Diabetic dermopathy: A subtle sign with grave implications

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Diabetic dermopathy (DD) is the most common cutaneous manifestation of diabetes mellitus. DD refers to atrophic, hyperpigmented macules characteristically located on the shins of patients with diabetes. They have an unfavorable association with the 3 most common microangiopathic complications of diabetes mellitus: neuropathy, nephropathy, and retinopathy. A relationship between DD and coronary artery disease has also been demonstrated. Thus, the presence of DD should prompt aggressive intervention to detect diabetes mellitus and prevent the development of ensuing complications. (J Am Acad Dermatol 2008;58:447-51.)

HISTORY

In the early 1960s, the Swedish physician Hans Melin[1] studied and characterized a "circumscribed brownish skin lesion" on the lower extremities of patients with diabetes. Melin[1] described these lesions in great detail and concluded that they were specific for diabetes mellitus. In 1965, Binkley[2] coined the term "diabetic dermopathy" (DD), reflecting his concept that DD is a cutaneous manifestation of diabetic microangiopathy.

DD has been known by many names, each characterizing its clinical presentation. It has been referred to as "atrophic lesions" by Melin,[1] "shin spots" by Danowski et al,[3] "pigmented pretibial patches" by Bauer et al,[4] and "spotted leg syndrome" by Murphy.[5] "Diabetic dermopathy" is currently the most widely used term. It represents their association with the complications of long-standing diabetes mellitus.

EPIDEMIOLOGY

DD is the most common cutaneous manifestation of diabetes mellitus.[2,6,7] The incidence of DD ranges from 9% to 55%.[1,6,8-12] This distribution may result from variations among the sample sizes and ethnicities of the study groups. For example, the lowest incidence was noted among Indian patients, whose complexion may render DD more difficult to detect.[12] Two studies conducted in Singapore reported that DD was present in 24% and 16% of 135 patients hospitalized with diabetes and 100 clinic patients with diabetes, respectively.[8,9] The most extensive study noted to date found that 13% of 457 patients with diabetes in Messina, Italy, had DD.[10]

DD is seen more frequently in older patients, especially those older than 50 years, and those who have had diabetes mellitus for a longer period of time.[1,3,6] It may affect male patients twice as often as female ones, but this is not consistently seen.[1,6,8,10,11]

Although DD has been reported in patients without diabetes[3] and many believe that it is not pathognomonic of diabetes mellitus, we argue that this is an improper assumption. The only study to have identified DD in patients without diabetes has a fatal flaw. Danowski et al[3] diagnosed DD in control subjects without diabetes clinically, without having biopsied any of the lesions on these control subjects. Those described could have been scars or other entities noted in the differential diagnosis below. Thus, one cannot conclude that DD occurs in patients without diabetes on the basis of that study. The prospect that DD is not specific for diabetes mellitus seems to have been propagated from the results of this one flawed study. Therefore, we consider DD to be pathognomonic for diabetes mellitus.

Abbreviations used:

DD:	diabetic dermopathy
IDDM:	insulin-dependent diabetes mellitus
NIDDM:	noninsulin-dependent diabetes mellitus

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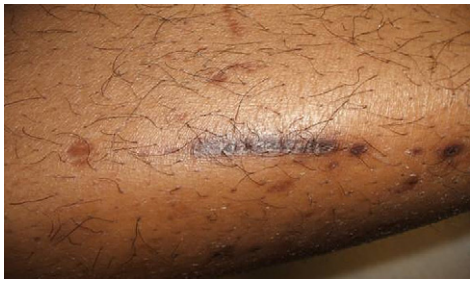

Fig 1. Diabetic dermopathy. Several well-demarcated, hyperpigmented, atrophic depressions, some linear, on shins of 55-year-old man with diabetes and long-standing noninsulin-dependent diabetes mellitus and peripheral neuropathy.

It is unclear whether DD affects patients with noninsulin-dependent diabetes mellitus (NIDDM) more commonly then those with insulin-dependent diabetes mellitus (IDDM). One study reports that 12.5% of 393 patients with NIDDM had DD, whereas none of the 64 patients with IDDM were affected.[10] The characteristics of the two groups in this study were quite different in terms of age and duration of diabetes. Patients with NIDDM were generally much older than those with IDDM and were also affected by the disease for a greater duration of time. Therefore, the preponderance of DD found among patients with NIDDM in relation to those with IDDM may be accounted for by the age difference among the patients studied.

The incidence of DD increases as the number of microangiopathic complications of diabetes mellitus rises. Although 21% of patients with DD do not have evidence of nephropathy, neuropathy, or retinopathy, the incidence of dermopathy increases from 52% in patients with one microangiopathic complication, to 81% in patients with all 3 ($P < .001$).[6] Interestingly, a relationship between the level of glycemic control, as measured by hemoglobin A_{1c}, and frequency of DD has never been demonstrated.[10]

ORIGIN

The origin of DD remains largely unknown. Melin[1] believed that it was the result of minor trauma to the shins that went unnoticed by patients. He tested this hypothesis by striking a rubber hammer against the shins of patients with diabetes. Contrary to the anticipation of Melin,[1] this crude experiment did not reproduce DD.

In 1972, Shelley[13] described a mottled appearance to the skin surrounding the lesions of DD and compared it with livedo reticularis, observing that DD may represent areas of relative ischemia that were particularly sensitive to local heat. In 1975, the effect of thermal trauma to the skin of patients with diabetes was evaluated with both hot and cold stimuli. This experiment also failed to reproduce DD.[14]

Laser Doppler technology has been used to evaluate blood flow to the lower extremities of patients with diabetes. Contrary to expectations, blood flow to DD is actually increased, rather than decreased, in relation to adjacent uninvolved sites.[15] Therefore, it is unlikely that DD represents local ischemia. However, it is still possible that impaired skin perfusion is involved in its development.[15]

Other possible explanations for DD have been proposed. DD may result from minor trauma in the setting of impaired wound healing.[14,15] It may occur secondary to subcutaneous nerve degeneration in patients with neuropathy.[16] However, the most convincing argument is in the relationship between DD and the microangiopathic complications of diabetes. This strong association suggests that DD may be another manifestation of the microangiopathic environment of diabetes mellitus.[14]

CLINICAL MANIFESTATIONS

DD consists of small, brown, well-demarcated, shallow depressions that have an atrophic appearance (Fig 1). They are typically less than 1 cm in diameter and round. Occasionally they are elongated and may reach 2.5 cm.[4] The atrophic appearance refers to a shallow depression and thin epidermis that resembles a scar. They are smooth and hyperpigmented. The intensity of brown pigmentation has been correlated with the degree of atrophy. Melin[1] noted that the most prominent atrophy was associated with the most pronounced hyperpigmentation. Conversely, less atrophic ones were typically a lighter brown.

DD is asymptomatic and does not itch or cause pain.[1] It is typically located bilaterally on the pretibial region and is asymmetrically distributed. Although it is rare, DD can occur on the upper extremities, thighs, trunk, and lower aspect of the abdomen.[1,10,17-20] The characteristic pretibial location and appearance of DD prompts many patients to dismiss DD as scars, likely from forgotten trivial trauma.[1,2]

The appearance of DD at its onset is scarcely documented. Melin[1] described a nonblanching red macule appearing spontaneously on the lower extremity that evolved into typical DD 2 days later.[1] Initial DD usually appears as several scaly, red to purple macules or papules that grow to reach a diameter of 5 to 12 mm during the course of 1 week. They then either persist or slowly resolve. They resolve as the typical shallow, hyperpigmented depressions of DD.[2,17,20,21]

The progression of the dermopathy is variable and does not appear to be affected by glycemic control.[8,10,20] Individual lesions persist for 18 to 24 months on average, but may remain indefinitely. They may fade slowly, leaving behind pigmentation without atrophy or may resolve completely. As older lesions fade, new lesions continuously form. Thus, the overall clinical picture does not change.[1,8,20,22,23]

ASSOCIATED FINDINGS

DD is associated with diabetes mellitus and its ensuing microvascular complications. Specifically, it has been linked with retinopathy, neuropathy, and nephropathy.[6,9,10,15,24] In one survey, 24% of patients with diabetes had DD and 39% had concomitant retinopathy. In this study retinopathy was present in only 7% of patients without dermopathy.[8] Furthermore, a 2007 study of 173 patients with diabetes in Tehran, Iran, found that 44% of patients with DD also had retinopathy, as opposed to the 15% who had retinopathy without DD ($P < .0001$).[11] This revealed a statistically significant association between diabetic retinopathy and dermopathy (odds ratio: 3.60; 95% confidence interval: 1.53-8.44; $P = .003$).[11]

In Israel, it was discovered that 66% of patients with retinopathy had signs of DD.[6] This study also reported the presence of DD in 62% of patients with neuropathy and in 63% of patients with nephropathy. This was found among 35% and 16% of patients with diabetes with neuropathy and nephropathy, respectively ($P < .01$).[6] Furthermore, as the number of coexistent microangiopathic complications increased from one to all 3, the incidence of DD increased from 52% to 81% ($P < .001$). However, it is important to note that 21% of patients with DD lacked any evidence of retinopathy, nephropathy, or neuropathy.[6]

Another study of 457 patients with diabetes in Italy found a significant correlation between neuropathy and dermopathy among patients with NIDDM. This work found that 27.5% of patients had neuropathy in the absence of DD, whereas a significantly greater proportion of patients with DD (42.9%) had concomitant neuropathy ($P < .005$). Patients with DD also had an increased frequency of retinopathy and nephropathy, but this association was not statistically significant.[10]

An association between DD and large-vessel disease has also been identified. Large-vessel disease was defined based on certain electrocardiographic abnormalities, a clinical history of coronary artery disease, or both. It was found that 53% of patients with NIDDM and DD were concurrently affected by coronary artery disease.[10] The results were statistically significant, yet more work is needed to validate this conclusion. The association between DD and coronary artery disease must be examined in a setting where the effect of age on prevalence of both of these findings is evaluated.

The association of DD with neuropathy, nephropathy, retinopathy, and coronary artery disease indicates that it may be a marker of the severity of diabetic complications.[25] In lieu of this, it is interesting that an association between the glycosylated hemoglobin level and the presence of DD has not been observed.[10]

DIAGNOSIS

DD is a clinical diagnosis. With the appropriate history and physical examination, the diagnosis of DD should be evident. The presence of multiple well-demarcated, hyperpigmented, atrophic "scars" on the shins of a patient with diabetes is highly suggestive of DD. Although patients without diabetes may rarely have one or two similar lesions, it has been suggested that the presence of 4 or more with typical features of DD is characteristic of diabetes mellitus.[26,27]

A biopsy is not routinely done. The histologic findings of DD are nonspecific; one may prefer to avoid cutting the distal lower extremities in patients with diabetes. However, when atypical features or rare distribution renders the diagnosis ambiguous clinically, a biopsy may be desirable.

HISTOPATHOLOGY

Histologic findings of the epidermis includes atrophy of rete ridges, moderate hyperkeratosis, and variable pigmentation of basal cells.[28] The papillary dermis exhibits telangiectasia, fibroblastic proliferation, and edema. Hyaline microangiopathy, extravasated erythrocytes, and hemosiderin deposits are universally seen.[2,8,28-30] Periodic acid—Schiff staining is essential to accentuate the mucopolysaccharide infiltrate in the vessel wall.[13]

A mild perivascular infiltrate composed of lymphoid and histiocytic cells is present.[7,28-30] Recently, this infiltrate was found to consistently contain an abundance of perivascular plasma cells, with an average of 2.2 plasma cells per vascular plexus. Thus, the presence of increased dermal perivascular plasma cells is suggested to be a rather specific indicator of DD, when present in the appropriate setting.[7]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of DD includes many entities listed in Table I. The initial lesions of DD may be mistaken for a fungal infection.[20] However, the

Table I. Differential diagnosis of diabetic dermopathy

Lesion	Appearance	Distribution
Diabetic dermopathy	Atrophic, depressed, hyperpigmented macules	Pretibial, rarely seen on thighs, trunk, and forearms
Neurotic excoriations	Pigmented, slightly atrophic scars, irregular in shape	Any part of body
Papulonecrotic tuberculids	Atrophic, circular, sharply demarcated scars, pale with pigmented border zone	Extremities
Schamberg's disease	Patches of orange/brown pigmentation with "cayenne pepper spots"	Lower extremities
Purpura annularis telangiectodes of Majocchi	Purpuric, telangiectatic, and atrophic patches with an annular arrangement of peripheral lesions	Begins on lower extremities, spreads to trunk and arms, or becomes generalized
Pigmented purpuric lichenoid dermatitis of Gougerot-Blum	Purpura, pigmentation, and papules present throughout pigmented plaques	Legs, thighs, and lower aspect of trunk
Stasis dermatitis	Hyperpigmentation and lichenification	Medial aspect of leg over medial malleolus
Angioma serpiginosum of Hutchinson	Groups of telangiectasia in a serpiginous arrangement	Lower extremities

Data from Melin[1] and Bauer et al.[4]

typical brown atrophic scars may sometimes require differentiation from Schamberg's disease (progressive pigmented purpuric dermatitis), purpura annularis telangiectodes, pigmented purpuric lichenoid dermatitis, stasis dermatitis, angioma serpiginosum of Hutchinson, healed lesions of papulonecrotic tuberculids, and neurotic excoriations.[1,4] Many of these entities can be distinguished from the others by distribution, appearance, and natural history.

TREATMENT

Treatment for the cutaneous element of DD is neither recommended nor effective.[19,22] The lesions themselves are asymptomatic and may persist indefinitely or resolve spontaneously without treatment.[1,23] The effect of glycemic control on their natural progression has yet to be established.

On the other hand, the conditions associated with DD require attention. First off, patients with DD must be evaluated for the presence of diabetes mellitus. If the patient does not meet the criteria for diabetes, re-evaluation of the diagnosis and biopsy should be considered. If the diagnosis of diabetes mellitus is made, particular attention should be placed on the detection and prevention of the associated complications. Retinopathy, neuropathy, and nephropathy are undoubtedly associated with DD.[6,9,10,15,24] Furthermore, coronary artery disease is present in 53% of patients with DD.[10] The major difference between any patient with diabetes and one with dermopathy is that the one with dermopathy is more inclined to develop microangiopathies. As with all patients with diabetes, to those with DD, glycemic control is paramount.

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