

REVIEW ARTICLE

Juvenile, insulin-dependent diabetes mellitus, type 1-related dermatoses

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Abstract

Juvenile insulin-dependent diabetes mellitus type 1 (IDDM) is a well-recognized worldwide entity, the significance of which has increased because of its recent upsurging trends, warranting attention on variety of its clinical expressions, in particular, pertaining to skin, an aspect seldom taken cognizance of. Hence an endeavour to recap the related dermatoses, such as limited joint mobility syndrome including sclerodermoid (scleroderma-like) changes, xerosis, necrobiosis lipoidica diabetorum, granuloma annulare, diabetic foot syndrome, has been made. Complexities relating to the recently explored issues of atopic dermatitis and drug hypersensitivity syndrome have also been covered adequately. In addition, the current concepts of the physiopathology of type 1 diabetes-related dermatoses are briefly recapitulated for clarity.

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Conflict of interest

None declared.

Introduction

Diabetes mellitus-related dermatoses are fairly well-recognized. Their overall incidence ranges from 11.4%¹ to 71%², which includes insulin-dependent diabetes mellitus (IDDM), type 1 and non-insulin-dependent diabetes mellitus (NIDDM), type 2. The former also known as juvenile diabetes, largely afflicts children. This entity is distinct from NIDDM because of its diverse undertones.³ The estimated recent trends from across the continents point to statistically significant increases in the incidence of IDDM, 4.0% in Asia, 3.2% in Europe and 5.3% in North America, whilst in Central America and the West Indies it has shown a perceptible decline of 3.6%.⁴ Environmental factors may be responsible for these variations.⁵ Most cases of IDDM, type 1 are the result of environmental factors interacting with a genetically susceptible person. This interaction leads to the development of autoimmune disease directed at the insulin-producing cells of the pancreatic 'islets of Langerhans'. These cells are progressively destroyed, with insulin deficiency usually developing after the destruction of 90% of islet cells.^{6,7} Without insulin replacement, such patients rapidly develop life-threatening hyperglycaemic ketoacidosis, for this reason, terms such as 'insulin-dependent,' 'ketosis-prone,' and 'brittle' diabetes have been applied to patients with type 1 disease. Abnormal carbohydrate metabolism, athero-

sclerosis, microangiopathy, neuron degeneration and impaired host mechanisms are the possible factors in the pathogenesis of cutaneous complications.⁸ Furthermore, type 1 diabetes patients develop more frequently autoimmune type of cutaneous lesions.⁹ In order to have an in-depth understanding of the issues at stake, it is necessary to have a comprehensive review on all related aspects.

Physiopathology

Diabetic complications appear to be multifactorial in origin. Its in-depth understanding is, therefore, imperative. The biochemical process of advanced glycation in particular, seems to be accelerated in diabetes as a consequence of chronic hyperglycaemia and increased oxidative stress.¹⁰ Advanced glycation involves the generation of a heterogeneous group of chemical moieties recognized as advanced glycated end products (AGEs). This is a non-enzymatic reaction with glucose interacting with proteins, lipids, and nucleic acids, and implicating key intermediates like methylglyoxal. Indeed, there is accumulating evidence that an interaction between an AGE and its receptor for advanced glycation end products (RAGE) generates oxidative stress and subsequently evokes vascular inflammation and thrombosis.¹⁰ AGE deposits in the skin can be identified using autoimmunofluorescence (AF) as a marker. An

independent association exists between skin AF and diabetic nephropathy, as also with diabetic neuropathy (but not diabetic retinopathy), in individuals affected by type 1 diabetes (T1D).¹¹ Accordingly, skin AF could be a useful predictor for the presence of microangiopathy. AGEs are responsible for the dermatoses like limited joint mobility syndrome (LJMS), in particular. Thus, AGEs are hypothesized to play a key role in the pathogenesis of diabetic complications primarily with respect to involvement of the neuro-vascular unit.¹⁰

Diabetic neuropathy is characterized by progressive nerve fibre loss that gives rise to clinical signs and symptoms such as pain, paraesthesia and loss of sensation. The nerve fibre loss takes the form of pan-modal pattern with proximo-distal gradient. Endoneurial microangiopathic change is also a permanent feature of peripheral nerve pathology and negatively correlates with nerve fibre density. The vascular change and distal nerve fibre loss of small calibre, in particular, at the site of epidermis, begin even in subjects with impaired glucose tolerance and precede loss of nerve fibres in the nerve trunk of lower extremities. Pathogenetic mechanisms underlying the progressive nerve fibre loss seem to be multifactorial. It includes polyol pathway, glycation, reactive oxygen species, and altered protein kinase C activity.¹² The dermal nerves may manifest changes analogous to those in sural nerve, and that in dorsal root ganglion.¹³ Electron microscopy has revealed thickening of the peri-neural cell basement membrane. The functional correlate to these morphological changes is unclear; however, peri-neural basement membrane thickening may be implicated in the drop-out of myelinated fibres.¹⁴ Autonomic neuropathy is a well-known complication of diabetes. Perhaps it is more common in T1D than in type 2 diabetes (T2D).¹⁵ Autonomic sudomotor dysfunction may be manifested by decreased sweating as a result of damage to sympathetic fibres of sweat glands. Anhidrosis is usually patchy, often involving the lower limbs. According to recent studies, sudomotor dysfunction has been linked to lipid peroxidation in early type 1 diabetes.¹⁶ Sudomotor dysfunction may be associated with increased risk of foot ulcer and should be included in the screening tests for identification of diabetic patients at risk of ulceration.¹⁷

Diabetic microangiopathy, a cardinal outcome of T1D, is characterized by laminated thickening of the walls of arterioles, capillaries, and venules throughout the body. AGE deposits may result in obliteration of the vascular lumen. Proliferation and hypertrophy of endothelial cells has been a subject of focus.^{18,19} Thickening of the basement membrane may impede the transfer of nutrients from the circulation, rendering surrounding areas more vulnerable to insult and perhaps interfering with the movement of leucocytes to damaged or infected areas.^{20,21}

Autoimmune diseases and auto-antibodies are frequently associated with T1D. The risk of developing several coexisting autoimmune diseases and conditions is especially high in 'autoimmune families' where the probands may manifest an additional autoimmune disease.²² These 'autoimmune families' may have some common susceptibility alleles leading to the expression of multiple

autoimmune diseases. The genes or mechanisms responsible for this susceptibility are yet to be elucidated.²² In addition, it has been observed that levels of serum IFN- α 2, IL-1 β , IFN- γ , and CXCL-10 are elevated in new-onset patients of T1D.²³ This may implicate that altered innate immunity exists in cellular subsets from T1D patients and raises the possibility that these alterations may be associated with disease mechanisms including infections.

Clinical connotation

It is pertinent, at this stage, to evolve a classification based on clinical manifestations of T1D-associated dermatoses concerning:

- 1 Related dermatoses
- 2 Autoimmune cutaneous lesions
- 3 Cutaneous infections
- 4 Cutaneous reactions to insulin treatment
- 5 Other dermatoses.

Related cutaneous lesions

Limited joint mobility syndrome

The entity was first described as 'diabetic hand syndrome'.²⁴ In the year 1974, the association between diabetes mellitus and conditions like stiff joints and short stature was reported in three children. Soon after,²⁵ it became evident that joint stiffness was a relatively common manifestation of childhood diabetes mellitus and was associated with thick, waxy skin.²⁶ Subsequently, this finding was called joint stiffness, limited joint mobility (LJMS), diabetic cheiroarthropathy, digital sclerosis, and may be hypothesized to belong to the same spectrum as Dupuytren's contractures²⁷ (fibromatosis) and sclerodermoid (scleroderma-like) skin lesions. The limited joint mobility syndrome (LJMS) is described as flexion contractures of the fingers. The proximal interphalangeal joints of the fourth and fifth fingers are frequently involved. The contractures are painless. They can be demonstrated by fanning the fingers, then either placing the palm of the hand on a flat surface or opposing the palms and fingers in a praying position. Should the patient not be able to oppose the entire palmar surface of the hand to the table or to the opposite hand even after gentle pressure by the examiner, contractures are confirmed. Occasionally, there is stiffness or resistance to passive extension without a fixed contracture. Contractures are not only confined to the fingers but may also involve the wrist, ankle, elbow, knees, toes, and cervical and thoracolumbar spine.²⁸ Earlier studies reported frequency of up to 30% among those with type 1 diabetes, under 22 years of age.²⁹ The prevalence of LJMS in type 1 diabetes, quoted in several studies of paediatric and adult diabetes clinics, ranges from 9% to 58%.^{26,30,31} LJMS syndrome has shown a steady decline over the past two decades possibly because of intensive glucose control, as there is some evidence that long-term glycaemic control influences the onset of this condition.^{32,33} A strong correlation has been found between sclerodermoid hand

lesions and the duration of type 1 diabetes.³⁴ LJMS has been correlated with increased frequency of microvascular complications. In a study, the likelihood of developing microvascular complications after 16 years of age was found to be 83% for diabetic individuals with LJMS compared to 25% for those without LJMS.²⁸ Limited joint mobility is frequently associated with waxy thickening of the dorsal skin of the hand.^{28,29} The thickening of the dorsal skin has been described as scleroderma-like.^{35,36} Thick, adherent skin on the digits and occasionally over the dorsum of the hand of 24% of 137 children³⁶ is on record. Digital sclerosis generally is of the fifth digit, may progress laterally to involve other fingers.³⁷ In most severe instances, there is a loss of transverse digital ridges on the dorsum of the finger. The changes are usually unassociated with dermal atrophy, pigmentary changes or telangiectasis. Histopathological examination of the diabetic hand syndrome shows a thick dermis, increased cross-linked collagen in the reticular dermis, and small amounts of mucin.³⁸ It is important to distinguish it from scleroderma because the latter may also present with sclerodactyly and diffuse or localized thickening of the skin. In evaluating patients with these findings, a history should focus on the other related symptoms found in scleroderma, such as dysphagia, calcinosis cutis, and difficulty breathing. Patients should carefully be assessed for the presence of autoantibodies, such as SCL-70, antinuclear antibody, anti-SS-A (Ro), and anti-SS-B (La) antibodies. The sclerodactyly in patients with these two disorders may be distinguished by the absence of Raynaud's phenomenon, atrophy, and telangiectases in patients with diabetes mellitus.³⁹

Glycosylation may be responsible for the increased and abnormal cross-linking observed in the dermal collagen that is less readily digested and extracted. Such changes could also contribute to the accumulation of collagen by interfering with degradation. Increase in lysyl oxidase activity may result in increased cross-linking, which could explain this accelerated ageing of collagen and subsequent resistance to collagenase digestion.⁴⁰ Fibroblast proliferation and protein synthesis have been described that could account for the clinical skin changes.^{41–43}

Stenosing flexor tenosynovitis/trigger finger

Stenosing flexor tenosynovitis (trigger finger) involving multiple digits is closely associated with LJM syndrome.⁴⁴

Xerosis, acquired ichthyosis and keratosis pilaris

Xerosis, skin dryness is one of the earliest and most common of the manifestations of type 1 diabetes. A recent study found xerosis in 22% of patients vs. 3% of control subjects.³⁴ In another series,⁹ only 6% of the patients had xerosis. Yet another study² registered 48% of the patients with ichthyosiform shin changes in their series of patients. The clinical observations are supported by objective findings of a reduced hydration state of the stratum corneum and decreased sebaceous gland activity in patients with diabetes, without any impairment of the stratum corneum barrier function.⁴⁵ Even in the absence of clinically apparent xerosis, patients with

diabetes have an impaired desquamation process.⁴⁶ Acquired ichthyosis (AI) occurs in patients in the absence of personal or family history of ichthyosis. It is a rare disease, clinical features of which may vary from symmetric xerosis and roughness to the scaling of large plaques.⁴⁷ 'Ichthyotic changes' of the shins were described in 48% of the patients in one survey of 238 type 1 diabetic individuals² but these changes appeared to be that of asteototic eczema rather than AI, besides, these features developed long before the onset of diabetes, without any histopathological assessment.⁴⁸ Only two cases of AI have thus far been reported, that too in insulin-dependent young patients.⁴⁸ The pathophysiological mechanism is still not well understood. It is speculated that ichthyosiform skin changes and thickening of the skin in diabetic individuals could be explained by structural changes in skin proteins attributable to advanced glycosylation.² An abnormal host immune response, probably against components of the granular cell layer, in particular, the keratohyalin granules, may have a role in the pathogenesis.⁴⁸ Insulin deficiency may result in a reduction in the synthesis of some structural proteins, which in turn may lead to these clinical changes.⁴⁸ In a study, keratosis pilaris proved to be significantly more prevalent amongst type 1 diabetic patients than in controls, and only one patient had atopic eczema. The age of the majority of type 1 diabetic individuals with keratosis pilaris (21 out of 27) was >10 years.³⁴ Skin xerosis may play a significant role in its development.⁴⁸

Necrobiosis lipoidica diabetorum

It was first described by Oppenheim in the year 1930, and was subsequently named necrobiosis lipoidica diabetorum (NLD) by Urbach in the year 1932.⁴⁹ Of those patients studied who were without diabetes at the start of the study but had abnormal glucose tolerance, it was hypothesized that approximately 90% eventually may develop diabetes. The female to male ratio was 3 : 1. It was observed that insulin-dependent diabetes mellitus patients developed NL considerably earlier, at a mean age of 22 years, whereas, in non-insulin-dependent diabetes mellitus and non-diabetic patients the mean age was 49 years.⁵⁰ It is most commonly seen in patients with type 1 diabetes, but may also occur in type 2 diabetes.⁵¹ Only a few instances have been reported of an association between NLD and diabetes in children.⁵² NLD begins as 1–3 mm well-circumscribed papules/nodules that extend with an active border to become waxy, atrophic, round plaques. Initially, they are red-brown in colour and eventually progress to become yellow, atrophy being a prominent feature affecting the centre of the plaque (Fig. 1).

In a study of 1557 patients under the age of 15 years with type 1 diabetes, only one patient (0.06%) was confirmed with NLD.⁵² In a review⁵³ of reported cases of NLD in children, it was observed to be more common in girls (at least 8 out of 11 patients). Most lesions occurred on the lower extremities. All the reported children had type 1 diabetes, except one case without diabetes and one who had type 2 diabetes. NLD may be associated with microangiopathic



Figure 1 Necrobiosis lipoidica diabeticorum depicting yellow-brown atrophic plaques over the right shin and left lower leg above the medial malleolus.

changes consisting of thickened basement membrane and capillary walls particularly, in pre-tibial lesions. Other proposed causative factors include obliterative endarteritis, immune-mediated vasculitis, delayed hypersensitivity, non-enzymatic glycosylation and other defects in collagen trauma, platelet aggregation, defective mobility of neutrophils and vascular insufficiency.^{50,54} Human Leucocytic Antigen (HLA) correlation has also been found in the form of high frequencies of HLA -DR4, -B8 and -CW 3, and low incidence of HLA -DR5 and DR7.⁵⁵ Histopathologically two patterns are seen, the first usually present in patients with diabetes mellitus is called palisading granulomatous dermatitis, while the second named 'tuberculoid' type is predominant in non-diabetic group.⁵⁶ Large areas of necrobiotic collagen are present in lower two-third of the dermis surrounded by cellular infiltrate of histiocytes, fibroblasts and lymphoid cells. Extra-cellular lipid deposits are also seen. Plasma cells are scattered among the degenerating fibres with variable number of Langerhans' foreign body giant cells, and blood vessels show endothelial proliferation with wall thickening. Atypical lesions are reported on the face and scalp.⁵⁷ A recent study suggests that children as well as adult diabetic individuals with NLD can be at high risk for nephropathy and retinopathy; NLD can be a clue for diabetic nephropathy and retinopathy⁵⁸.

Granuloma annulare

Granuloma annulare (GA): It is a benign self-limiting skin disease of unknown aetiology, common in childhood. It is usually asymptomatic, characterized by a ring of small, firm papules and/or nodules, occupying the backs of the forearms, hands, feet and face, often located around joints or knuckles (Fig. 2).

It is usually localized but may become generalized. The prevalence of diabetes is reported to be 4%–10% in patients with GA.⁵⁹



Figure 2 Granuloma annulare showing lesion on the left hand.

Classically, it occurs in middle-aged, almost invariably obese patients with NIDDM; however, there is evidence linking granuloma annulare and autoimmune thyroiditis/type 1 diabetes. In a review of clinical case histories of 100 patients with generalized granuloma annulare at the Mayo clinic, 13 patients were found to have thyroid disease while diabetes was diagnosed in 21 patients. Information about specific antibodies is not available in the study. There is only one reported case in the literature linking the association of granuloma annulare (which involved the skin and viscera) with Addison's disease but the patient had type 1 diabetes and myxoedema.⁶⁰ A disordered carbohydrate metabolism, with abnormal glucose tolerance tests or overt diabetes, appears to occur particularly in the generalized and perforating forms of the disease.⁵⁹ Histopathologically, necrobiotic granuloma is seen in three patterns: necrobiotic palisading granulomas, an interstitial form, and granulomas of sarcoidal or tuberculoid type. There are foci of degenerated collagen in the upper dermis and histiocytes between collagen bundles, and around degenerated collagen. The colloidal iron stain shows abundant mucin in the involved area. The vessel changes are not predominant and there are not many giant cells. There is marked reduction or absence of elastic fibres.⁶¹

Diabetic dermopathy

Diabetic dermopathy (DD) is the most common cutaneous manifestation of diabetes mellitus. DD refers to atrophic, hyperpigmented macules characteristically located on the shins of patients with diabetes. DD is found to vary from 12.5% to 40% in diabetic individuals of both type 1 and type 2 and is thought to represent an abnormal response to trauma in the skin of diabetic individuals.⁶² They have an unfavourable association with the three most common microangiopathic complications of diabetes mellitus: diabetic neuropathy, diabetic nephropathy, and diabetic retinopathy. A relationship between DD and coronary artery disease has also been demonstrated.⁶³ Thus, the presence of DD should

prompt aggressive intervention to detect diabetes mellitus and prevent the development of ensuing complications. No treatment is effective for lesions. By and large patients are asymptomatic, and do not respond to control of hyperglycaemia.¹⁹

Scleredema adultorum

Scleredema adultorum of Buschke is a fibromucinous connective tissue disorder of unknown aetiology that belongs to a group of scleroderma-like diseases.^{64,65} It is characterized by a localized induration of the skin with occasional erythema or pigmentation. The lesions are ill-defined, woody non-pitting plaques. The epidermis overlying the affected area wrinkles or takes a *peau d'orange* appearance when pinched. The lesions are usually confined to the nape, the neck, the shoulders and the upper part of the back. The face and the tongue can also be involved leading to difficulties in opening the eyes or the mouth, dysarthria or mastication troubles.⁶⁶ Scleredema may induce limitation in motion of upper limbs and is also a restrictive lung disorder. Association with obstructive sleep apnoea syndrome has been reported in a large study.⁶⁷ Cellulitis syndrome or delays in wound healing are possible.⁶⁸ Other organs such as heart, skeletal or ocular muscles, oesophagus, parotid glands, liver, pleura or peritoneum could also be involved on rare occasions.⁶⁹

The diagnosis is based on clinical presentation. Histological confirmation by punch or incision biopsy is not systematically required.⁷⁰ The specific histological findings are represented by the thickness of the dermis caused by both enlarged collagen bundles and the presence of clear spaces or 'fenestrations' between them, filled with mucopolysaccharides. Mucin deposit is more likely to be observed in the deep dermis and can be stained with Alcian Blue dye. However, the presence of glycoaminoglycan deposits stained by Alcian Blue is inconsistent and unreliable, and their absence does not exclude diagnosis. The normality of appendiceal structures is specific of scleredema unlike in scleroderma. There is no sign of inflammation.

The main mechanism of the accumulation of the extra-cellular matrix components seems to be represented by an abnormal expression of extra-cellular protein genes, type 1 and type 3 collagens, and fibronectin in skin rather than a decrease of clearing processes.⁷⁰ This gene dysregulation is observed in scleredema adultorum regardless of the presence of diabetes. The signals mediating the biosynthetic activation of fibroblasts are still unknown. Various aetiologies have been proposed including infection, autoimmunity, hyper-insulinism, or ischaemia without convincing demonstration.⁶⁵ Diabetes is observed in half of the cases of scleredema.⁷¹ Scleredema has been observed in patients suffering from either type 1 or type 2 diabetes mellitus, even if type 2 diabetes seems to be largely more frequent in the rare large series published in the literature.^{67,71} The more common features in the cases of scleredema diabeticorum are male gender, adult-onset and long duration of diabetes, poor metabolic control, requirement of insulin treatment and the presence of diabetes-specific complica-

tions.⁷² There is no consensual treatment. In the mildest of the cases, optimization of metabolic control and physiotherapy especially in case of motion or respiratory disability is recommended. For the rare progressing forms, various systemic treatments have been proposed including corticosteroids, D-penicillamine, cyclosporine, methotrexate, psoralen plus ultraviolet A (PUVA) therapy, prostaglandin E1, factor XIII or radiotherapy. But these approaches have been tried on very few patients or even mostly in a single patient. Success seems to be limited in most of the cases. The most enduring short-term beneficial effects in most severe cases have been observed with radiation therapy.⁷³

Xanthomas

The decreased lipoprotein lipase activity in IDDM results in the accumulation of serum triglycerides, whose levels are occasionally highly elevated to produce eruptive xanthomas.⁷⁴ Uncontrolled diabetes is a frequent underlying problem. They occur anywhere on the body, but particularly on the extensor surfaces of the limbs and the buttocks. The papules are discrete and dome-shaped but may coalesce to form plaques and nodules when they are called tubo-eruptive.⁷⁵ Tubo-eruptive lesions occur mainly over the elbows. Plane xanthomas typically develop in skin folds and especially in the palmar creases. The treatment priority is the patient's diabetes that is out of control. It is also necessary to diagnose and treat underlying lipid disorders.⁷⁶ Treatment of the hyperlipidaemia initially consists of diet and agents with lipid-lowering effect.⁷⁷ With correction of lipid status, after several weeks of systemic treatment, the lesions involute, sometimes with post-inflammatory hyper-pigmentation and occasionally scar.⁷⁸

Diabetic bullae

Approximately 0.5 percent of diabetic individuals develop diabetic bullae. Although not common yet, it is considered as a clinically distinct diabetic marker. Spontaneous and sudden appearance of bullae, on the hand and forearm is cardinal. Mechanical trauma or ultraviolet radiation in conjunction with nephropathy may be co-factor in the evolution of diabetic lesions. There has been speculation about the role of altered carbohydrate-, calcium-, magnesium metabolism or vascular insufficiency, microangiopathy or reaction imbalance secondary to renal failure in many of these patients.⁷⁹ These bullae have only been reported in adults, age varying from 40 to 77 years.⁸⁰ It is commonly seen in males, with long standing diabetes. The most common type is spontaneous and non-scarring with clear sterile fluid. It has a non-inflamed base. These are associated with long-established diabetes, diabetic peripheral neuropathy and good circulation to involve extremity.⁸¹

Rubeosis faciei

It is characterized by a facial blush, which lacks the warmth and elevated border of erysipelas and the telangiectasia of carcinoid flush.⁵⁰ In a recent study, the prevalence of rubeosis faciei in patients with type 1 diabetes was found to be high (7%)³⁴ and was

in consonance with a previous study.² It was weakly related to the disease duration. The prevalence in most previous studies in patients with type 2 diabetes was estimated to be in the range of 21–59%.^{81,82} Venular dilatation is prominent in the cheeks of diabetic patients with rubeosis faciei, and may be caused by hyperglycaemia-induced sluggish microcirculation.⁸³ Moreover, hypertension may exacerbate the capillary damage.⁸³ A relation of rubeosis faciei, however, with metabolic control could not be demonstrated in young patients with type 1 diabetes, and only one patient had concomitant hypertension.³⁴ Rubeosis faciei was not seen in any of the 64 patients of an Italian series of type 1 diabetic individuals.⁹

Acquired perforating dermatoses

Acquired perforating dermatoses (APD) are a group of disorders characterized by a common phenomenon called transepithelial elimination. APD occurs in a similar frequency in either types of diabetes (type 1 or type 2). The etiopathogenesis of APD is not clearly delineated. The widely accepted theory suggests that scratching is the main culprit behind these lesions. Scratching leads to local trauma and necrosis of the dermal layer, which is already compromised by microvasculopathy.⁸⁴ This dermal necrosis results in extrusion of dermal material through the epidermis. Other postulates regarding the etiopathogenesis are a foreign body reaction to the altered dermal collagen material and calcium salt deposition in a genetically predisposed patient.

Acquired perforating dermatoses consists of pruritic 2–10 mm hyperkeratotic, dome-shaped often umbilicated papules and nodules (Fig. 3) some of which may coalesce as a result of severe pruritus and rubbing to form small verrucous plaques. They may either be clustered or arranged in a linear distribution. The smallest lesions are pinhead-sized, follicular or perifollicular papules, while the largest lesions are dark brown nodules, with a central crust filling a central depression.



Figure 3 Acquired perforating dermatoses displaying multiple hyperkeratotic, dome-shaped umbilicated papules on the trunk.

Pruritus

Pruritus in the feet caused by tinea pedis and pudendal pruritus because of candidiasis have been reported to be highly prevalent in diabetic patients,⁸⁵ however, there is a scarcity of data of pruritus with diabetes. A higher prevalence of truncal pruritus in diabetic than in non-diabetic subjects has recently been demonstrated and it was observed in approximately 12% of general diabetic individuals. Two possible mechanisms are proposed for truncal pruritus. First, because sympathetic nerve function includes the sudomotor function,⁸⁶ sympathetic dysfunction may cause hypohydrosis and result in dry skin. A second mechanism could be the damage to sensory c-fibres by diabetic polyneuropathy (DPN). Superficial skin pain is considered to be caused by abnormal firing of the pain nerve fibre in patients with DPN.⁸⁷ Similarly, abnormal firing of the nerve fibre in pruritus may induce truncal pruritus.

Diabetic foot syndrome

The term diabetic foot syndrome is used to include all cutaneous manifestations namely xerosis, callus, fissures, erosions, numbness and pain, trophic ulcer, and gangrene (Fig. 4) of the foot that occur as a result of the following mechanisms:

Ischaemia

This is an outcome of premature peripheral vascular insufficiency secondary to atherosclerosis of large and medium-sized vessels, and microangiopathy. Cool, atrophic shiny skin along with dystrophic nails and hair loss are its clinical characteristics. The lesions are progressive and may ultimately lead to ulceration and gangrene of the tips of the toes.⁸⁰

Infection

Soft tissues infections of lower extremities are frequent. A mixed infection is usually found and non-clostridial gas gangrene may occur. Maceration between the fourth and fifth toe is very common leading to marked bacterial and fungal colonization.⁸⁸ In addition, onychomycosis is among the most significant predictors of foot ulcer.⁸⁹

Neuropathy

The peripheral neuropathy in diabetes is thought to be attributable to microangiopathy, affecting the intra-neural blood vessels.⁹⁰ In



Figure 4 Necrotic ulceration affecting the dorsum of left foot and leg.

early stages, the foot is frequently warm with good peripheral circulation. Numbness and pain may be present in 'glove and stocking' distribution prior to the loss of sensation. The neuropathy may result in blisters and ulcers developing over pressure areas usually as a result of painless trauma. The characteristic lesion in diabetic neuropathy is the perforating plantar ulcer/malum perforans. A small ulcer can belie considerable deep tissue destruction and may be complicated by osteomyelitis.⁸⁰ Ulcers are typically circular, punched out and associated with callus and concomitant loss of temperature, pain sensation and absence of ankle reflexes. Callosities along with dry, scaly fissured skin, is commonly seen as a result of hypohidrosis from autonomic neuropathy. Increased plantar pressure, especially beneath the metatarsal heads, and the resultant callus play an important role. Callus may result in an excess plantar pressure, which emphasizes the importance of early and mild chemical debridement of the hyperkeratotic tissue with keratolytics.⁹¹ The patients often already have xerosis of the plantar skin with scales, fissures, erosions and impaired barrier function, complicating the situation. Prompt neurological and vascular diagnostic studies, coupled with routine examination of the feet and primary prophylactic measures are most important. The most important therapeutic goals are optimal control of the diabetes mellitus, relieving pressure points and avoiding or reducing callus formation.⁹² Recently, a strong association has been observed between the degree of renal function impairment and diabetic foot.⁹³ Topical treatment includes the debridement of the ulcer. Stimulants of granulation tissue-like membranes or benzyl peroxide or absorbent dressings are useful. Amputation is indicated when vascular flow is inadequate or cannot be restored by modern surgical procedures.

Autoimmune cutaneous lesions

Vitiligo

Vitiligo is an autoimmune-mediated hypomelanotic disorder, with a prevalence of approximately 0.5% in the general population. T1D is found more commonly in vitiligo patients compared with the background population, with a frequency of up to 10%.⁹⁴ In populations of European origin, variants in the gene encoding NACHT leucine-rich-repeat protein-1 (NALP1) have been observed in vitiligo-associated multiple autoimmune diseases.⁹⁵ A significant association of HLA DR4 and vitiligo has also been reported.⁹⁶

Psoriasis

In a recent observational study with a population of 65, 449; 1061 incident cases of DM were diagnosed, 59% had a history of psoriasis, yielding a crude incidence rate ratio of 1.36 (95% CI 1.20–1.53). The risk increased with psoriasis duration and severity, and was not driven by high body mass index (BMI) alone.⁹⁷ Autoimmune loci on Chromosome 4q27 in psoriasis and psoriatic arthritis patients identical to those implicated in the pathogenesis of type 1 diabetes have been delineated.⁹⁸

Alopecia areata

A recent Genome – wide association study of alopecia areata revealed several risk loci in common with other forms of autoimmunity including T1D. The commonality with rheumatoid arthritis, type 1 diabetes and coeliac disease is particularly noteworthy in view of the significance of the NKG2D receptor in the pathogenesis of each of these three diseases.⁹⁹

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), an autosomal recessive syndrome defined by two of the following conditions namely chronic mucocutaneous candidiasis, hypoparathyroidism, or Addison's disease, may be associated with IDDM and other autoimmune conditions including vitiligo and alopecia areata. APECED is caused by mutations in the autoimmune regulator gene, mapping to 21q22.3.¹⁰⁰

Dermatitis herpetiformis

In a series comprising 1,104 consecutive patients with dermatitis herpetiformis (DH), 25 (2.3%) were affected by T1D and three of their first-degree relatives had type 1 diabetes, the frequencies being significantly higher than in the general population. Most DH patients with type 1 diabetes and with isolated type DH could adhere strictly to the gluten-free diet (GFD). The response was good or moderate in 84% of the DH patients with T1D and in 94% of the patients with isolated DH.¹⁰¹ HLA allele polymorphisms may be a possible explanation of the two diseases appearing together more frequently than expected.¹⁰²

Other autoimmune cutaneous lesions like chronic urticaria^{103–105} and thrombotic thrombocytopenic purpura¹⁰⁵ have also been reported in T1D.

Cutaneous infections

Skin infections occur in 20%–75% of all diabetic individuals. They are more frequent in NIDDM, and are associated with poor blood glucose control. The infections may either be fungal or bacterial. The former are more common than the latter.^{106–109}

Fungal infections

Dermatophytosis

Reported prevalence rates of dermatophytosis amongst type 1 diabetic individuals vary from 2.8%⁴⁰ to 84.6%.¹¹⁰ In a study¹¹¹ on 509 diabetic individuals, the most frequently isolated dermatophyte was *Trichophyton mentagrophytes*. Although, there may not be a correlation between the incidence of toe web space colonization with dermatophytosis with the criteria of patient gender and age, and duration of diabetes, yet the difference in the incidence according to type of diabetes was statistically significant. In NIDDM patients, the incidence of fungal isolation from toe webs is significantly higher (30.1%) than in IDDM (19.8%).¹¹¹

Candidiasis

Oral yeast colonization is higher in type 1 diabetic individuals than in type 2, which may be related to poorer glycaemic control in the former. *Candida albicans* is the most frequently isolated candidal species, others being *C. glabrata*, *C. parapsilosis*, *C. krusei*, and *C. tropicalis*.¹¹² Accurate identification of strains isolated from diabetic individuals is important, because they are more likely to carry species other than *C. albicans*, which might not be sensitive to certain antifungal agents. In addition, the culture and sensitivity testing would add to the value of selecting the appropriate antifungal drugs, rather than prescribing any type of antifungal just for the presence of clinical manifestations of candidal infection.¹¹² The risk factors for oral candidal infection in diabetic individuals are complex. The role of local factors such as low salivary flow rates and pH, smoking, wearing dentures, and poor oral hygiene, others focus on systemic factors such as patient age or disease types, degree of control, and the presence of complications, has been emphasized.¹¹² Patients with diabetes mellitus are at increased risk of vulvovaginal candidiasis (VVC). Besides, *Candida albicans*, they often have infection caused by non-*C. albicans* Candida species such as *C. glabrata*. There seems to be a significant link between hyperglycaemia and vulvovaginal candidiasis.¹¹³ In a prospective study comprising 35 patients with T1D (age 1.7–20 years), the predominant Candida species isolated were *C. albicans* (72.7%), *C. glabrata* (22.7%), *C. tropicalis* (2.3%), and *C. parapsilosis* (2.3%). The mean glycosylated haemoglobin (HbA1c) in diabetic patients from whom Candida species were isolated was significantly higher than that of patients without Candida infection. Most of the *C. glabrata* isolates were significantly resistant to ketoconazole.¹¹⁴ Limited response in the clinical symptoms and culture negativity following single dose fluconazole therapy in diabetic subjects with VVC may be explained by the high prevalence of *C. glabrata* in them.¹¹⁵

Mucormycosis

Mucormycosis is an acute, often rapidly fatal fungal infection that is an important but preventable cause of death in young patients with diabetes mellitus who have poor glycaemic control. In the majority of instances rhino-orbital-cerebral mucormycosis (ROCM) is associated with DM (60–80%) as seen in different series.^{116,117} Mucorales are ferrophilic fungi. Acidosis reduces the binding of iron to transferrin; in turn, the available free iron helps in proliferation of the mucorales.¹¹⁸ The characteristic clinical feature is a necrotic eschar over the nasal turbinates. Jugular venous thrombosis, cavernous sinus thrombosis, dissemination, and cranial nerve palsies are some its complications. Diagnosis may be confirmed by histopathological examination which may show pathognomonic changes of broad, irregular, non-septate, right-angled, branching hyphae are demonstrated by haematoxylin and eosin, and by specialized fungal stains. Vascular invasion and necrosis are the char-

acteristic consequences of the infective process. A neutrophil infiltrate is typical, and a granulomatous reaction may be observed.¹¹⁹

Malignant otitis externa

Malignant or progressive necrotizing otitis externa is an uncommon but severe infectious condition of the external auditory canal.³⁷ In a prospective study of 22 patients, 60% had diabetes (one out of four, insulin-dependent) and 13% were immunocompromised. The causal organism was *Pseudomonas aeruginosa* in 87% of cases.¹²⁰ In another study over a period of 10 years, of the 19 patients, 94.7% had diabetes (insulin-dependent in six cases). The causal germ was *P. aeruginosa* in 59% of cases.¹²¹ Pre-therapeutic investigations should include a computed tomography scan and a technetium scintigraphy to confirm diagnosis and assess extension. It is treated with parenteral antibiotic therapy using a third-generation cephalosporin (ceftazidime or ceftriaxone) and a fluoroquinolone (ciprofloxacin or ofloxacin) and, if there is no contraindication, hyperbaric oxygen may be used. Surgery is not indicated in malignant otitis externa other than local debridement.¹²⁰

Methicillin-resistant *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus aureus* (MRSA) is increasingly isolated from diabetic foot ulcers, and may be associated with an adverse prognosis. A study explored the relationship between MRSA isolation from foot ulcers and nasal MRSA carriage. Over a 12-month period, 65 consecutively attending patients with diabetic foot ulceration were recruited. Demographic information was collected, and the ulcer and nose swabbed bacteriologically using standard techniques. Mean age was 61 years, diabetes duration 14 years, and HbA1c 8.5%. 61% of them were male subjects and 15% with type 1 diabetes. Ulcers were neuropathic in 55%, ischaemic in 14% and neuro-ischaemic in 31%. MRSA was isolated from 12 (19%) ulcers, and 11 (17%) had nasal carriage. Of the MRSA-positive ulcer patients 7/12 (58%) had nasal MRSA carriage, compared to 4/53 (8%) with MRSA negative ulcers. Nasal MRSA carriage in diabetic patients may be significant risk factor for foot ulcer MRSA infection.¹²²

Necrotizing fasciitis

Necrotizing fasciitis (NF) is a potentially fatal bacterial infection of the subcutaneous soft tissues. The skin changes are characterized by prominent erythema (redness), induration, patchy necrosis, impairment and/or loss of sensations, associated with extensive undermining of the tissue following colossal necrosis of the fascia (Fig. 5).¹²³ Two cases of polymicrobial NF in adolescents with T1D and poor glycaemic control have been reported.¹²⁴ The perineal region was involved in both cases. One case was precipitated by apparently minimal trauma, the other by high-impact trauma. Diabetes mellitus has been identified as a common comorbidity and predictor of increased mortality in adult patients with NF.



Figure 5 Necrotizing fasciitis of the left buttock, illustrating extensive undermining of the tissue following colossal necrosis of the fascia.

The associations between diabetes and the incidence or outcome of NF in children and adolescents are not known. In all cases, early identification and aggressive surgical intervention are important for limiting morbidity and mortality.

Fournier's gangrene

Fournier's gangrene (FG) is a fulminant form of infective necrotizing fasciitis of the perineal, genital, or perianal regions caused by anorectal or urogenital and perineal trauma, more common in patients with diabetes mellitus and alcohol misuse. A 50-year-old post-menopausal obese female, who had poorly controlled IDDM suffered from recurrent Fournier's gangrene. Microbial evaluation of the obtained specimen from the lesions identified *Pep-tostreptococcus*, *Enterococcus* and *Escherichia coli*.¹²⁵

Clostridial gas gangrene

A case of non-traumatic clostridium infection has been reported, with rapid progression and a paucity of clinical signs in a patient with type 1 diabetes.¹²⁶ The diagnosis of this entity can be made confidently on the basis of four early clinical findings: (i) pain disproportionate to clinical findings or injury, (ii) marked tachycardia, (iii) discolored and oedematous skin, and (iv) Gram-staining of the bulla showing Gram-positive bacilli and few leucocytes.¹²⁷

Cutaneous reactions to insulin treatment

The incidence of insulin reaction varies from 10% to 56%, which may be immediate local/or general, delayed or biphasic and may occur within the first month of insulin therapy. Allergic reactions may be caused by impurities in the insulin preparation to beef or pork proteins, to the insulin molecule itself or to additional polypeptide preservatives or additives. The newer mono-component porcine insulin and purified human insulin have made these skin side-effects very rare with an incidence of 0.1% to 0.2%.¹²⁸

Insulin-induced lipoatrophy and lipohypertrophy is jointly referred to as lipodystrophy. It occurs at the site of injection or occasionally at distant sites. It presents as a depressed well-circumscribed area of skin, reflecting possibly a localized immune reaction to the insulin with associated loss of subcutaneous fat.¹²⁹ This reaction more commonly affects women in areas of substantial fat deposition. Lipohypertrophy presents as soft dermal nodules, clinically resembling lipomas, at the site of frequent injections, may be as a response to the lipogenic action of insulin. Chronically injected sites become hypoesthetic and this results in a delayed absorption rate.

Other dermatoses

Atopic dermatitis

It seems that type 1 diabetes has a Th1 (T-helper 1) immune reactivity pattern. There is often a reciprocal relationship between Th1 immune responses, which suggests that atopic dermatitis (AD), Th2 phenotype and type 1 diabetes Th1 Phenotype are unlikely to coexist in the same individual.¹¹³ This aspect has been investigated to find out the association between type 1 diabetes and AD but the results are debatable.¹³⁰

Drug hypersensitivity syndrome

Rapid loss of insulin secretion (fulminant diabetes) has been described following drug hypersensitivity syndrome (DHS).^{131–135} In three reported cases, findings for anti-islet cell or glutamic acid decarboxylase (GAD) antibodies were negative, indicating that the β -cell failure was not of autoimmune origin. In one report, the presence of antibodies was not described, but the onset of diabetes was associated with severe pancreatitis, which is also suggestive of a non-autoimmune cause.¹³³ One case has been reported of GAD-positive type 1 diabetes mellitus associated with DHS, following exposure to methimazole, implicating an autoimmune mechanism.¹³⁵

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