Cutaneous Manifestations of Diabetes Mellitus

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Introduction

Diabetes mellitus is a disorder with extensive clinical manifestations and changes in the skin are no exception. It has been estimated that about 30% of all diabetic patients manifest one or the other cutaneous manifestations. Cutaneous manifestations of diabetes are due to multiple factors. Some are caused by metabolic complications while others occur as a consequence of the three major diabetic complications namely microangiopathy, macroangiopathy and neuropathy. Some skin conditions are found to be strongly associated with diabetes that they are considered to be markers of the disease. Various classifications exist for the cutaneous manifestations of diabetes and two of them - a clinical and an aetiopathological classification are given below.

Classification of cutaneous manifestations of diabetes

A. Clinical classification

I. Cutaneous markers of diabetes
II. Cutaneous manifestations of diabetic complications.
   a) Infections
   b) Diabetic neuropathy
III. Complications of diabetic treatment
IV. Rare associations with endocrine and other syndromes.

Various cutaneous markers of diabetes mellitus

1. Necrobiosis lipoidica diabeticorum
2. Granuloma annulare
3. Diabetic dermopathy
4. Diabetic thick skin - Scleredema adulпорum of Bushke.
5. Acanthosis nigricans
6. Bullous diabeticorum
7. Pigmented purpuric dermatosis
8. Oral leukoplakia

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B. Classification based on aetiopathogenesis

<table>
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<th>Changes in collagen</th>
<th>Microangiopathy</th>
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<td>Astacotic skin of lower limb</td>
<td>Necrobiosis Lipoidica</td>
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<td>Dupyren’s Contracture</td>
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<td>Lichen Amyloid</td>
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<tr>
<td>Macrogangiopathy</td>
<td>Metabolic</td>
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<td>Atrophied, pale, cold skin</td>
<td>Pruritus</td>
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<td>Ischaemic ulcer</td>
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<td>Gangrene</td>
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<td>Infections</td>
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<td>Bacterial</td>
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<td>Folliculitis</td>
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<td>Fungal</td>
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<td>Mucormycosis</td>
<td>Skin tags</td>
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Pathophysiology and skin changes in skin of diabetes

The skin glucose content of diabetic patients with...
Diabetic dermopathy is the most common dermatosis associated with diabetes. They present as round or oval, red or brownish papules which become hyperpigmented, atrophic, scaly lesions.

Structural changes in skin of diabetes
1. Increase in number of mast cells in the dermis especially in the superficial layers, around blood vessels and skin appendages.
2. Increased capillary fragility.
3. Thickening of capillary walls due to peri-endothelial deposits of positive material.
4. Increase in the number of vessels in upper and lower dermal layers.

Cutaneous markers of diabetes
Necrosis lipoidica diabeti colorum (NLD)
This is a rare condition first described by Oppenheim in 1929 and named by Urtback in 1932. It has the strongest association with diabetes but is a rare complication seen in only 0.3% of diabetic patients. It is believed to be even more rare among Indians. Approximately 65% of patients with NLD have diabetes mellitus at the time of detection. It may precede diabetes in 15% of patients and hence is sometimes considered as a pre-diabetic marker.

Clinical features
It has a female preponderance being three times more common among women and usually occurs in the third or fourth decade of life.

Location: Most common - pretibial region - 90%
Initially the lesion consists of sharply demarcated erythematous papules. Later the classical lesion develops as non-scaIy, round, oral or irregularly spaced plaques which are firm in constituency with atrophic yellow centre, surface telangiectasia and violaceous or erythematous raised border.

Histology
Histologically the hallmark is necrobiosis which refers to the degeneration and thickening of the collagen bundles in the dermis with perivascular inflammatory infiltrates and endarteritis obliterans.

Granuloma annulare
This is a benign self limiting asymptomatic dermatosis that is most often seen on the extensor surface of joints of fingers, wrists and hands. The classic lesion is an annular plaque with flesh coloured papular borders and a flat centre. The pathogenesis of this condition is unknown.

Histology is characterised by focal degeneration of collagen in the dermis and palisaded arrangement of histiocytes around collagen bundles with abundant mucin.

Diabetic dermopathy (pigmented pre-tibial patches)
Also known as “Shin spots” or “Melin spots” or “Spotted leg syndrome” this condition was first described by Melin in 1964. It is the most common dermatosis associated with diabetes. It is however not specific to diabetes. Anterior and lateral aspects of the skin are most commonly affected (hence shin spots), but also occurs on the forearm, bony prominences and thighs. Lesions are distributed bilaterally but asymmetrically. They present as round or oval, red or brownish papules which later become hyperpigmented, atrophic, scaly lesions.

It occurs more often in male diabetics and is very frequent in those with duration of diabetes more than 10-15 years. Diabetic microangiopathy is thought to be responsible for this condition. Histology consists of extravasated RBCs and oedema and thick walled capillaries in the papillary dermis. Treatment is not required as it is a harmless condition.

Diabetic thick skin
a) A scleroderma like syndrome may follow acute bacterial or viral infections.
b) Scleredema Adulorum Diabeticorum of Bushke is characterised by induration and marked increase in dermal thickness of back and posterior upper neck in middle aged, overweight, poorly controlled NIDDM patients. It is due to deposition of mucopolysaccharides in the dermis. There is no effective treatment and it usually resolves spontaneously.
c) Thick skin and waxy joints: This classically occurs in children with insulin dependent diabetes of more than 5-10 years duration and is characterised by thickening of the skin and increased joint stiffness and limited joint
Diabetic foot is one of the most common complications, is dangerous and accounts for 70% of all non-traumatic amputations.

usually between third and fourth toes is another common manifestations. Other fungal infections that are common in diabetes are dermatomycosis, tinea versicolor and mucormycosis, the last one being more common in diabetic ketoacidosis.

b) Macroangiopathy or large vessel disease
Causes skin atrophy, hair loss, nail dystrophy, coldness of toes, pallor or elevation and delayed return of color following pressure on skin i.e., more than 15 seconds.

c) Diabetic foot
This is one of the most common complications, is dangerous and accounts for 70% of all non-traumatic amputations. Detailed description of this condition is outside the purview of this article but the commonest features of this include indolent perforating ulcers, accentuated plantar arches, increased predisposition to infections, hammer-toes, osteomyelitis and gangrene.

d) Metabolic complications and skin
1. Pruritis - considered as a classical symptom of diabetes and usually presents as generalised pruritis or genital pruritis.
2. Xanthoma - is due to associated hypertriglyceridemia; eruptive xanthoma is the commonest type and occurs in elbow, knees, buttocks, etc.
3. Yellow skin - is another skin manifestation.

Skin reactions to diabetic therapy

 Sulphonylureas
Various cutaneous reactions occur with first generation sulphonylureas such as Tolbutamide or Chlorpropamide. These usually develop in the first two months of treatment and may be either toxic or allergic. Two to three percent of people develop maculopapular rash. Other cutaneous manifestations include photosensitivity, erythema nodosum, Steven Johnson’s syndrome, alcohol induced flushing, pruritis, urticaria and erythema multiforme.

Insulin
Cutaneous reactions to insulin can be divided into localised, generalised and lipodystrophy. Local reactions include erythema, induration and occasionally ulceration. Generalised reactions are uncommon and include pruritis, urticaria and angioedema. These reactions can be overcome by switching over to purer forms of insulin e.g., Human Insulins. Table 1 outlines the skin reactions to insulin therapy.

Lipodystrophy
This term includes lipoatrophy and lipo hypertrophy and these are complications of insulin injections. Lipoatrophy presents as circumscribed depressed areas of skin due to decrease in subcutaneous fat. It is seen mostly with use of impure forms of insulin. It is believed to be due to a local immune response and lipolytic components of insulin. Changing over to pure forms of insulin and injection of purified insulin into the periphery of the lesion usually results in filling up of the depressed areas.

Lipo hypertrophy
This term refers to an increase in the amount of fat and presents as soft dermal nodule with normal surface epidermis. It is due to lipogenic action of insulin and can be avoided by rotation of sites and by using purified insulins.

Idiosyncratic reactions may include pigmentation, keloid and bilateral symmetrical plaques (Table 1).

Rare association with endocrine and other syndromes

1. Glucagonoma syndrome - Necrolytic migratory erythema
This rare syndrome is due to glucagon secreting islet cell syndrome and presents cutaneously as a polymorphous, erythematous eruption with superficial bullae at active borders. They are most frequently seen in the girdle area - groin, buttocks, thighs or in the peri-oral regions. They heal with superficial erosions. Associated features include diarrhoea, diabetes and venous thrombosis.
2. Cushings’ syndrome - skin atrophy, striae and hirsutism
3. Acromegaly - increased skin thickness and increased sweating
4. Haemochromatosis - bronze skin and diabetes
5. Ataxia Telangiectasia
6. Campbell de Morgan’s spots (Cherry angioma) - multiple cherry angioma in untreated diabetes

Summary

1. Various cutaneous conditions occur frequently in diabetics, although common skin lesions may occur by chance given the dictum that “two common diseases can co-exist without an aetiological connotation”.
2. Skin disorders affect about 30% of diabetic patients with
In diabetics, the ratio of skin to blood glucose is higher than in non-diabetics. Since glucose is the nutrient for saprophyte organisms that dwell in the skin, hyperglycaemia potentiates the growth of micro-organisms.

mobility leading to complications like Dupytren’s contracture, sclerosing tenosynovitis of palmar flexor tendon and Garrod’s knuckle pads.

The pathogenesis is a accumulation of large collagen fibres in the dermis associated with increased glycosylation of collagen. It is associated with an increased incidence of microvascular complications.

**Acanthosis nigricans**

This is an uncommon condition characterised by brown, velvety, hyperkeratotic plaques which are seen in flexural areas of skin like axilla, infra-mammary regions, back of neck, etc. It is seen in a large heterogeneous group of disorders with the common feature being insulin resistance.

**Pathogenesis**

Mechanism is uncertain but there is evidence of an epidermal growth factor which binds insulin-like receptors in keratinocytes and fibroblasts. Histologically the epidermis is extensively folded, slightly thickened and has a number of melanocytes.

A particular clinical syndrome has been reported in hyperandrogenic women with signs of virilization and accelerated growth and given the acronym HAIR-AN (Hyperandrogenism with insulin resistance and acanthosis nigricans).

Acanthosis nigricans can also occur in obesity and internal malignancy especially gastrointestinal malignancies.

**Bullous diabeticorum**

This is an uncommon condition with primarily acral distribution - mostly on the feet and sometimes on the hand. It is more common in men than women and has predilection for patients with long standing diabetes complicated by neuropathy. These lesions most often occur suddenly on non-inflamed skin without any history of trauma. Lesions consist of tense blisters on a non-inflammatory base which contain clear viscous fluid that is sterile.

Two major forms exist:
(a) Intra-epidermal heals without scarring
(b) Sub-epidermal heals with mild scarring

The exact aetiology is not understood but a recent study showed a reduced threshold to suction induced blister formation in diabetic patients. The blisters should be drained as otherwise it could lead to underlying necrosis, sometimes leading to superficial gangrene.

**Cutaneous manifestations of diabetic complications**

a) Infections

The effects of diabetes on host defence are multifactorial and are related to defects in both cellular and humoral immune system. Abnormalities of all aspects of phagocyte function have been described. These include decreased cell movement and impaired phagocytosis. In hyperglycemia, excess glucose is metabolised by aldose reductase through polyol pathway. Thus, NADPH decreases the ability of cells to mount an oxidative attack and thereby inhibits killing.

**Excess skin glucose**

As already mentioned, in diabetics, the ratio of skin to blood glucose is higher than in non-diabetics. Since glucose is the nutrient for saprophyte organisms that dwell in the skin, hyperglycaemia potentiates the growth of micro-organisms.

**Bacterial infections**

Common cutaneous bacterial infections include impetigo, cellulitis, folliculitis, furunculosis, carbuncles, and erysipelas. Organisms usually involved are staphylococcus aureus and beta hemolytic streptococci.

Erysipelas may be complicated by gangrene and necrotising fascitis. Pathogens involved are *E. coli*, Klebsiella, *Pseudomonas* and *Bacteriodes*.

Malignant external otitis caused by *Pseudomonas aeruginosa* can progress through cellulitis, perichondritis and osteomyelitis to cranial nerve damage and meningitis.

**Fungus infections**

Candida infection in diabetes can present as:
1. Pruritis vulvae and balanitis
2. Angular stomatitis
3. Atrophic glossitis
4. Paronychia
5. Erosi interdigitale blastomyceta - Infection of web spaces
almost all patients with diabetes of more than 15 years duration showing one or other of the skin manifestations of diabetes.

3. Certain skin manifestations precede diabetes and are considered as pre-diabetic markers. These include Necrobiosis Lipoidica Diabeticorum, Granuloma annulare and generalised pruritus.

4. Certain conditions like dermatitis are due to microangiopathy and may point to the presence of, or predict the occurrence of, other complications like retinopathy and nephropathy.

5. Diabetic neuropathic foot is one of the important causes of morbidity amongst diabetic patients in our country. Most of the foot ulcer patients in developing countries lack awareness and diabetic education.

6. Cutaneous complications of diabetic treatment like reactions to sulphonylurea drugs, insulin allergy and lipodystrophies should be thought of while initiating treatment of diabetes.

7. Cutaneous manifestations of diabetes must be recognised early so that early treatment can be instituted not only for the skin problem itself but also to ensure adequate metabolic control of diabetes to prevent their recurrence wherever possible.

**Suggested readings**


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**Table 1. Skin reactions to insulin therapy**

<table>
<thead>
<tr>
<th>Drug and reaction</th>
<th>Lesion</th>
<th>Pathogenesis</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>Animal source insulin</td>
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<td></td>
</tr>
<tr>
<td>Local immediate allergy</td>
<td>Erythema, ulcer induration</td>
<td>IgG mediated</td>
<td>Change to human insulin</td>
</tr>
<tr>
<td>Delayed allergy</td>
<td>Erythema, ulcer</td>
<td>Cell mediated</td>
<td>Change to human insulin</td>
</tr>
<tr>
<td>Generalised allergy</td>
<td>Pruritis, urticaria</td>
<td>IgE mediated</td>
<td>Change to human insulin</td>
</tr>
<tr>
<td>Human insulin</td>
<td></td>
<td></td>
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<tr>
<td>Idiosyncratic reaction</td>
<td>Rare</td>
<td>Change in tertiary</td>
<td>Desensitization</td>
</tr>
<tr>
<td>Lipatrophy depressed areas of skin</td>
<td>Keloid, pigmentation, plaques</td>
<td>Unknown</td>
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</tr>
<tr>
<td>Lipohypertrophy</td>
<td>Circumscribed response and lipolytic action of insulin</td>
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<tr>
<td></td>
<td>Local immune purified insulin into periphery of lesion</td>
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<tr>
<td></td>
<td>Lipogenic action of insulin</td>
<td>Rotate sites of of injection</td>
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