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REVIEW

CONTACT DERMATITIS | WILEY

Allergic contact dermatitis caused by glucose sensors and insulin pumps: A full review

Part 2. Case reports and case series, clinical features, patch test procedures, differentiation from irritant dermatitis, management of allergic patients and (proposed) legislation

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Abstract

During the past 8 years, a large number of reports have appeared on allergic contact dermatitis to glucose sensors and insulin pumps in paediatric and adult patients with type 1 diabetes mellitus. Isobornyl acrylate in one particular sensor sensitised many hundreds of (published) individuals, and many other allergens were discovered in a large number of sensors and pumps. Diagnostic procedures with patch tests proved very complicated, as manufacturers showed a serious lack of cooperation with dermatologists in providing information on the ingredients of their products and samples for patch testing. This two part article provides a full and detailed review of all aspects of the subject of allergic contact dermatitis to glucose sensors and insulin pumps. Part 1 provided a general introduction to sensors and pumps, a survey of the cutaneous adverse reactions that they have caused, a full account of the allergens in the diabetes devices and an overview of the glucose sensors and insulin pumps that have caused allergic contact dermatitis. This part 2 presents all published case reports and case series, clinical features of allergic contact dermatitis, patch test procedures, differentiation from irritant dermatitis, management of allergic patients and (proposed) legislation.

KEYWORDS

allergic contact dermatitis, colophonium, contact allergy, continuous subcutaneous insulin infusion, diabetes mellitus, diabetes medical device, glucose monitoring, glucose sensor, insulin pump, isobornyl acrylate, *N*,*N*-dimethylacrylamide

1 | INTRODUCTION

This is the second part of a full review of allergic contact dermatitis caused by glucose sensors and insulin pumps. Part 1 provided a general introduction to sensors and pumps, a survey of the cutaneous adverse reactions that they have caused, a full account of the allergens in the diabetes devices and an overview of the glucose sensors and insulin pumps that have caused allergic contact dermatitis.[1]

This part 2 presents all published case reports and case series, clinical features of allergic contact dermatitis, patch test procedures, differentiation from irritant dermatitis, management of allergic patients and (proposed) legislation.

2 | ALLERGIC CONTACT DERMATITIS FROM INSULIN PUMPS

Insulin pumps have been used since the mid-1970's to continuously deliver insulin, mainly to patients with type 1 diabetes mellitus. The older devices consisted of a needle that was inserted into the skin and fixed with a plastic butterfly and an adhesive patch, and was connected to a pump by a plastic cannula/catheter/tube. Several cases of allergic contact dermatitis (ACD) to these early pumps, or actually their infusion sets, were reported between 1985 and 2001, caused by the infusion needle (nickel), glues to fixate the needle to the cannula or plastic butterfly (epoxy resin, acrylates), or materials of the cannula itself (methyl methacrylate). These early reports are presented in paragraph 2.1.

Reports of ACD from modern insulin pumps and infusion sets began to appear from 2018 on with a case series of 4 patients from France who developed ACD from isobornyl acrylate (IBOA) in the Omnipod insulin pump.[2] Two patients were sensitised by the device itself after 4 months and 1 year. The other 2 already suffered ACD after the first use of the pump; they had previously become allergic to IBOA by the use of the glucose sensor FreeStyle Libre (FSL), which at that time had already sensitised a large number of patients using this device.[3] Since then, cases of allergic reactions have been reported to 8 different brands of insulin infusion sets and patch pumps (part 1, tab. 9). They are presented in paragraph 2.2. An overview of all allergic reactions to the pumps with brand, culprit allergen(s), number of patients and literature references is provided in part 1, paragraph 4.4 (tab. 9).

2.1 | Early reports of allergic contact dermatitis to insulin pumps

Cases of allergic contact dermatitis to insulin pumps, or actually to their infusion sets, were already reported in the period 1985–2001.[4–11] They are presented in some detail in Supporting Information S1.

2.2 | Allergic contact dermatitis to modern insulin pumps

Compared to glucose sensors, the number of reported cases of sensitization to and ACD from modern insulin pumps and infusion sets is modest. Allergic reactions to the Omnipod have been reported in nearly 20 patients, some of who had previously become sensitised to its ingredient IBOA from the use of the FSL sensor.[12,13] The other pumps/infusion sets (MiniMed Quick-set, MiniMed Sure-T, mylife Ypsopump Orbit, Omnipod DASH pump and the TouchCare A6) have each caused only 1 or 2 cases of allergic reactions in which the culprit allergen was established. This could possibly be explained by the fact that pumps are removed after 2–3 days (and then a new application follows to another part of the skin), whereas sensors may remain attached to the skin for 10–14 days, strongly increasing the risk of sensitization. Another possible explanation is that in the conventional pumps, the adhesive patches are separated from the housing of the pump by a cannula. This would preclude any contamination with allergens migrating from the housings, as has been the case with the Omnipod pump and the FSL sensor.

Several case series of ACD from insulin pumps and infusion sets have been reported.[14–16] They are presented in some detail in Supporting Information File 1. Case reports with 1 or 2 patients with ACD have also been published[17–28]; their key data are presented in Supporting Information Table S1.

3 | ALLERGIC CONTACT DERMATITIS FROM GLUCOSE SENSORS

The first report in 2017 of allergic contact dermatitis from IBOA in FreeStyle Libre (FSL) sensor by investigators from Belgium and Sweden[3] was followed by a multitude of similar reports from other centres and countries (part 1, paragraph 4.3.1). Other sensors that have caused ACD include Dexcom G4, Dexcom G6, Dexcom G7, Enlite and Guardian 4, of which Enlite has caused most reactions with colophonium (derivatives), IBOA, or both as culprit allergens.

Over 20 reports have presented case series of ACD to glucose sensors[29–49]; these are presented in some detail in Supporting Information File 2. There are also multiple case reports with 1–3 allergic patients available[13,14,17,18,20,21,23–28,33–35,42,46,50–74]; their key data are presented in Supporting Information Table S2.

4 | CLINICAL FEATURES OF ALLERGIC CONTACT DERMATITIS

Allergic reactions to diabetes devices usually manifest as dermatitis under the adhesive patch of the glucose sensor or the insulin infusion set/patch pump. As diabetes type 1, for which the devices are generally used, mostly starts in (early) childhood, many of the patients are children.[3,16,20,29,33,39,42,46] In case reports of ACD to sensors and pumps, >60% of the patients were younger than 18 years (Tables S1 and S2). The fact that the devices were primarily reimbursed by health insurers for children may also have played a role in this.

The time from the start of using a diabetes device to first appearance of dermatitis has varied from a few weeks to several years; typically, dermatitis started after 5–7 months.[3,13,14,16,33,35,36,37,41] The majority of these data relate to patients who became sensitised to IBOA in the FreeStyle Libre sensor. However, in the case reports, in

which over half of the patients had ACD to other sensors and to pumps, the median delay was similar with 5 months (Tables S1 and S2).

Thereafter, upon repeated contact, ACD usually emerges within one to a few days, but sometimes later.[14] Repeated applications in sensitised individuals often result in stronger allergic reactions with subsequent exposures and shorter time lags until dermatitis appears.[64] Some patients who have been sensitised by the use of a sensor or pump and who start using an alternative device may develop ACD to the new device within 1–3 days, when the allergen to which they have been sensitised previously is also present in the new device. This has occurred frequently in patients primarily sensitised to IBOA in the FSL sensor (e.g., References 12,13,20,21,24,26). However, when a device contains very low levels of the chemical to which the patient is allergic, it may take up to a few weeks before clinical ACD develops.[21]

The clinical picture of allergic reactions to diabetes devices may depend on the nature of the allergen, its concentration in the contact surface of the device, the strength of the sensitization, the contact time with the skin, the number of contacts and the degree of pre-existing skin damage, for example, from irritant dermatitis. Allergic reactions often present as subacute dermatitis with (sometimes severe) itching, erythema, mild swelling and scaling with well-defined borders in the form of the device's adhesive patch.[43] However, acute ACD with erythema, oedema, vesicles, oozing and erosions are not infrequent.[30,31,61,64,75] Bleeding, secondary infection,[53,72] abscesses,[53] scarring, and burning, stinging and pain have also been reported.[46,75,76] In a few individuals ulcers have been observed, sometimes referred to as 'burn wounds' by patients, which, given their diabetes status, may bear an additional risk of superinfection.[75] In one series of 70 patients, of who 63 had reactions to FSL and 7 to Enlite, 70% had severe dermatitis, defined as red, swollen, intensively itching, oozing, bleeding or blistering dermatitis at the sensor contact site, and 30% had mild dermatitis.[33]

Generally, the dermatitis is limited to the application surface of the adhesive patches or expands slightly to surrounding skin, which also applies to the more severe reactions.

Dermatitis usually heals within a week or so after removal of the device, sometimes leaving (post-inflammatory) hyperpigmentation[30,46] or (less frequently) hypopigmentation. Leukoderma at the site of previous ACD has also been observed.[10,63] In one of these cases, a potential role for hydroquinone monomethyl ether, which is present in the IBOA materials to prevent spontaneous polymerisation and which acts as a very potent depigmenting agent, was suggested.[63] It has been claimed that contact dermatitis to glucose sensors 'usually' manifests as acquired leukoderma,[77] which seems unlikely: leukoderma from diabetes devices has been reported only rarely[10,63] and in both cases appeared *after* dermatitis had developed.

Rare cases of 'contact dermatitis syndrome' with generalised itchy erythema, vesicles and pustules on both soles[65] and systemic contact dermatitis[72] have been reported.

The clinical aspect of allergic reactions to early insulin pumps was usually somewhat different from the more recent ones, presenting with dermatitis under the 'butterfly' of the infusion set[5,7] or linear-shaped lesions from allergic reactions to the cannula.[4,9] One patient allergic to nickel developed painful papulonodular dermatitis at the site of the inserted needle with an itchy vesicular eruption spreading over her abdomen.[8] Another nickel-allergic individual developed itchy papules around the needle site increasing to form a plaque 10 cm in diameter, later with papules spreading over the abdomen and buttocks with intense itching.[6] The latter may well have been a case of ACD and systemic allergic dermatitis from nickel entering the bloodstream from the needle.[6] These early cases are presented in paragraph 2.1.

The consequences of becoming sensitised to acrylates in glucose sensors or insulin pumps other than problems in finding safe alternative devices have not been well investigated. A few patients sensitised from diabetes devices have also suffered allergic reactions to acrylate nail cosmetics.[35,50] Some were already sensitised to these cosmetics before using diabetes devices.[35] A causal relationship between sensitization to a sensor or pump followed by allergic reactions to nail cosmetics has never been obvious, although it was suggested in one case.[50] This may well be explained by the fact that isobornyl acrylate, the acrylate responsible for by far most cases of allergic reactions to diabetes devices, has very limited tendency to cross-react to other acrylates and to methacrylates such as 2-hydroxyethyl methacrylate (HEMA), methacrylates being the usual allergens in acrylate nail cosmetics (part 1, paragraph 4.3.1).[78] One patient sensitised to IBOA later developed ACD from a disposable blood pressure cuff, which was found to contain IBOA and 2-phenoxyethyl acrylate.[59]

5 | DIAGNOSING ALLERGIC CONTACT DERMATITIS FROM DIABETES DEVICES: PATCH TEST PROCEDURES

Positive patch tests to one or more ingredients known to be present in diabetes devices that have caused cutaneous reactions suspected to be ACD confirm the diagnosis. However, the diagnostic process is complicated by difficulties in getting adequate information on what the medical devices are made of, obtaining information on how to patch test new suspected allergens and the collection of adequate patch test materials.[29] Indeed, information on the chemicals present in the adhesive patches and the housings of the devices is usually unavailable and most investigators have noticed a serious lack of cooperation from the manufacturers when requesting specific data on the ingredients of their products.[3,14,17,21,24,33,35,42,43,46,75,79] This makes targeted testing very difficult. As a consequence, most allergens could only be identified by performing gas chromatography–mass spectrometry analyses (GC–MS) of (ultrasonic bath) extracts of the devices (part 1, paragraph 4.2).[31] Only a few centers have the laboratory facilities and skilled personnel to perform such laborious and costly analyses.

We suggest to patch test patients with suspected ACD from diabetes devices with the European baseline series (or any other baseline series as appropriate), a diabetes device screening series, a (meth)

acrylate series, an isocyanate series, a plastic and glue series and, whenever possible, a piece of the adhesive of the device(s) that caused the dermatitis.[46,80] Patch test reactions first appearing after D4 are not infrequent, especially with acrylates, but also with isocyanates, and therefore a test reading after 1 week is absolutely necessary.[13,29,30,80]

In Table 1 a proposal for a diabetes device screening series containing 24 chemicals is shown largely based on the list of allergens that have caused ACD by their presence in glucose sensors, insulin pumps, or both, as shown in part 1, paragraph 4.3.6. Twelve of these are commercially available from Chemotechnique, 9 from Allergeaze. The other 12 can be purchased from a chemical company

TABLE 1 A proposal for a diabetes device screening series.

		Available from	
Allergens commercially available for patch testing	**Concentration[i]**	**Chemotechnique**	**Allergeaze**
Abietic acid	10.0%	+	+
Butyl acrylate	0.1%	+	+
Butylated hydroxytoluene (BHT)[c]	2.0%	+	+
4,4′-Diaminodiphenylmethane[b,d]	0.5%	+	+
Ethyl acrylate[e]	0.1%	+	+
Ethyl 2-cyanoacrylate	10.0%	+[g]	+[h]
1,6-Hexanediol diacrylate (HDDA)[a]	0.1%	+	
Hydroabietyl alcohol (Abitol)[c]	10.0%	+	+
Isobornyl acrylate (IBOA)[a]	0.1%	+	+[h]
Isophorone diisocyanate (IPDI)[b]	1.0%	+	
Methyl methacrylate[a]	2.0%	+	+
Tripropylene glycol diacrylate[a]	0.1%	+	

		Available from	
Chemicals not commercially available for patch testing	**Concentration[i]**	**Sigma-Aldrich**	**TCI chemicals**
2,4-di-*tert*-Butylphenol	1%	+	+
Carboxyethyl acrylate	0.1%	+	
Dicyclohexylmethane-4,4′-diisocyanate (DMDI)	1%		+
N,*N*-Dimethylacrylamide (DMAA)	0.3%	+	+
Dipropylene glycol diacrylate	0.1%		+
Hydroquinone monomethyl ether (4-methoxyphenol)	1%	+	+
Hydroxycyclohexyl phenyl ketone (1-benzoyl cyclohexanol)	5%	+	+
Isobornyl acrylate	0.3%	+	+
Isobornyl methacrylate	2%	+	+
2,2′-Methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate (MBPA)	1.5%		+
4,4′-Methylene diphenyl diisocyanate (MDI) (diphenylmethane 4,4-diisocyanate)[c]	0.5%	+	+
2-Phenoxyethyl acrylate[f]	0.1%	+	+
Phenoxypoly(ethyleneoxy)ethyl acrylate (PEEA) (Phenol, ethoxylated, esters with acrylic acid); PEEA contains monomers (2-phenoxyethyl acrylate), oligomers and polymers	0.1%[j]	+	+

Abbreviations: Allergeaze: test allergens available from www.smartpracticecanada.com and (not all) www.smartpracticeeurope.com; Chemotechnique, www.chemotechnique.se; Sigma-Aldrich: www.sigmaaldrich.com; TCI: TCI Chemicals, www.tcichemicals.com.
[a]May be present in a '(meth)acrylate series'.
[b]May be present in an 'isocyanate series'.
[c]May be present in a 'plastic and glue series'.
[d]Also included as a screening agent for MDI sensitization.[45,81]
[e]Frequently co-/cross-reacted with isobornyl acrylate in one large study.[38]
[f]Monomer of phenoxypoly(ethyleneoxy)ethyl acrylate (PEEA).
[g]'Currently not available due to temporary lack of high-grade raw material' (www.chemotechnique.se, October 22, 2024).
[h]Not available from www.smartpracticeeurope.com.
[i]All chemicals in petrolatum.
[j]Because of the presence of only 14% monomers (2-phenoxyethyl acrylate) this test concentration may be too low.

(e.g., Sigma-Aldrich, TCI chemicals, other companies) for preparing the test allergens. Table 1 shows these chemicals with their test concentration as used in literature and availability from two major chemical suppliers.

Of the chemicals in the list of allergens identified as causes of ACD from diabetes devices (part 1, paragraph 4.3.6) colophonium, epoxy resin and nickel are present in the baseline series. Some patients allergic to colophonium only react to the material tested at 60%.[29,31] Patients sensitised to modified colophonium or -derivatives such as hydroabietyl alcohol may have negative or ? + reactions to colophonium 20% in the baseline series (part 1, paragraph 4.3.2),[16,82,83] hence the suggested presence of abietic acid and hydroabietyl alcohol in the screening series.

Some of the allergens may already be present in a '(meth)acrylate series' or 'isocyanate series' used by the investigator. Included in the screening series are also some chemicals that have not caused ACD from their presence in diabetes devices; for these, there are other reasons for their presence in the series. Ethyl acrylate, for example, is the only acrylate that fairly often co-reacts/cross-reacts with IBOA (part 1, paragraph 4.3.1). 4,4′-Methylene diphenyl diisocyanate (MDI) has been identified by GC–MS in diabetes devices (part 1, tab S1 in the Supporting information) and 4,4′-diaminodiphenylmethane (MDA) is a good screening agent for MDI allergy.[45,81] Hydroquinone monomethyl ether (4-methoxyphenol) is present as inhibitor of spontaneous polymerisation in many acrylate raw materials used for the in-house preparation of patch test materials and should therefore be patch tested separately. We suggest isobornyl methacrylate, which is a frequent constituent of nail cosmetics[84] to be added to investigate cross-reactivity from IBOA sensitization.[44] 2-Phenoxyethyl acrylate, finally, is the monomer in phenoxypoly(ethyleneoxy)ethyl acrylate (PEEA), which has caused allergic reactions in diabetes devices and in which 2-phenoxyethyl acrylate is present in a concentration of nearly 15% (part 1, paragraph 4.3.4).

The test concentrations for chemicals not available for patch testing are based on the most recent published data. IBOA and DMAA were first tested at 0.1%. Later, it was found that a higher concentration of 0.3% identified allergic patients who had negative patch tests to 0.1%.[12,13,29,30,46] IBOA 0.3% was negative in 100 controls and no late-appearing reactions suggestive of patch test sensitization were recorded.[13]

2,2′-Methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate (MBPA) was first tested at 0.3% pet.,[30] but later 1.5% proved to identify more cases of sensitization without causing irritant reactions or late reactions in controls (part 1, paragraph 4.3.4).[31] Thus, a screening series is not static but should regularly be updated when new information becomes available. The medical device series used since 2020 in Malmö provides additional allergens which may be suitable for inclusion in a diabetes screening series.[13]

It should be realised that the performance of non-commercially prepared patch test materials, at the concentrations shown below (based on literature data), depends on the properties of the material purchased from a chemical company. It cannot be guaranteed that the test materials are non-irritant, safe, and adequate or optimal for detecting contact allergy. In addition, the series contains a large number of acrylates, which may in some patients result in fierce allergic reactions or false positives (irritant reactions), and the risk of active sensitization is unknown.

Therefore, the screening series, chemicals and the test concentrations shown in the table should not be considered as an *advice* from the authors. It is presented as an option for (inclusion in) a diabetes device screening series to be considered and critically evaluated by the readers. Also, prevailing and applicable legislation for use of such materials for investigating patients should always be taken into account.

Pieces of the device (notably the adhesive material(s)) can be tested 'as is'.[46] Unfortunately, the concentration of the culprit allergen is often very low, especially when the allergen has migrated into the patch from the housing, which frequently results in false-negative tests.[30] Prolonging the application time from 2 to 4 days may increase the sensitivity of the test.[31]

When the results of all patch tests are negative and the patient is strongly suspected of ACD, additional patch testing with ultrasonic bath extracts of the involved device is recommended.[80,85,86] It is preferable, but usually impossible, to make extracts from several devices of the same type. To increase the likelihood of extracting both polar and non-polar sensitizers, three extracting solvents with different physicochemical properties can be used—water, ethanol, and acetone.[80] Most investigators have used acetone for extraction (which is suitable for both polar and non-polar chemicals), some methanol (part 1, paragraph 4.2). A test reading after 1 week is mandatory unless positive reactions are noted already at the reading of D3 or D4. To substantially diminish the possibility of a false-positive reaction, patch testing in 20 consecutive dermatitis patients is necessary and should be negative.[80] Following this, GC–MS analyses should preferably be performed to identify potential allergens in the device(s) and these must, whenever possible, subsequently be patch tested in the patient and, when positive, in 20 controls. Unfortunately, false-negative reactions to extracts also occur.[30] Extracts giving a positive reaction can also be used for separation and identification based on patch testing with thin layer chromatograms, although very likely few centers will have the expertise and possibilities for such analyses.[29,80]

When patch testing reveals contact allergy to a chemical known to be present in the device or to the non-irritant extract, the diagnosis of ACD has been established. Depending on the patch test results and clinical data, authors from Malmö, Sweden (who have greatly contributed to the scientific literature on allergic reactions to diabetes devices) have recommended as alternative diagnoses ACD?, UCD (unspecified contact dermatitis) and ICD (irritant contact dermatitis). The suggested criteria for making these diagnoses can be found in Reference 80.

6 | NEGATIVE PATCH TESTS IN PATIENTS SUSPECTED OF ALLERGIC CONTACT DERMATITIS: IRRITANT CONTACT DERMATITIS?

Many patients suffering from diabetes mellitus who use a glucose sensor, insulin pump or both develop cutaneous reactions to one or more

of their devices, frequently dermatitis (part 1, paragraph 3). Initially, skin reactions to the newly developed glucose sensor FSL were considered to be irritant rather than allergic, caused by skin temperature, occlusion, humidity, and long exposure.[87,88] However, in 2017 isobornyl acrylate was found to be an important allergen in FSL causing ACD in 12 of 15 patients (80%) with skin reactions to this sensor.[3] Later, *N*,*N*-dimethylacrylamide was reported as another sensitizer in this sensor (part 1, paragraph 4.3.3).

Nevertheless, irritant contact dermatitis (ICD) is presumably the more common reaction pattern, which is less severe and less reproducible upon application at new sites than ACD. It may be assumed that only the patients with more severe and persistent symptoms suggestive of ACD are referred to a dermatologist for patch testing. Indeed, in a university hospital in Belgium, in 2019, only 5.5% of diabetes patients were referred to the patch test clinic for suspected ACD from the FSL sensor.[39] However, even in these selected patient groups, relevant contact allergies could not always be demonstrated and the question has been raised repeatedly whether such patients had ICD.[17,35,39,43,44] In a university center in Brussels, Belgium, of 52 patients who were referred for skin reactions to diabetes medical devices, relevant contact allergy could not be established in 17 (33%).[43] In other studies with case series of patients suspected of ACD to sensors, pumps or both, percentages of individuals in who the suspected contact allergy could not be verified by patch tests have varied widely: 7%,[3] 13%,[13] 13%,[46] 20%,[33] 24%,[16] 31%,[44] 32%,[39] 43%,[42] 67%,[35] and even 80%.[17]

In the Belgian study previously mentioned, all 52 patients, both those with ($n = 35$) and without ($n = 17$) relevant patch test reactions, presented a very similar clinical picture with an annular, squamous, well-defined itchy erythema under the sensor. The authors concluded that 'the clinical aspect, therefore, does not allow a distinction between ICD and ACD'. Also, the time between first symptoms and first use of the sensor was virtually the same for patients with ACD and suspected ICD (6–7 months). Following the first development of dermatitis, in both groups, all patients described progressive worsening and a decrease in the delay between sensor applications and appearance of the reaction, which was, according to the authors, more likely in ACD than ICD. Nevertheless, ICD was suggested to be present in the 17 patients (33%) in who no relevant contact allergies were found (with undiagnosed contact allergy as another possibility).[43] Subsequently, Swedish investigators argued that ICD was an unlikely diagnosis in many of the reported patients in the Belgian study.[80] They pointed out that there had not been a D7 reading, that the test concentration of 0.1% for IBOA and DMAA fails to identify a number of sensitised patients and that the temporal relationship between exposure and dermatitis in all patients argues in favour of the same mechanism for contact dermatitis in both (ACD and ICD) groups.[80]

Indeed, there are several possible explanations for not finding a relevant contact allergy in patients in who the cutaneous reaction to diabetes devices is strongly suspected to be ACD (sometimes termed 'false-negative reactions'):

1. Patch tests are read only at D2 and D3/4, but not at D7. Thus, late-appearing reactions at D7 (negative at D3/4), which are not infrequent with IBOA, DMAA and other acrylates,[80] are missed[13];
2. The test concentration used is too low and misses some cases of sensitization. IBOA and DMAA have long been tested at 0.1% pet. which we now know fails to identify a number of sensitizations which are picked up with testing at 0.3%.[12,13,29,30,46] Already in 2020 investigators from Sweden have advised to test these allergens at 0.3% pet.[80] However, it may be assumed that by far most centers still test with IBOA 0.1% pet., as this is the only IBOA test allergen currently available from the major commercial providers. On the same note: 2,2′-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate (MBPA) was first tested at 0.3% pet.,[30] but later 1.5% proved to identify more cases of sensitization (part 1, paragraph 4.3.4)[31];
3. One or more allergens known to be present in diabetes devices are not tested;
4. The allergic reaction is caused by an established allergen, the presence of which in diabetes devices is not known and which is not patch tested;
5. The allergic reaction is caused by a chemical in the device not previously described as an allergen (and therefore not tested);
6. No patch tests were performed with the device itself (usually the adhesive patch) tested 'as is', or extracts (mostly acetone), which might have been positive, establishing ACD after negative control testing)[3,20,38,46];
7. Patch tests *were* performed with pieces of the device, extracts or both, but were negative due to their low content of the allergen; such false-negative reactions are relatively frequent[30,38];
8. 8. The patient has a weak contact allergy, for which the usual application time of 2 days is too short to provoke the allergic response.[31]

It cannot be excluded, however, that some patients who are, based on patient history and clinical symptoms, strongly suspected of ACD, in fact have severe irritant contact dermatitis and therefore show no relevant contact allergy even when optimal patch testing has been performed. Patch test procedures in suspected cases of ACD from diabetes devices are discussed in paragraph 5.

7 | FREQUENCY OF ALLERGIC CONTACT DERMATITIS FROM DIABETES DEVICES

Few studies have investigated the frequency of ACD from diabetes devices in groups of patients using them, and some of these were flawed.[20,33,39,42,89] In a university hospital in Antwerp, Belgium, in the period December 2016 to April 2019, of 1036 patients (614 adults, 422 children) using FSL, 34 of the adult patients (5.5%) and 23 of the children (5.5%), total group 57 (5.5%), were referred to the dermatology department because of cutaneous adverse reactions to the sensor. When patch tested, 39/57 patients had positive reactions to

IBOA 0.1% pet., establishing ACD to the FSL sensor. Thus, the frequency of ACD to the device was 3.8% (39/1036).[39] This percentage is almost certainly an underestimation, as there was probably no late (D7) reading, and neither IBOA 0.3% nor DMAA were tested (these data were probably not available at the time), which inevitable has resulted in some false-negative reactions (paragraph 6). Also, as ACD can take months to even years to develop, some FSL users from this cohort may have developed ACD after the termination of the study. And finally, very likely not all patients with cutaneous reactions were referred for patch testing.[39]

In two university hospitals in Finland, between October 2017 and January 2019, 70 patients were patch tested because of suspected ACD from FSL ($n = 63$) or the Enlite sensor ($n = 7$).[33] 51 FSL users had positive reactions to IBOA 0.1%. In November 2018, there were 6567 FSL users in the 2 hospitals, and the frequency of ACD therefore can be calculated as 51:6567 = 0.8% (incorrectly stated to be 0.7%). There were 4 cases of ACD to Enlite in 385 users, which amounts to 1.0% (incorrectly stated as 0.8%).[28] Obviously, for the same reasons as given above, the actual figures are almost certainly higher. In addition, only patients who had to stop using the sensor or needed to use skin protectors under the sensor were referred for patch testing, indicating that patients with less severe allergic reactions were not patch tested.[33]

In a university hospital in Brussels, between January 2016 and July 2019, 215 children were followed-up for wearing a FSL sensor. Ten patients were patch tested because of cutaneous reactions to the sensor and 9 had a positive reaction to IBOA 0.1% pet. This means that 9/215 (4.2%) of the children who were wearing the glucose sensor FSL were sensitised to IBOA,[20] which is, again, highly likely an underestimation.

In a university hospital in Spain, between March 2019 and February 2020, all children ($n = 264$) with type I diabetes mellitus who were equipped with glucose sensors were investigated.[42] The data presented showed that 6.9% of the 275 sensors caused ACD in 14 of the 264 children (5.3%). However, the article contained many mistakes and in fact, the percentage of allergic reactions to sensors was not 6.9% but 4% and the percentage of patients with ACD to a sensor was not 5.3% but 3% (for details see Supporting information File 2, FreeStyle Libre 1, Spain, 2020).

An Italian study calculated/estimated the prevalence of ACD to diabetes devices at 8.4%, but the research (in which apparently no dermatologists were involved) contained many flaws and this percentage is almost certainly unreliable (Reference 89 partly also presented in Reference 90).

8 | MANAGING ALLERGIC CONTACT DERMATITIS FROM DIABETES DEVICES

After removal of the device that causes the skin reaction, ACD will heal spontaneously. In patients with severe dermatitis, topical corticosteroids will speed up the healing process. Next, measures must be taken to avoid recurrences of dermatitis. For this, simply relocating the culprit device is of no help in cases of ACD. Only complete avoidance of a culprit sensitizer or at least a substantial decrease in exposure to it is necessary to prevent progressively worsening and relapsing dermatitis.[75] Using an alternative device may solve the problem, but is risky, as it may well contain the same or cross-reacting allergens and using no diabetes devices anymore is the safest option. However, the use of glucose sensors and insulin pumps often considerably enhances the quality of life of the patients. Therefore, many of them are reluctant to stop using their device[40,43] and will first look for measures to alleviate the symptoms or, ideally, prevent the development of dermatitis completely. To achieve this, protective measures (secondary prevention) can be taken in patients who want to continue to use the culprit device. Alternatively, the patient can switch to another device that does not contain the allergen. Both options have proven to be rather challenging.

8.1 | Secondary prevention

There are three main strategies (sometimes used in combination) for secondary prevention while continuing the use of devices that causes allergic reactions: topical application of corticosteroids, applying barrier sprays before each new application, and applying a plaster between the skin and the adhesive patch of the device to stop the allergens from reaching the skin. It is often cited that the UK government website in 2019 stated that applying barrier creams, patches and sprays might affect the performance of the device; however, zero evidence was provided.[91] By far most experience has been gained with patients reacting to IBOA in FreeStyle Libre 1 (which is not used anymore). The results of most protective measures have been somewhat disappointing[3,17,33,39] and sometimes protective dressing even aggravated the dermatitis.[3] In one study, only 14 of 63 (22%) patients with ACD to their IBOA–containing glucose sensor were able to continue using the device, with all 14 requiring use of a barrier agent and still having residual dermatitis.[33]

8.1.1 | Topical corticosteroids

Twelve paediatric patients using diabetes devices who had developed local skin reactions under the adhesive patch of their sensor were treated with fluticasone propionate aqueous nasal solution on the skin area prior to adhesion of a new device. Five of the patients with moderate-to-severe local reactions had undergone 'allergic assessment demonstrating a positive response to their adhesive material'. In 10/12, there was no recurrence of local irritation nor dermatitis during almost 6 months of treatment.[92] It is uncertain how many of the children had ACD, possibly those who had undergone 'allergic assessment'.

Fluticasone propionate sprayed topically fortnightly at the site prior to application of the sensor led to a marked improvement in one patient.[52] In another report, the use of topical corticosteroids had very limited protective effect in an unspecified number of patients.[33]

8.1.2 | Barrier sprays

Many patients have tried film-forming barrier sprays to prevent the adverse cutaneous reactions under their diabetes devices. Most frequently used was Cavilon™ spray (3M, St. Paul, Minnesota, USA), which is commonly used for the prevention of incontinence-associated dermatitis and for ostomy care. Its ingredients are hexamethyldisiloxane, isooctane, acrylate terpolymer and polyphenylmethylsiloxane. Although there is a case report claiming success,[65] its protective power appears to be limited, as it shields the skin only for a few days, whereas sensors may remain in place for up to 2 weeks.[65]

In a Belgian study 16 patients of who 14 showed ACD to IBOA, had tried Cavilon to prevent their cutaneous adverse reactions. Five of these 16 patients (31%), all children, reported some improvement with this product, but only 2 continued its use. The first child, sensitised to IBOA, reported residual but acceptable itch and erythema, whereas the other child, not sensitised to IBOA, became completely free of symptoms. The 11 of 16 remaining patients (71%), all adults, experienced no benefit from Cavilon at all.[39] In another report, the use of Cavilon also had limited protective effect in an unspecified number of patients.[33] It should also be realised that ACD and severe irritant contact reactions to Cavilon have been reported in patients using the product for stoma care.[93]

8.1.3 | Plasters and dressings

Another possibility for trying to avoid relapses of ACD is to apply a physical barrier between the skin and the adhesive part of the sensor, for example, with sterile adhesive tapes (plasters) or hydrocolloid- or silicone-based dressings/plasters/plates. Examples of such dressing are Compeed™ sheets (HRA Pharma, Paris, France),[33,69] Cutimed® Hydro B (BSN Medical, Hamburg, Germany),[40,68] Eakin® Surround protectors (Eakin Healthcare, Comber, Ards, United Kingdom),[33] Hansaplast™ blister plasters (Beiersdorf, Hamburg, Germany),[26,40,68] Opsite® (Smith & Nephew, London, UK),[3] Stomahesive™ (Convatec Group plc, Paddington, London, UK),[24,25,40,54] and Tegaderm™ (3M, Minneapolis, MN, USA).[3,51,64,94]

In some case reports, protective success has been claimed for the use of Tegaderm,[64,94] Stomahesive,[24,25] Compeed,[69] and Hansaplast blister plaster.[26] In other case reports and case series, dressing barriers were unsuccessful in preventing development of dermatitis or had limited effect.[2,13,51] Authors from Australia presented 3 patients with ACD from IBOA, who were given Stomahesive as a barrier. Two patients could continue using their sensor without further development of ACD and the third had 'improvement' from the combination Stomahesive and a topical corticosteroid.[54] In a study from Poland, 3 of 10 Eakin Surround users were able to continue using FSL with no dermatitis.[33] In Germany, good results have been achieved with placing two or three overlapping Hansaplast blisters between the skin and the sensor. One patient 'was almost always able to keep his FSL in place for the full application time of 14 days' (meaning that dermatitis still developed) and in 9 or 10 other patients 'this worked well' in terms of 'mostly preventing ACD symptoms'. The authors also claimed success for Cutimed Hydro B in another 2 patients.[68] Seven of these patients (5 using Hansaplast and 2 Cutimed Hydro B) were presented in more detail by these authors in another publication, where they also claimed success with Stomahesive in one individual. The authors did mention, however, that the usage of these protective devices has some limitations.[40]

Thus, it appears that the use of hydrocolloid- or silicone-based plates underneath the sensor may help a subgroup of patients to tolerate the diabetes devices to which they are allergic. However, many patients still experience dermatitis to some extent.[75] Unfortunately, such protective skin barriers make wearing the devices less comfortable.[68] In addition, their centres have to be perforated so that the sensor filament or infusion cannula can reach the skin. This work-around sometimes prevents correct placing of the device, which may hamper its proper functioning.[68] Occlusion and additional costs for the plates are other critical points.[24,40,75] In addition, the patches have poorer resistance to water contact, requiring more frequent replacement of the sensor.[53] Finally the dressings, some of which may contain acrylates or (modified) colophonium, may well cause allergic reactions themselves.[95,96]

Generally, using these plates is regarded only as a temporary solution.[68,75] In the end, many patients, despite taking protective measures still have to give up on the use of their devices and look for an alternative device (paragraph 8.2).[36]

8.2 | Choosing an alternative sensor or pump

Many patients who have become sensitised to their device will try to continue its use by taking measures to prevent recurrences of dermatitis or ameliorating the symptoms (paragraph 8). When this proves to be unsuccessful, the use of an alternative device may be considered. Such a new device should not contain the allergen that has caused ACD in the patient or chemicals that may cross-react with it. For individuals in who the allergen has not been identified (paragraph 6) there is no alternative other than the 'by trial and error' method. Unfortunately, finding a suitable replacement device is equally difficult for patients with an established contact allergy, as there is virtually no information available on the composition of currently commercialised glucose sensors and insulin pumps.[13,16] Manufacturers do not need to disclose the chemical composition of their product[97] and most have shown a serious lack of cooperation when requested to provide specific data on the ingredients of their products.[3,14,17,21,24,33,35,42,43,46,79,97]

There is a great deal of information available, collected between 2016 and now, on the presence (part 1, paragraph 4.2, tabs 3 and S1 in the supporting information) or absence (part 1, paragraph 4.2, tables S2 and S3 in the supporting information) of specific allergens in specific sensors and pumps from chemical analyses (GC–MS) or (in a small minority) from information provided by the manufacturer. Some of this information is now outdated. Devices such as FSL and Dexcom G4 platinum, for example, are not available anymore, only their

successors. Also, product ingredients may be altered without a change of brand name or notification to the clinicians or the users.[30] Therefore, the information formerly acquired, although providing some direction in suggesting an alternative device, may not be accurate anymore. In addition, a negative GC–MS analysis for a certain chemical may not always completely rule out its presence in the product investigated and a guarantee that every possible allergen is identified cannot be given either.[97]

In clinics investigating patients with suspected ACD to diabetes devices, having updated and accurate knowledge on the composition of the products is necessary. Only then can recommendations on alternative products be given to patients with known allergy to protect them from re-exposure to their sensitizers. When no information is provided by manufacturers, the only option to acquire data on the composition of products is by chemical analyses of extracts, which should be repeated periodically because of possible changes in the product composition. However, chemical analyses of the products can only partly, and often with considerable delay, compensate for the lack of information provided by manufacturers on the composition of their products[15,80] and few centres have the opportunity to perform these investigations. Only a detailed labelling of the composition of these medical devices enables patients with known ACD to one of the components to avoid further skin reactions (paragraph 9).

9 | LEGISLATION

For reasons discussed in paragraph 8.2, it is important if not imperative for medical professionals to have access to detailed product descriptions of medical devices including their qualitative chemical composition in order to be able to perform appropriate patch testing, give advice to patients, and provide alternatives in case of allergies. As manufacturers continue to refuse collaboration and communication, several dermatologists have called attention to the need for (mandatory) full ingredient labelling of diabetes devices and other medical devices, both for existing products and for new devices entering the market.[16,43,46,74,80,97,98,99] An Editorial in 2019 clearly showing the need for EU legislation to require disclosure and labelling of the composition of medical devices[99] was followed in 2021 by a Position statement from 14 experts in contact allergy on behalf of the European Society of Contact Dermatitis (ESCD), European Environmental and Contact Dermatitis Research group (EECDRG), the European Academy of Dermatology and Venereology (EADV) Contact Dermatitis Task Force, and the European Academy of Allergy and Clinical Immunology (EAACI).[97] This position paper reviewed the scientific literature on allergic reactions to medical devices and the current regulatory framework adopted for medical devices. It showed the negative impact of the absence of product labelling on patient care, costs of illness to the patients and society, and on the quality of life of the patients who have become allergic to a device. The authors strongly recommend that the European Commission require full labelling for any device.[97] Furthermore it was encouraged to implement an obligation for manufacturers of medical devices to cooperate and disclose all information necessary for the management of patients who have suffered an adverse event. This particularly concerns full disclosure of the components (to the treating physician) of the device that has induced the reaction in order[95] and providing samples for patch testing.[16]

A large proportion of patients with ACD from diabetes devices is children. Many have used several sensors, pumps or both and develop several contact allergies. This emphasises the need for collaboration between the medical profession, the patient organisations and the companies producing the items, since these individuals will both need to and want to continue using diabetes devices, very likely for the rest of their lives.[29]

AUTHOR CONTRIBUTIONS

Anton de Groot: Conceptualization; investigation; visualization; project administration; writing – original draft; writing – review and editing. **Emma M. van Oers:** Conceptualization; investigation; visualization; writing – original draft; writing – review and editing. **Norbertus A. Ipenburg:** Formal analysis; visualization; writing – review and editing. **Thomas Rustemeyer:** Supervision; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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