# Cutaneous Manifestations in Diabetes Mellitus

35

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**Key Points**

- The most common skin manifestations in diabetes are cutaneous infections, xerosis, and inflammatory skin diseases
- Necrobiosis lipoidica may be viewed as the prototype of a diabetes-associated skin disease
- Granuloma annulare has a marked association with systemic diseases, particularly diabetes and rheumatic diseases
- Acanthosis nigricans has better outcomes with weight reduction and optimal blood glucose control
- Foot ulcerations are one of the most serious and disabling complications of diabetes and are the most common cause of nontraumatic foot amputation
- Patients with diabetes are more prone to infections than healthy individuals

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## General Epidemiology

Diabetes mellitus (DM) is a metabolic disorder affecting various organ systems, including the skin [1]. It involves a relative or complete insulin deficiency that leads to alterations in glucose, fat, and protein metabolism. In type 1 DM, insulin insufficiency results from a gradual, immune-mediated destruction of pancreatic β islet cells [2]. It is characterized by abrupt onset, insulin deficiency, a tendency to progress to ketoacidosis even in the early stages, and a dependence on exogenous insulin for survival [3]. In contrast, in type 2 DM, chronic hyperglycemia mainly results from end-organ (particularly the liver and skeletal muscles) insulin resistance. This condition is accompanied by a progressive, age-related decrease in pancreatic insulin release. A genetic predisposition and a strong association with obesity exist for type 2 DM [2].

DM is a rapidly growing pandemic. Around 415 million people worldwide, or 8.8% of adults, are estimated to have diabetes. If these trends continue, by 2040 some 642 million people, or one adult in ten, will have diabetes. Approximately 5.0 million adults died from diabetes in 2015, equivalent to one death every 6 s [4]. In addition, DM is the leading cause of new cases of blindness among adults [5].



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**Table 35.1** Dermatologic manifestations related to diabetes mellitus

| Specific | Nonspecific | Complications |
|---|---|---|
| Diabetic dermopathy | Skin tags | Diabetic foot syndrome |
| Necrobiosis lipoidica | Rubeosis faciei | Cutaneous infection |
| Granuloma annulare | Yellow skin | Diabetic hand syndrome |
| Acanthosis nigricans | Xerosis | |
| Diabetic bullae | Pruritus | |
| Scleredema diabeticorum | Psoriasis | |
| Kyrle's disease | Vitiligo | |
| | Lichen planus | |

Cardiovascular disease, kidney failure, and limb amputation also occur more often as a result of DM than from any other disease in the majority of high-income countries [4].

Complications related to diabetes are the result of metabolic, hormonal, environmental, and genetic factors manifesting in every organ system. The cutaneous manifestations range widely in severity (from mundane cosmetic concerns to life threatening), prevalence, and treatment response [6].

Skin disorders may be present in 30–79.2% of people with diabetes, and can occur as the first sign of diabetes or may develop at any time over the course of the disease [7–9]. The most common skin manifestations are cutaneous infections (47.5%), xerosis (26.4%), and inflammatory skin diseases (20.7%) [10].

The prevalence of cutaneous disorders seems to be similar between type 1 DM and type 2 DM patients, but type 2 DM patients develop more frequent cutaneous infections and type 1 DM patients manifest more autoimmune-type cutaneous lesions [1].

In this chapter, diabetes-related skin disorders are divided into those specifically or nonspecifically related to diabetes. In addition, skin complications associated with diabetes are also discussed (Table 35.1).

## Skin Manifestations

## Diabetes-Specific Skin Conditions

### Diabetic Dermopathy

Diabetic dermopathy, also known as shin spots, is considered one of the most common cutaneous lesions in diabetes, although it is not pathognomonic of DM [1]. It affects as many as 30–60% of DM patients [2].

#### Etiopathogenesis

The etiopathogenesis of diabetic dermopathy is unknown but probably represents a post-inflammatory lesion in poorly vascularized skin or a manifestation of microangiopathy [11].

#### Clinical Presentation

Lesions begin as multiple, discrete, erythematous, coin-shaped macules or annular rings and are prevalent on the shins [2]. Of unknown etiology, its progression is variable and it may fade slowly, leaving a pigmented area without atrophy, or it may resolve completely, with new lesions developing contiguously [5]. It is a dynamic process, with lesions at varied stages present at the same time [6]. The occurrence of lesions correlates with retinopathy, nephropathy, and neuropathy [2, 5]. Macules are asymptomatic and are not directly associated with increased local morbidity [2].

#### Complementary Examinations

Because the histopathology is relatively nonspecific, a skin biopsy is not necessary [6].

#### Therapeutic Approach

No treatment for diabetic dermopathy is necessary [2].

### Necrobiosis Lipoidica

Necrobiosis lipoidica (NL) has been shown to be associated with multiple systemic diseases,

including sarcoidosis, autoimmune thyroiditis, inflammatory bowel disease, ulcerative colitis, and rheumatoid arthritis. However, its most common systemic underlying disease is diabetes [12].

NL may be viewed as the prototype of a diabetes-associated skin disease. Although it is rare, its prevalence in adult patients is approximately 0.3–1.6%, occurring more frequently in women [3–7].

Most patients with NL will be diagnosed with diabetes at some point in their lives, and type 1 DM is more frequently associated with it [6, 9]. The presence of this disorder in diabetic patients is associated with a higher frequency of retinopathy and nephropathy [3]. Nevertheless, glycemic control has no effect on its course [9, 13].

### Etiopathogenesis

The cause of NL remains unknown. The leading theory involves microangiopathy as a result of glycoprotein deposition in the vasculature, resulting in the thickening of blood vessels [13].

### Clinical Presentation

The presence of NL is mainly based on a clinical diagnosis [8]. Clinically, NL lesions are localized on the lower two-thirds of the legs (pretibial regions) 90% of the time [14]. Lesions typically present as one to three asymptomatic, well-circumscribed papules and nodules with active borders that slowly coalesce into plaques [13]. Plaques are typically yellowish-brown, with elevated, erythematous borders, an atrophic center, and telangiectatic vessels visible through the skin [8] (Fig. 35.1). Their texture may be similar to that of wax [12, 14]. In isolated cases, lesions may affect the upper limbs, scalp, trunk, penis, or face [6, 12]. They may ulcerate spontaneously [12]. The Koebner phenomenon may also occur [13].

Although the majority of lesions do not result in pain, as a result the associated nerve damage up to 25% can be extremely painful, especially if ulcerated [13].

Squamous cell carcinoma is a rare complication that can arise in long-standing NL lesions, presenting also without ulceration [12, 13].

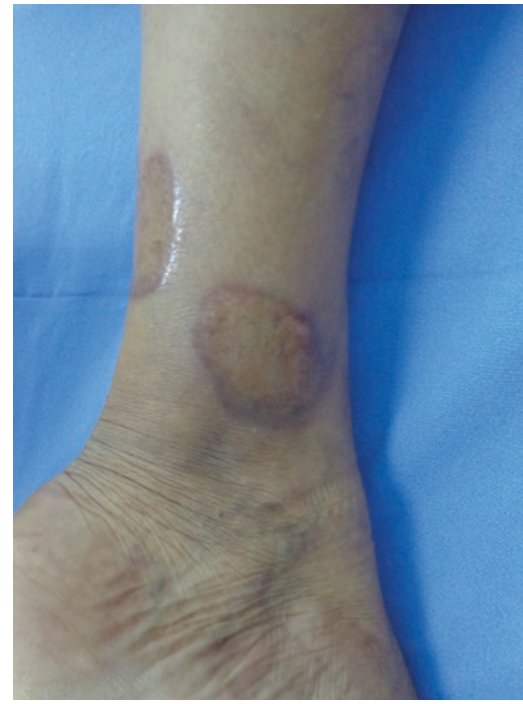

**Fig. 35.1** Necrobiosis lipoidica presenting as yellowish-brown plaques with well-delimitated borders and atrophic center (Photograph from the Department of Dermatology Collection, Universidade Federal de Santa Maria, Santa Maria, Brazil)

Differential diagnoses of NL include granuloma annulare, necrobiotic xanthogranuloma, morphea, sarcoidosis, and, in cases of ulceration, tuberous syphilis [9].

### Complementary Examinations

The characteristic histologic features are neutrophilic necrotizing vasculitis in the early stages and amorphous degeneration and hyalinization of dermal collagen (necrobiosis) in the later stages [3].

### Therapeutic Approach

It should be considered that NL is indolent, and up to 17% of lesions may resolve spontaneously. Therefore, decisions on the treatment of NL are individualized [12].

It is important to note that despite the numerous investigations carried out over the years, no treatment modalities have been shown to be completely satisfactory in treating NL [15].

Nevertheless, the primary treatment is currently the use of steroids, either topical, intralesional, or, rarely, systemic [7, 13]. Steroids should be applied to the active borders of lesions and not to atrophic areas. Steroid use in diabetic patients demands attention in order to prevent glucose dysregulation [13].

In addition to steroids, other treatments are possible, although they have only been successful in some cases or still lack scientific evidence of their effectiveness. Calcineurin inhibitors, topical retinoids, ultraviolet A phototherapy (PUVA) treatment, photodynamic therapy, and cyclosporine are some of the additional options [16]. Pentoxifylline, a potent anti-inflammatory agent with hemorrheologic effects, has been used to improve microcirculatory flow with some favorable results [17, 18].

In nondiabetic patients, baseline blood work should include a fasting blood glucose or glycosylated hemoglobin test to screen for diabetes or to assess glycemic control. If these are not diagnostic of diabetes they should be repeated on a yearly basis, as NL can be the first presentation of diabetes [12].

Lifestyle modifications, such as the avoidance of trauma, are important in minimizing the risk of NL complications [13].

## Granuloma Annulare

Granuloma annulare (GA) is a common idiopathic disorder, which occurs twice as frequently in women [19]. Clinical variants include localized, generalized, subcutaneous, micropapular, nodular, perforating, and (rarely) pustular generalized perforating GA [19, 20].

### Etiopathogenesis

Although the origin of this condition remains poorly understood, a marked association has been observed with certain systemic diseases, particularly diabetes and rheumatic diseases [3].

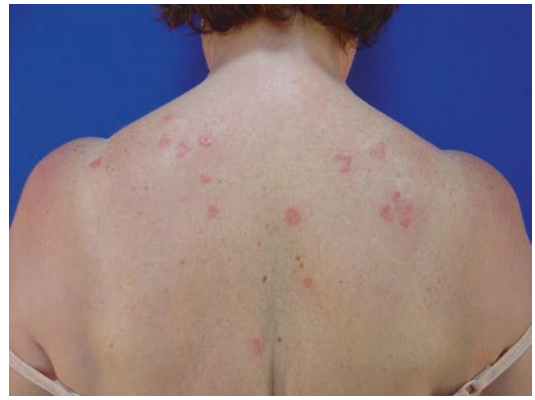

**Fig. 35.2** Granuloma annulare: multiple red annular plaques organized around a slightly depressed center (Photograph courtesy of Edison Covatti, Passo Fundo, Brazil)

### Clinical Presentation

The most common clinical form is localized GA, which accounts for approximately 75% of all cases [21]. It consists of pale red or violaceous papules that are firm and smooth to the touch. The lesions fuse into single or multiple annular plaques organized around a slightly depressed center [3] (Fig. 35.2). Lesions can occur anywhere on the body, but are more often found on the lateral or dorsal surfaces of the hands and feet. Symptoms are usually absent [20].

Subcutaneous or deep GA presents as a fixed nodule located on the legs, scalp, palms, or buttocks. Other less common variants include disseminated GA, characterized by a diffuse papular eruption, and a perforating form that presents as umbilicated papules with a central crust or scale and transepidermal elimination of necrobiotic connective tissue from the center [3].

Differential diagnosis for GA include other common annular skin conditions such as tinea corporis, pityriasis rosea, nummular eczema, psoriasis, or erythema migrans associated with Lyme disease. The lack of any surface changes to the skin is the key feature that distinguishes GA from these other skin conditions. Less common annular skin conditions (e.g., subacute cutaneous lupus erythematosus, erythema annulare centrifugum) have associated scaling and can be ruled out [22].

### Complementary Examinations

Regardless of the clinical presentation, histologically there is dermal or subcutaneous granuloma formation with collagen necrobiosis, mucin deposition and an infiltrate consisting of histiocytes and multinucleated giant cells. Perivascular lymphocytic infiltration is also frequently observed. The histiocytes may be present in an interstitial pattern without apparent organization, or may show a palisading pattern, surrounding areas with prominent mucin [20].

### Therapeutic Approach

GA treatment is frequently unnecessary because most of the lesions resolve spontaneously within 2 years of onset [3]. Nevertheless, the appearance of the lesions may require that some patients seek treatment [22].

For localized occurrences of this disease, topical corticosteroids are generally considered the first-line therapy. Depending on the site, high-potency corticosteroids with or without occlusion can be used. For nonresponsive cases, intralesional corticosteroids can be used [23]. Other options for localized disease treatment include calcineurin inhibitors, cryotherapy, or pulsed dye laser treatment. Generalized forms may be treated with one of a variety of systemic therapies, including dapsone, retinoids, niacinamide, antibiotics, antimalarials, phototherapy, or photodynamic therapy, all with only relative therapeutic success [3].

## Acanthosis Nigricans

Benign acanthosis nigricans (AN) is most commonly related to endocrinopathies [24]. Obesity is the major underlying disease, often associated with hyperinsulinism, DM, and insulin resistance. Cushing's syndrome, polycystic ovaries, thyroid diseases, hirsutism, Addison's disease, and acromegaly are other endocrine disorders associated with AN [24]. All of these conditions have a significant resistance to endogenous insulin in common [25].

AN also occurs rarely as a complication of an internal malignancy, particularly of the stomach, and secondary to some medications, including nicotinic acid [25] and repeated same-site insulin injections [26].

AN is more common in dark-skinned people and is found more commonly in the adult population, although it can be observed at any age [27].

### Etiopathogenesis

Elevated insulin concentrations result in the activation of IGF-1 (insulin-like growth factor 1) receptors on keratinocytes and fibroblasts, leading to epidermal cell proliferation and resulting in the clinical manifestation of hyperkeratosis and acanthosis. Other mediators may also contribute to this condition, such as EGFR (epidermal growth factor receptor) and FGFR (fibroblast growth factor receptor) [28].

### Clinical Presentation

Regardless of its underlying disease presentation, AN usually follows the same pattern [25]. Presentation is characterized by symmetric, skin-colored or brownish lesions 1 mm to 1 cm in size [24, 27]. The plaques are palpable with a velvety texture and may have a flat to wart-like appearance [28].

The lesions typically form in large skin folds, particularly in the axillae, posterolateral neck, groin, and abdominal folds. Any other part of the body can also be involved, such as the nipples and phalanges [2, 24, 27] (Figs. 35.3 and 35.4). Associated skin tags are common [2].

Papillomatous growths may be encountered on the eyelids, lips, and oral mucosa, as well as on the esophageal, laryngeal, and nasal mucosa [29], and the palms (tripe palms) and dorsal surfaces of large joints [30]. These generalized forms involving mucosa, however, are more often related to malignancies [27].

### Complementary Examinations

Histopathologically the lesions reveal papillomatosis, hyperkeratosis, and mild acanthosis. The dark color is due to the thickness of the keratin-containing superficial epithelium because there is no change in melanocyte number or melanin content [25].

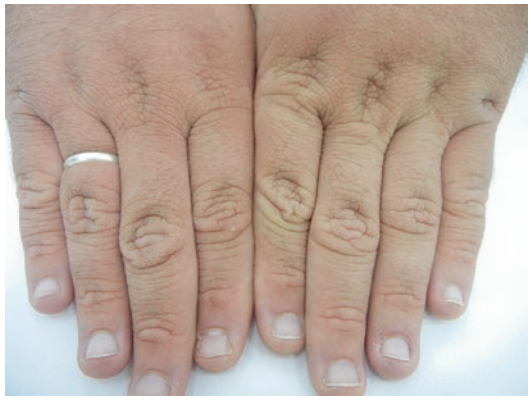

**Fig. 35.3** Papillomatous growths on the dorsal surfaces of the hands (Photograph from the Department of Dermatology Collection, Universidade Federal de Santa Maria, Santa Maria, Brazil)

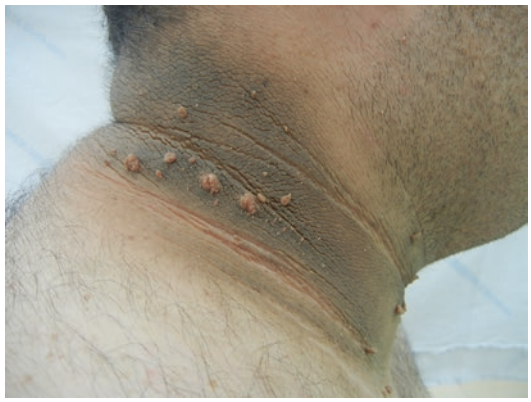

**Fig. 35.4** Dark velvety discoloration in acanthosis nigricans associated with skin tags (Photograph from the Department of Dermatology Collection, Universidade Federal de Santa Maria, Santa Maria, Brazil)

### Therapeutic Approach

AN has better outcomes with weight reduction and optimal blood glucose control [9, 31]. The use of agents capable of increasing the differentiation and decreasing the proliferation of keratinocytes, such as topical calcipotriene or oral and topical retinoids, may also be useful. Exfoliating agents, such as urea or ammonium lactate, and depigmenting agents can also be of benefit to some patients [31].

## Diabetic Bullosis

Bullosis diabeticorum (BD) is considered a rare and relatively harmless skin manifestation related to diabetic patients [32].

### Etiopathogenesis

Several hypotheses have been proposed to explain the production of the bullae, such as neurotrophic disturbance, alterations in carbohydrate metabolism resulting in bullae in a manner akin to chemical vesicants, a cationic imbalance due to diabetic nephropathy, immunoglobulin-mediated vasculitis, and ischemia. Nevertheless, the exact etiopathogenesis is still unknown [33].

### Clinical Presentation

Spontaneously occurring bullae without pain or any sign of inflammation generally not related to trauma or obvious physical cause are clinical features of BD. Bullae vary in size from a few millimeters to several centimeters and contain a clear, sterile fluid [33]. The main location for BD is on the distal extremities, especially the feet and lower legs, although hands and the forearms may also be involved [34] .Its evolution is self-limited and usually ceases within 2–5 weeks, without scarring. It especially occurs in patients with long-term DM [32–35].

Differential diagnoses can include epidermolysis bullosa acquisita, porphyria cutanea tarda, erythema multiforme, or drug eruption [32–35].

### Complementary Examinations

Histopathologic examinations have shown inconsistent levels of skin separation, and no specific signs have been found. Therefore, skin biopsy should be used only in case of continuous eruptions suggesting a chronic skin disease [32].

### Therapeutic Approach

Treatment is conservative. The blister must be kept intact in order to cover the lesion and pre-

vent secondary infection. The patient should be instructed to keep the wound clean and protected. Topical therapy is not required [35].

## Scleredema Diabeticorum

Scleredema adultorum (SA) of Buschke is a fibromucinous connective tissue disorder. When associated with DM, SA is known as scleredema diabeticorum (SD) [36].

### Etiopathogenesis

One proposed hypothesis for the pathogenesis of SD involves the glycosylation of collagen fibers leading to altered degradation. Another implicates hyperglycemia in stimulating fibroblasts and the synthesis of extracellular matrix components [37].

### Clinical Presentation

SD is characterized clinically by diffuse, symmetric, and nonpitting induration of the skin, usually involving the neck, shoulders, trunk, face, and arms. Hands and feet are characteristically spared. Differential diagnoses of scleredema include fibrosing disorders such as scleroderma and scleromyxedema [37].

### Complementary Examinations

Because of the inelasticity and induration of the thickened skin in scleredema, incisional biopsy is usually recommended to confirm the diagnosis. Histologic analysis shows a thickened dermis with increased deposition of glycosaminoglycans, mainly hyaluronic acid [37, 38]. However, diagnostic imaging may be helpful in accurately evaluating the activity of the disease in cutaneous sclerotic disorders [38].

### Therapeutic Approach

There is no standard therapeutic approach for SD. Systemic corticosteroids alone or in combination with cyclophosphamide may facilitate infections and aggravate the diabetic state. The therapeutic effect of PUVA, prostaglandin $E_1$, methotrexate, and cyclosporine is uncertain [9]. Glucose control has not been firmly associated with improvement of the disease [37].

## Kyrle's Disease

Perforating disorders are a group of unrelated pathologic abnormalities showing the common property of histopathologic transepidermal elimination, whereby the extrusion of altered dermal substances or foreign material through the epidermal channel occurs [39].

Elastosis perforans serpiginosa, reactive perforating collagenosis, perforating folliculitis, and Kyrle's disease (KD) are all classic perforating dermatoses. Clinical and histologic features of these diseases are not uniform and may resemble any of the four diseases [40].

KD is regarded as a genetically determined disease with onset occurring during adulthood, usually between the ages of 30 and 50 years and with a female-to-male ratio of up to 6:1 [41]. Chronic renal failure and/or DM usually accompany this skin disease [40].

### Etiopathogenesis

In patients with KD, keratin is the predominant eliminated material. This disorder of keratinization results in the development of dyskeratotic cells at multiple points. These cells have a limited capacity for proliferation. Eventually this results in depleted cells and a consequent defect in the epidermis [42].

### Clinical Presentation

KD is characterized by the eruption of asymptomatic, mildly pruritic pinhead-sized papules with silvery scales. These gradually enlarge to form reddish-brown papules and papulonodules with central keratotic cone-shaped plugs, which can be removed with a curette. The papules may be follicular or extrafollicular. Koebner's phenomenon is uncommon, although at times the lesions may

be linear [43]. The lower extremities are involved more frequently, but the upper extremities, head, and neck may also be affected [44].

### Complementary Examinations

Histologically there are large keratotic and parakeratotic plugs penetrating from the epidermis through the dermis. The plugs cause inflammatory responses and a foreign-body giant cell reaction in the dermis. Mild degenerative changes in the connective tissue with no increase in the elastic tissue may also be noted. KD can remain inactive for years, with a possible clearing of lesions when the associated illness is under control [44].

### Therapeutic Approach

Treatment of perforating disorders is difficult. Nevertheless, spontaneous resolution is possible [45]. Prognosis depends on the underlying disease and its response to treatment. In idiopathic cases and treatment-resistant secondary cases, topical steroids and topical and oral retinoids, along with UVB therapy, constitute the first-line therapies [46]. Narrowband UVB also appears to be an effective adjuvant phototherapeutic regimen [45].

## Nonspecific Skin Conditions Associated with Diabetes

### Skin Tags

Acrochordon or fibroepithelial polyps, commonly known as skin tags (STs), are one of the most common benign skin conditions [47].

Acrochordon is regarded as a sign of impaired glucose tolerance, DM, and increased cardiovascular (atherogenic lipid profile) risk [48]. STs may also play a role in the early diagnosis of metabolic syndrome [47].

### Etiopathogenesis

In hyperinsulinemia, insulin is able to activate IGF-1 receptors present on fibroblast and keratinocyte surfaces in a similar way to what occurs in the pathogenesis of AN [49]. Two studies have found the presence of human papillomavirus DNA in STs, at frequencies of 48% [50] and 88% [51].

### Clinical Presentation

STs are consisting of skin projecting from the surrounding skin, usually occurring on the eyelids, neck, and axillae [47].

### Complementary Examinations

There are no complementary examinations that need to be performed to investigate STs.

### Therapeutic Approach

Because they are generally of only cosmetic concern, treatment of STs is not required, and cutting the pedicles of the tags can be performed with microscissors and microforceps [52]. Cryotherapy and electrodesiccation can also be used [53].

Patients with STs also need suitable interventions, such as weight reduction, smoking cessation, and changes in dietary habits [47].

### Rubeosis Faciei

Rubeosis, also named rubeosis faciei and rubeosis faciei diabeticorum [54], is a relatively common skin manifestation associated with diabetes that may go unnoticed by patients and physicians [7].

### Etiopathogenesis

Hyperglycemia could lead to sluggish microcirculation, which becomes clinically evident from facial venous dilatation; its presence should lead to the evaluation of the patients for other more important microangiopathies, such as retinopathy [7].

### Clinical Presentation

Rubeosis presents as a flushing that can be observed more frequently in association with type 1 DM (21–59%). Rubeosis is more prominent in fair-skinned people and usually involves the face, neck, hands, and feet [1].

### Complementary Examinations

Rubeosis faciei is a clinical diagnosis and does not demand complementary examinations.

### Therapeutic Approach

No treatment is needed, although strict glycemic control can improve the appearance and prevent

complications related to microangiopathy in other organ systems [7, 54].

## Yellow Skin

Yellow pigmentation of the skin (xanthoderma) may be associated with carotenemia, hypothyroidism, liver disease, and renal disease. The frequency of this phenomenon in diabetic patients is unknown, and the relationship between skin color and blood carotenoid level is controversial [55].

### Etiopathogenesis

Not much is known about the relationship of diabetes and yellow skin. Traditionally yellow skin is considered to be related to carotenemia, whereby there are increased β-carotene levels in the blood, but it may also be associated with end products of advanced glycation [56].

### Clinical Presentation

Carotenemia is a clinical condition characterized by yellow pigmentation of the skin (xanthoderma) [55]. Carotene deposits are usually most notable in areas with a thick stratum corneum, such as the nasolabial folds, palms, and soles, as opposed to areas such as the conjunctivae and mucosa [57].

### Complementary Examinations

Tests for carotene levels can be performed but are generally unnecessary to evaluate yellow skin in diabetic patients.

### Therapeutic Approach

No treatment is required, although adjustments to the glycemic level may result in an improvement in the yellow discoloration of the patient's palms and soles.

## Xerosis

Rough skin or xerosis, commonly known as dry skin, results from a defect in the stratum corneum. This condition is negatively influenced by winter climatic conditions. DM, as well as other endocrine and metabolic disturbances, is also involved in this condition [58].

### Etiopathogenesis

Xerosis is considered to be related to an autonomic peripheral C-fiber neuropathy, and it has been speculated that other factors, such as stratum corneum adhesion and accelerated aging of the skin, may be involved in the development of xerotic skin changes in diabetic patients [59].

### Clinical Presentation

Dry skin can affect the extremities, trunk, or even the whole body. Cracking and fissuring of the epidermis can be visible.

### Complementary Examinations

No complementary examinations need to be performed to xerosis related to DM.

### Therapeutic Approach

Xerosis can be improved to various degrees by emollients, humectants, hydrating agents, and squamolytic agents [58].

Doctors should educate patients about the importance of skin hygiene, including applying fragrance-free creams or lotions within 3 min of bathing to trap moisture within the skin [7].

## Diabetic Pruritus

Pruritus is difficult to characterize and define. Various indirect definitions have been proposed that include a sensation which provokes the desire to scratch or an uneasy sensation of irritation in the skin [60].

Itching in people with diabetes frequently can be secondary to many of the skin conditions already mentioned. Nevertheless, chronic pruritus with no primary skin condition is thought to affect a considerable percentage of diabetic patients, with some studies suggesting it affects 3–49% of all diabetics [9].

A large-scale survey of 2,656 diabetic outpatients and 499 nondiabetic subjects was performed between November 2006 and August 2007. The prevalence of truncal pruritus of unknown origin in diabetic subjects was significantly higher than that in nondiabetic subjects [61].

Pruritus is a risk factor for self-injuring behavior in sensory polyneuropathies because itching

often induces scratching that can lead to clinically significant tissue damage [62].

### Etiopathogenesis

Itches originating in the skin are considered pruritoceptive and can be induced by a variety of stimuli, including mechanical, chemical, thermal, and electrical stimulation [63].

Diabetic polyneuropathy (small fiber neuropathy with damage to myelinated Aδ and nonmyelinated C fibers) and xeroderma (aggravated by age and hypohidrosis in diabetic autonomic neuropathy), as well as certain drugs (glimepiride, metformin, and tolbutamide), have all been implicated in the pathogenesis of diabetic pruritus [9].

### Clinical Presentation

Generalized pruritus is considered to be a sign of diabetes. Neuropathic pruritus may cause generalized truncal pruritus and localized itching, particularly in the genital areas of diabetic patients [64].

### Complementary Examinations

Skin biopsies are nonspecific and may only help if there is an underlying skin disease suspected as the cause of the symptoms.

One study showed a positive association between postprandial blood glucose and generalized pruritus, suggesting that better control of postprandial glucose might be beneficial to relieve generalized pruritus in diabetic patients [65].

### Therapeutic Approach

Symptomatic therapies may include high-dose antihistamines and pain-modulating drugs, such as gabapentin, pregabalin, or antidepressants. Therapy with emollients containing urea and in combination with substances that mitigate pruritus is essential [9].

## Psoriasis

Psoriasis is a chronic inflammatory disease associated with several comorbidities. A few decades ago, it was considered to be a disease exclusive to the skin, but today it is considered a multisystem disease. It is believed that 73% of psoriasis patients have at least one comorbidity [66]. There are reports of a significant association between DM and psoriasis in a large series of patients with psoriasis [48].

It has been suggested that psoriasis is an independent risk factor for the development of type 2 DM, whereby the severity of psoriasis correlates with the diabetic risk [67].

### Etiopathogenesis

Immune-mediated inflammatory processes, metabolic biomarkers, and environmental factors could be the potential links between psoriasis and diabetes [68].

There is probably an association between psoriasis and diabetes that is related the actions of T-helper 1 cytokines, which can promote insulin resistance and metabolic dysregulation (i.e., metabolic syndrome) and can promote inflammatory cytokines known to drive psoriasis [67].

### Clinical Presentation

Chronic plaque psoriasis (psoriasis vulgaris) is the most common form of the disease and accounts for approximately 90% of the cases. Typical psoriasis lesions are monomorphic, sharply demarcated, erythematous plaques covered by silvery lamellar scales. Extensor surfaces of the forearms and shins, periumbilical, perianal, and retroauricular regions and the scalp are the most common sites for these lesions [69].

### Complementary Examinations

Cutaneous psoriasis is a clinical diagnosis, and skin biopsy is rarely used. There are three main histologic features of these lesions: epidermal hyperplasia; dilated, prominent blood vessels in the dermis; and an inflammatory infiltration of leukocytes, predominantly into the dermis [70].

Despite recent advances in the systemic treatment of psoriasis, topical agents represent the primary treatment for a majority of patients with mild to moderate psoriasis, as well as for some with more severe cases of this disease [71].

### Therapeutic Approach

Topical therapies such as glucocorticosteroids, vitamin D derivatives, or combinations of both are usually sufficient to manage mild cases of this

disease. Topical calcineurin inhibitors are used at difficult-to-treat sites, such as the intertriginous areas or the face. A combination of phototherapy and systemic therapy is needed for patients with moderate to severe psoriasis. Established systemic drugs for the treatment of psoriasis include methotrexate, cyclosporine, acitretin, and, in some countries, fumaric acid esters. Biologics have also been developed and approved for the treatment of psoriasis over the past few years [69].

## Vitiligo

Vitiligo, an acquired pigmentary disorder of unknown origin, is the most frequent cause of depigmentation worldwide, with an estimated prevalence of 1% [72]. It is well known that vitiligo is associated with other autoimmune disorders, such as thyroid dysfunction, Addison's disease, insulin-dependent DM, and alopecia areata, showing that vitiligo shares a common genetic etiologic link with these autoimmune disorders. Insulin-dependent DM is found in 1–7% of patients with vitiligo, and conversely, 4.8% of all diabetic patients were found to have vitiligo [73].

### Etiopathogenesis

The leading theory of vitiligo's etiology involves an autoimmune cause linked to specific genetic mutations. Although the role of antimelanocyte antibodies in vitiligo is still not well known, high levels of circulating autoantibodies have been found in approximately 10% of patients, especially against tyrosinases 1 and 2 [74].

### Clinical Presentation

The most typical skin lesion is an asymptomatic, whitish macule or patch, with regular borders and sharp margins surrounded by normal or hyperpigmented skin [74].

### Complementary Examinations

Histologic examination and immunohistochemical studies with a large panel of antibodies generally show an absence of melanocytes in lesional skin, although sometimes a limited number of melanocytes can be observed [72].

### Therapeutic Approach

Topical therapy and narrowband UVB are the safest and most effective treatment options in most cases of vitiligo. Topical corticosteroids are still the primary treatment for localized forms of vitiligo because of their wide availability, low cost, and efficacy. Systemic therapy can be attempted in cases of disseminated vitiligo lesions, and in these cases steroids still remain the principal therapy. Surgical therapy could be useful in patients for whom medical therapy has failed [74].

## Lichen Planus

Lichen planus (LP) is an uncommon disorder affecting <1% of the general population [7]. Some studies have shown a significant association between LP and increased disturbances of glucose metabolism including DM, glucose intolerance, and insulin resistance [75, 76].

### Etiopathogenesis

LP is caused by an autoimmune process mediated by different types of cells and triggered by antigen alterations on the cell surface of the basal layer of the epithelium. In addition, epidermal cells have shown abnormalities in their enzymatic activity, as well as defective carbohydrate regulation in cases of LP, which might be connected with hormones essential for metabolic processes [75].

### Clinical Presentation

LP presents as grouped, symmetric, erythematous to violaceous, flat-topped, polygonal papules distributed mainly in the flexural aspects of the arms and legs, and can rarely appear on the trunk. The Koebner phenomenon is common, and the pruritus associated is intense and heals with postinflammatory hyperpigmentation [7].

### Complementary Examinations

Histologic examination of the skin or mucosal biopsies is useful to confirm the diagnosis in atypical cases, as well as to avoid inappropriate treatment in cases of severe disease [77].

### Therapeutic Approach

Because the cutaneous form of LP may resolve spontaneously, the goals of therapy are to shorten the time between the onset and resolution of the lesions and to reduce itching. Topical glucocorticoids are the first-line treatment. When topical treatments are ineffective, oral glucocorticoid therapy is sometimes used. Other options are phototherapy and oral aromatic retinoids [77].

## Skin Complications Associated with Diabetes Mellitus

### Diabetic Foot Syndrome

Diabetic foot syndrome is defined as a group of clinical manifestations associated with neurologic abnormalities and various degrees of peripheral vascular disease in the lower limbs of diabetic patients. Ulceration, infection, and/or destruction of the deep tissues can occur [78].

Approximately 30% of diabetics will suffer from metabolic polyneuropathy, which is characterized by symmetric, distal, chronic, insidious onset, and somatic (sensorimotor) and autonomic dysfunction. An inability to detect temperature changes, excessive pressure, and continued traumas develop. Atrophy and weakening of the intrinsic muscles of the foot lead to deformities and abnormal biomechanical loading of the foot. Autonomic neuropathy results in anhidrosis, causing dry skin, fissures, and callused areas with secondary ulceration [79, 80].

The other component of diabetic foot syndrome involves vascular disease. Ischemia reduces the supply of oxygen, nutrients, and soluble mediators that are involved in the skin repair process. Furthermore, hyperglycemia-induced nerve dysfunction leads to the dysregulation of nerve microvasculature and consequent neuropathy [81].

### Plantar Ulcers

Foot ulcerations are one of the most serious and disabling complications of DM and are the most common cause of nontraumatic foot amputation [82]. The prevalence of ulcers in the diabetic population ranges from 4% to 25% [81, 83]. Each patient with DM requires a comprehensive foot examination annually to identify risk factors for neuropathy and any evidence of neuropathy or ulceration [81].

#### Etiopathogenesis

Foot ulcerations are the result of neurologic abnormalities and various degrees of peripheral vascular disease. Both factors work in predisposing patients to ulcers and also making it difficult for ulcers to heal.

#### Clinical Presentation

The most common locations for foot ulcers are in the projections of the first, second, or fifth metatarsal bone, but may occur in other locations such as the heel and outer edge of the foot or toes. They are painless lesions because surface and depth sensitivity are impaired. Therefore, patients may continually traumatize the ulcerated location, making healing difficult [14].

Measurement of cutaneous pressure perception with the use of Semmes–Weinstein monofilaments is a validated screening test for the potential for neuropathy and ulcers. The loss of pressure sensation at four sites, as detected by the unperceived buckling of a 10-g monofilament, is highly predictive of subsequent ulceration. The four sites include the first, third, and fifth metatarsal heads, and the plantar surface of distal hallux. In addition, vibration testing with a 128-Hz tuning fork applied at a bony prominence is a useful test for peripheral neuropathy. The ankle jerk and patellar reflexes are also examined [81].

In purely neuropathic ulcers the foot is typically warm, pulses are palpable, and there is hypohidrosis. In contrast, in neuroischemic ulcers the foot is cold, pedal pulses are not palpable, and there is atrophy of the subcutaneous muscles and skin appendages [9].

#### Complementary Examinations

Radiography and other imaging modalities can help in detecting structural changes related to diabetic foot syndrome. Magnetic resonance imaging has high sensitivity and specificity for cases where infection with osteomyelitis is suspected [84].

### Therapeutic Approach

The management of a diabetic foot ulcer has better outcomes when a multidisciplinary team is involved [81]. A combination of prevention and infection control, pressure removal thorough relief shoes or devices such as casts or boots, debridement, and dressings are used in combination [78].

Considering that abnormal glucose levels affect the nature of infection and cellular immunity, optimizing glucose control was previously highlighted as crucial for wound healing. Nevertheless, evidence from a recent study was unable to conclude whether intensive glycemic control had a positive or detrimental effect on the treatment of foot ulcers in people with diabetes when compared with conventional glycemic control [85].

The importance of avoiding walking barefoot and potential trauma should be impressed on the patient. Appropriate footwear is essential. The removal of mechanical pressure from a neuropathic foot ulcer is central to the healing of the ulcer. Resting the foot and the use of a nonremovable, total-contact cast is associated with more rapid healing rates [81]. The use of orthopedic innersoles, in accordance with various "offloading" foot techniques using various material features, has also led to good results [14].

The use of moist dressings on clean granulating wounds improves the wound environment. They provide protection against further infection, maintain moisture balance and pH, absorb fibrinous fluids, and reduce local pain. The choice of dressing is further guided by patient requirements and treatment costs [81].

Debridement is the process whereby all materials incompatible with healing are removed from a wound. Several methods are currently used for debridement, including surgery, conventional dressings, larvae, enzyme preparations, polysaccharide beads, and hydrogels. The choice of method should be based on the available expertise, patient preferences, clinical context, and costs [86].

If there are any signs of infection, further investigation should be performed and then followed by the administration of systemic antibiotics according to antibiogram results [9, 81].

There is low- to moderate-quality evidence that suggests a beneficial effect of hyperbaric oxygen therapy when used as an adjunct to standard treatments for diabetic foot ulcers [87].

## Charcot Foot

Although Charcot foot does not primarily affect the skin, dermatologists should be familiar with this disorder, as its acute form may imitate erysipelas/cellulitis, deep vein thrombosis, or an acute gout attack [9, 88].

Charcot neuroarthropathy (CN) is an uncommon complication in diabetes that is characterized by severe deformity of the foot and/or the ankle that when not detected early will result in secondary ulceration, infection, and ultimately amputation [89].

Although Charcot foot occurs most often in patients with diabetic neuropathy, other predisposing conditions include alcoholic neuropathy, sensory loss caused by cerebral palsy or leprosy, and a congenital insensitivity to pain [90].

The prevalence of CN in diabetic patients ranges from 0.08% to 8.5%, and most patients who develop CN have had a known duration of diabetes of more than 10 years [84, 89].

### Etiopathogenesis

The interaction of several component factors (diabetes, sensorimotor neuropathy, autonomic neuropathy, trauma, and metabolic abnormalities of bone tissue) results in an acute localized inflammatory condition that can lead to varying degrees and patterns of bone destruction, subluxation, dislocation, and deformity [84].

### Clinical Presentation

Although Charcot foot is more common unilaterally, it can involve both extremities in up to 39% of cases [89]. The most common presentation is a neuropathic patient who sustains an unperceived injury, continues to walk until a severe inflammatory process leads to osteopenia, distention of the joint, and end-stage foot and/or ankle dislocation [89].

Musculoskeletal deformities in cases of Charcot foot can be very slight or grossly evident, most often owing to the chronicity of the

problem and the anatomic site involved. The classic rocker-bottom foot, with or without plantar ulceration, represents a severe chronic deformity and is typical for this condition [84].

All physicians treating diabetic patients should be vigilant in recognizing the early signs of an acute process such as unexplained pain, warmth, edema, or pathologic fractures in a neuropathic foot [84].

The patient often has no recollection of an inciting event or reports only a minor injury. Vital signs are typically stable. The patient may have already been treated for recurrent cellulitis. The edematous limb is often without any open wounds and has increased warmth and erythema, which resolves with the elevation of the foot [88]. If the swelling and rubor persist during this technique, an infectious process is likely to be present.

### Complementary Examinations

In the acute stage of CN, venous duplex ultrasonography will likely show negative results for deep vein thrombosis [88].

The erythrocyte sedimentation rate, C-reactive protein values, and white blood cell count are also usually found to be normal [91].

Results from radiography and other imaging modalities may detect subtle changes consistent with active CN or may be normal, emphasizing the importance of early utilization of advanced imaging [84, 88].

Magnetic resonance imaging allows for the detection of subtle changes in the early stages of active CN. It has high sensitivity and specificity for osteomyelitis and has become the test of choice for the evaluation of foot complications in diabetic patients [84].

### Therapeutic Approach

The modern approach to treating CN is to diagnose it as early as possible and to institute timely off-loading to avoid adverse outcomes [91].

Total contact casting is well recognized as the gold-standard treatment for CN in general, although it has not become a standard treatment in many diabetic foot clinics because of concerns about complications [91]. Immobilization can be achieved with either a nonremovable or removable cast for an average duration of 14 weeks [88].

Surgical treatment is indicated for chronic recurrent ulcerations and joint instability when patients present with unstable or displaced fracture dislocations. Treatment outcomes and complication rates vary between centers [91].

## Cutaneous Infections

Patients with DM are more prone to infections than healthy individuals [6, 9]. Moreover, diabetics exhibit a five-fold increase in complication risks compared with nondiabetics in cases of skin and soft tissue infections [9]. Incidences of infection correlate with mean blood glucose levels [6].

The disturbed skin barrier in diabetic patients and diabetes-induced vasculopathies, together with neuropathies, have been implicated in an increased vulnerability to infections. Recurrent bacterial infections, such as impetigo contagiosa, abscesses, erythrasma, folliculitis, erysipelas, or severe fungal infections, should alert physicians to screen for DM [8].

Treatment options for bacterial infections include the use of local antiseptics or antibiotic agents and, in cases of progressive soft tissue involvement or systemic signs of infection, the use of systemic antibiotics [6, 9].

Patients with diabetes are believed to be particularly susceptible to *Candida* infection because increased glucose concentrations permit the organism to thrive [9]. Thrush, angular cheilitis, candidal balanoposthitis, vulvovaginitis, and paronychia, as well as intertriginous candidiasis, are all common among diabetic patients. In contrast, the increased prevalence of dermatophytosis in diabetic patients is still a matter of controversy [8, 9].

Fungal infection of the nails is also common in diabetes [6]. Up to one-third of diabetics may have onychomycosis, which is a significant predictor of the development of foot ulcers in diabetes [92]. Therefore, treatment must not be neglected in these cases.

Furthermore, foot infections remain the most frequent diabetic complication requiring hospitalization and the most common precipitating event leading to lower extremity amputation [91].

Usually a consequence of an ulceration, the presence of a foot infection is generally indicated by the presence of systemic signs of infection or purulent secretions or by two or more local symptoms (redness, warmth, induration, pain, or tenderness). It is also important to note that local signs of infection can be diminished because of peripheral arterial disease and neuropathy. Osteomyelitis may affect up to two-thirds of patient with diabetic ulcers and may occur without pain [81].

Nasal and eyelid inflammatory lesions in diabetic patients deserve special attention. The possibility of mucormycosis, a rapidly progressive and potentially lethal infection caused by fungus primarily of the genera *Rhizopus* or *Mucor*, must not be ignored. Cutaneous mucormycosis is usually due to skin inoculation or local trauma introducing spores into the dermal layer, where vascular invasion by hyphae can cause infarction and necrosis of tissues. Rhino-orbital-cerebral and pulmonary infections are the most common presentations [93].

## Diabetic Hand Syndrome

The term "diabetic hand" is used to characterize complications of DM that occur in the hands. Although the term "diabetic hand" has no precise definition in the literature, Papanas and Maltezos propose defining it as a syndrome of musculoskeletal manifestations of the hand (mainly limited joint mobility, Dupuytren's contracture, and trigger finger) in diabetic patients that is usually associated with long-standing diabetes, suboptimal glycemic control, and microvascular complications. Neuropathic hand ulcers and diabetic hand infections are also cited by the authors as part of the definition of "diabetic hand" [94].

### Limited Joint Mobility Syndrome

Limited joint mobility syndrome (LJMS), diabetic sclerosis, the pseudosclerodermatous hand of the diabetic, and diabetic stiff hand are some of the diagnostic terms used in the medical literature referring to diabetic cheiroarthropathy (DCA) [95].

Increased nonenzymatic collagen glycosylation due to chronic hyperglycemia may lead to increased crosslinking between collagen molecules, thereby conferring an increased resistance to collagenases, manifesting clinically as stiffness [94].

Diagnosis is based on the following clinical features: progression of the painless stiffness of hands and fingers (prayer sign), fixed flexion contractures of the small joints of the hands and feet, impairment of fine motion, and impaired grip strength in the hands. As the syndrome progresses, it can also affect other joints [96].

It is important to diagnose LJMS because its presence is associated with the micro- and macrovascular complications of diabetes.

Because of the lack of curative treatment options, the suggested method to prevent or decelerate the development of LJMS is to improve or maintain good glycemic control. Daily joint-stretching exercises aimed at preventing or delaying the progression of joint stiffness may reduce the risk of inadvertent falls and will help maintain quality of life [96].

### Dupuytren's Contracture

Dupuytren's contracture (DC) is characterized by palmar fascia thickening, palmar and digital nodules, skin thickening and adherence, pretendinous band formation, and digital flexion contracture. DC affects 16–32% of diabetic patients and is more common among the elderly and those who have had DM for longer periods. It mainly affects the third and fourth fingers, rather than the fourth and fifth fingers, as typically occurs in cases associated with other etiologies [97]. Dupuytren's contracture has been treated with intralesional infiltration of corticosteroids, surgery, and physical therapy [97].

### Trigger Finger

Stenosing flexor tenosynovitis typically presents as fingers locked in flexion, extension, or both, more commonly involving the thumb, third finger, and/or fourth finger [97].

The treatment for stenosing flexor tenosynovitis includes a change in activities, the use of nonsteroidal anti-inflammatories, splinting, infiltrations, and, in more severe cases, surgery [97].

### Tropical Diabetic Hand Syndrome and Hand Infections

Tropical diabetic hand syndrome is a complication affecting patients with DM that is much less recognized that foot infections.

The syndrome encompasses manifestations that range from a localized cellulitis with variable swelling and ulceration of the hands to progressive, fulminant hand sepsis and gangrene affecting the entire limb [98].

Typically, patients have type 2 DM, are female, present in their fifth to sixth decade of life, and have poor metabolic control. Antecedent trauma (mild abrasion, laceration, insect bites) is often reported [94].

While tropical diabetic hand syndrome is essentially confined to the tropics, hand infections may also occur in the general diabetic population of the Western world. *Staphylococcus aureus* is the most common bacterial isolate, while infections by *Streptococcus*, *Klebsiella, Enterobacter*, *Proteus*, *Escherichia coli*, and various anaerobes may also be found [94].

Early diagnosis and treatment may lead to adequate recovery. Prognosis improves when appropriate blood glucose and insulin control, antimicrobial therapy, drainage, and debridement are performed promptly after diagnosis [99].

### Peripheral Neuropathy and Ulceration

Although diabetic foot problems related to peripheral neuropathy are well reported in the literature, we tend to forget the possible involvement of the hands. However, sensory impairment of the hands may occur in patients with severe neuropathy [100].

Screening for hand neuropathies is not a normal practice in most clinics unless patients are symptomatic (e.g., hand numbness or tingling). Such hand symptoms are, however, uncommon, and patients are unaware of neural dysfunction. Marked hand symptoms also seem to be more related to carpal tunnel syndrome than to neuropathy [100].

Hand examinations should not be neglected in patients with severe neuropathy in the feet and/or foot burns. Such patients need to be warned about the danger of hand burns [94].

Education on hand care should be given more attention, particularly in patients with lower extremity neuropathy. Patients in certain occupations (e.g., those that involve handling of hot materials or vibrating machinery) may be at particular risk, and the necessary precautions must be assured in their work environment [94].

**Conclusion**

DM and insulin resistance are related to a wide range of skin manifestations. Therefore, doctors should be aware of these skin conditions to best assist patients with this metabolic disorder.

## Glossary

**Acanthosis** Hyperplasia of the squamous epithelium.

**Acanthosis Nigricans** Dark pigmentation with a velvety texture in large skin folds.

**Acrochordon** Benign pedunculated skin growths usually occurring on the eyelids, neck, and axillae.

**Charcot foot** Complication in diabetes that is characterized by severe deformity of the foot and/or the ankle that when not detected early may result in secondary ulceration, infection, and amputation.

**Diabetic dermopathy** Also known as "shin spots," a specific skin condition associated with diabetes mellitus.

**Flushing** Redness of the skin together with a sensation of local warmth or burning.

**Koebner reaction** A phenomenon where new lesions appear along a site of trauma or irritation of the skin can. Examples: lichen planus, psoriasis.

**lichen planus** Inflammatory chronic skin condition of flat-topped erythematous to violaceous papules caused by an autoimmune process,

**Macule** A change in the color of the skin that is neither raised nor depressed, up to 1 cm in diameter.

**Melanocytes** Pigment cells responsible for producing melanin. In the human skin they are

found in the basal layer of the epidermis and hair follicles.

**Necrobiosis** Gradual degeneration and death of a cell.

**Necrobiosis lipoidica** Skin disease marked by one or more tender yellowish brown patches often associated with diabetes mellitus.

**Psoriasis** An autoimmune skin condition that changes the life cycle of skin cells. The majority of patients presents lesions as clearly defined red and scaly plaques.

**Scleredema** A dermatologic disorder characterized by hardening and thickening of the skin. When associated with diabetes mellitus is called "scleredema diabeticorum."

**Vitiligo** An acquired pigmentary disorder of unknown origin characterized by portions of the skin losing their pigment.

**Xanthoderma** Yellow pigmentation of the skin.

**Xerosis** Commonly known as "dry skin," results from a defect in the stratum corneum.

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