

## SKIN DISORDERS IN DIABETES MELLITUS

### A review of the diabetes-associated dermatoses and their implications for other disorders

S. Hödl

#### SUMMARY

In an overview, the pathogenesis, histopathology, and clinical picture of the diabetes-associated dermatoses are delineated. Special consideration is given to the connotations that these dermatoses have for extant or predictable disorders in other tissues, organs, or systems of the patient. Heeding the dermatological signals of diabetes mellitus permits timely measures to be initiated, thus preventing feared complications, particularly deleterious metabolic derangements.

Diabetes mellitus, non-enzymatic glycosylation, microangiopathy, macroangiopathy, diabetic dermopathy, diabetic bullae, necrobiosis lipoidica diabetorum, diabetic neuropathy, diabetic foot including commandments for self-care and medical management, diabetic heel, metabolic skin disorders including scleredema diabetorum and diabetic cheirography, infections, lipodystrophies as well as general measures in diabetes are reviewed.

#### KEY WORDS:

*diabetes mellitus, non-enzymatic glycosylation, diabetes mellitus connected skin conditions, general measures in diabetes*

---

#### INTRODUCTION

Nearly one-third of all diabetics exhibit skin changes. These are interpreted as consequences of the chronic metabolic derangements or the defective interaction of insulin with its receptors. Most of these dermatoses are already present when the metabolic derangements manifest themselves clinically. Some, however, may precede metabolic manifestation by a long time, or not appear until much later. In practice, their presence implies that long-term glucose control has been inadequate. Moreover, certain diabetes-associated skin changes permit conclusions as to the individual risk of possibly life-threatening complications in other organs or organ systems. Such complications are myocardial infarction, kidney failure,

arterial hypertension, apoplectic insult, ischemia of the brain and other parts of the body, blindness, diverse disorders of the connective tissue and nervous system, as well as repeated severe infections with correspondingly severe consequences. The dermatologist is obliged to call attention to these associations, so that timely measures can be taken to avert, or at least delay such complications.

Non-enzymatic glycosylation plays a central role in the pathogenesis of these changes. Chronic hyperglycemia gradually leads to chemically irreversible formation of glucose-protein complexes (so-called advanced glycosylation end products or AGEs), familiar as Maillard's fluorescent brown pigment of aged tissues. One such glycosylation



product is hemoglobin-A 1c (Hb A 1c). Its level can be utilized as a nutritionally dependent parameter reflecting the degree of blood glucose control. In normoglycemia, the proportion of HbA1c relative to total hemoglobin is below 5 %. A diabetic with good glucose control has HbA 1c levels of 6 - 7 %. Values of over 8 % indicate poor control and the need for correction of the therapy.

Glycosylation of collagen results in increased intermolecular linkage of structural proteins, and consequently, a decrease in their enzymatic degradation. The disturbed balance between collagen synthesis and degradation leads to accumulation of collagen, resulting in scleroderma-like conditions. These are known as limited joint mobility, i.e. diabetic cheiroopathy, or diabetic scleredema. Extravascular AGEs can bind covalently to extravasated serum proteins (IgG, IgM, albumin, LDL), and initiate obliterative processes in renal glomerula, as well as in retinal, coronary, cerebral, or peripheral vascular beds. The histological substrate in these processes is thickening of the basal membrane and vascular wall of capillaries and arterioles, which are permeated with PAS-positive material. Furthermore, diverse pathobiochemical tissue alterations must also be considered in the genesis of diabetes-associated dermatoses.

In the following, the most important diabetes-associated dermatoses (so - called diabetic dermadromes) will be described together with their possible implications for disorders in other parts of the body (1, 2, 3).

## 1. DERMATOSES OF VASCULAR ORIGIN IN DIABETES MELLITUS

### 1.1. MICRO-AND MACROANGIOPATHY

The occlusion of arterioles and capillaries leads to the development of small, livid areas, usually in an acral localization, which later become necrotic. The skin vasculature is affected mainly in the regions below the knee. Of special importance is the control of infections in the interdigital space, because enlargement of the necrotic area threatens due to infectious thrombosis and occlusion of the terminal vasculature. Macroangiopathic complications arise considerably sooner and more often in diabetics, with the tendency to progress rapidly. The microangiopathic changes must not necessarily parallel the large vessel disease. The characteristic nocturnal resting pain, which awakens the patient, is apparently caused by ischemic neuritis. This condition is improved by lowering the extremity and through increased cardiac action, for example by mobilization. These complaints are usually an indication for angiography with the purpose of vascular surgery.

### 1.2. PRETIBIAL PIGMENT SPOTS (FIG. 1)

These pigmented spots, also known as diabetic dermopathy or shin spots, exhibit the most frequent positive syntropy with diabetes mellitus. Their relationship to diabetes mellitus is significant, but not of a pathognomonic nature. This lesion is androtropic (has a predilection for the male sex) and presents as a pretibial, depressed, atrophic, pigmented lesion measuring a few millimeters to about 1 cm in diameter with a whitish wafer-like scale. It is indicative of poor arterial perfusion of the legs. These dermatologic changes may precede the clinical manifestation of diabetes. They correlate with its duration and severity, occurring more often in non-insulin-dependent DM. They may also correlate with peripheral neuropathy.



Fig. 1 Diabetic dermopathy (so-called shin spots) in a 53 year old male. Several atrophic hyperpigmented macules with watch-glass scales are located on the shin.



### 1.3. BULLOSIS DIABETICORUM (DIABETIC BULLAE) (FIG. 2 AND 3)

Bullous diabeticorum is observed almost exclusively in manifest diabetes mellitus. The lesions appear clinically as walnut-sized, combustiform bullae with highly viscous contents and a necrotic base. They show a predilection for the feet, particularly the toes, for the lower legs, and sometimes the backs of the hands. Histologically, the bullae are found in subepidermal as well as intraepidermal localization, and the dermis exhibits microangiopathic changes. In addition to the latter, pathobiochemical and neuropathic tissue alterations are presumably also involved in the pathogenesis of this lesion. It should direct attention to the presence of a so-called diabetic foot (see section 2.1), as well as to disorders of inner organs innervated by the autonomic nervous system. The following symptoms should be looked for:

Symptoms of Autonomic Neuropathy:

Heart:

resting tachycardia, restricted range of cardiac frequency, pronounced orthostatic regulatory disorder, cardiac arrest.

GI Tract:

disordered motility (gastroparesis, delayed or accelerated gastrointestinal transit with constipation or diarrhea). Delayed gastric emptying harbor the danger of postprandial hypoglycemia.

Urogenital Tract:

atonic urinary bladder with evacuation disorders (increased intervals between micturition, polyuria, urine retention, recidivating urinary tract infections).

Neurocochlear hearing deficiency in the high frequency range.

The decreased or missing perception of hypoglycemia, owing to a reduced secretion of catecholamines, is a special danger to these patients.

Overall, patients suffering from autonomic neuropathy have an increased risk of mortality.

### 1.4. NECROBIOSIS LIPOIDICA DIABETICORUM (FIG. 4)

Clinically, yellow-brown indurated plates are seen in the pretibial region, less often on the forearm, head, or trunk. Besides a microangiopathic pathogenesis, a delayed-type immune reaction is under discussion. Spontaneous remission is possible. This entity may long precede the clinical manifestation of the metabolic derangements!

## 2. DERMATOSES CAUSED BY DIABETIC NEUROPATHY

Chronic hyperglycemia and its associated toxic and neurometabolic derangements, together with microangiopathic changes in the Vasa nervorum, can lead to nerve damage. The autonomic nervous system is affected first, then the sensory and motor peripheral nerves. (See section 1.3 for symptoms of autonomic neuropathy in inner organs). In no other part of the body does the combination of neuropathies in these three systems appear as consistently as in the lower extremity, particularly the foot (so-called diabetic foot). Practically one-half of all diabetics suffer from peripheral neuropathy after 15 years duration of the disease.

### 2.1. DIABETIC FOOT (FIG. 5 AND 6)

It is the result of complex pathogenetic processes, and is characterized by an ungainly form, plantar callus formation at points of increased pressure, and dry, reddened scaly skin. (Table 1)

Furthermore, increased mechanical stress resulting from disordered foot posture as well as trophic changes lead to alterations in the skeletal structure of the foot (diabetic osteoarthropathy). Roentgenologically, two forms of bone destruction may be distinguished: either diffuse speckled demineralization of the entire foot skeleton (similar to Sudeck's atrophy), or a localized periarticular form.

#### 10 COMMANDMENTS FOR THE DIABETIC FOOT:

- have an experienced orthopedic shoemaker fabricate shoes designed to relieve pressure and make polyethylene sole inlays to distribute pressure
- wash and then thoroughly dry feet daily
- treat skin with ointments
- inspect feet daily using a hand mirror
- give attention to even the smallest injuries
- wear absorbent socks, never go barefoot
- do not cut toenails too short
- avoid sharp or pointed pedicure implements
- do not use hot water bottles, heating pads, or the like
- practice walking on a regular basis.

Medical Management of the Diabetic Foot :

1. Determine the degree of peripheral occlusive arterial disease.
2. Take steps to improve the circulation.
3. Rule out the presence of a neuropathy.
4. Eliminate risk factors, especially smoking.
5. Treat ulcerations and infections, immobilize the foot.
6. Multidisciplinary teamwork is required.

Table 1

Substrate	Sequel
-Macroangiopathy:	Vascular occlusion with subsequent gangrene of a large portion of an extremity.
-Microangiopathy:	Circumscribed necrosis, particularly in acral locations; pretibial pigment spots; Bullosis diabeticorum; necrobiosis lipidica.
-Autonomic Neuropathy:	Hypo-and anhidrosis due to motor dysfunction. Red, overheated (excessively warm) foot due to vasomotor paralysis ("sympathectomy syndrome"). Dry, whitish, scaly skin that facilitates bacterial invasion (DD: alcoholic polyneuropathy: moist skin with fetor, trophic disorders ("glossy skin").
-Sensory Neuropathy ("insensitive foot"):	Subjective complaints: paresthesias such as burning, tingling, or crawling sensations, aching, numbness, and sometimes also severe lancinating pain, particularly nocturnal resting pain which improves with movement (in contrast to intermittent claudication in peripheral occlusive arterial disease). Objective findings: a stocking-shaped pattern of impaired vibratory sense, pain, and temperature sensitivity with the attendant danger of unnoticed painless injuries.
-Motor Neuropathy:	Disordered synergism of the flexor-extensor system of the foot leads to increased pressure at certain points with subsequent callus formation, followed by associated, completely painless, deep punched-out ulcerations (Mal perforant du pied) with imminent danger of infection.

7. Delay amputation.

8. Patient training with special emphasis on self-observation of the skin.

9. Optimal glucose control on the basis of HbA1c levels!

## 2.2. DIABETIC HEEL

Pressure on the calcaneus is relieved and distributed by a special arrangement of connective and fatty tissues. The connective tissue forms vertically oriented tubes, in which the subcutaneous fatty tissue is oriented in a pillar-like fashion. When this pressure absorbing fatty tissue cushion is diminished by a reduced circulatory supply, normal mechanical forces in this region, such as occur while sleeping or wearing shoes, may lead to pressure necrosis. Especially diabetics with neuropathy are endangered, because they change their position too infrequently due to the sensory deficiency. Once the skin becomes necrotic, the fatty tissue undergoes colliquation necrosis, and all protection from pressure is lost. In addition, there is imminent danger of deep tissue infections. Bedridden diabetics therefore require comprehensive measures to prevent pressure necrosis in this region. It is essential to inspect the skin daily, and to monitor the proper seating of the heel guard (cotton or foam rubber cushion).

## 2.3. RUBEOSIS PLANTARUM

The skin appears reddened and excessively warm as a result of disordered vasomotor tone and the opening of arterio-venous shunts. It is possible that the latter effect may be the result of intermediary metabolic products. This entity may be the expression of poor glucose control in diabetes mellitus.

## 2.4. ERYTHROMELALGIA

This entity is characterized by painful attacks of pedal edema and hyperemia, probably caused by a functional disorder in the terminal vascular bed. Also under discussion as a possible cause is a disorder in prostaglandin metabolism, which could be the basis for the therapeutic effectiveness of acetylsalicylate.

## 2.5. "BURNING FEET SYNDROME"

This syndrome is closely related to erythromelalgia, however without acute hyperemia. The symptoms of severe burning or tingling sensations in the feet usually occur at night in the warmth of the bed. Relief is obtained by letting the feet hang out of bed. It occurs not only in diabetes mellitus, but also in chronic alcoholism, hepatic diseases, vitamin B deficiency, and INH-overdosis.



### 3. DERMATOSES OF METABOLIC AND ENDOCRINE CAUSES

In chronic hyperglycemia, collagen is subject to non-enzymatic glycosylation, i.e. intermolecular cross-linkage occurs. The result is an imbalance in collagen synthesis and degradation. The excess of collagen in the dermis leads to thickened skin which cannot be tented and has a limited range of displacement against the underlying structures.

#### 3.1. SCLEROEDEMA DIABETICORUM (FIG. 7)

Scleroedema diabeticorum is characterized by thickened, indurated, barely moveable skin on the nape of the neck, as well as the neck itself, upper back and shoulder regions. These areas are often erythematous and exhibit a relief reminiscent of an orange rind. This skin disorder may be associated with diabetic retinopathy, neuropathy, hypertension, and coronary artery disease. It may also be indicative of inadequate glucose control.

#### 3.2. DIABETIC CHEIROPATHY (SYNDROME OF LIMITED JOINT MOBILITY AND WAXY SKIN, DIABETIC SCLERODACTYLIA) (FIG. 8)

This painless affliction of the connective tissue occurs preponderantly in insulin-dependent juvenile diabetes, but also in maturity-onset insulin-resistant diabetes. Clinically, the skin takes on a taut, waxy appearance, displays scleroderma-like thickening, and cannot be tented. These changes occur preferentially on the extensor surfaces of the fingers as well as the metacarpal region, resulting in a dermatogenic restriction of joint mobility. In consequence, the hand cannot be placed flat on top of a table ("table top sign"), and it is impossible, actively or passively, to press both palms together without an intervening space. The reduced mobility may be objectified by making an inked handprint. This affliction is considered an early marker for microangiopathy of the skin, eyes, and kidneys. The severity of the microangiopathy appears to correlate with the restriction of movement, i.e. the degree of sclerosis. If optimal glucose control is attained soon enough, the condition will improve to an extent. A connection with the duration of diabetes does not seem established. Patients with diabetic cheiropathy are at high risk for developing retinopathy!

#### 3.3. BENIGN ACANTHOSIS NIGRICANS AND FIBROPAPILLOMA (SKIN TAGS)

Both of these conditions are indicative of insulin resistance in target tissues. Autoantibodies competitively bind to cellular insulin receptors, the unengaged insulin affects growth hormone receptors, and thus triggers an increase in

keratinocyte and fibroblast metabolism. This activity results in the development of the typical dirty-brown vegetations and the fibropapillomas in the intertriginous areas. The insulin resistance is associated with a strong tendency to ketoacidosis.

### 4. INFECTIOUS DERMATOSES

Increased tissue and serum glucose levels and ketoacidotic conditions appear to favor infections of the skin and other organs by impairing chemotaxis, phagocytosis, and bactericidal potency of neutrophilic granulocytes. In addition, local factors such as increased moisture content and alkalinized skin surface, as well as an impaired barrier function of the stratum corneum also facilitate infection.

Dermatoses caused by gram-positive organisms: furuncle, carbuncle, folliculitis, erysipelas.

Dermatoses caused by gram-negative organisms: folliculitis, gram-negative infections of the feet, malignant otitis externa, nonclostridial gas gangrene (*Proteus*, *E.coli*, *Pseudomonas*, *Klebsiellae*, *Bacteroides*) (Fig. 9)

Mycotic infections: *Candida* infections in (semi-) mucous membranes, intertriginous areas (*Erosio interdigitalis candidamycetica*), and nails.

Furthermore, infections with dermatophytes and molds, as well as corynebacteria appear to have a higher incidence in diabetics.

### 5. DIABETES-ASSOCIATED LIPODY - STROPHIES OF GENETIC ORIGIN

This is a heterogeneous group of diseases, which have in common a total or partial loss of the panniculus adiposus and insulin-resistant diabetes.

#### 5.1. CONGENITAL TOTAL LIPODYSTROPHY (SO-CALLED LIPODYSTROPHY DIABETES MELLITUS)

The entire panniculus adiposus is lacking at birth. Diabetes mellitus does not appear until the second decade of life. Cosanguinity is generally (often) the case, and the patients succumb to cirrhosis of the liver. There is a primary decrease in the number of insulin receptors, with subsequent hyperinsulinism.

#### 5.2. ACQUIRED TOTAL LIPODYSTROPHY

The onset of this affliction is in childhood or early adult life, usually following an infection. The growth rate of these



children is above normal, leading ultimately to an acromegaloid, Hercules-like habitus. Death generally results from liver failure. The pathogenesis of this disease lies in reduced insulin effectivity owing to decreased insulin affinity of the receptor.

### 5.3. ACQUIRED PARTIAL LIPODYSTROPHY (FIG. 10)

The reduction of the panniculus adiposus begins in childhood, but sometimes also in later adult life. Women are affected more often, and the age of manifestation is usually between 5 and 15 years. The most common form is characterized by cephalothoracic loss of adipose tissue, but increased fat deposits in the hips, gluteal region, and thighs, result in an androgynous habitus. The abdomen is enlarged by hepatomegaly. Further features are sunken cheeks due to loss of Bichat's fat-pad, a slender neck with conspicuous organ modelling, and a pseudoathletic habitus resulting

from the unmasked musculature of the shoulder girdle and thoracic region (3). Complications are mesangiocapillary nephritis, and portal cirrhosis of the liver as a consequence of increased circulating blood lipids which cannot be transferred to fat deposits.

### 6. RECOMMENDED MEASURES

1. Intensive compliance with the diabetic diet
2. Blood glucose control based on repeated HbA1c level determinations and supervision of blood pressure
3. Quarterly determination of urine status (microalbuminuria!), serum creatinine, ECG, eyegrounds, cerebral and peripheral vascular status, inspection of the lower extremities, especially the feet
4. Semiannual neurological testing of the peripheral nervous system and exploration for symptoms of autonomic neuropathy
5. Yearly testing of serum cholesterol and triglyceride levels.

## REFERENCES

1. Hanna W, Friesen D, Bombardier C, Gladman D, Hanna A (1987): Pathologic features of diabetic thick skin. *J Am Acad Dermatol* 16: 546-553
2. Huntley AC (1982) The cutaneous manifestations of diabetes mellitus *J Am Acad Dermatol* 7: 427-455
3. Jelinek JE (1986) The skin in diabetes. Lea & Febiger, Philadelphia

## AUTHORS ADDRESS

Stefan Hödl, M.D., Professor of Dermatology, Department of Dermatology, University of Graz, Auenbruggerplatz 8  
A - 8036 Graz, Austria

### Legends to the Illustrations:

Fig. 2 Diabetic bullae. This 95-year old diabetic female developed spontaneous bullae on the dorsal aspects of the toes. The bullae were partially sub- and partially intradermal, and contained a viscous fluid.

Fig. 3 Diabetic bullae in a 57-year old diabetic female. Two applanized bullae may be seen on the medial aspect of the left foot. The base of one blister displays superficial necrosis.

Fig. 4 *Necrobiosis lipoidica diabetorum*. A palm-sized indurated yellow plaque with teleangiectasias on the shin of a 22-year old insulin-dependent woman.

Fig. 5 Diabetic foot in a 62-year old man. The plantar aspect reveals the characteristic deformation of Charcot's foot. The skin is reddened, warm, scaly, and dry. Calluses indicate areas of abnormal pressure over the fifth metatarsal heads, the left one with a neuropathic ulcer.

Fig. 6 Diabetic foot. X-ray of the left foot of the patient depicted in Fig. 5. The fifth metatarsal-phalangeal joint is subluxated.

Fig. 7 *Scleroedema diabetorum* in a 71-year old obese insulin-dependent patient. The skin of the back and dorsal neck is markedly thickened, indurated, painful, and displays an orange rind pattern.

Fig. 8 Diabetic cheiropathy in a 65-year old female. Both hands exhibit thickened waxy skin, and resist flattening on a table ("table top sign") as a result of limited joint mobility.

Fig. 9 Gram-negative infection of the foot (*Pseudomonas*) in a 58-year old non-insulin-dependent woman.

Fig. 10 Acquired (partial) progressive lipodystrophy (cephalothoracic type) in a 14-year old insulin resistant diabetic girl. Beginning in childhood, an insidious loss of subcutaneous fat extends from the face (loss of buccal fat pads) down to the iliac crest.







