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Original Article-Triggers in Diabetic Ketoacidosis and Predictors of Adverse Outcome

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Abstract
Diabetic ketoacidosis (DKA) though much more common in type 1 diabetes, patients with type 2 diabetes mellitus are also susceptible to DKA. An analysis and overview of the different clinical characteristics of diabetic ketoacidosis in patients with type 1 and type 2 diabetes is needed.
Aims- To study the precipitating factors triggering diabetic ketoacidosis.2. To compare the clinical and biochemical characteristics of type 1 versus type 2 diabetes mellitus (DM) and to assess the outcome in patients with DKA.
Materials and Methods- This prospective study was conducted in 50 hospitalized patients with diabetic ketoacidosis. Patients were classified as having type 1 or type 2 on the basis of age and treatment history. Groups were compared for differences in clinical presentation, precipitating factors and biochemical profiles at the time of admission. Statistical analysis used: Statistical Package for the Social Sciences (SPSS) software (t- test)
Results: 50 cases of diabetic ketoacidosis admitted in emergency were selected for study. Male: Female ratio was 1:1. 27 (54%) were type 1 diabetes mellitus(DM) and 23(46%) type 2 DM on the basis of age and treatment history. 19(28%) were on insulin alone and 13(26%) cases were new patients presenting with DKA. In type 1 DM, the mean age was 23.5 years whereas it was 49.6 years for type 2 DM. 24(48%) episodes of DKA occurred in patients less than 30 and 8(16%) episodes were observed in those between 51- 70 years of age. Vomiting, pain abdomen, altered sensorium were common symptoms observed on presentation in addition to symptoms of precipitating factors like cough, burning micturition, fever etc. The trigger for the development of DKA was identified in44 (88%) patients. Commonest precipitating factor for DKA in Type 1 DM cases was noncompliance with insulin seen in 14(51.9%) followed by infections in 12(44.4%). In Type 2 DM cases most common precipitating factor was infection in 16 (69.8%). Mortality was 3(6%). They had associated comorbidities. The mean bicarbonate was 5.4 mEq/ L for the expired group and 14.5 mEq/L for the survived group (P value 0.02).
Conclusions: - A significant proportion of DKA occurs in patients with type 2 diabetes. DKA may be the first presentation of diabetes. A precipitating factor for the development of DKA should be searched for during initial evaluation for optimal management and favorable outcome. Overall infections account for majority of DKA in type 2 and omission of insulin in type 1DM. Very low bicarbonate levels at admission may predict mortality.

Keywords: Diabetic ketoacidosis, Infection, Precipitating Factors

Introduction
Diabetic ketoacidosis (DKA) is a medical emergency. Increased frequency of hospitalization for DKA may be due to increased prevalence of type 2 diabetes mellitus (DM) [1, 2]. DKA occurs in the setting of absolute or relative insulin deficiency combined with increased levels of counter regulatory hormones, such as glucagon, catecholamine's, cortisol and growth hormone under stressful conditions. DKA may be the first presentation of diabetes. Previously thought to occur only in patients with type 1 diabetes, diabetic ketoacidosis is now known to occur in patients with type 2 diabetes [3].
Initial evaluation of patients with DKA includes diagnosis and treatment of precipitating factors. Insulin omission with or without intercurrent illness is the most common precipitating factor, accounting for most of the cases of DKA [4]. Infection, trauma, myocardial infarction, surgery are some of the conditions which lead to an increase in insulin requirements and thus to DKA [5].

Diabetes mellitus is a chronic metabolic disorder that is gradually assuming pandemic proportions. An unfavorable social and economic environment is the basis of the high prevalence of DKA in our country. Several episodes of DKA can be prevented by effective public awareness programmes and education to healthcare providers [6]. An analysis and overview of the different clinical and biochemical characteristics of DKA between patients with type 1 and type 2 diabetes is needed, hence this study.

Aims and Objective

1. To study the precipitating factors triggering diabetic ketoacidosis.
2. To compare the clinical and biochemical characteristics of type 1 versus type 2 diabetes mellitus (DM) and to assess the outcome in patients with DKA.

Material and Method

This study was conducted in JA Group of Hospitals, G.R. Medical College, and Gwalior between April 2013 to November 2014. Ethical clearance was given by the ethical society of G.R. Medical College, Gwalior. Informed consent was taken by the subjects/ attendants in case of unconscious patients.

This prospective study was conducted in 50 hospitalized patients with diabetic ketoacidosis. The patients with Hyperosmolar hyperglycemic state (HHS) were excluded. The diagnosis of DKA was based on three 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 7.3 or lower and urinary ketones. The symptom profile, clinical and biochemical profile, precipitating events and the outcome was recorded for every selected case. Patients were classified as having type 1 or type 2 on the basis of age and treatment history. Groups were compared for differences in symptoms, precipitants, biochemical profiles at presentation. Precipitating events were searched for and if at all present recorded in the pre- typed proforma. Patients were managed by intravenous fluid, insulin infusion, electrolyte monitoring and correction as and when required in addition to addressing the precipitating factor. Analysis was done using Statistical Package for the Social Sciences (SPSS) software (t- test). Values < 0.05 were considered statistically significant.

Results

Table-1: Showing Treatment History of Patients Presenting With Diabetic Ketoacidosis.

Treatment	Number Of Cases With Dka	Percentage
Insulin	19	38.0
Insulin+Drugs	9	18.0
Newly Diagnosed	13	26.0
Total	50	100.0

Table-2: Showing Episodes of Diabetic Ketoacidosis in Various Age Groups

Age in years	No of cases	Percentage
15-30	24	48.0
31-50	18	36.0
51-70	8	16.0
Total	50	100.0

Table-3: Showing Clinical Presentation of Diabetic Ketoacidosis at the Time of Admission in Type 1 and Type 2 Diabetes Mellitus.

Clinical Presentation	Type 1 DM 27	%	Type 2 DM 23	%	Total
Fever	10	37.03%	7	30.43%	17
Vomiting	12	44.4%	10	43.47%	22
Abdominal Pain	11	40.74%	8	34.78%	19
Burning micturition	6	22.2%	3	13.04%	9
Cough	7	25.92%	5	21.73%	12
Altered Mental status	17	62.9%	9	39.1%	26

Table 4: Shows Precipitating Factors for Dka in Type 1 and Type 2 Diabetes Mellitus.

Precipitating Factors	Diabetes Mellitus Type 1 (27)	% Percentage	Diabetes Mellitus Type 2 (23)	% Percentage	Total (50)	% Percrentage
Omission Of Insulin Or Drugs	14	51.9	4	17.4	18	36
Infections						
Respiratory	1	3.7	5	21.7	6	12
Urinary	1	3.7	6	26.1	7	14
Gastrointestinal	2	7.4	0	0	2	4
Malaria	2	7.4	0	0	2	4
Tuberculosis	6	22.2	3	13.04	9	18
Diabetic Foot	0	0	1	4.3	1	2
Tubercular Meningitis	0	0	1	4.3	1	2
Total	12	44.4	16	69.6	28	56
Other Illnesses						
Coronary Artery Disease	0	0	2	8.7	2	4
Cerebrovascular Disease	0	0	2	8.7	2	4
Surgical	1	3.7	0	0	1	2
Unknown	2	7.4	4	17.4	6	12.0

Table-5: Comparison of Biochemical Parameters between Expired and Survived Groups Admitted With Diabetic Ketoacidosis

Patient Outcome	Expired (3)				Survived (47)				Total-50				P value- between expired and survived	
	Mean	± SD	Min	Max	Mean	± SD	Min	Max	Mean	± SD	Min	Max		
RBS	586.7	23.1	560	600	476.4	87.6	265	630	483.0	89.0	265	630	0.0005	Significant
HB%	9.3	2.8	6.9	12.4	10.2	1.8	6.4	14.9	10.2	1.9	6.4	14.9	0.65	Not significant
TLC	9666.7	3384.3	6800	13400	11066.0	4904.8	4600	27900	10982.0	4812.9	4600	27900	0.55	Not significant
Urea	29.3	14.2	14	42	42.9	26.2	12	124	42.1	25.8	12	124	0.21	Not significant
Creatinine	1.0	0.2	.74	1.19	1.0	0.5	.26	2.70	1.0	0.5	.26	2.70	0.99	Not significant
Na+	134.0	7.0	126	139	135.1	5.1	122	149	135.0	5.2	122	149	0.87	Not significant
K+	3.6	1.1	2.8	4.8	4.2	0.9	2.3	6.1	4.1	0.9	2.3	6.1	0.46	Not significant
PH	7.0	0.1	6.88	7.00	7.2	0.1	6.82	7.30	7.2	0.1	6.82	7.30	0.066	Not significant
HCO3	5.4	2.6	2.9	8.0	14.5	1.9	10.0	18.0	13.9	2.9	2.9	18.0	0.023	Significant

Review of prospectively collected data revealed the following. Out of 50 cases of diabetic ketoacidosis 27 (54%) were type 1 diabetes mellitus(DM) and 23(46%) type 2 DM on the basis of age and treatment history (Table-1). We observed that the maximum number of cases 19(28%) were on insulin alone and 13(26%) cases were new cases presenting with DKA therefore not on any treatment.

25 cases were male (50%) and 25 females (50%) M: F ratio was 1:1

Youngest patient was 15 years of age and the oldest patient 70 years. In type 1 DM, the mean age was 23.5 years whereas it was 49.6 years for type 2 DM. 24(48%) episodes of DKA occurred in patients less than 30, 18 (36%) episodes in persons between 31- 50 and 8(16%) episodes were observed in those between 51- 70 years of age.(Table- 2)

4(14.8%) patients with type 1 DM had history of previous hospitalization for DKA. However none of the patients with type 2 DM had a history of previous episode of DKA.

On admission vomiting was present in 12(44.4%) patients with type 1 DM and 10(43.5%) patients with type 2 DM. Pain abdomen was present in 11(40.7%) with type 1 and 8(34.8%) with type 2 DM. Neurological manifestations with altered sensorium was observed in 17(62.9%) with type 1 DM and 9(39.1%) with type 2 DM at the time of admission.

Other symptoms observed were the consequences of the precipitating factor. Fever in 10(37.03%) with type 1 DM and 7(30.43%) with type2 DM; cough in 7(25.9%) with type 1DM and 5(21.7%) with type 2 DM; and burning micturition in 6 (22.2%) with type 1DM and 3(13.04%) with type 2 DM. (Table-3)

Signs of dehydration were present in 17 (62.9%) with type 1 DM and 15(65.2%) with type 2 DM.

The trigger for the development of DKA was identified in44 (88%) patients.

Commonest precipitating factor in Type 1 DM cases was noncompliance with insulin in 14(51.9%) followed by infections in 12(44.4%). In Type 2 DM cases most common precipitating factor was infection in 16 (69.8%). (Table-4)

Overall infection was identified in 28 (56%) which included pulmonary tuberculosis in 9 (18%), tubercular meningitis in 1 (2%), respiratory tract infection in 6 (12%), urinary tract infection in 7(14%). Other infections including malaria, diabetic foot comprised 3(6%). Surgical emergency (gastric outflow obstruction) was identified in one(2%) patient with type 1 diabetes mellitus. 2 (4%) patients with type 2 diabetes presented with acute coronary syndrome and another 2(4%) patients with type 2 diabetes mellitus presented with cerebrovascular accidents.(Table- 4)

Patients previously diagnosed as having type 2 diabetes were found to be noncompliant with their diabetes therapy in 4(17.4%).

6(22.2%) and 3(13.0%) cases with type 1 DM and type 2 DM respectively had pulmonary tuberculosis. Overall 9(18%) cases had pulmonary tuberculosis which was also the commonest infection observed followed by urinary tract infection.

Mortality was 3(6%). 2 patients with type 1DM and 1 patient with type 2 DM expired. They had associated comorbidities. One patient with type 1DM had a surgical comorbidity and the two others had medical comorbidities. The mean bicarbonate was 5.4 mEq/ L for the expired group and 14.5 mEq/L for the survived group (P value 0.02). Mean blood sugar was 586.7 mg/dL for the expired group versus 483 mg/dL for the survived group (Pvalue 0.0005) Table-5

Discussion

Patients presenting with diabetic ketoacidosis may have type 1 or type 2 diabetes. Out of 50 cases 27(54%) were classified as type 1 DM and 23(46%) as type 2 DM based on age and treatment history. In a study by Newton *et al*. 21.7% patients had Type 2 diabetes [1].

In type 1 DM, the mean age was 23.5 years whereas it was 49.6 years for type 2 DM. The patients with DKA and type-2 DM were significantly older than patients with DKA and type-1 DM. Our study was somewhat similar to a study by Andrew E Edo where patients with T2DM were significantly older than those with T1DM (54 years vs. 23 years) [7].

Episodes of DKA were more frequent in the younger age group and the frequency of DKA declined with age. (Table-2)

Patients presented in emergency with either gastrointestinal symptoms namely vomiting and pain abdomen or altered sensorium as neurological presentation. Other symptoms were those of precipitating factors including fever, cough and burning micturition. (Table-3)

Neurological manifestations with altered sensorium was observed in 17(62.9%) with type 1 DM and 9(39.1%) with type 2 DM at the time of admission. When the neurological condition of the patients with DKA deteriorates despite improved metabolic parameters, presence of concomitant CNS infections should be seriously considered [5].

DM was a new diagnosis in 13(26%) presenting as DKA. 8 such patients were grouped under type 1 DM as they were young and 5 patients were grouped under type 2 as they were elderly. In a study by Andrew *et al*., over 50% of the patients presenting with DKA or HHS did not have previous history of DM [7].

This difference may be attributed to exclusion of HHS in our study. In yet another study 19.9% admissions were for newly diagnosed diabetes [1].

Much new-onset DKA can be prevented by increased awareness of early signs and symptoms of diabetes. Ketoacidosis occurs in both Type 1 and Type 2 diabetes although the frequency in type 1DM is higher [1].

An explanation for the development of DKA was identified in 44(88%). (Table-4). 6(12%) did not have any precipitating factor in our study. According to a study, in about 25 % of cases of DKA precipitating factor could not be identified [1].

Frequently identified precipitating factors included omission of insulin and infections. Overall infections accounted for nearly 28(56%) of DKA in our study and appeared to be the most frequent precipitant of DKA. An infection left untreated may adversely affect the short- and long-term control and outcome of diabetes. Infection is not a coincidental concomitant of DKA but an important triggering factor. Examinations of these patients should be supplemented with investigations aimed at documenting infection.

Commonest precipitating factor in type 1 DM was omission of insulin in 14/27 (51.85%) followed by infection in 12(44.44%) in our study.

Patients miss insulin doses for various reasons, for example, inaccessibility, unavailability and unaffordability of insulin, missed clinics, alternative therapies like herbs, prayers and rituals [8].

In type 2 DM infection was the commonest precipitating factor for DKA observed in 16/23 (69.56%). Worldwide, infection is the most common precipitating cause for DKA, occurring in 30-50% of cases [9].

Pulmonary Tuberculosis was the commonest infection 9(18%) followed by urinary tract infection in 7(14%) cases in our study. Pulmonary tuberculosis was observed in 6 (22.2%) patients with type 1 DM and 3 (13.04 %) patients with type 2 DM. However all these patients had radiological evidence of tuberculosis. None were sputum positive for acid fast bacilli. Diabetes and Tuberculosis often co-exist. Developing countries bear the brunt of diabetes and tuberculosis. Diabetes increases the risk of treatment failure, relapse and death among patients with tuberculosis [10].

There are concerns about the merging epidemics of tuberculosis and diabetes particularly in the low to medium income countries like India [11].

Optimal control of Diabetes is necessary for management of tuberculosis. Anti-tubercular drugs interact with oral hypoglycemic agents leading to suboptimal control. Diabetes and tuberculosis interact at many levels each exacerbating the other [12]. Integration of TB and DM services in our country may improve the diagnosis and management of dually affected patients.

Recurrence of DKA in type 1 DM was 4/27 (14.81%). However none of the patients with type 2 DM reported recurrence of DKA.

To conclude a significant proportion of DKA occurs in patients with type 2 diabetes. In a study the majority of DKA could not be classified as classical type 1 diabetes. Some of the newly diagnosed people presenting with DKA could be safely withdrawn from insulin treatment [13].

Mortality was 3 (6%) in our study. Two patients having type 1 DM expired and one patient with type 2 DM expired.All had associated comorbidities. Recent studies using standardized written guidelines for therapy have demonstrated a mortality rate of less than 5%, with higher mortality rates observed in elderly patients and those with concomitant life-threatening illnesses [9].

Another study has reported an overall mortality rate of 3.9%. [4] A very low serum bicarbonate level (mean bicarbonate 5.4 mEq/L) in our study was identified as a risk factor for mortality. High blood sugar was also significant in the expired group. (Table-5). Whether hyperglycemia per se predicts mortality is difficult to admit but very low sodabicarbonate levels may be a poor prognostic factor. Previous studies (not RCTs) have failed to find evidence of biochemical recovery with bicarbonate treatment even in severely ill patients [4].

Limitations

Firstly the sample size was small. Secondly patients presenting for the first time with DKA in elderly age group were presumed to be type 2. However this limitation will always remain because it is very difficult to decide who in future will not require insulin in a case of new diabetes with DKA. Only follow up of such patients will decide in how many, insulin can be safely withdrawn. Thirdly auto antibodies and c-peptide levels could not be done due to financial constraints.

Conclusion

A significant proportion of DKA occurs in patients with type 2 diabetes. A precipitating factor for the development of DKA should be searched for during initial evaluation for optimal management and favorable outcome. Overall infections account for majority of DKA in type 2 and omission of insulin in type 1DM. Radiological evidence of pulmonary tuberculosis exceeded other infections. Dual disease is a matter of concern. Very low bicarbonate levels at admission may predict mortality. Further studies on a large scale basis on tuberculosis and diabetes in DKA is warranted as it will enlighten us further in making strategies to further reduce mortality.

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