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Diabetes Research
and Clinical Practicejournal homepage: www.elsevier.com/locate/diabresInternational
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Allergic contact dermatitis in pediatric patients with type 1 diabetes: An emerging issue

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ARTICLE INFO

Article history:

Received 29 October 2019

Received in revised form

20 January 2020

Accepted 18 February 2020

Available online 19 February 2020

Keywords:

Adhesives

Atopy

Colophonium

Contact allergy

Sensitization

Skin reactions

ABSTRACT

Aims: Aim of our observational study was to assess the prevalence of allergic contact dermatitis among children and adolescents with type 1 diabetes who use technological devices for diabetes treatment and its management. Secondary outcome was to identify possible clinical and/or demographic variables that could be associated to contact dermatitis.

Methods: Among a total of 215 patients using insulin pumps and/or glucose sensors followed-up at our Pediatric Diabetes Centre between January and September 2018, 64 patients were enrolled and 42 (19 male and 23 female) completed the study. Demographic and clinical features of the study population were statistically analysed. All the patients underwent patch testing with specific allergens belonged to resin and acrylate classes.

Results: Eighteen patients experienced skin reactions suggestive of allergic contact dermatitis, demonstrating a prevalence of 8.4%. None of the demographic or clinical variables were associated to skin reactions. Colophonium was the most identified sensitizing allergen (87.5% of the cases).

Conclusions: The rate of sensitization to allergens included into diabetes devices among pediatric patients is higher than commonly assumed. Well-designed studies are needed to better investigate the association between type 1 diabetes and allergic contact dermatitis. Moreover, we suggest that manufactures should supply detailed information about adhesives in order to avoid dermatological complications and consequently a worsening of disease management and patients' quality of life.

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1. Introduction

Dermatological complications represent one of the most current issues related to the use of diabetes devices, such as con-

tinuous subcutaneous insulin infusion (CSII), continuous glucose monitoring (CGM), flash glucose monitoring (FGM), sensor-augmented pump (SAP). Despite advancements in technology which led to optimize the management of type 1

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<https://doi.org/10.1016/j.diabres.2020.108089>

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diabetes (T1D), in the last few years diabetes specialists observed an alarming increasing rate of skin issues related to the use of devices which are connected to the body of diabetic patients [1]. Binder et al. recently reported that 43% of patients experienced skin complications related to insulin infusion sets (IIS) [2]. Another study conducted in 143 patients using CSII demonstrated that almost 90% of individuals experienced dermatological issues, including pruritus, wounds, and nonspecific eczema [3]. The most relevant skin reactions due to medical diabetes devices are scarring, lipodystrophy, irritant contact dermatitis and allergic contact dermatitis (ACD). Scarring manifests as small hypo- or hyperpigmented lesions of fibrous tissue [4]. Lipodystrophy includes lipohypertrophy, that is the consequence of an abnormal growth of subcutaneous adipose tissue, and lipoatrophy, that is a localized loss of subcutaneous adipose tissue. Lipohypertrophy is quite common among diabetic patients. Its exact etiology is not known, but the insulin itself with its strong growth-promoting properties and repeated trauma caused by insertion of IIS seem to play a fundamental role [5]. Lipoatrophy is caused by an adverse immunological response to insulin therapy [6]. Irritant contact dermatitis occurs as a result of direct damage to the skin by chemical or physical agents resulting in a non-immune inflammatory reaction [7]. ACD is a type IV allergic hypersensitivity reaction, named also delayed-type or cell-mediated hypersensitivity. It is caused by a T cell-mediated immune reaction to usually harmless allergens which presents with erythema, edema, vesicles, oozing, and intense pruritus [8]. ACD may occur after skin exposure to chemical agents included in CGM, FGM and ISS adhesives, and it represents the most insidious among dermatological side-effects of these devices.

1.1. Aim of the study

The aim of our observational study was to assess the prevalence of ACD among children and adolescents with T1D who use technological devices for diabetes treatment and its management. Secondary outcome was to identify possible clinical and/or demographic variables that could be associated to the appearance of ACD.

2. Material and methods

The study included children and adolescents with T1D followed-up at our Pediatric Diabetes Centre between January and September 2018. Written informed consent from the parents of each child involved in the research study was obtained before the start of study procedures.

The study was conducted in accordance with the Helsinki Declaration, good clinical practice, and all applicable laws and regulations, and the study protocol was submitted and approved by the local Ethics Committee of University. Inclusion criteria comprised a diagnosis of diabetes for at least 6 months, use of CSII and/or CGM/FGM for at least 1 month. Exclusion criteria were prolonged exposure to sun or tanning lamps during the last 2 weeks, relapses of dermatological

complications at the time of enrollment, skin application of corticosteroids or immunomodulators in the last 2 weeks.

Anamnestic data included age, duration of diabetes, allergic comorbidities, other illness associated, scheme of insulin therapy, duration of the use of CSII and/or CGM/FGM, brand and model of IIS and/or sensor systems, occurrence and timing of skin reactions if present, family history of allergic diseases. The clinical examination aimed to highlight the integrity of the skin. Screening for a predisposition for atopic diseases was evaluated by skin prick test (SPT) for common aeroallergens. The evaluation of glycemic control was assessed by the last year mean value of glycated haemoglobin (HbA1c). All the patients selected in this study underwent patch testing with specific allergens belonged to resin and acrylate classes. Patch tests (Allergopharma® – Germany) were performed with Finn Chambers (diameter, 8 mm; SmartPractice®, Phoenix, Arizona) on Scanpor tape (Norgesplaster®, Vennesla, Norway). Each patch test panel consisted of three layers: the liner, a white polyethylene protected, writable paper; the panel, a clear polyurethane film coated on one side with a medical grade acrylic adhesive; the cover liner, a clear thin plastic layer fitted with removable blue-finger lift tabs. The chambers containing seven allergens (bisphenol-A type epoxy resin, butyl acrylate, butanediol 1–3 methacrylate, colophonium, ethyl acrylate, ethyl methacrylate, methyl methacrylate) were placed by means of hypoallergenic adhesive tape on the skin of the back. Every chamber was filled with 20–25 mg of test substance. Test chambers were removed after 2 days, and patch tests were read after 30 min and 1 day later.

Among a total of 215 patients using insulin pumps and/or glucose sensors followed-up at our Pediatric Diabetes Centre, 64 patients were enrolled and 42 (19 male and 23 female) completed the study. The mean age of the patients was 11.8 ± 3.6 (5–19) years and duration of diabetes was 5.3 ± 3.9 (1–16) years. All the patients who experienced skin reactions characterized by erythema, vesicle and itchy participated in the study, and they belonged to the group of “patients with ACD”. The remaining subjects were included in the group of “patients without ACD” (Fig. 1).

2.1. Statistical analysis

The numerical data were expressed as mean and standard deviations (S.D.) and the categorical variables as absolute frequencies and percentage. Examined variables were not normally distributed, such as verified by Kolmogorov Smirnov test; consequently the non-parametric approach was used. In order to compare patients with or without cutaneous skin reactions we applied the Mann Whitney test (for numerical parameters) and Chi Square test or Log-likelihood Ratio test or Exact Fisher test, as appropriate (for categorical variables). Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and diagnostic accuracy (DA) were evaluated for patch test. A P-value smaller than 0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS for Windows package, version 22.0.

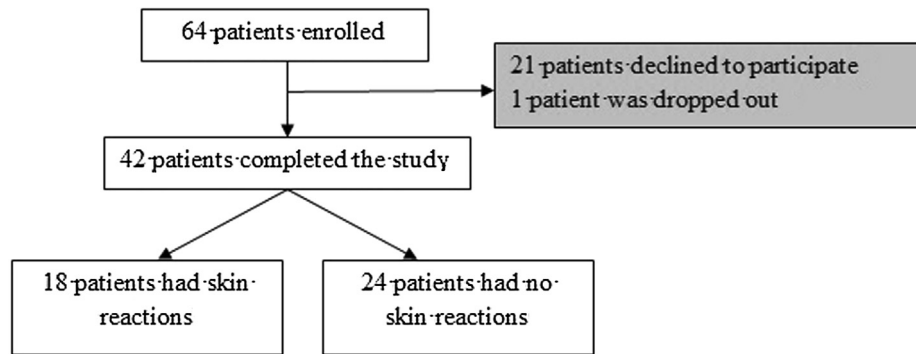


Fig. 1 – Flow-chart for patients' recruitment.

3. Results

Among a total of 215 T1D children and adolescents who use technological devices for diabetes treatment, 18 patients experienced skin reactions suggestive of ACD (Fig. 2), demonstrating a prevalence of 8.4%.

The demographic and clinical characteristics of the subjects are listed in Table 1. There was no significant difference in age and gender among two groups, as well as in diabetes duration, last year mean value of HbA1c and atopic predisposition between the groups. Among the patients with ACD, 27.8% had a history of allergic diseases: 3 patients had suffered from atopic dermatitis, 1 patient had been diagnosed allergic rhinitis and 1 patient had a history of atopic dermatitis, asthma and rhinitis. In the group of patients without ACD, 29.1% of individuals referred allergic comorbidities, such as rhinitis, asthma, food allergy, atopic dermatitis. SPT resulted positive in 22.2% among patients with a history of skin reactions, and in 29.1% of patients included in the other group.

Although the duration of use of CSII and/or CGM/FGM was not statistically associated to the appearance of ACD, we noticed that ACD was mostly present in those patients who had used technological devices for a few months. Conversely, half of the patients without ACD had used insulin pumps or glucose sensors for over two years without any adverse reactions. The distribution of CSII, CGM and FGM brands between the two groups, and its relationship with the total number of devices used in our Centre is shown in Table 2. We detected patch test positivity in 44.4% of patients with dermal problems and in 9.1% among the patients without dermal issues, revealing a significant difference ($p < 0.05$). Moreover, we evaluated sensitivity, specificity, negative predictive value, positive predictive value and diagnostic accuracy for patch test in our study population (Table 3).

Colophonium was the most identified sensitizing allergen (87.5% of the cases). One patient resulted positive to butyl acrylate and butanediol 1–3 methacrylate. Colophonium is a complex mixture of several compounds derived from pine



Fig. 2 – Various skin lesions suggestive of ACD on the surface of patients' body.

Table 1 – Demographic and clinical variables of patients with and without skin issues.

Variables	Patients with ACD	Patients without ACD	p value
Age (ys)	10.8 ± 4.1	12.5 ± 3.1	0.100
Sex (F / M)	9 (50.0%) / 9 (50.0%)	14 (58.3%) / 10 (41.7%)	0.591
Diabetes duration (ys)	6.1 ± 4.1	4.8 ± 3.9	0.178
HbA1c (%)	6.8 ± 0.8	6.9 ± 0.7	0.611
HbA1c (mmol/mol)	50.9 ± 8.6	51.8 ± 7.5	0.611
CSII and/or CGM/FGM duration			0.359
1–6 months	7 (38.9%)	4 (16.7%)	
6–12 months	2 (11.1%)	3 (12.5%)	
1–2 years	4 (22.2%)	5 (20.8%)	
2 years	5 (27.8%)	12 (50.0%)	
Allergic comorbidities (yes / no)	5 (27.8%) / 13 (72.2%)	7 (29.1%) / 17 (70.8%)	0.990
SPT positivity (yes / no)	5 (27.8%) / 13 (72.2%)	7 (29.1%) / 17 (70.8%)	0.990
Patch test positivity (yes / no)	8 (44.4%) / 10 (55.6%)	2 (9.1%) / 22 (90.9%)	0.010*

trees. Colophonium # is used, in both unmodified and modified forms, as a fast-acting adhesive for industrial, medical or other commercial uses [9,10]. Butyl acrylate and butanediol 1–3 methacrylate are complex chemicals which are used in paints, sealants, coatings, adhesives, fuel, textiles, plastics, and caulk.

4. Discussion

ACD is a common disorder of the skin in the pediatric age which may have previously been under-diagnosed [11]. The negative impact of ACD causes a decrease of quality of life secondary to pruritus, loss of sleep, and impairment of social life. In addition, it represents a significant economic burden for the community [12]. ACD is a type IV allergic cell-mediated reaction, caused by sensitization and immune reaction inside the skin. The sensitization is caused by allergen(s) entering both epidermis and dermis through an impaired skin barrier. These allergen(s) are bound with self-proteins to make complete antigens which in turn is recognized and expressed by dendritic cells of major histocompatibility complexes [13]. The symptomatic phase appears upon repeated exposure to allergen(s) leading to a clinical cutaneous response. The exposure can occur through epidermal route or less frequently by means of ingestion, inhalation, or intravenous routes [14]. Rates of contact sensitization in children are higher than commonly expected [15].

Our study showed that the prevalence of ACD in patients, who use the latest technological devices available to optimize the management of T1D, is estimated at 8.4%. As demonstrated in our study, the sensitization rate to certain allergens contained into IIS and glucose sensors, assessed by patch testing, is significant higher among those individuals who had skin reactions typical of ACD compared to the patients without any dermatological complications. Interestingly, despite these results over half the patients with a history of ACD showed patch test negativity. This data could be explained from different points of view. Although patch testing is useful to define the exact etiological diagnosis of contact allergy, it has several pitfalls. It was reported that the sensitivity of patch testing is approximately 70% [16]. The accuracy of patch testing is influenced by many variables.

The validity of patch test may be altered by inadequate concentrations of the tested substances. Moreover, it may be considered as poor if not tested under controlled conditions. A large experience in both the clinical and diagnostic aspects of contact allergy is needed to avoid wrong interpretations of the test. [17].

The accurate knowledge of potential allergens is fundamental to minimize the risk of false negatives. Recently, Herman et al. reviewed the cases of ACD induced by insulin pumps and glucose sensors since the 1970s. The authors described a wide range of identified harmful sensitizers, comprising several classes of acrylates and resins [18]. It is known that comprehensive and detailed information about adhesives used to secure infusion sets and sensors are rarely available. Adhesive manufacturers are often reluctant to disclose their exact composition. Moreover, different materials could be mixed. Therefore it is difficult to identify which component contained in the adhesive tapes induces contact allergy [19]. Failure to test for potential harmful sensitizers could further reduce the sensitivity of patch testing.

Our study revealed that ACD seems not be associated with either the duration of diabetes or the glyco-metabolic control. Interestingly, atopic predisposition should not be associated with the development of ACD among patients with T1D. Our results disagree with the previous conclusions of some authors who reported an association between CSII-related skin conditions and atopic history [3,20]. Unlike our study, those authors conducted their cross-sectional studies exclusively by means of face-to-face or online questionnaires, and they considered different forms of dermatological complications, including scars and lipodystrophies.

Based on our results, patients affected by T1D could be assimilated to the general population regarding the prevalence of ACD in atopic children which is comparable to that observed in non-atopic children [21].

ACD appeared within the first months of insulin pumps and/or glucose sensors use in most of our patients. This data may suggest that clinicians pay more attention after the first applications of ISS or glucose sensor adhesives. In those cases of skin reactions indicative of ACD, the use of hypoallergenic adhesive patches or supplemental tapes applied over the CGM/CSII adhesive patch is strongly recommended. This

Table 2 – Distribution of CSII, CGM and FGM brands among the two study groups and the correct percentages on the total number of technological devices users in our Centre.

Devices and brands	Total technological devices users in our Centre	Patients with ADC included in the study (% of total users)	Patients without ADC included in the study (% of total users)
CSII + CGM or FGM			
Medtronic®+ Enlite®	55	12 (21.8%)	8 (14.5%)
Omnipod®+Dexcom®	15	2 (13.3%)	3 (20.0%)
Movi®+ Dexcom®	15	0 (0.0%)	4 (26.7%)
Roche®+ Dexcom®	5	1 (20.0%)	1 (20%)
Omnipod® + Freestyle Libre®	6	0 (0.0%)	3 (50.0%)
Total	96	15 (15.6%)	19 (19.8%)
CSII			
Medtronic®	33	0 (0.0%)	0 (0.0%)
Omnipod®	6	1 (16.7%)	0 (0.0%)
Roche®	4	0 (0.0%)	3 (75.0%)
Ypsopump®	3	0 (0.0%)	0 (0.0%)
Total	46	1 (2.2%)	3 (6.5%)
CGM			
Dexcom®	7	0 (0.0%)	0 (0.0%)
FGM			
Freestyle Libre®	66	2 (3.0%)	2 (3.0%)
Total	215	18 (8.4%)	24 (11.2%)

Table 3 – Diagnostic patch test evaluation in our study population.

Patch test	Value	95% CI
Sensitivity	44.44%	21.53% to 69.24%
Specificity	91.67%	73.00% to 98.97%
Disease prevalence	42.86%	27.72% to 59.04%
Positive Predictive Value	80.00%	49.06% to 94.32%
Negative Predictive Value	68.75%	58.86% to 77.19%
Accuracy	71.43%	55.42% to 84.28%

preventive measure, in addition to ensuring the skin integrity, allows the patients to continue using the potentially harmful patch [7].

To date, there are few data about correlation between ACD and T1D. ACD is a disorder induced and maintained by environmental factors, which mainly has a T-helper 2 (Th2) pattern in its chronic form. T1D is also a chronic disease, and it is the result of an autoimmune Th1 cell-mediated destruction of the beta cells. Th1 and Th2 cells can be recognized by the pattern of cytokines they produce. Th1 cells specifically produce interferon-gamma and interleukin-2, and are mainly involved in intracellular infections and auto-immune diseases. Th2 cell-derived cytokines are IL-4 and IL-10, which are associated with extra-cellular infections and atopic disease. Th1 and Th2 cells reciprocally inhibit each other by production of their specific cytokines [22]. Engkilde et al. found an inverse relationship between ACD and T1D related to shared genetic factors and common environmental determinates [23]. However, based on the latest research, the presence of T1D does not reduce the risk to develop Th2 or cellular driven immunological responses. The potency of the sensitizer(s) and a prolonged exposure represent the pivotal factors for developing a contact allergy towards the allergen (s). Individual or specific characteristics of patients, such as

disrupted skin barrier or inflammatory activation of immunologic cellular system of the skin, could also play an important role for developing skin reactions [24]. The high prevalence of ACD among our patients with T1D supports this theory.

5. Conclusions

Diabetes specialists should thoroughly consider the diagnosis of ACD in their patients who have skin reactions characterized by erythema, vesicles and intense itchy. ACD may represent a quite frustrating condition for the patient, as it could increase diabetes-specific emotional distress and necessitate a change in a switch to multiple injection therapy, and for the physician as it could hamper the spread of new technology. However, there are few published data on the prevalence of and risk factors associated with ACD among patients with T1D. We suggest the opportunity for further studies to better investigate the association between ACD and T1D along with the underlying mechanisms. The execution of patch testing with potential harmful allergens before the application of CSII and/or FGM/CGM may be an attempt to early identify the patients at high risk of developing ACD.

Furthermore, we highlight the need for medical devices manufacturers to provide detailed information about adhesives, being aware that skin sensitization is quite typical after repeated exposure to the substances contained in these devices.

6. Authors' contributions

FL and GS had been in charge of the patients and drafted the paper; MFM helped to draft and write the paper; LC contributed to realize patch testing with the help of GC and IP; AA realized statistical analysis; GBP contributed to discussion and reviewed the paper; SP collected the data and wrote the paper; The paper has been read and approved by all the

authors and each author considers that the paper represents their honest work.

Authors' disclosure statement

No competing financial interests exist.

Acknowledgments

None.

Conflict Of Interest

The authors declare no conflict of interest.

Funding

The authors received no funding from an external source.

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