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The relationship between initial lactate levels and outcomes in patients diagnosed with diabetic ketoacidosis in the emergency department

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Ethics Committee Approval
Ethical approval was obtained from Şişli Hamidiye Etfal local ethics committee (ethics committee ruling number: 2193, date: 29.11.2022).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
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Abstract

Background/Aim: Diabetic ketoacidosis (DKA) is an endocrinological emergency frequently seen in emergency departments (ED). It can result in mortality if not treated appropriately. The aim of this study was to examine the relationship between baseline lactate levels and patient outcomes in DKA patients admitted to the emergency department (ED).

Methods: This retrospective cohort study was carried out in the ED of a tertiary hospital between May 2022 and November 2022 using the data of patients diagnosed with DKA. Patients with missing data, patients transferred from another hospital, patients with a diagnosis other than DKA, and patients who could not be followed up were excluded from the study. The primary outcome of the study was admission to the intensive care unit (ICU) and/or in-hospital mortality. The area under the curve (AUC) was calculated by receiver operating characteristic (ROC) regression analyses to predict critically ill patients with lactate levels.

Results: The study was completed with 95 patients. The mean age of the patients was 53.1 years and n = 46 were female. Twenty (21.1%) of these patients were admitted to the intensive care unit and 22 (23.2%) died. The statistical analysis showed that lactate levels were statistically significant in predicting critically ill patients ($P < 0.001$). ROC analysis showed that a lactate level of 2.6 mmol/dL could predict critically ill patients. The area under the curve was 0.823 (95% confidence interval: 0.731-0.894, sensitivity: 71.4, Specificity: 69.8), the Youden index was 0.476, and the *P*-value was 0.001.

Conclusion: According to the results of this study, there is a significant relationship between the initial lactate levels in DKA patients and patients who will require critical care. Therefore, lactate can be used as an appropriate follow-up tool in the management of DKA patients.

Keywords: Diabetic ketoacidosis, Lactate, Mortality

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Introduction

Diabetic ketoacidosis (DKA) is one of the acute complications of diabetes mellitus (DM) and can even result in death if not treated appropriately [1, 2]. The incidence of DKA has been shown to be 4.6-8 episodes per 1000 diabetic patients per year. It is thought to be responsible for 500.000 hospitalizations per year in the United States (USA) with a total cost of approximately $2.4 billion [3].

The incidence of DKA among diabetic patients is reported to be 0.4-0.8%. In 2009, 140,000 DKA patients were hospitalized in the United States of America (USA), and one-year hospital expenses were reported to be approximately 1 billion dollars [4]. DKA is more common in younger children and those with lower socioeconomic status. Low socioeconomic status and low educational levels reduce the compliance of the patients with the treatment and can cause DKA to recur more frequently. Mortality rates of DKA are found to be 1-5% [5].

Lactate is produced from most tissues in the body (kidney, erythrocyte, skeletal muscle, brain). Most lactate is metabolized by the liver followed by kidney and skeletal muscle [6]. The prognosis of patients can be evaluated with lactate follow-up via blood gases [7]. The increased blood level of lactate may be due to overproduction or lack of use. Both of these situations indicate a malfunction in the systems. Common causes of increased lactate include hypotension, hypoperfusion, infections, lack of oxygenation, circulation, pulmonary and hemoglobin transfer problems, malignancy, kidney failures, liver failures, diabetes, malnutrition, hypothermia, hyperthermia, dehydration, epilepsy, toxins, various operations, alcohol, drugs, sepsis, and excessive exercise [8]. The aim of this study was to examine the relationship between initial lactate levels and patient outcomes in DKA patients admitted to the emergency department (ED).

Materials and methods

This retrospective, observational study was conducted in the ED of the Şişli Hamidiye Etfal Training and Research Hospital in Istanbul, Turkey. The Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics committee approved the analysis and issued a waiver of consent (ethics committee ruling number: 2193; date: 29.11.2022). All patients over the age of 18 and diagnosed with DKA who applied to the ED of a tertiary hospital between May 2022 and November 2022 were included. Patients with missing data, patients transferred from another hospital, patients with a diagnosis other than DKA, and patients who could not be followed up were excluded. The diagnosis of DKA was made via blood glucose at presentation >250 mg/dL with ketonemia or blood acidemia (pH <7.3 or serum bicarbonate concentration <15 mEq/L) [5]. After a study form was created, the patients' age, gender, laboratory data at the time of application, and patient outcomes were recorded. Blood gas lactate levels were measured using a Hitachi 917 automated analyzer (Roche Diagnostics, Mannheim, Germany).

The primary outcome was admission to the intensive care unit (ICU) and/or in-hospital mortality. The sample size was based on the number of patients in studies with a 95% confidence interval [9]. At least 74 patients were needed considering a 0.5% margin of error.

Statistical analysis

Statistical analysis used SPSS v. 25.0 software package (SPSS Inc., Chicago, IL, USA) and MedCalc ver. 12.5 (MedCalc Software Ltd, Ostend, Belgium). Descriptive criteria included mean and standard deviation as a percentage distribution. The conformity of the data to the normal distribution was checked with the Kolmogorov-Smirnov test. The area under the curve (AUC) was calculated by receiver operating characteristic (ROC) regression analyses. We calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of lactate levels to assess performance; *P*-values below 0.05 were considered statistically significant.

Results

The study contained 95 patients after excluding three patients transferred from another hospital, 11 patients diagnosed other than DKA, and eight patients who could not be followed up during the period. The mean age of the patients was 53.1 years, and 46 were female. Of these patients, 15 (15.7%) were discharged, 38 (40%) were hospitalized, 20 (21.1%) were hospitalized in the intensive care unit, and 22 (23.2%) died. The patients included in the study were divided into two groups as critical (ICU admission and/or deceased) and non-critical (outpatient and/or inpatient unit). Some of their features were then compared. The blood gas data (HCO_3 and pH) of the patients in the critically ill group were lower than those in the non-critical group, but the lactate levels were higher ($P = 0.003$, $P = 0.001$ and $P = 0.001$, respectively) (Table 1).

Table 1: Comparison of various characteristics of patients with critical and non-critical diabetic ketoacidosis.

	Outpatient and/or Inpatient unit n = 53		ICU admission and/or Deceased n = 42		*P*-value
	Mean n	SD %	Mean N	SD %	
Age	49.2	18.8	57.1	21.3	0.58
Gender					0.019
Woman	20	37.7	26	61.9	
Man	33	62.3	16	38.1	
Systolic blood pressure (mmHg)	123.2	18.6	119.1	31.8	0.448
Diastolic blood pressure (mmHg)	74.9	11.9	71.1	20.9	0.289
Pulse rate (bpm)	93.4	15.7	107.1	21.9	0.001
Respiratory rate	17.2	4.9	25.9	8.9	0.001
SPO_2 (%)	97.0	2.7	93.8	8.4	0.010
Glucose (mg/dL)	553.9	193.1	634.9	210.3	0.054
Creatinine (mg/dL)	1.38	0.87	1.79	1.17	0.051
Blood urea nitrogen (mg/dL)	30.1	24.8	41.5	28.6	0.043
AST (IU/L)	23.0	20.9	54.8	123.4	0.068
ALT (IU/L)	21.2	18.6	36.7	75.8	0.153
Albumin (g/L)	35.3	16.2	29.9	15.4	0.117
Sodium (mEq/dL)	129.8	5.6	131.3	9.3	0.334
Potassium(mEq/dL)	4.8	0.8	5.0	0.9	0.304
Chloride (mg/dL)	91.9	7.0	92.9	10.1	0.560
pH	7.22	0.10	7.14	0.14	0.001*
PCO_2 (mmHg)	33.9	10.3	30.6	10.3	0.126
HCO_3 (mEq/dL)	14.7	4.4	11.8	4.9	0.003*
Lactate (mmol/dL)	2.26	0.74	3.91	1.68	0.001*

* Student's t-test

The statistical analysis showed that lactate levels were significantly higher in predicting critically ill patients ($P < 0.001$, Table 1). ROC analysis of lactate level could help predict critically ill patients: The area under the curve was 0.823 (95% CI 0.731-0.894), the Youden index was 0.476, and the *P*-value was 0.001. A lactate level cut-off of >2.6 mmol/L could identify critically ill patients with a sensitivity of 71.4% and a specificity of 69.8%. The positive predictive value was 65.2, and the negative predictive value was 75.5 (Figure 1, Table 2).

Figure 1: Receiver operating characteristic curve of lactate level predicting critically ill patients.

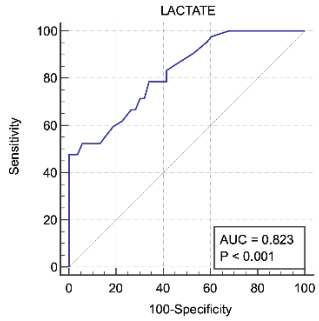

Table 2: Values of lactate level in predicting critical patients in diabetic ketoacidosis patients.

	AUC	Cut-Off	Sensitivity	Specificity	PPV	NPV	Youden Index
Lactate	0.823 (0.731-0.894)	>2.6	71.4	69.8	65.2	75.5	0.476

AUC: area under curve, PPV: positive predictive value, NPV: negative predictive value

Discussion

This study evaluated the relationship between initial lactate levels and outcomes in DKA patients admitted to the ED. We concluded that elevated lactate levels at the time of admission may predict in-hospital mortality and ICU admission.

Although DKA is mostly seen in type 1 DM, it can also occur in type 2 DM patients with precipitating conditions such as infection, trauma, or surgery that create a catabolic process [10]. The classic triad of DKA occurs as a result of hyperglycemia, ketonemia-ketonuria, metabolic acidosis, insufficient insulin activity, and the effect of contra-insulinary hormones. This hormonal disorder causes the substances transported from the tissues (muscle amino acids, lactate, and pyruvate as well as free fatty acids and glycerol from adipose tissue) to be actively converted into glucose and ketone bodies (beta hydroxy butyrate, acetoacetate, acetone). This in turn increases release into circulation. Osmotic diuresis develops, thus resulting in hyperglycemia (>250 mg/dl), ketoacidosis (pH <7.30), dehydration, and electrolyte loss [11].

DKA severity can be graded as mild, moderate, and severe depending on the level of metabolic acidosis and changes in mental status. As the disease worsens, mental status changes may progress from wakefulness to lethargy or even coma. Therefore, DKA is an important cause of mortality and morbidity in DM patients. Although overall mortality is less than 5% in experienced centers, it is the main cause of mortality in patients with type 1 DM and is responsible for 50% of deaths in patients with DM under 24 years of age [11].

Lactate is used as a prognostic tool in many diseases [12-14]. Normal blood lactate levels are 1 mEq/l. Even lactate levels >1.5 mEq/l have been shown to be associated with mortality [15]. It is thus desirable to keep lactate levels below 2 mEq/l in patient follow-ups. A lactate level of 4 mEq/l and above means a very high-risk mortality [16].

There are various studies in the literature examining lactate levels and outcomes of DKA patients. Taskin et al. [17] analyzed the data of 43 patients admitted to the ICU for DKA. They emphasized that low or high lactate levels at the time of admission would not make a difference in terms of mortality or ICU stay, but they emphasized that lactate kinetics should be used during patient follow-up. In another study conducted in Turkey, they concluded that lactate levels were significantly correlated with DKA severity (mild-moderate-severe) in 230 DKA patients presenting with ED [18]. Suwarto et al. [9] found that a lactate level >4 mmol/L could be used as an independent risk factor in estimating 5-day mortality from hospital admission. Our study was thus found to be compatible with the prior literature.

Limitations

This study does have some limitations. This single-center, retrospective design study was conducted in a relatively small population. The comorbidities of the patients were not examined and this may be an important factor in evaluating patient outcomes. Finally, only the lactate level at the time of application was examined—not dynamic changes in lactate levels.

Conclusion

DKA is a common endocrinological disease in EDs. It can result in mortality if not treated appropriately. Our results show that there is a significant relationship between the initial lactate levels in DKA patients and patients who will require critical care. Therefore, lactate can be used as an appropriate follow-up tool in the management of DKA patients.

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