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Prevalence and significance of lactic acidosis in diabetic ketoacidosis[☆]

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Abstract

Purpose—The prevalence and clinical significance of lactic acidosis in diabetic ketoacidosis (DKA) are understudied. The objective of this study was to determine the prevalence of lactic acidosis in DKA and its association with intensive care unit (ICU) length of stay (LOS) and mortality.

Methods—Retrospective, observational study of patients with DKA presenting to the emergency department of an urban tertiary care hospital between January 2004 and June 2008.

Results—Sixty-eight patients with DKA who presented to the emergency department were included in the analysis. Of 68 patients, 46 (68%) had lactic acidosis (lactate, >2.5 mmol/L), and 27 (40%) of 68 had a high lactate (>4 mmol/L). The median lactate was 3.5 mmol/L (interquartile range, 3.32–4.12). There was no association between lactate and ICU LOS in a multivariable model controlling for Acute Physiology and Chronic Health Evaluation II, glucose, and creatinine. Lactate correlated negatively with blood pressure ($r = -0.44$; $P < .001$) and positively with glucose ($r = 0.34$; $P = .004$).

Conclusions—Lactic acidosis is more common in DKA than traditionally appreciated and is not associated with increased ICU LOS or mortality. The positive correlation of lactate with glucose raises the possibility that lactic acidosis in DKA may be due not only to hypoperfusion but also to altered glucose metabolism.

Keywords

Diabetic ketoacidosis; Lactic acidosis; Diabetes; Acidosis

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1. Introduction

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus that occurs when circulating insulin levels are low or absent. This state is characterized by acidosis, hyperglycemia, and the presence of serum ketones. Diabetic ketoacidosis affects nearly 8 per 1000 persons with diabetes annually and is associated with a mortality of less than 5% [1–3].

Lactate levels have been found to be predictive of illness severity in several critical illnesses including sepsis, burns, ST-elevation myocardial infarction, postcardiac arrest, and trauma [4–11]. At present, there are very little data on the clinical significance of lactate levels in DKA or the association with disease severity. Furthermore, in the relatively small body of literature on this subject, there is controversy surrounding the prevalence of lactic acidosis in this population. Although Fulop et al [12] report that “elevations of blood lactate concentration are not uncommon in patients with hypovolemia, hypotension, and hyperventilation, which are abnormalities often found in patients with diabetic ketoacidosis”; other reports suggest that DKA and lactic acidosis are distinct entities that rarely occur concomitantly. In a study of lactic acidosis in 23 diabetics with clinically suspected DKA, Watkins et al [13] concluded that “lactic acid may contribute to the metabolic acidosis in patients with true diabetic ketoacidosis, but the blood lactate concentrations in these patients are not usually very high.” In a review article from 2001, Kitabchi et al [2] state that “measuring blood lactate concentration easily establishes the diagnosis of lactic acidosis (>5 mmol/L) because DKA patients seldom demonstrate this level of serum lactate.” This statement suggests that DKA should be differentiated from lactic acidosis because lactic acidosis in the setting of DKA is a rare event.

Based on previous data from non-DKA populations, one might expect that high lactate levels in DKA would be associated with clinical outcome measures such as increased mortality or increased ICU length of stay (LOS), as seen in other disease states. Watkins et al [13] concluded that persons with diabetes with “lactic acidosis generally have a serious underlying disorder and poor prognosis.” The clinical significance of the predictive value of lactic acidosis in DKA is important given the increasing practice of measuring this variable. At present, clinicians may associate a high lactate in DKA as an indicator of illness severity, but this assumption may not be valid. Our study aims to establish the prevalence and significance of lactic acidosis in patients with DKA. We hypothesized that lactic acidosis is common in DKA and that lactic acidosis would not be a predictor of clinical outcomes, specifically ICU LOS.

2. Materials and methods

We performed a retrospective chart review of patients presenting to the emergency department (ED) of an urban tertiary care hospital with 50,000 ED visits per year. The study was approved by the institutional review board, and waiver of the requirement for informed consent was obtained under institutional review board regulation.

Patients were identified through an electronic query of the ED registry. Consecutive adult (age, ≥ 18 years) patients admitted to the hospital through the ED between January 2004 and June 2008 with a diagnosis of DKA (*International Classification of Diseases, Ninth Revision*, code 250.1) were included for analysis. Patients who were transferred from other hospitals or who developed DKA during their hospitalization were not included in the analysis. Patients found to have serum bicarbonate less than 20 mEq/L, serum anion gap greater than 16 mEq/L, serum glucose greater than 250 mg/dL, urine ketones, and a lactate level drawn within 3 hours of arrival were included. Calculation of anion gap was performed in the hospital’s laboratory with the following equation: $[(Na^{+}) + (K^{+})] - [(HCO_3^{-}) + (Cl^{-})]$

–)], and the cutoff value of 16 in the current investigation is in agreement with previously established guidelines for DKA after adjusting for K⁺ (1). If an arterial or venous blood gas was performed within the first 3 hours, the patient was included only if the pH was less than 7.30. Patients without a lactate drawn within the first 3 hours of arrival to the ED were excluded. Patients with competing causes of lactic acidosis such as seizure within 3 hours of admission, linezolid use, or antiretroviral use were excluded. Patients with sepsis were included because infection is a common precipitant for DKA. Metformin use was not an exclusion criterion.

Complete medical records were reviewed and data extracted by trained research assistants. Pertinent demographics, including age, sex, and initial ED laboratory data and vital signs as well as comorbid diseases and suspected precipitants for DKA, were recorded. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated using admission laboratory values and vital signs measured in the ED. Emergency department vitals and laboratory data were used for APACHE II score calculation (as compared with values over a 24-hour period) because the initial data would be most appropriate given the timing of initial lactate measurements. Intensive care unit LOS and in-hospital mortality were also recorded. Data were collected using a standardized data collection form and subsequently entered into an electronic database (Access 2003; Microsoft Corporation, Redmond, Wash). Data analysis was performed using SAS software, version 9.1 (SAS Institute Inc, Cary, NC).

We defined lactic acidosis as a lactate level of 2.5 mmol/L or greater and a “high” lactate level as greater than 4.0 mmol/L, which is in agreement with previous investigations [14]. The primary end point for the study was ICU LOS, and the secondary end point was in-hospital mortality. Fisher exact tests were used to compare categorical variables between high-lactate and low-lactate groups. The Student *t* test or Wilcoxon rank sum tests were used if continuous variables were parametric or nonparametric. Spearman correlation coefficients were used to assess univariate relationships between continuous variables. A multivariable linear regression with ICU LOS as an independent variable was also constructed.

3. Results

There were 254 patients admitted between January 2004 and June 2008 with an admitting diagnosis of DKA, and 68 of these patients met the inclusion criteria for this study. The lactate levels observed in our cohort ranged from 1.2 to 8.3 mmol/L and are reported in Fig. 1. Lactic acidosis (lactic acid level, >2.5 mmol/L) was observed in 46 (68%) of 68 patients with DKA in this study. A high lactate level (>4 mmol/L) was observed in 27 (40%) of 68 patients. Only 1 patient in the high-lactate group had concomitant septic shock. The median lactate level was 3.5 mmol/L (interquartile range, 2.125–5.050).

The baseline characteristics of the patients in this study are presented in Table 1. The patients are divided into low-lactate (<4 mmol/L) and high-lactate (>4 mmol/L) groups. The patients in the high-lactate group had statistically significant older age, higher initial serum glucose levels, higher anion gaps, lower systolic blood pressures, and greater APACHE II scores. Although the higher lactate group tended to have a lower initial bicarbonate level and pH, these variables were not statistically different between the 2 groups. Patients in the high and low lactate level groups had similar comorbid illnesses and precipitants for DKA. The most common precipitant for DKA in this study was medication noncompliance, followed by infection and unknown causes. Only patients in the low-lactate group were taking metformin before their admission for DKA.

The average ICU LOS in the low-lactate group was 2.44 ± 1.60 days and 1.96 ± 1.09 days in the high lactate group ($P = .18$). There was no statistically significant correlation between

lactate levels and ICU LOS in a univariate model (Fig. 2). In a multivariable model controlling for APACHE II score, initial serum glucose, and initial creatinine, there was also no statistically significant association between lactate level and ICU LOS.

Initial glucose levels were strongly correlated with initial lactate levels (Fig. 3). There was a negative correlation between lactate and blood pressure (Spearman $r = 0.34$; $P = .004$). In-hospital mortality in this study was 2.9%. There was 1 death in the low-lactate group and 1 death in the high-lactate group. The patient in the high-lactate group who died also had sepsis. There was no statistically significant difference in mortality between the low- and the high-lactate groups using Fisher exact test ($P = 1.0$). Of note, there were no deaths in the cohort of patients without a measured blood lactate.

4. Discussion

Lactic acidosis is more common in DKA than traditionally appreciated. Although there is some disagreement in the literature about the association of lactic acidosis with DKA [12,13], our findings suggest that lactic acidosis commonly occurs in patients with DKA. Although metformin is known to cause lactic acidosis in diabetics, no patients in the high-lactate group were known to be using metformin in this cohort, suggesting that the degree of lactic acidosis observed in this study cannot be attributed to metformin use.

In our study, lactic acidosis was not associated with increased ICU LOS. In addition, there was no difference in mortality in the low- and high-lactate groups, although the overall mortality in the study was low. Our results suggest that lactic acidosis is not a predictor of worse clinical outcomes in DKA as it is in other diseases such as sepsis, burns, postcardiac arrest, and trauma [4–11].

Our results demonstrate that lactic acidosis is common in DKA, with 68% of patients having some degree of elevation and 40% of patients with levels greater than 4 mmol/L. Despite the high prevalence of lactic acidosis in patients with DKA, the mortality in this population remains low. Patients with DKA have much lower mortality than is observed in septic patients with similar lactate levels (Fig. 4). Howell et al [14] demonstrated that patients with sepsis who had a lactate greater than 4 mmol/L had a mortality of 28%. In our study of patients with DKA, the mortality in patients with a lactate greater than 4 mmol/L was 3.7%; however, if the single patient with sepsis is excluded, the mortality of patients in the high-lactate group was 0%. This suggests that lactate level alone is not a predictor of mortality and that the lactate level must be interpreted in the clinical context of a specific disease state. Our findings are consistent with data from Stroe et al [15], which demonstrated that lactate levels were not predictive of mortality in patients with DKA; however, this study was limited by a small sample size of only 29 patients.

The mechanism by which lactic acidosis occurs in DKA has yet to be completely described. Lactate levels were found to correlate positively with glucose levels in this study (Fig. 3). The positive correlation of lactate with glucose raises the possibility that lactic acidosis in DKA may be due not only to hypoperfusion but also to altered glucose metabolism. Glucose is initially metabolized in glycolysis to pyruvate, which, in aerobic conditions, will enter Krebs cycle for energy production. In anaerobic conditions or in states with altered metabolism, pyruvate may be shunted to produce lactic acid. Altered glucose metabolism in DKA may contribute to elevated lactate levels in these patients. Alternative mechanistic explanations of lactic acidosis in DKA must also be considered. James et al [16] reported lactic acidosis in sepsis and trauma in the absence of tissue hypoperfusion. James et al propose that production of epinephrine subsequently stimulates the activity of muscle Na⁺/K⁺ pumps, thereby generating excess lactate [16]. This epinephrine-response mechanism may play a role in patients with DKA because stress and insulin deficiency associated with DKA

enhances production of counter regulatory adrenergic hormones including epinephrine [17]. Furthermore, Bolli et al [17] also found that the epinephrine elevation is associated with severity of DKA. An alternative mechanism for lactic acidosis in DKA beyond tissue hypoperfusion may explain why lactic acidosis does not have the same significance as it does with sepsis in terms of severity of illness or mortality.

5. Limitations

The current investigation has several limitations. First, lactate levels were not collected in all patients who presented in DKA. Only 52% (68/132) of patients who were identified as meeting clinical criteria for DKA had a lactate level drawn within 3 hours of arrival to the ED. However, there were no deaths in the cohort of patients with DKA without a measured lactate. In addition, although mortality was not the primary end point, the low incidence of mortality observed in this study limits the power to detect a meaningful difference in this outcome variable. Future prospective studies are needed to further investigate the prevalence and clinical significance of lactic acidosis in patients with DKA.

6. Conclusion

Lactic acidosis is common in DKA. Lactic acidosis in patients with DKA is not associated with worse clinical outcomes, specifically increased ICU LOS. Lactate levels should, therefore, be interpreted in the context of a specific disease state.

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Fig. 1.
Initial lactate levels in patients with DKA.

Fig. 2.

Lactate levels and LOSs. In patients with DKA, lactate was not associated with ICU LOS ($P = .37$) or hospital LOS ($P = .39$). A, ICU LOS. B, Hospital LOS.

Fig. 3. Relationship of glucose levels and lactate. Initial glucose levels were correlated with initial lactate levels (Spearman correlation coefficient, 0.34; $P = .004$).

Fig. 4. Mortality in patients with DKA compared with patients with sepsis. The mortality of patients in DKA stratified by lactate levels is compared with the mortality for patients with sepsis obtained from data collected in the study of Howell et al [14].

Table 1

Patient characteristics, stratified by initial lactate levels

Patient demographics			
	Lactate <4 (n = 41)	Lactate ≥4 (n = 27)	P
Age	39.2 ± 17.0	49.7 ± 18.1	.018 ^a
Gender	36.6%, male 63.4%, female	22.2%, male 77.7%, female	.286
Data and vital signs			
Glucose (mg/dl)	622.6 ± 247.5	813.4 ± 310.8	.007 ^a
Bicarbonate MEq/L	9.7 ± 4.5	8.2 ± 3.9	.284
Anion gap	29.2 ± 6.0	36.1 ± 6.3	<.001 ^a
pH	7.11 ± 0.15 (n = 25)	7.09 ± 0.13 (n = 21)	.635
Systolic BP, min mm Hg	115.6 ± 27.4	103.7 ± 31.6	.003 ^a
Diastolic BP, min mm Hg	57.9 ± 17.2	49.7 ± 18.3	.065
APACHE II	14.6 ± 5.9	19.7 ± 7.0	.002 ^a
Comorbid diseases			
Hypertension	22 (53.6%)	12 (44.4%)	.621
Chronic renal insufficiency	4 (9.8%)	3 (11.1%)	1.000
Coronary artery disease	2 (4.9%)	4 (14.8%)	.206
Malignancy	4 (9.8%)	1 (3.7%)	.641
Precipitant for DKA			
Medication noncompliance	19 (46.3%)	10 (37%)	.466
Infection	11 (26.8%)	8 (29.6%)	1.000
Myocardial infarction	0 (0%)	1 (3.7%)	.397
Unknown	11 (26.8%)	8 (29.6%)	1.000
Other			
Type 2 diabetes	6 (14.6%)	2 (7.4%)	.463
Metformin use	4 (9.8%)	0 (0%)	.146

BP indicates blood pressure.

^aRepresents statistical significance using Wilcoxon rank sums for nonnormal variables and the Student *t* tests for normal variables and Fisher exact tests for categorical variables.