Predictors of Mortality in Pediatric Diabetic Ketoacidosis: The Role of Serum Lactate, Dehydration, and Admission Blood Sugar Levels

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KEYWORDS

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ABSTRACT

Background : Diabetic Ketoacidosis (DKA) is a severe complication of Type 1 Diabetes (T1D) in children, associated with significant morbidity and mortality. The mortality rate varies between <1% in developed countries and 3-13% in developing countries. Effective management of DKA necessitates accurate prognostic assessment to prevent adverse outcomes. This study investigates the role of serum lactate levels, severe dehydration, and admission blood sugar levels as predictors of mortality in pediatric DKA.

Methods: This prospective observational study was conducted over one year at SMGS Hospital, Jammu. It included pediatric patients (0-17 years) diagnosed with DKA. Data were collected on demographics, clinical features including severity of dehydration and laboratory findings including admission blood sugar , blood gas and urinalysis analysis, and treatment details. Outcomes assessed were length of hospital stay, intensive care requirements, and mortality.

Results: Fifty patients (50% male, median age 10.5 years) were studied. The mortality rate was 8%. Non-survivors had significantly higher mean serum lactate (7.95 mmol/L vs. 5.97 mmol/L; p=0.043) and blood sugar levels (521.5 mg/dL vs. 367.83 mg/dL; p=0.001) compared to survivors. Severe dehydration was present in 100% of non-survivors vs. 13.04% of survivors (p=0.0009). Despite these findings, multivariate regression did not identify any variable as an independent significant risk factor for mortality.

Conclusion: Elevated serum lactate levels, severe dehydration, and high admission blood sugar levels are associated with increased mortality in pediatric DKA. These findings highlight the need for precise assessment and management to improve outcomes. Further research is necessary to validate these predictors and optimize DKA management strategies.

Introduction

Type 1 Diabetes (T1D) is a prevalent chronic condition in children and often presents with Diabetic Ketoacidosis (DKA) as a severe, life-threatening complication. DKA is characterized by hyperglycemia, metabolic acidosis, and ketonemia or ketonuria[1]. It frequently represents the initial clinical manifestation of previously undiagnosed T1D, with incidence rates at diagnosis varying between 15% and 70% in Europe and North America[2].

Despite advancements in diabetes management, DKA remains a significant cause of morbidity and mortality in pediatric T1D patients. In developed countries, the mortality rate from DKA is <1%, while in developing countries, it is significantly higher, ranging from 3% to 13%[3]. Early recognition and effective management are crucial to preventing adverse outcomes. Assessing the prognosis in DKA is essential to avoid both overtreatment and long-term complications. This study aims to assess the role of serum lactate levels, severe dehydration, and admission blood sugar levels as predictors of mortality in pediatric DKA. The insights gained from this study are expected to enhance understanding of key predictors, potentially guiding and optimizing management strategies to improve outcomes for affected children.

Methods

This Prospective study was done in department of paediatrics , Govt Medical College Jammu over a period of 1 year from 1st may 2023 to 30th April 2024, which serves as a high-volume, resource-limited center for pediatric patients. All pediatric patients (aged 0-17 years) diagnosed with DKA and admitted during the study period were enrolled in this research study. DKA was defined according to standard clinical criteria: hyperglycemia (blood glucose >200 mg/dL), venous pH <7.3 or serum bicarbonate <15 mmol/L, and the presence of ketonuria. Each eligible study patient was followed during hospitalisation .Data were collected from all study patient medical records, including demographic characteristics (age, gender, consanguinity and body mass index), family history of diabetes ,undiagnosed or diagnosed diabetic in the past and intake of any indigenous treatment. History of precipitating illness , dose of insulin and compliance in known diabetics was also recorded in a preformed proformas. Symptoms complained by patients ,clinical signs and laboratory parameters were documented for each study patient at admission and during hospitalization. Clinical signs included assessment of dehydration ,signs of cerebral edema . Laboratory parameters included blood gas analysis , urinalysis for ketones serum lactate levels and CT head. Treatment details included fluid management , insulin therapy, , and use of pressors or mechanical ventilation. The outcomes of included the length of hospital stay, the requirement for intensive care measures (pressor support and mechanical ventilation), and mortality.

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data were presented as the means ± SD. The data normality was checked by using Shapiro-Wilk test.

The following statistical tests were applied for the results:

- The association of the variables which were quantitative in nature were analysed using Independent t test.
- The association of the variables which were qualitative in nature were analysed using Fisher's exact test as at least one cell had an expected value of less than 5.
- Multivariate logistic regression was used to find out independent significant risk factors of mortality.

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 25.0.For statistical significance, p value of less than 0.05 was considered statistically significant.

Results

Fifty patients were included in the study, with an equal gender distribution (50% male, 50% female) and a median age of 10.5 years. One-fourth of the patients were obese, and 24% were overweight based on Body Mass Index (BMI). Consanguinity was present in 60% of cases, while 34% had a family history of diabetes. Indigenous (non-allopathic) treatment was used by 22% of patients. Vomiting was the most common symptom (34%), followed by abdominal pain (32%). Newly diagnosed DKA cases accounted for 38% of the cohort, while 72% were known diabetics. Nineteen patients (38%) were first-time admissions for DKA, and 34% were second-time admissions. Acute respiratory illness was the most frequent precipitating factor (22%), followed by undifferentiated fever (16%). However, 44% of patients had no identifiable trigger. Signs of cerebral edema were observed in 18% of patients, and poor compliance with insulin was noted in 38% (table 1). Severe dehydration was present in 20% of cases, with 46% exhibiting mild dehydration. Median values at admission were: blood sugar 366 mg/dL, serum lactate 6 mmol/L, serum pH 7.09, and HbA1c 8%. Pressor support was required in 24% of patients, while 20% required mechanical ventilation. The median hospital stay was 10 days, and the mortality rate was 8%. The proportion of patients with severe dehydration was significantly higher in non-survivors (100% vs. 13.04%). Non-survivors had significantly higher mean blood sugar levels (521.5 ± 113.36 mg/dL vs. 367.83 ± 82.18 mg/dL; p=0.001) and serum lactate levels (7.95 ± 2.42 mmol/L vs. 5.97 ± 1.79 mmol/L; p=0.043) compared to survivors (table 2). Conversely, survivors had significantly higher mean serum pH at admission (7.08 ± 0.14 vs. 6.85 ± 0.1; p=0.002). Multivariate regression analysis did not identify any variable as an independent significant risk factor for mortality, likely due to the sample size (table 3).

Discussion

We defined stress hyperglycemia (SH) as blood glucose level above 140 mg/dl as per American Diabetes Association guidelines (ADA) for diagnosis of stress hyperglycemia (**Moghissi S et al 2009**). Our study found a significant association between elevated serum lactate levels at admission and mortality in pediatric DKA patients, adding important evidence to the ongoing debate about the prognostic value of lactate in this population. Previous research has established that lactic acidosis is associated with poor outcomes in various critical conditions, such as sepsis, septic shock, and trauma, where it has been independently linked to increased mortality in critically ill children [4]. Although some studies have suggested that lactic acidosis frequently occurs in DKA, others have reported conflicting findings regarding its impact on mortality in this context[5]. For instance, while lactic acidosis has been noted to be common in adult DKA patients, there remains a lack of pediatric-specific research focusing on its prognostic value in pediatric DKA[6]. Notably, some studies in adults have shown that lactic acidosis is not a strong predictor of mortality in DKA, contrasting with its recognized importance in other critical conditions[7,8]. However, studies involving pediatric patients have provided mixed results, with some indicating an association between initial lactate levels and mortality in intensive care settings[9]. Despite this, research specifically targeting the significance of lactate levels in pediatric DKA remains sparse [8].

Our study reported an 8% mortality rate, with a mean serum lactate level of 7.95 mmol/L in non-survivors, compared to 5.97 mmol/L in survivors (p = 0.043). Mortality in DKA is primarily due to cerebral edema, and all non-survivors in our study had cerebral edema[2]. Our findings align with emerging research on the role of lactate in cerebral edema. While cerebral edema is a well-known complication of DKA, its exact pathogenesis remains complex and multifactorial. Recent studies, such as one conducted on a rat model of cirrhosis, have shed light on the potential mechanisms linking lactate accumulation to cerebral edema[10]. In the context of chronic liver disease and minimal hepatic encephalopathy (HE), increased brain lactate was shown to play a primary role in the development of brain edema, surpassing the contributions of other factors like glutamine. The study found that inhibiting lactate synthesis could attenuate brain edema, suggesting that lactate is a critical factor in the osmoregulatory disturbances that lead to cerebral swelling[11]. Although the pathophysiology of cerebral edema in DKA differs from that in chronic liver disease, the role of lactate as a key contributor to cerebral edema may be a common link. In DKA, hyperglycemia, dehydration, and metabolic acidosis can lead to elevated lactate levels, which, as our study shows, are associated with increased mortality. The findings from the chronic liver disease study support the hypothesis that lactate may contribute to the development of cerebral edema in DKA, possibly through similar osmoregulatory mechanisms. Our results, combined with these insights, suggest that elevated lactate levels in pediatric DKA should not only be seen as a marker of severe metabolic disturbance but also as a potential contributor to the development of cerebral edema. This underscores the importance of closely monitoring and managing lactate levels in DKA patients to prevent this life-threatening complication.

Our findings contribute to this area by highlighting the significant association between elevated initial serum lactate levels and mortality in pediatric DKA. This supports the suggestion that lactic acidosis, while common in DKA, can serve as an important marker of disease severity and outcome in children[8]. Furthermore, a study by Alışkan and Kılıç also supports our findings, demonstrating that elevated lactate levels at the time of admission may predict in-hospital mortality and ICU admission[12]. Given the mixed evidence in the literature, our results underscore the need for further research to clarify the role of serum lactate as a prognostic marker in pediatric DKA. Such research should aim to establish standardized guidelines for the management of DKA patients with elevated lactate levels to improve outcomes.

Our study also identified severe dehydration as a significant predictor of mortality in pediatric DKA, as evidenced by our univariate regression analysis. The proportion of patients with severe dehydration was significantly higher in non-survivors compared to survivors (100% vs. 13.04%; $p = 0.0009$). This finding is particularly important given the challenges associated with accurately assessing dehydration in these patients. Dehydration in DKA results from osmotic diuresis due to hyperglycemia and ketonemia, compounded by nausea, vomiting, and reduced oral intake. While fluid therapy is crucial for correcting these deficits, the assessment of dehydration remains challenging[13]. Traditional clinical signs, such as changes in perfusion, blood pressure, and orthostatic hypotension, are often used but have shown poor correlation with actual dehydration levels measured by weight gain post-rehydration[14]. Studies have demonstrated that clinical signs such as dry mucous membranes, hyperventilation, sunken eyes, and lethargy, though correlated with dehydration, do not reliably predict its severity. Additionally, severe DKA does not always equate to severe dehydration, complicating treatment further[14]. This disparity between clinical assessment and actual dehydration underscores the need for more accurate tools and individualized fluid therapy protocols. Overestimation of dehydration can lead to overhydration, increasing the risk of cerebral edema, while underestimation may perpetuate hypoperfusion and tissue hypoxia, exacerbating the risk of mortality[15]. Therefore, our findings support the importance of careful and individualized assessment of dehydration in managing pediatric DKA to avoid these risks and improve patient outcomes.

Admission Blood Sugar Levels

One of the novel findings of our study is the significant association between admission blood sugar levels and mortality in pediatric DKA. We observed that non-survivors had significantly higher blood sugar levels at admission compared to survivors. This finding suggests that extreme hyperglycemia at presentation may reflect a more severe metabolic disturbance, contributing to worse outcomes. Interestingly, despite the well-established role of blood sugar control in the management of DKA, there is a noticeable gap in the literature regarding the direct relationship between admission blood sugar levels and mortality outcomes in pediatric DKA. To our knowledge, no previous studies have specifically examined this association in a pediatric population. This lack of data underscores the uniqueness of our findings and the potential importance of admission hyperglycemia as a prognostic marker.

Multivariate Regression Analysis

On performing multivariate regression, none of the factors mentioned above were identified as independent significant risk factors for mortality, as shown in Table 1.

Conclusion

Our study highlights elevated serum lactate levels at admission as a significant predictor of mortality in pediatric DKA, with higher lactate levels correlating with increased mortality. Severe dehydration and high admission blood sugar levels were also associated with worse outcomes, emphasizing the need for accurate assessment and management. Despite these findings, further research is needed to establish the role of these predictors and to improve patient outcomes in pediatric DKA.

Limitations

This study's single-center and small sample size may limit the generalizability of the findings and restrict the robustness of the conclusions. Additionally, variations in clinical management and the complexity of multivariate regression analysis may affect the interpretation of the results.

Table 1:- Patient characteristics distribution.

Patient characteristics	n(%)	Mean ± SD	Median(25th-75th percentile)	Range
Gender				
Female	25 (50.00%)	-	-	-
Male	25 (50.00%)			

Consanguinity	30 (60.00%)	-	-	-
Indigenous treatment	11 (22.00%)	-	-	-
Family history of diabetes	17 (34.00%)	-	-	-
Abdominal pain	16 (32.00%)	-	-	-
Vomiting	18 (36.00%)	-	-	-
Signs of cerebral edema	9 (18.00%)	-	-	-
Hospitalizations for DKA (Diabetic Ketoacidosis)				
First	19 (38.00%)	-	-	-
Second	17 (34.00%)			
Third	13 (26.00%)			
Fourth	1 (2.00%)			
Newly diagnosed / Known diabetic				
Newly diagnosed	14 (28.00%)	-	-	-
Known diabetic	36 (72.00%)			
Compliance with insulin				
First time admitted for DKA	14 (28.00%)	-	-	-
Good	17 (34.00%)			
Poor	19 (38.00%)			
Precipitating illness				
Absent	22 (44.00%)	-	-	-
Acute respiratory illness	11 (22.00%)			
Pneumonia	4 (8.00%)			
Undifferentiated fever	8 (16.00%)			
UTI	5 (10.00%)			
Dehydration grade				
Mild	23 (46.00%)	-	-	-

Moderate	17 (34.00%)			
Severe	10 (20.00%)			
Blood sugar at admission (mg/dL)	-	380.12 ± 93.61	366(325-432)	209-650
Serum lactate levels at admission (mmol/L)	-	6.12 ± 1.9	6(5-7)	3-11
Serum pH at admission	-	7.06 ± 0.15	7.09(7.03-7.148)	6.6-7.22

Table 2:-Association of patient characteristics with non-survivors and survivors.

Patient characteristics	**Non-survivors(n=4)**	**Survivors(n=46)**	**Total**	**P value**
Dehydration grade				
Mild	0 (0%)	23 (50%)	23 (46%)	0.0009*
Moderate	0 (0%)	17 (36.96%)	17 (34%)	
Severe	4 (100%)	6 (13.04%)	10 (20%)	
Blood sugar at admission (mg/dL)	521.5 ± 113.36	367.83 ± 82.18	380.12 ± 93.61	0.001†
Serum lactate levels at admission (mmol/L)	7.95 ± 2.42	5.97 ± 1.79	6.12 ± 1.9	0.043†
Serum pH at admission	6.85 ± 0.1	7.08 ± 0.14	7.06 ± 0.15	0.002†

† Independent t test, * Fisher's exact test

Table 3:Multivariate logistic regression to find out significant risk factors of mortality.

Variables	**Beta coefficient**	**Standard error**	**P value**	**Odds ratio**	**Odds ratio Lower bound (95%)**	**Odds ratio Upper bound (95%)**
Blood sugar at admission (mg/dL)	0.003	0.006	0.574	1.003	0.992	1.015
Serum lactate levels at admission (mmol/L)	0.280	0.327	0.391	1.323	0.697	2.511
Serum pH at admission	0.409	4.378	0.926	1.505	0.000	8025.757
Dehydration grade						
Mild				1.000		
Moderate	0.325	1.821	0.859	1.383	0.039	49.062
Severe	3.113	1.873	0.097	22.489	0.572	884.043

References

1. Lucier J, Dulebohn SC. Type 1 Diabetes. [Updated 2023 Mar 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507713/

2. Glaser N, Fritsch M, Priyambada L, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Pediatr Diabetes*. 2022; 23(7): 835-856. doi:10.1111/pedi.13406
3. Mastromauro C, Polidori N, Blasetti A, et al. Insulin resistance relates to DKA severity and affects insulin requirement in children with type 1 diabetes at onset. *Pediatr Diabetes*. 2022;23(8):1613-1620. doi:10.1111/pedi.13424
4. Loomba RS, Farias JS, Villarreal EG, Flores S. Serum Lactate and Mortality during Pediatric Admissions: Is 2 Really the Magic Number?. *J Pediatr Intensive Care*. 2022;11(2):83-90. Published 2022 Feb 18. doi:10.1055/s-0042-1743180
5. Cox K, Cocchi MN, Salciccioli JD, Carney E, Howell M, Donnino MW. Prevalence and significance of lactic acidosis in diabetic ketoacidosis. *J Crit Care*. 2012;27(2):132-137. doi:10.1016/j.jcrc.2011.07.071
6. Cully M, Thompson AD, DePiero AD. Is lactic acidosis predictive of outcomes in pediatric diabetic ketoacidosis?. *Am J Emerg Med*. 2020;38(2):329-332. doi:10.1016/j.ajem.2019.158449
7. Bhat JA, Masoodi SR, Bhat MH, Bhat H, Ahmad PO, Sood M. Lactic Acidosis in Diabetic Ketoacidosis: A Marker of Severity or Alternate Substrate for Metabolism. *Indian J Endocrinol Metab*. 2021;25(1):59-66. doi:10.4103/ijem.IJEM_753_20
8. Unal E, Pirinccioglu AG, Yanmaz SY, Yılmaz K, Taşkesen M, Haspolat YK. A DIFFERENT PERSPECTIVE OF ELEVATED LACTATE IN PEDIATRIC PATIENTS WITH DIABETIC KETOACIDOSIS. *Acta Endocrinol (Buchar)*. 2020;16(1):114-117. doi:10.4183/aeb.2020.114
9. Koliski A, Cat I, Giraldi DJ, Cat ML. Lactato sérico como marcador prognóstico em crianças gravemente doentes [Blood lactate concentration as prognostic marker in critically ill children]. *J Pediatr (Rio J)*. 2005;81(4):287-292.
10. Bosoi CR, Zwingmann C, Marin H, et al. Increased brain lactate is central to the development of brain edema in rats with chronic liver disease. *J Hepatol*. 2014;60(3):554-560. doi:10.1016/j.jhep.2013.10.011
11. Vaquero J, Chung C, Blei AT. Brain edema in acute liver failure. A window to the pathogenesis of hepatic encephalopathy. *Ann Hepatol*. 2003;2(1):12-22.

12. Alışkan H, Kılıç M. The relationship between initial lactate levels and outcomes in patients diagnosed with diabetic ketoacidosis in the emergency department. J Surg Med.2022;6(12):991-993.

13. EL-Mohandes N, Yee G, Bhutta BS, et al. Pediatric Diabetic Ketoacidosis. [Updated 2023 Aug 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470282/

14. Singhi S, Jayashree M. 'De hydration' assessment and replacement fluid therapy in diabetic ketoacidosis: is there an answer? [published correction appears in Pediatr Crit Care Med. 2012 May;13(3):373. Muralindharan, Jayashree [corrected to Jayashree, Muralindharan]]. *Pediatr Crit Care Med*. 2012;13(2):240-241. doi:10.1097/PCC.0b013e31822882e9

15. Yuen N, Anderson SE, Glaser N, Tancredi DJ, O'Donnell ME. Cerebral blood flow and cerebral edema in rats with diabetic ketoacidosis. *Diabetes*. 2008;57(10):2588-2594. doi:10.2337/db07-1410