Ketoacidosis in Newly Diagnosed Type 1 Diabetes in Children and Adolescents in Israel: Prevalence and Risk Factors

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ABSTRACT: **Background:** Diabetic ketoacidosis (DKA) as the first presentation of type 1 diabetes mellitus (T1DM) is a serious complication that is preventable.

Objectives: To identify risk factors for DKA at presentation of T1DM to delineate high-risk Israeli populations that could benefit from preventative measures.

Methods: Data for this multicenter retrospective study were collected from the medical files of three pediatric diabetes centers representing three districts in Israel. Inclusion criteria were diagnosis of T1DM, age at diagnosis ≤ 17 years, permanent residency in Israel, and documentation of the presence or absence of DKA at presentation.

Results: The study population included 607 patients of whom 438 met the inclusion criteria. The mean age at diagnosis was 9.1 ± 4.5 years. DKA was present at diagnosis in 156/438 patients (35.6%). The incidence of DKA was different among the three diabetes centers (P = 0.04). The DKA group was significantly younger than the non-DKA group (8.4 ± 4.5 vs. 9.5 ± 4.4, respectively, P = 0.008). DKA was significantly associated with maternal origin (Ashkenazi Jewish origin [lower] vs. non-Ashkenazi, P = 0.04) and with paternal education level (academic [lower] vs. non-academic education, P = 0.04). Stepwise logistic regression showed that maternal Ashkenazi Jewish origin has a protective effect on DKA (odds ratio [OR] 0.4, 95% confidence interval [95%CI] 0.21–0.74, P = 0.004) and that younger age is an independent risk factor (OR 1.06, 95%CI 1.01–1.1, P = 0.02).

Conclusions: A diabetes educational program targeting high-risk population groups may reduce the prevalence of DKA nationwide.

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KEY WORDS: type 1 diabetes mellitus (T1DM), diabetic ketoacidosis (DKA), risk factors, demographic variables

Diabetic ketoacidosis (DKA) is the major cause of mortality in children with type 1 diabetes mellitus (T1DM) [1]. Mortality from DKA is most frequently secondary to brain edema [2]. The incidence of T1DM has been steadily increasing in the western world [3], including Israel [4]. There is a wide geographic variation in the frequency of DKA, with the rate of DKA in newly diagnosed T1DM patients inversely correlated with its incidence [5]. It follows, therefore, that there would be a decrease in the DKA rate with an increase in the incidence of T1DM. While this is true in general, it is not the case among specific ethnic groups [4,6,7] or in specific geographic areas [7]. DKA at presentation of T1DM is more common in infants and toddlers (0–4 years of age), in families with low parental education levels, and in families of low socioeconomic status [7-9].

DKA at presentation of T1DM carries a high risk of complications, and its prevention should be a major goal of community health planning. An increased awareness of symptoms of new-onset diabetes in the general population and the primary care medical caregivers may enable earlier diagnosis and prevention of DKA, as has been shown by Vanelli et al [10]. However, implementation of such a widespread educational program is very costly, making it necessary to define groups at risk for DKA and focus these efforts on high-risk populations.

In the current study, we aimed to assess the prevalence of DKA in different regions of the country and to define the risk factors for DKA at presentation of T1DM in the Israeli population.

PATIENTS AND METHODS

STUDY POPULATION

Children aged ≤ 17 years at diagnosis of T1DM and whose diagnosis was established between January 1, 1990 to August 31, 2012 were enrolled in this study. T1DM was established based on the presence of pancreatic autoantibodies. Additional

*The first and second authors contributed equally to this study

criteria included permanent residency in Israel and documentation of the DKA status at presentation. DKA was defined as hyperglycemia above 200 mg/dl, pH below 7.30, bicarbonate less than 15 mEq/L, and the presence of ketonuria.

The data were collected from the medical files. The study was retrospective and included three pediatric diabetes centers in three different districts of Israel: Dana-Dwek Children's Hospital in Tel Aviv (central), Assaf Harofeh Medical Center in Zerifin (south-central), and Emek Medical Center in Afula (northeastern). The study was approved by the institutional review board at each participating center.

The extracted data included age at presentation, gender, ethnic origin, presence/absence of DKA at presentation, area of residence, first-degree relatives with T1DM, level of parental education, number of siblings, and co-morbidities. The subject's ethnic origin was categorized as follows: Ashkenazi Jewish, Sephardic Jewish, Ethiopian Jewish, Former Soviet Union Jewish, and Israeli Arab. The level of parental education was evaluated based on years of education and classified as academic (> 12 years of education) or non-academic (≤ 12 years of education).

STATISTICAL ANALYSIS

The statistical analyses of the results were conducted using the BMDP program [11]. Descriptive statistics are presented as mean ± standard deviation for continuous variables and as frequencies for categorical variables. Discrete variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. Comparison between continuous variables was performed using one-way analysis of variance (ANOVA). Stepwise logistic regression was applied to determine independent risk factors for DKA at presentation. Significance was set at $P = 0.05$.

RESULTS

Our study comprised 607 patients, of whom 438 met the inclusion criteria (114 from Dana-Dwek Children's Hospital, 104 from Assaf Harofeh Medical Center, and 220 from Emek Medical Center). The 169 excluded patients were above 18 years of age (n=15), not permanent residents in Israel (n=24), non-T1DM (maturity-onset diabetes of the young [MODY], Type 2 DM, or neonatal diabetes, n=115), or had missing data on DKA at presentation (n=15).

At presentation, 106 patients (35.6%) had DKA. The prevalence of DKA was 26% in Dana-Dwek Children's hospital, 41% at Assaf Harofeh Medical Center, and 38% at Emek Medical Center ($P = 0.04$).

The mean age at diagnosis of T1DM was 9.1 ± 4.5 years for the entire cohort. It was 8.4 ± 4.5 years for the DKA group compared to 9.5 ± 4.4 for the non-DKA group ($P = 0.008$) [Table 1].

Table 1. Demographic characteristics at presentation in DKA and non-DKA groups

	Overall	DKA	Non-DKA	*P*
Number	438	156 (36%)	282 (64%)	
Age (years) (standard deviation)	9.1 (4.5)	8.4 (4.5)	9.5 (4.4)	0.008
Gender				0.4
Female	245 (56%)	91 (37%)	154 (63%)	
Male	193 (44%)	65 (34%)	128 (66%)	
Maternal ethnicity				0.04
Ashkenazi Jewish	72 (17%)	16 (22%)	56 (78%)	
Sephardic Jewish	123 (29%)	45 (37%)	78 (63%)	
New immigrant*	65 (15%)	31 (48%)	34 (52%)	
Non-Jewish**	164 (39%)	62 (38%)	102 (62%)	
Paternal ethnicity				0.13
Ashkenazi Jewish	81 (19%)	19 (24%)	62 (76%)	
Sephardic Jewish	123 (29%)	48 (39%)	75 (61%)	
New immigrant*	63 (15%)	26 (41%)	37 (59%)	
Non-Jewish**	160 (37%)	60 (37%)	100 (63%)	
Paternal education				0.04
Academic	135 (33%)	39 (29%)	96 (71%)	
Non-academic	274 (67%)	109 (40%)	165 (60%)	
Maternal education				0.07
Academic	155 (38%)	48 (31%)	107 (69%)	
Non-academic	256 (62%)	102 (40%)	154 (60%)	
Diabetes center				0.04
Dana-Dwek Children's Hospital	114 (26%)	30 (26%)	84 (74%)	
Assaf Harofeh Medical Center	104 (24%)	43 (41%)	61 (59%)	
Emek Medical Center	220 (50%)	83 (38%)	137 (62%)	
Area of living				0.8
Urban	292 (67%)	103 (35%)	189 (65%)	
Rural	146 (23%)	53 (36%)	93 (64%)	
Co-morbidities				0.18
Without co-morbidities	317 (72%)	166 (74%)	201 (71%)	
With co-morbidities	121 (28%)	40 (26%)	81 (29%)	
First-degree relative with T1DM				0.18
No relative with T1DM	240 (74%)	98 (41%)	142 (59%)	
Relative with T1DM	83 (26%)	27 (32%)	56 (68%)	

DKA = diabetic ketoacidosis, T1DM = type 1 diabetes mellitus

*Ethiopian Jewish and Former Soviet Union Jewish

**Israeli Arabs

The prevalence of DKA was significantly associated with maternal origin (lower in Ashkenazi Jewish origin vs. non-Ashkenazi origin, $P = 0.04$). DKA at presentation was significantly associated with paternal education level (29% for academic vs. 40% non-academic, $P = 0.04$), and tended to be less associated with maternal education level (31% vs. 40%, respectively, $P = 0.07$) [Table 1].

The incidence of DKA at presentation among children with a first-degree relative with T1DM was lower compared to children without a family history, but the difference did not reach a level of significance (32% vs. 41%, respectively, $P = 0.18$). Gender, ethnicity, co-morbidities, and rural versus urban areas had no effect on the prevalence of DKA at presentation. A stepwise logistic regression model showed that maternal Ashkenazi Jewish origin appeared to have a protective effect on DKA at presentation, and that younger age appeared to be an independent risk factor [Table 2].

Table 2. Results of stepwise logistic regression

Step	Variable	Odds ratio	95% confidence interval	*P*
1	Maternal ethnicity	0.40	0.21–0.74	0.004
2	Age	0.94*	0.90–0.99	0.02

*for each additional year of age

DISCUSSION

We found that the overall prevalence of DKA at presentation of T1DM among Israeli children is relatively high (35.6%) compared to the prevalence in other developed countries [5,8,12]. The parameters that increased the risk for DKA at presentation included younger age, low socioeconomic level, low paternal education, and maternal origins.

The annual incidence of T1DM in Israel is 11.4 per 100,000 children aged 0–17 years [4]. This is lower than the incidence in the European population (up to 36.6 per 100,000 children) [13] and in the United States (24 per 100,000 children) [14]. The prevalence of DKA at presentation in our cohort is similar to previous reports from Israel [4,15,16]. The relatively high prevalence of DKA at presentation compared to other developed countries may be explained by the lower prevalence of T1DM in Israel and consequently a lower level of awareness to the early symptoms of T1DM on the part of the public and the primary care physicians.

Our finding that younger children have a higher prevalence of DKA at presentation is in agreement with previous reports [17,18], attributing that finding to a more aggressive disease due to a fast decline of β-cell function [19], which is further worsened by the higher incidence of inter-current infection precipitating acidosis [20], higher levels of dehydration, and the reduced ability of metabolic compensation in younger aged patients [20]. The higher rate of DKA may also be related to a delay in the diagnosis of T1DM due to unrecognized typical symptoms, such as polyuria and nocturia in a still not toilet-trained infant, and the high rate of inter-current illness that may have masked the symptoms of diabetes. The incidence of DKA at presentation among children with a first-degree relative with T1DM was lower compared to children without a family history, but unlike previous studies from Israel [21,22], the difference did not reach a level of significance. This might be explained by differences in the study populations.

We found that maternal Ashkenazi Jewish origin and parental academic education apparently had a protective effect on the presence of DKA. The differences in the incidence of DKA between diabetes centers may be related to the socioeconomic status of the population in each district [23], as noted by others [6,15,22,24].

To the best of our knowledge, this multicenter study is the first to show differences in the incidence of DKA between diabetes centers, reflecting differences between different regions in Israel.

The limitations of the study are its retrospective nature and lack of data on the marital status of the parents, their religious affiliation, and their household income.

The implementation of an educational program focusing on high-risk populations may potentially reduce the rate of DKA [10,25] as well as the morbidity and mortality that are associated with DKA in new-onset T1DM children. This could be provided by lectures conducted by teams of diabetologists, diabetes nurse educators, medical students, and parents of children with T1DM or young individuals with T1DM themselves to be held in schools and communicated via the media, as well as being part of courses attended by teachers, nurses, and primary physicians. In addition, posters displaying the presenting symptoms of T1DM could be distributed in local newspapers, schools, primary care clinics, and well-baby clinics.

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Capsule

Sustained T follicular helper cell response is essential for control of chronic viral infection

During chronic viral infections, both CD8 and CD4 T cell responses are functionally compromised. Alongside exhaustion of CD8 T cells during chronic viral infections, it has also been documented that the CD4 T cells have an increased propensity to differentiate toward CXCR5+ T follicular helper cell (T_{FH}) lineage. Whether these T_{FH} cells contribute to the immune response for chronic viral infection has remained unclear. Using chronic lymphocytic choriomeningitis virus (LCMV) infection in conjunction with an in vivo system where T_{FH} cells can be conditionally ablated, **Greczmiel** and colleagues established that these T_{FH} cells do in fact play an important protective function. Specifically, the authors have demonstrated that these T_{FH} cells are essential for the late emergence of neutralizing LCMV-specific antibodies that keep viral titers in check and ultimately allow mice to clear the virus. By supporting the generation of neutralizing antibodies, the authors showed that sustained activity of T_{FH} cells promotes control of the chronic infection in face of exhausted CD8 T cell responses.

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Capsule

Thyroid hormone inhibits lung fibrosis in mice by improving epithelial mitochondrial function

Thyroid hormone (TH) is critical for the maintenance of cellular homeostasis during stress responses, but its role in lung fibrosis is unknown. **Yu** et al. found that the activity and expression of iodothyronine deiodinase 2 (DIO2), an enzyme that activates TH, were higher in lungs from patients with idiopathic pulmonary fibrosis than in control individuals, and were correlated with disease severity. The authors also found that *Dio2*-knockout mice exhibited enhanced bleomycin-induced lung fibrosis. Aerosolized TH delivery increased survival and resolved fibrosis in two models of pulmonary fibrosis in mice (intratracheal bleomycin and inducible TGF-β1). Sobetirome, a TH mimetic, also blunted bleomycin-induced lung fibrosis. After bleomycin-induced injury, TH promoted mitochondrial biogenesis, improved mitochondrial bioenergetics and attenuated mitochondria-regulated apoptosis in alveolar epithelial cells both in vivo and in vitro. TH did not blunt fibrosis in *Ppargc1a*- or *Pink1*-knockout mice, suggesting dependence on these pathways. The authors concluded that the antifibrotic properties of TH are associated with protection of alveolar epithelial cells and restoration of mitochondrial function and that TH may thus represent a potential therapy for pulmonary fibrosis.

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