Original Article

Skin Changes in Newly Diagnosed Cases of Hypothyroidism

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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 (≥18years 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 seborrheic 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 seborrheic 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 Schwan 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 3rd 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. hypo-hidrosis and palmoplantar keratoderma secondary to decrease 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.[15,16,17,18]

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), CREAST syndrome, psoriasis, Cowden's syndrome, ANOTHER syndrome (alopecia, nail dystrophy, hypo-hydrosis and ephelides), acropachies, and atopic manifestations (urticaria, dermographism and angioedema.[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%), seborrheic dermatitis 36(34.3%), coarse scalp hairs 28(26.7%), slow nail growth 24(22.9%), brittle nails 19(18.1%), alopecia areata18(17.1%), chronic urticaria 18(17.1%), acanthosis nigricans15(14.3%), ivory yellow skin 13(12.4%), purpura ecchymosis 12(11.4%), ichthyosis 11(10.5%) and herpes simplex in 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, seborrheic keratosis and ephelides. The actinic keratosis, scleroderma, granuloma annulare, polymorphic light eruption and baker's naevus, 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(%)* *n=105*	*Females* *n = 65*	*Males* *n= 40*	*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)	35.306+37.31	26.96+27.19	**<0.0001**
➢ **Diabetes mellitus**	20(19%)	14(21.5%)	06(15%)	0.407
➢ **Dyslipidaemia**	12(11.4%)	8(12.3%)	04(10%)	0.718
➢ **Anaemia**	09(8.6%)	9(13.8%)	00(0%)	**0.014**
➢ **Hypertension**	23(22%)	19(29.2%)	4(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=5*	*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. Pruritis	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. Icthyosis	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. Myxoedema	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)

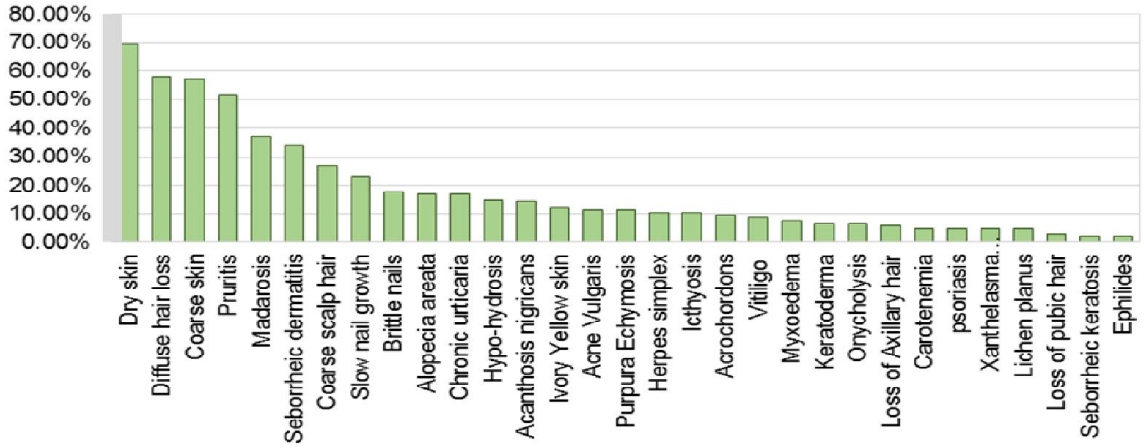

Figure 1: Bar graph representation of cutaneous findings observed in hypothyroid cases (n=105)

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.[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.[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 all who found xerosis i.e., dry skin in 67% of cases.[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 2nd 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.[12,23] Course skin was found in half of our cases, i.e., the 3rd 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.[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.[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.[23] Nail changes include slow nail growth (23%) and brittle nails (18%), however, Keen et all found nail changes in 2% cases which were very less than compared in our study.[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.[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.[25]

Chronic idiopathic urticaria was reported in 17% of our study. Dogra et al,[26] Lenzoff and Sussman[27] reported 15.6% and 624 patients respectively with chronic idiopathic urticaria and angioedema and noted thyroid disorder in 90 patients while Heymann[28] couldn't establish the mechanism of autoimmunity in urticaria. A study by Neerja puri showed 6% of patients of urticaria.[23]

In our study acanthosis nigricans was seen in 14.3% of patients while a study by Keen et al[24] showed acanthosis nigricans in only four patients which did not coincide with our study. An association between acanthosis nigricans and hypothyroidism have established by Kuroki et al.[29]

Ivory yellow skin was seen in 12.4% in our study while 6.52% & 5.12% in studies conducted by Keen et al [24] & Rai et al[30] respectively, which was lower than our study and does not coincide with their studies and Neerja puri showed 52.75% cases which were higher than our study.[23] Purpura ecchymosis was found in 11.4% of our study while Keen at al[24] reported 4.13% and Christianson HB[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 al[24] 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 al [24] found 7 patients in their study. While research conducted by Sedighe et al,[32] Gopal et al[33] have shown an association between vitiligo and hypothyroidism. Haritha et al[32] 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 puri[23] and Keen et al[24] found in 33.3% and 19.35% respectively in their studies which were higher than our study but Rai et al[30] found 7.2% patients which were less than our study

Carotenemia was found in 5% of our study which coincides 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 al[24] who found 1.52% and the least common finding in his study whereas the study by Dogra et al[26] noticed it in 3% of patients. Lichen planus was seen in 5% of our study while the study by K. Kirthi[32] 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 naevus 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.

Conclusion

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.

References

1. Khan YS, Farhana A. Histology, Thyroid Gland. In: Stat Pearls. Stat Pearls Publishing, Treasure Island (FL); 2020. PMID: 31869123.
2. Kim MJ et al. Changes in body compositions and basal metabolic rates during treatment of Graves' disease. International journal of endocrinology. 2018:1-8. DOI: https://doi.org/10.1155/2018/9863050
3. Alam MA, Quamri MA, Sofi G, Ansari S. Update of hypothyroidism and its management in Unani medicine. Journal of basic and clinical physiology and Pharmacology. 2020: 32(2):1-10. DOI: 10.1515/jbcpp-2020-0121
4. Rizzo LF, Mana DL, Serra HA. Drug-induced hypothyroidism. Medicina (Buenos Aires). 2017;77(5):394-404. PMID: 29044016.
5. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet. 2017,9 (23);390(10101):1550-62. DOI: 10.1016/S0140-6736(17)30703-1.
6. Chen X, Zheng X, Ding Z, Su Y, Wang S, Cui B, Xie Z. Relationship of gender and age on thyroid hormone parameters in a large Chinese population. Arch Endocrinol Metab. 2020 ;64(1):52-58. DOI: 10.20945/2359-3997000000179.
7. Safer JD. Thyroid hormone action on skin. Dermato-endocrinology. 2011;3(3):2111-2115. . DOI: 10.4161/derm.3.3.17027
8. Silva TS, Faro GB, Cortes MG, Rego VR. Primary hypothyroidism with exuberant dermatological manifestations. An Bras Dermatol. 2020;95(6):721-723. DOI: 10.1016/j.abd.2019.07.010.
9. Priyadarshani AM. Insights of hypercarotenaemia: A brief review. Clin Nutr ESPEN. 2018, 2(23):19-24. DOI: 10.1016/j.clnesp.2017.12.002.
10. Clayton RW et al. Neuroendocrinology and neurobiology of sebaceous glands. Biological Reviews. 2020 ; 95(3):592-624. DOI: https://doi.org/10.1111/brv.12579
11. Kasumagic-Halilovic E, Begovic B. Thyroid autoimmunity in patients with skin disorders. Thyroid Hormone. 2012:18:297. DOI: 10.5772/45980.

12. Haritha S, Sampath KK. Skin manifestations of hypothyroidism-A clinical study. Journal of dental and medical sciences 2013: 7(2);58-60.
13. Peeters RP. Subclinical hypothyroidism. New England Journal of Medicine. 2017: 29;376(26):2556-65. DOI: 10.1056/NEJMcp1611144
14. Chiovato L, Magri F, Carlé A. Hypothyroidism in Context: Where We've Been and Where We're Going. Adv Ther. 2019;36(Suppl 2):47-58. DOI: 10.1007/s12325-019-01080-8.
15. Biondi B, Cappola AR, Cooper DS. Subclinical Hypothyroidism: A Review. JAMA. 2019, 9;322(2):153-60. doi:10.1001/jama.2019.9052
16. Koehler VF, Reincke M, Spitzweg C. Hypothyreose – wann und wie behandeln? [Hypothyroidism-when and how to treat?]. Internist (Berl). German. 2018 ;59(7):644-653. DOI: 10.1007/s00108-018-0438-x.
17. Mihor A, Gergar M, Gaberščček S, Lenasi H. Skin microvascular reactivity in patients with hypothyroidism. Clin Hemorheol Microcirc. 2016 ; 64(1):105-114. DOI: 10.3233/CH-162062.
18. Chahine J, Ala CK, Gentry JL, Pantalone KM, Klein AL. Pericardial diseases in patients with hypothyroidism. BMJ 2019 ;105(13):1027-1033. DOI: 10.1136/heartjnl-2018-314528. 19.
19. Lázaro VA, Martínez AA. Skin changes associated to hypothyroidism. Endocrinologia y nutricion: organo de la Sociedad Espanola de Endocrinologia y Nutricion. 2013;60(6):345-7. DOI: 10.1016/ j.endoen.2012.08.014.
20. Muñoz-Ortiz J, Sierra-Cote MC, Zapata-Bravo E, Valenzuela-Vallejo L, Marin-Noriega MA, Uribe-Reina P, et al. Prevalence of hyperthyroidism, hypothyroidism, and euthyroidism in thyroid eye disease: a systematic review of the literature. Systematic reviews. 2020 ;9(1):1-2. DOI: https://doi.org/10.1186/s13643-020-01459-7
21. Mammen JSR, Cappola AR. Autoimmune Thyroid Disease in Women. JAMA. 2021;325(23):2392–2393. DOI: 10.1001/jama.2020.22196
22. Bains A, Tegta G R, Vedant D. A cross-sectional study of cutaneous changes in patients with acquired thyroid disorders. Clin Dermatol Rev 2019;3:72-7. DOI: 10.4103/CDR.CDR_2_18
23. Puri N. A study on cutaneous manifestations of thyroid disease. Indian journal of dermatology. 2012;57(3):247-248. DOI: 10.4103/0019-5154.96227
24. Keen MA, Hassan I, Bhat MH. A clinical study of the cutaneous manifestations of hypothyroidism in kashmir valley. Indian J Dermatol. 2013;58(4):326. doi:10.4103/0019-5154.113951.
25. Marahatta S, Agrawal S, Mehata KD. Alopecia Areata and Thyroid Dysfunction Association- A Study from Eastern Nepal. Kathmandu Univ Med J (KUMJ). 2018; 16(62):161-165. PMID: 30636758.
26. Dogra A, Dua A, Singh P. Thyroid and skin. Indian J Dermatol 2006;51:96-9. DOI: 10.4103/0019-5154.26927
27. Leznoff A, Sussman GL. Syndrome of Idiopathic chronic urticaria and angiodema with thyroid autoimmunity: A study of 90 patients. J Allergy Clin Immunol 1989;84:66-71. DOI: 10.1016/0091-6749(89)90180-2
28. Heymann WR. Chronic Urticaria and angioedema associated with thyroid autoimmunity; Review and therapeutic implications. J Am Acad Dermatol 1999;40:229-32. DOI: 10.1016/s0190-9622(99)70193-3.
29. Kuroki R, Sadamoto Y, Imamura M, Abe Y, Higuchi K, Kato K, Koga T, Furue M. Acanthosis nigricans with severe obesity, insulin resistance and hypothyroidism: improvement by diet control. Dermatology. 1999;198(2):164-6. DOI: 10.1159/000018096.
30. Rai D, Wahid Z, Zaidi AN. Cutaneous manifestations of thyroid disease. J Pak Assoc Dermatol. 2000;10:8–22
31. Christianson HB. Cutaneous manifestations of hypothyroidism including purpura and ecchymoses. Cutis. 1976;17:45–52. PMID: 1017224.
32. Sedighe M, Gholamhossein G. Thyroid dysfunction and thyroid antibodies in Iranian patients with vitiligo. Indian J Dermatol. 2008;53:9–11. DOI: 10.4103/0019-5154.39733
33. Gopal KV, Rama RG, Kumar YK, Appa R, Vasudev P, Srikant S. Vitiligo: a part of a systemic autoimmune process. Indian J Dermatol Venereol Leprol. 2007; 73:162–5.
34. Samson JF, Mathew PS, Libu GK, Jayakumar B. A study of cutaneous manifestations of hypothyroidism and hyperthyroidism. Kerala Medical Journal. 2011:52-4. DOI: 10.14260/jemds/2015/883