Gdański Uniwersytet Medyczny

**Rozprawa doktorska**

**lek. Mikołaj Cichoń**

# Kontaktowe zapalenie skóry u pacjentów z cukrzycą typu 1 leczonych ciągłym podskórnym wlewem insuliny oraz stosujących systemy do monitorowania glikemii.

# Contact dermatitis in patients with diabetes mellitus type 1 treated with continuous subcutaneous insulin infusion sets and using glucose monitoring systems.

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Spis treści

# Wykaz stosowanych skrótów

| | |
|---|---|
| ACD | alergiczne kontaktowe zapalenie skóry<br>(ang. *allergic contact dermatitis*) |
| BCA | ang. *β-carboxyethyl acrylate* |
| BIS-GMA | 2,2-bis[4(2-hydroksy-3-metakryl- oksypropoksy)fenyleno]propan<br>(ang. *2,2-bis(4-(2,3-epoxypropoxy)phenyl) propane*) |
| BIS-MA | dimetakrylan bisfenolu<br>(ang. *bisphenol A dimethacrylate*) |
| DMAA | N,N-dimetyloakrylamid<br>(ang. *N,N-dimethylacrylamide*) |
| DMAEMA | metakrylan N,N dimetyloaminoetylu<br>(ang. *2-(Dimethylamino)ethyl methacrylate*) |
| DPGDA | diakrylan glikolu dipropylenowego<br>(ang. *dipropylene glycol diacrylate*) |
| GC-MS | chromatografia gazowa sprzężona ze spektrometrią mas<br>(ang. *gas chromatography-mass spectrometry*) |
| IBOA | izobornyl akrylu<br>(ang. *isobornyl acrylate*) |
| ICD | kontaktowe zapalenie skóry z podrażnienia<br>(ang. *irritant contact dermatitis*) |
| ICDRG | Międzynarodowa Grupa Badająca Wyprysk Kontaktowy<br>(ang. *International Contact Dermatitis Research Group*) |
| MBPA | monoakrylan 2,2'-methylenebis(6-tert-butylo-4-metylofenolu)<br>(ang. *2,2'-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate*) |
| PEEA | ang. *phenoxypoly(ethylenoxy) ethylacrylate* |
| SL | seskwiterpeny laktonowe<br>(ang. *sesquiterpene lactones*) |
| UCD | nieokreślone kontaktowe zapalenie skóry<br>(ang. *unspecified contact dermatitis*) |
| 2-HEA | 2- akrylan hydroksyetylu<br>(ang. *2-hydroxyethyl acrylate*) |

# 1. Wprowadzenie

## 1.1 Przedstawienie problemu klinicznego

Kontaktowe zapalenie skóry jest powszechną dermatozą wywołaną przez bezpośredni kontakt skóry z czynnikami zewnętrznymi. W zależności od jej patomechanizmu wyróżnia się dwie główne postaci choroby: alergiczne kontaktowe zapalenie skóry (ACD – *allergic contact dermatitis*) oraz kontaktowe zapalenie skóry z podrażnienia (ICD – *irritant contact dermatitis*). Alergiczne kontaktowe zapalenie skóry to jednostka chorobowa wywołana przez swoistą reakcję immunologiczną na alergen kontaktowy, z którym w przeszłości był kontakt i tym samym doszło do uczulenia organizmu na niego. Niemożliwe jest wystąpienie alergicznego kontaktowego zapalenia skóry bez wcześniejszej ekspozycji na dany alergen. Natomiast w patomechanizmie kontaktowego zapalenia skóry z podrażnienia nie bierze udziału żaden ze znanych typów nadwrażliwości immunologicznej wg Gella-Coombsa. Dermatoza ta jest bezpośrednim wynikiem drażniącego i uszkadzającego działania czynników fizycznych, chemicznych lub mechanicznych na skórę. W przypadkach wątpliwych, w których nie można jednoznacznie określić typu kontaktowego zapalenia skóry, klasyfikuje się je jako nieokreślone kontaktowe zapalenie skóry (UCD – *unspecified contact dermatitis*).

Obecnie dzięki intensywnemu rozwojowi inżynierii biomedycznej coraz więcej pacjentów z cukrzycą typu 1 jest leczonych ciągłym podskórnym wlewem insuliny (tzw. pompami insulinowymi) oraz korzysta z systemów do ciągłego monitorowania poziomu glikemii (tzw. sensorów glukozy). Zwiększenie dostępu do tego typu urządzeń medycznych nie tylko poprawiło jakość życia osób z cukrzycą typu 1, ale również przyczyniło się do zdecydowanie lepszych wyników terapeutycznych w tej grupie pacjentów (1).

Niestety na przestrzeni ostatnich lat obserwuje się coraz więcej przypadków kontaktowego zapalenia skóry, zarówno alergicznego, jak i z podrażnienia, wynikającego ze stosowania pomp insulinowych oraz sensorów glukozy (2). Pacjenci skarżą się na przewlekły świąd oraz uczucie pieczenia skóry, jak i na wynikające z tego zaburzenia snu i znaczne pogorszenie jakości życia. Zmiana miejsca wkłucia pompy insulinowej lub aplikacji sensora pomiaru glikemii nie przynosi poprawy, gdyż zmiany skórne pojawiają się po aplikacji urządzenia na dotychczas zdrową skórę.

Za przyczynę ACD w tej grupie pacjentów uznaje się alergeny kontaktowe, głównie z grupy akrylanów, znajdujące się w elementach, które mocują wkłucie pompy insulinowej

do tkanki podskórnej i zabezpieczają sensor pomiaru glukozy na skórze (3). Alergeny mogą być również obecne w samym urządzeniu i przenikać przez klej lub plaster mocujący, powodując reakcję zapalną skóry. Głównym alergenem odpowiedzialnym za ACD w grupie pacjentów stosujących urządzenia dla diabetyków jest izobornyl akrylu (IBOA) (3,4). Zidentyfikowanymi czynnikami sprawczymi są również: kalafonia, żywica epoksydowa, siarczan niklu oraz inne pochodne akrylanów, które omówione zostaną w dalszej części rozprawy (2). W większości przypadków kontaktowego zapalenia skóry spowodowanego stosowaniem pomp insulinowych oraz/lub sensorów glukozy czynnik sprawczy pozostaje nieznany. Brakuje wieloośrodkowych danych co do częstości występowania ICD oraz ACD w tej grupie pacjentów. W badaniu przeprowadzonym przez Ahrensbøll-Friis i wsp. na podstawie 5-letniej obserwacji 76% pacjentów doświadczało ACD lub prawdopodobnego ACD (5). Z innego badania natomiast można wnioskować, iż nawet u 32,7% pacjentów przyczyną jest ICD (3).

Identyfikacja potencjalnych alergenów jest trudna i wymagająca, ponieważ producenci urządzeń dla diabetyków nie dysponują listą konkretnych akrylanów użytych podczas produkcji. Dlatego też wielu pacjentów otrzymuje diagnozę UCD. Aktualnie źródłem większości informacji na temat alergenów występujących w pompach insulinowych oraz sensorach glukozy są pojedyncze opisy przypadków oraz nieliczne prace oryginalne, przeprowadzone zwykle na małej grupie chorych. Jednocześnie zwraca się uwagę na potencjał drażniący akrylanów, co razem z przewlekłą okluzją skóry może powodować ICD (6). Jednakże definitywna diagnoza ICD nie jest możliwa bez wykluczenia potencjalnych alergenów. Problem kliniczny, chociaż bardzo istotny, pozostaje niewystarczająco dokładnie zbadany.

## 1.2 Cele pracy

I. Ocena częstości występowania alergicznego kontaktowego zapalenia skóry oraz kontaktowego zapalenia skóry z podrażnienia u pacjentów z cukrzycą typu 1 leczonych pompami insulinowymi oraz stosujących sensory pomiaru glikemii.

II. Określenie najczęstszych alergenów, które uczulają pacjentów leczonych pompami insulinowymi i stosujących sensory pomiaru glikemii.

III. Określenie związku pomiędzy rodzajem kontaktowego zapalenia skóry (ACD a ICD) a następującymi zmiennymi: wiek i płeć pacjenta; urządzenie powodujące kontaktowe zapalenie skóry; czas, po jakim pojawiły się pierwsze zmiany skórne; częstotliwość zmiany miejsca aplikacji sensora glukozy i/lub pompy insulinowej; wiek pacjenta w chwili rozpoznania cukrzycy typu 1; wiek pacjenta w chwili rozpoczęcia stosowania sensora glukozy i/lub pompy insulinowej.

IV. Określenie związku pomiędzy rodzajem urządzenia wywołującego kontaktowe zapalenie skóry (sensor glukozy, pompa insulinowa, sensor glukozy oraz pompa insulinowa) a następującymi zmiennymi: wiek i płeć pacjenta; czas, po jakim pojawiły się pierwsze zmiany skórne; częstotliwość zmiany miejsca aplikacji sensora glukozy i/lub pompy insulinowej; wiek pacjenta w chwili rozpoznania cukrzycy typu 1; wiek pacjenta w chwili rozpoczęcia stosowania sensora glukozy i/lub pompy insulinowej.

V. Podsumowanie aktualnego stanu wiedzy na temat kontaktowego zapalenia skóry spowodowanego stosowaniem pomp insulinowych i sensorów glukozy.

## 2. Wykaz publikacji wchodzących w skład rozprawy doktorskiej

**Łączna wartość wskaźnika oddziaływania (IF): 14,7**

**Łączna punktacja MEiN: 480**

1. Praca przeglądowa

**Contact dermatitis to diabetes medical devices**

Mikołaj Cichoń, Magdalena Trzeciak, Małgorzata Sokołowska-Wojdyło,
Roman J. Nowicki

*International Journal of Molecular Sciences*, 2023

IF: 4,9 | MEiN: 140 | Q1

2. Praca kazuistyczna

**Allergic contact dermatitis elicited by insulin infusion sets: first case reported in Poland**

Mikołaj Cichoń, Małgorzata Sokołowska-Wojdyło, Magdalena Trzeciak

*Contact Dermatitis*, 2023

IF: 4,8 | MEiN: 100 | Q1 |D1

3. Praca oryginalna

**Role of acrylates in the development of contact dermatitis in diabetic patients – a Polish dermatology tertiary center experience**

Mikołaj Cichoń, Małgorzata Myśliwiec, Magdalena Trzeciak

*Contact Dermatitis*, 2023

IF: 4,8 | MEiN: 100 | Q1 |D1

4. List do redakcji

**Allergic contact dermatitis caused by diabetes medical devices**

Mikołaj Cichoń, Magdalena Trzeciak, Roman J. Nowicki

*Alergologia Polska*

IF: 0,2 | MEiN: 140

## 3. Omówienie publikacji wchodzących w skład rozprawy doktorskiej

1) Praca przeglądowa

**Contact dermatitis to diabetes medical devices**

Mikołaj Cichoń, Magdalena Trzeciak, Małgorzata Sokołowska-Wojdyło,
Roman J. Nowicki

*International Journal of Molecular Sciences*, 2023

IF: 4,9 | MEiN: 140 | Q1

Pierwsza publikacja wchodząca w skład rozprawy doktorskiej stanowi przegląd dostępnej literatury opisującej problem kontaktowego zapalenia skóry wywołanego stosowaniem urządzeń medycznych dla diabetyków. Z racji na rzadko opisywany problem kliniczny w pracy ujęto również doświadczenia autorów w tym temacie, co zostało odpowiednio oznaczone w tekście.

W okresie marzec 2023 r. – czerwiec 2023 r. do przeglądu dostępnych artykułów naukowych dotyczących problematyki kontaktowego zapalenia skóry u osób stosujących sensory glukozy i pompy insulinowe użyto wyszukiwarek baz danych PubMed oraz Web of Science. Podczas przeglądu literatury nie zastosowano ograniczeń co do rodzaju artykułu, daty publikacji, czasopisma, w jakim dany artykuł się ukazał, czy wydawnictwa publikującego artykuł. Nie uwzględniono również ośrodka oraz afiliacji autorów. Do przeglądu literatury użyto następujących fraz: *diabetes medical devices*, *diabetes devices*, *insulin infusion sets*, *insulin pumps*, *continuous glucose monitoring system*, *flash glucose monitoring system*, *glucose monitoring system*, *glucose sensors*, *acrylate*, *acrylates*, *isobornyl acrylate*, *IBOA and contact dermatitis*, *IBOA and allergic contact dermatitis*, *IBOA and irritant contact dermatitis*. Zastosowano zarówno wyszukiwane „wsteczne" (przegląd piśmiennictwa zawartego w istotnych artykułach, tzw. *backward search*), jak i wyszukiwanie „do przodu" (wyszukiwanie istotnych artykułów, w których był cytowany artykuł oryginalny po jego opublikowaniu, tzw. *forward search*.)

Po wstępie, w którym zwrócono uwagę na istotność problemu klinicznego, w pracy szczegółowo omówiono każdy z alergenów, który w czasie pisania pracy był powiązany z występowaniem alergicznego kontaktowego zapalenia skóry w wyniku stosowania urządzeń dla diabetyków. Największą uwagę poświęcono IBOA, który jest najlepiej poznanym oraz najczęściej podawanym alergenem sprawczym (4). W kolejnych akapitach opisano inne,

rzadsze alergeny sprawcze, w tym zarówno pochodne akrylanów, jak i inne substancje. Przy każdym alergenie wskazano na konkretny model urządzenia do podawania insuliny i/lub sensora glukozy, w którym go zidentyfikowano. Przegląd wszystkich poznanych alergenów odpowiedzialnych za alergiczne kontaktowe zapalenie skóry wywołane urządzeniami dla diabetyków przedstawia Tabela 1 (stan na dzień publikacji). Lista alergenów jest ograniczona z racji na brak informacji co do ich stosowania podczas produkcji urządzeń. Większość autorów w celu potwierdzenia obecności danego alergenu w konkretnym sensorze lub pompie samodzielnie przeprowadza ich oznaczanie za pomocą chromatografii gazowej sprzężonej ze spektrometrią mas (GC-MS). Tym samym ostateczna diagnoza (ACD lub ICD) u większości pacjentów jest bardzo opóźniona.

Tabela 1 – Alergeny odpowiedzialne za alergiczne kontaktowe zapalenie skóry u pacjentów stosujących pompy insulinowe i/lub sensory glukozy. Wymienione alergeny zostały udokumentowane jako powodujące uczulenie (dodatni wynik testów płatkowych) oraz zidentyfikowane w urządzeniach dla diabetyków.

| **akrylany** | **inne alergeny** |
|---|---|
| izobornyl akrylu (IBOA) | kalafonia |
| monoakrylan 2,2′-methylenebis(6-tert-butylo-4-metylofenolu) (MBPA) | żywica epoksydowa |
| diakrylan glikolu dipropylenowego (DPGDA) | nikiel |
| cyjanoakrylany (n.p. 2-cyjanoakrylan metylu i 2-cyjanoakrylan etylu) | *1-Benzoylcyclohexanol* |
| *phenoxypoly(ethylenoxy) ethylacrylate* (PEEA) | |
| *β-carboxyethyl acrylate* (BCA) | |
| N,N-dimetyloakrylamid (DMAA) | |

Kolejna część pracy poświęcona została możliwym mechanizmom odpowiedzialnym za kontaktowe zapalenie skóry z podrażnienia. Należą do nich przewlekła okluzja skóry spowodowana aplikacją urządzenia oraz związany z tym wzrost wilgotności i zmiana pH skóry, a także mechanizm tarcia czy drażniące właściwości akrylanów. Zwrócono uwagę, że alergiczne kontaktowe zapalenie skóry i zapalenie skóry z podrażnienia mogą współwystępować, utrudniając ostateczną diagnozę.

Ostatni akapit publikacji odnosi się do leczenia i zapobiegania kontaktowego zapalenia skóry u pacjentów stosujących urządzenia dla diabetyków. Kluczowym elementem jest unikanie alergenów, co w przypadku badanej grupy pacjentów jest niezwykle trudne. Przykładowo pacjenci uczuleni na IBOA, którzy zmieniali urządzenie medyczne na nowe, pozbawione IBOA, nadal rozwijali kontaktowe zapalenie skóry. Przyczyną mógł być niezidentyfikowany dotąd alergen. Niestety w świetle obecnego stanu wiedzy – poza leczeniem objawowym polegającym na stosowaniu w stanach ostrych miejscowych glikokortykosteroidów oraz terapii podtrzymującej miejscowymi inhibitorami kalcyneuryny – nie ma idealnego rozwiązania terapeutycznego dla pacjentów. Dostępnym w Polsce sensorem glukozy, w składzie którego za pomocą GC-MS nie zidentyfikowano IBOA, jest Freestyle Libre 2 (12). Sensor ten, mimo że jest pozbawiony IBOA, był przyczyną kontaktowego zapalenia skóry u części pacjentów włączonych do badania (reakcja z podrażnienia lub nieznany alergen). Drugim sensorem pozbawionym IBOA jest zestaw do ciągłego pomiaru glikemii Eversense XL (Roche, Basel, Switzerland), którego czujnik umieszczany jest podskórnie oraz pozwala na kontrolę glikemii przez okres nawet 6 miesięcy. W przeprowadzonych badaniach w każdym z komponentów (sensor, transmiter, plastry mocujące) poziom IBOA był poniżej granicy oznaczalności (<0.10 μg/ml) (13). W trakcie prowadzenia badań żaden z pacjentów włączonych do badania nie korzystał z tego sensora. Pacjenci często sięgają po metody barierowe ochrony takie jak spreje barierowe, a skórę dookoła urządzenia dodatkowo zabezpieczają plastrami, na przykład do kinezjoterapii. Jednakże pomimo tych środków zapalenie skóry nie ustępuje ani nie zmniejsza swojego nasilenia, co może być spowodowane udowodnioną zdolnością akrylanów do penetracji przez środki ochrony osobistej takie jak rękawiczki gumowe (14–16).

Publikacja ta stanowi podsumowanie aktualnego stanu wiedzy na temat kontaktowego zapalenia skóry wywołanego przez urządzenia dla diabetyków.

2) Praca kazuistyczna

**Allergic contact dermatitis elicited by insulin infusion sets: first case reported in Poland**

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Druga publikacja to praca kazuistyczna przedstawiająca pierwszy oficjalnie opisany w Polsce przypadek zapalenia skóry spowodowanego stosowaniem trzech zestawów infuzyjnych firmy Medtronic (Quick-Set, Sure-T oraz Silhouette) kompatybilnych z pompą insulinową Medtronic 640 G (Medtronic, Minneapolis, USA). Opisany 15-letni pacjent chorujący na cukrzycę typu 1 od 8. roku życia stosował od wielu lat zamiennie wymienione zestawy infuzyjne. Po około 7 latach użytkowania w miejscu wkłuć zaczęły pojawiać się zmiany o charakterze kontaktowego zapalenia skóry, z nasilonym świądem oraz pieczeniem skóry, a okresowo również sączenie. Zmiany te rozwijały się po około 3 dniach od aplikacji każdego z trzech zestawów infuzyjnych, niezależnie od miejsca wkłucia. W wykonanych testach płatkowych stwierdzono uczulenie na między innymi IBOA. Dendooven et. al. zidentyfikowali wcześniej ten alergen w dwóch wkłuciach stosowanych przez pacjenta – Quick-Set oraz Sure-T, podczas gdy w zestawie Silhouette nie wykryto IBOA w zakresie granicy oznaczalności (17). Pacjent rozwijał zmiany skórne po każdym z wymienionych wkłuć w takim samym odstępie czasu, co może sugerować, że wkłucie Silhouette zawiera śladowe ilości IBOA, wystarczające do wywołania reakcji alergicznej.

Po roku od wystąpienia ACD na zestawy infuzyjne do obrazu klinicznego dołączyły bardzo podobne zmiany skórne wynikające ze stosowania sensora pomiaru glikemii Medtronic Guardian 3. W dostępnym piśmiennictwie nie ma publikacji opisujących reakcje alergiczne na stosowany przez pacjenta sensor. Nie są również znane alergeny występujące w tym urządzeniu. Możliwym wytłumaczeniem jest pierwotna sensytyzacja na nieznany dotąd alergen zawarty we wkłuciach od pompy insulinowej i rozwinięcie alergii kontaktowej na sensor glukozy. Poza uczuleniem na IBOA we wcześniej wykonanych testach płatkowych pacjent miał dodatni wynik testów płatkowych w kierunku seskwiterpenów laktonowych (SL), jednak wynik ten nie miał istotnego klinicznie znaczenia. Najpewniej jest to przykład reakcji krzyżowej (ang. *cross-reactivity*) pomiędzy akrylanami a SL, na co jako pierwsi uwagę zwrócili Herman i wsp.(18). Późniejsze badania wskazują, iż nawet 44%

pacjentów uczulonych na IBOA prezentowało również dodatnie reakcje krzyżowe w testach płatkowych na SL (19). Sugeruje się, że na skutek zmian konformacyjnych wiązań pojedynczych w IBOA, cząsteczka ta upodabnia się do pierścienia alfa-metyleno-gamma-butyrolaktonowego odpowiedzialnego za reakcje krzyżowe SL.

W leczeniu ostrej fazy zapalenia zastosowano miejscowe glikokortykosteroidy z następczą terapią proaktywną za pomocą inhibitorów kalcyneuryny (takrolimus miejscowo stosowany raz dziennie dwa razy w tygodniu), co przyniosło znaczną poprawę kliniczną.

3) Praca oryginalna

**Role of acrylates in the development of contact dermatitis in diabetic patients – a Polish dermatology tertiary center experience**

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IF: 4,8 | MEiN: 100 | Q1 |D1

Trzecia publikacja składająca się na rozprawę doktorską to praca oryginalna przedstawiająca wyniki badań. Jest to pionierska, pierwsza w Polsce praca oryginalna przedstawiająca wyniki badań na temat kontaktowego zapalenia skóry spowodowanego stosowaniem urządzeń dla diabetyków. Jednocześnie jest to jedna z niewielu prac oryginalnych w Europie i na świecie, w której przedstawiono wyniki badań na większej grupie pacjentów. Do tej pory zdecydowaną większość prac stanowiły opracowania kazuistyczne.

Głównym celem pracy było określenie roli akrylanów w rozwoju kontaktowego zapalenia skóry spowodowanego stosowaniem urządzeń medycznych dla diabetyków. W badaniu przeanalizowano liczne zależności socjodemograficzne takie jak: związek pomiędzy rodzajem kontaktowego zapalenia skóry a następującymi zmiennymi: wiek i płeć pacjenta; urządzenie powodujące kontaktowe zapalenie skóry; czas, po jakim pojawiły się pierwsze zmiany skórne; częstotliwość zmiany miejsca aplikacji sensora glukozy i/lub pompy insulinowej; wiek pacjenta w chwili rozpoznania cukrzycy typu 1; wiek pacjenta w chwili rozpoczęcia stosowania sensora glukozy i/lub pompy insulinowej. Ponadto analizie poddano związek pomiędzy rodzajem urządzenia wywołującego kontaktowe zapalenie skóry (sensor glukozy, pompa insulinowa, sensor glukozy oraz pompa insulinowa) a następującymi zmiennymi: wiek i płeć pacjenta; czas, po jakim pojawiły się pierwsze zmiany skórne; częstotliwość zmiany miejsca aplikacji sensora glukozy i/lub pompy insulinowej; wiek pacjenta w chwili rozpoznania cukrzycy typu 1; wiek pacjenta w chwili rozpoczęcia stosowania sensora glukozy i/lub pompy insulinowej. Do analizy statystycznej użyto testu niezależności chi-kwadrat Pearsona, testu Manna-Whitneya oraz testu Kruskala-Wallisa z poziomem istotności statystycznej $p < 0.05$. Do badania włączono 15 pacjentów, w tym 11 dzieci (6 dziewczynek oraz 5 chłopców; średnia wieku 11,2 lata) oraz 4 osoby dorosłe (1 kobieta oraz 4 mężczyzn; średnia wieku 32,3 lata). Każdy z pacjentów prezentował kontaktowe zapalenie skóry spowodowane stosowaniem pompy insulinowej i/lub sensora pomiaru glikemii. Trzynastu pacjentów było użytkownikami zarówno pomp

insulinowych, jak i sensorów glukozy, a dwóch korzystało tylko z sensora. Następujące sensory glukozy były używane i powodowały kontaktowe zapalenie skóry: Freestyle Libre, Freestyle Libre 2 (Abbott Diabetes Care, Witney, UK), Dexcom G6 (Dexcom Inc., San Diego, CA, USA) i Medtronic Guardian 3 (Medtronic, Minneapolis, USA). Sensory Medtronic Enlite oraz Eversense XL (Roche, Basel, Switzerland) nie były używane przez żadnego z pacjentów. Wśród pomp insulinowych będących przyczyną zmian skórnych znalazły się: pompy Medtronic 640G, Medtronic 715 i Medtronic Veo 754 (z kompatybilnymi wkłuciami infuzyjnymi QuickSet, Silhouette and Sure-T), pompa mylife YpsoPump z wkłuciem infuzyjnym Orbit soft oraz Orbit micro (Ypsomed, Burgdorf, Switzerland), pompa Accu-Chek z wkłuciem infuzyjnym Rapid-D link (Roche Diabetes Care, Indianapolis, USA) oraz mikropompa Equil z zestawem infuzyjnym Soft i kaniulami długości 6 mm oraz 9 mm (MicroTech Medical [Hangzhou] Co. Zhejiang, China). Wśród pacjentów nie było użytkowników pompy insulinowej Omnipod (Insulet Corp., Acton, MA, USA).

Lista oraz stężenia testowanych alergenów kontaktowych ujęte zostały w Tabeli nr 2. Testy płatkowe przeprowadzono oraz odczytano zgodnie z wytycznymi Międzynarodowej Grupy Badającej Wyprysk Kontaktowy. Wyniki przeprowadzonych testów płatkowych z użyciem alergenów przedstawionych w tabeli u pacjentów włączonych do badania prezentowały się następująco – 3 pacjentów (20%) miało dodatnie wyniki testów płatkowych: wszyscy 3 pacjenci byli uczuleni na IBOA, a dodatkowo jeden z nich miał dodatni wynik na 2-HEA. Spośród wymienionych 3 pacjentów: pierwszy pacjent rozwinął ACD na IBOA zawarty w sensorach Freestyle Libre oraz Dexcom G6; drugi pacjent prezentował UCD na sensor Medtronic Guardian 3 (alergen nieznany lub reakcja z podrażnienia) i ACD na wkłucia Medtronic Sure-T, Silhouette oraz Sure-T zawierające IBOA (w przypadku wkłucia Silhouette istnieje duże prawdopodobieństwo, że IBOA jest poniżej granicy oznaczalności (7)); trzeci pacjent rozwinął ACD na IBOA obecne we wkłuciu Orbit od pompy insulinowej YpsoPump. Warto zauważyć, że trzeci pacjent był również uczulony na 2-HEA (dodatni wynik testów płatkowych), jednak alergen ten jak dotąd nie został oznaczony w tej pompie insulinowej. Nie można jednak wykluczyć, że on również jest alergenem sprawczym. Pierwszy pacjent, uczulony na IBOA, rozwinął zmiany skórne również po zamianie sensora z Freestyle Libre na Dexcom G6, który jeszcze do niedawna uważany był za sensor wolny od IBOA i był jedną z nielicznych alternatyw dla pacjentów z uczuleniem na IBOA. W latach 2018 oraz 2019 stężenie IBOA mierzone za pomocą GC-MS w kleju stosowanym przy Dexcom G5 oraz Dexcom G6 wynosiło poniżej

granicy oznaczalności (<0.10 μg/ml IBOA rozpuszczonego w metanolu) (8,9). Niestety na początku 2020 r. zmianie uległ klej mocujący Dexcom G6 do skóry – zawartość IBOA wynosiła 0.1–0.7 μg w plastrze oraz 0.8–1.3 μg w ekstrakcie z samego sensora Dexcom G6. Potwierdzeniem tego są również obserwacje z przeprowadzonych badań, w których niektórzy pacjenci uczuleni na IBOA oraz stosujący Dexcom G6 prezentowali kontaktowe zapalenie skóry (10).

Aż 12 pacjentów (80%), pomimo obecności kontaktowego zapalenia skóry, nie miało żadnego dodatniego wyniku testów płatkowych. Nie jest jednak w pełni poprawne traktowanie tych przypadków zapalenia jako ICD, gdyż diagnoza ta wymaga wykluczenia udziału potencjalnych alergenów, co z powodu braku informacji od producenta o składzie komponentów urządzeń nie jest w pełni możliwe (11). Ponadto możliwa jest sensytyzacja na alergen zawarty w używanych w przeszłości urządzeniach i rozwinięcie zapalenia skóry po zmianie na inne urządzenie, również zawierające jeszcze niepoznany alergen. W artykule zwrócono także uwagę na zapalenie skóry wywołane przez dotąd nieopisywane w literaturze urządzenia dla diabetyków takie jak sensory Medtronic Guardian 3 oraz Freestyle Libre 2. Analiza GC-MS wykazała, że w sensorze Freestyle Libre 2 nie ma IBOA, co może wskazywać, że przyczyną zapalenia skóry jest nieznany alergen lub reakcja z podrażnienia (12). Nie wykazano statystycznie istotnego związku między wymienionymi zmiennymi socjodemograficznymi a rodzajem kontaktowego zapalenia skóry oraz urządzeniem wywołującym kontaktowe zapalenie skóry.

Publikacja ta dowodzi trudności w diagnostyce pacjentów z kontaktowym zapaleniem skóry spowodowanym stosowaniem pomp insulinowych oraz sensorów glukozy. Ze względu na duże nasilenie zmian skórnych jeden z pacjentów był skłonny zaprzestać korzystania z urządzeń i powrócić do tradycyjnej insulinoterapii i do pomiarów glikemii poprzez nakłucie opuszki palca i odczyt z użyciem glukometru. Zważając na nieliczne doniesienia naukowe, opierające się głównie na pracach kazuistycznych, przeprowadzone badanie dostarcza nowych informacji w temacie kontaktowego zapalenia skóry wywołanego stosowaniem pomp insulinowych oraz sensorów glukozy u pacjentów z cukrzycą typu 1.

Tabela 2. Lista oraz stężenia testowanych alergenów kontaktowych.

| alergen | stężenie |
|---|---|
| **1**. siarczan niklu | 5.0% |
| **2**. żywica epoksydowa | 1.0% |
| **3**. balsam peruwiański | 25.0% |
| **4**. kalafonia | 20.0% |
| **5**. diakrylan butano-1,4-diolu | 0.1% |
| **6**. dimetakrylan butano-1,4-diolu | 2.0% |
| **7**. akrylan butylu | 0.1% |
| **8**. metakrylan butylu | 2.0% |
| **9**. diakrylan dietylenoglikolu | 0.1% |
| **10**. metakrylan N,N dimetyloaminoetylu (DMAEMA) | 0.2% |
| **11**. akrylan etylu | 0.1% |
| **12**. dimetakrylan glikolu etylenowego | 2.0% |
| **13**. metakrylan etylu | 2.0% |
| **14**. diakrylan 1,6-heksanodiolu | 0.1% |
| **15**. akrylan 2-hydroksyetylu (2-HEA) | 0.1% |
| **16**. 2-hydroksyetylometakrylan | 2.0% |
| **17**. 2,2-bis[4(2-hydroksy-3-metakryl-oksypropoksy)fenyleno]propan (BIS-GMA) | 2.0% |
| **18**. 2-hydroksypropylometakrylan | 2.0% |
| **19**. akrylan izobornylu (IBOA) | 0.1% |
| **20**. dimetakrylan bisfenolu (BIS-MA) | 2.0% |
| **21**. metakrylan metylu | 2.0% |
| **22**. N,N'-metylenobisakrylamid | 1.0% |
| **23**. diakrylan trietylenoglikolu | 0.1% |
| **24**. dimetakrylan trietylenoglikolu | 2.0% |
| **25**. triakrylan trimetylopropanu | 0.1% |
| **26**. diakrylan glikolu tripropylenowego | 0.1% |

| | |
|---|---|
| **27**. metakrylan tetrahydrofurfurylu | 2.0% |
| **28**. dimetakrylan tetraetylenoglikolu | 2.0% |
| **29**. dimetakrylan uretanu | 2.0% |

4) List do redakcji

**Allergic contact dermatitis caused by diabetes medical devices**

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*Alergologia Polska*

IF: 0,2 | MEiN: 140

Ostatnia publikacja wchodząca w skład rozprawy doktorskiej ma na celu zwiększenie świadomości lekarzy mających pod swoją opieką pacjentów z cukrzycą typu 1 na temat kontaktowego zapalenia skóry w wyniku stosowania urządzeń dla diabetyków. Zwrócono uwagę, że chociaż pompy insulinowe i sensory pomiaru glikemii są fundamentem leczenia cukrzycy typu 1 i znacząco podnoszą jakość życia pacjentów, to obserwuje się co raz więcej wywołanych przez nie przypadków kontaktowego zapalenia skóry. W pracy podkreślono istotę diagnostyki alergologicznej oraz wskazano, iż pacjenci zmagający się z problemem kontaktowego zapalenia skóry powinni mieć przeprowadzone testy płatkowe z uwzględnieniem pochodnych akrylanów, a w szczególności IBOA, aby móc wskazać przyczynę kontaktowego zapalenia skóry.

# 4. Wnioski

I. Kontaktowe zapalenie skóry spowodowane stosowaniem pomp insulinowych oraz sensorów glukozy to istotny problem kliniczny i duże wyzwanie diagnostyczne. Źródłem mogą być zarówno zestawy infuzyjne insuliny, jak i sensory pomiaru glikemii.
Do tej pory wiedza w tym temacie opierała się głównie na pracach kazuistycznych. Po raz pierwszy w Polsce udało się włączyć do badania większą grupę pacjentów i poddać ich specjalistycznej diagnostyce, uzyskując znaczące wyniki. Wyniki przedstawionych badań wypełniają również lukę w badaniach na temat kontaktowego zapalenia skóry spowodowanego urządzeniami dla diabetyków, które prowadzone są aktualnie w Europie i na świecie.
Zgodnie z wynikami przeprowadzonych badań kontaktowe zapalenie skóry częściej jest spowodowane sensorami – może to być zarówno klej mocujący urządzenie do skóry, jak i samo urządzenie. U większości pacjentów nie udało się zidentyfikować dokładnej przyczyny kontaktowego zapalenia skóry – nie można wykluczyć podłoża alergicznego, jak i zapalenia skóry z podrażnienia. Takich pacjentów powinno się diagnozować jako UCD. Wbrew oczekiwaniom i utartym standardom nie zawsze można postawić konkretną diagnozę ACD lub ICD, szczególnie w przypadku pacjentów stosujących urządzenia dla diabetyków. Jest to innowacyjne podejście w temacie diagnostyki kontaktowego zapalenia skóry, dzięki któremu nie przypisuje się pacjentowi jednostki chorobowej, do której rozpoznania czasami nie ma wystarczająco danych.

II. Zaledwie u 20% pacjentów zdiagnozowano ACD, a głównym alergenem sprawczym był IBOA. Prawdopodobnym alergenem jest również 2-HEA, którego obecność w urządzeniach musi jednak zostać zidentyfikowana, by ostatecznie uznać ten związek za alergen sprawczy. Podczas diagnostyki oraz przeprowadzania testów płatkowych wśród pacjentów z kontaktowym zapaleniem skóry spowodowanym stosowaniem urządzeń dla diabetyków należy zatem zawsze uwzględnić IBOA oraz 2-HEA. Istnieje potrzeba stworzenia serii testów płatkowych skierowanych do grupy pacjentów z kontaktowym zapaleniem skóry wywołanym stosowaniem urządzeń dla diabetyków. Pozwoliłoby to z większym prawdopodobieństwem określić tło zapalenia skóry. Alergiczne kontaktowe zapalenie skóry nie jest aż tak częstym problemem jak można by przypuszczać, co niesie za sobą istotne

implikacje kliniczne, gdyż łatwiej jest pomóc pacjentom doświadczającym zapalenia skóry z podrażnienia niż prezentującym alergię kontaktową.

III. W badaniu nie wykazano istotnie statystycznego związku pomiędzy rodzajem kontaktowego zapalenia skóry (ACD a ICD) a następującymi zmiennymi: wiek i płeć pacjenta; urządzenie powodujące kontaktowe zapalenie skóry; czas, po jakim pojawiły się pierwsze zmiany skórne; częstotliwość zmiany miejsca aplikacji sensora glukozy i/lub pompy insulinowej; wiek pacjenta w chwili rozpoznania cukrzycy typu 1; wiek pacjenta w chwili rozpoczęcia stosowania sensora glukozy i/lub pompy insulinowej.

IV. W badaniu nie wykazano istotnie statystycznego związku pomiędzy rodzajem urządzenia wywołującego kontaktowe zapalenie skóry (sensor glukozy, pompa insulinowa, sensor glukozy oraz pompa insulinowa) a następującymi zmiennymi: wiek i płeć pacjenta; czas, po jakim pojawiły się pierwsze zmiany skórne; częstotliwość zmiany miejsca aplikacji sensora glukozy i/lub pompy insulinowej; wiek pacjenta w chwili rozpoznania cukrzycy typu 1; wiek pacjenta w chwili rozpoczęcia stosowania sensora glukozy i/lub pompy insulinowej.

V. Aktualny stan wiedzy na temat kontaktowego zapalenia skóry spowodowanego stosowaniem pomp insulinowych oraz sensorów glukozy opiera się w dużej mierze na seriach przypadków klinicznych oraz badaniach retrospektywnych z niewielką grupą badaną. Zważając jednak na rosnącą liczbę pacjentów, głównie pediatrycznych, z diagnozą cukrzycy typu I, można się spodziewać wzrostu przypadków odnotowywanego kontaktowego zapalenia skóry w wyniku stosowania pomp insulinowych oraz sensorów pomiaru glikemii. Istotnym aspektem, który mógłby znacznie przyśpieszyć proces diagnostyczny i stworzyć alternatywne rozwiązania dla pacjentów, byłoby oznaczenie przez producentów poszczególnych alergenów użytych podczas produkcji urządzeń. Wyniki badań wskazują na pilną potrzebę wyeliminowania IBOA podczas produkcji urządzeń dla diabetyków.

# 5. Streszczenie w języku polskim

Wstęp:

Wprowadzenie sensorów glukozy oraz pomp insulinowych zrewolucjonizowało leczenie cukrzycy typu 1. Na przestrzeni ostatnich lat pojawiły się pojedyncze opisy przypadków kontaktowego zapalenia skóry wywołanego stosowaniem urządzeń dla diabetyków. Główną rolę w rozwoju ACD i ICD u pacjentów stosujących pompy insulinowe i sensory glukozy przypisuje się akrylanom, a w szczególności IBOA.

Cele:

Główny cel badania to ocena częstości występowania alergicznego kontaktowego zapalenia skóry oraz kontaktowego zapalenia skóry z podrażnienia u pacjentów z cukrzycą typu 1 leczonych pompami insulinowymi oraz stosujących sensory pomiaru glikemii. Kolejne cele badania to wytypowanie najczęstszych alergenów kontaktowych, które uczulają pacjentów stosujących urządzenia dla diabetyków, oraz analiza związku pomiędzy rodzajem kontaktowego zapalenia skóry i urządzeniem wywołującym kontaktowe zapalenie skóry a licznymi zmiennymi socjodemograficznymi. Ostatni cel badania to podsumowanie aktualnego stanu wiedzy na temat kontaktowego zapalenia skóry u pacjentów stosujących sensory glukozy oraz pompy insulinowe.

Wyniki:

W opublikowanych wynikach pracy oryginalnej 20% pacjentów miało dodatni wynik testów na poszczególne akrylany: trzech było uczulonych na IBOA, a jeden z nich dodatkowo na 2-HEA. Wszyscy trzej pacjenci korzystali z sensorów glukozy oraz z pomp insulinowych – jeden z pacjentów rozwinął ACD w wyniku stosowania sensora, jeden w wyniku stosowania sensora i pompy, a jeden miał ACD spowodowane stosowaniem wyłącznie pompy insulinowej. U dwunastu pacjentów (80%) nie stwierdzono żadnego uczulenia na alergeny badane, a kontaktowe zapalenie skóry zaklasyfikowano jako UCD. Kontaktowe zapalenie skóry częściej powodowały sensory. Nie wykazano statystycznie istotnego związku pomiędzy zmiennymi socjodemograficznymi pacjentów a rodzajem kontaktowego zapalenia skóry lub wywołującym je urządzeniem. Pierwszy oficjalnie opisany przypadek w Polsce dotyczył pacjenta płci męskiej, który rozwinął ACD w wyniku stosowania zarówno sensora pomiaru glikemii, jak i pompy insulinowej. W testach płatkowych wykazano uczulenie na IBOA, który jest użyty podczas produkcji stosowanych przez pacjenta

zestawów infuzyjnych insuliny. Warto zauważyć, że u pacjenta pierwotne zmiany w przebiegu kontaktowego zapalenia skóry dotyczyły tylko zestawu infuzyjnego insuliny, a dopiero po roku do obrazu klinicznego dołączyły zmiany kontaktowe w wyniku stosowania sensora glukozy. Można zatem podejrzewać, iż poprzez stosowanie pompy insulinowej doszło do pierwotnego uczulenia na IBOA, który może występować w sensorach glukozy stosowanych przez pacjenta. Nie można również wykluczyć, że w sensorze glukozy obecne są jeszcze niezidentyfikowane alergeny lub substancje drażniące. Dane dostępne w literaturze, które zostały podsumowane w artykule poglądowym, pozostają spójne z wynikami przeprowadzonego badania. IBOA pozostaje najlepiej poznanym i zarazem najczęstszym alergenem odpowiedzialnym za rozwój ACD u pacjentów stosujących urządzenia dla diabetyków. Jednocześnie u większości pacjentów identyfikacja alergenu sprawczego nie była możliwa, co wskazuje na obecność niezidentyfikowanych alergenów w urządzeniach lub tło z podrażnienia.

Wnioski:

U większości pacjentów stosujących sensory glukozy i pompy insulinowe nie udało się zidentyfikować alergenu odpowiedzialnego za kontaktowe zapalenie skóry. Wskazuje to na obecność niepoznanych jeszcze alergenów kontaktowych lub reakcję z podrażnienia. Rozpoznanie kontaktowego zapalenia skóry z podrażnienia wymaga z kolei wykluczenia potencjalnych alergenów kontaktowych obecnych w urządzeniach dla diabetyków, co jest obecnie niezwykle trudne. W grupie pacjentów z rozpoznanym alergicznym kontaktowym zapaleniem skóry to IBOA był najczęstszym alergenem sprawczym. Wyniki podkreślają istotne trudności w diagnostyce kontaktowego zapalenia skóry w grupie pacjentów z cukrzycą typu 1. Istnieje pilna potrzeba stworzenia serii testów płatkowych skierowanych do grupy pacjentów obciążonych cukrzycą i kontaktowym zapaleniem skóry wywołanym stosowaniem urządzeń dla diabetyków. Wśród alergenów testowanych powinny znaleźć się pochodne akrylanów, a w szczególności IBOA oraz 2-HEA. Ponadto oznakowanie przez producentów alergenów użytych podczas produkcji urządzeń dla diabetyków umożliwiłoby identyfikację nowych alergenów sprawczych i przyśpieszyłoby proces diagnostyczny. Dzięki temu pacjenci z cukrzycą, u których stwierdzono alergię kontaktową, mogliby świadomie wybierać urządzenia pozbawione alergenów, na które są uczuleni.

# 6. Streszczenie w języku angielskim

Introduction:

The introduction of glucose sensors and continuous subcutaneous insulin infusion systems was a milestone in the treatment of diabetes mellitus type I. In recent years a few cases of contact dermatitis towards glucose sensors and insulin infusions sets were reported. Acrylates, especially IBOA, are considered to play the major role in the development of ACD and ICD in diabetic patients.

Aim:

The main aim of the doctoral thesis was to assess the frequency of ACD and ICD in patients with diabetes mellitus type 1 experiencing contact dermatitis from using insulin pumps and glucose sensors with focus on acrylate derivates as the causative factors. Following aims were to select the most common culprit contact allergens causing ACD and to analyze the relationship between socio-demographic features of patients and type of contact dermatitis as well as the diabetes medical device causing contact dermatitis. The final goal was to conclude the current state of knowledge about contact dermatitis elicited by insulin infusion sets and glucose monitoring devices.

Results:

In the published original article three patients (80%) reacted to the following acrylate allergens: three patients reacted to IBOA and one of them additionally to 2-HEA. The results were of clinical relevance. All three patients were using insulin pumps and glucose sensors – in one patient contact dermatitis was towards the glucose sensor, in one patient towards the glucose sensor and insulin pump and in one patient only towards the insulin pump. Twelve patients did not show any skin reaction towards the allergens tested and were classified as UCD. Glucose sensors were more often responsible for contact dermatitis. No statistical significance was found between the type of diabetes medical device or type of contact dermatitis and socio-demographic features of the patients. The first officially reported case of ACD due to diabetes medical devices described a young male patient who elicited ACD to both, insulin infusion set and glucose sensor. In patch tests the patient was positive towards IBOA which is used in the production of insulin infusion sets used by the patient. Interestingly, initially contact dermatitis was limited to the insulin pump used and one year later new contact lesions from glucose sensor appeared. Probably the patient was

primarily sensitized to IBOA from insulin infusion sets, which might be present in the glucose sensor used. Another explanation is the presence of unknown allergens or irritants in the glucose sensors. The results obtained in our study are coherent with the current state of knowledge, which was summarized in the review article. IBOA remains the most known and common contact allergen responsible for ACD in patients using diabetes medical devices. At the same time, the identification of culprit allergen in most patients was not possible, showing that the causative contact allergens are not discovered yet, or that the contact dermatitis is irritant.

Conclusions:

In most patients the identification of causative allergens was not possible. Either the triggering allergen remains unknown or the contact dermatitis is irritant. Diagnosis of irritant contact dermatitis requires exclusion of most common contact allergens, what so far remains an immensely difficult task. In the group of patients with the diagnosis of allergic contact dermatitis the most common contact allergen was IBOA. Results show significant difficulties with the diagnosis of contact dermatitis in diabetes patients. There is an urgent need to create a patch tests series for diabetes patients, in which acrylate allergens, including IBOA and 2-HEA, would be present. Disclosing the precise chemical composition of the medical devices by the manufacturers would help in identifying the so-far unknown, potential allergens and facilitate the final diagnosis for many patients. Such information would allow patients suffering from contact dermatitis to choose from diabetes medical devices which are free from the sensitizing allergens.

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ORIGINAL ARTICLE

CONTACT DERMATITIS WILEY

# Role of acrylates in the development of contact dermatitis in diabetic patients—A Polish dermatology tertiary centre experience

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## Abstract

**Background:** In recent years, an increasing number of contact dermatitis cases triggered by acrylates contained in diabetes medical devices have been reported. Acrylates seem to play a major role in the development of irritant contact dermatitis and allergic contact dermatitis (ACD) in diabetic patients.

**Objectives:** To study a group of patients with contact dermatitis caused by diabetes medical devices with a focus on acrylates as possible allergens responsible for contact dermatitis.

**Patients and Methods:** Fifteen patients with diabetes mellitus type 1 and contact dermatitis from diabetic devices were patch tested to 25 acrylate allergens.

**Results:** Three patients (20%) reacted to the following allergens: three patients reacted to isobornyl acrylate (IBOA) and one of them additionally to 2-hydroxyethyl acrylate (2-HEA); results were of clinical relevance. All three patients were using insulin pumps and glucose sensors (GS)—in one patient contact dermatitis was towards the insulin pump and the GS, in one patient only towards the insulin pump and in one patient only towards the GS. Twelve patients (80%) did not show any skin reaction towards the allergens tested.

**Conclusion:** A majority of diabetic patients showed no reactions towards any acrylate allergen tested; yet, the presence of untested allergens must be kept in mind. IBOA proved to be a cause of ACD in diabetes patients. 2-HEA might be another culprit allergen, but its presence in the devices must first be confirmed.

KEYWORDS
2-hydroxyethyl acrylate, adhesives, allergic contact dermatitis, diabetes, glucose sensors, insulin infusion sets, irritant contact dermatitis, isobornyl acrylate

## 1 | INTRODUCTION

The introduction of glucose sensors (GS) and continuous subcutaneous insulin infusion (CSII) systems was a milestone in the treatment of diabetes mellitus type I (DM type I). With accurate glycaemic control, these devices reduce diabetes' long-term complications and enhance the patients' quality of life, hence increasing the compliance with medication.[1] The two main categories of GS are flash glucose monitoring (FGM) systems and continuous glucose monitoring (CGM) systems. FGM users scan the sensor to measure interstitial glucose levels; no calibrations according to self-monitoring of blood glucose are necessary.[2] Conversely, CGM systems provide real-time measurement of glucose levels but some do require more frequent calibrations based on fingerprick tests.[3] In line with new international guidelines, it is strongly recommended that children, adolescents and young adults (<25 years old) with DM

  

type 1 should use CGM systems as soon as possible after the diagnosis.[4]

However, in recent years, several adverse cutaneous reactions towards GS and CSII were reported. Isobornyl acrylate (IBOA), found in many diabetes devices, is considered to be the main culprit allergen.[5] Beside acrylates, allergens such as colophony, nickel sulphate or epoxy resin are also listed as culprits.[6] However, some patients do not present any skin reaction to tested allergens, indicating difficulties with patch testing and diagnosis of contact dermatitis from medical devices.

## 2 | PATIENTS AND METHODS

### 2.1 | Patients

The study was conducted between May 2022 and April 2023 at the Department of Dermatology, Venereology and Allergology, Medical University of Gdansk, Poland in cooperation with the Department of Paediatrics, Diabetology and Endocrinology, Medical University of Gdansk, Poland. Fifteen patients with DM type I with adverse cutaneous reactions at the application sites of GS and CSII were enrolled in the study. Skin lesions were typical for contact dermatitis (CD). Of the 15 patients, 11 were children (6 girls and 5 boys; mean age 11.2) and 4 were adults (1 woman and 3 men; mean age 32.3). Thirteen patients were using both GS and CSII and two patients were using GS only. Six patients had contact dermatitis to both GS and CSII, seven patients to GS only and two had skin lesions due to CSII only. The following GS were used by our patients: Freestyle Libre, Freestyle Libre 2 (Abbott Diabetes Care, Witney, UK), Dexcom G6 (Dexcom Inc., San Diego, CA, USA) and Medtronic Guardian 3 (Medtronic, Minneapolis, USA). There were no Medtronic Enlite users. Those patients with CSII devices used Medtronic 640 G, Medtronic 715 and Medtronic Veo 754 (with QuickSet, Silhouette and Sure-T infusion sets), mylife YpsoPump with Orbit infusion set (Ypsomed, Burgdorf, Switzerland), Accu-Chek with Rapid-D link infusion set (Roche Diabetes Care, Indianapolis, USA) and Equil micropump with soft infusion sets (MicroTech Medical [Hangzhou] Co. Zhejiang, China). The Omnipod pump (Insulet Corp., Acton, MA, USA) is not registered in Poland and was not used by any patients. None of the patients had previous history of sensitisation towards acrylates in everyday life.

Some patients tried to protect the skin around the device with overtapes to minimise the irritation. Skin protectors included sterile adhesive tapes (plasters), hydrocolloid plasters, kinesiology tapes and skin barrier sprays. Despite the additional protective measures, the dermatitis did not alleviate.

### 2.2 | Patch tests

Patch tests (Finn Chamber AQUA, SmartPractice, Phoenix, Arizona) with 25 acrylates (Chemotechnique Diagnostics, Vellinge, Sweden) were placed on the patients' backs with readings performed on day (D) 2, D3 and D7 in accordance with the guidelines of the European Society of Contact Dermatitis.[7] Apart from acrylates, patients were also patch tested with nickel, colophony and epoxy resin. These are the allergens from the Polish Baseline Series, which proved to be the culprits of contact dermatitis in some diabetic patients.[6]

An overview of the allergens used to patch test is presented in Table 1.

Positive patch tests to allergens, together with clinical relevance and information about their presence in certain diabetes medical devices, either from the manufacturer or from the literature, allowed for the diagnosis of allergic contact dermatitis (ACD). Negative patch tests were treated as unspecified contact dermatitis (UCD; possible ACD−exclusion of the possible role of an untested allergen required).[8] Two patients with history of atopic dermatitis had irritant reactions at

**TABLE 1** An overview of the allergens used to patch test patients with contact dermatitis elicited by diabetes medical devices.

| Allergen | Vehicle | Concentration |
|---|---|---|
| 1. 1,4-Butanediol diacrylate | pet. | 0.1% |
| 2. 1,4 Butanediol dimethacrylate | pet. | 2.0% |
| 3. Butyl acrylate | pet. | 0.1% |
| 4. Butyl methacrylate | pet. | 2.0% |
| 5. Diethyleneglycol diacrylate | pet. | 0.1% |
| 6. *N,N*-Dimethylaminoethyl methacrylate | pet. | 0.2% |
| 7. Ethyl acrylate | pet. | 0.1% |
| 8. Ethyleneglycol dimethacrylate | pet. | 2.0% |
| 9. Ethyl methacrylate | pet. | 2.0% |
| 10. 1,6-Hexanediol diacrylate | pet. | 0.1% |
| 11. 2-Hydroxyethyl acrylate (2-HEA) | pet. | 0.1% |
| 12. 2-Hydroxyethylmethacrylate | pet. | 2.0% |
| 13. 2,2-Bis(4-(2-hydroxy-3-methacryloxypropoxy)phenyl) propane, (BIS-GMA) | pet. | 2.0% |
| 14. 2-Hydroxypropylmethacrylate | pet. | 2.0% |
| 15. Isobornyl acrylate (IBOA) | pet. | 0.1% |
| 16. 2,2-Bis(4-methacryloxy)phenyl propane | pet. | 2.0% |
| 17. Methyl methacrylate | pet. | 2.0% |
| 18. *N,N*-Methylene-bisacrylamide | pet. | 1.0% |
| 19. Triethyleneglycol diacrylate | pet. | 0.1% |
| 20. Triethyleneglycol dimethacrylate | pet. | 2.0% |
| 21. Trimethylolpropane triacrylate | pet. | 0.1% |
| 22. Tripropyleneglycol diacrylate | pet. | 0.1% |
| 23. Tetrahydrofurfurylmethacrylate | pet. | 2.0% |
| 24. Tetraethyleneglycol dimethacrylate | pet. | 2.0% |
| 25. Urethane dimethacrylate | pet. | 2.0% |
| 26. Nickel sulphate hexahydrate | pet. | 5.0% |
| 27. Colophony | pet. | 20.0% |
| 28. Epoxy resin | pet. | 1.0% |

Abbreviation: pet.: petrolatum.

the edge of the chamber application sites. After removing them, erythematous papules were visible (rim/edge effect). These lesions, however, diminished and were not present during the follow up readings (decrescendo sign).

### 2.3 | Statistical analysis

For statistical analysis, Pearson's chi-squared test ($\chi^2$), Mann–Whitney U test (MWU) and Kruskal–Wallis one-way analysis of variance (ANOVA) were used with statistical significance level of $p < 0.05$.

### 2.4 | Ethical approval

The study was approved by the Local Ethics Committee of the Medical University of Gdansk for studies involving humans (NKBBN/88/2022). Patients gave written consent to have patch tests performed and for photographs of their skin lesions to be taken and used.

## 3 | RESULTS

Fifteen patients were enrolled in the study and patch tested. Patients' demographic and clinical data, type of devices used, features and patch test results are presented in Table 2. Three of the fifteen patients showed positive reactions towards acrylates tested—three patients reacted to IBOA on D2, D3 and D7 and one of them had additional positive results towards 2-hydroxyethyl acrylate (2-HEA) on D2, D3 and D7. The presence of IBOA in the devices confirmed ACD. Of the three patients, one elicited contact dermatitis towards Freestyle Libre and Dexcom G6, one to Medtronic Guardian 3 and Medtronic Sure-T, Silhouette and Quick-Set infusion sets and one to Orbit microinfusion set. Additionally, one patient had positive results towards nickel sulphate on D2, D3 and D7, one to colophonium on D2 and one to epoxy resin in D2 and D3. Twelve patients did not have any positive skin reactions towards any of the acrylates patch tested.

There was no statistically significant relationship between the type of contact dermatitis (UCD or ACD) and sex ($\chi^2$: $p = 0.438$; $V = 0.20$) or age of patients ($\chi^2$: $p = 0.372$; $V = 0.36$). Also, there was no link between the type of contact dermatitis and the diabetes medical devices used ($\chi^2$: $p = 0.520$; $V = 0.30$) or time after which the dermatitis appeared ($\chi^2$: $p = 0.315$; $V = 0.49$). The three patients with ACD first elicited skin lesions from within a few hours up to 7 months, whereas for patients with UCD, it was most often either 1–3 days or up to half a year for the lesion to appear. However, patients with UCD less often changed the application sites of the devices ($\chi^2$: $p < 0.05$; $V = 0.85$). There was no correlation between the type of contact dermatitis presented and the age at which patients were diagnosed with DM I (MWU: $p = 1.000$; $r = 0.00$), or age at which patients started to use GS/CSII (MWU: $p = 0.273$; $r = 0.30$). For the patients with ACD the mean age of DM I diagnosis was 11 years, whereas for patients with UCD it was 8 years. No link was shown between the type of medical device triggering skin lesion (GS or CSII) and sex and age of patients ($\chi^2$: $p = 0.689$; $V = 0.22$ and $\chi^2$: $p = 0.754$; $V = 0.25$, respectively). Furthermore, no connection between medical device used and time after which contact dermatitis appeared ($\chi^2$: $p = 0.635$; $V = 0.38$) as well as between medical devices used and the frequency of changing their application sites (ANOVA: $p = 0.118$; $V = 0.68$) was found. In the group of patients using GS only, GS was changed every 7, 10 or 14 days, whereas users of CSII changed application site every 3 days. No relationship between use of GS or CSII causing dermatitis and the age at which these devices were used the first time was observed ($p = 0.243$; $\eta^2 = 0.08$).

The most often reported sensations accompanying dermatitis were itching, erythema and scaling. Four patients described pain in the affected area and two patients experienced sleep deprivation due to the lesions. Because of the severity of dermatitis, one patient had to switch from GS to fingerprick tests and one patient was close to resigning from GS use altoghether. Interestingly, patients with severe dermatitis were not diagnosed with ACD. Prior to application of GS or CSII all patients said they disinfected the skin—four were using alcohol free, octenidine-based antiseptics, ten were using alcohol-based (2-propanol, 1-propanol, 2-diphenylol or isopropyl based) antiseptics and one patient was interchangeably using both.

## 4 | DISCUSSION

With cutaneous adverse effects being the most common reason for discontinuation of CGM use, it is crucial to determine the potential role of allergens in triggering contact dermatitis.[9] Numerous publications have proven that acrylates are allergens responsible for ACD in occupational settings, especially in medicine, dentistry, printing industry, cosmetology and the adhesive/coatings industry. An increasing number of cases describing adverse cutaneous reactions towards diabetes medical devices are being reported worldwide, with acrylates being mentioned as the main culprits of ACD. In the production of diabetic devices, acrylates are mainly found to be part of adhesives used to attach devices to the skin or are used to join plastic components together. To date, there is a paucity of data comparing prevalence of ICD and ACD in diabetic patients. Asarani et al. provided a systematic review of cutaneous manifestations related to GS use from 54 eligible studies—allergic skin reactions were reported in four trials and comprised 4.3% of all adverse skin reactions.[10] On the other hand, Ahrensbøll-Friis et al., in a 5-year-period study established that over 76.0% of GS and CSII users with contact dermatitis proved to have ACD or probable ACD.[11] However, there are a few studies showing the incidence of ICD in diabetic patients. In a study performed by Herman et al., 32.7% of patients tested had no positive reaction in patch tests, suggesting ICD.[5]

Although the problem of contact dermatitis elicited by diabetes medical devices has already been highlighted in recent years, many manufacturers of GS/CSII still do not label their products with

**TABLE 2** Contact dermatitis from diabetes medical devices: patients' demographic and clinical data, type of devices, features, and results of the patch tests.

| | | | Reaction to medical device | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Patient no. | Age | Sex | GS | CSII | Positive patch tests to acrylate allergens (D2/D3/D7) | Time between GS/CSII application and the onset of symptoms | Atopic dermatitis history | Other concomitant diseases | Positive patch test results to nickel, colophony or epoxy resin (D2/D3/D7) |
| 1. | 17 | F | Dexcom G6<br>FreeStyle Libre | – | IBOA (+/++/+++) | 3 days (both) | – | – | Ni (++/++/+++)[a] |
| 2. | 18 | M | Guardian Sensor 3 | Paradigm medtronic 640 G (Quick-set, Sure-T, Silhoutte) | IBOA (+/+/+) | Few hours (both) | – | – | ER (+/+/–) |
| 3. | 12 | M | Dexcom G6 | – | – | 3 days | – | Allergic asthma coeliac disease | – |
| 4. | 9 | M | Guardian Sensor 3 | – | – | Few hours | yes | – | |
| 5. | 11 | M | Guardian Sensor 3 | Paradigm Medtronic 640 G (Sure-T) | – | 4 months (GS) 7 months (CSII) | – | – | Co (+/–/–) |
| 6. | 7 | F | Guardian Sensor 3 | Paradigm Medtronic (Quick-set, Sure-T) | – | 1–3 days (both) | – | – | – |
| 7. | 9 | F | FreeStyle Libre | – | – | 2 days | – | – | – |
| 8. | 14 | F | – | Mylife YpsoPump (Orbit infusion set) | 2-HEA (+/++/+)<br>IBOA (+/++/+) | 7 months | – | Coeliac disease | – |
| 9. | 6 | F | Guardian Sensor 3 | – | – | 14 days | – | – | – |
| 10. | 6 | M | Dexcom G6 | Paradigm Medtronic Veo | – | 4 years (both) | – | – | – |
| 11. | 14 | F | FreeStyle Libre | Accu-Chek Rapid-D Link | – | 1 month | – | – | – |
| 12. | 32 | M | – | Equil micropump, (soft infusion sets – 6 and 9 mm) | – | 2 days | – | – | – |
| 13. | 33 | F | FreeStyle Libre<br>FreeStyle Libre 2 | – | – | 6 months (both) | – | – | – |
| 14. | 36 | M | FreeStyle Libre 2 | – | – | 12 days | Yes | – | – |

TABLE 2 (Continued)

| Patient no. | Age | Sex | Reaction to medical device: GS | Reaction to medical device: CSII | Positive patch tests to acrylate allergens (D2/D3/D7) | Time between GS/CSII application and the onset of symptoms | Atopic dermatitis history | Other concomitant diseases | Positive patch test results to nickel, colophony or epoxy resin (D2/D3/D7) |
|---|---|---|---|---|---|---|---|---|---|
| 15. | 28 | M | FreeStyle Libre 2 | Paradigm Medtronic 715 (Quick-set) | – | 3 days | – | – | – |

Abbreviations: 2-HEA, 2-hydroxyethyl acrylate; Co, colophonium; CSII, continuous subcutaneous insulin infusion; D2, day 2; D3, day 3; D7, day 7; ER, epoxy resin; F, female; GS, glucose sensor; IBOA, isobornyl acrylate; M, male; Ni, nickel; –, not applicable.
[a]Despite sensitization towards nickel, the patient did not present any signs of contact dermatitis resulting from contact with this metal in everyday life.

allergens that might be present. This fact delays and makes the diagnosis of ACD more difficult, as the clinical aspect alone does not allow precise differentiation between ICD and ACD. We made attempts to obtain information about acrylate allergens used in the production of certain GS and CSII, but the responses we received were in vast majority of cases inaccurate and unspecific (e.g. "adhesives contain acrylates" or "polyacrylates are present") or there was no response at all. Considering that acrylates and acrylate derivatives (methacrylates and cyanoacrylates) comprise for an expansive group of chemical compounds, such inadequate information about their potential presence in medical devices hampers diagnosis of ACD.

Acrylate polymers are formed in a process of polymerisation of monomers. Monomers are the causative agents of most documented cutaneous reactions, in contrast to polymers, which usually are inert. However, trace amounts of monomers can almost always be present in polymers.[12] Acrylates and their derivates have potency to induce irritation in contact with skin as well as to sensitise individuals and trigger allergic skin reactions upon repeated exposure.

### 4.1 | Irritant potency of acrylates

ICD accounts for ~80% of all cases of contact dermatitis[13] and results from direct damage to epidermal cells by external toxic agents (e.g., chemicals, metal ions or plants) or ambient environmental factors (humidity, occlusion and temperature). Although the pathogenesis of ICD for a long time was thought to be non-immunological, it is thought that immune system does play a role in causing ICD with upregulation of proinflammatory cytokines such as IL-1α (interleukin-1 alpha), IL-1β (interleukin-1 beta) and TNF-α (tumour necrosis factor alpha) upon damage to keratinocytes.[14] According to literature, diacrylates show the highest irritant potency, monoacrylates show moderate potency and methacrylates are considered weak irritants.[12] Glycidyl methacrylate,[15] cyanoacrylates,[16] butanediol diacrylate,[17] hexanediol diacrylate[17] and tetraethylene glycol diacrylate[18] are documented culprits of ICD. Although the amounts of residual acrylate monomers in medical devices are low, the exact concentrations able to elicit ICD are not described.

In our study, 12 patients (80%) had negative patch tests to acrylates. Most of them developed dermatitis within 1–3 days after the first attachment of the device to the skin, in line with the typical onset time of acute/subacute ICD forms and confirming that previous sensitisation is not required to elicit ICD. Two of these twelve patients, one with dermatitis due to Medtronic Veo CSII and the other due to FreeStyle Libre 2 GS, had their first skin lesions after 1 year or more of sustained use. According to Bains et al. and Patel and Nixon, a chronic subtype of ICD can develop over years as a result of skin exposure to weak irritants and repetitive micro injuries to the skin barrier.[13,19] The rash in vast majority of patients was well-demarcated and always started at the area of direct contact of the device with skin, without spreading to nearby sites. Interestingly, three patients with UCD reduced the contact time of GS/CSII with the skin by more frequent reapplications and reported positive

outcomes. The gradual resolution of skin reactions after the cessation of exposure, known as 'decrescendo sign', indicates an irritant reaction rather than an allergic one. Apart from the chemical irritant properties of acrylates, environmental factors also contribute to the development of ICD in diabetic patients; yet, they are very often neglected or ignored. Repeated occlusion for prolonged periods reduces the perspiration rate and increases humidity, leading to skin barrier disruption and making individuals more susceptible to irritants such as heat or sweat. It can also promote the penetration of acrylates through the skin barrier. Small acrylic monomers can permeate protective rubber surfaces (like disposable gloves), which can explain the ineffectiveness of additional skin protectives.[20]

Nonetheless, the diagnosis of ICD in our group of patients is not necessarily an appropriate one. First of all, the role of untested allergens in elicitation of contact dermatitis has to be excluded before a diagnosis of ICD. Currently, we do not know the composition of the adhesives used by manufacturers and identifying the culprit allergen (apart from the already known as IBOA or MBPA in particular devices) sometimes resembles a 'trial and error' method. Many patients experience contact dermatitis from devices containing IBOA but have negative patch tests. Second, it is theoretically possible that a patient may be sensitised to an allergen in the first device after several months of use and upon switching to another device containing the same allergen develops contact dermatitis. In such scenario, we cannot classify the reactions as ICD.

## 4.2 | Allergic potency of acrylates

All acrylates have a potential to sensitise and, in line with type IV hypersensitivity reactions, produce the clinical symptoms of ACD during reexposure. Polyfunctional acrylates show the highest potential to sensitise whereas monoacrylates and their corresponding methacrylates are weaker sensitisers.[12] Although ACD is less common than ICD, the clinical significance is much greater as elimination of the culprit allergen is of tremendous importance.

In 2017, IBOA was identified in FreeStyle Libre and proved to be the major culprit of allergic reactions, something which has been confirmed in many subsequent studies.[21] Later, IBOA became allergen of the year 2020 and to date is the most well-known allergen responsible for ACD in patients using diabetic medical devices.[22] Other acrylates reported to elicit ACD include *N,N*-dimethylacrylamide,[23] 2-ethyl cyanoacrylate,[24] dipropylene glycol diacrylate,[25] β-carboxyethyl acrylate and phenoxypoly(ethylenoxy) ethylacrylate.[26] Recently, 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate (MBPA) was identified as a new component in the adhesive of Dexcom G6 model.[27]

The three patients who had positive IBOA patch tests were using the following sets: i) the first patient was using FreeStyle Libre and Dexcom G6 sensors; ii) the second patient was a user of the Guardian 3 sensor and Medtronic Sure-T, Silhouette and Quick-Set infusion sets; iii) the third patient was using the Orbit microinfusion set. Although IBOA was eliminated from FreeStyle Libre 2 in 2020, as was confirmed by Oppel et al.,[28] it was present in the first generation of FreeStyle Libre.[21] Also, initially the Dexcom G6 was thought to be an IBOA-free alternative.[29] However, in another study performed by Svedman et al. all diabetic patients reacted positively to IBOA and gas chromatography–mass spectrometry detected IBOA in Dexcom G6 sensors.[30,31] Therefore, it is probable that the first patient got initially sensitised towards IBOA from Dexcom G6 and reacted to IBOA present in FreeStyle Libre. Both Dexcom G6 and FreeStyle Libre triggered skin reactions after about 3 days of use. This also supports the finding that Dexcom G6 is not free from IBOA. The second patient was primarily sensitised from the use of IBOA-containing infusion sets and 1 year later developed contact dermatitis from the Guardian 3 sensor with the culprit allergen remaining unknown.[32] Relevant to the third patient, Enberg et al. reported a case of a 6-year-old who had ACD due to IBOA contained in the new Orbit microinfusion set linked with MyLife YpsoPump.[33] Our patient, who is a user of the same set, besides IBOA also reacted to 2-HEA (Figure 1). It is probably the first case of ACD elicited by the Orbit microinfusion from Poland. There are no data on whether Orbit microinfusion contains 2-HEA and we are currently investigating the potential presence of 2-HEA in this device in cooperation with the Department of Pharmaceutical Chemistry, Medical University of Gdansk.

Two patients using Dexcom G6, four patients using Guardian 3, two users of FreeStyle Libre and three users of FreeStyle Libre 2 had no positive patch tests results, despite clinical presentation of contact dermatitis. Possible explanations for that may be that

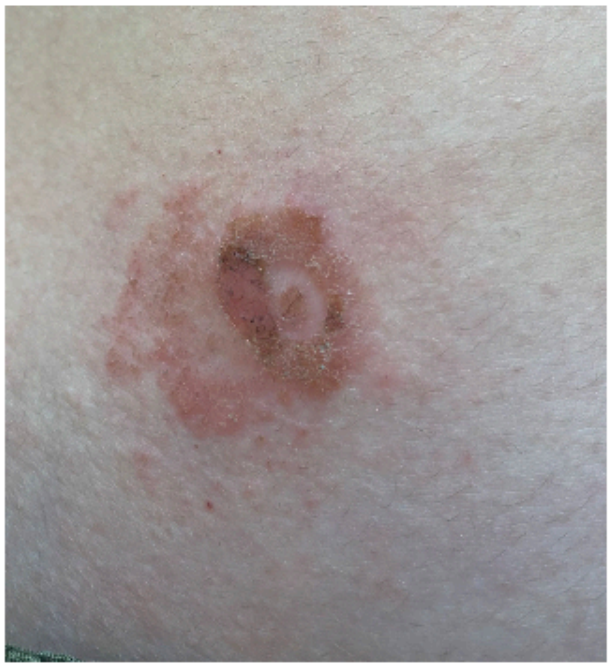

**FIGURE 1** Allergic contact dermatitis to isobornyl acrylate (IBOA) contained in mylife YpsoPump with orbit infusion set. The patient is also sensitised towards 2-hydroxyethyl acrylate (2-HEA), though its presence in this device is not yet confirmed.

disrupted skin barrier and genetic or immunological pathways predispose some patients to allergic skin reactions caused by acrylates, whereas others without those predispositions do not develop ACD. Still, the easiest explanation is the presence of an allergen we are not yet aware of. Furthermore, to the best of our knowledge, there are presently no reports on substances reported as culprit sensitisers in FreeStyle Libre 2 or Medtronic Guardian 3 sensors.

One patient, despite sensitisation towards nickel, did not present any signs of contact dermatitis resulting from contact with this metal in everyday life. One patient had a positive result to epoxy resin on D2 and D3, but negative in the following reading on D7. There was no clinical relevance either. Another patient, a user of Medtronic Sure-T insulin infusion set, had positive results towards colophonium on D2, but no reaction was observed on D3 and D7. Passanisi et al.[34] reported a patient with severe ACD caused by colophonium contained in the Medtronic Enlite sensor, which presence was then confirmed by the manufacturer. However, there is no data whether any of the Medtronic insulin infusion sets contain this allergen. Therefore, the patient could be treated as UCD. The final diagnosis requires identification of the allergen in the device.

A limitation of the study is a relatively small study group. However, from our observations in our region (Pomeranian Voivodeship, northwestern Poland) contact dermatitis affects ~1%–2% of patients with DM1 and not every patient is seeking dermatological help, mainly those with severe and exaggerated contact dermatitis. Logistical challenges (living far away from Gdansk; inability to attend follow up readings) prevented some patients from taking part in the study. Patients suffered from contact dermatitis to diabetes medical devices only. They did not present any other clinical signs of contact allergy towards any of the commonly observed allergens. Therefore, the entire standard series (Polish Baseline Series) was not tested, but only the targeted allergens that were most likely to elicit dermatitis. Moreover, we did not want to expose patients to new allergens. Incapability of carrying out patch tests with some suspected allergens (like MBPA or phenoxyethanol used in disinfectants) is another limitation.

In conclusion, although certain acrylates contained in diabetes medical devices have been proven to elicit contact dermatitis (e.g., IBOA), our study showed that in many situations the causative factor has not yet been identified. It highlights the difficulties in patch testing and diagnosis of contact dermatitis in diabetic patients using medical devices.

## AUTHOR CONTRIBUTIONS

**Mikołaj Cichoń:** Writing – original draft; funding acquisition; conceptualization; investigation; writing – review and editing; methodology; visualization; data curation; resources. **Małgorzata Myśliwiec:** Resources; supervision; formal analysis; methodology; project administration; writing – review and editing. **Magdalena Trzeciak:** Funding acquisition; writing – review and editing; project administration; formal analysis; supervision; resources; investigation; methodology.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

Research data are not shared.

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# Contact Dermatitis to Diabetes Medical Devices

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**Abstract:** Skin adverse reactions to diabetes medical devices have been reported frequently over recent years. Adhesives attaching glucose sensors and continuous insulin infusion sets to the skin are proven to cause both allergic contact dermatitis and irritant contact dermatitis in patients with diabetes mellitus. Several allergens contained in adhesives and/or parts of medical devices are documented to cause allergic contact dermatitis, with acrylate chemicals being the most common culprit-especially isobornyl acrylate (IBOA), but also 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate or cyanoacrylates. Epoxy resin, colophonium and nickel were also identified as causative allergens. However, repetitive occlusion, maceration of the skin and resulting disruption of the skin barrier seem to have an impact on the development of skin lesions as well. The purpose of this study is to highlight the burden of contact dermatitis triggered by diabetes medical devices and to show possible mechanisms responsible for the development of contact dermatitis in a group of diabetic patients.

**Keywords:** allergic contact dermatitis; irritant contact dermatitis; diabetes medical devices; glucose sensors; insulin pumps; isobornyl acrylate; IBOA; 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate; MBPA



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## 1. Introduction

The management of diabetes mellitus (DM) has been vastly improved due to the broader access to technological devices such as glucose sensors (GS) and continuous subcutaneous insulin infusion (CSII) sets. The two main categories of GS are flash glucose monitoring (FGM) and continuous glucose monitoring (CGM). FGMs do not require calibration with self-measurements of glucose levels from finger prick tests, but users need to scan the sensor manually. On the other hand, CGMs provide real-time tracking of interstitial glucose levels, though some of them still require calibration [1]. Avoiding short-term complications of DM (such as diabetic ketoacidosis or frequent hypoglycemia episodes) and long-term complications (such as retinopathy, nephropathy or neuropathy) is essential and more accurate glycemic control facilitated by early use of GS and CSII by minimizes these risks. Use of medical devices also increases patients' compliance with medication and enhances their quality of life [2]. Although the management of DM1 has been revolutionized by technological achievements, the incidence rate of dermatological complications resulting from using diabetes medical devices is increasing. The incidence of DM type 1 and DM type 2 continues to rise in Europe [3]. Over recent years, cases of irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD) caused by diabetes medical devices have been reported, with acrylates being the most common culprit in the latter [4]. Apart from contact dermatitis, other cutaneous adverse effects frequently seen include skin infections, unspecified skin eruptions, urticaria or oedema [5]. Berg et al. report that almost 90% of patients using CSII experienced adverse skin effects with non-specific eczema being present most frequently in 25.7% of patients [6]. Since skin adverse effects remain the most common reason for discontinuation of CGM, it is crucial to determine the role of allergens

in triggering contact dermatitis and the mechanisms beyond it [7]. This article focuses on allergens eliciting ACD as well as on the factors leading to ICD in diabetic patients.

*Materials and Methods*

A review of the literature concerning the problem of contact dermatitis in patients with diabetes who use medical devices was conducted using PubMed and Web of Science between March 2023 and June 2023. No restrictions were placed on article types, publication date, country, journal or publisher. The following terms were searched for: diabetes medical devices, diabetes devices, insulin infusion sets, insulin pumps, continuous glucose monitoring system, flash glucose monitoring system, glucose monitoring system, glucose sensors, acrylate, acrylates, isobornyl acrylate, IBOA and contact dermatitis, allergic contact dermatitis and irritant contact dermatitis. A backward search (scanning the references included in relevant articles), as well as forward search (search for relevant articles in which the original article was cited after being published), was also conducted. Since the clinical problem of contact dermatitis elicited by diabetes medical devices is not that widely explored and covered in the literature yet and many studies are currently being performed, personal observations were also included (these are appropriately indicated in the text).

## 2. Contact Dermatitis Triggered by Diabetes Medical Devices

Contact dermatitis (CD) is a very common inflammatory skin disease characterized by pruritic, eczematous-scaling lesions sometimes accompanied by vesicles or impetiginization. The two main types of contact dermatitis are ACD and ICD, whose clinical pictures in most cases are indistinguishable. ICD is more frequent and stands for approximately 80% of all contact dermatitis cases [8], whereas the prevalence of ACD is as much as 20% [9]. Statistically, contact dermatitis affects women twice as often as men with the onset of symptoms between 12 and 16 years of age in 15% [10,11]. Notably, the coexistence of ACD and ICD at the same time is possible. Since DM1 accounts for about 85% of all diabetes cases in patients under the age of 20, with a peak between 10 and 14 years old, most device users are children and adolescents [12]. Therefore, dermatological problems that stem from the use of either GS or CSII sets are most common in the younger group of patients.

Whilst several report studies and case series have been published across the past few years, there is a paucity of reliable systematic reviews or meta-analysis presenting the actual incidence rate of ACD and ICD triggered by diabetes medical devices. Nonetheless, contact dermatitis elicited by the use of insulin pumps and/or glucose sensors can be either allergic or irritant [13].

### 2.1. Risk Factors

There are risk factors for the development of local skin reactions to diabetes medical devices. One of them is the use of diabetes devices in the past, which could contain allergens (such as IBOA), regardless of the presence of skin lesions. Svedman et al. pinpointed that patients sensitized through the use of one medical device are not free from future episodes of ACD when using another product [14]. Another risk factor is atopic dermatitis history and consequent epidermal barrier disruption or other epidermal barrier disorders (e.g., fillagrin deficiency). Such conditions facilitate the penetration of allergens through the skin barrier leading to more prompt sensitization. Furthermore, patients with skin barrier abnormalities have lower inflammatory thresholds for external irritant factors and are more likely to develop ICD [15].

### 2.2. Allergic Contact Dermatitis

ACD is an example of a type IV hypersensitivity reaction according to Coombs and Gell classification, in which dermal dendritic cells (DCs) and epidermal DCs (Langerhans cells) play a key role in sensitization and elicitation phases. During the sensitization process, an individual is first exposed to an allergen (hapten), which reacts with DCs and, as a hapten-peptide complex, migrates to regional lymph nodes of the skin and prime naïve Th-cells.

DCs present the haptens on their major histocompatibility complex molecules (MHC) to antigen-specific T-cell receptors (TCRs) leading to the formation of hapten-specific memory and effector T-cells. Upon re-exposure, the hapten is recognized by already sensitized hapten-specific T-cells, which migrate to the skin. Following this, hapten-specific cytotoxic CD8+ T lymphocytes, via proinflammatory cytokine cascade, elicit skin lesions that are clinically seen as ACD [16,17]. DCs, by priming the naïve T-cells, act as a link between the innate and adaptive immune system. (Meth)acrylates are suspected to be the major contact allergens found in medical adhesives.

What is currently being investigated is why not all individuals exposed to an allergen become sensitized towards it and, consequently, might develop ACD. Genetic tendencies and environmental factors seem to predispose certain groups and put them at higher risk of developing ACD [18]. Family members tend to develop ACD more frequently, which suggests the role of genetics but also pinpoints environment and ethnicity as risk factors [18]. Mutations in the genes encoding proteins of the epidermal skin barrier (e.g., filaggrin) [19] or genetically influenced polymorphism for enzymatic activities (e.g., higher N-acetyltransferase activity is linked with contact dermatitis) play a role as well [20,21]. Gene polymorphisms in coding regions of enzymes such as glutathione S-transferases M1 and T1 [22] or angiotensin-converting inhibitors [23] are associated with an increased risk for ACD. Cytokine gene polymorphisms for promoters for tumor necrosis factor alpha [24] or interleukin 16 [25] are genetic risk factors directly connected to the immunological response.

#### 2.2.1. Patch Testing

The gold standard in the diagnosis of ACD is patch testing. When suspecting ACD connected to diabetes medical devices, acrylate-series patch tests including IBOA should be performed. From our observations, acrylate allergens very often do not give positive results until the last reading taken after 7 days, so it is crucial to perform all three readings after 48 h, 72 h and 7 days. The difficulties of patch testing and diagnosis of cases with contact dermatitis from medical devices have been discussed by Ulriksdotter et al. as the role of an untested allergen in the development of dermatitis must be kept in mind. Frequently, the causative allergen is not identified [26]. Cases with negative patch tests could be described as possible ACD or unspecified contact dermatitis.

The question arises whether diabetic patients should undergo patch testing prior to using the device. There is, however, no unequivocal answer. This difficult topic is not covered in any guidelines and should be treated in a patient-oriented way. The decision on performing patch tests (or not) is strongly dependent on the clinical picture and symptoms patients present. If a patient has a history of contact allergy to glues, sealants, adhesives, etc., it seems reasonable to extend diagnostics with patch tests as possible results towards epoxy resin, colophony or isobornyl acrylate can help with choosing the appropriate device free from these allergens, thus preventing possible elicitation of ACD. On the other hand, exposing patients to new allergens during patch tests and possible sensitization, even if they do not present clinical symptoms of contact allergy towards any allergens, remains highly questionable. The identification of the causative allergen(s) in patients with contact allergy towards medical devices is immensely challenging, sometimes resembling the 'trial and error' method. Finally, not every patient using insulin pumps and/or glucose sensors eventually elicits contact dermatitis. Unfortunately, we have not found any official data describing the percentage of patients with DM experiencing contact dermatitis from the medical devices they use. From our observations, this number fluctuates by a few percent, though the trend is upward in recent years (personal observations M.C. and M.T.).

In the following paragraphs, we outline the contact allergens eliciting ACD and evaluate the factors contributing to ICD in the users of diabetic medical devices.

2.2.2. Isobornyl Acrylate

Acrylates are created by polymerization of monomers derived from (meth)acrylic acid. Acrylic monomers are proven to cause the most documented cutaneous reactions. In contrast, acrylic polymers are relatively inert, though every polymerized acrylate very often contains trace amounts of residual monomers [27]. It has been shown that all types of acrylates have the potential to sensitize, with monoacrylates being considered weaker sensitizers and multifunctional acrylates as stronger allergens [27].

Isobornyl acrylate (IBOA; CAS 5888-33-5), the 2020 American Contact Dermatitis Society Allergen of the Year, is a liquid and reactive acrylate monomer widely used in plastic material and ink manufacture. In everyday life, IBOA can be found in glues, adhesives, resins, inks and solvents, in which it offers good resilience, flexibility and hardness [28]. Therefore, it is also a perfect compound for the manufacture of adhesives used to attach GS and CSII sets to the skin. On safety sheets, it is classified as an irritant substance. As Foti et al. report, IBOA may sometimes play the role of a hidden allergen collected as an impurity during the industrial process [29]. In the past, IBOA, though repeatedly identified in occupational components, was rarely the cause of ACD and remained in the shadow of other acrylates responsible for ACD such as 2-hydroxyethyl methacrylate or ethylene glycol dimethacrylate [30,31]. The first reports of IBOA-induced ACD in diabetic patients are from 1995 when two young women experienced eczema at the sites of insulin pump attachment [32]. IBOA was one of the allergens detected in the UV-cured (ultraviolet-cured) glue used to fix the needle into the plastic set. Both patients had positive patch test results for this acrylate. In 2016, the accidental presence of IBOA in the FreeStyle Libre sensor (FreeStyle Libre; Abbott Diabetes Care, Alameda, CA, USA) was established by a group of Belgian dermatologists [28]. From this moment onward, more and more diabetic patients with similar skin lesions were patch tested towards IBOA, proving this acrylate to be the culprit in many cases. In Finland, 81% of the patients experiencing adverse skin reactions to FreeStyle Libre were sensitized towards IBOA [33,34]. In the years since, it has been confirmed that, apart from FreeStyle Libre, IBOA is a contact allergen detectable in: (i) the housing [35] (1.11 ± 0.12 µg/mL), adhesive [35] (0.26 µg/mL) and in the Enlite sensor itself [36] (10 µg/sensor) (Medtronic, Fridley, MN, USA); (ii) a tubeless insulin pump Omnipod [37] (5 µg/patch and 190 µg/sensor) (Insulet Corporation, Billerica, MA, USA); (iii) insulin infusions sets Paradigm MiniMed Quick-Set and Paradigm MiniMed Sure-T [38] (Medtronic, Fridley, MN, USA); (iv) insulin infusion set Accu-Chek Insight Flex (Roche Diabetes Care, Indianapolis, IN, USA) [38]; (v) in all following parts of the Medtrum A6 TouchCare (Medtrum Technologies, Shanghai, China): 1 µg in the sensor, 3 µg in the sensor adhesive patch, 30 µg in the insulin pump reservoir, 6 µg in the reservoir patch adhesive [39]. Initially, gas-chromatography-mass-spectrometry (GC-MS) analysis showed that the related Paradigm Minimed Silhouette infusion does not contain IBOA within detection limits [38], but a recent report of a 15-year-old boy from Poland suggests that the Silhouette set might still contain IBOA in untraceable amounts, but enough to elicit contact dermatitis [40]. Unfortunately, despite the ongoing saga of skin reactions towards diabetes medical devices, it has already been reported that the relatively new insulin pump system YpsoPump (Ypsomed, Burgdorf, Switzerland) also contains IBOA, and the first cases of ACD elicited by this device are known [41]. An alternative for IBOA-sensitized patients was supposed to be the monitoring system Dexcom G6 (Dexcom Inc., San Diego, CA, USA), which was recommended as an IBOA-free device. According to studies performed between 2018 and 2019, IBOA concentrations in the adhesives of Dexcom G5 and Dexcom G6, measured with GC-MS, were below the limit of quantification, which was 0.10 µg/mL for IBOA diluted in methanol [35,42]. In 2020, the modification of the adhesive in Dexcom G6 appeared, and an increasing number of patients started to experience skin problems towards this sensor. The company confirmed that, in order to obtain better skin fixation, an acrylate derivate was exchanged (no precise name of the substance was given), but at the same time it was maintained that the Dexcom G6 system is IBOA-free [43]. Svedman et al. investigated the culprit of ACD in 11 patients using Dexcom G6 and,

contrary to the previous findings, identified IBOA in the new 'IBOA-free' adhesive patches (0.1–0.7 µg/patch) and in extracts of the sensors (0.8–1.3 µg), whereas extracts from the plastic parts were free from IBOA. The detection limit for IBOA diluted in acetone in this study was 0.01µg/mL. These outcomes, together with positive patch test results, proved IBOA as the contact allergen responsible for the majority of contact allergies in the group of patients using Dexcom G6 [14]. However, most of the patients used IBOA-containing devices (Omnipod insulin pump or Freestyle Libre sensor) prior to switching to Dexcom G6. These case reports pointed out that the issue of switching to 'allergen-free' and more useful devices might not always free the patients from future contact reactions. However, the aforementioned studies aiming to detect IBOA in the Dexcom G6 sensor set different analytical limits. In one of them, the limit of quantification (LOQ) for IBOA in methanol was 0.10 µg/mL (no IBOA was detected), whereas the limit of detection (LOD) for IBOA in acetone in another study was 0.01 µg/mL (IBOA detected). The LOQ is the lowest analytical concentration of a substance that can be precisely and accurately measured by an analytical procedure, meeting the usually international acceptance criteria for bias or imprecision [44,45]. However, LOQ and LOD are not equivalent, and cannot be used interchangeably. The major differentiating factor between them is the underlying accuracy and precision. LOQ must always be reported with suitable trueness, reliability and quality criteria, whereas for LOD, no quantification is required. It is designed to show the lowest concentration of a substance in a sample that is greater than zero (the absence of the substance) [46]. If the same limits were set in the studies identifying IBOA in Dexcom G6, the outcomes would be more reliable and, maybe, more cohesive. On the other hand, it is generally acknowledged that even trace amounts of a contact allergen can elicit ACD, so the clinical value of either LOD or LOQ might be disputed. Furthermore, different solvents to dilute IBOA were used (methanol vs. acetone), which might have influenced the final results as well. An actual alternative for IBOA-sensitized patients can be the Eversense XL continuous monitoring system (Roche, Basel, Switzerland), whose sensor is placed underneath the skin in the upper arm, allowing for continuous measures of glucose levels for up to 6 months. In none of the components of the Eversense (implanted sensor, transmitter, two types of adhesive patches) was IBOA found (LOQ < 0.10 µg/mL), making it a viable option for patients with IBOA allergy [47]. Additionally, GC-MS analysis of the new generation FreeStyle Libre 2 sensor did not detect any IBOA residue [48].

#### 2.2.3. Other Acrylate Chemicals

##### 2,2′-Methylenebis(6-*tert*-butyl-4-methylphenol) Monoacrylate (MBPA)

Apart from IBOA, Svedman et al. identified a new allergen in the adhesive of the newer DexcomG6-2.2′-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate (MBPA; CAS 61167-58-6), which so far had not been linked with the problem of skin reactions to diabetes medical devices [49]. Therefore, the authors suspect that both IBOA and MBPA could be contact allergens present in Dexcom G6. Further investigation was performed by Oppel et al., who in patients using Dexcom G6 with no previous history of IBOA-sensitization performed patch tests for MBPA in three concentrations (0.1%, 0.3% and 0.5%) and to 2.2′-methylenebis(6-*tert*-butyl-4-methylphenol) (MBP; CAS 119-47-1) also in three concentrations (0.1%, 0.5% and 1.0%) [43]. MBP is a substance related to MBPA but without the acrylate group. In line with previous studies, 0.1% IBOA was patch tested as well. For IBOA and MBP, there were no positive patch tests. Patients reacted to MBPA, with the strongest reaction to 0.5% concentration (no reaction towards MBPA 0.1% was observed). Furthermore, in the same study, MBPA and MBP were detected in the Dexcom G6 new series from 2020 (LOQ MBPA 0.40 µg/mL and LOQ MBP 0.46 µg/mL), while in the series 2018/2019 their presence was not shown. This study showed that MBPA is an actual contact allergen in the new Dexcom G6 series responsible for ACD in patients not sensitized to IBOA [43]. Presumably, MBPA was the acrylate added to support the fixation of Dexcom G6, though the presence of IBOA must be still borne in mind.

Dipropylene Glycol Diacrylate (DPGDA)

DPGDA (CAS 57472-68-1) has been previously linked with occupational dermatitis in the painting industry, accounting for 18% of positive patch test results in a group of patients allergic to acrylic monomers [50]. In 2022, three cases of ACD caused by DPGDA in the Omnipod were reported. All patients reacted to 0.1% DPGDA and two of them additionally towards 0.01% concentrations [51]. Though the same authors, detected the presence of IBOA in the Omnipod before, other acrylates, such as DPGDA could not be identified, probably due to less sensitive GC-MS used in the past [37].

Cyanoacrylates

Cyanoacrylates (e.g., methyl-2-cyanoacrylate [CAS: 137-05-3] or ethyl-2-cyanoacrylate [CAS: 7085-85-0]), thanks to their ability to polymerize rapidly, can form very strong bonds with metals, plastics, rubbers and biological tissues, and are used mainly in the production of fast-acting glues [27]. In 2016, fabric parts of the Dexcom G4 Platinum containing cyanoacrylates (ethyl-2 cyanoacrylates) were responsible for ACD in diabetic patients [52,53]. Subsequent studies in 2017 confirmed the presence of ethyl cyanoacrylate in this device, a fact that has also been confirmed by the manufacturer [4,54]. In 2020, in the extract of the sensor and the insulin reservoir of Medtrum A6 TouchCare (Medtrum Technologies, China, Shanghai), GC-MS analyses indicated ethyl-2-cyanoacrylate [39].

Phenoxypoly(ethylenoxy) Ethylacrylate (PEEA) and $\beta$-Carboxyethyl Acrylate (BCA; CAS 24615-84-7)

Along with the first detection of IBOA in a medical device in 1995, other acrylate chemicals proved to be culprits in contact allergy cases, namely PEEA and BCA [32]. BCA was later reported to be one of allergens responsible for an epidemic of occupational dermatitis from acrylic glue amongst Polish workers involved in the production of electric coils for television displays [31]. In 2001, PEEA was also the culprit allergen in ACD in a 38-year-old woman with diabetes treated with an insulin pump [55].

N,N-Dimethylacrylamide (DMAA; CAS 2680-03-7)

DMAA is an easily polymerized monomer used as a precursor in the synthesis of hydrogels and polymer coatings and was highlighted to sensitize (0.1% DMAA in PET) and elicit ACD in seven patients using FreeStyle Libre. When analyzed with GC-MS, DMAA was found in the extract of the sensor ($\approx$2 $\mu g/cm^2$) but was not detected in the adhesive sensor patch (<0.5 $\mu g/cm^2$). Six out of seven patients were concomitantly sensitized towards IBOA, which is also present in FreeStyle Libre [56]. DMAA was also shown to be contained in the extracts from the Enlite sensor [36].

2.2.4. Non-Acrylic, Clinically Important Allergens Found in Diabetes Medical Devices

Epoxy Resin

Epoxy resin, a well-known cause of ACD, is believed to be the first discovered contact allergen to trigger ACD in two users of an insulin pump (Actrapid autosyringe infusion set). Both patients were positive for epoxy resin (one patient additionally to p-tert-butylphenol-formaldehyde), which the manufacturer was using to bind tubes and needles [57].

Colophonium

Colophonium (known as colophony or rosin) is a mixture of >100 compounds derived from pine trees [58]. The exact composition of colophonium varies as it is dependent on the type of pine trees it is derived from, as well as on the extraction and storage techniques. The exact list of allergenic compounds in colophonium is yet to be characterized [59]. Colophony has many uses in industry, but one of them is as a fast-acting adhesive material. Passanisi et al. described two patients, an 8-year-old girl using an Enlite sensor and a 10-year-old boy treated with an Omnipod insulin pump, who experienced eczematous pruritic lesions at application sites. Patch testing revealed that both patients were sensitized

towards colophonium 20% in PET. The presence of colophonium in the adhesive on the glucose sensor and in the adhesive on the insulin pump was confirmed by the manufacturers [60]. Colophonium-related substances, such as methyldehydroabietate, were also detected in all extracts acquired from the glucose sensor and the insulin reservoir of Medtrum A6 Touchcare System (Medtrum Technologies, Shanghai, China) [39]. The manufacturer confirmed the device contains up to 15% of modified colophonium. Svedman et al., by observing the reactivity pattern of patch tests performed in a group of diabetic patients, postulated the potential presence of colophonium derivates in Dexcom G6. However, this has not been confirmed and requires further investigation [14].

Nickel

Nickel remains the most common allergen that gives positive results in patch tests and can be found in many items and workplaces [17]. There are two reports describing ACD caused by nickel-containing needles in infusion sets [61,62]. However, these cases were reported a long time ago (in 1985 and 1998) and to date, we have not come across other similar reports. Possibly due to the high awareness of its sensitization properties, nickel has been removed from the composition of diabetes medical devices used nowadays. From our experience, the information we received from the manufacturers does confirm the absence of nickel in the devices. Nonetheless, nickel should be considered as a potential culprit and suspected allergen in the group of diabetic patients.

1-Benzoylcyclohexanol

1-Benzoylcyclohexanol is a UV photoinitiator compound contained in UV-cured glue. There is one report of 1-Benzoylcyclohexanol causing ACD in a user of an insulin pump [32].

2.2.5. Cross-Interactions or Co-Reactions?

Sensizitation to methacrylates may induce cross-reactivity to acrylates, but not vice versa [50]. However, studies show that compounds that are not listed on safety data sheets are sometimes still present in commercial products abundant in acrylate chemicals, and this supports the suggestion of possible concomitant positive patch test reactions, rather than cross-reactions [63]. Taking into account insufficient cooperation with the medical devices' manufacturers, who are hesitant to share the exact composition of all parts of their diabetes devices, we cannot rule out co-reactions in patients patch tested for several acrylates. Though not clearly stated, it is generally believed that IBOA does not cross-interact with other acrylate derivates, a belief that is supported by the statement of occupational dermatologists performing extended series with acrylate patch tests [28]. Nonetheless, none of the available (meth)acrylates in patch test services can be a marker for contact allergy towards IBOA, and every patient with contact dermatitis elicited by diabetes devices should be patch tested for IBOA. There are documented cross-reactions between acrylates (methyl-acrylate and ethyl-acrylate) and dimethyl fumarate (or its isomer dimethyl maleate), though the latter has not yet been linked with diabetic medical devices [64]. Clear labeling of the composition of device components would definitely help in further investigation of cross-reactions and co-reactivity between acrylates.

As stated previously, in a group of seven patients with skin reactions to FreeStyle Libre, all were sensitized to DMAA and six of them additionally to IBOA. The presence of both compounds was confirmed by the manufacturer, clearly pointing to co-reactions between IBOA and DMAA in these cases.

Recent studies have shown that 44% of patients with FreeStyle Libre-associated IBOA allergy have positive patch test results to sesquiterpene lactone mix (SLM) [38]. Interestingly, SLM has not been identified in FreeStyle Libre and IBOA patch test materials, nor has IBOA been demonstrated in any of the SLM patch test materials. Though the striking occurrence of concomitant patch test results towards IBOA and SLM requires further studies, the authors theorize that SLM can cross-react with IBOA [38,65]. A possible explanation for this phenomenon could be a common precursor for IBOA and SLM or (non)enzymatic

reactions which, by triggering conformational changes, make IBOA mimic the α-methylene-γ- butyrolactone ring present in SLM responsible for cross-reactivity.

The summary of allergens causing ACD in patients using diabetes medical devices is presented in Table 1.

**Table 1.** Allergens responsible for contact dermatitis in diabetic patients using insulin infusion sets and/or glucose sensors. Only the allergens that patients were sensitized towards and whose presence in the devices was confirmed are listed.

| Acrylate Allergens | Non-Acrylate Allergens |
|---|---|
| isobornyl acrylate (IBOA) [14,28,32,35–39,41] | colophonium [39,60] |
| 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate (MBPA) [43,49] | epoxy resin [57] |
| dipropylene glycol diacrylate (DPGDA) [51] | nickel [61,62] |
| cyanoacrylates (e.g., methyl-2-cyanoacrylate and ethyl-2-cyanoacrylate) [39,52–54] | 1-Benzoylcyclohexanol [32] |
| phenoxypoly(ethylenoxy) ethylacrylate (PEEA) [32,55] | |
| β-carboxyethyl acrylate (BCA) [32] | |
| N,N-dimethylacrylamide (DMAA) [36,56] | |

### 2.3. Irritant Contact Dermatitis (ICD)

ICD is caused by the direct toxic effect of an irritant compound which disrupts the skin barrier and triggers innate immune response with release of proinflammatory cytokines [66]. The first cases of dermatitis to medical devices were treated as ICD, since the repetitive occlusion, friction and increased humidity underneath adhesives are well-known irritants. On the other hand, damaged skin barriers are more permeable to allergens contained in the devices which, in turn, can lead to sensitization and possible evolution to ACD. Additionally, the coexistence of ACD and ICD is possible.

Reliable data concerning the prevalence of ICD in diabetic patients are not available. Herman et al. report that approximately 1/3 of patients experiencing adverse cutaneous effects from diabetes medical devices had no positive patch test results, suggesting ICD as a diagnosis of exclusion [13]. This number, however, could be overestimated as the lack of full labeling of ingredients contained in devices hampers the identification of allergens and irritants. The discovery of IBOA as the major culprit allergen altered the initial assumptions related to ICD and shifted the diagnostic process toward determining the already known and new allergens present in the devices. At the same time, the irritant potential of acrylates is undoubted; thus, the conception that some groups of patients might actually suffer from ICD rather than ACD cannot be neglected.

The overview of factors contributing to the development of contact dermatitis in diabetic patients is presented in Figure 1.

### 2.4. Systemic Contact Dermatitis

Another form of rarely observed contact dermatitis is systemic contact dermatitis (SCD) (also known as Baboon Syndrome) in which a patient first becomes cutaneously sensitized towards an allergen and upon a systemic re-exposure develops a sequela of systemic symptoms such as malaise, fatigue, fevers, vomiting and musculoskeletal disorders [67]. The pathophysiology of SCD is still poorly understood. Though previously SCD was thought to be a type I hypersensitivity reaction, the general consensus is now that SCD is a type IV hypersensitivity reaction [68]. So far, there are no reports linking the use of diabetes medical devices and SCD.

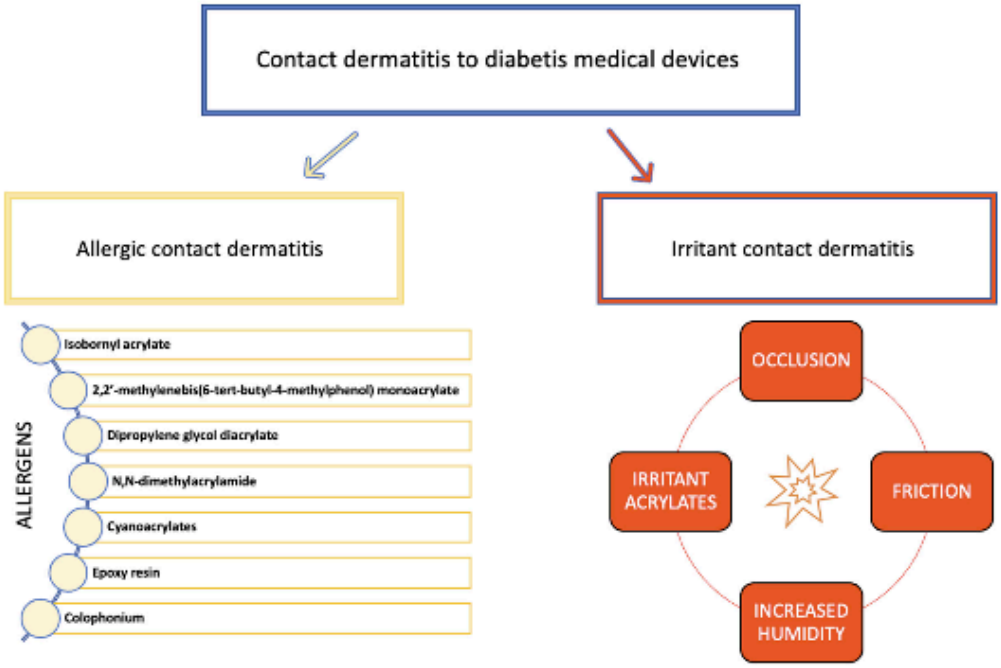


**Figure 1.** Factors contributing to the development of contact dermatitis from diabetes medical devices.

### 3. The Difficulties of Allergen Avoidance

The principal treatment of ACD is avoidance of culprit allergens, something that is not easy to implement in the case of GS or CSII users. In cases of ACD, relocation of the device to a different body region is not helpful. According to the most recent guidelines, children and young adults under 25 years old should use CGMs [69]. In comparison to finger prick self-measurements, CGMs are more effective in minimizing hypoglycemia incidents and are proven to reduce hemoglobin A1c (HbA1c), even in patients who are not on insulin, likely due to a positive impact on the patient's lifestyle and behavioral changes [70–72]. In Poland, a patient must meet specific requirements to receive reimbursement for a diabetes medical device. Once the patient receives the GS/CSII, a change of the device 'on demand' is possible in most cases only at the patient's cost, which, for a majority of them, is not affordable due to the high prices of diabetic devices. Moreover, bearing in mind cross-reactions between acrylates, we cannot guarantee the patient that the new GS/CSII, which in theory should be free from the culprit allergen, will not elicit contact dermatitis to another allergen. In cases of ICD, a possible way to reduce the symptoms of contact dermatitis could be to reduce the attachment time of the device to the skin. However, the number of insulin infusion sets or sensors a patient can obtain per month at reimbursed prices is strictly determined. Therefore, any additional use of infusion sets or sensors resulting from more frequent reapplications must be covered by the patients themselves, posing a financial challenge.

Since avoidance of allergens is in many cases difficult to implement or even impossible, patients try different barrier methods with varying success. These include barrier sprays, hydrocolloid dressings, BB kinesiotherapy tapes and others. However, barrier methods have substantial drawbacks: (i) applying extra protective layers underneath the medical device can result in false readings of glucose levels and/or inappropriate insulin infusions, (ii) the surface of the skin might not be dry enough to secure the adhesive and hence the device may detach after its application, (iii) sometimes barrier methods can elicit ICD or ACD and may lead to an exacerbation of dermatitis. Finally, it is generally recognized that

acrylates (such as methyl methacrylate [MMA], 2-hydroxyethyl methacrylate [HEMA], triethylene glycol dimethacrylate [TEGDMA]) can penetrate protective barriers such as latex, vinyl and nitrile gloves [30,73,74]. This can possibly explain why users allergic to IBOA-containing devices do not experience the desired alleviation of skin symptoms upon using the skin barriers. Notably, occlusives on the skin might lead to even higher exposure to acrylates [31].

Practice shows that some patients who have changed GS from IBOA-containing FreeStyle Libre to 'allergen-free' Dexcom G6 or FreeStyle Libre 2 still experience contact dermatitis. It is postulated that either previous sensitization can somehow trigger contact dermatitis when using IBOA-free devices or that there are still allergens that have not yet been identified (personal observations M.C. and M.T.). Manufacturers usually do not provide a list of exact chemicals contained in devices or generally state that 'polyacrylates' are present without specification; sometimes we fail to obtain any information about the composition. Unfortunately, the 'trial-error' scheme is in some cases the only solution for patients who give up on their devices due to itching, pain or sleep deprivation. In acute contact dermatitis, topical corticosteroids (TCS) are the first-line treatment. As the use of TCS cannot be a long-term solution due to the side effects, patients can be recommended to use topical calcineurin inhibitors (tacrolimus; pimecrolimus) to control the subinflammatory process.

## 4. Conclusions

The identification of IBOA as the major contact allergen in diabetes medical devices was the praeludium to further research of other allergens that might be present in glucose sensors and insulin infusion sets. The management of diabetes device contact allergy is challenging, as avoidance of allergens is not always achievable and the 'allergen-free' equivalents can still elicit contact dermatitis due to the presence of untested allergens or via irritant, toxic pathways. As long as the precise chemical compositions of the medical devices are not officially disclosed by the manufacturers, the burden of contact dermatitis amongst patients using diabetes sets will be considerable.

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CONTACT POINT

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# Allergic contact dermatitis elicited by insulin infusion sets: First case reported in Poland

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**KEYWORDS:** adhesives, allergic contact dermatitis, case report, children, diabetes, insulin infusion sets, isobornyl acrylate

Over the past years, irritant and allergic skin reactions caused by diabetes medical devices have been reported. We present a patient with type 1 diabetes mellitus (DM) who developed allergic contact dermatitis (ACD) from three different MiniMed infusion sets (Medtronic, Minneapolis, USA).

## CASE REPORT

A 15-year-old nonatopic boy with Type 1 DM presented with dermatitis at application sites of his insulin pump (Figure 1). Since the age of 8 he had been using alternatingly three MiniMed infusion sets: QuickSet, Sure-T and Silhouette. Recently, lesions appeared on his left thigh where the infusion sets were placed. Every consecutive use of insulin sets resulted in new, equally severe lesions developing within 3 days of use, regardless of the type of set used. His glucose sensor, the Medtronic Guardian 3 (Medtronic, Minneapolis, USA), did not provoke skin reactions until 1 year after the onset of skin lesions induced by the insulin kits.

Patch tests (Finn Chamber AQUA, SmartPractice, Phoenix, Arizona) were performed with the Polish Baseline Series (Chemotechnique Diagnostics, Vellinge, Sweden)[1] along with several parts of the devices tested "as is." Following an occlusion of 2 days (D), readings were performed on D2, D3 and D7, showing positive reactions on D2 to epoxy resin (+), quaternium 15 (+), sesquiterpene lactone mix (SLM) (+), methylisothiazolinone (+), formaldehyde (+) and on D3 to cobalt chloride (+), epoxy resin (++), SLM (+), quaternium 15 (++), methylisothiazolinone (+), formaldehyde (+++), methylisothiazolinone and methylchloroisothiazolinone mix (+), all of unclear relevance. No reactions occurred to the parts of the devices.

Six months later patch tests with 25 acrylates (Chemotechnique Diagnostics) were carried out (Table S1). A positive reaction to isobornyl acrylate (IBOA) (++) was observed on D2 and D3 which disappeared by D7.

## DISCUSSION

There are no official reports about allergic reactions from diabetes devices in Poland. However, an increasing number of such cases are currently reported, especially in paediatric patients.[2] Interestingly, our patient appears to be primarily sensitized from the use of IBOA-containing insulin infusion sets, with additional ACD developing from his glucose sensor 1 year later, the culprit allergen(s) in the latter currently being unknown (new introduction of IBOA in this device, or ACD from other skin sensitizers present in this sensor?).

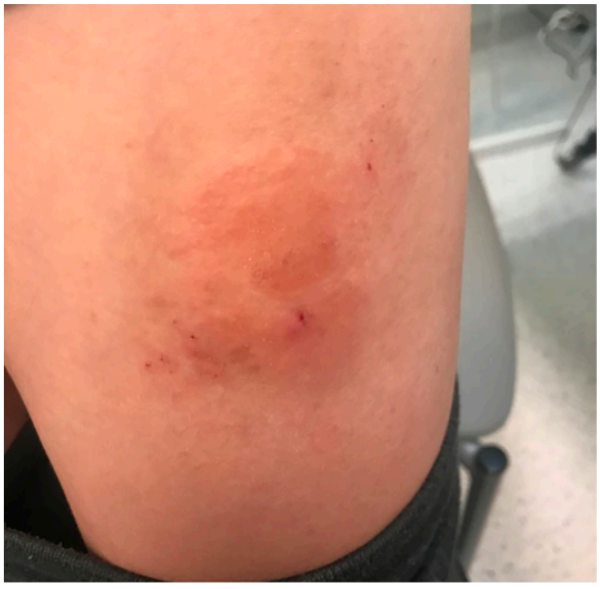

**FIGURE 1** Allergic contact dermatitis (ACD) on the patient's thigh elicited by a MiniMed insulin infusion set.

Dendooven et al. found that Quick-set and Sure-T contained trace amounts of IBOA, whereas in the Silhouette no IBOA was found within detection limits.[3] However, our patient reacted to the all three infusion sets, within the same timeframe, which might indicate that the Silhouette set might still contain IBOA. Other acrylates reported as responsible for ACD from insulin infusion sets include: dipropylene glycol diacrylate,[4] 2-ethyl cyanoacrylate,[5] phenoxypoly(ethylenoxy) ethylacrylate and β-carboxyethyl acrylate.[6] The positive reaction to SLM observed in our patient probably reflects cross-reactivity between SLM and IBOA, which was initially observed by Herman et al.[7] Also in a study performed by Dendooven et al., 44% patients with positive patch test reaction to IBOA were co-sensitized to SLM.[3] It has been suggested that co-sensitization to IBOA and SLM may be due to cross-reactivity.[8] A possible theory is that, due to conformational changes in single bonds, IBOA may mimic the α-methylene-γ-butyrolactone ring present in SLM responsible for cross-reactivity. Moreover, there is no evidence for clinical relevance of positive patch test reactions to SLM in IBOA-sensitized patients, which was also the case in our patient. Regarding the potential relevance of some of the other positive reactions observed in our case: (i) epoxy resin can be used to fix the plastic tube to the needle in insulin pumps,[9] yet the manufacturer did not confirm its presence in the sets; (ii) isothiazolinone derivatives can also be found in adhesives, yet again their presence remains unconfirmed.[10] In conclusion, although apparently rarer than glucose sensors, our case suggests that also insulin infusion sets can be a primary source of sensitization and ACD from IBOA.

## AUTHOR CONTRIBUTIONS

**Mikołaj Cichoń:** Conceptualization; investigation; writing – original draft; methodology; visualization; validation. **Małgorzata Sokołowska-Wojdyło:** Supervision; formal analysis; writing – review and editing; methodology; investigation. **Magdalena Trzeciak:** Supervision; formal analysis; writing – review and editing; methodology; investigation.

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## CONFLICT OF INTEREST

The authors declare none to declare.

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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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# 9. Pozostałe osiągnięcia naukowe

## 9.1. Publikacje naukowe niewchodzące w skład rozprawy doktorskiej

**Łączna wartość wskaźnika oddziaływania (IF): 10,2**

**Łączna punktacja MEiN: 425**

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Mikołaj Cichoń, Paulina Zielińska, Jan M. Zaucha, Ewa Zarzycka, Magdalena Trzeciak

*Journal of European Academy of Dermatology and Venereology*

IF: 8,2 | MEiN: 140 | Q1 | D1

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*Children*

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*Dermatologia po Dyplomie*

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Mikołaj Cichoń, Wioletta Barańska-Rybak

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MEiN: 5

## 9.2. Prezentacje ustne na konferencjach naukowych

Sumarycznie: 7

Pierwszy autor: 7

Zjazd Sekcji Forum Młodych Polskiego Towarzystwa Dermatologicznego, Łódź, 24–25 października 2024 r.

Mikołaj Cichoń, Tatsiana Damps, Jolanta Gleń, Wojciech Biernat, Roman J. Nowicki

„Linijna IgA dermatoza pęcherzowa o wieloczynnikowej etiologii – opis przypadku”

**Prezentacja ustna w sesji przypadków klinicznych**

Zjazd Sekcji Forum Młodych Polskiego Towarzystwa Dermatologicznego, Łódź, 24–25 października 2024 r.

Mikołaj Cichoń, Katarzyna Rychlik, Aleksandra Wilkowska, Roman J. Nowicki

„Grzybica drobnozarodnikowa owłosionej skóry głowy o ciężkim przebiegu – opis przypadku”

**Prezentacja ustna w sesji przypadków klinicznych**

32. Zjazd Polskiego Towarzystwa Dermatologicznego, Lublin, 31 maja–3 czerwca 2023 r.

Mikołaj Cichoń, Małgorzata Myśliwiec, Magdalena Trzeciak

„Kontaktowe zapalenie skóry u pacjentów z cukrzycą typu 1 stosujących pompy insulinowe oraz sensory monitorowania glikemii – wyniki badań własnych”

**Laureat sesji prac oryginalnych**

XXII Konferencja Naukowo-Szkoleniowa Alergia-Astma-Immunologia Kliniczna, Łódź, 15–17 czerwca 2023 r.

Mikołaj Cichoń, Magdalena Trzeciak

„Alergiczne kontaktowe zapalenie skóry spowodowane izobornylem akrylu zawartym w nowej pompie insulinowej”

**Pierwsza Nagroda w sesji Clinical Study**

32. Zjazd Polskiego Towarzystwa Dermatologicznego, Lublin, 31 maja–3 czerwca 2023 r.
Mikołaj Cichoń, Magdalena Trzeciak, Roman J. Nowicki
„Czy potrzebna jest aplikacja mobilna pomagająca kontrolować przebieg atopowego zapalenia skóry?"
**Prezentacja ustna w Sesji Alergologia I**

Zjazd Sekcji Forum Młodych Polskiego Towarzystwa Dermatologicznego, Łódź, 20–21 października 2022 r.
Mikołaj Cichoń, Jan M. Zaucha, Magdalena Trzeciak
„Pokrzywka indukowana zimnem – czy to tylko pokrzywka fizykalna?"
**Prezentacja ustna w sesji przypadków klinicznych**

Zjazd Sekcji Forum Młodych Polskiego Towarzystwa Dermatologicznego, Łódź, 20–21 października 2022 r.
Mikołaj Cichoń, Małgorzata Sokołowska-Wojdyło, Magdalena Trzeciak
„Alergiczne kontaktowe zapalenie skóry wywołane przez izobornyl akrylu (IBOA) u pacjentów stosujących pompy insulinowe i sensory pomiaru glukozy – seria przypadków klinicznych"
**Prezentacja ustna w sesji przypadków klinicznych**

## 9.3. Plakaty na konferencjach naukowych

Sumarycznie: 3

Pierwszy autor: 3

XXIII Konferencja Naukowo-Szkoleniowa Alergia-Astma-Immunologia Kliniczna, Łódź, 13–15 czerwca 2024 r.

Mikołaj Cichoń, Małgorzata Myśliwiec, Magdalena Trzeciak

„Alergiczne kontaktowe zapalenie skóry u pacjentów z cukrzycą typu 1 stosujących sensory pomiaru glikemii oraz pompy insulinowe."

**Nalepszy plakat w sesji Clinical Study**

XV Sympozjum naukowo-szkoleniowe Polskiego Towarzystwa Dermatologicznego „Polska Akademia Dermatologii i Wenerologii", Kraków, 20–22 czerwca 2023 r.

Mikołaj Cichoń, Małgorzata Myśliwiec, Magdalena Trzeciak

„9-letnia pacjentka z alergicznym kontaktowym zapaleniem skóry wywołanym przez pompę insulinową – na tropie nowych alergenów akrylanowych."

12th International Symposium for Atopic Dermatitis, Montreal, 17–19 października 2022 r.

Mikołaj Cichoń, Mariusz Baran, Magdalena Trzeciak

„Mobile application – could it help with patients' education and management of atopic dermatitis?"