Original Article

Clinical and biochemical profile, precipitants and prognostic factors of diabetic ketoacidosis: A retrospective study from a tertiary care center of north India

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ARTICLE INFO

ABSTRACT

Background: We aimed to retrospectively investigate the clinical and biochemical profile of Diabetic ketoacidosis (DKA) patients and various precipitating and prognostic factors.
Methods: This was a hospital-based retrospective observational study, conducted in a tertiary care hospital in north India, from March 2014 to March 2017.
Results: Among 50 patients who satisfied the study criteria, 10 (20%) had DKA as their first presentation. Most common symptoms were nausea and vomiting (74%). Noncompliance was the major precipitating cause in 26 cases (52%) followed by infections in 18 cases (36%). The mean value of blood sugar at presentation was 406.8 ± 130.4 mg/dl with serum ketone 5.38 ± 1.56 mmol/l and mean pH 7.128 ± 0.157 with severe DKA in 14 (28%) patients. Mean duration of hospital stay was $8.2. \pm 5.0$ days, and low hemoglobin ($p = 0.019$) and high pulse rate ($p = 0.025$) were independent predictors of a longer stay.
Conclusion: With intensive care, mortality did not occur; however, non-compliance remained the most common precipitating cause of DKA followed by infections.

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1. Introduction

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome (HHS) are acute life-threatening complications of diabetes requiring admission in the emergency department and critical care units. DKA is a clinico-biochemical syndrome characterized by a severe insulin deficient state leading to hyperglycemia, ketosis, and high anion gap metabolic acidosis. Acute management includes aggressive fluid resuscitation, insulin infusion, correction of electrolyte disturbances and care of treatable precipitant factor like an infection. Untreated or ineffectively treated patients have invariably high mortality [1—3]. The overall incidence of DKA is 4—8% with a mortality of <1% with intensive management in developed countries [3—7]. However, Indian studies have shown a higher incidence with mortality reaching up to 30% [8—15].

The two most common precipitating factors of DKA (and HHS) remain exogenous insulin deficiency (noncompliance or under-treatment) and infections [3,6]. Previous Indian studies found infection (chiefly pneumonia or urinary tract infection) as a principal recognized cause of DKA precipitations [8,10—15].

Despite India often being considered as the diabetic capital of the world, studies on DKA are few, especially from the parts of north India. In the present study, we aimed to retrospectively investigate the clinical and biochemical profile of DKA patients admitted in a tertiary care hospital of northern India, as well as underlying precipitating factors and prognostic factors (in terms of the time of DKA resolution, duration of hospital stay and in-hospital mortality).

2. Methods

Study population: This was a hospital-based retrospective observational study, conducted in a medical emergency of a tertiary care hospital in north India, from March 2014 to March 2017.
Case definition: Patients aged above 13 years admitted to the

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emergency medical outpatient department or emergency medicine ward of Internal Medicine with clinically suspected and laboratory confirmed DKA were included. DKA was diagnosed according to American Diabetes Association guidelines including serum glucose $\geq$ 250 mg/dl (14 mmol/l), blood pH $\leq$ 7.30, bicarbonate $\leq$ 18 mEq/L, serum anion gap > 10 mEq/L, and presence of ketosis [3]. DKA was further classified according to the severity based on pH and bicarbonate; i.e., mild DKA-pH 7.25–7.30, bicarbonate >14; moderate DKA-pH 7.00–7.24, bicarbonate 10–14; and severe DKA- < pH 7.00, bicarbonate <10 [3].

Standard protocol approvals and patient consent: The Institutional Ethics Committee approved the study.

Data collection: The number of patients enrolled during the study period determined the sample size. All the clinical details were obtained from the case records of the medical records department (MRD) of the institution. On enrollment, a clinical research form including a clinical profile (medical history, sociodemographic data and physical examination), laboratory data (capillary blood sugar levels, blood gas analysis, serum or urine ketone level, serum electrolytes, renal function tests, complete blood counts, cultures of blood or other body fluids blood), and treatment details regarding fluid management, insulin therapy, antimicrobial therapy and mechanical ventilation were filled. The case files with incomplete records were excluded from the study.

Statistical analysis: We used Statistical Package for the Social Sciences (SPSS), version 16 for Windows, for data analysis, and recorded discrete data as frequency and percentage, and symmetrically distributed continuous data as mean $\pm$ SD. Regression analysis and correlation were performed using ANOVA. $p < 0.05$ was considered statistically significant.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

Baseline characteristics: We enrolled 50 patients aged 13 years and above with DKA according to ADA definition. The most common type of diabetes was type 1 DM (74%), followed by type 2 DM (18%) and latent autoimmune diabetes of adults (8%). The mean age was 29.4 $\pm$ 14.4 years (ranging from 13 to 70 years), which corresponded to a younger group of type 1 DM patients. The male to female ratio was 3:2.

Clinical presentation of DKA: Among the 50 patients, 10 (20%) had DKA as their first presentation of diabetes, and 13 (26%) had one or more episodes of DKA in the past (recurrent DKA).

Nausea or vomiting was the most common complaint, seen in 74% of patients. Other common presenting complaints were shortness of breath (54%), abdominal pain (52%), fever (52%) and altered mental status (48%). Osmotic symptoms of hyperglycemia such as polyuria were seen only in 18% of DKA cases.

Regarding hemodynamic parameters at presentation, mean systolic and diastolic blood pressure) were 113.9 $\pm$ 16.3 and 71.8 $\pm$ 9.8 mm of Hg respectively, and four patients had hypotension. Tachycardia was seen in 58% patients and mean pulse rate was 104.6 $\pm$ 18.2 per min (Table 1).

Microvascular complications of diabetes such as neuropathy, retinopathy or nephropathy were present in 18% patients, and 6% had macrovascular disease including coronary artery disease and peripheral artery disease.

Laboratory abnormalities and diagnosis: The mean value of blood sugar at presentation was 406.8 $\pm$ 130.4 mg/dl with mean

Table 1
Clinical and laboratory profile of DKA patients on admission with the mean value and range.

S No.	Parameter	Mean value	Range
	Hemodyanamic parameters		
1	Pulse rate (per minutes)	104.6 $\pm$ 18.2	74–160
2	Systolic BP (mm Hg)	113.9 $\pm$ 16.3	80–150
3	Diastolic BP (mm Hg)	71.8 $\pm$ 9.8	40–90
	DKA parameters		
4	Glucose (mg/dl)	406.8 $\pm$ 130.4	161–600
5	pH	7.128 $\pm$ 0.157	6.8–7.4
6	Bicarbonate (mEq/l)	8.2 $\pm$ 5.0	1–19
7	Anion gap	23.4 $\pm$ 6.7	11–37
8	Serum ketone (mmol/l)	5.38 $\pm$ 1.56	0.8–10.0
	Biochemical parameters		
9	Sodium (mEq/l)	137.0 $\pm$ 6.4	121–151
10	Potassium (mEq/l)	3.9 $\pm$ 1.0	1.3–5.9
11	Blood urea (mg/dl)	62.2 $\pm$ 51.4	14–261
12	Creatinine (mg/dl)	1.35 $\pm$ 1.18	0.4–5.2
	Hematological parameters		
13	Hemoglobin (gm/dl)	10.9 $\pm$ 2.3	7–15
14	Peripheral leucocyte (per mm^3)	13270 $\pm$ 7293.56	3900–33100
15	Platelets (per mm^3)	221520 $\pm$ 136666	27000–683000

serum ketone level 5.38 $\pm$ 1.56 mmol/l. Regarding blood gas analysis on admission, mean pH was 7.128 $\pm$ 0.157, mean bicarbonate 8.2 $\pm$ 5.0 meq/L and the mean anion gap was 23.4 $\pm$ 6.7 (Table 1). Out of 50 cases, we observed mild DKA in 11 (22%), moderate in 25 (50%) and severe DKA in 14 (28%) patients.

Complete blood counts demonstrated that mean hemoglobin was 10.9 $\pm$ 2.3 gm/dl and 70% patients had anemia (according to World Health Organization criteria, i.e., hemoglobin <12 g/dl in women and <13 g/dl in men). Mean white cell count was 13270 $\pm$ 7293.56 per mm^3 and 44% of patients had leucocytosis. Mean platelet count was 221520 $\pm$ 136666 per mm [3].

Biochemistry panel showed hyponatremia and hypokalemia as commonest electrolyte disturbance; each was seen in 34% of patients. Mean serum levels of sodium and potassium were 137.0 $\pm$ 6.4 meq/dl and 3.9 $\pm$ 1.0 meq/dl, respectively. Mean values of blood urea and serum creatinine were elevated (62.2 $\pm$ 51.4 mg/dl and 1.35 $\pm$ 1.18 mg/dl, respectively), reflecting the intravascular volume depletion in DKA patients.

Management of DKA and precipitating causes: Normal saline was fluid of choice for initial resuscitation (bolus dosing) as well as for maintenance fluid replacement. Mean amount of required fluid was 1.26 $\pm$ 0.51 L in the initial first-hour resuscitation and 4.13 $\pm$ 1.96 L in the first 24 h of hospitalization. Short-acting regular insulin was administered as a continuous infusion without an initial bolus dose and was adjusted according to hourly blood glucose monitoring. Endotracheal intubation or mechanical ventilation was required in 18% of patients given poor Glasgow Coma Scale, respiratory failure or hemodynamic instability. 24% of DKA patients received vasopressors for hypotension not responding to intravenous fluids, noradrenaline being the initial vasopressor of choice. Treating physicians decided to start empirical antibiotics in a majority (78%) of the DKA patients; however, only 36% of patients had documented infections during further evaluation.

Among the 50 patients, nonadherence to the antidiabetic treatment was the major precipitating cause of DKA, found in 26 cases (52%). Infections were the next common precipitating factors (18 cases, 36%). Lung was the most frequent site of infection (7 out of 18 cases) with community-acquired pneumonia (5), pulmonary tuberculosis (1), and fungal pneumonia (1). Four patients had urinary tract infection, in which three had *Escherichia coli* in urine culture. Less common infections were acute meningoencephalitis (2 cases) and acute gastroenteritis (2 cases).

Prognosis: In our study, the mean duration of hospital stay was

Table 2
Comparison of various Indian DKA studies [8–15].

Authors & publication year	Matoo VK et al. (1991) [8].	Adhikari et al. (1997) [9].	Seth P et al. (2015) [10].	Aggarwal A et al. (2016) [11].	Chaudhary R et al. (2016) [12].	Mahesh MG et al. (2017) [13].	Singh AK et al. (2017) [14].	Sonowani S et al. (2018) [15].	Present Study
Sample size (n) && % of T1DM cases	143 NA	43 37.2%	60 20%	270 62.6%	52 17%	110 NA	120 66.7%	120 Only Type 2 DM	50 74%
Commonest presentations	NA	NA	Nausea/vomiting abdominal pain	NA	Dehydration, nausea vomiting & polyuria/ polydipsia	Vomiting, generalised weakness & abdominal pain	Nausea/vomiting dehydration & abdominal pain	Nausea/vomiting & abdominal pain	Nausea/vomiting, dyspnea, abdominal pain & fever
Main precipitating factors	1. Infection (30%) 2. Non-compliance (20%)	NA	1. Infection (73.3%) (lung - 40.9%; UTI - 27.3%) 2. Non-compliance (66.6%)	1. Infection (60%) (lung - 34%; UTI - 20%) 2. Non-compliance (18.9%)	1. Infection (49.6%) (lung – 34.7%; UTI - 9.6%) 2. Non-compliance (19.2%)	1. Infection (52%) (UTI - 27%; lung - 21%; cellulitis - 24%) 2. Non-compliance (21%)	1. Infection (59.2%) (lung – 41.7% (tuberculosis - 23.3%); UTI -17.5%) 2. Non-compliance (33.3%)	1. Infection & non-compliance combined (53%) (lung - 24%; UTI -22%)	1. Non-compliance (52%) 2. Infections (36%) (lung - 14%; UTI - 8%)
Severe DKA (%)	NA	NA	NA	50%	30.8%	NA	NA	4%	22%
Mortality	23.7%	16.3%	10%	30%	10.3%	9.1%	6.7%	7%	None

Abbreviation: T1DM: type 1 diabetes mellitus, NA: not available.

8.2.±5.0 days with a range of 1—24 days. Survival records showed no mortality during the hospital stay, but one patient left against medical advice. Response to medical treatment and intensive care was evaluated by assessing the duration of hospital stay. High pulse rate (p = 0.025) and low hemoglobin (p = 0.019) at presentation were significantly associated with longer length of hospital stay.

4. Discussion

Using ADA criteria for DKA, retrospective data of 50 patients admitted in the medical emergency department were analyzed. The majority of our patients were younger and had type 1 diabetes. Incidence of new-onset diabetes presenting as DKA, which ranges from 10 to 27% in various studies, was 20% in our study [16,17].

Among the remaining 80% (40/50) previously diagnosed cases, about one third (13 patients) had recurrent DKA (one or more DKA episodes in the past). Recurrent DKA is a highly morbid condition which usually results from exogenous insulin deficiency (noncompliance or undertreatment) [18,19]. Using the T1D Exchange Clinic Registry in the United States of America, Weinstock RS et al. found that 4.8% type 1 diabetic patients developed a recurrence of DKA in 1 year [20]. However, another study from North America detected 55.5% of cases of recurrent DKA, mainly due to poor adherence to insulin treatment [21].

We found noncompliance is the commonest precipitant of DKA, and the next common was an infection. Most of the Indian studies have shown infection as a leading cause of DKA precipitation (Table 2). Concurring with previous studies, we found the focus of infection in the lung or urinary tract in the majority of the cases. A large Israel study of 220 patients showed that lack of exogenous insulin (due to missed insulin, changed insulin therapy) was the principal precipitant; however, severe DKA was commonly precipitated by infections [22].

Despite having 22% severe DKA cases and 18% of patients requiring mechanical ventilation, we observed no mortality, correlating with <1% mortality in DKA with intensive care, worldwide. Regarding the length of hospital stay or resolution of ketoacidosis, none of the DKA parameter (blood glucose, blood pH, serum bicarbonate or ketone level) showed a significant association, as observed in previous studies [16]. We found that for a more extended stay in the hospital, low hemoglobin and high pulse rate were independent predictors.

Therefore, in conclusion, our study detected DKA as a multisystem disorder; i.e., an endocrine emergency which usually presents with gastrointestinal or nervous system complaints, precipitated by infections of the respiratory or urinary tract and low hemoglobin predicts prolonged hospital stay.

Our study is limited by its retrospective design and small sample size, as approximately twice the number of the sample size case files had incomplete data and thus not included in the study.

5. Conclusion

Even though the progress in intensive care and sepsis management in India have made DKA to have <1% mortality, poor compliance remains the leading cause of DKA (as well as recurrent DKA). Patients and their caretakers should receive education regarding diabetes, its complication, and insulin therapy before hospital discharge.

Funding

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.06.002.

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