SKIN DISEASES IN DIABETES MELLITUS

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Summary

Diabetes is a metabolic disorder of epidemic proportions, with increasing prevalence. The skin is directly affected by chronic hyperglycemia and the complex physiopathogenic reactions triggered by it. The authors present the most common skin diseases that are associated with diabetes mellitus, with the description of the etiopathogenic correlations, the clinical picture and the therapeutic strategy.

***Key words**: diabetes mellitus, hyperglycemia, skin manifestation, diagnosis, treatment.*

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Introduction

Diabetes mellitus (DM) is a heterogeneous syndrome, with multiple aetiologies, with hyperglycaemia as a common element. It is characterized by a complex disorder in regulating the body's energy metabolism due to absolute or relative insufficiency of insulin. The biochemical changes that these disorders cause lead to functional cellular changes, followed by irreversible anatomical lesions in numerous tissues and organs. [1]

According to data for 2017, provided by the International Diabetes Federation (IDF), 425 million adults have diabetes worldwide, the prevalence being of one of 11 adults. These figures are constantly rising, with the number of diabetes patients forecast to increase to 629 million by 2045. These data associate an increase in mortality through the complications of diabetes, but also with the economic costs. At present, 12% of global health expenditure is for diabetes. The prevalence in Europe is estimated at 8.5%, and in Romania it is 11.6%. [2]

DM complications are the leading cause of morbidity and mortality in diabetic patients. They are classified into acute, potentially fatal (severe hypoglycaemia, ketoacidosis) or chronic, debilitating, due to macro and diabetic micro-angiopathy (cardiovascular disease, retinopathy, nephropathy, neuropathy, etc.).

Aetiopathogenic cellular and extracellular skin processes in DM

The skin is directly affected by the complex pathophysiological processes triggered by chronic hyperglycaemia. The intracellular excess of glucose overloads the glucose metabolism pathways, causes the dysfunction of the mitochondria and the endoplasmic reticulum, with the generation of reactive oxygen species and the appearance of the cellular injury.

Chronic hyperglycaemia generates the emergence of advanced glycation end products (AGEs), following a series of non-enzymatic reactions between reduced carbohydrates and proteins or lipids. This process, normally with

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aging, is accelerated in DM and contributes to the development of diabetic microangiopathy. The AGE molecules present intracellularly alter cellular function and transport, and extracellular alter the biological structure and function of the dermal and basal membrane proteins. Dermal collagen is subjected to fragmentation and cross-linking processes, becoming rigid and resistant to proteolytic digestion. Coupling AGE with the specific RAGE receptor activates oxidative stress, apoptosis and triggers the inflammatory process by activating the transcription NFkB factor. In addition, the structure of dermal collagen is altered by the action of metalloproteinases 1, 2 and lysyl oxidase, present in concentrations significantly increased in non-diabetic skin. Clinical studies, carried out over a 10 years' period, have shown a direct correlation between the level of cutaneous AGE (measured by auto-fluorescence), the duration of diabetes, the onset of nephropathy and retinopathy. [3,4]

In vitro tests in animal models with induced diabetes have shown to affect keratinocytes by inhibiting proliferation, migration and differentiation, decreasing the number of basal cells and increasing the number of corneocytes. The lipid film on the surface of the skin is altered by the free fatty acids and cholesterol synthesis decrease, and lowering of the antioxidant protection system. [5]

Diabetic microangiopathy has also been described at the skin level.The pathogenesis of this process is complex, involving inflammation, endothelial dysfunction, decreased nitric oxide production, accumulation of excess AGE, oxidative stress, abnormal activity of growth factors, etc.

Histopathological evidence shows thickening of the vascular walls, oedema and hyperplasia of endothelial cells. The capillary density may be reduced. Capillary permeability is increased for albumin and water. Glycosylation of the erythrocyte membrane decreases their deformation capacity and contributes to obstruction of the capillary lumen, with the onset of ischemia. Also, diabetic patients have increased fibrinogen concentrations and procoagulant status. [6]

Impairment of the peripheral nervous system, somatic and vegetative, is a common chronic complication in DM, with various clinical manifestations. In developed countries, DM is the main cause of ***peripheral neuropathy***. Diabetic neuropathy is not a direct cause of death, but is a major cause of various forms of morbidity associated with DM. The most common form of diabetic neuropathy is symmetrical sensory-motor peripheral polyneuropathy, commonly associated with autonomic neuropathy. Approximately 60–70% of diabetics have medium or severe forms of neuropathy. Up to 50% of diabetic polyneuropathies can be asymptomatic and the respective patients have a high risk of not being aware of the lesions present in the legs. [7]

Peripheral neuropathy diagnosis is set by: testing the painful sensitivity, the vibrational sensitivity (using a 128 Hz tuning fork), the pressure sensitivity with a 10 g monofilament placed on the plantar face of both haloes and metatarsal joints, Achilles reflex assessment. For cutaneous neurovegetative disorder electro-physiological and sudomotor tests can be performed. These are clinical examinations that are easy to perform but that show advanced neuropathy. Skin biopsy allows the measurement of the density of the intraepidermal nerve fibres, their loss being correlated with the severity of the peripheral neuropathy. Other techniques for early assessment of the presence of nerve damage are corneal confocal microscopy and confocal reflectance microscopy. Testing the neurovascular response after the application of thermal stimuli, acetylcholine or capsaicin, followed by assessment by the Doppler technique, is also a method of early detection of nerve damage, before the appearance of the clinical picture. [8]

There is no specific treatment for underlying nerve damage, other than improving glycaemic control, which may slow the progression, but does not cancel out the neuronal destruction already present.

According to published studies, between 30% and 90% of patients present at least one dermatological manifestation during DM. Sometimes it is the first clinical manifestation of an undiagnosed DM or prediabetes. Also, certain conditions are considered markers of inadequate glycaemic control. [9]

Skin manifestations in DM

The skin disorder encountered in DM is diverse and has variability in prevalence, severity, therapeutic response or association with the type of DM. They can be classified as follows:

- skin diseases clearly associated with DM: diabetic dermopathy, necrobiosis lipoidica, generalized granulloma annulare, diabetic bullae, scleredema diabeticorum, eruptive xanthomatosis, benign acanthosis nigricans;
- common skin conditions, commonly found in diabetes: bacterial and fungal skin infections, generalized or localized itching, skin fibroids, facial rubeosis, palmar erythema, yellow coloration of the skin and nails, Dupuytren's contracture, diabetic cheiroarthropathy, vulgar psoriasis, vitiligo, lichen planus;
- macro and micro skin manifestations secondary to diabetic angiopathy;
- dermatological adverse effects of antidiabetic therapy: insulin lipodystrophy etc.

Diabetic dermopathy affects between 9 and 55% of diabetic patients, more commonly men over 50 years and with a long history of DM.It is considered the specific skin manifestation of diabetic microangiopathy. Of the patients with diabetic dermopathy, 52% associate with a microangiopathy complication, and 81% have all 3 complications (neuropathy, retinopathy, and nephropathy). [2, 8, 9] The evolution of the disease does not seem to correlate with the value of glycated haemoglobin. The condition is asymptomatic. Clinically, erythematous macules appear pretibial, bilateral, sometimes squamous at onset, which in time become atrophic, brown, simultaneously with the appearance of new lesions. Theevolution is variable. The diagnosis is generally clinical, and the histopathological aspect is non-specific: epidermal atrophy with hyperkeratosis, proliferation of dermal collagen, hyaline angiopathy, extravasation of erythrocytes, perivascular lymphocyte infiltrate, and hemosiderin deposit. Treatment is ineffective and is often unnecessary. [10,11]

Necrobiosis lipoidica (NL) is a rare chronic inflammatory dermatosis, affecting 3% of diabetics, especially those with a juvenile form. Histopathological appearance is of palisadic granuloma in the dermis and hypodermis, consisting of lymphocytes, plasmocytes, eosinophils, histiocytes, collagen degeneration, and lymphocyte perivascular infiltrate, thickening and obliteration of the dermal vessels, sclerosis, extracellular lipid deposit and nerve fibres loss. Alpha tumour necrosis factor has high concentrations in the serum and skin of these patients.

NL affects women more frequently (ratio of women to men 3: 1), in the fourth decade of life for non-diabetic patients and in the third decade for diabetic patients. DM is present in 11-65% of patients with NL, and non-diabetic patients are at higher risk of developing diabetes in the future. In patients without diabetes, associations with primary hypertension, obesity, dyslipidaemia, glucose intolerance, thyroid disorders were observed.

Patients with necrobiosis lipoidica have oval or irregular plaques, sometimes confluent, with a raised margin, initially light brown or erythematous, progressing to yellow-coloured indurated plaques and telangiectasias on the surface, central atrophy with perforating ulceration. Election localization is pretibial, often symmetrical, but in 15% of cases there are injuries to the hands, forearms or scalp.

The following factors are implicated in the aetiopathogenesis of this condition: microangiopathy, immunological vasculitis, delayed hypersensitivity reaction, collagen synthesis and structure abnormalities, and traumatic factor. The presence of increased platelet aggregation in patients with lipoid necrosis is demonstrated by the therapeutic effect of aspirin. Patients receiving aspirin or pentoxifylline had a significant improvement in the clinical appearance of the lesions and healing of the ulcers in 2-4 weeks. Local treatment consists of dermatocorticoids or tacrolimus, and generally corticosteroids in large doses over a short period. [11-13]

Generalized granuloma annulare(GGA) is the form of granuloma annulare that associates in 60-70% of DM cases. It mainly affects women (sex ratio 6: 1), often past 40 years.The aetiology is unknown. It is assumed that a cellular mediated immune inflammatory response of T lymphocytes is triggered by certain trigger factors (e.g. local trauma, insect bite, vaccine, viral

infections, etc.). GGA cases associated with other pathologies have been described: autoimmune thyroiditis, malignancies, chronic HBV or HIV infection. Some cases are iatrogenic, after administration of allopurinol, cationic inhibitors, and diclofenac, anti TNF, calcitonin or some chemotherapeutics. The clinical appearance is of multiple asymptomatic, arciform or oval lesions, with a diameter of 1-5 cm with the margin formed by the coalescence of small firm papules, discrete erythematous, with the hypo or hyperpigmented centre, without atrophy. GGA lesions are frequently located in the trunk, cervical and extremities. Histopathologically, palisadic or interstitial lymphohistiocytic granuloma, collagen degeneration, mucin deposits, absent or reduced elastic fibres are observed in the dermis. Treatment is difficult. The following are used: dermatocorticoids, calcineurin inhibitors, corticotherapy, antimalarials, retinoids, dapson, doxycycline, infliximab, etc. [13-15]

Diabetic bullae disease is a rare condition, with uncertain aetiopathogenesis, clinically characterized by large bubbles, filled with clear or serohematic fluid, arranged at the extremities. The lesions heal spontaneously within a few weeks, usually without scarring, but they can recur, evolving into a few years. Treatment is symptomatic. This condition is not correlated with the duration of diabetes or glycaemic control.

Diabetic scleredema manifests through thickening and diffuse induration of the skin, with symmetrical disposition.The disease begins at the level of the face and neck, then continues to the trunk and root of the lower limbs, with respect to the abdomen and lower limbs. It particularly affects obese men with old diabetic disease and major complications.

Xanthomas are accumulations of lipids in the skin and subcutaneous cellular tissue. Eruptive xanthomas are rare clinical forms of xanthomas, manifested by an eruption with a sudden onset, consisting of multiple coalescing, sometimes itchy, yellow papules, with localization of election on the buttocks and extension parts of the limbs. They frequently associate a significant hypertriglyceridemia, of primary or secondary aetiology to an uncontrolled DM, primitive biliary cirrhosis, nephrotic syndrome, hypothyroidism, drug use (beta blockers, oestrogens, etc.). Eruptive xanthomas may be the first clinical manifestation of a DM. Treatment of eruptive xanthomas begins with the treatment of dyslipidaemia that they report. They remit within 6-8 weeks of gaining adequate metabolic control. [15, 16]

Benign Acanthozis Nigricans (AN) is a skin condition commonly associated with metabolic or endocrine disorders.AN is the most common cutaneous manifestation that accompanies obesity, its presence being directly correlated with the increase in body mass index. The aetiopathogeny of AN implies the presence of insulin resistance, respectively compensatory hyperinsulinemia, a disorder of metabolism that precedes and accompanies DM. Increased insulin levels stimulate excessive proliferation of keratinocytes and fibroblasts via insulin-like growth factor-1 (IGF-1), epidermal (EGF) and fibroblastic (FGF) growth receptors. Clinically, it is characterized by grey or brown hyperpigmentation, imprecisely delimited, thickening of the skin, itching, with symmetrical affectation of the armpits, groin areas, laterocervical, antecubital and popliteal fosses, umbilical region. The histopathological aspect is papillomatosis, moderate hyperkeratosis and hyperpigmentation. AN is present in various genetic syndromes (HAIR-AN, type B, congenital lipodystrophy, Wilson's disease, Lawrence-Seip syndrome, telangiectasia ataxia, etc.), autoimmune diseases (dermatomyositis, scleroderma, lupus erythematosus, Hashimoto's thyroiditis), gigantism or acromegaly. HAIR-AN syndrome (type A), present in 1-3% of patients with polycystic ovary syndrome, is associated with hyperandrogenism, insulin resistance and AN. These patients have an increased risk for DM. AN can be iatrogenic, after systemic administration of corticosteroids, niacin, synthesis oestrogens, but also locally secondary to insulin injections. The presence of AN in obese adolescents is considered an early warning signal for the DM type 2 development. AN can be treated by dietary hygiene and weight loss, local application of chemical keratolytics, emollients, laser therapy, and retinoids are generally administered. Drugs

that lower insulin resistance may be a therapeutic option for AN. [17-19]

Skin infections are,in most studies, the most common skin manifestation associated with DM.These may reveal undiagnosed diabetes or may be a sign of inadequate glycaemic control [8-10]. The presence of vascular complications and neuropathy, together with a supposed immune deficiency induced by DM, contributes to the appearance of infections. Hyperglycaemia and acidosis inhibit the ability of diapedesis, phagocytic activity of polymorphonuclear leukocytes and CD4 T lymphocytes function. Also, the production of interleukins 1, 6, 10 by monocytes and interferon ă by T lymphocytes is low.

Gold staphylococcus and haemolytic beta streptococci are the most common pathogenic germs involved in the occurrence of impetigo, erysipelas, folliculitis, boils and furunculosis, ectima. Diabetic patients frequently have relapsing forms, difficult to control, with progression to severe forms of cellulite or gangrene. Necrotizing fasciitis, a severe infection of the fascia and subcutaneous tissue, rapidly extensive and with 40% mortality, is more common with diabetics. Pseudomonas aeruginosa colonizes nails and interdigital spaces. External malignant otitis is a serious infection of the external auditory canal, caused by pseudomonas aeruginosa, manifested by severe otalgia, otorrhea, the appearance of granulation tissue and evolution towards osteitis and paralysis of the cranial nerves. Patients affected are most commonly diabetic or immunocompromised. [20]

Recurrent candidiasis mucocutaneous infections are relevant for the presence of DM.

Skin manifestations secondary to diabetic angiopathy and neuropathy

At the skin level, xerosis is noticed or, on the contrary, a damp leg, warm to touch, nail dystrophies and / or onychomycosis, decreased distal hair. Xerosis is commonly reported in diabetic patients with peripheral neuropathy and impaired microcirculation. The use of emollients for the treatment of kerosis decreases the possibility of local bacterial or fungal infection and reduces the formation of callus. [8] At the same time as worsening of peripheral neuropathy and ischemia, plantar cracks, callus appear on the pressure zones, followed by neuropathic or neuro-ischemic ulcerations. The ulceration is delimited by an annular hyperkeratotic area. Necrosis has a tendency of progression to the deep musculaponeurotic and bone structures, resulting in osteolysis and osteoarthritis. The onset of ulcers is the last stage of the "diabetic foot" and precedes most of the amputations suffered by diabetics. [8-10]

Diabetic foot is a powerful complication of DM that affects between 1-6% of patients, usually with long-term and neglected disease. Lesions interact simultaneously with the skin, subcutaneous tissue, nerves, vessels, and bone tissue. The diabetic foot diagnosis implies the presence of at least 3 of the following lesions: diabetic neuropathy, diabetic micro and/or macroangiopathy, diabetic osteoarthropathy, perforating foot ulceration. Infection is a common complication of the diabetic foot, and local signs can sometimes be masked because of peripheral neuropathy and / or severe ischemia. [11]

In a clinical study performed on 2,511 patients with foot ulcers it was found that the risk of amputation is increased by: the presence of comorbidities (retinopathy, chronic kidney disease, oedema presence, and walking disability), disease duration, multiple ulcerations, deep infection presence, severity of peripheral artery disease, patient's non-compliance. [21]

International guidelines for the prevention and management of diabetic foot recommend prophylaxis measures and an integrated multidisciplinary approach to the patient, to significantly reduce the risk of lower limb amputations. Clinical examinations should be performed at least annually and in patients with risk factors for ulceration, more often. Adopting a routine prophylactic program also lowers the risk of amputation and improves the quality of life of these patients. This program includes: educating the patient and his / her family, examining and maintaining daily foot care, quitting smoking, adopting a healthy lifestyle, wearing appropriate footwear, early identification and treatment of newly emerging lesions, adequate metabolic control. [22]

Musculoskeletal symptoms associated with DM are common, but more commonly seen in

patients with old diabetes who have retinopathy, nephropathy and inadequate glycaemic control. These symptoms, apart from the diabetic foot, are frequently located in the hands, constituting the *diabetic hand syndrome*, often associated with sclerodactyly. The diabetic hand includes: limiting joint movements, flexor tenosynovitis, carpal tunnel syndrome, Dupuytren's contracture. Glycosylation of proteins, peripheral neuropathy, alteration of microcirculation, collagen deposition in the skin and periarticular, are presumed aetiopathogenic mechanisms. Clinical symptoms in the diabetic hand impair the patient. They present the limitation of the joint movements, because of the thickening and fibrosis of the skin and of the periarticular tissue. Also, the flexion and extension of the fingers is limited, with the appearance of deformations and functional impotence. There is also the presence of nodules and localized thickening of the fingers tendons, accompanied by pain. Diabetic hand diagnosis is generally clinical. The following tests can be performed: the prayer test, the wrist-flexion test, and Tinel's sign. Skin biopsy reveals an increased mass of collagen in the dermis, which is disorganized, sometimes fragmented, with few dermal vessels and thickened walls. Adequate glycaemic control, together with medical and orthopaedic recovery interventions, can significantly improve these conditions. [23,24]

Sudomotor dysfunction is one of the clinical symptoms of autonomic neuropathy. In the initial phases, the thermoregulatory hyposweating with distal localization, proximal compensatory hyposweating, with evolution towards anhidrosis, appear.

Sympathetic denervation contributes to the opening of arteriovenous shunts. Peripheral neuropathy affects the healing ability of skin lesions, because of decreased synthesis of nerve growth factor (NGF), insulin like growth factor (IGF) and neurotrophins. [25]

Conclusions

Diabetes affects, structurally and functionally, all the components of the skin organ.

Skin disorders associated with diabetes are common and have a strong impact on the patients' life quality.

Their early detection provides indications of the existence of prediabetes or neglected diabetes.

Proper metabolic control of diabetic patients is the most important factor for the prevention of chronic complications, but also for the therapeutic response of the present skin manifestations.

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Conflict of interest
NONE DECLARED

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