

## Skin Manifestations of Diabetes Mellitus

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### Abstract

Skin disorders are common in diabetic patients and may also act as clues for diagnosis in undiagnosed cases. These manifestations may be summarized in five categories including non-infectious, infectious, treatment-related and miscellaneous manifestations as well as diabetic foot ulcer.

The most common non-infectious disorder occurring in up to 70% of patients is diabetic dermopathy. Infections with staphylococcus aureus and streptococcus hemolytic group A, and dermatophytoses are seen frequently in diabetics. Moreover, severe and life-threatening infections such as necrotizing fasciitis, malignant external otitis and rhinocerebral mucormycosis may be seen especially in elderly diabetics. Diabetic foot ulcer is also a major problem in longstanding diabetes and needs particular attention. Complications due to treatment of diabetes are also found in some patients.

In conclusion, skin manifestations must be considered as an important issue in any patient, especially in obese ones. Improved metabolic control as well as using newly introduced drugs may help reduce or even resolve these problems.

**Key Words:** Skin, diabetes, cutaneous.

## Introduction

Diabetes Mellitus (DM) refers to a group of metabolic disorders with a common presentation of hyperglycemia. There are two common types of DM. In Type 1, there is absolute or near-total insulin deficiency; while in type 2, the problem originates from insulin resistance, impaired insulin secretion and raised glucose production (1).

Skin disorders are common in diabetic patients and the prevalence up to 30% has been reported in these patients (2). Generally, these

manifestations appear during the period of disease in known cases of DM, but they may also be the first presentation of the disease or appear many years before the diagnosis of DM (3).

As expected, autoimmune skin disorders are more frequently observed in type 1 DM while infectious skin diseases are more prevalent in type 2 diabetic patients (4,5).

Cutaneous manifestations of DM can be categorized into 5 groups: 1-Non-infectious skin disorders 2-Infectious skin disorders 3-

Skin disorders related to treatment of diabetes  
4- Diabetic foot ulcer 5-Other manifestations

### 1-Non-infectious Skin Disorders

#### Acanthosis Nigricans (AN)

AN is associated with insulin resistance and can be found in the absence of diabetes. There are two types of insulin resistance. Type A is the result of mutations in the gene encoding insulin receptor; so, insulin receptor signaling through tyrosine kinase activity is blocked or diminished. AN is seen in the form of HAIR-AN syndrome, the acronym of hyperandrogenism, insulin resistance, and acanthosis nigricans. AN is usually severe and generalized in type A and it appears in infancy or early childhood. AN also may be found less frequently in type B which is also less severe and extensive. Type B results from autoantibodies to insulin receptor. It is seen in middle-aged females and is usually associated with autoimmune disorders namely systemic lupus erythematosus and Sjögren's syndrome (6).

AN presents as hypertrophic, hyperpigmented velvety plaques in body folds especially axillae and flexural areas of the posterior neck (7). It also may be found less commonly in locations like groin, umbilicus, areolae, submammary regions, and hands (8). Figure 1 shows the lesion in the neck region. Although this lesion is mainly asymptomatic, it can present as a painful, malodorous, or macerated



Figure 1. Acanthosis Nigricans

lesion (3). The dark color is due to thickness of keratin-containing superficial epithelium, not change of melanocyte number, or melatonin content (8).

AN is usually considered benign, because it is commonly seen in type 2 diabetes mellitus (8), obesity (9), total lipodystrophy (10) and polycystic ovarian syndrome (11) which share the feature of insulin resistance; but rarely it may be a complication of an internal malignancy, particularly of the stomach (12) or secondary to some drugs (e.g. nicotinic acid) (13).

#### Diabetic dermopathy (Shin spots)

The most prevalent finding in diabetes mellitus is seen in 7 to 70% of diabetic patients (14) (Figure 2); however it can be seen in 20% of non-diabetics as well. Men are affected twice as women (15) and the mean age of its onset is 50 years (16). The lesion presents initially as dull-red macules of 0.5-1 cm diameter which eventually resolve as shallow, hyperpigmented, and depressed scars (17). Common involved sites include extensor side of lower legs and may appear even before the metabolic disorder. Also, they can be found on forearms, thighs and lateral malleoli (16). Because shin spots occur more prevalently in diabetic patients with such end organ damages as retinopathy, neuropathy and nephropathy, the potential role of microangiopathy has been postulated as the underlying factor for the development of these lesions (18).

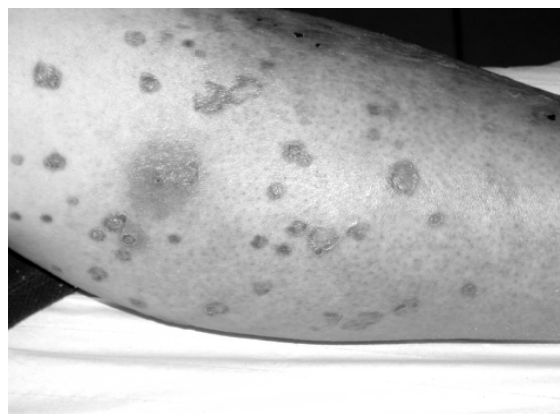


Figure 2. Diabetic dermopathy (Shin spots)



Figure 3. Necrobiosis Lipoidica Diabeticorum

#### **Necrobiosis Lipoidica Diabeticorum (NLD)**

This lesion occurs only in 0.3% of diabetic patients; although its prevalence is more than 2% in type 1 diabetic patients (17,19). Two-third of patients are insulin-dependent (20). It affects females three times the males and is common in third and fourth decades of life (21). NLD often occurs in pretibial region of legs but may also involve forearm, trunk, face, scalp, palms and soles (17,21) (figure 3). This lesion starts with a slowly spreading oval patch which turns to a plaque with yellow-brown atrophic center, waxy surface and telangiectasia which may become ulcerative. Studies show that blood glucose control does not affect the course of NLD (15,17).

#### **Diabetic thick skin**

Unlike the normal aging, skin thickness increases with age in diabetic patients (16). Three forms of diabetic thick skin may be seen. The first is general asymptomatic measurable thickening of the skin. The second form which is clinically apparent is seen in 20-30% of the patients and varies from pebbled knuckles (Huntley's papules) which consist of multiple group papules on extensor parts of fingers, on the knuckles or in periungual regions, to diabetic hand syndrome. The latter

has a variable prevalence of 8-50% (22) and consists of limited joint mobility, flexion contracture, and trigger finger (23). Limited joint mobility may be demonstrated as "prayer sign" which means patients' inability to press their palms together completely without a gap remaining between opposed palms and fingers (24). It may be further complicated by Dupuytren contracture (25).

The third form is so-called scleredema diabeticorum is seen in 2.5-14% of diabetic population (15). It occurs in both types of diabetes mellitus without any gender or racial predilection (3). The most common sites of involvement are neck and upper back. This form clinically presents as significant bilateral and painless thickening and induration of skin on the dorsum of fingers (sclerodactyly) and proximal inter-phalangeal joints which may extend to forearms, arms and back (3). A peau d'orange appearance usually with decreased sensitivity to pain and touch also may occur in affected areas. These progressive and often permanent lesions must be differentiated from "scleredema of Buschke", a rare disorder occurring after an upper respiratory infection, affecting face, arms, and hands which clears spontaneously (16).

#### **Skin tag (Acrochordon)**

Small, flesh-colored to dark brown, pinhead-sized and larger, sessile and pedunculated papillomas frequently occur on the neck, in axilla and on the eyelids (17). Several studies have shown the association between multiple acrochordons and insulin resistance (26-29). In a study performed on a large population with skin tags, the prevalence of diabetes and impaired glucose tolerance was more than 25% and 8%, respectively. So, skin tag may be considered as a sign of impaired glucose tolerance, diabetes and increased cardiovascular risk (30,31). Also, the prevalence of diabetes has been reported to be about 66% to 75% in subjects with skin tags (3).

#### **Diabetic bullae (Bullosis diabeticorum)**

These non-inflammatory, painless blisters occur more often in type 1 diabetic patients and in patients with long-standing diabetes with peripheral neuropathy. There is no gender predilection (32). They appear with various sizes on the plantar surfaces and margins of the feet (33) and occasionally on the hands and legs. The incidence rate is about 0.16% per year (17) and the prevalence rate is 0.5% (16,17). These lesions usually resolve spontaneously without scarring in few weeks (15,17,34). Appearance of the lesions is related to following periods of relative hypoglycemia (17).

#### **Granuloma annulare**

Ring-shaped or oval lesions with raised border of skin-colored or erythematous papules commonly occur on the lateral or dorsal surfaces of hands and feet. Histologic findings are similar to NLD. Its association with diabetes is not clearly established (3,16,17).

#### **Eruptive xanthoma**

Firm, non-tender, yellow papules with an erythematous halo on the extensor surfaces of knees and elbows, back, and buttocks (16,21) are seen in less than 0.1% of diabetic patients (35). In diabetes mellitus and familial hypertriglyceridemia, there is an increased level of triglycerides due to lack of lipoprotein lipase activity as well as chylomicron and very low density lipoprotein (VLDL) clearance disorder which is in association with development of these eruptions. They tend to heal by lipid and carbohydrate metabolism control (16).

#### **Perforating disorders**

These lesions appear as 2-10 mm dome-shaped papules and nodules with a hyperkeratotic plug in patients with renal failure, type 2 and type 1 diabetes mellitus. Its prevalence is up to 10% in patients under dialysis (36,37). Common sites include the limbs, trunk and dorsal surface of hands. They may Koebnerize (16,21). These chronic lesions may heal by avoidance of scratching and trauma (16).

#### **Yellow skin (Carotenoderma)**

Yellowish discoloration of skin, especially of palms and soles due to increased levels of carotenoids (i.e. pigments of green and yellow vegetables) may rarely occur in diabetic individuals (3,17).

#### **Vitiligo**

This lesion which is characterized by depigmented areas of the skin is more associated with type 1 diabetes mellitus. Its prevalence is 1-7% in diabetic subjects compared to 0.2-1% in general population. The mechanism is unclear but some postulated that it may be part of Polyglandular Autoimmune Syndrome type 2 (PAS2) (16).

### **2-Infectious Skin Disorders**

#### **Fungal Infections:**

- ***Candidiasis***

Infections by *Candida albicans* are common in diabetic patients, especially in patients with poor metabolic control; and often involve the mouth, ungual folds, genitalia and intertriginous regions (38). They may be an early manifestation of undiagnosed diabetes. *Perlèche* is a classical sign of diabetes in childhood (16) and is attributed to high glucose content of saliva (39). Localized female genitalia infection has a strong association with diabetes. Candidal balanitis, balanoposthitis, intertrigo and phimosis may be seen in male diabetic patients (17,39,40).

- ***Dermatophytoses***

The most common superficial infections are caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Epidermophyton floccosum*. Intertriginous or interdigital infections by *T. mentagrophytes* present as areas with maceration and surface scaling with active margins. Onychomycosis and *tinea pedis* must be monitored and treated because they act as a route of entry for other infections (16).

- ***Rhinocerebral mucormycosis***

This rare but potentially life-threatening infection mainly occurs in elderly diabetics with diabetic ketoacidosis; although it may

also affect the patients who are metabolically well-controlled (41-43). The fungi responsible for it belong to Zygomycetes. Clinical presentations include fever, facial cellulitis, periorbital edema, proptosis, facial numbness (due to involvement of trigeminal nerve branches) and black scars in nasal mucosa or palate (due to ischemic necrosis of tissues caused by fungal vascular invasion). The infection may also spread from ethmoid sinus to frontal lobe; and from sphenoidal sinus to cavernous sinus, resulting in cavernous sinus thrombosis, carotid artery involvement and cranial nerves paralysis (3).

#### **Bacterial infections**

Infection by staphylococcus aureus and streptococcus hemolyticus group A is common in diabetics (21). The most common infections include impetigo, folliculitis, furunculosis, carbuncles, ecthyma, cellulitis and erysipelas. In obese diabetics, corynebacterium minutissimum causes erythrasma which is characterized by shiny, hyperpigmented, pruritic patches in intertriginous regions (16,44). Necrotizing fasciitis is not common but is potentially a lethal infection of skin and soft tissues (45) and is typically caused by a mixture of bacteria including streptococcus pyogenes, staphylococcus aureus, anaerobic streptococci, and bacteroides (46). This condition must be considered in any diabetic patient with cellulitis and systemic manifestations of infection (3). Malignant external otitis is uncommon but may be a life-threatening infection caused by pseudomonas aeruginosa and is often seen in elderly patients with diabetes (16). It starts with cellulitis but progresses to chondritis, osteomyelitis and cerebritis. Clinical examination reveals tenderness of pinna and periauricular regions, and swollen external auditory canal with purulent discharge (3).

### **3-Skin Disorders Related to Treatment of Diabetes**

#### **Skin reactions to insulin**

Insulin injection may cause local and/or generalized allergic reactions which are attributed to impurities in insulin preparations, preservatives, additives or the insulin molecule itself. Immediate local reaction, probably IgE-mediated, starts with erythema and become urticarial and usually subsides in one hour (16,39). This lesion may progress to a generalized erythema and urticaria but anaphylaxis is rare. The most common type of reaction is a delayed type hypersensitivity reaction which starts as a pruritic nodule at the site of injection, usually 2 weeks after the initiation of insulin therapy. It may last for days and may resolve with hyperpigmentation and scar. Biphasic reactions consisting of immediate and delayed types rarely occur and are accompanied by a general malaise similar to serum sickness (16). With the advent of human recombinant insulin, these reactions are reported in less than 1% of patients (15). Other skin disorders associated with insulin injection include lipoatrophy, lipohypertrophy, keloids, hyperkeratotic papules, purpura and local pigmentation. Lipoatrophy of subcutaneous fat presents as delineated and depressed areas at the locations of insulin injections, 6-12 months after the initiation of treatment. This lesion is more common in children and obese women. Mechanism is unclear but some theories have been suggested; namely lipolytic components in insulin preparation and immune complex-mediated inflammatory process. It may rarely resolve spontaneously (39). Lipohypertrophy appears with lipoma-like soft nodules in the areas with repeated insulin injections. This lesion probably results from local adipocyte stimulation by insulin (3). It can be prevented by rotating the injection site (21,47). Simultaneous appearance of lipoatrophy and lipohypertrophy in a patient is possible (16).

#### **Skin reactions to oral hypoglycemic agents**

Most cutaneous reactions are related to sulfonylureas (especially the first generation drugs) which may be due to similar structure to sulfonamides (3,16). The most common

manifestations are maculopapular eruptions. Other reactions include generalized erythema, urticaria, lichenoid eruptions, erythema multiforme, exfoliative dermatitis, erythema nodosum, and photosensitivity reactions (16). Adverse effects due to using metformin are erythema multiforme (48), leukocytoclastic vasculitis (49,50), psoriasiform eruption (51), photosensitivity, erythema, exanthema, pruritus and urticaria (52). Edema has been reported as a side effect of using thiazolidinediones (52). There are also reports of generalized erythema multiforme and acute generalized exanthematous pustulosis induced by acarbose (53,54).

### 4-Diabetic Foot Ulcer

Diabetic foot is a complex of several pathologies including neuropathy, peripheral arterial disease, trauma and infection (55,56), of which, the neuropathy seems to be the most important factor (56). Poor metabolic control predisposes the patients to impaired wound healing by impairing collagen cross-linking and matrix metalloproteinase activity (57).

Recent studies have shown that incidence and prevalence rates of diabetic foot ulcer are 1-

4% and 4-10%, respectively (58). The lifetime risk is near 25% (59). There are several types of classifications for the ulcers, based on different aspects of them; for example, they may be classified based on the underlying pathogenesis (60), depth of ulcer and extent of gangrene (Wagner-Meggitt classification) (61) or a combination of the factors (PEDIS classification) (62).

### 5-Other Manifestations

Pruritus, periungual telangiectasia, calciphylaxis, lichen ruber planus, etc.

### Conclusion

With regard to the high prevalence of skin manifestations in diabetic patients and considering that they may precede the development of overt disease in some subjects, particular attention should be paid to these findings, especially in high risk individuals. In addition, improved metabolic control and using advanced types of insulins and equipment may alleviate or even resolve these problems.

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