



Insulin pump therapy is associated with higher rates of mild diabetic ketoacidosis compared to injection therapy: A 2-year Swedish national survey of children and adolescents with type 1 diabetes

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Funding information

the Swedish state under the agreement between the Swedish government and the county councils, the ALF agreement (ALFGBG720791, VGFOUBD495431, VGFOUBD518351, VGFOUREG564611, VGFOUREG757511, VGFOUREG757651).

Abstract

Objectives: Diabetic ketoacidosis (DKA) in type 1 diabetes (T1D) can occur during both insulin pump therapy (continuous subcutaneous insulin infusion, CSII) and insulin injection therapy (multiple daily injections, MDI). The primary aim of this study was to compare CSII and MDI regarding DKA frequency. A secondary aim was to compare metabolic derangement between CSII and MDI at hospital admission for DKA.

Research Design and methods: Children 0–17.99 years with established T1D admitted for DKA in Sweden from February 1, 2015 to January 31, 2017 were invited to participate. Data regarding demographics, laboratory data, CSII or MDI, and access to ketone meters and CGM were provided through questionnaires and medical records. The Swedish National Diabetes Registry (SWEDIABKIDS) was used to compare the distribution of CSII and MDI in the national population with the population admitted for DKA, using the chi-square goodness-of-fit test. Distribution of CSII and MDI was then categorized in clinical severity grades for mild (pH 7.20–7.29), moderate (pH 7.10–7.29) and severe DKA (pH <7.10).

Results: The distribution of CSII at DKA admission was significantly larger than in the national pediatric population with T1D (74.7% vs. 59.7%, $p = 0.002$). CSII was over-represented in mild DKA (85.2% vs. with CSII, $p < 0.001$), but not in moderate/severe DKA (57.9% with CSII, $p = 0.82$). Mean HbA1c at hospital admission was 73.9 mmol/mol with CSII and 102.7 mmol/mol with MDI.

Conclusions: CSII was associated with higher risk of mild DKA than MDI. MDI was associated with markedly higher HbA1c levels than CSII at hospital admission for DKA.

KEYWORDS

child, diabetes mellitus type 1, diabetic ketoacidosis, insulin infusion systems, registries

1 | INTRODUCTION

Insulin pump therapy (Continuous Subcutaneous Insulin Infusion, CSII) or insulin injection therapy (Multiple Daily Injections, MDI) are the standard options for comprehensive treatment of type 1 diabetes (T1D) in children.^{1,2} Both options share the principle of basal-bolus insulin regimes, with a continuous basal rate (CSII) or a basal dose given once or twice daily (MDI), and bolus doses administered during meals or if blood glucose levels are too high. However, regardless of insulin delivery mode, diabetic ketoacidosis (DKA) can develop in children with T1D in case of absolute or relative insulin deficiency.³

The use of CSII is increasing internationally and has become the predominant type of treatment for children with T1D in many countries. In Sweden, all children with new-onset T1D start treatment with MDI at onset of diabetes. Sooner or later, the majority move on to CSII therapy, and in Sweden more than 70% of the children with T1D used CSII in 2020.⁴ It is recommended to start with CSII at onset of diabetes for preschool children.⁵ Although considerably more expensive, CSII offers several potential advantages over MDI. Bolus doses can be given in low doses, and adjustments are possible in small increments, while only adjustments to half units can be made with MDI. CSII thus allows for a more flexible administration of insulin and enables fine-tuning of daily basal insulin requirements, which can be important on many occasions, such as before or during physical activity or increased insulin resistance associated with sick days. CSII may also increase comfort by eliminating the need for subcutaneous injections several times daily. In Sweden, no difference is found between CSII and MDI regarding HbA1c levels on a national level,⁶ while studies from other countries have found lower HbA1c levels associated with CSII.⁷⁻⁹ CSII could hypothetically be associated with increased risk of DKA, since this treatment mode only uses rapid- or short-acting insulins with short half-lives, leading to rapid depletion of insulin depots in case of interruption of insulin delivery. However, studies have shown mixed results regarding DKA incidence rates when comparing CSII with MDI. CSII has been associated with higher,^{10,11} lower,^{7,8} or practically equal^{12,13} DKA incidence rates compared with MDI in various populations.

Monitoring glucose levels is central in diabetes management. All families should have access to capillary glucose tests. In addition, access to blood ketone tests at home is recommended by many authors since these tests may reduce hospitalizations for DKA.¹⁴⁻¹⁶ DKA prevention measures using blood ketone meters are taught at diabetes onset and at CSII initiation. It is also included for both MDI and CSII users when refreshing sick day knowledge. Continuous Glucose Monitoring (CGM) is available for many patients with T1D in economically privileged countries. CGM utilizes subcutaneous sensors for continuous monitoring of glucose levels with a high degree of accuracy.^{17,18} The use of CGM has increased quickly,^{7,19} and is used by more than 95% of children in Sweden (2020).⁴ Besides advantages in increasing comfort, for example by enabling uninterrupted physical activity and minimizing the need for capillary glucose tests, better glycemic control has been shown in several studies.^{7,13,19-21} Through alert functions, CGM could also help avoid hyper/hypoglycemic

events by alerting the child/caregiver if subcutaneous glucose levels are too high or too low. Integration of CSII and CGM allows for automatic suspension of the basal rate when the glucose level is low. Hybrid closed-loop CSII systems can adjust the basal rate automatically and give small automatic corrections. The main intentions of these advanced systems are maintenance good of metabolic control and avoidance of hypoglycemic or hyperglycemic events, including DKA.²²⁻²⁶

DKA incidence rates in children with established T1D are relatively low in Sweden from an international perspective, with annual incidences of hospital admission for DKA below 1% in the total national T1D pediatric population.⁴ Since DKA is associated with significant risk of acute morbidity and mortality, may cause long-term morbidity, and entails a substantial healthcare cost, it is nonetheless imperative to keep the incidence rate of DKA as low as possible.²⁷⁻²⁹

The primary objective was to compare the distributions of CSII and MDI in the national pediatric T1D population with the population admitted to hospital for DKA.

Secondary objectives were to analyze the effect of CSII and MDI on the level of acidosis at hospital admission for DKA and to compare HbA1c levels between CSII and MDI in DKA.

2 | METHODS

This study is part of a two-year national prospective study, including all children 0-17.99 years with both new-onset and established T1D admitted to hospital for DKA in Sweden from February 1, 2015 to January 31, 2017. Children with new-onset T1D and DKA participated in a separate part, described in detail by Wersäll et al. in a recent publication.³⁰

This part of the study deals with DKA in children with established T1D. There were no exclusion criteria. All pediatric centers caring for children with diabetes agreed to participate prior to the inclusion period. Study data were collected using two questionnaires [in Swedish, available upon request]. Parents/caregivers, together with their children if 15 years of age or above, filled out a questionnaire regarding demographic data, insulin treatment mode (CSII or MDI), access to capillary ketone meters, and CGM use at the time of admission. The attending physician or nurse filled out a second questionnaire regarding laboratory and physiological parameters at hospital admission and during hospital care. In some cases, missing data from the questionnaires were added from medical records. Both questionnaires were administered at hospital admission or shortly thereafter and could be filled out either in web-based or paper format. The web-based questionnaires were created using a web survey program (SurveyMonkey®, SVMK Inc.). Access to the web-based survey required a code provided to physicians and nurses only, who then gave access to the parents/caregivers.

Data from the pediatric part of the Swedish National Diabetes Register (SWEDIABKIDS) were used to estimate total patient-years for CSII and MDI in the national pediatric population with T1D during the study period, and to compare the number of DKA cases included

in the study with the number DKA cases registered in SWEDIABKIDS. Data on patient-years with CSII or MDI were derived from the current type of insulin treatment registered in SWEDIABKIDS during routine outpatient visits. Data on CSII and MDI usage was not available during the entire study period for those children who turned 18 years before January 31, 2017, since adult patients are no longer registered in SWEDIABKIDS. Therefore, the mean reported treatment time with CSII and MDI during the study period for the whole population in SWEDIABKIDS was expected to be less than 2 years.

2.1 | Statistics

The distribution of children with CSII and MDI at hospital admission in the study population was compared with the distribution of CSII and MDI in the national population during the study period using a chi-squared goodness-of-fit test. The null hypothesis was that the distribution of CSII and MDI among DKA cases was the same as the distribution of CSII and MDI in the national pediatric diabetes population during the study period. The significance level was set to 0.05. pH values at hospital admission were compared between CSII and MDI using the Mann-Whitney U test and univariate and multivariable regression analyses, adjusting for sex, age, and access to ketone meters and CGM, with robust estimation of the variance for the multivariable analysis.³¹ The distribution of CSII and MDI was then categorized according to clinical severity grades,³ into mild DKA (pH 7.20–7.29), moderate DKA (pH 7.10–7.19), and severe DKA (pH <7.10) for comparison with the distribution of CSII and MDI in the national population

with T1D during the study period. HbA1c levels were compared between CSII and MDI in DKA using the Mann-Whitney U test.

If a child had experienced multiple episodes of DKA during the study period, only the first episode was included in the study.

SPSS v. 27 (IBM Corporation) was used for all calculations, tables, and graphs.

2.2 | Ethics

Approval for this study was granted from the regional research ethics committee in Vastra Gotaland, Gothenburg, Sweden (registration number 748-14), who granted permission for the conduction of the study nationally. All included individuals consented to take part in the study, either by their caregivers or by caregivers and the child if above the age of 15 years.

3 | RESULTS

3.1 | The Swedish National Diabetes Registry

In SWEDIABKIDS, 7958 children 0–17.99 years were registered with at least one routine elective visit for T1D to a pediatric diabetes outpatient clinic during the study period. Treatment mode (CSII or MDI) was registered during at least one routine visit in 7832 children, in whom the treatment time was 84,130 months (59.7%) with CSII and 56,755 months (40.3%) with MDI (Figure 1). Including only the first

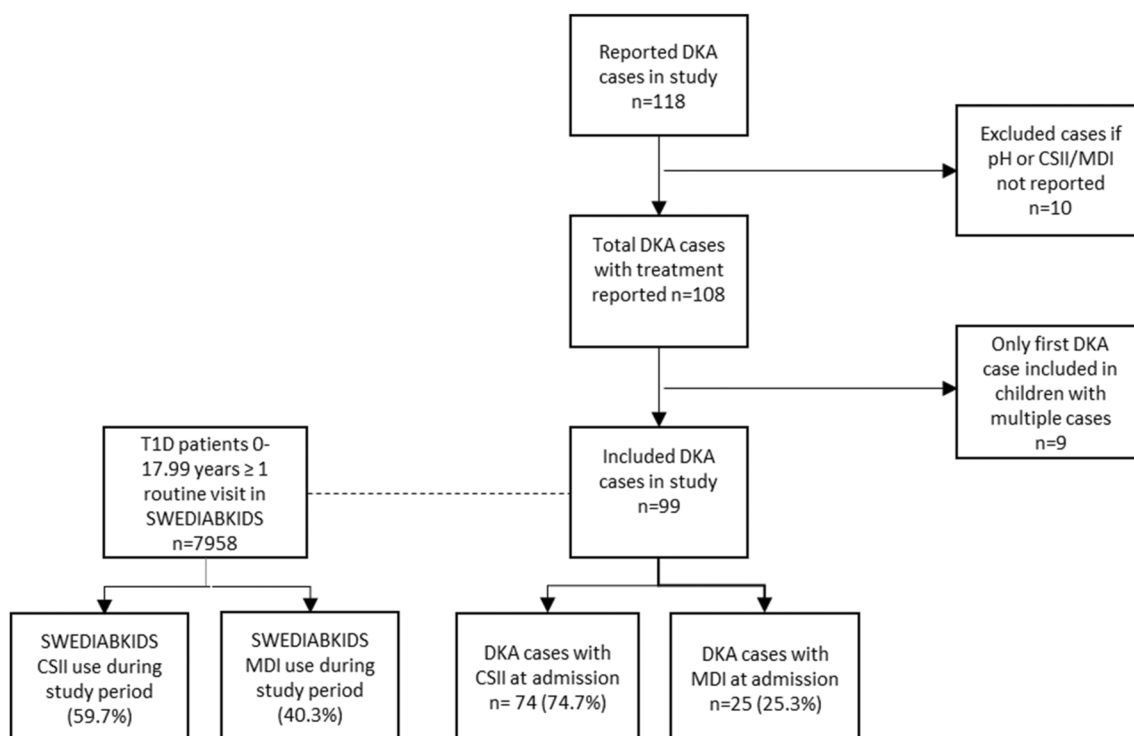


FIGURE 1 Flow chart describing diabetic ketoacidosis (DKA) cases included in the study.

TABLE 1 Study results divided between mild and moderate/severe diabetic ketoacidosis (DKA). Only the first episode is included for children with multiple admissions

			All DKA cases included in study	Mild DKA cases	Moderate/severe DKA cases ^a
			pH <7.30	pH <7.30–7.20	pH <7.20
Number of cases		CSII	74/99 (75%)	52/61 (85%)	22/38 (58%)
		MDI	25/99 (25%)	9/61 (15%)	16/38 (42%)
Sex	Female	CSII	38/73 (52%)	25/51 (49%)	13/22 (59%)
		MDI	13/25 (52%)	6/9 (67%)	7/16 (44%)
	Male	CSII	35/73 (48%)	26/51 (51%)	9/22 (41%)
		MDI	12/25 (48%)	3/9 (33%)	9/16 (56%)
Age in years ^b	Mean (SD)	CSII	12.7 (3.6)	12.9 (3.6)	12.4 (3.7)
		MDI	13.7 (2.7)	13.6 (3.4)	13.8 (2.4)
	Median (min–max)	CSII	13.6 (3.3–17.9)	13.5 (3.8–17.7)	13.9 (3.3–17.9)
		MDI	13.9 (8.2–17.7)	15.3 (8.2–17.7)	13.8 (9.9–17.0)
Ketone meters		CSII	52/53 (98%)	36/36 (100%)	16/17 (94%)
		MDI	15/22 (68%)	6/8 (75%)	9/14 (64%)
CGM		CSII	39/70 (56%)	27/49 (55%)	12/21 (57%)
		MDI	7/25 (28%)	5/9 (56%)	2/16 (13%)
pH	Mean (SD)	CSII	7.22 (0.071)	7.26 (0.025)	7.13 (0.054)
		MDI	7.15 (0.091)	7.24 (0.027)	7.11 (0.078)
	Median (min–max)	CSII	7.25 (6.96–7.29)	7.27 (7.20–7.29)	7.14 (6.96–7.19)
		MDI	7.16 (6.96–7.28)	7.23 (7.20–7.28)	7.13 (6.95–7.19)
HbA1c ^c mmol/mol	Mean (SD)	CSII	73.9 (18.1)	71.8 (17.2)	77.7 (19.5)
		MDI	102.7 (23.3)	87.4 (9.2)	108.2 (24.6)
	Median (min–max)	CSII	66 (41–132)	64.5 (41–111)	78.0 (50–132)
		MDI	100 (63–139)	91.0 (75–98)	111.5 (63–139)
HbA1c%	Mean (SD)	CSII	8.9 (3.8)	8.7 (3.7)	9.3 (3.9)
		MDI	11.6 (4.3)	10.2 (3.0)	12.1 (4.4)
	Median (min–max)	CSII	8.2 (5.9–14.2)	8.1 (5.9–12.3)	9.3 (6.7–14.2)
		MDI	11.3 (7.9–14.9)	10.5 (9.0–11.1)	12.4 (7.9–14.9)

^aSevere DKA was seen in four children with CSII and five children with MDI.

^b*n* = 95.

^c*n* = 74.

DKA event in patients with multiple events, there were 118 DKA cases calculated from Swediabkids during the study period February 1, 2015 to January 31, 2017.

3.2 | Description of study data

There were 114 cases of DKA with reported ongoing CSII or MDI treatment, of whom 108 cases had reported pH values at the time of hospital admission. Eight children had multiple DKA episodes during the study period. Two DKA episodes were reported in four individuals with MDI, and three individuals with CSII. One child with CSII reported three DKA episodes. When including only the first hospital admission for DKA in children with multiple DKA events, the study captured 99/118 (84%) of all patients with DKA compared to Swediabkids. Of these, there were 74/99 (74.7%)

cases with CSII and 25/99 (25.3%) cases with MDI treatment (Table 1 and Figure 1).

Among children with reports on access to ketone meter for home use, 52/53 (98.1%) of the CSII users and 15/22 (68.2%) of the MDI users reported having had access to ketone meters at the time of admission for DKA. Regarding CGM, 39/70 (55.7%) of the CSII users and 7/25 (28.0%) of the MDI users had CGM at admission.

MDI users with DKA had higher mean HbA1c levels than the national pediatric population with MDI (102.7 vs. 59.2 mmol/mol, 11.6% vs. 7.6%). CSII users with DKA also had higher HbA1c levels than the national pediatric population with CSII, but to a lesser degree (73.9 vs. 58.8 mmol/mol, 8.9% vs. 7.5%). HbA1c levels >70 mmol/mol at admission for DKA were seen in 18/19 (94.7%) of children with MDI and 27/55 (49.1%) of children with CSII.

Out of 38 participating hospitals with pediatric emergency wards, seven did not report any DKA cases during the study period. These seven

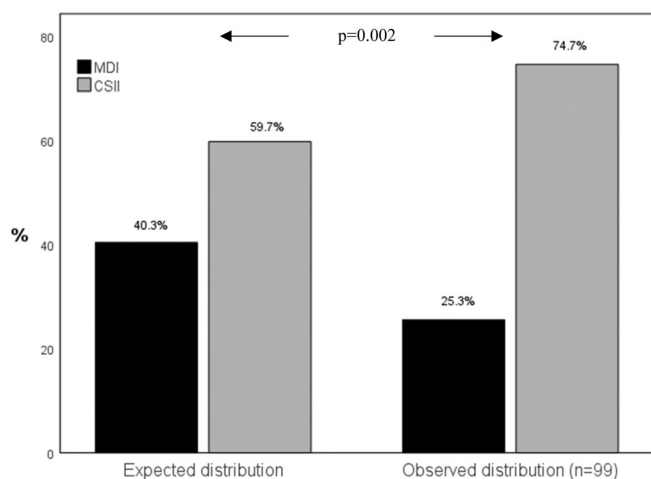


FIGURE 2 Comparison of expected and observed distributions of multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII) at hospital admission for diabetic ketoacidosis.

hospitals were small and comprised only 8% of the total pediatric population with T1D registered to them during the study period, and the mean proportion of children with T1D and CSII for these hospitals was 66%.^{32,33}

3.3 | Analyses of study data

There was a significant difference between the observed and the expected distributions of CSII and MDI in the population of DKA admissions ($\chi^2 = 9.317$, $p = 0.002$, chi-square goodness-of-fit test, Figure 2).

Median pH at admission for DKA was 7.25 (max 7.29 min 6.96) in the CSII group and 7.16 (max 7.28 min 6.95) in the MDI group. The Mann-Whitney U test showed a significant difference in pH distributions between CSII and MDI ($p < 0.001$). In univariate regression analyses of pH regarding effects of insulin delivery mode (CSII or MDI), sex, age, CGM and access to ketone meters, CSII was significantly associated with a higher mean pH value ($p = 0.001$, CI -0.110 to -0.029) as was access to home ketone meters ($p = 0.046$, CI -0.152 to -0.001). In adjusted multivariable regression analyses, only insulin treatment mode had a significant effect on pH, with CSII being associated with a higher mean pH value than MDI ($p = 0.028$, CI -0.103 to -0.006). No significant interactions were found between the independent variables.

Children with mild DKA (pH 7.20–7.29) had a significantly larger distribution of CSII than the national pediatric T1D population (85.2% vs. 59.7%, $p < 0.001$, chi-square goodness-of-fit test, Figure 3). Children with moderate DKA (pH 7.10–7.19), had a similar distribution of CSII to the national population (62.1% vs. 59.7%, $p = 0.80$). There were only nine children with severe DKA (pH < 7.10), of which five had MDI and four CSII. When severe and moderate DKA were combined, moderate/severe DKA had a distribution of CSII similar to the national population (57.9% vs. 59.7%, $p = 0.82$, chi-square goodness-of-fit test, Figure 3).

Children with CSII had significantly lower HbA1c levels than MDI (Table 1, $p < 0.001$, Mann-Whitney U test), also when subgrouped into mild DKA ($p = 0.046$) and moderate/severe DKA ($p = 0.002$).

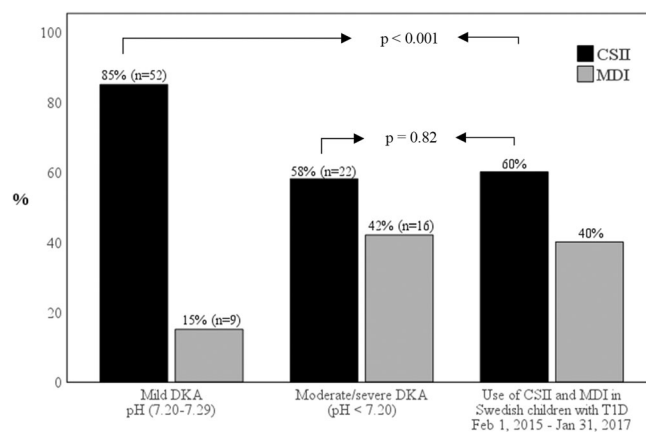


FIGURE 3 Distribution of continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI) in mild and moderate/severe diabetic ketoacidosis (DKA) compared with use of CSII and MDI in the national population.

4 | DISCUSSION

The main finding is that DKA was more common in children with CSII compared to the distribution of CSII in the national pediatric population. This is in line with previous studies from Sweden, although the incidence rate of DKA in children with CSII is lower today (1.1 per 100 patient-years during February 1, 2015–January 31, 2017 compared to 3.6 per 100 patient-years in 2000).¹¹ The results suggest that DKA could still be a more significant problem in children with CSII compared with MDI. However, when the DKA cases were divided into clinical severity grades (mild, moderate and severe DKA),³ overrepresentation of CSII compared to MDI was only seen in the group with mild DKA (pH 7.20–7.29, Figure 3). The pH differences between CSII and MDI among admissions for DKA can thus be explained by the fact that CSII was overrepresented in mild DKA, and not because children with MDI and DKA had more severe DKA.

Several studies from other countries have shown opposite results, with significantly lower relative frequencies of DKA in children treated with CSII compared with MDI.^{7,8} There could be many explanations for these differences in study outcomes. One explanation might be that children with mild DKA may not always be admitted to hospital, and thus not included in studies finding DKA less common with CSII. Another possible explanation could be differences in other countries regarding socioeconomic and sociodemographic patterns between the populations with CSII and MDI.

CGM has been associated with lower frequencies of DKA in several international studies.⁷ CGM use in children with DKA was only 58% for CSII and 29% for MDI, compared to an overall figure of 80%–90% in SWEDIABKIDS during the study period. Thus, the children with DKA did not utilize publicly available technology (CGM is reimbursed in Sweden) at the time of hospital admission. With higher use of CGM, users will get warning signals in the form of hyperglycemia alerts, prompting them to check for blood ketones if an insulin correction dose does not have the intended effect. In this study, 98% of the CSII users had access to blood ketone meters, while only 68% of MDI users had access to these despite a national recommendation of

prescribing blood ketone meters to all children at diabetes onset. Access to ketone meters may have guided the CSII users to seek medical help earlier, thus preventing the progress to more severe DKA.

Since the current prevalence of CGM in Sweden is 98.8% in CSII users and 95% in MDI users,⁴ it could be hypothesized that the risk of DKA should have decreased. However, the overall rate for DKA in children with established diabetes has been constantly low and has shown little variation during the past decade (between 0.5% and 1% since 2011). The rate of high HbA1c values is decreasing among Swedish children. In 2020 only 6.7% had HbA1c >70 mmol/mol.⁴ In 2015 the rate was 12.5% and in 2016 10.5%. The results in this study indicate that children with MDI and DKA, largely, might belong to a group with high HbA1c levels. In contrast, the HbA1c levels among children with CSII and DKA are more in line with the HbA1c levels in the national population with T1D.

This study should be interpreted in relation to international rates of DKA in children with T1D, which are higher than in Sweden.^{34,35} A lower DKA incidence in Sweden might reflect increased awareness among patients and caregivers. The significant overrepresentation of CSII among hospital admissions for mild DKA could reflect a management problem in this group.³⁶ Interruption of insulin administration via CSII results in quicker ketogenesis than missed doses with MDI, where a long-acting insulin provides an insulin depot. It is also possible that some children with mild DKA, with either MDI or CSII, were self-treated at home and never admitted to hospital. For mild DKA, the ISPAD 2018 guidelines state that subcutaneous insulin and oral rehydration can be used initially, which should apply to most mild DKA episodes in this study.³ This simplified management could reduce the burden of hospital admission for both the individual and the health care system. For children with insulin pumps without automatic suspension and repeated DKA episodes, addition of long-acting basal insulin may be beneficial in selected cases.³⁷

Regarding DKA in the group of children with MDI, this study shows significantly higher HbA1c levels compared to children with CSII. Children with MDI also had low access to ketone meters at home. This emphasizes the importance of exploring the total situation of this group of children, including a social and psychological investigation and thorough follow-up, in the same manner as is recommended for recurrent DKA in ISPAD Guidelines.³

A limitation in this study is that the total treatment time since the start of CSII treatment until DKA admission was impossible to obtain from SWEDIABKIDS. Such data would have permitted a more precise estimation of the relative risk of DKA comparing CSII and MDI. However, risk estimation of DKA in the pediatric population with T1D is difficult due to the inherent practical and ethical problems in designing blinded, randomized controlled trials. Another limitation is the lack of socioeconomic or ethnic data in statistical analyses. Specific demographic data, such as socioeconomic factors and ethnicity, is not part of SWEDIABKIDS and was beyond the scope of this study.

A strength with this study is that it is a national population-based design that included all children 0–17.99 years with T1D admitted to hospital for DKA during 2 years. Furthermore, a high-quality national register (SWEDIABKIDS) was used to compare the background pediatric population with T1D.

Hybrid Closed Loop systems that might decrease the risk of DKA were not standard features of CSII treatment at the time of study

inclusion.^{22,23,26} However, an interrupted insulin delivery will cause ketosis and risk of progression to DKA regardless of which insulin delivery mode is used.

5 | CONCLUSIONS

Compared with the distribution of CSII in the national pediatric population with T1D, the distribution of CSII was significantly higher in children admitted to hospital for DKA. However, this overrepresentation of CSII was seen in mild DKA. Raised awareness of the risk of rapid development of insulin deficiency is essential during treatment with CSII.

Children treated with MDI who developed DKA had significantly higher HbA1c levels at hospital admission, which should raise concerns of management difficulties and call for extensive interventions by the diabetes team.

AUTHOR CONTRIBUTIONS

Johan H. Wersäll participated in concept/design, data collection, performed the main data analysis and interpretation. Peter Adolffson participated in data collection, data analysis and interpretation. Gun Forsander participated in data collection, data analysis and interpretation. Ragnar Hanas participated in concept/design, data collection, data analysis and interpretation. All authors participated in drafting, critical revision and final approval of the article.

ACKNOWLEDGMENTS

This study was supported by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF agreement (ALFGBG720791, VGFOUBD495431, VGFOUBD518351, VGFOUREG564611, VGFOUREG757511, VGFOUREG757651). The authors want to express gratitude to all patients, caregivers and Swedish pediatric diabetes clinics that have contributed with data, and to Jan Ekelund, senior statistician at Centre of Registers, Western Healthcare Region, Gothenburg.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared since they involve personal identification data from medical records and SWEDIABKIDS.

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REFERENCES

1. Danne T, Phillip M, Buckingham BA, et al. ISPAD clinical practice consensus guidelines 2018: insulin treatment in children and adolescents with diabetes. *Pediatr Diabetes*. 2018;19(Suppl 27):115-135.
2. Sherr JL, Tauschmann M, Battelino T, et al. ISPAD clinical practice consensus guidelines 2018: diabetes technologies. *Pediatr Diabetes*. 2018;19(Suppl 27):302-325.

3. Wolfsdorf JI, Glaser N, Agus M, et al. ISPAD clinical practice consensus guidelines 2018: diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *Pediatr Diabetes*. 2018;19(Suppl 27):155-177.
4. Annual Report of the Swedish National Paediatric Diabetes Registry (SWEDIABKIDS). 2020; Accessed February 2022. https://www.ndr.nu/pdfs/Arsrapport_Swediabkids_2020.pdf.
5. Sundberg F, Barnard K, Cato A, et al. ISPAD guidelines. Managing diabetes in preschool children. *Pediatr Diabetes*. 2017;18(7):499-517.
6. Fureman AL, Lilja M, Lind T, Sarnblad S, Bladh M, Samuelsson U. Comparing continuous subcutaneous insulin infusion and multiple daily injections in children with type 1 diabetes in Sweden from 2011 to 2016—a longitudinal study from the Swedish National Quality Register (SWEDIABKIDS). *Pediatr Diabetes*. 2021;22(5):766-775.
7. Cardona-Hernandez R, Schwandt A, Alkandari H, et al. Glycemic outcome associated with insulin pump and glucose sensor use in children and adolescents with type 1 diabetes. Data from the International Pediatric Registry SWEET. *Diabetes Care*. 2021;44(5):1176-1184.
8. Karges B, Schwandt A, Heidtmann B, et al. Association of insulin pump therapy vs insulin injection therapy with severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with type 1 diabetes. *JAMA*. 2017;318(14):1358-1366.
9. Szypowska A, Schwandt A, Svensson J, et al. Insulin pump therapy in children with type 1 diabetes: analysis of data from the SWEET registry. *Pediatr Diabetes*. 2016;17(Suppl 23):38-45.
10. Brorsson AL, Viklund G, Ortvist E, Lindholm OA. Does treatment with an insulin pump improve glycaemic control in children and adolescents with type 1 diabetes? A retrospective case-control study. *Pediatr Diabetes*. 2015;16(7):546-553.
11. Hanas R, Lindgren F, Lindblad B. A 2-yr national population study of pediatric ketoacidosis in Sweden: predisposing conditions and insulin pump use. *Pediatr Diabetes*. 2009;10(1):33-37.
12. Blair J, McKay A, Ridyard C, et al. Continuous subcutaneous insulin infusion versus multiple daily injections in children and young people at diagnosis of type 1 diabetes: the SCIPI RCT. *Health Technol Assess*. 2018;22(42):1-112.
13. Bratke H, Margeisdottir HD, Assmus J, Njolstad PR, Skrivarhaug T. Does current diabetes technology improve metabolic control? A cross-sectional study on the use of insulin pumps and continuous glucose monitoring devices in a Nationwide pediatric population. *Diabetes Ther*. 2021;12(9):2571-2583.
14. Vanelli M, Mastroianni C, Fainardi V, et al. Clinical utility of beta-hydroxybutyrate measurement in the management of physiological ketosis at home in children under 5. *Acta Bio-Med: Atenei Parmensis*. 2019;90(2):215-220.
15. Laffel LM, Wentzell K, Loughlin C, Tovar A, Moltz K, Brink S. Sick day management using blood 3-hydroxybutyrate (3-OHB) compared with urine ketone monitoring reduces hospital visits in young people with T1DM: a randomized clinical trial. *Diabetic Med*. 2006;23(3):278-284.
16. Klocker AA, Phelan H, Twigg SM, Craig ME. Blood beta-hydroxybutyrate vs. urine acetoacetate testing for the prevention and management of ketoacidosis in type 1 diabetes: a systematic review. *Diabetic Med*. 2013;30(7):818-824.
17. Bailey TS, Chang A, Christiansen M. Clinical accuracy of a continuous glucose monitoring system with an advanced algorithm. *J Diabetes Sci Technol*. 2015;9(2):209-214.
18. Laffel L. Improved accuracy of continuous glucose monitoring systems in pediatric patients with diabetes mellitus: results from two studies. *Diabetes Technol Ther*. 2016;18(Suppl 2):S223.
19. DeSalvo DJ, Miller KM, Hermann JM, et al. Continuous glucose monitoring and glycemic control among youth with type 1 diabetes: international comparison from the T1D exchange and DPV initiative. *Pediatr Diabetes*. 2018;19(7):1271-1275.
20. Bergenstal RM, Tamborlane WV, Ahmann A, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med*. 2010;363(4):311-320.
21. Foster NC, Miller KM, Tamborlane WV, Bergenstal RM, Beck RW, Network TDEC. Continuous glucose monitoring in patients with type 1 diabetes using insulin injections. *Diabetes Care*. 2016;39(6):e81-e82.
22. Breton MD, Kanapka LG, Beck RW, et al. A randomized trial of closed-loop control in children with type 1 diabetes. *N Engl J Med*. 2020;383(9):836-845.
23. Lee MH, Paldus B, Krishnamurthy B, et al. The clinical case for the integration of a ketone sensor as part of a closed loop insulin pump system. *J Diabetes Sci Technol*. 2019;13(5):967-973.
24. Nevo-Shenker M, Phillip M, Nimri R, Shalitin S. Type 1 diabetes mellitus management in young children: implementation of current technologies. *Pediatr Res*. 2020;87(4):624-629.
25. Nimri R, Battelino T, Laffel LM, et al. Insulin dose optimization using an automated artificial intelligence-based decision support system in youths with type 1 diabetes. *Nat Med*. 2020;26(9):1380-1384.
26. Tauschmann M, Thabit H, Bally L, et al. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. *Lancet*. 2018;392(10155):1321-1329.
27. Aye T, Mazaika PK, Mauras N, et al. Impact of early diabetic ketoacidosis on the developing brain. *Diabetes Care*. 2019;42(3):443-449.
28. Ghetti S, Kuppermann N, Rewers A, et al. Cognitive function following diabetic ketoacidosis in children with new-onset or previously diagnosed type 1 diabetes. *Diabetes Care*. 2020;43(11):2768-2775.
29. Donzeau A, Piffaretti C, Jossens A, et al. Time trend in excess mortality in children with type 1 diabetes from 1987 to 2016 in mainland France. *Pediatr Diabetes*. 2021;23:38-44.
30. Wersäll JH, Adolfsson P, Forsander G, Ricksten SE, Hanas R. Delayed referral is common even when new-onset diabetes is suspected in children. A Swedish prospective observational study of diabetic ketoacidosis at onset of type 1 diabetes. *Pediatr Diabetes*. 2021;22(6):900-908.
31. Dudgeon P. Some improvements in confidence intervals for standardized regression coefficients. *Psychometrika*. 2017;82(4):928-951.
32. Annual Report of the Swedish National Paediatric Diabetes Registry (SWEDIABKIDS). 2015; Accessed December 2021. https://www.ndr.nu/pdfs/Arsrapport_Swediabkids_2015.pdf.
33. Annual Report of the Swedish National Paediatric Diabetes Registry (SWEDIABKIDS). 2016; Accessed December 2021. https://www.ndr.nu/pdfs/Arsrapport_Swediabkids_2016.pdf.
34. Cengiz E, Xing D, Wong JC, et al. Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D exchange clinic registry. *Pediatr Diabetes*. 2013;14(6):447-454.
35. Maahs DM, Hermann JM, Holman N, et al. Rates of diabetic ketoacidosis: international comparison with 49,859 pediatric patients with type 1 diabetes from England, Wales, the U.S., Austria, and Germany. *Diabetes Care*. 2015;38(10):1876-1882.
36. Dogan ADA, Jorgensen UL, Gjessing HJ. Diabetic ketoacidosis among patients treated with continuous subcutaneous insulin infusion. *J Diabetes Sci Technol*. 2017;11(3):631-632.
37. Alemzadeh R, Parton EA, Holzum MK. Feasibility of continuous subcutaneous insulin infusion and daily supplemental insulin glargine injection in children with type 1 diabetes. *Diabetes Technol Ther*. 2009;11(8):481-486.

How to cite this article: Wersäll JH, Adolfsson P, Forsander G, Hanas R. Insulin pump therapy is associated with higher rates of mild diabetic ketoacidosis compared to injection therapy: A 2-year Swedish national survey of children and adolescents with type 1 diabetes. *Pediatr Diabetes*. 2022;23(7):1038-1044. doi:10.1111/pedi.13377