Introduction to Cutaneous Manifestations of Diabetes Mellitus

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Diabetes mellitus (DM) is a chronic endocrinopathy affecting almost every organ and system; and the skin, the largest organ in the body, is not an exception.

It affects individuals regardless of ethnicity, age or socio-economic level, and the number of patients drastically increased and tends to continue to increase globally.

The term "diabetes" comes from the Greek language and means "to go through" making reference to the quick passing of fluids the patient drinks due to increased thirst, from intake to urination. Physicians used to taste urine, therefore, the term "mellitus," which comes from the Latin and refers to the sweet or honey-like flavor glucose gives [1].

DM is caused by a deficiency or improper use (resistance) of insulin (I). The pancreas produces insulin which is necessary for glucose to be transported from the bloodstream into cells, thus providing energy.

I deficit is accompanied by chronic hyperglycemia, responsible for glucose following other non-insulin dependent metabolic pathways in order to reduce sugar concentration on the skin, through the polyols pathway, sugar autoxidation, non-enzymatic glycation (NEG)—[2]. But in turn, they create an unbalance between the antioxidant capacity, which is diminished, and a higher free radical (FR) production, which results in "oxidative stress" with the subsequent vascular inflammation and prothrombotic state, thus playing an essential role in the development of DM complications [3].

Unfortunately, this mechanism reinforces itself, since under hyperglycemia or oxidative stress conditions, as in the case of DM, NEG is accelerated and more AGEs products are generated. There is sufficient evidence showing that the interaction

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between AGEs and their AGE receptor (RAGE) causes oxidative stress, thus closing a vicious circle. More recently, it was also proven that the AGE-RAGE axis is in turn interrelated to the renin-angiotensin system and that both are involved in vascular damage, one of the most significant complications of diabetes [4, 5].

Therefore, all these biochemical alterations (hyperglycemia, insulin deficiency, NEG increase) are responsible for DM complications (microangiopathy, neuropathy, alteration of the immune response, etc.) and they are closely linked to its cutaneous manifestations [6, 7].

Insulin, a multifunctional hormone involved in regulating many cellular processes, is essential for normal proliferation, differentiation and cutaneous metabolism at skin level. It acts on the epidermal cells, specially, on keratinocytes and on the dermal cells, such as fibroblasts. These cells express the insulin receptor (IR), which is activated through its binding to I. Since the I-IR binding accelerates cellular processes, it is logical that higher activity levels are found in proliferating or differentiating epithelia; while IR activation is minimal in keratinocytes which are already fully differentiated.

Hyperglycemia and the alteration of I signaling pathways with a lower IR expression are directly involved in the development of chronic complications of DM because they lower the use of glucose by keratinocytes, as well as differentiation and proliferation [8].

Since DM is a disease that progresses with chronic hyperglycemia due to an I deficiency, the skin will be directly affected in multiple cellular processes, such as poor wound healing [9, 10].

Many theories have been formulated in order to explain how hyperglycemia may generate neural and vascular disorders which are typical of this disease. They may be divided into those emphasizing the direct toxic effect of hyperglycemia and its derivatives on tissue (such as oxidants, hyperosmolarity or glycosylated products), among which the skin is no an exception, and those assigning pathophysiological relevance to a continued alteration of cellular signaling pathways (such as changes in phospholipids or kinases) induced by glucose metabolism products [11].

Diabetes mellitus (DM) expresses itself on the skin through a wide range of signs and symptoms, some of which remain unexplained despite extensive research work [12]. But it has been proven that the impact of DM on the skin stems from the acute metabolic disorder, dermatosis being a sign of increased blood glucose, as in the case of candidiasis, and more frequently, from chronic complications of a prolonged diabetes, such as ulcers [13].

It is estimated that 30% of diabetic patients present cutaneous manifestations during the course of their disease. If we add lesions due to frequent complications, such as vasculopathy and neuropathy, this percentage would increase to ALMOST 100%. Sometimes, cutaneous disease is the first sign of undiagnosed DM. But more frequently, cutaneous changes are observed in patients with diagnosed but poorly managed DM, in that case, their identification by the dermatologist, together with proper metabolic control, may help prevent some of these dermatoses as well as more serious complications. Most of them are related to the long-term effects of

Table 4.1 DM cutaneous manifestations classification [17, 18]

Group 1	Cutaneous markers of DM	30%
Group 2	Cutaneous infections	
Group 3	Dermatoses most frequently related to DM	
Group 4	Cutaneous alterations caused by DM treatment	
Group 5	Vasculopathy-related cutaneous manifestations	almost 100%
Group 6	Neuropathy-related cutaneous manifestations	

DM on skin collagen and microcirculation. In fact, some cutaneous disorders may be a warning to suspect microvascular complications such as diabetic dermopathy or bullous diabeticorum [14]. It is worth highlighting that skin may also be affected by the adverse effects of glucose-lowering drugs.

Cutaneous infections are more frequent in patients diagnosed with T2DM, while autoimmune alterations are more common in Type 1 diabetic patients [15].

There is a correlation between the duration of the disease and the onset of cutaneous lesions, being long-standing diabetics the ones that present the most devastating cutaneous lesions; although they may also appear in the short term [16].

There are different classifications for cutaneous manifestation of DM, below we include one that divides them into six groups (Table 4.1).

In the following chapters, we will refer to each group and their cutaneous manifestations.

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