Frequency of Dermatological Side Effects of Continuous Subcutaneous Insulin Infusion in Children and Adolescents with Type 1 Diabetes

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- lipoatrophy

Abstract

Background: The incidence of type 1 diabetes is rising, particularly in young infants. The treatment with continuous subcutaneous insulin infusion (CSII) offers certain benefits and has gained popularity. Insulin-pump therapy could be associated with cutaneous-adverse effects. The purpose of our study was to investigate the frequency and characterization of skin-related complications in patients with CSII.

Methods: In a single center setting, 54 patients (28 male, 26 female) on CSII therapy aged between 3 and 20 years participated in our study. Data including duration of diabetes, duration of CSII, pump model, catheter material, frequency of catheter switch and hygiene procedures at time of puncture were collected through a standardized questionnaire and photographs of affected areas of the skin were made. Statistical analysis was done to verify an association with gender, patients´ age, HbA1c values, and body mass index.

Results: Our observation revealed skin complications at the site of catheter insertion in 43% (8 f, 15 m) of our patients. A frequent occurrence of scars (24%, 6 f, 7 m), lipohypertrophic areas (20%, 4 f, 7 m) and eczema (11%, 1 f, 5 m) was observed. Furthermore, 6% (1 f, 2 m) showed changes in pigmentation and 6% (1 f, 2 m) lipoatrophy. The catheter localization had to be switched due to skin-complications in 24% (6 f, 7 m) whereas none of our patients discontinued insulin-pump therapy.

Conclusion: Skin-related complications during CSII are frequent and regular examination of the insertion sites is crucial. To verify the occurrence of lipoatrophy associated with insulin pump therapy – an otherwise rare complication – larger studies would be needed.

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Abbreviations

BMI	body-mass-index
HbA1c	glycated hemoglobin
CSII	continuous subcutaneous insulin infusion
T1DM	type I diabetes mellitus

Introduction

The incidence of type 1 diabetes (T1DM) is steadily rising worldwide. Whereas the annual global increase is estimated at 3.9% [1], the incidence increase in Europe is 5.0% and in Austria 5.5% [2, 3]. A distinct shift to the age-group of 0–4 years at onset can be observed and one can expect this trend to continue in the future [1]. Furthermore, it is likely for patients with severe diabetes to present complications at a younger age. To delay or prevent long-term complications, an appropriate diagnosis and maintenance of good metabolic control are therefore crucial. To optimize glycemic control, continuous subcutaneous insulin infusion (CSII) therapy is a treatment method allowing the most physiological substitution of insulin. It has gained popularity, in particular in infants and young children [4]. Many studies have been published showing the benefits of CSII in children, such as improvement of HbA1c, a decrease of severe hypoglycemic events [5, 6] and reduced rates of diabetic ketoacidosis [7].

Since the introduction of highly purified recombinant human insulin, dermatological adverse effects as seen with bovine insulin preparations became rare. These side effects (e.g. lipoatrophy) may not only have serious cosmetic effects, but can also affect insulin absorption kinetics and therefore glycemic control [8]. Even if CSII was reported to be used successfully in resolving cutaneous side effects from insulin injections

such as lipoatrophy [9], dermatological complications from insulin pump therapy are documented [10–13].

The objective of our study was to evaluate the type and frequency of dermatological side effects in children and adolescents with T1DM with CSII. Furthermore, we aimed to verify if the skin manifestations are associated with certain parameters such as catheter localization sites, frequency of set change, catheter sets and needle material used in addition to the patient's age, body mass index (BMI) and glycemic control.

Methods

The observational study was performed in a single center setting. 54 (87%, 28 male, 26 female) of 62 patients with CSII therapy agreed to participate in our cross-sectional study, while 8 patients refused to take part in the investigation. Written informed consent was obtained from parents and children. The study design was approved by the Ethics Board of the Medical University of Innsbruck (AN 4740; 314/4.11). Data collection was performed during the patients´ visit to the outpatient's clinic of the Pediatric Department at the University Hospital of Innsbruck. Data such as the preferable and previously used insertion site region, interval between set changes, hygienic practices, person who changes catheter, and the switch of insertion sites due to adverse effects were obtained through a standardized questionnaire. Anthropometric measures including patient´s age, weight, height and body-mass index as well as data concerning diabetes history such as HbA1c-value, duration of disease and CSII-therapy, catheter sets, and type of insulin pump were obtained from medical reports. The insertion sites were assessed by the same individual for dermatological abnormalities and digitally photographed using identical settings. The observed cutaneous changes were categorized in scars, eczema or eczema-like lesions, pigmentary abnormalities, lipohypertrophy and lipoatrophy.

Statistical analysis was performed with SPSS version and the Mann-Whitney test was applied for group comparisons of continuous variables and the Fisher's exact test for categorical variables. Values were reported as a median and interquartile range and a 2-sided p-value < 0.05 was considered to be statistically significant.

Results

In total, 54 of 62 (87%) patients were included in the study, 28 (52%) were male, 26 (48%) female. The median age of our patients was 9.6 years, ranging from 3.1 to 20.5 years of age. 7 preschoolers (5 and less years of age) participated; 21 were between 6–10 years, 18 were between 11–15, and 8 patients were 16 years and older.

Patient characteristics such as age and BMI as well as diabetes duration and duration of CSII treatment are shown in **Table 1**.

The dermatological complications searched for were scars, lipohypertrophy, eczema like lesions, pigmentary changes and lipoatrophy. The frequency of occurrence of dermatological side effects during insulin pump therapy in the study group and separated for boys and girls is outlined in **Table 2**.

We further assessed if the incidence of dermatological complications is associated with anthropometric measurements. No significant association could be found between skin alterations and age, BMI, or sex. Skin-related side-effects did not significantly associate with the duration of the disease itself (p = 0.96) or the duration of CSII therapy (p = 0.12). HbA1c-values did not differ in the population with or without dermatological complications (p = 0.69) (**Table 2, 3**).

The most preferable localization for catheter insertion as shown in **Fig. 1** was the buttock (46%), in particular in young infants. 22% of the patients inserted the catheter in the subcutaneous tissue of the abdomen and 11% in the thigh. Only 15% of our patients used 2 different insertion regions and 6% more than 2. Certain skin alterations could be found predominantly at distinct insertion sites. For instance, pigmentary changes were predominantly found at the buttock and lipoatrophy at the leg. Nevertheless, no statistically significant association between catheter localization and the frequency of dermatological alterations was found. There was no significant decrease in skin complications in those patients who used more than just one insertion site.

39% managed the catheter switch themselves. The youngest patients and most school-age patients (up to 11 years) (61%) required assistance from their parents (**Table 4**).

44% (n = 24) changed the insulin catheter every second day (38% of them (n = 9) experienced dermatological complications), 50%, (n = 27) switched the catheter every third day with skin altera-

Table 1 Characteristics of all patients and for males and females separately. Data are indicated as median (interquartile range).

	All (n = 54) (IQ-range)	Male (n = 28) (IQ-range)	Female (n = 26) (IQ-range)	p-values
Age (years)	9.6 (7.1–13.8)	8.5 (7.0–11.9)	11.9 (7.0–14.4)	0.23
BMI (kg/m²)	16.4 (15.2–19.6)	15.9 (15.3–19.1)	18.5 (15.0–21.7)	0.19
BMI-SDS/LDS	−0.07 (−0.62–0.51)	−0.09 (−0.6–0.29)	0.03 (−0.72–0.86)	0.40
HbA1c (%)	7.7 (7.3–8.5)	8.0 (7.4–8.7)	7.4 (7.1–8.3)	0.08
Duration of diabetes (years)	3.9 (2.6–6.2)	3.6 (2.4–5.6)	4.3 (2.9–6.3)	0.43

Table 2 Frequency and type of dermatological complications in all patients, respectively in male and female patients.

Dermatological complications	All patients (n = 54)	Male (n = 28)	Female (n = 26)	p-values *
Scars	13 (24%)	7 (25%)	6 (23%)	1.00
Lipohypertrophy	11 (20%)	7 (25%)	4 (15%)	0.51
Eczema-like lesions	6 (11%)	5 (18%)	1 (4%)	–
Pigmentary changes	3 (6%)	2 (7%)	1 (4%)	–
Lipoatrophy	3 (6%)	2 (7%)	1 (4%)	–
General Frequency	23 (43%)	15 (54%)	8 (31%)	0.11

* Because of the small number of cases Fisher exact tests were only applied for scars and lipohypertrophy

tions seen in 48% (n=13) (Table 4). Lipoatrophy was observed only in patients with an interval of 3 or more days between set changes.

35% (n=19) of our patients used teflon needles vs. 65% (n=35) steel needles (Table 4). 53% (n=10) of the patients using teflon needles experienced any dermatological side effects compared to 37% (n=13) using steel needles. No significant association between the frequency of skin alterations and the material of the catheter needle was found (p=0.39). Concerning the insulin infusion set used (Table 5), no association to skin complications could be detected.

None of our patients had to discontinue CSII therapy because of dermatological side effects.

Table 3 Comparison of patients with and without skin alterations, median (IQ range), Mann-Withney-Test.

	With cutaneous side effects (n=23) (IQ-range)	Without cutaneous side effects (n=31) (IQ-range)	p-value
Age (years)	9.4 (6.2–12.0)	11.5 (7.1–14.3)	0.22
BMI (kg/m²)	15.8 (15.0–19.4)	16.4 (15.5–20.9)	0.27
HbA1c (%)	7.6 (6.2–8.5)	7.7 (7.3–8.8)	0.69
Duration of disease (years)	3.9 (2.7–6.3)	3.9 (2.4–6.1)	0.96
Duration of pump therapy (years)	2.5 (1.8–3.8)	2.0 (1.1–3.3)	0.12

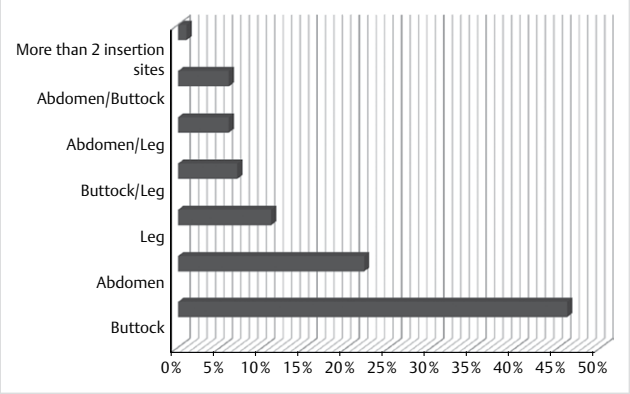

Fig. 1 Frequency of different insertion sites of the insulin-pump catheter used by children and adolescents with insulin pump treatment.

Table 4 Details on catheter insertion habits and CSII infusion set characteristics of the study population (n=54).

Person inserting catheter	
Parent	24 (44%)
Child	21 (39%)
Parent and child	9 (17%)
Frequency of catheter insertion	
Every 2nd day	24 (44%)
Every 3rd day	27 (50%)
Less common than every 3rd day	3 (6%)
Material of catheter needle	
Teflon	19 (35%)
Steel	35 (65%)

Discussion

Skin complications, other than infections can be frequently observed in adults and children with insulin pump therapy [14,15]. The age of our study population ranged from 3 to 20 years of age and concordant to other pediatric reports [11] no age-dependency in the frequency of cutaneous side effects was found. Furthermore, duration of diabetes and duration of insulin pump therapy did not influence the frequency of skin complications. The adverse effect on glycemic control due to impaired absorption of insulin as previously described [8] could not be observed in our patients as there was no difference in the HbA1c values compared to the general study group. Although obesity is described to be associated with an increased incidence of skin alterations [10,16] we were unable to replicate this finding in our study group, which may be explained by the low median BMI of 16.4 in the observed group of patients.

In contrast to adults who typically use the abdomen as a recommended insertion area, in children the gluteal region is the most preferable insertion site. Our results underline the findings of the study by Schober et al. [11] that revealed that the buttock is a safe insertion area for small children even if diapers are worn frequently – no association between the age and insertion site and the frequency of cutaneous side effects could be observed (p=0.22) (Table 3). Even if all the patients who experienced lipoatrophy use the upper leg as an insertion site we cannot determine any association between the catheter localization and cutaneous side-effects as lipoatrophy was observed again after switching the catheter localization. In our pediatric population parents were involved most of the time in the procedure of the catheter insertion.

In comparison to the study published by Conwell that showed a benefit in using infusion sets with non-metal catheters inserted at 90° [10], we observed an advantage in using metal catheters. 37% of patients using steel catheters (vs. 53% using teflon sets) experienced skin complications, regardless of the time interval between insertions and hygiene procedures for CSII site preparations. In particular, 2 of the 3 patients with lipoatrophy were using teflon catheters. Even though not statistically significant, this supports the hypothesis that the degree of irritation is directly caused by the amount of movement of the inserted Teflon catheter. Experiments to prove this hypothesis are ongoing.

As previously reported, skin alterations in pediatric patients with pump treatment appear frequently as scarring [10,11,17].

Table 5 Skin alterations (in general as well as specific) for the most commonly seen alterations and differentiated for the use of teflon vs. steel needle catheters. Absolute numbers of patients given in % in brackets.

	General skin alterations		Specified skin alterations			
Catheter type	Skin alterations	Scars	Lipohypertrophy	Eczema	Hyperpigmentation	Lipoatrophy
Teflon	10 (53%)	6 (32%)	5 (26%)	1 (5%)	1 (5%)	2 (11%)
Steel	13 (37%)	7 (20%)	6 (17%)	5 (14%)	2 (6%)	1 (3%)

In our study, a quarter of our patients revealed scars which may be a result of chronic irritation of the epidermis. Lipohypertrophic areas in the subcutaneous fat tissue are known to be caused by both bolus and continuous insulin application. With a frequency of 20%, it was the second prevalent cutaneous side-effect, again going concordant with published data [10,18].

Other chronic side effects seen were lipoatrophy and pigmentary changes, whereas eczema and eczema-like skin alterations were observed as acute adverse effects, either resulting from allergic reactions to bandages or skin irritation due to disinfection agents.

Most interestingly, 3 of our patients (6%) experienced lipoatrophy while on CSII treatment. This is unexpected given that lipoatrophy – like many of the cutaneous side effects of diabetes therapy – has decreased since the introduction of purified recombinant insulin [19,20]. Furthermore, the finding is of interest as a switch to CSII is recommended in the literature in cases of lipoatrophy and insulin injections [21,22]. Similar to our observation and some published case reports [23,24], a Canadian study reported 2 out of 50 diabetes patients developing lipoatrophy during CSII therapy [10]. Insulin-induced lipoatrophy is a subcutaneous fat atrophy at the site of injection which is not only relevant because of the serious cosmetic impact it may cause to a young patient, but it may also influence glycemic control because of the variability of absorption at the site of lipoatrophy. In the early 20th century the repeated mechanical trauma from needle injections [25] was a proposed mechanism leading to lipoatrophy and could possibly still play a role in the pathogenesis of lipoatrophy. The long-term insertion of either teflon or steel catheters could lead to an irritation resulting in mechanical trauma. Compared to the steel variety, the mechanical trauma and movement of a teflon catheter might be more pronounced and may explain the higher frequency of cutaneous side effects associated with this material. On the other hand, an immunological response to insulin crystals [26] is hypothesized in the pathogenesis of lipoatrophy. Subclinical, subacute inflammatory reactions may be involved in the pathogenesis since the destructive process seems to improve by the administration of anti-inflammatory medications such as corticosteroids or disodium cromoglycate ointment [27–31].

In our study group the number of patients with lipoatrophy is too small to be able to demonstrate any association with patient's age, adiposity or features of diabetes mellitus history. We can only describe that 2 of the 3 who developed lipoatrophy used teflon catheters; in all 3 patients lipoatrophic areal declined under treatment with disodium cromoglycate ointment. All of them changed the catheter set every 3 days and 2 switched the insertion site and developed lipoatrophy again. Although the total number of 3 seems low, it is of concern, as we have not seen lipoatrophy in patients with insulin injection therapy for years. Therefore, the occurrence of lipoatrophy in CSII patients suggests further investigations in larger patient groups with CSII.

In conclusion, our observation showed that dermatological side effects during CSII therapy are frequent. It is therefore crucial to inspect the insertion sites at every patient´s visit to prevent or improve cutaneous complications. As this is a single centre observation with a limited number of patients we conclude that extended prospective surveys with a higher number of patients would allow further assessment of differences between teflon and steel needle catheters. Furthermore, a prospective randomized study in a higher number of patients would enable to estimate the prevalence of certain dermatological complications such as lipoatrophy and to identify potential risk factors.

Conflict of interest: None.

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