Received: 12 July 2023 | Accepted: 23 January 2024

DOI: 10.1111/jdv.19908

JEADV JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

SYSTEMATIC REVIEW

Prevalence of dermatitis including allergic contact dermatitis from medical devices used by children and adults with Type 1 diabetes mellitus: A systematic review and questionnaire study

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Abstract

Use of medical devices (MDs), that is, glucose sensors and insulin pumps, in patients with Type 1 diabetes mellitus (T1D) has proven an enormous advantage for disease control. Adverse skin reactions from these MDs may however hamper compliance. The objective of this study was to systematically review and analyse studies assessing the prevalence and incidence of dermatitis, including allergic contact dermatitis (ACD) related to MDs used in patients with T1D and to compare referral routes and the clinical investigation routines between *clinics being part of the European Environmental and Contact Dermatitis Research Group* (*EECDRG*). A systematic search of PubMed, EMBASE, CINAHL and Cochrane databases of full-text studies reporting incidence and prevalence of dermatitis in persons with T1D using MDs was conducted until December 2021. The Newcastle–Ottawa Scale was used to assess study quality. The inventory performed at EECRDG clinics focused on referral routes, patient numbers and the diagnostic process. Among the 3145 screened abstracts, 39 studies fulfilled the inclusion criteria. Sixteen studies included data on children only, 14 studies were on adults and nine studies reported data on both children and adults. Participants were exposed to a broad range of devices. Skin reactions were rarely specified. It was found that both the diagnostic process and referral

routes differ in different centres. Further data on the prevalence of skin reactions related to MDs in individuals with T1D is needed and particularly studies where the skin reactions are correctly diagnosed. A correct diagnosis is delayed or hampered by the fact that, at present, the actual substances within the MDs are not declared, are changed without notice and the commercially available test materials are not adequately updated. Within Europe, routines for referral should be made more standardized to improve the diagnostic procedure when investigating patients with possible ACD from MDs.

BACKGROUND

Diabetes mellitus (DM) represents a major, increasing health problem worldwide, affecting approximately 463 million people.[1] The Global Burden of Disease study identified DM as the cause of 10–20 years of life lost due to disability.[2] DM, especially dysregulated insulin-dependent diabetes mellitus (IDDM), is associated with an increased incidence of severe, potential life-threatening comorbidities.[3] Many of the complications might be delayed or even avoided through improved glycaemic control.[4–6] Different medical devices (MDs) such as glucose sensors, continuous glucose monitoring (CGM), intermittently scanned continuous glucose monitoring (isCGM) as well as insulin pumps have been developed improving glucose control and diabetes-related quality of life for a growing population of both children and adults.

As a result, in many European countries, the use of MDs for use in IDDM is increasing. In Sweden in 2021, more than 85% of adults and more than 98% of children with IDDM used CGM or isCGM.[7] However, the use of MDs is associated with a series of different possible cutaneous side effects[8,9] which have been extensively reported, albeit mostly in case reports and small case series.[10–14] These studies reported that some patients even had to stop using their MDs because of the severity of the skin problems. However, the actual prevalence of dermatitis due to MDs, particularly allergic contact dermatitis (ACD), has not been established and will vary due to the size of the exposed population, how long the products have been available for the population, what type of products have been provided and their recommended exposure time. When evaluating patients with dermatitis from MDs, a correct diagnosis is essential. Dermatitis in patients exposed to MDs may have different aetiologies, irritant dermatitis, but foremost ACD, which if diagnosed, might be avoided by a correct change (of the content) of the MD. ACD is diagnosed through patch testing, with a baseline series and with aimed testing with specific contact allergens in a defined correct concentration. Because potential contact allergens are usually not declared by the manufacturer, chemical analyses are often required. Then, when substances included in MDs are finally identified, they are often not commercially available for patch testing. Therefore, patch testing with (extracts of) the patient's own materials is often required, supplemented by in-house prepared, non-commercialized patch test preparations.

It can therefore be assumed that within Europe, and probably also elsewhere, ACD related to MDs in IDDM patients can only be diagnosed correctly in specialized dermatological referral centres. As the advantages of these MDs are huge, knowledge of causes of dermatitis is limited and referral routes are not standardized, many individuals with the condition might never be referred. Therefore, there is a high risk that individuals with dermatitis from MDs are left undiagnosed, misdiagnosed or untreated, which, eventually, may also compromise adequate management of their DM.

This study aimed to systematically review and analyse studies of prevalence and incidence of dermatitis, especially ACD, related to the use of MDs in close prolonged contact to the skin (e.g. CGM, isCGM and insulin pumps) for treatment and monitoring of Type 1 diabetes (T1D).

MATERIALS AND METHODS

Review

Following a pre-specified protocol, a data search was performed from 1946 in Medline, EMBASE, Cochrane, CINAHL, Center, Google and Google Scholar, in addition to hand search until December 2021. Predefined search terms and MeSH (medical subject headings) and keywords were developed in collaboration. The searches are described in Appendix S1. Reference lists of included studies and conference abstracts have also been screened, and Google has manually been searched for potential additional studies.

Study selection

Population-based cross sectional, cohort or nested case–control studies that reported incident and prevalent dermatitis in individuals with T1D using MDs were included. Inclusion criteria were epidemiological studies that reported on contact dermatitis, irritant dermatitis, contact allergy or any dermatitis possibly related to MDs in persons with diagnosed T1D. For intervention studies, studies were not selected based on treatment, though these data were extracted for comparison purposes. No language restrictions were applied. Studies that included less than 10 patients, or studies that did not assess the exposures and outcomes of interest, were excluded. The reasons for

exclusion are reported in Appendix S2. The following outcomes were assessed: dermatitis using a broad definition, contact dermatitis, ACD, contact allergy and clinical relevance. Descriptive data and details on the study settings were collected.

Eligibility assessment and data extraction

Two reviewers independently assessed the eligibility of studies based on the title and abstract. In the second screening phase, full text papers were assessed independently by the two reviewers. A data extraction form was developed and piloted by reviewers on a random selection of included studies designed to describe the characteristics of studies to be included, as set out in the recommendations in the Cochrane Handbook section-5.4. Two reviewers extracted the data from included studies using this form. Extracted data items included characteristics of each study, study methodological quality items and the outcomes of interest for each study using a standardized data extraction as recommended in the Cochrane Handbook section-5.5. All disagreements were resolved by consensus involving a third reviewer.

Study quality assessment

Following the Cochrane Collaboration's recommendation, to present potential biases for each study instead of using scores to rate quality, a set of quality appraisal items was applied. These include biases in sample selection, validity of measures of disease and educational outcome, appropriateness of statistical analysis and adjustment for confounders when applicable using the Newcastle–Ottawa quality assessment scale, NOS. The NOS was used for longitudinal studies and an adopted version for cross-sectional studies. The primary outcome was prevalence (point prevalence, 1-year prevalence and/or lifetime prevalence), incidence and type of dermatitis such as ACD related to MDs placed on the skin; secondary outcomes included prevalence and incidence across age, sex and quality assessment using NOS. A particular focus was on publications using data from 2000 and onwards.

Statistical analysis

Articles that met the inclusion criteria were recorded in table format to perform a systematic and narrative synthesis on the available evidence. When numbers were provided in the original articles but not percentages, percentages were calculated. We studied all MDs together and reported combined for any reaction on any MD. We also studied each type of MDs individually; if studies included combinations of different types of MDs, we distinguished the separate adverse reactions if possible. Data were summarized descriptively, and we planned to perform a meta-analysis including exploring sources of heterogeneities if possible. This review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, Appendix S3).

Questionnaire

A questionnaire was developed and adjusted by EECDRG members from nine European countries to survey the management and routine procedures for referred IDDM patients with suspected contact allergy to MDs and to report the trends and number of patients referred and tested in different centres in Europe. The questionnaire (Appendix S4) was distributed as a web-based survey on SUNET (SUNET NOC, Stockholm, Sweden) or a paper questionnaire (pdf file) sent by email. All EECDRG members received the questionnaire and could respond from March to August 2022. These data are described and reported in numbers and proportions. The proportions of patients with a contact allergy to MDs between age groups (children <18 years vs. adults, ≥18 years) were compared using the chi-squared test using IBM SPSS Statistics for Windows (version 27.0; IBM Inc., New York, USA).

RESULTS

Systematic review

Among the 3145 screened abstracts, 39 studies fulfilled the inclusion criteria and reported on T1D only (Figure 1, Table 1[8,9,15–51]). The results from these studies are presented in Table 1. Seven studies also included participants with T2D (Table 2[52–58]).

Several case reports and case series focusing particularly on ACD were excluded as they only reported the proportion of ACD for those investigated for dermatitis but did not include data on the total number of patients exposed to MDs. Reviews were also excluded as they did not contain original data.

Of the included studies with patients with T1D, none differentiated between men and females, 16 studies reported data of in total 1532 children,[16–31,40–47] 14 studies on altogether 3131 adults[8,15,27–29,31–39] and nine studies on both adults and children[9,23–26,48–51] ($n = 863$). Participants were exposed to different MDs as described in Table 1. Most studies did not have an assessment of the prevalence of dermatitis as primary aim and the type of dermatitis was seldom specified, only three papers published data on the prevalence of ACD. Most studies had a poor study quality according to the Newcastle–Ottawa Scale which was used to assess the quality of the included studies regarding the assessment of the prevalence in a general population of persons with IDDM (Tables 1 and 2). Of the included studies, there was one international multi-centre study,[31] eight from the USA,[17,25,30,39,40,46,47,50] one from Saudi Arabia,[26] two from Israel[45,49] and the others from Europe.[9,15,18–24,27–29,33,34,36–38,41–44,48,51]

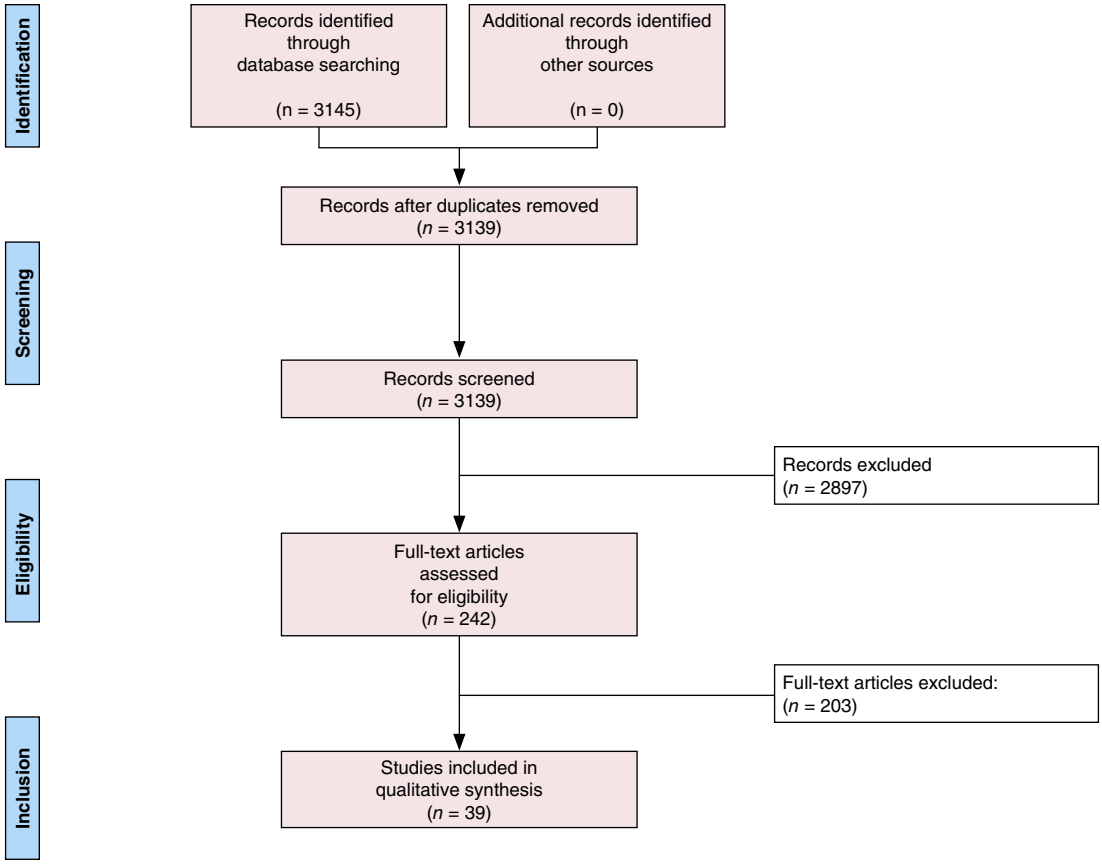

FIGURE 1 Prisma flow chart.

Of the included studies, 14 were cross sectional,[8,9,15–26] and 25 involved some longitudinal data.[27–51] In the longitudinal studies the follow-up time [the time of observation] was between 7 days and 3 years. Nine longitudinal studies had a follow-up of less than 6 months.[26,32,33,39,41–43,46,50] There was one study with a cross-sectional assessment and another assessment after 7 years,[28] no data was collected in between. Many studies were excluded in the title and abstract screening phase due to low numbers; about 50 articles reported on less than 10 participants. A few studies ($n = 3$) had the primary aim to assess the prevalence of dermatitis related to MDs in persons with T1D.[32,34] Possible skin reactions to glucose sensor systems were assessed in 18 studies[20,21,24,27,29,30,32,34–36,40–43,46–49] only, 10 studies[16,17,22,23,26,28,33,37,39,45] assessed insulin pump systems only, and 11[8,9,15,18,19,25,31,38,44,50,51] both glucose sensor systems and insulin pump systems. There was one study with data on the incidence and this was calculated indirectly.[51] When assessing the numbers of participants, we used the number of persons which were finally included in the data analysis of the studies, as several studies did not report the numbers which were invited and participated.

The outcomes were self-reported by the participants in 17 studies, physician-diagnosed in 14 studies (only three of them by a dermatologist), and both self-reported and physician diagnosed in six studies. Two studies did not specify the assessment of the outcomes.

The prevalence of dermatitis ranged from about 5% to more than 10% in both adults and children in studies with good quality; the proportion of children with any dermatological reaction to MD was about 7%; the proportion of children with contact allergy to MD was about 5%, but how this was diagnosed differed. In good quality studies, the proportion of adults with any dermatological reaction to MD was between about 6% and 10% and the proportion of adults with allergic contact dermatitis to MD was not directly assessed.

Questionnaire

Responses from 11 clinical centres with different sizes of referral areas and populations were included. Most centres had contact with diabetes clinics to facilitate the referral process. In some of the centres skin symptoms from MD were regularly

TABLE 1 Articles with Type 1 diabetes mellitus.

	Publication (year, country)	Participants, Number[a], children[b], adults or mixed Mean, SD, median age, range (years)	Diabetes medical device(s) used (*n*, if not all patients)	Exposure time Before study (BS) During study (DS)	Outcome (definition) A. Skin reaction/irritation, unspecified B. Symptoms/signs specified[c] C. Diagnosis specified D. Patch testing performed with substances	Diagnosis Physician diagnosed or self-reported	Outcome (results) A. Current B. Ever had C. Specified time frame (during study period) D. Not specified	Quality assessment
Cross-sectional studies								
1	Berg et al. (2018, Denmark)[8]	118, adults Median: 46	CGM (48) CSII (117)	BS: CSII: mean 5 years minimum: 4 months CGM/CSII: minimum 4 weeks	B	Self-reported	CSII: A: 34.2%. B: 79.5%. CGM: A: 35.4%. B: 71.4%.	Moderate
2	Christensen et al. (2019, Denmark)[15]	111, adults Median: 46.2 (20.5–73.5)	CGM (51) CSII (111)	BS: CGM: 32.4 months CSII: 64.8 months DS (CGM and CSII): 4 months	B	Self-reported	CSII-users: A: 58.6%. Last 4 months: 64.9%. CGM-users: A: 45.1%. Last 4 months: 74.5%.	Moderate
3	Berg et al. (2018, Denmark)[9]	144, mixed Median Herlev: 11.54 HillerØd: 12.96 (2–20)	CGM (76) CSII (143)	BS: CSII Herlev: 3.29 years HillerØd: 3.94 years CGM/CSII: minimum 4 weeks	B	Self-reported	CSII-users: A: 62.9%. B: 89.5% CGM-users: A: 46%. B: 79.5%.	Moderate
4	Conwell et al. (2008, Canada)[16]	50, children Mean: 13.3 ± 3.5	CSII infusion set	BS: CSII: Mean: 2.8 years Minimum 6 months	B	Physician diagnosed	A: Erythema: 66% Subcutaneous nodules (erythematous) 42% Subcutaneous nodules (non-erythematous) 20% Epidermal abrasion 8%	Poor
5	Eastman et al. (2002, USA)[17]	66, children[a] Mean: 11.9 ± 3 years (7–17)	GlucoWatch (a glucose monitor)	BS: unknown	B	Physician diagnosed	A: Erythema: *Extraction site*: Forearm: 66% Other application sites: 67% *Adhesive site*: Forearm: 49% Other application sites: 53%	Poor
6	Herman et al. (2020, Belgium)[18]	12, children Mean: 11.5 (4–17)	CGM CSII infusion set (3)	BS: unknown.	D: European baseline series isobornyl acrylate, N,N-dimethylacrylamide, a piece of the adhesive part as is, (meth) acrylates, plastic and glues series Costunolide and dehydrocostus lactone, alantolactone	Physician diagnosed[d]	A: Contact allergy to IBOA: 4.2%.	Poor
7	Lombardo et al. (2020, Italy)19	139, children Mean: 11.1 (4–17)	CGM CSII	BS: minimum 1 month	B	Self-reported	A: Patch pump or glucose sensor: 51.1% *Patch pump*: 20.0% *CGM*: 57.1% *FGM*: 39.1%	Poor

(continues)

TABLE 1 (Continued)

	Publication (year, country)	Participants, Number[a], children[b], adults or mixed Mean, SD, median age, range (years)	Diabetes medical device(s) used (*n*, if not all patients)	Exposure time Before study (BS) During study (DS)	Outcome (definition) A. Skin reaction/irritation, unspecified B. Symptoms/signs specified[c] C. Diagnosis specified D. Patch testing performed with substances	Diagnosis Physician diagnosed or self-reported	Outcome (results) A. Current B. Ever had C. Specified time frame (during study period) D. Not specified	Quality assessment
8	Vergier et al. (2019, France)20	347, children Age: mean/median unknown	CGM	BS: average 285 days	A	Self-reported	B: 22.2%	Good
9	Vidal-Albareda et al. (2020, Spain)21	264, children Median: 8 (4–17)	CGM	BS: unknown	D: Baseline series, acrylate series, IBOA 0.1% pet, colophonium, adhesive "as is"	Physician diagnosed[d]	D: ACD 5.3% *Contact allergy among 14 tested*: IBOA: 35.7% Colophonium: 14.3% Ethyl cyanoacrylate: 7.1% Freestyle adhesive: 41.7% (5/12) Dexcom adhesive: 0% (0/5) Enlite adhesive: 40.0% (2/5)	Good
10	Schober et al. (2009, Austria)[22]	78, children Mean/median: unknown	CSII	BS: minimum 4 months	B	Physician diagnosed	A: <6 years/>6 years Nodules 30%/21% Erythema 25%/26.3% Blisters 10%/7.9% Abscess 12.5%/7.9%	Poor
11	Binder et al. (2015, Austria)[23]	54, mixed Median: 9.6 (3.1–20.5)	CSII	BS: median 2.0–2.5 years	B	Physician diagnosed	A: 43%. Pigmentary change: 6% Ezcema-like: 11%	Good
12	Hyry et al. (2019, Finland)[24]	70, mixed Median: 25 (2–73)	CGM	BS: unknown	D: IBOA 0.1% pet., colophonium, ethyl cyanoacrylate, baseline series, dental series, or acrylate series	Physician-diagnosed[d]	D: ACD to IBOA: Freestyle Libre: 0.7% Enlite: 0.8%.	Poor
13	Rigo (2020, USA)[25]	121, mixed Mean: 13.9 ± 4.8 years (3–25)	CGM (85) CSII (119)	BS: unknown	B	Self-reported	D: Overall skin reaction: 59.5% (72/121) Red 35% (25/72) Itchy 31% (22/72) Painful 22% (16/72) Rash 22% (16/72) Skin change 13% (9/72) Infection 11% (8/72) Psoriasis exacerbation 3% (2/72) Eczema exacerbation 1% (1/72)	Poor
14	Al Hayek et al. (2018, Saudi Arabia)[26]	64, mixed Mean/median: unknown (13–19)	CSII	BS: minimum 12 months	B	Self-reported	C: Changes in pigmentation: 39.1% Occurrence of scars: 17.2% Local skin irritations: 35.9%	Poor

TABLE 1 (Continued)

	Publication (year, country)	Mean, SD, median age, range (years)	Participants, Number[a], children[b], adults or mixed Diabetes medical device(s) used (*n*, if not all patients)	Exposure time Before study (BS) During study (DS)	Outcome (definition) A. Skin reaction/irritation, unspecified B. Symptoms/signs specified[c] C. Diagnosis specified D. Patch testing performed with substances	Diagnosis Physician diagnosed or self-reported	Outcome (results) A. Current B. Ever had C. Specified time frame (during study period) D. Not specified	Quality assessment
Longitudinal studies								
15	Bolinder et al. (2016, Sweden, Austria, Germany, Spain, Netherlands)[27]	252, adults	CGM	BS: unknown DS: 6 months	B	Unknown	D: Skin reaction: 25.8% (65/262)	Good
16	Chantelau et al. (1989, Germany)[28]	116, adults Mean: 29 ± 1 year	CSII (8)	BS: 0 DS: unknown	B	Self- reported and physician diagnosed	D: 134 cases of subcutaneous inflammation (self- reported), 0.26 cases of inflammation per patient-year Erythema: 51% Subcutaneous nodules: 19% Inflammation requiring antibiotic treatment: 1.7%	Poor
17	Charleer et al. (2020, Belgium)[29]	1913, adults Mean/median: unknown	CGM	BS: unknown DS: 89% minimum 12 months	A	Self-reported	D: Skin irritation: 11%	Moderate
18	Chase et al. (2005, USA)[30]	99, children Mean: 12.3 ± 2.7	GlucoWatch	BS: unknown DS: 6 months	A, B	Physician diagnosed and self-reported.	C: Skin irritation last 6 months: 100% Acute changes: 55% Nonacute changes (any): 51%	Moderate
19	Feig et al. (2017, Canada, England, Scotland, Spain, Italy, Ireland, USA)[31]	160, adults (18–40)	CGM CSII	BS: unknown DS: unknown	B	Physician diagnosed	C: Pregnancy group: 48% (49/103). Planning pregnancy group: 44% (23/52)	Moderate
20	Garg et al. (2009, USA)[32]	14, adults Mean: 33 ± 6	CGM	BS: unknown DS: 15 days	A	Physician diagnosed and self-reported	C: *Adhesive area*: Dexcom seven: 27% FreeStyle Navigator: 58% *Insertion site reactions*: Dexcom seven: 4.2% FreeStyle Navigator: 65%	Good
21	Grimm et al. (1987, France)[33]	47, adults Mean: 30 ± 7	CSII	BS: unknown DS: 4 months	A	Self-reported	D: Minor skin problems: 64%.	Poor
22	Lind et al. (2017, Sweden)[34]	156, adults Mean: N/A	CGM	BS: unknown DS: 26 weeks	B, C	Self-reported	C: Skin and subcutaneous tissue disorders: 5.8% Contact dermatitis: 0.6% Eczema: 0.6% Skin reaction: 0.6% Skin ulcer: 1.9%	Good

(continues)

TABLE 1 (Continued)

	Publication (year, country)	Participants, Number[a], children[b], adults or mixed Mean, SD, median age, range (years)	Diabetes medical device(s) used (*n*, if not all patients)	Exposure time Before study (BS) During study (DS)	Outcome (definition) A. Skin reaction/irritation, unspecified B. Symptoms/signs specified[c] C. Diagnosis specified D. Patch testing performed with substances	Diagnosis Physician diagnosed or self-reported	Outcome (results) A. Current B. Ever had C. Specified time frame (during study period) D. Not specified	Quality assessment
23	Mastrototaro et al. (2006, USA)[35]	20, adults Mean: 40.4	CGM	BS: unknown DS: average 317 days	A	Self-reported	C: 42% itching/skin irritation.	Poor
24	Oskarsson et al. (2018, Europe)[36]	81, adults Median: 42	CGM	BS: unknown DS: 6 months	B	Self-reported	C: Insertion-site symptoms experienced by 42.0% (34/81) participants Erythema: 28.4% (23/81) Rash: 9.9% (8/81)	Good
25	Pfutzner et al. (2015, Germany)[37]	22, adults Mean: 39 ± 11	CSII	BS: unknown DS: 6 months	A	Self-reported and physician diagnosed	C: Erythema: 3.5% Rash: 3.2% Injection site reddening: 2.2% Skin irritation: 2.1% Injection site reactions (patient reported) 4-days use: 59, 2 days use: 33 Injection site reactions Health Care Professionals (HCP) 4 days use = 27, 2 days use = 11	Good
26	Šoupal et al. (2020, Czech republic)[38]	94, adults Mean: 32.3–35 (different groups)	CGM CSII	BS: unknown DS: 3 years	A	Unknown	C: 4 allergic reactions to glucose sensor use	Poor
27	Thrasher et al. (2018, USA)[39]	27, adults Mean: 42.2 ± 14.6	CSII	BS: minimum 6 months DS: 8 weeks	A	Physician diagnosed	C: No hypersensitivity reactions or allergic reactions on either treatment Mild infusion site reaction reported in 4.0% patients on SAR-Lis No patients on Ly-Lis reported an infusion site reaction Four patients reported pain or swelling at the infusion site as the reason for unscheduled infusion set changing	Moderate
28	Chase et al. (2003, USA)[40]	40, children Mean: 11.9 (7–17)	GlucoWatch	BS: unknown DS: 6–9 months	B	Self-reported	C: One individual had more than a mild skin reaction to the device	Moderate
29	Diabetes Research in Children Network Study Group et al. (2007, UK)[41]	30, children Mean: 11.2 (4–17)	CGM	BS: minimum 6 months DS: 13 weeks	B	Physician diagnosed	C: Acute skin changes: 29% Nonacute changes: 39%	Poor
30	Edge et al. (2017, UK)[42]	89, children Mean: 10.2 (4–17)	CGM	BS: unknown DS: up to 14 days	B	Physician diagnosed and self-reported	C: 6%	Moderate

TABLE 1 (Continued)

	Publication (year, country)	Participants, Number[a], children[b], adults or mixed Mean, SD, median age, range (years)	Diabetes medical device(s) used (*n*, if not all patients)	Exposure time Before study (BS) During study (DS)	Outcome (definition) A. Skin reaction/irritation, unspecified B. Symptoms/signs specified[c] C. Diagnosis specified D. Patch testing performed with substances	Diagnosis Physician diagnosed or self-reported	Outcome (results) A. Current B. Ever had C. Specified time frame (during study period) D. Not specified	Quality assessment
31	Giani et al. (2018, Italy)[43]	17, children Mean: 13.7	CGM	BS: unknown DS. 2 weeks	A	Physician diagnosed	C: 5.9% (1/17)	Poor
32	Massa et al. (2019, Belgium)[44]	20, children Median 10.4 (8.1–13.2)	CGM CSII	BS: CSII mean 3.1 (0.8–6.0) years isCGM mean 0.8 (0.7–1.0) years DS: 6 months	B, C	Physician diagnosed	C: Signs of skin irritation/inflammation: 45% (9/20). Contact dermatitis: 10% (2/20).	Poor
33	Rachmiel et al. (2019, Israel)[45]	113, children Mean: 9.1 ± 4.1	CSII	BS: never used DS: 12 months	A	Self-reported	C: Omnipod-users: 22.2% Medtronic-users: 22.3% Animas-users: 22.2%	Poor
34	Slover et al. (2018, USA)[46]	145, children Mean: 13.1 ± 3.9	CGM	BS: unknown DS: 7 days	A	Physician diagnosed	C: Skin assessments ($n = 777$): Redness/irritation: 15.7% Small red/pink dot: 41.6% Redness: 18.9%	Poor
35	Tsalikian et al. (2012, USA)[47]	23, children Mean: 3.0 ± 0.8	CGM	BS: unknown DS: 6 months	B	Physician diagnosed and self-reported	C: (self-reported): 70% (16/23) At the 26-weeks visit (physician diagnosed): 15% (3/20)	Poor
36	Bozzetti et al. (2003, Italy)[48]	74, mixed Mean 18.5 (7–25)	GlucoWatch	BS: unknown DS: unknown	A	Self-reported	C: 77%	Poor
37	Landau et al. (2018, Israel)[49]	71, mixed Mean: 13.4 (4.1–23.8)	CGM	BS: unknown DS: 6–12 months	A	Physician diagnosed	C: 12.7%	Poor
38	Messer et al. (2017, USA)[50]	127, mixed Range: 4–45	CGM CSII	BS: CSII min 6 months DS: 42 days	A	Self-reported	C: 24.4% (25/127)	Poor
39	Weng et al. (2019, Denmark)[51]	138, mixed Median: 12.8 (8.8–14.8)	CGM CSII	BS: median CSII: 3.71 years CGM: 1.01 years	B	Self-reported	C: last 5 months (eczema) CSII: 31% CGM (all types): 41% All dermatological complications: FreeStyle Libre: 21% Enlite: 58%	Poor

Abbreviations: ACD, allergic contact dermatitis; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; IBOA, isobornyl acrylate; isCGM, intermittently scanned continuous glucose monitoring; *n*, number.

[a]Number of participants; individuals exposed to device(s) investigated.

[b]≤18 years.

[c]Most important findings reported.

[d]Dermatologist.

TABLE 2 Studies including participants also with T2D.

	Publication (year, country)	Participants, Number[a], children[b], adults or mixed Mean, SD, median age, range (years)	Diabetes medical device(s) used (*n*, if not all patients)	Exposure time Before study (BS) During study (DS)	Outcome (definition) A. Skin reaction/ irritation, unspecified B. Symptoms/ signs specified[c] C. Diagnosis specified D. Patch testing performed with substances	Diagnosis Physician diagnosed or self-reported	Outcome (results) A. Current B. Ever had C. Specified time frame (during study period) D. Not specified	Quality assessment
Cross-sectional study								
1	Pyl et al. (2020, Belgium)[52]	57, mixed IBOA-allergic: 24.5 years (9–53)	CGM	BS: unknown	A, D	Physician diagnosed	ACD by isobornyl acrylate: 3.8% Cutaneous adverse events: 5.5%	Poor
Longitudinal studies								
2	Deiss et al. (2020, Europe and South Africa)[53]	3023, adults	Eversense (glucose monitor)	BS: unknown DS: unknown	A	Physician diagnosed and self-reported	Adhesive patch location site irritation: 0.66%	Moderate
3	Deshmukh et al. (2020, UK)[54]	10,370, mixed Mean: 38.0 ± 18.8	CGM	BS: unknown DS: unknown	B	Self-reported	3% itching, redness, rash, or allergic reaction	Moderate
4	Haak et al. (2017, Europe)[55]	149, adults (intervention group) Mean: 59.3 ± 9.6	CGM	BS: unknown DS: 6 months	A	Self-reported	Nine participants reported 16 device-related adverse events	Moderate
5	Ramirez-Rincon et al. (2016, Colombia)[56]	183, mixed Mean: 32 ± 15.4	CGM CSII	BS: unknown DS: 12 months	A	Self-reported	Sensor allergy: 3 months: 13.1, 6 months: 13.7, 12 months: 12.6 Infusion set allergy: 3 months: 2.2, 6 months: 2.7, 12 months: 1.6	Moderate
6	Tierney et al. (2001, USA)[57]	355, adults Mean: 48.2, 46.5	GlucoWatch (glucose monitor)	BS: unknown DS: unknown	B	Self-reported	Edema and erythema scores: 0: 83.4%, 1: 84.9%, 3: 1.2%, 4: 0.09%	Poor
7	Hoss et al. (2013, USA)[58]	62, adults	CGM	BS: unknown DS: 14 days	B	Physician diagnosed	Pain: 3.6% (2/55) Itching: 1.8% (1/55)	Poor

Abbreviations: *n*; number.

[a]Number of participants; individuals exposed to device(s) investigated.

[b]≤18 years.

[c]Most important findings reported.

reported to the European Medicine Agency (EMA) or national equivalent (Table 3).

Diagnostic procedure

All patients were patch tested with the national baseline series. Six centres had a test series locally defined for diabetes patients with suspected contact allergy to MDs. The sets of tested allergens varied (Table 4). Patch testing with individually acquired test substances was based on the clinician's evaluation in all centres. Most of the additional allergens tested were purchased from Chemotechnique diagnostics (Chemotechnique MB Diagnostics AB, Vellinge, Sweden) and Smart Practice (Phoenix, Arizona, United States). Some allergens were prepared in-house, purchased from different chemical manufacturers or provided by other collaborating departments and colleagues.

Outcomes

In 2021, the proportions of referred DM patients with suspected contact allergy to MDs ranged from 0.4% to 4% of the tested patients in different clinics (Table 3). Contact allergy rates are shown in Table 5. Overall, in 2021, 117 DM patients with suspected contact allergy to MDs were referred. Contact allergy to MDs was diagnosed in 54 (46%) patients. The odds of having positive reactions to allergens tested were similar in female and male patients (49% vs. 43%, p-value = 0.57). Of all DM patients investigated, 34 (29%) were children. The overall proportion of children diagnosed with contact allergy to substances in MDs was 50%, whereas, in adults, the proportion was 46%, p-value = 0.68. During the past 5 years, the overall number of DM patients tested for suspected contact allergy to MDs increased, as well as the proportion of patients with contact allergy to MDs diagnosed in seven centres. The number of test substances identified in or suspected in MDs or related to contact allergy to MDs used for patch testing increased in nine centres.

Recommendations to patients

Recommendation of change of device when a contact allergy was found was given by almost all centres; however, none could routinely provide a list of 'safe' alternatives, as allergens in the products differ, products differ over time, there is lack ingredient labelling and, in some countries, no alternatives were available. Recommendations to alleviate symptoms differed between centres (Table 6).

DISCUSSION

The review performed clearly highlights that skin reactions due to MDs are seldom the main outcome of studies. Indeed, larger studies evaluating MDs for DM patients have mostly focused on MDs and diabetes-specific health outcomes, and, regarding adverse events, mainly noted the frequency of skin reactions without diagnostically defining the true nature of these cutaneous adverse events.

The present study indicates that skin problems are common in individuals with IDDM that use MDs and that the problem is most likely underdiagnosed. The present review, even if the evaluation of skin reactions differed, showed a high risk of dermatitis in patients with IDDM using MDs. However, among children with dermatitis, an ACD was found in only 5%, thus a much lower proportion of ACD than what was found in the present questionnaire survey where the overall ACD proportion was 50% among children with MD-related dermatitis when investigated at centres specialized in contact allergy. This highlights that dermatitis, and specifically contact allergy to MD, seems to be underdiagnosed and that the estimates might be higher than those summarized from the systematic review. Thus, the lack of well-performed large epidemiological studies with defined diagnosis of the dermatitis (i.e. ACD or irritant contact dermatitis) does not, unfortunately, allow any conclusion on the prevalence and incidence of dermatitis such as ACD in this patient group. There is a lack of larger studies, both longitudinal prospective studies on MD naïve patients and on a population already exposed to MDs.

Skin reactions were often self-reported, rarely observed by a dermatologist and were seldom reported as well-defined diagnoses (for example irritant contact dermatitis and ACD). In only three studies, patch testing was performed.

Some studies used a prospective design, which is usually advantageous, although the follow-up time was often less than 6 months which is the typical the mean minimum period to develop an ACD to MDs. The usually short follow-up period in the included studies makes ACD even more difficult to assess and will make it often impossible to draw any conclusions as to the safety as sensitization may effectively occur later. Cross-sectional studies need exact information on previous exposures in the population, and exposure time of the MDs, even though this includes a high risk of recall bias, when the investigation is performed.

A drawback of this review was the fact that many publications reporting ACD in patients using MDs are case reports. However, in this review, a comprehensive search using a predefined protocol aiming also to assess study quality was performed. The aim was to ensure study quality and size. As the study aim was to identify prevalence and incidence of dermatitis related to MDs, we excluded reviews, case reports and studies with small number of patients, even if of high quality[59] or when new allergens were identified. The included studies rarely reported on possible confounding factors for the prevalence of ACD, population-based studies were lacking, and the proportion of participation was often unclear increasing the risk of selection bias.

TABLE 3 Demographic data for centers patch testing diabetes mellitus patients with suspected contact allergy to medical devices.

	City, country	Referral area (population, estimated)	All patch-tested patients in 2021	DM patients referred in 2021			Having collaboration with diabetes clinic(s)/report cases to EMA or a national equivalent
			N	Total, *n* (%)	Male, *n*	Female, *n*	
1	Amsterdam, Netherlands	The whole country (17.44 M)	1452	40 (2.75)	15	25	Yes/only relevant contact allergy and irritant reactions
2	Barcelona, Spain	Part of Catalonia, Spain (0.30 M)	500	10 (2.00)	6	4	Yes/all adverse skin reactions
3	Copenhagen (Gentofte), Denmark	Capital region (1.84 M)	477	15 (3.14)	7	8	Yes/all adverse skin reactions
4	Copenhagen (Bispebjerg), Denmark	Capital Region (1.84 M)	667	4 (0.59)	4	0	No/only relevant contact allergy reactions
5	Leeds, United Kingdom	Leeds & Harrogate (0.88 M)	845	0 (0)	0	0	No/no report
6	Malmö, Sweden	The southern part (1.34 M)	946	18 (1.90)	6	12	Yes/all adverse skin reactions
7	Göttingen, Germany	central part (0.32 M)	70	3 (4.29)	1	2	No/only relevant contact allergy reactions to MDs, IBOA
8	Antwerp, Belgium	North Belgium (Flanders) (6.59 M)	436	9 (2.06)	3	6	Yes/only relevant contact allergy reactions
9	Coimbra, Portugal	Coimbra-center of Portugal (0.15 M)	273	2 (0.73)	1	1	Yes/adverse skin reactions are seldom reported
10	Perugia, Italy	Umbria (1.0 M)	1100	9 (0.82)	4	5	Yes/all adverse skin reactions
11	Bari, Italy	Puglia (4.03 M)	1500	7 (0.47)	4	3	Yes/only relevant contact allergy reactions
Total	11 centres, 9 countries		8266	117 (1.42)	51	66	

Note: Types of medical devices used in different countries are not available.

Abbreviations: DM, diabetes mellitus; EMA, The European Medicine Agency; IBOA, isobornyl acrylate; M, million; MDs, medical devices;

TABLE 4 Patch testing routine for diabetes mellitus patients with suspected contact allergy to medical devices, in different centres.

	City, country	Test with 'special' patch test series for DM patients with suspected contact allergy to MDs	Additional testing for DM patients with suspected contact allergy to MDs was introduced (year)[a,b]	Test with other existing series, such as glue or acrylate	Patch test with ultrasonic bath extract of the MDs	Additional patch test allergens with suspected chemicals contained in MDs			
						IBOA	DMAA	DPGDA	MBPA
1	Amsterdam, Netherlands	Yes	2017	Yes	No	0.1%	0.5%	0.1%	
2	Barcelona, Spain	No	2019	Yes	No	0.1%	[c]		
3	Copenhagen (Gentofte), Denmark	Yes	2017	Yes	No	0.1% 0.3%	0.1% 0.3%	0.1% 0.01%	
4	Copenhagen (Bispebjerg), Denmark	No	2020	Yes	No	0.1%			
5	Leeds, United Kingdom	Yes	2019	Yes	No	0.1%			
6	Malmö, Sweden	Yes	2017	No	Yes	0.1% 0.3%	0.1% 0.3%	0.1%	1.5%
7	Göttingen, Germany	No	2019	Yes	No	0.1%			
8	Antwerp, Belgium	Yes	2016	Yes	No[d]	0.1% 0.3%	0.1%	0.1%	0.1%[e]
9	Coimbra, Portugal	No[b]	2020	Yes	No	0.1%			
10	Perugia, Italy	Yes	2019	Yes	No	0.1%			
11	Bari, Italy	No	2018	No	No	0.1%			
	All centres, *n*	6		9	1	11	4	4	2

Note: All clinics patch-tested the patients with their baseline series and additional allergens when contact allergy to medical devices was suspected. The allergens were occluded for 2 days on Day (D) 0. Most clinics read the results on D2 or D3 on the first reading and D3 or D4 on the second reading. Only two clinics read on D7 routinely. Occasionally, additional readings might be performed depending on the clinical assessment of the clinicians.

Abbreviations: DM, diabetes mellitus; DMAA, N,N- Dimethylacrylamide; DPGDA, Dipropylene glycol diacrylate; IBOA, isobornyl acrylate; Irganox, 2,2′-methylenebis(6-tert-butyl-4-methylphenol)monoacrylate; MBPA, 2,2′-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate; MDs, medical devices.

[a]Most of the clinics had tested with suspected allergens for individuals before developing special patch test series for DM patients.

[b]No separated 'dedicated' series but tested with acylates, including ECA and IBOA and other allergens depending on the patient's history and space availability on the back.

[c]The allergen will be included for patch testing in 2022.

[d]Pieces of MDs were usually tested.

[e]The concentrations have been changed in 2022 (1.5%, 1%, 0.5%, 0.3% and 0.1%).

TABLE 5 Diabetes mellitus patients with adverse skin reactions to medical devices investigated in 2021.

			DM patients tested		Contact allergy patients	
			N = 113		*N* = 53	
	City, country		*n*	*n* (%)	*n* (% of patients tested)	
1	Amsterdam, Netherlands		40		20 (50.0)	
		Adults		35 (87.5)		15 (42.9)
		Children		5 (12.5)		5 (100)
2	Barcelona, Spain		10		1 (10.0)	
		Adults		4 (40.0)		0
		Children		6 (60.0)		1 (16.7)
3	Copenhagen (Gentofte), Denmark		15		4 (26.7)	
		Adults		9 (60.0)		2 (22.2)
		Children		6 (40.0)		2 (33.3)
4	Copenhagen (Bispebjerg), Denmark	Adults	4	1 (25%)	0	
		Children		3 (75%)		
5	Malmö, Sweden		18		12 (66.7)	
		Adults		12 (66.7)		7 (58.3)
		Children		6 (33.3)		5 (83.3)
6	Göttingen, German		3		1 (33.3)	
		Adults		2 (66.7)		1 (50.0)
		Children		1 (33.3)		0
7	Antwerp, Belgium		9		8 (88.9)	
		Adults		8 (88.9)		7 (87.5)
		Children		1 (11.1)		1 (100)
8	Coimbra, Portugal		2		2 (100)	
		Adults		1 (50.0)		1 (100)
		Children		1 (50.0)		1 (100)
9	Perugia, Italy		9		4 (44.4)	
		Adults		4 (44.4)		2 (50.0)
		Children		5 (55.6)		2 (40.0)
10	Bari, Italy		7		2 (28.6)	
		Adults		7 (100)		2 (28.6)
		Children		0		0
	All centres[a]		117		54 (46.2)	
		Adults		83 (70.9)		38 (45.8)
		Children		34 (29.1)		17 (50.0)

Abbreviation: DM, diabetes mellitus.

[a]The centre in UK had no patient referred in 2021.

The questionnaire part of the study further indicated that there are no standard diagnostic routines for this patient group. It is important to correctly diagnose patients with skin reactions to MDs as different kinds of skin reactions have different implications and should be treated differently.

The questionnaire survey shows that patients with IDDM referred with MD-related problems were referred to all centres and that all centres performed extensive investigations to help patients to obtain a correct diagnosis. Most centres reported that the number of patients with IDDM for assessment of ACD has increased. However, as there was rarely a straightforward referral route from diabetes clinics to the diagnosing centres, it is impossible to establish the prevalence of DM patients with skin reactions from MDs, particularly ACD. There was a high proportion of contact allergy among investigated patients, but it was not possible to estimate how often patients with skin reactions from MDs were referred. Among our patients, a high contact allergy rate was noted (>45%), similar to rates found in patients with hand eczema.[60]

In patients with hand dermatitis, displaying an impaired skin barrier and high exposure to possible contact allergens,

TABLE 6 Recommendations and management for diabetes mellitus patients with contact allergy to medical devices.

	City, country	Glucocorticosteroid cream	Glucocorticosteroid-containing nasal spray	Barrier protection (ex. hydrocolloid dressing)	Barrier cream/patch/spray	Change of medical devices	Others
1	Amsterdam, Netherlands		☑	☑	☑	☑	
2	Barcelona, Spain	☑			☑		
3	Copenhagen (Gentofte), Denmark	☑		☑		☑	
4	Copenhagen (Bispebjerg), Denmark					☑	
5	Leeds, United Kingdom		☑			☑	
6	Malmö, Sweden					☑	
7	Göttingen, Germany		☑	☑	☑	☑	
8	Antwerp, Belgium	☑	☑	☑	☑	☑	Methotrexate
9	Coimbra, Portugal	☑		☑		☑	
10	Perugia, Italy					☑	
11	Bari, Italy	☑					
	All centres, *n*	5	4	5	4	8	

the recommendation is that the patient group should be patch tested, whereas no such guideline currently exists for the group of patients with dermatitis, and possible ACD, from MDs.

The questionnaire indicated differences in the diagnostic procedure, both regarding patch test materials and patch testing with patients own material. When diagnosing an ACD due to allergens found in MDs there are several prerequisites.[61] Knowledge of present and prior exposure is necessary to enable correct patch testing and relevance assessment. The allergens commercially available are limited. Among the new allergens recently found in MDs, isobornyl acrylate was identified in 2016 and commercially available a few years later. Although several allergens in test series already have proven to be of clear-cut relevance, new substances in MDs, such as N,N-dimethylacrylamide, are not included in commercially provided test series. Further, there is no consensus on which allergens should be tested due to different exposures. However, as the products are quickly spread on the global market, it would be possible to identify a minimum of patch test allergens, and screening series has been proposed.[62] Even if this is done, there are several pitfalls in the diagnostic procedure that need to be highlighted. As MD contain ingredients that are not labelled the diagnostic procedure must include aimed testing with possible sensitizers present in the MD, with patient's own material and extracts thereof. To identify the culprit agent, or relevance of positive test, additional chemical analysis is often necessary. As the MDs used are chemically complex products with several components produced by different manufacturers, several possible allergens might be identified and the patient has to be retested with additional allergens to ensure that the culprit agent(s) is (are) correctly identified. False-negative reactions may appear after a usual final reading on Day 3 or 4; therefore, patch test reading should be performed on Day 7 and also later if needed.[63–65]

Due to the lack of data on ACD related to MDs and studies published in easily accessible literature aimed to endocrinologists and diabetes nurses, as well as a lack of standardized referral routes, health care professionals treating patients with IDDM might be unaware of the necessity to refer this patient group to specific test centres. Moreover, dermatologists need robust diagnostic procedures for this patient group. The need for labelling of MDs regarding possible allergens has already been emphasized in dermatological literature.[66] Labelling of products used would help the endocrinologists to possibly avoid exposing the patients to substances the patients are allergic to. Additionally, knowledge of the actual culprit allergens and the prevalence of contact allergy will enable primary preventive measures.

In conclusion, this review highlights a major research gap with no population-based study assessing the prevalence of ACD from MDs in persons with IDDM. The prevalence of exogenous dermatitis and particularly ACD in patients using MDs is still not well defined and further research is needed. This study also indicates the need of improved knowledge about the chemical substances contained in MDs, better

regulation on full labelling of MD, improvement of the commercially available allergens, and guidelines regarding referral routes and diagnostic procedures.

ACKNOWLEDGEMENTS

We would like to acknowledge the medical librarian Marika Svalstedt for assistance with the literature search.

FUNDING INFORMATION

None declared.

CONFLICT OF INTEREST STATEMENT

LK, JU, KT, TA, TB, MB, FC, NH, JJ, TR, MW: No COI in relation to this work. OA is investigator, consultant and/or speaker for Leo Pharma, Abbvie, Sanofi, L'Oréal/La Roche Posay and Bioderma/NAOS. AGA is or recently was a speaker and/or advisor for and/or has received research funding from Almirall, Amgen, AstraZeneca, Avene, Celldex, Escient Pharmaceutials, Genentech, GSK, Instituto Carlos III-FEDER, Leo Pharma, Menarini, Novartis, Sanofi–Regeneron, Servier, Thermo Fisher Scientific and Uriach Pharma/Neucor. MG is investigator, consultant and/or speaker for Abbvie, Astra-Zeneca, Leo Pharma, Lilly, Novartis, Pfizer, Sanofi and Takeda. LS is or recently was an investigator/speaker for Abbvie, Almirall, LeoPharma, Lilly, Novartis, Pfizer and Sanofi. CS participates in the IDEA project sponsored by the International Fragrance Association (IFRA).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: von Kobyletzki LB, Ulriksdotter J, Sukakul T, Aerts O, Agner T, Buhl T, et al. Prevalence of dermatitis including allergic contact dermatitis from medical devices used by children and adults with Type 1 diabetes mellitus: A systematic review and questionnaire study. J Eur Acad Dermatol Venereol. 2024;00:1–18. https://doi.org/10.1111/jdv.19908