Diabetes is the most common endocrine disorder, affecting 8.3% of the population (1). Skin disorders will be present in 79.2% of people with diabetes (2). A study of 750 patients with diabetes found that the most common skin manifestations were cutaneous infections (47.5%), xerosis (26.4%), and inflammatory skin diseases (20.7%) (2). Individuals with type 2 diabetes are more likely than those with type 1 diabetes to develop cutaneous manifestations. Cutaneous disease can appear as the first sign of diabetes or may develop at any time in the course of the disease. This review provides a brief overview of skin conditions that primary care providers (PCPs) may encounter when treating patients with diabetes.

Conditions Associated With Insulin Resistance

Acanthosis Nigricans

Acanthosis nigricans (AN) is likely the most readily recognized skin manifestation of diabetes (3). It is present in up to 74% of obese adult patients and can be predictive of the existence of hyperinsulinemia (4). The presence of AN is a prognostic indicator for developing type 2 diabetes. There is also a possible genetic predisposition or increased sensitivity of the skin to hyperinsulinemia in different ethnic groups. At the same obesity rates, prevalence of AN is lowest in whites (0.5%), higher in Hispanics (5%), and even higher in African Americans (13%) (5).

AN is a hyperpigmented velvety thickening of skin folds, presenting predominantly in the neck, axilla, and groin areas (Fig. 1). Possible additional presentations could include skin tags and hyperkeratosis. Heredity, obesity, endocrine disorders, certain drugs, and malignancy are associated with AN. Benign AN type 2 is related to type 2 diabetes, and pseudo-AN type 3 is associated with the metabolic syndrome. Type 2 diabetes-related AN has an insidious onset and initially presents as hyperpigmentation. Both underlying conditions present with insulin resistance (3). Children aged 8–14 years who had AN were found to have insulin resistance, and 25% had disturbed glucose metabolism at the time of the study (6). Microscopically, AN presents as papillomatosis and hyperkeratosis (epidermis in irregular folds, exhibiting various degrees of acanthosis).

Treatment consists of treating the underlying cause. Significant weight loss resolves AN type 2 and type 3.
Topical or systemic retinoids and topical retinolytics may be used to manage symptoms (7).

**Acrochordons**

Acrochordons, or fibroepithelial polyps, skin tags, and soft fibromas, are pedunculated outgrowths of normal skin on a narrow stalk, most commonly located on the eyelids, neck, axillae, and groin (Fig. 1). They are found in ~25% of adults, and their number and prevalence increases with age (6). Familial history, obesity and AN have been related to acrochordons; the relationship between hyperinsulinemia and skin tags has been well established (8).

Acrochordons are benign lesions, but may become symptomatic with abrasion or necrosis. Red or black skin tags are the result of twisting of the base, which cuts off the blood supply. The diagnosis of acrochordons is made by clinical appearance. Rarely, they may look suspicious for malignancy and should be sent for histological testing. Treatment is usually cosmetic or for cases involving irritation. Excision may be performed with forceps, fine-grade scissors, cryosurgery with liquid nitrogen, or electrodessication (9).

**Diabetic Dermopathy**

Population studies from Sweden demonstrate that diabetic dermopathy (DD) affects 33% of patients with type 1 diabetes, 39% of patients with type 2 diabetes, and 2% of control subjects (9). However, a more recent study found that DD is present in only 0.2% of people with well-controlled type 2 diabetes (10).

This condition presents as small (<1 cm), well-demarcated, atrophic depressions, macules, or papules on the prebuttocks, and is considered to be a sign of insulin resistance (Fig. 2). Lesions heal and disappear within 1–2 years on their own, leaving atrophic hypopigmentation at the site of origin (3). Little is known about the relationship of DD to diabetes. On cadaveric skin biopsy, 4 of 14 samples demonstrated moderate to severe arterial wall thickening, and 11 of 14 samples demonstrated mild basement membrane thickening. Stain findings suggested the presence of hemosiderin and melanin depositions in the epidermis of affected patients (11).

No current treatment exists or is necessary for DD, which is asymptomatic and does not lead to morbidity (3).

**Eruptive Xanthoma**

Eruptive xanthoma (EX) presents on the buttocks, elbows, and knees as sudden onset crops of yellow papules with an erythematous base (Fig. 3) (12). EX is rare and occurs more often in patients with poorly controlled type 2 diabetes. The sudden appearance of EX can be worrisome to patients and may prompt a visit to the physician.

These lesions can be the first sign of diabetes. The decrease in lipoprotein lipase activity seen in insulin-dependent diabetes results in an accumulation of serum triglycerides. Occasionally, when the serum triglyceride level reaches 2,000 mg/dL, lipids will deposit in the skin (13). Cutaneous presentation is associated with hypertriglyceridemia types I, III, IV, and V or secondary hyperlipidemias. Types I, III, IV, and V show high concentrations of very-low-density lipoprotein and chylomicrons. EX lesions tend to resolve spontaneously within weeks (14).

Diagnosis can be made clinically and confirmed with a biopsy of the lesions. It is important to obtain fasting lipid levels at presentation. People with EX are at higher risk from hypertriglyceridemia of early coronary artery disease and pancreatitis (13). Treatment should aim to lower the triglyceride concentration with diet modification and systemic medications to reverse this condition and decrease complications (15,16).

**Rubeosis Facei**

Rubeosis facei (RF), a relatively common skin manifestation associated with diabetes, is a microangiopathic complication. It may go unnoticed by patients and physicians. However, if recognized, it should alert physicians to look for other microangiopathic complications such as retinopathy (17). RF presents as a flushing to the face. This condition is seen in 3–5% of people with diabetes. In a study of 150 participants comparing facial redness association with diabetes, Gitelson et al. (18) showed that 59% of patients with diabetes had markedly red faces compared to slightly red or not red (21 and 20%, respectively).

The appearance of RF correlates with poor glucose control. No treatment is needed. Strict glycemic control can improve the appearance and prevent complications of microangiopathy in other organ systems (12,19).

**Epidermal Necrolysis/Stevens-Johnson Syndrome**

Stevens-Johnson syndrome is a rare mucocutaneous necrotizing condition diagnosed in 1–6 cases per million people annually worldwide (20). A more severe form called toxic epidermal necrolysis is diagnosed at a rate of 0.4–1.2 cases per million people per year (21). Because of their similar etiology, pathogenesis, and clinical and histological presentation, it has been
Necrobiosis lipoidica (NL) is rare, appearing in 0.3–1.6% of people with type 1 diabetes, more often in women than men (12,32). Typical lesions of NL occur in young and middle-aged patients and present most commonly on the pretibial skin as irregular, painless ovoid plaques with a yellow atrophic center and a red to purple periphery. The lesions are usually multiple and bilateral. Lesions may ulcerate spontaneously or from trauma (33,34). Of the patients with NL, 11–65% have type 1 diabetes at the time of cutaneous diagnosis (34). Ninety percent of people with NL who do not have diabetes eventually develop diabetes (mostly type 1 diabetes) (12). Glycemic control has no effect on the course of NL (16).

NL is a benign condition, and dermatology referral is not usually necessary. The cause of NL is currently unknown. Proposed causes are localized trauma, microangiopathy, immunoglobulins and fibrin deposition, and metabolic changes (32,35). Although NL is benign, its appearance is cosmetically distressing to the patient (Fig. 4).

The mainstay of treatment is currently steroids, either topical, intralesional, or, rarely, systemic. Steroids are cost-effective and have low side-effect profiles. Steroid use is beneficial to control the initial erythema in early lesions but fails to help with the atrophic component of the lesions and can worsen atrophy. Stockings are advised to help with stasis changes and protect from trauma (35). Other treatments that have been used include pentoxifyllin, cyclosporine, ticlopidine infliximab, and thalidomide. Some case reports have shown benefit from nicotinamide, clofazimine, chloroquine, and topical tretanoin. These later treatments do require dermatology referral to manage medications and potential side effects (32,36).

Vitiligo
Vitiligo affects 0.3–0.5% of world population, making it the most common depigmenting disorder. Patients present with patches of depigmentation of skin and hair (Fig. 5).

Possible etiologies are both environmental and polygenetic. This condition affects males and females equally (37). Out of several subtypes, generalized vitiligo is most common. It is associated with autoimmune diseases in 20–30% of cases. The most common associations are with Hashimoto’s thyroiditis, Grave’s disease, rheumatoid arthritis, psoriasis, type 1 diabetes (usually adult-onset), pernicious anemia, systemic lupus erythematosus, and Addison’s disease (38). A 2009 study of 50 patients with type 1 diabetes reported that 4% of subjects had vitiligo (39). Genetic vitiligo (GV) is most often a gradually progressive disorder and is unresponsive to treatment. However, some cases do stop progressing. GV complications are long duration,
Bullosis Diabeticorum

Bullosis diabeticorum, or diabetic bullae, are seen in 0.5% of individuals with type 1 diabetes. This condition is seen more often in men and in those with longstanding peripheral neuropathy. The lesions arise spontaneously and are primarily on the dorsa and the sides of the lower legs and feet. Occasionally, they are seen on the forearms and hands. The lesions present as clear bulla on non-inflamed bases. They are painless and contain sterile fluid. Lesion size can range from a few millimeters to a few centimeters (16).

Blister pathology is currently unknown. Diabetic bullae typically appear in individuals who have had type 1 diabetes for many years. However, this condition may be the first sign of diabetes (41). Lesions resolve on their own in 2–5 weeks. Differential diagnosis includes bullous pemphigoid, which can be ruled out by submitting a biopsy of the lesion for direct and indirect immunofluorescence. The lesions resemble those in acquired epidermolysis bullosa, porphyria cutanea tarda, autoimmune or impetiginous bullae, erythema multiforme, or drug eruption (42). Dermatologists often make the diagnosis of diabetic bulla; after diagnosis, this condition can be managed by PCPs.

The treatment is focused on infection prevention (19). If the bullae become large and symptomatic, they can be aspirated, leaving the roof intact to protect the skin barrier (16). Individuals may use saline compresses for symptomatic relief. Topical antibiotics or steroids are generally not necessary (41).

Other Diabetes-Related Conditions

Psoriasis

Psoriasis is a chronic, inflammatory, polygenic skin disorder with environmental triggers such as trauma, medications, and infection. Psoriasis is characterized by erythematous scaly papules and plaques with pustular and erythrodermic eruptions occurring most commonly in areas of friction such as scalp, elbows, knees, hands, feet, trunk, and nails. Koebner phenomenon is a well-documented factor, in which a plaque develops on the site of the injury. Histologically, Koebner phenomenon presents with alterations in epidermal growth (elongated rete ridges with dilated blood vessels, thinned suprapapillary plate, and differentiation), intermittent parakeratosis, and multiple biochemical, immunological, and vascular abnormalities (e.g., lymphocyte and neutrophil infiltration).

This condition can develop at any age, with the most common onset between 15 and 30 years of age; it is uncommon in people <10 years of age. It affects 2–3% of the U.S. population. Approximately 9% of people with diabetes (type 1 or type 2) has psoriasis (42). Recent research shows that psoriasis may raise predisposition for developing diabetes mellitus, just as it does for heart attack and stroke. A 13-year study with 52,000 participants concluded that people with psoriasis have a 49–56% greater risk of developing type 2 diabetes later in life (43).

Most people with psoriasis will be treated by a dermatologist. Treatment consists of topical and systemic immunomodulators, as well as ultraviolet light and laser application. Topical treatments are effective in most cases; however, they carry a 40% adherence rate because of time-consuming application and cosmetic inappropriateness (44). Both cream and ointment should be prescribed. Phototherapy with ultraviolet A, ultraviolet B, and psoralen has been used for several decades and has shown good response in mild cases (45).

Lichen Planus

Lichen planus is an uncommon disorder affecting <1% of the general population. Onset is common in middle age (30–60 years of age). However, the prevalence of lichen planus in people with type 1 or type 2 diabetes has been noted to be 2–4% (39,46). Lichen planus may affect the skin (termed “cutaneous,” with several variants), the oral cavity (“oral”), the genitalia (“vulvar” or “penile”), the scalp (“lichen planopilaris”), the nails, or the esophagus (47,48).

Lichen planus presents as grouped, symmetric, erythematous to viola-
PRACTICAL POINTERS

Xerosis
Xerosis is another name for dry skin. It is the second most common skin manifestation in people with diabetes. In a study of 100 patients with diabetes and skin lesions, xerosis was present in 44% of the patients (50). Patients with renal disease also frequently suffer from xerosis.

No referral to a dermatologist is necessary for xerosis. PCPs should educate patients about the importance of skin hygiene, including applying fragrance-free creams or lotions within 3 minutes of bathing to trap moisture within the skin.

Scleroderma Diabeticorum
Scleroderma diabeticorum is a condition of thick, indurated, erythematous plaques occurring on the upper back and neck. Lesions may have erythema. This condition is seen in 2.5–14% of individuals with diabetes (51). The condition is more common in obese middle-aged men with type 2 diabetes. Patients with scleroderma diabeticorum are often asymptomatic; however, neck and back pain may occur. The diagnosis is often made clinically, although a definitive diagnosis is confirmed by skin biopsy.

The pathogenesis of scleroderma diabeticorum is thought to be linked to increased stimulation of insulin and nonenzymatic glycosylation of collagen. This causes increased collagen cross-linking, rendering the collagen fibers resistant to degradation by collagenase and leading to increased amounts of collagen.

Treatments have showed limited benefits. Some treatment options include steroids, methotrexate, and ultraviolet light phototherapy (15,52). Differential diagnosis includes Scleroderma Buschke, also associated with type 1 diabetes. Scleroderma Buschke presents as thickening mainly on the neck, shoulders, and upper limbs, often after an upper-respiratory infection. This condition clears spontaneously in a period of months or years. Women are affected more often than men. Scleroderma diabeticorum involves the fingers, hands, and trunk. It is in the family of diabetic thick skin called morgue and is the most severe, systemic scleroderma (53).

Granuloma Annulare
Granuloma annulare (GA) presents as erythematous to flesh-colored papules coalescing to form an oval or ring lesion. GA often presents asymptptomatically but can cause pruritus or a burning sensation (54). The association between granuloma annulare and diabetes is controversial. One retrospective study showed a 12% association between GA and diabetes (55). Another study reported diabetes in 21% of 100 cases of generalized granuloma annulare (GGA) and in 9.7% of 1,350 cases of localized GA (56). Skin lesions may often precede diabetes. Struder et al. (55) suggest that patients with recurrent localized granuloma annulare or the disseminated form be given a glucose tolerance test.

The pathogenesis of GA is currently unknown. Treatment options are topical steroids, intralesional steroids, isoretinoin, dapsone, antimalarias, and phototherapy. Untreated lesions may spontaneously regress; this is more common in the localized form of GA than in the disseminated form (57). Localized forms can be treated easily and followed by PCPs. Recurrent GA or disseminated GA can be worked up by PCPs and referred to a dermatologist. GGA tends to be idiopathic. However, it has been associated with diabetes and with diseases such as autoimmune thyroiditis, HIV, hepatitis C, Epstein-Barr virus infection, sarcoidosis, and internal malignancies (58).

Acquired Perforating Dermatosis
Acquired perforating dermatosis presents as dome-shaped papules and nodules with hyperkeratotic plugs. This condition is characterized by...
the transepidermal elimination of some component of the dermis. The cutaneous perforating disorders have classically been divided into four types: elastosis perforans serpiginosa, reactive perforating collagenosis, perforating folliculitis, and Kyrle’s disease. Perforating disorders have been associated with chronic renal failure, dialysis, and diabetes. Acquired perforating dermatitis is seen in both type 1 and type 2 diabetes (15,16,59). In most cases, the renal disease is a complication of diabetic nephropathy (60). The lesions of acquired perforating dermatosis are most commonly seen on the trunk and extremities and tend to be pruritic.

It has been thought that the mechanism of action may be derived from epidermal trauma, a foreign-body reaction to the collagen in the dermis, or metabolic products from uremia (59,61). Dialysis has not shown therapeutic value, but renal transplant has been shown to be effective in clearing the lesions (60). Treatment options include avoidance of scratching, topical or systemic steroids, phototherapy, retinoids, and antihistamines.

**Onychodystrophy**

Onychodystrophy presents as excessive nail thickening and deformity, which may cause accumulation of debris and subsequent infection of the toe that should be treated as a diabetic ulcer. Poorly fitting shoes may cause repeated trauma and worsening of the injured site (61). In patients with diabetes, onychodystrophy is the result of poor peripheral circulation and diabetic neuropathy. The condition itself may cause diabetic foot ulcers (62). Proper nail care, well-fitting shoes, and immediate attention to nail infections are important.

**Periungual Telangiectasias**

Periungual telangiectasias present as nail fold erythema, dilated blood vessels visible to the naked eye, fingertip tenderness, and thick cuticles. Telangiectasias arise in the nail beds of people with diabetes after loss of capillary loops and dilation of remaining capillaries. The condition is present in up to 49% of people with diabetes (63). Some patients also experience fingertip tenderness. No treatment is necessary for this condition.

**Infections Associated With Diabetes**

**Cutaneous Infections**

Infections form the largest group of cutaneous conditions affecting people with diabetes. In a 2009 study of 50 patients, 55% of those with diabetes had infectious skin manifestations at some time (39). Another study reported a 61% prevalence rate in skin infections in people with diabetes (64). Cutaneous infections include candidiasis, dermatophytosis, and bacterial infections. These are described in more detail below.

**Candidiasis**

Mucocutaneous candidiasis is caused most commonly by Candida albicans and presents as red plaques with characteristic white adherent exudate and satellite pustules. The risk of infection is increased with hyperglycemia, which favors Candida proliferation. Candidal vulvovaginitis is the most common of all cases, and perianal candidiasis is also common in both males and females. Other presentations include thrush (infection of oral mucosa and perleche), angular cheilitis, intertrigo (infection of skinfolds and erosio interdigitalis blastomysetica chronica), finger web space infection, paronychia (infection of soft tissue around the nailplate), and onychomycosis (infection of the nail) (3). Common cutaneous fungal infections are summarized in Table 1.

Rarely, critically ill patients with diabetic ketoacidosis (DKA) may be diagnosed with mucormycosis, an acute, severe, soft-tissue infection caused by Mucor, Rhizopus, and Absidia species. Saprophytic fungi prefer the low pH environments seen during DKA and thrive in hyperglycemia. Some fungi also utilize ketones as nutritional substance (3).

An estimated 50–75% of cases of rhinocerebral mucormycosis occur in patients with diabetes (65). Mucormycosis is progressive and poorly responds to systemic antifungals. Treatment options include itraconazole, fluconazole, amphotericin B, and voriconazole. This condition is often fatal.

**Dermatophytosis**

Tinea or dermatophytoses are superficial infections of the skin, hair, and nails by fungus. Tinea corporis, tinea pedis (Fig. 6), and onychomycosis (Fig. 7) are common dermatophyte infections.
infections encountered in people with diabetes. In a 2013 study of 76 patients with tinea corporis, the main predisposing factor was xerosis (66). In a 2001 study of 171 people with diabetes compared with 276 control subjects, the most common infection in people with diabetes was tinea pedis, followed by distal subungual onychomycosis (65). This study did not show a correlation between dermatophytosis and duration or type of diabetes or its complications.

Trichophyton rubrum, Trichophyton mentagrophytes, and Trichophyton tonsurans are the most common dermatophytes. Because dermatophyte infections are so common in the general population, no dermatology referral is necessary. Treatment consists of topical antifungals or systemic antifungal medication. Table 2 summarizes common fungal infections and the topical and oral antifungal therapies used to treat them.

**Bacterial Infections**

Cutaneous bacterial infections are more common, as well as more severe, in people with diabetes. Diabetic foot ulcers are the leading type of morbidity in diabetes. They develop because of decreased sensation from diabetic neuropathy and unrecognized injury, with subsequent infection. White blood cell dysfunction resulting from increased glucose levels allows bacteria to proliferate. Staphylococcal folliculitis or skin abscesses are among the most common bacterial infections in uncontrolled diabetes. They respond well to antibiotics and surgical drainage. *Pseudomonas aeruginosa* is another common diabetic foot ulcer organism.

External ear canal infection caused by *Pseudomonas aeruginosa* is also frequent in people with diabetes. Pseudomonads thrive in moist...
environments full of oxygen. Lesions can be recognized by characteristic green-blue pigment, as well as fluorescence with Wood’s lamp application. Microscopically, pseudomonads are identified as gram-negative rods. Patients may present with otalgia, otorhea, hearing loss, and edema and erythema of the external ear canal.

Treatment consists of drying the area and applying topical antibiotics to uncomplicated infections. Malignant external otitis media requires immediate recognition and systemic antibiotics such as fluoroquinolones, plus an antipseudomonal antibiotic (e.g., antipseudomonal penicillin, antipseudomonal cephalosporin, monobactam, aminoglycoside, or carbapenem). Higher doses and surgical debridement are required to prevent spreading of the infection to bone and the nervous system (67). Urgent treatment of otitis externa is important because of its potential to rapidly spread to bone and cranial nerves, which could lead to mortality (68).

Summary
Diabetes is the most common endocrine disorder, and many cutaneous disorders are associated with diabetes. Knowledge of these skin conditions can aid PCPs in the diagnosis of diabetes and the treatment of its associated skin conditions. Most conditions can be managed by PCPs, but referral to a dermatologist may be warranted in some cases. As the incidence and prevalence of diabetes increases, skin manifestations associated with diabetes will become more common. Thus, PCPs should familiarize themselves with their presentation and treatment.

Duality of Interest
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