

ORIGINAL ARTICLE

Skin Problems Associated with Insulin Pumps and Sensors in Adults with Type 1 Diabetes: A Cross-Sectional Study

Anna Korsgaard Berg, BSc,^{1,2} Kirsten Nørgaard, MD, DMSci,^{2,3}
Jacob P. Thyssen, MD, PhD, DMSci,⁴ Claus Zachariae, MD, DMSci,⁴ Eva Hommel, MD, DMSci,⁵
Karen Rytter, RN,⁵ and Jannet Svensson, MD, PhD^{1,2}

Abstract

Background: In the future, widespread use of closed-loop infusion (artificial pancreas) systems to treat type 1 diabetes (T1D) may significantly improve glycemic control and enhance treatment flexibility. However, the infusion sets and plasters necessary for these treatments can cause dermatological complications that may hamper the spread of the new technology; few studies have investigated these complications in adults. The aim of this study was to describe the dermatological complications associated with continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM) in adults.

Methods: A total of 118 adult patients from two different diabetes clinics completed a questionnaire concerning the dermatological complications associated with their CSII and/or CGM treatment, other treatment variables, duration of diabetes, allergies, skin care, and other pathologies.

Results: CGM or CSII use was associated with current eczema, scars, and wounds. In total, 34% of CSII users and 35% of CGM users currently had one or more skin lesions due to the use of these devices. We found no significant association with glycated hemoglobin (HbA1c) levels, a history of atopic dermatitis, or other skin pathologies. However, multivariate analysis revealed associations with a history of atopy and CSII-associated dermatological complications.

Conclusions: Dermatological complications were present in one in every three patients and represent a significant challenge to using CSII and CGM to treat adults with T1D. Prospective studies on the causes of these complications will be required to develop preventive strategies and ensure that optimal diabetes treatment approaches that take advantage of the latest technology can be implemented.

Keywords: Adults, Continuous glucose monitoring, Continuous subcutaneous insulin infusion, Dermatological complications, Type 1 diabetes.

Introduction

THE CORRECT AMOUNT OF INSULIN to obtain good metabolic control is crucial for patients with type 1 diabetes (T1D) in avoiding long-term complications.¹ Treatment with continuous subcutaneous insulin infusion (CSII) is becoming

more widespread² because it offers rapid and precise insulin dosing, lower blood glucose variability, increased flexibility, and improved quality of life.^{2–5} Continuous glucose monitoring (CGM) is often combined with CSII or an insulin pen to adjust insulin doses⁶ and can reduce glycated hemoglobin (HbA1c) levels in both CSII⁷ and pen users.⁸

¹Department of Pediatrics, Copenhagen Diabetes Research Center (CPH-DIRECT), Copenhagen University Hospital, Herlev and Gentofte, Herlev, Denmark.

²Faculty of Health Science, University of Copenhagen, Denmark.

³Department of Endocrinology, Copenhagen University Hospital, Hvidovre, Denmark.

⁴Department of Dermatology and Allergy, Copenhagen University Hospital, Herlev and Gentofte, Hellerup, Denmark.

⁵Steno Diabetes Center Copenhagen, Gentofte, Denmark.

Unfortunately, the use of CSII and/or CGM is associated with dermatological complications such as eczema, itch, wounds, infections, lipohypertrophy, lipoatrophy, and scars.⁹ However, the number of studies on skin problems in adults using CSII or CGM has been limited,^{10–13} and few have investigated the predictors of dermatological complications.^{3,9,14,15}

Dermatological complications can affect insulin absorption or even lead to discontinuation of treatment with CSII and CGM, which improves glycemic control more effectively than multiple daily injections with insulin pens.^{2,6} Therefore, avoiding dermatological complications may be essential for improving metabolic control in patients and reducing the risk of long-term complications.^{5,16,17}

The development of closed-loop artificial pancreas systems to treat patients with T1D provides hope that in the near future, these systems may improve metabolic control and result in less blood glucose variability.¹⁸ The prerequisites for closed-loop subcutaneous systems are similar to the current components of open-loop treatment, an infusion set in the skin and patches for CGM. Therefore, dermatological complications must be elucidated to develop artificial pancreas systems that do not aggravate skin issues.^{16,17,19,20} The open-loop systems will as well continue to be used by many patients in the next decades. We examined whether dermatological complications were associated with HbA1c levels and whether previous atopic dermatitis, allergies, or asthma may predispose a patient using CSII or CGM to dermatological complications.

Materials and Methods

Our study was a cross-sectional questionnaire-based study in two large Danish specialist diabetes clinics with long-standing experience in providing CSII and CGM treatment. The population for our study was a random sample of patients with T1D who were aged 18 years or older and had been using CSII, CGM, or both for more than 4 weeks. We recruited patients from the Department of Endocrinology, Hvidovre University Hospital, and Steno Diabetes Center, Copenhagen. Recruitment for the project was performed on random dates when all device-using patients attending the outpatient clinic were invited to participate. The only exclusion criteria were lack of Danish language skills and inability to complete the

questionnaire. A similar study was performed in children, as reported elsewhere.²¹

Our online questionnaire could be completed at home or in the hospital waiting area. Dermatologists and endocrinologists participated in the development of the questionnaire. The background outcomes included in the questionnaire were HbA1c levels, body mass index (BMI), T1D duration, CSII type, CSII duration, CGM type, CGM use, CGM duration, and procedure for changing equipment.

For dermatological complications associated with treatment, the patients were asked about both current and previous dermatological complications. Each currently visible dermatological lesion associated with CSII/CGM was categorized by the participant according to which of the eight pictures shown in Figure 1 it resembled most. As an alternative to using the pictures, the participant could provide a text description of the skin lesion. These alternative answers were categorized into one of the eight groups or an additional category (“other”). The patients used a five-point scale (“no problem” to “very big problem”) to rate the discomfort caused by each visible skin lesion.

Self-reported history of atopic disease, other dermatological pathologies, and skin care data were also collected. Atopy was defined as a current immunoglobulin E-mediated allergy, atopic dermatitis, or asthma. A history of atopic dermatitis was defined according to the United Kingdom Working Party diagnostic criteria, but excluding visible dermatitis.²² Frequency of infusion set-change data was obtained from CSII consultation reports for a subset of patients to compare with the self-assessed information from the questionnaire. The full questionnaire is available on request. This study was approved by both the Danish Data Agency and the National Ethics Committee. All participants provided written and oral informed consent before participation.

Statistical analysis

Descriptive statistics were used and the characteristics of participants were expressed as medians with interquartile ranges. Quadratic splines demonstrated that the durations of treatment with both CSII and CGM were not linear. CSII and CGM duration categories were assigned according to the number of patients in each group.

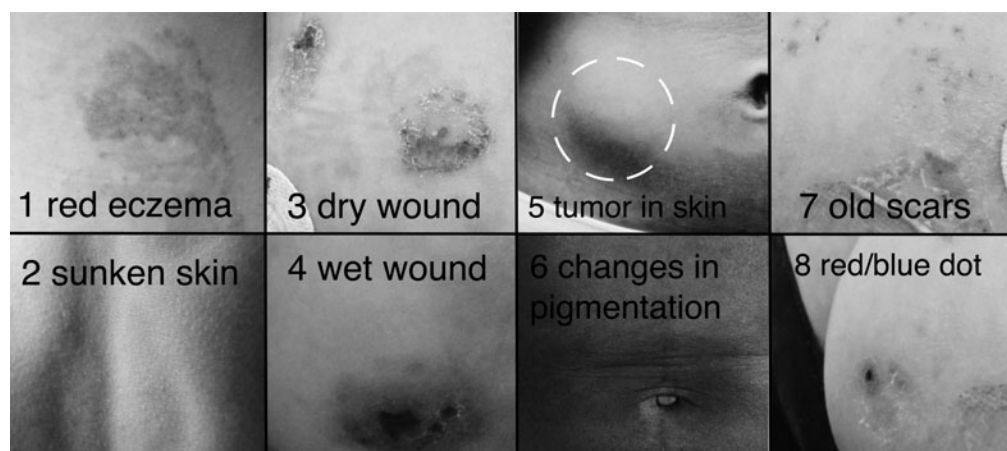


FIG. 1. The eight photographs presented to the patients to characterize their type of skin problem. The eight photographs presented to patients to help them categorize their dermatological complications.

To determine the factors associated with dermatological complications, both univariate and multivariate logistic regression analyses were used. Odds ratio (OR) will be given combined with 95% confidence intervals (CIs). Both the appearance of all types of currently visible dermatological complication and a subgroup, including only current eczema, wounds, and scars, were used as dichotomous outcomes. The multivariate analysis tested each potentially associated factor for possible confounding by age, sex, BMI, and the durations of CGM and CSII treatments. Mantel-Haenszel Chi-square was used to determine differences between the discomfort scores. A two-sided *P*-value of <0.05 was considered statistically significant. Microsoft Excel (Microsoft Corporation, Redmond, WA) and SAS (ver. 9.4; SAS Institute, Inc., Cary, NC) software were used for statistical analyses.

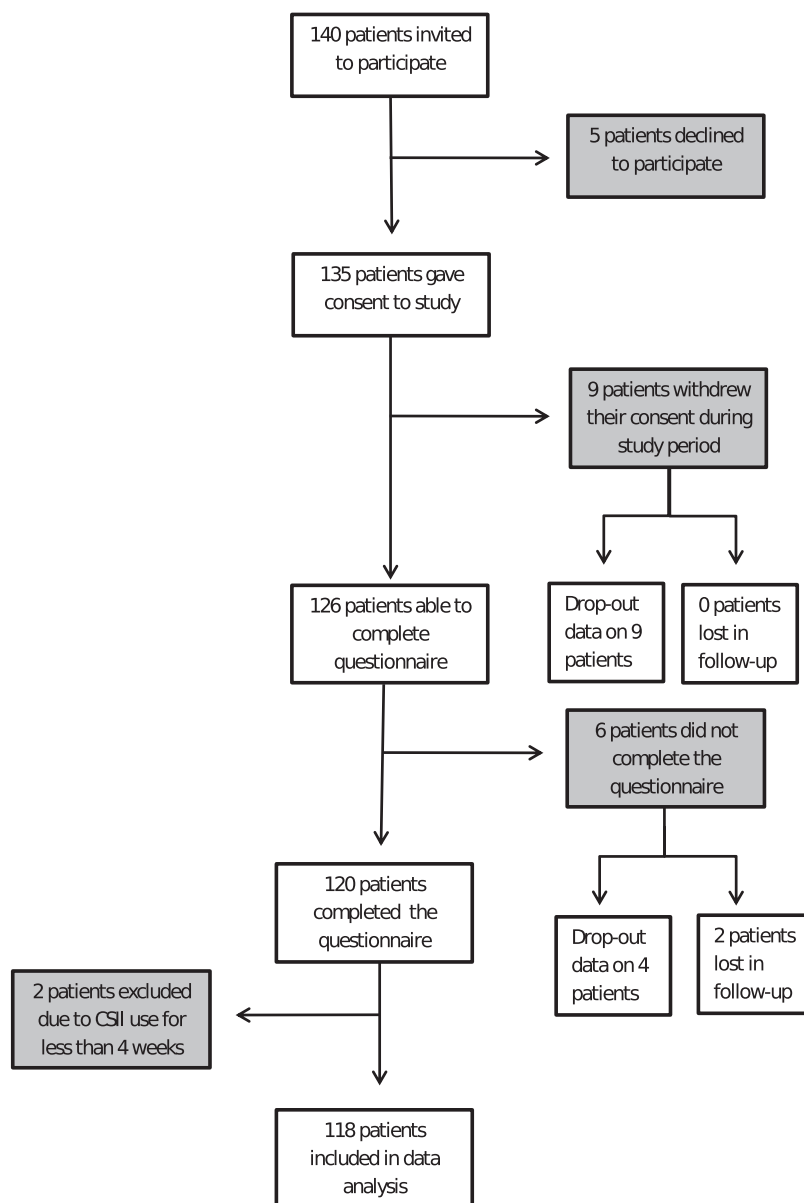
Results

Of the 140 patients asked to participate in the study, 85.7% (120) completed the questionnaire. However, two patients

were later excluded because they did not use CGM and had CSII treatment for <4 weeks. A flowchart for patient inclusion in the study is shown in Figure 2. Of the remaining 118 patients, 99.2% (117) were currently using CSII and 40.7% (48) were using CGM. Patients from the two hospitals were pooled because basic characteristics such as age, gender, BMI, duration of diabetes, and duration of pump use did not differ between the two groups. The participants had a median age of 46 years, median duration of diabetes was 24 years, and median pump duration was 5 years. Of participants, 59% were female.

In total, 79.5% of the patients had previously experienced dermatological complications due to CSII at some point, compared with 71.4% who had experienced complications due to CGM. Itch was the most common symptom, whereas eczema and wounds were the most common complications among both CSII and CGM users. More than one-third of the patients currently had dermatological complications that were associated with using either CSII (34%) or CGM (35%).

FIG. 2. Flowchart showing the patient inclusion process. A total of 140 patients were invited to participate, and 120 patients completed the questionnaire. Dropout data available on 13 patients were used in a dropout analysis.



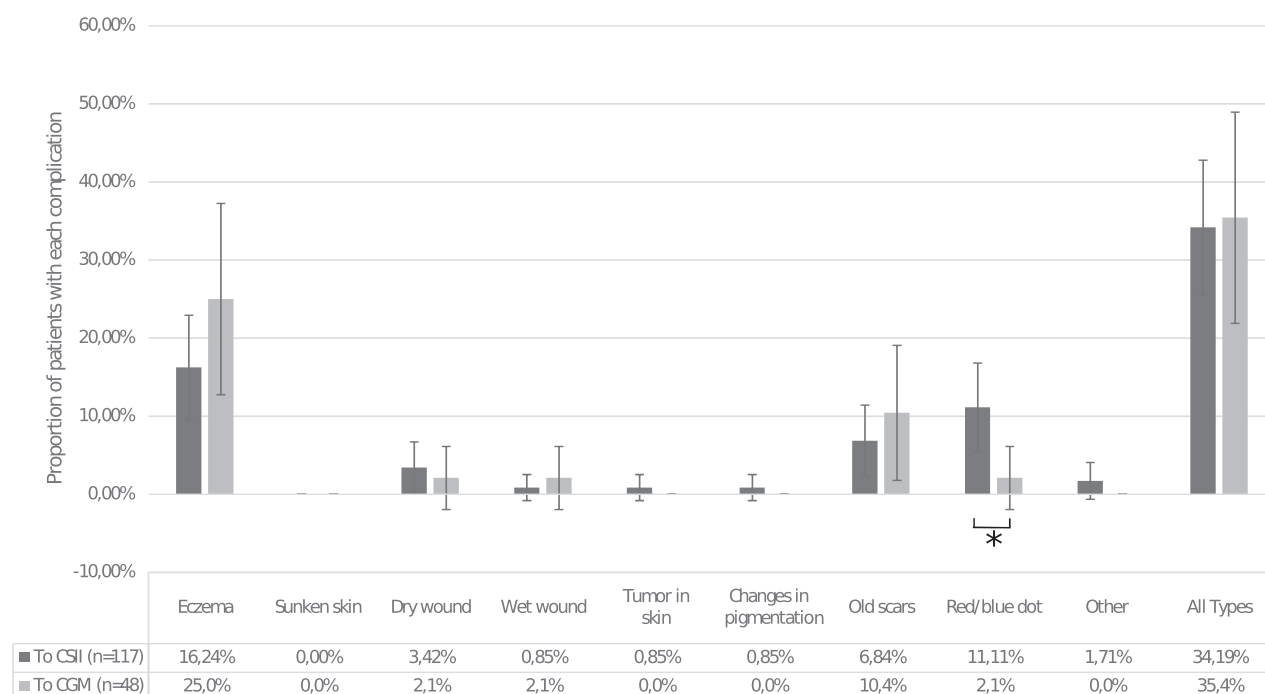


FIG. 3. The distribution of current dermatological complications associated with both CSII and CGM is shown with 95% confidence intervals. There is a significant difference between the frequencies of the subtype “Dot” between CSII and CGM users ($P < 0.05$). CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion.

The duration of this skin lesion had been more than a week for 60% of the reactions. Eczema was the most frequent type of complication, especially for the CGM users (Fig. 3). Only two participants using CSII and two using CGM described their complications using the alternative option instead of the eight pictures: three of them described their complications as “infections” and the other described a “hematoma.”

There was a significant difference in the frequency of the “red/blue dot” (Fig. 1) complication type between CSII users (11%) and CGM users (2%). For comparison, the analysis of the 13 dropouts shown in Figure 2, who did not complete the questionnaire or withdrew their consent, the frequencies of previous dermatological complications were 58.3% for CSII-users and 33.3% for CGM-users. Of the 117 patients using CSII, 36% had changed their infusion set earlier than planned within the last 6 months due to dermatological complications. Of those patients currently suffering from dermatological complications, 57.5% changed their infusion set earlier than planned for the same reason.

Clinical characteristics of patients currently with and without CSII-associated dermatological complications are given in Table 1. The univariate regression analysis revealed no significant differences related to age, gender, HbA1c levels, BMI, duration of diabetes, sensor use, atopy, or atopic dermatitis. This was still the case after adjustment for relevant confounders in the multivariate analyses, with the exception of a history of atopy, which had an OR of 2.58 [95% CI: 1.09–6.15; $P = 0.032$]. For the duration of CSII-use, we found a higher incidence in the group of use between 3 and 7 years. In CSII users, the OR for having eczema, wounds, or scars increased if they were using CGM (OR: 2.50 [95% CI: 1.05–5.9; $P = 0.038$]) and were unchanged after adjustment for relevant confounders. No significant differences in the frequency of CSII- or CGM-associated dermatological

complications were found among the different system types or brands; however, Medtronic’s CSII and CGM systems accounted for more than 60% of the systems being used.

The same variables investigated for CSII were analyzed for CGM, and no significant differences were found between patients currently with and without CGM-associated dermatological complications. The multivariate analyses also showed no association with HbA1c levels, duration of use, age, or atopy. Current dermatological complications associated with CSII and CGM were linked (OR: 10.0 [95% CI: 2.5–39.4; $P = 0.001$]). Dermatological complications associated with CSII or CGM were not associated with psoriasis or dermatological pathologies related to diabetes such as necrobiosis lipoidica diabetorum, vitiligo, diabetic bullae, acanthosis nigricans, or dermopathy, neither to the use of hand hygiene in procedures, frequency of showering, swimming, or doing sport. A sensitivity analysis, excluding those with <6 months use of CSII and CGM, did not change the results significantly. Only four patients did use steroid lotion, one used it daily, and three only occasionally.

Figure 4 shows the distribution of the discomfort scores and demonstrates that skin problems associated with CGM (mean = 2.8) were rated significantly worse than those associated with CSII (mean = 2.4; $P = 0.017$ using an unpaired t -test). According to these patients, mean scores for the dot were less bothering than the others, but eczema, scar, and wound did not differ significantly on the five-point scale with Mantel-Haenszel Chi-square.

Discussion

This study shows that dermatological complications associated with using both CSII and CGM are a significant problem for adult patients with T1D. The frequency of

TABLE 1. CURRENT DERMATOLOGICAL COMPLICATIONS ASSOCIATED WITH CONTINUOUS SUBCUTANEOUS INSULIN INFUSION

	Descriptive statistics (median and IQ-range)		Univariate analysis ^a	
	Patients with skin problems ^b (n = 40)	Patients without skin problems ^b (n = 77)	OR for skin problems	P-value
Age, years	40.5 (35.6–48.8)	48.4 (35.7–58.7)	0.90 (0.79–1.04) ^c	0.15
Gender, females, %	58	60	0.91 (0.42–1.98)	0.82
HbA1c, mmol/mol	58.50 (52.46–69.00)	58.48 (51.00–68.00)	1.01 (0.98–1.03) ^d	0.63
HbA1c, %	7.5 (7.0–8.5)	7.5 (6.8–8.4)	1.07 (0.82–1.38) ^c	0.63
BMI, kg/m ²	25.28 (23.68–27.75)	25.06 (22.54–27.45)	1.04 (0.94–1.16)	0.45
Diabetes duration, years	25.0 (17.8–35.2)	22.7 (14.5–36.5)	1.00 (0.97–1.03)	0.88
Use of CGM, ^f %	43	39	1.16 (0.53–2.52)	0.71
CSII duration 0–3 years, n (%)	10 (26)	28 (74)	1	
CSII duration 3–7 years, n (%)	21 (51)	20 (49)	2.94 (1.14–7.58)	0.03
CSII duration >7 years, n (%)	9 (24)	29 (76)	0.87 (0.31–2.46)	0.79
Days between set change	3.0 (2.6–3.5)	3.0 (3.0–3.8)	0.88 (0.61–1.27) ^g	0.49
Former or current atopic dermatitis, ^f %	10	13	0.74 (0.22–2.54)	0.64
History of atopy, ^f %	48	30	2.12 (0.97–4.68)	0.06

^aUnivariate analysis using logistic regression with OR and P-value shown. Significant result is shown in bold.

^bSkin problems characterized as current dermatological complications due to CSII.

^cOR per 5-year increase in age.

^dOR per 1-mmol/mol increase in HbA1c.

^eOR per 1% increase in HbA1c.

^fFor binary outcomes, the proportion of patients (%) with CGM, atopic dermatitis, and a history of atopy is shown. Atopic dermatitis is defined according to United Kingdom criteria²² and a history of atopy is defined as the presence of atopic dermatitis, asthma, or an immunoglobulin E-mediated allergy.

^gOR per day of infusion set change.

CSII, continuous subcutaneous insulin infusion; IQ, interquartile; OR, odds ratio; BMI, body mass index; CGM, continuous glucose monitoring; HbA1c, glycated hemoglobin.

current dermatological complications was 34% for CSII users and 35% for CGM users. Eczema was the predominant type of dermatological complication, especially among CGM users, with a frequency of 25%. In studies with pediatric patients, the frequency of current dermatological complications

associated with CGM was 0%–55%.^{21,23–25} This study is, to our knowledge, the first to investigate dermatological complications associated with CGM use in adults, and here, we demonstrate the problem is relevant to this patient group as well. Our results are consistent with the frequency data on

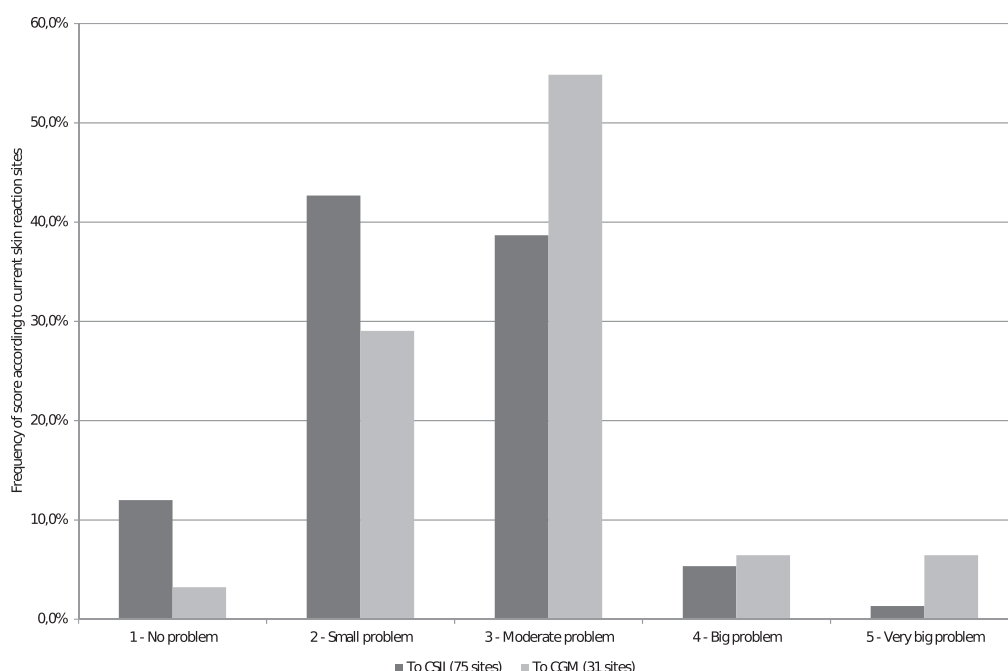


FIG. 4. Patients scored each current dermatological complication according to their perception of how big a problem it was. The mean scores for problems associated with CSII (2.4) and CGM (2.8) were significantly different ($P=0.017$) with t -test.

CSII-associated dermatological complications obtained by other studies (26%–43%).^{12,13} Studies from the 1980s also described CSII-associated dermatological complications, particularly erythema and infections. However, improved recommendations relating to hygiene and infusion set change procedures have significantly reduced the prevalence of CSII-associated infections.^{10,11,26}

In this study, we showed that dermatological complications were not associated with HbA1c levels. In contrast, Linkeschova et al. found that abscesses were related to HbA1c levels.³ Our findings seem to indicate an association between atopy and dermatological complications, although significant only after adjustment using multivariate analysis (OR: 2.58). This is consistent with similar findings in Danish pediatric patients²¹ and suggests that further investigations into associations with atopic history should be performed. In our study, the insertion-site vacuum dot or red/blue dot (Fig. 1) was significantly more frequent among CSII users compared with CGM users. This highlights a need to examine carefully the mold and materials used to make the infusion set.

Skin problems increase over time, but seem to diminish in long-term users. This might be due to older age in this group or selection bias, where those with skin problems have changed back to pen treatment. Prospective studies with long-term follow-up are needed to identify the reason for lower risk in those with long-term use. Authors have strongly recommended that infusion sets are changed at approximately day 3, due to the high frequency of skin problems and other adverse events.^{14,15} In our study, the patients generally reported changing their infusion sets on approximately day 3, possibly explaining why we found no association with infusion set changes. We also showed that CSII users who were also using CGM had higher frequencies of current specific types of complications such as eczema, wounds, and scars, but not of current dermatological complications in general. This may be because allergic or irritant contact dermatitis is developing as a result of CGM use or because CGM use is changing the immune response to CSII. Previous case studies have shown that contact dermatitis can develop in response to both infusion sets and glucose sensors.^{27–30}

Current CSII-associated dermatological complications were linked to an increased number of unplanned infusion set changes, compared to patients with no complications. Unscheduled infusion set changes may make the procedure more stressful and encourage carelessness. The frequency of especially lipohypertrophy (represented by “tumor in skin”) is, in this study, significantly low (<1%) compared to previous studies finding 26% in a patient survey.³¹ The description or naming of the lipohypertrophy or investigation by a trained investigator might have increased the prevalence of this dermatologic complication. The low reporting of lipohypertrophy have although been found in other survey studies.¹³ In CSII users, the presence of dermatological complications suggests the patient runs a high risk of developing dermatological complications in response to CGM also; therefore, skin protection and a high level of skin care should precede the initiation of CGM in these patients. This highlights the possibility that the mechanisms responsible for the development of CSII- and CGM-associated dermatological complications are similar.

Information regarding types of adhesive and materials used in both infusion set and patches has been difficult to

obtain from the manufacturers, and since no differences were found among different sensor and pump types, significant differences are not assumed to persist between types. Since very few used other cannulas than Teflon, we were unable to test association with different types of infusion sets. Regarding problems primarily associated with the glue/plaster, we did a subgroup analysis of eczema, wounds, and scars. It could have been interesting to look at associations to certain subtypes of dermatological complications, but unfortunately, our study did not have enough power to calculate this.

Allergic contact dermatitis in response to an active substance in the patch, metal, or coating that is present in both the CSII and CGM patch will produce a reaction to both devices. This will often result in eczema and possibly wounds, explaining the strong association we found with eczema and wounds. The association with scars could be caused by deep scratches or infections, since eczema traditionally does not lead to scarring of the skin. Screening active substances in the patch, metal, or coating for potential allergenic effects should be considered before initiating CGM if CSII-associated complications might be due to overlapping ingredients/glue in infusion sets and sensors. In comparison with the similar study in children and adolescent, this study shows lower frequency of dermatological complications, possibly due to a more sensitive skin in the pediatric age group.²¹

Despite the dermatological complications, most patients continue to use CSII and CGM. Apparently, patients tolerate these dermatological complications despite the discomfort (Fig. 4). Because only users were included in our study, we have no information regarding patients who discontinued CSII treatment. Some studies have shown that CSII discontinuation rates are quite low (~4%).³² The association of skin problems and duration of CSII between 3 and 7 years could possibly be because patients with skin problems discontinue the use of CSII, develop tolerance, or just caused by insufficient numbers of individuals increasing the risk of a type 2 error. An older study showed that 20% of patients who discontinued CSII treatment attributed this decision to dermatological complications.³²

Skin reactions are a major factor in the reduced use or discontinuation of CGM in both children and pregnant women,^{33,34} and studies have shown that discontinuation rates are ~35%–42%.^{35,36} From our experience, many patients are using different barrier crème, film, and additional patches to reduce the skin reactions. None of the treatments has been studied in a structured way, but are developed based on trial and error. There is a clear lack of prospective studies aiming at prevention or treatment of skin reactions in CSII and CGM users. Reducing skin reactions should certainly improve treatment satisfaction in these patients, and systematic methods of preventing and treating skin problems must be found.

The high attendance rate reduces selection bias and is one of the strengths of our study. The questionnaire was short and could be completed at home; this meant the study was flexible and probably helped to retain participants. Our dropout analysis shows as well that skin problems are present in the 13 participants who did not fill out the questionnaire. The limitations imposed by self-reporting and categorization of dermatological problems are obvious, but we targeted a high specificity for the different pathologies by using pictures. There was some selection for participants with a greater

frequency of previous dermatological complications. To reduce selection bias, patients were recruited on random dates, and nearly all patients asked (135/140) participated (Fig. 2).

Dermatological complications increase the number of infusion set changes in CSII patients. In addition, they necessitate the excessive use of patches, barrier crèmes, and so on. Therefore, dermatological complications are expensive, as well as causing the patient discomfort. The development of artificial pancreas systems, which combine an infusion set and a CGM, is ongoing. The effects of dermatological complications on insulin absorption and the accuracy of blood-glucose measurements are unclear. More studies on dermatological complications in adults are needed to direct the new technology, to reduce variation and costs, and to enhance its security. Randomized clinical trials or prospective studies will be required to determine methods for prevention and treatment. In addition, infusion sites must be inspected routinely during consultations to identify dermatological complications as early as possible.

In conclusion, this study demonstrates that dermatological complications are far more common than anticipated and could represent a significant additional burden of diabetes. As expected, CSII- and CGM-associated dermatological complications are linked. No other significant clinical association was found, but prospective studies will be necessary to determine preventive and treatment strategies.

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Author Contributions

A.K.B.: participated in planning and obtaining funding of study, generating the questionnaire, collecting and analyzing data, and writing the first draft of the article. K.N.: participated in generating the questionnaire, recruiting patients at Hvidovre University Hospital, and critically reviewing the article. J.P.T.: participated in generating the questionnaire and critically reviewing the results of data analysis and the article. C.Z.: participated in planning the study, generating the questionnaire, and critically reviewing the results of data analysis and the article. E.H.: participated in discussing the study, recruiting patients at the Steno Diabetes Center Copenhagen, and critically reviewing the article. K.R.: participated in discussing the study, recruiting patients at the Steno Diabetes Center, and critically reviewing the article. J.S.: participated in initiating, planning, and obtaining funding for the study, generating the questionnaire, analyzing data, and critically reviewing the article. All co-authors approved the final version before publication. Author contributions are in accordance with the Vancouver Guidelines: <http://icmje.org/>

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Author Disclosure Statement

No competing financial interests exist for A.K.B. K.N. serves as an adviser to Medtronic, Abbott, and Novo Nordisk. She owns shares in Novo Nordisk, has received research grants from Novo Nordisk and Roche Diabetes Care, and has received fees for speaking on behalf of Medtronic, Roche Diabetes Care, Rubin Medical, Sanofi, Novo Nordisk, Zeal and Pharma, and Bayer AG. J.P.T.'s spouse is employed at Novo Nordisk. C.Z. owns shares in Novo Nordisk. E.H. serves as an adviser to Abbott and Novo Nordisk, and owns shares in Novo Nordisk. K.R. owns shares in Novo Nordisk. J.S. serves as an adviser to Medtronic, Janssen, and Novo Nordisk. She owns shares in Novo Nordisk, and has received fees for speaking on behalf of Medtronic, Sanofi, Novo Nordisk, and Bayer AG.

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Address correspondence to:

Anna Korsgaard Berg
Herlev Ringvej 75, Dept. E, Opg. 82—Level 04
Herlev 2730
Denmark

E-mail: anna.korsgaard.berg.02@regionh.dk