Diabetologia (1988) 31: 567-575

Diabetologia

The skin in diabetes mellitus

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The skin, in common with most other organs, suffers the effects of the metabolic disturbance of diabetes mellitus. Indeed, if any two of the multiple cutaneous conditions said to be associated with diabetes are considered, 100% of patients have skin involvement [1]. We do not intend simply to list the many and varied dermatological manifestations of diabetes, but Table 1 gives a selection of the most important. Neither will we discuss in detail aspects of cutaneous infection which are common in diabetes, nor the specialised and often reviewed problem of the diabetic foot. Rather it is our intention to discuss the fundamental changes in cutaneous structure and function induced by diabetes, and the relationship of these to the pathogenesis of skin disorders.

The effects of diabetes on the skin

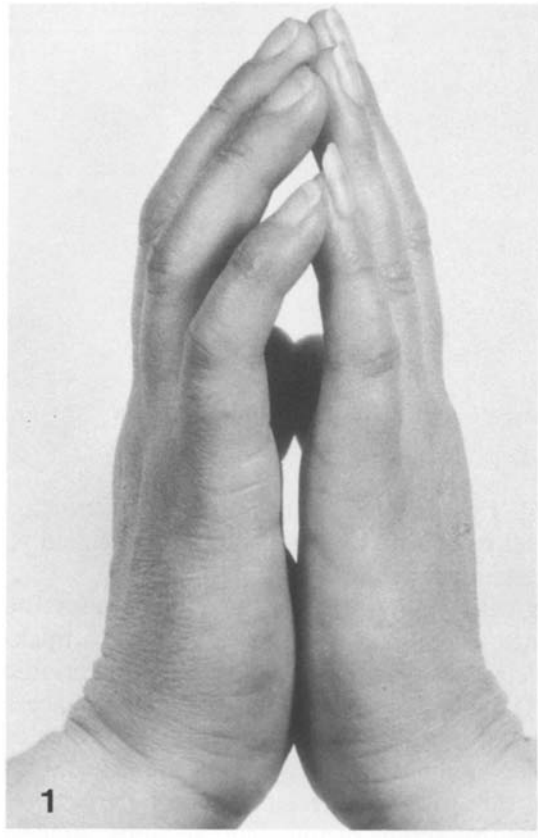
The histological changes induced by diabetes are well described [2, 3]. There is thickening of dermal collagen, with increased cross linking from non-enzymatic glycosylation [4], as in normal aging skin [2, 5]. The "browning" process by which glycosylation of proteins stabilises them has been extensively reported [6, 7], and affects skin collagen [6], and keratin [8]. There is no increased collagen synthesis, unlike systemic sclerosis [9], but skin thickness is increased [10]. There is loss of elastic fibres and clumping of residual elastic tissue [2, 11]. Individual elastic fibres are frayed and disrupted, and separated by microfibrillar dense zones which occur around the edges of fibrils [12]. There is loss of anchoring fibrils in the basement membrane of the epidermis, and this, coupled with the thickened and inflexible dermis may predispose to injury from minor trauma [12]. In general these cutaneous changes appear to be related to duration of disease [13], as well as to the quality of glycaemic control. They are said to be irreversible [14], though there are isolated reports of reduced skin thickness with improved diabetic control [14], as well as spontaneously [15].

It is thought possible that these changes are produced in part by the relative ischaemia of the skin in diabetes [16]. This may be due to micro- or macro-vascular disease, or to arterio-venous shunting related to autonomic neuropathy.

Histologically, the skin floridly demonstrates the characteristics of diabetic vascular disease, with thickening of the vessel walls and deposition of (Periodic Acid Schiff) positive material thought to be excess basement membrane [2]. The origin and significance of these changes remain unknown, but the studies of Braverman, using three-dimensional computerised reconstructions of serial histological sections suggest that this appearance may be due to the veil cells surrounding the vessels, rather than the basement membrane itself [17]. The vascular changes found throughout the skin are similar to those caused by ultra-violet exposure and the normal aging process, but in diabetes are found not only in non-light exposed areas such as the buttock, but also in young, complication-free patients [2]. They increase from thigh to foot, and are most marked in the capillaries

Table 1. Conditions said to be related to diabetes mellitus, either causally, or by epidemiological data only

Infections
Thick skin and stiff joints
Foot ulceration
Necrobiosis Lipoidica
Granuloma annulare (?)
Shin spots
Diabetic blisters
Acanthosis nigricans
Scleredema
Lipodystrophy
Treatment related conditions:
Lipo-atrophy
Lipo-hypertrophy
systemic allergy
flushing
Skin tags
Yellow nail syndrome
Vitiligo
Lichen planus
Psoriasis
Pemphigoid
Granuloma annulare (?)



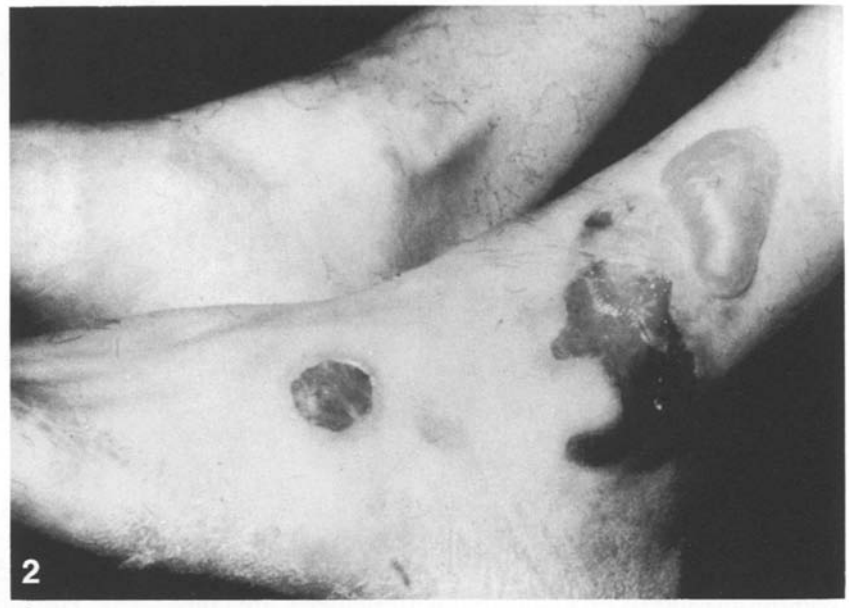


Fig. 1. The prayer manoevre, demonstrating thickened skin with limited extension of the interphalangeal joints

Fig. 2. Diabetic blistering, with one intact blister and two eroded areas. The surrounding skin is normal

[18]. It is suggested that they may occur as a consequence of failure of vascular responsiveness [19], which leads to a loss of protection of the small vessels from postural changes in venous pressure.

Skin appendages in diabetes

Sebaceous gland

Though the sebaceous gland is under hormonal control, there are no reports of abnormalities of glandular dysfunction in diabetes itself. There are, however, well-reported instances of excess sebum production and even severe acne vulgaris in patients with other endocrinological disorders of which diabetes may form a part. Thus, severe acne is a marker for both growth hormone excess [20] and Cushing's syndrome. No structural abnormalities of sebaceous glands have been reported.

Sweat glands

There are many reports of abnormalities of sweating in diabetes. Decreased sweating, often with compensatory hyperhidrosis elsewhere [21] is the result of autonomic neuropathy, and defective re-innervation is said to be the cause of gustatory sweating, in which eating is associated with inappropriate localised facial sweating [22].

Cutaneous features of vascular insufficiency

Diabetic thick skin and stiff joints: cheiro-arthropathy

This pseudosclerodermatous condition is said to occur in as many as 30% of diabetic patients [23]. In its fully developed form, the changes are obvious, with thickening of the skin resulting in loss of full extension of the fingers, followed by a degree of fixed flexion [24]. Less severe forms may be detected by the "prayer" manoeuvre (Fig. 1), but enthusiastic use of this test leads to the detection of abnormalities in many normal people [25]. This suggests that, at worst, it is simply a normal variant, and at best a sign which requires cautious interpretation. Cutaneous changes are often accompanied by joint stiffness which rarely causes major disability, and for which there is little effective therapy [26]. Cheiro-arthropathy is described as reversible, which suggests that browning is not the cause [15], and there is no correlation between the amount of non-enzymatic glycosylation and the presence of limited joint mobility [27].

In cross-sectional studies, cheiro-arthropathy has been shown to be associated with other complications of diabetes [23], and indeed might be a marker for the most severe renal and ophthalmic lesions [28]. However, this association probably indicates that all these features of the disease are more likely in those who have had diabetes longer or whose glycaemic control has been poor.

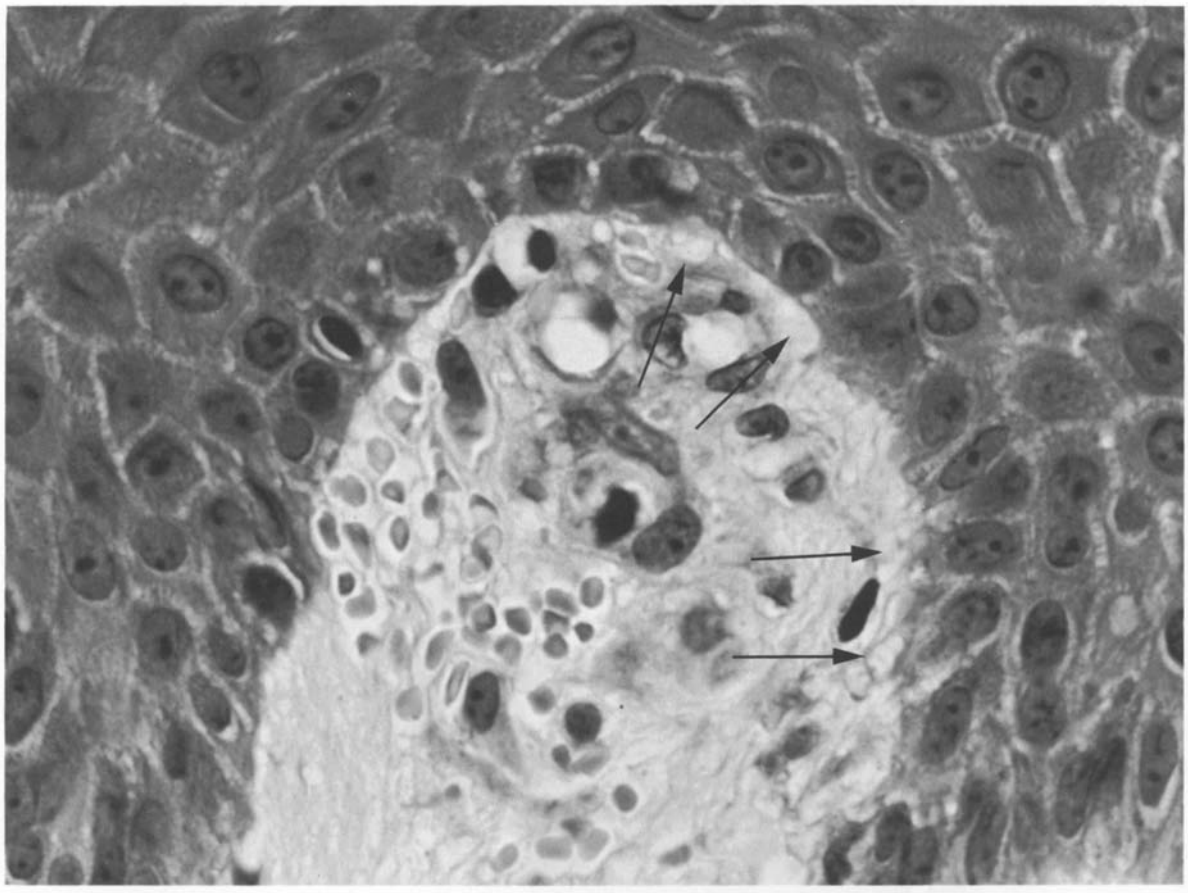


Fig. 3. Photomicrograph of skin biopsy from clinically non-specific area of excoriated papules on the trunk of a patient with long standing, multiply complicated non-insulin-dependent diabetes mellitus. (Haemotoxylin and eosin, ×780). Note the sub-epidermal vacuolation indicated by the arrows

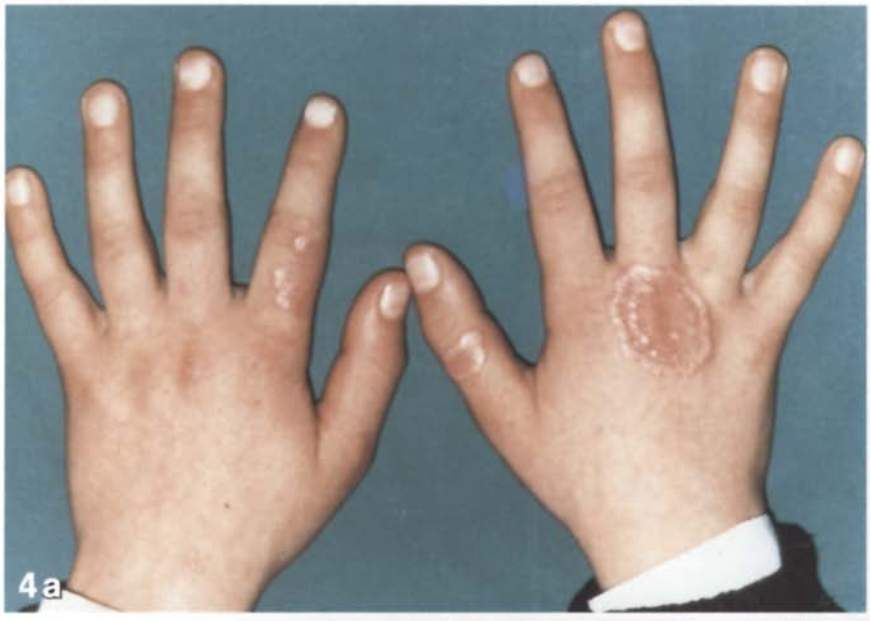
Scleredema diabeticorum

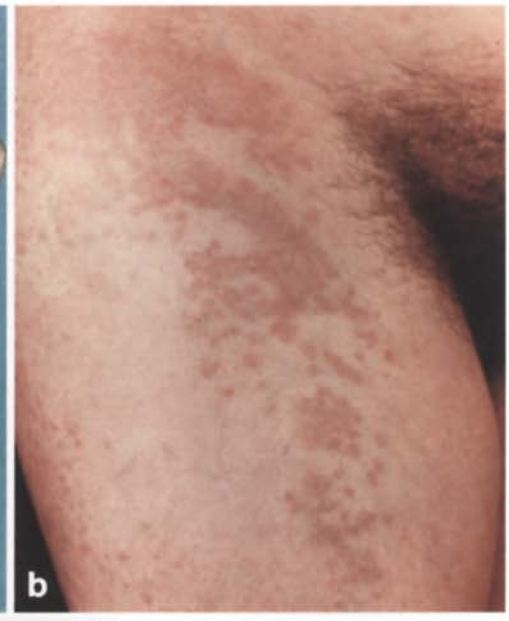
We include this uncommon condition in this category because it is produced by changes in dermal collagen [29]. This is thickened, even to the extent of replacing the sub-cutaneous fate, and increased amounts of intercellular substances, particularly hyaluronic acid, are present [30]. These changes are localised to the face, neck and shoulders where they produce changes in texture that are clinically obvious [31]. In non-diabetic subjects a similar, but self-limiting condition occurs (Scleredema of Bushke) and may follow a systemic infection, typically streptococcal [32]. There are also suggestions of an infective basis in diabetes [33], though the evidence is limited. If infection is responsible, it is of interest that Borrelia burgdorferi may induce changes in collagen in localised scleroderma [34].

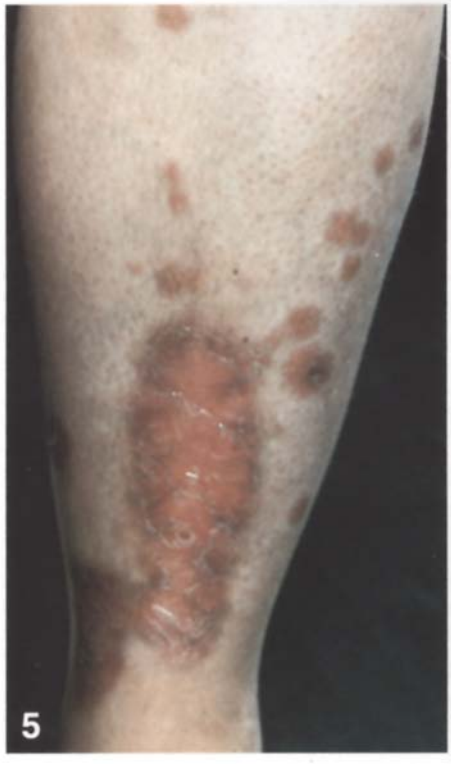
Bullosis diabeticorum

Since its description in 1963 by Rocca and Peraya [35], diabetic blistering has been the subject of many single case reports and small series [36–38], notable only for their heterogeneity. The clinical picture seems reasonably clear, with symmetrical spontaneous blistering of the extremities tending to occur in patients with multiple other complications of their disease [39] (Fig. 2). The histology is less well documented however, with blisters being both sub- [37, 38] and intra-epidermal [36], or mixed [40], with and without immunoreactants [40], and either scarring [35] or non-scarring [41]. Suggested aetiologies have been numerous, ranging from immunological [41], to those related to calcium and magnesium imbalance secondary to renal disease [38], and including that due to ultraviolet light [41]. More recently, the clinical and histological features of four similar cases have been reported [42], and suggest that the aetiology may be related to the effects of vascular insufficiency on dermal rigidity and dermo-epidermal adhesion. The histology was consistent in that the blister was sub-epidermal with electron-microscopy showing dermo-epidermal vacuolation in para-lesional skin.

Interestingly, this para-lesional vacuolation has been seen around the non-specific papular and excoriated lesions of the limbs and trunk in other patients with long standing diabetes (unpublished data), (Fig. 3) and this reinforces the suggestion that trauma has a role in the development of blistering, and also that these non-specific lesions may be part of the same spectrum of cutaneous aging change.







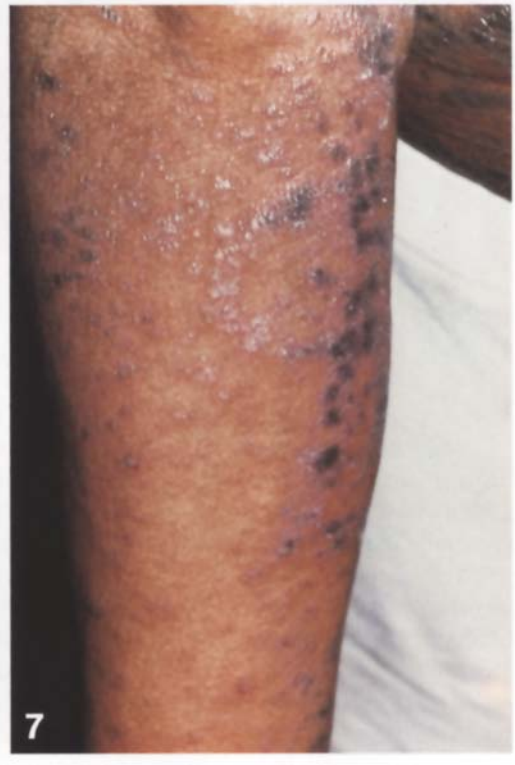


Fig.4. **(a)** Localised and **(b)** diffuse granuloma annulare

Fig.5. Necrobiosis lipoidica diabeticorum. One lesion shows early superficial ulceration

Fig.7. Typical lichen planus of the wrist and forearm in an Asian patient, showing the characteristic purple colour, with prominent Wickham's striae

It is possible that the same is true of diabetic shin spots. These occur on the shins of both diabetic patients and non-diabetic subjects, and are atrophic and pigmented in appearance [43]. It has been suggested that they may represent the sites of earlier blistering lesions [37], but this has not been confirmed.

Table 2. The differential diagnosis of diabetic blistering

Bullosis diabeticorum
Bullous pemphigoid
Epidermolysis bullosa acquisita
Porphyria cutanea tarda
Bullous impetigo
Oedema blisters

Blistering lesions need to be properly documented, not only because the differential diagnosis is large (Table 2), but also because of the risks of secondary infection and non-healing if the lesions are inappropriately managed.

Granuloma annulare

The relationship of this common condition to diabetes mellitus is not clear [44–46]. Clinically there are two forms, localised and generalised. The localised variety

is often confined to the knuckles and characterised by skin coloured dermal papules arranged in annular configurations [47] (Fig.4). It may also occur on the feet, where the lesions may have a central purple discolouration [47]. Subcutaneous lesions occur and are found, like localised disease, in a younger age group than the generalised form. The generalised type may have a variety of appearances, from large numbers of dermal papules similar to the localised variety but much more extensive, to more diffuse dermal plaques [47]. Some lesions may be perforating with epidermal ulceration [47].

Granuloma annulare is characterised histologically by degeneration of superficial dermal collagen with an accompanying granulomatous inflammation, and is similar in the diffuse and localised forms [47]. There may be accompanying evidence of small vessel occlusion and occasionally a definite vasculitis, with fibrinoid change and nuclear dusting secondary to the endothelial injury [48]. It is indistinguishable from the histology of rheumatoid nodules [49], and a relationship between rheumatoid arthritis and diabetes has been reported but not confirmed [50].

It has been suggested that granuloma annulare might be a marker for diabetes [44], but this has not been clearly established. Conflicting evidence has been provided by steroid provocation tests [51, 52], measurement of enzymes known to be abnormal in diabetes [53], and epidemiological studies [54]. Dermatological dogma has it that generalised granuloma annulare is most likely to be associated with diabetes, and that all those who present in this way should have diabetes mellitus excluded [47]. However, the basis for this dogma is open to dispute. Moreover, a recent study [54] reported that it was the *localised* variety of granuloma annulare that was related to diabetes. If there is an association between either or both forms, the skin condition may or may not predate the onset of diabetes. There has been a suggestion that successful treatment of the diabetes may lead to resolution of the granuloma annulare [46], but this has not been confirmed. We have all seen patients with granuloma annulare in whom its occurrence directed our attention to their diabetes, particularly in the elderly. The balance of evidence seems to favour the dermatological dogma, with an added caution in elderly patients with localised granuloma annulare.

Necrobiosis lipoidica

Necrobiosis lipoidica (diabeticorum) is unequivocally related to diabetes mellitus [55]. About 50% of patients with this cutaneous disorder will have diabetes [55, 56]. Occurring most often on the shins, the clinical appearance is characteristic, with a purple edge, yellow atrophic centre, and frequent ulceration [47] (Fig.5). Histologically, it is remarkably similar to granuloma annulare although it shows more extensive collagen degeneration, but similar granulomatous inflammation [57].

The pathogenesis of necrobiosis and granuloma annulare is unknown. The most commonly held view is that the basis of the collagen degeneration is vascular, with small vessel thrombosis [58] and abnormal platelet function [59]. Treatment with aspirin and dipyridamole [60], and with fibrinolytic drugs has been advocated, though benefit was not proven in a small controlled trial [61]. Others believe that the vascular lesion is itself the result of an immune vasculitis [62], or delayed hypersensitivity [63], but the evidence is limited. There is also evidence for an intrinsic abnormality of collagen production, though this could still be a secondary phenomenon [64].

Treatments such as potent topical steroids or local steroid injections, and topical psoralen phototherapy [65] remain unproven. Patients should be advised about the danger of trauma to the area, and should use simple emollients topically, as well as taking advantage of the very effective camouflage produced by appropriately coloured masking creams. In a limited number of severely affected patients, skin grafting may be successful.

Insulin related conditions

Acanthosis nigricans

Acanthosis nigricans is uncommon [66] and is even less commonly associated with diabetes [67]. The appearances are unmistakable, with warty hyperpigmentation in flexures and around the neck (Fig.6), where there may be associated skin tags [66]. When it does occur with diabetes, it is always associated with marked insulin resistance and raised insulin levels [68]. This combination can and often does occur in the absence of clinical diabetes [68], when it may be linked to other endocrine diseases (Cushings, acromegaly) or to simple obesity. Two groups of patients are described: the first (Type B syndrome) has circulating antibodies to the insulin receptor [69], the second or Type A syndrome is linked with genetic defects in the receptor function or in post receptor pathways and may show hyper-androgenism [68]. Either may have diabetes. The cause of epidermal proliferation is unknown. Insulin is a potent growth factor [70], and most investigators feel that the high levels of insulin are the main stimulus to cutaneous overgrowth [71]. It is suggested that this effect is mediated through activation of receptors for other growth factors, particularly insulin-like growth factor (IGF) [72], for which insulin has a significant affinity [71]. Other possibilities are insulin like growth factors themselves, or androgens [73], which can produce acanthosis nigricans when given as replacement therapy [74].

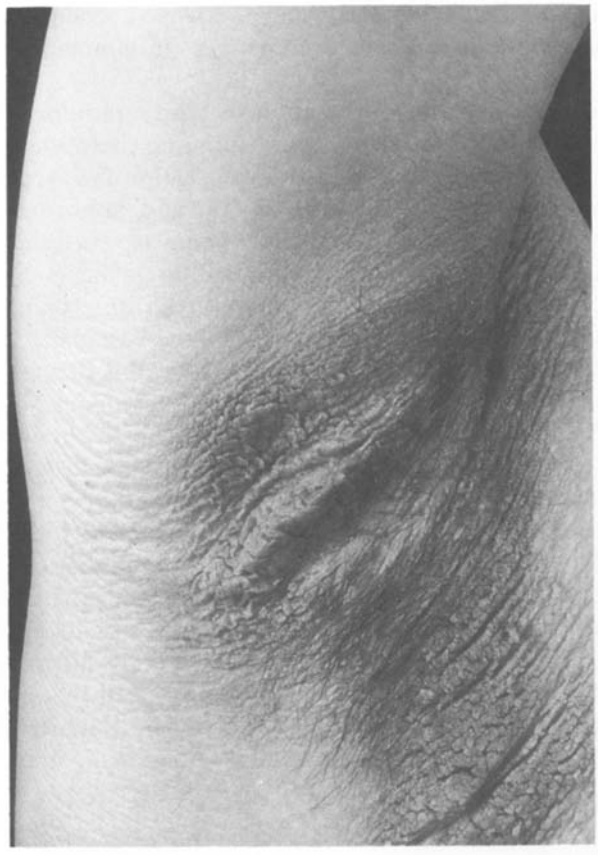


Fig.6. Acanthosis nigricans of the axilla

Skin tags of soft fibromata are very common lesions of the obese [75]. They are also seen very frequently in patients with acanthosis nigricans [66]. The finding of diabetes in three-quarters of patients with skin tags in one study [76] is not born out in clinical practice elsewhere, but it is an interesting possibility that these common lesions of only cosmetic importance may be related to growth factor excess of one sort or another.

Insulin induced lipohypertrophy

Occasionally with the older insulins, and more often with highly purified pork insulin, there may be a local reaction producing fat hypertrophy [77]. This results initially in a relatively anaesthetic, mobile nodule at the site of repeated injections, but may ultimately result in large sheets of hypertrophied fatty tissue. Because the area is anaesthetic, patients tend to favour this area for injection and thus compound the problem, which resolves eventually if the area is avoided for injections [78]. This complication is most likely to be related to the trophic actions of insulin acting locally [79], with large quantities of insulin accumulating at the sites of repeated injection because of unreliable absorption. It has also been described after subcutaneous infusion of insulin [80].

Diabetes as an immunological condition

The onset of Type 1 (insulin-dependent) diabetes mellitus is almost certainly immunologically mediated. The subject has been much discussed and well reviewed [81]. A number of cutaneous diseases have been related to diabetes, and are likely to be so related by virtue of a common immunological background.

Vitiligo

This characteristic skin complaint, with usually symmetrical patches of depigmentation [82] occurs more frequently in patients with both insulin and non-insuliln treated diabetes [83, 84]. There is no evidence that it occurs specifically in those patients who have circulating antibodies and other organ specific auto immune disease, and it is not related to any specific HLA type. It is unlikely that vitiligo can be produced by the metabolic upset of diabetes, and if the relationship is confirmed, must occur because of common immunological abnormalities. If this is correct, there should be a similar increase in the frequency of, for instance alopecia areata, and lichen sclerosus et atrophicus. No such relationship is described [85].

Bullous pemphigoid

Bullous pemphigoid characteristically affects the elderly, with urticated erythematous plaques (often peripheral) preceding the development of sub-epidermal blisters [86]. This bullous disorder is diagnosed on the basis of sub-epidermal IgG demonstrated on immuno-biopsy of para-lesional skin [87]. The antibody is directed against a basement membrane component situated in the lamina lucida of the basement membrane zone [88], and can be demonstrated in the serum of affected patients by indirect techniques [89]. It has been recently suggested that pemphigoid also occurs more frequently in diabetes [90]. If true, it is possible that the explanation is the same as that suggested for vitiligo, although it is possible that the changes in collagen lead to antigenic changes that precipitate the disease.

The relationship between these two conditions, pemphigoid and diabetes, whatever the explanation, has considerable importance. It is not sufficient to assume that a bullous disorder occurring in diabetic patients is bullosis diabeticorum. Any blistering disorder now needs full investigation, to exclude not only relatively common causes of bullae, e.g. staphylococcal bullous impetigo, and drug reactions, but most importantly bullous pemphigoid for which there is specific treatment. There are obviously clinical pointers: pemphigoid is usually extensive, persistent and itchy while bullosis diabeticorum is usually localised and transient, with a tendency to recur. These latter features have all been described with pemphigoid however; therefore, skin biopsy for histology and immunofluo-

rescence studies, circulating auto-antibodies, blister fluid for culture and immunology and porphyrin studies are all essential in the work up of diabetic patients with blistering.

Lichen planus

Lichen planus has been described in association with diabetes on a number of occasions [91, 92], and it is suggested that this association is more than by chance. Clinically, lichen planus is recognised by the presence of flat topped polygonal papules, having a purple colour and classically situated on the wrists, often with oral or genital lesions. There may be Wickham's striae, giving a white tracery to the surface [93] (Fig. 7). The histological picture is also characteristic, with a hyperplastic granular layer, saw-toothed acanthosis, and a high dermal lymphocytic infiltrate [93]. A similar condition, both clinical and histological, occurs in graft versus host disease, indicating that lichen planus too is likely to have an immunological basis [94]. Recent reports suggest that there is no association of other autoimmune conditions with lichen planus [95], and even the link with diabetes is unproven, since both are relatively common conditions.

Cutaneous reactions to insulin

Most reports of insulin reactions (local urticarial reactions, systemic allergic reactions of varying degrees including anaphylaxis, and lipo-atrophy) inevitably refer to the old pork and beef insulins which have now been replaced with more purified porcine, semisynthetic and synthetic human insulin [96]. The basis for most reactions was immunological, with the allergen in most cases being one or other of the impurities in the preparation [97], though the number of potential allergens, including insulin itself, was extremely large [98]. Some form of cutaneous reaction to insulin is said to occur in up to 10% of patients [98], and the vast majority of these were local, with systemic reactions being extremely rare [99], but potentially amenable to desensitisation [100].

Lipo-atrophy

Most insulin reactions were atrophic lesions at the site of insulin injection, and were the result of local inflammatory reactions to the injection, induced by antibodies to one of its components (zinc, impurities or insulin itself) [101]. Hollowed areas appeared at the sites of injections [102], and illustrate well the common response of skin to deep inflammation, such as that produced by a panniculitis. Such deep seated atrophy is a feature of the panniculitis of both (Systemic Lupus Erythematosus) and sarcoidosis of the skin [103], it is not a feature specific to insulin reactions. Repeated injections to the same site are said to predispose to this problem [78], which could be corrected by injection of a monocomponent insulin into the atrophic area, suggesting that allergy to impurities is more common than to insulin itself [104]. Presumably the lipogenic effect of insulin was responsible for this recovery, though lipo-atrophy can occur very rarely even with the monocomponent insulins [105].

Infections

Cutaneous infections of all types are found frequently in uncontrolled diabetes. There is evidence, well reviewed recently [106], that neutrophil chemotaxis, phagocytosis and killing are all abnormal in diabetes, and that the degree of the abnormality relates at least in part to levels of hyperglycaemia. Chemotactic function may also be abnormal in non-diabetic first degree relatives of diabetic patients, suggesting a more inherent defect in these cells. Cell-mediated immunity is deficient, again partly related to hyperglycaemia [107]. There is no evidence of impairment of specific cutaneous defences, such as changes in the normal skin flora, or defects in Langerhans cell function, though these in particular have not been specifically investigated.

Conclusions

The skin is one of the major organ systems involved in diabetes. Certain changes occur inevitably in this disease, and are undoubtedly the cause of many of the skin disorders seen in patients with diabetes. Other skin disorders are related to common disease processes, and still others are simply unexplained statistical observation.

Acknowledgement. We would like to thank Dr. W. Jeffloate for helpful criticism and advice about this manuscript.

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Received: 30 May 1988

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