■ *Original Article*

Clinical profile of diabetic ketoacidosis in adults

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Abstract

Introduction: Diabetic ketoacidosis (DKA) is a potentially life-threatening complication of diabetes mellitus. Recent epidemiological studies indicate that hospitalizations for DKA in the U.S. are increasing. Epidemiological studies from India are limited. We undertook this observational study to analyse the clinical profiles of DKA in adults in south India. **Methods:** This study was conducted in at a tertiary care center in Andhra Pradesh for one year from Aug 2010 to July 2011. Diagnosis of DKA was made by the presence of (1) Plasma glucose level of 250mg/dl or higher (2) Serum bicarbonate level of 15mEq/lt or lower (3) Arterial blood pH of 7.3 or lower or a venous blood pH of 7.25 or lower (4) Presence of moderate or large urine ketones. All the patients were treated with institutional treatment protocol. **Results:** Of 27 patients, 22(81%) had type2 diabetes and 5(19%) had type 1 DM .10 were females and 17 males. Age of the patients ranged between 18 to 70 years, with an average of 45.3 years. Precipitating factors were present in 60% of the admissions. Non-compliance or discontinuation of drug therapy was seen in fifty per cent of patients. Average length of hospital stay was slightly longer in type 1 than type 2 DM patients **Conclusion:** A significant proportion of DKA occurs in patients with type 2 diabetes and many of these cases can be prevented with proper patient education and effective communication with a health care provider during an inter-current illness.

Keywords: DKA, type-2 diabetes mellitus

Introduction

Together with hyperglycemic coma, diabetic ketoacidosis (DKA) is the most severe acute metabolic complication of diabetes mellitus (DM).[1] Defined by the triad hyperglycemia, acidosis, and ketonuria, DKA can be inaugural or complicate known diabetes.[2] Although DKA is evidence of poor metabolic control and usually indicates an absolute or relative imbalance between the patient's requirements and the treatment, DKA-related mortality is low among patients who receive standardized treatment, which includes administration of insulin, correction of hydroelectrolytic disorders, and management of the triggering factor (which is often cessation of insulin therapy, an infection, or a myocardial infarction).[3,4]

In general, DKA is always described to be closely linked to type 1 DM. The occurrence of DKA has been thought to indicate the underlying significant and irreversible ß-cell damage that classifies these diabetic patients as type 1 DM However, many DKA patients do have clinical course and metabolic features of type 2 DM. There is a strong, almost dogmatic, errant perception by physicians that DKA is a complication that occurs only in patients with

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type 1 diabetes. But in fact, DKA does occur in type 2 diabetes; however, it rarely occurs in the absence of a precipitating event.

Recent epidemiologic studies estimate that hospitalizations for DKA have increased during the past 2 decades.[5] Part of this increased frequency of admissions may be related to the increased prevalence of type 2 diabetes. With the changes in the frequency of DKA and the increased incidence of DKA in patients with type 2 diabetes mellitus, the question may be posed of whether there has been any change in the clinical or laboratory characteristics of the patients with DKA who present to the emergency department.

In India, there have been few investigations focusing on the type 2 diabetic patients who suffered from DKA episodes. We therefore undertook to examine the clinical characteristics of diabetic patients who presented with DKA to our hospital.

Objective

To study the clinical profile of DKA episodes in adult diabetic.

Methods

The patient population included in this study was adult diabetics aged 18 years and above who had been admitted in ICU under General Medicine of our hospital due to DKA during one year period from Aug 2010 to July 2011.

The diagnosis of DKA was made in the emergency department by the presence of 3 laboratory findings: a plasma glucose level of 250 mg/dL or higher; a serum bicarbonate level of 15 mEq/L or lower, an arterial blood pH of 7.30 or lower, or a venous blood pH of 7.25 or lower; and moderate or large urinary ketones.[6]

Intravenous insulin was administered according to the standard institutional treatment algorithm. Additional hydration and electrolyte replacement were left to the discretion of the treating physicians, although following the American Diabetes Association practice guidelines was encouraged[6]. The insulin infusion was discontinued 2 hours after the administration of subcutaneous insulin once patients had resolution of their metabolic status, including a ketone-free urine sample, and were able to tolerate oral feedings.

Data collection: According to standardized procedure, we recorded the following information prospectively: (1) demographics (2) co morbidities; (3) characteristics of the diabetes (4) presenting complaints at admission (including systemic, respiratory, gastrointestinal, and neurological symptoms; bedside blood and urine dipstick quantification of glycemia, glycosuria, and ketonuria; (5) precipitating factors, (6) vital signs, (7) biochemical profile and (8) events and treatments during the first 24 h after admission and data concerning clearance of ketonuria, evaluated at 6-hour intervals with use of reagent strips (graded with 0–5 plus signs).

Patients were assigned to the type 2 diabetes group if they were previously diagnosed as having diabetes and at some time in their disease, other than a time consistent with the "honeymoon period," were managed with diet and exercise alone or with oral hypoglycemic agents or were noncompliant with their insulin regimen for more than 3 weeks preceding admission. Patients with newly diagnosed diabetes were assigned to the type 2 group if they tested negative for autoimmune antibody or if they had phenotypic features of type 2 diabetes (such as obesity, acanthosis nigricans, or a family history of type 2 diabetes) and were noted to have a stressful event (eg, infection) that precipitated the episode of DKA. Based on recent evidence that indicates similar biochemical profiles and physical characteristics, patients with idiopathic type 1diabetes (type 1B) were included in the type 2 diabetes subgroup for purposes of analysis.[7]

A stressful event was defined by: (1) clinical or biochemical evidence of any infections, (2) inflammatory, painful, or physically traumatic process, and (3) use of any drugs likely to elevate plasma catecholamine or cortisol levels. Infection was either clinically or microbiologically documented. Clinically documented infection (considered as a "probable" infection) was defined according to its site as one of the following: urinary tract infection (characterized by micturition disorders, frequency, burning

sensations during voiding, low-back pain), respiratory infection (cough, expectoration, chest pain, focal crackles), ear-nose-throat infection (rhinorrhea, odynophagia, headache), gastrointestinal infection (diarrhea, abdominal pain, obstruction, peritonitis), meningoencephalitis (headache, vomiting, stupor, coma), or skin and soft-tissue infection. Microbiologically documented infection (considered as a "definite" infection) was defined according to the results of the tests done to document infection. Routine tests at admission to detect presence of infections were done like blood culture, chest radiography, urine culture: stool tests, sinus radiography, lumbar puncture, abdominal sonography, bronchoscopy with protected brushing, skin-swab testing as indicated by clinical manifestations. Infection of the gastrointestinal tract was considered only if the clinical manifestations described above were associated with a microbiologically documented infection, an abnormal abdominal sonogram, or perioperative evidence of peritonitis.

Results

During the study period, 33 adult patients were admitted to medical ICU with suspected episodes of DKA but 6 patients did not achieved the diagnostic criteria of DKA and were excluded.

22 episodes (81%) occurred in the type 2 DM and 5 episodes (19%) in the type 1 DM. 10 were females (37%) and 17 males (63%). This reflects the male dominance of the disease and the current epidemiology of DKA in rural area of Khammam, Andhra Pradesh. The age of male patients ranged from 22 years to 65 years, the average being 43.1. The age of female patients were ranged from 18 years to 70 years with an average of 49 years. The female to male ratio is 1: 1.7.

Table 1: Age distribution of study population

Age in years	Male	Female
<20	0	1
20-30	4	0
30-40	1	0
40-50	7	3
50-60	2	4
60-70	3	1
70-80	0	1
Total	17	10

In this study, age of the patients was ranged between 18 to 70 years, with an average of 45.3 years. The maximum number of cases was found between 40 to 50 years (45%) in case of type 2 diabetes and 20 to 30 years (80%) in type 1 diabetes. Only 4.5% of the type 2 diabetic patients were < 30 years old whereas more than 50% were older than 50 years. Precipitating factors were identified in 60% of cases. The major precipitating factors of total episodes included infection (43%), chronic kidney disease (25%) and acute myocardial infection (12.5%). Newly diagnosed diabetes accounted for 18.5% of cases. Among the infections, urinary tract infections were most common, followed by septicemia and pneumonia. The incidence of occurrence of DKA with infections was more in type 1 DM than type 2. Infections as precipitating event was identified in 60% of episodes of DKA in type 1 where as only one third of patients (33%) with type 2 DM had infection. In type 2 DM some stressful events like associated medical conditions; family related matters etc were seen in majority of cases (60%) which eventually lead to development of DKA. Non-compliance or discontinuation of drug therapy was seen in 50% of patients. However, in the type 1 DM, poor drug compliance accounted for only 20% of cases. Some episodes of DKA revealed no obvious precipitating factors, 20% in type 1 DM and 14 % of type 2 DM. Symptoms present at the time of presentation along with the duration are summarized in Table 2.

Table 2: Clinical characteristics of patients presenting with DKA

Symptom	Frequency, % of admissions	Symptom duration Mean ± SD
Nausea, vomiting	40	3.3±1.8
Breathlessness	36	6.4±9.1
Fever	28	11.2±10.4
Altered sensorium	28	4.8±4.96
Abdominal pain	24	2.3±1.8
Chest pain	16	5.3±5.9

Table 3: Laboratory characteristics of patients presenting with DKA

Component	Low frequency (%)	Normal frequency (%)	High frequency (%)
Glucose	0	0	100
Arterial pH	100	0	0
Bicarbonate	100	0	0
Sodium	72	28	0
Potassium	12	52	36
Blood urea nitrogen	0	76	24
Creatinine	0	68	32
Serum osmolality	0	100	0

Compared with those patients with normal or low potassium levels, the patients with hyperkalemia at the time of presentation had correspondingly higher plasma glucose levels and lower serum sodium levels.

Table 4: Comparison of laboratory parameters between type 1 and type 2 DM at presentation

Variables	Type 1 DM	Type 2 DM
No. of admissions	5	22
Glucose (mg/dL)	439.6	507
Arterial pH	7.114	7.28
Bicarbonate (mEq/L)	10.1	11.3
Sodium (mEq/L)	135.8	130.42
Potassium (mEq/L)	5.34	4.22
Blood urea nitrogen(mg/dL)	30.4	38.47
Creatinine (mg/dL)	1.2	1.5
Serum osmolality (mmol/L)	296.4	280.25

Overall patients had cleared their urine ketones at an average of 50 hours after being initiated on an insulin infusion.

With regard to complications associated with treatment of DKA, 2 patients had a blood glucose level of less than 70 mg/dl at some point during the insulin infusion. One of these episodes occurred after the patient received a subcutaneous injection of insulin in anticipation of discontinuing the intravenous insulin infusion but failed to tolerate the associated meal. None of the episodes of hypoglycemia were reported to be clinically significant. Hypokalemia occurred in 16% of patients during the insulin infusion but was not clinically significant and were detected during routine electrolyte monitoring. None of the patients developed cerebral oedema and there were no deaths. One patient developed acute respiratory distress syndrome within few hours of presentation to the emergency department.

The average length of hospitalization was slightly longer in type 1 DM patients than in the type 2 DM patients (8 days vs 6.5 days; p-value = 0.48).

Discussion

Diabetic ketoacidosis (DKA) was classically considered to occur only in persons with type 1 diabetes mellitus. Hyperglycemia in type 2 diabetes was thought to lead only to hyperosmolar hyperglycemic state (HHS) without ketosis. Our results indicate that a large percentage of patients (81%) from rural population of Andhra Pradesh, India who present with DKA have type 2 diabetes in adult population. Similar findings have been reported by a Chinese study.[8] They reported DKA in 71.5% in type 2 DM. There are some possible explanations for this finding. First of all, type 1 DM is predominantly a disease of whites; it is rare in Indians and Chinese. Secondly, most of the type 1 diabetic onset develops in the pediatric period. The clinical features of DKA occurring among the adult patients may therefore present with different characters. Balasubramanyan and colleagues reviewed the clinical profiles of 141 adults admitted to the hospital with diabetic ketoacidosis.[9] At presentation, 39% of patients were considered to have type 1diabetes, 53% were considered to have type 2 diabetes, and 8% were not classified. However, a retrospective review found that among adult patients presenting with DKA, 47% had known type 1 diabetes, 26% had known type 2 diabetes and 27% had newly diagnosed diabetes.[10]

An underlying deficiency of insulin, with elevation in counter-regulatory hormones, is found in DKA. There are three proposed mechanisms of DKA in type 2 diabetics: 1) Insulinopenia, 2) Elevation of counter regulatory stress hormones, and 3) Increase in free fatty acids. Some authors/studies believe that only the first one of these, insulinopenia, is significant in type 2 diabetics.[11]

In the largest study of DKA in type 2 diabetics, Linfoot[11] found, using c-peptide concentration as a marker for insulin, a significant decrease in plasma

c-peptide concentration at the time of DKA presentation in type 1 diabetics and ketosis-prone type 2 diabetics. The stressors precipitating DKA have been postulated to cause a relative rather than a definitive deficiency of insulin. Possible causes for this relative insulin deficiency include impairment of insulin secretion due to chronic exposure of insulin secreting or islet cells to high levels of glucose of free fatty acids.[12] Additional causes are hypokalemia, which can impair insulin secretion, and prolonged fasting, which increases the rate of ketosis, and may decrease insulin secretion.

Although elevation of counter-regulatory stress hormones and free fatty acids are postulated mechanisms, Linfoot found that the plasma concentrations of the stress hormones and free fatty acids were not significantly different in ketosis prone and non ketosis prone, type 2 diabetics.[11] Thus he believed the predominant mechanism for ketosis in these patients is the deficiency or decrease in insulin secretion. We did not measure the C-peptide levels and therefore we can only hypothesize about the possible role of insulinopenia in the development of DKA in our patients. However, it is hard to ignore the possible role of counter regulatory hormones in these patients as 60% of these patients were having a stressful event prior to development of DKA. Increased secretion of glucagon (as well as other counteregulatory hormones such as cortisol, catecholamines, and growth hormone) in response to stress from *1*) overwhelming infection *2*) infarction of tissue *3*) other severe illness further suppress insulin secretion to perpetuate a downward spiral.

In our study of adult DKA patients, the mean age was 45.3 years, with insignificant male predominance for both types of diabetes. However, type 2 diabetic patients were significantly older than that of type 1. There is a common perception that significant\physical stress (other than the effects of persistent hyperglycemia per se) is a prerequisite for patients with type 2 diabetes to develop DKA.[13, 14] However, we found that about 40% our type 2 patients had no identifiable antecedent or concurrent stressful condition. DKA appears to be precipitated by transient insulinopenia. An adequate insulin secretory response is restored in these patients by aggressive management of diabetes.

Infection is the major precipitating factor, occurring in 43% of our patients, with urinary tract infections and pneumonia being the most common infections. Similar reports have been described by other investigators also.[2,3] We found that in many instances, an acute illness, such as cerebro-vascular accident or myocardial infarction, has precipitated the DKA by the release of counter regulatory hormones. Therefore, DKA should be considered in patients with diabetes who have a concurrent infection, stroke, myocardial infarction, or other serious illness. These intercurrent illnesses should be sought and treated aggressively.

Omission of insulin therapy for a variety of reasons has also been shown to be the leading precipitating cause of DKA in urban, African American patients with known diabetes.[15] In our study also nearly fifty per cent patients discontinued treatment prior to development of DKA. Many of our "previously diagnosed" type 2 patients had no obvious precipitating cause other than prolonged omission of oral hypoglycemic therapy. However, since we did not collect data on other behaviors that might have influenced progression to DKA, such as diet and physical activity, future prospective studies should examine comprehensively the impact of treatment compliance in precipitating DKA in patients with type 2 diabetes.

The observation that stopping insulin for economic reasons is a common precipitant of DKA[3]. The rate of insulin discontinuation and a history of poor compliance accounts for more than half of DKA admissions in inner-city and minority populations.[3.16] Several cultural and socioeconomic barriers, such as low literacy rate, limited financial resources, and limited access to health care, in medically indigent patients may explain the lack of compliance and why DKA continues to occur in such high rates in inner-city patients.

Although nonspecific, the symptoms of nausea, emesis, and abdominal pain are related to the presence of ketonemia. It was observed that symptoms of osmotic diuresis did not bring people to medical attention, but nausea, vomiting, and abdominal pain do. Unfortunately, the classic symptoms of DKA may not always be apparent.[17]

Almost 50% of patients in our study presented with nausea, vomiting and abdominal pain.

The laboratory data for our patients presented in Tables 3 are consistent with results that would be predicted for DKA. Potassium levels will tend to be high because of the physiologic compensation of the metabolic acidosis and the hyperosmolarity and insulin deficiency present, although it is known that total body stores of potassium are depleted in DKA.[17, 18] A little less than one fifth of the patients had newly diagnosed diabetes, accounting for approximately 20% of the admissions which is consistent with other reports.[16] Hypoglycemia and hypokalemia are two common complications with overzealous treatment of DKA with insulin and bicarbonate, respectively, but these complications have occurred less often with the low-dose insulin therapy.[6]

Cerebral edema, which occurs in 0.3–1.0% of DKA episodes in children, is extremely rare in adult patients during treatment of DKA. None of our patients developed cerebral edema during the course of hospitalization.

In community-based studies, more than 40% of African-American patients with DKA were >40 years of age and more than 20% were >55 years of age.[19]

Conclusion

Most patients with DKA have type 1 diabetes; however, patients with type 2 diabetes are also at risk during the catabolic stress of acute illness 2. Contrary to popular belief, DKA is more common in adults than in children. A significant proportion of DKA occurs in patients with type 2 diabetes and many of these cases can be prevented with proper patient education and effective communication with a health care provider during an inter-current illness.

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