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Diabetes mellitus and its skin manifestations - dermatology for diabetologists

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Abstract

Introduction: Diabetes Mellitus (DM) one of the most common chronic disease in Europe, can affect every part of the body including the skin. Metabolic changes during the progress of diabetes mellitus , influence the occurence of various dermatoses such as Acanthosis nigricans, Necrobiosis lipoidica diabeticorum, bullosis diabeticorum, eruptive xanthomatosis and diabetic dermopathy. On the other hand, there are allergic skin reactions as a consequence of insulin infusion, diabetic pills treatment and using diabetic devices like insulin pumps and glucose monitors that can improve patiens glycemic control and their quality of life.

Aim of the study: The aim of our study is to present skin manifestations associated with diabetes mellitus patients. The importance of early detection skin changes and its significance are also analysed.

Material and methods: We searched electronic databases, using keywords such as „Diabetes Mellitus” , „ Skin dermatoses assosiated with diabetes mellitus „ and „Acanthosis Nigricans”

Conclusions: Human skin is a reflection of the processes that take place in the body. The characteristc dermatoses that appear on it, can be a clue for the doctor and help him in the diagnostic process and proper control of diabetes. Technological progress has led to the develompent of specialized devices to control the glycemia of patients, however, this is often associated with the deterioration in the well-being of patients and the benefits of treatment ,by reverse allergic skin reactions to contact with the equipment.

Key words: Diabetes Mellitus; Cutaneous manifestations; Dermatoses; Allergic contact dermatitis

Introduction

Diabetes is a group of metabolic diseases with significant morbidity and mortality. [1] The common feature of diabetes is hyperglycemia associated with a defect in insulin secretion or action. Chronic hyperglycemia in diabetes leads to damage, dysfunction, and failure of various organs. [11] The incidence of diabetes continues to rise, and according to WHO projections, by 2025, 8 billion people worldwide will be affected by diabetes. [4] Among the complications of diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, and macrovascular complications such as coronary artery disease, peripheral arterial disease, and cerebrovascular disease are commonly mentioned. However, little is said about skin-related complications, which develop in 30-70% of patients during the course of the disease. [2] It is essential to emphasize the role of early detection of skin changes associated with diabetes in expediting the diagnostic process and initiating hyperglycemia treatment as quickly as possible.

Skin Manifestations of Diabetes

For the purpose of this work, skin changes can be divided into five groups

1. Infectious skin changes resulting from diabetes
2. Skin changes in the course of diabetes
3. Skin Diseases Co-occurring with Diabetes

4. Conditions that may precede or accompany diabetes
5. Skin Adverse Reactions to Specialized Diabetological Equipment

1. Infectious skin changes resulting from diabetes

Soft tissue and skin infections are more common in patients with diabetes than in the healthy population. It has been shown that the skin pH in these patients is higher, promoting bacterial colonization. Moreover, vascular disorders and diabetic polyneuropathy make patients less sensitive to pain, which, in the event of an injury, may lead to unawareness, causing infection and deepening of wounds. [2] Bacterial infections are often caused by Staphylococcus Aureus and Group B-hemolytic Streptococci. Staphylococcus aureus is responsible for conditions such as cellulitis, purulent skin infections, recurrent folliculitis, and infectious eczema. Carbunculosis, characterized by the formation of multiple boils on the lower limbs and feet, is a common cause of hospitalization among diabetics, accompanied by pain and inflammation, often requiring appropriate antibiotic therapy and surgical intervention. [18]

Group A beta-hemolytic Streptococci are the etiological factor of bullous impetigo. As the name suggests, this disease entity in diabetic patients is characterized by an aggressive course with the formation of blisters filled with bloody content, usually located on the shins. High fever and pain at the sites of blister occurrence are accompanying symptoms of bullous impetigo. [7] Erythrasma is a skin infection caused by Corynebacterium minutissimum bacteria, which, under appropriate conditions, colonize the stratum corneum of the epidermis, leading to the development of erythematous lesions in the groin, interdigital spaces of the feet, and skin folds. The skin is often moist and itchy, with a delicately wrinkled surface. C. minutissimum produces a substance called coproporphyrin, which, when exposed to Wood's lamp, induces an orange-red fluorescence. This phenomenon is used for the rapid diagnosis of erythrasma. [26]

Fungal infections in this group of patients are mainly caused by Candida Albicans, with growth closely correlated with higher blood glucose levels. Candida Albicans is responsible for oral and tongue candidiasis, as well as angular cheilitis. Yeast infections between the fingers and skin folds are also common. In women, C. albicans causes vaginal candidiasis, characterized by intense itching, burning, and abundant discharge with an unpleasant odor. Fungal infections are less common in men than in women. [7] Balanitis and post-inflammatory phimosis may be early signs of diabetes in men. The treatment of yeast infections requires stabilizing the patient's glycemic level

and using specialized antifungal medications such as nystatin, clotrimazole, or fluconazole. Dermatophytosis is a separate fungal disease, leading to fungal infections of the feet and nails in diabetic patients. [26]

The first changes that diabetic patients may notice are dryness, cornification, skin cracking, and slow skin regeneration. Clinical studies have shown that keratinocytes, the main cells of the epidermis, are inhibited in their differentiation by hyperglycemia and hyperinsulinemia. Additionally, in patients with fasting serum glucose levels higher than 110 mg/dL and HbA1c >5.8%, skin moisture was lower than in patients with fasting serum glucose levels lower than 110 mg/dL. These changes are easily overlooked by both patients and doctors because they are not characteristic and are not accompanied by pain symptoms. This is extremely dangerous because neglect at the beginning will deepen the pathology within the epithelium and contribute to the development of infection portals. [1] [2] [14] [15]

2. Skin changes in the course of diabetes

Diabetic erythema (Rubeosis faciei) often occurs in patients with uncontrolled glycemia. Superficial vessels on the face dilate due to microcirculation disorders, leading to the formation of chronic bright red erythema on the cheeks and neck. [2] Treatment is mainly causal and involves regulating the patient's carbohydrate metabolism and avoiding caffeine and nicotine. [18]

Sclerotic skin edema is a consequence of excessive collagen glycation due to hyperglycemia. [18] It occurs more frequently in adults and begins with thickening of the skin in the back and lateral neck area, then spreading to the upper back, arms, and torso. The diseased skin is tough and thick, resembling the peel of an orange. It usually does not cause symptoms but can impede mobility, especially around the back, over time. [25]

Pseudo-scleroderma syndrome develops in about 8 to 50% of diabetic patients. The skin of the hands thickens, hindering mobility in the interphalangeal joints, nodules form on the surface of the finger extensors or ankles, and the patient becomes clumsy in movements with a weakened grip. Patients suspected of having this condition are tested by asking them to fold their hands in a prayer-like gesture. Those with pseudo-scleroderma syndrome are unable to fully close the gaps between opposing fingers, known as Dürer's hands. [27]

Diabetic pemphigus is rarely detected in diabetic patients, characterized by vesicular or blister-like lesions on non-inflammatory skin, mainly on the hands and feet. The blisters are tense and filled with lymphatic fluid rarely stained with blood. After rupture, the skin at the site of the lesion heals without leaving a scar. The entire process occurs painlessly, but there have been cases where patients reported a burning sensation. Diabetic pemphigus is diagnosed in men with unstable long-term diabetes and peripheral neuropathy. One of the mechanisms of blister formation considers trauma, most often found in patients with peripheral neuropathy due to the loss of feeling in the distal parts of the limbs. Other considered causes are the influence of UV radiation, microangiopathy, and disorders of calcium metabolism. [2] [10] [18]

Diabetic dermopathy is well-defined brown spots, approximately 1 cm in size, with a central indentation. They are most commonly located on the shin bone but can also appear on the arms, thighs, calves, or abdomen. The color intensity significantly correlates with the intensity of skin atrophy. It occurs with a frequency ranging from 9% to 55% in diabetic patients and is considered the most common skin change in those with diabetes [16]. It is believed that men over 50 years old and those with a long history of diabetes are most susceptible to developing these changes. The pathogenesis is not fully understood, but the most commonly described explanation in scientific publications is that diabetic dermopathy arises as a consequence of microvascular changes. The correlation between the progression of microangiopathic changes and the frequency of diabetic dermopathy is still being studied. At present, it is believed that patients with a greater number of complications are more prone to developing diabetic dermopathy. Therefore, despite the fact that the changes undergo spontaneous regression within 18-24 months, extended diagnostics for retinopathy, neuropathy, or diabetic nephropathy should be conducted [18].

Eruptive xanthomas (yellow bumps) are associated with dyslipidemia and also accompany individuals with diabetes. They take the form of numerous well-defined yellow nodules on straight parts of limbs, arms, and buttocks. Xanthomas can be asymptomatic or cause itching, burning, and sensitivity to touch. They form due to the local deposition of lipids in the skin. Treatment is mainly causal and involves controlling hyperlipidemia and daily glycemia in patients. When the body's condition is regulated, changes regress without additional medical intervention. In isolated cases where the primary disease therapy is ineffective, surgical procedures, laser, or local cryotherapy may be applied [12] [20] [21].

3. Skin Diseases Co-occurring with Diabetes

Acanthosis Nigricans was first described in 1889 in correlation with obesity. Now, cases are increasingly documented when it appears with diseases involving insulin resistance, such as PCOS or Cushing's disease. From a pathophysiological perspective, such changes likely result from the action of insulin or insulin-like growth factor (IGF-1), which stimulate the proliferation of epidermal cells. Other mediators mentioned in publications that may influence the formation of changes include fibroblast growth factor (FGF) and tyrosine kinase receptors. Dark acanthosis is typically asymmetrical skin thickening with a gray-brown color, most commonly located on the neck, underarms, wrists, or skin folds. Besides the obvious aesthetic aspect that can worsen psychological well-being, patients do not experience somatic discomfort. The frequency of occurrence is the same for women and men, with an increasing trend in older individuals. Diagnosis, in most cases, should be limited to dermatoscopy; however, in some cases, a biopsy may be indicated to differentiate dark acanthosis from other discolorations. [2] [8] [17]

Hidradenitis suppurativa (inverse acne) is a chronic inflammatory skin disease that begins in hair follicles and, in collaboration with bacterial infection, leads to the formation of painful inflammatory nodules, abscesses, and skin fistulas. It is most commonly located in areas where the skin rubs against itself, such as the underarms, breasts, and groin, but as the disease progresses, it can affect body regions such as the neck, limbs, or skin behind the ears. It is worth noting that there is a difference in the distribution of lesions depending on gender. Everything indicates that diabetes is the most common comorbid disease for hidradenitis suppurativa. Pain, unpleasant odor from the exudate seeping from the lesions, scar formation, and the continuous relapse of the disease process are just some of the symptoms experienced by patients with inverse acne. In essence, they are more prone to psychosocial discomfort than in the case of other dermatological diseases such as atopic dermatitis or psoriasis. Diagnosis is established based on the presence of typical lesions: nodules, abscesses, scars, fistulas, in typical locations - armpits, groin, inguinal areas occurring chronically, with a frequency of more than 2 times within 6 months. [5] [6] .

4. Conditions that may precede or accompany diabetes

Necrobiosis lipoidica diabeticorum is a chronic granulomatous skin disease, estimated to occur in 0.3% to 1.2% of diabetic cases, and it affects women in 77% of instances. It is more commonly associated with insulin-dependent diabetes than type 2 diabetes. The pathogenesis of the disease is unknown; however, the most popular and frequently mentioned theory in the literature is microangiopathy resulting from the deposition of glycoproteins in blood vessels, causing their thickening. [9] Changes occur bilaterally in the shin areas, upper limbs, scalp, and face. Initially, they take the form of small red-brown nodules surrounded by erythema, then enlarge, changing color to yellow-brown with atrophy of the central part of the epidermis. Teleangectasias may develop in the affected skin, most likely due to collagen degeneration. A significant portion of the changes is painless, but with damage to nearby nerves, the pain can be very intense, hindering the patient's daily functioning. Moreover, 33% of cases may ulcerate. Despite many years of research, the most effective treatment method has not been developed yet. Currently, locally administered glucocorticoids and antiseptic agents such as iodine, chlorhexidine, or silver solutions are used, and research is ongoing on other treatment options. [3] [19]

Granuloma annulare is a skin and subcutaneous tissue disease that takes the form of reddish nodules with a lighter center, non-atrophic in nature, and raised red-purple borders, resembling a ring. The lack of atrophy distinguishes this disease entity from lipoid necrobiosis in diabetes and facilitates appropriate differential diagnosis. The nodules are most commonly located on the distal parts of the limbs and heal with hypo or hyperpigmentation. Their presence is asymptomatic or may be associated with itching. [2] [18] In patients with diabetes, the frequency of occurrence is approximately 0.3%, with a female predominance. In the group of patients with diagnosed granuloma annulare, the frequency of coexisting diabetes, mainly type 2, ranges from 21% to 77%. [25] Treatment is applied locally using phototherapy, corticosteroids, and calcineurin inhibitors.

5. Skin Adverse Reactions to Specialized Diabetological Equipment

The increased incidence of diabetes in recent years, associated with rapid economic development, urbanization, and the establishment of unhealthy dietary habits, has somewhat necessitated the improvement of the entire process of diabetes treatment and glucose control. Specialized equipment, such as continuous glucose monitoring sensors and insulin pumps, has been

invented to facilitate the work of doctors and improve the quality of life for patients. But is it really so? As many as 49% of cases of adverse skin reactions result in dark red scars, as a side effect of using personal insulin pumps. Frequent punctures in the same area lead to epidermal cornification with overproduction of collagen in the papillary layer of the dermis [13]. Scar formation not only causes discomfort for the patient but also hinders the proper absorption of insulin. In a study involving 30 patients using personal insulin pumps, scientists used non-invasive optical coherence tomography (OCT) and performed skin biopsies at infusion sites. The results confirmed that the skin at infusion sites has altered structure, inflammation, fibrosis, and fat tissue necrosis [23]. Another complicating factor in the treatment process using an insulin pump is bacterial infections at the puncture site, most commonly caused by Staphylococcus epidermidis and Staphylococcus aureus. Proper skin care and hygiene, as well as the replacement of infusion sets every 2-3 days, are essential to minimize the risk of infection [24]. Most diabetological devices come with patches coated with adhesive to secure them to the skin. Many allergic contact reactions to adhesive components, such as ethyl acrylate, isobornyl acrylate, or colophony (resin), have been documented [30]. In 2018, four such cases were documented using the Omnipod pump. Gas chromatography coupled with mass spectrometry detected isobornyl acrylate, which was not part of the adhesive but was used in other parts of the sensor. The allergy resulted from its migration to the patch [29]. A similar reaction to isobornyl acrylate was observed in patients using the FreeStyle Libre continuous glucose monitoring system in 2017. It was found that this substance was not part of the adhesive but of the plastic parts of the device, penetrating the patch and causing allergic contact reactions in patients. It is worth noting that allergic reactions were confirmed through patch tests on patients each time [22]. In contrast to continuous glucose monitoring sensors requiring a patch, Eversence® is a new subcutaneously implanted system for several months that does not require the use of adhesive agents. However, adverse reactions associated with the use of this system occurred in 14.3% of patients. Interventions during the implantation and removal of the device caused mild skin inflammation, discoloration, infections, skin atrophy, and impaired skin regeneration [13].

Summary

In the context of future care for patients with diabetes, it is crucial to strive for a comprehensive approach that considers both metabolic control and monitoring of skin reactions to modern therapies. The future of examining skin changes in diabetes mellitus holds promising advancements driven by innovative technologies. Emerging diagnostic tools, such as artificial intelligence and advanced imaging techniques, are likely to revolutionize the early detection and characterization of skin manifestations associated with diabetes. We must not forget the basics in

medicine, a well-conducted physical examination of the skin in outpatient care can prevent the worsening of changes caused by poorly controlled glycemia and protect the patient from unfavorable prognostic consequences. The role of collaboration among physicians specializing in diabetology, dermatology, and primary care doctors should be emphasized. By working together, they can achieve satisfactory outcomes in patient care. The best prevention against skin complications in diabetics is maintaining glycemic control and proper skin hygiene. It is recommended that patients regularly perform skin self-examinations, paying special attention to the feet, shins, and skin folds. [1][2][11][15][30]

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