



Lactate kinetics in intensive care unit admissions due to diabetic ketoacidosis

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ABSTRACT

Aims: We conducted this study to investigate the clinical significance of lactate kinetics in patients admitted to the intensive care unit (ICU) for diabetic ketoacidosis (DKA).

Methods: This retrospective study was conducted between November 1, 2016, and December 31, 2020. Serial lactate measurements (at the hospital admission, ICU admission, and in 24 hours periods until 48 hours of ICU stay) of the patients admitted to our ICU with a diagnosis of DKA were recorded.

Results: Forty patients were included in the study (mean age: 50.6±19.4 years, female 60%). Eighty-five percent (n=34) of patients had increased (>2 mmol/L) blood lactate levels on admission. There was no significant difference between the low (lactate <4 mmol/L) and high-lactate (lactate ≥4 mmol/L) groups in mortality (p=0.195), ICU stay (p=0.966) and hospital length of stay (LOS) (p=0.274). However, the group with less than 40% decrease in lactate level from hospital admission to ICU had significantly higher Acute Physiology and Chronic Health Assessment II score [24 (12-46) vs. 18 (2-27), p=0.007], longer ICU stay [5 (1-40) vs. 3 (2-8) days, p=0.032], and higher mortality rate [6 (26.1) vs. 0 (0.0), p=0.030]. Additionally, non-survivors (n=6) had significantly higher lactate levels at hospital admission [3.0 (1.3-15.0) vs. 5.1 (3.9-13.5) mmol/L, p=0.017], and ICU admission [2.3 (0.6-9.4) vs. 5.0 (2.4-16.0) mmol/L, p=0.010] than survivors.

Conclusions: Although the ICU LOS and mortality did not differ between initial high and low-lactate groups in the present study, the lactate kinetics, especially in the early treatment period, can guide referral to the ICU level of care and determine the DKA patients at higher risk of death.

Introduction

Diabetic ketoacidosis (DKA) is primarily characterized by hyperglycemia, ketonemia, and acidosis with an increased anion gap. The number of cases with DKA has been increasing in the last two decades (1,2). The mortality rate of DKA varies across the world due to psychosocial and economic diversities; mainly, it has been reported as less than 1% (3,4). Although the risk of death is low, intensive care units (ICU) are still the places where these patients are primarily treated, and the prolongation of the ICU stays leads to an increase in hospital costs and ICU overcrowding. In addition, there are no specific criteria for determining whether the patients with DKA should be treated in the ICU or not.

Increased blood lactate concentration, a significant prognostic predictor for many clinical conditions in critically ill patients, is also typical in patients with DKA (5). This may occur due to impaired glucose metabolism with hypoperfusion and poorly understood mechanisms such as the glyoxal pathway and alternative energy substrate in DKA. In addition, there are still controversies regarding the role of increased lactate levels in the course of DKA. Unfortunately, there are insufficient data to suggest that the lactate kinetics in DKA patients may help evaluate treatment response over time and ICU outcomes (6).

This study investigated the clinical significance of lactate kinetics in patients admitted to ICU for DKA.

Methods

Study Population

This retrospective study included patients with DKA hospitalized in the medical ICU between November 01, 2016 and December 31, 2020. The study was approved by the Gülhane Faculty of Medicine, Local Ethics Committee (number: 2020/504, date: 16.06.2016) and performed following the Helsinki Declaration. Patients who had (1) plasma glucose level greater than 250 mg/dL, (2) presence of ketone in serum (3 mmol/L) or urine ($\geq 2+$), and (3) plasma bicarbonate level less than or equal to 18 mEq/L and/or blood pH less than or equal to 7.30 were included. Patients under 18 years of age and those found to have other causes of lactic acidosis, such as convulsions, use of linezolid or antiretroviral agents, were excluded.

Data Collection

Demographic characteristics (age, sex), history and type of diabetes mellitus (DM) (type 1 or 2), precipitants for DKA, history of metformin use, comorbidities, and Acute Physiology and Chronic Health Assessment (APACHE) II scores which calculated in the first day of ICU admission were recorded. Systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure at the ICU admission were obtained. Additionally, arterial blood gas analysis results (pH, lactate, HCO_3 levels), plasma glucose and other laboratory data at hospital admission, hemoglobin A1c (HbA1c) (glycosylated hemoglobin) levels measured during the hospital stay or in the last three months before hospital admission were obtained. Hospital length of stay (LOS), ICU LOS, and in-hospital mortality were recorded.

Patients were grouped into two as low (lactate < 4.0 mmol/L) and high-lactate (lactate ≥ 4.0 mmol/L) on admission. Additionally, the serial measurements of lactate levels in 24 hours periods until 48 hours of ICU stay, or ICU discharge, whichever came first, were recorded. Laboratory data including plasma glucose, pH, bicarbonate, sodium, and osmolality measured simultaneously with lactate screening (at hospital admission, ICU admission, 24th hr, 48th hr of ICU stay) were obtained.

As there are no published data on the optimal ratio of decrease in lactate levels to predict response to treatment and/or prognosis in patients with DKA, and the magnitude of lactate reduction following treatment is highly variable in different patient populations (7), we defined a 40% decrease in lactate levels as the threshold in the early treatment period (between hospital and ICU admissions) for prognosis prediction. Thus, the patients were grouped into two by 40% or higher decrease in lactate levels from hospital admission to ICU admission. Two previous studies strengthen the feasibility of this approach. Walker et al. (8) suggested a cut-off level of 36% in lactate clearance in the first 6 hours of treatment for mortality prediction

in severe sepsis and septic shock patients who were referred to ICU from the emergency department (ED). In another study, Hernandez et al. (9) reported a $>50\%$ decrease in lactate levels in the first 6 hours of resuscitation in patients with septic shock. The time (hours) between these two analyses was recorded. The two groups were compared for mortality, APACHE II score, ICU, and hospital LOS.

Statistical Analysis

Distribution normality for continuous variables was determined by the Shapiro-Wilk test, skewness and kurtosis coefficients, and histogram graphics. The mean (standard deviation) was used to represent parametric continuous variables, and the median (minimum-maximum) was used to represent nonparametric continuous variables. Categorical variables were expressed as numbers (percentage distributions). Independent samples t-test was used to compare parametric variables, and the Mann-Whitney U test was used to compare nonparametric variables. The chi-square test or Fisher's exact test was used for the comparison of categorical variables. Correlations were tested using the Spearman correlation analysis. $P < 0.05$ was considered statistically significant. The data analysis was performed using the IBM Statistical Package for Social Sciences statistics 25.0 (IBM.Corp., Armonk, NY, 2017).

Results

There were 43 patients with the diagnosis of DKA. After excluding three patients due to missing data, the study population included 40 patients. The mean age of patients was 50.6 ± 19.4 (19-81) years, and 24 (60%) patients were female. While 15 (37.5%) patients had type 1 DM, 25 (62.5%) patients had type 2 DM. The poor compliance with the treatment ($n=25$, 62.5%) was identified as the most common precipitating factor, followed by infections ($n=10$, 25%), newly diagnosed DM ($n=1$, 2.5%) and other causes ($n=4$, 10%). Two patients had chronic kidney disease that did not require renal replacement therapy, and three patients had advanced stage malignancy without hepatic involvement. Eighteen patients had been prescribed oral metformin before admission. The median ICU and hospital LOS were 4.0 (1.0-40.0) and 9.0 (2.0-77.0) days, respectively. The overall mortality rate was 15% ($n=6$).

Eighty-five percent ($n=34$) of patients have increased lactate levels (> 2 mmol/L) on admission. High lactate levels (lactate ≥ 4 mmol/L) were observed in 16 (40%) of patients. The comparison of demographic, clinical, and laboratory data of low-lactate and high-lactate groups are presented in Table 1. There was no significant difference between the two groups in terms of age, gender, APACHE II score, type of DM, metformin use, blood pressures at ICU admission, duration of DM, glucose, pH, bicarbonate, sodium, urea, creatinine, leukocyte count, hemoglobin, platelet, C-reactive protein, procalcitonin, aspartate

Table 1. Comparison of the diabetic ketoacidosis patients according to lactate levels at hospital admission

Variables	Low-lactate <4.0 mmol/L n=24 (60.0%)	High-lactate ≥4 mmol/L n=16 (40.0%)	p value
Age, years, median (min.-max.)	51.5 (19-81)	53 (19-80)	0.413 ^Y
Gender, female, n (%)	16 (66.7)	8 (50.0)	0.469 ^a
Type of DM, n (%)			0.739 ^a
Type 1	10 (41.7)	5 (31.3)	
Type 2	14 (58.3)	11 (68.8)	
Metformin use, n (%)	11 (45.8)	7 (43.8)	1.000 ^a
APACHE II, median (min.-max.)	18.0 (2-46)	22.5 (12-41)	0.078 ^Y
Blood pressures, mmHg			
Systolic, mean±SD	121.2±17.1	120.7±24.0	0.939 ^B
Diastolic, median (min.-max.)	66.5 (32.0-79.0)	68.5 (45.0-89.0)	0.171 ^Y
Mean, mean±SD	84.3±10.8	87.1±13.3	0.467 ^B
HbA1c †, %, mean±SD	12.5±2.4	10.6±1.5	0.029^{B*}
Duration of DM [§] , years, median (min.-max.)	10.0 (0.0-39.0)	8.0 (2.0-45.0)	0.510 ^Y
pH, mean±SD	7.10±0.1	7.12±0.1	0.658 ^B
Glucose level, mg/dL, median (min.-max.)	563.0 (159.0-1378.0)	397.0 (161.0-837.0)	0.050 ^Y
Bicarbonate, mEq/L, median (min.-max.)	5.7 (2.1-21.9)	9.7 (2.4-32.3)	0.136 ^Y
Sodium, mmol/L, mean±SD	130.0±7.8	133.9±4.6	0.091 ^B
Osmolality, mOsm/kg, median (min.-max.)	300.7 (263.1-352.7)	304.6 (287.7-349.6)	0.890 ^Y
Hemoglobin, g/dL, mean±SD	13.3±2.2	12.8±2.7	0.582 ^B
WBC, x10 ³ /mm ³ , mean±SD	16.0±6.7	16.9±6.3	0.657 ^B
Platelet, x10 ³ /mm ³ , median (min.-max.)	296.0 (47.0-652.0)	335.5 (181.0-559.0)	0.194 ^Y
Urea, mg/dL, median (min.-max.)	53.5 (21.0-240.0)	48.5 (31.0-216.0)	0.720 ^Y
Creatinine, mg/dL, median (min.-max.)	1.15 (0.73-6.40)	1.42 (0.64-13.0)	0.782 ^Y
Albumin, g/dL, mean±SD	3.34±0.66	3.45±0.70	0.637 ^B
AST, U/L, median (min.-max.)	20.5 (5.0-119.0)	26.5 (8.0-407.0)	0.240 ^Y
ALT, U/L, median (min.-max.)	14.0 (4-43)	21.5 (0-309)	0.047^{Y*}
Bilirubin (total), mg/dL, median (min.-max.)	0.51 (0.10-4.30)	0.49 (0.10-3.90)	0.841 ^Y
CRP, mg/L, median (min.-max.)	56.63 (0.44-421.80)	30.78 (2.50-190.00)	0.773 ^Y
Procalcitonin, ng/mL, median (min.-max.)	0.70 (0.01-16.35)	1.34 (0.02-249.00)	0.256 ^Y
ICU LOS, days, median (min.-max.)	4.0 (1.0-22.0)	3.5 (2.0-40.0)	0.966 ^Y
Hospital LOS, days, median (min.-max.)	9.0 (2.0-43.0)	7.5 (2.0-77.0)	0.274 ^Y
In hospital mortality, n (%)	2 (8.3)	4 (25.0)	0.195 ^d

^aChi-square test, ^BIndependent samples t-test, ^YMann-Whitney U test, ^dFischer's Exact test, *p<0.05, †A total of 28 patients (18 in low lactate group 10 in high lactate group) with available HbA1c levels included in the analysis.
[§]A total of 26 patients (16 in low lactate group, 10 in low lactate group) with available DM history included in the analysis.
DM: Diabetes mellitus, APACHE II: Acute Physiology and Chronic Health Evaluation II, WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, ICU: Intensive care unit, LOS: Length of stay, min.-max.: Minimum-maximum, SD: Standard deviation

aminotransferase, total bilirubin levels, serum osmolality, ICU and hospital LOS or mortality. However, the patients in high-lactate group had significantly lower HbA1c (12.5±2.4 vs. 10.6±1.5%, p=0.029) and higher alanine aminotransferase levels [14.0 (4.0-43.0) vs. 21.5 (0.0-309.0) U/L, p=0.047] than patients in low-lactate group.

The serial change of lactate levels of the survivors (n=34) and non-survivors (n=6) over time is presented in Figure 1. The median lactate levels were [3.0 (1.3-15.0) vs. 5.1 (3.9-13.5) mmol/L,

p=0.017] in survivors and in non-survivors on admission, [2.3 (0.6-9.4) vs. 5.0 (2.4-16.0) mmol/L, p=0.010] at ICU admission, [1.3 (0.3-3.5) vs. 1.4 (0.9-11.8) mmol/L, p=0.425] at the 24th hour of the ICU stay, and [1.3 (0.5-4.7) vs. 1.6 (0.7-5.4) mmol/L, p=0.370] at the 48th hour of the ICU stay, respectively.

In patients with or without %40 or more decrease in lactate levels, there was no significant difference in time from hospital admission to ICU admissions (2.25 vs 3.22 hours, p=0.556). However, the group with less than 40% decrease in lactate levels

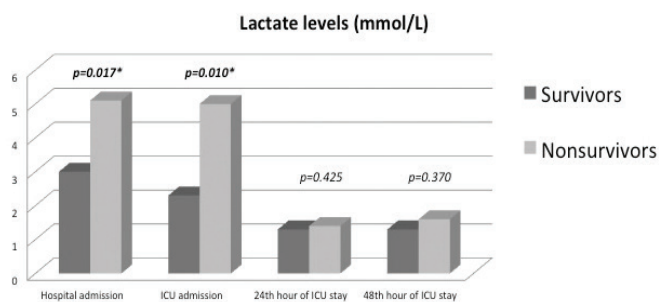


Figure 1. The serial change of lactate levels of survivors and non-survivors over time
ICU: Intensive care unit

Table 2. Comparison of the diabetic ketoacidosis patients according to decrease of lactate levels by ≥40% from hospital admission to intensive care unit admission

	Total n=40	Decrease in lactate <40% n=23 (57.5%)	Decrease in lactate ≥40% n=17 (42.5%)	p value
Time between hospital and ICU admission, hours, median (min.-max.)	2.82 (0.47-76.37)	2.25 (0.47-39.87)	3.22 (0.60-76.37)	0.556 ^a
APACHE II, median (min.-max.)	18 (2-46)	24 (12-46)	18 (2-27)	0.007^a*
ICU LOS, days, median (min.-max.)	4 (1-40)	5 (1-40)	3 (2-8)	0.032^a*
Hospital LOS, days, median (min.-max.)	9 (2-77)	11 (2-43)	8 (2-77)	0.329 ^a
In hospital mortality, n (%)	6 (15)	6 (26.1)	0 (0.0)	0.030^b*

^aMann-Whitney U test, ^bFischer's Exact test, *p<0.05.
ICU: Intensive care unit, APACHE II: Acute Physiology and Chronic Health Evaluation II, LOS: Length of stay, min.-max.: Minimum-maximum

had significantly higher APACHE II score [24 (12-46) vs 18 (2-27), p=0.007], longer ICU stay [5 (1-40) vs 3 (2-8) p=0.032], and higher mortality rate [26.1 (6) vs 0 (0.0), p=0.030] (Table 2).

In correlation analysis, low to moderate significant correlations were found between the initial lactate level and APACHE II score (r=0.336, p=0.034) and HbA1c level (r=-0.493, p=0.008). However, there was no correlation between the initial lactate level and ICU LOS (p=0.211), hospital LOS (p=0.603), systolic, diastolic and mean arterial blood pressures (p=0.758, p=0.659 and p=0.268, respectively), glucose (p=0.090), pH (p=0.838), bicarbonate (p=0.456), osmolality (p=0.844), and other laboratory tests (not shown).

Discussion

We hypothesized in the present study that serial changes in lactate level might be more informative than a single admission level in DKA patients. In parallel with previous data (5), there was no difference in mortality and ICU LOS between the on admission high and low-lactate groups in our study. However, it was shown that there was no death among patients who showed more than 40% decrease in lactate level within the median 3.22 hours before the ICU admission. It was also observed that these patients stayed for a shorter period in the ICU than the patients who could not achieve this decrease. Therefore, it can be thought that decreasing lactate levels in DKA patients, especially in the ED, may help predict the prognosis and decide on the unit (ICU, ED, or general medical ward) where the patient will be managed.

DKA is a common complication of DM, and it constitutes up to 28% of diabetes-related hospital admissions (10). Many DKA patients are still being treated in ICUs. The main reasons for this preference are the presence of varying degrees of metabolic acidosis, frequent monitoring requirements for blood gas, vital signs, urine output, and serum electrolyte level, and the necessity of intravenous insulin infusion (10-12). However, overcrowding of ICU beds and increased hospital costs must be considered when selecting the ICU level of care to treat these patients. In a study by Marinac and Mesa (13), DKA patients were retrospectively grouped in five severity grades using diastolic blood pressure and some laboratory data (serum bicarbonate, osmolality, anion gap, and base excess). According to their scoring system, the authors reported that more than one-third of all DKA admissions to the ICU were not appropriate in this cohort.

Additionally, previous studies showed that these patients, especially with non-severe DKA, could be safely managed in non-ICU settings such as ED and general medical wards (14-16). Nevertheless, the exact criteria for deciding which patient with DKA should be admitted to the ICU have not been fully established yet. The lactate kinetics in the early period of DKA treatment may help this decision.

The inadequate tissue perfusion due to volume depletion was considered the leading cause of elevated lactate levels in DKA patients. Consequently, relative hypoxemia causes an increase in lactate levels by stimulating anaerobic glycolysis (17,18). However, there was no difference in blood pressures between initial high and low-lactate groups in the current study. As explained above, it is thought that tissue hypoxia may not be the only mechanism responsible for elevated lactate levels in DKA patients. Previously, Cox et al. (5) reported a positive correlation between serum lactate and glucose levels in patients with DKA. This finding may indicate a relationship between lactate levels and altered glucose metabolism. On the contrary,

no correlation was found between initial lactate and glucose levels in the current study, and even a negative correlation was found between HbA1c and lactate levels.

The reason for the increase in intra-erythrocyte glucose during DKA is that erythrocytes do not need insulin for glucose uptake. The increased intra-erythrocyte glucose is converted first to pyruvate and then to L-lactate through aerobic glycolysis. The remaining amount of glucose is first transformed into methylglyoxal and then to D-lactate with the glyoxalase system. This system also allows the formation of D-lactate in plasma during DKA (19-21). Lu et al. (21) reported that D-lactate levels increased significantly with increased methylglyoxal production during DKA and that high D-lactate levels were significantly correlated with a rising anion gap and decreased bicarbonate levels and thus were associated with DKA severity. The lactate formed during DKA can be used for gluconeogenesis and can be directed to other tissues as an alternative energy substrate due to cellular glucose deficiency. This can be attributed to another mechanism that stimulates the activity of muscle Na⁺/K⁺ pumps via the increased catecholamine production due to stress and insulin deficiency in DKA (22,23). As a result, lactate, which increases as an alternative energy substrate for tissues during DKA, can be expected to decrease after the administration of insulin infusion. Therefore, it can be thought that the decrease in lactate level with the initiation of treatment in DKA patients is not only due to rehydration but also due to the decrease in the need for energy substrate with the initiated insulin infusion. The serial measurements of lactate levels may thus be more informative than a single measurement in DKA patients. A systematic review by Vincent et al. (7) on lactate kinetics in critically ill patients suggested that assessing lactate kinetics at 1-2 hour intervals may be more predictive for mortality than baseline values. This recommendation may also be helpful for DKA patients.

The mortality rate in adult DKA patients varies across the world. In the US and UK, the mortality rate has been reported to be less than 1% (24,25). However, in low-income countries, the in-hospital mortality rate has been reported to be as high as 30% (26,27). Mortality in adult DKA patients is more likely to result from underlying comorbid diseases, cardiopulmonary complications, or metabolic disorders (hypokalemia/hypoglycemia), which occur during therapy (28). In our study, the overall mortality rate is higher than previously reported. This may be related to the older age of the study population [30% (n=12) of patients were 65 years of age or older], had a high APACHE II score (20.7±9.10), and had high HbA1c (11.87±2.32) levels indicating long term bad metabolic status.

Additionally, in terms of comorbidities, three patients had advanced stage malignancy without hepatic involvement. Furthermore, a quarter of patients had an infection as a precipitating factor. In a study by Azevedo et al. (12), the in-hospital mortality rate was 4% in cases admitted to the ICU due to DKA, while it was reported as 9% in severe DKA cases.

Another study by Pasquel et al. (29) revealed that lower bicarbonate levels on admission were significantly related to increased mortality rates. Similarly, in our study, 28 patients had bicarbonate levels less than 10 mEq/L, which could be considered severe DKA. The higher mortality rate observed in our study can be explained by poor comorbid conditions, long-term inadequate medical care, and a high rate of infections.

This study has some limitations. The first is its retrospective design, which may contribute to the results due to other undocumented factors it hides. The lactate metabolism may differ significantly in type 2 DM patients because of more frequent liver involvement than in type 1 DM patients. Evaluation of these two different types of diabetes together may have affected our results. Since our entire study population consisted of critically ill patients and a standard treatment protocol was used independent of diabetes type, we included both types of DM patients in our analyses. In addition, none of the patients included in our study had known chronic liver disease or concomitant fulminant liver failure. The other potential limitation of this study is that the total number of included patients remains small. Additionally, in this study, plasma L-lactate and D-lactate levels were not studied separately. While L-lactate is a marker of tissue hypoxia, D-lactate is a marker of metabolic disarrangements. Therefore, our assessment of the possible pathophysiological mechanisms of changes in lactate kinetics has been limited.

Conclusion

Although the ICU LOS and overall mortality did not differ between initial high and low-lactate groups, the lactate kinetics, especially in the early treatment period, can guide referral to ICU and determine the DKA patients at higher risk of death. Our results could be confirmed with further studies, including higher numbers of patients to test DKA lactate kinetics.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey Gülhane Faculty of Medicine, Local Ethics Committee (number: 2020/504, date: 16.06.2016) and performed following the Helsinki Declaration.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: G.T., M.Y., H.Ş., İ.S.G., Data Collection or Processing: G.T., S.Y., H.S., Analysis or Interpretation: G.T., H.Ş., İ.S.G., M.Y., Literature Search: G.T., S.Y., H.Ş., H.S., S.T., Writing: G.T., M.Y., L.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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