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Clinical profile and outcome of children with diabetic ketoacidosis admitted in a tertiary care centre in Kerala during the pre and post COVID period

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Abstract

Objective: To study clinical profile and outcome of children admitted with diabetic ketoacidosis in our tertiary care centre during the pre and post covid period (Jan 2016 – Jan 2022).

Materials and Methods: Hospital-based cohort study among the children admitted with DKA in the department of Paediatrics. We abstracted the data of children, satisfying the inclusion criteria as per the pre-designed proforma based on ISPAD 2018 guidelines.

Participants: 46 children admitted with diagnosis of DKA during the study period, in a tertiary care centre in Kerala.

Results: Total of 46 admissions with DKA including 16 readmissions in 30 children were enrolled in the study. Majority (95.65%) were Type 1 DM with mean age of 11.6 years and male to female ratio of 1.1:1. There were 11.5 admission per year after the Covid 19 outbreak, compared to 5.8 cases per year during the pre-covid period. Most of the patients (60.9%) had only a short duration of symptoms (≤ 3 days) at presentation, and vomiting was the commonest symptom (63%), followed by polyuria, polydipsia (60.9%). 47.8% patients presented with mild DKA followed by 34.8% as severe DKA and majority (60.9%) needed 4 to 7 days of hospital stay.

Conclusion: DKA is a leading cause of morbidity and mortality in children with diabetes. There is a significant increase in the frequency of children getting admitted with DKA in the post Covid period which may be due to the delay in diagnosing the condition because of sedentary life style during lockdown, unhealthy eating habits and poor utilization of health care system by the public during the early surge of COVID peak.

Keywords: Diabetic ketoacidosis, type 1 diabetes, type 2 DM, ISPAD guidelines

Introduction

Diabetes mellitus is an endocrine disorder affecting millions of paediatric population leading to significant morbidity and mortality^[1]. Diabetic ketoacidosis (DKA) is a major life-threatening medical emergency of diabetes mellitus requiring urgent medical attention and expert management^[2]. The prevalence of DKA in paediatric age group is increasing by 3% per year^[1]. DKA occurs in both type 1 and type 2 diabetes and is characterized by significant elevation of glucose and ketones in blood. It results from relative or absolute lack of insulin combined with elevated counter regulatory hormones^[3]. Biochemical criteria for diagnosis of DKA as per ISPAD guidelines 2018 include:

- Hyperglycemia >11 mmol/L (≈ 200 mg/dL)
- Venous pH <7.3 or bicarbonate <15 mEq/L and
- Ketonemia (blood beta hydroxybutyrate ≥ 3 mmol/L or moderate or large ketonuria^[4]).

Risk factors for newly diagnosed DKA include younger age, delayed diagnosis, lower socioeconomic status and residence in a country with a low prevalence of type 1 DM. Omission of insulin, limited medical access and faulty insulin delivery are the risk factors for DKA in previously diagnosed DM^[4]. About 25-40% of type 1 DM clinically presents as DKA at the time of initial diagnosis whereas the risk for DKA in a previously diagnosed type 1 DM is 1-8%. Mortality rate of DKA in developed countries ranges from 0.15-0.31% compared to higher rates (up to 13%) in developing countries due to better medical facilities, early diagnosis and proper treatment^[2, 5].

Clinical presentation of DKA includes dehydration, tachypnoea, nausea, vomiting, abdominal pain, confusion, drowsiness and loss of consciousness [3]. The potential complications of DKA include cerebral venous thrombosis, mucormycosis, pancreatitis, sepsis, acute kidney injury, electrolyte imbalances, thrombotic thrombocytopenic purpura and cerebral edema [3, 6]. There is an increased incidence of DKA following Covid pandemic and one of the reasons being lower rate of healthcare use, potentially leading to delayed medical attention [7]. In our study, the clinical profile and outcome of children admitted with DKA in the hospital is evaluated for 4 years before and 2 years after the Covid19 pandemic.

Materials and Methods

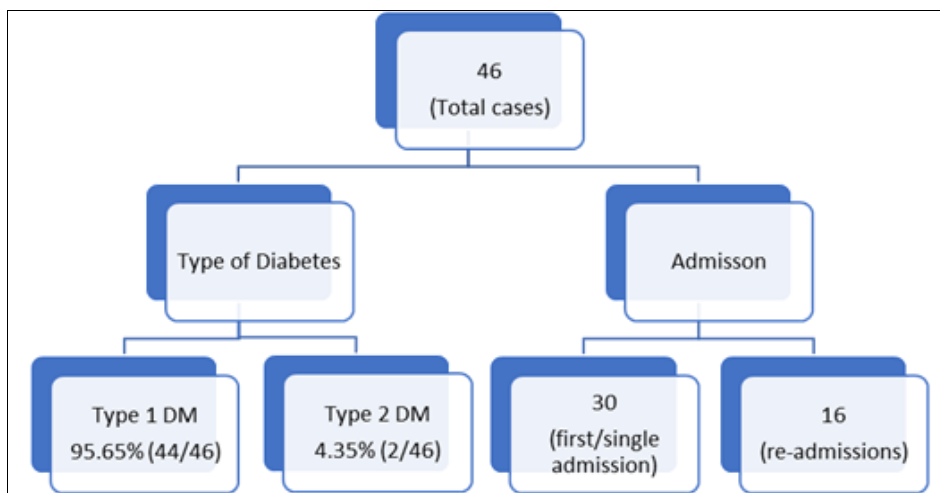
This is a hospital-based cohort study conducted in a tertiary care center in Kerala among the children admitted with DKA in the department of Pediatrics 6 years from Jan 2016 to Jan 2022. We abstracted the data of 46 children, satisfying the inclusion criteria as per the prepared proforma based on ISPAD 2018 guidelines including age, sex, clinical symptoms, laboratory parameters, co morbidities, family history, relevant treatment details and final diagnosis [4]. The biochemical criteria for the diagnosis of diabetic ketoacidosis (DKA) are, hyperglycaemia (blood glucose >11 mmol/L (≈200 mg/dL), venous pH <7.3 or serum bicarbonate <15 mmol/L, ketonemia (blood β-hydroxybutyrate ≥3 mmol/L) or moderate or large ketonuria

[4]. According to ISPAD and BSPED guidelines DKA is categorized as mild (venous pH <7.3, bicarbonate <15mmol/L), moderate (pH<7.2, bicarbonate <10 mmol/L), severe (pH <7.1, bicarbonate <5 mmol/L) [4, 8]. Hyponatraemia and hyponatremia are defined as serum sodium values of >145 mmol/L and <135 mmol/L respectively whereas hyperkalemia and hypokalemia are defined as serum potassium value of >6 mmol/L and <3.5mmol/L respectively [9].

Data collected as per the proforma were entered in the Microsoft excel and statistical analysis was done using SPSS version 20. All the variables were represented by frequency and percentage and analysed by Chi –square test or Fisher’s exact test. A p value of <0.05 was set as statistically significant.

Results

Total of 30 children who satisfied the inclusion criteria were enrolled in the study over a period of 6 years from January 2016 to January 2022. There was a total of 46 admissions with DKA, out of which 16 were re-admissions (Flow chart - 1). Out of the total 46 admissions, majority (95.65%) were Type 1 DM and only 2 cases were Type 2 DM, and 39.13% (18/46) were newly diagnosed DM. The mean age of presentation was 11.6 years and the male to female ratio was 1.1:1. Majority of the children (67.4%) were more than 10 years old, which is statistically significant (p value 0.018).



Flow Chart 1

Among the patients admitted with DKA, majority (67.4%) had blood sugar value of 300- 500 mg/dL which is statistically significant compared to only 23.9% of patients who had significant high blood sugar values of more than

500mg/dL. There was a significant increase in the frequency of DKA admission to 11.5 cases per year after the Covid 19 outbreak, compared to 5.8 cases per year during the pre-covid period (Table 1).

Table 1: Demography, initial blood sugar and frequency of DKA.

Variables	Frequency	Percent	p - value
Sex			
Male	24	52.2%	0.768
Female	22	47.8%	
Age (Years)			
≤ 10	15	32.6%	0.018
> 10	31	67.4%	
Episodes of DKA			
Single	30	65.2%	0.039
Multiple	16	34.8%	
GRBS at Admission			

200 - 300	4	8.7%	0.000
301 - 500	31	67.4%	
> 500	11	23.9%	
Frequency per Year			
Pre-COVID (<2020)	5.8		--
Post-COVID (> 2020)	11.5		

Most of the patients (60.9%) had only a short duration of symptoms (≤ 3 days) at presentation, compared to only 4.3% children who presented with long duration of symptoms of > 30 days which is statistically significant. Vomiting was the commonest presenting symptom (63%), followed by osmotic symptoms like polyuria and polydipsia (60.9%), abdominal pain (41.3%), acidotic breathing

(32.6%), weight loss (19.6%), fever (17.4%) and altered sensorium (15.6%). DKA was precipitated by preceding illness like diarrhea, skin or throat infection or acute respiratory infection, was identified 15.2%, whereas for majority of the cases (84.8%), a precipitating illness could not be identified (Table 2).

Table 2: Clinical Features and precipitating factors for DKA.

Duration of Presenting Illness before Admission (Days)	Number out of 46	%
≤ 3	28	60.9%
4 - 7	6	13.0%
8 - 14	5	10.9%
15 - 30	5	10.9%
> 30	2	4.3%
Clinical feature		
Vomiting	29	63.0%
Polyuria / Polydipsia	28	60.9%
Abdominal Pain	19	41.3%
Breathlessness	15	32.6%
Acidotic Breathing	15	32.6%
Fever	9	19.6%
Recent Weight Loss	9	19.6%
Altered Sensorium	7	15.2%
Diarrhoea	3	6.5%
Shock	3	6.5%
Comatose at Admission	1	2.2%
Precipitating Factor		
Unknown	39	84.8%
Diarrhea	3	6.5%
Skin Infection	2	4.3%
Tonsillitis	1	2.2%
ARI	1	2.2%

Severity of DKA was distributed as mild DKA (47.8%), moderate DKA (17.4%) and severe DKA (34.8%). All of them were dehydrated at the time of admission among which 3 (6.5%) were presented with shock. Dehydration was treated with fluid boluses according to severity and clinical evaluation, with 10 ml/kg (63%), 15ml/kg (23.9%) and 20ml/kg (13%). Acidosis was corrected within 24 hours in 71.4% of patients, 17.1% by 24-48 hours and 11.4% required > 48 hour. Bolus subcutaneous insulin was started after stopping the insulin infusion within 24 hours in 54.3% cases, whereas 23.9% needed 24-48 hours and 21.7%

required >48 hours. In 80.43% children, the blood sugar value was corrected to less than 250mg/dL within 6 hours of initiation of insulin infusion, however 6.5% children required >12 hours for the same. Most of the patients (52.2%) had hyponatremia at the time of presentation whereas 4.3% had hypernatremia. Hypokalemia was present among 13% cases, but 6.5% presented with hyperkalemia, whereas 80.4% had normal potassium levels. Majority (60.9%) needed 4 to 7 days of hospital stay, whereas 21.7% required ≤ 3 days and 17.4% were discharged after 7 days (Table 3).

Table 3: Severity, clinical variable and hospital stay of DKA patients.

Variables	Frequency	Percent	p - value
Severity of DKA			
Mild	22	47.8%	0.040
Moderate	8	17.4%	
Severe	16	34.8%	
Number of Fluid Bolus			

10 ml/kg	29	63.0%	0.000
15 ml/kg	11	23.9%	
20 ml/kg	6	13.0%	
Time taken for correction of acidosis (Hours)			
≤ 24	25	71.4%	0.000
24 - 48	6	17.1%	
> 48	4	11.4%	
Duration of insulin infusion (Hours)			
≤ 24	25	54.3%	0.010
24 - 48	11	23.9%	
> 48	10	21.7%	
Duration to correct Blood sugar to < 250 (Hours)			
≤ 6	31	67.4%	0.000
6 - 12	12	26.1%	
> 12	3	6.5%	
Sodium			
	No.	%	
Hyponatremia	2	4.3%	0.000
Hyponatremia	24	52.2%	
Normal	20	43.5%	
Potassium			
Hypokalemia	6	13.0%	0.000
Hyperkalemia	3	6.5%	
Normal	37	80.4%	
Number of Hospital Stay (Days)			
≤ 3	10	21.7%	0.000
4 - 7	28	60.9%	
> 7	8	17.4%	

Discussion

The present study included 46 admissions, corresponding to 30 patients. Out of 46 cases 34.7% (16/46) of cases were readmission. Among the 46 children 95.65% of cases were type 1 DM whereas 4.3% were type 2 DM, all the readmission for DKA were Type 1 DM. In our cohort, 39.13% of cases were newly diagnosed type 1 DM whereas a study from Lucknow showed that 80% of DKA admissions were newly diagnosed DM and 20% were previously diagnosed diabetes [2]. A study from Brazil reported 59.6% of DKA admissions as newly diagnosed DM [10]. Increased prevalence of DKA among newly diagnosed type 1 DM were also reported from Saudi [1, 3].

The mean age of the study group was 11.6 years which was similar to many national and international studies [1, 2, 10]. The prevalence of DKA was 32.6% among ≤10 years whereas 67.93% was > 10 years of age ($p < 0.018$) which is similar to the study from Saudi in which 33% of cases were ≤10 years and 67% cases were > 10 years [1].

There was a slight male preponderance (male: female = 1.09:1) in our study, however it was not statistically significant, in contrast to most of the national and international studies which showed female preponderance [1, 2, 10].

The frequency of DKA was nearly doubled during post Covid years compared to pre Covid era (average case per year-11.5: 5.8). A study from Germany also reported a significant increase in frequency of DKA in the post Covid period, which may be attributed to multiple reasons like fear of approaching health care system, psycho-social factors, reduced medical services and lower health care use, leading to delayed diagnosis of diabetes [7].

Commonest presenting symptom was vomiting (63%), followed by osmotic symptoms like polyuria and polydipsia (60.9%), abdominal pain (41.3%) and acidotic breathing (32.6%) in contrast to the study from Uttar Pradesh, which showed respiratory distress as the most common presenting

symptom (77.5%), but 65% cases had polyuria/polydipsia similar to our study [2]. Higher rates of polyuria and polydipsia (96%) were reported from Saudi Arabia, however osmotic symptoms were lower (54.5%) in a study from Delhi [11, 12]. Majority of the children had symptoms ≤3 days (60.87%) before getting admitted to the hospital, whereas only 4.35% had symptom for >30 days, which signifies the importance of public awareness of the common symptoms of diabetes and related complications like DKA including polyuria, polydipsia, vomiting and abdominal pain.

Precipitating factor for DKA was unknown among 84.8% of patients and 15.2% had infective etiology, and diarrhoea was the commonest predisposing event. Infections are thought to be the most important precipitating factor among DKA patients in contrast to our study and some have reported possible intercurrent infections up to 45% [2, 13].

Electrolyte abnormalities are common in DKA patients and the present study reveals statistically significant hyponatremia with normokalemia, similar to the report by D Prasad from India [2].

Severity of DKA was distributed as mild DKA (47.8%), moderate DKA (17.4%) and severe DKA (34.8%). The mean pH at the time of admission was 7.09 which is similar to the report from North India (pH 7.07), whereas MA Naeem *et al*, showed mean pH as 7.15 [1, 2].

6.5% of patients presented with shock and dehydration which was treated with fluid boluses according to severity. Majority required treatment with 10 ml/kg (63.04%) in contrast to a study from Saudi which showed more than half not requiring any fluid boluses [1]. The fluid therapy is aimed at replacing the fluid deficit in case of inadequate vascular volume, however judicious use of fluid is advised as shock with haemodynamic compromise is uncommon [14, 15].

Acidosis was corrected within 24 hours in 67.4% of patients and majority of the patients were discharged within 4 to 7

days (mean hospital stay of 5.6 days) which is comparable to the data from North India [2].

None of the participants in our study developed cerebral oedema and the reported incidence of cerebral edema in DKA patients in pediatric population is 0.5- 1% in some studies [16, 17]. Predicted mortality in DKA according to literature ranges from 0.15% to 0.35% in developed countries and 3.4% to 13.4% in developing countries including India [18, 19]. There was no mortality during the study period and adhering to a protocol based on ISPAD guidelines would help to reduce mortality and morbidity while managing DKA in children.

Conclusion

DKA is a leading cause of morbidity and mortality in children with diabetes. There is a significant increase in the frequency of children getting admitted with DKA in the post Covid period compared to the pre Covid era. Most of the reported cases are adolescents with mean age of 11.6 years and 47.8% cases presented with mild DKA followed by severe (34.8%) and moderate DKA (17.4%) respectively. In this study majority presented with gastrointestinal symptoms like vomiting, followed by osmotic symptoms (polyuria and polydipsia). In our cohort, 65.2% of patients presented with the first episode of DKA and most of them were previously diagnosed DM and the duration of the presenting illness was less than 3 days. Majority of the cases, insulin infusion was changed to bolus doses within 24 hours, along with correction of acidosis and stabilization of clinical condition. Precipitating factors could not be identified in 84.8% and diarrhea was the predominant infection which precipitated DKA. Majority of the patients required fluid boluses of 10 ml/kg and the duration of hospital stay was 3- 7 days before discharge.

Strength of our study is that, it is one of the fewer recent studies from south India assessing the clinical profile of DKA and highlighting the recent increase in frequency of DKA in pediatric population post-Covid period which may be due to fear of approaching health care system during the early surge of Covid peak, psycho-social factors, reduced medical services and lower health care use, leading to delayed diagnosis of diabetes. Our study will open a platform for future comparison studies and may help the clinicians to improve the management and care of patients with DKA.

Key Messages

What is already Known: DKA is a paediatric emergency leading to significant morbidity and mortality in children with female preponderance. The prevalence of DKA in paediatric age group is increasing by 3% per year and 25-40% of type 1 DM clinically presents as DKA at the time of initial diagnosis whereas the risk for DKA in a previously diagnosed type 1 DM is 1-8%. Mortality rate of DKA in developed countries ranges from 0.15-0.31% compared to higher rates (up to 13%) in developing countries due to better medical facilities, early diagnosis and proper treatment.

What this study adds: The frequency of children getting admitted with DKA in the post Covid period has significantly increased compared to the pre Covid era. The mean age of presentation is 11.6 years and majority (47.8%) presenting with mild DKA. Majority presented with gastrointestinal symptoms like vomiting, followed by

osmotic symptoms and 65.2% of patients presented with the first episode of DKA and the duration of hospital stay was 3- 7 days before discharge. The recent increase in frequency of DKA in pediatric population post-Covid period which may be due to fear of approaching health care system during the early surge of Covid peak, psycho-social factors, reduced medical services and lower health care use, leading to delayed diagnosis of diabetes.

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Details of contribution by authors

MK, JVF, DG, ACB involved in conception, design, acquisition of data, analysis and interpretation of data. All authors are accountable for drafting of the manuscript, critical revision of manuscript for important intellectual content and the final version to be published.

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