 doi:10.20944/preprints202101.0570.v1

Review

Skin involvement in paediatric patients with type 1 diabetes

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Abstract

Skin involvement is an overlooked aspect in the management of paediatric patients with type 1 diabetes. A comprehensive search of published literature using the PubMed database was carried out using the following key terms: “children”, “pediatric/paediatric patients”, “skin”, “skin disorders”, “type 1 diabetes”. Dermatological side effects are frequently observed among diabetic children and adolescents. Insulin-induced lipodystrophies and allergic contact dermatitis caused by insulin pumps or glycaemic sensors are the most common skin reactions in these patients. Furthermore, several diabetes-associated skin diseases such as necrobiosis lipoidica, granuloma annulare, vitiligo, and bullosis diabeticorum may already be present in paediatric age. Paediatric diabetes specialists should pay attention to their patients’ skin so as to recognize these disorders, identify the potential causes, and choose the most suitable treatment. Finally, the evaluation of skin concentrations of advanced glycation end-products using non-invasive diagnostic techniques may be used to assess the risk of chronic complications of diabetes as early as adolescence.

Keywords

Advanced glycation end-products, contact dermatitis, granuloma annulare, insulin, lipoatrophy, lipohypertrophy, necrobiosis lipoidica, skin autofluorescence.

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1. Introduction

Type 1 diabetes (T1D), previously defined "insulin-dependent diabetes" or "juvenile-onset diabetes", is a chronic disease caused by cellular-mediated autoimmune destruction of the pancreatic β-cells leading to absolute insulin deficiency (1). T1D is one of the most common endocrine disorders in childhood and adolescence, and its incidence is progressively increasing worldwide (2). Diabetes management is based on intensive insulin therapy, regular physical activity, healthy nutrition, and close glucose level monitoring. Intensive insulin treatment has the role of mimicking normal insulin secretory patterns using a combination of basal and bolus insulin by multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) (3). The introduction of real-time continuous glucose monitoring (CGM) systems has remarkably improved the way glucose levels are monitored. CGM systems are minimally invasive devices that use a subcutaneous sensor to measure changes in interstitial glucose values (4). Integration of CGM with CSII devices has led to the development of algorithm-controlled pumps, which work as hybrid closed loop systems that can both suspend insulin delivery to prevent hypoglycaemia and automatically administer additional insulin to correct hyperglycaemia (5).

Despite recent advances in the management of T1D, skin involvement still remains one of the most overlooked aspects in the approach to paediatric patients with T1D. Dermatological complications due to insulin injections or adhesives used to hold insulin pumps and glucose sensors in place on the patient skin are quite frequent (6,7). Some rare skin diseases have been reported to be associated with T1D in children and adolescents (8,9). Finally, skin concentrations of advanced glycation end products (AGEs) have been correlated with the occurrence of microvascular and macrovascular complications, including cardiovascular disease in patients with T1D (10).

In this manuscript, we provide an updated review of literature focusing on: i) cutaneous complications due to insulin therapy and CGM devices, ii) skin disorders that may be associated with T1D, iii) the role of skin AGEs as a potential predictive marker of microvascular and macrovascular complications in diabetes. To accomplish this, we performed a comprehensive

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search of published literature using the PubMed MEDLINE database up to December 2020. We used the following combination of keywords: “children”, “pediatric /paediatric patients”, “skin”, “skin disorders”, “type 1 diabetes”. English-language articles which were available as full-text were included. Particular emphasis was placed on all high-quality studies (randomized controlled studies, observational studies, reviews, and meta-analysis).

2. Lipodystrophy

Lipodystrophy is a common complication in insulin treated patients, which could affect insulin absorption and cause unexplained brittle glycaemic control (11). Lipodystrophy includes two main subtypes, lipohypertrophy and lipoatrophy *(Figure 1)*. The exact pathophysiological mechanism of insulin-induced lipodystrophy remains unknown. Improper injection technique is considered to be a major cause of the occurrence of this skin complication. Several data demonstrate that there is a large gap between patient practices of insulin administration techniques and guideline recommendations (12–14). Although insulin-induced lipodystrophy is quite frequent among paediatric and adult patients suffering from T1D, awareness of this issue is still inadequate among healthcare professionals (15).

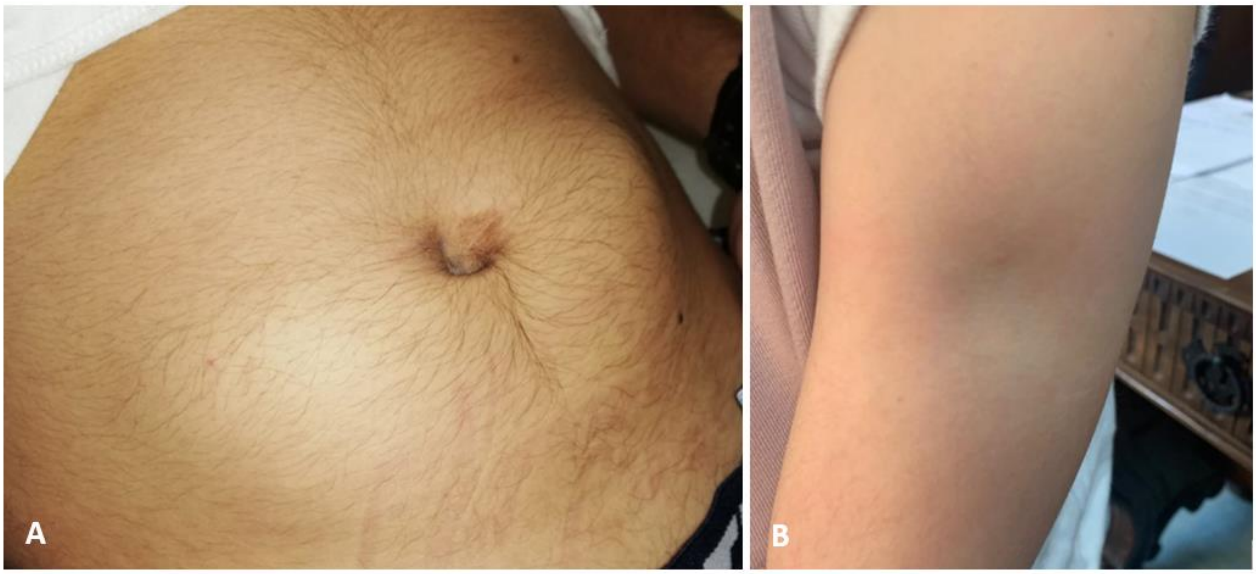

Figure 1. In A, insulin-induced lipohypertrophic areas located on both sides of the abdomen in a 15-year-old male patient treated with multiple insulin injections. In B, a lipoatrophic area

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appeared on the application site of continuous subcutaneous insulin infusion on the left arm of a 9-year-old patient

2.1. Lipohypertrophy

Lipohypertrophy (LH) is characterized by the appearance of a thickened, swollen lesion in the adipose tissue around subcutaneous insulin injection sites (16,17). Histologically, the hypertrophic adipocytes appear twice as large as those from normal subcutaneous areas and contain several small lipid droplets (18). According to numerous studies conducted on paediatric patients treated with MDI therapy, the prevalence of LH varies from 39% to 60.6% (18–22). Arms seem to be the most common site for LH as they are usually the preferred site of insulin injection among children (20,21).

Over time, areas of LH become hyposensitive, hence patients tend to inject insulin at the same site as it becomes painless. Lack of regular rotation of insulin injection sites and use of small injection areas are the most relevant factors associated with the occurrence of LH (21,23). Some authors have revealed the association between LH and body mass index (20,24). Particularly, LH has been reported to be less common in obese and overweight patients. However, this finding could be distorted by the fact that LH areas are more easily seen in normal or lean patients. Indeed, detection of LH requires both careful examination and palpation of injection areas as some lesions can be more easily felt than seen (25). Recently, Barola et al. (23) have demonstrated that patients treated with regular insulin plus long-acting analogues had a 3.2-fold higher risk of LH than rapid plus long-acting analogues users with the same mean injection frequency. These authors hypothesized that rapid-acting insulin analogues with their improved pharmacokinetic actions could spare adipocytes from the lipogenic action (23).

Although the occurrence of LH is more frequently related to MDI therapy, children and adolescents using insulin pump therapy may also experience this dermatological side-effect. Recently, some authors reported that LH occurs in approximately 20% of paediatric patients treated with CSII (26,27).

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Insulin administration in LH areas leads to inconsistent absorption, with the potential for worsening of glycaemic control, as demonstrated by several studies that have shown higher glycated haemoglobin (HbA_1c) values in patients with LH (18,19,21,23). LH may also be considered a rare cause of diabetic ketoacidosis in paediatric patients (28). Gupta et al. (22) also reported a significant association of LH with unexplained hypoglycaemia rate and glycaemic variability as assessed by ambulatory glucose monitoring. Finally, a prospective multicentre study demonstrated that LH does not adversely impact the accuracy of CGM sensors (29).

Topical application of specific gel on the LH area might be considered to reduce the swollen lesion. However, emphasizing the concept of injection site rotation at each outpatient ambulatory visit is paramount to prevent the occurrence of LH.

2.2. Lipoatrophy

Lipoatrophy (LA) is clinically characterized by evident cutaneous depression and palpable atrophy of subcutaneous adipose tissue at the insulin injection site (18). The development of LA may be the result of an immune-mediated inflammatory response to insulin or excipients of the injection solutions (30). Histological examination may reveal increased mast cell infiltration in lipoatrophic areas. Degranulation of mast cells mediates the inflammatory process characterized by local production of pro-inflammatory cytokines such as tumour necrosis factor-α (TNF- α) and interleukin-6. This process may induce de-differentiation of adipocytes in the subcutaneous tissue, resulting in LA (31,32). Macrophages, lymphocytes, immunoglobulin (Ig)M, IgA, complement component 3, fibrinogen and fibrin have also been isolated from areas of LA (33).

In the past, this condition affected 10% to 55% of patients treated with non-purified bovine/porcine insulin preparations (34). Since the 1950s, the prevalence of LA has drastically decreased due to the introduction of human purified insulin. In recent years, LA has been associated with insulin analogues (e.g. Lispro, Glargine, Detemir, Aspart) (35–37). Cases of LA have also been reported in patients treated with CSII using rapid insulin analogues (38,39). A single-centre systematic evaluation of 678 children and adolescents with T1D revealed an LA prevalence of 2.4%

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(40). Another recent observational study found that LA was present in 3 out of 176 paediatric patients (1.7%) affected by T1D (18).

Salgin et al. reported that LA was associated with an increased risk of Hashimoto's thyroiditis and coeliac disease in female patients (41). These findings support the hypothesis that the development of LA may be caused by an autoimmune inflammatory mechanism that could be triggered by the subcutaneous administration of any insulin (42). The occurrence of LA has also been correlated with a longer diabetes duration (40). The association between LA and an increased risk of hypoglycaemic episodes is still debated.

Specific treatment of LA is currently unavailable. Changing between different insulin preparations, switching from MDI therapy to insulin infusion pump, local treatment with sodium cromolyn to prevent mast cell proliferation, subcutaneous administration of corticosteroid to inhibit the inflammatory process, are some therapeutic options used in case reports or in small series of affected patients (32,40,43). A controlled, randomized, open-label parallel study in young people with type 1 diabetes treated with CSII found that switching from the previous insulin analogue to the zinc-free insulin glulisine significantly reduced the prevalence and size of lipoatrophic areas over 12 months (44). However, further investigations in larger samples of people with T1D and LA are awaited to confirm this finding.

3. Allergic contact dermatitis

Allergic contact dermatitis (ACD) is a delayed-type hypersensitivity reaction caused by a T cell-mediated immune response to usually harmless substances. ACD is clinically characterized by the appearance of erythema, oedema, vesicles, oozing, and intense itch (45) *(Figure 2)*. ACD may occur after exposure to chemical agents included in the adhesives that hold insulin infusion sets, patch pumps, and CGM devices in place on patients' skin. Reactions typically require a long period of exposure to be induced but may occur more rapidly after persistent exposure due to reactivation of memory Th1 cells. Pre-existing skin diseases such as atopic dermatitis, recurrent taping at the

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same site of insertion, and careless removal of adhesive tapes are all factors that may increase the risk of developing ACD. Patch testing is crucial for diagnosing ACD and identifying the culprit allergen (46). However, this diagnostic investigation is not always feasible as the exact composition and preparation of adhesives used by various manufacturers are rarely available (6).

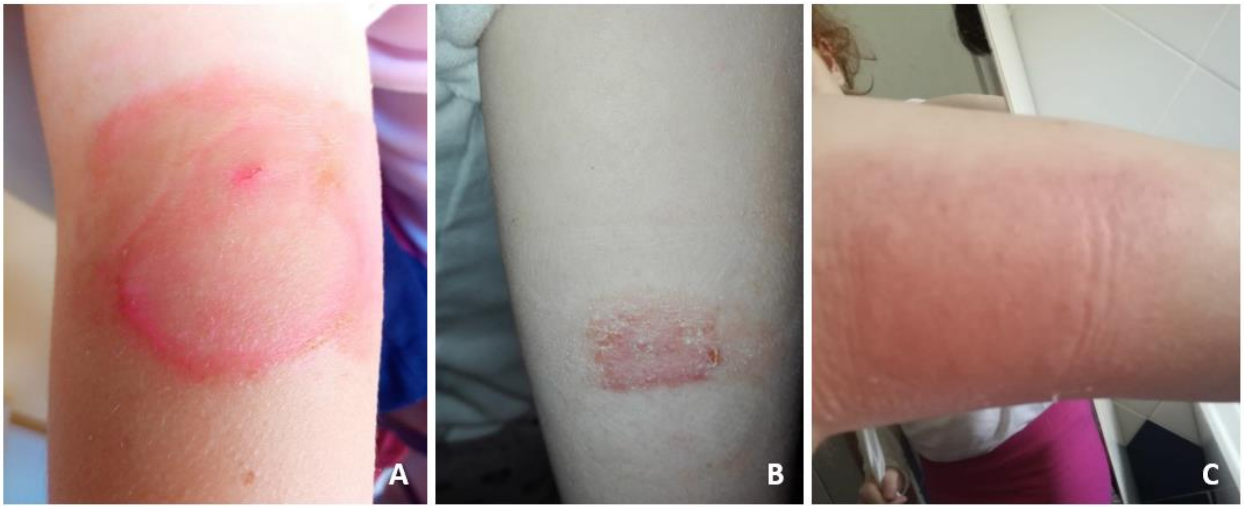

Figure 2. Three cases of allergic contact dermatitis caused by continuous glucose monitoring devices (A, C) and patch pump (B). All these patients wore diabetes management devices on their arms.

Although it is widely considered that ACD represents an emerging issue, the exact prevalence of contact sensitization among children and adolescents with T1D has not yet been well established. Recently, Lombardo et al. reported that ACD was present in 18 out of 215 paediatric patients (8.4%) using CSII and/or CGM devices (47). Another single-centre study showed a 5.5% prevalence of ACD among children using Freestyle Libre®, which is an intermittently scanned CGM device (48). The longer insertion time of these technological devices than in the past may allow the allergen to easily forward sensitization (49). In the last few years, several case reports and observational studies have been reported on paediatric patients with contact sensitization to chemical agents included in devices used for the management of diabetes *(Table 1)* (50–61).

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Table 1. Summary of case reports and clinical studies concerning allergic contact dermatitis caused by diabetes management devices in children and adolescents with type 1 diabetes.

Ref	Article type	Age	Type of device	Onset of dermatitis following the use of device	Sensitizer(s)
50	Case report	2 yrs	Glucose sensor	7 days	Ethyl cyanoacrylate
51	Case report	9 yrs	Glucose sensor	Unknown	Ethyl cyanoacrylate
52	Observational study (6 paediatric patients)	Mean age 9.6 yrs	Glucose sensor	Unknown	Isobornyl acrylate (66.6% of patients)
53	Case report	10 yrs	Both glucose sensor and insulin patch pump	5 months	Isobornyl acrylate
54	Case report	16 yrs	Both glucose sensor and insulin patch pump	2 months	Isobornyl acrylate
55	Case report	8 yrs	Glucose sensor	2 weeks	Colophonium
55	Case report	10 yrs	Insulin patch pump	6 years	Colophonium
56	Case report	8 yrs	Glucose sensor	Few days	Isobornyl acrylate
57	Observational study (16 paediatric patients)	Mean age 11.5 yrs	Glucose sensor	Unknown	Isobornyl acrylate in all patients and sesquiterpene lactones in 50% of patients
58	Observational study (30 paediatric patients)	Not available	Glucose sensors	Unknown	Isobornyl acrylate and colophonium
59	Observational study (18 paediatric patients)	Mean age 10.9 yrs	Glucose sensors and insulin pumps	From few weeks to more than 2 years	Colophonium in 41.1% of patients, butanediol 1-3 methacrylate and butyl acrylate in 5.5% of patients
60	Observational study (12 paediatric patients)	Mean age 11.5 yrs	Glucose sensor	From 2 months to 16 months	Isobornyl acrylate in 83.3% of patients, sesquiterpene lactone

					in 41.6% of patients, hydroxypropyl methacrylate, ethylacrylate, hydroxyethylacrylate, butyl acrylate, and colophonium in 8.3% of patients
61	Observational study (30 paediatric patients)	Mean age 8 yrs	Glucose sensors and insulin pumps	Unknown	Colophonium or its derivates* in 46.6% of patients, isobornyl acrylate in 16.6% of patients, butyl acrylate and ethyl cyanoacrylate in 3.3% of patients

* Abitol and abietic acid

Isobornyl acrylate (IBOA) and colophonium have been reported to be the most identified allergens. IBOA is a photopolymerizable acrylate monomer and is used, in its liquid form, in coatings, sealants, glues, adhesives, paints, and inks and also as a plasticizer in various plastic materials (62). It has qualities of hardness combined with flexibility, and impact resistance. IBOA can also be easily released into materials flowing over surfaces made from it (63). Colophonium is a natural substance derived from pine trees. Although the skin sensitizing and skin-irritant effects of colophonium are well known, the actual harmful components have not yet all been characterized. Abietic acid seems to be the most sensitizing among all its derivatives (59). Colophonium is commonly used, in both unmodified and modified forms, as a fast-acting adhesive for industrial, medical, or other commercial uses (64). Reactions to cyanoacrylate, N,N-dimethylacrylamide, butyl acrylate, butanediol 1–3 methacrylate, and sesquiterpene lactones have rarely been reported (47,50,57,65).

ACD also has a psychological impact on young patients with T1D and their parents since it is perceived as an additional burden for diabetes-specific emotional distress (66). Some patients need to switch from CSII to MDI therapy, others are forced to suspend CGM and to re-start the more

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annoying self-blood glucose monitoring (47). Furthermore, the persistence of ACD represents an impediment to the achievement of optimal glycaemic control (67).

Avoidance of the sensitizing allergen is the landmark of ACD treatment. However, identification of the harmful agents is not always possible, as discussed above. The application of various barrier agents to prevent hypersensitivity reactions has been proposed as an alternative approach to manage ACD caused by the adhesives of glucose sensors and insulin pumps. These protective agents may be used in the form of hypoallergenic (hydrocolloid and/or silicone-based) patches, and liquid or crème barriers (6). Unfortunately, these skin protective tolls are not very useful in the event of severe ACD (67). A recent observational study demonstrated the preventive effect of fluticasone propionate aqueous nasal solution, sprayed topically prior to CGM device insertion among youths with T1D (68). However, further studies are needed to evaluate the long-term safety and effectiveness of the use of this nasal steroid.

4. Type 1 diabetes-associated skin disorders

4.1. Necrobiosis lipoidica

Necrobiosis lipoidica (NL) is a chronic inflammatory granulomatous skin disease associated with collagen degeneration (9). It is clinically characterized by erythematous papules, which may slowly progress into yellow-brown, telangiectatic plaques with atrophic centre and raised violaceous borders (*Figure 3)*. Histological examination may reveal granulomatous inflammation of the subcutaneous tissue and blood vessels, thickening of capillary basement membrane, and obliteration of vessel lumen (69). NL usually appears on the lower extremities and more rarely on hands, fingers, face, and scalp (70). The prevalence of NL in paediatric age varies from 0.06% to 2.3% (71,72). It is estimated that almost two-thirds of patients with NL have or will develop T1D (69). The pathogenetic mechanism is still unclear. Immuno-complex vasculitis and collagen abnormalities have been described as potential promoting factors of this inflammatory granulomatous skin disease. A multicentre retrospective study on children, adolescents and young

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adults with T1D showed a strong correlation between hyperglycaemia and the occurrence of NL (73). Furthermore, tighter glucose monitoring seems to improve or prevent this skin disorder (74). Ulceration is the most frequent complication of NL occurring in 25-35% of cases. Rarely, squamous cell carcinoma may develop in the affected skin area (75). Differential diagnosis includes amyloidosis, erythema nodosum, granuloma annulare, lupus panniculitis, and sarcoidosis. There is currently no standardized effective treatment of NL. Topical, systemic or intra-lesional steroids, cyclosporine A, hydroxychloroquine, laser surgery, tacrolimus, and photochemotherapy with topical PUVA have been used over the years with conflicting results (76–80). Biological agents such as etanercept and infliximab have been suggested as an effective therapeutic alternative mainly in ulcerative NL unresponsive to prior conventional regimens (81). Spontaneous remission of NL is quite rare (69,70).

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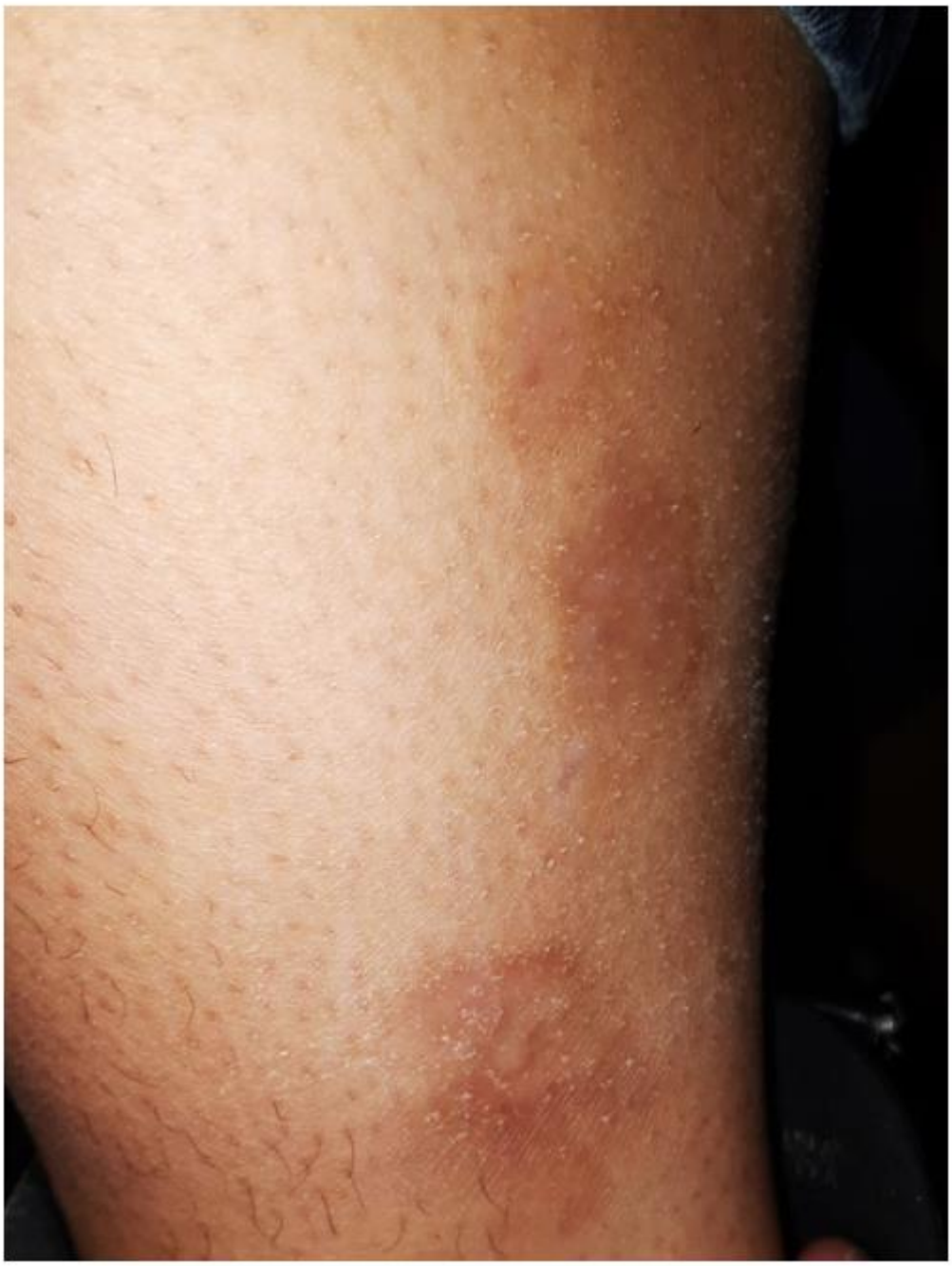

Figure 3. Telangiectatic plaques suggestive of necrobiosis lipoidica occurring in the lower left leg of a 14-year-old girl with type 1 diabetes.

4.2. Granuloma annulare

Granuloma annulare (GA) is the most common non-infectious granulomatous skin disease. It consists of painless, non-itchy erythematous plaques or papules arranged in an annular configuration that usually appear on the upper extremities (82). Skin lesions may also be

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localized on dorsal surfaces of the feet and other bony prominences (83). There are five different subtypes of GA characterized by distinct clinical features: localized GA, generalized GA, perforating GA, linear GA, and subcutaneous GA. Localized and subcutaneous GA can occur simultaneously and have been reported almost exclusively in young children (84). Lesions are histologically characterized by focal collagen degeneration, inflammation with interstitial histiocytes, and mucin deposition. A perivascular lymphocytic infiltrate admixed with eosinophils may also be present (85). So far, the aetiology of GA is unknown. Some authors have suggested a possible relationship to T1D, especially in childhood (86,87). Associations between GA and other autoimmune diseases such as autoimmune thyroiditis have also been reported (88,89). Therefore, GA development could be related to underlying immunological mechanisms. Differential diagnosis includes both malignant diseases (e.g. synovial sarcoma malignant peripheral nerves sheath tumour, malignant fibrous histiocytoma, and rhabdomyosarcoma) and benign diseases (e.g. hemangioma, nodular fasciitis, plexiform fibrohistiocytic tumour, and infantile myofibromatosis) (84). Sporadic cases of coexistence of GA and NL in paediatric patients with T1D have been described in literature, suggesting that these two skin disorders may share the same pathogenetic process (90). GA is a benign and usually self-limiting condition. Intralesional steroid injection is the first-line therapy for recurrent lesions. Other therapeutic approaches include phototherapy, hydroxychloroquine, TNF- α inhibitors, cryotherapy, and surgical excision. However, there appears to be no difference in the duration of lesions between untreated and treated patients (82).

4.3. Bullosis diabeticorum

Bullosis diabeticorum (BD), also known as diabetic bullae or bullous eruption of diabetes mellitus is a cutaneous disorder characterized by the sudden appearance of painless tense blisters or bullae within normal-appearing, non-inflamed skin (91). Bullae may be single or multiple, varying in size from a few millimetres to several centimetres and are distributed asymmetrically (92). Lesions usually occur on the distal portions of the body such as the feet,

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distal legs, hands, and forearms. They are rarely present on the trunk. Bullae contain a serous fluid, which may rarely be haemorrhagic (93). Histological examination reveals the presence of intraepidermal blisters with inconsistent levels of skin layer separation. Direct immunofluorescence staining is generally negative for C3, IgM, IgA, and IgG (91). The prevalence of BD varies from 0.16% to 2% among diabetic patients (93–95). It occurs more frequently in adults with a long duration of diabetes, but cases of BD have also been reported in young children with T1D (96,97). The relationship between poor glycaemic control and bullae development is controversial. Physical factors such as vibration, high temperature, and long-standing pressure on the proximal lower extremities seem to facilitate bullae formation (98). In patients with nephropathy, exposure to ultraviolet light has been hypothesized to be a risk factor for the occurrence of BD (93). Other causes of bullous lesions such as infectious skin disease, porphyria cutanea tarda, pseudoporphyria, epidermolysis bullosa acquisita, and localized bullous pemphigoid should be considered in the differential diagnosis (91). BD is more frequently a self-limited condition and blisters usually heal spontaneously within a few weeks. The most common complication is represented by infections of subcutaneous tissue, whereas osteomyelitis and tissue necrosis are very rare (93,99). Topical and systemic antibiotics may be used to prevent infections. Surgical management should be considered in the event of long persistence of bullae (100).

4.4. Vitiligo

Vitiligo is an acquired skin disease characterized by the selective loss of melanocytes resulting in depigmented macules and patches. It is the most common depigmenting disorder affecting 0.1%-2% of the population worldwide (101). Three different patterns of vitiligo exist: focal, segmental, and generalized. Focal and segmental vitiligo patterns are characterized by ≤ 10% body surface area involvement and have a stable clinical evaluation. Generalized vitiligo pattern involves > 10% of body surface area, has a bilateral and symmetrical distribution, and is clinically characterized by an alternation between remissions and relapses (102). According to

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recent advances in understanding of the pathogenesis, vitiligo is currently classified as an autoimmune disease (101). It has been estimated that 2% to 10% of T1D patients have vitiligo (103). So far, curative treatment is not available. Phototherapy is the most used therapeutic approach. Particularly, excimer is preferred for small areas and narrowband UVB is more useful for diffuse vitiligo. Phototherapy may also be combined with other medications such as steroids and topical calcineurin inhibitors (104).

5. Skin advanced glycation end-products

Advanced glycation end-products (AGEs) are the result of non-enzymatic reactions between sugar and amino groups of proteins (105). The accumulation of AGEs is physiologically accelerated in diabetic patients. The excessive production of AGEs caused by chronic hyperglycaemia has deleterious effects on endothelial tissue and has been hypothesized to be related to the development of macrovascular and microvascular complications of diabetes (106,107). The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study showed that skin concentrations of AGEs were associated with the progression of media-intima thickness (108). Therefore, skin AGEs have since been considered a potential marker for assessing the risk of chronic complications in patients with diabetes (10). Skin biopsy was the only diagnostic procedure to evaluate skin AGE accumulation until the advent of non-invasively techniques such as skin autofluorescence (SAF) and skin intrinsic fluorescence (SIF). The correlation between SAF and impaired renal function, neuropathy, and cardiovascular events in adult patients with T1D has been well documented (109–111). The evaluation of skin AGEs has also recently been investigated in children and adolescents suffering from T1D. Several studies reported that skin AGE levels were significantly higher in young people with T1D compared to healthy control group (112–114). Interestingly, accumulation of skin AGEs has also been demonstrated in children newly diagnosed with T1D compared to children without diabetes (112). The association between

SAF/SIF values and HbA1c has been debated. Although AGEs may be considered an alternative tool to provide information on cumulative hyperglycaemic states, van der Heyden et al. reported that some patients had an elevated SAF despite a HbA1c value within target, suggesting that genetic factors could influence the level of glycation of HbA1c or the production of AGEs (114). Conversely, other researchers found SAF/SIF to be associated with mean HbA1c over the preceding year (115–117). Indeed, skin AGEs reflect the memory of glycometabolic stress, thus skin AGE levels are more correlated with long-term HbA1c rather than concurrent HbA1c. SAF appears to increase faster in older adolescents (114,116). A recent cross-sectional study conducted on adolescents with T1D showed that higher SAF was associated with retinopathy, defined as the presence of at least one microaneurysm or haemorrhage using seven-field stereoscopic fundal photography, and cardiac autonomic dysfunction defined as abnormal standard deviation of mean normal-to-normal (NN) intervals for age and gender. Authors found no association between SAF and the other complication outcomes (peripheral nerve dysfunction, pupillometry abnormalities or elevated albumin excretion rate) (116). According to these findings, SAF could be considered a useful non-invasive screening tool to predict microvascular complications also in paediatric patients with T1D. However, longitudinal studies are awaited to confirm the role of skin AGE assessment as potential surrogate risk marker for chronic complications.

6. Conclusions

In recent years, the management of T1D has greatly improved due to the introduction of novel insulin analogues and technological devices that allow to maintain glycaemic levels within normal range for long periods throughout the day and, thus, reduce the risk of long-term microvascular complications. The skin of children and adolescents with T1D is increasingly stressed by subcutaneous insulin administration and the application of adhesives that connect insulin pumps and glycaemic sensors to their bodies. The prevalence of dermatological side

effects such as lipodystrophy and contact dermatitis is quite high in these patients and may hamper the achievement of optimal glycaemic control. Furthermore, T1D-associatied skin diseases (e.g. necrobiosis lipoidica, granuloma annulare, bullosis diabeticorum, vitiligo) may also appear in paediatric age. Paediatric diabetes specialists should familiarize themselves with these skin disorders to recognize them and choose the most suitable treatment. Therefore, physical examination of the patient's skin should be carefully performed at each outpatient visit. Finally, non-invasive diagnostic procedures such as SAF and SIF that measure skin concentrations of AGEs could be considered potential routine screening tests to evaluate the risk of chronic complications of diabetes as early as adolescence.

Author contributions: SP drafted and wrote the paper with the help of GS; FL conceived the study design and revised the paper.

Funding: This research received no external funding.

Informed Consent Statement: Informed consent was obtained by patients and their parents to the publication of pictures included in this paper.

Acknowledgments: Not applicable.

Conflict of interests: The authors declare no conflict of interest.

 doi:10.20944/preprints202101.0570.v1

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