Frequency and severity of ketoacidosis at diagnosis among childhood type 1 diabetes in Khartoum state, Sudan

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Abstract

Background: Diabetic ketoacidosis (DKA) is a potentially life threatening acute complication of Type I diabetes mellitus (T1DM). This study aimed to determine the frequency and clinical characteristics of pediatric DKA at diagnosis of new-onset T1DM in Khartoum during 2000- 2017 period.

Methods: The study was retrospective and involved review of medical files of children (<15 years) with T1DM in the city hospitals and diabetes centers.

Results: The overall frequency of DKA among T1DM children at onset of disease diagnosis was 17.6% (173/982). The episodes of DKA increased from 26% in first 6- year period (2000-2005) to 46.3% in the last 6-year period (2011-2012; p<0.001). No significant difference in the frequency of DKA was observed according to gender (p=0.9) and age (p=0.24). Compared to other age groups, the severity of DKA (pH<7.1) was higher in pre-school children (p<0.01). Approximately, 5% of patients were complicated with cerebral edema with a mortality rate of 1.7%.

Conclusion: The DKA frequency at diagnosis of childhood T1DM in Khartoum was lower than previous reports. In addition, the severity of DKA was high among pre-school age children with a relatively high mortality rate when compared to the global rate.

Keywords: Ketoacidosis; mortality; onset; DKA; T1DM; Sudan; Khartoum.

Introduction

Diabetic ketoacidosis (DKA) is a serious complication of type 1 diabetes mellitus (T1DM) that can be life threatening.[1,2] The condition is associated with a considerable morbidity and mortality.[3-5] It is estimated that each year, 65000 children aged less than 15 years develop T1DM each year, among them, 12.8-80% suffer from DKA at time of diagnosis.[7]

According to the literature, DKA is classified as one of the major health problems in sub-Saharan Africa, and this was attributed to the poor healthcare infrastructure, poverty and ignorance.[8] The prevalence of DKA among T1DM children in sub-Saharan Africa is high, ranging between 70-80% due to the lack of facilities and insulin storage.[9] The majority of workers in different health stations in sub-Saharan Africa are not well oriented and trained to

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deal with DKA and its complications that could lead to a severe fatal form of the condition.[8]

The high incidence rate of childhood T1DM in Sudan suggests high DKA episodes[11,13] In a previous study that was conducted in 1994 in Khartoum and included 90 DKA episodes among T1DM children, 24% of cases occurred in newly diagnosed patients.[12] However, the recent prevalence of pediatric DKA in Sudan is still not known.[10,11]. The present study examined DKA in Khartoum city, the capital of Sudan. Khartoum is located at the confluence of the Blue Nile and White Nile that merge to form Nile River. The total population of Khartoum is about 8 million. According to a previous study, the incidence of T1DM in Khartoum among children was about 1/10,000[11]. In Khartoum, T1DM children receive treatment at a variety of health facilities such as primary medical centers, specialized diabetes clinics and hospitals. The aim of the current study was to investigate the frequency and clinical picture of DKA at onset of the diagnosis of childhood T1DM in Khartoum city during the period from 2000 to 2017. The study findings are expected to enhance awareness about DKA amonghealth care providers in Sudan, and the subsequent effective management interventions.

Materials and Methods Study design and subjects

The study is retrospective used records of children at diagnosis of T1DM whom admitted at 31 hospitals/diabetes centers distributed in Khartoum city, Sudan. These include five public hospitals, eight private hospitals, two diabetes centers and sixteen medical centers. Among the involved hospitals, five were tertiary facilities, while the rest were primary facilities. The majority of the DKA cases were managed in the Intensive Care Unit (ICU) that is available in most hospitalsspan style="font-family:'Times New Roman'">. The admission to ICU was according to doctors' recommendations and the severity of the case. DKA data were extracted from January 2000 until December 2017 including age, gender and laboratory data. The study period was divided into three equal intervals of 6 years each based to three campaign programs aimed to improve intervention of emergency medicine. T1DM was confirmed using the criteria of the World Health Organization. In addition, DKA was diagnosed according to the international guidelines consensuses that use the following criteria: blood pH < 7.3 and/or bicarbonate

<15 mEq/ accompanied with hyperglycemia and positive ketonuria. Cases with DKA were categorized into severe (pH<7.1), moderate (pH: 7.1-7.2) and mild (pH >7.2).[14] Inclusion criteria were: children with T1DM at onset of diagnosis aged ≤ 15 years old. Exclusion criteria were: patients with DKA due to reasons other than T1DM (such as starvation) and patients with incomplete data. A total of 153 cases were excluded. Research Ethics Committee of Omdurman Islamic University, Khartoum, Sudan that follows the 1964 Declaration of Helsinki principles approved the study. DKA children were divided into 3 groups according to age of diagnosis: 0 - <5 years, 5 - <10 years, and 10 - 15 years.

Demographics and biochemical parameters
Demographic information (age and sex) and clinical data were collected from patient files. Among collected biochemical parameters include glucose, HbA1c, pH, bicarbonate and potassium that were measured at the emergency unit prior the time of admission to the hospital.

Statistical analysis
The data were analyzed with GraphPad Prism statistical software (version 5, San Diego, CA, USA). For comparison of categorical variables, Pearson's Chi-Squared and Fisher Exact (when n < 5) test were used. The One-way ANOVA was used for three group comparisons. The linear regression test was used to test the trend in DKA frequency over time. The P value < 0.05 was used to indicate significant differences.

Results
The frequency of DKA in TIDM during the study period was 982 (503 female, 51.2%); of these cases 173/982 (17.6%) (93 female, 53.8%) had DKA at time of T1DM diagnosis. The mean age of children who had DKA at diagnosis was 5.9±2.3 years. When the study period was divided into 3 intervals of 6 years each (Table 1), the frequency of DKA at time of T1DM diagnosis was higher (P<0.001) in the last period (2012-2017, 46.3%) than the first period (2000-2005, 26.0%) and second period (2006-2011, 27.7%). In addition, the frequency of incidence/trend of DKA was similar among boys and girls (Table 1, P=0.94). Figure (1) shows the trend in DKA frequency over the study duration. A significant increase in the frequency of DKA with time was observed (r=0.72, P<0.01). Moreover, the frequency of DKA was similar in all age groups (range: 15.7% – 18.3%, P=0.24).

Table 1: Distribution of DK at the time of T1DM diagnosis during the study period (2000- 2017) according to age and gender.

	First period (2000-2005) n =45		Second period (2006-2011) n =48		Third period (2012-2017) n =80		Whole period (2000-2017) n =173		P value (trend)
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	
Total (n=173)	45 (26.0%)	-	48 (27.7%)	-	80 (46.3%)	-	173 (100%)	-	0.01*
Gender									
Boys	21 (46.7%)	42.9-50.4	23 (47.9%)	44.2-51.7	36 (45.0%)	41.3-48.8	80 (46.2%)	42.5-50.0	0.94
Girls	24 (53.3%)	49.6-57.0	25 (52.5%)	49.3-56.9	44 (55.0%)	51.5-58.9	93 (53.8%)	50.1-57.5	0.94
Age									
Group 1 (0-4 years)	13 (28.9%)	25.1-32.5	13 (27.1%)	23.4-30.8	24 (30.0%)	26.4-33.9	50 (28.9%)	25.3-32.6	0.24
Group 2 (5 - 9 year)	26 (57.8%)	54.1-61.6	28 (58.3%)	54.6-62.2	43 (53.75%)	50.2-57.8	97 (56.1%)	52.4-59.7	0.26
Group 3 (10-15 years)	6 (13.3%)	9.7-17.2	7 (14.6%)	10.9-18.5	13 (16.25%)	12.7-20.0	26 (15.0%)	11.3-18.8	0.12

Chi-square was used to calculate p value (Fisher exact test was used when sample size less than 5). *: Significant ($P<0.05$). [a]: significant compared to Group 2 ($P<0.05$). [b]: significant compared to Group 2 ($P<0.01$).
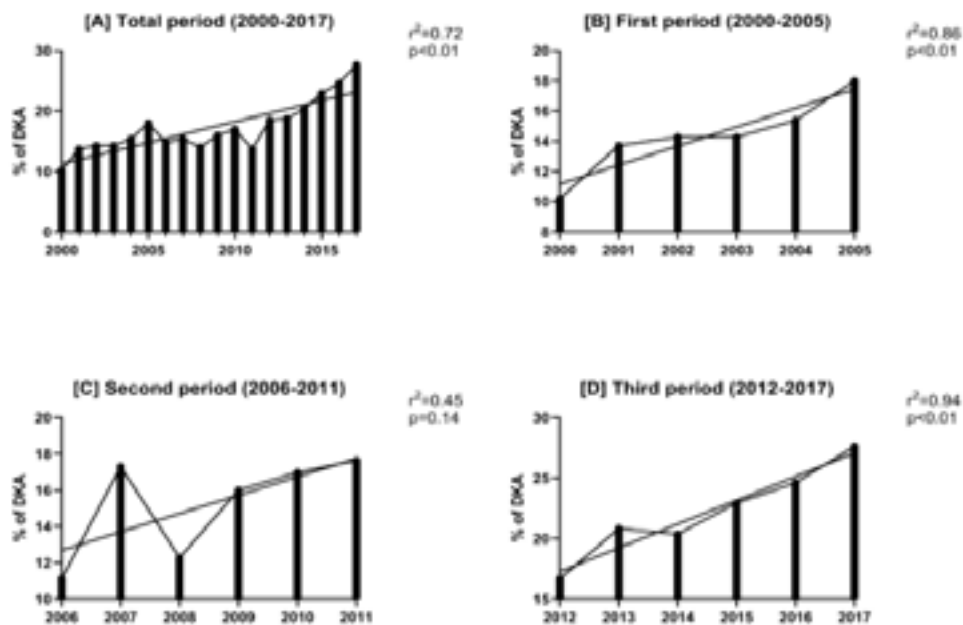

Figure 1. Trend in DKA among children with type 1 diabetes:

[A] Total period (2000-2017)

[B] First period (2000-2005)

[C] Second period (2006-2011)

[D] Third period (2012-2017)

Tertiary care centers have low mortality rate than others, some died, cases did not get reported because of treatment with alternative medicine which is available in Sudan.

The clinical picture of DKA was divided into three types; mild, moderate and severe according to pH values (Table 2). The severity of DKA was lower in age group 2 (5 – <10 years) than other groups (P=0.03). When each period was considered separately, the severity of DKA was higher among the age group 1 of the third period (P<0.001, Table 2).

Table 2: Frequency of DKA at the time of T1DM diagnosis according to severity during the study period (2000-2017).

	First period (2000-2005) n =45		Second period (2006-2011) n =48		Third period (2012-2017) n =80		Whole period (2000-2017) n =173		P value (trend)
	n (%)	95% (CI)	n (%)	95% (CI)	n (%)	95% (CI)	n (%)	95% (CI)	
Mild symptoms (pH>7.2)									
Group 1	4 (8.9%)	5.2-12.7	5 (10.4%)	6.8-14.2	4 (5.0%)	1.3-8.6	13 (7.5%)	3.7-11.0	0.31
Group 2	5 (11.1%)	7.4-14.8	4 (8.3%)	4.6-12.1	8 (10.0%)	6.2-13.5	17 (9.8%)	6.1-13.5	0.86
Group 3	2 (4.4%)	0.8-8.1	3 (6.2%)	2.4-9.9	3 (3.75%)	0.06-7.2	8 (4.6%)	0.9-8.2	0.65
Moderate symptoms (pH= 7.1-7.2)									
Group 1	8 (17.8%)	14.1-21.5	7 (14.6%)	11.0-17.9	11 (13.75%)	10.3-17.4	26 (15.0%)	11.3-18.7	0.65
Group 2	19 (42.2%)	38.6-46	22 (45.8%)	42.1-49.3	34 (42.5%)	38.8-46.2	75 (43.3%)	39.6-47.1	0.83
Group 3	3 (6.7%)	3.0-10.1	3 (6.3%)	2.4-9.9	9 (11.25%)	7.5-14.9	15 (8.7%)	4.9-12.4	0.47
Severe symptoms (pH<7.1)									
Group 1	1 (2.2%)	-1.4-5.8	1 (2.1%)	-1.6-5.7	9 (11.25%)[b]	7.5-14.9	11 (6.4%)[a]	2.6-10.1	0.03*
Group 2	2 (4.4%)	0.8-8.1	2 (4.2%)	0.5-7.8	1 (1.52%)	-2.4-4.9	5 (2.9%)	-0.8-6.4	0.52
Group 3	1 (2.2%)	-1.4-5.8	1 (2.1%)	-1.6-5.7	1 (1.25%)[b]	-2.4-4.9	3 (1.7%)[a]	-0.2-5.4	0.82

Chi-square was used to calculate p value (Fisher exact test was used when sample size less than 5).
*: Significant (P<0.05). [a]: significant compared to Group 2 (P<0.05). [b]: significant compared to Group 2 (P<0.01).

Table 3 shows a comparison of biochemical parameters between the three age groups. The mean level of glucose was found to be higher in group1 (0 – 4 years) than other age groups (P<0.01), whereas HbA1c, pH, bicarbonate and K+ were similar in all age groups (P>0.05, Table 3).

Over the examined periods, eight children had cerebral edema at admission according to the clinical diagnosis supported with radiological evidence. Five children out of the eight were fully recovered without complications, whereas three children passed away.

Table 3: Comparison of biochemical data in different age groups at admission.

	Group 1		Group 2	Group 3
	Mean±SE	95% (CI)	Mean±SE 95% (CI)	Mean±SE 95% (CI)
Glucose (mmol/L)	28.60±0.30*	27.8±29.4	26.4-0.59 24.9-27.9	26.2±0.50 24.9-27.5
HbA1c (%)	12.14±0.38	11.1-13.2	11.8±0.58 10.2-13.4	11.1±0.48 9.7-12.4
pH	7.14±0.02	7.05-7.23	7.20±0.02 7.11-7.29	7.20±0.02 7.09-7.31
Bicarbonate (mmol/L) K$^+$(mmol/L)	14.4±0.3	13.1-15.7	15.3±0.1 14.8-15.7	15.8±0.4 13.7-17.8
	5.2±0.05	4.4-6.0	5.0±0.03 4.2-5.8	5.0±0.03 4.2-5.8

Group1: 0 - <5 years, group2: 5 - <10 years and group3: 10 – 15 years. P value was calculated using ANOVA test. * Significant compared to group 2&3 (p<0.01). SE: standard Error.

Discussion

The current study examined the frequency of DKA among children with T1DM in Khartoum, Sudan over the past 18 years. The overall frequency of DKA at onset of T1DM diagnosis was 17.6%. The episodes of DKA increase with the years. In addition, the severity of DKA was higher in pre-school age children than other age groups.

The reports about DKA frequency in children with T1DM in Sudan are rare. A study by Elamin et al, that examined DKA among children in Sudan between 1977 and 1986 showed a frequency of 81% at the time of T1DM diagnosis.[10] Another study that examined the records of a central hospital in Khartoum in 1994 reported 90 DKA episodes of which, 22 (24%) cases had the condition at diagnosis.[12] In the current study, the overall frequency of DKA in children with T1DM at diagnosis in Khartoum during the study period (2000-2017) was 17.6%. This frequency is slightly lower than that reported in the 1994 study. When compared to other countries, the percentage (17.6%) is comparable with previous studies conducted in Canada (18.6%) and Sweden (16%).[15,16] However, high frequency of DKA among children with T1DM was reported in countries such as Egypt, Serbia, Saudi Arabia, USA, UK and others.[17-24]

The current study showed a trend of increase in the severity of DKA among children with T1DM over the study period with an overall frequency of 12.3%. This frequency is comparable to that reported in Kuwait,

Spain, France, Finland and Italy.[18,25-30] However, relatively higher frequencies were reported in other countries such as Saudi Arabia, UK and others.[19,22,27,28,31,32] Current findings also showed that the severity of DKA in pre-school age children was elevated from 7.6% to 33.3% across the study period. The high frequency of severe DKA among preschool age children is in agreement with previous studies conducted in Saudi Arabia, Serbia and Ethiopia.[21,33-35] Thus, more attention should be given to children with T1DM of this age group to prevent acute complications and severe consequences of the disease.

The study reported a relatively higher frequency of diagnosed DKA cases in the last period than earlier ones. This might be attributed to the improvement in the registration/archivingf DKA cases in the last period. More studies are required to confirm this finding.

About 1.7% of DKA children with T1DM had cerebral edema and were reported died because of the severity of their conditions. Worldwide mortality rate from DKA comprises between 0.3-1% that attributed to cerebral edema.[36] In a previous study from Sudan, a rate of death from children with DKA of about 4% was reported.[37] Thus, the present findings indicate significant improvements in the management of severe DKA cases in Sudan. Alternatively, the number of deaths might be underreported in the current study. This could be due to the fact that the diagnosis of cerebral oedema is very expensive and limited facilities offer MRI and CT scan in Sudan. It is possible that many children with DKA at diagnosis

plausibly die off before the diagnosis was made. However, the reported rate in the current study is twice the mortality rate from DKA reported in developed countries[6] and within the range reported in developing countries.[38] In Sudan, the poor socioeconomic status and low parental awareness about the risk factors of developing DKA in T1DM patients could contribute to the observed high mortality rate from DKA.[35]

Among the limitations of the current study is that biochemical parameters (like blood urea nitrogen and sodium) were not recorded in the majority of the patients' files. In addition, no information about sociodemographic data of the patients was available. Moreover, the incomplete/absence of registration of patients in private and public hospitals is common in Sudan. Thus, the reported findings did not cover all cases of DKA during the examined period. Furthermore, differences in the frequency of severe DKA and mortality rate were observed among examined tertiary and primary health care facilities. The reasons behind such differences need more investigations. Finally, in Sudan, the use of alternative medicine is very common, and this might underestimate the frequency and death rate from DKA.

In conclusion, the frequency of DKA among children at diagnosis of T1DM in Khartoum is lower than previous reports. The severity of DKA is high among pre-school age children. DKA mortality rate is lower than previously reported, but is still higher than global rate.

Authors Contributions
All authors participate in all research stages, data collection, analysis, writing and reviewing the final draft.

Conflict of Interest
Authors have nothing to declare.

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