Cutaneous manifestations of diabetes mellitus

Tammie Ferringer, MD, O. Fred Miller III, MD*

Department of Dermatology, Geisinger Medical Center, 100 North Academy Avenue, Danville, PA 17822, USA

Diabetes mellitus (DM), the most common endocrine disorder, affects an estimated 11 million in the United States. Ninety percent have type II, non-insulin-dependent (NIDDM), whereas 10% have insulin-dependent type I (IDDM) [1]. At least 30% of diabetics have some cutaneous involvement during the course of their disease [1]. Although the overall prevalence of cutaneous disorders does not seem to differ between type I and type II diabetes patients [2], type II patients do develop more frequent cutaneous infections, whereas type I patients develop more autoimmune-type cutaneous lesions [2,3]. Cutaneous manifestations generally appear subsequent to the development of the diabetes, but may be the first presenting sign or even precede the diagnosis by many years. The cutaneous findings can be classified into four major groups: (1) skin diseases associated with diabetes, such as necrobiosis lipoidica (NL), diabetic dermopathy, and diabetic bullae; (2) cutaneous infections; (3) cutaneous manifestations of diabetic complications, such as neuropathic foot ulcers; and (4) skin reactions to diabetic treatment. This article outlines the major skin findings in DM and summarizes recent studies and reports.

Cutaneous conditions associated with DM

Necrobiosis lipoidica

Necrobiosis lipoidica (NL) appears in 0.3% to 1.6% of diabetics [2]. Only 11% to 65% of patients with NL have DM at the time of cutaneous diagnosis [4,5]. Of those without diabetes, approximately 90% eventually develop diabetes, have abnormal glucose tolerance, or report one or both parents with diabetes [2]. Consequently, nondiabetic patients with NL should be evaluated and followed for development of diabetes. The general consensus is that diabetic control has no effect on the course of NL. Cohen et al [6], however, believe that the pathogenesis of NL differs in diabetics versus nondiabetic patients and tighter glucose control could reduce the incidence of NL in diabetics.

Necrobiosis lipoidica is three times more common in women. IDDM patients develop NL considerably earlier at a mean age of 22 years, whereas NL appears in NIDDM and nondiabetic patients at a mean age of 49 years [7].

Initially, an erythematous, slowly enlarging irregular plaque with an elevated border, NL becomes more brownish yellow, telangiectatic, porcelain-like, and depressed. NL may present as single or multiple plaques that often coalesce. Classically, NL occurs bilaterally on the pretibial or medial malleolar areas [7]. NL involving the hands, forearms, abdomen, face, and scalp is less consistently associated with diabetes [8,9]. Although not painful and often insensate to pinprick and fine touch, NL may ulcerate spontaneously or from trauma, resulting in pain, especially if secondarily infected [10]. Spontaneous gradual resolution is noted in 13% to 19% after 6 to 12 years, but residual atrophic scarring persists [1,8].

Etiologically, NL may be associated with microangiopathic changes consisting of thickened basement membranes and capillary walls, particularly in pretibial lesions. These changes are less common in NL sites elsewhere on the body, however, indicating that microangiopathy may not be necessary for development of lesions [8]. If microangiopathy is responsible for NL, other microvascular complications, such as retinopathy and nephropathy, should correlate with NL. A few studies have supported these associations.
One noted such a direct correlation in adolescents with NL and IDDM [11]. Other proposed causative factors include obliterative endarteritis, immune-mediated vasculitis, other immune factors, delayed hypersensitivity, nonenzymatic glycosylation and other defects in collagen, trauma, platelet aggregation, defective mobility of neutrophils, and vascular insufficiency [7].

Histologically, the dermis shows degenerated collagen surrounded by a horizontal palisade of histiocytes with minimal mucin and interspersed lymphocytes, plasma cells, and foreign body giant cells. Treatment includes potent topical steroids with or without occlusion, intralesional steroids at the active border, or rarely systemic steroids. Topical psoralen plus ultraviolet A (PUVA), cyclosporine, high-dose nicotinamide, clofazimine, pentoxifylline, aspirin, and dipyridamole have been tried with varying success [12–15]. Attempts at local excision and grafting are usually complicated by recurrences at the borders [16]. Based on the collagen destruction in NL, topical retinoids have been used to enhance collagen formation [12]. Laser treatment of the telangiectases may improve the appearance and reduce trauma-related bleeding [17]. Benzoyl peroxides have been reported to be useful in ulcerated lesions [8].

Granuloma annulare

The association of localized granuloma annulare (GA) with diabetes has not been clearly established. Four patients with nodular GA and DM were reported from one facility [18]. Several studies, which used glucose or prednisone-glucose tolerance provocative testing for diabetes, support the view that generalized GA, especially in older patients, is associated with diabetes [19]. Other studies have not been confirmatory. Despite the controversy, it is reasonable to screen all patients who present with generalized GA for abnormal glucose tolerance.

No universally accepted theory explains the cause of the usually asymptomatic, occasionally pruritic lesions of generalized GA [2,20]. Histologic features include focal degeneration of collagen in the upper and mid-dermis, palisaded histiocytes around collagen bundles, and abundant dermal mucin.

Although localized GA frequently resolves spontaneously without scarring, the generalized variant has a more protracted course with rare spontaneous resolution. Sporadic therapeutic success has been reported with topical, systemic, and intralesional steroids; isotretinoin; chlorambucil; freezing; chloroquine; potassium iodide; niacinamide; chlorpropamide; dapsone; antimalarials; and PUVA [7,20].

Diabetic dermopathy

Affecting 7% to 70% of diabetics, predominantly men over the age of 50, diabetic dermopathy, also known as shin spots and pigmented pretibial papules, is considered the most common cutaneous manifestation of DM [8,21,22]. Diabetic dermopathy, however, is not pathognomonic of diabetes because 20% of non-diabetics show similar lesions. Although a correlation with higher hemoglobin A1c values has been noted in one study, most believe diabetic dermopathy is not related to blood glucose control [2]. Similar to NL, shin spots may precede abnormal glucose metabolism [19].

Shin spots appear as multiple, bilateral, asymmetric, annular, or irregular red papules or plaques on the extensor surface of the lower legs with gradual evolution into atrophic hyperpigmented finely scaled macules. Lesions may also be observed on the forearms, thighs, and the lateral malleoli [10]. Older lesions may persist or disappear while new lesions appear.

Histologically, the epidermis is thin with thickened vessels in the papillary dermis, showing increased periodic acid–Schiff–positive (PAS) diastase-resistant material. There is often a mild perivascular lymphohistiocytic infiltrate with scattered hemosiderin deposits associated with hemorrhage. Unlike NL, the collagen change is much less marked and necrobiosis is absent [16].

The genesis of shin spots is unclear. The frequency of changes over bony prominences suggests that trauma may be a modifying factor, especially in diabetics with neuropathy. Blunt trauma did not elicit lesions in one study but another investigator induced lesions with heat and cold injury [23,24]. Evidence also exists for and against the role of microangiopathy. The thick-walled capillaries are present in lesions and in adjacent noninvolved skin. Several investigators have reported a correlation of microangiopathic changes of diabetic dermopathy with the presence of retinopathy, neuropathy, and nephropathy, whereas others have been unable to substantiate these findings [21,22,24–26]. Capillary changes may predispose to, but are not likely to be the sole cause of shin spots.

The differential diagnosis includes NL, stasis dermatitis, pigmented purpuric eruption, or posttraumatic scarring. No treatment is effective for these generally asymptomatic, nonulcerated lesions [27,28].

Diabetic bullae

Approximately 0.5% of diabetics develop diabetic bullae or bullosis diabeticorum, a clinically distinct
These bullae have only been reported in adults (40 to 77 years old), more commonly in men, with long-standing diabetes and neuropathy [2,29]. There have been a few reports of diabetic bullae leading to the diagnosis of DM [30,31]. These painless bullae on a noninflamed base suddenly appear most commonly on the dorsa and sides of the lower legs and feet, sometimes in association with similar lesions on the hands and forearms or on the hands alone. Ranging in size from a few millimeters to several centimeters the bullae contain clear, sterile fluid.

Two different types of bullae have been described: the more frequent nonscarring lesions with a histologic intraepidermal split without acantholysis [32,33]; and the occasionally hemorrhagic bullae that heal with scarring, slight atrophy, and have a histologic subepidermal split [34]. Histologic differences may be explained by different pathogeneses or by biopsies taken at different stages of development [7].

Although the pathogenesis of these blisters is not well understood, some evidence supports trauma with a reduced threshold to suction blister-induced formation in type 1 diabetics [35]. Multiple bullae at widely separated sites, however, argue against trauma as a pathogenic factor [7]. Other suggested causes include immunologic factors; disturbed metabolism of calcium, magnesium, or carbohydrates; microangiopathy; vascular insufficiency; or ultraviolet light in conjunction with nephropathy [13,16,29,30,36,37].

The differential diagnosis includes bullous pemphigoid, epidermolysis bullosa acquisita, porphyria cutanea tarda, bullous impetigo, erythema multiforme, and coma blisters. Bullous diabeticorum remains a diagnosis of exclusion with negative immunofluorescent studies, porphyrin levels, and cultures.

The bullae heal spontaneously in 2 to 5 weeks but may recur in the same or new anatomic locations [38]. If large and symptomatic, the bullae can be aspirated with an intact blister roof providing a physiologic wound covering.

**Acanthosis nigricans**

Acanthosis nigricans (AN) presents clinically as hyperpigmented velvety plaques in body folds, mostly the axillae and neck [4]. Other locations include the groin, umbilicus, areolae, submammary regions, and hands (tripe hands) [2].

Acanthosis nigricans is seen in situations of insulin resistance, including type II DM, obesity, and total lipodystrophy. In these cases the pathogenesis may be related to insulin binding insulin-like growth factor receptors on keratinocytes and dermal fibroblasts, stimulating growth [39]. In a study of 223 patients with AN, nearly 50% of patients in their fifth decade had NIDDM, whereas only 4 of the 99 patients under age 20 had documented NIDDM. Impaired glucose tolerance without a diagnosis of DM, however, was present in a larger proportion of the younger patients [4]. Because AN can also be seen as a complication of carcinoma (particularly of the stomach), secondary to medications, such as nicotinic acid or corticosteroids, and in various other endocrinopathies, work-up becomes necessary in the diabetic patient to rule out other underlying disorders [16].

Histopathologically, the lesions reveal papillomatosis, hyperkeratosis, and mild acanthosis. The dark color is related to the thickness of the keratin-containing superficial epithelium, not to any change in melanocyte number or melanin content [4].

Although generally asymptomatic, retinoic acid and salicylic acid may be effective for cosmetic improvement [8]. Weight control is clearly of benefit. Clinical improvement with dietary fish oil supplement has been reported [40].

**Acquired perforating dermatosis**

The cutaneous perforating disorders, characterized by the transepidermal elimination of some component of the dermis, have classically been divided into four types: (1) elastosis perforans serpiginosa, (2) reactive perforating collagenosis, (3) Kyrle’s disease, and (4) perforating folliculitis. All four of these major perforating disorders have been reported in patients with chronic renal failure, diabetes, or both. In 1989, Rapini et al [41] helped to clarify the issue of perforating disorders in patients with systemic disease, such as chronic renal failure or DM, by proposing the term acquired perforating dermatosis. Acquired perforating dermatosis consists of pruritic, 2- to 10-mm, hyperkeratotic, dome-shaped, often umbilicated papules and nodules usually on the extensor limbs, trunk, dorsal hands, and less so the face [19]. A linear configuration suggests koebnerization. Histologically, transepidermal channels filled with keratin, pyknotic nuclear debris, inflammatory cells, elastin, and collagen traverse an acanthotic epidermis. With maturity, elastin disappears and collagen acquires a more basophilic staining in a cup-shaped plug [42]. Elements of both elastic material and collagen may represent different stages or different types of lesions of a single pathologic process.

Although acquired perforating dermatosis is often associated with hemodialysis, some cases have occurred before initiation of dialysis [43]. The dermal theory of pathogenesis proposes that the metabolic derangements associated with chronic renal failure...
and diabetes induce superficial dermal connective tissue changes and trigger transudative elimination. Because ultrastructurally the eliminated collagen fibers show normal periodicity, the collagen might be biochemically but not morphologically altered [42,44]. Another theory proposes that the primary defect resides in the dermis. Pruritus caused by uremia or diabetes may result in epidermal injury secondary to scratching, whereas the altered blood supply of diabetic vasculopathy results in localized dermal necrosis and extrusion of dead tissue through the epidermis [42,44]. Lesions can often be reproduced by superficial scratching and tend to be distributed on trauma-prone areas [44,45]. One study of eight diabetics reported thickened (PAS) positive vessel walls in the surrounding dermis suggesting an etiologic role of microangiopathy [44]. These lesions are chronic but may heal after months if scratching and trauma are avoided. Reported treatments include topical keratolytics, topical and systemic retinoids, PUVA, UVB, topical and intralesional steroids, oral antihistamines, and cryotherapy [42,44,46]. Dialysis does not have therapeutic value. Renal transplantation has resulted in clearance of the dermatosis [43].

Lichen planus

Numerous reports have studied the association of diabetes and lichen planus, especially oral lichen planus. The prevalence of decreased glucose tolerance in patients with oral lichen planus varies widely between 1.6% and 85% [47,48,99]. In two of these studies, the prevalence of diabetes in patients with oral lichen planus did not differ from that of diabetes in the general population [47,49]. No one of these studies used the same methods and criteria used. Some studies diagnose DM at lower values than those recommended by the World Health Organization [50]. Also, 12% to 14% of the general population has abnormal glucose tolerance tests [51]. Lundstrom [51] did not support the observation that erosive lichen planus occurs in a higher percentage of diabetics with oral lichen planus than in nondiabetics [52,53]. One report found a higher frequency of lichen planus on the tongue in diabetics [52]. Fewer studies have examined the frequency of lichen planus in known diabetics. Although most reports do not differentiate the type of diabetes, the reported rates vary from 0.55% to 5.76% of diabetics having clinical and less often histologic evidence of oral lichen planus. Petrou-Amerikanou et al [50] reported a prevalence of oral lichen planus in type I diabetics of 5.76%, significantly higher than the control population. The difference in prevalence between type II diabetics and controls did not meet statistical significance. Some authors argue that what seems clinically to be oral lichen planus may actually be lichenoid reactions to drugs, such as nonsteroidal anti-inflammatory drugs, antihypertensives, and oral hypoglycemic agents [54]. Withdrawal and rechallenge of these medications in those affected have not been studied. Two studies, however, did not find a statistical association between oral lichen planus and medications known to cause lichenoid mucosal reactions [50,55].

Diabetic thick skin

Three forms of diabetic thick skin have been identified. First, diabetics in general have an asymptomatic, often unnoticed, but measurable increase in skin thickness. Second, the diabetic hand syndrome (syndrome of limited joint mobility, cheiroarthropathy, waxy skin and stiff joints, scleroderma-like syndrome, and diabetic sclerodactyly) consists of scleroderma-like skin changes in the fingers with limited joint mobility. Third, diabetic sclerodema is distinct from the self-resolving sclerodema adultorum of Buschke seen in children after a streptococcal infection. The abnormality in diabetic thick skin consists of abnormal collagen, which may be caused by hyperglycemic accelerated nonenzymatic glycosylation. These glycosylation end products lead to increased cross-linking rendering the collagen fibers resistant to degradation by collagenase, which in turn leads to excessive accumulation of abnormal collagen [56]. Other theories abound: insulin acting as a growth factor can cause overproduction of collagen [57]; decreased local oxygen pressure secondary to microangiopathy may increase collagen and glycosaminoglycan synthesis by fibroblasts [58]; and polyol accumulation caused collagen hydration [9]. Quantitative estimations of skin thickness have been determined by microscopic measurement, caliper measurement, ultrasonography, and radiologic investigation [9]. Normally, skin thickness varies based on body site, age, and sex. Typically, the skin thickens until adulthood then decreases in thickness after age 20. Several groups have found an increase in skin thickness of the forearm in insulin-dependent diabetics in comparison with age and sex-matched nondiabetic controls [59,60].

Originally described in insulin-dependent adolescent diabetics, the diabetic hand syndrome has been subsequently reported in non–insulin-dependent diabetic patients. With an 8% to 50% prevalence variation [56] the syndrome begins with stiffness of the
metacarpophalangeal and proximal interphalangeal joints, generally the fifth digit, and then progresses to the other fingers [7]. The limitation of movement initially involves active and later passive extension. Flexion limitations may occur in the end stage. Limited joint mobility can be demonstrated by inability to flatten the hand on a tabletop and by failure of palmar approximation (the prayer sign). Although the joints are not directly involved, the abnormal stiffening of the collagen in the periarticular tissue [7] leads to joint limitations in one third to one half of patients. The thickening of the skin can also be manifested by pebbling of the fingers (Huntley’s papules or finger pebbles), which are multiple grouped minute papules on the extensor surfaces of the fingers, on or near the knuckles or periungual areas [61]. Palmar fascia thickening (Dupuytren’s contracture) further complicates the diabetic hand syndrome [16,62].

Most authors have been unable to find a correlation between the development of the diabetic hand syndrome and long-term glycemic control [21,56,63,64]. Studies vary in support of the relationship between the diabetic hand syndrome and the duration of diabetes [21,56,62]. The literature suggests that this disorder is a marker for other diabetes-related microvascular complications, such as retinopathy, neuropathy, and nephropathy [9,56,62,63,65].

Diabetic scleredema is characterized by diffuse nonpitting induration of the skin with loss of skin markings over the upper back, neck, and shoulders with occasional extension to the face, arms, chest, and abdomen [8]. Although usually asymptomatic, neck discomfort and back pain may accompany severe cases of this chronic disorder, most common in poorly controlled non–insulin-dependent diabetic obese men. Although diabetic scleredema occurs in 2.5% to 14% of diabetics [66,67], 94% of adult patients with scleredema have diabetes [10]. Histologic findings include markedly thickened dermis, increased numbers of mast cells, fenestration of collagen, accumulation of hyaluronic acid, and the absence of edema and sclerosis. Potent topical and intralesional steroids, strict glucose control with an insulin infusion pump, penicillamine, intralesional insulin, bath-PUVA, low-dose methotrexate, prostaglandin E1, and pentoxifylline provided limited therapeutic success [58,68,69].

Xanthoma

Eruptive xanthomas present as sudden crops of small, discrete, yellow, erythematous-based papules over the buttocks, elbows, and knees [2]. Often presenting as a Koebner phenomenon, the lesions may be pruritic or tender [7]. Multiple xanthomas may coalesce and form tuberous xanthomas [28]. Eruptive xanthomas appear in association with elevated levels of triglyceride-rich lipoproteins, including chylomicrons and very low-density lipoprotein. The lipid changes appear in association with familial hypertriglyceridemia or insulin deficiency with uncontrolled IDDM resulting in lack of adequate lipoprotein lipase activity and impaired clearance of chylomicrons and very low-density lipoprotein [19]. Polyphagia in uncontrolled diabetes accelerates formation of very low-density lipoprotein and chylomicrons [37]. Histologically, foamy, lipid-laden histiocytes with a mixed lymphocytic and neutrophilic infiltrate accumulate in the dermis [70]. Control of the diabetes or underlying hyperlipidemia leads to xanthoma resolution.

Rubeosis facei

Although difficult to quantify, flushed face or rubeosis facei has been reported in 3% to 59% of diabetics [2]. Blond and red-haired persons appear more erythematous because of reduced cutaneous melanin to obscure the erythema. The red color may be caused by microangiopathy, increased solar sensitivity, or dehydration [27]. Tighter glucose control might improve the appearance [2].

Yellow skin

In carotenemia, the yellow pigment concentrates in areas of prominent sebaceous activity and in areas with a thick stratum corneum, such as the palms, soles, and face. Unlike jaundice the sclerae are not discolored [28]. Earlier studies reported carotenemia in more than half of diabetics and yellow skin in 10% of this population. The reports may have been due to a diabetic diet high in yellow fruits, vegetables, and butter; impaired conversion of carotene to vitamin A in the diabetic liver; or hyperlipidemia accompanying diabetes [16,37]. A recent study has found normal carotene levels in diabetic patients with yellow skin [19]. Perhaps the carotene may have disproportionate accumulation in the skin despite normal blood levels or the skin color may not be caused by carotene but by dermal collagen glycosylation with yellow end-stage glycosylation products [9].

Other

Vitiligo, Werner’s syndrome, pseudoxanthoma elasticum, lipoid proteinosis, Kaposi’s sarcoma
pigmented purpuric dermatosis, clear cell syringoma [1], and dermatitis herpetiformis [16] may be associated with diabetes. Various disease processes with cutaneous manifestations may involve secondary diabetes including hemochromatosis; hepatic porphyrias, especially porphyria cutanea tarda; and lipodystrophies, such as Lawrence-Sea syndrome and partial lipoatrophy.

**Cutaneous infections associated with diabetes mellitus**

Skin infections occur in 20% to 50% of poorly controlled diabetics, most commonly type II diabetics [2,3]. Poor diabetic control might be the cause or the consequence of the concurrent infection. The infectious disorders can be of fungal or less commonly bacterial origin [3] and may be related to abnormal microcirculation, hypohidrosis, peripheral vascular disease, diabetic neuropathy, decreased phagocytosis and killing activity, impaired leukocyte adherence, and delayed chemotaxis seen in diabetics [7,8,13].

**Bacterial infections**

Pyodermic infections, such as impetigo, folliculitis, furunculosis, carbuncles, erythema, and erysipelas, can be more severe and widespread in diabetic patients. Leg ulcer infection can rapidly progress to gangrene and amputation.

Fatal in over 50% of patients [19], malignant otitis externa caused by Pseudomonas aeruginosa, especially in elderly diabetic men, can progress to chondritis, osteomyelitis, and bacterial meningitis. Green fluorescence on Wood’s lamp examination identifies Pseudomonas toe web infection clinically similar to dermatophytosis [9].

Erythrasma, caused by gram-positive Corynebacterium minutissimum, identified with Wood’s light coral fluorescence, presents as reddish tan scaling patches of the upper inner thighs, axillae, toe web spaces, and submammary creases in obese patients. Extensive erythrasma occurs with increased frequency in diabetes [1,19].

**Fungal infections**

Little controversy exists about the increased frequency and severity of Candida infections in poorly controlled diabetics. A classic cutaneous complication in childhood diabetics and occasionally in diabetic adults, presenting as white, curdlike material adherent to an erythematous, fissured oral commissure, angular stomatitis may be caused by increased concentrations of salivary glucose [9].

Frequently recurrent, candidal paronychia presents as painful nail fold erythema, swelling, and separation from the nail margin with subsequent nail dystrophy. Pseudohyphae and spores on potassium hydroxide preparation support a candidal diagnosis. Purulent drainage may indicate secondary bacterial involvement. Treatment involves drainage of abscess, control of the blood sugar, keeping the digits dry, and topical antifungal solutions. Less common than paronychia, occlusion and retention of moisture lead to interdigital infections most commonly between the third and fourth fingers (erosio interdigitale blastomycetica) or between the fourth and fifth toes.

In women, Candida commonly infects the inframammary area and the genitalia with severe pruritus vulvae. Genital infections in elderly uncircumcised men with diabetes include balanitis and phimosis.

Authors sustain [71–73] and negate [74–76] the correlation between the prevalence of dermatophytosis and blood levels of glucose. Because maceration and skin breaks can serve as portals of entry for bacteria leading to cellulitis and potentially serious limb-threatening infections, tinea pedis should be aggressively managed in diabetics.

**Cutaneous manifestations of diabetic complications**

**Diabetic foot**

Foot ulcerations account for significant morbidity and mortality in the diabetic population and are responsible for 70% of annual US lower limb amputations. The economic impact of medical and surgical therapy, rehabilitation, loss of work, and mortality is staggering [77–79]. An understanding of the pathophysiology of diabetic foot complications results in appropriate therapy, healing, and the avoidance of many amputations. Adequate blood supply should preclude amputation. Proper evaluation of diabetic feet identifies peripheral neuropathy (60% to 70%), peripheral ischemic vascular disease (15% to 20%), and combined clinically significant neuropathy and vascular disease (15% to 20%) as the cause of ulcerations [80,81]. If a surgical revascularization procedure can correct the ischemic state, adherence to principles of wound therapy effect healing. In a setting of diminished or absent sensation, foot deformity, and adequate blood supply, neuropathic ulcers usually heal within weeks if treated with aggressive debridement [82] and offloading with
various devices, or most effectively with a total contact cast [83,84]. Any use of topical growth factors or bioengineered skin grafts cannot replace a needed revascularization procedure, debridement, and ulcer offloading [85,86]. Because of the prevalence of bacterial colonization of foot ulcerations, the need for antibiotic therapy rests on clinical evaluation and judgment [70]. Osteomyelitis can often be cured surgically with rongeur and excision of infected small foot bones [87,88]. Prevention of foot complications remains paramount through daily foot inspection; foot care guidelines; and prevention of pressure, friction, and callus formation with appropriate footwear [89–91].

**Diabetic gustatory sweating**

In response to eating certain foods, long-standing diabetics with neuropathy and nephropathy experience gustatory sweating in areas supplied by the superior cervical ganglion on the face and neck. This may be caused by axonal degeneration and aberrant sprouting of nerve fibers [92]. Gustatory sweating may resolve postrenal transplant suggesting an etiologic role of nephropathy. Effective treatment consists of oral anticholinergics, clonidine, and topical glycopyrrolate [92].

**Cutaneous reactions to diabetic treatment**

**Insulin**

Insulin allergy may be local or systemic and usually occurs within the first month of insulin therapy. Erythematous or urticarial pruritic nodules at the site of the injection, may appear immediately, within 15 minutes to 2 hours of injection, or delayed with onset 4 or more hours after injection [19]. Allergic reactions may be caused by impurities in the insulin preparation; to beef or pork proteins; to the insulin molecule itself; to additional polypeptides (proinsulin); to preservatives (parabens); or to additives (zinc) [19,93]. A local reaction has also been reported in a patient allergic to latex caused by small amounts of latex rubber antigens in the insulin injection materials (insulin vial and syringe) [94]. The highly purified or recombinant insulins have reduced allergy prevalence to 0.1% to 0.2% [2]. Treatment may be unnecessary because of spontaneous resolution. The patient’s technique should be observed to ensure that the injection is not intradermal. Substitution of a more purified insulin is the treatment of choice. Systemic allergic reactions to insulin manifested as generalized urticaria and rarely anaphylaxis may necessitate discontinuation of insulin for other forms of therapy or may require desensitization.

Lipoatrophy and lipohypertrophy (lipodystrophy) can coexist in the same patient. Lipoatrophy presenting as circumscribed depressed areas of skin at the insulin injection site 6 to 24 months after starting insulin and occasionally at distant sites [8,16] seems to occur more in children and women in areas of substantial fat deposits, such as the thighs [16]. The cause may be related to lipolytic components of the insulin preparation or an immune complex–mediated inflammatory process with release of lysosomal enzymes [1]. Other theories include cryotrauma from refrigerated insulin; mechanical trauma caused by angle of injection; contamination with surface alcohol [95]; and local hyperproduction of tumor necrosis factor-α from macrophages induced by injected insulin [96]. Because duration of injected insulin deposition may also be a complicating factor, Murao et al [96] suggest substituting rapidly acting insulin to avoid lipoatrophy. Spontaneous improvement after rotating injection sites is rare but has been reported. Use of purified and recombinant human insulin has resulted in decreased lipoatrophy [8]. Lipohypertrophy presenting as soft dermal nodules, clinically resembling lipomas, at the site of frequent injections may be a response to the lipogenic action of insulin [2]. Chronically injected sites become hypoesthetic; however, absorption from these areas is very erratic [10]. Lipohypertrophy can be treated and prevented by injection site rotation. Other local cutaneous complications of insulin injection include keloids, hyperkeratotic papules, purpura, and localized pigmentation [27].

**Oral hypoglycemic agents**

Most cutaneous reactions to oral antidiabetic medications have been reported with the first-generation sulfonylureas, such as chlorpropamide and tolbutamide. One percent to 5% of patients taking sulfonylureas develop cutaneous reactions [2] within the first 2 months of treatment, most commonly maculopapular eruptions that often disappear despite continuation of the drug [2]. Other reported cutaneous reactions include generalized erythema, urticaria, photosensitivity, lichenoid eruptions, erythema multiforme, exfoliative dermatitis, and erythema nodosum [97]. In 10% to 30% chlorpropamide may cause a disulfiram-like reaction consisting of marked flushing, headache, tachycardia, and shortness of breath beginning 15 minutes after alcohol consumption and gradually resolving over the following hour [16].
This reaction pattern seems to be inherited in an autosomal-dominant pattern [1]. With increasing use, second-generation sulfonylureas, such as glyburide, glipizide, and glimepiride, have also been reported in association with cutaneous reactions. The most frequent reactions associated with glyburide include erythema, exanthems, photosensitivity, pruritus, and urticaria [97]. Similar reactions have also been reported with metformin. Reports of cutaneous reactions are still limited with the newer classes of antidiabetics including acarbose and rosiglitazone [97]. One case of erythema multiforme caused by acarbose has been reported [98].

Summary

Diabetes is a common disease with many cutaneous manifestations encountered by dermatologists. Diabetes and the skin may be linked by association (eg, necrobiosis lipoidica); infection; diabetic complication (eg, neuropathic ulcer); or treatment reaction. Review of recent studies and reports focuses on pathogenesis and treatment of these many diabetic cutaneous changes.

References


