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Updates in the Management of Cutaneous Manifestations of Diabetes Mellitus

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Abstract: Diabetes mellitus is a chronic disease of metabolic dys-regulation involving the abnormal metabolism of glucose. Diabetes has a significant impact on the healthcare costs of the Western world. Nearly all patients with diabetes eventually develop cutaneous manifestations of the disease. Cutaneous signs of the disease can heighten the suspicions of a physician regarding the diagnosis of diabetes. This article will focus on the clinical features, pathogenesis and modern treatment modalities of the various dermatologic manifestations of the disease ranging from the more benign granuloma annulare to the more sinister diabetic ulcer.

Key words: Cutaneous manifestations · Diabetes mellitus · Diabetic Ulcers · Recent Advances · Vitiligo

INTRODUCTION

Diabetes mellitus (DM) is a heterogenous group of metabolic disorders characterized by elevated serum glucose levels resulting from defects in insulin production, insulin action, or a combination. Complications include retinopathy, nephropathy and neuropathy. The two main types of diabetes of are Type 1 insulin-dependent DM, which is characterized by the destruction of insulin-producing beta cells of the pancreas creating the absolute need for exogenous insulin and Type 2 noninsulin-dependent mellitus, which is associated with older age, obesity, physical inactivity and family history. Type 2 diabetes is increasingly being diagnosed in children and adolescents. Diabetes has been implicated as the single largest cause of end-stage renal disease, the main reason for non-traumatic amputation and an independent risk factor for cardiovascular disease [1]. Nearly one-third of diabetic patients have some type of dermatologic manifestation. With time, the skin of all diabetic patients is affected in some form or another. Cutaneous signs of DM are extremely valuable to the clinician. For example, diabetic bullae, diabetic dermopathy, necrobiosis lipoidica diabeticorum and the scleroderma-like syndrome of waxy skin with limited joint mobility can alert the physician to the diagnosis of diabetes[2, 3]. Eruptive xanthomas reflect the status of glucose and lipid metabolism. This review article will focus on the clinical features, the pathogenesis and modern treatment strategies of the cutaneous manifestations of diabetes.

Necrobiosis Lipoidica Diabeticorum: Necrobiosis lipoidica diabeticorum (NLD) is a degenerative disease of collagen in the dermis and subcutaneous fat with an atrophic epidermis and granulomatous dermis. The initial lesions of NLD are well-circumscribed erythematous plaques with a depressed, waxy telangiectatic center [4, 5]. In early lesions, a neutrophilic vasculitis is evident. With the passage of time, granulomatous lesions evolve into a sclerotic stage of the reticular dermis and subcutaneous fat [6-8]. One-third of lesions may progress to ulcers if predisposed to any trauma. The vast majority of lesions occur on the pre-tibial region of the lower extremities. When NLD occurs in regions other than the legs, there is less of an association with diabetes. NLD affects women more than men and only 0.3 to 0.7 percent of people with diabetes ever develop the lesions [4, 9].

The etiology of NLD has not been clearly defined. Most popular theories suggest that a micro-angiopathic basis with neuropathy leads to the degradation of collagen [4, 10]. Few studies have found a correlation between NLD and the micro-vascular effects of diabetic retinopathy and nephropathy [4, 10, 11]. An immunologic role, such as the release of cytokines from inflammatory cells, may lead to destruction of the collagenous matrix.
At present, there is no standard therapy for necrobiosis lipoidica. The majority of the literature on the management of necrobiosis lipoidica refers to anecdotal reports. The main modalities of treatment options include non-steroidal anti-inflammatory agents, intra-lesional, systemic, or topical corticosteroids and even laser surgery [3, 4, 7]. A randomized, double-blind, Swedish trial of aspirin and

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dipyridamole combination versus a placebo did not reveal any significant benefit [12].

Acanthosis Nigricans: Acanthosis nigricans is a disorder characterized by a velvety, light brown to black hyper-pigmented, cutaneous thickening usually on the back, the sides of the neck, the axillae and flexural surfaces. Lesions of acanthosis nigricans show marked hyperkeratosis and papillomatosis with mild acanthosis and hyperpigmentation [4]. The first cutaneous sign is hyperpigmentation followed by intensified hypertrophy of the epidermis.

The exact mechanism of acanthosis nigricans is unknown. There are eight types of acanthosis nigricans, the most common type being obesity-associated acanthosis nigricans [13]. Malignancy has also been associated with acanthosis nigricans. The first major breakthrough association of acanthosis nigricans with insulin resistance came from a study by Kahn [14]. Insulin resistance contributes a significant role in noninsulin-dependent diabetes and in a number of syndromes [14-16]. Insulin resistance may be caused by preceptor defects (autoantibodies against insulin), receptor resistance (genetic or functional defects in the insulin receptors) and/or post-receptor abnormalities (genetic or functional defects, such as abnormal signal transduction pathway, leading to inability to activate the enzyme tyrosine kinase) [17-22]. There have been suggestions that insulin at high concentrations may stimulate insulin-like growth factor receptors on keratinocytes [23], thereby promoting epidermal cell proliferation.

There is no cure for acanthosis nigricans. The principal management should be targeted at the underlying problem [13, 16]. Overweight individuals have considerable improvement with weight reduction. In patients with malignancy, elimination of the tumor may decrease the prominence of acanthosis nigricans.

Diabetic Dermopathy: Diabetic dermopathy also known as shin spots, is considered the most common cutaneous finding in diabetes. According to one study, 40 percent of diabetic patients in an Israeli hospital had diabetic dermopathy, which was statistically significant in patients over the age of 50 [24]. Diabetic dermopathy appears as round to oval atrophic hyperpigmented lesions on the pretibial areas of the lower extremities. The lesions are usually bilateral and have an asymmetrical distribution. Histologically, lesions show edema of the papillary dermis, thickened superficial blood vessels, extravasation of erythrocytes and a mild lymphocytic infiltrate [7, 25, 26]. The extravasated erythrocytes leave hemosiderin deposits, which provide the brownish hyperpigmentation. The lesions of diabetic dermopathy resolve spontaneously, leaving scars behind [2].

Diabetic Thick Skin: Physicians have noticed that patients with DM tend to have thicker skin than those without. This has been confirmed using ultrasound [27]. Diabetic thick skin has been separated into three main categories: 1) scleroderma-like changes of the hand associated with stiff joints and limited mobility; 2) measurable skin thickness that is clinically insignificant; and 3) scleredema diabeticorum. Thickening of the dorsum of the hands may occur in a third of patients with diabetes [7]. Other signs of increased skin thickening include pebbled or rough skin, known as Huntley's papules, over the interphalangeal joints, particularly the knuckles. Waxy skin and stiff joints have been correlated with increasing age and duration of diabetes, more so for Type 1 DM, rather than the glycemic value [4, 28]. The term scleredema describes a clinical picture of thickening of the skin and non-pitting induration of which there are two types. The first, scleredema of Buschke, can occur at any age and is usually subsequent to a viral or streptococcal infection. The posterior neck and upper part of the back are frequently affected. Scleredema diabeticorum has the same distribution as scleredema of Buschke, but the skin thickening extends to the upper extremities, including the hands.

Histologically, large disorganized collagen bundles in a thickened dermis are separated by clear spaces with small amounts of acid muco-polysaccharides. Diabetic scleredema may be difficult to distinguish clinically from scleroderma. Hanna and Friesen reveal that, diabetic thick skin has distinct light and electron microscopic features from those seen in scleroderma [29]. Unlike scleroderma, diabetic thick skin seldom has collagen fibers below 60nm and bimodality of fibers was not observed [29]. Some studies have mentioned an increased synthesis of type 3 collagen (small fibers) in scleroderma, resulting in a bimodal distribution of collagen size.[29-32] Another study mentioned an increase in hyaluronic acid in diabetic scleredema with a predominance of dermatan sulfate in scleroderma [29, 33]. The pathogenesis of diabetic thick skin has not been clearly defined. Potential explanations include the hydration of collagen secondary to polyol accumulation [4, 34] and nonenzymatic glycosylation of collagen [4, 35]. There is no treatment for this condition although strict glycemic control may be beneficial [36].

Diabetic Bullae: Diabetic bullae are usually confined to the hands and feet. The blisters occur spontaneously and most are non-scarring. Patients tend to have adequate circulation in the affected extremities but have signs of diabetic peripheral neuropathy. There are three types of diabetic bullae. The most common type is sterile and fluid-containing and heals without scarring. Histology shows intra-epidermal cleavage without acantholysis [7]. The second type is hemorrhagic and heals with scarring. Histology depicts cleavage below the dermo-epidermal junction with destruction of anchoring fibrils [7, 37]. The third type involves mostly multiple non-scarring bullae on sun-exposed, tanned skin. Histology reveals cleavage at the lamina lucida [37, 38]. One study mentioned an association with long-term Type 2 DM [39] with peripheral neuropathy and another study mentioned a connection with chronic Type 1 DM [4]. The pathogenesis of these lesions has not been clearly elaborated. Therapy of diabetic bullae focuses on preventing infection.

Yellow Skin: Yellow nails and skin associated with diabetes is a benign condition with no known significance. The pathological cause of yellow skin remains in controversy. The change may be due to either elevated levels of carotene or non-enzymatic glycosylation of dermal collagen [4]. One glycosylation end product, 2-(2-furoyl)-4(5)-(2-furanyl)-1H-imidazole, has a yellow hue, which could provide the characteristic color of yellow skin [3, 16]. The yellow color is best appreciated at the distal hallux of the nails, palms and soles. There is no current treatment for this condition.

Diabetic Ulcers: Diabetic patients form the single largest group of non-traumatic amputations in the United States [40]. For the majority of diabetic patients, the initial condition that leads eventually to amputation begins with a skin ulcer. Diabetic foot ulcers are separated into two categories: ischemic and neuropathic ulcers [40]. Peripheral neuropathy plays a central role in nearly four-fifths of diabetic patients. The most common neuropathy is a mixed distal motor and sensory neuropathy [4, 41]. In the majority of cases, ulceration occurs as a consequence of the loss of protective sensation. The combination of motor and sensory neuropathy along with mechanical factors plays a role in the pathogenesis of neuropathic ulcers [4, 42]. Clinical signs of paresthesias with loss of temperature and pain sensation along with disturbances in sweating are prevalent in neuropathic diabetic ulcers. The pathogenesis of ischemic ulcers involve diabetic atherosclerotic disease. The ischemic patient will present with disproportionately excruciating pain associated with a superficial ulcer, while the neuropathic patient is unaware of a large, deep ulcer. The ischemic patients will often elicit a history of intermittent claudication, foot pain on leg elevation and pain relieved with resting [40].

Prevention of foot ulcers is critical. Clinicians should routinely examine the feet of diabetic patients. A nylon monofilament test provides a method of early determination for the loss of peripheral sensation and identifies patients at risk for ulceration. Education in foot care, proper footwear, avoidance of burns and trauma and close medical follow up are steps needed for the prevention of diabetic ulcers [40]. Glycemic control will diminish the progression of peripheral neuropathy, a key factor in the development of ulcers. Smoking cessation must be emphasized. Patient compliance along with physician intervention, are the mainstays of the prevention strategy of diabetic ulcers.

Treatment of diabetic ulcers becomes necessary once preventive measures have failed. Many diabetic ulcers fail to heal because patients continue to put weight on their affected lower extremities. Approximately 90 percent of ulcers can be treated by relieving weight from the ulcerated area, treatment of infections with systemic antibiotics and arterial perfusion restoration [43]. A common mistake is the use of wet-to-dry dressings on a clean ulcer bed [40]. The removal of the dry dressing interrupts the healing process of re-epithelialization. The preservation of a wet saline dressing maintains a moist wound environment. New adjunctive therapies, such as becaplermin gel (recombinant platelet-derived growth factor), show modest benefit in improving granulation tissue and wound repair [44]. The role of growth factors and cytokines in the process of wound healing is an area of ongoing investigation. Bioengineered skin equivalents promote more rapid healing [45]. These innovative therapies are not substitute for basic management of diabetic ulcers, such as adequate offloading, treatment of infections and debridement [40, 44]. The decision to perform vascular surgery depends on the severity of the vascular impairment, the surgical risks and rehabilitation potential. The therapeutic goal of the treatment of diabetic ulcers is the eventual healing and avoidance of amputation, thereby improving function and quality of life.

Diabetic Cutaneous Infections: Well-controlled diabetic patients are no more susceptible to infections than the normal population [3]. Patients with uncontrolled DM and

ketosis are more predisposed to severe systemic and cutaneous bacterial infections [3, 4]. Bacterial infections of the skin, usually caused by staphylococcus aureus and beta-hemolytic streptococci, include impetigo, erysipelas, cellulitis and necrotizing fasciitis [4, 46]. Obese patients with DM have a higher predisposition to erythrasma caused by corynebacteria minutissimum. [4, 46]. Systemic antibiotic therapy and surgical debridement are indicated for severe infections, particularly for necrotizing fasciitis. Candida is one organism correlated with increased serum glucose levels and an early indicator of undiagnosed DM [3, 4, 47]. Commonly affected areas involve the nail folds and the web spaces of the fingers and toes. Normalization of blood glucose and use of topical and systemic anti-fungals are the main modalities of treatment. Patients with DM are also at risk for rhino-cerebral mucormycosis, an extensive life-threatening infection beginning in the nasal passages and spreading into the orbit and cerebrum [4, 48]. Treatment consists of debridement and intravenous fungal therapy, such as amphotericin B. Malignant otitis-externa caused by pseudomonas aeruginosa is a rare but serious infection in elderly people with diabetes. Initially, there is a purulent discharge and severe pain in the external auditory meatus, which then progresses to cellulitis and then to meningitis [4, 7, 48]. Treatment involves surgical debridement and intravenous anti-pseudomonal antibiotics. Patients with malignant otitis-externa have high mortality rates [49].

Perforating Dermatosis: The majority of patients with adult-onset acquired perforating dermatosis have kidney failure associated with diabetes.[50] Itching and scratching accompany this entity, also known as Kyrle's disease or reactive perforating collagenosis. The lesions are located primarily on the extensor surfaces of the lower extremities but can occur on the face and trunk. The lesions are described as a few millimeters in diameter, papular, often with a keratotic plug. Another feature consists of the elimination of collagen and elastin throughout the affected epidermis. Histologic examination of these lesions reveals a hyperplastic epidermis surrounding a plug of degenerated material, which has elements of leukocytes, collagen and nuclear debris [3, 4, 51]. Acquired perforating dermatosis is difficult to treat. Retinoic acid has shown some benefit along with topical anti-histamines to alleviate the pruritus [52]. A Chinese study showed a reduction of pruritus with the use of trans-cutaneous electrical nerve stimulation [53]. A German article mentioned two patients being successfully treated with allopurinol [54].

Eruptive Xanthomas: Eruptive xanthomas in the context of DM are accompanied by hyperlipidemic and hyperglycemic states. The lesions are described as waxy, yellow papules surrounded by an erythematous rim and usually occur on the extensor surfaces and popliteal region. Histologic samples depict lipid-laden histiocytes and a mixed lympho-neutrophilic infiltrate in the dermis. The main treatment option is strict control of the hyper-lipidemic and hyperglycemic condition associated with the DM [55].

Other Dermatoses: There is some evidence of higher incidence of vitiligo in diabetic patients [56]. Patients with vitiligo have family histories of autoimmune diseases, such as Addison's disease, Hashimoto's thyroiditis and pernicious anemia. Vitiligo has a higher incidence among adults with diabetes; therefore, it is recommended to evaluate for diabetes among late-onset vitiligo [57]. One-fourth of porphyria cutanea tarda patients have diabetes [56]. Diabetes generally precedes the onset of porphyria, a possible result of the non-enzymatic glycosylation of the heme-pathway [56-58]. Granuloma annulare is a chronic, asymptomatic dermatosis with a predilection for the dorsum of the hands, feet and elbow. The lesions may be difficult to distinguish from necrobiosis lipoidica diabeticorum and are self limited. The generalized form may have an association with DM [59]. Nearly one-half of diabetic patients with psoriasis develop psoriasis before diabetes, but the association between diabetes and psoriasis has not been clearly defined [56]. Similarly, the association between diabetes and lichen planus, Kaposi's sarcoma and skin tags remain controversial [56].

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