

Cutaneous Adverse Effects from Diabetes Devices in Pediatric Patients with Type 1 Diabetes Mellitus: a Systematic Review

Alicia Podwojniak, Joseph Flemming, Isabella J. Tan, Hira Ghani, Zachary Neubauer, Anne Jones

Submitted to: JMIR Dermatology
on: April 23, 2024

Disclaimer: © The authors. All rights reserved. This is a privileged document currently under peer-review/community review. Authors have provided JMIR Publications with an exclusive license to publish this preprint on its website for review purposes only. While the final peer-reviewed paper may be licensed under a CC BY license on publication, at this stage authors and publisher expressly prohibit redistribution of this draft paper other than for review purposes.

Table of Contents

Original Manuscript..... 5

Supplementary Files..... 31

0..... 31



Cutaneous Adverse Effects from Diabetes Devices in Pediatric Patients with Type 1 Diabetes Mellitus: a Systematic Review

Alicia Podwojniak¹ BSc; Joseph Flemming¹ MSc, BSc; Isabella J. Tan² BSc; Hira Ghani³ DO; Zachary Neubauer⁴ BSc; Anne Jones¹ DO, MPH

¹Rowan-Virtua School of Osteopathic Medicine Stratford US

²Rutgers Robert Wood Johnson Medical School New Brunswick US

³Department of Dermatology Northwestern Feinberg School of Medicine Chicago US

⁴Sidney Kimmel Medical College of Jefferson University Philadelphia US

Corresponding Author:

Alicia Podwojniak BSc

Rowan-Virtua School of Osteopathic Medicine

113 Laurel Rd

Stratford

US

Abstract

Background: Continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusions (CSII) are the current standard treatment devices for type 1 diabetes (T1D) management. With a high prevalence of T1D beginning in pediatrics and carrying into adulthood, insufficient glycemic control leads to poor patient outcomes. Dermatologic complications such as contact dermatitis, lipodystrophies, and inflammatory lesions are among those associated with CGM and CSII, which reduce glycemic control and patient compliance.

Objective: This systematic review aims to explore the current literature surrounding dermatologic complications of CGM, CSII, and the impact on patient outcomes.

Methods: A systematic review of the literature was carried out using PRISMA 2020 guidelines utilizing five online databases. Included articles were those containing primary data relevant to human subjects and adverse CGM and CSII devices in pediatric populations of which greater than 50% of the sample size were ages 0-21. Qualitative analysis was chosen due to the heterogeneity of outcomes.

Results: Following the application of exclusion criteria, 25 studies were analyzed and discussed. The most common complication covered is contact dermatitis with 12 identified studies. 6 studies concern lipodystrophies, 4 cover nonspecific cutaneous changes, and the remaining 3 cover unique cutaneous findings such as granulomatous reactions and panniculitis.

Conclusions: The dermatologic complications of CGM and CSII pose a potential risk to long-term glycemic control in T1D, especially in young patients where skin lesions can lead to discontinuation. Increased manufacturer transparency is critical and further studies are needed to expand upon the current preventative measures such as device site rotation and steroid creams, which lack consistent effectiveness.

(JMIR Preprints 23/04/2024:59824)

DOI: <https://doi.org/10.2196/preprints.59824>

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✓ **Please make my preprint PDF available to anyone at any time (recommended).**

Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.

Only make the preprint title and abstract visible.

No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✓ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**

Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain visible to all users.
Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <http://www.jmir.org/preprint/59824>, the full manuscript will be available to all users.



Original Manuscript

Title: Cutaneous Adverse Effects from Diabetes Devices in Pediatric Patients with Type 1 Diabetes Mellitus: a Systematic Review

Abstract

Background: Continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusions (CSII) are the current standard treatment devices for type 1 diabetes (T1D) management. With a high prevalence of T1D beginning in pediatrics and carrying into adulthood, insufficient glycemic control leads to poor patient outcomes. Dermatologic complications such as contact dermatitis, lipodystrophies, and inflammatory lesions are among those associated with CGM and CSII, which reduce glycemic control and patient compliance.

Objective: This systematic review aims to explore the current literature surrounding dermatologic complications of CGM, CSII, and the impact on patient outcomes.

Methods: A systematic review of the literature was carried out using PRISMA 2020 guidelines utilizing five online databases. Included articles were those containing primary data relevant to human subjects and **adverse reactions to CGM and CSII devices** in pediatric populations, of which greater than 50% of the sample size were ages 0-21. Qualitative analysis was chosen due to the heterogeneity of outcomes.

Results: **Following the application of exclusion criteria, 25 studies were analyzed and discussed. An additional 5 studies were identified after the initial search and inclusion. The most common complication covered is contact dermatitis, with 13 identified studies. Seven studies concern lipodystrophies, 5 cover nonspecific cutaneous changes, and the remaining 3 cover unique cutaneous findings such as granulomatous reactions and panniculitis, and 2 discuss user acceptability.**

Conclusion: The dermatologic complications of CGM and CSII pose a potential risk to long-term glycemic control in T1D, especially in young patients where skin lesions can lead to discontinuation. Increased manufacturer transparency is critical and further studies are needed to expand upon the current preventative measures such as, device site rotation and steroid creams, which lack consistent effectiveness.

Keywords: insulin pumps, continuous glucose monitoring, type 1 diabetes, lipohypertrophy, contact dermatitis, lipodystrophy

Introduction:

Type 1 diabetes (T1D) is a chronic metabolic disease that results from the autoimmune destruction of pancreatic beta islet cells with subsequent loss of endogenous insulin production. With a growing global incidence, inadequate surveillance of glucose monitoring, dietary management, and insulin injections pose a lifelong threat and burden to patients [1]. Although T1D treatment has improved significantly since the development of exogenous insulin in 1921, the acute risks of hypoglycemia and associated long-term morbidity from poor glycemic control necessitate an imminent need for more sustainable treatment [1]. T1D carries high morbidity, mortality, and poor quality of life [2]. There may be associated profound psychological distress and subsequent poor adherence to treatment [3].

Continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion (CSII) are currently the standards of care for managing T1D. CGMs are devices that monitor glucose levels within the interstitial fluid of subcutaneous adipose tissue every few minutes, replacing the need for manual finger sticks but requiring device replacement every 1-2 weeks [4]. CGMs can be used concomitantly with manual exogenous insulin or with automated insulin pumps, which are programmed to dose and release insulin. Closed loop systems allow the CGM and insulin pump to communicate and automatically dose depending on measured glucose levels. Flash glucose

monitoring (FGM) require patients to scan their cellular device over the CGM to obtain the data [4]. For CSII devices, infusion set cannulas are inserted subcutaneously, set onto the skin with adhesives, and connected via plastic tubing to the electronic device [2].

Contact dermatitis, local erythematous reactions, infection, and lipodystrophies are among the most commonly reported potential cutaneous side effects from using these devices [5]. Such reactions can lead to discontinued use and reliance on manual insulin administration, which has been shown to be less effective at optimizing glycemic control [4]. Primarily in pediatric patients, in whom tolerance for adverse skin reactions may be reduced, we suspect that identification and subsequent resolution of cutaneous adverse effects will promote increased adherence and optimized glycemic control. This systematic review aims to identify the existing cutaneous adverse reactions related to subcutaneous insulin infusion systems and continuous glucose monitoring devices in pediatric patients.

Methods:

This systematic review was conducted utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines using PubMed, SCOPUS, Embase, Cochrane, and Web of Science databases [6]. A flow diagram of the study selection process is available in Figure 1. This manuscript is registered on Prospero No. CRD42023489106. Using the NLM Medical Subject Heading (MeSH) to determine the best selection of potential search terms, the following were derived and used: (“insulin infusion System” OR “insulin infusion systems” OR “insulin pump” OR “implantable programmable insulin pump” OR “CGM” OR “continuous glucose monitor”) AND (“skin manifestation” OR “skin” OR “skin reaction” OR “cutaneous manifestation” OR “cutaneous reaction” OR “cutaneous” OR “dermatologic manifestation” OR “dermatologic reaction” OR “dermatologic”) AND (“pediatric” OR “child”). The following inclusion criteria were applied: original articles that involved primary data, i.e. [randomized controlled trials (RCT), retrospective studies, case studies, case series], human-only studies, literature published within the

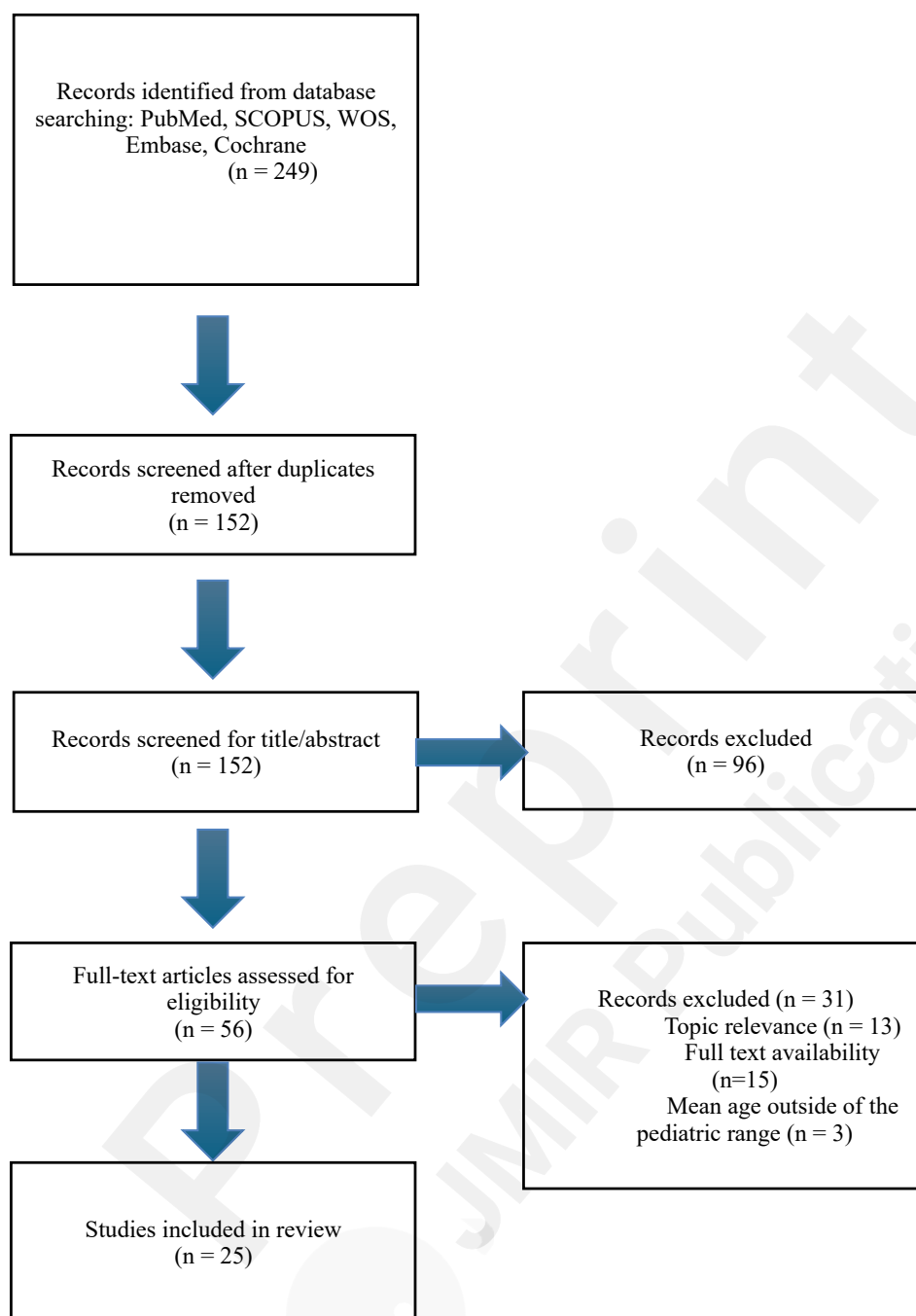
last five years (2018-2023), international studies, and studies about adverse cutaneous reactions to insulin infusion systems in pediatric patients. Exclusion criteria included abstracts, articles lacking full text, studies still in progress, articles that did not include mention of adverse cutaneous reactions to insulin infusion systems in pediatric patients, studies that had less than 50% pediatric patients or a mean age range outside of (0-18) years old.

Duplicate studies following initial retrieval were identified and sorted through by two reviewers (A.P. and J.F.) to ensure there were no further duplicates. After removing duplicates, the abstracts and titles were screened for the inclusion criteria (A.P.) **After the title and abstract appraisal, two reviewers independently conducted a full-text review** (A.P. & J.F.). The remaining studies then continued to the data extraction phase. The risk of bias was assessed by A.P. and J.F. using the JBI Critical Appraisal Checklist, which allows assessment of risk grading and scoring at low, moderate, or high [7]. Following these steps, data were extracted from the shortlisted articles, focusing on dermatologic reactions as the primary outcome. Secondary outcomes were device adherence and the efficacy of insulin infusion as measured by HbA1c. Given the heterogeneity of studies included in the review, a qualitative analytic approach was chosen.

Results:

The initial search retrieved 249 studies, of which 157 were duplicates. **Of the** remaining 152 articles, 56 were included in the abstract appraisal, and 96 were excluded due to the article type, wrong patient population, or not being relevant to the topic. Quality full-text appraisal included 25 studies. Of these, **the initial search yielded** 12 papers discuss contact dermatitis, 6 discuss lipodystrophy, 4 discuss nonspecific cutaneous changes and burden, and 3 describe other unique cutaneous reactions. **Additional 5 papers were added to supplement the identified articles, although they were not identified via the initial search terms.** A table of findings is summarized in (**Table 1**) and the basis of levels of study type is outlined according to The Centre for Evidence-Based Medicine Levels of Therapeutic Studies [8].

Figure 1. Flow diagram of the systematic study selection process.



Nonspecific Cutaneous Outcomes

Two qualitative surveys report generalized skin complaints as barriers to using CGMs and CSII devices [9,10]. Increased complications were seen in those who used both devices rather than just one (69% vs. 39%). Erythema, pruritus, pain, rash, skin change, infection, and existing skin condition exacerbation were the most commonly self-reported complications in descending order [9].

22% of respondents reported discontinuing the use of the devices as a result of these complications, and only 7% reported visiting a dermatologist to manage these complications. Genève et al. reported 33.8% reported skin reactions, with reactions in 30.4% of those who utilized CSII and 23.5% of those using CGM devices. Erythema (89.6%), itching (82.1%), presence of vesicles (35.8%), and squamous lesions (26.9%) were most commonly reported [11]. Detrimental consequences of these lesions included irregular usage (21.9%), device discontinuation (4.3%), device model change (13.1%), school absences (10.9%), sleep disturbance (35.5%), and discontinuing hobbies (13.2%) [11].

Sorenson et al. investigated the subcutaneous changes, including echogenicity, vascularity, and device distance via ultrasound, resulting from one year of device usage. Subcutaneous hyperechogenicity frequency, a measure of lipohypertrophy, and vascularization increased significantly over time for CSII devices ($P < .001$ and $P = 0.009$) but not for CGM. Subcutaneous hyperechogenicity did not predict poor glycemic control by HbA1c in this study ($P = .11$) [12].

It was also noted that among patients using FGM, adverse events were more frequently reported compared to those using self-monitoring of blood glucose (SMBG). These included premature sensor losses (31.8% vs. 12.4%; $P = 0.001$), skin reactions (18.2% vs. 2.6%; $P < 0.001$), and local pain (6.8% vs. 0%; $P < 0.001$) [13].

Allergic Contact Dermatitis

Seven studies and six case reports describe allergic contact dermatitis with various identified culprit allergens. Most cases were due to tapes and adhesives, and many others were attributable to allergens within the housing of the pump or sensor [14,15]. Isobornyl acrylate (IBOA) was identified as the primary culprit allergen, with positive patch testing results in 4 studies [14-17]. Abitol, colophonium [14,18] benzoyl peroxide [14]15, N-Ndimethylacrylamide (DMAA), colophonium, sesquiterpene lactone, and various acrylates [16,17], were also identified as contributors in a variety of device types and brands. A wide variety of commonly used devices were used. There was some

overlap regarding brand and product type [adhesive, plastic, plaster, and CGM or CSII]. Many patients had often used and failed at least one or two other devices with various compositions, suggesting cross-reactivity among products and brands [17]. Additional reactions include pruritus, fluid leakage, hyperpigmentation, bleeding, infection, and scarring, which were treated with topical corticosteroids and moisturizers [15]. Hypoallergenic bandage barrier use was the most reported solution to minimize the reaction, with a 43.7% improvement in one study [18]. Additional **prevention measures were** hydrocolloid and silicone-based plaster barriers, topical steroids, topical antibiotics, emollient creams, and topical antihistamines [19].

Five studies reported the need for complete discontinuation or switching to a different device [15-17,29]. This metric was not included in two articles [14,18]. Effects on glycemic control were generally not included, except **in two** articles that did not identify a significant difference in HbA1c among patients with or without allergic contact dermatitis without commenting on the discontinuation or continuation of devices [18,19].

Five case reports (n=6) were identified in this review that describe pediatric patients presenting with contact dermatitis from their diabetes devices. Two of these cases (n=3) describe patients without a history of atopic dermatitis (AD) who developed contact dermatitis reactions from multiple infusion sets and CGMs, with alternating brand use and site placement [19,20]20,21. IBOA and other acrylates were identified [20] along with dipropylene glycol diacrylate (DPGDA) [21] as culprit allergens. In two of these patients, successful switching of devices resolved the lesions [21]. Two cases (n=2) report the presentation of patients with a history of AD who developed contact dermatitis, in which the first began as an exacerbation of AD [22] and the second progressed to severe, systemic contact dermatitis reaction with subsequent infections requiring hospitalization [23]. IBOA was a contributing allergen in both cases, while Dicyclohexylmethane-4,4₀-diisocyanate (DMDI) [22] and 4-tert-butylcatechol (PTBC) [22]23 were also identified. Discontinuation and switching of devices yielded a positive outcome in one case [23] and was not reported in the other [22]. The last case describes the development of contact dermatitis from CSII, CGM, and an

adhesive barrier wipe used between sensor changes that contained isopropyl alcohol and colophony. Before wipe use, the patient did not react to the devices on their own. The authors suggest a sensitization that occurred due to wiping and progressed with subsequent exposure to the devices, as her patch testing results were positive for IBOA, sesquiterpene lactone, and colophony [24]. It is not reported whether the patient discontinued use because of her reaction.

In one case series investigating allergic reactions to the FreeStyle Libre glucose sensor, seven patients underwent patch testing with isobornyl acrylate (IBOA) and N,N-dimethylacrylamide (DMAA)[25]. Results revealed sensitization to both IBOA and DMAA in six patients, with one patient showing a reaction solely to DMAA[25]. Gas chromatography-mass spectrometry (GC-MS) analysis confirmed the presence of IBOA in adhesive patches and both IBOA and DMAA in sensor extracts, suggesting that both compounds, commonly found in adhesives of medical devices like glucose sensors, should be considered during patch testing for suspected allergic reactions[25].

Lipodystrophies

Several studies examined the incidence of lipodystrophies, including lipohypertrophy (LH) and lipoatrophy (LA), from the use of CGMs or CSII devices. Bleeding, bruising, and pain at the injection site were commonly reported regardless of injection type [26]. Rates of lipohypertrophy (LH) were significantly higher in the MDI group compared to the CSII group ($P=.001$)[26]. A similar, nonsignificant finding was seen in Vibetskaya et al. [27]. In contrast, Burgmann et al. found a higher incidence of LH associated with CSII compared to MDI (46.8% versus 42.2%) [228 as opposed to the aforementioned studies [26,27]. For those with LH, higher average insulin doses were required to maintain metabolic control (0.97U/kg/day vs 0.78U/kg/day), and HbA1C was increased [26] Significantly elevated HbA1c levels were noted in two studies ($P=.022$; $P<.001$) indicating a therapeutic detriment related to the incidence of LH [28,29]. Increased daily insulin usage was not significantly associated with LH [27]29. The incidence of hypoglycemic episodes was significantly greater in those with LH ($P=.007$) [24]. Incidence of LH was significantly decreased in relation to

adequate site rotation ($P=.02$; $P=.026$). [26,29] Overall, quality of life impairment was reported as low or absent in 95% of patients regardless of insulin therapy modality, [28] and zero participants discontinued the use of these devices. In a sample of 151 participants, Lombardo identified a prevalence of lipohypertrophy at 44.3%, and of lipodystrophy 0.9%. Lipodystrophies were associated with negative consequences in glycemic control [30].

Xatzipsalti et al. described two cases in which children with LA were resistant to standard treatment modalities and experienced regression of LA following laser treatment. First, a 6-year-old child was found to have sites of LA on the right upper thigh and bilateral buttocks. LA did not improve after switching to insulin glulisine or with the administration of 4% sodium chromoglycate (SCG) [31]. Due to the failure of conservative treatments, a CO2 laser, which generates a D-pulse that targets deep subcutaneous tissue, was directed at sites of LA on the bilateral buttocks [31]. Nine months following treatment, a dramatic reversal of LA sites on the buttocks was observed, whereas the LA site of the right upper thigh showed little to no improvement where SCG treatment was continued [31]. The same authors further discussed an identical treatment course in a 9-year-old patient [31].

Kordonouri et al. conducted an RCT to determine the effectiveness of zinc-free insulin formulations in reducing LA. All subjects had similar subcutaneous fat levels at baseline and were treated with zinc-containing insulin for six months. Following this, seven children were switched to the zinc-free insulin glulisine while the remainder continued zinc-containing insulin treatment, and the intervention group showed improved relative fat thickness ($P=.003$), number ($P=.015$) and size of atrophic sites ($P=.008$) [32].

Other skin manifestations

While most reported insulin-related dermatologic complications fall into the categories described previously, rare cases of more complex pathology also exist. Perez et al. describe a case of CSII use leading to inflammatory nodules and friable papules on the upper extremities of a young

child. Erosions, subcutaneous nodules, and a pink vascular papule were additionally present on the bilateral buttocks. Biopsy revealed a neutrophilic and granulomatous inflammation at insulin pump injection sites [33]. Switching from CSII to MDI reduced the development of these lesions [33]. Smith et al. describe a case of a 13-year-old with T1D with previously well-controlled glycemic levels with an HbA1c of 7.2% who developed painful, persistent nodules at all insulin injection sites hours after injection. Following nodule development, the patient's HbA1c rose to 12.5% [34]. Histopathologic analysis revealed the patient had a panniculitis reaction to exogenous insulin, which was proposed to result from insulin auto-antibodies forming IgG complexes with exogenous insulin, leading to a Type III hypersensitivity reaction. Edwards et al. report worsening glycemic control paired with inflammatory dermatologic lesions associated with various insulin preparations in a 17-year-old girl. Following negative allergy testing to various insulin prep additives such as zinc, a type III hypersensitivity reaction was determined to be causative [35].

User Acceptability

User acceptability is crucial in type 1 diabetes management due to the notable prevalence of adverse cutaneous reactions. Ensuring that devices such as continuous glucose monitoring devices and insulin pumps are comfortable and well-tolerated helps maintain consistent use and adherence to treatment regimens. This, in turn, promotes better diabetes control and reduces the risk of complications associated with fluctuating blood glucose levels.

One article examined the critical need to reduce "user burden" in diabetes care technology for broader adoption and improved adherence. Surveys of 1,348 individuals, including people with diabetes and parents of children with diabetes, highlighted concerns about current CGM devices[36]. Respondents expressed a strong preference for a proposed fully implanted CGM system that eliminates skin-attached components. Specifically, surveys revealed that only 8-17% of patients with type 1 diabetes currently adopt CGM technology, emphasizing the potential of less obtrusive systems to increase usability and adherence rates[36]. These findings underscore the importance of patient-

centered design in enhancing diabetes care technologies to achieve broader adoption and better patient outcomes.

In another study involving 67 young patients aged 13 to 19 years with T1D using FGM systems, user acceptability was notably high. Results indicated that 95.5% of participants found sensor application less painful than routine finger-stick tests, and 85% rated the system as comfortable[37]. Additionally, 94% appreciated the small size of the FGM and 89.6% felt it did not disrupt their daily activities[37]. The majority (91%) reported strong compatibility of the FGM with their lifestyle, and many participants preferred FGM over traditional blood glucose monitoring methods for being less painful (83.6%), more discreet (83.6%), and easier to use (95.5%)[37]. Overall, the study concluded with strong evidence of high acceptability and satisfaction among young patients with T1D using FGM systems.

Table 1: Summary of identified studies.

Authors	Cutaneous manifestation	N=; % affected	Mean age (years) unless otherwise stated	% Discontinued use of insulin devices	Glycemic control outcomes	Quality of Study ^a
Rigo et al. [9]	Nonspecific cutaneous reactions	121; 60%	13.9	22%	Not included	2b
Hilliard et al. [10]	Nonspecific cutaneous reactions	55; nonspecific	5	Not included as a measure specific to cutaneous reaction	Not included	2b
Geneve et al. [11]	Nonspecific cutaneous reactions	198; 33.8%	11.75	4.3%	Not included	2b
Messaoui [13]	Nonspecific cutaneous reactions	334	13.6	Not included as a measure specific to cutaneous reaction	Not included	2b

Sorensen et al. [12]	Ultrasound determined subcutaneous changes	161	11	N/a	No effect of hyperechogenicity (an indicator of lipohypertrophy) on HbA1c	2b
Ahrensboell-Friis et al. [14]	Contact dermatitis	30; 100%	13.8	Not included	Not included	2b
Alves de silva et al. [15]	Contact dermatitis	15; 100%	9.3	26% d/c current device and switched to another, 0% totally d/c use of any device	Not included	2b
Lombardo et al. [18]	Contact dermatitis	139; 56%	11.1	0.01%	Not included	2b
Herman et al. [16]	Contact dermatitis	12; 100%	11.5	16%	Not included	2b
Huang and Dekoven et al. [24]	Contact dermatitis	1; 100%	11	Not included	Not included	4
Enberg et al. [22]	Contact dermatitis	1; 100%	6	Discontinued use and changed brands	Not included	4
Lyngstadaas et al. [23]	Contact Dermatitis, systemic dermatitis, and infection	1;100%	8 months	Discontinued use and changed brands	Not included	4
Cichoń et al. [20]	Contact dermatitis	1; 100%	15	Not included	Not included	4
Ulriksdotter et al. [21]	Contact dermatitis	2; 100%	8, 10	Discontinued use and changed	Not included	4

				brands		
Svedman et al. [17]	Contact dermatitis	8; 100%	8	Discontinued use and changed brands prior to study	Not included	2b
Passanissi et al. [19]	Contact dermatitis	21; 100%	12.1	38.1% discontinued use	No significant change in glycemic control as measured by HbA1C	2b
Mowitz et al. [25]	Contact dermatitis	4; 100%	9.75	75% discontinued use/switched brands	Not included	4
Demir et al. [26]	Lipohypertrophy	254; 17.1%	14.9	Not included	Nonsignificant changes increased HbA1C associated with LH Increased number of hypoglycemic episodes for those with LH (p=0.007)	2b
Lombardo et al. [30]	Lipohypertrophy Lipoatrophy	151; LH: 44.3% LA: 0.9%	11.9	Not included	Difference in correlation variation (p = 0.036) and blood glucose standard deviation score (p = 0.021) among patients with lipodystrophies	2b
Vitebskaya et al. [27]	Contact dermatitis Lipohypertrophy	50; CD: 45% LH: 63%	12	Not included	Not included	2b
Burgmann et al. [28]	General dermatologic complication	369; 91.8%	12.3	0% discontinued use	Increased HbA1c in those with LH (p=0.022)	2b

	Lipohypertrophy	369; 46.8%				
Deeb et al. [29]	Lipohypertrophy	104; 39%	12.11	Not included	Increased HbA1c in those with LH (p<0.001)	2b
Xatzipsalti et al. [31]	Lipoatrophy	2; 100%	6, 9	Insulin-induced, changed insulin types without improvement	Not included	4
Kordonouri et al. [32]	Lipoatrophy	14; 100%	14.7	N/a	Nonsignificant changes in HbA1c	1b
Perez et al. [33]	Granulomatous reaction	1; 100%	6	Switch from CSII to MDI improved lesions	Not included	4
Smith et al. [34]	Panniculitis reaction	1;100%	13	Not included	HbA1C rise from 7.2% to 12.5% following development of nodules	4
Edwards et al. [35]	Panniculitis	1; 100	17	Multiple changes trialed and failed	Not included	4
Engler et al. [36]	User acceptability	114	10.7	Not included	Not included	2b
Al Hayek [37]	User acceptability	67	13-19	Not included	Not included	2b

^aFrom the Centre for Evidence-Based Medicine, [8]

Discussion

Principle Results

Currently, several chemicals are believed to contribute to ACD, including IBOA, butyl acrylate, abietic acid, abitol, and colophony. IBOA is overwhelmingly identified as the causative agent [14-16, 20,22,23] and is well known as a causative agent in a variety of these devices.

Additional reports exist, identified outside of our original search, whereby an 8-year-old girl develop

ACD to IBOA [38], and a case series of both adults and children, in which 4 patients reacted to IBOA and one to colophonium [39]. In 2020, IBOA earned the American Contact Dermatitis Society Allergen of the Year title [40]. Manufacturer acknowledgment of IBOA in their devices is mixed, with some companies denying awareness of its presence in products [41].

Nevertheless, the overwhelming evidence of IBOA as an agent of contact dermatitis should be sufficient to produce consumer warnings and patient transparency. Such allergens often exist on the adhesive [10,14-16,22] but have also been found on plastics, plaster, or other aspects of the devices [15,18,20-22]. Thus, transparency of chemicals within every component of the various devices is critical to ensure the optimal opportunity to undergo patch testing and prevent adverse dermatologic outcomes. Further, sequiterpene lactone is a co-reactor with IBOA in ACD cases involving diabetic devices and was identified as a causative agent in many of the studies identified in this review [13,24]. This finding illustrates the potential for co-reactivity among devices if a child switches to another device, again prompting the need for increased manufacturer transparency. The overwhelming incidence of contact dermatitis from these devices suggests the need for screening measures for cutaneous complications and patch testing for pediatric patients with T1D to optimize their continued use of these beneficial devices.

Progression of these reactions, such as subsequent infection and long-term scarring, can perpetuate worse outcomes for patients [15,23]. Particularly in toddlers or pediatric patients with less body surface area, minimizing risk and optimizing area availability are potential predictors for ongoing management. In the Defining, Reviewing, and Monitoring Skin Pathology in Type 1 Diabetes Study (DERMIS) study, the authors used noninvasive optical coherence tomography OCT imaging and skin biopsies to identify skin changes in long term CSII users, (average age 48.1). Fibrosis, eosinophilia, increased vessel density, increased IGF- I and TGF- β 3, and fat necrosis were identified[42].

Lipodystrophies serve as another barrier to optimizing the use of these devices. Insulin injection pens were identified as having higher rates of lipodystrophies in some studies than

continuous insulin pumps, but the reverse was true in others [26-28]. Infusion site rotation was determined to be a feasible means of avoiding adverse lipodystrophy reactions, suggesting the need for proper patient education regarding appropriate insulin administration on an individual basis to maintain quality of life regardless of dermatologic complications [26]. Components of insulin formulations are also known to contribute to cutaneous reactions [13,32,34,35,42-44]. It is, therefore, important to identify and isolate reactions from pump components, insulin components, or the nature of a continuous infusion of reaction-provoking insulin. Increased insulin dosage, however, was not found to increase rates of LH development [29], suggesting an increased need for studies of the exact cause. Additional potential confounding causative agents must be identified and filtered to better characterize these reactions [45]. Granulomatous reactions were a rare finding in this review, with two suggested mechanisms of pathogenesis. First, the altered immune response in T1D and chronic local trauma from insulin injections may lead to a granulomatous tissue reaction. Alternatively, zinc crystals bound to insulin molecules may cause neutrophilic chemotaxis, lysis of those neutrophils leading to enzyme release and further zinc dispersion, and increased chemotaxis in an inflammatory cycle [33,46]. Interestingly, the switch to MDI from CSII led to fewer reactions [33], which contradicts the finding of lipodystrophies [26,27].

Identifying effective prevention and maintenance strategies for these cutaneous side effects is critical for patients, parents, and medical providers. Preventing exposure to the offending agents is the primary defense, as effective treatments do not exist to allow for continued use of the products. Colophony was another agent identified in patch testing results, although in this review, it was pertaining to wipes used as a barrier to protect the skin [23,24]. Additional preventative measures identified included silicone-based plasters and hydrocolloid creams, with topical steroids, antibiotics, and emollient creams as therapeutics [19]. The suggested use of barriers such as plasters and adhesives is often cumbersome and requires frequent change, thus decreasing a patient's tolerance to their usage. Significant cost burdens related to managing these cutaneous effects have been identified as another barrier to continued use. Despite these measures, some patients are still unable to tolerate

these effects, leading to discontinued use. Interventions such as laser therapy should be further explored to restore and optimize surface area for device use and insulin administration [31]. A small case series identified topical fluticasone nasal spray prior to CGM application as a successful means of reducing irritation and dermatitis, crediting its anti-inflammatory properties[47].

Additionally, the introduction of a standardized skin reaction report form, as proposed in one study, could incentivize healthcare providers (HCPs) to systematically evaluate and document skin conditions associated with diabetes management devices [48]. This approach holds promise in addressing potential underreporting of adverse events, thereby enhancing the accuracy and comprehensiveness of data collection [48]. By promoting consistent documentation practices, such a tool could yield valuable insights into the prevalence and severity of skin reactions among individuals using these devices. Ultimately, this initiative may contribute to optimizing patient care, informing device selection, and driving advancements in device design aimed at minimizing dermatological complications in diabetes management.

Limitations

Limitations to this review include confounding variables among insulin length of use, duration of T1D, and unclear manufacturer components. Additionally, some studies had small sample sizes and subjective measurements, often reported by a parent or guardian.

Conclusion

For pediatric patients with an early age of diagnosis, the lengthened period of need for and exposure to such devices creates an increased risk, and skin reactions contribute as a key reason for treatment discontinuation [49]. Current practices to minimize these cutaneous burdens in pediatric patients include changing site placement, changing devices or brands, and using creams or steroids. Often, these practices are ineffective due to cross-reactivity within the products, high costs, and decreased unaffected surface area with each subsequent cutaneous reaction. These adverse cutaneous reactions can predispose individuals to chronic scarring with psychological sequelae [50]. This

review highlights the complex challenges of cutaneous reactions in pediatric type 1 diabetes patients using insulin infusion and glucose monitoring devices. Increased longitudinal research is required to determine the long-term consequences of discontinued use of the devices and transition to lifelong manual monitoring. Alternative manufacturing practices also need to be considered to optimize patient outcomes. As the current gold standard of insulin-dependent diabetes management depends on continuous devices [50], it is crucial to minimize obstacles to their use and promote lifelong compliance.

Conflicts of Interest: The authors have no conflicts of interest to disclose.

Supplemental information:

Detailed search term strategy: Using the NLM Medical Subject Heading (MeSH) to determine the best selection of potential search terms, the following were derived and used:

("Insulin Infusion System" OR "insulin infusion systems" OR "Insulin pump" OR "Implantable Programmable Insulin Pump" OR "CGM" OR "continuous glucose monitor") AND ("Skin Manifestation" OR "skin" OR "skin reaction" OR "cutaneous manifestation" OR "cutaneous reaction" OR "cutaneous" OR "dermatologic manifestation" OR "dermatologic reaction" OR "dermatologic") AND ("pediatric" OR "child")

References:

1. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. Jan 04 2014;383(9911):69-82. doi:10.1016/S0140-6736(13)60591-7. PMID: 23890997
2. Elian V, Popovici V, Ozon EA, et al. Current Technologies for Managing Type 1 Diabetes Mellitus and Their Impact on Quality of Life-A Narrative Review. Life (Basel). 2023;13(8):1663. Published 2023 Jul 30. doi:10.3390/life13081663. PMID: 37629520
3. Tareen R.S., Tareen K. Psychosocial aspects of diabetes management: Dilemma of diabetes

- distress. *Transl Pediatr.* 2017;6:383–396. doi: 10.21037/tp.2017.10.04. PMID: 29184819
4. Sora ND, Shashpal F, Bond EA et al. Insulin pumps: review of technological advancement in diabetes management. *Am J Med Sci* 2019; 358: 326–331. PMID: 31655714.
 5. Jedlowski PM, Te CH, Segal RJ, Fazel MT. Cutaneous adverse effects of diabetes mellitus medications and medical devices: a review. *Am J Clin Dermatol.* 2019;20(1):97-114. PMID: 30361953.
 6. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. PMID: 33782057
 7. Aromataris E, Fernandez R, Godfrey C, Holly C, Kahlil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an Umbrella review approach. *Int J Evid Based Healthc* 2015;13(3):132-40. PMID: 26360830
 8. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. *Plast Reconstr Surg.* 2011 Jul;128(1):305-310. doi: 10.1097/PRS.0b013e318219c171. PMID: 21701348.
 9. Rigo RS, Levin LE, Belsito DV, Garzon MC, Gandica R, Williams KM. Cutaneous Reactions to Continuous Glucose Monitoring and Continuous Subcutaneous Insulin Infusion Devices in Type 1 Diabetes Mellitus. *J Diabetes Sci Technol.* 2021;15(4):786-791. doi:10.1177/1932296820918894. PMID: 32389062
 10. Hilliard ME, Levy W, Anderson BJ, Whitehouse AL, Commissariat PV, Harrington KR, Laffel LM, Miller KM, Van Name M, Tamborlane WV, DeSalvo DJ, DiMeglio LA. Benefits and Barriers of Continuous Glucose Monitoring in Young Children with Type 1 Diabetes. *Diabetes Technol Ther.* 2019 Sep;21(9):493-498. doi: 10.1089/dia.2019.0142. Epub 2019 Jul 9. PMID: 31287721;
 11. Genève P, Adam T, Delawoevre A, et al. High incidence of skin reactions secondary to the use of adhesives in glucose sensors or insulin pumps for the treatment of children with type 1

- diabetes. *Diabetes Res Clin Pract.* 2023;204:110922. doi:10.1016/j.diabres.2023.110922. PMID: 37769906
12. Sørensen FMW, Svensson J, Kinnander C, Berg AK. Ultrasound Detected Subcutaneous Changes in a Pediatric Cohort After Initiation of a New Insulin Pump or Glucose Sensor. *Diabetes Technol Ther.* 2023;25(9):622-630. doi:10.1089/dia.2023.0137. PMID: 37279034.
13. Messaaoui A, Tenoutasse S, Crenier L. Flash Glucose Monitoring Accepted in Daily Life of Children and Adolescents with Type 1 Diabetes and Reduction of Severe Hypoglycemia in Real-Life Use. *Diabetes Technol Ther.* 2019;21(6):329-335. doi:10.1089/dia.2018.0339
14. Ahrensboell-Friis U, Simonsen AB, Zachariae C, Thyssen JP, Johansen JD. Contact dermatitis caused by glucose sensors, insulin pumps, and tapes: Results from a 5-year period. *Contact Dermatitis.* 2021;84(2):75-81. doi:10.1111/cod.13664. PMID: 32677709.
15. Alves da Silva C, Bregnhøj A, Mowitz M, Bruze M, Andersen KE, Sommerlund M. Contact dermatitis in children caused by diabetes devices. *Contact Dermatitis.* 2022;87(5):406-413. doi:10.1111/cod.14166. PMID: 35634681
16. Herman A, Darrigade AS, de Montjoye L, Baeck M. Contact dermatitis caused by glucose sensors in diabetic children. *Contact Dermatitis.* 2020;82(2):105-111. doi:10.1111/cod.13429. PMID: 31657469.
17. Svedman C, Bruze M, Antelmi A, et al. Continuous glucose monitoring systems give contact dermatitis in children and adults despite efforts of providing less 'allergy- prone' devices: investigation and advice hampered by insufficient material for optimized patch test investigations. *J Eur Acad Dermatol Venereol.* 2021;35(3):730-737. doi:10.1111/jdv.16981. PMID: 33034101.
18. Lombardo F, Passanisi S, Tinti D, Messina MF, Salzano G, Rabbone I. High Frequency of Dermatological Complications in Children and Adolescents with Type 1 Diabetes: A Web-Based Survey. *J Diabetes Sci Technol.* 2021;15(6):1377-1381. doi:10.1177/1932296820947072. PMID: 32757778

19. Passanisi S, Salzano G, Galletta F, et al. Technologies for Type 1 Diabetes and Contact Dermatitis: Therapeutic Tools and Clinical Outcomes in a Cohort of Pediatric Patients. *Front Endocrinol (Lausanne)*. 2022;13:846137. Published 2022 Mar 15. doi:10.3389/fendo.2022.846137. PMID: 35370980
20. Cichoń M, Sokołowska-Wojdyło M, Trzeciak M. Allergic contact dermatitis elicited by insulin infusion sets: First case reported in Poland. *Contact Dermatitis*. 2023;88(5):404-406. doi:10.1111/cod.14281. PMID: 36700556.
21. Ulriksdotter J, Svedman C, Bruze M, Mowitz M. Allergic contact dermatitis caused by dipropylene glycol diacrylate in the Omnipod® insulin pump. *Br J Dermatol*. 2022;186(2):334-340. doi:10.1111/bjd.20751. PMID: 34510410.
22. Enberg J, Hamnerius N, Mowitz M. Allergic contact dermatitis caused by a new insulin pump system containing isobornyl acrylate. *Contact Dermatitis*. 2023;88(4):326-328. doi:10.1111/cod.14274. PMID: 36607276
23. Lyngstadaas AV, Holm JØ, Krogvold L, Måløy AK, Ingvaldsen CA. A toddler with systemic contact dermatitis caused by diabetes devices. *Skin Health Dis*. 2023;3(4):e234. Published 2023 Apr 8. doi:10.1002/ski2.234. PMID: 37538326
24. Huang C, DeKoven J. An unexpected source of glucose monitor-associated allergic contact dermatitis [published online ahead of print, 2021 Feb 17]. *Contact Dermatitis*. 2021;10.1111/cod.13815. doi:10.1111/cod.13815. PMID: 33598976.
25. Mowitz M, Herman A, Baeck M, et al. N,N-dimethylacrylamide-A new sensitizer in the FreeStyle Libre glucose sensor. *Contact Dermatitis*. 2019;81(1):27-31. doi:10.1111/cod.13243
26. Demir G, Er E, Atik Altınok Y, Özen S, Darcan Ş, Gökşen D. Local complications of insulin administration sites and effect on diabetes management. *J Clin Nurs*. 2022;31(17-18):2530-2538. doi:10.1111/jocn.16071. PMID: 34622517
27. Vitebskaya AV, Amshinskaya JR, Grabovskaya OV Dermatological Complications of Insulin Therapy in Children with Type 1 Diabetes: Cross-Sectional Study. *Current Pediatrics* .

- 2020;19(1):26-34. <https://doi.org/10.15690/vsp.v19i1.2082>
28. Burgmann J, Biester T, Grothaus J, Kordonouri O, Ott H. Pediatric diabetes and skin disease (PeDiSkin): A cross-sectional study in 369 children, adolescents and young adults with type 1 diabetes. *Pediatr Diabetes*. 2020;21(8):1556-1565. doi:10.1111/pedi.13130. PMID: 32985057
29. Deeb A, Abdelrahman L, Tomy M, et al. Impact of Insulin Injection and Infusion Routines on Lipohypertrophy and Glycemic Control in Children and Adults with Diabetes. *Diabetes Ther*. 2019;10(1):259-267. doi:10.1007/s13300-018-0561-7. PMID: 30617932
30. Lombardo F, Bombaci B, Alibrandi A, Visalli G, Salzano G, Passanisi S. The Impact of Insulin-Induced Lipodystrophy on Glycemic Variability in Pediatric Patients with Type 1 Diabetes. *Children (Basel)*. 2022;9(7):1087. Published 2022 Jul 20. doi:10.3390/children9071087
31. Xatzipsalti M, Alvertis H, Vazeou A. Laser treatment for lipoatrophy in children with diabetes type 1. *Diabetol Int*. 2021;13(2):452-455. Published 2021 Oct 3. doi:10.1007/s13340-021-00547-w. PMID: 35463860
32. Kordonouri O, Biester T, Weidemann J, et al. Lipoatrophy in children, adolescents and adults with insulin pump treatment: Is there a beneficial effect of insulin glulisine?. *Pediatr Diabetes*. 2020;21(7):1285-1291. doi:10.1111/pedi.13094. PMID: 32738019
33. Perez VA, Husain S, Magro CM, Strom MA, Williams KM, Levin LE. A newly described cutaneous reaction at sites of insulin pump use in a child with Type 1 diabetes. *Pediatr Dermatol*. 2021;38(1):239-241. doi:10.1111/pde.14438. PMID: 33169884.
34. Smith RJ, Khurana M, Rubin AI, Kublaoui B, Perman MJ, Murthy AS. Painful nodules on the abdomen of a teenage male. *Pediatr Dermatol*. 2021;38(2):e12-e13. doi:10.1111/pde.14430. PMID: 33870568.
35. Edwards M, Liy-Wong C, Byrne A, Cowan KN, Ahmet A. Insulin Reactions: What Do You Do When Your Treatment's the Trigger?. *Can J Diabetes*. 2023;47(2):190-192. doi:10.1016/j.cjcd.2022.08.006. PMID: 36137870

36. Engler R, Routh TL, Lucisano JY. Adoption Barriers for Continuous Glucose Monitoring and Their Potential Reduction With a Fully Implanted System: Results From Patient Preference Surveys. *Clin Diabetes*. 2018;36(1):50-58. doi:10.2337/cd17-0053
37. Al Hayek AA, Robert AA, Al Dawish MA. Acceptability of the FreeStyle Libre Flash Glucose Monitoring System: The Experience of Young Patients With Type 1 Diabetes. *Clin Med Insights Endocrinol Diabetes*. 2020;13:1179551420910122. Published 2020 Mar 16. doi:10.1177/1179551420910122
38. Mine Y, Urakami T, Matsuura D. Allergic contact dermatitis caused by isobornyl acrylate when using the FreeStyle® Libre. *J Diabetes Investig*. 2019;10(5):1382-1384. doi:10.1111/jdi.13023
39. Aerts O, Herman A, Mowitz M, Bruze M, Goossens A. Isobornyl acrylate. *Dermatitis*. 2020;31(1):4-12. PMID: 31913984.
40. Teufel-Schäfer U, Huhn C, Müller S, Müller C, Grünert SC. Severe allergic contact dermatitis to two different continuous glucose monitoring devices in a patient with glycogen storage disease type 9b. *Pediatr Dermatol*. 2021;38(5):1302-1304. doi:10.1111/pde.14767. PMID: 34418148.
41. Mastroilli C, Rizzuti L, Cangelosi AM, Iovane B, Chiari G, Caffarelli C. Long-acting insulin allergy in a diabetic child. *Int J Immunopathol Pharmacol*. 2017; 30 (2): 174-177. doi:10.1177/0394632017700431. PMID: 28368217
42. Kalus A, Shinohara MM, Wang R, et al. Evaluation of Insulin Pump Infusion Sites in Type 1 Diabetes: The DERMIS Study. *Diabetes Care*. 2023;46(9):1626-1632. doi:10.2337/dc23-0426
43. Jacquier J, Chik CL, Senior PA. A practical, clinical approach to the assessment and management of suspected insulin allergy. *Diabet Med*. 2013;30(8):977-985. doi:10.1111/dme.12194. PMID: 23601039

44. Schernthaner G. Immunogenicity and allergenic potential of animal and human insulins. *Diabetes Care*. 1993;16 Suppl 3:155-165. doi:10.2337/diacare.16.3.155. PMID: 8299472.
45. Gentil S, Strollo F, Ceriello A. AMD-OSDI Injection Technique Study Group. Lipodystrophy in Insulin-Treated Subjects and Other Injection-Site Skin Reactions. Are We Sure Everything is Clear?. *Diabetes Ther*. 2016; 7(3): 401-409. doi:10.1007/s13300-016-0187-6. PMID: 27456528
46. Jordaan HF, Sandler M. Zinc-induced granuloma--a unique complication of insulin therapy. *Clin Exp Dermatol*. 1989;14(3):227-229. doi:10.1111/j.1365-2230.1989.tb00938.x
47. Paret M, Barash G, Rachmiel M. "Out of the box" solution for skin problems due to glucose-monitoring technology in youth with type 1 diabetes: real-life experience with fluticasone spray. *Acta Diabetol*. 2020;57(4):419-424. doi:10.1007/s00592-019-01446-y
48. Freckmann G, Buck S, Waldenmaier D, et al. Skin Reaction Report Form: Development and Design of a Standardized Report Form for Skin Reactions Due to Medical Devices for Diabetes Management. *J Diabetes Sci Technol*. 2021;15(4):801-806. doi:10.1177/1932296820911105
49. Asarani NAM, Reynolds AN, Boucher SE, de Bock M, Wheeler BJ. Cutaneous complications with continuous or flash glucose monitoring use: systematic review of trials and observational studies. *J Diabetes Sci Technol*. 2020; 14(2): 328-337. PMID: 31452386
50. Calabrò PF, Ceccarini G, Calderone A, et al. Psychopathological and psychiatric evaluation of patients affected by lipodystrophy. *Eat Weight Disord*. 2020;25(4):991-998. doi:10.1007/s40519-019-00716-6. PMID: 31144218.
51. Burckhardt MA, Smith GJ, Cooper MN, Jones TW, Davis EA. Real-world outcomes of insulin pump compared to injection therapy in a population-based sample of children with type 1 diabetes. *Pediatr Diabetes*. 2018;19(8):1459-1466. doi:10.1111/pedi.12754. PMID: 30129154.

Abbreviations:

T1D, type 1 diabetes mellitus;
CGM, continuous glucose monitor;
CSII, CGM, continuous **glucose monitoring (device)**;
ACD, allergic contact dermatitis;
IBOA, isobornyl acrylate;
FGM, **flash glucose monitoring (device)**;
PRISMA, Preferred Reporting Items for Systematic Reviews and Metaanalysis;
RCT, randomized controlled trial;
DMAA, N-Ndimethylacrylamide;
DPGDA, dipropylene glycol diacrylate;
DMDI, Dicyclohexylmethane-4,4_o-diisocyanate;
PTBC; 4-tert-butylcatechol;
LA, lipoatrophy,
LH; lipohypertrophy; S
CG, sodium chromoglycate

Supplementary Files

Untitled.

URL: <http://asset.jmir.pub/assets/51802582c621944d7012f1440d4872ba.docx>