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Indian Journal of Postgraduate Dermatology

Original Article

Cutaneous Manifestations in Patients with Endocrine Diseases

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Received: 04 April 2025
Accepted: 05 June 2025
EPub Ahead of Print: 12 January 2026
Published: 22 January 2026

DOI
10.25259/IJPGD_84_2025

Quick Response Code:

ABSTRACT

Objectives: The objective of the study is to systematically characterise the types and patterns of cutaneous manifestations observed in patients with various endocrine disorders and to differentiate and document the specific and non-specific dermatological changes linked to endocrine abnormalities.

Materials and Methods: After obtaining ethics committee clearance and written informed consent from individual study participants, patients who attended the dermatology outpatient department of our tertiary care hospital with endocrine diseases from January 2021 to December 2022 were included. A pre-set pro forma was used to collect data on demography and clinical findings including dermatological manifestations and laboratory parameters. We noted the different endocrinal diseases along with the mucocutaneous findings in the study participants. We classified the mucocutaneous manifestations associated with endocrinal diseases into specific and non-specific.

Results: Over a 2-year observational period, 150 patients diagnosed with endocrinal disorders who attended the outpatient department were included in the study. The distribution of these endocrinal conditions was as follows: Diabetes mellitus in 88 patients (58.66%), hypothyroidism in 39 patients (26%), hyperthyroidism in 12 patients (8%) and Cushing's syndrome in six patients (4%). Most common mucocutaneous manifestations noted amongst the study cohort were generalised pruritus, dry coarse skin and diffuse hair fall. Amongst individuals diagnosed with diabetes mellitus, the predominant cutaneous findings were generalised pruritus (25 patients, 28.41%) and dermatophytoses, specifically tinea cruris and tinea corporis (10 patients, 11.36%). In those with hypothyroidism, the most common issues were generalised pruritus (15 cases, 38.46%) and dry, coarse skin (13 cases, 33.33%). The most common manifestations reported in patients with hyperthyroidism were generalised pruritus (4 cases, 33.33%) followed by warm moist skin (3 cases, 25%).

Conclusion: All 150 patients who attended the dermatology OPD with endocrinal disorders along with any mucocutaneous findings, points to the importance of detailed dermatological evaluation in patients with endocrinal diseases to offer comprehensive care, which points to the importance of detailed dermatological evaluation in patients with the former to offer comprehensive care to the affected. Awareness of specific mucocutaneous features of endocrinal diseases may help the dermatologist to offer proper evaluation and early diagnosis of endocrinal diseases.

Keywords: Cutaneous manifestations, Diabetes mellitus, Endocrinal disorders, Pruritus

INTRODUCTION

Skin and its appendages frequently reflect the changes and disorders involving the internal milieu, and thus, examination of these important structures may provide vital clues to diagnosis and guide patient's work up in the proper direction. Clinicians can observe, diagnose and track endocrine

illness through the skin. The health and quality of life of an individual are profoundly impacted by the dermatologic signs and symptoms of endocrinopathies.[1] Hormones are known to be essential in regulating physiologic processes in each system of the body, including the skin. Endocrine diseases, through excess or deficiencies of hormones, can result in changes in cutaneous function and morphology and lead to complex symptomatology.[2] Patients with endocrine diseases may present with different cutaneous manifestations, some of which are specific to these disorders, while others are non-specific or secondary to metabolic changes [Table 1].[3]

Diabetes mellitus is a clinical syndrome characterised by hyperglycaemia due to either deficiency or decreased effect of insulin. This insulin deficiency whether actual or relative affects the metabolism of carbohydrate, protein, fat, water and electrolytes. Such long-term metabolic derangement is frequently associated with permanent and irreversible functional and structural damage to the cells in various tissues and organs.[4]

The clinical syndrome of excessive thyroid activity is known as 'thyrotoxicosis'. It presents commonly as 'Grave's disease' with a triad of enlarged toxic goitre, exophthalmos and dermopathy. Less common causes include thyroiditis, toxic multinodular goitre, toxic adenoma and exogenous thyroid hormone use. Cutaneous findings seen are warm, moist, smooth skin and flushing due to increased cutaneous blood flow and peripheral vasodilatation, palmar erythema, hyperhidrosis, diffuse scalp hair thinning, fine thin hair, increased incidence of alopecia areata, onycholysis, koilonychia, clubbing, pretibial myxedema, thyroid acropachy, generalised pruritus, chronic urticaria, vitiligo (increased incidence) and hyperpigmentation (localised/generalised).

In the hypothyroid state, there is slowdown of the metabolism of all tissues.

It may result from congenital hypothyroidism (cretinism), primary hypothyroidism in adults (autoimmune), Sheehan's syndrome, pituitary tumour, goitrous hypothyroidism, lack of TSH/TRH production and Hashimoto's thyroiditis.

Cutaneous changes seen are pale cold; scaly wrinkled skin absence of sweating; ivory yellow skin colour (carotenaemia); puffy oedema of hands, face and eyelids; eczema craquele; xanthomatosis (tuboeruptive xanthoma secondary to hyperlipidaemia); coarse sparse scalp hair; loss of pubic, axillary and facial hair; loss of lateral third of eyebrows, brittle and striated nails; purpura and ecchymoses; punctate telangiectasis on arms and fingertips and delayed wound healing. The most prominent feature is a dermal accumulation of mucopolysaccharides (hyaluronic acid and chondroitin sulphate) that lead to puffiness of the skin.[5]

MATERIALS AND METHODS

The study was conducted in Outpatient Department of Dermatology, Venereology and Leprosy of a tertiary care hospital over a period of 2 years. 150 patients were enrolled based on inclusion and exclusion criteria and study duration. Patients with previously diagnosed endocrine disorders who presented to the dermatology outpatient departments, having cutaneous manifestations and consented to participate were included in the study. Study was initiated after permission from Institutional Review Board. Written informed consent of patients was taken. Pro forma containing detailed history including demographic data was taken and a detailed clinical examination was carried out. Routine investigations and specific investigations were reviewed and noted. A biopsy report if suggested by the consultant was reviewed.

RESULTS

The study included 150 patients in total, of whom 90 (60%) were female and 60 (40%) were male. Out of a total of 150 patients, 88 patients (58.66%) had diabetes mellitus. Forty four (50%) of the 88 patients were men. The most common non-infectious manifestations were generalised pruritus (28.41%), followed by, acanthosis nigricans (10.2%), acquired reactive perforating collagenosis (6.84%), dry coarse skin (6.82%), acrochordons with acanthosis nigricans (5.69%), lipodystrophy (4.55%), xanthelasma palpebrarum (2.28%), acquired icthyosis (1.1%) and granuloma annulare (1.1%) [Table 2]. The most common infectious manifestations were tinea cruris/corporis (11.36%), followed by candidal balanoposthitis (5.69%) and vaginal candidiasis (4.55%).

Out of 150 patients, 39 had hypothyroidism out of which eight were males (20.51%) and 12 had hyperthyroidism out of which four were males (33.33%). The most common non-infectious manifestations in hypothyroidism were generalised pruritus (38.46%) followed by dry coarse skin (33.33%), Melasma (12.83%), diffuse hair fall (12.83%), acrochordons (7.69%), vitiligo (5.13%), chronic spontaneous urticaria (5.13%), oral/cutaneous lichen planus (5.13%), alopecia areata (5.13%) and pretibial myxedema (5.13%). Infectious manifestation seen was tinea cruris/corporis (7.68%).

Common manifestations of hyperthyroidism were generalised pruritus (33.33%) followed by warm moist skin (25%), chronic spontaneous urticaria (16.67%) and pretibial myxedema (16.67%) [Table 3].

Three patients had polycystic ovarian syndrome, all had hirsutism and one patient additionally had lower face acne. One patient with hypopituitarism and macroadenoma presented with hirsutism. The patient having hypogonadotropic hypogonadism had acanthosis nigricans

Table 1: Skin lesions showing association with endocrinopathies.

Lesions	Associated conditions
Acanthosis nigricans	Acromegaly, hyperprolactinaemia, diabetes mellitus, Cushing's syndrome, excessive androgen production
Acne	Cushing's syndrome, hyperprolactinaemia, excessive androgen production
Acquired ichthyosis	Hypothyroidism
Acquired perforating dermatosis	Diabetes mellitus
Alopecia areata/universalis	Hypoparathyroidism, autoimmune polyglandular syndrome-1, hyperthyroidism
Androgenetic alopecia	Hyperprolactinaemia, excessive androgen production
Asteatotic eczema	Hypothyroidism
Atopic dermatitis	Hyperthyroidism
Autoimmune bullous disease	Diabetes mellitus, hypoparathyroidism, hyperthyroidism
Calciphylaxis	Hyperparathyroidism, diabetes mellitus
Cherry angioma	Hyperprolactinaemia
Chronic urticaria	Hyperthyroidism, diabetes mellitus
Cutis verticis gyrata	Acromegaly
Dermatophytic infections	Diabetes mellitus, Cushing's syndrome
Eruptive xanthoma	Diabetes mellitus
Erythrasma	Diabetes mellitus
Foot ulcers	Diabetes mellitus
Generalised Myxedema	Hypothyroidism
Granuloma annulare	Diabetes mellitus
Hyperpigmentation	Addison's disease, ectopic ACTH syndrome, Cushing's disease, hyperthyroidism, POEMS syndrome
Hypertrichosis	Cushing's syndrome
Langerhans cell histiocytosis	Diabetes insipidus, hypopituitarism
Lipoatrophy/lipohypertrophy	Diabetes mellitus
Loss of pigmentation	Hypopituitarism
Metastatic calcification	Hyperparathyroidism
Mucosal or cutaneous candidiasis	Autoimmune polyglandular syndrome-1, diabetes mellitus, Cushing's syndrome
Necrobiosis lipoidica	Diabetes mellitus
Necrolytic migratory erythema	Glucagonoma syndrome
Oral lichen planus	Diabetes mellitus, hypothyroidism
Osteoma cutis	Pseudohypoparathyroidism
Palmar and plantar erythema	Diabetes mellitus
Palmoplantar keratoderma	Hypothyroidism
Periungual telangiectasia	Diabetes mellitus
Pretibial myxedema	Hyperthyroidism
Primary cutaneous amyloidosis	Hyperparathyroidism, pheochromocytoma
Psoriasis (generalised or pustular)	Hypoparathyroidism
Pseudomonas infection	Diabetes mellitus
Scleredema	Diabetes mellitus
Shin spots or pretibial pigmented papules	Diabetes mellitus
Skin tags (acrochordons)	Acromegaly, diabetes mellitus
Staphylococcal pyoderma (carbuncle and furuncle)	Diabetes mellitus, Cushing's syndrome
Striae	Cushing's syndrome
Subcutaneous ossification	Albright's hereditary osteodystrophy
Telogen effluvium	Hyperthyroidism, hypothyroidism
Ungual dystrophy	Hypoparathyroidism
Vitiligo	Hypoparathyroidism, diabetes mellitus, autoimmune polyglandular syndrome-1, hypothyroidism, hyperthyroidism
Xanthoma disseminatum	Diabetes insipidus

ACTH: Adrenocorticotropic hormone, POEMS: Polyneuropathy, Organomegaly, Endocrinopathy, M-protein and Skin changes

Table 2: Cutaneous manifestations of diabetes mellitus in the present study.

S. No.	Diabetes mellitus	Male	Female	Total no. (%)
1.	Generalised pruritus	11	14	25 (28.41)
2.	Tinea cruris, corporis	6	4	10 (11.36)
3.	Acanthosis nigricans	1	8	9 (10.2)
4.	Acquired reactive perforating collagenosis	3	3	6 (6.84)
5.	Dry coarse skin	2	4	6 (6.82)
6.	Acrochordons with acanthosis nigricans	-	5	5 (5.69)
7.	Candidal balanoposthitis	5	-	5 (5.69)
8.	Lipodystrophy	3	1	4 (4.55)
9.	Vaginal candidiasis	-	4	4 (4.55)
10.	Erythrasma	4	-	4 (4.55)
11.	Lipodermatosclerosis	2	1	3 (3.41)
12.	Vitiligo	3	-	3 (3.41)
13.	Trophic ulcer	2	1	3 (3.41)
14.	Xanthelasma palpebrarum	1	1	2 (2.28)
15.	Herpes zoster	1	1	2 (2.28)
16.	Necrobiosis lipoidica		2	2 (2.28)
17.	Diabetic dermopathy	1	1	2 (2.28)
18.	Onychomycosis	2	-	2 (2.28)
19.	Cutaneous/oral lichen planus	1	1	2 (2.28)
20.	Digital gangrene	1	-	1 (1.13)
21.	Macular amyloidosis	-	1	1 (1.13)
22.	Granuloma annulare	-	1	1 (1.13)
23.	Pyoderma gangrenosum	-	1	1 (1.13)
24.	Scleredema diabeticorum	-	1	1 (1.13)
25.	Eczema	-	1	1 (1.13)
26.	Erythema nodosum	1	-	1 (1.13)
27.	Furunculosis	1	-	1 (1.13)
28.	Acute paronychia	1	-	1 (1.13)
29.	Left leg cellulitis	-	1	1 (1.13)
30.	Acquired ichthyosis	1	-	1 (1.13)
31.	Pretibial pigmented patch	1	-	1 (1.13)
32.	Psoriasis	1	-	1 (1.13)
33.	Stasis dermatitis	-	1	1 (1.13)
	Total	55	58	113*

*The numbers may add up to more than 88 patients because of the simultaneous involvement of more than one manifestation

and sparseness of hair over androgen-dependent sites. Cushing's syndrome was seen in six patients [Table 4].

Two of these patients (one male and one female) with Cushingoid habits, such as moon face and weight gain (>5% bodyweight after 1 month of therapy), who were receiving glucocorticoid therapy (iatrogenic) were included in the study [Figures 1a-h and 2a-c].

DISCUSSION

The skin serves as a window for clinicians to understand, diagnose and monitor endocrine disease. Dermatologic manifestations of endocrinopathies contribute significantly to an individual's health and quality of life.[1] The endocrine and integumentary systems interact through a cohort of complex mechanisms. Dysregulation of endocrine hormones, as seen in many endocrinopathies, often results in clinically significant dermatologic disease.[1] Cutaneous manifestations in our study were divided according to the endocrine diseases into diabetes mellitus, hypothyroidism, hyperthyroidism, Cushing's syndrome, polycystic ovarian syndrome, hypogonadotropic hypogonadism and hypopituitarism with microadenoma. Poorly controlled or undiagnosed diabetics have a greater susceptibility to bacterial and fungal infections of the skin. Following factors are contributory to infections in diabetics:

- Impaired microcirculation
- Hypohidrosis
- Suppression of cell-mediated immunity.

Candidal infections, especially vulvovaginitis and balanoposthitis, are more prevalent in diabetics than in the general population. Paronychia, oral thrush and disseminated candidiasis may occur in uncontrolled diabetics.[6,7] Recurrent infections are more common in diabetics.

Investigations including histopathological evaluation were reviewed as and when required. The youngest patient in our study was 18 years old while the oldest patient was 81.

In our study, the incidence of generalised pruritus was maximum (28.41%) in diabetes mellitus which was consistent with the study done by Goyal *et al.*,[8] i.e. 30%. In infective aetiologies, the incidence of fungal infections was maximum (23.88%) in the present study which was found closer to Goyal *et al.* study[8] (16%) and Chatterjee *et al.* study[9] (16.3%) than in comparison with Greenwood study[10] where incidence was higher (40%). The incidence of erythrasma in the present study was 4.55% which was more compared to the study done by Chatterjee *et al.*[9] (1.76%). The incidence of herpes zoster in the present study was 2.28% which was also more compared to the study done by Roslind *et al.*[11] (1%). Incidence of furunculosis was 6% in study done by Goyal *et al.*[8] and 3.82% in study done by Chatterjee *et al.*[9] which was more as compared to 1.13% in the present study.

Table 3: Cutaneous manifestations in disorders of thyroid gland in the present study.

S. No.	Hypothyroidism	Male	Female	Total no. (%)
1.	Generalised pruritus	2	13	15 (38.46)
2.	Dry coarse skin	2	11	13 (33.33)
3.	Melasma	-	5	5 (12.83)
4.	Diffuse hair fall	1	4	5 (12.83)
5.	Acrochordons	1	2	3 (7.69)
6.	Tinea cruris, corporis	1	2	3 (7.68)
7.	Vitiligo	1	1	2 (5.13)
8.	Chronic spontaneous urticaria	1	1	2 (5.13)
9.	Oral/cutaneous lichen planus	1	1	2 (5.13)
10.	Alopecia areata	1	1	2 (5.13)
11.	Pretibial myxedema	-	2	2 (5.13)
12.	Atopic dermatitis-like features	-	1	1 (2.56)
13.	Pyoderma gangrenosum	-	1	1 (2.56)
14.	Hirsutism	-	1	1 (2.56)
15.	Lipodermatosclerosis	-	1	1 (2.56)
16.	Onychomycosis	1	-	1 (2.56)
	Total	12	47	59*
S. No.	**Hyperthyroidism**	**Male**	**Female**	**Total no.**
1.	Generalised pruritus	2	2	4 (33.33)
2.	Warm moist skin	1	2	3 (25)
3.	Chronic spontaneous urticaria	2	-	2 (16.67)
4.	Pretibial myxedema	-	2	2 (16.67)
5.	Acanthosis nigricans	1	-	1 (8.33)
6.	Lipodermatosclerosis	-	1	1 (8.33)
7.	Onycholysis	-	1	1 (8.33)
	Total	6	8	14

*The numbers may add up to more than 51 patients because of the simultaneous involvement of more than one manifestations

Candidal balanoposthitis was seen in 5.69% of patients in our study while a study done by Goyal *et al.*[8] showed 9% of patients and study done by Chatterjee *et al.*[9] showed 11.91% of patients with candidal balanoposthitis. Onychomycosis was noted in 2.28% of patients. Incidence of acanthosis nigricans in diabetes mellitus was found to be 15.91% which was very close to Roslind *et al.*[11] study where acanthosis nigricans was seen in 13% of diabetic patients. Lipodystrophy was seen in 4.55% of patients at the sites of insulin injection in our study, which was consistent with the study done by Goyal *et al.*[8] (4%). 3.41% of patients had trophic ulcers in diabetes mellitus in the present study, which was found closer to Roslind *et al.*[11] study (2%). The incidence of acquired reactive perforating collagenosis in the present study was 6.84% which was higher as compared to Roslind *et al.*[11] study (2%). Incidence of dry skin in diabetic patients was 6.82% in our study because of autonomic diabetic neuropathy which was low as compared to Goyal *et al.*[8] study (44%), Chatterjee *et al.*[9] study (25.58%) and Roslind *et al.*[11] study (21%) where higher percentage of patients presented with dry skin. The incidence of acquired ichthyosis in the present study was only 1.13%, which was not consistent with the study done by Goyal *et al.*[8] (10%). Psoriasis and eczema were found in 1.13% of patients with diabetes each, which were comparable with the study done by Goyal *et al.*,[8] where 2% of patients had similar findings. The incidence of vitiligo in diabetes mellitus in the present study was 3.41% and that of cutaneous/oral lichen planus was 2.28% which was higher than the study done by Chatterjee *et al.*[9] (1.76% and 0.44%, respectively). Incidence of scleredema diabeticorum (1.13%), granuloma annulare (1.13%) and gangrene (1.13%) was found very close to Roslind *et al.*[11] study (1%, 1% and 2%, respectively). Macular amyloidosis was seen in 1.13% of patients in our study which was higher as compared to Chatterjee *et al.*[9] study (0.58%) and lower as compared to Goyal *et al.*[8] study (4%) whereas other cutaneous manifestations which we encountered were lipodermatosclerosis (3.41%), pyoderma gangrenosum (1.13%), erythema nodosum (1.13%), cellulitis (1.13%), pretibial pigmented patch (1.13%) and stasis dermatitis (1.13%).

In our study, the second most common (26%) endocrinological disorder was hypothyroidism. The incidence of generalised pruritus was maximum, i.e. 38.46% which was higher in comparison with study done by Bains *et al.*[12] (16.81%), Keen *et al.*[13] (17.17%) and Paswett *et al.*[14] (10%). Incidence of dry coarse skin was 33.33% in our study which was lower than the study done by Bains *et al.*[12] (67.25%) and Keen *et al.*[13] (51.17%) but was higher than the study done by Paswett *et al.*[14] (15%). Diffuse hair falls in hypothyroidism was present in 12.83% and alopecia areata was present in 5.13% of patients which was consistent with the study done by Paswett *et al.*[14] (13%) and Bains *et al.*[12] (5.3%), respectively. Chronic spontaneous urticaria, vitiligo and oral/cutaneous lichen planus were seen in 5.13% of patients which were consistent with the study done by Paswett *et al.*[14] (8%, 6% and 2%, respectively). Autoimmunity is the reason behind the association. The incidence of melasma in hypothyroidism in the present study was higher (12.83%) as compared to Bains *et al.*[12] study (9.73%). Pretibial myxedema in hypothyroidism in the present study was seen in 5.13% of patients whereas it was 2% in study done by Paswett *et al.*[14] Incidence of other cutaneous manifestations was as follows:

Table 4: Cutaneous manifestations in various other endocrine disorders.

Disease	Manifestations	Male (%)	Female (%)	Total no. (%)
Polycystic ovarian syndrome	Hirsutism alone	-	2 (66.67)	2 (66.67)
	Hirsutism with acne vulgaris	-	1 (33.33)	1 (33.33)
	Total	-	3 (100)	3 (100)
Hypopituitarism with macroadenoma	Hirsutism	-	1 (100)	1 (100)
Hypogonadotropic hypogonadism	Acanthosis nigricans with sparseness of hair over androgen-dependent sites	1 (100)	-	1 (100)

Figure 1: (a) Xanthelasma palpebrarum, (b) Moon facies, (c) Acanthosis nigricans, (d) Acquired ichthyosis, (e) Acquired reactive perforating collagenosis, (f) Granuloma annulare, (g) Hirsutism, (h) Striae in Cushing's syndrome.

Pyoderma gangrenosum (2.56%), hirsutism (2.56%), lipodermatosclerosis (2.56%) and onychomycosis (2.56%).

Hyperthyroidism was seen in 8% of the patients in our study. Generalised pruritus was the most common (33.33 %) symptom which was in line with Bains *et al.*[12] study (30.76%) followed by warm moist skin (25%) which was less common than the Bains *et al.*[12] study (53.84%) but was considerably more in line with Puri study[15] (23.98%). The incidence of pretibial myxedema was 16.67% in our study which was found surprisingly equal to the study done by Puri, i.e. 16.67%.[15] Chronic spontaneous urticaria in hyperthyroidism was seen in 16.67% of patients which was closer to Bains *et al.*[12] study (15.38%). The incidence of onycholysis was 8.33% which was discordant with the study done by Puri[15] (28.6%). On the other hand, lipodermatosclerosis and acanthosis nigricans were the other most common cutaneous symptoms observed in hyperthyroidism (8.33%).

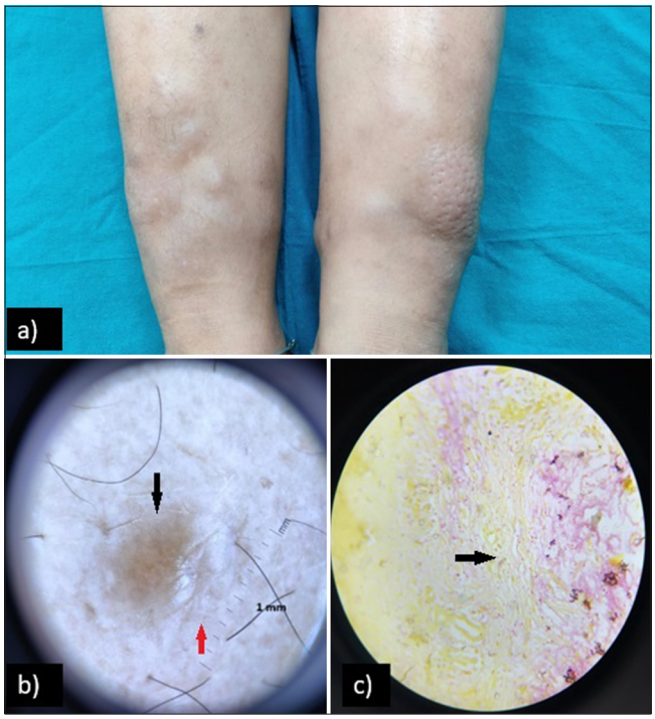

Figure 2: (a) Pretibial myxedema. (b) Dermoscopy of pretibial myxedema showing yellowish-white structureless areas with irregular pigmentation (black arrow) and telangiectasias (red arrow). (c) Histopathology of pretibial myxedema showing separation of collagen bundles by large amount of mucin in the dermis (black arrow) (Hematoxylin and eosin stain, 40× magnification).

Other patients had polycystic ovarian syndrome (PCOS) (2%), hypogonadotropic hypogonadism (0.67%) and hypopituitarism with microadenoma (0.67%). Hirsutism alone was present in 66.67% patients of PCOS which was consistent with the study done by Spritzer *et al.*[16] where 70–80% of patients with PCOS had hirsutism. Hirsutism was predominantly of lateral type. The sparseness of hairs over androgenic sites was found in patients with hypogonadotropic hypogonadism due to decreased androgen levels while acanthosis nigricans were noted in the patients which could be attributed to ongoing hormonal therapy. In patients with hypopituitarism with macroadenoma, predominantly central-type hirsutism was noted.

Limitation

Study was conducted at a single tertiary referral centre and small sample size was the limitation. At least some patients have been missed who attended the outpatient department with hitherto undetected endocrine diseases as no evaluation was carried out to rule out endocrine diseases in dermatology patients.

CONCLUSION

Overall, generalised pruritus was the most common manifestation observed in the majority of patients with endocrinal disorders. This study highlights the importance of an integrated approach between dermatology and endocrinology. By systematically documenting various cutaneous changes in endocrinal disorders, diagnostic accuracy is enhanced, promoting earlier intervention and improved patient outcomes. Hence, this study supports the inclusion of cutaneous evaluation in the routine assessment of patients with suspected or confirmed endocrinal diseases.

Ethical approval: The research/study was approved by the Institutional Review Board at NHL Institutional Review Board, dated 23 December 2020.
Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.
Financial support and sponsorship: Nil.
Conflicts of interest: There are no conflicts of interest.
Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Mehboobkhan KS, Jagati A, Mahajan R, Chaudhary RG, Baxi K, Rout P, *et al*. Cutaneous Manifestations in Patients with Endocrine Diseases. Indian J Postgrad Dermatol. 2026;4:1-8. doi: 10.25259/IJPGD_84_2025