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High prevalence of skin reactions among pediatric patients with type 1 diabetes using new technologies: the alarming role of colophonium

AUTHORS

Fortunato Lombardo[1], Stefano Passanisi[1], Lucia Caminiti[2], Andrea Barbalace[1], Alessandra Marino[1], Mauro Iannelli[1], Maria Francesca Messina[1], Giovanni Battista Pajno[2], Giuseppina Salzano[1].

[1] Department of Human Pathology in Adult and Developmental Age "Gaetano Barresi", University of Messina.

[2] Department of Human Pathology in Adult and Developmental Age "Gaetano Barresi", Allergy Unit, University of Messina.

RUNNING TITLE

Skin reactions due to diabetes devices: our experience.

CORRESPONDING AUTHOR

Stefano Passanisi. Via Consolare Valeria 1, 98124, Messina, Italy. Phone number: +393880511623. Fax number: +390902213170. Email address: spassanisi87@gmail.com

KEYWORDS

Allergy, colophonium, continuous subcutaneous insulin infusion, patch test, sensor-augmented pump, sensitization, skin reactions.

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ABSTRACT

In the last few years the increasing use of devices for diabetes treatment, such as continuous subcutaneous insulin infusion pumps, flash glucose monitoring, continuous glucose monitoring systems, sensor-augmented pumps and automated insulin delivery devices, has resulted in important improvements in disease management. Meanwhile, **the longer a patient uses a device, the greater the likelihood of developing a skin reaction.** Allergic contact dermatitis is the most **frequently described skin side effect** caused by adhesive tapes contained in the insulin infusion sets or glucose sensor sets and used **to connect these devices to the body**. We describe 18 patients, followed-up at our Pediatric Diabetes Centre, who experienced dermatological complications due to diabetes device use from January 2018 to December 2018. All the patients were patch tested with allergens from a 'standard' series and from a "plastics and glues" series. Patch tests resulted positive in 66.7% of patients. Colophonium was the most frequent isolated sensitizing allergen (41.1% of cases). It is complex mixture of >100 compounds derived from pine trees. Colophonium is commonly used, in both unmodified and modified forms, as a fast-acting adhesive for industrial, medical or other commercial uses. Its presence in the adhesive of the insulin **sets and** glucose sensors was confirmed by the manufacturer of some devices brand. On the basis of our results, we stress the importance of contacting manufacturers for product information. We also highlight that there should be stricter legal restrictions to label medical adhesives, even if only small amounts of colophonium are used.

BACKGROUND

Intensive treatment regimens of patients affected by type 1 diabetes (T1D) are often based on the use of advanced medical devices such as continuous subcutaneous insulin infusion pump (CSII), continuous glucose monitoring (CGM), flash glucose monitoring (FGM), sensor-augmented pump (SAP), predicted low glucose suspend system (PLGS). CSII attempts to more closely replicate physiological blood insulin levels, improves glycaemic control, improves quality of life scores (1,2). CGM provides instantaneous real-time display of glucose levels, alerts and alarms for actual or impending hypo- and hyperglycemia, and it characterizes glycaemic variability (3, 4). FGM allows to visualize the current glucose value very quickly and to show the glucose trend value through an arrow and a graph (5).

SAP system combines insulin pumps and CGM technologies, provides more flexible treatment, improves glycated haemoglobin (HbA1c) levels, minimizes intra-day glycemic variability and consequently reduces the risk of chronic complications (6). The most recent automated insulin delivery systems, such as PLGS, **consistently** reduce the rate of hypoglycaemia. These systems use an automation algorithm, which allows to modify the basal insulinization rate based on the expected glucose value (7). Despite these important improvements in the **treatment** of the disease, skin reactions caused by **devices used for management of diabetes** have been increasingly described in the literature in the last few years (8-13). Allergic contact dermatitis (ACD) represents the most insidious among dermatological complications. It is a type IV allergic hypersensitivity reaction, caused by a T cell-mediated immune reaction to usually harmless allergens which presents with erythema, edema, vesicles, oozing, and intense pruritus (14). Reactions typically take a long period of exposure to induce initially, but may occur more rapidly after repeated exposure due to reactivation of memory Th1 cells. Patch test is essential to make diagnosis of ACD, and to identify the offending agents (15). Recently, some authors have experienced the emerging role of colophonium as one the most harmful substances contained into the adhesive tapes used by T1D patients (10, 16). Colophonium is a natural substance derived from Pineaceae trees. It is used in a wide range of consumer and occupational products because of its tackiness, and is a known sensitizer (17).

The aim of this study was to describe the prevalence of and risk factors associated with allergic contact dermatitis among pediatric T1D patients.

MATERIAL AND METHODS

A retrospective analysis selected all patients, followed-up at our Pediatric Diabetes Centre, who experienced dermatological complications due to diabetes device use from January 2018 to December 2018. Every patient if of age, or at least one parent if underage, gave their written informed consent before the patient's inclusion in the study. 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. Data analysed included patient demographic and clinical variables. All the patients selected in this study were patch tested with allergens from a 'standard' series and from a "plastics and glues" series. 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 fourteen allergens were placed by means of hypoallergenic adhesive tape on uninvolved 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 minutes and 1 day later. Furthermore, all the patients undertook the skin prick tests (SPT) with inhaled allergens to screen for a predisposition to atopic diseases.

The study population comprised 18 patients (12.1% of 148 patients using CSII and/or CGM/FGM) . Demographic and clinical data of the patients, and information about their devices are reported in table 1. Mean age of our patient population was 10.9 years (range 5-18) with an equal distribution between male and female. Mean duration of diabetes was 6.1 years. Of the 18 patients, 12 (66.6%) used Medtronic® pump and Enlite® as CGM. The on-body insulin infusion sets which connected to the pump were different: the majority of them used MiniMed Mio infusion set, 4 subjects applied MiniMed Mio Advance, and only 1 patient used MiniMed Mio 30 infusion set. Two patients (11.8%) used Roche® pump with

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Accu-Check Flexlink infusion set, and DexCom® G5 as CGM. Finally, 2 patients used Omnipod® pump, and the remaining 2 children used Freestyle Libre® as FGM. Three patients (16.7%) showed mild patchy, follicular, or homogenous erythema with or without infiltration, 7 children (38.9%) presented erythematous lesions with infiltration and discrete vesicles, 8 patients (44.4%) showed severe skin lesions characterized by coalescing vesicles and bullous reaction (Figure 1). These dermatological complications appeared within the first month of CSII and/or CGM-FGM use in 10 patients (55.6%), within the first year in 4 subjects (22.2%), after one year in the remaining individuals (23.5%). Atopy history was present in 27.8% of subjects: 3 patients had presented atopic dermatitis, 1 patient had been diagnosed allergic rhinitis and 1 patients had a history of atopic dermatitis, asthma and rhinitis. SPT resulted positive in 4 patients (22.2%). Almost all the patients presented a good **glycemic** control as demonstrated by the last year mean value of HbA1c (6.8 ± 0.8%). Of the 18 patients, one patient was switched back to multiple daily injections and 3 patients were forced to discontinue continuous **glucose** monitoring system. Patch tests resulted positive in 12 patients (66.6%). Colophonium was the most identified sensitizing allergen (58.8% of positive patch tested patients). One patient resulted positive to butyl acrylate and butanediol 1-3 methacrylate. Other identified allergens are reported in table 1.

DISCUSSION

In the last few years diabetes specialists have increasingly focused on the elevated rate of skin reactions among pediatric and adolescent patients **using** CSII and/or CGM/FGM. Berg et al reported that almost one **of** two patients using advanced technology treatment modalities for diabetes, experience skin issues (3). These dermatological complications could carry several implications. Persistent skin problems could increase diabetes-specific emotional distress (18). Cutaneous symptoms related to CSII use could necessitate a change in a switch to multiple injection therapy, as demonstrated in one of our described patients. The inability to use CGM systems could be related to a worsening of glycaemic control, as we observed among the patients who were forced to discontinue CGM and FGM usage. Finally, these dermatological concerns may hamper the spread of the new technology.

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Despite the magnitude of this problem, there is a clear lack of studies aiming at identification of the major causes of these complications. Some authors found a possible association between atopy and dermatological complications (3, 19), even though only 22.2% of our study population had a history of atopic diseases. Recently, Messer et al suggested a practical comprehensive guidance for skin care with diabetic devices. In order to preserve skin integrity those authors highlighted the importance of promoting considerations about device correct placement, skin care prophylaxis and careful removal techniques. They suggested the application of various barrier agents to minimize risk of hypersensitivity reactions, such as the use of hypoallergenic adhesive patches or supplemental tapes applied over the CGM/CSII adhesive patch (20). Despite of these preventing measures, when managing ACD, avoidance of the sensitizing antigen represents the milestone of the treatment. Therefore, the identification of the harmful agents contained in the components of the **adhesives used to secure infusion sets and sensors** to the skin plays a paramount role. Patch testing with all molecules included into the insulin infusion sets or glucose sensor sets is essential. However, this diagnostic investigation is not always feasible. In most cases, the exact composition of **adhesives** is unknown, and information from the manufacturers is generally missing or incomplete (21). In our study population, colophonium was the most frequent isolated sensitizing allergen. It is complex mixture of >100 compounds derived from pine trees. Although the skin-sensitizing and skin-irritant effects of colophonium are well known, the actual allergens have not yet all been characterized. Abietic acid seems to be the most sensitizing among all its components. Colophonium is commonly used, in both unmodified and modified forms, as a fast-acting adhesive for industrial, medical or other commercial uses (22, 23). The presence of colophonium in the adhesive of the insulin pump or glucose sensors was confirmed by the manufacturers of some devices brand.

According to EU legislation (EC) No. 1272/2008, colophonium is classified as an 'R43 chemical skin sensitizer' (24). Therefore, products containing >1% colophonium must be labelled with the risk phrase 'May cause sensitization by skin contact'. However, medical adhesives are excluded from EC No. 1272/2008, and are included in 93/42/EEC on medical devices (25). Therefore, the R43 restriction is not applicable, and suppliers may be unaware of the presence of colophonium in their medical adhesives.

Butyl acrylate is a chemical which is used in paints, sealants, coatings, adhesives, fuel, textiles, plastics, and caulk. Butanediol 1-3 methacrylate is a complex chemical and it is used as the monomer resin in some windscreen repair kits, dental materials and as bone cement for fixing prosthetic devices in orthopaedic surgery. Thus far, their presence in the components of CSII and/or CGM/FGM has not been validated.

CONCLUSION

On the basis of our experience, we stress the importance that **physicians** contact manufacturers to require the declaration of all well-known sensitizers contained in the product information of **adhesives**. We also highlight that the competent authorities should impose stricter legal restrictions on the use of even small amounts of colophonium in medical adhesives.

AUTHORS' CONTRIBUTIONS

SP collected the data and drafted and wrote the paper; GS and MFM helped to draft and write the paper; LC contributed to realize patch testing with the help of AB, AM and MI; GBP contributed to discussion and reviewed the paper. FL had been in charge of the patients and contributed to discussion of the paper; The paper has been read and approved by all the authors and each author considers that the paper represents their honest work.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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Table 1. Patients' demographical and clinical data, and patch tests results

Age (ys)	10.9 ± 4.4
Female (%)	9 (50%)
Duration of diabetes (ys)	6.1 ± 4.1
Last year mean value HbA1c (%)	6.8 ± 0.8
Atopy history	5 (27.8%)
Allergic asthma + allergic rhinitis + atopic dermatits	1
Allergic rhinitis	1
Atopic dermatitis	3
Positive skin prick tests	4 (22.2%)
Dust mites	2
Dust mites + grass pollen	1
Dust mites + olive tree pollen	1
Technological devices	
Freestyle libre®	2 (11.8%)
Omnipod®	2 (11.8%)
Medtronic® pump + Enlite® sensor	12 (66.6%)
MiniMed Mio Advance	4
MiniMed Mio 30 infusion set	1
MiniMed Mio infusion set	7
Roche® pump + DexCom® sensor	2 (11.8%)
Accu-Check Flexlink infusion set	2
Skin issue features	
Mild patchy, follicular, or homogenous erythema with or without	3 (16.7%)
infiltration	7 (38.9%)
Erythematous lesions with infiltration and discrete vesicles	8 (44.4%)
Coalescing vesicles and bullous reaction	
Time of appearance of skin manifestations	
0-1 month	9 (52.9%)
1-6 months	1 (5.8%)

6-12 months	3 (17.6%)
>12 months	3 (17.6%)
Positive patch tests	12 (66.7%)
Balsam of Peru	1
Butanediol 1-3 methacrylate	1
Butyl acrylate	1
Cobalt chloride	1
Colophonium	7
Neomycin sulphate	1

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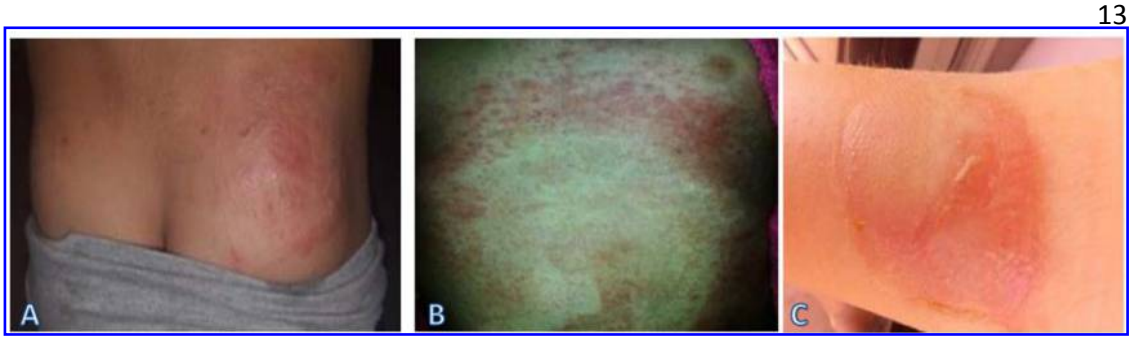

Figure 1. Various skin lesions due to diabetes devices on the buttocks, abdomen and arm of different patients (A, mild patchy, follicular, homogenous erythema; B, erythematous lesions with infiltration and discrete vesicles; C, coalescing vesicles and bullous skin lesions).

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