

# Cutaneous manifestations of diabetes mellitus: clinical meaning

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## ABSTRACT

**Background.** Diabetes mellitus as a chronic disease it is associated to multiple complications. As other organs, skin is affected showing different manifestations.

**Objective.** The aim of this study was to determinate the different types of skin lesions in diabetes mellitus and to analyze their prevalence and their clinical correlation with other systemic complications of this disease. Finally, to make a comparative statistical study between patients with and without diabetic dermopathy (DD).

**Methods.** We included 125 diabetics in a six month period. They were only Internal Medicine Department's in-patients.

**Design.** We made a protocolled, transversal, descriptive and observable study.

**Results.** The 88% had type 2 diabetes mellitus. 57% were female and the mean age was 58.9 years. Eighty-eight patients had DM chronic complications: 35% DD, 32% nephropathy, 26% retinopathy, 41% neuropathy and 15% macroangiopathy. The average of cutaneous lesions per patient was 4.4. The 90.4% had cutaneous manifestations, being the most frequent: xeroderma (69%), dermatophytosis (52.8%), peripheral hypotrichia (39%), DD (35%). After doing a comparative analyze between patients with and without DD, we found, in the first group more frequently ( $p < 0,05$ ) the followings variants: male sex, over 50 years old, retinopathy, sensitive neuropathy, macroangiopathy, diabetic foot and tinea pedis.

**Conclusions.** The cutaneous lesions more frequently found in diabetic patients were xeroderma, tinea pedis, onychomycosis, peripheral hypotrichia and DD. As we found a statistic significant association between DD and some systemic complications of DM, we propose to use this cutaneous sign as a marker of internal complications (Dermatol Argent 2010;16(2):117-121).

## Keywords:

*diabetes mellitus, cutaneous manifestations.*

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## Introduction

Due to the high prevalence of diabetes mellitus (DM) and increased morbidity and mortality related to the presence of chronic complications, this study aims to determine the clinical features of skin lesions present in diabetic patients admitted in our hospital. It was also examined the injuries frequency of presentation and their clinical correlation to other chronic complications of this disease. Finally, we performed a comparative statistical analysis between patients with and without diabetic dermopathy (DD).

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**PHOTO 1.** Pretibial circumscribed brown atrophy.

## Material and methods

A protocolled study, descriptive, observational and transversal was performed from March to August 2007. The statistical analysis used measures of central tendency,  $\chi^2$  and Student's test. The criterion of significance was set for an alpha less than 5% ( $p < 0.05$ ).

Inclusion criteria: every diabetic patient who was admitted to the Hospital Medical Clinic Luis Lagomaggiore was chosen for this study.

Exclusion criteria: ambulatory patients or admitted for other service areas.

125 patients were included, which were carefully evaluated by a dermatologist and a physician.

For this skin lesions study, it was recorded in the protocol the presence or absence of the following conditions: xeroderma, onychomycosis, tinea pedis, peripheral hypotrichosis, DD, thickening-skin syndrome, diabetic foot, mucocutaneous candidiasis, fibroma pendulum, intertrigo, inner eyebrow separation, seborrheic keratoses, facial flushing, erysipelas cellulitis, acanthosis nigricans, vitiligo, psoriasis, pretibial myxedema, folliculitis, erythrasma, gas gangrene, necrobiosis lipoidica, granuloma annulare, Bullosis diabeticorum, erythema simile erysipelas, ecthyma, impetigo, perforating folliculitis and eruptive xanthomas.

It was considered DD or pretibial brown atrophy circumscribed in pretibial macules, usually atrophic, hyperpigmented, round or oval-shaped, spread bilaterally but not symmetrically (**Photo 1**).

Chronic complications were established in accordance with clinical and instrumental evaluation. Macroangiopathy was diagnosed based on clinical pathologic history and/or electrocardiographic evidence of coronary disease. Retinopathy was diagnosed by ophthalmoscopy, nephropathy by the presence of proteinuria, and peripheral neuropathy by the

**TABLE 1. Risk factors.**

Pathology	%	N
Xeroderma	69	86
Dermatophytosis	52,8	66
Onychomycosis.	49	61
Tinea pedis	39	49
Peripheral hypotrichia	39	49
Diabetic dermopathy	35	44
Skin thickening syndrome	25	31
Diabetic foot	24	30
Candidiasis	17	21
Fibroids pendulums	11	14
Intertrigo	10	12
Inner eyebrow separation	10	12
Seborrheic keratoses	8	10
Flush	4	5
Erysipelas / cellulitis	4	5
Acanthosis nigricans	3	4
Vitiligo	2	3
Psoriasis	2	3
Folliculitis.	1	1
Erythrasma	1	1
Gas gangrene	1	1

presence of a positive rate (three complications of microangiopathy). Adequate metabolic control could not be documented due to lack of availability of HbA1c in our hospital.

## Results

Of the 125 diabetic patients hospitalized in the Department of Medical Clinic of the Hospital Luis Lagomaggiore, it was observed that 88% ( $n = 110$ ) had type 2 DM and the remaining 12% type 1 DM. The mean age was  $58.9 \pm 15.43$  years, with a maximum of 85 years and a minimum of 16 years old. 55% of patients ( $n = 69$ ) were older than 60 years. Females predominated slightly, representing 57% of the patients.

The reason for hospitalization was associated with skin lesions such as cellulitis, erysipelas and/or diabetic foot in 22% ( $n = 28$ ) of cases. The average hospital stay was  $9.98 \pm 7.21$  days, which is higher than the general average of our hospital, which is 8 days. Mortality was 8%, but in only one case was it directly related to a skin lesion, corresponding to gas gangrene in the genital region of a patient.

50.4% of patients ( $n = 63$ ) had more than 10 years of diagnosis. Associated comorbidities were presented in 111 patients (89%), and the most common were hypertension (60%) and obesity (45%). In 70% of patients ( $n = 80$ ) some of the chronic complications of this disease was presented such as DD, nephropathy, retinopathy, neuropathy and macroangiopathy (**Figure 1**).

70% of patients had evidence of infection. The skin infection was present in 35 patients (28%). Skin lesions were observed in 113 patients, 90.4% of cases. The most frequently observed were: xeroderma, dermatophytosis, peripheral hypotrichosis, DD, among others (Table 1). The mean number of skin diseases per patient was  $4.4 \pm 2.89$ . In no case it was diagnosed necrobiosis lipoidica, granuloma annulare, eruptive xanthomas or Bullosis diabeticorum.

Given that DD is one of the most common skin lesions found in this disease, we performed a statistical analysis comparing diabetic patients with DD ( $n = 44$ ; 35%) and without DD ( $n = 81$ ).

We found that in the male gender, of age over 50 years, the presence of retinopathy, sensory neuropathy, macroangiopathy, diabetic foot and/or tinea pedis were significantly more frequent in diabetic patients with DD. In addition it was found that DD patients presented a longer evolution of their illness (Table 2). No significant differences in the type of DM were found, regarding the presence of nephropathy and mortality.

Regarding the relationship between the incidence of DD and the number of chronic complications (retinopathy, nephropathy, neuropathy and macroangiopathy) in each patient, we found the following information:

- DD in patients without complications: 6 of 40 (15%)
- DD in patients with 1 complication: 14 of 27 (34.14%)
- DD in patients with 2 complications: 10 of 19 (52.63%)
- DD in patients with 3 complications: 11 of 18 (61.11%)
- DD in patients with 4 complications: 4 of 7 (57.14%)

## Comments

DM constitutes a heterogeneous group of disorders characterized by the secretion and/or inadequate action of insulin that determines hyperglycemia and alterations in the metabolism of carbohydrates and lipids.<sup>1</sup> The prevalence in the Western world is of 5 to 7% of the population. It is estimated that one in four individuals over 54 years has DM.<sup>2</sup>

Several multicenter studies have shown that adequate metabolic control is essential to prevent chronic complications. Chronic hyperglycemia is associated with long-term damage of almost all organs and skin is no exception.<sup>3</sup>

It has been estimated that over 30% of patients with diabetes mellitus present cutaneous manifestations of the disease in early stages of the disease and up to 100% during the course it.<sup>2,4</sup> This significant percentage of diabetic patients with dermatological conditions determine the clinical importance of a thorough skin examination at each visit.

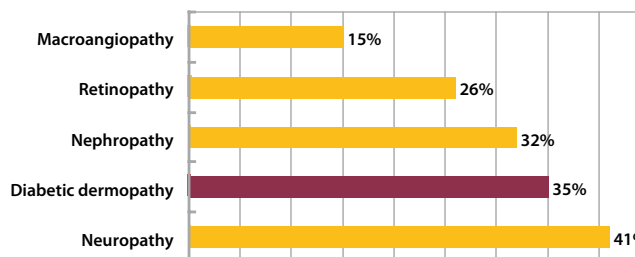
The physiopathology of the skin lesions is explained mainly by the damage caused by diabetic microangiopathy. This is associated with abnormalities in skin perfusion, temperature control and hair loss.<sup>5</sup>

**TABLE 2. Differences and similarities between patients with and without DD**

	With DD %/n	Without DD %/n	P
Male	65,9 / 29	31,2 / 25	0,00015
Age > 50 years	81,8 / 36	48,1 / 39	0,00024
Diabetic retinopathy	38,6 / 17	18,5 / 15	0,013
Sensitive neuropathy	54,5 / 24	24,7 / 20	0,00084
Macroangiopathy	36,4 / 16	18 / 14	0,017
Diabetic foot	41,5 / 20	11,3 / 10	0,000034
Tinea pedis	54,5 / 24	30,9 / 25	0,0095
Evolution time (years $\pm$ SD)	15,1 $\pm$ 10,4	10 $\pm$ 9,4	0,0018
Diabetes mellitus type 2	90,9 / 40	86,4 / 70	NS
Nephropathy	54,5 / 24	24,7 / 20	NS
Mortality	13,6 / 6	4,9 / 4	NS

DD: diabetic dermopathy. SD: standard deviation. NS: not significant.

**FIGURE 1. DM complications.**



It has been demonstrated a diffuse thickening of the basement membrane (BM) with a progressive increase in permeability and injury by microvascular occlusion. This increased thickness is the result of a reduction in the degradation rather than increased synthesis of the components of the membrane. Also occurs due to non-enzymatic glycosylation of proteins such as laminin, collagen type IV and heparan sulfate, key elements of its structure.<sup>6</sup> Other mechanisms are also described such as the excess of sorbitol formation, oxidative damage and overstimulation of protein kinase C.<sup>5</sup> This heightened vascular permeability leads to increase in dermal deposits of collagen type IV, loss of albumin and a greater tendency to platelet aggregation, which further worsens the case.<sup>6</sup>

The following injuries are described as clearly derived from microangiopathic damage: facial rubeosis, necrobiosis lipoidica, DD, Bullosis diabeticorum, erythema simile erysipelas, diabetic foot, periungual telangiectasias and purple pigmentous.<sup>6</sup>

Our data demonstrate that most diabetic patients presented skin lesions, only 12% of cases had no skin lesions. These findings are similar to those of the series of Foss et al., which reports a high percentage (81%) of skin lesions,<sup>1</sup> whereas in Romano et al. lower rates were observed

(60%).<sup>4</sup> It is important to note that the latter study, unlike ours, was conducted on ambulatory diabetic patients. This discrepancy in sample selection may explain the numerical differences because patients requiring hospitalization, in general, are less well-controlled patients with greater number and severity of complications.

The mean number of skin diseases per patient was 4.4, slightly higher than that provided from other series such as Foss et al., who found a mean of 3.7. This series of 403 diabetic patients reported the following skin lesions among the most frequent: dermatophytes 82.6%, xeroderma 20.8%, benign skin tumors 23.5%, candidiasis 12.9% and acne 4.7%.<sup>1</sup>

In the series of Romano et al., over a total of 457 diabetics, it showed that the skin lesions were clearly different depending on the type of DM. In type 1 DM were the most common injuries were vitiligo and psoriasis while in type 2 DM they were infections in 20.6% of cases and DD in 12.5%.<sup>4</sup> In our experience, primarily with respect to the DD, there was no statistically significant difference between both types of DM. With regard to skin infections in diabetic patients it is clear that the incidence is higher in poorly controlled patients with chronic complications.<sup>1</sup> In addition, they present with severe clinical manifestations, have more resistance to treatment and are more likely to relapse.<sup>5,6</sup> This is explained by the alteration of tissue irrigation and decreased chemotaxis of neutrophils and phagocytosis.<sup>1</sup>

With regard to bacterial infections, there are conflicting data about its increase incidence in diabetic patients.<sup>4,6,7</sup> It is known that dermatophytosis have a significant increase in patients affected by this disease, mainly in DM type 1 (tinea pedis: 32% in DM vs. 7% in controls). In our series we observe dermatophytosis in 52.8% of cases, from which 49% (n = 61) were onychomycosis and 39% (n = 49) Tinea pedis: the observed frequency of incidence was lower than in the series published by Foss.<sup>1</sup>

Candidiasis occurs more frequently in elderly and/or with poor metabolic control and may be taken as an early marker of undiagnosed DM.

In our study candidiasis was diagnosed in 17% of patients, compared with 12.9% in the series of Foss.<sup>1</sup>

The DD is one of the most common skin manifestations in diabetic patients. Was described in 1960 by Hans Melin and classified by Perez and Kohn in 1994 as one of the cutaneous manifestations strongly associated with DM.<sup>4,6,8,9</sup> Like necrobiosis lipoidica, it is now considered as pathognomonic of the disease.<sup>9</sup>

The incidence of this disease varies from 9 to 55%<sup>1,4,7,9</sup> and was of 35% in our series of cases. It is more frequent in male patients, over 50 years and with DM of longer evolution time and poor metabolic control (higher HbA1c levels).<sup>9</sup>

Its incidence increases with the number of severe complications: microangiopathic (nephropathy, retinopathy and

neuropathy) and macrovascular (CAD), in this way it is considered as a cutaneous indicator of systemic DM disease.<sup>3,7,9</sup>

Abdollahi et al. conducted a study that showed significant statistical association between DD and retinopathy, the condition was found in 44% of patients with DD vs. 15% in patients with retinopathy without DD (n = 173, p <0.0001).<sup>10</sup> An Italian study conducted on 457 non-insulin dependent diabetic patients correlated DD with neuropathy. They found that 42.9% of diabetics presented both neuropathy and DD at the same time, with respect to 27.5% of patients with diabetic neuropathy in the absence of DD (p <0.005).<sup>4</sup> Even Kiziltan et al. found that DD was a skin indicator of neuropathy as important as the diabetic foot.<sup>11</sup>

It has also been published an association of DD and arteriopathy. Romano et al. found that 53% of patients with noninsulin-dependent DM and DD also suffered from coronary artery disease.<sup>4,9</sup> In our series, the presence of DD was associated with statistical significance to male gender, of age over 50 years and the presence of retinopathy, sensory neuropathy, macroangiopathy and diabetic foot. These findings are consistent with the literature mentioned above and the publication of Shemer, which also mentioned statistical significance with nephropathy.<sup>7</sup>

## Conclusions

We emphasize that our study demonstrates the high incidence of dermatological diseases in diabetic patients, observing more than 4 lesions per patient. The most common skin lesions found were xeroderma, tinea pedis, onychomycosis, peripheral hypotrichia and DD among others and due its pathological significance, we highlight DD and diabetic foot. Unlike what the literature suggests, our data showed few cases of acanthosis nigricans.

By detecting statistical significant association between DD and other systemic findings of DM, we support the recent concept of using this cutaneous manifestation as a marker of internal complications. Thus, this provides a better therapeutic clinical behavior that allows us to anticipate unfavorable diseases.

We emphasize that this work, based on the local population and especially hospitalized patients, is the first study in our community. Patients included, due to required hospitalization, reflect a group with poor metabolic control of their disease and, therefore, a higher skin condition and complications with diabetes.

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