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Lactate Levels in Diabetic Ketoacidosis: Is There an Association Between the Severity of Acidosis and Length of Hospital Stay with Elevated Lactate Levels?

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ABSTRACT

Introduction: This study aimed to investigate the prevalence of lactic acidosis, its effect on the duration of intensive care unit (ICU) stay and hospital stay, and other factors affecting morbidity in patients with diabetic ketoacidosis (DKA).

Methods: We reviewed the records of 56 patients, including 26 (46.4%) girls and 30 (53.6%) boys, under 18 years of age, diagnosed as DKA. The cut-off value for elevated lactate levels was set at ≥2 mmol/L. The length of hospital stay, ICU stay, and mortality rate were recorded.

Results: There was no statistically significant correlation between length of hospital and ICU stay with lactate levels. In addition, no statistically significant relationship was found between the time of transition to subcutaneous therapy and lactate. There was a statistically significant positive correlation between lactate level, respiration rate, glucose level, and pediatric risk of mortality III score.

Conclusion: Lactic acidosis is common in pediatric patients with DKA. Although lactate levels were reported to be a significant independent predictor of morbidity and mortality in adult ICU patients, no effect was found on the length of hospital stay, ICU stay, and the time to transition to subcutaneous therapy with lactate levels in pediatric DKA patients.

Keywords: Type 1 diabetes, lactate, PRISM III score, lactic acidosis

Introduction

Diabetic ketoacidosis (DKA) is the most frequent acute complication of type 1 diabetes and the leading cause of diabetes-related fatalities (1,2). Ketoacidosis is a pediatric emergency, and approximately 15-67% of children with diabetes present with ketoacidosis upon diagnosis (2). Although the incidence of ketoacidosis-related mortality is reported to be 0.15-0.31% in Western countries, it is as high as 6-24% in developing countries (2,3). The factors that can influence mortality and morbidity in critically ill patients during ketoacidosis treatment should be recognized. The lactate level is increasingly being used as a predictor of illness severity and prognosis in critical condition. In the adult intensive care unit (ICU), high lactate levels are major independent predictors of mortality (4). According to the 2018 guidelines of the International Society of Pediatric and Adolescent Diabetes (ISPAD), while hyperglycemic hyperosmolar conditions were more prevalent, lactic acidosis could also occur in DKA cases. In DKA, the anion gap is usually between 20 and 30 mmol/L, with anion gaps greater than 35 mmol/L suggesting the presence of concomitant lactic acidosis (5). Increased lactate levels are common in patients with diabetes and are thought to be caused by increased anaerobic glycolysis due to tissue hypoperfusion and hypoxemia (6,7). However, its role in DKA is not well-defined. Our study aimed to investigate the prevalence of lactic acidosis, its effect on the duration of intensive care and hospital stay, and other factors affecting morbidity in patients with DKA.

Methods

A total of 56 patients with DKA aged 35-210 months, who were admitted to University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital between May 2019 and December 2022, were included in the study. According to the ISPAD 2018 guidelines, DKA is characterized by hyperglycemia (blood glucose >11 mmol/L or ~200 mg/dL), venous pH <7.3, serum bicarbonate <15 mmol/L, ketonemia (blood ß-hydroxy-butyrate ≥3 mmol/L), or moderate to severe ketonuria (5). Patients who were referred to another center after the start of treatment and those who were referred to another center during treatment were excluded from the study.

Venous blood gas samples were obtained from all patients within 1 hour of admission to the emergency room. Patients were categorized into

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three groups according to their venous blood pH value and bicarbonate (HCO_3) levels: mild (pH <7.30, HCO_3 <15 mmol/L), moderate (pH <7.20, HCO_3 <10 mmol/L), and severe (pH <7.10, HCO_3 <5 mmol/L) ketoacidosis groups (5). The following information was obtained retrospectively from patient files: age at admission, gender, body mass index, age of diabetes diagnosis, length of hospital stay, Glasgow Coma Score, respiration rate, heart rate, body temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MBP). For patients who were followed up at the ICU, the length of ICU stay and pediatric risk of mortality III (PRISM III) score were evaluated (8). The PRISM III score calculation included 17 parameters; SBP, heart rate, temperature, mental status, pupillary response, acidosis, pH, pCO_2, total CO_2, pO_2, glucose, serum potassium, creatinine, blood urea nitrogen, total white blood cell count, platelet count, prothrombin time, and activated partial thromboplastin time.

Laboratory results were used to obtain data on glucose, blood pH, sodium, potassium, calcium, bicarbonate, anion gap, lactate in blood gas, pO_2 and pCO_2 in venous blood gas, leukocyte count, hemoglobin, platelets, C-reactive protein, glycosylated hemoglobin A1c (HbA1c) at diagnosis, C-peptide, urea, creatinine, and urinary ketone values. The length of hospital stay, length of ICU stay, and mortality rate were recorded. Each patients assessment included only one episode of ketoacidosis. Patients with heart failure, hepatic insufficiency, or history of drug use (metformin, acetaminophen and acetylsalicylic acid) that could cause lactic acidosis were excluded from the study. Although different studies have suggested different normal serum lactate levels, the cut-off value for elevated lactate levels was set at ≥2 mM in the present study (4,9). The relationship between the degree of acidosis, high lactate levels, and C-peptide levels and ICU and hospital stays was investigated.

The study was approved by the University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (2022/514/218/16, date: 28.01.2022).

Statistical Analysis

The IBM Statistical Package for the Social Sciences Statistics Standard Concurrent User v. 26 (IBM Corp., Armonk, New York, USA) software was used for data analysis. Descriptive statistics were presented as number of units (n), percentage (%), mean ± standard deviation, median, minimum, and maximum values. The Shapiro-Wilk test was used to assess the standard distribution hypothesis of numerical variables, whereas the Levene's test was used to test group homogeneity. The independent samples t-test or the Mann-Whitney U test was applied to compare numerical variables between the lactate <2 and lactate ≥2 groups. The Kruskal-Wallis test was used to compare the length of hospital stay among the pH groups, with multiple comparisons conducted using the Dunn-Bonferroni test. The relationship between numerical variables was examined using Spearman's correlation analysis. A p-value of <0.05 was considered statistically significant.

Results

The study files of 56 patients reviewed, including 26 (46.4%) girls and 30 (53.6%) boys. The median age of the participants was 123.5 months (range, 35-210 months). Forty (71.4%) patients were newly diagnosed, whereas sixteen (28.6%) were previously diagnosed. The age at diagnosis varied from 35 to 209 months, with a median age of 103.5 months. Thirty-four patients (60.7%) were followed up in the ICU, and the median length of stay was 2 days. The descriptive features of the patients are summarized in Table 1.

Table 1. Descriptive characteristics of patients (n=56)

Variables	Statistics
Age, (months)	
$\bar{X}$ ± SD	123.75±49.06
Median (minimum-maximum)	123.5 (35.0-210.0)
Sex, n (%)	
Girls	26 (46.4)
Boys	30 (53.6)
Diagnosis, n (%)	
Newly diagnosed	40 (71.4)
Previously diagnosed	16 (28.6)
Age at diagnosis (months)	
$\bar{X}$ ± SD	106.98±46.03
Median (minimum-maximum)	103.5 (35.0-209.0)
Body mass index (kg/m²)	
$\bar{X}$± SD	17.48±3.48
Median (minimum-maximum)	16.55 (10.8-27.4)
Admission to the ICU, n (%)	
Yes	34 (60.7)
No	22 (39.3)
Length of ICU stay (days)	
$\bar{X}$ ± SD	2.52±2.13
Median (minimum-maximum)	2.0 (1.0-14.0)
When were normal lactate levels achieved? (hours)	
$\bar{X}$± SD	7.01±5.66
Median (minimum-maximum)	4.0 (1.0-24.0)
Lactate (mM)	
$\bar{X}$ ± SD	2.84±1.16
Median (minimum-maximum)	2.5 (1.2-6.1)
Glucose (mg/dL)	
$\bar{X}$ ± SD	518.01±126.41
Median (minimum-maximum)	497.0 (268.0-897.0)
pH	
$\bar{X}$ ± SD	7.05±0.12
Median (minimum-maximum)	7.07 (6.8-7.3)
GFR (mL/min/1.73 m²)	
$\bar{X}$ ± SD	115.17±24.64
Median (minimum-maximum)	112.50 (74.5-197.0)
Creatinine (mg/dL)	
$\bar{X}$ ± SD	0.77±0.21
Median (minimum-maximum)	0.720 (0.41-1.43)
HCO_3 (bicarbonate) (mmol/L)	
$\bar{X}$ ± SD	9.52±3.81
Median (minimum-maximum)	9.0 (4.0-24.0)
Mean arterial pressure (mmHg)	
$\bar{X}$ ± SD	84.44±12.64
Median (minimum-maximum)	87.0 (53.0-111.0)

SD: Standard deviation, min: Minute, ICU: Intensive care unit, GFR: Glomerular filtration ratio

In terms of acidosis severity, 7 (12.5%) patients were classified into the mild group, 18 (32.1%) in the moderate group, and 31 (55.4%) in the severe group. We found a statistically significant difference between these groups in terms of acidosis severity and length of hospital stay. The total length of hospital stay was significantly longer in the severe acidosis group than in the moderate and mild acidosis groups. The relationships between the mild, moderate, and severe acidosis groups and the total length of hospital stay are summarized in Table 2.

We found no difference among 3 groups in terms of lactate level and cardiac apex beat, SBP, DBP, and MBP (rho: 0.115, p=0.399; rho: 0.019, p=0.892; rho: 0.027, p=0.844; and rho: -0.023, p=0864, respectively), and we found a positive correlation between the lactate level and respiratory rate (rho: 0.307; p=0.022).

No significant correlation was found among the 3 groups regarding the time to transition to subcutaneous therapy and lactate level (rho: 0.141; p=0.309).

There was no correlation between lactate and heart rate, SBP, DBP, MBP, length of hospital stay, length of ICU stay, time of transition to subcutaneous therapy, or C-peptide level (Table 3). Lactate level was positively correlated with respiration rate, glucose level, and PRISM III score, and there was a negative correlation between lactate and pH.

There was no correlation between the time of transition to subcutaneous therapy and lactate level (rho: 0.141; p=0.309). No significant relationship was found between the PRISM III score and length of hospital stay (rho: 0.227; p=0.198), and the PRISM III score and length of ICU stay (rho: 0.112; p=0.528). A significant positive relationship between C-peptide levels and pH was found (rho: 0.384; p=0.006).

Table 2. A comparison of length of hospital stay based on the severity of acidosis

	Severity of acidosis			Test statistics	
	Mild, (n=7)	Moderate, (n=18)	Severe, (n=31)	H	p
LOHS (days)					
Median (minimum-maximum)	7 (4-9)[a]	7 (3-10)[a]	9 (3-21)[b]	10,137	0.006

H: Kruskal-Wallis test; superscripts ([a]) and ([b]) indicate groups with statistically significant differences. Groups with the same superscripts were statistically similar. LOHS: Length of hospital stay

Table 3. Correlations between lactate level and other variables

	Lactate	
	rho	p
Heart rate	0.115	0.399
Systolic blood pressure	0.019	0.892
Diastolic blood pressure	0.027	0.844
Respiration rate	**0.307**	**0.022**
Mean arterial pressure	-0.023	0.864
Length of hospital stay	-0.134	0.325
Length of ICU Stay	-0.089	0.616
Time from transition to subcutaneous treatment	0.141	0.309
Glucose	**0.301**	**0.024**
PRISM III score	**0.606**	**<0.001**
C-peptide levels	-0.116	0.426
pH	**-0.435**	**0.001**

Rho: Spearman correlation coefficient; bold values indicate statistical significance. ICU: Intensive care unit, PRISM III: Pediatric risk of mortality III

There was no statistical difference between the high and normal lactate groups based on age and gender (Table 4). The lactate ≥2 group had significantly higher glucose and creatinine levels. The lactate groups had statistically similar sodium, potassium and HbA1c values. The pH and bicarbonate values of the lactate ≥2 group were lower than the lactate <2 group. No significant difference was found between the groups in terms of $PaCO_2$ levels. The lactate ≥2 group had statistically higher anion gap values. We found no differences among the groups in SBP, DBP, time to transition to subcutaneous treatment, or C-peptide levels.

There was no correlation between length of stay and anion gap, glucose, sodium, potassium, and lactate (Table 5).

No comorbidities or deaths were recorded in our study group.

Discussion

The current study examined pediatric patients with DKA admitted to the emergency department. Our study aimed to identify the factors contributing to prolonged hospital stays and to determine the effect of lactic acid levels on transition to subcutaneous treatment and length of hospitalization. Lactate levels showed a statistically significant positive correlation with respiration rate, glucose levels, and PRISM III score, whereas a statistically significant negative correlation with pH was noted.

Studies involving non-diabetic patients reported that high lactate levels were associated with longer ICU stay and increased mortality in critically ill patients as well as in patients with sepsis who were admitted to the ICU for follow-up (10-12).

In their extensive retrospective study, Khosravani et al. (4) found that a lactate level of ≥2 mmol/L upon admission was an important predictor of mortality among adults admitted to ICUs. Kruse et al. (9) conducted a systematic review of 33 articles and determined that single lactate measurements at hospital admission were valuable for predicting adverse outcomes. They recommended close monitoring for patients with lactate levels ≥2.5 mM at admission. The study found an acceptable correlation between lactate levels in arterial and venous blood samples, suggesting that venous sampling is associated with minimal risk and inconvenience for patients. They reported a negative correlation between pH and lactate. However, a relationship was found between lactate levels and length of hospital stay (9).

In 2021, Masharani et al. (13) reported data from 79 adults hospitalized for DKA. Increased blood glucose levels and hydrogen ion concentrations were correlated with higher lactate levels. A decrease in the glomerular filtration rate was also related to a higher lactate (13). Because metformin therapy may increase lactate levels by decreasing renal clearance, no patients were treated with metformin in the present study.

James et al. (14) reported that lactic acidosis in patients may be due to sepsis or trauma in the absence of tissue hypoperfusion. The authors suggested that the activity of the muscle Na-K pump increases

Table 4. Comparisons based on lactate levels

	Lactate level		Test statistics	
	<2, (n=8)	**≥2, (n=48)**	**Test value**	**p-value**
Lactate level (mmol/L)	1.65 (0.25)	2.65 (1.48)	*z*=4.508	**<0.001**
Age (months)	134.2±57.6	122.0±47.9	*t*=0.650	0.518
Gender (girls/boys)	6/2	20/28	χ^2=3.063	0.127
Glucose (mg/dL)	419.7±83.4	534.3±125.4	*t*=2.484	**0.016**
Creatinine (mg/dL)	0.54 (0.24)	0.77 (0.29)	*z*=2.917	**0.002**
Sodium (mmol/L)	132.2±3.8	131.2±4.9	*t*=0.525	0.602
Potassium (mmol/L)	4.11±0.71	4.47±0.64	*t*=1.438	0.156
HbA1c (%)	12.56±1.82	12.93±1.99	*t*=0.498	0.620
pH	7.18±0.12	7.04±0.11	*t*=3.381	**0.001**
Bicarbonate (mmol/L)	14.05 (5.98)	8.25 (4.65)	*z*=2.369	**0.016**
$PaCO_2$ (mmHg)	26.37±11.47	23.82±7.32	*t*=0.836	0.407
Anion gap	19.1±5.1	23.1±4.9	*t*=2.072	**0.043**
Systolic blood pressure (mmHg)	110.0 (27.5)	110.0 (20.0)	*z*=0.285	0.792
Diastolic blood pressure (mmHg)	72.5 (28.7)	72.5 (20.0)	*z*=0.071	0.954
Time to transition to subcutaneous treatment (hour)	11.4 (3.1)	12.7 (1.7)	*z*=1.793	0.075
C-peptide level (ng/mL)	0.41 (0.71)	0.34 (0.25)	*z*=0.357	0.727

Data are expressed in mean ± standar deviation or median (interquartile range), *z*: Mann-Whitney U test, *t*: Independent samples t-test, χ^2: Chi-squared test, and bold p-values are statistically significant. HbA1c: Hemoglobin A1c

with increased epinephrine levels and thus causes increased lactate production (14). In patients with DKA, insulinopenia and stress may activate counterregulatory hormones and cause an increase in epinephrine levels (15). Bolli et al. (15) reported that increased epinephrine levels may increase the severity of ketoacidosis. Increased lactic acid levels in patients with sepsis and trauma are often associated with tissue hypoperfusion, whereas in patients with DKA, they are associated with increased levels of counterregulatory hormones. This explains why lactic acidosis is not an important indicator of mortality in patients with DKA, as it is in those with sepsis and trauma.

It was reported in relevant studies with adult patients that lactic acidosis was prevalent in DKA patients and that elevated lactate levels were not correlated with the length of ICU stay and mortality (6,13,16). Only a few studies have investigated elevated lactate levels associated with DKA in the pediatric age group. Cully et al. (17) evaluated 92 pediatric patients and reported that lactate levels were >2.5 mmol in 63.7% of the patients and that lactate levels were associated with glucose levels during admission; these findings were similar to those of adult studies. A study involving pediatric cases monitored in the ICU for severe ketoacidosis found a negative relationship between lactate levels and the recovery time from DKA (18). Nevertheless, lactate levels were positively correlated with glucose levels.

Elevated lactate levels were a common finding in our study, and the lactate level was found to be ≥2 mmol in 85.7% of the patients. The findings of our study are consistent with those of the current literature. There was no correlation between lactate levels, transition to subcutaneous treatment, and length of hospital stay.

Table 5. Correlation between length of hospital stay and anion gap, glucose, sodium, and potassium levels

	Length of hospital stay	
	rho	**p**
Anion gap	-0.054	0.692
Glucose	-0.088	0.518
Sodium	0.035	0.796
Potassium	-0.242	0.073
Lactate	-0.134	0.325

rho: Spearman's correlation coefficient

Furthermore, there was no obvious difference in lactic acid levels, transition to subcutaneous therapy, or length of hospital stay between the groups. Patients with severe ketoacidosis had longer hospital stays than those with mild or moderate ketoacidosis. This was attributed to the fact that patients with severe ketoacidosis were primarily monitored in intensive care, which delayed diabetes education. Although higher lactate levels were associated with poorer clinical outcomes in patients with trauma, sepsis, and burns, lactate levels were not associated with increased morbidity and mortality in patients hospitalized due to DKA (19-21). Similarly, elevated lactate levels did not increase morbidity and mortality in the current study.

Inadequate tissue perfusion due to volume depletion and relative hypoxemia are the main causes of lactate elevation in patients with DKA. Despite higher blood glucose levels in patients with DKA, tissue glucose secretion is insufficient because of insulinopenia. This causes a hypoglycemic response in the tissues, especially brain tissue. As a result, lactate production can meet the brain's need for fuel, which is known as "alternative fuel hypothesis" (7). Hyperlactatemia is frequent in patients with DKA and is not linked to unfavorable outcomes. The results suggest that a thorough assessment and empirical treatment of sepsis solely based on elevated lactate levels might be unnecessary.

No deaths due to DKA or related complications were recorded. Only one patient was intubated because of unconsciousness upon admission and required dialysis because of a gradual increase in creatinine levels. A study in Türkiye reported that only 1 patient was lost due to sepsis and multiorgan failure among 119 patients with DKA who were followed up in the pediatric ICU. In the relevant study, the median length of ICU stay was 2 days, and the median length of hospital stay was reported 8 days (22).

Study Limitations

The present study has certain limitations. Clinical and laboratory data were retrospectively recorded in patient files. Due to the limited sample size, studies with larger sample sizes are required to ascertain the clinical importance of lactic acidosis in pediatric patients with DKA in emergency services.

Conclusion

Lactic acidosis is common in pediatric patients with DKA. Nevertheless, its clinical significance remains unclear. Thus, serum lactate levels alone should not be used as a predictor of outcomes in pediatric DKA. Lactic acid levels are expected to return to normal in patients with DKA who receive appropriate intravenous fluid and insulin replacement. In patients with persistently high lactic acid levels despite improvement in hyperglycemia, we recommend that patients be further evaluated for underlying diseases.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (2022/514/218/16, date: 28.01.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Surgical and Medical Practices - E.S., U.Y.; Concept - E.S., F.H.E.; Design - E.S., U.Y., M.T.K.; Data Collection or Processing - E.S., U.Y., M.T.K.; Analysis or Interpretation - M.T.K., Y.A., F.H.E.; G.E.; Literature Search - E.S., Y.A.; Writing - E.S.

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