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Hypoalbuminemia: A poor prognostic harbinger in diabetic ketoacidosis

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Abstract:

The incidence of DKA at the global level has been reported to be between 0 and 56 episodes per 1000 person-year in people with diabetes depending on the population and setting. Diabetes ketoacidosis (DKA) is a life-threatening emergency disease with high mortality in resource-restricted areas and 50 cases (2019-2021) of Acharya Vinoba Bhave Rural Hospital, Wardha, and ICU were compared to 50 diabetic controls. The patients in the DKA group had a reduced serum albumin; the non-survivors had even less (2.56 ±1.07 versus 3.40 ±0.65 g/dL; p=0.040). Regression established that albumin was not only an independent predictor of mortality (OR -6.069; 95% CI -1.149-8.010; p=0.045). High-risk patients can be detected during routine, simple albumin testing at the time of admission and directed towards higher degrees of treatment.

Keywords: Diabetic ketoacidosis (DKA), serum albumin, prognostic marker

Background:

Diabetic ketoacidosis (DKA) is an acute metabolic complication of diabetes that is potentially fatal, which is typified by hyperglycaemia, ketonemia and metabolic acidosis **[1]**. Its prevalence worldwide is between 0 and 56/1000 person/year among patients and health facilities **[2]**. DKA mortality in-hospitals in low and middle-income nations such as India stand at 30 percent, which is a lot higher than the <1 percent in high-income nations **[3]**. A prospective Emergency Department cohort study provided 5.8% mortality in DKA without delay and 19.2% death two years later and hypoalbuminemia was an independent variable predicting mortality **[4]**. Globally, insulin non-adherence causes 40-44% of DKA episodes and the urinary tract and respiratory infection are the most common factors that trigger the condition in developing countries **[5]**. Low access to essential healthcare and inadequate glycaemic control also increase the risks of DKA in resource-restrained areas **[6]**. The most common plasma protein which is produced exclusively by the liver, serum albumin, controls oncotic pressure, transport of drugs and antioxidant defense; hypoalbuminemia (<3.5 g/dL) is linked with high morbidity, mortality and extended hospital stay **[7]**. Insulin deficiency has a direct negative effect on the albumin mRNA and production of the liver by impairing the gene transcription of albumin itself **[8]**. It was verified by animal research that diabetes induced by alloxane lowered the synthesis of albumin to 20 percent of the normal level and that was reverted by the replacement of insulin **[9]**. The rate-limiting ketogenic enzyme, mitochondrial HMG-CoA synthase, is inhibited by albumin; its loss allows the unregulated ketone body production and continues DKA **[10]**. Ketonuria was identified in 62.5% of hypoalbuminemic patients with acute hyperglycaemia in hospitalized patients with T2DM (OR: 3.15; p = 0.02), which makes albumin a predictor of insulin deficiency and risk of ketosis **[11]**. The level of serum albumin in 48 hours was the predictor of 28 day mortality in critically ill patients, using binary logistic regression **[12]**. A large ICU-based study proved that low serum albumin predisposed both the ICU and hospital mortality regardless of the APACHE-II scores **[13]**. Therefore, it is of interest to assess the serum albumin as a prognostic index in DKA patients and compare the levels with diabetic controls.

Materials and Methods:

This is a hospital-based case-control study of the Department of Medicine and the Medicine Intensive Care Unit (MICU) of the Acharya Vinoba Bhave Rural Hospital (AVBRH), a 1,200-bed tertiary care teaching hospital that serves as the rural community of Central India, Sawangi (Meghe), Wardha and Maharashtra, India. The research was conducted within two years between October 2019 and November 2021. The sample included two groups: cases were adult patients (age above 18 years) admitted to the MICU having a confirmed diagnosis of DKA, which is the simultaneous presence of random blood glucose above 250 mg/dL, arterial pH level below 7.30 and 1+ ketones in the urine sample on a dipstick, including both Type 1 and Type 2 diabetes mellitus. To reduce the confounding effect of diabetes on serum albumin, age and sex-matched diabetic patients who were not ketotic and had been recruited at the Medicine OPD and wards were used as controls. Both groups excluded patients with pregnancy, chronic kidney disease, chronic liver disease, chronic diarrhoea, other ketotic states (alcoholic or starvation ketosis) and other metabolic acidoses and post-CPR status. To all the participants, detailed socio-demographic, clinical and anthropometric data were collected, consisting of type and duration of diabetes, hypertension and coronary artery disease history and stroke and precipitating factors (infections and insulin non-adherence). The blood pressure was taken three times a day when in recumbent position by a mercury sphygmomanometer and averaged and BMI was determined through Quetelet formula. Laboratory examinations (CBC, liver function tests: total protein, serum albumin, bilirubin, AST, ALT, ALP), renal tests (urea, creatinine, electrolytes), random blood glucose, HbA1c, arterial blood gas and urine ketones were all done on validated analyzers and within 30 minutes of admission and under aseptic conditions. Three scoring systems were used to determine the severity of the disease and they include APACHE IV, qSOFA and the Glasgow Coma Scale (GCS). Cases were all traced to their clinical outcome of discharge or in-hospital death. Statistical testing was done by the use of SPSS version 20.0 (IBM Corp., USA). The continuous variables were described in the form of mean and standard deviation and compared through independent sample t-test, whereas the categorical variables were represented in frequencies and percentages and compared with the help of the chi-square test. To determine independent predictors of in-hospital mortality, multiple linear regression was performed in which the p-value

of <0.05 was deemed statistically significant. The participants were enrolled in the study based on the Declaration of Helsinki, with all of them having been informed of the study by the written informed consent or the legally acceptable representatives of the individuals on their behalf in the local language (Marathi) and approved the study by the Institutional Ethics Committee of Datta Meghe Institute of Medical Sciences (Deemed University) in Sawangi (Meghe), Wardha (Ref. No. DMIMS (DU)/IEC/Aug-2019/8216, dated 03/10/2019).

Table 1: Baseline demographic and anthropometric characteristics

Characteristics	Cases of Diabetic Ketoacidosis (n=50)	Diabetic Controls (n=50)	Mean Difference	P-value
Age (years)	46.68 ± 13.25	47.42 ± 13.99	-0.74	0.78
Gender (Males)	32 (64.0%)	32 (64.0%)	N/A	0.83
Gender (Females)	18 (36.0%)	18 (36.0%)	N/A	N/A
Height (cm)	162.62 ± 5.06	163.06 ± 3.70	-0.44	0.005
Weight (kg)	65.94 ± 10.20	78.40 ± 10.89	-12.46	<0.001
Body Mass Index (kg/m²)	25.01 ± 4.28	29.53 ± 4.34	-4.51	<0.001
Systolic Blood Pressure (mmHg)	121.64 ± 17.58	126.20 ± 14.96	-4.56	0.16
Diastolic Blood Pressure (mmHg)	77.64 ± 9.89	78.80 ± 9.17	-1.16	0.54
Mean Arterial Pressure (mmHg)	92.31 ± 11.79	94.60 ± 10.23	-2.29	0.302

Table 2: Complete blood count and arterial blood gas profiles

Clinical Parameter	Cases (Mean ± SD)	Controls (Mean ± SD)	Mean Difference	P-value
Hemoglobin (g/dL)	11.27 ± 1.92	11.83 ± 2.45	-0.56	0.205
Total Leukocyte Count (cells/mm³)	14594.00 ± 10418.28	9568.00 ± 5133.10	5026	0.003
Hematocrit (%)	33.87 ± 5.75	35.50 ± 7.38	-1.62	0.22
Arterial pH	7.27 ± 0.07	7.45 ± 0.07	-0.179	<0.001
Fraction of Inspired Oxygen (FiO2 %)	93.44 ± 3.84	97.69 ± 1.43	-4.25	<0.001
Arterial pO2 (mmHg)	97.02 ± 5.34	96.02 ± 1.40	0.99	0.206
Arterial pCO2 (mmHg)	39.46 ± 2.92	40.82 ± 2.78	-1.36	0.019
Bicarbonate (mEq/L)	20.76 ± 1.91	21.66 ± 1.83	-0.89	0.018

Table 3: Biochemical parameters

Biochemical Parameters	Cases (Mean ± SD)	Controls (Mean ± SD)	P-value
Aspartate Aminotransferase (SGOT, IU/L)	38.02 ± 24.19	47.57 ± 45.03	0.19
Alanine Aminotransferase (SGPT, IU/L)	32.50 ± 18.98	36.74 ± 34.64	0.45
Alkaline Phosphatase (ALP, IU/L)	157.23 ± 115.19	97.18 ± 35.78	0.001
Total Bilirubin (mg/dL)	0.98 ± 0.55	0.86 ± 1.14	0.52
Total Serum Protein (g/dL)	6.25 ± 1.13	7.11 ± 0.94	0.001
Serum Albumin (g/dL)	3.31 ± 0.72	3.76 ± 0.69	0.002
Serum Globulin (g/dL)	3.01 ± 0.51	3.37 ± 0.73	0.005
Blood Urea (mg/dL)	40.66 ± 27.86	30.84 ± 23.69	0.06
Serum Creatinine (mg/dL)	1.07 ± 0.61	1.31 ± 1.61	0.31
Random Blood Sugar (mg/dL)	331.34 ± 39.78	207.82 ± 30.66	0.001
Hemoglobin A1c (HbA1c, %)	10.98 ± 2.47	8.93 ± 2.80	<0.001

Table 4: Biochemical profiles and final outcome (Discharged vs. Deceased)

Clinical/Biochemical Parameter	Discharged Patients (n=43)	Deceased Patients (n=3)	P-value
Height (cm)	163.23 ± 4.68	162.66 ± 6.65	0.844
Body Mass Index (kg/m²)	24.70 ± 3.92	25.71 ± 6.56	0.681
Hemoglobin (g/dL)	11.36 ± 1.87	10.23 ± 2.53	0.329
Total Leukocytes (cells/mm³)	14472.09 ± 10894.50	18366.67 ± 9806.80	0.55
Arterial pH	7.23 ± 0.13	7.14 ± 0.22	0.324
Random Blood Sugar (mg/dL)	333.65 ± 38.69	312.00 ± 64.61	0.364
Total Serum Protein (g/dL)	6.37 ± 1.09	5.43 ± 1.19	0.158
Serum Albumin (g/dL)	3.40 ± 0.65	2.56 ± 1.07	0.04
SGOT (AST) (IU/L)	36.34 ± 22.75	66.33 ± 34.03	0.037
SGPT (ALT) (IU/L)	32.41 ± 19.69	31.66 ± 4.51	0.948

Table 5: Multiple linear regressions for independent risk factors of mortality

Predictive Variable	Odds Ratio (OR)	95% Confidence Interval	Regression Coefficient	P-value
Height	0.045	0.008 to 0.083	2.426	0.018
Gender (Sex)	-4.06	-6.006 to -1.087	-2.301	0.024
Body Mass Index	0.128	0.021 to 0.235	2.378	0.02
Total WBC	2.069	0.000 to 0.000	0.753	0.454
Arterial pH	-0.016	-0.126 to 0.093	-0.295	0.769
Serum Albumin	-6.069	-8.010 to -1.149	-1.746	0.045
Total Protein	0.042	-0.036 to 0.120	1.064	0.291
Hemoglobin A1c	-0.005	-0.020 to 0.009	-0.728	0.046

Results and Discussion:

The research recruited 50 cases of DKA and 50 diabetic controls and both matches well on age (46.68 ± 13.25 vs. 47.42 ± 13.99 years; p = 0.780) and gender (64% males in each group; p = 0.830) so that the groups can be compared and the effects of age or sex are minimized. Nevertheless, the body weight (65.94 ± 10.20 vs. 78.40 ± 10.89 kg; p <0.001) and BMI (25.01 ± 4.28 vs. 29.53 ± 4.34 kg/m^2; p <0.001) of DKA were also much lower than controls (**Table 1**). The observation is in agreement with the established catabolic nature of DKA, in which intense insulin deficiency facilitates increased lipolysis, protein breakdown and negative nitrogen balance, which cause excessive weight and muscle mass loss. Similar results were also obtained by Agarwal *et al.* **[14]** who documented that patients with DKA in tertiary care hospitals in India were more likely to have leaner body habitus, which was attributed to poor metabolic reserve and late referral pattern in resource limited facilities. This also aligns well with Tabrah & Al-Bakri **[15]**. Who studied 200 DKA patients in Baghdad and found that 70% of patients had normal BMI and 12% were underweight, confirming the lean body habitus characteristic of DKA admissions particularly in type 1 diabetes-predominant cohorts where insulin deficiency drives lipolysis and muscle catabolism. Blood pressure measurements - systolic blood pressure, diastolic blood pressure and mean arterial pressure did not differ between the two groups (p >0.05), which indicated the hemodynamic compensation was preserved at admission in the majority of cases. An increased total leukocyte count of the DKA cases compared to controls was significantly higher (14,594 ± 10,418 vs. 9,568 ± 5,133 cells/mm^3; p = 0.003) (**Table 2**). Slovis *et al.* **[16]** observed that leukocyte counts between 10, 000-15,000/mm^3 are normal in DKA and are manifestations of cortisol and catecholamine surge stress demargination, whereas a count above 25,000/mm^3 is an indicator to evaluate sepsis. Stress leukocytosis and not overt infection was more plausible in most instances in our group of 14,594/mm^3 TLC, although without microbiological information, it could not be completely ruled out. The DKA cases had significantly lower pH (7.27±0.07 versus 7.45±0.07; p = 0.001), lower FiO_2 (93.44±3.84 versus 97.69 ± 1.43; p = 0.001), lower pCO_2 (39.46 ±2.92 versus 40.82 ±2) ALP was found to be significantly higher in DKA cases (157.23 ± 115.19 vs. 97.18 ± 35.78 IU/L; p = 0.001) and the SGOT, SGPT and total bilirubin levels were similar between groups. The increase of ALP in DKA can indicate the hepatic stress because of the increased fatty acid flux and ketogenesis, which is the unstudied side of DKA pathophysiology. Markedly, total serum protein (6.25 ± 1.13 vs. 7.11 ±0.94 g/dL; p=0.001), serum albumin (3.31 ±0.72 vs. 3.76 ±0.69 g/dL; p=0.002) and serum globulin (3.01 ±0.51 vs. 3.37 ±0.73 g/dL; Cheng *et al.* **[17]** have shown that ketosis risk is negatively related to serum albumin level in hospitalized patients with T2DM, showing a prevalence of ketonuria of 48% in subjects with hypoalbuminemia compared to 30% in normoalbuminemic controls (OR: 2.15; 95% CI: 1.26-3.57; p = 0.004) and hypothesized that hypoalbuminemia reflects the depletion of secretory reserves of insulin. Karthikeyan and Rajaragupathy **[10]** also postulated that albumin can be a co-regulator of ketogenesis - inhibiting ketogenesis rate-limiting enzyme, hydroxymethylglutaryl-CoA synthase so that hypoalbuminemia in insulin-deficient conditions eliminates this inhibition and initiates uncontrolled ketogenesis. The serum albumin is not only a nutritional marker but an active player in DKA pathogenesis according to this mechanistic model, a fact that justifies the fact that albumin levels are significantly low in our cases of DKA. The levels of random blood glucose (331.34 ± 39.78 vs. 207.82 ± 30.66 mg/dL; p = 0.001) and HbA1c (10.98 ± 2.47 vs. 8.93 ± 2.80% p = 0.001) were significantly more elevated in cases of DKA, which substantiated the presence of chronically poor glycaemic control as the predisposing factor to the development (**Table 3**). This is in line with the study by Cheng *et al.* **[17]** that indicated a negative relationship between serum albumin and HbA1c (r = -0.293; p <0.001), whereby the lesser the albumin the poorer the glycaemic burden. Out of 50 cases of DKA, 43 were fully discharged and 3 passed away in the hospital. The mean serum albumin of deceased patients was much lower than that of the survivors (2.56 + 1.07 vs. 3.40 + 0.65 g/dL; p = 0.040), which proved to be a strong and clinically significant correlation between hypoalbuminemia and in-hospital DKA mortality (**Table 4**). This is very close to the finding of Hang *et al.* **[18]** who with the help of MIMIC-III critical care database (n=589 DKA patients in ICU) found that serum albumin in non-survivors was lower in comparison with that of survivors (2.9±0.7 vs 3.4±0.7 g/dL; p=0.001) and albumin was an independent factor of the BUN-to-albumin ratio is independent predictor of the in-hospital all-cause mortality in DKA. Our cohort, dead patients with DKA also demonstrated a much higher level of SGOT (66.33 ± 34.03 vs. 36.34 ±22.75 IU/L; p = 0.037) indicating that hepatocellular stress was also a contributing factor to adverse outcomes, which is also reflected in the report by Agarwal *et al.* **[14]** where high levels of transaminases had a significant correlation with DKA mortality.In the multiple linear regression model, serum albumin proved to be an important independent predictor of mortality (OR: - 6.069; CI: -1.149 to -8.010; p = 0.045), which validates the claim that hypoalbuminemia is an independent predictor of high mortality rate in the conditions of other covariates (**Table 5**). Rabi *et al.* **[17]** hypoalbuminemia was notably linked with higher overall mortality rates (71% vs. 52%) and increased 28-day mortality (50% vs. 39%), even after adjusting for age, comorbidities and disease severity. Agarwal *et al.* **[14]** confirmed this when they found serum albumin to be one of the important biochemical predictors on the study on Univariate analysis of 270 DKA patients with non-survivors showing a mean albumin of 2.79±0.61 g/dL as compared to 3.37±0.83 g/dL in survivors (p=0.001), which is strikingly similar to our results. HbA1c (p = 0.046) and gender also had an independent predictive value of death according to our study (p = 0.024). The same findings were made by Agarwal *et al.* **[14]** who found that male sex was an important and independent predictor of good outcome (OR: 7.93; 95% CI: 3.99-13.51) due to the high rates of female mortality because of late health-seeking behavior and socio-economic conditions in the tertiary care environment of developing countries. It is important to note

that, even though the difference in the arterial pH and WBC count is much higher between DKA cases and controls, neither of them was statistically significant predictors of mortality in our regression analysis. This coincides with the work of Agarwal *et al.* **[14]** who also discovered that pH and bicarbonate had no significant relationships with final outcome when subjected to multivariate analysis ($p>0.05$) indicating that initial acid-base severity is not predictive as strongly of final outcome compared to underlying nutritional-metabolic reserve. Hang *et al.* **[18]** also supported the same by showing that BAR, which utilizes serum albumin as a crucial denominator, was better than pH as a predictive of long-term DKA mortality in patients in the ICU. The combined importance of albumin and HbA1c as independent variables in our model is therefore the sum of the cases of acute nutritional depletion and chronic glycaemic load as the two fatal determinants of DKA mortality.

Conclusion:

DKA patients have significantly low serum albumin levels than diabetic controls and hypoalbuminemia itself is an independent predictor of in-hospital mortality. Frequent check of serum albumin and HbA1c at admission is an easy, cost-efficient prognostic measure aiding clinicians in the management of DKA. Timely provision for escalation of care and possible improved survival outcomes can be achieved by early recognition of hypoalbuminemic DKA patients, especially in environmentally constrained tertiary care.

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