REVIEW

Skin manifestations in rare types of diabetes and other endocrine conditions

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Abstract

As the most visible and vulnerable organ of the human organism, the skin can provide an impression of its state of health. Rare forms of diabetes and endocrinopathies are often diagnosed late or primarily misinterpreted due to their rarity. Skin peculiarities associated with these rare diseases may be indicative of the underlying endocrinopathy or form of diabetes. At the same time, rare skin changes in diabetes or endocrinopathies can also be a major challenge for dermatologists, diabetologists and endocrinologists in optimal patient and therapy management. Active collaboration between these different specialist groups can therefore lead to increased patient safety, better therapeutic success and more targeted diagnostics.

Key Words

- rare types of diabetes
- rare endocrinopathies
- cutaneous effects of rare diabetes
- rare dermatologic changes in endocrine disorders

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Background

With its many functions, such as mechanical and antimicrobial barrier protection, heat regulation or sensory perception, the human skin represents an essential organ also allowing for the assessment of an organism`s general condition. Consequently, as in certain hereditary endocrine diseases for example, the skin can also provide information about the severity of the underlying disease or can even be indicative of the condition itself. Diseases of endocrine organs often lead to cutaneous changes, which may either be an indirect effect of hormone dysregulation or a direct consequence of the same – often endocrine disorder or endocrine-immunologic pathomechanism responsible for endocrine organ dysfunction (1). Dermatological manifestations related to endocrine disorders range from mild to severe or are even life-threatening and can be specific or non-specific for the underlying disease. Moreover, some skin manifestations may occur early in the disease course and may therefore help in the early recognition and treatment of the endocrine disorder.

By definition, rare diseases affect only a small number of people and therefore cause specific problems arising from their rarity. The European Union considers a disease as rare when it affects less than 1 in 2000 citizens. (3). The status of 'rare' can vary from region to region. Some diseases are common in principle but can occur in rare variants. Medical and scientific knowledge about rare diseases is far from sufficient (3). Rare diseases have long been neglected by the medical sciences and policy makers, so that despite recent efforts scientific knowledge and appropriate health policy measures are still insufficient in this pivotal medical field. Although a cure for most rare diseases has still not been found, adequate symptomatic treatment and medical care improve the quality of life and increase the life expectancy of affected individuals. Impressive progress has been made in the treatment of some rare diseases, which should be motivating for more intense research efforts and further strengthen social solidarity as it is driven by ENDO-ERN, the European Reference Network on Rare Endocrine Conditions,

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for example. European reference networks are virtual networks of experts that aim to provide optimal care for people with rare diseases. Collaboration between specialised centres facilitates the exchange of highly specialised expertise throughout the European Union and thus allows access to medical expertise without patients having to travel. ENDO-ERN aims to improve the care of rare endocrinopathies and rare forms of diabetes (3, 4, 5, 7). For this purpose, a Europe-wide network for patient-oriented, structured, targeted and scientific cooperation is in place. ENDO-ERN is supported by the European Societies of Adult and Paediatric Endocrinology. It brings together the expertise of 71 centres from 19 countries in the field of rare endocrine diseases (https://endo-ern.eu).

This review aims to inform about possible skin changes in diabetes, including its rare forms and rare endocrinopathies and to try to enhance the interdisciplinary expertise of dermatologists, diabetologists and endocrinologists concerning this issue.

General and rare skin changes in diabetes and pancreatic endocrine dysfunction

Diabetes mellitus is the most common endocrine disease with a steadily increasing prevalence (7). The disease gradually causes changes in all organs, with more than one-third of people with diabetes developing skin changes of varying severity in the course of the disease. Cutaneous changes can even be the first clinical signs of a manifesting diabetic metabolic condition. Diabetes mellitus can affect the skin through primarily diabetes-induced changes in skin metabolism but also through associated complications such as vasculopathies, neuropathies or immunological impairment and ensuing skin infections.

Especially the hyperglycaemia-induced, non-enzymatic glycation of cell structures plays a decisive role in the pathogenesis of diabetic complications according to the current understanding. The accumulation of glycated proteins and amino acids leads to a disturbance of the intracellular signalling cascades, resulting in a functional impairment of keratinocyte and fibroblast proliferation, differentiation and migration (8). Among other things, this results in a disturbed barrier function and delayed wound healing. In addition, a reduced synthesis of collagen 1, a functional impairment of proliferation and adhesion of diabetic endothelial cells, as well as a relative decrease in VEGF secretion by mesenchymal stem cells and wound fibroblasts, have been observed in diabetic skin (9, 10). Finally, adipose stem cells from diabetic mice showed a marked decrease in adipogenic and osteogenic differentiation potential.

Children and adolescents with type 1 diabetes frequently reveal skin changes as well. Consequently, the PediSkin study cohort of 369 paediatric patients with

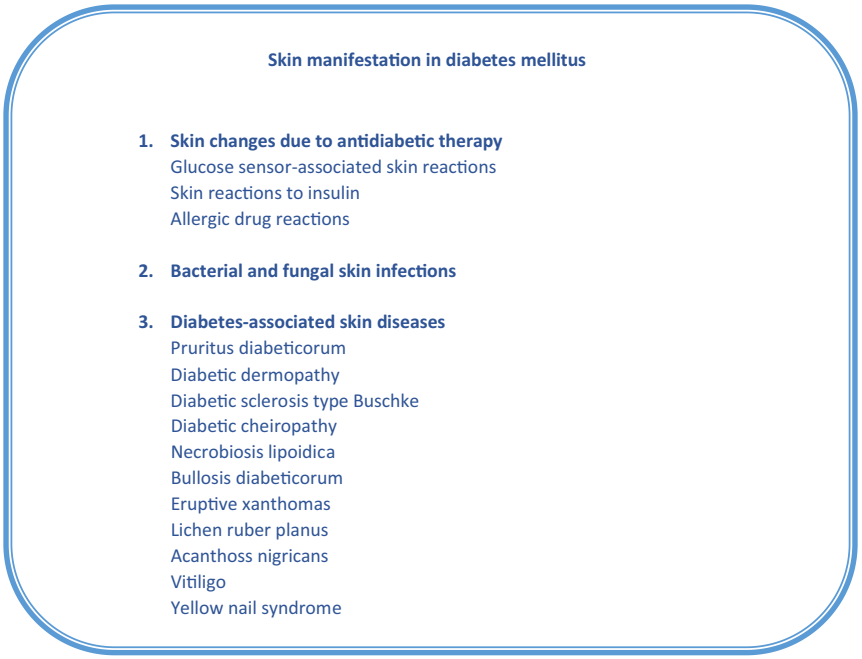

Figure 1
Skin changes in diabetes mellitus.

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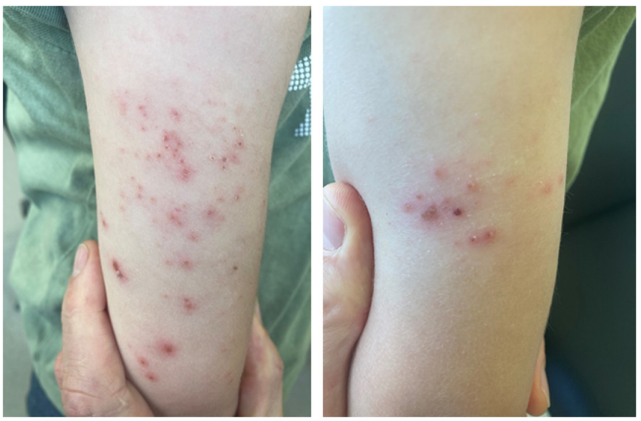

Figure 2
Skin changes in childhood diabetes. Skin irritation and scratching artefacts caused by a CGM sensor.

type 1 diabetes (55% male, 12.3 ± 4.3 years) showed skin abnormalities in 91.8% of diabetic individuals. The most common problems were sensor- or catheter-associated skin lesions (76%) (11).

A brief summary of skin changes occurring in people with diabetes is displayed in Fig. 1.

Skin changes resulting from antidiabetic therapy

Injection- or device-related skin changes: Treatment of insulin-dependent diabetes is inevitably accompanied by the s.c. administration of insulin. This can be done by pen via a s.c. single injection, for example, in the case of a basal bolus principle, or permanently by insulin pump in the context of a continuous s.c. insulin injection. Both forms of therapy lead to typical skin changes that are caused by the injection itself, such as lipohyper- or lipohypotrophies. In addition to blood glucose measurement, blood glucose is nowadays measured in the form of flash glucose measurement or continuous glucose measurement (CGM) via a glucose sensor. During pump therapy or sensor diagnostics, the skin comes into close contact with the patch or other components of the sensor. This may lead to irritative and eczematic reactions, which can often be treated well with topical emollients and anti-inflammatory agents. Additionally, allergic contact dermatitis, for example to isobornyl acrylate or the components of the plastic housing of the sensors, can also occur if the pump or sensor systems are worn for a long time (Fig. 2) (12, 13).

Allergic drug reactions (14): All drugs used in diabetes therapy – both oral antidiabetics (e.g. sulfonylureas and metformin) and insulin preparations – can trigger allergic reactions of the immediate type (e.g. urticaria, angioedema and severe anaphylaxis) or the delayed type such as leukocytoclastic vasculitis, erythema multiforme, maculopapular rash or severe bullous drug reactions. These can also occur due to sweeteners as well as due to medications prescribed for the treatment of concomitant diseases. Interestingly, sulfonylureas are well-known elicitors of photoallergic reactions.

Skin reactions to insulin (14, 15): Local reactions after s.c. insulin application in the form of pruritus, erythema and induration are rare. With the introduction of highly purified human insulin preparations and new delivery systems, the incidence has decreased significantly. Although rare, circumscribed adipose tissue dystrophy (usually atrophy, very rarely hypertrophy) represents a characteristic side effect in insulin injection sites. An immunological reaction within the adipose tissue is assumed, although clinical signs of inflammation are usually absent. The changes usually manifest within the first 2 years after the start of therapy. Prophylactically, a constant change of the injection site and, if necessary, a change of the insulin preparation is recommended.

Skin changes in response to oral antidiabetics: Bullous pemphigoid (BP) is an acquired subepidermal autoimmune vesicular blistering disease with cellular humoral immune response to BP-180 and BP-230 antigens. BP can be triggered by several drugs. Several reports revealed an association between BP and gliptin (=dipeptidyl peptidase-4 inhibitors (DPPIs), partly with mucosal affection, the leading one being vildagliptin, followed by sitagliptin and linagliptin. DPPI is thought to interfere with the pathogenesis of BP via alteration of the antigenic properties of the basement membrane. Many cell types in the skin express DPP-4, including keratinocytes, epithelial cells and T cells. DPP-4 is a cell surface plasminogen receptor that activates plasminogen and leads to the formation of plasmin. Plasmin is a serine protease that binds BP-180 in the immunodominant NC-16A domain and is found in lesional skin as well as in BP blister fluid. Inhibition of plasmin by DPPI could lead to changes in proper BP-180 binding and induce antigenicity. Inhibition of DPP-4 increases the activity of eotaxin and other proinflammatory cytokines and may lead to eosinophil activation and blister formation. The time of first blister formation is between 2 and 26 months. Healing occurs on average 3 weeks after discontinuation of the DPPI and usually does not require any steroid therapy (16).

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Skin infections

The impaired barrier function, high glucose concentrations in the epidermis and immune system impairment facilitate the adherence and proliferation, sometimes invasion and spread of bacteria and fungi in diabetic individuals. Hence, bacterial and fungal Infections are observed in every second patient suffering from diabetes. Especially recurrent bacterial skin infections such as folliculitis, abscesses, erysipelas, impetigo contagiosa and extensive fungal infections should lead to the suspicion of diabetes mellitus, and adequate screening should be initiated. About a quarter of diabetics reveal clinical signs of candida infection. Especially in women, chronic recurrent vulvovaginal candidiasis can be a sign of a diabetic metabolic condition (14). Fungal infections of the nails, also known as onychomycosis or tinea unguium, are a common phenomenon in the general population and are not rarely associated with aesthetic/psychosocial impairment and, potentially, secondary complications such as paronychia. In diabetics, fungus-infested thickened nail plates in the presence of advanced peripheral arterial occlusive disease can increase the risk of diabetic foot syndrome (17). Interdigital or palmoplantar fungal infections in the foot area (tinea pedis) are also dangerous, as the ensuing maceration and skin barrier impairment often facilitates bacterial infections, particularly bacterial cellulitis (erysipelas). Therefore, the early and effective treatment of fungal infection of the skin and nails is of pivotal medical importance in diabetic individuals.

Diabetes-associated idiopathic or autoimmune skin diseases

Pruritus diabeticorum (14, 15, 18)

Skin dryness and itching are found in over 30% of diabetics. Although its exact aetiology is still unknown, skin dryness (xerosis cutis) may be a consequence of sweat gland insufficiency due to dysfunction of sympathetic nerves. In addition, reduced sebum production leads to a further disturbance of the skin barrier. Scratching further impairs the skin barrier and activates cytokine pathways, which usually leads to an intensification of the symptoms (itch–scratch cycle). Treatment of pruritus diabeticorum is multimodal consisting of emollients, topical glucocorticoids and immunomodulators and systemic antihistamines, for example. Also, mild skin care with synthetic detergents rather than alkalic soaps and the avoidance of potential contact allergens factors such as fragrances in cosmetics is highly recommendable.

Diabetic dermopathy (15, 19): The disease is diagnosed in up to 10% of adult patients with diabetes, while it is very rarely encountered in children. Clinically, multiple reddish to brownish, annular, slightly atrophic plaques are found, especially on the extensor surfaces of the legs. The aetiology of diabetic dermopathy is still unclear, although microangiopathy and the influence of microtrauma are suspected causes. Histologically, hyaline deposits are found in the dermal vessels. An initial necrobiosis lipoidica (see below) can also be considered as a differential diagnosis. As diabetic dermopathy is an asymptomatic and benign condition, no treatment is required. However, further assessment and treatment of diabetes and associated complications may be required. Diabetic dermopathy is often associated with damage to nerves and blood vessels that can cause more serious problems, such as peripheral neuropathy, diabetic ketoacidosis, common infections, kidney disease, eye problems and arthropathies. Proper metabolic control can help reduce the likelihood of diabetic dermopathy.

Buschke's scleredema (15, 19, 20): The disease is particularly common in male senior citizens with type 2 diabetes. Over months and years, pathologically enhanced glycation leads to skin remodeling, especially of the dermis. As a rule, symmetrical, painless, waxy and thickened skin areas appear on the neck first and then spread to the face, thorax, arms, palms and finally fingers (mostly little fingers). Depending on the extent of skin thickening, joint mobility may be restricted, and contractures may occur, leading to reduced arm mobility in the shouldevr area. Other causes of scleredema (paraproteinaemia and neoplasia) as well as scleroderma must be considered as critical differential

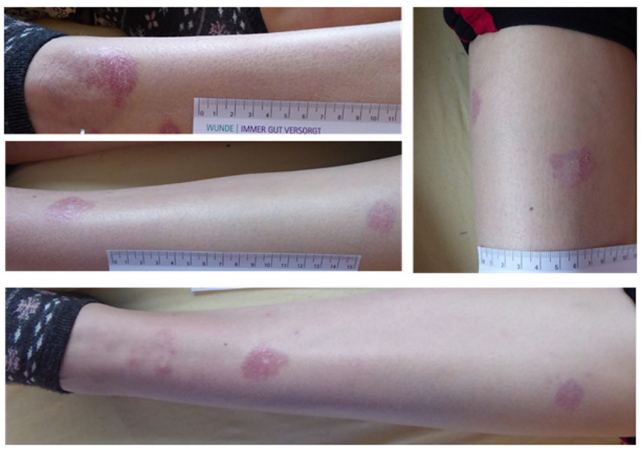

Figure 3
Skin changes in childhood diabetes. Typical skin lesions of necrobiosis lipoidica in a girl suffering from type 1 diabetes and low metabolic control.

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diagnoses. As a rule, the course of Buschke's scvleredema is chronically progressive. Therapeutically, the setting of the underlying disease is decisive. As a symptomatic measure, the interaction of long-wave UVA radiation with a photosensitising substance (psoralen and UVA (PUVA) therapy), but also the sole application of UVA1, has led to a decrease in symptoms in some patients.

Diabetic cheiroarthropathy (21): Clinically, this rare disease entity, like Buschke's scleredema, causes a waxy thickening of the skin and is mainly located to the hands, particularly the fingers and palms. In the course of the disease, however, the forearms and thighs can also be affected. The cause is thought to be a microangiopathy, a disorder of collagen synthesis due to non-enzymatic collagen glycation and mucin deposits. Histologically, there are clearly thickened collagen clumps next to mucin deposits. As important differential diagnoses, Buschke's scleredema and scleroderma must be considered. The disease has an important indicator function because it may precede the onset of diabetes mellitus. Furthermore, diabetic cheiropathy is associated with an increased risk of diabetic retinopathy and neuropathy.

Necrobiosis lipoidica (15, 19, 22): This is a rare granulomatous dermatosis of unclear aetiology, as can be seen in Fig. 3. Pathophysiological mechanisms include inflammatory microangiopathy and the effect of elevated tumour necrosis factor-alpha levels. Fibroblasts show abnormal collagen metabolism and impaired glucose transport. According to recent statistics, the average age of onset is slightly over 50 years. While 0.5–1% of diabetics display necrobiosis lipoidica, up to 65% of individuals with necrobiosis lipoidica patients develop diabetes mellitus. Disease severity is independent of the severity of the underlying diabetic condition. Necrobiosis lipoidica is also associated with other conditions such as Hashimoto's thyroiditis, hypercholesterolaemia, obesity or nicotine abuse. Clinically, sharply demarcated, irregularly configured brown-yellowish plate-like atrophic plaques are found mainly on the extensor surfaces of the lower legs (approximately 85%). As a complication, ulcerations occur in 15–35% of patients. Very rarely, squamous cell carcinoma can develop in very long-standing necrobiotic lesions. Xanthogranuloma, granuloma anulare and sarcoidosis should be considered for differential diagnosis. The disease course is chronic, although spontaneous healing is observed in about 10–20% of cases after 6–12 years. Systemic medications such as ciclosporin A, adalimumab, fumaric acid and corticosteroids may be

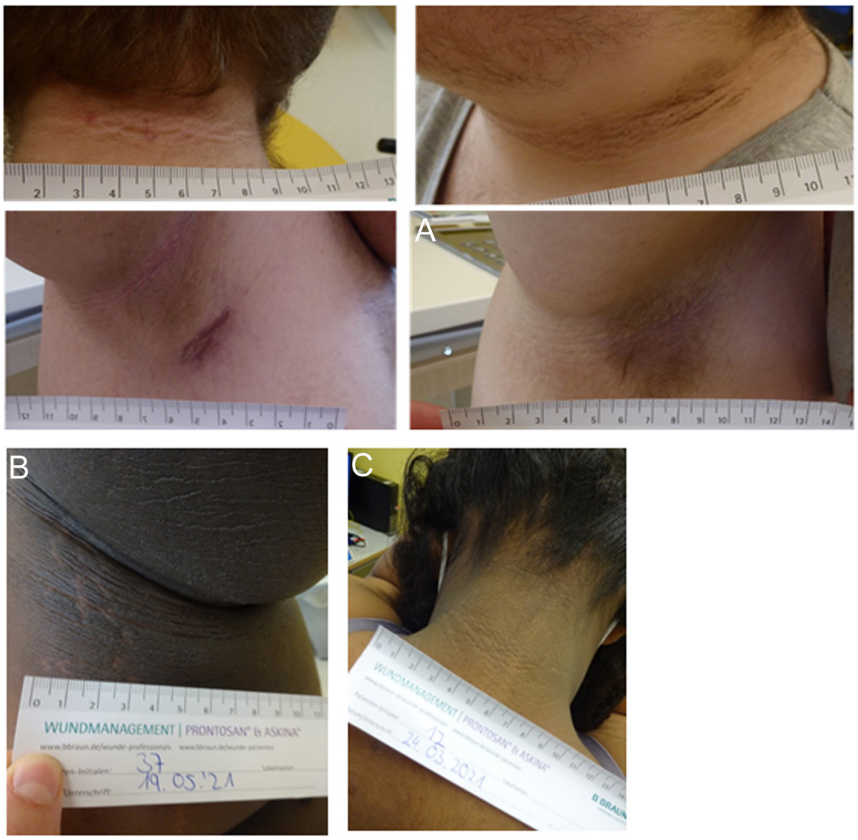

Figure 4
Typical skin changes of acanthosis nigricans at cervical (A), axillary (A, B) and nuchal (C) localisation in a youth with paediatric diabetes and poor metabolic control.

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used therapeutically. Treatment of the diabetic metabolic condition does not regularly lead to regression of the changes.

Bullosis diabeticorum/bullous disease of diabetes (14, 22, 23): The disease is very rare and occurs in less than 1% of diabetics. For still unknown reasons, mostly serous, rarely haemorrhagic, tense blisters without signs of perilesional inflammation occur mainly on the extensor sides of the lower legs and on the dorsum of the feet (Fig. 4). Histologically, there is junctional blister formation. Direct immunofluorescence examination usually shows negative findings, allowing differentiation from autoimmune-mediated bullae. Electron microscopy of newly appeared bullae may reveal separation in a subepidermal location in the lamina lucida or below the lamina densa. Spontaneous healing may take several weeks. Bursting of the blisters can lead to local infections or even poorly healing wounds. The external application of antiseptics and hydrocolloid plasters is therapeutically useful. The external application of glucocorticosteroids is controversially discussed. Especially in cases of recurrent skin blistering, autoimmune bullous diseases such as BP or pemphigus should be considered.

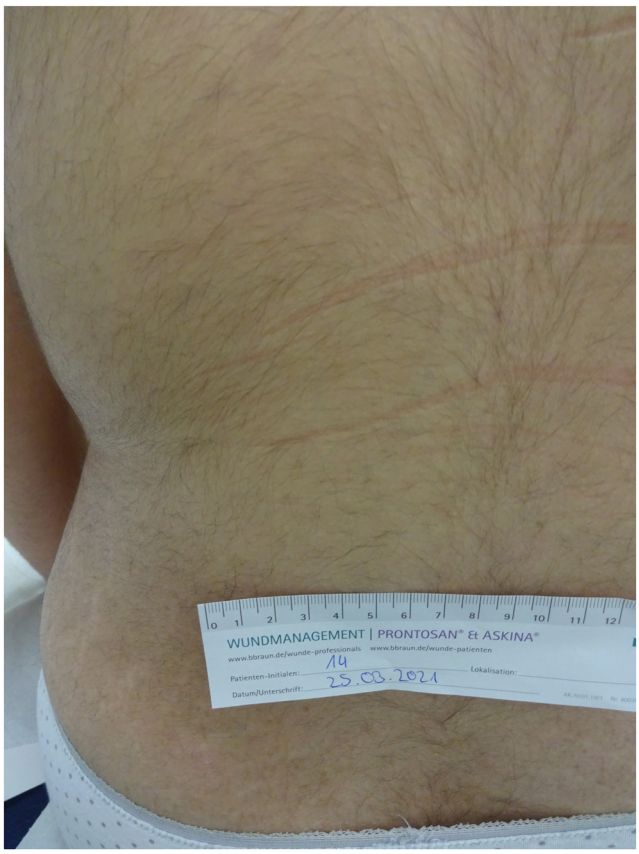

Figure 5
Typical skin changes of striae distensae and accompanying hirsutism in a teenage girl with type 2 diabetes mellitus and polycystic ovarian syndrome.

Eruptive xanthomas (15, 19): Xanthomas are observed in patients who have uncontrolled or poorly managed diabetes with hypertriglyceridemia, as well as in individuals who abuse alcohol excessively even with controlled diabetes. Clinically, reddish-yellowish, grouped papules on a slightly erythematous base are found mainly on the hips, back and extensor sides of the extremities. Treatment of the underlying disease is excision, curettage or laser therapy.

Lichen planus (15, 24, 25): In the context of lichen ruber planus, a cellular autoimmune reaction against basal keratinocytes leads to the formation of inflammatory, red and intensely pruritic, slightly shiny papules that tend to aggregate. In up to 50% of cases, the oral mucosa is also affected showing reticular whitish plaques on the buccal mucosa. The nails may also be affected revealing onychodystrophy or pterygium, for example. About 25% of adult patients with lichen ruber suffer from diabetes mellitus, but the disease is also associated with other autoimmune diseases and hepatopathies. Spontaneous regression may occur within 6–12 months. Malignant transformation has rarely been observed in adults with a chronic course of oral lichen ruber. Glucocorticosteroids, acitretin, cyclosporin A, methotrexate, azathioprine and PUVA are used therapeutically.

Acanthosis nigricans (15, 19, 26): Blurred, two-dimensional, grey-brownish to dark brown, flat hyperkeratoses are found in symmetrical distribution, especially in the axillary region and the head and neck areas (Fig. 4 and 5). The cause is thought to be an elevated insulin level due to a defect or absence of the insulin receptor, leading to keratinocyte proliferation. Acanthosis nigricans occurs hereditarily in insulin-resistant diabetes mellitus (often accompanied by hypertension), while the acquired form is often encountered in patients with metabolic syndrome (obesity magna). In rare cases only, it is also associated with neoplasia (especially adenocarcinoma of the gastrointestinal tract), so that neoplasia should always be excluded when the disease is present in adult patients. The so-called 'finger pebbles' are considered to be an acral variant of acanthosis nigricans: a seeding of tiny flat papules on the extensor sides of fingers and toes. The expression can increase or decrease depending on the blood sugar level.

Vitiligo (27): Vitiligo is a common skin disease with a worldwide point prevalence of just over 0.5%. The pathogenesis is multifactorial. Cytotoxic reactions against melanocytes in the context of autoimmune processes and

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an increase in intracellular H_2O_2 levels are the main causes. An association with numerous other autoimmune diseases is suspected. However, only Hashimoto's thyroiditis and Graves' disease are confirmed concomitant illnesses in about 30% of affected individuals. Vitiligo rarely occurs in the presence of diabetes mellitus alone, and no causal relations between the two diseases have been established. Clinically, sharply delineated whitish macules are found, sometimes accompanied by depigmented scalp and beard hair (poliosis), nail changes (pachyonychia) or perilesional depigmentation of melanocytic nevi (halo nevus). Therapy is generally difficult, although recent investigations have reported an at least partial response to topical tacrolimus ointment.

Yellow nail syndrome (24): The syndrome is very rare, and the connection with diabetes mellitus is questionable. There is a yellowish to grey-greenish discolouration, and thickening of individual or all nails, lymphedema of the legs (approximately 80%) and chronic respiratory diseases are further symptoms of this syndrome. The yellowish nail discolouration is possibly caused by non-enzymatic glycation. More often, the discolouration occurs as a solitary symptom in diabetics. Onychomycosis should always be considered as a differential diagnosis and ruled out by mycology. Spontaneous improvement up to complete remission is not infrequently observed. Vitamin E and fluconazole are used therapeutically, although controlled therapeutic studies have not been performed so far.

Particular rare forms of diabetes and skin lesions

Congenital/neonatal diabetes

Transient neonatal diabetes mellitus, or TNDM, is the most common form of neonatal diabetes mellitus. The diabetogenic metabolic state usually normalises by the 18th month of life. Diabetes that occurs within the first month of life and persists for more than 14 days is called neonatal diabetes mellitus. If the diabetes is only transient, the condition is called TNDM. If it remains permanent, it is called permanent neonatal diabetes mellitus. Neonatal diabetes is classified as ADA (American Diabetes Association) class 3 and is a form of maturity onset diabetes of the young (MODY). The exact incidence of TNDM is currently unclear. Presumably, the condition occurs in 1:95,000 to 1:400,000 live births and is therefore very rare. The exact cause of TNDM is currently (2020) unknown. The HLA types DR3 and DR4, which are characteristic of diabetes mellitus type 1, are often found. In 30–40%, there is a positive family history (28, 29).

Depending on the pathogenesis, a distinction is made between three forms (Table 1).

Skin manifestations

In neonatal diabetes, intrauterine growth retardation is common and is usually associated with low birth weight. Basically, there are no typical skin signs in this condition, although dry skin related to dehydration or macroglossia, omphalocele and various accompanying craniofacial dysmorphia can be noted only by inspection of the child when evaluating the visual aspect.

Maturity onset diabetes of the young

Maturity onset diabetes of the young (MODY) is based on mutations of genes that are needed in glucose metabolism. Inheritance is usually monogenic autosomal dominant. MODY already manifests itself in childhood or adolescence and is not yet insulin dependent in the beginning. The proportion of MODY diabetics among all diabetics is 2–5%. The following heterogeneous gene mutations can lead to the MODY phenotype (Table 2).

Skin manifestations

No specific or disease-indicating stigmata, dysmorphic signs or other skin affections have been described for the

Table 1 Overview of the variant types of TNDM including the affected gene focus and localisation.

Type of congenital diabetes	Affected gene	Localisation	Frequency
TNDM 1	PLAGL1 and HYMAI genes	Associated with aberrations in chromosomal region 6q24.	70%
TNDM 2	Activating, autosomal, dominantly inherited mutations in the ABCC8 gene	Chromosome 11	N/a
TNDM 3	Activating, autosomal,dominantly inherited mutations in the KCNJ11 gene	Chromosome 11	N/a

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Table 2 Different types of MODY diabetes including the affected gene focus, its localisation, and frequency.

Type of MODY	Affected gene	Gene localisation	Frequency
MODY 1	HNF4A (hepatocyte nuclear factor-4-alpha), hepatic transcription factor	Chromosome 20 q13.12	5% of cases
MODY 2: chromosome	Glucokinase	7 p13	10–15% of cases, but the commonest subtype of monogenic diabetes in the paediatric diabetes clinic (27)
MODY 3	HNF1A (hepatocyte nuclear factor-1-alpha), hepatic transcription factor	Chromosome 12 q24.2;	With 65% of cases, the most common form of MODY in Europe that results in familial symptomatic diabetes; manifestation occurs in early puberty
MODY 4	PDX1 (pancreas/duodenum homeobox protein-1)	Chromosome 13 q12.1	N/a
MODY 5	TCF2 (hepatic transcription factor-2), hepatic transcription factor	Chromosome 17 cen-q21.3	N/a
MODY 6	NEUROD1 (neurogenic differentiation 1)	Chromosome 2 q32	N/a
MODY 7	KLF11 (Krueppel-like factor 11)	Chromosome 2 p25	N/a
MODY 8: chromosome 9 q34	CEL (carboxyl ester lipase)	Chromosome 9 q34	N/a
MODY 9	PAX4 (paired box gene 4)	Chromosome 7 q32	N/a
MODY 10	INS (insulin gene)	Chromosome 11 p15.5	N/a
MODY 11	BLK (B-lymphoid tyrosine kinase)	Chromosome 8 p23	N/a
PNDM	Permanent neonatal diabetes mellitus; activating mutations in ABCC8 or KCNJ11 gene	Chromosome 11	N/a
TNDM	Transient neonatal diabetes mellitus	Among others due to imprinting defects on chromosome 6	N/a

different forms of MODY diabetes. This, coupled with its rarity, makes the diagnosis particularly difficult (28).

Alström syndrome

Alström syndrome is a rare hereditary disease characterised by a variety of symptoms. These include, among others, photophobia and increasing blindness of the patients, metabolic disorders and sensorineural hearing loss. In addition, several organ systems, such as the heart or kidney, can be affected. Alström syndrome is a very rare disease. About 270 cases have been described in the literature so far (2017). Alström syndrome is inherited in an autosomal recessive manner. The cause of the disease is a mutation in the ALMS1 gene at gene location 2p13.1. Normally, this gene encodes a protein located in the centrosome of almost all body cells. For this reason, Alström syndrome is classified as a ciliopathy. The exact function of the ALMS1 protein is still unknown today (2017). The first symptom of Alström syndrome is usually photophobia and nystagmus shortly after birth. Progressive visual loss due to dystrophy of the retina with blindness of the children by the age of 12 also occurs. Mild-to-moderate sensorineural hearing loss follows in most cases by the age of 6. Endocrine l abnormalities include hyperinsulinaemia, hyperthyroidism or hypothyroidism, high androgen levels in femalesand low testosterone levels in males and marked obesity. Other problems include cardiac abnormalities such as dilated cardiomyopathies, progressive heart failure and slowly progressive renal failure coupled with haemorrhagic urinary tract infections and hypogonadism in males with infertility. The diagnosis of Alström syndrome is made on the basis of the constellation of symptoms. In about half of all cases, the diagnosis can be confirmed by genetic testing with detection of the mutation in the ALMS1 gene (30, 31).

Skin symptoms

There is no specific skin change associated with Alström syndrome However, acanthosis nigricans associated with the typical marked obesity, often accompanied with short stature and scoliosis, can be seen by visual inspection. Alström syndrome patients usually present with early baldness. The underlying mechanism is completely unknown. The combination of baldness and high insulin resistance is typical in both female and male patients with Alström syndrome.

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Bardet–Biedl syndrome

Bardet–Biedl syndrome (BBS) is a monogenetic hereditary disease belonging to the group of ciliopathies. The syndrome manifests itself with multiple malformations caused by mutations on different chromosomes or gene loci. BBS is a comparatively rare disease. The incidence is between 1:15,000 and 1:160,000. The damage can affect different genes. Fifteen genes have been identified so far (2014), including BBS1 to BBS8, BBS10 to BBS12, CCDC28B, CEP290, TMEM67, MKS1 and MKKS. Biochemical analyses of human BBS proteins have shown that BBS proteins organise into a common multiprotein complex called a 'BBSome'. BBSomes are thought to be responsible for transporting intracellular vesicles to the base of cilia. How the mutations occur has not yet been clarified. Incest promotes the occurrence of the hereditary disease. Inheritance is autosomal recessive – consequently, only homozygous carriers of the mutation contract the disease. BBS is associated with marked obesity, diabetes mellitus, short stature and hypogonadism.

Skin changes

On visual inspection, syn- and polydactyly occur frequently in BBS. Apart from the typical manifestations of insulin resistance and the onset of diabetes and obesity, no specific skin manifestations are known.

Wolfram syndrome

Wolfram syndrome is a rare neurodegenerative hereditary disease with a functional disorder of the endoplasmic reticulum. Characteristic symptoms are diabetes insipidus, diabetes mellitus, optic atrophy and deafness, which also gave rise to the acronym DIDMOAD syndrome. The mode of inheritance is autosomal recessive. The cause is mutations of the genes WFS1, WFS2 or CISD2 on chromosome 4. WFS1 with the gene locus 4p16.1 consists of eight exons and is clearly more frequently affected. Mutation analyses show an increased probability of occurrence of mutations on exon 8. The WFS1 gene codes for the glycoprotein tungramine in the ER. This consists of nine transmembrane segments and is involved in calcium homeostasis. It presumably functions as a calcium channel. Dysfunction of the protein causes increased cytosolic calcium concentration with subsequent hyperactivity of the enzyme calpain 2. This most likely causes the gradual demise of beta cells and neurons and is accompanied by characteristic phenotypic features. The main clinical features of Wolfram syndrome are juvenile diabetes mellitus (without autoimmunity or HLA association) and optic atrophy in the first decade of life. Bilateral optic atrophy manifests as reduced visual acuity and loss of colour vision. Later, sensorineural hearing loss and diabetes insipidus occur. The disease is progressive and often leads to premature death due to respiratory failure (32, 33, 34).

Skin manifestations

Again, no typical skin manifestations are associated, but visual inspection reveals that patients are often dystrophic and short in stature. There is also ptosis and progressive testicular atrophy.

Other skin changes in endocrine disorders associated with altered insulin action or release

polyglandular autoimmune syndrome type 1

Type 1 polyglandular autoimmune syndrome, also known as autoimmune polyendocrinopathy–candiditis–ectodermal dystrophy (APECED), is a rare immunodeficiency syndrome caused by a mutation in the autoimmune regulatory gene. It is characterised by chronic mucocutaneous candidiasis (CMC), hypoparathyroidism, adrenal insufficiency and primary hypogonadism (35).

CMC is a characteristic feature of APECED. It is usually the first symptom of the disease (about 60% of patients), appearing in early childhood as candida-induced diaper dermatitis, mucositis and onychomycosis. Candidiasis affects all patients under 40 years of age and can be oral, cutaneous, gastrointestinal or genitourinary. Hyperpigmentation may occur in patients with adrenal insufficiency, although adrenal insufficiency is present in only about 5% of cases. In addition, people with APECED often have autoimmune and other diseases, which may include dentin hypoplasia, keratoconjunctivitis, urticarial eruptions, alopecia areata or vitiligo (36).

IPEX (immune dysregulation polyendocrinopathy enteropathy) syndrome

IPEX syndrome is a life-threatening, congenital, autoimmune disease with multiorgan impairment (e.g. intractable diarrhoea, endocrinopathies, dermatitis and immunodeficiency). It is one of the autoimmune polyendocrine syndromes and is caused by mutations

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in the FOXP3 gene, which codes for the forkhead box protein P3. This protein regulates the development and function of regulatory T cells (CD4+ and CD25+). As a consequence, the skin develops severe inflammatory symptoms, leading to neonatal or early infantile erythrodermy. Affected babies present with generalised scaling and erythema, chronic and debilitating pruritus and frequent skin infections. The disease is inherited in an X-linked recessive manner. Without early diagnosis and treatment, the course of IPEX syndrome is usually fatal within the first 2 years of life. Some patients survive into childhood. The only curative therapy at present (2019) is autologous haematopoietic stem cell transplantation (HSCT), especially in the early stages of the disease. HSCT significantly increases life expectancy. Supportive measures are immunosuppressive therapies with systemic glucocorticoids, cyclosporine A, tacrolimus, sirolimus and azathioprine. If necessary, insulin and thyroid hormones are substituted. In severe cases, parenteral nutrition is usually necessary (37).

Skin changes in other rare endocrinopathies

Carney complex (CNC) is a medical condition characterized by the development of multiple myxomas, which are benign tumors that can occur in different parts of the body. In addition to myxomas, people with CNC may also experience hormonal imbalances, skin pigment spots, and occasionally malignant neoplasms. It is a syndrome with patchy pigmentation of the skin, hormonal overactivity and myxomas. Skin pigmentation abnormalities include lentigines and blue nevi. The prevalence of CNC is not known, but it is a rare disease with about 160 index cases described to date. The most common symptoms from the endocrine side are acromegaly, thyroid and testicular tumours and Cushing's syndrome (CS) independent of adrenocorticotropic hormone (ACTH). One of the putative CNC genes (PRKAR1A) is located in chromosomal region 17q22-q24 and encodes the regulatory subunit (R1A) of protein kinase A. Heterozygous inactivating mutations in the PRKAR1A gene have been found in 45–65% of CNC index cases. But they may be present in 80% of families in which the disease manifests mainly as CS. The most common treatment for CS caused by PPNAD is bilateral adrenalectomy.

Type 1 endocrine neoplasia multiplex

Multiple endocrine neoplasia type 1 (MEN1) is a disease caused by the inactivation of the tumour-suppressor gene menin (*MEN1*) and is inherited in an autosomal dominant manner. MEN1 is characterised by parathyroid adenomas, pancreatic islet cell tumours and anterior pituitary tumours (10). The estimated incidence is 1–10/100,000 (38). The most common functional enteropancreatic tumour in MEN1 is gastrinoma, which may arise from the pancreas or duodenum. Up to 80% of patients with MEN1 have either multiple gastric ulcers due to gastrin-stimulated increased secretion of gastric acid or asymptomatic elevated gastrin levels. Insulinomas are the second most common functional pancreatic tumour and can precipitate hypoglycaemia. The tumours are often small and varied. The age of manifestation is often < 40 years.

Skin manifestations

To diagnose MEN1, the presence of cutaneous lesions is included as one of the criteria. If a person has two or more of these criteria, it is considered diagnostic. However, if there is a family history of MEN1, only one cutaneous lesion is required for diagnosis (38). Cutaneous lesions in MEN1 patients include angiofibromas, collagenomas and lipomas. In a 1997 study of skin lesions in MEN1 patients, angiofibroma was found to be the most common skin manifestation, with a prevalence of 88% in MEN1 patients, and most commonly occurring on the face. These lesions were described as 'telangiectatic, skin-coloured, pink or light brown papules'. Collagenomas were found in 72% of patients and were 'skin-coloured or slightly hypopigmented, dome-shaped, well-circumscribed, firm, round or oval papules', usually occurring on the upper trunk, neck and shoulders. Lipomas were present in 34% of patients and were located on the trunk, limbs and scalp. Café-au-lait-macules were observed in 38% of patients but were not considered diagnostically significant. Other manifestations included hypopigmented confetti-like macules (6%) and gingival papules (6%).

Type 2 endocrine neoplasia multiplex

Multiple endocrine neoplasia type 2 (MEN2) is a consequence of proto-oncogene activating mutations in *RET*. Multiple endocrine neoplasia, type 2A (MEN2A) is a hereditary syndrome characterised by medullary carcinoma of the thyroid, pheochromocytoma, parathyroid hyperplasia or adenomas (causing hyperparathyroidism) and occasionally skin lichen amyloidosis. The clinical presentation depends on the glands involved. Hereditary medullary thyroid carcinoma

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is a distinct variant of MEN2A. Diagnosis includes genetic testing. Hormone determinations and imaging techniques are used to localise the tumours. If possible, surgical removal of the tumours is performed. Medullary thyroid carcinoma and pheochromocytoma are common in both MEN2A and MEN2B. In addition, parathyroid adenomas are common in MEN2A (10–15%) and mucinous neuromas in MEN2B (39).

Skin manifestations

MEN2A is associated with cutaneous lichen amyloidosis which is estimated to occur in 51% of cases. These lesions are usually located between the scapulae or on the extensor surface of the limbs. Pruritus usually is the initial symptom due to the deposition of an amyloid-like substance. This leads to scratching of the affected areas, resulting in rather characteristic scaly, pigmented and papular skin lesions. MEN2B is associated with mucosal neuromas. These appear as warty papules and nodules. They may also be present on the inner eyelid, causing thickening, or on the lips and on the anterior third of the tongue and the oral mucosa (40).

Pseudohypoparathyroidism

In pseudohypoparathyroidism (PHP), symptoms of parathyroid hypofunction (hypoparathyroidism) appear without a deficiency of parathyroid hormone (PTH) in the blood. The parathormone effect is absent due to phasic or permanent disturbances at the parathormone receptor or intracellular signalling cascades. A familial accumulation indicates that genetic causes refer to a group of disorders characterised by inactivating mutations of GNAS (guanine nucleotide binding protein, alpha stimulating; which encodes for the Gs alpha unit of the G-protein-coupled receptor). Clinically, it involves a failure of the end organ (kidney and bone) to respond to PTH. These syndromes may present the phenotype of hereditary Albright's osteodystrophy (AHO) or a normal phenotype. Patients with AHO often present with hypocalcaemia, hyperphosphataemia and elevated PTH.

Skin manifestations

Short stature, obesity, brachydactyly and s.c. calcifications are characteristics of the AHO phenotype (41). The skin may be dry, scaly, hyperkeratotic and oedematous in PHP. In addition, thinning of the skin and s.c. tissue may occur. Nails may be dull and brittle and usually present a transverse ridge. Loss of scalp and body hair may occur. Eczematous and hyperkeratotic dermatitis and maculopapular eruptions have also been reported.

Cushing's syndrome

CS is characterised by a cluster of clinical features caused by chronic glucocorticoid excess. Cortisol excess can be either ACTH dependent or ACTH independent. Depending on the cause, CS can be caused by (i) hypersecretion of ACTH from the pituitary gland (Cushing's disease), (ii) ectopic secretion of ACTH from non-pituitary tumours and (iii) excessive secretion of cortisol from the adrenal glands.

Skin manifestations

The most common sign of glucocorticoid excess is central obesity of the face, neck, body and abdomen, producing a typical cushingoid appearance. Fat deposits on the cheeks produce the classic facial mottling (moon face) and are often accompanied by s.c. fat deposits on the back and neck (buffalo hump). Excess cortisol inhibits collagen synthesis, resulting in skin atrophy and easy bruising after minimal trauma. Patients with CS may also have purplish (purple) and broad (>1 cm in diameter) striae on the abdomen and lower flanks. In addition, hyperpigmentation may also occur in patients with chronic ACTH-dependent CS (ectopic ACTH syndrome is more common than in patients with pituitary ACTH hypersecretion).

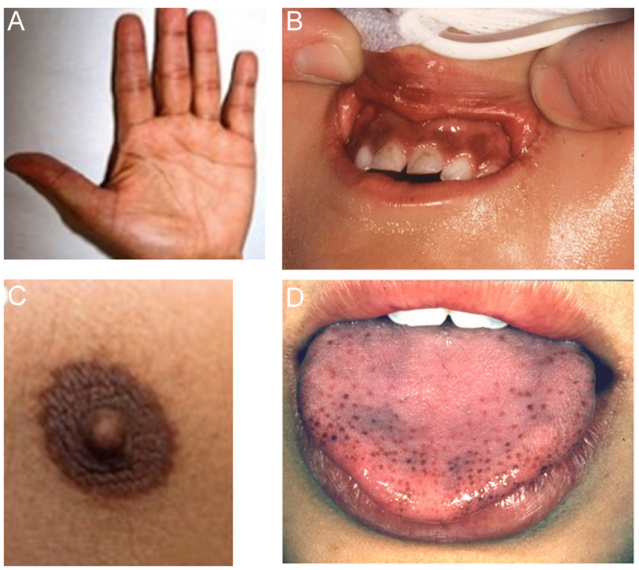

Figure 6
Characteristic skin lesion in a girl with Cushing's syndrome. In addition to the facial mottling with incipient acne vulgaris, there is also an accumulation of fat in the neck area.

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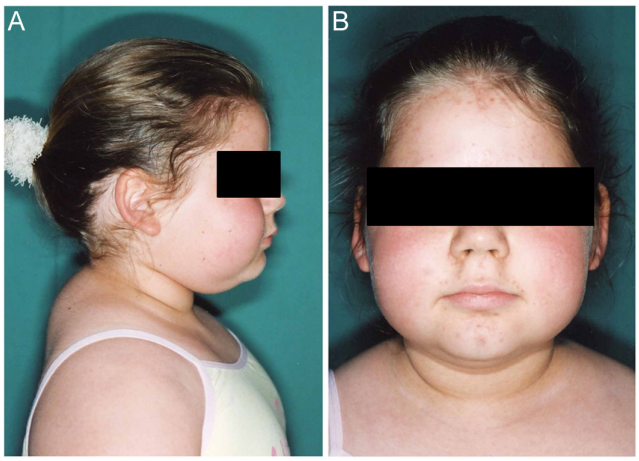

Figure 7
Classic skin changes that are indicative of hyperpigmentation, for example in the context of adrenal insufficiency. The hyperpigmentation can manifest itself all over the body. Here is an example on the hands (A), the gums (B), the nipple (C) and the tongue (D).

Other cutaneous manifestations include acanthosis nigricans due to insulin resistance (42, 43) (Fig. 6).

Primary adrenal insufficiency

Primary adrenal insufficiency is a condition in which the adrenal glands no longer produce cortisol. The most common cause is Addison's disease, an autoimmune disease of the adrenal glands (44).

Skin manifestations

Hyperpigmentation of the skin and mucous membranes is the most important dermatological sign in Addison's disease and occurs in >90% of patients. It arises secondary to cortisol deficiency causing an increase in ACTH and melanocyte-stimulating hormone, which increases melanin synthesis (Fig. 7). Hyperpigmentation occurs mainly in sun-exposed areas and areas with increased friction. Patients may have darker hair and nail colour. Hyperpigmentation may disappear once patients are adequately treated with a corticosteroid. Patients with Addison's disease are at increased risk of other autoimmune diseases, including vitiligo, which occurs in approximately 10% of patients (45).

Conclusion

In summary, one can try to classify the skin manifestations in endocrine disorders and diabetes diseases according to a certain pattern. In the relatively common type 2 diabetes, in addition to typical changes such as acanthosis nigricans or therapy-associated peculiarities of the skin, rare skin symptoms such as necrobiosis lipoidica can also occur. These rare skin symptoms must also be recognised and correctly interpreted by the treating diabetes specialist. On the other hand, certain skin symptoms can also be indicative of a certain condition underlying the organism. Here, perfidious knowledge of the skin affections of even rare forms of diabetes and endocrinopathies is important in order to accelerate the diagnosis and not to allow any misdiagnosis. Further knowledge of skin afflictions in rare forms of diabetes and endocrinopathies is of enormous importance to counter this phenomenon. Further collaborative sharing opportunities, such as those offered by virtual platforms like ENDO-ERN, are desirable to optimise this process of learning from each other.

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