

## Chapter 2

# Pancreas Disease and Diabetes Mellitus

Franco Rongioletti

### Key Points

- The main disease concerning the endocrine function of the pancreas is diabetes mellitus.
- Cutaneous manifestations are common in diabetes mellitus, with approximately 30% of patients experiencing some cutaneous involvement during the course of their illness.
- They can be classified as (1) non-infectious, including diseases with strong and weak associations with diabetes; (2) infectious; (3) related to complications because of vasculopathy and neuropathy; (4) related to complications of diabetes treatment.
- Skin manifestations generally appear during the course of diabetes but they may be first presenting sign or even precede the diagnosis of diabetes by many years.
- Patients with type 2 diabetes are more prone to develop skin infections, whereas those with type 1 more often have autoimmune-related diseases.

**Keywords** Diabetic skin conditions • Non-infectious • Infectious • Diabetic vasculopathy • Neuropathy • Iatrogenic

### 2.1 Introduction

Diabetes is a common metabolic disease characterized by high serum glucose levels and disturbances of carbohydrate and lipid metabolism that is estimated to affect 151 million people. Famous diabetic sufferers include actresses Sharon Stone and Elizabeth Taylor who went on to lead highly successful lives, despite being diagnosed diabetes

at an early stage. Clinically, diabetes mellitus can be classified as type 1 and type 2. Type 1 diabetes mellitus, characterized by a specific autoimmune destruction of the insulin-secreting  $\beta$ -cells in the pancreatic islets, comprises 5–10% of all diabetes. Type 2 diabetes mellitus, which accounts for 80–90% of all cases, affects older and overweight patients and is characterized by a resistance to the action of insulin and inadequate insulin secretion from the pancreas. Other rare forms of diabetes include maturity onset diabetes of the youth characterized by familial incidence of hyperglycemia with monogenic autosomal dominant inheritance, gestational diabetes, drug-induced or chemically induced diabetes mellitus such as steroid diabetes. Hyperglycemia is common to all types of diabetes and leads to complex metabolic and immunologic dysfunctions that induce various patterns of pathology. Of particular importance to the development of clinical symptoms are microangiopathy, macroangiopathy, polyneuropathy, and changes to connective tissue texture [1].

Dermatologic problems are common in diabetes (Table 2.1), with approximately 30% of patients experiencing some cutaneous involvement during the course of their illness [2, 3]. Autoimmune skin lesions are more common in type 1 diabetics, whereas infectious involvement of the skin is more prevalent in type 2 diabetes mellitus [4]. Skin manifestations generally appear during the course of the disease in patients known to have diabetes, but they may also be the first presenting sign of diabetes or even precede the diagnosis by many years.

### 2.2 Clinical and Pathological Aspects of Skin Manifestations

Cutaneous manifestations in the setting of diabetes can be classified as following: (1) *non-infectious*, (2) *infectious*, (3) *related to complications because of vasculopathy and neuropathy*, and (4) *related to complications of diabetes treatment*.

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**Table 2.1** Skin manifestations associated with diabetes

Estimated prevalence (%)	Disease	Diabetes type	Comment
7–70	Diabetic dermopathy	Type 1 and type 2	Most common manifestation Sign of retinopathy, neuropathy, and nephropathy
20–30	Diabetic hand syndrome	Type 1 and type 2	Increase with age and limits joint mobility
50	Acquired perforating dermatosis	Type 2 > type 1	Patients with kidney failure
2.5–14	Scleroderma	Type 2	Permanent condition in long-standing diabetes
0.3–1.6	Necrobiosis lipoidica	Type 1 and type 2	Weak association in diabetics but 75% of affected patients have diabetes
0.5	Bullosis diabeticorum	Type 1 and type 2	Weak association. Long-standing diabetes with neuropathy
0.3	Granuloma annulare	Type 1 > type 2	Controversial association Weak link between disseminated form and type 1 diabetes
0.1	Eruptive xanthomas	Type 1 and type 2	Associated with high triglyceride-rich lipoproteins
1–7	Vitiligo	Type 1 > type 2	Sign of autoimmune syndrome
4.6–9	Psoriasis	Type 1 and type 2	Metabolic syndrome
0.3 (skin) 40 (nail)	Yellow skin and nails	Type 2 > type 1	Palms, soles, and hallux nails
0.8–59	Rubeosis faciei	Type 2 > type 1	Functional microangiopathy
2.5–22	Xerosis	Type 1 and type 2	Sometimes, acquired ichthyosis-like pattern
1.3–3	Skin tags	Type 1 and type 2	Controversial association
20–40	Prurigo/pruritus	Type 1 and type 2	Controversial association; lack of evidence-based studies
1–37	Lichen planus	Type 1 and type 2	Controversial association, some evidence for oral lichen planus
90	Acanthosis nigricans	Type 2	Strong association in selected patients (obese young women of Afro-American and Hispanic ancestry)
49	Periungual telangiectasia	Type 1 and type 2	Common, functional microangiopathy
Unknown	Erysipela-like erythema (acral erythema)	Type 2 > type 1	Microcirculatory compromise mimicking erysipela
4.1	Palmar (plantar) erythema	Type 1 and type 2	Functional microangiopathy

## 2.2.1 Non-infectious Skin Manifestations

### 2.2.1.1 Necrobiosis Lipoidica

*Necrobiosis lipoidica* (NL) is a chronic granulomatous condition that occurs in all races and at any age, but it usually appears in the third and fourth decades and is three times more common in women. Although NL occurs in only 0.3–1.6% of diabetics, it precedes the onset of diabetes mellitus in 15% of patients [5], and 75% of patients with NL have or will develop diabetes mellitus [6]. Patients with type 1 diabetes develop NL at an earlier mean age than those with type 2 and those without diabetes. Familial cases of NL not associated with diabetes have been reported [7, 8]. The lesion starts as an asymptomatic, red-brownish papule that evolves into a non-scaling plaque with a yellow atrophic center, surface telangiectases, and an erythematous or violaceous border that may be elevated (Fig. 2.1). In most cases, the lesions are multiple, bilateral, and confined to the shins, but involvement of the face, scalp, trunk, upper extremities, penis, and abdomen at insulin injection sites has

been reported. Ulceration occurs in up to 35% of cases, resulting in pain. Rarely, squamous cell carcinoma has been reported in older, ulcerated lesions. The Koebner phenomenon has been unusually associated. Sensory loss because of nerve damage, hypohidrosis, and alopecia has been reported [9]. Laboratory findings are not helpful in the diagnosis of NL, as it relies on histopathology. Histologically, NL is characterized by an interstitial and palisaded, necrobiotic granulomatous inflammation with histiocytes and a variable numbers of Langhans and foreign body giant cells in the lower two-thirds of the reticular dermis, extending into the septa of subcutaneous tissue (Fig. 2.2a). Aggregates of lymphoid cells with numerous plasma cells are typically present around the deeper vessels (Fig. 2.2b). Vasculopathy with thickening of the blood vessel walls and proliferation of the endothelial cells are found, especially in patients with diabetic microangiopathy (Fig. 2.2c) NL may also present with a collection of more typical epithelioid granulomas and less degenerated collagen and vasculopathy. This form seems to have a weaker association with diabetes than the classic one. Direct immunofluorescence studies show

IgM, IgA, C3, and fibrinogen in the blood vessels and at the dermoepidermal junction.

The main differential diagnosis is with necrobiotic xanthogranuloma, which is characterized by yellowish, indurated, often periorbital plaques and the presence of a monoclonal gammopathy, and histologically with granuloma annulare (GA) in which patchy, superficial, discrete foci of granulomatous inflammation with mucin deposition are observed.

The exact cause is unknown. NL diabeticorum has been considered as an antibody-mediated vasculitis with secondary collagen degeneration. Other factors implicated in the pathogenesis of NL include diabetic microangiopathy, impaired

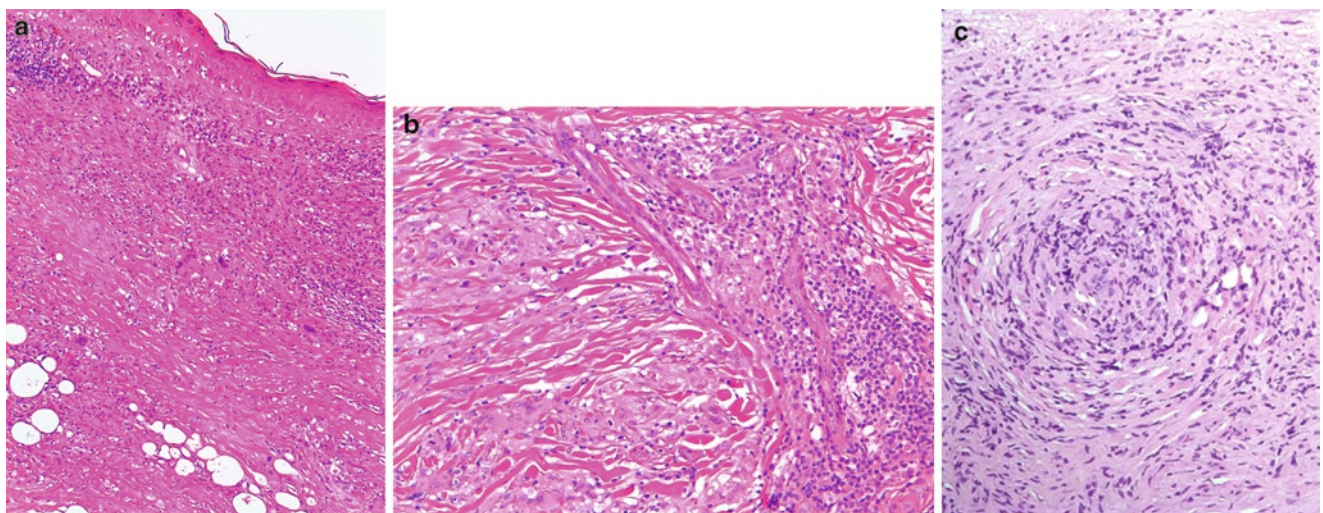
neutrophil migration, hyperlipidemia, venous reflux, and borrelia infection [10]. The findings of Glut-1 (human erythrocyte glucose transporter) expression in the areas of sclerotic collagen suggest that these abnormalities in glucose transport by fibroblast may have a role.

### 2.2.1.2 Diabetic Dermopathy

*Diabetic dermopathy* (DD) (i.e., *shin spots* and *pigmented pretibial papules*) is the most common cutaneous manifestation of diabetes occurring in 7–70% of all diabetic patients. It occurs twice as frequently in men compared with women, and the mean age is 50 years [4]. DD is commonly seen in diabetics with other end-organ damage such as retinopathy, neuropathy, and nephropathy. Coronary artery disease is present in 53% of patients with DD. Rarely, DD may precede abnormal glucose metabolism. Lesions consist of asymptomatic, bilateral, asymmetrical, well-demarcated, annular or irregular atrophic, brownish macules of 4–12 mm in diameter on the shins (Fig. 2.3). Involvement of the thighs and abdomen has been reported. The lesions do occur in patients without diabetes, but four or more lesions with typical features of DD are considered characteristic of diabetes mellitus [11]. Histopathology is not specific, especially in early lesions, and the diagnosis is a clinical one. Well-developed, atrophic macules exhibit epidermal atrophy, angioplasia of the superficial capillary plexus with hyaline microangiopathy, hemosiderin deposition, and a slight perivascular infiltrate of lymphocytes with plasma cells [12]. DD requires differentiation primarily from purpura pigmentosa chronica and stasis



**Fig. 2.1** Necrobiosis lipoidica on the shin



**Fig. 2.2** Necrobiosis lipoidica. (a) Interstitial and palisaded, necrobiotic granulomatous inflammation with histiocytes and giant cells in the lower reticular dermis, extending into the subcutis. (b) Infiltrate with

plasma cells and granulomatous features. (c) Microangiopathy in deep dermis (HE stain)



**Fig. 2.3** Diabetic dermopathy

dermatitis. Atrophy and involvement of the shins in addition to diabetes are helpful. The cause is obscure but alterations in skin blood flow as part of diabetic microangiopathy and unnoticed trauma have been implicated.

### 2.2.1.3 Granuloma Annulare

*Granuloma annulare* (GA) is a benign self-limited, granulomatous inflammatory disease. When discussing skin conditions in the setting of diabetes, GA is always mentioned but the link between the two conditions has been debated. Recent studies have failed to show conclusively any link between GA and type 2 diabetes [13], although a weak link with type 1 diabetes has been demonstrated. This correlation seems to be more likely with the disseminated form than with localized variants [14]. GA has also been associated with autoimmune diseases like SLE, thyroid disease, HIV infection, giant cell arteritis, lymphoproliferative conditions, and solid tumors [15].

GA is typically a papular disease which can be divided into a localized, disseminated (more than ten lesions involving trunk and limbs), or linear type. The most common presentation is the localized, papular form (80% of cases) that occurs before the age of 30, most commonly in children and it is twice as often in females. The lesions typically are located on the dorsa of the hands and feet and are characterized by multiple, small, skin-colored or erythematous papules that coalesce into an arcuate or annular pattern (Fig. 2.4).



**Fig. 2.4** Granuloma annulare



**Fig. 2.5** Granuloma annulare papular type

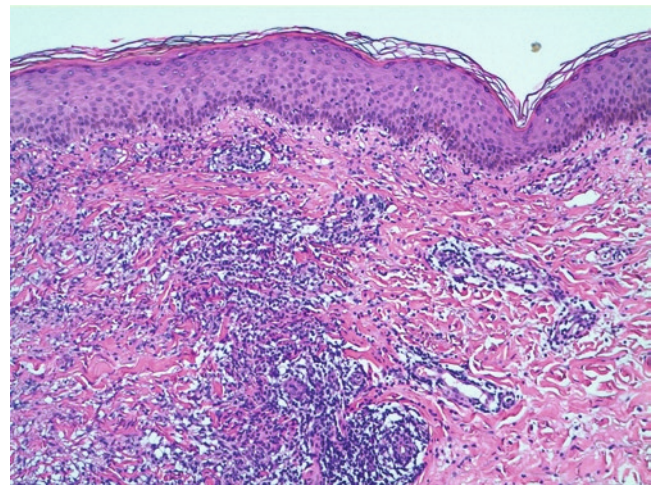
The pure (micro) papular form without annular pattern is less frequent (Fig. 2.5). Disseminated, papular GA occurs in 15% of cases, prevailing in middle-aged and elderly patients. It is characterized by hundreds to thousands of small, skin-colored-to-erythematous papules that are distributed symmetrically on the extremities and trunk. Disseminated GA is the most common clinical pattern in HIV infection. Other main clinical variants include: perforating type with central umbilication or crusts, subcutaneous (deep) type (also known as pseudo-rheumatoid nodule) most commonly observed in children, and patch type characterized by red-brown patches without evident papular component or scale that may or may not have an annular configuration on the trunk and extremities (Fig. 2.6). GA is usually asymptomatic but an acute-onset, painful acral form has been described. Any atypical form of GA should alert to the possibility of a paraneoplastic link [16]. Follicular pustular cases have been rarely described as well as atypical site of involvement such as the face, the palms, and penis. Systemic involvement such as anterior uveitis is an exceptional event [17].

Three histological patterns are typically recognized: necrobiotic granuloma (classic) pattern, interstitial or “incomplete” form, and the sarcoidal or tuberculoid type.

The classic (necrobiotic granuloma pattern) consists of areas of degenerated collagen filled with mucin surrounded by histiocytes and a variable numbers of multinucleate giant cells in a peripheral rim, forming a palisaded pattern (Fig. 2.7). Occasionally, neutrophils or nuclear fragments are seen inside the granuloma. Vessel involvement with fibrinoid deposition and endothelial swelling and true vasculitis are rarely found and are said to be predictive of associated systemic disease [18]. A perivascular infiltrate of lymphocytes with some eosinophils may also be seen. In subcutaneous GA, areas of necrobiosis are often larger than in the superficial type and are located into deep dermis and/or subcutis. Eosinophils are said to be more common in this variant. In perforating GA, a central epidermal perfora-



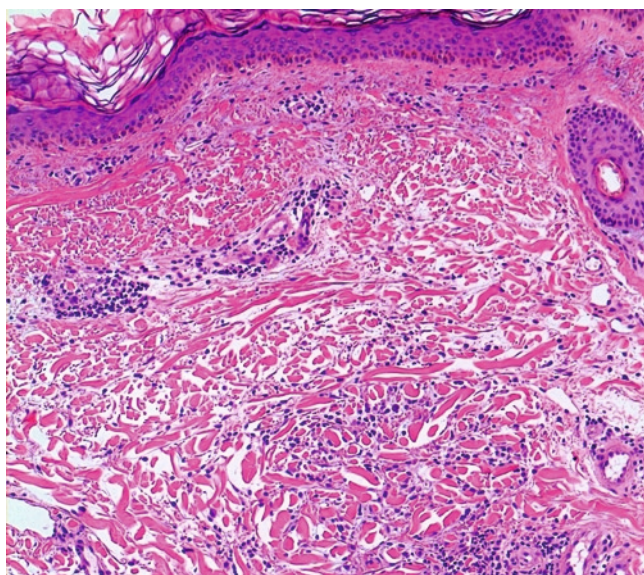
**Fig. 2.6** Granuloma annulare patch type



**Fig. 2.7** Granuloma annular, necrobiotic pattern (HE stain)

tion communicates with underlying necrobiotic granuloma. The interstitial or “incomplete” form is the most common pattern, in which lymphocytes and histiocytes infiltrate between collagen fibers in the absence of areas of degenerated collagen with interstitial mucin (Fig. 2.8). The non-necrobiotic sarcoidal or tuberculoid type of GA is the least common pattern. Immunohistochemistry reveals a broad, intense expression of CD68/PGM1 in the histiocytic population [19].

GA is diagnosed based on clinical and pathological correlation and no laboratory tests are helpful. Although the pathogenesis of GA remains uncertain, GA is considered



**Fig. 2.8** Interstitial type of granuloma annulare (HE stain)

a Th1 inflammatory-delayed reaction with the release of cytokines, including macrophage inhibitor factor, which cause histiocytes to accumulate in the necrobiotic areas and to release lysosomal enzymes that result in degenerated connective tissue. A genetic component plays a role as familial cases have been reported and the generalized form has been significantly associated with HLA-BW35. An immunoglobulin-mediated vasculitis also has been proposed. Triggering pathogenetic associations include insect bites, Bartonella and Borrelia infection [20], HIV, Epstein-Barr virus, herpes zoster, hepatitis C virus, trauma, intralesional skin tests, erythema multiforme, exposure to ultraviolet light, and scars secondary to herpes zoster.

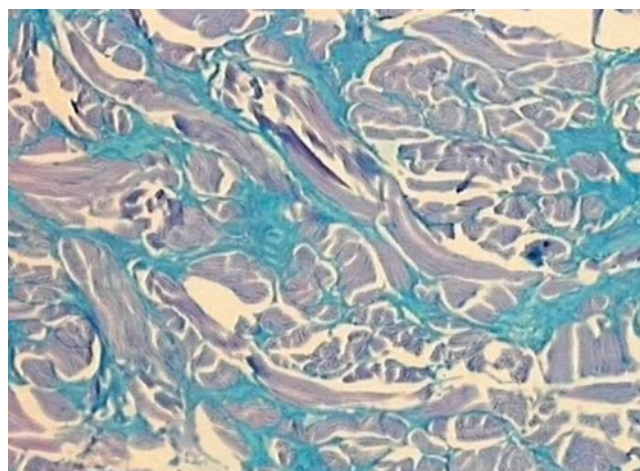
#### 2.2.1.4 Diabetic Thick Skin

*Diabetic thick skin* is seen both in type 1 and type 2 diabetic patients. Diabetic patients with neurological disorders have a significant increase in skin thickness versus diabetic patients without neuropathy. Two forms are described: *scleredema* and *diabetic hand syndrome*, which share a common histopathology characterized by thickened dermis and deposition of mucin. As for pathogenesis, an irreversible glycosylation of collagen and resistance to degradation by collagenase could lead to an accumulation of collagen. Alternatively, excess stimulation by insulin, microvascular damage, and hypoxia could increase the synthesis of collagen and mucin.

*Scleredema diabeticorum* occurs in 2.5–14% of patients with obesity and long-standing, poorly controlled diabetes, with micro and macroangiopathies (see also Chap. 18). The



**Fig. 2.9** Scleredema diabeticorum



**Fig. 2.10** Scleredema with large collagen bundles separated from one another by clear spaces filled with mucin (Alcian blue stain)

clinical findings are characterized by symmetric non-pitting induration of the posterolateral aspects of the neck and upper back (Fig. 2.9), occasionally extending to the deltoid and lumbar regions. A *peau d'orange* appearance of the skin can occur, often with decreased sensitivity to pain and touch. The onset is subtle and the involvement persistent. Systemic manifestations may include serositis, dysarthria, dysphagia, myositis, parotitis, and ocular and cardiac abnormalities. Histopathology discloses thickening of the reticular dermis, with large collagen bundles separated from one another by clear spaces filled with mucin, resulting in fenestration of the dermis (Fig. 2.10). Direct immunofluorescence is usually negative, but IgG and C3 have been found at the dermal–epidermal junction. Mucin also accumulates in skeletal

**Fig. 2.11** Diabetic thick skin of the hand (pebble hands)



muscle and the heart. Diabetic scleredema does not undergo spontaneous resolution.

Thickening of the skin on the dorsum of the hands, also known as *diabetic hand syndrome* or *diabetic sclerodactyly*, occurs in 20–30% of both diabetic type 1 and diabetic type 2 patients [21]. Clinical presentations range from pebbled knuckles (or Huntley papules) that are multiple minute papules, grouped on the extensor side of the fingers, on the knuckles, or on the periungual surface that progress to stiffness of the metacarpophalangeal and proximal interphalangeal joints, limiting joint mobility (Fig. 2.11). Cheiroarthropathy, known as the prayer sign, is the inability to appose the palmar surfaces when pressing the hands together and is considered an indicator of limited joint mobility. Dupuytren contracture (or palmar fascial thickening) may further complicate diabetic hand syndrome. The thickening is measurable by ultrasonography and tends to increase with age. The histopathologic findings of diabetic sclerodactyly show a thick dermis, increased cross-linked collagen in the reticular dermis, and small amounts of mucin. It is important to distinguish between diabetic thick skin and scleroderma.

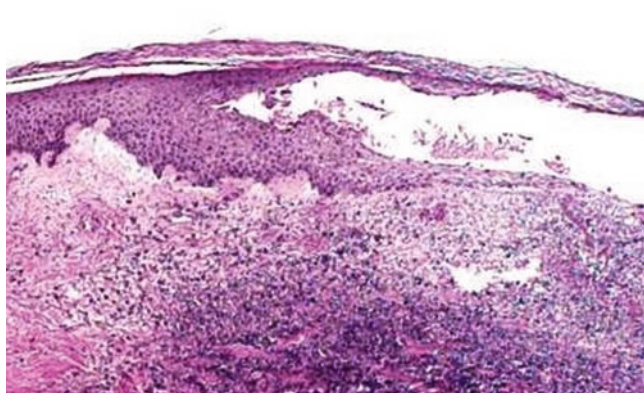
#### 2.2.1.5 Bullosis Diabeticorum

*Bullosis diabeticorum* or *diabetic bullae* or *bullous disease of diabetes* is a non-inflammatory blistering condition occurring in 0.16–0.5% of patients with type 2 diabetes. The bullae are seen more frequently in adult men with long-standing diabetes and neuropathy but they may also be the first



**Fig. 2.12** Bullosis diabeticorum

presentation of diabetes [22]. Diabetic bullae most often present as painless, tense, superficial bullae that occur in an acral distribution, mostly on the legs and feet (Fig. 2.12). Complications such as secondary bacterial infection, hemorrhage, or osteomyelitis may occur. Diabetic bullae have a heterogeneous histologic presentation as the blister may appear in a subcorneal, intraepidermal, or subepidermal location (Fig. 2.13). Dermal changes such as capillary wall thickening and dermal sclerosis reflect the patient's underlying diabetes mellitus. Caterpillar bodies typical of porphyria have been rarely reported. Direct immunofluorescence studies are negative. Trauma, diabetic neuropathy, and microangiopathy all could play a role. The differential diagnosis



**Fig. 2.13** Subepidermal and intraepidermal bulla of bullous diabeticorum (HE stain)

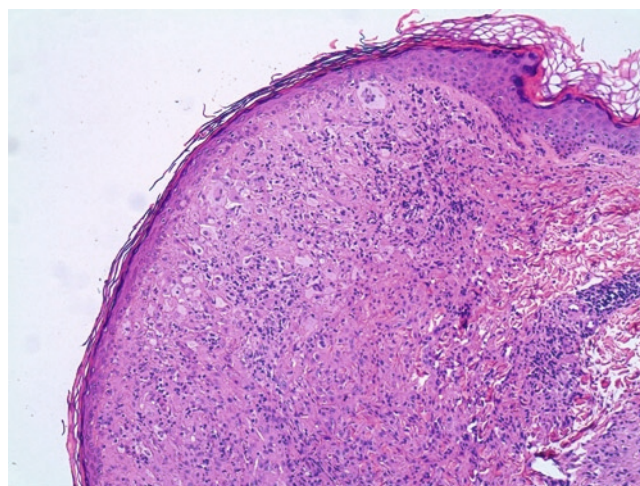


**Fig. 2.14** Eruptive xanthomas

includes autoimmune bullous disorders, porphyria, and pseudo-porphyria

#### 2.2.1.6 Eruptive Xanthomas

*Eruptive xanthomas* occur in the setting of chylomicronemia and hypertriglyceridemia caused by genetic abnormalities. Diabetes mellitus is a common cause of hypertriglyceridemia (diabetic lipemia), and the resultant eruptive xanthomas may be the first sign of an underlying untreated diabetes, usually of type 2 [23]. The incidence of eruptive xanthomas in diabetics is estimated at 0.1%. Eruptive xanthomas may also appear following alcohol abuse or ingestion of drugs such as estrogens or retinoids, or in the setting of hypothyroidism. Eruptive xanthomatosis manifests itself with the sudden appearance of yellowish-orange-to-red-brown, firm papules surrounded by a 1–4 mm wide erythematous halo (Fig. 2.14). They appear in crops on the buttocks, extensor surfaces of the extremities, and flexural creases. Pruritus and Koebner reaction may be present. Histologically, foamy macrophages



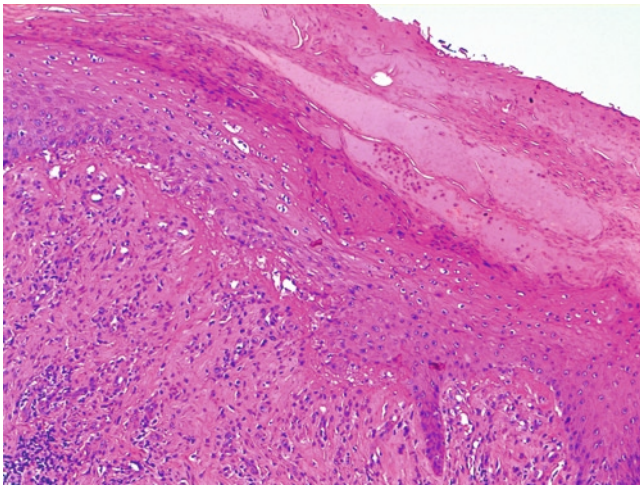
**Fig. 2.15** Histopathology of eruptive xanthoma (HE stain)

with extracellular lipid deposits are present in the papillary and upper reticular dermis with an admixed inflammatory infiltrate of lymphocytes and neutrophils (Fig. 2.15). Touton type giant cells are usually absent.

#### 2.2.1.7 Acquired Perforating Dermatoses

Acquired perforating dermatosis is a rare disorder seen in adult patients, especially those presenting with type 2 and type 1 diabetes mellitus (50%) and with chronic renal failure (73%) [24]. Most of the patients with diabetes mellitus (90.9%) had chronic renal failure because of diabetic nephropathy. It is characterized clinically by itching, hyperkeratotic, sometimes umbilicated or follicular papules and nodules with a central core, situated primarily on the extensor surfaces of the lower (Fig. 2.16a) and upper extremities, often in a linear fashion (Fig. 2.16b). Koebner phenomenon is seen in 32% of patients. The histological features are not uniform, and may resemble any of the four classic perforating disorders: *elastosis perforans serpiginosa*, *reactive perforating collagenosis*, *perforating folliculitis*, or *Kyrle's disease*. This classification is based primarily on the nature of the eliminated material and the type of epidermal disruption. In general, epidermal invagination filled with a keratotic plug admixed with basophilic cellular debris and neutrophils are the key features. If Masson trichrome and elastic van Gieson stains are negative in the epidermis and in the crater at the base of the lesion, the overall histological appearance is consistent with Kyrle's disease (Fig. 2.17). If vertically orientated collagen bundles are seen at the base of the cup-shaped invagination with transepidermal elimination, the overall histological appearance is consistent with reactive perforating collagenosis (Fig. 2.18a, b). If histochemical staining shows transepidermal elimination of degenerated elastic fibers, the overall histological appearance

**Fig. 2.16** Acquired perforating dermatoses in diabetic. (a) Kyrle's disease. (b) Reactive perforating collagenosis showing a linear arrangement due to Koebner phenomenon (Courtesy of James W. Patterson, Charlottesville, VA, USA)



**Fig. 2.17** Early lesion of Kyrle's disease with a central cup-like keratotic plug within an epidermal invagination (HE stain)

is consistent with elastosis perforans serpiginosa. When transepidermal elimination of collagen and elastic fibers occurs in many follicles, the features are consistent with perforating folliculitis (Fig. 2.19a, b). In diabetic patients, PAS staining may reveal thickening of the vessel walls in the upper dermis. The cause of APD is unknown, but it has been related to intense pruritus and subsequent scratching, to diabetic microangiopathy and hypoperfusion of dermal structures with an increase in matrix metalloproteinases, epidermal, or dermal change related to metabolic derangements, and to deposition of substances that cannot be removed with dialysis.

### 2.2.1.8 Acanthosis Nigricans

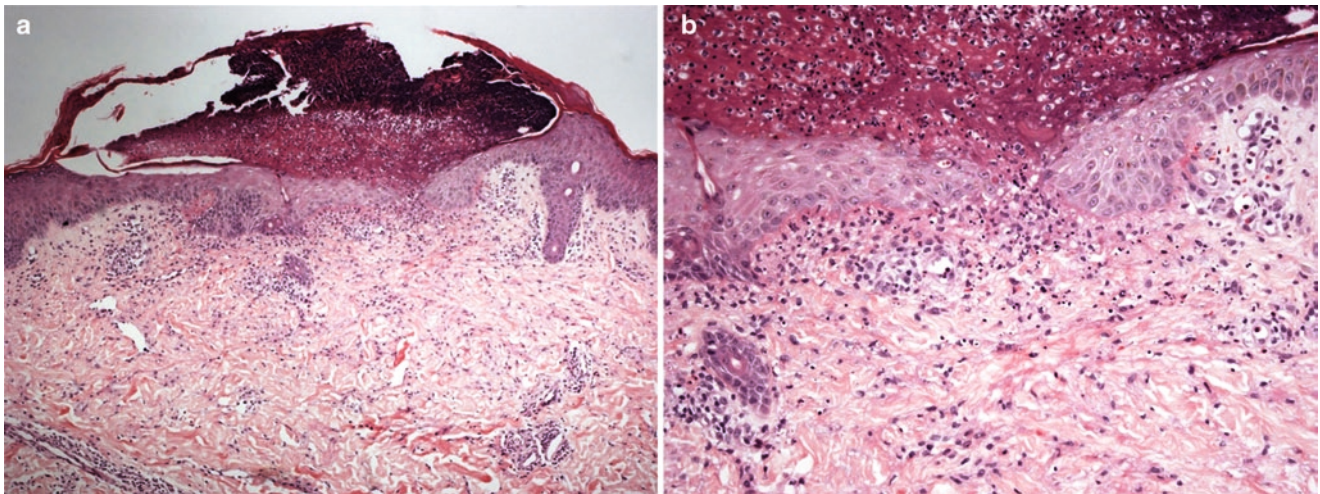
Acanthosis nigricans is a cutaneous manifestation of insulin-resistant diabetic patient and may indicate increased risk of

type 2 diabetes mellitus [25]. Insulin resistance is the most common association of acanthosis nigricans in the younger age population. However, it can occur as a sign of malignancy (particularly stomach cancer), as an adverse effect of certain drugs (i.e., nicotinic acid and corticosteroids), in various endocrinopathies (i.e., acromegaly, Cushing syndrome, and leprechaunism), and associated with obesity (see also Chap. 9). Acanthosis nigricans presents as hyperpigmented, velvety plaques involving typical areas such as the posterior neck, the axilla, and flexural surfaces (Fig. 2.20). Although the lesions are generally asymptomatic, they can be painful, malodorous, or macerated. Acrochordons (skin tags) are often found in and around the affected areas. Histologic examination reveals hyperkeratosis, papillomatosis, and slight irregular acanthosis with minimal or no hyperpigmentation (Fig. 2.21). The dermal papillae project upward as finger-like projections, with occasional thinning of the adjacent epidermis. Clinical hyperpigmentation is secondary to the hyperkeratosis and not to increased melanocytes or increased melanin deposition. The pathogenesis is most likely related to high levels of circulating insulin, which binds to insulin-like growth factor receptors to stimulate the growth of keratinocytes and dermal fibroblasts.

### 2.2.1.9 Miscellanea

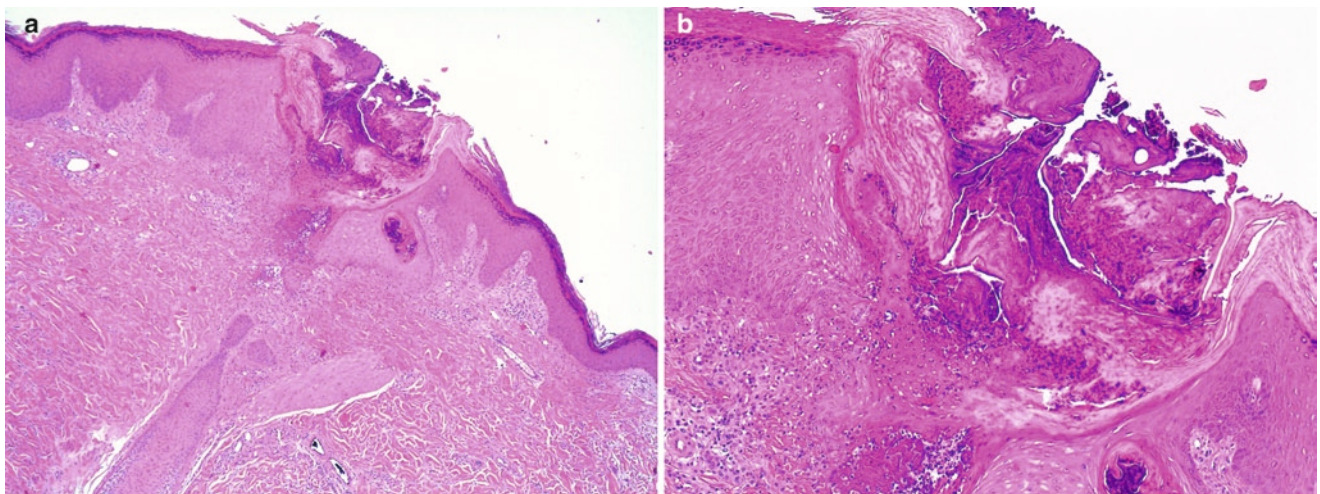
“Yellow nails and skin” is a benign condition associated with diabetes whose significance is unknown. The tinctoral change may be due to either high levels of carotene or non-enzymatic glycosylation of dermal collagen. The yellow color is best appreciated at the distal hallux of the nails, palms, and soles (Fig. 2.22).

The association between diabetes and lichen planus is controversial. Some studies have showed a significantly



**Fig. 2.18** Reactive perforating collagenosis. (a) Epidermal invagination filled with a keratotic plug admixed with basophilic cellular debris (HE stain) (Courtesy of James W. Patterson, Charlottesville, VA, USA).

(b) Transepidermal elimination of collagen fibers (Courtesy of James W. Patterson, Charlottesville, VA, USA)



**Fig. 2.19** Perforating folliculitis. (a) Transepidermal elimination of basophilic cellular debris and neutrophils throughout the follicle. (b) Close-up of follicular transepidermal elimination (HE stain)



**Fig. 2.20** Acanthosis nigricans with skin tags on the axilla

higher prevalence of lichen planus, especially oral lichen planus, in type 1 diabetic patients [26].

Vitiligo occurs with increased frequency in type 1 diabetic patients. From 1 to 7% of all diabetic patients have vitiligo versus 0.2 to 1% of the general population [4]. The association is based on autoimmune mechanisms and is a warning sign for polyglandular autoimmune syndrome.

Although skin tags are common lesions, over 25% of patients with acrochordons had diabetes and 8% had impaired glucose tolerance in a controlled study [4]. Acquired ichthyosis, especially in type 1 diabetic patients [27], is commonly described, while pruritus associated with diabetes mellitus, although commonly reported, is a controversial

association. The described pruritus is often localized to the vulva or anus and usually is due to candidal infection. Cutaneous signs of diabetic microangiopathy are periungual telangiectasia, palmar (plantar) erythema, rubeosis faciei, and erysipelas-like erythema, which is a well-demarcated erythema on the lower leg or dorsum of the foot that corre-

lates with radiological evidence of underlying bone destruction, and incipient gangrene.

### 2.2.2 Cutaneous Infections

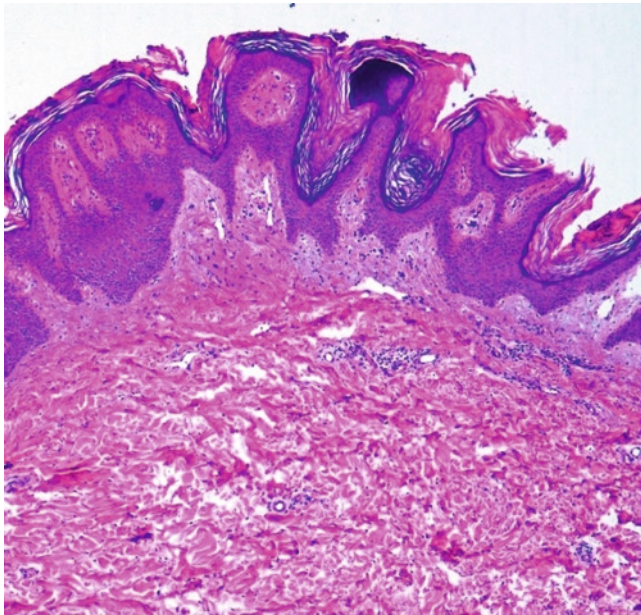
Skin infections occur in 20–50% of diabetic patients (more often in those with type 2 diabetes) and are often associated with poor glycemic control.

#### 2.2.2.1 Bacterial Infections

Pyodermic infections such as folliculitis, furunculosis, impetigo, erysipelas, and cellulitis are more severe and widespread in diabetics and are caused by *Staphylococcus aureus* or hemolytic streptococci. Staphylococcal sepsis can complicate even the smallest wound. Necrotizing fasciitis is a life-threatening condition that may occur in diabetics (Fig. 2.23). This infection is typically polymicrobial, involving group A streptococci, enterococci, *S. aureus*, enterobacteriaceae, and various anaerobes.

Non-clostridial gas gangrene occurs in 17% of diabetics admitted to the hospital for gangrene or ulceration.

Erythrasma is a brown-red discoloration of the intertriginous areas of the skin due to *Corynebacterium minutissimum*. It is seen with increased frequency in obese diabetics.



**Fig. 2.21** Histopathology of acanthosis nigricans (HE stain)



**Fig. 2.22** Yellow palms in a diabetic type 2



**Fig. 2.23** Necrotizing fasciitis in a diabetic with poor glycemic control



**Fig. 2.24** Intertrigo and vulvovaginitis in a diabetic woman

### 2.2.2.2 Candida Infections

*Candida* infections may be an early sign of undiagnosed diabetes and commonly develop in patients with poorly controlled disease. They include candidal angular stomatitis (perleche), median rhomboid glossitis, paronychia, erosion interdigitale blastomycetica characteristically involving the web space between the middle and fourth finger, vulvovaginitis with intertrigo (Fig. 2.24), balanitis, and phimosis.

### 2.2.2.3 Dermatophyte Infections

Although dermatophyte infections are not more frequent in diabetics compared with controls, tinea pedis and onychomycosis because of *Trichophyton rubrum* and *Trichophyton mentagrophytes* can result in significant morbidity as they can act as a portal of entry for bacterial infection.

### 2.2.2.4 Rare Infections

A few infections, such as malignant otitis externa, and rhinocerebral mucormycosis occur almost exclusively in patients with diabetes. Malignant otitis externa involves middle-aged, diabetic patients and is usually due to *Pseudomonas aeruginosa*. Infection starts with severe ear pain and otorrhea in the external auditory canal and spreads to adjacent soft tissue, cartilage, and bone.

Mucormycosis is caused by various ubiquitous molds (Phycomycetes). Invasive disease occurs in patients with poorly controlled diabetes and ketoacidosis. Fungi colonize the nose and paranasal sinuses with periorbital or perinasal pain, swelling, and induration, spreading to adjacent tissues by invading blood vessels and causing soft tissue necrosis, bony erosion, and cerebral abscesses (Fig. 2.25).



**Fig. 2.25** Rhinocerebral mucormycosis in a diabetic

## 2.2.3 Complications Due to Diabetic Neuropathy and Vasculopathy

Diabetic foot ulcers are common complications that occur in 15% of diabetic patients at some time during their lifetime. A total of 12–24% of individuals with a foot ulcer requires amputation (Fig. 2.26). Indeed, diabetes is the leading cause of non-traumatic lower extremity amputations. Foot complications occur in both forms of diabetes (type 1 and type 2) and are related more to the period of time that the illness has been present than to the age of onset. A number of factors are involved in the development and maintenance of a diabetic foot ulcer, including: sensorimotor and autonomic polyneuropathy, mechanical overload, peripheral arterial disease and infection. Diabetic peripheral neuropathy causes altered or complete loss of feeling in the foot and/or leg. There are two types of diabetic foot: (a) neuropathic foot that is warm, painless with palpable pulses,

characterized by diminished sweating and dry skin prone to fissuring; (b) neuroischemic foot that is cool, painful, and pulseless characterized by thin, shiny skin. The typical perforating foot ulcer is a circular deep ulcer with a hyperkeratotic ring on areas most subjected to weight bearing, such as the heel, plantar metatarsal head areas (Fig. 2.27), the tips of the most prominent toes (usually the first or second), and the



**Fig. 2.26** Diabetic foot undergone to amputation for necrosis of toes



**Fig. 2.27** Perforating foot ulcer

tips of hammer toes. Histologically, changes are related to the time of biopsy and are not specific. Hyperkeratosis is conspicuous, particularly at the edges of the lesion. The dermis is hypertrophic with a greater degree of fibrosis, frequently disrupting the normal structure of the extracellular matrix. An inflammatory infiltrate, mainly represented by leukocytes and macrophages, is present with variable granulation tissue [28].

Calciphylaxis, also known as calcific uremic arteriolopathy, is a small-vessel vasculopathy accompanied by mural calcification with intimal proliferation, fibrosis, and thrombosis (see also Chaps. 5 and 21). Poor-healing, necrotizing skin ulcers with a livedo-like reticular pattern are seen. In renal failure patients, women, white, obese, or diabetic patients (especially those with type 2 diabetes) are considered at risk [29]. Penile necrosis has been described in patients with a long history of diabetes, who were on dialysis [30].

#### **2.2.4 Complications Due to Diabetes Treatment**

Maculopapular rash, generalized erythema, and urticarial reactions may be induced by first-generation sulfonylureas such as chlorpropamide and tolbutamide in the first month of therapy and may resolve spontaneously, even if therapy is not stopped. Second-generation sulfonylureas (glipizide and glimepiride) are less likely to cause skin reactions. Metformin, the first choice oral drug in type 2 diabetes, may cause leukocytoclastic vasculitis.

Allergic reactions due to insulin range from IgE-mediated local erythematous reactions to more generalized reactions with angioedema and urticaria, and to delayed reactions characterized by an itching nodule at the site of injection. Biphasic reactions, with immediate itching and burning at the injection site, followed by a more sustained induration and generalized reaction 4–8 h later may occur. Such reactions may result from the insulin itself or from impurities, preservatives, additives, or retarding agents such as zinc or protamine and occur within 1–4 weeks of starting treatment. The use of recombinant human insulin preparations has decreased the incidence of insulin reactions to a rate of 0.1–2.4%. Lipoatrophy characterized by depressed areas at injection sites is actually rare (Fig. 2.28) while lipohypertrophy clinically mimicking lipomas can still occur due to the lipogenic action of insulin. Keloids, hyperkeratotic papules, localized hyperpigmentation, and purpuric reactions have also been reported.



**Fig. 2.28** Insulin lipoatrophy

## 2.3 Treatment and Prognosis

NL tends to chronicity. No robust studies have demonstrated any particularly effective therapy to date. Topical and intralesional corticosteroids are empirically considered as a first-line treatments lessening the inflammation of early active lesions and the active borders, but worsening the atrophy. Many recent therapies have been tried with variable success including topical tacrolimus, topically applied bovine collagen, mycophenolate mofetil, cyclosporin A, UVA1 therapy, photodynamic therapy, and pulse dye laser. Excision and grafting have been successful, but recurrence may occur. Anti-tumor necrosis factor alpha (TNF- $\alpha$ ) agents such as etanercept and infliximab have been used for refractory, ulcerative NL [31]. Treatment of the hyperglycemic state does not change the cutaneous lesions, although improvement following pancreas transplantation has been reported [32]. Because localized trauma can cause NL to ulcerate, protection of the legs with elastic support stockings and leg rest is useful.

The evolution of DD is variable and does not appear to be affected by glycemic control. The lesions may persist or resolve spontaneously with scar formation and recur in crops. Treatment is not very effective. Particular attention should be placed on the detection and prevention of diabetic complications such as retinopathy, neuropathy, nephropathy, and coronary heart disease, as patients with DD are more inclined to develop microangiopathies.

No well-designed randomized controlled studies have demonstrated any particularly effective therapy for GA. Localized disease generally is self-limited and resolves within 2 months to 2 years, whereas disseminated disease may last 3–4 years or as long as 10 years. For localized disease,

topical or intralesional glucocorticoids, tacrolimus and pimecrolimus, imiquimod, pulse dye laser, and cryotherapy have been used with variable success. Because localized GA is self-limited, a “wait and see approach” is also warranted. For disseminated disease, treatment modalities include retinoids, antibiotics, nicotinamide, dapsone, pentoxifylline, cyclosporine, fumaric acid esters, antimalarials, photodynamic therapy, and ultraviolet therapy including UVA1 phototherapy [33]. Regarding TNF- $\alpha$  inhibitors, there are reports reflecting resolution of the disease with this treatment modality while others show no benefit [34]. Lesions may resolve after biopsy. Recurrences occur in 40% of cases.

No effective treatment is known for scleredema diabeticorum. Control of the hyperglycemia does not have any influence on the skin. Many treatments have been tried with variable success. Phototherapy such as UVA1, cyclosporine, low-dose methotrexate, intravenous immunoglobulin therapy, and electron-beam therapy have all been reported to be of benefit [35, 36]. Aggressive therapies, however, should be limited to individuals with disabling disease or systemic manifestations.

There is no therapy for diabetic hand, although strict glycemic control may be helpful. Physical therapy is recommended to prevent limitations in the range of motion [37].

Diabetic bullae heal spontaneously without scarring in 2–6 weeks, but they may be recurrent. Blisters may turn into chronic foot ulcers with complications [38]. Glycemic control does not appear to have a direct correlation with blister formation.

Eruptive xanthomas usually resolve spontaneously over weeks and may result in hyperpigmented scars. Adequate treatment involves controlling the underlying hyperlipidemia with strict dietary therapy. Weight reduction and carbohydrate intake restriction are helpful in cases associated with diabetes. Eruptive xanthomas may herald the risk of atherosclerotic disease and acute pancreatitis.

Different treatments have been tried for acquired perforating dermatosis with variable results, such as topical or intralesional steroids, phototherapy including narrowband UVB, topical, and systemic retinoids, systemic antihistamines, antibiotics, and allopurinol [39]. Although there have been some reports of the spontaneous disappearance of perforating disorders with the stabilization of diabetes and renal disease, most cases of perforating disease continue for years unless treated.

The most effective treatment for acanthosis nigricans is lifestyle alteration. Weight reduction and exercise can reduce insulin resistance. Keratolytics such as ointments containing salicylic or retinoic acid can be used to reduce thicker lesions in areas of maceration in order to decrease odor. Oral agents that have shown some benefits include etretinate, isotretinoin, metformin, and dietary fish oils. Dermabrasion and laser therapy may also be used to reduce the bulk of the lesion.

Foot ulcers in diabetes require multidisciplinary assessment, usually by diabetes specialists, dermatologists, and surgeons. Treatment consists of appropriate bandages, strict infection control, skin grafts, skin substitutes, debridement, and arterial revascularization [40]. Hyperbaric oxygen therapy reduce the risk of amputation and may improve the healing.

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