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Dr. K Muralidhar Reddy
Associate Professor, Department of Paediatrics, Narayana Medical College, Nellore, Andhra Pradesh, India

Dr. Prudhivi Srinivas
Assistant Professor, Department of Paediatrics, Narayana Medical College, Nellore, Andhra Pradesh, India

Corresponding Author:
Dr. Prudhivi Srinivas
Assistant Professor, Department of Paediatrics, Narayana Medical College, Nellore, Andhra Pradesh, India

A study on clinical and biochemical profile, precipitants, and prognostic factors of diabetic ketoacidosis

Dr. K Muralidhar Reddy and Dr. Prudhivi Srinivas

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Abstract
Background: Diabetic ketoacidosis (DKA) is a life-threatening acute complication of diabetes mellitus (DM) that mostly affects type 1 diabetics and some type 2 diabetics. DKA is defined by hyperglycemia, ketoacidosis, and ketonuria. The real yearly incidence rate of DKA is difficult to determine, however, population-based studies have found rates ranging from 4.6 to 8 occurrences per 1,000 diabetic patients.
Objectives
1. To find out the metabolic derangements occurring in DKA in 1st 48 hrs. of admission and to determine its relation with the duration of insulin infusion and hospital stay.
2. To find out the various precipitating factors.
3. To find the relation between various precipitating factors, biochemical abnormalities, mortality and morbidity of DKA.

Material & Methods
Study Design: Hospital-based descriptive study.
Study area: The study was conducted in the Department of Paediatrics.
Study Period: 1 year.
Study population: All confirmed cases of DKA were admitted to the paediatric department.
Sample size: The study consisted of a total of 34 subjects.
Sampling Technique: Simple Random technique.
Inclusion criteria: All confirmed cases of DKA were admitted to the paediatric department.
- 5 ml of venous blood was drawn for estimation of urea, creatinine, and electrolytes namely sodium and potassium. Serum sodium and potassium were checked by the ion-selective electrode method protocol. Blood urea and Serum creatinine were evaluated automated chemistry analyser.
- Arterial blood was drawn in the heparinized syringe for blood gas analysis. Acidosis, Chloride, bicarbonate and ionised calcium were measured by ABG machine, using the Ion Selective Electrode method. ABG was interpreted as the presence or absence of acidosis and the type of acidosis present.

Results: On applying the chi-square test, a significant reduction in the duration of insulin infusion was demonstrated in children whose electrolyte levels normalised at 24 hours. When the duration of insulin infusion in patients who had normal and abnormal electrolytes at 24 hours was compared, it was found that all patients who had normal electrolytes at 24 hours required insulin infusion less than 24 hours.
Conclusion: Diabetic patients must be educated about ketoacidosis symptoms and must adhere to medication to prevent DKA, early detection, and treatment, as well as consequences. Simple lifestyle changes, patient education on not missing insulin doses, particularly during illness, and giving patients with an adequate insulin regimen can significantly minimize DKA occurrence.

Keywords: Diabetes mellitus, Diabetic ketoacidosis, Hyperglycemia, Lipolysis

1. Introduction
Diabetes mellitus (DM) is a major public health issue worldwide, and with approximately 17% of total global cases, India holds the dubious distinction of being the diabetic capital of the world [1, 2]. Diabetic ketoacidosis (DKA) is a hyperglycemic crisis that often necessitates hospitalization to the emergency department (ED) or critical care unit. Exogenous insulin insufficiency (poor compliance or control) and infections (mostly lung, urinary tract, or skin and soft tissue) are the most common causes of this potentially fatal illness [3-6]. Global and current Indian data reveal a falling trend in mortality in DKA patients down to <1% [2, 5-7].
Diabetic ketoacidosis (DKA) is a life-threatening acute complication of diabetes mellitus

(DM) that mostly affects type 1 diabetics and some type 2 diabetics. DKA is defined by hyperglycemia, ketoacidosis, and ketonuria [8-10]. The real yearly incidence rate of DKA is difficult to determine, however, population-based studies have found rates ranging from 4.6 to 8 occurrences per 1,000 diabetic patients [11, 12]. The majority of DKA cases are caused by missing insulin doses, which can be attributed to negligence or low socioeconomic level [13].

Infections, cerebrovascular accidents, alcohol/drug misuse, pancreatitis, myocardial infarction, trauma, and carbohydrate-metabolizing medications are all potential causes of DKA [14]. According to the American Diabetes Association, the mortality rate from DKA is 5% [15, 16]. It is critical that people with DKA are identified early and receive medical attention as soon as feasible [14].

Objectives

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Exclusion criteria

Patients who were partially treated for DKA in outside hospitals will be excluded.

Ethical consideration

Institutional Ethical committee permission was taken before the commencement of the study.

Study tools and Data collection procedure

Children were enrolled based on inclusion criteria after obtaining written informed consent from the parents/guardians. Diagnosis of DKA was made based on the standard definition.

The following details were noted in the data collection form

- Age and Sex
- Presence of pre-existing diabetes: If found to have pre-existent diabetes, duration of diabetes, insulin requirement, glycosylated haemoglobin (HbA1C) and the interval between DKA and last available HbA1C were noted.
- Family history of diabetes.
- The presence of any identifiable precipitating cause like infection, stress or insufficient intake was noted.
- Height was measured using a stadiometer for children > 2 years and recumbent length was measured using an infantometer for children < 2 years using standard techniques.
- The weight of the patient was measured by the electronic weighing scale with a least count of 50 gm with the child wearing light clothing.
- Body mass index calculated by using standard formula = weight in kg/height in m^2.
- Anthropometric measures were interpreted using a WHO chart for < 5 years of age and an IAP chart for children > 5 years of age and classified accordingly.
- 5 ml of venous blood was drawn for estimation of urea, creatinine, and electrolytes namely sodium and potassium. Serum sodium and potassium were checked by the ion-selective electrode method protocol. Blood urea and Serum creatinine were evaluated automated chemistry analyser.
- Arterial blood was drawn in the heparinized syringe for blood gas analysis. Acidosis, Chloride, bicarbonate and ionised calcium were measured by ABG machine, using the Ion Selective Electrode method. ABG was interpreted as the presence or absence of acidosis and the type of acidosis present.
- The above-said investigations were done at the time of initiation of treatment, 12 hrs., 24 hrs., 36 hrs. and 48 hrs. All the children admitted were treated as per standard DKA protocol. All DKA children were monitored using the chart given below.

Date & Time	HR	RR	BP	Perfusion	GCS	blood sugar	corrected Na	Insulin infusion	IVF	Remarks

For children who recovered or died before 48 hours, investigations were done only till that time. The time of stopping insulin infusion was noted for all patients. The clinical outcome of the child and duration of hospital stay were also noted.

Statistical analysis

Collected data entered in the Microsoft Excel sheet. Data analysis was done By SPSS software Version 20. Continuous variables were categorised as either normal or abnormal and the patients in either category were reported as proportion. Duration of insulin infusion and duration of hospital stay in various categories were analysed using box and whisker plot methods.

Observations & Results

A total of 34 patients were treated in our hospital PICU during the study period and were included in the study.

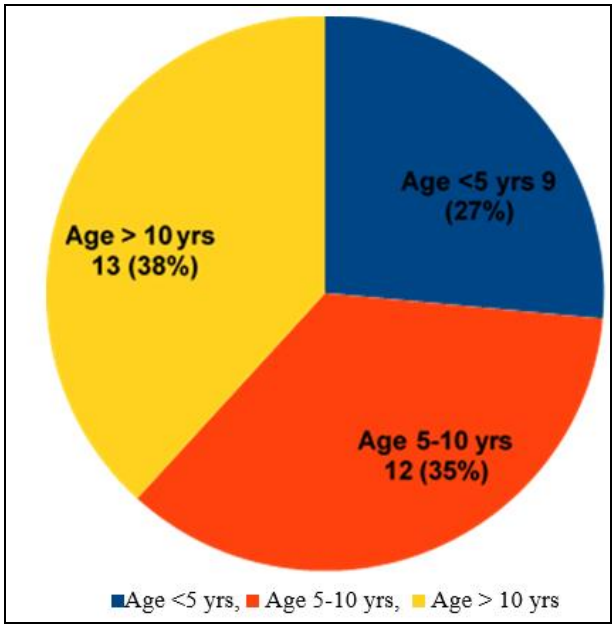

Fig 1: Age distribution in the study population

- Range: 02 to 12 years (10 years).
- Mean age: 8.41 ± 3.40 years.
- Almost half of the patients were more than 10 years (38.2%) of age and the least common age group was 2 years.

Calculated as male: female ratio

The number of males (17) and females (17) in the study was the same. Hence the Male-female ratio in this study was 1:1. 29.4% of children with DKA had pre-existing diabetes while the rest 70.6% were new onset DKA.

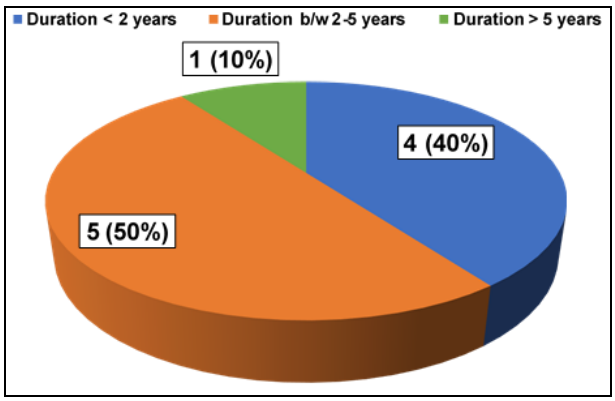

Fig 2: Duration of diabetes in pre-existing diabetic patients

Out of 10 children with pre-existing diabetes, half of them were diabetics for 2-5 years and 40% were diabetics for <2 years. Only 10% of cases had diabetes for more than 5 years.

Table 1: Preceding HbA1C status in pre-existing diabetic group

S. No.	HbA1C status	No. of subjects	Percentage
1.	7.5-9	04	40
2.	>9	06	60
Total		10	100

None of the children with pre-existent diabetics who presented with DKA had optimal glycaemic control as evidenced by HbA1C levels. 40% had sub-optimal control (HbA1C 7.5 to 9) while 60% had poor control (HbA1C more than 9).

Half of the patients with pre-existing diabetes mellitus required 1-1.5 µ/kg/day of insulin, while only 20% were on < 1 µ/kg/day of insulin. A small fraction i.e., 20% of patients required more than 1.5 µ/kg/ day. Positive family history was present in 26% of cases only.

Table 2: Precipitating cause of DKA

S. No.	Precipitating cause	No. of patients	Percentage
1.	Infection	11	32.3
2.	Insufficient insulin dose	04	11.8
3.	Skipped insulin dose	05	14.7
4.	Unknown	14	41.2
Total		34	100

In this study, the majority of patients (41.2%) had an unknown precipitating cause. 11 Patients (32.3%) were having some kind of infection. 4 patients (11.8%) had insufficient insulin intake and skipped insulin doses in 5 patients (14.7%).

While analysing the anthropometric data of children less than 5 years, it was found that 33% were under-weight as per weight for age and 11% of children were at risk of overweight as per BMI. The remaining children had normal anthropometric measurements.

In this study, we obtained the following results at the time of admission

- **Sodium:** 26.5% had hyponatremia, 64.7% were in normal range and 8.8% had hypernatremia.
- **Potassium:** 29.4% had hypokalaemia, 47.1% had normal range and 23.5% were in hyperkalaemia.
- **Chloride:** 91.2% had a normal range and 8.8% had hyperchloremia.
- **Bicarbonate:** 100% was in acidotic range.

In this study, we obtained the following results 24 hours after the time of admission

- **Sodium:** 8.8% had hyponatremia, 41.2% were in the normal range, 26.5% had hypernatremia and 23.5% were not taken due to acidosis correction or death.
- **Potassium:** 38.2% had hypokalaemia, 38.2% had normal range, and 23.2% were not taken acidosis correction or death.
- **Chloride:** 58.8% had normal range, 17.6% had hyperchloremia and 23.5% were not taken acidosis correction or death.
- **Bicarbonate:** 76.5% was in the acidotic range and 23.5% were not taken acidosis correction or death.

In this study, we obtained the following results at 48 hours after the time of admission

- **Sodium:** 17.6% was in the normal range, 5.9% had hypernatremia and 76.5% were not taken due to acidosis correction or death.
- **Potassium:** 14.7% had hypokalaemia, 8.8% had normal range, and 76.5% were not taken due to acidosis correction or death.
- **Chloride:** 20.6% had normal range, 2.9% had hyperchloremia and 76.5% were not taken due to

acidosis correction or death.

- **Bicarbonate:** 17.6% was in the acidotic range, 5.9% were in the normal range and 76.5% were not taken due to acidosis correction or death.

In this study, Pre-renal failure was seen in 32.4% of children at the time of admission, which decreased to 26.5% of children at 12 hours, 14.7% at 24 hours, and none at 36 and 48 hours. Renal failure was seen in 11.8% of children at the time of admission, 8.8% of children at 12 hours and 24 hours, and 5.9% of children at 36 hours and 48 hours.

In this study, 26.5% of children recovered with insulin infusion in less than 12 hours, 32.4% within 24 hours and 29.4% within 48 hours. Only 11.8% of children required insulin infusion beyond 48 hours.

Table 3: Length of hospital stay in DKA patients

S. No.	Length of hospital stay (in weeks)	No. of subjects	Percentage
1.	<1	06	17.6
2.	1-2	17	50.0
3.	>2	11	32.4
Total		34	100

In this study, 17.6% of patients stayed in the hospital for less than 1 week, 50% stayed for 1 to 2 weeks and 32.4% of patients stayed for more than 2 weeks.

The outcome of this study is mentioned in terms of number of discharges and number of deaths. No of Discharges was 30 which accounts for 88.2% of patients. Deaths were 4, which accounts for 11.8% of patients.

Table 4: Relation between metabolic derangements and hospital stay duration at 24 hours

S. No.	Duration of stay at hospital (in weeks)	Metabolic derangements (%)		Total No. of Subjects (%)
		Yes	No	
1.	<1	00(0.00)	02(100)	06(100)
2.	1-2	17(81.0)	4 (19.0)	21(100)
3.	>2	09(81.8)	02(18.2)	11(100)
Total		26(76.5)	8 (23.5)	34(100)
Statistical significance		Chi-square value=6.91; p-value<0.05;Significantassociation		

The duration of stay is longer in patients who had abnormal electrolyte levels at 24 hours – Only 2 of the patients with normal electrolyte levels at 24 hours stayed beyond 2 weeks. On applying the chi-square test, a significant reduction in the duration of hospital stay was demonstrated in children whose electrolyte levels normalised at 24 hours.

Table 5: Relation between metabolic derangements and insulin infusion duration at 24 hours

S. No.	Insulin infusion duration (in hours)	Metabolic derangements (%)		Total No. of subjects (%)
		Yes	No	
1	<12	01 (12.5)	07 (87.5)	08 (100)
2	12-24	13 (92.9)	01 (7.1)	14 (100)
3	24-48	08 (100.0)	00 (0.00)	08 (100)
4	>48	04 (100.0)	00 (0.00)	04 (100)
Total		26 (76.5)	8 (23.5)	34 (100)
Statistical significance		Chi-square value=24.0; p-value<0.05;Significantassociation		

On applying the chi-square test, a significant reduction in the duration of insulin infusion was demonstrated in children whose electrolyte levels normalised at 24 hours. When the duration of insulin infusion in patients who had normal and abnormal electrolytes at 24 hours was compared, it was found that all patients who had normal electrolytes at 24 hours required insulin infusion less than 24 hours.

In children with normal electrolyte levels at 24 hours, the Median duration of stay = 9.5 days, and the Interquartile range = 9.25 days. In contrast, for children with abnormal electrolyte levels at 24 hours, the Median duration of stay = 12 days, Interquartile range = 3.25 days. When the duration of insulin infusion was compared between the patients who had normal and abnormal electrolytes at 24 hours of admission, the median (IQR) of the former group was 11 hours and that of the latter group was 22 hours.

Discussion

This review has brought out different electrolyte abnormalities at presentation and at different time intervals in children hospitalised for DKA.

Sodium

In this study, at the time of admission, 26.5% population were hyponatremic, 64.7% were in the normal range and 8.8% had hypernatremia. The study done by Kanwal SK *et al*. [17] observed that at the time of admission, only 20% were hypernatremic. Another study done by Andrew E Edo [18] showed that about 36.9% had hyponatremia and 1.2% had hypernatremia at admission. A study conducted by Hamza Mulath *et al*. [19] titled "Serum sodium and potassium levels as prognostic indicators in paediatric diabetic ketoacidosis" showed Hyperkalaemia at presentation was significantly associated with mortality, hyponatremia at the time of admission was found to be significantly associated with prolonged hospital stay and abnormal sodium and potassium levels persisting at the end of 24 hours was significantly associated with the need for prolonged insulin infusion. Serial monitoring of sodium in this study showed that with treatment hyponatremia decreased and hypernatremia increased up to 24 hours after which sodium levels gradually stabilised to normal level. At the end of 48 hours of admission, only 5.9% of patients have sodium disturbances in the form of hypernatremia.

All others had normal sodium levels or had their acidosis corrected or expired.

Potassium

In this study at the time of admission, 29.4% had hypokalaemia, 47.1% had normal potassium levels and 23.5% had hyperkalaemia. In a study conducted by Andrew E Edo [18], he observed that 21% had hyperkalaemia at admission and only 3% had hypokalaemia. Similarly, a study conducted by Kanwal SK *et al*. [20] showed only 14.5% had hypokalaemia. Moulik *et al*. [21] observed in their study that 59.6% were hypokalaemia. The study by Moulik *et al*. showed that there was a significant fall in potassium level 6 hours after therapy with 100% of malnourished children and 72.7% of children with normal nutrition developing hypokalaemia during therapy. This is similar to the findings of our study which showed that the prevalence of hypokalaemia increases from 29% at admission to a maximum of 47.1% at 12 hours. Following this potassium levels tend to normalize so that at 48 hours only 14.7% hypokalaemia.

Chloride

In this study estimation of chloride level showed that 8.8% had hyperchloremia on admission which increases to a maximum of 23.5% at 24 hours. Thereafter chloride levels tend to normalise with only 2.9% having hyperchloremia at 48 hours. A study conducted by Mahesh Ramanan *et al*.(2021) titled "Sodium chloride or Plasmalyte-148 evaluation in severe diabetic ketoacidosis" showed Plasmalyte-148, compared to sodium chloride 0.9%, may lead to faster resolution of metabolic acidosis in patients with DKA without an increase in ketosis. In a study conducted by Vandana Arya, Kavitha *et al*. (2021) also showed PlasmaLyte was superior to Normal saline when used as a resuscitation fluid in children with shock, in terms of better improvement of acid-base balance after fluid bolus therapy, a lower rise in serum chloride level.

Bicarbonate

Bicarbonate levels which is the hallmark of metabolic acidosis were observed in all patients on admission. The percentage of children with low bicarbonate levels gradually reduced with treatment but 17.6% had low bicarbonate levels even at 48 hours after therapy. All patients had high anion gap metabolic acidosis at presentation withtreatment the number of patients with high anion gap metabolic acidosis decreased gradually with only a few patients having high anion gap metabolic acidosis at the end of 48 hours. Normal anion gap metabolic acidosis was seen in 9.1% at 12 hours and 24 hours, 6% at 36 hours and at 48 hours hyperchloremia could be attributed to normal anion gap metabolic acidosis observed in this study.

Renal failure in DKA

In this study during the time of admission, 11.8% had renal failure and 32.4% had pre-renal failure. In a study conducted by Mullai Baalaaji, Muralidharan Jayashree *et al*.[22] (2018) titled "Predictors and Outcome of Acute Kidney Injury in Children with Diabetic Ketoacidosis" showed Twenty-eight children developed AKI during the hospital stay; 20 (71.4%) recovered with hydration alone. Serum chloride at 24 hours was independently associated with AKI. Children with AKI had prolonged acidosis and PICU stay and higher mortality. A study conducted by C.F. Otieno *et al*. [23] on adults observed that 71.5% had abnormal renal parameters. Against this Moulik *et al*. [24] observed that only 9% had renal failure at admission. This deranged renal function was transient as evidenced by the gradual decrease in the proportion of children with renal failure with treatment. At 48 hours after treatment, only 5.9% had renal failure. It was observed in our study that most of the electrolyte disturbances were maximum at 12 hours after which they started to decline gradually. The duration of insulin infusion and hospital stay were compared for children with normal and abnormal electrolytes at 24 hours. Children with electrolyte disturbances at 24 hours had a statistically significant longer duration of insulin infusion requirement and significant prolongation of hospital stay. There is no study with similar data available for comparison.

Conclusion

Diabetic patients must be educated about ketoacidosis symptoms and must adhere to medication to prevent DKA, early detection, and treatment, as well as consequences. Simple lifestyle changes, patient education on not missing insulin doses, particularly during illness, and giving patients with an adequate insulin regimen can significantly minimize DKA occurrence.

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