Dermatology of the diabetic foot and lower limb

Jean Mooney

Diabetes predisposes people to a range of systemic pathologies, including those of the skin, and the majority of people with diabetes will develop disease-related skin complications during the course of their condition. Here, the author presents an overview of the more common dermatological pathologies related to concomitant diabetes, with special attention to those of the foot and lower limb.

Diabetes predisposes people with the condition to a range of systemic pathologies. These typically present approximately 20 years after diagnosis in people with type 1 diabetes, but around 10 years post-diagnosis in those with type 2 diabetes (Giligor and Lazarus, 1981), or may even precede and inform a type 2 diabetes diagnosis (Diabetes UK, 2004).

In addition to the widely known late-stage complications of diabetes (vasculopathy, nephropathy, retinopathy, polyneuropathy) the majority of people with diabetes also develop disease-related skin complications over the course of their condition (Wahid and Kanjee, 1998; Mahajan et al, 2003; Nigam and Pande, 2003; Van Hattem et al, 2008; Wani et al, 2009).

Dermatological problems in diabetes occur as a result of abnormal carbohydrate metabolism, accumulation of advanced glycation end-products (AGEs) in soft tissues and joint ligaments, limb atherosclerosis (macroangiopathy), dermal microangiopathy, limb and dermal neurone degeneration and impaired immune mechanisms (Jennifer and John, 2003; Wani et al, 2009).

Background

Dermatological conditions are significant in the context of diabetes for a number of reasons (Shemer et al, 1998; Bhat et al, 2006; Ayub et al, 2009). Skin changes may be:

- Diagnostic of diabetes or insulin resistance. For example, diabetic dermopathy, necrobiosis lipoidica diabeticorum (NLD), diabetic bullosis, and eruptive xanthomatosis tend to affect only people with diabetes. Lichen planus (LP), NLD and acanthosis nigricans (AN) are more common in people who subsequently go on to develop diabetes or show current insulin resistance. Individuals with type 1 diabetes tend to develop autoimmune-related skin lesions such as vitiligo and LP, whereas those with type 2 diabetes are more prone to develop bacterial and fungal skin infections (*Table 1*).
- Indicative of worsening glycaemic control or progression to a range of diabetes-related complications, with one in 20 people with diabetes-related skin lesions also having diabetic nephropathy, neuropathy or retinopathy (see *Appendix 1*).
- Adverse reactions to antidiabetes drugs (e.g. erythema multiforme assocaiated with

Article points

1. The majority of people with diabetes develop disease-related skin complications at some time over the course of their condition.
2. Dermatological problems in diabetes occur as a result of the abnormal carbohydrate metabolism and systemic changes brought about by their condition.
3. Skin lesions can act as diagnostic indicators, and alert the clinician to impending type 2 diabetes or the onset of underlying or unsuspected secondary systemic complications of diabetes.
4. A thorough knowledge of the dermatological manifestations of diabetes is an essential part of the clinical skill set of healthcare professionals involved in diabetes care.

Key words:
- Dermatology
- Diabetes-related skin pathologies

Jean Mooney is a Consultant Podiatrist, Royal Hospital Chelsea, London.

Page points

1. The risks associated with skin breakdown and ulceration in the diabetic lower limb are great. For this reason a clinical examination must review all aspects of the skin of the lower leg and foot.
2. Skin signs of macrovascular disease include cold superficial tissue, hair loss, nail dystrophy and soft tissue atrophy in the foot.

Table 1. Prevalence of diabetes-related skin pathologies in a diabetic population (Ayub et al, 2009).

Skin pathology	Prevalence (%)
Skin infections	31
Foot gangrene/ulcers	13
Pruritus	7
Vitiligo	6
Yellow skin	4
Diabetic dermopathy	4
Skin tags (acrochordons)	4
Acanthosis nigricans	3
Eruptive xanthoma	3
Necrobiosis lipoidica diabeticorum	2
Diabetic bullae	1
Pigmented purpura	<1

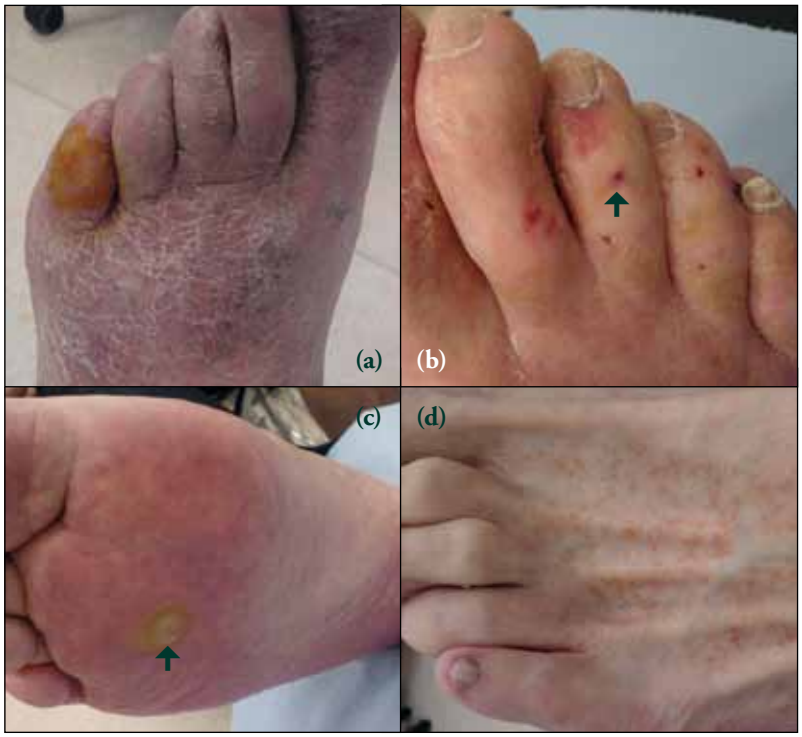

Figure 1. Diabetic feet with compromised vascularity manifesting as: (a) profound peripheral vascular disease (note the hairless skin and the fungal infection) and associated neuroischaemic ulceration of the fifth toe; (b) patchy tissue necrosis (↑); (c) plantar erythema with a patch of hyperkeratosis (↑); (d) pigmented purpura ("cayenne pepper spots") with clawing of the toes.

metformin use [Burger and Goyal, 2004]), or reactions to the administration of those drugs (e.g. insulin therapy [Richardson and Kerr, 2003]); and

- Progress to life- and/or limb-threatening infection and/or ulceration in the foot or lower limb.

Clinical examination

The risks associated with skin breakdown and ulceration in the diabetic lower limb are great. For this reason a clinical examination must review all aspects of the skin of the lower leg and foot for ulceration, joint deformity, discoloration, erythema, corn and/or callosity, haemorrhagic callus, interdigital maceration, infection and nail dystrophies (Boulton et al, 2008). Overall skin texture should be assessed, and evidence of oedema, dyshidroses, fissures or tinea pedis noted (Bristow, 2008). Nails should be examined for dystrophy, involution, paronychia, and onychomycosis. Neurological and vascular integrity should be tested, the skin temperature recorded, especially noting any differences between one foot and the other: a hotter foot may indicate infection, underlying active Charcot neuroarthropathy or skin inflammation indicative of possible ulceration, while a cold foot may indicate peripheral ischaemia (McGee and Boyko, 1998; Lavery et al, 2004; Armstrong et al, 2007; Lavery et al, 2007).

Angiopathy and neuropathy: clinical signs in the skin

Skin signs of macrovascular disease – otherwise known as peripheral vascular disease – include cold superficial tissue, hair loss, nail dystrophy and soft tissue atrophy in the foot, skin pallor on limb elevation and mottling and cyanosis with limb dependency and, in its ultimate form, ischaemic ulceration (*Figure 1a*) and distal gangrene.

Microvascular disease caused by arterio-venous shunting, capillary basement membrane thickening, glycation of erythrocyte membranes and increased plasma viscosity induces generalised compromise of capillary circulation with resultant reduced

Page points

1. This article will focus on non-ulcerative skin pathologies, seen primarily within the foot and lower limb, that are strongly associated with diabetes.
2. Acquired perforating dermatosis is rare. It typically affects people with diabetic nephropathy, those with renal failure and is noted in up to 10% of those on renal dialysis.
3. Diabetic bullae are a putative cause of neuropathic foot ulcers, affecting 1% of people with diabetes, with a 2:1 male:female ratio.

superficial tissue viability, patchy tissue necrosis and neuropathy (*Figure 1b*).

Reduced capillary function also causes erysipelas-like erythema (cold red skin of the foot) or microvenular dilatation, noted as facial flushing, periungual telangectasias and plantar erythema (*Figure 1c*). Extravasated erythrocytes from compromised capillaries cause pigmented purpura, or "cayenne pepper spots" (*Figure 1d*) of anterior tibial and dorsal foot skin, especially in older people with diabetes.

Distal polyneuropathy causes anhidrosis (*Figure 1a*), skin fissures and arteriovenous shunting (secondary to autonomic dysfunction), hyperkeratosis and trophic ulceration (with sensory loss) in areas of excess plantar pressure within the diabetic "claw foot", itself due to motor neuropathy and loss of joint mobility (Huntley and Drugge, 2009).

Non-ulcerative skin pathologies of the diabetic lower limb

The above text has summarised some of the dermatological effects of the systemic complications of diabetes within the lower limb that are all too familiar to the healthcare professional involved in the care of the person with diabetes and the diabetic foot. The remainder of this article will focus on some of the non-ulcerative skin pathologies, seen primarily within the foot and lower limb, that are strongly associated with diabetes.

Acquired perforating dermatosis (Kyrle's disease)

Acquired perforating dermatosis is rare. It typically affects people with renal failure, is noted in 10% of those on renal dialysis and can occur in diabetes. Lesions present as 2–10 mm diameter, pruritic, dome-shaped nodules with a central hyperkeratotic plug, mainly on the limbs, but also on the trunk, dorsa of the hands, and sometimes the face. Lesions show the Koebner phenomenon, and readily ulcerate if scratched.

Healing occurs within several months if lesion trauma can be avoided. Treatments such as topical keratolytics, psoralens with ultraviolet-A light, ultraviolet-B light, topical and systemic retinoids, topical and intralesional steroids, oral antihistamines and cryotherapy, are suggested (Morton et al, 1996; Ferringer and Miller, 2002; Saray et al, 2006).

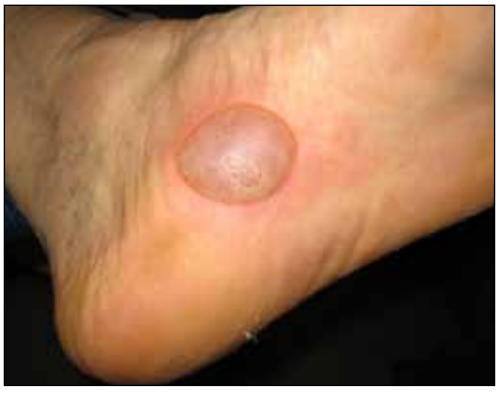

Figure 2. An example of bullous disease of diabetes, a marked blister manifest on the foot or leg skin in people with long-standing diabetes, distal sensory neuropathy and and nephropathy.

Bullous disease of diabetes (diabetic bullae; bullosis diabeticorum)

Bullous disease of diabetes (*Figure 2*) is characterised by marked blister formation of foot and leg skin in people with long-standing diabetes (Junkins-Hopkins, 2009), distal sensory neuropathy and nephropathy (Chakrabarty et al, 2002), independent of quality of glycaemic control (Ghosh et al, 2009). It is a putative cause of neuropathic foot ulcers and affects 1% of people with diabetes, with a 2:1 male:female ratio and a wide age range of onset (Larsen et al, 2008).

Blisters that are characteristically large (several centimetres in diameter), tense and irregular in outline form as intra-epidermal clefts filled with clear fluid; more unusually, haemorrhagic blisters form at the dermo–epidermal junction (Chakrabarty et al, 2002). Surrounding skin shows little or no inflammation. The differential diagnosis should exclude other causes of blisters (Ghosh et al, 2009).

Treatment is straightforward, involving protection of affected skin areas until lesions resolve. Very tense blisters may require aspiration, compression dressings and possible topical antibiotics. Blisters usually heal spontaneously without scarring within 2–3 weeks, unless subdermal tissues become involved or infection supervenes.

Page points

1. People with diabetes tend to develop stiffer skin with increasing disease duration, especially those with type 1 diabetes.
2. Causes of stiff skin include hydration of dermal collagen and generalised non-enzymatic glycosylation of dermal collagen with accumulation of advanced glycation end-products within soft tissues.
3. Granuloma annulare is a relatively common dermal pathology characterised by asymptomatic papules and annular plaques.

Diabetic dermopathy

Diabetic dermopathy (DD; "shin spots"; *Figure 3*) is the most common diabetic dermal pathology, affecting 7–70% of people with diabetes (Shemer et al, 1998), and preceding other signs of abnormal glucose metabolism. There is a close association between DD and severe systemic microvascular complications (Ferringer and Miller, 2002), indicating the likelihood of secondary diabetes-related complications (Sibbald et al, 1996).

Typically, DD affects men more than women, presenting as bilateral, round-to-oval, asymmetrical hyperpigmented patches of pretibial, lateral malleolar and dorsal foot skin (Van Hattem et al, 2008). Lesions are characterised by dermal oedema and local extravasation of erythrocytes (Binkley et al, 1967; Bauer and Levan, 1970) that break down *in situ* leaving haemosiderin deposits, which cause the characteristic irregular, blotchy, brownish skin pigmentation. Early DD skin changes do not cause marked symptoms, but the characteristic hyperpigmentation persists (Jelinek, 1994).

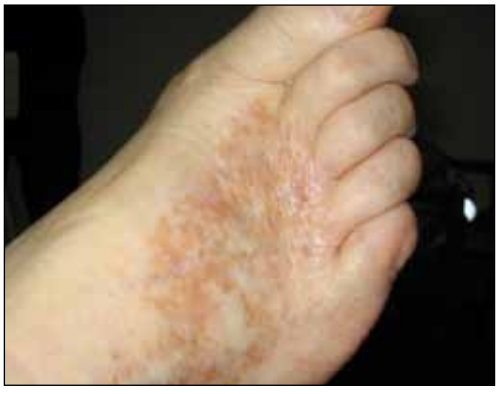

Figure 3. An example of diabetic dermopathy ("shin spots"), the most common diabetic dermal pathology.

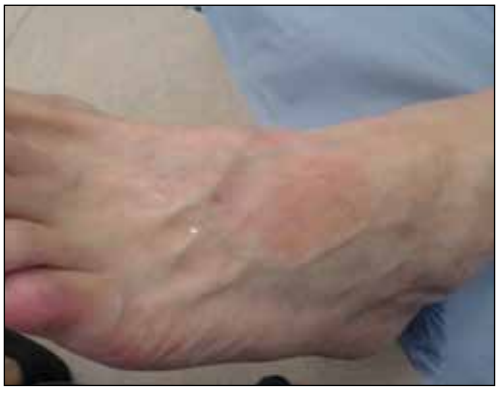

Figure 4. An example of granuloma annulare, a relatively common dermal pathology characterised by asymptomatic papules and annular plaques.

Diabetic thick skin

People with diabetes tend to develop stiffer skin with increasing diabetes duration, especially those with type 1 diabetes (Brik et al, 1991). Skin stiffness occurs as an increase in skin thickness, and/or scleroderma-like changes with associated reduced foot, hand and digit mobility (Huntley and Walter, 1990), "pebbling" of knuckle skin (Libecco and Brodell, 2001), diabetic hand syndrome (inability to extend the wrists and flatten the palms), DuPuytren's contracture (Huntley, 1982), reduced or absent subtalar joint motion (Delbridge et al, 1988) and sensory neuropathy (Van Hattem et al, 2008).

Causes of stiff skin include hydration of dermal collagen and generalised non-enzymatic glycosylation of dermal collagen with accumulation of AGEs within soft tissues (Buckingham et al, 1984; Perez and Kohn, 1994; Hashmi et al, 2006). There is no treatment for the condition, although strict glycaemic control appears to be of some benefit (Lieberman et al, 1980).

Granuloma annulare

Granuloma annulare (GA; *Figure 4*) is a relatively common dermal pathology characterised by asymptomatic papules and annular plaques, often of sun-exposed skin areas precipitated or exacerbated by chronic stress or triggered by certain drug regimens.

GA shows familial incidence, occurs in all races and age groups, although is rare in infancy (Cyr, 2006), and younger women are more commonly affected (female:male ratio 2:1; Kakourou et al, 2005). As many as one in eight people with type 1 diabetes develop GA (Studer et al, 1996). It also occurs in type 2 diabetes (Ghadially et al, 2009), developing at an earlier stage of the condition's natural history than NLD (Davison et al, 2010). GA has a weak association with underlying lymphoma (Li et al, 2003) and the differential diagnosis should exclude sarcoidosis (Cyr, 2006).

GA lesions vary in form and appearance. Initially, erythematous 1–2 mm papules

Page points

1. Yellowing of the nails and plantar skin is seen in diabetes and appears to be due to the long-term accumulation of carotene and advanced glycation end-products.
2. People with poorly controlled diabetes are more prone to anaerobic infections; these require urgent, aggressive intervention and intravenous antibiotic therapy to prevent subsequent limb amputation.
3. Candidal infections within the feet frequently cause web-space intertrigo with web spaces showing marked inflammation and peeling.

form (in dorsal foot and extensor lower leg skin); these gradually coalesce into arcs or annular plaques up to 5 cm in diameter with depressed hyperpigmented centres. A more generalised form may cause widespread leg and plantar skin involvement. A subcutaneous form presents as solitary, firm, non-tender, skin-coloured or pinkish isolated nodules attached to underlying fascia of pretibial and dorsal skin (Argent et al, 1994). A perforating form causes lower limb ulceration and later scarring, especially in older people (Penas et al, 1997).

GA lesions improve in winter and worsen in summer, and usually resolve spontaneously within 2–24 months of onset (Cyr, 2006).

Yellow skin and nails

Yellowing of the nails and plantar skin is seen in diabetes, especially in older people with type 2 diabetes. The discoloration is non-significant, and appears to be due to the long-term accumulation of carotene and AGEs within skin and nail tissue (Perez and Kohn, 1994; Norman, 2001). It is most marked in the hallux nail and weight-bearing parts of the plantar surface, especially in areas of hyperkeratosis.

Cutaneous infections

People with well-controlled diabetes are no more susceptible to infections than the normal population. However, those with poor glycaemic control, reduced tissue perfusion and microangiopathy, generalised peripheral vascular disease, peripheral neuropathy, and the decreased immune response that characterises diabetes are especially prone to systemic and skin infections (Perez and Kohn, 1994; Norman, 2001).

Bacterial infections: As the acute inflammatory response is reduced in diabetes, signs of impending or current bacterial infection with *Staphylococcus aureus* and beta-haemolytic streptococci, causing skin and superficial tissue infections, such as cellulitis and necrotising fasciitis, are masked. Antibiotic therapy is usually required.

People with poorly controlled diabetes are more prone to anaerobic infections (e.g. *Clostridium* species). These require urgent, aggressive intervention and intravenous antibiotic therapy to prevent subsequent limb amputation. *Pseudomonas* readily colonises interdigital spaces or contaminates existing skin wounds or fissures.

People who are obese and have diabetes are especially susceptible to erythrasma, caused by *Corynebacterium minutissimum* infection (Meurer and Szeimies, 1991), presenting in the foot as inflamed, pustular skin areas or pruritic interdigital fissures that resemble tinea or candidal infection. Erythrasma is confirmed by coral pink fluorescence under ultraviolet (Wood's) light and treated with topical or systemic erythromycin (Ferringer and Miller, 2002; Morales-Trujillo et al, 2008; Huntley and Drugge, 2009).

Fungal infections: Genital or oral thrush due to *Candida* (yeast; monilia) infection indicates poorly controlled or undiagnosed diabetes (Norman, 2001) and is often the pre-diagnostic presenting symptom (Lugo-Somolinos and Sánchez, 1992). Candidal infections within the feet frequently cause web-space intertrigo with web spaces showing marked inflammation, peeling and maceration, painful, raw apposing surfaces, with serous discharge, crusting and a characteristic yeasty smell, paronychia (marked nail-fold inflammation, swelling, tenderness, separation of the eponychium from the nail plate, and resultant nail plate dystrophy) or nail plate infection (the nail becomes white, friable and dystrophic). Treatment includes normalisation of blood glucose together with topical antifungal medications (e.g. topical imidazoles or 1% terbinafine; Meurer and Szeimies, 1991).

Dermatophyte infections (tinea pedis) of foot skin or nails caused by *Epidermophyton floccosum, Trichophyton rubrum* or *T. mentagrophytes* present as mildly inflamed, pruritic areas with peeling and parakeratosis of plantar skin (*Figure 5a*) and maceration and fissuring of interdigital

skin (*Figure 5b*). Perimeter heel skin shows frank hyperkeratosis and marked fissuring, extending into non-weight bearing heel skin as chronically inflamed areas of scaling and parakeratosis (*Figure 5c*). Nail infections present as white superficial onychomycosis, or as intermediate nail plate involvement causing white, yellow or brown discoloration, dystrophy and friability of all or part of the nail plate and matrix (*Figure 5d).*

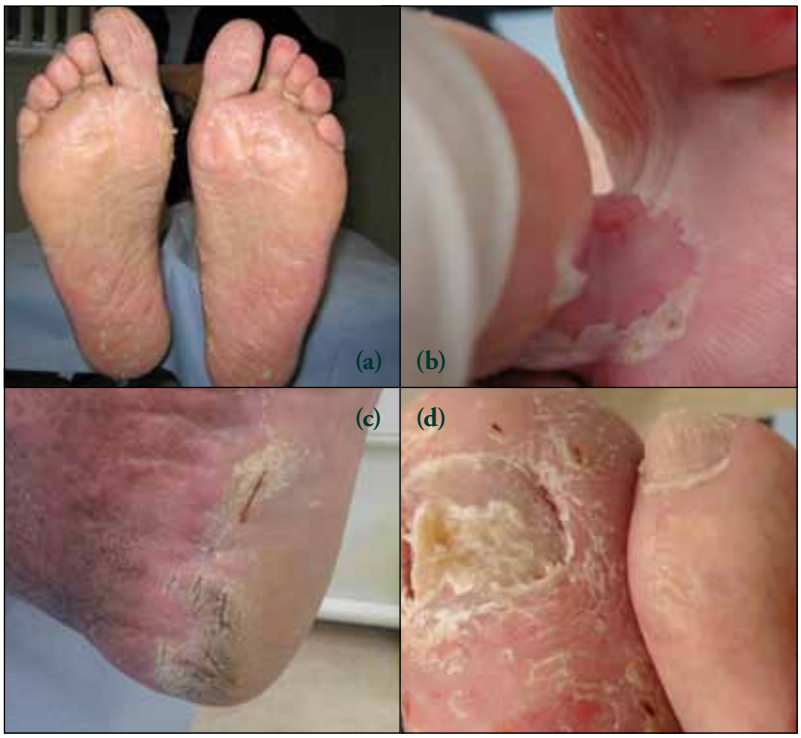

Figure 5. Fungal infections of the diabetic foot may involve (a) wide areas of plantar skin; (b) interdigital skin; (c) perimeter heel skin (note the hyperkeratosis and marked fissuring that extends to non-weight bearing heel skin); or (d) the nail plate (note the white, friable and dystrophic nail).

Page points

1. Lichen planus is an intensely itchy, chronic inflammatory disease of skin and/or mucous membranes; people with lichen planus show an increased prevalence of diabetes, insulin resistance and metabolic syndrome.
2. Necrobiosis lipoidica diabeticorum lesions typically develop in relation to mild trauma, ulcerate readily if subjected to ongoing trauma, and are more common in women than men, and in type 1 than type 2 diabetes.

People with poorly controlled diabetes may also be prone to more rare fungal infections such as *Phycomycetes* (Van Hattem et al, 2008).

As fungal infections, especially in skin, predispose to secondary bacterial infection, they should be monitored and treated with fungicidal preparations, such as terbinafine (topical 1% cream, or systemically), especially in people with coexisting neurovascular compromise or intertrigo.

Lichen planus

LP (*Figure 6*) is an intensely itchy (pruritic), chronic inflammatory disease of skin and/or mucous membranes characterised by crops of shiny, violaceous, polygonal papules, varying from 1 mm to >1 cm in diameter, covered by a fine parakeratotic scale (Wickham's striae). Lesions form as a delayed hypersensitivity immunological reaction, causing local inflammation and keratinocyte destruction (Neimann et al, 2006; Dreiher et al, 2008).

Cutaneous LP most commonly affects the flexor surfaces of limbs, although a chronic, pruritic, hypertrophic presentation may affect ankle skin and the extensor surfaces of the legs. Skin lesions may be discrete or arranged in lines or circles, showing the Koebner effect. Ten per cent of those affected also show related nail dystrophies (Chuang and Stitle, 2010).

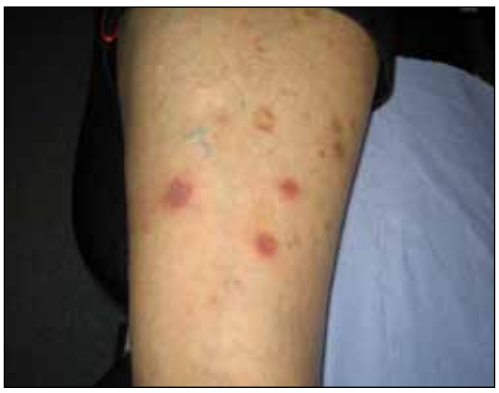

Figure 6. An example of lichen planus; a chronic inflammatory disease of the skin and/or mucous membranes characterised by crops of shiny, violaceous, polygonal, papules.

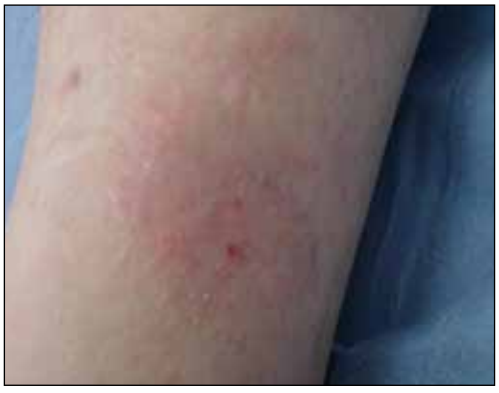

Figure 7. An example of necrobiosis lipoidica diabeticorum; lesions typically develop in relation to mild trauma, ulcerate readily if subjected to ongoing trauma, and are more common and in type 1 than type 2 diabetes.

In the majority of cases, skin lesions resolve within 6–18 months of onset, but affected skin areas show a characteristic slow-to-fade local hyperpigmentation.

LP affects approximately 1% of the adult population, although it can occur at any age (Balasubramaniam et al, 2008). People with LP show an increased prevalence of diabetes, insulin resistance and metabolic syndrome (i.e. high blood pressure, carbohydrate intolerance and dyslipidaemia). Onset is often stress related (Manolache et al, 2008) and those affected may also develop other immune-related diseases, for example vitiligo, alopecia, myasthenia gravis, pernicious anaemia or hepatitis C infection (Powell et al, 1974; Lowe et al, 1976; Dreiher et al, 2008; Bigby, 2009).

Necrobiosis lipoidica diabeticorum

NLD (*Figure 7*), particularly of pretibial skin, is a marker lesion for diabetes and its systemic complications (e.g. nephropathy and retinopathy; Kelly et al, 1993). Although only 1% of people with diabetes develop NLD, more than half of cases occur in those with diabetes (Cohen et al, 1996). Many people with diabetes show NLD lesions before diabetes diagnosis, and a quarter develop lesions soon after disease onset (Perez and Kohn, 1994).

Lesions typically develop in relation to mild trauma, ulcerate readily if subjected to ongoing trauma, and are more common in women than men, and in type 1 than type 2 diabetes (Meurer and Szeimies, 1991; Petzelbauer et al, 1992; Perez and Kohn, 1994; Marinella, 2002; Ahmed and Goldstein, 2006).

NLD occurs as chronic inflammatory degeneration of skin collagen. Initially lesions form as well-circumscribed, ovoid, sometimes pruritic, erythematous plaques several centimetres in diameter, which fade over time

to form insensate depressed, waxy areas of atrophic epidermis through which enlarged dermal vessels (telangectasia) may be visible.

The exact cause of the disease is unknown, but poor glycaemic control (Cohen et al, 1996), abnormal cytokine production, diabetic microangiopathy (Kelly et al, 1993) and an abnormal inflammatory response in association with distal sensory neuropathy (Barnes and Davis, 2010) are implicated in lesion genesis.

Treatment options include tight glycaemic control (Cohen et al, 1996), systemic non-steroidal anti-inflammatory agents, systemic, intralesional or topical corticosteroids (Ferringer and Miller, 2002) and topical immunosuppressive drugs (Nguyen et al, 2002; Stanway et al, 2004; Ahmed and Goldstein, 2006).

Pruritus

Pruritus (chronic skin irritation) complicates diabetes-related chronic renal failure and renal dialysis (Etter and Myers, 2002), but not acute renal failure. Apart from the ongoing discomfort of the condition, constant scratching traumatises skin, predisposing to secondary infection and skin ulceration.

Of unknown causes, pruritus is strongly associated with low urine output (<500 mL/24 hours; Bencini et al, 1985; Picó et al, 1992) and the accumulation of metallic ions and histamine (Weisman and Graham, 1998) that is characteristic of reduced renal function.

Conclusion

Diabetes currently consumes 5% of the NHS budget, although only 3.5% of the English population has the condition (NHS Information Centre, 2006). The type 2 presentation (90% of diabetes cases) is predicted to increase ten-fold by 2030 (Bagust et al, 2002), and 50% of these cases will already have secondary complications at diagnosis (Diabetes UK, 2004).

Indicators, such as skin changes and dermatological pathologies, that alert the clinician to impending diabetes or the onset of underlying or unsuspected secondary systemic complications of diabetes, form a vital part of early disease recognition. Recognition and appropriate management of diabetes-related dermatological pathologies of the foot and lower limb are of special importance in that their diagnosis and careful management may prevent progression to ulceration and infection, which are themselves strongly linked to increased morbidity and mortality (Davis et al, 2006). ■

Page points

1. Pruritus (a chronic skin irritation) complicates diabetes-related chronic renal failure and renal dialysis, but not acute renal failure. Pruritus is strongly associated with low urine output and the accumulation of metallic ions and histamine.
2. Recognition and appropriate management of diabetes-related dermatological pathologies of the foot and lower limb are of special importance in relation to their progression to ulceration, morbidity and mortality.

APPENDIX I. Systemic effects of diabetes and related conditions are listed in association with related dermatological presentations.

Insulin resistance
- Lichen planus

Metabolic syndrome
- Eruptive xanthomatosis

Established diabetes
- Diabetic dermopathy
- Necrobiosis lipoidica diabeticorum (NLD)

Poor glycaemic control
- Bacterial infections
- Yeast (*Candida*) infections
- Dermatophyte infections

Systemic neurovascular complications
- Ischaemic ulcers
- Cold feet or hot feet
- Skin and fibro-fat pad atrophy
- Bounding pulses
- Plantar erythema
- Polyneuropathy
- Trophic ulcers
- Charcot joint formation
- Abnormal neuro-inflammatory response
- Exuberant callous formation in high-pressure areas

Distal sensory neuropathy
- Diabetic bullae
- Trophic ulcers

Retinopathy
- Diabetic bullae
- Sensory neuropathy
- NLD

Nephropathy
- Pruritus
- Distal sensory neuropathy
- Acquired perforating acanthosis (Kyrle's disease)
- Diabetic bullae
- NLD
- Calciphylaxis

Early end-stage to chronic renal failure
- Pruritus

Accumulation of advanced glycation end-products
- Diabetic claw foot with reduced sub-talar joint movement and high plantar pressures
- Poor capillary perfusion and tissue compromise
- Diabetic thick skin
- Yellow skin and nails
- DuPuytren's contracture

Diabetes-related autoimmune disease
- Vitiligo

Hyperinsulinaemia
- Acanthosis nigricans of skin folds

Hypercholesterolaemia
- Acrochordons ("skin tags") of eyelids, neck and upper chest skin

Ahmed I, Goldstein B (2006) Diabetes mellitus. *Clin Dermatol* **24**: 237–46

Argent JD, Fairhurst JJ, Clarke NM (1994) Subcutaneous granuloma annulare: four cases and review of the literature. *Pediatr Radiol* **24**: 527–9

Armstrong DG, Holtz-Neiderer K, Wendel C et al (2007) Skin temperature monitoring reduces the risk for diabetic foot ulceration in high-risk patients. *Am J Med* **120**: 1042–6

Ayub J, Ahmed K, Muhammad Z, Qayum I (2009) Prevalence of cutaneous manifestations of diabetes mellitus. *J Ayub Med Coll Abbottabad* **21**: 76–9

Bagust A, Hopkinson PK, Maslove L, Currie CJ (2002) The projected health care burden of type 2 diabetes in the UK from 2000 to 2060. *Diabet Med* **19** (Suppl4): 1–5

Balasubramaniam P, Ogboli M, Moss C (2008) Lichen planus in children: review of 26 cases. *Clin Exp Dermatol* **33**: 457–9

Barnes CJ, Davis L (2010) *Necrobiosis lipoidica*. Available at: http://bit.ly/bv3Lt2 (accessed 31.01.11)

Bauer M, Levan NE (1970) Diabetic dermangiopathy: a spectrum including pretibial pigmented patches and necrobiosis lipoidica diabeticorum. *Br J Dermatol* **83**: 528–35

Bencini PL, Montagnino G, Citterio A et al (1985) Cutaneous abnormalities in uremic patients. *Nephron* **40**: 316–21

Bhat YJ, Gupta V, Kudyar RP (2006) Cutaneous manifestations of diabetes mellitus. *Int J Diabetes Dev Ctries* **26**: 152–5

Bigby M (2009) The relationship between lichen planus and hepatitis C clarified. *Arch Dermatol* **145**: 1048–50

Binkley GW, Giraldo B, Stoughton RB (1967) Diabetic dermopathy: a clinical study. *Cutis* **3**: 955–8

Boulton, AJM, Armstrong DG, Albert S et al (2008) Comprehensive Foot Examination and Risk Assessment: a report of the Task Force of the Foot Care Interest Group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. *Diabetes Care* **31**: 1679–85

Brik R, Berant M, Verdi P (1991) The scleroderma-like syndrome of insulin-dependent diabetes mellitus. *Diabetes Metab Rev* **7**: 120–8

Bristow I (2008) Non-ulcerative skin pathologies of the diabetic foot. *Diabetes Metab Res Rev* **24** (Suppl1): S84–9

Buckingham BA, Uitto J, Sandborg C et al (1984) Scleroderma-like changes in insulin-dependent diabetes mellitus: clinical and biochemical studies. *Diabetes Care* **7**: 163–9

Burger DE, Goyal S (2004) Erythema multiforme from metformin. *Ann Pharmacother* **38**: 1537

Chakrabarty A, Norman RA, Phillips TJ (2002) Diabetic bullae in cutaneous manifestations of diabetes. *Wounds* **14**. Available at: http://bit.ly/i2ezkI (accessed 31.01.11)

Chuang T-Y, Stitle L (2010) *Lichen planus*. Available at: http://bit.ly/cRGQfm (accessed 31.01.11)

Cohen O, Yaniv R, Karasik A, Trau H (1996) Necrobiosis lipoidica and diabetic control revisited. *Med Hypotheses* **46**: 348–50

Cyr PR (2006) Diagnosis and management of granuloma annulare. *Am Fam Physician* **74**: 1729–34

Davis WA, Norman PE, Bruce DG, Davis TM (2006) Predictors, consequences and costs of diabetes-related lower extremity amputation. *Diabetologia* **49**: 2634–41

Davison JE, Davies A, Moss C et al (2010) Links between granuloma annulare, necrobiosis lipoidica diabeticorum and childhood diabetes: a matter of time? *Pediatr Dermatol* **27**: 178–81

Delbridge L, Perry P, Marr S et al (1988) Limited joint mobility in the diabetic foot: relationship to neuropathic ulceration. *Diabet Med* **5**: 333–7

Diabetes UK (2004) *Diabetes in the UK 2004: A report from Diabetes UK*. Diabetes UK, London. Available at: http://bit.ly/emkpcw (accessed 31.01.11)

Dreiher J, Weitzman D, Davidovici B et al (2008) Psoriasis and dyslipidemia: a population-based study. *Acta Derm Venereol* **88**: 561–5

Etter L, Myers SA (2002) Pruritus in systemic disease: mechanisms and management. *Dermatol Clin* **20**: 459–72

Ferringer T, Miller F (2002) Cutaneous manifestations of diabetes mellitus. *Dermatol Clin* **20**: 483–92

Ghadially R, Szabo AZ, Garg A (2009) Granuloma annulare. Available at: http://bit.ly/aWr9f (accessed 31.01.11)

Ghosh SK, Bandyopadhyay D, Chatterjee G (2009) Bullosis diabeticorum: a distinctive blistering eruption in diabetes mellitus. *Int J Diabetes Dev Ctries* **29**: 41–2

Giligor RS, Lazarus GS (1981) Skin manifestations of diabetes mellitus. In: Rifkin H, Raskin P (eds) *Diabetes Mellitus*. RJ Brady, Louisiana, MO: 313–21

Hashmi F, Malone-Lee J, Hounsell E (2006) Plantar skin in type II diabetes: an investigation of protein glycation and biomechanical properties of plantar epidermis. *Eur J Derm* **16**: 23–32

Huntley AC (1982) The cutaneous manifestations of diabetes mellitus. *J Am Acad Dermatol* **7**: 427–55

Huntley AC, Walter RM (1990) Quantitative evaluation of skin thickness in diabetes mellitus: relationship to disease parameters. *J Med* **21**: 257–64

Huntley AC, Drugge R (2009) Diabetes in skin disease. In: *The Electronic Textbook of Dermatology*. Available at: http://bit.ly/hBPULl (accessed 31.01.11)

Jelinek JE (1994) Cutaneous manifestations of diabetes mellitus. *Int J Dermatol* **33**: 605–17

Jennifer L, John E (2003) Diabetes mellitus. In: Irvin MF, Arthur Z, Klaus W et al (eds) *Dermatology in General Medicine*. 6th edn. McGraw Hill, New York, NY: 1651–61

Junkins-Hopkins JM (2009) *Bullous Disease of Diabetes*. Available at: http://bit.ly/cR7pUi (accessed 31.01.11)

Kakourou T, Psychou F, Voutetakis A et al (2005) Low serum insulin values in children with multiple lesions of granuloma annulare: a prospective study. *J Eur Acad Dermatol Venereol* **19**: 30–4

Kelly WF, Nicholas J, Adams J, Mahmood R (1993) Necrobiosis lipoidica diabeticorum: association with background retinopathy, smoking, and proteinuria. A case controlled study. *Diabet Med* **10**: 725–8

Larsen K, Jensen T, Karlsmark T, Holstein PE (2008) Incidence of bullosis diabeticorum – a controversial cause of chronic foot ulceration. *Int Wound J* **5**: 591–6

Lavery LA, Higgins KR, Lanctot DR et al (2004) Home monitoring of foot skin temperatures to prevent ulceration. *Diabetes Care* **27**: 2642–7

Lavery LA, Higgins KR, Lanctot DR et al (2007) Preventing diabetic foot ulcer recurrence in high-risk patients: use of temperature monitoring as a self-assessment tool. *Diabetes Care* **30**: 14–20

Li A, Hogan DJ, Sanusi ID, Smoller BR (2003) Granuloma annulare and malignant neoplasms. *Am J Dermatopathol* **25**: 113–6

Libecco JF, Brodell RT (2001) Finger pebbles and diabetes: a case with broad involvement of the dorsal fingers and hands. *Arch Dermatol* **137**: 510–11

Lieberman LS, Rosenbloom AL, Riley WJ, Silverstein JH (1980) Reduced skin thickness with pump administration of insulin. *N Engl J Med* **303**: 940–1

Lowe NJ, Cudworth AG, Clough SA, Bullen MF (1976) Carbohydrate metabolism in lichen planus. *Br J Dermatol* **95**: 9–12

Lugo-Somolinos A, Sánchez JL (1992) Prevalence of dermatophytosis in patients with diabetes. *J Am Acad Dermatol* **26**: 408–10

Mahajan S, Koranne RV, Sharma SK (2003) Cutaneous manifestation of diabetes mellitus. *Indian J Dermatol Venereol Leprol* **69**: 105–8

Manolache L, Seceleanu-Petrescu D, Benea V (2008) Lichen planus patients and stressful events. *J Eur Acad Dermatol Venereol* **22**: 437–41

Marinella M (2002) Necrobiosis lipoidica diabeticorum. *Lancet* **360**: 1143

McGee SR, Boyko EJ (1998) Physical examination and chronic lower-extremity ischemia: a critical review. *Arch Intern Med* **158**: 1357–64

Meurer M, Szeimies RM (1991) Diabetes mellitus and skin diseases. *Curr Probl Dermatol* **20**: 11–23

Morales-Trujillo ML, Arenas R, Arroyo S (2008) [Interdigital erythrasma: clinical, epidemiologic, and microbiologic findings]. *Actas Dermosifiliogr* **99**: 469–73 [Article in Spanish]

Morton CA, Henderson IS, Jones MC, Lowe JG (1996) Acquired perforating dermatosis in a British dialysis population. *Br J Dermatol* **135**: 671–7

Neimann AL, Shin DB, Wang X et al (2006) Prevalence of cardiovascular risk factors in patients with psoriasis. *J Am Acad Dermatol* **55**: 829–35

Nguyen K, Washenik K, Shupak J (2002) Necrobiosis lipoidica diabeticorum treated with chloroquine. *J Am Acad Dermatol* **46** (Suppl2): 34–6

NHS Information Centre (2006) *National Quality and Outcomes Framework Achievement Data for England 2005–06*. NHS, London. Available at: http://bit.ly/h8zDtz (accessed 31.01.11)

Nigam PK, Pande S (2003) Pattern of dermatoses in diabetics. *Indian J Dermatol Venereol Leprol* **69**: 83–5

Norman A (2001) Dermal manifestations of diabetes. In: Norman R (ed). *Geriatric Dermatology*. Parthenon, New York, NY: 143–54

Penas PF, Jones-Caballero M, Fraga J et al (1997) Perforating granuloma annulare. *Int J Dermatol* **36**: 340–8

Perez MI, Kohn SR (1994) Cutaneous manifestations of diabetes mellitus. *J Am Acad Dermatol* **30**: 519–31

Petzelbauer P, Wolff K, Tappeiner G (1992) Necrobiosis lipoidica: treatment with systemic corticosteroids. *Br J Dermatol* **126**: 542–5

Picó MR, Lugo-Somolinos A, Sánchez JL, Burgos-Calderón R (1992) Cutaneous alterations in patients with chronic renal failure. *Int J Dermatol* **31**: 860–3

Powell SM, Ellis JP, Ryan TJ, Vickers HR (1974) Glucose tolerance in lichen planus. *Br J Dermatol* **91**: 23–5

Richardson T, Kerr D (2003) Skin-related complications of insulin therapy: epidemiology and emerging management strategies. *Am J Clin Dermatol* **4**: 661–7

Saray Y, Seçkin D, Bilezikçi B (2006) Acquired perforating dermatosis: clinicopathological features in twenty-two cases. *J Eur Acad Dermatol Venereol* **20**: 679–88

Shemer A, Bergman R, Linn S et al (1998) Diabetic dermopathy and internal complications in diabetes mellitus. *Int J Dermatol* **37**: 113–15

Sibbald RG, Landolt SJ, Toth D (1996) Skin and diabetes. *Endocrinol Metab Clin North Am* **25**: 463–72

Stanway A, Rademaker M, Newman P (2004) Healing of severe ulcerative necrobiosis lipoidica with cyclosporin. *Australas J Dermatol* **45**: 119–22

Studer EM, Calza AM, Saurat JH (1996) Precipitating factors and associated diseases in 84 patients with granuloma annulare: a retrospective study. *Dermatology* **193**: 364–8

Van Hattem S, Bootsma AH, Thio HB (2008) Skin manifestations of diabetes. *Cleve Clin J Med* **75**: 772–87

Wahid Z, Kanjee A (1998) Cutaneous manifestations of diabetes mellitus. *J Pak Med Assoc* **48**: 304–5

Wani MA, Hassan I, Bhat MH, Ahmed QM (2009) Cutaneous manifestations of diabetes mellitus: a hospital-based study in Kashmir, India. *Egyptian Dermatology Online Journal* **5**. Available at: http://bit.ly/i9GXQm (31.01.11)

Weisman K, Graham RM (1998) Systemic disease and the skin. In: Champion RH, Burton JL, Burns DA, Breathnach SM (eds). *Rook/Wilkinson/Ebling: Textbook of Dermatology*. 6th edn. Blackwell Science, Oxford: 2703–58