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Diabetic ketoacidosis (DKA) at diagnosis among youth with type 1 and type 2 diabetes: results from SEARCH (US) and YDR (India) registries

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Abstract

Background: There is significant global variation in the prevalence of DKA at diagnosis among youth with T1D. However, data for youth with T2D are limited, even in developed countries. We compared the prevalence of DKA at diagnosis among individuals with T1D and T2D from the SEARCH for Diabetes in Youth (SEARCH) and the Registry of people with diabetes in India with young age at onset (YDR) registries.

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Author contributions: N.T, D.D, V.M, R.F.H and E.J.M.-D conceptualized the study and oversaw the data harmonization. T.C.O, M.G.K, C.W.H, S.P.I., A.A and P.P harmonized and transformed data into the common data model (OMOP). S.P.I., C.W.H and T.C.O conducted data analysis. P.P and N.T prepared the first draft of the manuscript and provided oversight for study analyses. S.V.M contributed to data collection. All authors reviewed and edited the manuscript and contributed to discussion. All authors have read and approved the final manuscript.

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Methods: We harmonized the SEARCH and YDR data sets to the structure and terminology in the OMOP Common Data Model (v5). Data used in the analysis were from youth with T1D and T2D diagnosed before 20 years and newly diagnosed between 2006 and 2012 in YDR and between 2009 and 2012 in SEARCH.

Results: There were 5,366 U.S. youth (4,078 with T1D, 1,288 with T2D) and 2335 Indian youth (2108 with T1D, 227 with T2D). More than one third of T1D youth enrolled in SEARCH had DKA at diagnosis which was significantly higher than in YDR (35.3% vs 28.7%, p<0.0001). The burden of DKA in youth with T1D was significantly higher among younger age groups; this relationship was similar across registries (p=0.4). The prevalence of DKA among T2D in SEARCH and YDR were 5.5% and 6.6% respectively (p=0.4).

Conclusions: There is significant burden of DKA at diagnosis with T1D among youth from U.S. and India, especially among the younger age groups. The reasons for this high prevalence are largely unknown but are critical to developing interventions to prevent DKA at diagnosis.

Keywords

Diabetic ketoacidois; Type 1 diabetes; Type 2 diabetes; SEARCH for Diabetes in Youth registry; YDR registry

Introduction

An absolute or relative lack of insulin and the consequent unrestricted flux of carbohydrate, amino acid and lipid nutrients to the blood results in diabetic ketoacidosis (DKA) in individuals with diabetes mellitus[1]. DKA is characterized by hyperglycemia, ketonemia and metabolic acidosis. DKA is a potentially life-threatening acute complication and a common presentation of type 1 diabetes (T1D) at diagnosis. Children and adolescents with type 2 diabetes (T2D) may present with some degree of metabolic de-compensation at diagnosis including ketosis, symptomatic hyperglycemia, and DKA[2].

DKA and subsequent cerebral edema continues to be a leading cause of morbidity and mortality among children and adolescents with diabetes[3,4]. One in four survivors of DKA with cerebral edema also suffer from residual morbidity[5]. Previous reports suggest that DKA at diagnosis is associated with adverse neuro-cognitive outcomes and is an independent predictor of poor longer-term glycemic control among individuals with T1D[6–8].

Recent studies suggests that DKA at diagnosis is more common in populations with lower socioeconomic status and a lower background prevalence of T1D[9]. There are limited data comparing the prevalence and trends in prevalence of DKA among children and adolescents with either T1D or T2D, even in countries with high prevalence of youth onset diabetes. An earlier analysis from the SEARCH registry reported a high but stable trend in the prevalence of DKA among T1D and a 10% yearly decline in DKA among United States (U.S.) youth with T2D at diagnosis[10]. However, such data are limited in countries like India, where the absolute number of individuals with youth onset diabetes is quite high. Exploring similarities or variations in DKA burden at diagnosis between countries could provide insights in to developing context specific preventive strategies to reduce mortality and morbidity associated with DKA at diagnosis of diabetes.

Methods

Data for this analysis were obtained from the collaborative partnership between SEARCH for Diabetes in Youth (SEARCH) registry in the U.S. and the Registry of People with Diabetes with Youth Age at Onset (YDR) in India.

SEARCH for Diabetes in Youth

The SEARCH registry is a multi-ethnic, population-based registry with five sites across the U.S. ascertaining physician-diagnosed non-gestational incident diabetes cases among individuals aged 19 years or younger. Detailed information about SEARCH is published elsewhere[11,12]. Each site conducts active surveillance under the Health Insurance Portability and Accountability Act (HIPAA) waivers of consent using networks of endocrinologists, healthcare providers, hospitals and community health centers, and clinical and administrative data systems along with electronic medical records. Cases are confirmed as valid after review of medical records or by the referring physician. All registered participants are asked to complete an Initial Participant Survey (IPS) and medical record abstractions are conducted within 6 months from diagnosis for all registered cases to validate the diagnosis of diabetes and obtain information about DKA. DKA at diagnosis with diabetes at was considered to be present if, in the context of hyperglycemia, any of the following were present: blood bicarbonate level <15 mmol/L, pH <7.25 (venous) or <7.30 (arterial or capillary), and/or a DKA diagnosis mentioned in the medical records[10].

Registry of People with Diabetes with Youth Age at Onset (YDR)

The YDR registry is an observational multicenter clinic-based registry enlisting all cases of physician-diagnosed diabetes, diagnosed at the age of 25 years or younger, who were registered at a designated registry reporting center on or after January 1, 2000, residing within assigned geographical areas. More detailed information about YDR is published elsewhere[11,12]. Individuals are classified into various diabetes categories based on the assessment of the principal investigator at the reporting center using symptom-based clinical criteria agreed upon by the registry expert group prior to initiation of data collection in 2006. YDR data collection is coordinated by the ICMR through regional collaborating centers and their interacting reporting centers. All individuals have a proforma (registration and clinical extract) completed by the participant and physician to obtain information on socio-demographics, clinical profile, anthropometrics and laboratory measurements of the individual. Data from the period 2000–2006 were collected retrospectively in a structured format from medical records; while data from 2006–2012 were collected prospectively and completed by both the participant and physician at the time of registration, which is referred to here as the baseline visit. There are eight regional collaborating centers across India who provide cases to YDR. For this project, data from three of the eight regional collaborating centers (one in Chennai (Madras Diabetes Research Foundation) and two in New Delhi (All India Institute of Medical Sciences (AIIMS) and the University College of Medical Sciences, Delhi) were used. DKA information was obtained from self-report or documented DKA from medical records at the time of registration[10]. Since the average duration of diabetes at registration was 6.2 months for T1D and 7.0 months for T2D, DKA data was obtained within approximately 6 months from diagnosis.

Selected data from SEARCH and YDR were harmonized to the structure and terminology in the Observational Medical Outcomes Partnership (OMOP) Common Data Model (v5). We assigned common concept IDs for DKA and other variables in both registries. Uniform programs were run on the databases to generate the result tables. The analysis was conducted at each site without the physical transfer of data between sites. Hence, we were restricted from performing any multivariable adjusted analysis across the data sets. Additional details of data harmonization are provided in a previous article by Hockett et al. within this special edition.

Statistical Analysis

Data used in the analyses were from youth with T1D and T2D, aged less than 20 years and newly diagnosed between 2006 and 2012 in YDR and between 2009 and 2012 in SEARCH. The period prevalence of DKA at diagnosis (per 100 youth with type 1 or type 2 diabetes) was calculated as the proportion presenting with DKA at the time of diagnosis. The prevalence was also calculated by age group and gender. We compared the prevalence of DKA at diagnosis across registries using chi-square test. The linear trend in prevalence of DKA in both the registries was tested using chi square test for linear trend. All of the tests were 2-sided and a p-value of 0.05 was considered statistically significant.

Results

Characteristics of individuals with diabetes

Data from 5,366 SEARCH (4,078 with T1D, 1,288 with T2D) and 2,335 YDR (2,108 with T1D, 227 with T2D) youth were analyzed. The demographic characteristics of the study population in both SEARCH and YDR according to diabetes type are shown in Table 1. Both T1D and T2D individuals from YDR were older at diagnosis compared to SEARCH. The proportion of females with T2D was significantly higher in SEARCH. However, there was no difference in gender distribution between the registries for individuals with T1D.

Period Prevalence of DKA in SEARCH and YDR, by Diabetes Type

The prevalence of DKA at diagnosis by diabetes type and demographic characteristics are shown in the Table 2. More than one third of T1D youth enrolled in SEARCH had DKA at diagnosis which was significantly higher than YDR (overall 35.3% vs 28.7%, $p<0.0001$), in each age-group and among both boys and girls. The burden of DKA among individuals with T1D was significantly higher among younger age groups in both SEARCH and YDR and this relationship was similar across registries ($p=0.4$). For T2D, the numbers were much smaller; however, there were no statistically significant differences in the prevalence of DKA between SEARCH and YDR overall (5.5% vs 6.6%, $p=0.4$), by age-group or gender. None of the individuals with T2D diagnosed below 10 years had history of DKA at diagnosis.

Temporal Trends in the Prevalence of DKA in SEARCH and YDR, by Diabetes Type

In SEARCH, the prevalence of DKA significantly increased from 2009 to 2012 ($p<0.001$). In YDR the DKA prevalence was relatively stable at high levels all the years (2006 to 2012) with no statistically significant linear trend (Figure 1).

Discussion

Our study revealed a significant burden of DKA at diagnosis among individuals with youth-onset T1D from both India and the U.S., especially among those in the younger age groups. The burden of DKA at diagnosis among individuals with T2D was similar in both the registries. The prevalence of DKA at diagnosis with T1D increased over time in SEARCH but remained relatively stable (at high levels) in YDR.

Our current prevalence estimates of DKA at diagnosis with T1D for SEARCH are higher than the estimates from other U.S. studies and the earlier reports from SEARCH itself[10]. There are no such data from India to compare the findings from YDR reported here. For T2D, the current study estimates that 5.5% of individuals with youth-onset T2D in SEARCH present in DKA at diagnosis, which is lower than earlier published estimates from SEARCH (11.7% in 2002–03 to 5.7% in 2008–10)[10]. In both SEARCH and YDR the prevalence of DKA among individuals with T2D was more pronounced in the 10–14 age group compared to youth in 15–19 age group. This is consistent with earlier reports from SEARCH[10].

DKA prevalence estimates among individuals with T1D for both SEARCH and YDR reported in the current analysis, are much higher than those from UK, Canada and Finland, reported a decade ago[13,14]. The EURODIAB project (2001) reported DKA prevalence at diagnosis ranging from 11% to 67% in 11 centers across Europe[15]. A recent systematic review summarizing data from 65 studies comprising over 29,000 children in 31 countries concluded that the frequency of DKA at diagnosis ranged from 12.8% to 80%, with highest frequencies in the United Arab Emirates (80%), Saudi Arabia (59%) and Romania (67%), and the lowest in Sweden(14%) and Canada (19 %)[9]. Further, the prevalence of DKA at diagnosis was inversely associated with gross domestic product (GDP) of the countries[9]. There is large heterogeneity in the published literature on DKA at onset/diagnosis, in terms of sample size, period of study, design and method of case identification. Hence, comparisons of our estimate with other studies should be done with caution[16].

The prevalence of DKA at diagnosis seems to be inversely associated with the background prevalence of T1D in the countries[9]. Given the lower incidence of T1D in India, we expected a higher prevalence of DKA among the Indian population compared to U.S.. However, the results were contrary to our expectations, with higher prevalence of DKA in all the age groups in SEARCH compared to YDR. This could be due to several reasons with the distinct possibility of recall or recording bias and underreporting of DKA events in YDR. A principal reason for this could be the difference in methods used to ascertain and confirm the diagnosis of DKA in the two registries. Given the process flow in YDR, the information on DKA was captured from self-report or hospitalization records at the time of registration at a reporting center. Further, there could be a time lag between the date of diagnosis and registration of participants at the reporting centers. In contrast, SEARCH not only had direct access to medical records but was able to confirm the diagnosis of DKA through lab data including serum bicarbonate levels. Since YDR is a clinic-based registry, there could also be referral bias with likely impact on the estimated frequency of DKA.

There is a global variation in mortality associated with DKA at diagnosis among children and adolescents with diabetes. In developed countries, the overall mortality varies from 0.15% to 0.35% while in countries like India and Bangladesh, clinic-based studies report rates ranging from 3.4% to 13.4%[17]. Cerebral edema, sepsis and renal failure are the major precipitating factors of DKA-related mortality in the developing world[17]. These differential mortality rates may explain the differences seen in the estimated prevalence of DKA across countries. Therefore, the lower prevalence of DKA at diagnosis reported by YDR compared to SEARCH likely reflects a worrisome higher DKA-associated mortality, before T1D is diagnosed, which we were unfortunately unable to study. More efforts are needed to quantify the population level mortality associated with DKA at diabetes diagnosis in India.

The high burden of DKA among younger age groups in both the registries is concerning. Delayed diagnosis, relatively aggressive metabolic deterioration and difficulty in early diagnosis of symptoms in toddlers with T1D make them vulnerable to develop DKA[15]. Increasing parental awareness and improving health system preparedness to closely monitor children with genetic risk of T1D have shown promising results in the past[18]. However, it remains unclear whether the high propensity for DKA in younger children is a consequence of a particularly aggressive form of diabetes.

Data on temporal changes in DKA prevalence vary between reports from different parts of the globe with some studies reporting a declining trend[14,19], while others finding no change[13,20]. Our analysis showed a statistically significant upward trend in the prevalence of DKA among U.S. children and adolescents with T1D after 2009–2010. This is different from earlier reports from SEARCH that showed a high but stable trend between 2002 and 2009[10]. The reasons for this increasing trend in DKA at diagnosis of T1D among SEARCH youth in recent years need to be further explored. In YDR, the burden of DKA remained relatively stable during the study period ($p=0.1$); however, this should be interpreted with caution given the limitations mentioned above. Nevertheless, in both countries, the burden of DKA at diagnosis among individuals with T1D remains unacceptably high.

This report is the one of the first studies to systematically harmonize and compare data on DKA at diagnosis from Asian Indian and U.S. populations. To the best of our knowledge, this is the first study to compare DKA at diagnosis among youth with T2D between U.S. and Indian populations. For both registries, data were collected independent of the present study and over a similar time period. However, the study has several important limitations. As mentioned earlier, there were significant differences in the method of DKA ascertainment between the registries. Moreover, we were unable to study the effect of a potentially high burden of DKA-associated mortality before diagnosis of T1D in India. The sample sizes for T2D in both registries were small and not adequately powered for trend analyses. Further, SEARCH did not have DKA information for years 2006–2008. We were only able to conduct a descriptive analysis of the harmonized data, as there was no physical transfer of data between the registries. However, this comparison is an important first step in our understanding of DKA burden at diagnosis with diabetes in youth, which should lead to further research on potential explanations for observed differences.

Our data show a significant burden of DKA at diagnosis among a racially/ethnically diverse U.S. and an Asian Indian cohort of youth with T1D, especially among the younger age groups. These findings have serious public health implications as the DKA associated hospitalizations and subsequent morbidities dramatically increase the cost of diabetes care. Effective interventions to increase awareness and improve access to health care are required in both countries to prevent DKA at diagnosis among youth onset diabetes.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention and the National Institute of Diabetes and Digestive and Kidney Diseases.

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Abbreviations:

DKA	Diabetic Ketoacidosis
T1D	Type 1 Diabetes Mellitus
T2D	Type 2 Diabetes Mellitus

OMOP	Observational Medical Outcomes Partnership
YDR	Registry of People with Diabetes with Youth Age at Onset
U.S.	United States

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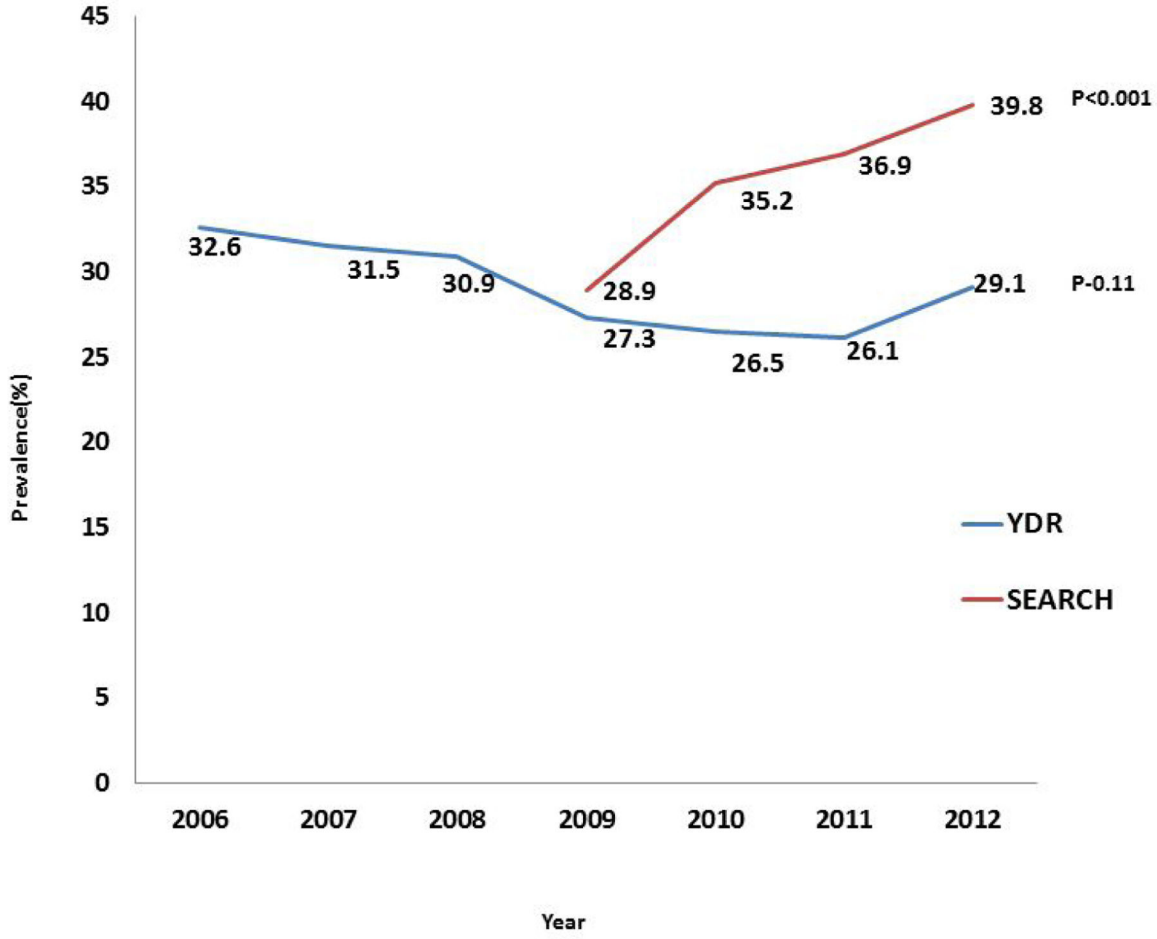

Figure 1:
Trend in DKA prevalence at diagnosis among individuals with T1D in SEARCH (2009–2012) and YDR (2006–2012).

Table 1:

Demographic characteristics of SEARCH (2009–2012) and YDR (2006–2012) youth by diabetes type.

	T1D			T2D		
	SEARCH (2009–2012*) n=4,078	**YDR (2006–2012*) n=2,108**	**p-value**	**SEARCH (2009–2012*) n=1,288**	**YDR (2006–2012*) n=227**	**p-value**
Age at diagnosis, *mean* ± *SD*	10.0 ± 4.5	10.4 ± 5.0	<0.001	14.8 ± 2.8	16.1 ± 2.8	<0.001
Age at diagnosis, *n (%)*						
0–4 yrs	652 (16.0)	332 (15.7)	<0.001	1 (<0.01)	0 (0)	<0.001
5–9 yrs	1,315 (32.2)	646 (30.6)		59 (4.6)	10 (4.4)	
10–14 yrs	1,482 (36.3)	688 (32.6)		595 (46.2)	59 (26.0)	
15–19 yrs	629 (15.4)	442 (20.9)		633 (49.1)	158 (69.6)	
Gender						
Female, n (%)	1,882 (46.1)	993 (47.1)	0.3	829 (64.3)	111 (48.9)	<0.001
Male, n (%)	2,196 (53.9)	1115 (52.9)		459 (35.6)	116 (51.1)	

*year of diagnosis

Table 2.

Prevalence of DKA at diagnosis in SEARCH (2009–2012) and YDR (2006–2012) youth, by diabetes type.

	T1D					T2D				
	SEARCH (2009–2012*)		YDR (2006–2012*)		p-value	SEARCH (2009–2012*)		YDR (2006–2012*)		p-value
	n	%	n	%		n	%	n	%	
Crude Prevalence (per 100)	4,078	35.3	2,108	28.7	<0.0001	1,288	5.5	227	6.6	0.4
Prevalence by age at diagnosis										
0–4 yrs^	652	43.7	332	36.7	<0.0001	-	-	-	-	
5–9 yrs^	1,315	35.2	646	30.0	<0.0001	-	-	-	-	
10–14 yrs	1,482	35.4	688	30.5	<0.0001	595	6.9	59	8.4	0.5
15–19 yrs	629	26.6	442	18.1	<0.0001	633	4.6	158	6.3	0.2
Prevalence by gender										
Female	1,882	35.1	993	28.7	<0.0001	829	4.2	111	7.2	0.2
Male	2,196	35.4	1,115	28.8	<0.0001	459	7.8	116	6.0	0.9

* year of diagnosis

^ None of the individuals with T2D diagnosed below 10 years had history of DKA at diagnosis