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REVIEW ARTICLE

Cutaneous Manifestations of Diabetes Mellitus: A Review

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Abstract Diabetes mellitus is a widespread endocrine disease with severe impact on health systems worldwide. Increased serum glucose causes damage to a wide range of cell types, including endothelial cells, neurons, and renal cells, but also keratinocytes and fibroblasts. Skin disorders can be found in about one third of all people with diabetes and frequently occur before the diagnosis, thus playing an important role in the initial recognition of underlying disease. Noninfectious as well as infectious diseases have been described as dermatologic manifestations of diabetes mellitus. Moreover, diabetic neuropathy and angiopathy may also affect the skin. Pruritus, necrobiosis lipoidica, scleredema adultorum of Buschke, and granuloma annulare are examples of frequent noninfectious skin diseases. Bacterial and fungal skin infections are more frequent in people with diabetes. Diabetic neuropathy and angiopathy are responsible for diabetic foot syndrome and diabetic dermopathy. Furthermore, antidiabetic therapies may provoke dermatologic adverse events. Treatment with insulin may evoke local reactions like lipohypertrophy, lipoatrophy and both instant and delayed type allergy. Erythema multiforme, leukocytoclastic vasculitis, drug eruptions, and photosensitivity have been described as adverse reactions to oral antidiabetics. The identification of lesions may be crucial for the first diagnosis and for proper therapy of diabetes.

Key Points

Skin alterations occur in about 30% of people with diabetes and may be precursors of the disease.

People with diabetes may experience infectious skin diseases, such as fungal and bacterial infections, as well as non-infectious disorders, such as pruritus, necrobiosis lipoidica, and granuloma annulare.

Insulin and oral antidiabetic drugs may cause cutaneous adverse reactions.

1 Introduction

Diabetes mellitus is the most common metabolic disease with a progressively growing number of newly diagnosed patients [1]. This disease is a global health problem and has a big impact on health systems [1]. The elevated glucose may also affect the skin, leading to noninfectious and infectious dermatological conditions and symptoms. About one third of all diabetes patients have some cutaneous clinical manifestation in the course of the disease [2]. Furthermore, some antidiabetic therapies may occasionally induce skin complications. In this review, the most common dermatological signs of diabetes are described with the aim to help dermatologists and physicians to identify undiagnosed diabetes and to inform them about associated symptoms and conditions.

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2 Prevalence and Incidence

About 415 million people worldwide are affected by diabetes [3]. In the US, 29.1 million people (9.3% of the population) had diabetes in 2014 [4]. The incidence and prevalence of diabetes is still increasing around the world, with approximately 642 million people predicted to be affected by the year 2040 [3]. Almost 80% of all diabetic patients have type 2 diabetes. Five to ten percent of people with diabetes have type 1 diabetes. Diabetes also appears in 7% of all pregnancies, frequently as gestational diabetes.

3 Pathogenesis

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [5].

Type 1 diabetes mellitus (T1D) is defined by destruction of the pancreatic β cells, which are responsible for insulin production [6]. About 70–90% of T1D patients have an immune-mediated loss of β cells, characterizing a type 1A diabetes mellitus (T1DA) [6, 7]. Autoantibodies against insulin, tyrosine phosphatases, islet cells, and glutamate decarboxylase can generate the pancreatic β-cell destruction. T1DA shows a genetic predisposition and a positive family history is common. Around 40% of T1DA patients have a human leukocyte antigen (HLA) locus mutation, commonly on chromosome 6q21.3 [8]. Over 10–30% of T1D patients show no genetic association or autoimmune mechanism [6]. They have idiopathic disease and are classified as type 1B diabetes mellitus (T1DB) [7]. The exact pathogenesis of this condition is still not clearly understood [8].

Autoimmune processes normally precede the outbreak of the T1D. Toxins or infections may trigger the onset of the disease [8]. Insulin replacement therapy is always required from the very beginning of T1D.

Type 2 diabetes mellitus (T2D) is responsible for more than 80% of the cases of diabetes. T2D is commonly caused by insufficient insulin activity (insulin resistance), impaired pancreatic β-cell action, or abnormal hepatic metabolism of glucose [9, 10]. Most patients with T2D are overweight or obese [11]. As for T1D, a genetic predisposition has been described for T2D [8]. A positive family history is also common. The physiopathological pathways of T2D have not been ascertained completely. Raised levels of pro-inflammatory cytokines, reactive oxygen species, adipokines, and free fatty acids have been associated with insulin resistance [12].

Gestational diabetes (GD) is characterized by a hyperglycemia first recognized during pregnancy and is most commonly a forerunner of type 2 diabetes [13]. It is present in about 7% of all pregnancies in the US [14]. Around 25% of women with GD develop T2D after pregnancy [15]. Insulin resistance has been reported in women with GD before pregnancy and therefore plays an important role in the pathology of this disease [16].

Diabetes can also be caused by rare genetic variations such as a mutation of the insulin receptor gene, characterizing a type A insulin resistance, or monogenic autosomal dominant inheritance, causing the maturity onset diabetes of the young (MODY) [17, 18].

The latent autoimmune diabetes of the adult (LADA) is a form of autoimmune diabetes characterized by the presence of diabetes-associated autoantibodies, most commonly glutamic acid decarboxylase 65 antibodies [19]. LADA has genetic similarities with both type 1 and type 2 diabetes and is also known as type 1.5 diabetes [19].

The physiopathological mechanisms of diabetes may modify skin metabolism and homeostasis, promoting diabetes-associated dermatological complications.

4 Diagnosis

The World Health Organization (WHO) has established two diagnostic criteria for diabetes [20]:

- fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), or
- 2-hour plasma glucose ≥11.1 mmol/L (200 mg/dL).

The American Diabetes Association (ADA) adopts any of the following criteria for the diagnosis of diabetes [21]:

- fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), or
- 2-hour plasma glucose ≥11.1 mmol/L (200 mg/dL), or
- random plasma glucose ≥11.1 mmol/L (200 mg/dL) in a patient with classic symptoms of hyperglycemia (i.e., polyuria, polydipsia, polyphagia, weight loss) or hyperglycemic crisis, or
- hemoglobin A1c (HbA1c) ≥48 mmol/mol (≥6.5%); the test should be performed in a laboratory using a method that is certified by the National Glycohemoglobin Control and Complications Trial (DCCT) reference assay.

Skin disorders of people with diabetes frequently precede the diagnosis of the disease and may therefore be important for its initial identification.

5 Diabetes-Induced Abnormalities of Skin Metabolism

The elevated level of serum glucose stimulates direct cell damage as well as indirect impairment through advanced glycation end products (AGEs) [22].

Hyperglycemic changes directly affect keratinocytes and fibroblast activities causing changes in protein synthesis, proliferation, and migration [23]. Furthermore, increased levels of glucose lead to dysfunction in vasodilatation through inhibition of nitric oxide (NO) molecules [23]. The sugar alcohol sorbitol is upregulated in hyperglycemia and promotes mitochondrial danger and consequently reactive oxygen species [24].

AGEs are formed after a non-enzymatic reaction of glucose with other molecules such as proteins, nucleotides, and lipids [22, 23]. The binding of AGEs with their specific receptor (RAGE) promotes a nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation with consequent production of proinflammatory cytokines [23, 25]. AGEs may also induce free-radical production causing oxidative stress [26]. Further reactions of AGEs with type 1 collagen or epidermal growth factor receptor suppress skin regeneration [27].

6 Skin Manifestations of Diabetes Mellitus

6.1 Pruritus

Chronic pruritus is a common skin manifestation of diabetes [28]. It is often associated with xerosis cutis. About 3–49% of people with diabetes have itching, considerably impairing their quality of life [29]. The generalized itching may occur in clinically inconspicuous dry skin or be associated with erythematous papules or with prurigo nodularis (Fig. 1) [29].

Diabetic polyneuropathy with correlated dysfunction of sweating due to impairment of the sympathetic nerve system may play a role in the pathogenesis of diabetic pruritus [30].

Therapy includes normalizing glucose levels accompanied by basic skin care with emollients such as urea-containing moisturizers, amended by topical antipruritics such as polidocanol or menthol [31]. However, in some cases of prurigo nodularis, these measures will not be sufficient, and topical corticosteroids such as mometasone furoate or betamethasone dipropionate, or intralesionally injected corticosteroids such as triamcinolone acetonide, will be needed [32, 33]. Likewise, topical capsaicin can also be applied several times daily (3–6 times/day) in those cases [33]. Oral antihistamines (promethazine hydrochloride at night) or antidepressants (doxepin at night) can be used in refractory cases [32]. Non-sedating antihistamines and selective serotonin reuptake inhibitor (SSRI) antidepressants may also reduce pruritus [34, 35]. Ultraviolet phototherapy is also a therapy option in case of refractory disease [32].

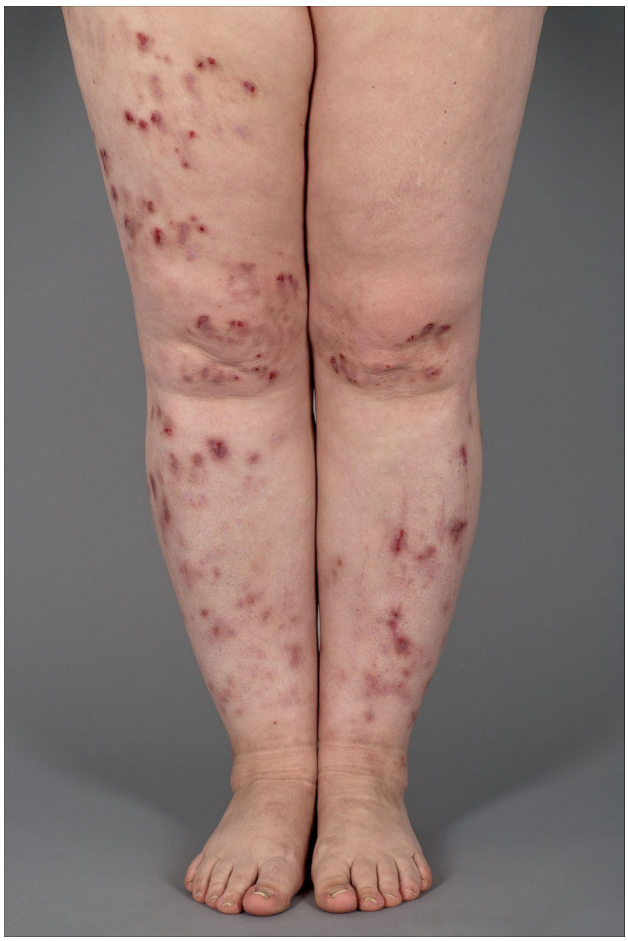

Fig. 1 Prurigo nodularis: excoriated erythematous papules and nodules in a diabetic patient

6.2 Necrobiosis Lipoidica

Necrobiosis lipoidica (NL) normally begins with erythematous papules, which evolve slowly, developing into a yellow-brown plaque with an atrophic center and telangiectasia (Fig. 2). NL is a non-pruritic chronic inflammatory granulomatous disease with a degeneration of collagen. The disease is encountered in 0.3–1.2% of all diabetes patients, with higher prevalence in women than in men, and it is commonly localized in the ventral area of the legs, often in a symmetrical distribution [36–38]. In 35% of patients lesions may ulcerate, commonly complicated by secondary bacterial infections [36].

The pathogenetic mechanisms are still unknown. Histopathology exhibits dermal collagen degeneration with

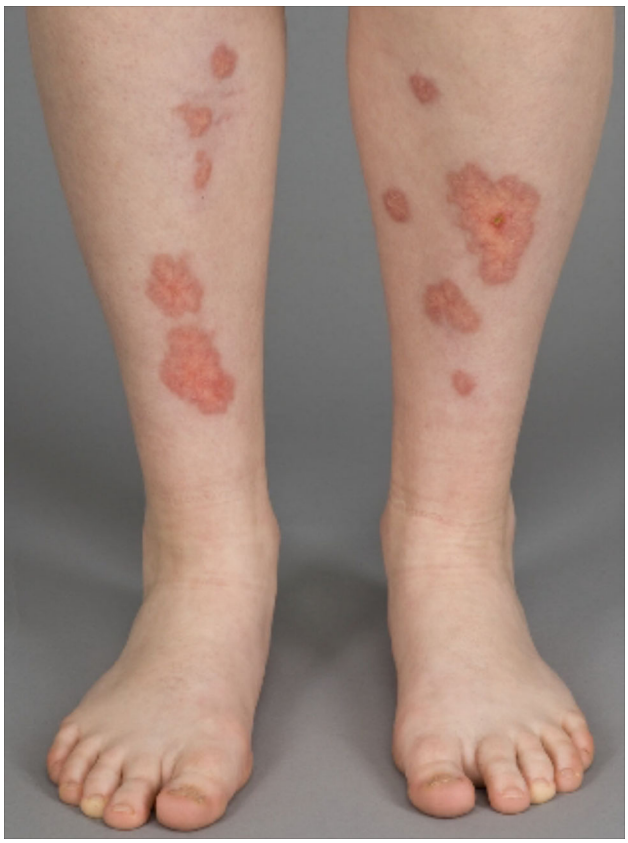

Fig. 2 Necrobiosis lipoidica: non-pruritic yellow-brown plaque with an atrophic center and telangiectasia

a granulomatous inflammatory infiltrate in a sandwich-like pattern beneath an atrophic epidermis [39].

NL lesions are usually chronic, but in some cases may improve spontaneously [40]. However, in most cases healing will result in atrophic scars. Treatment is difficult and unsatisfactory [41]. Topical therapy with corticosteroids such as clobetasol, or tacrolimus as well a systemic therapy with cyclosporine or anti-tumor necrosis factor-α (anti-TNF-α) antibodies may be attempted [41–43]. Intralesional steroids such as triamcinolone should also be applied to the active borders of NL lesions. The treatment of NL atrophic areas with intralesional steroids may worsen the atrophy and the risk of ulceration with this treatment should be considered [40, 44].

6.3 Scleredema Adultorum of Buschke

Scleredema adultorum of Buschke (SAB) is characterized by scleroderma-like extensive induration of the skin on the back, neck, shoulders, and face. It is defined by dermal deposition of collagen and mucopolysaccharides, which results in skin thickening, stiffness, and impairment of motility, particularly of the shoulder area. SAB is a rare disorder, which may be under-recognized. Apart from diabetes, SAB may also be encountered in other systemic diseases such as cancer, paraproteinemias, and infections.

The physiopathology is still not completely understood and probably involves both enhanced collagen synthesis by fibroblasts as well as a reduced degradation of collagen with consequent reduction of skin elasticity [45]. Skin specimens show extended collagen fibers and mucin deposits without epidermal alteration [45].

SAB shows a slowly progressive course. The skin sclerosis may reduce joint flexibility in the case of finger involvement. Huntley's papules, aggregated small erythematous papules, may be present. In extensive disease, the total skin organ as well as inner organs like the lung may be involved [45].

Phototherapy (especially by the use of UVA1), physiotherapy, and systemic therapy with penicillin are some options for the treatment of SAB [45]. Electron-beam therapy can also be applied [46]. Despite the different therapy modalities, SAB remains a frequently therapy-resistant disease [47].

6.4 Bullosis Diabeticorum

In patients with a long diabetes history, tense serous blisters without signs of skin inflammation may occur [48]. The bullae are painless and predominantly occur on the lower extremities, especially on the feet and soles. Bullosis diabeticorum (BD) may appear as the initial clinical finding of diabetes, and hands and trunk may also be affected. About 0.5% of people with diabetes develop blistering in the course of disease [48, 49]. BD blisters emerge rapidly and heal in the course of a few weeks [50].

The pathological mechanism has not been completely ascertained. A combination of angiopathy and neuropathy may play a role in the physiopathology of BD [51]. The HbA1c level represents the average glycemic control over the past 2–3 months and may be helpful in the analysis of blood sugar in patients with a long diabetes history. The histopathological analysis shows subepidermal blistering with sparse or even absent inflammatory infiltrate, in contrast to bullous pemphigoid (BP), which is an important differential diagnosis that can be ruled out by the use of direct immunofluorescence technique and blood sampling for detection of BP antibodies [51].

Therapy is mainly symptomatic and consists of preventing a secondary bacterial infection and promoting adequate serum glucose control.

6.5 Granuloma Annulare

Erythematous papules, aggregating to roundish formations on the dorsal surface of feet and hands or joints, characterize the clinical findings of granuloma annulare (GA)

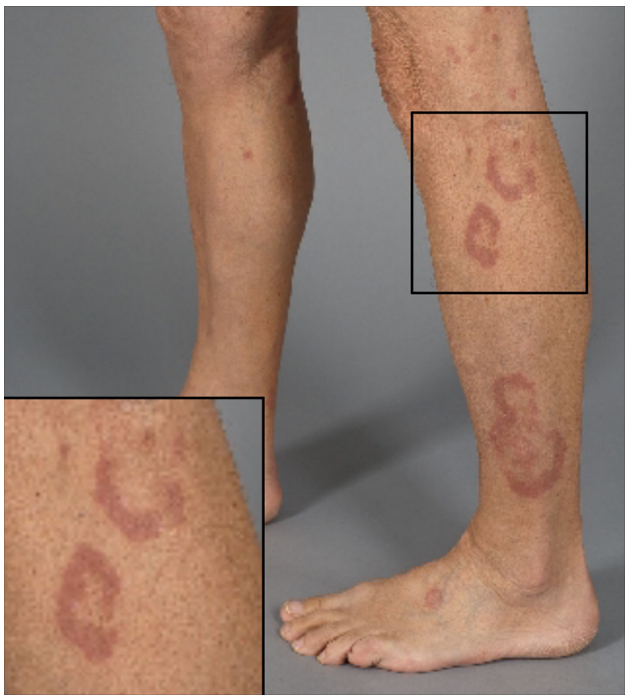

Fig. 3 Granuloma annulare: annular and semicircular plaques with central healing

(Fig. 3). This disease often appears in people with diabetes, but the association of GA and diabetes has been controversial [52]. Association with infectious diseases, like hepatitis and HIV, and tumors, such as lymphoma and carcinoma, is also described [53–55]. The course of the disease is frequently asymptomatic and the lesions heal with a central involution with hypo- or hyperpigmentation.

The pathogenesis remains unclear and the histological findings show palisaded lympho-histiocytic granuloma with mucin deposition [56].

Most lesions heal without therapy. Disseminated forms of GA are cosmetically disturbing and may be slightly itchy. Lesions can be treated with topical corticosteroids or calcineurin inhibitors, and in disseminated conditions, UV light therapy, such as PUVA, or systemic therapy with dapsone may be used [53, 57]. Pentoxifylline and antimalaria agents (hydroxychloroquine) have also been successfully used to treat GA [58].

6.6 Acanthosis Nigricans

Intertriginous hyperpigmented plaques characterize acanthosis nigricans (AN). Neck and axillae are commonly affected in diabetes (Fig. 4) [59]. Hyperinsulinism promotes keratinocyte hyperproliferation due to the binding of insulin to insulin-like growth factor receptors [59]. The increase in fasting insulin may precede the elevation of HbA1c; AN commonly antecedes the diabetes diagnosis

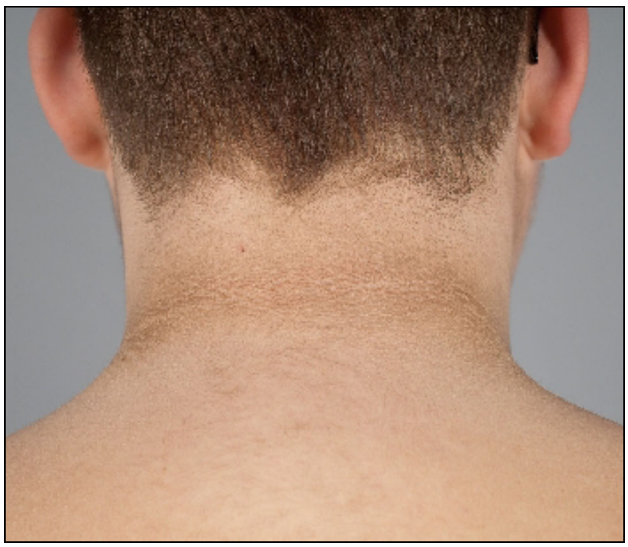

Fig. 4 Acanthosis nigricans: intertriginous hyperpigmented plaques. Neck and axillae are commonly affected

and may appear in the prediabetic state with normal HbA1c values [60]. Histopathological investigation confirms keratinocyte hyperproliferation with papillomatosis and acanthosis and a hyperpigmented epidermis [61].

AN has also been observed in polycystic ovary syndrome and obesity, and may manifest as a paraneoplastic syndrome in gastrointestinal malignancies [62–64]. In addition, drug-induced cases have been reported [65].

6.7 Vitiligo

Vitiligo is characterized by a sharply delineated loss of skin pigmentation (Fig. 5), often in a spotted manner. It often affects extremities, face, and neck as well as trunk, in a symmetrical distribution, and is easy to diagnose. It is a highly prevalent skin alteration with a prevalence of 2–10% in T1D patients, occurring spontaneously with progressive course [66]. Although the condition does not cause much physical impairment, patients may have disturbances in mental health and quality of life due to its disfiguring appearance [67].

As an autoimmune disease, it occurs frequently with other autoimmune disorders such as thyroid illnesses [68].

Most treatment attempts in vitiligo remain unsatisfactory, such as use of topical corticosteroids, topical calcineurin inhibitors, UV irradiation, laser light, as well as skin grafting. UV irradiation is the most commonly used therapy and may be assessed as monotherapy or in association with another treatment. Stable disease may also be surgically treated. Topical calcineurin inhibitors, such as tacrolimus or pimecrolimus, show less adverse effects in comparison with topical corticosteroids [69].

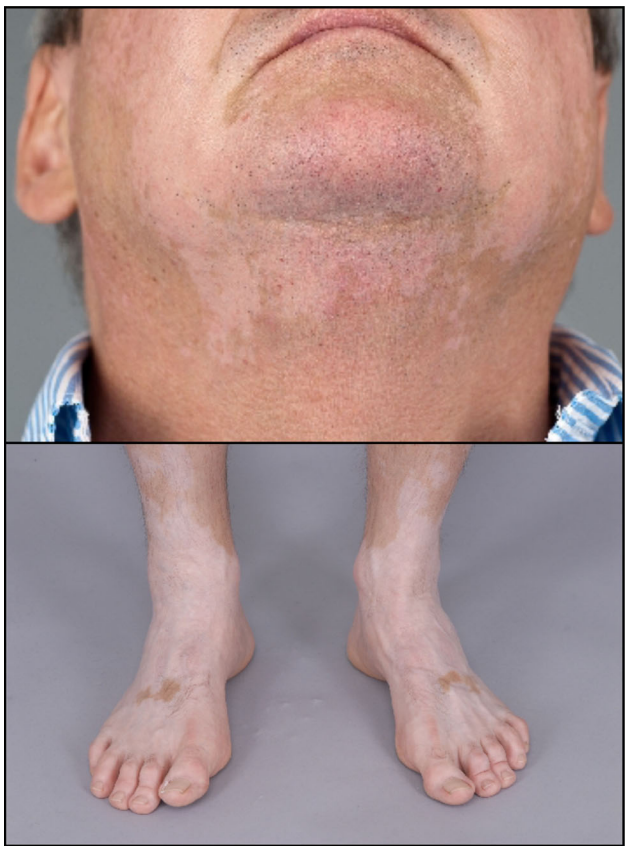

Fig. 5 Vitiligo: depigmentation with convex borders

6.8 Skin Tags

Hyperproliferation of keratinocytes due to hyperglycemia and insulin stimulation may stimulate skin tags, characterized by either hyperpigmented or skin colored fibroma, usually localized on eye lids, neck, axillae, or groin. About 70% of patients with skin tags have diabetes [70]. Most of the fibroma are asymptomatic and no therapy is necessary; however, many patients want them to be removed as they may cause skin irritation and are disturbing.

6.9 Carotenodermia

Yellowish skin and nails have been attributed to carotenodermia in people with diabetes, and yellow nails are frequent in diabetes patients [71]. The pathology likely involves a non-enzymatic glycation promoting the rise of serum levels of carotenoids with consequent deposition in the skin [72].

6.10 Lichen Planus

Around one quarter of lichen planus patients have diabetes [73]. The clinical findings show the typical pruritic polygonal erythematous papules with white striae (Wickham striae), characteristically located on ankles and wrists, with optional involvement of the mucosa. Lichen planus belongs to the skin diseases that may be provoked mechanically, also known as Koebner's phenomenon, which is also observed in psoriasis.

Other systemic diseases can also be associated with lichen planus, like liver and intestinal pathologies and thymoma [74].

A large number of therapies are available to treat lichen planus. Topical corticosteroids, topical calcineurin inhibitors, phototherapy, systemic retinoids, systemic corticosteroids, methotrexate, hydroxychloroquine, or dapsone can be applied [75].

6.11 Acquired Reactive Perforating Collagenosis

Acquired reactive perforating collagenosis (ARPC) is a rare skin disease but is over-represented in people with diabetes. It is also observed in patients with chronic renal insufficiency and hyperuricemia [76–78]. The pathogenesis remains unknown and histologic findings show a transepithelial elimination of collagen, more evident in the papillary dermis [77, 78]. Although it is rare, the clinical picture is typical: characteristically, pruritic erythematous umbilicated nodules or plaques with adherent crusts are found (Fig. 6) [77, 78]. Koebner's phenomenon is common. Therapy with topical and oral retinoids or corticosteroids has been described [79].

ARPC can be topically treated with class II–III corticosteroids and antiseptic agents [78]. Intralesional triamcinolone can also be applied. Systemic corticosteroids, systemic retinoids, and allopurinol have been successfully used to treat ARPC [78, 80].

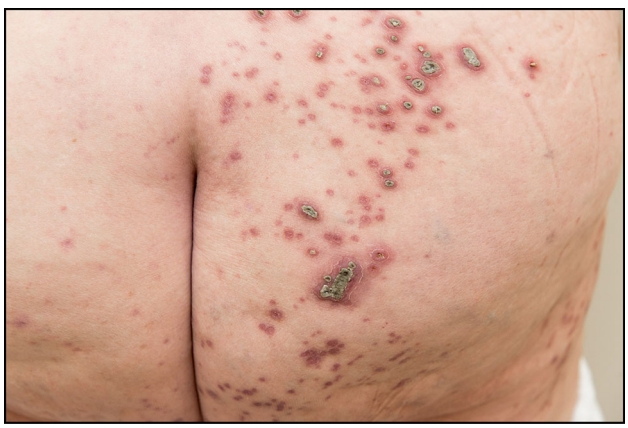

Fig. 6 Acquired reactive perforating collagenosis: pruritic erythematous umbilicated nodules or plaques with adherent crusts

7 Diabetic Angiopathy and Neuropathy-Associated Skin Diseases

7.1 Diabetic Foot Syndrome

The combination of diabetic angiopathy, neuropathy, and mechanical trauma plays an important role in the pathogenesis of diabetic foot syndrome (DFS), which occurs in 15–25% of all people with diabetes [81]. Around one quarter of patients with DFS develop complications, including infections and osteomyelitis, which may lead to amputation. It has been shown that these patients have a higher mortality, as 50% die within 3 years after amputation [82, 83].

The pathogenesis involves initially unrecognized trauma within skin areas of neuropathy and callus, which is often the case on the plantae and tips of toes (Fig. 7). Due to hyperglycemia, impaired chemotaxis, cell proliferation, and migration, the healing process is badly disturbed [23]. Furthermore, enhanced proinflammatory chemokines disturb wound healing, leading to diabetic ulcers [84]. In the course of DFS, the neuropathy and angiopathy evolves and leads to orthopedic disorders as well as to muscle atrophy and bone deformation causing the Charcot foot [85]. Further secondary bacterial infection can cause osteomyelitis.

Based on the cause, DFS can be subclassified as ischemic, neuropathic or mixed. The ischemic form is characterized by the presence of angiopathy, in which clinical findings show intermittent claudication with arching or cramping pains in the calf muscles [86]. A peripheral nerve dysfunction without another cause except the diabetes characterizes the neuropathic form [87]. The mixed form involves the association of both ischemic and neuropathic forms.

Interdisciplinary team-ordered therapy is very important in the treatment of DFS [83]. Hyperkeratotic tissue should be removed with wound debridement, and a topical antiseptic and wound dressing therapy should create an adequate precondition for recovery. Orthopedically adapted shoes, which release areas of pressure and impaired microcirculation, are important measures to prevent progression of the condition.

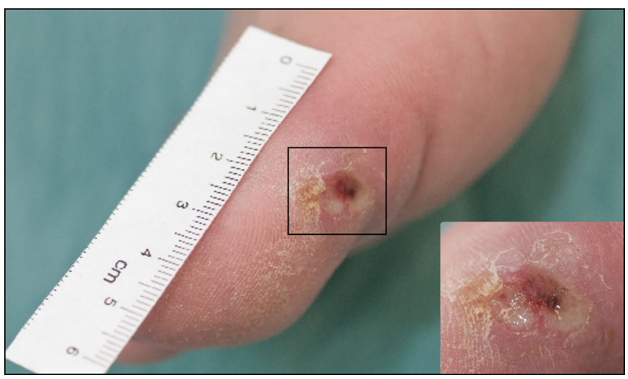

Fig. 7 Diabetic foot syndrome: hard-to-heal ulcer on the big toe in a patient with diabetic angiopathy and neuropathy

7.2 Diabetic Hand Syndrome

Similar to DFS, diabetes may also provoke musculoskeletal disorders on the hands like limited joint mobility (LJM), Dupuytren's disease (DD), and carpal tunnel syndrome (CTS) [88].

LJM is characterized by thickening and stiffness of periarticular connective tissue of the small joints of the hand, causing limited extension of the fingers, and is present in about 30–40% of patients with diabetes [88]. There is no specific therapy for LJM.

DD is caused by fibrosis and consequent thickening and shorting of palmar fascia, resulting in flexion contractures [89]. DD is present in 16–42% of people with diabetes and can be treated with physical therapy or with surgery in severe cases [89].

Sensory loss, paresthesia or a burning sensation in the median nerve innervation area of the hand are clinical signs of CTS [90]. CTS occurs in about 14% of patients without diabetic polyneuropathies and in up to 30% of patients with diabetic polyneuropathies [90]. Splinting and local injection of corticosteroids or NSAIDs can be applied [91]. Surgery may be required in some severe cases [91].

7.3 Diabetic Dermopathy

Also known as shin spots, diabetic dermopathy is present in about 40% of diabetes patients and may result from minor trauma [92]. It is a frequent manifestation of a diabetic organic disease, such as nephropathy, retinopathy or neuropathy [92, 93].

The disease tends to appear in lower extremities and in older men. The clinical finding shows asymptomatic erythematous maculae or papules with rapid growth [94]. The lesions have a recurrent course but improve spontaneously. The healing involves formation of brown hypotrophic scars.

8 Common Skin Infections in Diabetes Patients

Hyperglycemia leads to important metabolic and immunological alterations, so that people with diabetes tend to be more susceptible to skin infections. Moreover, the skin pH value is higher in diabetes patients and promotes bacterial colonization [95]. Diabetic neuropathy and angiopathy play an important role in the infection, as mechanical traumata may remain painless and therefore unrecognized, which facilitates microbial entry [23]. Secondary bacterial infection complicates wound healing. Bacterial and mycological

infections are frequent in people with diabetes [96]. About half of patients present an infectious episode in the course of their disease [82]. A high serum glucose level predisposes patients to these episodes.

8.1 Bacterial Skin Infections

Staphylococcus aureus is a Gram-positive organism that normally constitutes the microbiota of the skin and is commonly involved in folliculitis, abscesses, and impetigo contagiosa [96]. Recurring pyogenic skin infections should give reason to investigate for diabetes.

Small pustules on hair follicles characterize a folliculitis. In most cases, topical antibiotic therapy is sufficient. Abscesses are fluctuating, painful, warm, red pus-filled nodes [97]. Surgical incision with consequent pus and debris drainage and cavity cleaning is the most satisfactory treatment of abscesses. Additional antibiotic therapy can be helpful in case of insufficient drainage, or of abscesses on the face or genitoanal region. Impetigo contagiosa is a superficial bacterial infection caused by *Staphylococcus aureus* and/or β-hemolyzing streptococci, clinically characterized by yellow-crusted erosions with optional blistering [97]. The typical lesions appear individually or numerously on the face or extremities. Therapy with topical antibiotics, such as retapamulin, fusidic acid, or mupirocin, and antiseptic agents can be used if disease is localized [98]. Diffuse impetigo contagiosa should be treated with systemic penicillin or, in case of penicillin resistance, with systemic oxacillins, first-generation cephalosporins or co-trimoxazole [98, 99]. Oxacillins and first-generation cephalosporins may not be used in case of methicillin resistance [98].

β-Hemolyzing group A streptococci may also cause ecthyma and cellulitis [96, 97]. Ecthyma is characterized by small ulcers that show clearly erythematous demarcation and usually manifest on the lower extremities in warm climates [97]. Systemic therapy with penicillin is needed together with local antiseptic therapy. Erysipelas and cellulitis are extensive dermal streptococci infections that are clinically identified by warm brilliant erythema with discernible delimitation together with fever, impaired general condition, and leukocytosis (Fig. 8) [100]. Initial epidermal injury is a prerequisite for the bacterial penetration. The gold standard therapy is systemic penicillin [101]. Necrotizing fasciitis is a rare complication of streptococcal infection which is also statistically over-represented in diabetic patients [96]. Besides streptococci, *S. aureus* or anaerobic bacteria may be involved [102]. Fournier's gangrene is a serious perineal or genitoanal variant with a high rate of mortality [103].

The skin from the otorhinolaryngological tract is also prone to be involved in bacterial infections in diabetes. Malignant external otitis is an invasive bacterial otological infection commonly caused by *Pseudomonas aeruginosa* and can have a lethal course [104]. The microangiopathy and the pH alteration under hyperglycemia play an important role in the infection process [95, 105]. The infection normally starts asymptomatically and causes earache with purulent effluvium [105]. In complicated cases it can involve the peripheral soft tissue up to the skull and neurologic system causing meningitis and cerebritis [105].

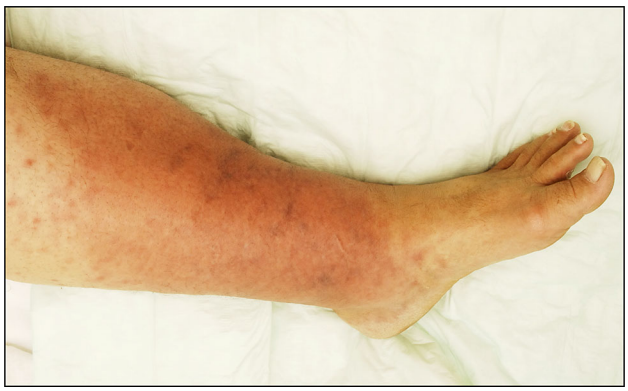

Fig. 8 Erysipelas: warm brilliant erythema with edema and discernible delimitation

8.2 Fungal and Candida Skin Infections

Comparable to the bacterial infections, the skin alterations caused by hyperglycemia predispose to mycological infections [106].

Candidiasis is a common fungal infection in people with diabetes [107]. *Candida albicans* is the most prevalent pathogen and affects skin and mucosae. Recurring candidiasis is an important sign of diabetes, which enables identification of patients with pre-diabetic status in some cases [107, 108]. Clinically it shows a pruritic erythematous rash, which evolves to vesiculopustules followed by maceration and fissuring. Mucosal infections appear as whitish papules and plaques and erythematous erosions. Periungual infection like paronychia with erythema and pus drainage of the nail walls is also common.

Infection caused by dermatophytes, such as skin dermatophytosis or onychomycosis, is also common in people with diabetes. As tinea pedis is associated with micro-fissuring, it may play an important role in secondary bacterial infection, as shown above (Fig. 9) [104, 107]. Consequently, tinea should be diagnosed and treated carefully in people with diabetes. The most prevalent dermatophytes are *Trichophyton rubrum*, *Trichophyton interdigitale* and *Candida parapsilosis* [109].

Fungal infection of the otorhinolaryngological tract can cause a rare but lethal disease called rhinocerebral mucormycosis [110]. A special class of fungi named

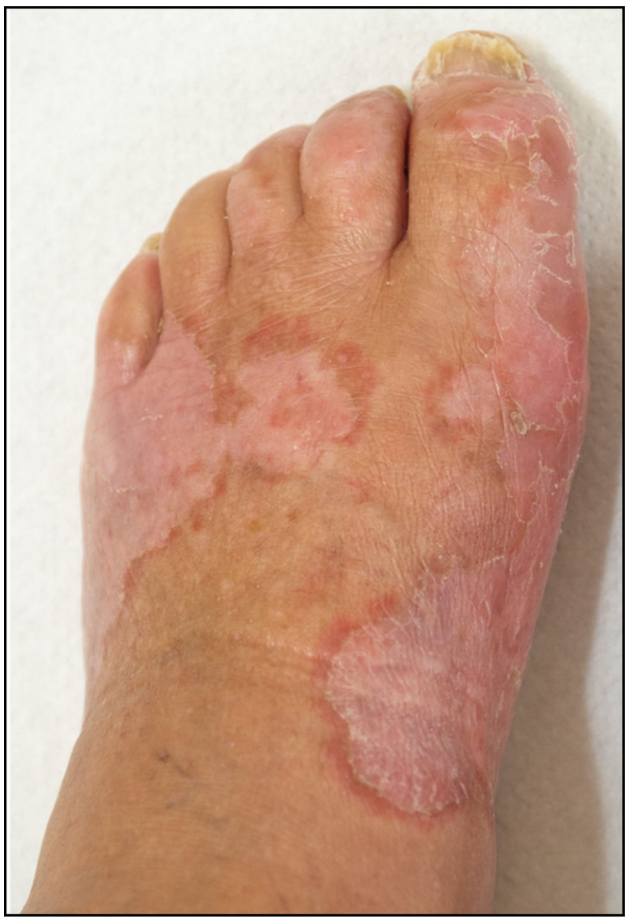

Fig. 9 Tinea pedis and onychomycosis: sharply marginated erythema associated with toenail dystrophy

Zygomycetes, like *Rhizopus*, *Rhizomucor* and *Absidia*, is responsible for the infection. It normally appears in elderly patients with unregulated serum glucose levels, but can also attack under adequate therapy [111]. Clinically, it initiates with a sinusitis with purulent nasal discharge, which evolves to a rash, facial erythema, and edema with fever in a form of cellulitis. The fungus can also break into nerves causing numbness and vessels resulting in necrosis, normally manifested on nasal or palate mucosa [112]. In complicated cases, the sphenoid sinus, cavernous sinus and carotid artery can be involved. The gold standard therapy is intravenous amphotericin B with surgical debridement of necrosis [112].

9 Complications of Anti-Diabetic Therapy

9.1 Skin Reactions Caused by Insulin

Continuous insulin application can provoke some skin reactions such as lipohypertrophy, lipoatrophy, local infections, subcutaneous nodules or insulin allergy.

Lipohypertrophy is the most frequent local reaction of subcutaneous insulin treatment and affects approximately 27% of people with diabetes [113]. It is defined by adipocyte hypertrophy of the local insulin injection site. The physiopathology might be associated with an activation of adipocytes by insulin [113]. The clinical findings show soft dermal lipoma-like nodules with variable size. This common complication also affects the local absorption of insulin, compromising the hypoglycemic therapy [114].

On the other hand, lipoatrophy is a recurrent adverse effect of insulin therapy and is characterized by atrophy of subcutaneous adipose tissue at the insulin injection site [113]. The exact pathological mechanism is still unknown, but is supposed to involve an immune-mediated reaction [115–117]. Vascular deposits of immunoglobulins are believed to promote an inflammatory cascade, leading to blockade of the adipocyte physiology [116]. Introduction of purified insulin has led to falling incidence of lipoatrophy. Continuous subcutaneous insulin infusion (CSII) may also prevent the development of lipoatrophy [118]. Despite the reduction of the incidence of lipoatrophy under CSII, some rare cases have been described in patients receiving CSII with lispro analog [118].

The risk of local bacterial infections is positively correlated to the number of daily insulin injections, while it is less uncommon in patients using insulin pumps [93].

Insulin allergy may range from localized symptoms to generalized reaction, depending on the underlying immunologic mechanism, which may be either IgE-mediated and occurring immediately after insulin injection, or of delayed type, leading to localized or generalized eczema [119]. Local reactions appear either as hives or as eczematous with erythema, papules, and vesicles on the injected site, together with pruritus [120]. Systemic manifestations may involve urticaria and angioedema as well as palmar and plantar pruritus and disseminated itching and flushing [120]. Life-threatening systemic reactions with dyspnea and hypotension have been reported in rare cases [119, 121]. If allergy to insulin injections is suspected, thorough allergy work ups are necessary, including determination of specific IgE towards insulins as well as cutaneous testing (skin prick test, intradermal test, patch test), in order to identify the responsible drug as well as alternatives [120].

9.2 Skin Reactions Induced by Oral Antidiabetics

Oral antidiabetics have been reported to cause systemic reactions such as erythema multiforme, leukocytoclastic vasculitis, allergic drug eruptions, and photosensitivity [122, 123]. In spite of their widespread use, these adverse events are very rare.

Sulfonylurea derivatives, such as glibenclamide, chlorpropamide and tolbutamide, are the most common agents associated with skin reactions and are responsible for non-specific reactions, such as photosensitivity, to allergic reactions [124–126]. These drugs have been identified as causes of lichenoid or psoriasiform drug eruptions by some authors [125, 127, 128]. On rare occasions, drug-associated pemphigus vulgaris has also been attributed to sulfonylurea therapy [129, 130].

Metformin is a commonly used antidiabetic drug included in the biguanide group, acting in the suppression of hepatic gluconeogenesis. Leukocytoclastic vasculitis and psoriasiform drug eruption induced by metformin have been reported [122, 131]. Acarbose acts by inhibiting the α-glucosidase enzymes and has been reported as a possible trigger of erythema multiforme exudativum and generalized exanthematous pustulosis [132, 133].

10 Conclusion

Diabetes mellitus is the most common metabolic disease, and early diagnosis is important to prevent complications like angiopathy, neuropathy, and nephropathy. Skin alterations appear in about 30% of people with diabetes. They may be precursors of diabetes and should therefore be recognized. Not only should patients with diabetes be seen by dermatologists at regular intervals, but also the diagnosis of diabetes should be considered in previously unrecognized patients showing typical skin conditions, such as recurring candidiasis. Furthermore, antidiabetic drugs may cause adverse skin effects, including allergic reactions that require elaborate allergy work-ups.

Compliance with Ethical Standards

Conflict of interest A. L. Lima, T. Illing, S. Schliemann, and P. Elsner declare that they have no conflicts of interest.

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