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ORIGINAL ARTICLE

Ketoacidosis at diagnosis of type 1 diabetes: Effect of prospective studies with newborn genetic screening and follow up of risk children

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We studied the frequency of diabetic ketoacidosis (DKA) in children at diagnosis of type 1 diabetes (T1D) in a region where newborn infants have since 1995 been recruited for genetic screening for human leukocyte antigen (HLA)-conferred disease susceptibility and prospective follow up. The aim was to study whether participation in newborn screening and follow up affected the frequency of DKA, and to follow the time trends in DKA frequency. We first included children born in Oulu University Hospital since 1995 when the prospective studies have been ongoing and diagnosed with T1D <15 years by 2015 (study cohort 1, *n* = 517). Secondly, we included all children diagnosed with T1D <15 years in this center during 2002-2014 (study cohort 2, *n* = 579). Children who had an increased genetic risk for T1D and participated in prospective follow up had low frequency of DKA at diagnosis (5.0%). DKA was present in 22.7% of patients not screened for genetic risk, 26.7% of those who were screened but had not an increased risk and 23.4% of children with increased genetic risk but who were not followed up. In study cohort 2 the overall frequency of DKA was 18.5% (13.0% in children <5 years, 14.0% in children 5-10 years and 28.6% in children ≥10 years at diagnosis; *P*<.001). In children <2 years the frequency of DKA was 17.1%. Participation in prospective follow-up studies reduces the frequency of DKA in children at diagnosis of T1D, but genetic screening alone does not decrease DKA risk.

KEYWORDS

diagnosis and children, ketoacidosis, type 1 diabetes

1 | INTRODUCTION

Diabetic ketoacidosis (DKA), a metabolic derangement characterized by the triad of hyperglycemia, acidosis, and ketosis, is commonly observed at diagnosis of type 1 diabetes (T1D) in children. The frequency varies between 15% and 80% and correlates inversely with the background incidence of T1D.[1–3] In some studies, DKA at diagnosis seems to have decreased[4,5] while other studies have reported stable or even increased frequencies of DKA.[6–8]

An alarming fact is that DKA is most common in the youngest children at diagnosis of T1D. Children younger than 5 years and especially children under 2 years of age at diagnosis are at a high risk for DKA.[7,9,10] Although young children have been reported to have a short duration of symptoms before the diagnosis of T1D, a delay in diagnosis due to various reasons, for example concurrent infections and misdiagnosis, may also occur.[11] Education about the initial symptoms of T1D and importance of early diagnosis may be challenging in the population level, but there are some published reports of the effectiveness of medical information on the frequency of DKA. For instance an 8-year campaign focusing on medical information on the early symptoms of diabetes reduced the incidence of DKA in children with newly diagnosed T1D in Italy.[12] Similarly, a 2-year intervention

period with education regarding T1D offered at child care centers, schools, and doctors' offices resulted in a decreased frequency of DKA at initial diagnosis.[13] It is also known that children with a first-degree relative (FDR) (mother, father and siblings) with T1D have a reduced risk for DKA at diagnosis.[14]

Several prospective studies have followed from birth children at increased genetic risk of T1D. These studies provide the risk information to all families participating in newborn genetic screening. Intensive follow up of children with increased disease risk may increase the awareness of symptoms thus resulting in an earlier diagnosis and prevention of DKA. In the Diabetes Autoimmunity Study in the Young (DAISY) children screened for genetic risk and observed regularly had a less severe onset of the disease characterized by a reduced hospitalization rate and lower mean HbA1c at onset.[15] The German BABYDIAB study reported that the children with an affected FDR and regular follow up had lower HbA1c and a reduced frequency of DKA (pH < 7.30) at diagnosis as compared with community controls, 3.3% vs 29.1%, $P < .001$.[16] Young children (<2 and <5 years) participating in the international TEDDY (The Environmental Determinants of Diabetes in the Young) study had a significantly lower rate of DKA at diagnosis of T1D when compared with data collected during similar periods from studies and registers in all TEDDY-participating countries.[17] In the first 100 children observed in the TEDDY study and diagnosed with T1D (age: 0.69-6.27 years) the risk of DKA was low (8%). In addition, 36% of these children had no symptoms of diabetes before diagnosis.[18]

The aim of the current study was to determine the risk of DKA in children at diagnosis of T1D in Oulu University Hospital where the prospective follow-up studies have been going on since 1995 with the hypothesis that such studies may have a decreasing effect on the overall risk of DKA in the population. In addition, we wanted to analyze the frequency of DKA at diagnosis of T1D in this center in 2002 to 2014 to follow our earlier observations, and to compare the risk of DKA in children with increased genetic risk who did or did not participate in the prospective follow up.

2 | METHODS

Our study includes children with newly diagnosed T1D at Oulu University Hospital (Figure 1). For the current analyses we constructed 2 study cohorts in order to address the specific study questions. Majority of the children (n = 485) were included in both cohorts. Study cohort 1 comprised the children who were diagnosed with T1D under the age of 15 years by December 2014 and who were born in 1995-2012, during the time period when 2 prospective T1D studies recruited all newborn infants in Oulu University Hospital for human leukocyte antigen (HLA) screening and subsequent follow up. The Finnish T1D Prediction and Prevention (DIPP) Study in Finland is based on screening for HLA-DR/DQ-conferred susceptibility to T1D in infants born in the university hospitals of Turku, Oulu and Tampere.[19] The Environmental Determinants of Diabetes in the Young (TEDDY) study is an international, longitudinal, observational investigation with a goal to identify environmental triggers of T1D in children genetically at risk.[20] With the DIPP and TEDDY studies, information of T1D, and screening for disease associated risk genes were offered to all families with a newborn baby. The infants with the defined HLA-DR/DQ genotypes associated with an increased risk for T1D were invited to regular clinical, immunological, and metabolic follow-up, in order to detect possible signs of islet autoimmunity associated with an increased risk of the disease.[21,22] The DIPP study started to recruit newborns for HLA screening in Oulu in September 1995, and the recruitment is still ongoing. The TEDDY Study screened newborn infants during 2004-2010 in Oulu. In both the DIPP and TEDDY studies, HLA-DR/DQ-conferred genetic risk for T1D was analyzed from cord blood.[19,23] As the genetic inclusion criteria for TEDDY and DIPP were only partly overlapping there were children with an increased disease risk not eligible to TEDDY who were recruited to DIPP in 2004 to 2010. The group of subjects with prospective follow up included children who had completed at least 1 visit to the study center as well as children who had participated regularly in the follow-up study until their diagnosis. During the first study center visit, a lot of information on T1D and preclinical diabetes was given to the family. In addition, if the child seroconverted to positivity for islet autoantibodies, a more intense follow up with further information and possibilities for discussions with the study personnel was organized. For the purposes of the current study the information on the participation in the prospective follow up was generated from the Oulu University Hospital patient registry at the time of diagnosis.

In study cohort 1 the total number of children was 517, mean age at diagnosis was 6.30 years (range: 0.52-14.87 years). Of these children 227 of 517 (43.9%) were younger than 5 years, 194 of 517 (37.5%) were 5.0-9.99 years and 96 of 517 (18.6%) were 10.0-14.99 years at diagnosis.

Study cohort 2 comprised all the children who had been diagnosed with T1D under the age of 15 years in Oulu University Hospital during 2002 to 2014 (n = 579, boys 341, 58.9%). We have earlier studied the frequency of DKA at diagnosis of T1D in 1982 to 2001 in Oulu University Hospital,[4] and found that DKA was decreasing during this 20-year period. Now we wanted to follow whether a further decrease since 2001 had occurred. The children in study cohort 2 were born in 1987-2012. Their mean age at diagnosis was 7.53 years (range 0.52-14.99 years). There were 185 of 579 (32.0 %) children aged 0-4.99 years, 205 of 579 (35.4%) children aged 5.00-9.99 years and 189 of 579 (32.6 %) children 10.00-14.99 years old at diagnosis. A total of 41 of 579 (7.1%) children were under 2 years of age at diagnosis.

The information on the duration of the symptoms before diagnosis was received from the patient registry and the estimated weight loss (%) was assessed based on the Finnish growth charts by weight at diagnosis and expected weight by height.[24] Standard laboratory methods were used to analyze venous pH, HbA1c, and β-hydroxybutyrate values in the hospital laboratory and the information on the values were collected from the hospital register. DKA was defined as a venous pH <7.30 and considered severe if pH was <7.10. The study was approved by the local ethics committee.

2.1 | Statistical analyses

The frequency of DKA was analyzed with 2 approaches by categorizing the children into the 2 study cohorts described above. In study

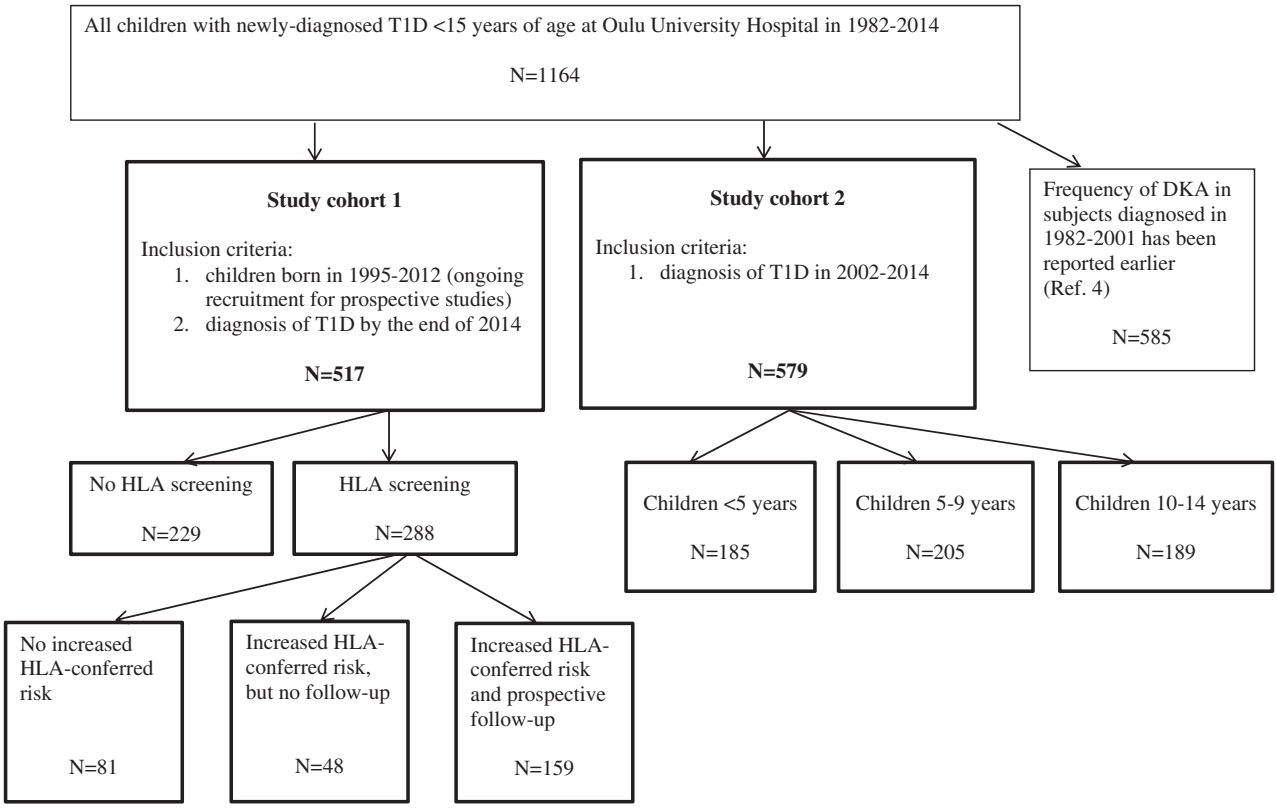

FIGURE 1 The flow chart represents the study cohort 1 and 2. All children living in the catchment area of Oulu University Hospital and who were diagnosed with T1D under the age of 15 years in 1982 to 2014 were registered (n = 1164). Frequency of DKA in children diagnosed in 1982 to 2001 (n = 585) was reported earlier.[4] In the study cohort 2 (n = 579) the frequency of DKA in children diagnosed thereafter, in 2002 to 2014, was analyzed to follow the trend in the frequency of DKA at diagnosis in various age groups. In the study cohort 1 (n = 517) we included children who were born in 1995 to 2012, when recruitment for the prospective DIPP and TEDDY studies was ongoing in Oulu University Hospital, and who were diagnosed with T1D by the end of 2014. The study cohort 1 was divided into 4 subgroups based on whether the children had or had not been (i) screened for human leukocyte antigen (HLA) (n = 288 and n = 229, respectively), (ii) had no increased HLA-conferred risk (n = 81), (iii) had an increased HLA-conferred risk but did not participate in the follow up (n = 48), or (iv) had an increased HLA-conferred risk and participated in the follow up (n = 159). Note that the study cohort 1 and 2 overlap with 485 children belonging to both groups

cohort 2 the frequency of DKA at diagnosis was compared in different age groups (<2 years, 0-4.99, 5.0-9.99, and 10.0-14.99 years at diagnosis), by gender, and in 3 time periods (1/2002-4/2006, 5/2006-8/2010, and 9/2010-12/2014) to identify the possible secular change in the frequency of DKA. In study cohort 1, the frequency of DKA was analyzed in the groups defined based on participation in the HLA screening and follow up in the prospective diabetes studies (Figure 1).

Data analysis was performed by using SPSS for Windows statistical software (version 20.0; SPSS, Chicago, Illinois). Student's 2-tailed t test for independent samples was used for pair-wise comparisons when comparing variables with normal distributions. The Mann-Whitney U test was applied for unequally distributed variables. Distributions were analyzed by cross-tabulation and χ^2 statistics. Univariate analysis with age-standardization was used while comparing continued variables when analyzing groups based on participation of the screening and follow up. When analyzing the 3 age groups, 1-way analysis of variance was used for variables with normal distributions and the Kruskal-Wallis test for unequally distributed variables. A 2-tailed P value of <.05 was considered to indicate statistical significance.

3 | RESULTS

In study cohort 1 representing 517 children born since September 1995 the overall frequency of DKA was 17.6% and that of severe DKA 3.5% at diagnosis of T1D. No difference was seen in the frequency of DKA between females and males (19.4% vs 16.6%, respectively P = .408). Similarly, the frequency of severe DKA was not significantly different between the sexes (females 5.1% vs males 2.4%; P = .099). In total 288 of 517 children (55.7%) had been screened from cord blood for HLA-conferred risk for T1D. The comparison of the children based on participation in the screening for HLA-conferred disease risk and the prospective follow up is presented in Table 1. The frequency of DKA was the lowest (5.0%) in children who had an increased HLA-associated genetic risk and were followed in a prospective diabetes study when compared with children with no HLA screening and children with HLA screening but no follow-up (P < .001). Severe DKA was seen in only 1/159 (0.6% of the children) who participated in both genetic screening and follow-up. This was an 11-year-old boy whose family had taken part only in the first information visit to the DIPP center at the age of 3 months. When comparing the age groups and participation in the prospective follow up, we found that children diagnosed at the age of

TABLE 1 Diagnostic characteristics of children born in 1995 to 2012 and diagnosed with type 1 diabetes in 1997 to 2014 (cohort 1)

	Cord blood HLA screening and participation in a longitudinal follow-up study				
	No HLA screening	No increased HLA-conferred risk at screening	Increased HLA-conferred risk at screening, but no follow up	Increased HLA-conferred risk and prospective follow up	*P*-value
Number of children (*N* = 517)	229	81	48	159	
Boys/girls	133/96	48/33	28/20	89/70	.961
Mean age at diagnosis (y, 95% CI)	6.75 (6.26-7.23)	6.92 (6.15-7.70)	5.50 (4.60-6.40)	5.60 (5.01-6.12)	.002
Duration of symptoms before diagnosis, days (95% CI)	14.9 (13.0-16.8)	17.7 (14.3-21.1)	13.7 (10.0-17.3)	5.7 (4.4-7.1)	<.001
Estimated weight loss, % (95% CI)	7.1 (6.3-7.9)	7.8 (6.7-8.8)	6.1 (4.3-7.9)	2.9 (2.3-3.5)	<.001
pH (95% CI)	7.34 (7.32-7.36)	7.31 (7.29-7.35)	7.35 (7.32-7.38)	7.39 (7.38-7.39)	<.001
Blood β-hydroxybutyrate, mmol/l (95% CI)	2.66 (2.32-2.99)	3.13 (2.51-3.74)	2.46 (1.62-3.29)	0.77 (0.55-0.99)	<.001
Blood HbA1c, % (95% CI)	10.77 (10.46-11.08)	11.39 (10.75-12.02)	10.42 (9.68-11.17)	8.52 (8.21-8.84)	<.001
Blood HbA1c, mmol/mol (95% CI)	94.2 (90.8-97.6)	101.0 (94.0-107.9)	90.4 (82.3-98.6)	69.6 (66.2-73.1)	<.001
DKA, pH < 7.30, % (95% CI)	22.7 (17.2-28.2)	26.3 (16.7-35.9)	23.4 (11.3-35.5)	5.0 (1.6-8.4)	<.001
Severe DKA, pH < 7.10, % (95% CI)	4.4 (1.7-7.1)	6.3 (1.0-11.6)	4.3 (0-10.1)	0.6 (0-1.8)	.098

Abbreviations: CI, confidence interval; DKA, diabetic ketoacidosis; HLA, human leukocyte antigen.

The subjects are grouped on the basis of cord blood screening for disease-associated HLA genotypes and participation in a prospective follow-up study. Data are expressed as frequencies and means (95% CI). Distributions were analyzed by cross-tabulation and χ^2 statistics. Univariate analysis with age-standardization was used while comparing continuous variables. *P* value of <.05 was considered to indicate statistical significance and presents the differences between the 4 groups based on the screening and participation of the prospective follow-up studies.

10-14 years had participated in a prospective diabetes study less frequently (18/96, 18.8%) than children who were 5-9 years old (61/194, 31.4%) or younger than 5 years old at diagnosis (80/227, 35.2%; *P* = .015).

In study cohort 2 that included all the 579 children diagnosed with T1D during 2002 to 2014 the overall frequency of DKA was 18.5% and the frequency of severe DKA 3.5% at presentation. The median pH was 7.37 (interquartile range [IQR] 7.32-7.40), the median blood β-hydroxybutyrate 1.2 mmol/L (IQR 0.3-4.0) and the median blood HbA1c 91.3 mmol/mol (IQR 72.7-113.1), 10.5% (IQR 8.8-12.5). The median duration of symptoms before diagnosis was 14.0 days (IQR 4.0-21.0). We found no differences in the frequency of DKA or severe DKA between females and males (20.4% vs 17.2%, *P* = .322 and 5.1% vs 2.4%, *P* = .079; respectively). When comparing children younger than 2 years at diagnosis (*n* = 41) with older children (*n* = 538), the frequency of DKA and severe DKA was observed to be almost equal (DKA occurred in 17.1% of children <2 years old vs 18.6% in older children, *P* = .807 and severe DKA occurred in 2.4% of children <2 years vs 3.6% in older children, *P* = .703). The comparison of the 3 age groups (0-4.9 years, 5.0-9.9 years, and 10.0-14.9 years) is presented in Table 2. The frequency of DKA was found to increase by age at diagnosis (13.0% in children under 5 years of age, 14.0% in children 5-9 years of age, and 28.6% in 10-14 -year-old children; *P* < .001). Similarly, severe DKA was seen most frequently in the oldest children (6.9% vs 2.2% in children <5 years and 1.5% in children 5-9 years, *P* = .008). The frequency of DKA did not change over the 3 time periods (20.8% in 1/2002-4/2006, 17.4% in 5/2006-8/2010, and 17.6% in 9/2010-12/2014, *P* = .638).

4 | DISCUSSION

We report the frequency of DKA at the clinical diagnosis of T1D from a single clinical center in Finland, which treats all children with newly diagnosed T1D who live in the catchment area. Our center has recruited newborn infants and their families for more than 20 years for prospective clinical follow-up studies where genetic disease risk is assessed from cord blood and regular follow up is offered to the families with a child carrying a genotype associated with an increased disease risk. We confirm that participation in a preclinical follow-up study reduces the frequency of DKA at diagnosis. However, genetic screening alone was not associated with a decreased DKA risk.

While analyzing the children born since 1995, when the DIPP study started in Oulu University Hospital, the DKA risk was found to be the lowest (5%) in the group of children who carried HLA-DR/DQ conferred susceptibility to T1D and were observed prospectively in a follow-up study. Our observation of the low frequency of DKA at the time of diagnosis of T1D is in line with earlier studies on children taking part in preclinical follow up.[15,16,18] However, in children with increased genetic risk but not participating in a follow-up study or in children without risk genotypes and thus not invited for follow up, the risk of DKA was similar in comparison with the total group of children born since September 1995. Thereby, it seems that the identification of an increased risk at newborn screening does not decrease the frequency of DKA at clinical diagnosis. Indeed, the frequency of DKA was the highest in children with no increased genetic risk (26.3%), that is higher than in children who were not screened at all. This is worrisome, because some families may mistakenly think that their children with no increased genetic risk are protected and will never develop T1D and may therefore not become concerned in response to emerging symptoms.

The overall frequency of DKA at diagnosis of T1D in children in Finland has been relatively low since the 1980s.[25] In our earlier study, the DKA frequency was 22.4% in 1982 to 1991 and 15.2% in 1992 to 2001 in Oulu University Hospital. In the most recent time period in 2002 to 2014 in the current study, the frequency of DKA was 18.5%. The mean age at diagnosis has become younger, being

TABLE 2 Comparison of the 3 age groups of children diagnosed with type 1 diabetes during 2002 to 2014 in Oulu University Hospital, Finland (cohort 2)

	Age at clinical diagnosis of type 1 diabetes			
cf	<5.0 y	5.0-9.9 y	10.0-14.9 y	*P*-value
Number of children	185	205	189	
Boys/girls	114/71	112/93	115/74	.301
Duration of symptoms before diagnosis, days (95% CI)	11.4 (9.5-13.2)	14.3 (11.7-16.8)	19.4 (16.1-22.8)	<.001
Estimated weight loss, % (95% CI)	4.6 (3.9-5.2)	6.3 (5.5-7.1)	8.3 (7.4-9.3)	<.001
pH (95% CI)	7.37 (7.36-7.38)	7.36 (7.35-7.37)	7.32 (7.29-7.33)	<.001
Blood β-hydroxybutyrate, mmol/l (95% CI)	1.90 (1.55-2.24)	1.99 (1.67-2.31)	2.48 (2.09-2.86)	.001
Blood HbA1c, % (95% CI)	9.58 (9.27-9.90)	10.37 (10.00-10.75)	12.00 (11.48-12.53)	<.001
Blood HbA1c, mmol/mol (95% CI)	81.2 (77.8-84.7)	89.9 (85.8-93.9)	107.7 (101.9-113.4)	<.001
DKA (pH < 7.30), % (95% CI)	13.0 (8.1-17.8)	14.0 (9.2-18.2)	28.6 (22.2-35.0)	<.001
Severe DKA (pH < 7.10), % (95% CI)	2.2 (0.1-4.3)	1.5 (0-3.1)	6.9 (3.3-10.2)	.008

Abbreviations: CI, confidence interval; DKA, diabetic ketoacidosis.

Data are expressed as frequencies and means (95% CI). Distributions were analyzed by cross-tabulation and χ^2 statistics. One-way analysis of variance was used for variables with normal distributions and the Kruskal-Wallis test for unequally distributed variables. *P* value of <.05 was considered to indicate statistical significance and presents the differences between the 3 age groups.

7.5 years in the current study cohort vs 8.3 years in children diagnosed in 1982 to 2001.[4] Low frequencies of DKA at diagnosis (12.8%-16%) have also been published from Sweden.[26,27] In many other countries the frequency of DKA at diagnosis vary a lot, and very high frequencies up to 80% at diagnosis have been reported.[2] T1D is a well-known disease in Finland among both the public and the healthcare staff, because the incidence of T1D is the highest in the world. The awareness of the disease and its symptoms leads likely to earlier diagnosis. This may also limit generalization of the present results to other countries. We did not observe further decline in the overall frequency of DKA, when comparing the 3 time periods within the latest 13-year period (2002-2014). It is possible that the frequency of DKA at the time of diagnosis has achieved such a low level among the Finnish children that it does not decrease further without extra efforts.

The most positive result was the remarkably decreased DKA frequency seen in the very young children under the age of 2 years at diagnosis. In the Finnish nationwide study in 1986 to 1989, the frequency of DKA among such children was 53.3%,[9] and in our earlier analysis the frequency in this age group was 50.0% in 1982 to 1991 and 39.1% in 1992 to 2001 in Oulu University Hospital.[4] In the whole of Finland in 2002 to 2005, the frequency of DKA in the youngest children at diagnosis was still 30.1%.[28] In the current study, the frequency of DKA in the children younger than 2 years of age was clearly lower, 17.5%, and did not differ from the DKA frequency in older children. The finding is exceptional because high frequencies of DKA (53%-69%) are still reported in this very young age group.[6,7] Our observation shows that the ongoing prospective studies have a significant effect on the awareness among the families and healthcare personnel of this potentially life-threatening disease.

When comparing the frequency of DKA at diagnosis in the different age groups we found the frequency to be the lowest (13%) among children under 5 years age at diagnosis. An appreciable change in DKA frequency has occurred in this age group in Finland. In the Finnish nationwide study conducted in 1986 to 1989, the frequency of DKA in this age group was 22.1% at diagnosis[9] and in our earlier study, it was 32.1% in 1982 to 1991 and 17.7% in 1992 to 2001 in Oulu University Hospital.[4] According to the data from the Finnish Pediatric Diabetes Register during 2002 to 2005, the frequency of DKA in this age group was 16.5%.[28] The current low frequency of DKA in children diagnosed under 5 years of age in the Finnish population is similar to that observed in the international TEDDY study (13.1%).[17] Again, our finding may be the result of the increasing awareness of T1D in families with young children because of the ongoing longitudinal diabetes studies in our country. It is also noteworthy that in many developed countries the frequency of DKA is still inversely associated with age at diagnosis.[7,29,30]

The most severe disquietude concerns the high frequency of DKA (28.6%) in children aged 10 to 14 years. In the Finnish Pediatric Diabetes Register the frequency of DKA in this age group was 26.2% at clinical diagnosis.[28] It appears that unfortunately the frequency of DKA is not decreasing among teenagers in Finland. The underlying reasons are not apparent, and many factors may have an impact. During recent years the school healthcare has changed considerably, and the children cannot meet the school health nurse as often as earlier. Many families have been broken up, and the children may live in more than 1 family. The parents may not oversee their adolescents as carefully as earlier, because the teenagers often take care of themselves quite well. In addition, the adolescents may have difficulties to speak with their parents or other adults about their personal health problems. In the future, it would probably be worthwhile to offer diabetes information to adolescents for instance at schools to prevent DKA in this age group.

A limitation of the study is the lack of data on the socioeconomic status of the children and their families preventing analysis of the possible effect of this factor on DKA. However, the parents of the children participating in the prospective follow-up studies may be more conscious and active than the parents not participating. The strength of this study is the fact that nearly all children are born in public hospitals in Finland, and all children diagnosed with T1D are treated in these hospitals. Thus the families in this study represent the general population.

In conclusion, participation in the cord blood screening to detect increased HLA-conferred risk for T1D without any follow up did not have any effect on the frequency of DKA at diagnosis of T1D. Instead, children who had increased genetic susceptibility for T1D and participated in prospective follow-up studies had very infrequently DKA at diagnosis. Overall, during 2002 to 2014 the frequency of DKA at diagnosis of T1D was low among children aged below 10 years, and particularly in those under 2 years in Finland in the region where prospective birth cohort studies aimed at prediction and prevention of T1D are ongoing. In the future, more attention should be paid to adolescents to make earlier diagnosis of T1D and prevent DKA at disease presentation.

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Conflict of interest

The authors declare no potential conflict of interests.

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