DIABETES MELLITUS AND THE SKIN

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Summary

The authors present in short the main metabolic and physiological perturbations wich favorise the aparition of multiple dematoses during the evolution of diabetes mellitus. The authors classified from an evolutive point of view those dermatoses in two groups: the first group dermatoses without a well established correlation with the age of diabetes (with the possibility to be developed at any time during the diseas"s evolution, even before) and the second group with a well established correlation in time with the diabetes, including dermatoses as more frequent as the diabetes is older.

That review article continues with description of the most important associations between diabetes and skin diseases. The first group includes necrobiosis lipoidica, granuloma annulare, acanthosis nigricans and Buschke"s scleredema, with a comprehensive clinical and histological description. The second group includes diabetic dermopathy, bulosis diabeticorum, diabetic hand, eruptive xanthomas, Huntley"s papules of the fingers and with a more detailed description the diabetic foot.

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Diabetes mellitus is a profound metabolic disorder that disrupts glucose homeostasis, either by decreasing natural insulin production or by reducing glucose uptake at the tissue level, generally due to the development of anti-insulin antibodies.

Since glucose is the nutritional basis of every type of cell and the only source of cellular energy, the disruption of glycaemic homeostasis produces adverse effects in all organs and tissues of the human body over time; the first organs to be affected are the kidneys, the circulatory system and the peripheral nervous system, followed by the immune system in general, the eyes and last but not least the skin and mucous membranes.

Although diabetes is commonly associated with a permanently elevated blood glucose level, the most dangerous situations occur when blood glucose fluctuates too much (with the extremes being hyperglycaemic coma and the opposite, hypoglycaemic coma), while glycaemic homeostasis becomes inadequate to the immediate needs of all organs, including the skin and mucous membranes. Basically, over time, all fundamental physiological functions will be affected.

At the level of the skin, cutaneous and mucosal xerosis develops, directly induced by elevated glucose levels, promoting chronic pruritus and various infections, bacterial on the skin and predominantly candidal on the mucous membranes.

Elevated blood glucose leads gradually, but inevitably over time, to the chemical phenomenon of glycosylation of dermal proteins (analogous to haemoglobin glycosylation) with

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cutaneous consequences clinically manifested as pseudosclerosis and various other signs.

The same elevated blood glucose also provides an increased supply of nutrient substrate for bacterial and fungal pathogens, which explains the higher frequency of infections, particularly their chronic and recurrent nature.

In addition, there is also a reduction in the effectiveness of both local non-specific defence mechanisms and the specific immune response, due to an altered balance between LTh and LTs lymphocytes.

Peripheral sensory polyneuropathy is the underlying cause of chronic hyperkeratotic plantar ulcers, known as mal perforans, occurring exclusively in the feet.

Microangiopathy affects the retina and the peripheral nervous system, and subsequently, in association with diabetic macroangiopathy, leads to dry gangrene and other complex changes in the feet, resulting in the so-called diabetic foot.

Cutaneous manifestations directly related to diabetes mellitus, or at least favoured by it, are numerous, some more common, others rare and often with multifactorial aetiology – such as acanthosis nigricans, which is associated with diabetes mellitus, but also with morbid obesity or the presence of internal malignancies. We will provide an overview of the main dermatoses associated with diabetes mellitus and a more detailed description of the so-called diabetic foot, arguably the most complex and difficult to treat pathology associated with diabetes mellitus.

Some dermatoses are significantly more frequent in diabetes mellitus, but they also occur in other pathological contexts, do not depend on the quality of glycaemic control and do not correlate with its course (over time) – they may appear before the onset of diabetes mellitus, concurrently with it or later, at any time. They are: necrobiosis lipoidica, granuloma annulare (single or multiple), acanthosis nigricans and Buschke's scleredema.

Other dermatoses are strongly correlated with the course of diabetes mellitus, in the sense that they occur only after its onset, their frequency increases linearly with the duration of diabetes mellitus and they depend directly on the quality of glycaemic control. They are: diabetic dermopathy, facial diabetic rubor, bullosis diabeticorum, palmoplantar anhidrosis with compensatory facial hyperhidrosis, xanthosis of the skin and nails (rare, non-icteric yellow), eruptive xanthomas, diabetic foot and frequent fungal infections (to some extent also bacterial), with a clear tendency to recur and, especially, become chronic (nail, skin, genital involvement).

Necrobiosis lipoidica

The condition presents clinically as one or more plaques, rarely unilateral, often bilateral and symmetrical, located on the lower legs, always well delimited, with a dark red background and yellow-brown areas throughout, and invariably exhibit telangiectasias. The margins are active, expanding, slightly raised, in contrast to the atrophic centre. In 30% of cases, hyperchronic ulcers develop on the surface of the plaques. The Koebner phenomenon is also observed in this dermatosis. Subjectively, the plaques are asymptomatic.

The name of the condition derives from its typical histological appearance, which combines the degeneration of collagen fibres – necrobiosis, with extracellular lipid deposits forming lipoid accumulations.

Evolutionarily, necrobiosis lipoidica develops after the onset of diabetes mellitus in 60% of cases, appears approximately concurrently with diabetes mellitus in 25% of cases, and precedes diabetes mellitus in 15% of cases, sometimes by several years.

The mainstay of treatment consists of local injections of corticosteroids, combined with topical corticosteroid creams from the category with minimal atrophogenic effects, in order not to exacerbate the already existing atrophy.

Granuloma annulare

Granuloma annulare, sometimes also referred to as necrobiotic papulosis, consists of an eruption of erythematous papules arranged in a very characteristic circular pattern, which may be single or multiple. Rarely, it may also present as an approximately circular plaque, erythematous, with slightly raised margins. The condition is asymptomatic, regardless of appearance or extent. In children and young adults, a single erythematous papular ring usually appears, whereas in adults over 50 years of age, the

condition usually presents as multiple rings, sometimes disseminated. The female-to-male ratio is 2:1.

It must be differentiated from many other typical annular eruptions – from the common ones, such as tinea corporis and pityriasis lichenoides chronica, to the rare ones, such as forms of subacute lupus erythematosus, erythema gyratum repens as a paraneoplastic phenomenon, elastolytic granuloma, chronic migratory erythema of Lyme disease, necrolytic migratory erythema associated with pancreatic disorders, and non-specific annular erythemas, such as those that may occur in psoriasis but are not characteristic.

The histological appearance is characteristic and consists of necrobiotic granulomas.

The pathological associations are multiple: diabetes mellitus, primary or secondary hyperlipidaemias, but also Hashimoto's thyroiditis, HIV infections and lymphomas or other malignant tumours. In children, approximately 50% of cases are idiopathic.

Only topical therapy is required, consisting of corticosteroids without atrophogenic effects, applied for an extended period of time – between 3 and 6 months, sometimes under occlusive dressings.

Acanthosis nigricans

Five different types of acanthosis nigricans (AN) have been described, according to their almost specific pathological associations. AN may appear as a paraneoplastic manifestation, in the context of malignant obesity, sometimes merely on a background of metabolic syndrome, or in association with certain medications (contraceptives, STH, stilbestrol); approximately half of the cases are idiopathic, while the diabetic form is associated with type 2 insulin-resistant diabetes mellitus.

The clinical manifestation is the same in all forms, presenting as lichenified and pigmented areas ranging all the way up to black, asymptomatic, with typical topographical localisation in the major folds – axillary, inguinal, and lateral cervical, but exceptionally, it may also appear on extensor surfaces such as the elbows and knees.

In the form associated with diabetes mellitus, cutaneous changes are driven by hyperinsulinaemia, which activates IGF-1 (insulin-like growth factor 1) present on the surface of keratinocytes and fibroblasts, which leads to lichenification of the skin, with impaired physiological desquamation followed by oxidation of the excess stratum corneum, which consequently acquires a dark colour.

It does not have a characteristic histological appearance, nor is there any treatment recognised as effective.

The de novo identification of AN requires glycaemic control, neoplastic evaluation, and a thorough history of the patient's medications or family history.

Buschke's scleredema

Buschke's scleredema (SB) presents as an asymptomatic sclerodermoid plaque with typical topographical localisation on the upper third of the back, the neck and proximal limbs, with diffuse margins. The onset is insidious, and the evolution over time is extremely slow, but once established, it becomes permanent and does not regress spontaneously.

It is mostly idiopathic, more common in obese and male individuals. It may be a paraneoplastic manifestation that requires a thorough oncological evaluation. In approximately 2.5 – 14% of cases, according to various studies, it is associated with diabetes mellitus. It is not preceded by cutaneous infections and is not influenced by glycaemic control when associated with diabetes mellitus. It may also be associated with AIDS, hyperparathyroidism, malignant insulinoma, rheumatoid arthritis and Sjogren's syndrome.

Unlike typical scleroderma, the dermal thickening results from the deposition of large amounts of glycosaminoglycans, which can be histologically rendered evident by specific staining, rather than from the alteration of collagen fibres. Histologically, SB is classified as a mucinosis.

The treatments are exclusively systemic, chronic and of limited efficacy. High-dose penicillin has proven to be effective, with the active agents actually being the metabolites of penicillin, penicilloic and penicillanic acids, with antisclerogenic effect. Cyclophosphamide, cyclosporine and PUVA-therapy may also be attempted.

Diabetic dermopathy

In terms of clinical appearance, it is identical to the pigmented stasis dermatitis seen in the varicose complex of the lower leg and shares the same basic mechanism, namely the deposition of haemosiderin within local macrophages. In diabetic dermopathy, however, there is no impairment of venous blood flow with chronic hypoxia, but there is a general slowing of macrophage functions due to altered glycaemic homeostasis.

Bullosis diabeticorum

It consists of purely bullous eruptions on the lower legs and sometimes the forearms, apparently spontaneous, containing serous-citrine or haemorrhagic fluid, with the haemorrhagic appearance being more common in diabetic patients receiving anticoagulant (Eliquis, Pradaxa) or antiplatelet (Aspirin) therapy.

It appears more frequently in males with type 1 diabetes mellitus, with an incidence of approximately 0.5% among all diabetic patients.

Diabetic hand

Diabetic hand, or diabetic cheiroarthropathy, occurs in approximately 5-8% of all diabetic patients, through a process of sclerosis of the skin on the hands, accompanied by Dupuytren's contracture, carpal tunnel syndrome and limited joint mobility. Because it was depicted by A. Durer in a 1508 engraving in which he drew his own hands, the condition is also referred to as "Durer's Hands".

Eruptive xanthomas

Eruptive xanthomas have an incidence of approximately 1% in type 1 diabetes mellitus and 2% in type 2 diabetes mellitus. The condition for their occurrence is an elevated level of triglycerides, over 2000 mg/dl. Their formation is favoured by the reduced activity of lipoprotein lipase, secondary to insulin deficiency. They may appear at any stage of diabetes mellitus. Clinically, they present as small, shiny, pinkish-yellow papules, which are asymptomatic and preferentially located on the extensor surfaces – the knees and buttocks.

Huntley's papules of the fingers (finger pebbles)

It is an extremely rare manifestation, presenting as numerous shiny and asymptomatic micropapules that develop on the fingers and the dorsal surfaces of the hands. It is basically a form of diabetes-induced scleroderma; histologically, it is characterised by altered collagen fibres and hyperkeratosis, with changes present at the level of the dermal papillae, accounting for the micropapular clinical appearance.

Diabetic foot

The pathological changes in the feet in diabetic patients are multiple and accumulate over time, resulting in a complex of conditions collectively referred to as the diabetic foot.

Xerosis with hyperkeratosis and persistent heel fissures create entry points for common bacterial infections – erysipelas-like streptococcal skin infections and staphylococcal cellulitis-like infections, on a background of impaired non-specific and specific defence, which become chronically recurrent.

The interdigital skin favours the localisation of chronic candidiasis, more frequently than various dermatophyte infections, due to the increased supply of nutrient substrate in the form of glucose, specific to the genus Candida.

At the nail level, typical dermatophytic mycoses are more frequent, more difficult to treat and also tend to be recurrent.

Peripheral sensory polyneuropathy, frequently encountered, induced by perineural microangiopathy and neuronal protein glycosylation, ultimately leads to local trophic disturbances, clinically manifested as atonic ulcers (also called plantar mal perforans). These ulcers develop predominantly on areas of maximum pressure, such as the base of the hallux or the heel, but may also occur on the lateral surface of the toes. Clinically, they are characterised by the surrounding hyperkeratotic ring, the hyperchronic persistence, and the absence of painful sensation in the ulcer base. They progress slowly from superficial ulcers to deep ulcers, eventually leading to denudation of the underlying bone through necrosis and chronic osteitis. Treatment requires balanced control of diabetes mellitus, systemic medication for neuropathy,

and local application of moist pro-epithelialising and antiseptic dressings.

Diabetic microangiopathy, and particularly macroangiopathy, lead over time to dry, necrotic gangrene of the toes, with extremely painful arterial ulcers and autoamputations.

Proper treatment of the diabetic foot requires dedicated medical practices and a medical team consisting of a diabetologist, dermatologist, neurologist, vascular surgeon and possibly a podiatrist, working together efficiently.

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Conflict of interest
NONE DECLARED

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