Amongst all n(%),n=105 | Females 65(62%) | Males 40(38%) | p-value |
|--------------------------|------------------------|-----------------|---------------|---------|
| 1. Dry skin              | 73(69.5%)              | 50(76.9%)       | 23(57.5%)     | 0.036   |
| 2. Diffuse hair loss     | 61(58.1%)              | 45(69.2%)       | 16(40%)       | 0.003   |
| 3. Coarse skin           | 60(57%)                | 42(64.6%)       | 18(45%)       | 0.049   |
| 4. Pruritus               | 54(51.4%)              | 38(58.5%)       | 16(40%)       | 0.066   |
| 5. Madarosis              | 39(37.1%)              | 22(33.8%)       | 17(42.5%)     | 0.373   |
| 6. Seborrheic dermatitis | 36(34.3%)              | 27(41.5%)       | 9(22.5%)      | 0.046   |
| 7. Coarse scalp hair     | 28(26.7%)              | 16(24.6%)       | 12(30%)       | 0.545   |
| 8. Slow nail growth      | 24(22.9%)              | 12(18.5%)       | 12(30%)       | 0.172   |
| 9. Brittle nails          | 19(18.1%)              | 11(16.9%)       | 8(20%)        | 0.691   |
| 10. Alopecia areata      | 18(17.1%)              | 10(15.4%)       | 8(6.8%)       | 0.542   |
| 11. Chronic urticarial   | 18(17.1%)              | 11(16.9%)       | 7(17.1%)      | 0.939   |
| 12. Hypo-hydrosis        | 16(15.2%)              | 10(15.4%)       | 6(15%)        | 0.958   |
| 13. Acanthosis nigricans | 15(14.3%)              | 10(15.4%)       | 5(12.5%)      | 0.682   |
| 14. Ivory Yellow skin    | 13(12.4%)              | 8(12.3%)        | 5(12.5%)      | 0.977   |
| 15. Acne Vulgaris        | 12(11.4%)              | 6(9.2%)         | 6(15%)        | 0.367   |
| 16. Purpura Echymosis    | 12(11.4%)              | 8(12.3%)        | 4(10%)        | 0.718   |
| 17. Ichthyosis            | 11(10.5%)              | 4(6.2%)         | 5(12.5%)      | 0.092   |
| 18. Herpes simplex       | 11(10.5%)              | 7(10.8%)        | 4(10%)        | 0.901   |
| 19. Acrochordons          | 10(9.5%)               | 3(4.6%)         | 7(17.5%)      | 0.029   |
| 20. Vitiligo              | 9(9.1%)                | 5(7.7%)         | 4(10%)        | 0.682   |
| 21. Myxedema              | 08(7.6%)               | 5(7.7%)         | 3(7.5%)       | 0.971   |
| 22. Keratoderma           | 08(6.7%)               | 4(6.2%)         | 4(10%)        | 0.471   |
| 23. Onycholysis           | 7(6.6%)                | 4(6.2%)         | 3(7.5%)       | 0.788   |
| 24. Loss of Axillary hair | 06(5.7%)               | 2(3.1%)         | 4(10%)        | 0.138   |
| 25. Carotenemia           | 05(4.8%)               | 4(6.2%)         | 1(2.5%)       | 0.360   |
| 26. Psoriasis             | 05(4.8%)               | 3(4.6%)         | 2(5%)         | 0.928   |
| 27. Xanthelasma palpebrum| 05(4.8%)               | 1(1.5%)         | 4(10%)        | 0.048   |
| 28. Lichen planus         | 05(4.8%)               | 3(4.6%)         | 2(5%)         | 0.928   |
| 29. Loss of pubic hair    | 03(2.9%)               | 2(3.1%)         | 1(2.5%)       | 0.863   |
| 30. Seborrheic keratosis  | 02(1.9%)               | 0(0%)           | 2(5%)         | 0.069   |
| 31. Ephilides             | 02(1.9%)               | 2(3.1%)         | 0(0%)         | 0.263   |
| 32. Actinic keratosis     | 0(0%)                  | 0(0%)           | 0(0%)         | -       |
| 33. Scleroderma           | 0(0%)                  | 0(0%)           | 0(0%)         | -       |
| 34. Granuloma annulare    | 0(0%)                  | 0(0%)           | 0(0%)         | -       |
| 35. Polymorphic light eruption | 0(0%) | 0(0%) | 0(0%) | - |
| 36. Becker naevus         | 0(0%)                  | 0(0%)           | 0(0%)         | -       |

(Test of significance Chi-square test, significant p-value<0.05)
Discussion

In our study, there were 105 patients in which 62% were females and 38% were males which coincides with the earlier studies which showed female predominance by Haritha et al.\textsuperscript{12} We may conclude that female predominance may be due to an increased prevalence of autoimmune disorders in females and this autoimmunity is an important cause of hypothyroidism as well.\textsuperscript{21}

The commonest skin finding of hypothyroidism in our study was dry skin that is observed in approx. 2/3rd of our cases. This coincides with the study by Bains et al who found xerosis i.e., dry skin in 67% of cases.\textsuperscript{22} Varying results are observed in different studies. The reasons could be environmental factors, skin types, age, gender and regional differences.

Dry skin was followed by diffuse hair loss (58%) which is 2\textsuperscript{nd} most common finding of hypothyroidism in our study which is lower than observations by Haritha and Neerja et al showing 34.8% and 33.3% respectively.\textsuperscript{12,23} Course skin was found in half of our cases, i.e., the 3\textsuperscript{rd} most common finding in our study which is higher and does not coincide with the study by Keen et al who found it in 65% of cases.\textsuperscript{6} This may also be contributed to the environmental and other factors mentioned earlier.

Pruritis was seen in 27% of patients in our study while Keen et al found it less common i.e., 17.7% finding in his study.\textsuperscript{24} Madarosis (i.e., loss of eyebrows) was seen in 37% of patients in our study but Neerja et al found it in 22.2% which is lower than our study.\textsuperscript{23} Nail changes include slow nail growth (23%) and brittle nails (18%), however, Keen et al all found nail changes in 2% cases which were very less than compared in our study.\textsuperscript{24} The nail health depends on multiple factors in addition to thyroid disorders, regional deficiency of calcium and other nutrients may be responsible for this high prevalence in our cases.

Skin changes secondary to autoimmunity like alopecia areata are observed to be approx. 17% in certain other studies.\textsuperscript{23,24} Alopecia secondary to hypothyroidism is mediated via hormone that affects the initiation and duration of the hair growth cell cycle. The normal telogen anagen hair relationships can be restored by thyroid hormone replacement. A significant association is found between alopecia areata and thyroid disorders by Marahatta et al in his study as well.\textsuperscript{25}

Chronic idiopathic urticaria was reported in 17% of our study. Dogra et al\textsuperscript{26} Lenzoff and Sussman\textsuperscript{27} reported 15.6% and 624 patients respectively with chronic idiopathic urticaria and angioedema and noted thyroid disorder in 90 patients while Heymann\textsuperscript{28} couldn’t establish the mechanism of autoimmunity in urticaria. A study by Neerja puri showed 6% of patients of urticaria.\textsuperscript{23} In our study acanthosis nigricans was seen in 14.3% of our study which is lower than than observations by Kuroki et al\textsuperscript{29} reported 52.75% cases which were higher than our study.\textsuperscript{23} Purpura ecchymosis was found in 11.4% of our study while Keen et al\textsuperscript{24} reported 4.13% and Christianson HB\textsuperscript{31} reported 4.05% of patients which was lower than our study.
Ichthyosis was seen in 10.5% of our study while Haritha et al showed 38% of ichthyotic patients in their studies which was a higher percentage compared to our study. Herpes simplex was seen in 10.5% of patients in our study and Keen et al24 in their study suggested that it’s an association of disease. Thyroid hormone (T3) participates in the regulation of herpes simplex replication during reactivation but in vivo suggested that T3 suppressed herpes simplex virus replication.

Vitiligo was seen in 0.5% of our study while Keen et al24 found 7 patients in their study. While research conducted by Sedighe et al,32 Gopal et al33 have shown an association between vitiligo and hypothyroidism. Haritha et al32 found three patients in their study which was less than our study and findings were not coincide with a study conducted by Samson et al.34 Palmoplantar keratoderma was seen in 7% of patients while Neerja pur23 and Keen et al24 found in 33.3% and 19.35% respectively in their studies which were higher than our study but Rai et al30 found 7.2% patients which were less than our study. Carotenemia was found in 5% of our study which coincide with the study by Keen et al.24 Xanthelasma palpebrum was seen in 5% of patients which did not coincide with a study by Keen et al24 who found 1.52% and the least common finding in his study whereas the study by Dogra et al26 noticed it in 3% of patients. Lichen planus was seen in 5% of our study while the study by K. Kirthi32 was not coinciding with our study, they found 3% cases of lichen planus in their study. Other associated diseases like seborrheic keratosis and ephelides were noticed as less common finding only 2 cases in our study. There were no cases reported of actinic keratosis scleroderma, granuloma annulare, polymorphic light eruption and baker naevas in our study.

There is limited regional data addressing skin changes of hypothyroidism. This study provides us with the various skin changes secondary to hypothyroidism in our population. There are certain limitations in our study like the small sample size and short duration of the study and lack of regional local data available. The authors recommended a better sample size and careful interpretation of data and further regional studies in this context with the prolonged duration of the study. The results of this study will help us with an earlier diagnosis and better management of patients that can prevent the systemic complications of hypothyroidism.

We conclude that the relationship between the skin and the thyroid gland is complex. Skin acts as an important diagnostic window to diseases affecting internal organs including thyroid disorders. Certain dermatological manifestations help in the early diagnosis and management of patients by early detection of changes in skin, hairs and nails secondary to hypothyroidism. Authors recommended screening for thyroid functions in patients presenting with suggestive dermatological manifestations irrespective of age and gender.

**Conclusion**

We are thankful to all participants who were involved in this study and others who have helped either directly or indirectly.

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