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Original Research Article

DIABETIC KETOACIDOSIS: A PROSPECTIVE STUDY ON CLINICAL PROFILE AND ASSESSMENT OF ITS PROGNOSIS BY APACHE-II SCORE

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ABSTRACT

Background: To study the clinical course and outcome and the role of biochemical markers in patients admitted with diabetic ketoacidosis (DKA).
Materials and Methods: It was a prospective (observational), hospital-based study done in all patients of both sexes, who were diagnosed with diabetic ketoacidosis according to ADA* criteria. A detailed history of the participants and laboratory tests including all routine blood investigations like complete hemogram, Blood sugar –random, fasting, postprandial, and HBA1C, serum ketones, Renal function tests, Liver function tests, Arterial blood gas analysis, chest Xray, ECG were done for all the patients at admission and as per the clinical requirement.
Results: The present study determined that there was male predominance. GCS score along with APACHE II was helpful in estimating the various elements indicating towards the prognosis of DKA at the time of admission. It was found that various biochemical markers like ketonuria and hyperglycemia mark DKA and maximum patients had mild GCS (13-15). Infection was found to be one of the most predisposing factors of DKA. There was no significant difference in the APACHE II parameters on DKA between deceased and discharged patients.
Conclusion: The comparison of APACHE II score among two groups of the patients did not show any significant difference. There was no suitable cut-off point for APACHE II score to predict DKA. APACHE II score cannot be applied in the predicting of DKA in hyperglycemic patients.
Keywords: Diabetic Ketoacidosis, APACHE II, Infection. ADA* criteria.

INTRODUCTION

Diabetes mellitus is a clinically and genetically heterogeneous group of metabolic disorders that manifest in an abnormally high level of glucose in the blood. The hyperglycemia is a result of an insulin secretion deficiency caused by pancreatic β- cell dysfunction or resistance to the action of insulin in the liver, adipose tissue, and muscle or a combination of these issues. Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) constitute two opposite spectrum of decompensated diabetes that remains the main causes of morbidity and mortality in diabetic patients inspite of well-developed diagnostic criteria and treatment protocols. Further, Diabetic ketoacidosis (DKA) is a serious and potentially life-threatening complication of diabetes mellitus. It is characterized by a triad of hyperglycemia, high anion gap metabolic acidosis, and ketonemia and represents a state of insulin deficiency and concurrent elevation in counterregulatory hormones.

DKA is accountable for > 500,000 hospital days / year at an estimated annual direct medical expense and indirect cost of 2.4 billion USD4. Many patients with DKA have autoimmune type 1 diabetes; also, patients with type 2 diabetes maintains the risk during the catabolic stress of acute illness such as trauma, surgery, or infections. The physical signs include evidence of dehydration with evidence of hypotension, fruity breath from acetone, increased respiratory rate and kussmaul's breathing. The study

done in 2006 shows that incidence remains high between 4.6 - 8 percent for every 1000 subjects and remains an important cause of mortality in diabetic patients which is rarely caused by a metabolic complication of hyperglycemia or metabolic acidosis, and it is usually related to the underlying medical illness that bring about metabolic compensation. The second most important contributor to the development of DKA is inadequate insulin treatment, commonly seen as a result of noncompliance, especially in the young population. [1,2]

DKA has also been reported with the mismanagement of insulin pumps and undetected leakage of the infusion system or at the time of religious fasting. In some cases, medications, such as corticosteroids, pentamidine, and terbutaline, have been identified as stimulus for DKA. Cocaine use is responsible for repeated missed dose of insulin administration, but it also has marked effects on counter-regulatory hormones. It was found to be an important factor for the development of DKA. [3]

Management is directed towards treating the precipitating factors and coordinating fluid resuscitation, insulin therapy and electrolyte replacement along with continuous monitoring of the patient. Patients with DKA need four things Fluid therapy, Insulin therapy, Potassium, bicarbonate, and phosphate therapy and Education. In patients with shock, early venous access with large-bore cannulas should be placed, basic measures (oxygen, cardiac monitor, regular measurement of pulse and blood pressure) were be instituted. Consider central line only in severely ill patients for monitoring. In patients with low GCS, nasogastric tubes were inserted to prevent aspiration as a resuscitative measure. A urinary catheter was inserted in haemodynamically unstable and who need strict urine output measurement.

Hypoglycemia defined by blood glucose level below 70 mg/dL is the most common complication of DKA which can be managed by repeated monitoring of blood glucose levels and adjustment of insulin dose timely. If DKA is not resolved and blood glucose level is below 200–250 mg/dL, decrease in insulin infusion rate and/or addition of 5% or 10% dextrose to current intravenous fluids can be implemented. Commercially available home glucose-ketone meters which measures β-hydroxybutyrate levels on a fingerstick blood specimen, which help in early detection of ketoacidosis and to guide insulin therapy at home and, possibly, may prevent hospitalization for DKA 12. Ketonemia and ketonuria are trait, as is a serum bicarbonate level of 18 mEq/L or less (less than 5 mEq/L is indicative of severe DKA). These biochemical changes are frequently associated with an increased anion gap, increased serum osmolarity and increased serum uric acid. A prognostic biomarker provides information about the patient's overall outcome, regardless of therapy, while a predictive biomarker gives information about the effect of a therapeutic intervention and target for therapy.[4]

APACHE II with 12 physiological variables is the most widely used model which has incorporated chronicity of health and effects of age influenced according to their relative impact. It has score with range of 0-71. APACHE II score is used within 24 hours of ICU admission with poor value recorded for each component part of physiological variable. The principal diagnosis responsible to ICU admission is put in APACHE II as a category so as to observe the predicted mortality based on principal diagnosis at admission. 16 APACHE II score of 25 correspond to a predicted mortality of 50% and a score >35 signifies a predicted mortality of 80%. The distribution and mean APACHE score were compared within the two periods. There was a 52% ($P < 0.01$) reduction in ICU mortality in the second period. The application of APACHE II to control for case mix allowed the valid conclusion of a real reduction in ICU mortality. The study concluded that baseline biochemical parameters such as APACHE II score, and phosphate level were important predictors of the DKA- associated mortality.

MATERIAL AND METHODS

It was a prospective (observational), hospital-based study done during 1st January 2021 to 31st December 2021 over a period of 12 months in Department of General medicine, Government general hospital, Nizamabad.

Inclusion Criteria

All patients of both sexes, who were diagnosed with diabetic ketoacidosis according to ADA* criteria.

Exclusion Criteria

Patients not willing to participate and those patients with ketonuria but without evidence of metabolic acidosis on Arterial blood gas.

(* The American Diabetes Association diagnostic criteria for DKA are as follows:

- Elevated serum glucose level (greater than 250 mg per dL [13.88 mmol per L])
- An elevated urine ketone level
- A pH less than 7.3 and
- A serum bicarbonate level less than 18 mEq per L (18 mmol per L)

Patients fulfilling the above-mentioned inclusion and exclusion criteria were included in the study. A detailed history of the participants was recorded as per the attached format. Laboratory tests including all routine blood investigations like complete hemogram, Blood sugar –random, fasting, postprandial, and HBA1C, serum ketones, Renal function tests, Liver function tests, Arterial blood gas analysis, chest Xray, ECG were done for all the patients at admission and as per the clinical requirement. Other special investigations as per the individual case requirements were carried out. The clinical course of each patient in the hospital was monitored and recorded. All the above data were recorded and tabulated.

Statistical Analysis

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Continuous data was represented as mean and standard deviation.

Chi-square test of Fischer's exact test (for 2x2 tables only) was used as test of significance for qualitative data. Yates correction was applied wherever chi-square rules were not fulfilled (for 2x2 tables only). Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs such as bar diagram and Pie diagram.

RESULTS

The study was done for 100 patients diagnosed with diabetic ketoacidosis presented to the medicine department. The study evaluated clinical and laboratory parameters that affect DKA outcomes at a tertiary care center and accessed its prognosis by APACHE II. Out of total 100 patients, maximum 48% of the patients were aged from 41-60 years. Minimum patients were in the age group of < 20 years. The mean age was 55.44. [Table 1]

years. 56 of the patients were male and 44 of the patients were female.

Out of 44 female patients, majority of the patients belonged to 41-60 years of age group. However, out of 56 male patients, majority of the patients belonged to 41 and above age group. [Table 1]

Out of total 100 patients, maximum 74% of the patients had a history of diabetes. Out of 100 patients majority of patients (n= 71) had poor glycemic control (HbA1c > 8). [Table 2]

Out of total 100 patients, 4 of the patients were deceased and 96 of the patients were discharged. Amongst the deceased patients the degree of ketonuria +4 and +2. Furthermore, among the discharged patients the degree of ketonuria was +2 in majority. [Table 3]

Out of 100 patients, 74 are known diabetics, among them 39 of patients received OHA, followed by insulin and OHA with insulin which was 16 and 8 respectively.

Out of 100 patients, among known diabetic majority of the patients (n = 35) had irregular frequency of treatment. [Table 4]

Out of 4 deceased patients, majority of them belonged to >40 years. Furthermore, out of 96 discharged patients, majority of the patients belonged to 41- 60 years of age group. [Table 5]

Among the 4 deceased patients, 2 of the patients were male and 2 of the patients were female. Among the 96 discharged patients, 42 of the patients were female and the remaining 54 of the patients were male. [Table 6]

Among the 4 deceased 2 are known diabetic and 2 were newly diagnosed. [Table 7]

The precipitating factors of DKA was irregular treatment followed by infection like UTI and cellulitis. [Table 8]

Out of 4 deceased, GCS score of Moderate- Severe. Among the 96 discharged patients, GCS score of majority of the patients (n=82) was mild. [Table 9]

There was no significant difference in the APACHE II parameters on DKA between deceased and discharged patients (except for HCO3) as their p value was >0.05. [Table 10]

Among the 4 deceased and 96 discharged patients, majority of the patients had pH group <7.10. [Table 11]

The majority of the patients had APACHE II score 11-20 with the expected mortality was 19.63%.

Out of total 100 patients, 4 (4 %) of the patients were deceased and 96 (%) of the patients were discharged. [Table 12]

Table 1: Age and Sex distribution

		Sex		Total
		Female	Male	
Age Group (Years)	<20	2	4	6
	21-40	5	6	11
	41-60	22	26	48
	>60	15	20	35
Total		44	56	100

Table 2: Known diabetics and Blood sugar levels in present study

Known diabetics or first time diagnosed diabetics	Frequency	Percentage
First time diagnosed diabetics	26	26
Known diabetics	74	74
Blood sugar levels		
250-350	15	15%
351-450	34	34%
451-550	30	30%
551-650	17	17%
>651	4	54%
HbA1c		
<7	2	2
7-8	27	27
8.1-9	46	46
9.1-10	17	17

> 10	8	8
total	100	100

Table 3: Degree of ketonuria by dipstick method in patients who recovered and those who succumbed

Ketones	Deceased	Discharged	Total
+4	2	8	10
+3	1	22	23
+2	1	42	43
+1	0	24	24
Total	4	96	100

Table 4: Treatment received in past and Frequency of treatment

Treatment received	Frequency	Percent
Diet	3	4%
Insulin	16	21.6%
Insulin + OHA	8	10.8%
None	8	10.8%
OHA	39	52.7%
Total	74	100.0
Frequency of treatment		
Irregular	35	47.2%
None	8	10.8%
Regular	31	41.85

Table 5: Age wise outcome of patients

			Outcome		Total	P-value
			Deceased	Discharged		
Age Group (Years)	<20	Count	**0**	**6**	**6**	>0.05
		% within Outcome	0%	6.25%	6.25%	
	21-40	Count	0	11	11	
		% within Outcome	0.0%	11.45%	11.45%	
	41-60	Count	2	46	48	
		% within Outcome	50.0%	48.0%	48%	
	>60	Count	2	33	35	
		% within Outcome	50%	34.37%	35.0%	
Total		Count	4	96	100	
		% within Outcome	100.0%	100.0%	100.0%	

Table 6: Sex wise outcome in patients

			Outcome		Total	P-value
			Deceased	Discharged		
Sex	Female	Count	2	42	44	>.05
		% within Outcome	50.0%	43.75%	44%	
	Male	Count	2	54	56	
		% within Outcome	50.0%	56.25%	56%	
Total		Count	4	96	60	
		% within Outcome	100.0%	100.0%	100.0%	

Table 7: Known diabetics or first time diagnosed diabetics and its outcome

			Outcome		Total	P-value
			Deceased	Discharged		
Known diabetic	No	Count	2	24	26	>0.05
		% within Outcome	50.0%	26.9%	26.7%	
	Yes	Count	2	72	74	
		% within Outcome	50.0%	73.1%	73.3%	
Total		Count	4	96	100	
		% within Outcome	100.0%	100.0%	100.0%	

Table 8: Incidence of precipitating events in DKA patients

Precipitating Factors	Frequency	Percent
Irregular treatment	35	35%
UTI	8	8%
Acute Gastroenteritis	7	7%

Diabetic Foot	4	4%
Septic Shock	2	2%
Cerebrovascular Accident	3	3%
Surgery	4	4%
Cellulitis	6	6%
Pneumonia	3	3%
New Onset Diabetes	26	26%
Viral Fever	2	2%

Table 9: Glasgow coma scale and its outcome

			Outcome		Total	P-value
			Deceased	Discharged		
GCS	Severe (3-9)	Count	2	4	6	<0.05
		% within Outcome	50%	4.1%	6%	
	Moderate (10-12)	Count	2	10	12	
		% within Outcome	50%	10.41%	12%	
	Mild (13-15)	Count	0	82	82	
		% within Outcome	50%	85.4%	82.0%	
Total		Count	4	96	100	
		% within Outcome	100.0%	100.0%	100.0%	

Table 10: APCAHE II score parameters

	Outcome	N	Mean	Std. Deviation	P-value
temperature	Deceased	4	37.6888	1.22877	>0.05
	Discharged	96	37.4058	1.37047	
PaO2	Deceased	4	87.250	10.2365	>0.05
	Discharged	96	86.810	13.6064	
MAP	Deceased	4	91.6913	21.00973	>0.05
	Discharged	96	94.6769	13.07821	
pulse	Deceased	4	106.75	18.737	>0.05
	Discharged	96	96.73	14.819	
Respiratory rate	Deceased	4	25.50	4.472	>0.05
	Discharged	96	24.40	3.851	
WBC	Deceased	4	16779.863	11230.8977	>0.05
	Discharged	96	12964.696	10931.9323	
HCO3	Deceased	4	9.350	3.8049	<0.05
	Discharged	96	13.192	2.6938	
serum Na	Deceased	4	134.63	12.328	>0.05
	Discharged	96	135.58	7.130	
serum potassium	Deceased	4	3.988	.8823	>0.05
	Discharged	96	3.977	.7139	
serum creatinine	Deceased	4	1.938	1.1686	>0.05
	Discharged	96	1.610	1.0863	
hematocrit	Deceased	4	37.800	6.2840	>0.05
	Discharged	96	36.623	5.3674	

Table 11: PH and its outcome

			Outcome		Total	P-value
			Deceased	Discharged		
PH Group	<7.10	Count	3	49	52	>0.05
		% within Outcome	75%	51.%	52%	
	7.11-7.25	Count	1	47	48	
		% within Outcome	25 %	48.9%	48%	
Total		Count	4	96	100	
		% within Outcome	100.0%	100.0%	100.0%	

Table 12: APACHE II score and mortality

APACHE II Score	Expected mortality %	No. of patients	deceased	discharged
0-10	11.00%	10	0	10
11-20	19.63%	58	1	57
21-30	49.10%	18	2	16
31-40	73.00%	8	1	7

DISCUSSION

Diabetes mellitus is commonly encountered universal disease known for ages together. It belongs to the category of metabolic disorder which includes hyperglycemia as common phenotype. Diabetic ketoacidosis is one of the medical emergencies which requires earlier detection and treatment to reverse biochemical and clinical course of disease. The obstinate persistent mortality rate of DKA is cause of great worry and challenging for diabetologist all over the world. The annual incidence of DKA from

population-based studies is estimated to range from 4 to 8 episodes per 1,000 patient admissions with diabetes.[4] The present study consisted of 100 patients who presented with diabetic ketoacidosis. The results of the table were analysed and discussed.

In the current study, the number of males was 56 and the number of females was 44. Therefore, male predominance was visible in the current study which was similar to the study of Matoo et al,[5] in JAPI, where males were more than females. According to study by Avinash et al,[6] favorable outcome was found significantly associated with sex and was significantly higher (33.4%) in males compared to females. Furthermore, according to the study of Bedaso et al,[7] the number of males was higher than that of the number of females, the results were in accordance to the current study. According to the given studies, the average age of patients admitted with DKA is between 40 to 60 years.[8]

In the current study the majority of the patients belonged to 41-60 years of age group. Supporting the current study, Bedaso et al,[7] had majority of the patients in 41-60 years age group. Kitabchi et al,[9] concluded that most patients with DKA were between the ages of 18 and 44 years (56%) and 45 and 65 years (24%), with only 18% of patients <20 years of age.

Barski et al,[10] concluded that advanced age was an independent predictor of mortality. As shown in table no .5, maximum patients were having blood glucose level more than 350. 4 patients were having BSL > 650 mg/dl. Glucose more than 300 mg/dL after 12 hour of standard protocol treatment is an independent risk factor for mortality. In the study done by Mahesh et al,[11] patients with RBS more than 300 mg% at or after the first 12 hours were 32.7% of which 22.2% had resistant RBS and expired. A p-value was found to be 0.002 which is statistically very significant.

In the current study majority of the patients who deceased had +4 ketones whereas among the discharged patients majority of them had +2 ketones. In contrast to the current study, Ahuja et al,[12] majority of the patients among the deceased patients the majority of them had no urinary ketones. Similarly, among the discharged patients majority of them had no urinary ketones.

In the current study the previous mode of treatment was OHA in majority of the cases. Similarly, according to the study of Agarwal et al,[1] the previous treatment history in majority of the patients was OHA.

In the current study the majority of the patients were irregular for the diabetic treatment. Similarly, according to the study of Seth et al,[13] majority of the patients were irregular for the treatment for diabetes.

In the present study, infection contributed to the maximum as precipitating factors of DKA with dehydration (n=9) being second common.

The descending order of frequency includes infections (52%), skipping of anti-diabetic treatment (35%), undiagnosed diabetes (26%). Among infections, urinary tract infection is the commonest (8%) followed by cellulitis and respiratory infections.

In most of the studies, the precipitating factors are infection, skipping of medication, undiagnosed diabetes and comorbid conditions as shown in the given studies. Ahuja W. et al,[12] concluded in the study that infections and missed insulin dose were frequently seen as the predisposing factors and was similar in the study given by Hartalkar A .et al,[14] Rahim et al,[15] reported about 33% patients had infective etiology, about 33% had poor adherence to insulin therapy and no definite precipitating factor found in about 25%. In a study from Kenya, about 34% patients were noncompliant to insulin therapy, 23.4% had infective focus. Even in studies from India and Korea, the most common cause was poor adherence to therapy. A study in Pakistan reported that among type 2 diabetes mellitus patients, 63% developed DKA due to infection. According to the study done by Sonawani S et al,[16] has revealed that DKA patients were having more than one precipitating factor like 53% who had poor compliance also had infection like pneumonia (24%) and UTI (22%). DKA patients also presented with stroke (7%) and MI (6%) as the precipitating factors. Hence, it can be said that presence of non-compliance to treatment is an important precipitating factor which indicates that prevalence of DKA can be reduced by proper education of patients about their illness and harm of non-compliance. Welch et al,[17] studied T2DM patients presenting with DKA and reported that multiple precipitating factors are required in diabetic patients to develop DKA, which is in agreement to the present study findings.

In the current study majority of the deceased had severe GCS score while among the discharged patients, majority of them had mild GCS score. However, the results of Agarwal et al,[1] matched the current study as the majority of deceased patients had severe GCS score and the majority of the discharged patients had mild GCS score. In the study by Otieno et al,[18] concluded that altered level of consciousness was a major predictor of mortality in DKA patients. Hence, additional, larger studies are needed to show the association between GCS and mortality.

In the current study, majority of the patients had pH group <7.10. However, on the contrary as per the study of Rahim et al,[15] the majority of the patients had pH group 7-7.24. Furthermore, the study by Agarwal et al,[-] had majority of the patients in the <7.10 pH group.

Out of total 100 patients, 4 (4%) of the patients were deceased and 96(96%) of the patients were discharged. In the study by Agarwal A et al at final evaluation, of the 270 patients, 189 patients were discharged (70.0%), while 81 patients were deceased (30.0%) as shown,[1] The results with the studies where mortality rates ranged from 2.5% to 9% which is similar to our study. This may be because the aforementioned study had mortality rates that were reported and associated with DKA alone and excluded mortality attributable to factors that precipitated DKA. Other factors that contributed to higher mortality in the present study could be due to

limited resources in developing countries, greater patient load in tertiary care health centers, and late referrals.[19]

In the present study the majority of the patients had APACHE II score 11-20 with the expected mortality was 19.63%. The study done by Friere et al,[20] in 1506 patients in ICU showed that high APACHE II score in the first 24 hours after ICU admission predicted hospital mortality in an in MICU. A study done by Efstathiou et al,[21] on the patients with DKA admitting ICU showed that the higher the score in the first 24 hours after ICU admission, the higher the mortality rate. A study conducted by Matic et al,[22] on 129 patients regarding the selection of ventilator mode by APACHE II score showed that if the score > 20, the patients required aggressive method of mechanical ventilation; but if the score < 20, non-aggressive method should be applied. A study performed by Nfonoyim et al,[23] on 30 patients with DKA showed that APACHE II score was suitable for decision making about the patient admission in ICU and it reduced the costs of wrong ICU admission. A research done by Chiavone et al,[24] on 521 patients in ICU showed that APACHE II score was useful for the severity classification of the disease but APACHE II score was a weak predictor of mortality rate of the patients.

The APACHE II score calculated at presentation was found to be significantly (P<0.001) associated with the final outcome. Patients who had higher mean ± SD APACHE II score of 25.0±9.74 had significantly increased mortality compared to those with a lower mean 15.0±5.95 score. We were not able to identify any other studies that showed direct correlation between APACHE II score and mortality in DKA. (1) So from the current study it was proved that APACHE II score can be used for predicting the prognosis in the the DKA patients.

Limitations

The main limitation of this study is the small number of patients recruited for the study. Similar type of studies can be conducted in a larger group, may be multicentric, which will help in the risk stratification of patients with DKA at the time of admission.

CONCLUSION

DKA is a life threatening disease if not treated and diagnosed on time. This was prospective observational study, and patients were assessed at the time of admission. The present study determined that there was male predominance. GCS score along with APACHE II was helpful in estimating the various elements indicating towards the prognosis of DKA at the time of admission. It was found that various biochemical markers like ketonuria and hyperglycemia mark DKA. In current study we had maximum patient with mild GCS (13-15). Infection was found to be one of the most predisposing factors of DKA. There was no significant difference in the APACHE II parameters on DKA between deceased and discharged patients.

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