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Clinical utiliy of serum lactate levels in diabetic ketoacidosis in adult patients admitted to emergency department

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Abstract

Aim: To evaluate serum lactate and its clinical utility for disease severity among patients admitted to the emergency department with diabetic ketoacidosis (DKA) diagnosis.

Materials and Methods: This is a retrospective data review that included patients 18 years of age and admitted to the department with a DKA diagnosis. Patients with a blood glucose level of 250 mg/dL between 01 January 2016 to 30 June 2021 with DKA were included. Patients without arterial blood gas or urine ketone analyses or diagnosed with isolated hyperglycemia were excluded. DKA was defined as a blood glucose level 250 mg/dL, pH <7.3, HCO_3<18 mEq/L, and urine ketone positivity at admission. The DKA severity was graded based on the degree of metabolic acidosis based on pH and HCO_3 levels.

Results: 230 patients were included (82 mild, 126 moderate, and 22 severe DKA). The median age was 44 years, and 50.4% of patients were male. Patient age (p=0.27), sex (p=0.63), and blood glucose levels (p=0.69) were similar between DKA groups. However, DKA severity was moderately and negatively correlated with pH (r=-0.44, p<0.001), weakly and negatively correlated with HCO_3(r=-0.25, p<0.001), and moderately and positively correlated with lactate (r=0.41, p<0.001).

Conclusion: The primary outcome of this study was that serum lactate level is significantly correlated with DKA moderate, and monitoring the normalizing levels while treating the DKA may be utilized as a marker of efficiency in the emergency department.

Introduction

Lactate is an internal bioproduct of anaerobic metabolism, produced mainly in muscle tissue by reduction from pyruvate by lactate dehydrogenase enzyme [1]. It is primarily excreted from the liver and kidneys to a small extent. The lactate levels are tightly controlled, and the elevated levels are associated with either increased production, decreased clearance, or multifactorial etiology [2, 3]. Previous studies reported that serum lactate levels could predict or monitor the severity of several critical pathologies like sepsis, burns, cardiovascular emergencies, including myocardial infarcts and post-cardiac arrest, and trauma [4]. Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus characterized by acidosis, hyperglycemia, and elevated serum ketone levels [5]. In addition, diabetes, particularly DKA, is a severe condition that may lead to hyperlactatemia and lactic acidosis (LA) [6]. Furthermore, DKA affects about 8 of 1000 diabetic patients, and mortality rates may reach 5% [7]. These relatively high rates imply the importance of assessing potential biomarkers to evaluate and monitor the clinical severity. Nevertheless, evidence of elevated lactate levels and DKA severity is scarce and needs further assessment in different clinical settings [8]. Based on the associations between the lactate levels and the severity of critical pathologies, we hypothesized that serum lactate levels might also be associated with DKA. Therefore, this study evaluated serum lactate and its clinical utility for disease severity among patients admitted to the emergency department with a DKA diagnosis.

Materials and Methods

This study was conducted as a retrospective chart review at the Emergency Medicine Department of the Tepecik Education and Research Hospital of Health Sciences University between 01.01.2016 and 06.30.2021. Hospital records were screened for patients who were 18 years of age and

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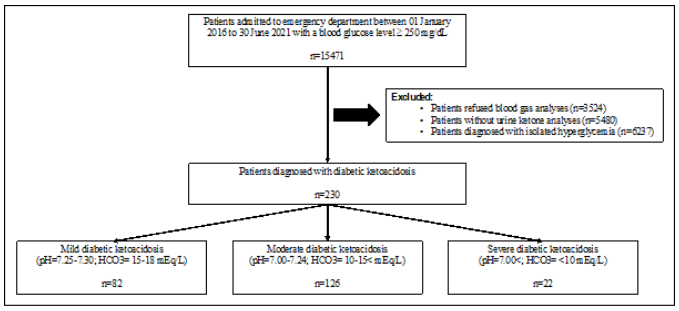

Figure 1. Study flowchart: inclusion, exclusion, and categorization of patients.

admitted to the emergency department with a DKA diagnosis, and patients who met the inclusion criteria were included in the study. The eligibility assessment flowchart is depicted in Figure 1. Accordingly, 15471 patients who were admitted with a blood glucose level of 250 mg/dL

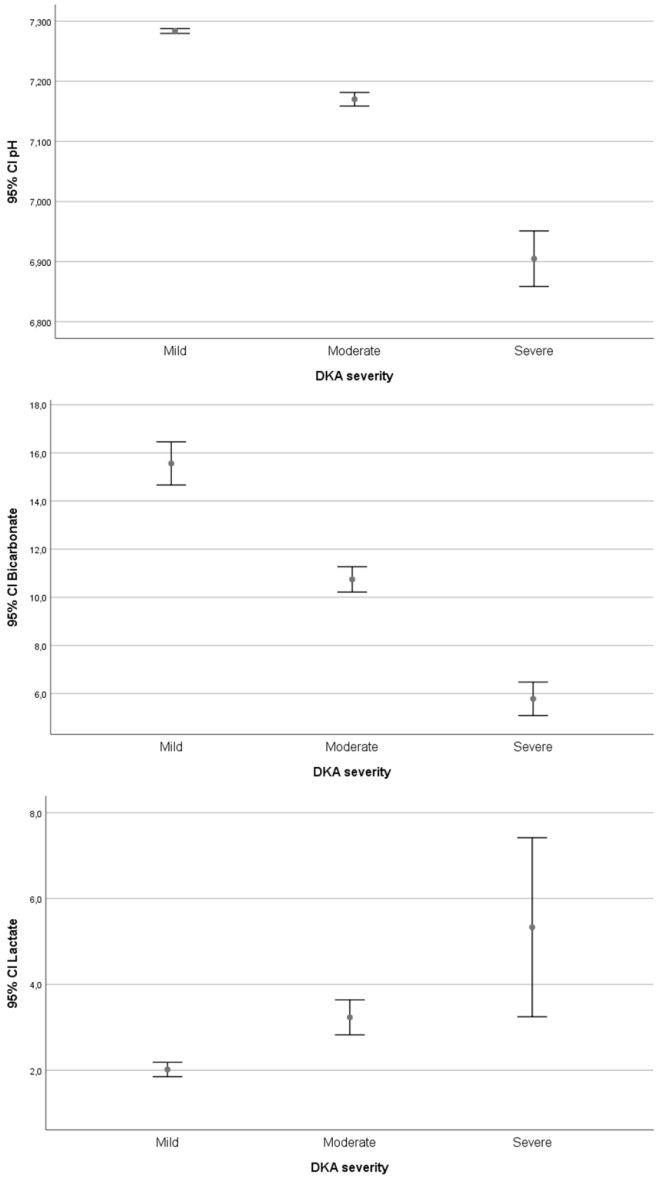

Figure 2. pH, bicarbonate, and lactate according to DKA severity groups.

were identified in the initial screening, and after exclusion due to refusing arterial blood gas testing (n=3524), absence of urine ketone testing (n=5480), and a diagnosis of isolated hyperglycemia (n=6237), remaining 230 patients diagnosed with DKA were included in the analysis. Multiple records for a patient at different times were regarded as an individual visits and evaluated separately. The local ethical committee (Health Sciences University, Tepecik Training and Research Hospital Non-Interventional Research Ethics Committee) approved the study protocol on 14/07/2021 as 2021/07-26. The available demographic and clinical data were collected from the electronic hospital records and included age, sex, DKA severity (mild, moderate, severe), blood glucose level, urine ketones, blood gas analysis (pH, bicarbonate – HCO3, lactate), anion gap, sodium (Na) and chlorine (Cl) levels. The anion gap was calculated as [Na-(Cl+HCO3)]. DKA diagnosis was defined as a blood glucose level 250 mg/dL at admission, pH <7.3, HOC3<18 mEq/L, and urine ketone positivity. The DKA severity was graded based on the degree of metabolic acidosis (pH and HCO3) as mild (pH=7.25-7.30; HCO3= 15-18 mEq/L), moderate (pH=7.00-7.24; HCO3= 10-15<mEq/L), and severe (pH=7.00<; HCO3= <10 mEq/L). The primary outcome of this study is the association of lactate levels with DKA severity.

Statistical analyses

The Statistical Package for the Social Sciences for Windows version 22.0 (SPSS v.22.0, IBM Inc., Armonk, NY, USA) was used for all statistical analyses. Continuous variables were presented as mean ± standard deviation (SD). Categorical data were presented as frequency and percentages. Comparisons between independent groups were conducted with the Kruskal-Wallis test and Chi-square test, respectively. The correlations between DKA severity and lactate levels were analyzed using Spearman's rho. The statistical significance level was a type-I error level of 5% ($p<0.05$).

Results

Analyses were conducted with demographic and clinical data of 230 DKA patients after excluding ineligible cases in the initial screening. The DKA severity categories included 82 patients in the mild, 126 patients in the moderate, and 22 in the severe DKA groups. The basal demographics and clinical data are presented in Table 1. The median age was 44 years (IQR: 33, range:18-89 years), and 50.4% of patients were males. Comparisons between DKA severity categories revealed that patient age ($p=0.27$), gender ($p=0.63$), and blood glucose levels ($p=0.69$) were similar between groups. However, the pH, HCO_3, and lactate comparisons showed significant gradual differences between severity groups ($p<0.001$, each). The correlation analyses to assess the association of biomarkers with disease severity revealed moderate and negative correlation with pH ($r=-0.44$, $p<0.001$), weak and negative correlation with HCO_3 ($r=-0.25$, $p<0.001$), and moderate and positive correlation with lactate ($r=0.41$, $p<0.001$) Table 2.

Discussion

DKA is the most common high-anion gap metabolic acidosis type and an acute complication of diabetes char-

Table 1. Comparisons of demographic and clinical features between DKA severity groups.

	Mild (n=82)	Moderate (n=126)	Severe (n=22)	p
Age (years), mean ± SD	48 ± 20	43 ± 20	48 ± 19	0.273
Sex (male), n (%)	42 (51.2)	63 (50)	10 (45.5)	0.634
Blood glucose (mg/dL), mean ± SD	548 ± 196	552 ± 166	548 ± 165	0.686
pH, mean ± SD	7.28 ± 0.02	7.17 ± 0.06	6.91 ± 0.10	<0.001*
Bicarbonate (mEq/L), mean ± SD	15.6 ± 4.1	10.7 ± 3.0	5.8 ± 1.6	<0.001*
Lactate (mmol/L), mean ± SD	2.0 ± 0.8	3.2 ± 2.3	5.3 ± 4.7	<0.001*

*:Both Kruskal-Wallis non-parametric analysis of variances test and Jonckheere-Terpstra non-parametric analysis of trend test results were statistically significant at the <0.001 level.

Table 2. Correlations of pH, bicarbonate, and lactate with DKA severity.

	r	p
pH	-0.436	<0.001
Bicarbonate	-0.248	<0.001
Laktat	0.412	<0.001

acterized by hyperglycemia, increased ketone levels, and acidosis, which may progress to death in severe cases [5]. Increased serum lactate was previously reported as a common finding in DKA, but its role in etiopathogenesis is not adequately evaluated or reported to have little or no impact on prognosis [9, 10]. Therefore, the primary outcome of this study is the association of lactate levels with DKA severity which the analyses revealed that serum lactate increases in parallel to the DKA severity, which is evident with a moderately positive and statistically significant correlation. For other parameters of metabolic acidosis, the HCO_3 and pH, significant correlations were also apparent with the disease severity. However, DKA severity was irrelevant to the patient's age, gender, and hyperglycemia levels. Recent studies reported that hyperlactatemia had no evident impact on the prognosis of DKA, such as its prognostic characteristics in sepsis, despite being a common biochemical finding in DKA patients [10, 11]. When the etiology of increased lactate levels is considered, possible initiators are either increased production in anaerobic circumstances, decreased clearance, or interaction of multiple pathogenesis pathways [12-14]. Moreover, certain drugs, including metformin, may disturb oxidative phosphorylation and significantly induce lactic acid production, which may be an underlying factor of elevated lactate levels in DKA patients taking metformin [11, 12]. Apart from the biochemical mechanisms of high serum lactate levels in DKA, its utility as a surrogate biomarker to predict the outcome of DKA is the question of this present study. Although we did not evaluate the outcome in DKA, significant associations between biochemical parameters of metabolic acidosis, particularly the serum lactate, with DKA severity suggests that it is a potentially helpful surrogate marker in the emergency room, in which there is limited time for intervention to the critical DKA cases. For mild, moderate, or severe DKA, the median lactate levels were 1.9, 2.8, and 3.3 mmol/L. These levels cannot be considered cut-off levels to determine the DKA severity but may be used as a clue for the initial clinical interventions. There is a lack of evidence regarding lactate levels in DKA severity groups. This is the first study in the literature that reported these levels to the best of our knowledge. Nevertheless, we are also aware that numerous previous studies evaluated lactate levels in critically ill patients to predict outcomes. Still, those studies were mainly conducted on patients with cardiogenic shock, sepsis, or trauma [15-17]. In a study that analyzed the large-scale database of Surviving Sepsis Campaign, including 28,150 patients, a cut-off level of 4 mmol/L was reported to be associated with adverse outcomes in septic patients, and authors recommended utilizing lactate levels as a surrogate marker to monitor the initial clinical interventions to reach efficiency [18, 19]. This report is appropriate with our results of median lactate levels of 3.3 mmol/L, which could be monitored during the treatment of these patients in the emergency department. However, our study has several notable limitations. First, the structure of the study was retrospective and was designed as a single center.

Conclusion

To the best of our knowledge, this is one of the low-numbered reports on the associations of lactate with DKA severity in adult patients admitted to emergency medical services. Based on our results, serum lactate level is significantly correlated with DKA severity, and we suggest utilizing it as a marker of efficiency while treating the DKA in the emergency department.

Ethics approval

The local ethical committee (Health Sciences University, Tepecik Training and Research Hospital Non-Interventional Research Ethics Committee) approved the study protocol on 14/07/2021 as 2021/07-26.

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