EPIDEMIOLOGY OF SKIN LESIONS IN DIABETES MELLITUS

Numerous skin lesions are associated with either type 1 or type 2 diabetes mellitus, specific chronic complications of the disease, use of antidiabetic drugs, and certain endocrine and metabolic disorders that cause secondary diabetes mellitus.

CLASSIFICATION OF DERMATOLOGIC LESIONS IN DIABETES MELLITUS

There is considerable uncertainty about the pathogenesis of the many cutaneous conditions affecting diabetic patients in no small part because of our inadequate understanding of the metabolic basis of diabetes mellitus itself.

There is no strict classification of skin lesions related to diabetes mellitus, therefore grouping them under the following headings will give us an idea about various types of skin lesions occurring in diabetes. So, one would know what are the dermatologic conditions occurring in a diabetic (1).

Dermatologic lesions associated with but not specific for diabetes mellitus (disease markers)
- Pruritus
- Necrobiosis lipoidica diabeticorum

Skin alterations due to diabetic complications
- Diabetic foot
- Cutaneous infections associated with diabetes
  - furunculosis
  - carbuncle
  - pyodermas
  - candidiasis
  - dermatophytosis
- Erythrasma
- Xanthomatosus
- Xanthelasma
- Pycomycetes
- Malignant otitis media

Dermatologic changes associated with neurovascular complications
- Macroangiopathy
• Microangiopathy
• Diabetic neuropathy

**Dermatologic complications of diabetes treatment**

- with oral hypoglycemic drugs
- with insulin

**Endocrine syndromes with skin alterations and diabetes mellitus**

- Migratory necrolytic erythema in glucagonoma

**Dermatoses that are more common in diabetes mellitus**

- Perforating dermatosis
- Vitiligo
- Lichen planus
- Eruptive xanthomas
- Kaposi’s sarcoma
- Bullous pemphigoid
- Dermatitis herpetiformis
- Psoriasis

**VARIOUS TYPES OF DERMATOLOGIC LESIONS IN DETAIL**

**Dermatologic lesions associated with but not specific to diabetes mellitus (disease markers)**

**Pruritus**

Generalized pruritus was once considered a typical symptom of diabetes but its frequency is unknown. Studies have failed to provide a statistical basis for this belief (2,3). A higher rate of pruritus is found in liver diseases, uremia, parasitic infestation, endocrine disorders (thyroid), malignant diseases, hematologic and metabolic diseases, and as a side effect of some drugs. Generalized pruritus is associated with diabetes complications of chronic renal insufficiency, occasionally neuropathy (irritation of nerve endings can be the cause). High levels of urea in the blood cause the skin to itch. Candidiasis or dermatophytosis may underlie pruritus in diabetic patients. Anogenital pruritus is often caused by candidiasis in diabetic patients (4).

Some fungal infections most commonly occurring in diabetics are jock itch, athlete’s foot and ringworm. Jock itch appears as a red, itchy area that will spread from genitals outward over the inside of the thighs. Jock itch is more common in men than in women. When athlete’s foot occurs the skin between the toes will become itchy and sore. It may also crack, peel or blister. Ringworm is identified by ring-shaped, red scaly patches that can itch or blister. Ringworm can appear on the feet, groin, trunk, scalp or nails. Itching in the legs in elderly diabetics is not a feature of hyperglycemia but rather a manifestation of xerosis. Simple lubricants and low potency corticosteroid application should prove helpful.

**Necrobiosis lipoidica diabeticorum**

The disease is very rare, occurring in 7% of diabetic patients (5). These relatively asymptomatic lesions are three times more common in women than in men. It is one of the cutaneous markers of diabetes. At the time of diagnosis 10% of the people will develop diabetes within 5 years or have abnormal glucose tolerance or history of the disease in at least one parent (6). The condition occurs at any age but it generally favors young adults at a mean age of 34 years. In insulin users, the onset is considered to occur much earlier than in type 2 diabetics or nondiabetics (7). The lesions are characteristically found on the anterior and lateral surfaces of lower legs, i.e. in the pretibial and medial malleolar region. They may also be present on the face, arms and trunk. There may be one or several lesions, either unilateral or bilateral. The lesion begins as a small, dusky-red elevated nodule with a sharply circumscribed border. It slowly enlarges to turn into a plaque of irregular outline, flattened, and eventually depressed as the dermis becomes more atrophic.

The color turns more brownish-yellow except for the border, which may remain red. Coalescing or enlarging lesions may in time encompass the entire anterior tibial area. The epidermis is smooth or slightly scaly and atrophic. Delicate vessels can be seen through the surface. The lesions may be anesthetic or have reduced sensation to pin prick and to fine touch due to destruction of cutaneous nerves (8).
The chronic lesions of necrobiosis lipoidica diabeticorum (NLD) are indolent; shallow, often painful ulcers frequently appear in long-standing lesions. In the early stages, NLD may resemble granuloma annulare or sarcoid, but a well-developed plaque is characteristic and easily recognized. The primary pathologic changes are in the lower dermis, where collagen is markedly altered with focal areas of loss of normal structure, swelling, basophilia, and distortion of the bundles (necrobiosis). Cross-striations and diameters of collagen fibers are irregular. Although the amount of collagen is actually decreased, the relative proportions of types I and III are preserved. Fibroblasts cultured from skin lesions have been reported to produce less collagen. There is also the loss and fragmentation of elastic fibers. There is increased collagenase in the lesional skin. In these areas, there are aggregations of inflammatory cells. The late appearance of foam cells accounts for the designation ‘lipoidica’.

The vasculature is always involved, with endothelial proliferation and occlusion of the lumina of arterioles and venules (9,10). Capillary walls are thickened with focal deposits of PAS-positive material that may also be present in the lumen. The nature of the association with diabetes and its pathogenesis remains unclear. Because NLD occurs in both IDDM and NIDDM, its pathogenesis cannot be related to genetic factors, underlying autoimmune disease, or other causes of diabetes. It can be reasonably assumed that the granulomatous response is secondary to alterations in dermal collagen. It is not clear whether this is secondary to an underlying vascular disease or develops independently. The latter would ascribe the changes in dermal collagen and vasculature to some primary disorder of connective tissue (as yet unknown). However, the invariable presence of arteriolar changes deep into and within the areas of collagen degeneration suggests an interrelation between the two components of NLD (11). It has been hypothesized that increased platelet aggregation may be a trigger factor in vascular changes (12). Immunoglobulins, complement (C3 and C4) (13), and fibrinogen are present in blood vessels in lesional and, in some cases, nonlesional skin (14). These findings are in concordance with the presence of inflammatory changes in adjacent clinically normal skin. The treatment of NLD is not very satisfactory. Progression of lesions does not correlate with normalization of hyperglycemia. Local therapy with topical application of glucocorticoids under occlusion or by intralesional injection may afford some improvement of active lesions. There have been some enthusiastic reports on the use of aspirin and dipyridamole, but these were not confirmed in a rigorous double-blind trial (15). Favorable effects were obtained with very small doses of aspirin: 3.5 mg/kg every 48 to 72 h (16). Other helpful agents are clofazimine, nicotinamide, and pentoxifylline. Ultraviolet light treatment has been found to control this condition when it is flaring.

Granuloma annulare
It is a benign necrobiotic condition associated with lesions similar to NLD, the only difference being the absence of epidermal atrophy. This is a skin disease usually seen in children and young adults. It is occasionally associated with diabetes. Skin signs are characterized by red spots in the initial stages that expand outwards in a ring-like fashion. The hands, especially the fingers, on dorsal or lateral aspect of the hands and elbows (forearms), are commonly affected. When granuloma annulare is widespread it may be associated with underlying diabetes mellitus. The skin lesions may precede the symptoms and signs of diabetes mellitus. Patients with widespread granuloma annulare need to be screened for diabetes mellitus. Mostly it is asymptomatic and resolves spontaneously.

Diabetic dermopathy
It is the most common skin lesion occurring in diabetics (17). It is prominent in males who are more than 50 years of age (18). It is seen even in euglycemic, endocrine diseases and also in healthy individuals. The presence of small blood vessel changes has led to the term diabetic dermopathy (17). The lesions are asymptomatic, irregularly shaped patches occurring primarily over the anterior lower legs; their surfaces are depressed and they have a light brown color. The pigmentation is due to deposition of hemosiderin in histiocytes and extravasated superficial erythrocytes. These lesions can occur on upper arms, thighs, and any bony prominences. Lesions appear in crops and gradually resolve over 12 to 18 months. The disorder is asymptomatic requiring no treatment except for protecting the area from any trauma and secondary infection. Use of bio-occlusive dressing is recommended.
Scleroderma-like syndrome, reduced joint mobility, waxy skin syndrome

These terms are synonymous denoting one and the same skin disorder (17,19). As many as one third of diabetic patients (both IDDM and NIDDM) have tight, thickened waxy skin over the dorsum of the hands. Reduced joint motion probably is the earliest complication of diabetes mellitus, a characteristic finding in children and adolescents after only 10 years of diabetes duration. The metacarpophalangeal and proximal intraphalangeal joints are usually first involved. Reduced extension, initially active, then also passive, is observed. Flexion may for long remain completely preserved. Clinical signs include impossible extension of the palm on the table and impossible clasping hands as in prayer. Restriction of passive extension of the interphalangeal and metacarpophalangeal joints is most important from the diagnostic point of view (20,21). The skin becomes thickened, with a waxy appearance, in about one third of patients (22). Such skin resembles sclerodermic skin. Histologically, dermal collagen thickening and elastic fiber reductions are observed (23,24). This cutaneous manifestation can accompany MODY and is considered to be associated with poor prognosis in terms of prediction of retinopathy and nephropathy (25,26). However, there are no substantial evidence supporting the above concept (27).

Acanthosis nigricans

This disorder is characterized by velvety papillomatous hyperplasia of the disease, and diabetes. Mild forms also occur in obesity without evident endocrine disorder. It appears likely that a common pathogenetic mechanism accounts for acanthosis nigricans linked to endocrinopathy. Studies of patients showed the epithelium with intense hyperpigmentation, which was most pronounced in the axillary, inguinal, and inframammary folds, and in the creases of the neck.

In more severe forms it may be more generalized and accompanied by verrucous patches on knuckles and other extensor surfaces, hyperkeratosis of the palms and soles, and other hyperplastic lesions. Acanthosis nigricans is associated with two types of disorders. The more severe form is usually found in patients with advanced malignant disease. The more limited form is more frequently found in association with a variety of endocrinopathies (28), including acromegaly, Cushing’s syndrome, and polycystic ovary. A variety of endocrine diseases and acanthosis nigricans suggest that insulin resistance is a common denominator even in the absence of overt diabetes. It was first shown to be associated with insulin resistance in patients with the rare syndrome of lipoatrophic diabetes (29). Subsequently, acanthosis nigricans has been associated with all three types of insulin resistance:

- type A, in which insulin resistance is due to receptor defects resulting in decreased insulin binding;
- type B, in which insulin resistance is conferred by effects of circulating antireceptor antibodies; and
- type C, in which postreceptor defects including abnormalities in signal transduction such as autophosphorylation of the receptor and activation of tyrosine kinase inhibit insulin action (1,30).

Histologic examinations reveal marked hyperkeratosis and papillomatous lesions (31), although the epidermis is mildly acanthotic, i.e. thickened (32). The use of keratolytic agents such as salicylic acid can improve the appearance cosmetically, if desired.

Diabetic bullae

Diabetic bullae are very rare but characteristic of diabetes mellitus. They occur in adult males. The bullae appear spontaneously, commonly in the dorsum and sides of the lower legs, especially feet. Sometimes they are associated with similar lesions on the forearm and hands. Bullae may range from millimeters to few centimeters. The lesions are often bilateral, containing clear sterile fluid. There is no surrounding erythema. Generally, the bullae heal in several weeks without significant scarring, although they may recur (33). These blisters are not the result of trauma or infection (34). The bullae are subepidermal, and ultrastructural studies have demonstrated the plane of separation to be in the basement membrane zone above the basal lamina. In some cases the distribution of lesions in light exposed areas suggests porphyria cutanea tarda, but abnormalities of porphyrin metabolism have not been found. Neither trauma nor immune mechanisms have been implicated. The cause of this rare manifestation of diabetes is unknown. At least 75 percent of patients have significant diabetic retinopathy, and in one series of three patients dermopathy and cutaneous angiopathy were present (17). The localization of the plane of separation suggests that weakness in the basement
membrane zone is an underlying factor. That this may be the case is suggested by the presence of a reduced threshold to formation of suction blisters on the forearms of insulin-dependent diabetics (35). Usually they do not require any treatment apart from prevention of secondary infection which can be done by the application of bio-occlusive dressings.

**Skin alterations due to diabetic complications**

**Neurovascular and ischemic changes and foot ulceration (diabetic foot)**

Diabetic foot is a serious complication which results from confluence of multifactorial pathogenic mechanisms. Neuropathy (motor, sensory and autonomic) and diabetic angiopathy are the contributing factors for its development, the neuropathy being the major factor. Laceration which may be complicated with necrosis, gangrene and osteomyelitis, accentuated plantar arches and hammer toes with interdigital maceration leading to bacterial and fungal infections, and loss of the ankle jerk and vibration sensation are the features of the diabetic foot. Because of its serious nature it requires special attention. Prevention is by far more relevant than cure. Hence care of the foot must become a routine in diabetic patients.

**Cutaneous infections associated with diabetes**

Poorly controlled or undiagnosed diabetics have a greater susceptibility to bacterial and fungal infections of the skin. The most frequently encountered infections are staphylococcal pyodermas such as furunculosis and carbuncles, candidiasis, erythrasma and dermatophytosis.

*Furunculosis (boils).* The word ‘boil’ has been derived from the German language and refers to ‘swelling’. There is extended involvement of the hair follicle including the perifollicular region in the dermis and subcutaneous tissue, i.e. there is folliculitis as well as perifolliculitis. It is caused by *Staphylococcus (S.) aureus*. Boils are common during adolescence and early adult age. In India these are more common during the rainy season. Isolated furuncles appear, and many lesions may develop together. In other cases crops of lesions keep appearing. Generally, the subjects are healthy but have poor hygiene or are carriers of *S. aureus*. Factors like diabetes mellitus, exfoliative dermatitis and intake of systemic steroids may be responsible for their increased frequency and greater severity.

A furuncle usually begins as a tender area, which rapidly develops into an inflammatory indurated nodule of 2 to 3 cm in diameter. Within the next few days the area becomes necrotic and discharges pus from a point at the follicular opening. Those furuncles, which do not discharge on the surface are called ‘blind boils’.

*Carbuncle.* A carbuncle may be said to be a group of boils which show deep infection of contiguous follicles with *S. aureus*. The infection spreads from one follicle to the other usually not *via* the surface but through the subcutaneous tissue. The lesion starts as a painful, tender, firm to hard indurated lump with a course similar to but more protracted than that of a furuncle. It is associated with intense inflammatory changes in the surrounding and underlying tissues. Pus is discharged not necessarily through the follicular openings but from any point. The common sites are the back of the neck, shoulders, hips and thighs. It is frequently associated with diabetes mellitus. If the underlying conditions are controlled and appropriate therapy instituted, healing takes place leaving a scar, otherwise toxemia and even death may follow.

*Pyodermas.* The advent of antibiotics and tighter control of diabetes has markedly reduced the incidence and morbidity of pyodermas which were formerly considered as serious complications. Lower extremities constitute a particular hazard for the diabetic patient. The associated atherosclerosis and peripheral neuropathy lead to ulceration and gangrene as well as poor wound healing.

*Candidiasis (monoliasis).* *Candida albicans* is a common complication in poorly controlled diabetics (36). They show considerable improvement when diabetes is controlled. Candidal infections of the skin may resemble those caused by other dermatophytes but are most common where the skin is moist and in contact with itself, e.g. groins, perineum, breasts, axillae. Nail infections start at the base, forming ridges, often accompanied by paronychia. Paronychia is the infection of the web space between the middle and fourth finger. In the mouth, white curd-like patches are seen, which can be scraped away leaving a bleeding base (37). Atrophy of the gums and angular stomatitis are common in the elderly.
Vulvovaginal candidiasis. It commonly presents with itching, soreness, and a thick creamy white discharge. In severe cases, there is beefy red erythema of the vaginal mucosa and vulval skin with curdy white flecks of discharge. The lesion may spread to the perineum and groins. The perianal area is often affected. Candidal vulvovaginitis may be chronic and recurrent. Factors that predispose to candidal vaginitis include pregnancy, diabetes mellitus, oral contraceptive or antibiotic administration, and occlusive tight fitting garments (38).

Balinitis or balanoposthitis. Balanitis is common among the elderly and uncircumcised patients. Balanoposthitis usually presents with itching, pain, erosions, cracks and whitish scales on the terminal portion of the prepuce. Diabetes mellitus is often the underlying disease. In diabetic or immunosuppressed patients, a severe edematous, ulcerative balanitis may occur. Phimosis has been observed as a common complaint in diabetic men and recurring candidal infection is usually the cause.

Investigations: The yeast may be identified microscopically or by culture from swabs or scrapings from the lesions, and be cultured from the blood in systemic disease. Underlying local or systemic defects should be sought.

Management: Most important is to correct or control the underlying predisposition. Cutaneous candidiasis is treated with a topical azole ointment. Mucosal infection usually responds well to lozenges or suspension of nystatin or amphotericin. Persistent infections and nail infections require oral fluconazole or itraconazole. Systemic infections should be treated with intravenous amphotericin or with amphotericin plus flucytosine.

Dermatophyositis (tinea infections) ringworm infections. It is encouraged by the sharing of wash places and ringworm is due to the infection by dermatophyte fungi. There are three main genera: *Trichophyton* (skin, hair, and nail infections); *Microsporum* (skin and hair), and *Epidermo-phyton* (skin and nails).

Clinical features: These depend upon the site and the species of fungus involved.

*Tinea pedis* (athlete’s foot). This is the most common type of fungal infection in humans. The sharing of wash places and swimming pools encourages it. Infrequent washing of socks and the use of occlusive footwear encourage relapses. It may present in three main ways: soggy interdigital scaling, diffuse powdery scaling of the soles (which is often unilateral and which picks out skin creases), and recurrent bouts of vesication of the soles. The organisms involved are usually *T. rubrum*, *T. mentagrophytes var. interdigitale* and *E. floccosum*.

*Tine unguum* (tinea of the nails). Toe nail infection is more common than finger nail infection and is often accompanied by *tinea pedis*. Usually only a few nails are infected. The changes first occur at the free edge of the nail, which becomes yellow and crumbly. Thickening of the nail and separation of the nail from the nail bed may follow. *T. rubrum* is a frequent cause.

*Tinea manuum* (tinea of the hands). It is usually asymmetric and involves the palms (dry, powdery scaling picking out the creases) more often than the backs of the hands.

*Tinea cruris* (tinea of the groin). It affects men more than women and causes well-demarcated redness and peripheral scaling of the groins and upper thighs. A few vesicles or pustules are usually seen within the lesions. The eruption is often unilateral or asymmetric, and itchy.

*Tinea corporis* (tinea of the trunk). It is the archetypal ‘ringworm’ eruption. Erythematous scaly plaques expand slowly and clear in the center, leaving a ring-like pattern. Peripheral scaling, a few vesicles and pustules are characteristic.

Erythrasma

As the name suggests the initial lesions are reddish (in fact, reddish-brown) but as the disease is asymptomatic, patients are not generally observed at this stage. After a period of time, the lesions become brownish-black (like a silver nitrate stain) with irregular but very well defined borders. They are smooth but later appear creased and even finely scaly. The sites of predilection of clinical disease are the genitocrural folds, axillae and submammary regions. The Coryneforms causing erythrasma are seen in large sections of the population in the interdigital web spaces where they produce only mild scaling. The lesions fluoresce coral-red under Wood’s light or ultraviolet-A (UVA) light, due to coproporphyrin III production by the bacteria. If the patient has recently taken a bath, the fluorescence may not be observed as the porphyrin is soluble in water.
Xanthomatosis

Eruptive xanthomas are a characteristic but uncommon complication of diabetes mellitus associated with a more sustained hyperlipidemia affecting plasma triglycerides and cholesterol more than phospholipids, and hyperglycemia with glycosuria. The decreased lipoprotein lipase activity in insulin-dependent diabetics results in the accumulation of serum triglycerides, whose levels are occasionally highly elevated to produce eruptive xanthomas.

Cutaneous xanthomas result from deposition of lipid in the histiocytes in the dermis or subcutaneous tissue. Xanthomas tend to appear rapidly in crops as multiple, small, reddish-yellow nodules of up to 0.5 cm in diameter. They present in clusters primarily on the extensor surfaces and buttocks. The lesions are much smaller and more inflammatory than tendinous and tuberous xanthomas, which are associated with hypercholesterolemia and may be pruritic initially. Rapid regression of these lesions occurs when hyperlipidemia is brought under control.

Xanthelasma

It occurs in most hyperlipidemic states including diabetes. It does not regress with therapy for diabetes. A yellowish discoloration of the skin of the palms, soles and nasolabial folds due to the deposition of carotene present in excess quantities in plasma may be associated with hyperlipidemia even in the absence of xanthomatosis in diabetes.

Phycomycetes infection

Sometimes hyperglycemia may permit organisms that are nonpathogenic to produce infection in traumatized skin, which may lead to gangrene and loss of the limb. There are various factors, which help the phycomycetes establish and lead to the infection. These factors include pre-existing leg ulcers, nonhealing surgical wounds, deep seated fungal infections, etc. Treatment must be aggressive, consisting of correcting acid-base balance, debridement of devitalized tissue, and intravenous antifungal therapy. Patients with uncontrolled diabetes mellitus and ketosis may be predisposed to deep fungal infections or rhinocerebral mucormycosis of the turbinates, septum, palate, maxillary and ethmoid sinuses (38).

Malignant otitis media

It is caused by Pseudomonas aeruginosa. It is an uncommon but a very serious infection. Initially there is purulent discharge and pain in the external ear canal. It occurs commonly in diabetic men. It begins as a cellulitis and can progress to chondritis, osteomyelitis, and infective cerebritis. It usually has fatal outcome. So, the treatment includes the use of antipseudomonas antibiotics and debridement of devitalized tissue if necessary (38).

Dermatologic changes associated with neurovascular complications of diabetes

Macroangiopathy

Patients with diabetes mellitus have a slightly higher incidence and prevalence of large-vessel disease compared with control subjects (39). In patients with IDDM or NIDDM, both low-density lipoprotein cholesterol and VLDL triglycerides are risk factors (40). Atherosclerosis of the arteries of the legs results in skin atrophy, hair loss, coldness of the toes, nail dystrophy, pallor on elevation, and mottling on dependence (33). A reliable sign of large vessel disease is dependent rubor with delayed return of color (>15 seconds) after pressure has been applied to the skin (41).

Microangiopathy

The role of diabetic microangiopathy is not completely understood. The signs include diabetic dermopathy, pigmented purpura, erysipelas such as erythema, NLD, periungual telangiectases, and diabetic foot (42). Other signs of microangiopathy include cutaneous reactive hyperemia and reduced capillary flow on cold or warm challenges of patients with IDDM and those with NIDDM, as measured by laser Doppler flowmetry (43-47). The thickening of the vessel walls, perivascular deposition of material reactive with periodic acid-Schiff stain, and clumping of the elastic fibers in the papillary dermis are produced by a combination of intimal hyperplasia and increased deposition of type IV collagen within and around the vessel wall. The space between the pericytes and the endothelial cells is wider, and the cytoplasmic process that formed the contact point between them is longer and thinner than normal, suggesting a possible explanation for increased
permeability (48). The capillary leakage leads to the loss of albumin and water, and the platelets have a higher tendency to aggregate. As a result, increased whole blood and plasma viscosity creates a sluggish microcirculation (41).

**Diabetic ruberosis** is a peculiar rosy reddening of the face, sometimes of the hands and feet, which may be observed in longstanding diabetics. It has been attributed to diabetic microangiopathy or a decreased vascular tone.

**Diabetic neuropathy**

Elderly patients in whom the onset of diabetes is insidious are especially at risk of developing diabetic neuropathy. A common neuropathy in diabetes mellitus is a distal, symmetric, mixed polyneuropathy involving both the motor and the sensory nerves (49).

The skin manifestations of autonomic neuropathy in diabetes mellitus are disturbances in sweating and peripheral hyperemia with erythema, edema, and atrophy. Motor neuropathy of the feet leads to imbalance between flexor and extensor muscles, displacement of fat pads, and subluxation of digits (50).

Typical signs of sensory neuropathy in diabetes mellitus are paresthesias with the loss of temperature and pain sensation, as well as aching and burning of the legs that are worse at night. The combination of motor and sensory neuropathy along with mechanical factors and microangiopathy plays a major role in the development of the diabetic foot (42).

Immunohistochemical studies of nerves in diabetic skin have demonstrated depletion of neuropathies. The antidepressant drugs such as desipramine and amitriptyline that inhibit the membrane pump mechanism for the reuptake of neuropeptides have proved effective in diabetic peripheral neuropathy (50).

**Dermatologic complications due to the treatment of diabetes**

**Oral hypoglycemic drugs**

The cutaneous complications of oral hypoglycemic agents are few. They occur more commonly with first generation sulphonylureas such as chlorpropamide and tolbutamide, and usually develop in the first two months of treatment. They may be either toxic or allergic in nature.

Phototoxic reactions presenting as excessive sunburn after exposure to sunlight occur in a few patients (52). Allergic skin reactions are uncommon and are similar for all hypoglycemic drugs belonging to the sulphonylurea group. They are usually mild and self-limited. Patients may present with intermittent or persistent pruritus or a maculopapular rash. Other cutaneous reactions which may occur occasionally include urticaria and erythema multiforme, which may progress to the Stevens-Johnson syndrome. Other rare skin manifestations include erythema nodosum and purpura as well as exacerbation of porphyria cutanea tarda and generalized hypersensitivity reactions.

The chlorpropamide alcohol flush occurs in patients taking this drug. The reaction usually begins within 15 min after ingestion of alcohol. It causes flushing, headache, tachycardia and dyspnea that gradually subsides after an hour. Second generation sulphonylureas, which are now widely used, produce fewer cutaneous side effects. The allergic skin reactions to sulphonylureas often disappear while the patient is receiving a maintenance drug regimen.

**Insulin**

Cutaneous complications due to insulin therapy used to be common before the advent of newer insulins. Allergic reactions to insulin may be immediate or delayed. Serious generalized reactions such as urticaria and anaphylaxis are rare. The immediate local reaction is probably IgE-mediated. It starts as erythema, becomes urticarial within 30 min and subsides within an hour. The delayed reaction is the most common reaction. It is due to delayed hypersensitivity. About 2 weeks after the initiation of insulin therapy, a pruritic nodule develops within 1 or 2 days at the site of injection, lasts for days and heals with hyperpigmentation and scarring. Localized induration, ulceration and scar formation, cutaneous abscess formation and development of keloids may result from faulty injection techniques. Idiosyncratic reactions are very rare and include pigmentation and occasionally keloid formation. Skin reaction resembling acanthosis nigricans has been reported.
Lipoatrophy. Insulin lipoatrophy and lipohypertrophy, which are the complications of insulin injection, are rare after the introduction of newer insulins. Lipoatrophy presents as circumscribed atrophic plaques showing atrophy of the subcutaneous fat at the site of insulin injection, and rarely shows complete resolution. It may be due to a local immune response to insulin injection (53).

Lipohypertrophy. It presents as a soft dermal nodule. The overlying skin appears normal at the site of injection. It may be due to the lipogenic action of insulin.

Insulin edema. Edema of the abdomen and legs is a more common and usually a self-limiting complication which appears shortly after starting or increasing the dose of insulin. It is commonly seen in women (54) and is unrelated to cardiac or renal disease. The pathogenesis is unclear. Ephedrine is the drug of choice (55).

Endocrine syndromes with skin alterations and diabetes mellitus

Glucagonoma

It is the most characteristic endocrine syndrome manifesting with skin alterations and diabetes mellitus. This syndrome is often diagnosed late and mostly by a dermatologist. The dermatosis is the presenting clue. The syndrome is usually caused by tumors of the alpha-cell, glucagon secreting portion of the pancreas. It has four components:

- hypersecretion of glucagon,
- diabetes that is usually mild,
- weight loss, and
- necrolytic migratory erythema.

The chronic, fluctuating dermatosis is characterized by an annular and figurative erythema that forms bullae and erosions. The periphery of these lesions extends with vesiculopustules. The lesions tend to coalesce before healing which starts within weeks, as they are replaced by new ones. They commonly occur in the intertriginous areas, perioral regions and on extremities. Histologically, they resemble pustular psoriasis, with features of intracellular edema in the upper epidermis, acanthosis and subcorneal pustulosis (56). Necrolytic migratory erythema resolves after excision of the pancreatic tumor, which in the majority of cases is the treatment of choice (57).

Dermatoses reported to be more common in diabetics than in nondiabetics

Kaposi’s sarcoma

It is a multiple idiopathic hemorrhagic sarcoma, which manifests primarily as multiple vascular nodules in the skin and other organs. It predominantly affects males. The lesions begin in the legs as multiple, purple macules, nodules or plaques. Later, other areas of the skin, mucous membranes and internal organs may be involved. Edema of the legs is frequent and may even be a prodrome. Histologic picture reveals accumulation of spindle cells forming vascular slits containing erythrocytes (58). Diabetes mellitus has been reported with greater than expected frequency in classic Kaposi’s sarcoma, however, confirmation is still needed (59).

Perforating dermatosis

There are several acquired cutaneous disorders having as a common histologic denominator the transepidermal elimination of degenerative material, chiefly collagen and elastic fibers. Many are seen in patients with chronic renal failure, particularly those on dialysis and with IDDM or NIDDM. The size of these papules ranges from 2 to 10 mm in diameter, often with a keratotic plug. They favor the extensor surface of the trunk and extremities, and are itchy with little tendency to spontaneous resolution. Most patients are middle aged, often black, and more often men than women. Improvement of itchy lesions is not achieved easily but topical retinoic (60) and ultraviolet therapy (61) has been useful.

Vitiligo

It is a disease with a diminished or absent function of melanocytes resulting in macular depigmentation. It is found mostly in periorificial regions and also on the extensor aspect of the extremities. It is asymptomatic but emotionally stressful, particularly in people with dark skin. Vitiligo occurs with a greater incidence than expected (+4.8%) in patients with maturity onset diabetes (62) and type 2 diabetes (63). It has also been
reported in association with IDDM and other autoimmune disorders of the adrenal and thyroid or gastric parietal cells.

**Lichen planus**

An increased incidence of diabetes mellitus and abnormal insulin response to glucose challenge have been claimed in patients with lichen planus (64). This seems particularly so in adults, especially those with the erosive oral form (65). There were various studies of lichen planus and its relationship with diabetes mellitus, which have led to a conclusion that there are two types of lichen planus, i.e. the immunogenic type and the metabolic defect type, both being associated with diabetes mellitus (66,67).

**Yellow nails**

The lesion involves distal hallux and is quite common in diabetic individuals (68). It is one of the important markers of diabetes mellitus. The earliest sign is yellow or brown color of the distal part of the hallux nail plate. Later, a canary-yellowish discoloration occurs on the nails. It can involve finger nails and other toe nails during the later stage of the disease.

**Eruptive xanthomas**

They commonly occur in hyperlipidemic status. Frequently, the underlying problem is uncontrolled diabetes. The eruptions are multiple, firm, yellowish in color, waxy papules ranging from 1 to 4 mm in diameter, appearing in crops. They are mostly located on the extensor surfaces. The firm nontender papules are present on the knees, elbows, back, buttocks and trunk (69). These lesions are itchy, sometimes tender, surrounded by erythematous halo. They show Koebner’s phenomena (70). The unifying factor in hyperlipidemic status is decreased lipoprotein lipase activity or increased LDL, making chylomicrons less able to compete LDL for lipoprotein lipase. The net result is an increase in plasma chylomicrons (71). There is some evidence that eruptive xanthomas in diabetics result from macrophages incorporating plasma lipoprotein forming foam and xanthoma cells (71). With correction of hyperlipidemia and hyperglycemia, the lesions involute, sometimes with postinflammatory hyperpigmentation and occasionally scars.

**Bullous pemphigoid**

There are very few studies relating bullous pemphigoid and diabetes. The relationship between the two awaits for confirmation. Theoretically, their association may be due to the lower threshold of diabetes in traumatically induced blisters or on the basis of antigenic changes at the level of lamina lucida because of enzymatic glycosylation. Steroids and sometimes even immunosuppressive drugs may be appropriate.

**Dermatitis herpetiformis**

The HLA association of diabetes and dermatitis herpetiformis may be a possible explanation for the two diseases appearing together more frequently than expected (72).

**Psoriasis.** It is a multifactorial disease of unknown origin. There is a distinct pattern of associated diseases existing in patients with psoriasis. Systemic disorders such as hypertension and diabetes are often seen in these patients. The reasons for these diseases to occur in psoriasis patients have been related to nutritional factors of hypercaloric dietary habits (73).

**REFERENCES**


