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 retinoytics 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 electrodesiccation (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 pretibia 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 deposits 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 faciei (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
In most cases, EN begins on first exposure to an inciting drug, within 8 weeks of the first dose. The dipeptidyl peptidase-4 inhibitor sitagliptin has been associated with cases of Stevens-Johnson Syndrome (23). It could present with fever, headache, rhinitis, cough, malaise, burning eyes, and dysphagia (24). In 1–3 days, EN progresses to mucocutaneous ulcers, necrosis and detachment of epidermis, severe stomatitis, and ocular involvement (25). Initial dusky red, purpuric macules are distributed symmetrically over the face, upper trunk, and proximal limbs, with distal limbs relatively spared (26). These lesions progressively coalesce and develop dark necrotic centers as they spread down the trunk. Nickolsky’s sign—displacement of epidermis with lateral pressure—is positive over the blistering epidermis.

The pathophysiology of EN is under-investigated. Presence of a strong cell-mediated immunological response involving natural killer cells and CD8+ T lymphocytes specific for the causative agent has been noted. This reaction also involves monocytes and granulocytes (27). Other factors that amplify the reaction are still being investigated. The end result of hypersensitivity is a full-thickness keratinocyte apoptosis of the epidermis and mucous membranes (28). Although drugs and their components are the most common etiologies, viruses, *Mycoplasma pneumoniae*, and immunizations are also suspected. More than 100 medications have been identified as causes of EN (29). If a person develops EN while on sitagliptin, the drug’s manufacturer recommends discontinuing therapy as soon as a hypersensitivity reaction is noted (30).

EN is a life-threatening emergency. Current treatments include withdrawal of all medications that would not be life-threatening. Discontinuation of medications started in the past 8 weeks is particularly important. EN is treated supportively as a massive burn, with emphasis on preservation of intact skin and supportive symptomatic measures. Patients presenting with EN should be transferred to a qualified intensive care unit as soon as possible (31). Immunosuppressive drugs have not proven to be helpful (24).

**Conditions Associated With Type 1 Diabetes**

**Necrobiosis Lipoidica**

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 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 afflicts 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,
Koebner phenomenon, leukotrichia, and mucosal involvement (37).

Dermatological therapy attempts to reduce T-cell response and induce melanocyte migration and regeneration. Corticosteroids with ultraviolet B or calcineurin inhibitors or systemic psoralen and ultraviolet A (PUVA) light are first-line treatments. Calcipotriol, topical PUVA, excimer laser, corticosteroid pulse therapy, and surgical melanocyte grafting are some of the treatment options. These treatments are long and complicated by numerous side effects. Use of sunscreen is recommended but also controversial because of ultraviolet B stimulation of melanocytes and the possibility of repopulation, as well as photo-adaptation of vitiligo-affected skin. Moderate exposure to sun is recommended.

The psychosocial impact of vitiligo can be substantial, and patient support groups are available. Numerous nontraditional treatments are attempted by patients but should be investigated for safety before administration (40).

Bullous Diabeticorum

Bullous 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).

Blisters 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 epidermolytic bullous, 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 purulent 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-
ceous, flat-topped, polygonal papules distributed mainly in flexural aspects of arms and legs and rarely can appear on the trunk (“Blaschkoid” or “zosteriform”) and inverse (“intertriginous”) (48). Variants may include ulcerative and perforating types. Koebner phenomenon is common, and pruritus associated with lichen planus is intense and heals with post-inflammatory hyperpigmentation.

Clinically, cutaneous lichen planus presents as flat-topped, violaceous papulosquamous eruptions on the skin. It is classically described as the “four Ps”: pruritic, purple (violaceous), polygonal, and papules or plaques. Papules may be isolated and a few millimeters in diameter or may coalesce to form larger plaques (48). Fine white lines may be visible on the surface of papules or plaques and are known as “Wickham’s striae.” Diagnosis can be made based on clinical findings. If clinical recognition is questionable, a biopsy is indicated. Etiology of the condition is unknown. It is suspected that CD8+ T cells and a Th1 immune response (cell-mediated mechanism against keratinocytes) is involved (49).

Most cases of lichen planus will be managed by a dermatologist. Treatment of cutaneous lichen planus is focused on pruritus control (47). The potency of topical steroids used depends on the site involved. On the trunk and extremities, high- to low-potency corticosteroids are indicated, whereas on the face and intertriginous areas, medium- to low-potency ointments are used. This is because of steroid-induced atrophy. Treatment efficacy should be checked in 3 weeks. With generalized involvement, light therapy may be added to the treatment plan. Intraleisonal corticosteroids are applied to thicker lesions (49). Systemic glucocorticoids, phototherapy with PUVA and ultraviolet B, and oral acitretin can be beneficial in people who are not candidates for topical steroid therapy. Few studies have been conducted on treatments because of the typical spontaneous remission of lichen planus (47,48).

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 GA is currently unknown. Treatment options are topical steroids, intralesional steroids, isotretinoin, dapsone, antimalarials, 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...
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 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.

TABLE 1. Common Cutaneous Fungal Infections

<table>
<thead>
<tr>
<th>Infection</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Candidal vulvovaginitis</td>
<td>Infection of vaginal mucosa</td>
</tr>
<tr>
<td>Perianal candidiasis</td>
<td>Infection of perineum and perianal area</td>
</tr>
<tr>
<td>Thrush</td>
<td>Infection of the oral mucosa</td>
</tr>
<tr>
<td>Perleche</td>
<td>Infection of labial commissures of mouth angles</td>
</tr>
<tr>
<td>Intertrigo</td>
<td>Infection of skinfolds</td>
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<tr>
<td>Erosion interdigitalis blastomysetica chronica</td>
<td>Infection of finger web space</td>
</tr>
<tr>
<td>Paronychia</td>
<td>Infection of the soft tissue around the nail plate</td>
</tr>
<tr>
<td>Onichomycosis</td>
<td>Infection of the nail</td>
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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, otorrhea, 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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