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Study of Diabetic Ketoacidosis with Special References to the Biochemical Prognostic Marker

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Abstract

Background: Diabetes Mellitus is a clinically and genetically heterogeneous group of metabolic disorders that manifest in an abnormally high level of glucose in the blood. Diabetic Ketoacidosis (DKA) represent extremes in the spectrum of decompensated diabetes. The mortality in patients with Diabetic Ketoacidosis is rarely caused by a metabolic complication of hyperglycemia or metabolic acidosis and it is usually related to the underlying medical illness that precipitates 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. **Methods:** The present study was conducted for period of 2 years. It is a hospital based prospective observational study of 60 Diabetic Ketoacidosis patients. The biochemical prognostic markers were studied. **Results:** The study was done for 60 patients diagnosed with Diabetic Ketoacidosis presented to the medicine department. The mean age was 55.44 years. So from the current study it was proved that, serum phosphorus and APACHE II score can be used for predicting the prognosis in the the DKA patients. The mean serum phosphate among the deceased patients (n = 8) was more as compared to the discharged patients (n = 52). Out of 60 patients, highest patients (n = 38) had infection (AFI, LRTI, pneumonia. UTI, sepsis pancreatitis, enterocolitis, AKI, viral fever) as their precipitating factors**. Conclusion:** APACHE II score and serum phosphorus is an important biochemical marker in the prognosis of DKA. APACHE II score is directly proportional to mortality index in DKA.

Keywords: APACHE II, Diabetic Ketoacidosis, Glasgow Coma Scale, Serum Phosphate

1. Introduction

Diabetic Ketoacidosis (DKA) is potentially life-threatening complication of Diabetes Mellitus characterized by a triad of hyperglycemia, high anion gap metabolic acidosis, ketonemia and represents a state of insulin deficiency and concurrent elevation in counter regulatory hormones.

The study done in 2006 shows that incidence remains high between 4.6-8% for every 1000 subjects and remains a prominent cause of mortality in diabetic patients. DKA remain important causes of morbidity and mortality among diabetic patients despite well-developed diagnostic criteria and treatment protocols.

A prognostic biomarker provides information about the patient's overall outcome, regardless of therapy, whilst a predictive biomarker gives information about the effect of a therapeutic intervention. A denoting biomarker can be a quarry for therapy. Phosphate depletion is common in Diabetic Ketoacidosis. Initially intracellular phosphate moves to extracellular compartment due to acidosis, dehydration. So patients with Diabetic Ketoacidosis can present with hyperphosphatemia.

APACHE II was designed to measure the severity of disease for adult patients admitted to intensive care units. The APACHE score was found to correlate directly with hospital mortality. The uses of APACHE II include

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risk stratification, comparison of the quality of care and prognosis.

This study will evaluate the clinical and biochemical parameters that affect outcomes in patients with DKA at a tertiary care centre.

2. Aims and objectives

To study the clinical course and outcome of patients and to assess and evaluate the role of biochemical markers in predicting prognosis of Diabetic Ketoacidosis (Serum Phosphate, APACHE 2).

3. Material and Methods

This prospective observational study conducted over a period of 2 years (Aug 17 to Dec 2019) in Department of Medicine at Dr. Vasantrao Pawar Medical College, Hospital and Research Centre, Nashik, Maharashtra, India. The cases included were 60 DKA patients of both sexes and various age groups. All these patients were examined and data were recorded in standardized proforma. An institutional ethical clearance was obtained prior to start the study and informed consent was taken after explaining the purpose of study.

The formula for sample size:

$\frac{(Z^2p^*q)}{L^2}$

Z =1.96 (critical value)

p = prevalence of disease – 0.63%

q = 1-p

L = Margin of error/ allowable error – 2% - 0.02

$\frac{(1.96)^2\ [0.63\ (1-0.63)]}{(0.02)} = 60$

3.1 Inclusion Criteria

All patients of both sexes, who were known diabetics diagnosed with DKA according to ADA* criteria.

- 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)

3.2 Exclusion Criteria

Patients not willing to participate and those with ketonuria but without evidence of metabolic acidosis on ABG will be excluded.

3.3 Methodology

A detailed history of the participants was recorded as per the attached format. Laboratory tests including all routine blood investigation. All the above data were recorded and tabulated.

APACHE 2 score (Calculated from age and 12 routine physiological examination).

- Partial oxygen pressure.
- temperature (rectal).
- mean arterial pressure.
- pH.
- Heart rate.
- Respiratory rate.
- Serum sodium.
- Serumpotassium.
- Serumcreatinine.
- Heamatocrit.
- White blood count.
- Glassgow coma scale.

3.4 Statistical Analysis

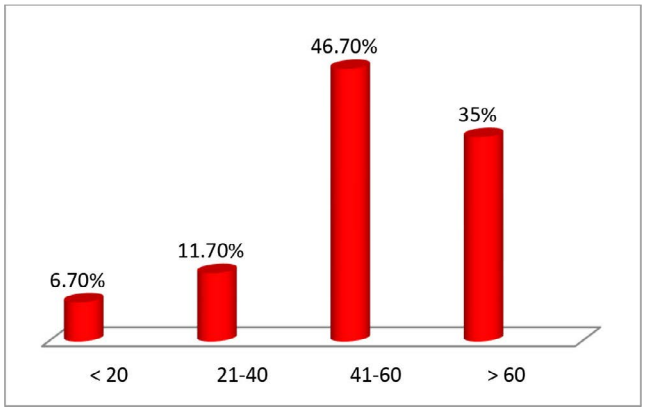
The collected data was analyzed at the end of the study by using appropriate statistical test that is odd's ratio. The results were tabulated and inferences were drawn.

4. Results

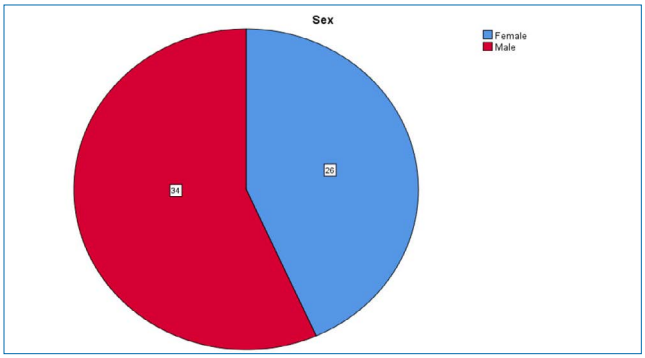
The study was done for 60 patients diagnosed with DKA presented to the medicine department. The study evaluated clinical and laboratory parameters that affect DKA outcomes at a tertiary care center.

Out of total 60 patients, 46.7% of the patients were aged from 41-60 years. The mean age was 55.44 years (graph no.1). Out of total 60 patients, 34 of the patients were male and 26 of the patients were female (graph no. 2). Out of 60 patients, the blood sugar level of 33.3% patients was between 351 and 450 (Table no. 1).

As shown in Graph no. 3, out of total 60 patients, 8 of the patients were deceased and 52 of the patients were discharged. Amongst the deceased patients the degree of



Graph No 1. Age Group



Graph No 2. Sex Distribution

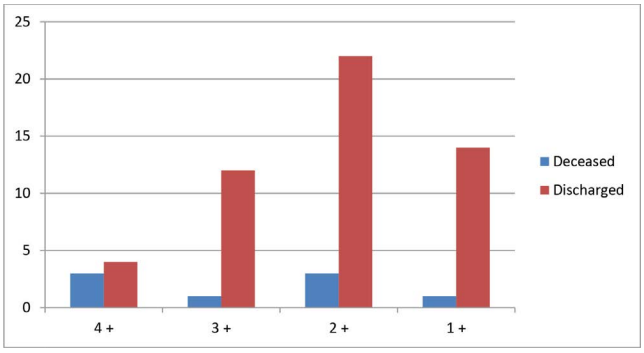
Table 1. Blood sugar levels at the time of admission

BSL	No. of patients	Percentage
250-350	9	15
351-450	20	33.3
451-550	18	30
551-650	10	16.7
>651	3	5
Total	60	100%

ketonuria +4 and +2 had 3 patients each. Furthermore, among the discharged patients the degree of ketonuria was +2.

As shown in Table 2, 38 patients had infection (AFI, LRTI, pneumonia, UTI, sepsis pancreatitis, enterocolitis, AKI, viral fever) as their precipitating factors followed by which was dehydration (n = 9).

Out of 8 deceased, GCS score of 5 patients was severe. Among the 52 discharged patients, GCS score of 41 was mild (Table 3).



Graph No 3. Degree of ketonuria by the dipstick in the patients who recovered and those who succumbed (X axis = degree of ketonuria, Y axis = no. of patients)

Table 2. Incidence of precipitating events in DKA patients

Precipitating Factors	Frequency	Percent
Infection	38	63.3%
dehydration	9	15.3%
Non compliance	5	8.3%
Others	8	13.3%

As shown in table 4, except for HCO_3 (p value <0.05) there was no significant difference in the APACHE II parameters on DKA between deceased and discharged patients (p value >0.05).

Among the 8 deceased and 52 discharged patients, 34 patients had pH group <7.10 (Table 5).

As shown in graph no. 4, 38 patients had Serum phosphorus level >4.5.

Serum phosphorus levels was significantly different between deceased and discharged patients as the p value was <0.05. It was higher for deceased patients (Table 6).

Out of total 60 patients, 8 (13%) of the patients were deceased and 52 (87%) of the patients were discharged (graph no. 5).

36 patients had APACHE II score 11-20 with the expected mortality was 19.63% (Table 7).

5. Discussion

The present study consisted of 60 patients who presented with Diabetic Ketoacidosis. The results of the table were analyzed and discussed.

5.1 Incidence of Age Distribution

In the current study, the number of males was 34 and females was 26. Therefore, male predominance was visible in the current study which was similar to the study of Matoo et al in JAPI, where males were more than females[6].

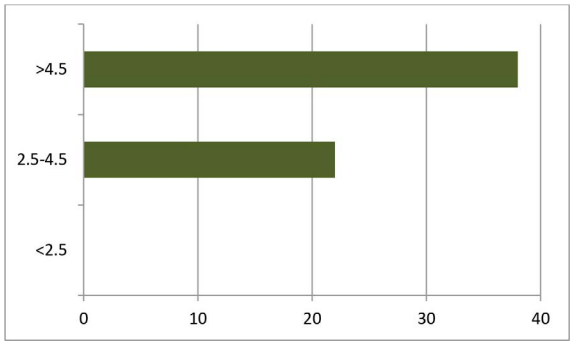
According to Agarwal A et al.[7] favorable outcome was found significantly associated with sex and was

Table 3. Glassgow coma scale and its outcome

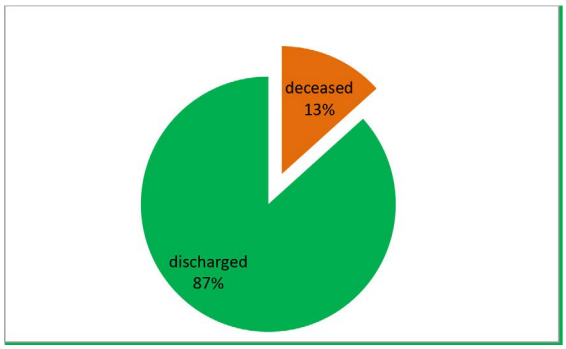
			Outcome		Total	P-value
			Deceased	Discharged		
GCS	Severe (3-9)	Count	5	5	10	<0.05
		% within Outcome	62.5%	9.6%	16.7%	
	Moderate (10-12)	Count	2	6	8	
		% within Outcome	25.0%	11.5%	13.3%	
	Mild (13-15)	Count	1	41	42	
		% within Outcome	12.5%	78.8%	70.0%	
Total		Count	8	52	60	
% within Outcome		100.0%	100.0%	100.0%		

Table 4. APCAHE II score parameters

	Outcome	N	Mean	Std. Deviation	P-value
Temperature	Deceased	8	37.6888	1.22877	>0.05
	Discharged	52	37.4058	1.37047	
PaO_2	Deceased	8	87.250	10.2365	>0.05
	Discharged	52	86.810	13.6064	
MAP	Deceased	8	91.6913	21.00973	>0.05
	Discharged	52	94.6769	13.07821	
Pulse	Deceased	8	106.75	18.737	>0.05
	Discharged	52	96.73	14.819	
Respiratory rate	Deceased	8	25.50	4.472	>0.05
	Discharged	52	24.40	3.851	
WBC	Deceased	8	16779.863	11230.8977	>0.05
	Discharged	52	12964.696	10931.9323	
HCO_3	Deceased	8	9.350	3.8049	<0.05
	Discharged	52	13.192	2.6938	
Serum Na	Deceased	8	134.63	12.328	>0.05
	Discharged	52	135.58	7.130	
Serum Potassium	Deceased	8	3.988	.8823	>0.05
	Discharged	52	3.977	.7139	
Serum Creatinine	Deceased	8	1.938	1.1686	>0.05
	Discharged	52	1.610	1.0863	
Hematocrit	Deceased	8	37.800	6.2840	>0.05
	Discharged	52	36.623	5.3674	



Graph No 4. Incidence of hyperphosphatemia



Graph No. 5. Final outcome of DKA patients

significantly higher (33.4%) in males compared to females. The possiblilty might be remarked to decreased health seeking behavior among females and because decision-making power lies with the male sex in our country, leading to very infrequent visits to primary care health center for disease treatment, leading to late referrals of female patients to tertiary care health centers.

5.2 Incidence of Sex Distribution

In the current study the majority of the patients belonged to 41-60 years of age group.

Supporting the current study, Bedaso et al[8] majority of the patients were in 41-60 years age group.

Kitabchi et al[9] concluded that most patients were between the ages of 18-44 years (56%) and 45-65 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; however, the final outcome was not statistically significantly associated with age.

Table 5. pH and its outcome

			Outcome		Total	P-value
			Deceased	Discharged		
pH Group	<7.10	Count	7	27	34	>0.05
		% within Outcome	87.5%	51.9%	56.7%	
	7.11-7.25	Count	1	25	26	
		% within Outcome	12.5%	48.1%	43.3%	
Total		Count	8	52	60	
% within Outcome		100.0%	100.0%	100.0%		

Table 6. Serum phosphorus and its outcome

	Outcome	N	Mean	Std. Deviation	P-value
Serum phosphorus	Deceased	8	5.700	.6928	<0.05
	Discharged	52	4.690	.8852	

Table 7. APACHE II score and mortality

APACHE II score	Expected mortality %	No. of patients	deceased	discharged
0-10	11.00%	7	0	7
11-20	19.63%	36	1	35
21-30	49.10%	15	6	9
31-40	73.00%	2	1	1

5.3 BSL at the time of Admission and its Outcome in DKA Patients

48 patients were having BSL>350. 3 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[11].

In the study done by Mahesh et al[12], 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

5.4 Degree of Ketonuria by the Dipstick in the Patients who recovered and those who Succumbed

In the current study majority of the patients had +4 ketones among the deceased whereas among the discharged patients majority of them had +2 ketones.

In contrast to the current study, Ahuja et al[13] 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.

5.5 Distribution of Precipitating Factors in DKA

In the present study, infection contributed to the maximum (n = 38) as precipitating factors of DKA with dehydration (n = 9) being second common.

Ahuja W. et al[13] 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%.

5.6 GCS and its Outcome

In the current study 5 of the deceased had severe GCS score while among the discharged patients 41 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.[16] concluded that altered level of consciousness was a major predictor of mortality in DKA patients. Larger studies are required to prove.

5.7 PH and its association with DKA

In the current study, 34 of the patients had pH group <7.10. However, on the contrary as per the study of Rahim et al.[17] the majority patients had pH group 7-7.24.

5.8 Incidence of Hyperphosphatemia

Out of 60 patients, 38 patients had Serum phosphorus level >4.5.

The initial hyperphosphataemia is reflective of intravascular volume depletion and pre-renal renal impairment[18].

In this study done by Agarwal A et al.[1] says that increased level of serum phosphate at presentation was associated with increased mortality. It was found that serum phosphate was a significant and independent predictor of final outcome.

Kebler et al.[18] also concluded that hyperphosphatemia is common in DKA, prior to therapy.

5.9 Serum Phosphorus Level with its Outcome

Table 8. Serum phosphorus levels and outcome

Study	Mean Serum phoshphate	No. of patients
Current study	Deceased	5.700 ± .692
	Discharged	4.690 ± .885
Agarwal et al.	Deceased	5.00 ± 1.46
	Discharged	4.38 ± 3.07

In the current study, the mean serum phosphate among the deceased patients was more as compared to the discharged patients. Similar results were obtained in by Agarwal et al.[1] where the mean serum phosphate of the deceased was higher than the discharged patients (Table 8).

5.10 Final Outcome of DKA Patients

Out of total 60 patients, 8 (13%) of the patients were deceased and 52 (87%) of the patients were discharged.

At final evaluation, of the 270 patients, 189 patients were discharged (70.0%), while 81 patients were deceased

(30.0%) as shown in the study by Agarwal A et al.[1]. The study by Ellemannet al.[19], where mortality rates ranged from 2.5% to 9% which is similar to our study.

5.11 APACHE II Score and Mortality

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 ICU showed that high APACHE II score in the first 24 hours after ICU admission predicted hospital mortality in an in MICU.

The current study proved that serum phosphorus and APACHE II score can be used for predicting the prognosis of DKA patients.

6. Limitations

Small number of patients recruited for the study, less time. Same 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.

7. Conclusion

DKA is a life threatening disease if not treated and diagnosed on time. GCS score along with APACHE II was helpful in estimating the various elements indicating towards the prognosis of DKA at the time of admission. Infection was found to be one of the most predisposing factors of DKA. The phosphate levels proved to be important predictors of DKA. Hyperphosphatemia was seen in patients with DKA on admission. There was no significant difference in the APACHE II parameters on DKA between deceased and discharged patients (except for HCO_3).

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