Dermatological complications of insulin therapy in children with type 1 diabetes

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Summary

Dermatological complications at insulin administration sites, like lipohypertrophy, lipoatrophy and erythema, are common in children with type 1 diabetes. These complications can be painful, disfiguring and may influence glycaemic control. Studies on epidemiology and etiology are needed before prevention or treatment is possible.

The aim of this study is to determine the prevalence of common dermatological complications in children with type 1 diabetes and to assess associations between dermatological complications and possible risk factors.

In this cross-sectional study 231 children with type 1 diabetes were included. Dermatological complications were assessed and a questionnaire with possible risk factors was completed. Data were evaluated using χ^2 tests.

The results showed that lipohypertrophy was present in 34.8% of the children, lipoatrophy in 8.1% and erythema in 24.6%. Lipohypertrophy was associated with multiple daily injection therapy (p=0.03) and insufficiency of alternating administration sites (p<0.001). Lipoatrophy was not influenced by type of insulin therapy (p=0.44) but was found to be associated with less frequent injection site alternation in patients using multiple daily injections (p=0.01). Also, HbA1c level was positively associated with lipoatrophy (p=0.01). Erythema of the skin was more frequently diagnosed in children with continuous subcutaneous insulin pump therapy (p<0.001). A history of cutaneous infections and dry skin on exam day were independently associated with erythema at insulin administration sites (p<0.001 and 0.04, respectively).

Dermatological complications are a common problem in children with type 1 diabetes making frequent examination of the skin in these children an important aspect of their medical care.

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Key words

children; dermatological complications; diabetes mellitus type 1; insulin therapy

Introduction

Dermatological complications at insulin administration sites, like lipohypertrophy, lipoatrophy and erythema, are a common problem in patients with type 1 diabetes. These complications can hinder insulin absorption[1] and influence glycaemic control.[2] Additionally, they alter the cosmetic appearance of the skin.

Although the causes of these dermatological complications are not completely understood, several hypotheses are postulated. Lipohypertrophy is thought to occur because of repeated stimulation of adipocytes by the injection of insulin, probably due either to traumatic injury caused by needles or to the direct effects of insulin.[3–4] Lipoatrophy is characterised by a reduction in size of lipid droplets and adipocytes without a reduction in number of adipocytes.[5] It is considered to be immunologically induced by insulin crystals.[6] Part of the inflammatory response is initiated by a local hyperproduction of tumor necrosis factor-α by macrophages, leading to a dedifferentiation of adipocytes.[7] Mast cells presumably contribute to this destructive immune process.[8–9] Erythema at insulin administration sites may either be caused by cutaneous infections or by a hypersensitivity or allergy to insulin, preservatives, catheter, needles, adhesive material or a combination of these.[4]

Studies on the prevalence of cutaneous complications of insulin therapy in children are scarce and the reported data show wide variation. The prevalence of lipohypertrophy in children and adolescents with type 1 diabetes is reported as between 1.8% and 54.9%, depending on the study population.[3,10–14] Fewer data are available on lipoatrophy and erythema. In children using continuous subcutaneous insulin infusion (CSII), lipoatrophy was reported in 0.9%[11] and 4.0%[12] of the children and erythema at insulin administration sites was described in 25.6%[13] and 66.0%,[12] respectively.

In order to reduce dermatological complications of insulin therapy, risk factors should be identified. Only a few studies are reported on this subject. Associations between lipohypertrophy and HbA1c, diabetes history, manner of insulin administration and insulin dose were found in some published studies.[3,14–15] In one study, erythema was reported to occur more often in children with allergic skin reactions to a variety of allergens.[13] No risk

factors for the development of lipoatrophy are reported.

Before better prevention and treatment of these complications of insulin therapy is possible, assessment of risk factors in the development of skin problems is needed. In this study we aim to determine the prevalence of lipohypertrophy, lipoatrophy and erythema at insulin administration sites in children with type 1 diabetes treated with subcutaneous insulin. Our secondary objective is to evaluate more associations between dermatological complications and proposed risk factors, including gender, age, duration of diabetes mellitus and mode of insulin administration.

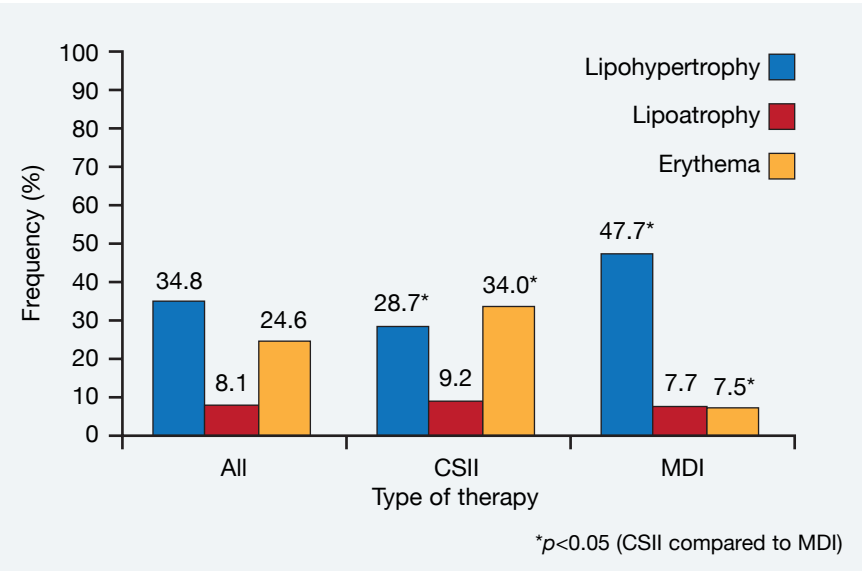

Figure 1. Prevalence of dermatological complications of subcutaneous insulin administration

Methods

In this cross-sectional study children and adolescents with type 1 diabetes attending the outpatient clinic of the Children's Diabetes Centre Nijmegen, The Netherlands, were recruited between September 2010 and September 2011. Our centre is a reference centre of expertise for secondary and tertiary paediatric diabetes care. At the moment of the study 257 children suffering from type 1 diabetes attended our clinic. Because of procedural and organisational reasons, data of 231 patients were complete enough for further analyses.

During a single routine clinical visit, insulin injection sites (abdomen, thighs and buttocks) were examined by meticulous inspection and palpation of the skin and subcutaneous tissue. All examinations of the skin were performed by experienced paediatric diabetes nurse practitioners. The presence of lipohypertrophy, lipoatrophy and erythema was scored as 1=absent or 2=present (either mild or severe). Lipohypertrophy and lipoatrophy were defined as a visible and/or palpable node or pit, respectively, at an insulin administration

Demographical data
Age
Gender
Diabetes history
Duration of type 1 diabetes
Current HbA1c
Reactivity of the skin
Atopy (eczema, bronchial asthma, hay fever)
Dry skin
Anamnestic cutaneous infections
Cutaneous reactions to other medication
Insulin administration
Type of therapy (CSII, MDI)
Washing hands before administration
Local use of alcohol before administration
Use of pain relief (cold packs or lidocaine-prilocaine emulsion)
Sufficiency of alternating administration sites (use of multiple sites in rotating manner)
Administration characteristics
1. CSII specific administration characteristics
Frequency of replacement of CSII catheter
Insertion of new CSII set before removing old
2. MDI specific administration characteristics
Sufficient injection technique (slow subcutaneous injection)
Reuse of needles (more than once)
Injection through clothing
Physical characteristics
Wounds
State of finger prick sites

Table 1. Data obtained as potential risk factors

site. Erythema was defined as visualised redness at administration sites. All examinations and questions were part of the usual care. Additional data, taken from chart and standard questions by our nurse practitioners, were obtained as shown in table 1.

The prevalence of lipohypertrophy, lipoatrophy and erythema were determined and the influence of all proposed risk factors was assessed using χ^2 tests. χ^2 testing for trend was used for age, duration of type 1 diabetes, current HbA1c and frequency of replacement of CSII catheter.

Subgroup analysis was performed in children using multiple daily injections (MDI) or CSII. Children using a subcutaneous insulin injection port (Insuflon) were excluded from subgroup analysis, because of the small sample size of this group. Statistical analysis was performed with SPSS software version 17.0. Values are reported as median with interquartile range. A p-value <0.05 was considered statistically significant.

Results

Demographic data and diabetes characteristics are shown in table 2. Children using MDI were approximately 2.5 years older than children using CSII. Other characteristics did not differ between CSII and MDI groups. All children were treated with human insulin analogues.

The subcutaneous insulin injection port was mainly used in children shortly after the diagnosis of diabetes, which is reflected in the short duration of type 1 diabetes and the relatively low HbA1c. The prevalence of dermatological complications is shown in figure 1.

In addition to the manifestation of a single dermatological complication, 16 children had a combination of lipohypertrophy and erythema, 5 had a combination of lipoatrophy and erythema, 4 had both lipohypertrophy and lipoatrophy and 2 suffered from all three dermatological complications.

	All children	CSII	MDI	Subcutaneous insulin injection port
n	231 (100%)	146 (63%)	69 (30%)	16 (7%)
Age (years)	14.0 (7.0)	12.5 (7.0) *	15.0 (4.0) *	11.0 (5.0)
Gender (male/female)	116/115	70/76	38/31	8/8
Duration of type 1 diabetes (years)	6.0 (8.0)	6.0 (7.0)	6.0 (7.0)	1.0 (1.0)
Current HbA1c (mmol/mol)	64.0 (19.0)	67.0 (20.0)	61.0 (21.0)	60.0 (13.8)

*p<0.05 (CSII compared to MDI)

Table 2. Demographic data and diabetes characteristics in children using CSII, MDI or subcutaneous insulin injection ports

Lipohypertrophy

Lipohypertrophy most often occurred in children treated with MDI (p=0.03). Insufficiency of alternating administration sites was clearly associated with lipohypertrophy in all children (p<0.001). Furthermore, lipohypertrophy was present in all children (n=3) who injected insulin through their clothes. HbA1c levels did not correlate with the occurrence of lipohypertrophy in our study.

Lipoatrophy

No significant difference was found between the occurrence of lipoatrophy and the different insulin delivery systems (p=0.44). A positive correlation was found between the occurrence of lipoatrophy and HbA1c (p=0.01). In the group using MDI, children who alternated their injection sites less, had more lipoatrophy (p=0.01).

Erythema

Erythema was seen more often in children using CSII than MDI (p<0.001). Children with a history of cutaneous infections in the past or dry skin on exam day were prone to develop erythema at administration sites (p<0.001 and 0.04, respectively), whereas an atopic constitution or skin reactions to other medication showed no association with the occurrence of erythema (p=0.33 and p=0.64, respectively). The development of erythema was not associated with the frequency of CSII catheter replacement (p=0.46).

Surprisingly, in our study the use of disinfectant alcohol (n=33, 15.5%), hand washing before administration (n=113, 54.9%) or the reuse of needles (n=24, 11.4%) did not influence the incidence of dermatological changes.

The remaining factors surveyed did not show statistically significant associations with the occurrence of lipohypertrophy, lipoatrophy or erythema. An overview of all results is shown in Table 3, 4 and 5.

Discussion

Dermatological complications are a common problem in children with type 1 diabetes. These complications may hinder insulin absorption,[1–2] influence glycaemic

	Lipohypertrophy		Lipoatrophy		Erythema	
	Present (n=78)	Absent (n=146)	Present (n=18)	Absent (n=205)	Present (n=55)	Absent (n=169)
Age (yr)	13.0 (5.3)	14.0 (7.5)	13.5 (5.3)	13.0 (7.0)	12.0 (7.0)	14.0 (6.0)
Male gender (%)	48.7	52.1	61.1	49.8	54.5	49.1
Duration of type 1 diabetes (yr)	6.0 (7.0)	5.0 (8.0)	5.0 (5.3)	5.0 (8.0)	5.0 (7.3)	6.0 (8.0)
HbA1c (mmol/mol)	66.0 (19.0)	62.0 (19.0)	70.0 (16.5)	63.0 (19.0)**	66.5 (19.8)	63.0 (19.5)
Atopy (%)	23.1	26.2	22.2	25.5	29.6	23.1
Dry skin (%)	25.1	31.7	33.3	31.9	42.6	27.8*
Cutaneous infections (%)	19.2	17.9	16.7	18.6	40.7	10.7**
Cutaneous reactions to other medication (%)	13	6.9	5.6	9.4	7.4	9.5
Insufficiently alternating sites (%)	57.7	17.1**	58.5	30.2*	35.8	31.1
Wounds (%)	24.4	20.7	35.3	21.0	47.3	13.8**
Problems at finger prick sites (%)	32.1	20.1	29.4	24.4	25.5	24.6

*p <0.05 ** p <0.01

Table 3. Associations between proposed risk factors and dermatological complications of subcutaneous insulin therapy in all children

control, lead to pain and itching and can be disfiguring. In our population, 51% of the children with type 1 diabetes suffered from one or more skin problems.

Lipohypertrophy was the most frequent complication with a prevalence of 34.8%. This value is within the broad range of 1.8% to 54.9% that was previously reported in children and adolescents with type 1 diabetes.[3,10–14] In our MDI group, almost half of the children had lipohypertrophy. Our study confirms earlier data that lipohypertrophy develops more often in patients who frequently use the same injection sites.[15] Children in the MDI group tended to alternate sites less frequently than children in the CSII group and laid a higher burden on the skin and subcutaneous tissue of their administration sites by pinching and inserting needles more often. In addition, injection of insulin reaches higher forces compared to continuous subcutaneous infusion,[16–17] which might lead to more direct stress on the subcutaneous tissue when using MDI. Although lipohypertrophy was associated with a longer duration of diabetes in previous studies,[3, 14–15] we did not observe a statistically significant association (p=0.08). This could be explained by differences in insulin injection regimens, in injection sites or in types of diabetes in our study population.[14–15] In contrast to one earlier study,[3] we did not find an association between HbA1c and lipohypertrophy, possibly because of an over all lower average HbA1c in our study group.

Few data on the incidence of lipoatrophy in patients with type 1 diabetes are reported. Reliable, bedside measurements of subcutaneous fat are not available and recognition of lipoatrophy sites mainly depends on purposeful search by the examiner. We report a relatively high incidence of lipoatrophy as compared to other studies.[11–12] This could be related to a higher number of children being referred to our tertiary centre for lipoatrophy. Additionally, our approach differed from that of Pavlovic *et al*[11] since in our study an experienced paediatric diabetes nurse practitioner performed the exams with detailed instructions to identify the specific skin complications at insulin administration sites. In the aforementioned study, the skin complications where quantified by a dermatologist who was more focused on the skin manifestations of diabetes, like fungal infections. Potential risk factors for the development of lipoatrophy have not been assessed in prior published studies, to our knowledge. We demonstrated a significant correlation between lipoatrophy and HbA1c and insufficient administration site alternation in children treated with MDI. This could be accounted for by a repetitively provoked local autoimmune reaction or by mechanical injury. We did not find a significant difference in the occurrence of lipoatrophy between children using CSII and MDI, but this could be due to the small number of patients with lipoatrophy in our study.

Local erythema at the insulin infusion site is a serious problem, mainly in children treated with CSII. The prevalence in our study group was comparable to the percentages reported before.[12–13] Since we did not make a difference between mild and severe erythema, our results are possibly overestimated since erythema can occur as a variation of normal. We found more erythema in children with cutaneous infections, which can

	Lipohypertrophy		Lipoatrophy		Erythema	
	Present (n=41)	Absent (n=102)	Present (n=13)	Absent (n=129)	Present (n=93)	Absent (n=48)
Age (yr)	12.0 (7.0)	12.5 (8.0)	12.0 (5.5)	12.0 (8.0)	12.0 (6.8)	13.0 (8.0)
Male gender (%)	48.8	47.1	46.2	53.5	52.1	45.2
Duration of type 1 diabetes (yr)	6.0 (6.5)	6.0 (7.0)	5.0 (3.5)	6.0 (7.0)	5.0 (7.0)	6.5 (7.0)
HbA1c (mmol/mol)	68.5 (20.8)	64.0 (18.8)	70.0 (29.5)	65.5 (19.0)*	66.5 (21.0)	65.5 (18.8)
Atopy (%)	24.4	24.8	23.1	25.0	29.8	21.5
Dry skin (%)	41.5	37.6	38.5	38.8	44.7	35.5
Cutaneous infections (%)	29.3	22.8	23.1	25.0	44.7	14.0†
Cutaneous reactions to other medication (%)	17.1	7.9	7.7	10.9	8.5	11.8
No hand washing (%)	28.2	42.0	61.5	35.2	34.8	39.6
No use of local alcohol (%)	75.6	78.2	84.6	76.6	80.9	76.3
Use of pain relief; cold packs (%)	17.1	27.5	38.5	22.5	25.0	22.6
Use of pain relief; lidocaine-prilocaine emulsion (%)	34.1	32.4	23.1	34.1	39.6	30.1
Insufficiently alternating sites (%)	48.8	19.4†	41.7	26.8	32.6	25.0
Number of days that CSII is in site (%)	3.0 (1.3)	3.0 (1.0)	2.5 (1.5)	3.0 (1.0)	3.0 (1.4)	3.0 (1.0)
Removing old CSII set before inserting new (%)	17.1	31.4	15.4	29.1	19.1	32.6
Wounds (%)	34.1	27.7	41.7	28.7	50.0	19.6†
Problems at finger prick sites (%)	39.0	23.0	33.3	27.1	25.0	29.3

*p <0.05 †p <0.01

Table 4. Associations between proposed risk factors and dermatological complications of subcutaneous insulin therapy in children treated with CSII

probably be explained by contamination of the insulin administration sites, either directly or through other wounds. Theoretically hand washing and local use of alcohol should reduce the occurrence of erythema. Surprisingly, these measures did not correlate with a reduction in erythema in our study. However, these data may be biased by the likelihood that patients with a history of erythema may be more attentive to hand washing and are frequently advised to use local alcohol. Another explanation might be that aseptic inflammation plays an important role in the development of erythema, thus limiting the effect of antibacterial actions. Finally, erythema could arise as a hypersensitivity reaction to the CSII material. As in the study by Conwell *et al.*[12] we did not find an association between the development of erythema and the frequency of CSII catheter replacement. We suggest that these data are biased by the fact that our clinic instructs patients with erythema at infusion sites to replace the insulin infusion set more often.

In conclusion, our study demonstrates that dermatological complications at insulin administration sites are a common problem in children with type 1 diabetes. Therefore, we stress the importance of examining patients regularly for lipohypertrophy, lipoatrophy and erythema, preferably by minute inspection and palpation of the skin and subcutaneous tissue at all used insulin injection sites. Objective bedside techniques should be developed to examine dermatological complications in a standardised way.

Longitudinal studies are necessary to register the natural history of the dermatological complications and the effect of proposed treatment. The identification of potential risk factors for the development of dermatological complications can be used for better counselling to prevent or treat the dermatological complications.

Preventive measures can be taught to all patients, such as rotating administration sites and not injecting through clothes. One manner to prevent the use of areas with lipohypertrophy or lipoatrophy might be the use of subcutaneous insulin injection ports. Though frequently recommended, actions to prevent erythema, like the local use of alcohol, washing hands before insulin administration and the insertion of a new CSII set before removing the old, have not been proven to be effective and should be further studied.

	Lipohypertrophy		Lipoatrophy		Erythema	
	Present (n=31)	Absent (n=34)	Present (n=5)	Absent (n=60)	Present (n=5)	Absent (n=62)
Age (yr)	15.0 (5.0)	15.0 (5.3)	15.0 (5.5)	15.0 (4.8)	14.0 (8.5)	15.0 (4.0)
Male gender (%)	64.7	51.6	80.0	56.7	60.0	56.5
Duration of type 1 diabetes (yr)	7.0 (7.5)	4.0 (5.5)	10.0 (7.0)	5.0 (6.5)	10.0 (9.0)	6.0 (7.0)
HbA1c (mmol/mol)	63.0 (20.0)	57.0 (19.0)	69.0 (24.5)	60.0 (16.0)	69.0 (28.3)	60.0 (21.0)
Atopy (%)	19.4	29.4	20.0	25.0	20.0	24.2
Dry skin (%)	22.6	14.7	20.0	18.3	20.0	17.7
Cutaneous infections (%)	6.5	5.9	0.0	6.7	0.0	6.5
Cutaneous reactions to other medication (%)	10.0	3.0	0.0	6.8	0.0	6.6
No hand washing (%)	67.7	52.9	20.0	63.6	60.0	60.7
Insufficiently alternating sites (%)	64.5	14.7†	100.0	36.7†	40.0	41.0
Insufficient injection technique (%)	19.4	2.9	0.0	11.7	20.0	9.7
Reuse of needles (%)	35.5	29.4	0.0	33.3	20.0	33.3
Injection through clothing (%)	14.3	0.0*	0.0	5.0	0.0	6.3
Wounds (%)	9.7	2.9	20.0	5.0	0.0	6.5
Problems at finger prick sites (%)	25.8	11.8	20.0	20.0	20.0	19.7

*p <0.05 †p <0.01

Table 5. Associations between proposed risk factors and dermatological complications of subcutaneous insulin therapy in children treated with MDI

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HE van Munster performed the statistical analysis and wrote the manuscript. CPM van de Sande collected data and contributed to interpretation of the data. PG Voorhoeve contributed to interpretation of the data and reviewed and edited the manuscript. AAEM van Alfen designed the study, contributed to interpretation of the data and reviewed and edited the manuscript.

All authors have contributed significantly, and all authors are in agreement with the content of the manuscript in this form.

KEY POINTS

- Dermatological complications at insulin administration sites are a common problem in children with type 1 diabetes. The frequency of lipohypertrophy, lipoatrophy and erythema was respectively 34.8, 8.1 and 24.6%.
- Important risk factors affecting the prevalence of dermatological complications are insufficiently alternating injection sites (more lipohypertrophy and lipoatrophy) and the type of insulin therapy (more lipohypertrophy when using MDI, more erythema when using CSII).
- We recommend regular examination for dermatological complications by minute inspection and palpation of the skin and subcutaneous tissue at all used insulin administration sites.

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