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

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Table of Contents

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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.

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Keywords: insulin pumps, insulin infusion, continuous glucose monitor, type 1 diabetes, pediatric, cutaneous reaction, lipoatrophy, lipohypertrophy, allergic contact dermatitis, glycemic control, dermatologic reaction, lipodystrophy, granulomatous reaction, panniculitis

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 poses 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 the management of 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 for the CGM and insulin pump to communicate and automatically dose depending on respective measured glucose levels. Flash CGMs (fCGM) require the patient to scan their cellular device over the CGM to obtain the data [4]. For CSII devices, infusion set cannulas are inserted subcutaneously and 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 that can occur from use of 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 the following databases: PubMed, SCOPUS, Embase, Cochrane, Web of Science [6]. A flow diagram of the study selection process is available in Figure 1. This manuscript is registered on Prospero No. CRD42023489106. 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

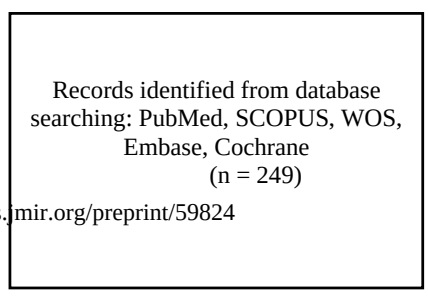
included: abstracts, articles lacking full text, studies still in progress, articles that did not include mention of adverse cutaneous reactions to insulin infusion systems in pediatric patients, studies that had less than 50% pediatric patients or a mean age range outside of (0-18) years old.

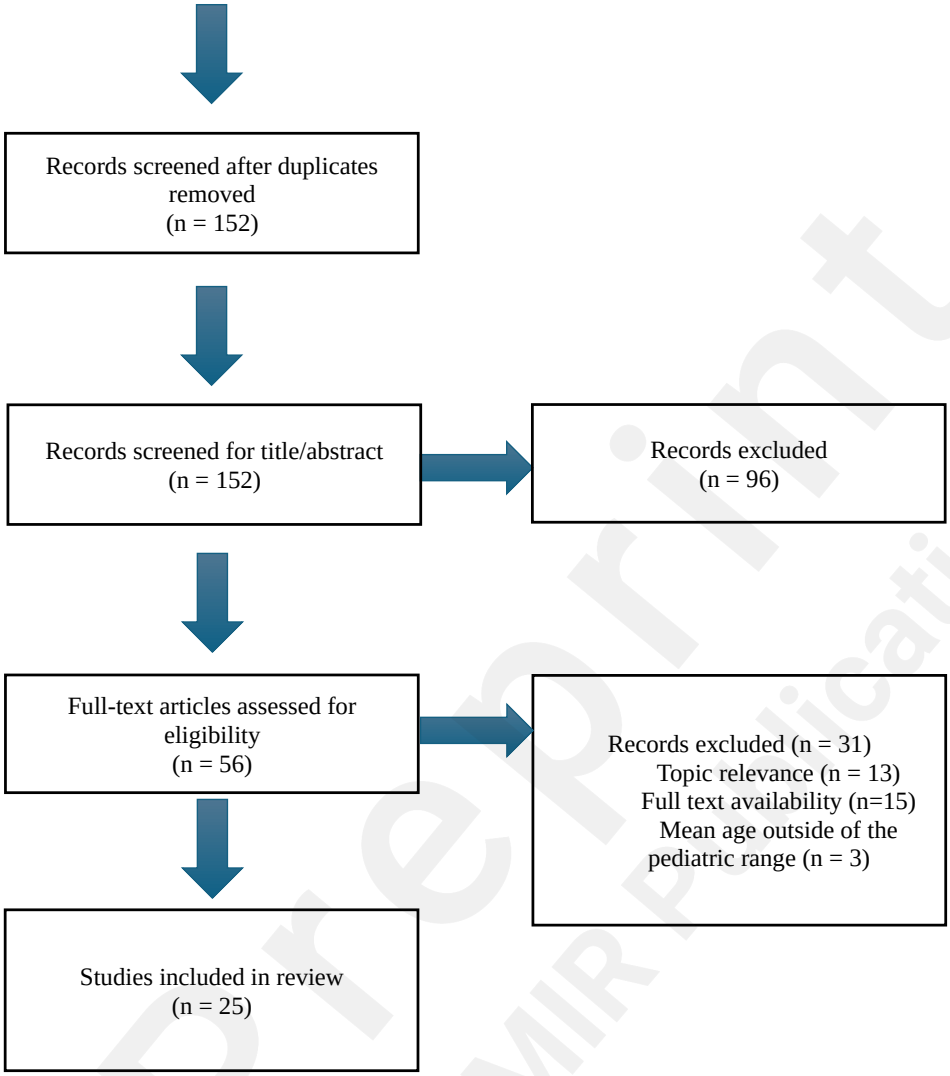
Duplicate studies following initial retrieval were identified and sorted through by two reviewers (A.P. and J.F.) to ensure there were no further duplicates. Following the removal of duplicates, the abstracts and titles were screened for the inclusion criteria (A.P.) After the title and abstract appraisal, full-text review was conducted independently by two reviewers (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, allowing assessment of risk grading, scored 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. With 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 having relevance to the topic. Quality full-text appraisal included 25 studies. Of these, 12 papers discuss contact dermatitis, 6 discuss lipodystrophy, 4 discuss nonspecific cutaneous changes and burden, and 3 describe other unique cutaneous reactions. 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 further only 7% reported visiting a dermatologist for management of 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 to 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 was not a predictor of poor glycemic control by HbA1c in this study ($P = .11$) [12].

Allergic Contact Dermatitis

Seven studies and six case reports describe allergic contact dermatitis with various identified culprit allergens. A majority of cases were due to tapes and adhesives, and many others were attributable to allergens within the housing of the pump or sensor [13,14]. Isobornyl acrylate (IBOA) was identified as the primary culprit allergen, with positive patch testing results in 4 studies [13-16].[1]Abitol, colophonium [13,17] benzoyl peroxide [14], N-Ndimethylacrylamide (DMAA), colophonium, sesquiterpene lactone, and various acrylates [15,16], 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]. Often, many patients had already used, and failed, at least one or two other devices with various compositions, suggesting cross-reactivity among products and brands [16]. Additional reactions include pruritus, fluid leakage, hyperpigmentation, bleeding, infection, and scarring, which

were treated with topical corticosteroids and moisturizers [14]. Hypoallergenic bandage barrier use was the most reported solution to minimize the reaction, with a 43.7% improvement in one study [17]. Additional measures of prevention were hydrocolloid and silicone-based plaster barriers, topical steroids, topical antibiotics, emollient creams, and topical antihistamines [18].

The need for complete discontinuation or switching to a different device was reported in five studies [14-16,18]. This metric was not included in two articles [13,17]. Effects on glycemic control were generally not included, except 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 [17,18].

5 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]. IBOA and other acrylates were identified [19] along with dipropylene glycol diacrylate (DPGDA) [20] as culprit allergens. In two of these patients, successful switching of devices resolved the lesions [20]. 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 [21] and the second progressed to severe, systemic contact dermatitis reaction with subsequent infections requiring hospitalization [22]. IBOA was a contributing allergen in both cases while Dicyclohexylmethane-4,4_0-diisocyanate (DMDI) [21] and 4-tert-butylcatechol (PTBC) [22] were also identified. Discontinuation and switching of devices yielded a positive outcome in one case [22] and was not reported in the other [21]. 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 have a reaction 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 [23]. It is not reported whether the patient discontinued use because of her reaction.

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 [24]. Rates of lipohypertrophy (LH) were significantly higher in the MDI group compared to the CSII group (*P*=.001)[24]. A similar, nonsignificant finding was seen in Vibetskaya et al [25]. In contrast, Burgmann et al found a higher incidence of LH associated with CSII compared to MDI (46.8% versus 42.2%) [26] as opposed to the aforementioned studies [24,25] 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 [24] Significantly elevated HbA1c levels were noted in two studies (*P*= .022; *P* <.001) indicating a therapeutic detriment related to the incidence of LH [26,27]. Increased daily insulin usage was not significantly associated with LH [27]. 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).[24, 27] Overall, quality of life impairment was reported as low or absent in 95% of patients regardless of insulin therapy modality, [26] and zero participants discontinued the use of these devices.

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) [28]. 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 [28]. 9

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 [28]. A largely identical treatment course was further discussed in a 9-year-old patient by the same authors [28].

Kordonouri et al. carried out 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 6 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) [29].

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 [30]. Switching from CSII to MDI reduced the development of these lesions [30]. 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% [31]. Histopathologic analysis revealed the patient had a panniculitis reaction to exogenous insulin, proposed to be the result of 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 [32].

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***
Rigo et al.	Nonspecific cutaneous reactions	121; 60%	13.9	22%	Not included	2b
Hilliard et al.	Nonspecific cutaneous reactions	55; nonspecific	5	Not included as a measure specific to cutaneous reaction	Not included	2b
Geneve et al.	Nonspecific cutaneous reactions	198; 33.8%	11.75	4.3%	Not included	2b
Sorensen et al.	Ultrasound determined subcutaneous changes	161	11	N/a	No effect of hyperechogenicity (indicator of lipohypertrophy) on HbA1c	2b
Ahrensbøll-Friis et al.	Contact dermatitis	30; 100%	13.8	Not included	Not included	2b
Alves de silva et al.	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.	Contact dermatitis	139; 56%	11.1	0.01%	Not included	2b
Herman et al.	Contact dermatitis	12; 100%	11.5	16%	Not included	2b
Huang and Dekoven et al.	Contact dermatitis	1; 100%	11	Not included	Not included	4
Enberg et al.	Contact dermatitis	1; 100%	6	Discontinued use and changed brands	Not included	4
Lyngstadaas et al.	Contact Dermatitis, systemic dermatitis and infection	1;100%	8 months	Discontinued use and changed brands	Not included	4
Cichoń et al.	Contact dermatitis	1; 100%	15	Not included	Not included	4
Ulriksdotter et al.	Contact dermatitis	2; 100%	8, 10	Discontinued use and changed brands	Not included	4
Svedman et al.	Contact dermatitis	8; 100%	8	Discontinued use and changed brands prior to study	Not included	2b
Passanissi et al.	Contact dermatitis	21; 100%	12.1	38.1% discontinued use	No significant change in glycemic control as measured by HbA1C	2b
Lombardo et al.	Contact dermatitis	42; 100%	11.8	Not included	No significant change in glycemic control as measured by HbA1C	2b
Demir et al.	Lipohypertrophy	254; 17.1%	14.9	Not included	Nonsignificant changes, increased HbA1C associated with LH Increased number of	2b

					hypoglycemic episodes for those with LH (p=0.007)	
Vitebskaya et al.	Contact dermatitis Lipohypertrophy	50; CD: 45% LH: 63%	12	Not included	Not included	2b
Burgmann et al.	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 at al.	Lipohypertrophy	104; 39%	12.11	Not included	Increased HbA1c in those with LH (p<0.001)	2b
Xatzipsalti et al.	Lipoatrophy	2; 100%	6, 9	Insulin-induced, changed insulin types without improvement	Not included	4
Kordonouri et al.	Lipoatrophy	14; 100%	14.7	N/a	Nonsignificant changes in HbA1c	1b
Perez et al.	Granulomatous reaction	1; 100%	6	Switch from CSII to MDI improved lesions	Not included	4
Smith et al.	Panniculitis reaction	1;100%	13	Not included	HbA1C rise from 7.2% to 12.5% following development of nodules	4
Edwards et al.	Panniculitis	1; 100	17	Multiple changes trialed and failed	Not included	4

*From the Centre for Evidence-Based Medicine, http://www.cebm.net [8]

Discussion

Principle Results

12 papers in this review discussed the development of ACD as a significant barrier to device usage. Currently, there are several chemicals believed to contribute, including IBOA, butyl acrylate, abietic acid, abitol, and colophony. IBOA is overwhelmingly identified as the causative agent [13-15, 19, 21,22] and is well known as a causative agent in a variety of these devices. In 2020, IBOA earned the title of American Contact Dermatitis Society Allergen of the year [33]. Manufacturer acknowledgment of IBOA in their devices is mixed, with some companies denying awareness of its presence in products [34]. Nevertheless, the overwhelming evidence of IBOA as an agent of contact dermatitis should be sufficient to produce consumer warnings and patient transparency. The presence of such allergens often exists on the adhesive [10, 13-15,21], but has also been found on plastics, plaster, or other aspects of the devices [14,17,19-21]. 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 [15,23]. This finding illustrates the potential for co-reactivity among devices if a child switched 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 cause perpetuated worse outcomes for patients [14,22]. Particularly in toddlers or other pediatric patients with less body surface area, minimizing risk and optimizing area availability serve as potential predictors for ongoing management.

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 compared to continuous insulin pumps, but the reverse was true in others [24-26]. 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 [24]. Components of insulin formulations are also known to contribute to cutaneous reactions [12,29,31,32,35-38]. 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 [27], 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 [39]. Granulomatous reactions were a rare finding in this review, with two suggested mechanisms of pathogenesis. First, the altered immune response in T1D combined with 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 [30,40]. Interestingly, the switch to MDI from CSII led to fewer reactions [30], which is a contradictory finding to those of lipodystrophies [24,25].

Identifying effective prevention and maintenance strategies for these cutaneous side effects is of critical importance 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]. Additional preventative measures identified included silicone-based plasters and hydrocolloid creams, with topical steroids, antibiotics, and emollient creams as therapeutics [18]. Suggested use of barriers such as plasters and adhesives is often cumbersome and requires frequent changing, 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 [28].

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, oftentimes 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 [41]. 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 [42]. 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 [43], 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")

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Abbreviations:

T1D, type 1 diabetes mellitus;
CGM, continuous glucose monitor;
CSII, continuous insulin infusion (device);
ACD, allergic contact dermatitis;

IBOA, isobornyl acrylate;
fCGM, flash continuous glucose monitor;
PRISMA, Preferred Reporting Items for Systematic Reviews and Metaanalysis;
RCT, randomized controlled trial;
DMAA, N-Ndimethylacrylamide;
DPGDA, dipropylene glycol diacrylate;
DMDI, Dicyclohexylmethane-4,4_0-diisocyanate;
PTBC; 4-tert-butylcatechol;
LA, lipoatrophy,
LH; lipohypertrophy; S
CG, sodium chromoglycate

Supplementary Files

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