Diabetes Mellitus

41

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Abbreviations

AN	Acanthosis nigricans
BD	Bullosis diabeticorum
CN	Charcot neuroarthropathy
DM	Diabetes mellitus
DPN	Diabetic peripheral neuropathy
EGFR	Epidermal growth factor receptor
FGFR	Fibroblast growth factor receptor
GA	Granuloma annulare
IGF-1	Insulin-like growth factor 1
KD	Kyrle's disease
LP	Lichen planus
NL	Necrobiosis lipoidica
SA	Scleredema adultorum
SD	Scleredema diabeticorum
STs	Skin tags

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.
- Many cutaneous manifestations of DM have better outcomes with optimal blood glucose control.
- Foot ulcerations are one of the most serious and disabling complications of diabetes, being nonhealing ulcers an important cause of lower extremity amputation.
- Patients with diabetes are more prone to infections than healthy individuals.

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 skele-

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tal muscles) insulin resistance. This condition is accompanied by a progressive, age-related decrease in pancreatic insulin release.

DM is one of the most important global health emergencies of this century. Around 463 million people worldwide, or 9.3% of adults, are estimated to have diabetes. A 51% increase in its prevalence by 2045, with 700 million people, or 10.9% of the worldwide population, is estimated [4]. In addition, diabetic retinopathy is the leading cause of new cases of blindness among adults in developed countries [5]. Other well-established complications of DM are cardiovascular disease, kidney failure, and limb amputation. More recently, the casual link between DM and cancers, dementia, infections, and liver disease have also been recognized [6].

In 80% of the cases, type 2 DM is identified. On second place comes type 1 DM, with up to 10% of the cases. DM also appears in 7% of all pregnancies, mostly as gestational diabetes [7].

Complications related to diabetes are the result of metabolic, hormonal, environmental, and genetic factors manifesting in every organ system. The cutaneous commitment ranges in severity (from mundane cosmetic concerns to life threatening), prevalence, and treatment response [8].

One or more skin disorders may be present in 30–92% 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 [9–12]. The most common skin manifestations are cutaneous infections (47.5%), xerosis (26.4%), and inflammatory skin diseases (20.7%) [13].

The prevalence of cutaneous disorders seems to be comparable between type 1 DM and type 2 DM patients; however, cutaneous infections are more common in type 2 DM 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 41.1).

Table 41.1 Dermatologic manifestations related to diabetes mellitus

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

Skin Manifestations

Diabetes-Specific Skin Conditions

Diabetic Dermopathy

Diabetic dermopathy is also known as shin spots, pigmented pretibial patches, diabetic dermangiopathy, or spotted leg syndrome [14]. Although not pathognomonic, it is considered one of the most common cutaneous lesions in DM, affecting up to 70% of adult patients [15].

Etiopathogenesis

The etiopathogenesis of diabetic dermopathy is unknown but may be related to deficient wound healing due to decreased skin vascularization, local thermal trauma, or to local subcutaneous nerve degeneration [14].

Clinical Presentation

Lesions begin as multiple, discrete, erythematous, coin-shaped asymptomatic macules or annular rings and are prevalent on the shins [2]. Its progression is variable. Lesions may fade slowly, leaving a pigmented area without atrophy, or it may resolve completely, with new lesions developing contiguously [16]. Lesions at varied stages can be present at the same time [8]. Its occurrence correlates with retinopathy,

nephropathy, and neuropathy [2, 16]. In fact, diabetic dermopathy tend to precede microvascular complications [14].

Complementary Examinations

Due to the nonspecific histopathology, a skin biopsy is usually 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 DM [17].

NL may be viewed as the prototype of a diabetes-associated skin disease. Its prevalence in adult patients is approximately 0.3–1.6%, occurring more frequently in women [3, 8, 9].

Most patients with NL will be diagnosed with DM at some point in their lives, and type 1 DM is more frequently associated with it [8, 11]. The presence of this disorder in diabetic patients is associated with a higher frequency of retinopathy and nephropathy [3]. Nevertheless, glycemic control seems to have no effect on its course [11, 18].

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 [18].

Clinical Presentation

The presence of NL is mainly based on a clinical diagnosis [10]. Clinically, NL lesions are localized on the lower two-thirds of the legs (pretibial regions) 90% of the time [19]. Lesions typically present as one to three asymptomatic, well-circumscribed papules, and nodules with active borders that slowly coalesce into plaques [18]. Plaques are typically yellowish-brown, with elevated, erythematous borders, an atrophic center, and telangiectatic vessels visible through the skin [10] (Fig. 41.1). Their texture may be similar to that of wax [17, 19]. In isolated cases, lesions may affect the upper limbs, scalp, trunk, penis, or face [8, 17]. A quarter of patients may present spontaneous ulceration [17]. The Koebner phenomenon may also occur [18].

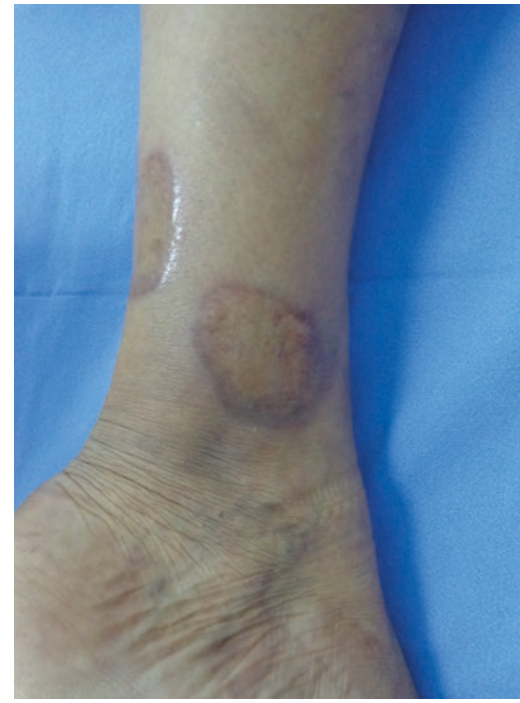

Fig. 41.1 Necrobiosis lipoidica presenting as yellowish-brown plaques with well-delimitated borders and atrophic center. (Photograph from the Department of Dermatology Collection, Universidade Federal de Santa Maria, Santa Maria, Brazil)

As a consequence of the associated nerve damage, up to 25% of the lesions can be extremely painful, especially if ulcerated [18].

Squamous cell carcinoma is a rare complication that can arise in long-standing NL lesions, presenting with or without ulceration [17, 18, 20].

Differential diagnoses of NL include granuloma annulare, necrobiotic xanthogranuloma, morphea, sarcoidosis, and, in cases of ulceration, tuberous syphilis [11].

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 [17].

The primary treatment is currently the use of steroids, either topical, intralesional, or, rarely, systemic [9, 18]. Their topical application should be only over the active borders of lesions and not on the atrophic areas. Steroids use in diabetic patients should be handled carefully in order to prevent glucose dysregulation [18].

In addition to steroids, other treatments are possible, although scientific evidence of their effectiveness still lacking. Calcineurin inhibitors, topical retinoids, ultraviolet A phototherapy (PUVA) treatment, photodynamic therapy, and cyclosporine are some of the additional options [21]. Pentoxifylline, a potent anti-inflammatory agent, has been used to improve microcirculatory flow with some favorable results [22, 23]. The use of Janus kinase inhibition combined with intralesional corticosteroid is also mentioned as an option for refractory NL [24].

Baseline blood work should assess glycemic levels. If these are not diagnostic of DM, they should be repeated yearly, as NL can be the first presentation of the disease [17].

Lifestyle modifications, such as the avoidance of trauma, are important in minimizing the risk of NL complications [18].

Granuloma Annulare

Granuloma annulare (GA) is a common idiopathic disorder, which occurs twice as frequently in women [25]. Clinical variants include localized, generalized (more than 10 lesions), subcutaneous, micropapular, nodular, perforating, and (rarely) pustular generalized perforating GA [25, 26].

Etiopathogenesis

Although the origin of this condition remains poorly understood, association with certain systemic diseases, such as DM, dyslipidemia, thyroid disease, malignancies, rheumatic diseases, and infections, such as human immunodeficiency virus, has been observed [3, 27].

Clinical Presentation

The most common clinical form is localized GA, which accounts for approximately 75% of all cases [28]. 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. 41.2). Lesions can occur at any area, being the lateral or dorsal surfaces of the hands and feet the most common. Symptoms are usually absent [26].

Subcutaneous or deep GA presents as a nodule located on the legs, scalp, palms, or buttocks. Less commonly, disseminated GA appears as a diffuse papular eruption. A perforating form 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 includes other common annular skin conditions such as tinea corporis, pityriasis rosea, nummular eczema, psoriasis, or erythema migrans associated with Lyme disease. However, these skin conditions do not typically develop without surface changes. Less common annular skin conditions (e.g., sub-

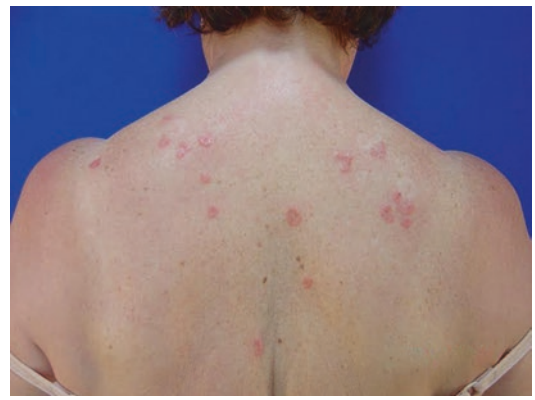

Fig. 41.2 Granuloma annulare: multiple red annular plaques organized around a slightly depressed center. (Photograph courtesy of Edison Covatti, Passo Fundo, Brazil)

acute cutaneous lupus erythematosus, erythema annulare centrifugum) have associated scaling and can be ruled out [29].

Complementary Examinations

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 common. Histiocytes may be present in an interstitial unorganized arrangement, or may show a palisading pattern, surrounding areas with prominent mucin [26].

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 [29].

For localized occurrences, topical corticosteroids are generally considered the first-line therapy. Depending on the site, high-potency corticosteroids with or without occlusion can be used. Nonresponsive cases can be handled with intralesional corticosteroids [30]. Other treatment options for localized include calcineurin inhibitors, cryotherapy, or pulsed dye laser treatment. Generalized forms may demand systemic therapies, including dapsone, retinoids, niacinamide, antibiotics, antimalarials, phototherapy, or photodynamic therapy [3].

Acanthosis Nigricans

Benign acanthosis nigricans (AN) is most commonly related to endocrinopathies, being obesity 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 [31].

AN also occurs rarely as a complication of an internal malignancy, particularly of the stomach, and secondary to some medications, including nicotinic acid [32]. AN can also develop on areas of repeated same-site insulin injections [33].

AN is more frequent in dark-skinned people and is found more commonly in the adult population, although it can be observed at any age [34].

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) [35].

Clinical Presentation

Regardless of its underlying disease presentation, AN usually follows the same pattern [32]. Presentation is characterized by symmetric, skin-colored or brownish lesions 1 mm to 1 cm in size [31, 34]. The plaques are palpable with a velvety texture and may have a flat to wart-like appearance [35].

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, 31, 34] (Figs. 41.3 and 41.4). Associated skin tags are common [2].

Papillomatous growths may be encountered on the eyelids, lips, and oral mucosa, as well as

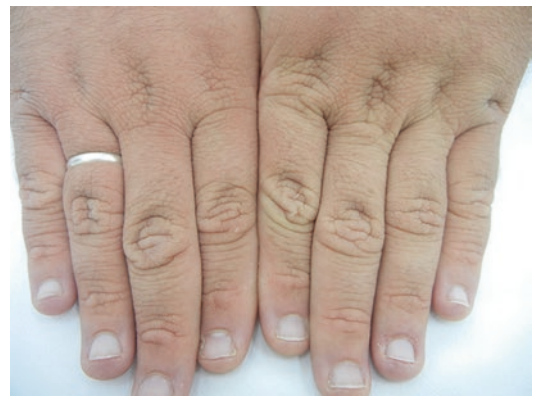

Fig. 41.3 Papillomatous growths on the dorsal surfaces of the hands. (Photograph from the Department of Dermatology Collection, Universidade Federal de Santa Maria, Santa Maria, Brazil)

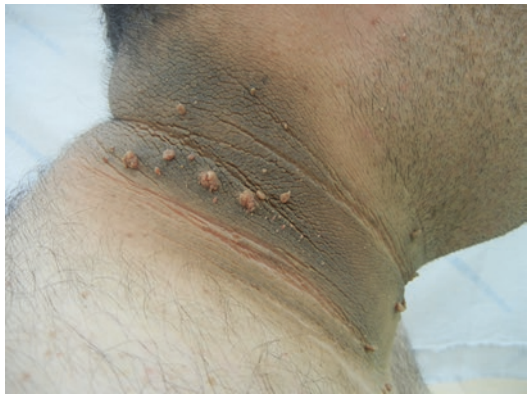

Fig. 41.4 Dark velvety discoloration in acanthosis nigricans associated with skin tags. (Photograph from the Department of Dermatology Collection, Universidade Federal de Santa Maria, Santa Maria, Brazil)

on the esophageal, laryngeal, and nasal mucosa [36], and the palms (tripe palms) and dorsal surfaces of large joints [37]. These generalized forms involving mucosa, however, are more often related to malignancies [34].

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 [32].

Therapeutic Approach

AN has better outcomes with weight reduction and optimal blood glucose control [11]. 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 [38].

Diabetic Bullosis

Bullosis diabeticorum (BD), or diabetic bulla, is a noninflammatory and relatively harmless blistering condition related to diabetic patients [39]. BD is poorly understood and considered to be rare [40].

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 [41].

Clinical Presentation

Clinical features of BD are spontaneously occurring painless bullae without inflammation signs. Bullae are tense and vary from a few millimeters to several centimeters of diameter, containing a clear and sterile fluid [41]. 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 [42]. Its evolution is self-limited and usually lasting 2–5 weeks, without scarring [40–43].

Differential diagnoses can include epidermolysis bullosa acquisita, pemphigus, contact dermatitis, insect bites, burns, porphyria cutanea tarda, erythema multiforme, or drug eruption [40–43].

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 [40].

Therapeutic Approach

Treatment is conservative. The blister must be kept intact in order to cover the lesion and prevent secondary infection. The patient should be instructed to keep the wound clean and protected. No topical therapy is required [43].

Scleredema Diabeticorum

Scleredema adultorum (SA) of Buschke is a connective tissue disorder, also known as scleredema diabeticorum (SD), when associated with DM.

The annual prevalence of SD in DM has been reported to be between 2.5% and 14%. SD is mostly seen in obese patients with poorly controlled diabetes [44].

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 [45].

Clinical Presentation

SD is characterized clinically by diffuse, symmetric, and nonpitting induration of the skin. Neck, shoulders, trunk, face, and arms are the most affected areas. Hands and feet are characteristically spared. Differential diagnoses of scleredema include fibrosing disorders such as scleroderma and scleromyxedema [45].

Complementary Examinations

Because of the inelasticity and induration of the thickened skin in scleredema, incisional biopsy is usually recommended. Histologic analysis is characterized by thickened dermis with increased deposition of glycosaminoglycans, mainly hyaluronic acid [45, 46]. Diagnostic imaging may be helpful in accurately evaluating the activity of the disease in cutaneous sclerotic disorders [46].

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 [11]. Glucose control has not been firmly associated with improvement of the disease [45].

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 [47].

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 [48].

KD is regarded as a genetically determined disease with onset occurring usually between the ages of 30 and 50 years and with a female-to-male ratio of up to 6:1 [49]. Chronic renal failure and/or DM usually accompany this skin disease [48].

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 [50].

Clinical Presentation

KD is characterized by the eruption of asymptomatic or 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 [51]. The lower extremities are involved more frequently; however, the upper extremities, head, and neck may also be affected [52].

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 [52].

Therapeutic Approach

Treatment of perforating disorders is difficult. Nevertheless, spontaneous resolution is possible [53]. 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 phototherapy, constitute the first-line therapies [54].

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 [55].

Acrochordon is regarded as a sign of impaired glucose tolerance, DM, and increased cardiovascular (atherogenic lipid profile) risk [56]. STs may also play a role in the early diagnosis of metabolic syndrome [55].

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 [57]. Studies have found the presence of human papillomavirus DNA in STs, at frequencies of 48% [58] and 88% [59].

Clinical Presentation

STs are consisting of skin projecting from the surrounding skin, usually occurring on the eyelids, neck, and axillae [55].

Complementary Examinations

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

Therapeutic Approach

Treatment is only necessary due to cosmetic reasons. Surgical excision, cryosurgery, or electrodessication can be applied [10, 60].

Patients with STs also need suitable interventions, such as weight reduction, smoking cessation, and changes in dietary habits [55].

Rubeosis Faciei

Rubeosis, also named rubeosis faciei and rubeosis faciei diabeticorum [61], is a relatively common skin manifestation associated with DM that may be unnoticed by patients and physicians [9].

Etiopathogenesis

Hyperglycemia could lead to sluggish microcirculation, which becomes clinically evident from facial venous dilatation [9].

Clinical Presentation

Rubeosis presents as a flushing that can be observed more frequently in association with type 1 DM (21–59%). It 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 [9, 61].

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 [62].

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 [63].

Clinical Presentation

Carotenemia is a clinical condition characterized by yellow pigmentation of the skin (xanthoderma) [62]. 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 [64].

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 pigmentation.

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, may also present with xerosis [65].

Etiopathogenesis

Xerosis is considered to be related to an autonomic peripheral C-fiber neuropathy. Stratum corneum adhesion and accelerated aging of the skin may be involved in the development of xerotic skin changes in diabetic patients [66].

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 [65].

Doctors should educate patients about the importance of skin hygiene, including applying fragrance-free creams or lotions right after bathing to trap moisture within the skin [9].

Diabetic Pruritus

Pruritus can be defined as a sensation which provokes the desire to scratch or an uneasy sensation of irritation in the skin [67].

Itching in people with DM frequently can be secondary to many of the skin conditions already mentioned. Nevertheless, it is estimated that chronic pruritus with no underlying skin condition might affect 3–49% of all diabetics [11].

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 [68].

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 [69].

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 [11].

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 [70].

Complementary Examinations

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

A 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 [71].

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 [11].

Psoriasis

Psoriasis is a chronic inflammatory disease considered to be a multisystem disease associated

with several comorbidities. It is believed that 73% of psoriasis patients have at least one comorbidity [72]. Moreover, psoriasis is a significant independent risk factor for developing type 2 DM, whereby the severity of psoriasis correlates with the risk for DM [73, 74].

Etiopathogenesis

Immune-mediated inflammatory processes, metabolic biomarkers, and environmental factors could be the potential links between psoriasis and diabetes [75].

There is probably an association between psoriasis and diabetes that is related to 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 [73].

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 affected areas [76].

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 [77].

Therapeutic Approach

Despite recent advances in the systemic treatment of psoriasis, topical agents represent the primary treatment for a majority of patients including some with more severe cases of this disease [78].

Glucocorticosteroids, vitamin D analogues, or combinations are well-established options. Topical calcineurin inhibitors are advantageous at difficult-to-treat sites, such as the intertriginous areas or the face [76]. Additionally, there are not enough evidences to support the recommendation of coal tar and *Liquor Carbonis Detergens* for the treatment of plaque psoriasis [78]. Moreover, it is known that long-term use of topical corticosteroids may be associated with significant systemic absorption interfering with DM control [79].

A combination of phototherapy and systemic therapy might be necessary 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 [76].

Methotrexate should be administered with caution in diabetic patients. Chronic kidney disease that is common in DM could reduce renal clearance of the drug increasing the chances of toxicity. Moreover, cyclosporine use is significantly associated with the risk of developing DM. On the other hand, PUVA and narrowband UVB therapy are not expected to cause significant changes in metabolic parameters [79].

Lack of response to the classic systemic treatment or phototherapy, contraindications, or intolerance to at least one of the systemic treatments, are conditions for the indication of the treatment with immunobiologics (etanercept, infliximab, adalimumab, ustekinumab, guselkumab, ixekizumab, secukinumab) [78]. Biological therapies tend to affect less negatively metabolic parameters as conventional treatments do [79].

Vitiligo

Vitiligo, an acquired pigmentary disorder of unknown origin, is the most frequent cause of depigmentation worldwide, with an estimated prevalence of 1% [80]. 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. 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 [81].

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 [82].

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 [82].

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 [80].

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 [82]. Tacrolimus monotherapy seems to have good efficacy and tolerability; however, only small trials and case series provide this evidence [83]. Systemic therapy can be indicated for 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 [82].

Lichen Planus

Lichen planus (LP) is an uncommon disorder affecting <1% of the general population [9]. Some studies have shown a significant association between LP and increased disturbances of glucose metabolism including DM, glucose intolerance, and insulin resistance [84, 85].

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 [84].

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 [9].

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 [86].

Therapeutic Approach

Most cutaneous form of LP may resolve spontaneously. Therefore, the goals of therapy are to shorten the time between the onset and resolution of the lesions and to reduce symptoms. Topical glucocorticoids are the first-line treatment. Oral glucocorticoid therapy is sometimes used when topical treatment failed. Other options are phototherapy and oral aromatic retinoids [86].

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 [87].

At least 50% of individuals with diabetes develop diabetic peripheral neuropathy (DPN), being distal symmetric polyneuropathy the most frequent presentation. DPN is a sensory neuropa-

thy with autonomic nervous system involvement. Motor features might also be present in advancing disease [88].

As a result from DPN, an inability to detect temperature changes, excessive pressure, and continued traumas develop. Atrophy and weakening of the intrinsic muscles of the foot lead to abnormal biomechanical loading of the foot. Anhidrosis, causing dry skin, fissures, and callused areas with secondary ulceration occur [87, 88].

The other component of diabetic foot syndrome involves vascular disease. The supply of oxygen, nutrients, and soluble mediators that are involved in the skin repair process are reduced. Furthermore, hyperglycemia-induced nerve dysfunction leads to the dysregulation of nerve microvasculature and consequent neuropathy [89].

All patients with diabetes should have an annual foot review to identify any evidence of DPN, peripheral vascular disease or ulceration [90].

When evaluating the pedal skin, areas of increased pressure represented by hyperkeratotic tissue and/or subdermal hemorrhaging should be noted. Foot deformities also need to be addressed. Moreover, atrophied skin, pigment changes and reduced or absent hair in the area are indicative of vascular disease [91].

The loss of pressure sensation at four sites (first, third, and fifth metatarsal heads, and the plantar surface of distal hallux), as detected by the unperceived buckling of a 10-g monofilament (Semmes-Weinstein Sensory testing), is highly predictive of subsequent ulceration. 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 should also be examined [89].

Plantar Ulcers

Foot ulcerations are one of the most significant complications of DM, being non-healing ulcers an important cause of lower extremity amputation [92]. The risk of diabetic patients developing a foot ulcer across their lifetime has been estimated to be 19–34% [93]. More than half of diabetic foot ulcerations (DFU) become infected and 20% ultimately lead to amputation [91].

Etiopathogenesis

Peripheral neuropathy, peripheral vascular disease and abnormal foot mechanics predispose patients to develop DFU and also make it difficult for ulcers to heal [91].

Additionally, the healing process is also negatively affected by impaired chemotaxis, cell proliferation and cell migration. Furthermore, enhanced pro-inflammatory chemokines disturb wound healing in DM [7].

Clinical Presentation

Ischemic wounds occur typically in a poorly perfused foot, around the lateral fifth metatarsal head and medial first metatarsal head. Subcutaneous muscles and skin appendages are atrophic. Pedal pulses are likely to be nonpalpable. Additionally, purely neuropathic wounds are commonly painless, occurring in the warm foot in pressure-bearing areas, often surrounded by callus tissue. Toenails might be thickened, yellow and crumbling. Autonomic neuropathy might result in either dry or very moist skin [11, 90].

Wound examination should evaluate the extent and depth of the ulcer, its base consistency (granular, fibrotic or necrotic), and the conditions of the periwound skin (viable, nonviable, hyperkeratotic). The presence of exudate, malodor, and signs of infection are also relevant [91].

Infection is generally indicated by the presence of systemic signs 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 subtle due to peripheral arterial disease and neuropathy. Osteomyelitis may affect up to two-thirds of patient with diabetic ulcers and might present painless [89].

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 [94].

Therapeutic Approach

A combination of prevention and infection control, pressure removal thorough relief shoes or devices such as casts or boots, debridement, and dressings are recommended [87].

Intensive glycemic control potentially improves the incidence of diabetic foot ulcer, decreases the risk of amputation, and improves sensory nerve function compared with less intensive control [92].

The removal of mechanical pressure from a neuropathic foot ulcer is paramount to the healing process. Appropriate footwear, the importance of avoiding walking barefoot and potential trauma should be addressed to the patient. Resting the foot and the use of a nonremovable, total-contact cast is associated with more rapid healing rates [89]. The use of orthopedic innersoles, in accordance with offloading foot techniques using various material features, has also led to good results [19].

Debridement is the process whereby all materials incompatible with healing are removed from a wound. Several methods can be applied, including surgery, conventional dressings, larvae, enzyme preparations, polysaccharide beads, and hydrogels [95].

The use of 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 [89].

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 [11, 89].

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 [95].

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 [11, 96].

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 properly detected will result in secondary ulceration, infection, and ultimately amputation [97].

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 [98].

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 [94, 97].

Etiopathogenesis

The interaction of several component factors (diabetes, sensorimotor neuropathy, autonomic neuropathy, trauma, and metabolic abnormalities of bone tissue) results in a localized inflammatory condition that can lead to varying degrees and patterns of bone destruction, subluxation, dislocation, and deformity [94].

Clinical Presentation

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 [97].

Musculoskeletal deformities in cases of Charcot foot can be very slight or grossly evident, most often owing to the chronicity of the problem. The classic rocker-bottom foot, with or without plantar ulceration, represents a severe chronic deformity and is typical for this condition [94].

In the acute phase, the majority of patients complain of unilateral edema with no inciting event or reports of only a minor injury associated. Vital signs are typically stable and 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 [96].

Although some of the differential diagnosis includes infection, osteomyelitis, deep vein thrombosis, and cellulitis, any of these conditions can be present concomitantly with the CN [91].

Complementary Examinations

In the acute stage of CN, venous duplex ultrasonography will likely show negative results for deep vein thrombosis [96].

The erythrocyte sedimentation rate, C-reactive protein values, and white blood cell count are also usually found to be normal [99].

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 [94, 96].

Magnetic resonance imaging allows 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 [94].

Therapeutic Approach

Total contact casting is recognized as the gold-standard treatment for CN, although it has not become a standard treatment in many diabetic foot clinics due to concerns about complications [99]. Immobilization can be achieved with either a nonremovable or removable cast for an average duration of 14 weeks [96].

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 [99].

Due to a high percentage of recurrence (40%) and the difficulty on correcting the etiopathogenesis of the problem, wound closure in DFU shall be seen in terms of remission instead of resolution [93].

Diabetic Hand Syndrome

Unlike DM-related conditions of the foot, diabetic hand complications occur less frequently and in a ratio of 1:20 [100].

The term “diabetic hand” is used to characterize complications of DM that occur in the hands. 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, which is usually associated with long-standing diabetes, suboptimal glycemic control, and microvascular complications. Neuropathic hand ulcers and diabetic hand infections might also occur [101].

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 most likely unaware of neural dysfunction [102].

Additionally, the tropical diabetic hand syndrome (TDHS) 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 [103].

Patients with TDHS tend to be female type 2 diabetic patients in their fifth to sixth decade of life and with poor metabolic control. Antecedent trauma (mild abrasion, laceration, insect bites) is often reported [101].

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 [104].

While THDS 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 [101].

Cutaneous Infections

Due to hyperglycemia leading to metabolic and immunological alterations, diabetic persons are more prone to skin infections than healthy individuals [8]. Moreover, diabetics exhibit a fivefold increase in complication risks compared with nondiabetics in cases of skin and soft tissue infections [11]. Incidences of infection correlate with mean blood glucose levels [8].

The disturbed skin barrier in diabetic patients and diabetes-induced vasculopathies, together with neuropathies, has been implicated in an increased vulnerability to infections. Therefore, recurrent bacterial infections, such as impetigo, abscesses, erythrasma, folliculitis, erysipelas, or severe fungal infections, should alert physicians to screen for DM [10].

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 [8, 11].

Additionally, patients with diabetes are believed to be particularly susceptible to *Candida* infection because increased glucose concentrations permit the organism to thrive [11]. Thrush, angular cheilitis, candidal balanoposthitis, vulvovaginitis, and paronychia, as well as intertriginous candidiasis, are common among diabetic patients [10, 11].

Fungal infection of the nails is also common in diabetes [8]. Up to one-third of diabetics may have onychomycosis, which is a significant predictor of the development of foot ulcers in diabetes [105]. Therefore, treatment must not be neglected in these cases.

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 be considered. Vascular invasion by hyphae can cause infarction and necrosis of tissues. Rhinoorbital-cerebral and pulmonary infections are the most common presentations [106].

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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