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

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Funding Information
Swedish Government and the County Councils, Grant/Award Numbers: VGFOUREG757651, VGFOUREG757511, VGFOUREG564611, VGFOUBD518351, VGFOUBD495431, ALFGBG720791

Abstract

Objective: Delayed treatment for new-onset diabetes Type 1 (T1D) can lead to diabetic ketoacidosis (DKA) with potentially devastating consequences. This prospective observational study aimed to characterize pediatric patients with DKA at hospital admission, regarding parental awareness of diabetes-related symptoms and delayed referrals from primary health care providers to pediatric emergency wards.

Research Design and Methods: Patients 0–18 years admitted to hospital with new-onset T1D and DKA between 2015 and 2017 were invited to participate. Questionnaires were filled out separately by the caregivers and by the attending hospital staff. Data from the Swedish National Diabetes Registry (SWEDIABKIDS) were used for comparison. Delayed referral was defined as a primary healthcare contact due to diabetes-related symptoms 0–4 weeks before hospital admission without immediate referral, or registered elevated glucose levels at primary healthcare centers without immediate referral.

Results: The study included 237 patients, among which parental suspicion of new-onset diabetes before healthcare contacts was reported in 39%. Parental suspicion of diabetes was associated with higher pH values at diagnosis. Patients in contact with primary health care providers before hospital admission had a delayed referral in 43% of the cases. Delayed referral was associated with lower pH values at hospital admission. Symptoms leading to primary healthcare contacts were similar regardless of whether delay occurred or not.

Conclusions: Parental suspicion of diabetes was associated with milder DKA at hospital admission. Delayed referral was seen in a considerable proportion of children with primary healthcare contacts for symptoms associated with diabetes. Increased awareness of diabetes symptoms is of paramount importance.

Keywords
children, delayed referral, diabetic ketoacidosis, symptoms, Type 1 diabetes
INTRODUCTION

New-onset Type 1 diabetes (T1D) is a medical emergency condition. Caregivers should be aware of symptoms of T1D and of the need for prompt medical evaluation of the child if such symptoms appear. According to national and international guidelines, primary health care providers who suspect new-onset T1D in a child should arrange immediate referral to the nearest hospital with pediatric emergency ward capabilities. Initial contacts by telephone with medical professionals are becoming increasingly common within the primary health care sector in many countries. It is essential to maintain a low threshold for advising patients or caregivers to seek prompt physical medical evaluation if symptoms that could be attributed to diabetes are reported. In Sweden, the usual way of referral of a child with new-onset diabetes to a pediatric emergency ward is from a general practitioner since children usually do not see a pediatric specialist during an initial primary healthcare visit.

Urine and blood glucose tests as well as ketone tests should be performed liberally in primary health care settings. Primary healthcare centers universally have access to blood glucose testing but usually not to blood ketone meters, and pH levels in blood cannot be measured in primary healthcare centers. All pediatric care is free of charge and paid for by the public healthcare system in Sweden, including patient visits to primary healthcare centers and laboratory tests such as tests for blood ketones (if available) and blood glucose.

Both Swedish and international (International Society for Pediatric and Adolescent Diabetes [ISPAD]) guidelines recommend that children with elevated glucose levels should be urgently referred to a pediatric emergency ward regardless of symptoms. However, several international reports have shown that pediatric patients whose blood glucose levels were above the normal range in a primary health care setting were not referred to a hospital on the same day.

Untreated new-onset T1D eventually leads to diabetic ketoacidosis (DKA). DKA can have devastating consequences in the acute setting and has been associated with long-term adverse effects on glycemic control and cognition, which makes it imperative to avoid this complication whenever it is possible. Internationally, many cases of DKA among patients with new-onset diabetes are attributed to a missed diagnosis or delays in referral. These cases, along with patients’ or caregivers’ delay in seeking medical evaluation, plausibly explain all cases of DKA in pediatric emergency wards. Theoretically, DKA could be entirely avoidable in new-onset diabetes if the general population were aware enough to seek medical care immediately if diabetes-related symptoms are present, and if a delay in the management of such cases were eliminated. Interventional studies aiming at bringing down DKA in pediatric patients with new-onset diabetes by information campaigns have, in some cases, been quite successful. In contrast, others have shown less effectiveness.

The primary aim of this prospective observational study was to describe the status of patients 0–17.99 years of age with new-onset T1D and DKA at hospital admission, with the main focus to characterize patients whose caregivers had suspected new-onset diabetes before contacting healthcare services, and patients with delayed referral to hospital after contacts with the primary healthcare system. The secondary aims were to analyze the effects of parental suspicion of diabetes and delayed referral on pH levels at hospital admission for DKA.

METHODS

A national 2-year prospective observational study from February 1, 2015 to January 31, 2017 was performed in which all children 0–17.99 years old admitted to hospital with new-onset diabetes and DKA in Sweden were included. Data on pre-admission events and admission parameters were collected using two questionnaires. In one questionnaire, parents/caregivers (together with their children if 15 years of age or above) were asked to fill out data regarding symptoms and health care contacts within 4 weeks before admission. In a second questionnaire, the attending physician or a nurse were asked to fill out data regarding the patient’s in-hospital parameters and care. Both questionnaires were administrated at hospital admission or shortly thereafter. The questionnaires could be filled out either in web-based format or in paper format. The web-based questionnaires were created using a web survey program (SurveyMonkey®, SVMK Inc., Palo Alto, CA). Access to the web-based survey required a code, which was provided to physicians and nurses only.

Data from the National Pediatric Diabetes Registry (SWEDIABKIDS) were compared with the questionnaires to account for possible missing individuals with DKA in either the study population or the register. SWEDIABKIDS covers more than 98% of children and adolescents with diabetes up to the age of 17.99 years in Sweden. The frequency of DKA in SWEDIABKIDS was calculated including only children with registered pH values.

Definition of delayed referral

Delay was defined as:

a. primary healthcare contacts for any or a combination of the classic diabetes symptoms described in Table 2 within 1–28 days before admission for DKA, with no referral to a hospital with a pediatric emergency ward the same day, or,

b. healthcare contacts the same day as hospital admission on the initiative of the caregiver, without referral by the primary health care provider or,

c. identification of hyperglycemia not resulting in a referral the same day, regardless if symptoms were present or not.

In contrast, “no delay” was defined as a patient who was referred to a hospital with a pediatric emergency ward the same day as the health care visit.

Primary healthcare contacts could be physical contacts with a doctor or a nurse, or telephone contact with a medical professional from the Swedish National Healthcare Service. In case of multiple contacts with primary healthcare providers, the first contact within
28 days was chosen as the reference point, if that contact was established due to symptoms described in Table 2 or if elevated blood or urinary glucose levels had been measured.

DKA was defined as pH < 7.30 and ketosis according to ISPAD Guidelines, and further divided into clinically relevant pH groups (severe DKA: pH < 7.10, moderate DKA: 7.10–7.19 and mild DKA: 7.20–7.29).6

The type of presentation was divided into two groups according to where the first contact was established: (1) hospital (HOSP) or (2) primary health care (PRIM). PRIM was further divided into delay (PRIM-D) or no delay (PRIM-ND).

2.2 | Statistics

pH was described and analyzed both as a continuous variable and a categorical variable according to clinically relevant groups of DKA severity. Descriptive statistics of baseline characteristics and healthcare events before admission for DKA were performed. The effects on pH of sex, age, and caregiver’s reported suspicion of diabetes before seeking medical assistance were analyzed with a linear regression model using a robust estimate of the variance.12 Delay was expected to be possibly affected by pH and vice versa, and for this reason, it was not included in the multivariable linear regression model. Due to the skewed distribution of pH values, median values were presented in descriptive tables. The association between delay and pH was evaluated using a Mann-Whitney U test for distribution comparison and Hodge-Lehmann’s test for median differences. Telephone consultations were included in the principal analysis. SPSS version 27 (IBM Corporation, Armonk, New York, NY) were used for all calculations, tables, and graphs.

2.3 | Ethics

Approval for the study was granted by the regional ethical review board in Vastra Gotaland, Gothenburg, Sweden.

3 | RESULTS

3.1 | Description of data from SWEDIABKIDS

The SWEDIABKIDS register includes records of 1710 patients with new-onset T1D during the study period, of which 1375 (80.4%) had reported data on pH (Figure 1). Of these, 299/1375 (21.7%) presented with DKA. There were another 30 patients without reported pH values in SWEDIABKIDS whose pH values were found in the study and thus had DKA. Patients with DKA in SWEDIABKIDS had a higher mean HbA1c than patients without DKA (108.9 vs. 91.2 mmol/mol, 12.12% vs. 10.5%, p < 0.0001, t-test).

3.2 | Description of study data

The study included 237 patients with DKA, of which 215 patients were found in the SWEDIABKIDS register. There were 92/237 (39%) cases in which parents/caregivers reported suspicions of new-onset T1D before taking contact with medical professionals.

Data regarding health care contacts before admission was available for 215/237 (91%) patients (Figure 1). Of these, 126 (59%) patients reported that primary healthcare contacts occurred prior to hospital admission, of which delay or no delay could be evaluated in 112 cases. There were 99 patients with physical contacts and 13 patients with telephone contacts as first primary healthcare contact. Demographic data and laboratory parameters are reported in Table 1.

3.3 | Primary health care contacts

Symptoms described by the patients and/or their caregivers leading to primary health care contacts are presented in Table 2. The distributions of symptoms between PRIM-D and PRIM-ND were similar and classic symptoms of thirst, polyuria, tiredness, and weight loss were the most common in both groups. In 48/112 (43%) of the cases, the patients were not referred immediately to a hospital emergency ward (PRIM-D). When divided into age groups, delay was found in 5/10 (50%) of children between 0 and <2 years, 12/22 (55%) between 2 and 7 years, and 31/80 (39%) between 8 and 17.99 years. PRIM-ND and PRIM-D are compared according to DKA severity in Table 3. In 30/81 (37%) of the cases with primary health care contacts, parents/children reported that they were informed about another diagnosis than diabetes by the primary health care provider. The most commonly assumed diagnosis in these cases was gastroenteritis, which was reported in 6/81 (7.4%) cases. See Table S1 for a complete list of diagnoses assumed by the primary health care provider.

In 54/126 (43%) of the patients with primary healthcare contacts before admission, the caregiver and/or the patient reported having suspected a diabetes diagnosis before contacting a primary health care provider. In 21/54 (39%) of these cases, the patient did not get an immediate referral to hospital after the primary health care contact. The caregivers, children, or physicians, reported that urinary glucose or blood glucose levels were not tested in 27/99 (27%) of the cases with physical contacts at a primary health care center. When both thirst and polyuria were reported as the main symptoms in these cases, urinary or blood sugar were not tested in 13/56 (23%). In PRIM-D there were only 20 (42%) patients with reports that blood glucose or urinary glucose had been tested at the primary health care center, in whom either thirst, polyuria or a combination of both symptoms were reported as reasons for contacting the primary health care by patients or their caregivers.

3.4 | Analysis of effects of demographics, suspicion of diabetes before healthcare contacts and delayed referral on metabolic status at admission for DKA

The distribution of pH values between HOSP, PRIM-ND, and PRIM-D is presented in Figure 2 and between PRIM-ND and PRIM-D in Figure 3. There was a significant difference in pH distribution and median
pH values between PRIM-D and PRIM-ND (Mann–Whitney U test, $p = 0.018$, Figure 3; Hodge-Lehmann’s test for median difference estimate $-0.040$ C.I. $-0.080$ to $-0.010$), but not between HOSP and PRIM-D ($p = 0.067$). In the whole population (HOSP, PRIM-ND, and PRIM-D), reported suspicion of diabetes before healthcare contacts strongly predicted less severe pH levels ($p < 0.001$, C.I. $0.053–0.125$).

In the multivariable model including sex and age, both increasing age ($p = 0.037$, C.I. $0.000–0.008$) and parental suspicion of diabetes ($p < 0.001$, C.I. $0.058–0.129$) predicted higher pH levels with no significant interactions found between the independent variables (Table S2).

There were 11 patients (5%) who showed symptoms of cerebral edema according to Muir’s criteria, with five patients (2%) fulfilling diagnostic criteria of cerebral edema. Of these, two patients were treated with mannitol or hypertonic saline with good outcome.

4 | DISCUSSION

The frequency of DKA at onset is inversely related to the prevalence of T1D. Sweden has a high incidence of T1D but a low relative incidence of DKA compared with most other countries. In Sweden, DKA at onset has varied between 20% and 25% during 2015–2018. The proportion of DKA, according to SWEDIABKIDS at diagnosis, was 21.7% during our study period. This proportion is higher than the previous figure of 16%, reported in a similar Swedish study during 1999–2000. The findings in this study indicate that a considerable proportion of patients with healthcare contacts due to diabetes-related symptoms before admission for DKA was not immediately referred to an emergency ward. In our study, severe or moderate DKA ($pH < 7.2$) seemed more common in patients with a delayed referral, which could indicate that delayed referral contributed to a worsened metabolic status at presentation. Since pH values were not measured at the time of contact with the primary healthcare providers, it is not possible to know how many patients who had developed DKA already at the time of consultation. Although it could be assumed that immediately referred patients were those with more typical symptoms, it is nonetheless evident from Table 2 that symptoms at presentation were quite similar regardless of whether the patient was immediately referred or not.

Patients in the lowest pH group had more specific symptoms of acidosis (tachypnea, vomiting from ketonemia) but lower frequencies
of the classic diabetes symptoms of thirst and polyuria. The latter finding could have contributed to an overlooked diagnosis of more severe ketoacidosis, resulting in not being referred. Patients not expressing or showing obvious signs of dehydration, for example, thirst or polyuria, thus, seem to be at risk of a missed DKA diagnosis. Although classic symptoms were relatively common in the two groups

### TABLE 1  Characteristics of patients with new-onset T1D and DKA with or without primary healthcare contacts before hospital admission

|                     | No healthcare contacts (HOSP) | Healthcare contacts before admission | Total |
|---------------------|------------------------------|-------------------------------------|-------|
| N (%)               | 89 (41%)                     | 126 (59%)                          | 215   |
| Median age (range)  | 11.4 (0.49–17.4)             | 10.0 (0.62–17.9)                   | 10.7 (0.49–17.4) |
| Sex                 |                              |                                     |       |
| Female              | 36 (38%)                     | 58 (62%)                            | 94    |
| Male                | 53 (44%)                     | 68 (56%)                            | 121   |
| PRIM-ND             |                              |                                     |       |
| Median pH (range)   | 7.21 (6.82–7.29)             | 7.18 (6.88–7.29)                   | 7.19 (6.82–7.29) |
| Mean HbA1c mmol/mol (min-max) | 109 (68–177) | 110 (62–165) | 110 (62–177) |
| Mean HbA1c % (min-max) | 12.1 (8.4–18.4) | 12.2 (7.8–17.3) | 12.2 (7.8–16.1) |

*n = 80.

### TABLE 2  Symptoms described at healthcare contacts within 4 weeks before hospital admission for new-onset Type 1 diabetes and diabetic ketoacidosis (DKA)

| Distribution of symptoms at first primary healthcare contact between PRIM-ND and PRIM-D | Distribution of symptoms by age groups at first primary healthcare contact |
|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
|                                                                                     | 0–<2 | 2–<8 | 8–17.99 years | 0–17.99 years |
| Thirst                                                                               | 64    | 48    | 112           | 12   | 25 | 89 | 126 |
| PRIM-ND                                                                             | 47 (73%) | 29 (60%) | 76 (68%) | 4 (33%) | 17 (68%) | 57 (64%) | 78 (62%) |
| PRIM-D                                                                             | 48 (75%) | 25 (52%) | 73 (65%) | 4 (33%) | 16 (64%) | 55 (62%) | 75 (60%) |
| Polyuria                                                                            | 40 (63%) | 33 (69%) | 73 (65%) | 8 (67%) | 13 (52%) | 53 (60%) | 74 (59%) |
| Tiredness                                                                            | 32 (50%) | 25 (52%) | 57 (51%) | 2 (17%) | 7 (28%) | 50 (56%) | 59 (47%) |
| Weight loss                                                                         | 17 (27%) | 9 (19%) | 26 (23%) | 1 (8%) | 5 (20%) | 22 (25%) | 28 (22%) |
| Nausea                                                                              | 16 (25%) | 12 (25%) | 28 (25%) | 3 (25%) | 6 (24%) | 20 (22%) | 29 (23%) |
| Vomiting                                                                            | 10 (16%) | 9 (19%) | 19 (17%) | 2 (17%) | 5 (20%) | 11 (15%) | 20 (16%) |
| Abdominal pains                                                                     | 3 (5%) | 4 (8%) | 7 (6%) | 0 | 0 | 7 (8%) | 7 (6%) |
| Breathing                                                                            |                   |                   |                   |                   |                   |                   |
| Visual problems                                                                     |                   |                   |                   |                   |                   |                   |

Note: It was possible to determine delay in 112/126 patients. Distribution of symptoms by PRIM-ND (patients with immediate referral to hospital from a primary healthcare provider) and PRIM-D (patients with delayed or no referral to hospital from a primary healthcare provider), and distribution of symptoms compared by age groups.

### TABLE 3  Comparison of severity of diabetic ketoacidosis (DKA) between PRIM-ND (patients immediately referred to hospital from a primary healthcare provider) with PRIM-D (patients with a delayed referral from a primary healthcare provider)

| DKA severity | Severe (pH < 7.10) | Moderate (pH 7.10–7.19) | Mild (pH 7.20–7.29) | Total (pH <7.29) |
|--------------|--------------------|--------------------------|---------------------|-----------------|
| PRIM-ND      | N (%)              | 12 (48%)                 | 15 (43%)            | 30 (67%)        | 57 (54%) |
| PRIM-D       | N (%)              | 13 (52%)                 | 20 (57%)            | 15 (33%)        | 48 (46%) |
with higher pH, a large proportion of these patients were not immediately referred.

Many children in whom elevated blood glucose levels were confirmed, were not directly referred to hospital. One explanation for the delay could be that some general physicians and other health care staff are not fully aware of the existence of diabetes in children and adolescents. Another explanation could be that general practitioners assume the diagnosis of Type 2 diabetes when an elevated blood glucose level is found, thus missing the urgency of the situation.

A growing concern is the risk of long-term neurological consequences of DKA. Schoenle et al. reported in 2002 that impaired intellectual development in boys with diagnosis <6 years was associated with DKA at diagnosis. A study from 2019 found that a single episode of moderate or severe DKA (as was more common in the group with delayed referral in our study) was associated with lower cognitive scores and altered brain growth. Similarly, an Australian study from 2014 showed significant impairment on cognitive tests after DKA. A delayed DKA diagnosis may thus result in both a short-term risk of treatment complications and life-long neurological impairment for the child, making it paramount to find measures to avoid DKA both at diagnosis and afterwards. Both primary health care providers and the general population therefore need to achieve and maintain higher awareness of symptoms that could be related to new-onset diabetes. Misdiagnosis has been shown to be significantly associated with the incidence of DKA in other studies.

Studies describing interventions to bring down the incidence of DKA among patients with new-onset T1D have shown mixed results. Some interventions have shown remarkable effects. For example, an Italian poster campaign which lowered the incidence of DKA to nearly zero in individuals above the age of 6 years, and a Turkish study showed a two-fold decrease in the rate of DKA after a 2-year national diabetes awareness program was initiated. However, interventions in Austria and Wales did not show any significant effects of diabetes awareness interventions. The scope of interventions has commonly been to educate primary health care providers, caregivers and children about the possibility of a diabetes diagnosis in patients with
typical symptoms or to remind primary health caregivers to immediately refer patients with an elevated blood glucose value to the nearest hospital with a pediatric emergency department.

Since the only way to avoid DKA in patients with new-onset T1D is to initiate insulin therapy urgently, a high level of alertness among health care providers regarding diabetes-related symptoms must be maintained. Blood glucose and ketone tests and immediate referral must be carried out in cases where diabetes is suspected. Many patients in this study (59%) had primary healthcare visits before admission, a proportion which is substantially higher than what was found in a large meta-analysis in which 39% of children who presented with DKA had been seen at least once by a doctor before diagnosis. A delay for more than 48 h has been associated with increased risk of DKA. An increase in routine glucose testing of children in the primary health care setting would likely be able to better identify cases of new-onset diabetes. A specialized pediatric outpatient system with pediatricians serving mainly for this age group instead of general practitioners may have been better equipped to diagnose children with new onset diabetes earlier. However, reports from countries that have this system implemented still show high percentage of DKA at onset.

In our study, 39% of the caregivers reported that they suspected diabetes before any contacts with medical professionals were taken. In these cases significantly higher pH values were recorded at hospital admission. Such awareness of symptoms related to diabetes was associated with a lower risk of DKA in a UK study. For the group with primary healthcare contacts before hospital admission, it is therefore remarkable that delayed referral was seen in 43% of the cases where caregivers had suspected diabetes prior to taking contact with a primary health care service.

We found that classic symptoms were common both in PRIM-D and PRIM-ND, in similar proportions as in a UK study (polyuria 76%, polydipsia 86%). Tiredness and weight loss were also very common with similar proportions in both groups. Alertness to these symptoms could probably speed up a referral, thus preventing DKA in many cases and leading to a milder DKA in others. The similar distributions of symptoms in PRIM-ND and PRIM-D could indicate that delay in diagnosis is more of a doctor’s delay than patient’s delay. The higher HbA1c values in DKA patients versus non-DKA patients in SWEDIABKIDS were similar to findings in other studies.

When looking at registry data for DKA, one might assume that pH would not be measured in patients whose clinical condition did not indicate DKA. Missing data would then indicate an absence of DKA. If this were true, the frequency of DKA in SWEDIABKIDS would have been 299/1710 (17.5%). However, when combined with our study data, 30 cases with missing data turned out to be non-registered DKA cases, giving a DKA frequency of at least 329/1710 (19.2%). Thus, it is evident that valid DKA frequencies in registries can only be calculated based on cases with registered pH values, that is, missing values cannot be interpreted as non-DKA as discussed by Cherubini et al.

The reason for a patient being included in our study, but not in SWEDIABKIDS, may be due to missing data in SWEDIABKIDS. One explanation is that some patients with diabetes (refugees, asylum seekers, etc.) have temporary national identification numbers, while only permanent national identification numbers are registered in SWEDIABKIDS.

This study has some limitations and strengths. The study did not include patients with new-onset Type 1 diabetes without DKA. It would have been of interest to investigate this group to increase power in determining the incidence of delayed referral for the total group of children with new-onset T1D. However, if all patients with new-onset T1D would have been included during the study period, it would not have been possible to determine how many cases of DKA that could have been prevented with an immediate referral, since pH and ketones are not measured at primary care contacts. Misdiagnosis was significantly associated with the incidence of DKA in a Polish study and DKA was shown to be 74% more common if the diagnosis was delayed in a meta-analysis. Another limitation is that caregivers, if they reported suspicions of diabetes before contacting healthcare services, did not report where they got knowledge about diabetes prior to contacting healthcare services. This information would have been useful also to discuss possible ways of improving public knowledge about new-onset diabetes. Further limitations related to methodology are uncertainty whether “diabetes-related symptoms” were communicated the same way in the questionnaires as they were in the contacts between the health care provider and the patients/caregivers, and the possibility of bias since all participants in the study already knew they had diabetes at the time they answered the questionnaire. There are also limitations in the absence of secondary enuresis among the choices in the list of symptoms in the questionnaire (no parents mentioned this as a symptom), and in that only patients with primary health care were asked about symptoms.

A strength of this study is that it was national and population-based, and that the response rate of the questionnaire included 72% of reported cases of DKA in SWEDIABKIDS. Furthermore, we included 2 years of data to account for year-to-year differences. Another strength is that we included all types of primary healthcare providers, not only general practitioners. However, the results of this study are produced in the health care environment that is present in Sweden, and may not be applicable to countries with a health care system that differs markedly.

5 CONCLUSIONS

Even in a country with a very high incidence of T1D like Sweden, symptoms of T1D are not always recognized by general practitioners and other healthcare providers, and the majority of caregivers seem to be unaware of the possibility of diabetes when their children present such symptoms. Most children presented with classic diabetes symptoms, with similar proportions and elevated blood glucose levels in both the delay and non-delay groups at the primary healthcare contact. Nonetheless, as many as 43% of these children were not immediately referred to a pediatric...
emergency ward, indicating a substantial doctor's delay. Improved knowledge and general awareness of diabetes symptoms among both caregivers and among medical professionals working in the primary healthcare sector are paramount in improving this situation and preventing DKA.

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 (ALFGGB720791, VGFOUBD495431, VGFOUBD518351, VGFOURS564611, VGFOURED757511, VGF OUREG757651). The authors want to express gratitude to all Swedish pediatric diabetes clinics that have contributed with data and to Jan Ekelund, senior statistician at Center of Registers, Western Healthcare Region, Gothenburg.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

Johan H. Wersäll participated in concept/design, data collection, performed the main data analysis and interpretation. Peter Adolfsson participated in data collection, data analysis and interpretation. Gun Forsander participated in data collection, data analysis and interpretation. Sven-Erik Ricksten participated in 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.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Wersäll JH, Adolfsson P, Forsander G, Ricksten S-E, 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;1–9. https://doi.org/10.1111/pedi.13229