The Role of Serial Serum Phosphate Levels in Predicting Outcomes in Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

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Abstract- Background: Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are acute, life-threatening complications of diabetes mellitus associated with significant metabolic and electrolyte disturbances. While many biochemical markers are monitored, the prognostic value of serum phosphate levels in predicting patient outcomes remains a key area of investigation. This study aimed to evaluate the role of serial serum phosphate levels as a predictor of outcome in patients with DKA and HHS.

Methods: A cross-sectional study was conducted from July 2022 to June 2024, involving 50 patients with type 2 diabetes mellitus admitted with DKA or HHS to the Alluri Sitarama Raju Academy of Medical Sciences, a tertiary care center in Eluru, India. Serial serum phosphate levels were measured at admission and during the hospital stay. Data on demographics, clinical parameters (HbA1c, BMI, RBS), duration of ICU and hospital stay, and mortality were collected. Statistical analysis was performed using chi-square tests, and the sensitivity and specificity of serum phosphate as a prognostic marker were calculated.

Results: The mean age of the study population was 43.12 ± 5.8 years, with a male predominance (72%). The mean admission RBS was 631.48 mg/dL, and the mean serum phosphate was 2.9 mg/dL. A significant association was found between hypophosphatemia (serum phosphate <2.5 mg/dL) and adverse outcomes. Mortality was significantly higher in the hypophosphatemic group compared to the normophosphatemic group ($p<0.05$). Furthermore, patients with hypophosphatemia had a significantly longer duration of both ICU stay (mean 11 vs. 6.75 days, $p<0.0001$) and total hospital stay (mean 14 vs. 9.75 days, $p<0.0001$). Low serum phosphate demonstrated a sensitivity of 78.57% and a specificity of 88.89% for predicting mortality.

Conclusion: Hypophosphatemia upon admission is a significant predictor of adverse outcomes in patients with DKA and HHS. It is strongly associated with increased mortality, as well as prolonged ICU and hospital stays. Routine monitoring of serial serum phosphate levels can serve as a valuable prognostic tool, helping to risk-stratify patients and guide clinical management in these hyperglycemic emergencies.

Keywords: Diabetic Ketoacidosis, Hyperglycemic Hyperosmolar State, Serum Phosphate, Hypophosphatemia, Prognosis, Mortality

INTRODUCTION

Diabetes mellitus (DM) has become a global pandemic, with its prevalence rapidly increasing, particularly in developing nations like India (11, 12). Among the most severe acute complications of DM are diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS). Both are medical emergencies characterized by profound hyperglycemia and severe metabolic derangements that can lead to significant morbidity and mortality if

not managed promptly and effectively (1, 9).

DKA is defined by the triad of hyperglycemia, ketonemia, and metabolic acidosis, resulting from absolute or relative insulin deficiency (5). HHS, in contrast, is characterized by extreme hyperglycemia, hyperosmolarity, and severe dehydration, typically without significant ketosis (9). The management of these conditions is complex, involving meticulous fluid resuscitation, insulin therapy, and correction of electrolyte imbalances.

Phosphate is a crucial intracellular anion, essential for numerous cellular processes, including energy metabolism (as a component of adenosine triphosphate, ATP), oxygen transport (via 2,3-diphosphoglycerate), and maintenance of acid-base balance (16). During hyperglycemic crises, significant shifts in phosphate occur. Osmotic diuresis leads to substantial urinary phosphate losses, while insulin therapy drives phosphate from the extracellular to the intracellular space, often resulting in hypophosphatemia (15). Severe hypophosphatemia can have profound clinical consequences, including respiratory muscle weakness, cardiac dysfunction, hemolysis, and rhabdomyolysis (3, 8).

Despite established treatment guidelines, predicting outcomes in patients with DKA and HHS remains challenging. Several studies have investigated potential prognostic markers, with serum phosphate levels emerging as a candidate of interest (17, 19). However, the evidence regarding its utility is not definitive, and the practice of routine phosphate monitoring and replacement is still debated (15). This study was designed to investigate the association between serial serum phosphate levels and clinical outcomes—specifically mortality, duration of ICU stay, and duration of hospital stay—in patients with DKA and HHS in a tertiary care setting in India.

MATERIALS AND METHODS

Study Design and Setting

This was a cross-sectional study conducted at the Department of General Medicine, Alluri Sitarama Raju Academy of Medical Sciences (ASRAMS), Eluru, Andhra Pradesh, India. The study was carried out over a period of two years, from July 2022 to June 2024.

Study Population

A total of 50 patients admitted to the medical ward and ICU with a diagnosis of DKA or HHS were enrolled in the study.

- Inclusion Criteria:
  - Patients aged >18 years.
  - Diagnosed with type 2 diabetes mellitus.
  - Presenting with DKA or HHS based on standard diagnostic criteria.
  - Provided written informed consent.
- Exclusion Criteria:
  - Patients with a prior diagnosis of type 1 DM or gestational DM.
  - Patients with a history of renal transplantation, pancreatitis, or severe burns.

Data Collection

Upon admission, a detailed history was taken, and a thorough clinical examination was performed for each patient. The following data were collected and recorded in a pre-designed proforma: demographic details (age, sex), clinical parameters (BMI, duration of diabetes, previous episodes of DKA/HHS), and precipitating factors.

Venous blood samples were collected at admission and serially during the hospital stay for biochemical analysis. The following investigations were performed: random blood sugar (RBS), glycated hemoglobin (HbA1c), complete blood count, renal function tests, liver function tests, serum electrolytes (including sodium, potassium, and phosphate), and arterial blood gas (ABG) analysis. Urine ketones were also measured.

Study Outcomes

The primary outcomes measured were in-hospital mortality, duration of Intensive Care Unit (ICU) stay, and total duration of hospital stay.

Ethical Considerations

The study was conducted after obtaining approval from the Institutional Ethics Committee of ASRAMS Medical College, Eluru. Written informed consent was obtained from all participants or their legally acceptable representatives before their enrollment in the study. Patient confidentiality was maintained throughout the study.

Statistical Analysis

The collected data were entered into a Microsoft Excel spreadsheet. Statistical analysis was performed using

the Statistical Package for the Social Sciences (SPSS) version 26.0. Qualitative data were expressed as frequencies and percentages and analyzed using the Chi-square test. Quantitative data were expressed as mean ± standard deviation. A p-value of <0.05 was considered statistically significant. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of serum phosphate levels for predicting mortality were calculated. Hypophosphatemia was defined as a serum phosphate level of <2.5 mg/dL.

RESULTS

Demographic and Clinical Characteristics

A total of 50 patients were included in the study. The mean age of the study population was 43.12 ± 5.8 years. The majority of the patients were male (36, 72%), while 14 (28%) were female. The mean HbA1c was 11.5%, indicating poor long-term glycemic control. The mean BMI was 32.2 ± 4.2 kg/m², and the mean duration of diabetes was 10.8 ± 1.2 years. The vast majority of patients (90%) had no prior history of DKA. The baseline characteristics are summarized in Table 1.

Table 1: Baseline Characteristics of the Study Population (n=50)

Characteristic	Value
Age (years), mean ± SD	43.12 ± 5.8
Gender, n (%)	
Male	36 (72%)
Female	14 (28%)
HbA1c (%), mean	11.5
BMI (kg/m²), mean ± SD	32.2 ± 4.2
Duration of Diabetes (years), mean ± SD	10.8 ± 1.2
Previous DKA, n (%)	5 (10%)
RBS at admission (mg/dL), mean	631.48
Serum Phosphate at admission (mg/dL), mean	2.9

Serum Phosphate Levels and Clinical Outcomes

At admission, 13 patients (26%) had hypophosphatemia (<2.5 mg/dL), 24 patients (48%) had serum phosphate levels between 2.5-3.5 mg/dL, and 13 patients (26%) had levels between 3.5-4.5 mg/dL.

A statistically significant association was observed between admission serum phosphate levels and all three primary outcomes.

Mortality:

The overall mortality rate in the study was 30% (15 out of 50 patients). Mortality was significantly higher in the hypophosphatemic group. Of the 14 patients with hypophosphatemia on admission, 11 (78.6%) died, compared to only 4 deaths (11.1%) among the 36 patients with normal phosphate levels (p<0.05) (Table 2).

Table 2: Association between Admission Serum Phosphate and Mortality

	Mortality: Yes	Mortality: No	Total
Hypophosphatemia (<2.5 mg/dL)	11	3	14
Normophosphatemia (≥2.5 mg/dL)	4	32	36
Total	15	35	50

Chi-square test, p<0.05

Duration of ICU and Hospital Stay:

Patients with hypophosphatemia had significantly longer stays in both the ICU and the hospital. The mean duration of ICU stay was 11 days for the hypophosphatemic group versus 6.75 days for the normophosphatemic group (p<0.0001). Similarly, the mean total hospital stay was 14 days for the hypophosphatemic group compared to 9.75 days for the normophosphatemic group (p<0.0001) (Table 3).

Table 3: Association between Admission Serum Phosphate and Duration of Stay

	Hypophosphatemia Group (n=13)	Normophosphatemia Group (n=37)	p-value
Mean ICU Stay (days)	11	6.75	<0.0001
Mean Hospital Stay (days)	14	9.75	<0.0001

Prognostic Accuracy of Serum Phosphate

As a predictor of mortality, an admission serum phosphate level of <2.5 mg/dL demonstrated a sensitivity of 78.57% and a specificity of 88.89%. The positive predictive value (PPV) was 73.33%, and the negative predictive value (NPV) was 91.43%.

DISCUSSION

This study investigated the prognostic significance of serial serum phosphate levels in patients with DKA and HHS. Our findings demonstrate a strong and statistically significant association between hypophosphatemia at admission and adverse clinical outcomes, including increased mortality and prolonged ICU and hospital stays.

The mean age of our cohort (43.1 years) is comparable to that reported in other studies by Xie et al. (45.4 years) and Betdur et al. (42.6 years), but younger than some Western cohorts, reflecting the earlier onset of type 2 DM in the Indian population (19, 22). The high mean HbA1c (11.5%) highlights the background of poor glycemic control that predisposes these patients to hyperglycemic crises.

The central finding of our study is the powerful predictive value of hypophosphatemia. The mortality rate in the hypophosphatemic group was over seven times higher than in the normophosphatemic group. This aligns with findings from several other studies. For instance, Betdur et al. found that the mean phosphate level was significantly lower in patients who did not survive (2.14 mg/dL) compared to those who recovered (3.03 mg/dL) (19). Similarly, a study by Camp et al. found a four-fold increase in mortality in hospitalized patients with severe hypophosphatemia (17). Our results reinforce the concept that the degree of hypophosphatemia reflects the severity of the underlying metabolic derangement. Phosphate depletion in DKA/HHS is multifactorial, stemming from osmotic diuresis and intracellular shifts during insulin treatment. Severe depletion can impair ATP production, leading to cellular dysfunction in multiple organ systems, which likely contributes to the increased mortality risk (16).

In addition to mortality, we found that hypophosphatemia was associated with a significantly longer duration of care, with an average of 4 extra days in the ICU and hospital. This suggests that patients with low phosphate levels have a more complicated and protracted recovery course. This increased length of stay has significant implications for healthcare resource utilization and costs. The prolonged stay may be due to complications directly attributable to hypophosphatemia, such as respiratory muscle weakness delaying weaning from mechanical ventilation, or it may simply be that hypophosphatemia is a marker for a more severe overall illness state that requires longer treatment.

The prognostic accuracy of admission hypophosphatemia was robust in our study, with a high specificity (88.89%) and a very high negative predictive value (91.43%). This suggests that a normal serum phosphate level on admission is a strong indicator of a more favorable prognosis, while a low level should alert clinicians to a high-risk patient requiring more intensive monitoring and potentially more aggressive management.

LIMITATIONS

Our study has several limitations. First, it was a single-center study with a relatively small sample size (n=50), which may limit the generalizability of our findings. Second, due to the cross-sectional design, we can only establish association, not causation. It is unclear whether hypophosphatemia is a direct cause of poor outcomes or simply a marker of disease severity. Third, we did not analyze the impact of phosphate replacement therapy on outcomes, which is an important area for future research.

CONCLUSION

In conclusion, our study demonstrates that hypophosphatemia on admission is a powerful and independent predictor of adverse outcomes in patients with DKA and HHS. It is strongly associated with increased in-hospital mortality and prolonged ICU and hospital stays. These findings underscore the importance of routine monitoring of serum phosphate levels in the management of hyperglycemic crises. An admission serum phosphate level can serve as a simple, readily available, and valuable tool for early risk stratification, helping clinicians to identify high-risk patients who may benefit from more intensive monitoring and care. Further large-scale, prospective studies are warranted to confirm these findings and to evaluate the potential benefits of early phosphate repletion in the high-risk hypophosphatemic population.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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