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The relationship between lactate and thiamine levels in patients with diabetic ketoacidosis[★]

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Abstract

Purpose—Thiamine functions as an important cofactor in aerobic metabolism and thiamine deficiency can contribute to lactic acidosis. Although increased rates of thiamine deficiency have been described in diabetic outpatients, this phenomenon has not been studied in relation to diabetic ketoacidosis (DKA). In the present study, we hypothesize that thiamine deficiency is associated with elevated lactate in patients with DKA.

Materials and Methods—This was a prospective observational study of patients presenting to a tertiary care center with DKA. Patient demographics, laboratory results, and outcomes were recorded. A one-time blood draw was performed and analyzed for plasma thiamine levels.

Results—Thirty-two patients were enrolled. Eight patients (25%) were thiamine deficient, with levels lower than 9 nmol/L. A negative correlation between lactic acid and plasma thiamine levels was found ($r = -0.56$, $P = .002$). This relationship remained significant after adjustment for APACHE II scores ($P = .009$). Thiamine levels were directly related to admission serum bicarbonate ($r = 0.44$, $P = .019$), and patients with thiamine deficiency maintained lower bicarbonate levels over the first 24 hours (slopes parallel with a difference of 4.083, $P = .002$).

Conclusions—Patients with DKA had a high prevalence of thiamine deficiency. Thiamine levels were inversely related to lactate levels among patients with DKA. A study of thiamine supplementation in DKA is warranted.

Keywords

Thiamine; Thiamine deficiency; Lactic acidosis; Diabetic ketoacidosis; Diabetes mellitus

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1. Introduction

Diabetic ketoacidosis (DKA) is a potentially life-threatening disorder characterized by hyperglycemia, ketonemia, and metabolic acidosis. Although the overall mortality of DKA has improved over recent decades, the incidence and financial burden of DKA remain high. Diabetic ketoacidosis accounts for 4 to 8 of every 1000 admissions for diabetes, or approximately 100 000 hospital admissions annually [1]. With medical expenditures at approximately \$13 000 per admission, the annual cost of DKA approaches \$1 billion per year [1,2].

Thiamine deficiency is a well-documented phenomenon among diabetic outpatients [3–5]. In experimental models, insulin deficiency leads to poor enteral thiamine absorption and decreases thiamine reuptake in the renal proximal tubule [6,7]. Severe thiamine deficiency can trigger acute lactic acidosis [8]. Thiamine functions as a cofactor in mitochondrial oxidative decarboxylation, converting pyruvate to acetyl-CoA and α -ketoglutarate to succinyl-CoA for use in the citric acid (Krebs) cycle [9]. In the absence of thiamine, pyruvate cannot enter the Krebs cycle and, instead, is converted to lactic acid. Lactic acidosis is an increasingly well-recognized phenomenon in DKA, with recent studies suggesting that the overall prevalence may be as high as 68% [10].

Multiple studies have explored the impact of thiamine replacement therapy on diabetic microvascular disease with promising results. Thiamine supplementation has been shown to prevent diabetic retinopathy in rats, reduce urinary microalbumin, improve diabetic neuropathy, and reverse hyperglycemia-induced endothelial dysfunction [6,7,11]. To date, however, the prevalence and significance of thiamine deficiency have not been studied in relation to DKA.

In the present study, we hypothesize that thiamine deficiency is associated with higher lactate levels in patients presenting to the emergency department (ED) with DKA.

2. Materials and methods

2.1. Study design

This was a prospective observational study of patients presenting to an urban tertiary care center with a diagnosis of DKA. Patients were enrolled consecutively between November 2009 and June 2012. The study was approved by the institutional review board at Beth Israel Deaconess Medical Center.

2.2. Study participants

Inclusion criteria consisted of adult patients (age ≥ 18 years), serum glucose level higher than 250 mg/dL, bicarbonate of 20 mEq/L or less, anion gap greater than 16 mEq/L, pH less than 7.30, and the presence of urine ketones. Those patients with competing causes of lactic acidosis including seizure activity within 3 hours of admission, primary myocardial infarction, sepsis, carbon monoxide poisoning, cyanide toxicity, current use of linezolid, or antiretroviral medications were excluded. Other exclusion criteria included ongoing thiamine supplementation and pregnancy.

2.3. Data collection

Patient demographics, comorbid conditions, vital signs, suspected trigger of DKA, laboratory test results including venous lactate levels, morbidity, and outcomes data were recorded and entered into an online database (REDCap, version 4.3.5). A one-time blood draw was performed at the time of enrollment, and the blood sample was analyzed for

plasma thiamine levels. The median time elapsed between lactate and thiamine measurement was 69.5 minutes (interquartile range [IQR], 14.3–152.5 minutes).

2.4. Procedures

Blood samples collected for analysis of plasma thiamine levels were centrifuged at $3000 \times g$ for 10 minutes, after which 1 mL was aliquoted into cryotubes and frozen. Blood was protected from light during the collection and freezing process. Frozen samples were sent to Quest Diagnostics. At Quest Diagnostics, plasma was deproteinized and incubated with acid phosphatase to convert thiamine phosphate esters to free thiamine. The free thiamine was then oxidized to thiochrome by the addition of alkaline potassium ferricyanide. The thiochrome was then separated from other interfering substances by high-performance liquid chromatography and measured fluorometrically. The amount of total thiamine in a given sample was proportional to the amount of thiochrome formed.

Absolute thiamine deficiency was determined using previously established standard laboratory values from Quest Diagnostics. Specifically, absolute thiamine deficiency was defined as a level less than or equal to 9 nmol/L.

2.4. Outcomes

The primary outcome was the relationship between thiamine and lactate levels. Secondary outcomes included severity of acidosis, gastrointestinal symptoms, hospital length of stay, and mortality.

2.5. Statistical analysis

All analyses were performed using JMP Pro, a component of SAS (Cary, NC). Simple descriptive statistics were used to describe the study population. Thiamine and lactate levels were converted logarithmically because of the nonnormality of the data. Subsequent goodness-of-fit testing of the transformed data revealed normal distributions.

Linear regression was used to evaluate the relationship between thiamine and lactate levels in patients with DKA. Severity of illness was identified a priori as a potential confounder and was controlled for using the APACHE II score. Multivariate regression analyses were also performed, controlling for factors found to be different between the thiamine-deficient and thiamine-sufficient groups. Results are reported for both the unadjusted and adjusted analyses. A mixed-model approach with patients as the random factor and thiamine group, time and their interaction as fixed factors were used to compare bicarbonate in thiamine-deficient and thiamine-sufficient patients over time. A *P* value less than .05 was considered statistically significant.

3. Results

A total of 32 patients presenting to the ED with a diagnosis of DKA were enrolled in the study. Baseline characteristics are displayed in Table 1. Diabetic ketoacidosis triggers were medication nonadherence (34.3%), infection (12.5%), newly diagnosed diabetes (16.0%), and insulin pump malfunction (3%). The cause was unknown in 34.3%. The reference range of plasma thiamine as defined by Quest Diagnostics is 9 to 44 nmol/L. The median thiamine level of our patient population was 14 (IQR, 8.5–18) nmol/L, and 8 patients (25%) were found to have absolute thiamine deficiency with levels less than 9 nmol/L. Twelve patients (38%) identified as African American. Of those, 6 (50%) had an absolute thiamine deficiency. Three (9.4%) patients were identified as having chronic alcoholism, none of whom were thiamine deficient.

Twenty-eight (87.5%) of the 32 enrolled patients had lactate levels measured in the ED. The overall median lactate level was 2.4 (IQR, 1.5–4.6) mmol/L. The median lactate levels in the thiamine-deficient and thiamine-sufficient groups were 5.8 (IQR 2.6–7.7) and 1.9 (1.3–3.6) mmol/L, respectively ($P = .006$). Fourteen (50.0%) patients had lactic acidosis with lactate greater than 2.5 mmol/L, and 7 (25.0%) had lactate greater than 4 mmol/L.

A statistically significant inverse association between lactic acid levels and blood thiamine levels was found ($r = -0.56$, $P = .002$; Fig. 1). This relationship remained significant after adjustment for severity of illness using the APACHE II score ($r = -0.57$, $P = .009$). Thiamine-deficient patients were found to have higher heart rates, respiratory rates, and low bicarbonate levels. The relationship between thiamine and lactate persisted after controlling for these factors ($r = -0.57$, $P = .0184$). A direct relationship between thiamine level and admission serum bicarbonate was noted ($r = 0.44$, $P = .019$), and patients with thiamine deficiency maintained lower serum bicarbonate levels over the first 24 hours (slopes are parallel with a difference of 4.083, $P = .002$; Fig. 2). Admission bicarbonate was negatively correlated with intensive care unit length of stay ($r = -0.35$, $P = .048$).

Thiamine-deficient patients had higher rates of vomiting (87.5% vs 37.5%, $P = .01$) and abdominal pain (75% vs 21%, $P = .006$). Patients with thiamine deficiency also had longer median intensive care unit lengths of stay compared with those without (5 [IQR, 2.25–7.25] vs 3 days [IQR, 2–5]), but this difference did not reach statistical significance ($P = .24$). The overall in-hospital mortality rate was 0%.

5. Discussion

In the present study, we found an inverse correlation between plasma thiamine and lactate levels such that patients with lower thiamine levels had higher levels of lactate. This relationship remained significant after correcting for potential confounders including severity of illness. Patients with thiamine deficiency had lower bicarbonate levels on admission and maintained lower bicarbonate levels over the first 24 hours. In addition, patients with thiamine deficiency were more likely to have abdominal pain and vomiting.

Plasma thiamine levels were measured directly in this study, and thiamine deficiency was defined as a plasma thiamine less than 9 nmol/L per laboratory standard. Using this criterion, 25% of patients with DKA exhibited an absolute thiamine deficiency. In a prior study by our group, 0 of 30 patients presenting to the ED with minor complaints were found to be thiamine deficient [12]. Thiamine deficiency is a known phenomenon among diabetic outpatients and may be related to poor enteral thiamine absorption and/or decreased renal reuptake [6,7]. Thiamine deficiency in our cohort may have been exacerbated by depletion from metabolic stress [13].

Most of those patients with thiamine deficiency were African American. One study of preoperative bariatric patients found that 31% of African Americans, as compared with 6.8% of whites and 47.2% of Hispanics, were thiamine deficient. This was attributed to differences in nutritional intake [14]. Future studies should include a specific focus on thiamine deficiency in both African Americans and other ethnic minorities.

Fourteen (50.0%) patients with venous lactate measured in the ED were found to have lactic acidosis with lactate levels greater than 2.5 mmol/L, and 7 (25.0%) had lactate greater than 4 mmol/L. These results are comparable with those found in a retrospective review of 68 patients previously published by our research group. In that study, 68% of patients with DKA had lactate levels greater than 2.5 mmol/L, and 40% had lactate greater than 4 mmol/L [11]. Taken together, these findings suggest that lactic acidosis in DKA is more common than previously appreciated.

To date, research exploring the consequences of thiamine deficiency in diabetes has focused primarily on the relationship of thiamine deficiency to diabetic microvascular disease [7,8]. In the pediatric literature, one study of 15 patients found that thiamine deficiency is common in those with DKA and that insulin administration may further reduce thiamine levels [15]. This study is the first to report on the connection between thiamine deficiency and lactic acidosis in patients with DKA. Our group has previously shown that thiamine levels exhibit a negative correlation with lactate in patients with sepsis [12]. Whereas elevated lactate levels in critical illness are often taken to reflect tissue hypoperfusion in response to a low-flow state, our analyses suggest that thiamine deficiency may be an independent and reversible factor.

In addition to higher lactate levels, those patients with thiamine deficiency were more likely to have abdominal pain and vomiting. Whether thiamine deficiency could potentially be the cause of these complaints is unclear; however, in 2 prospective studies of patients who were deprived of thiamine, gastrointestinal complaints including nausea, vomiting, and abdominal pain were common [16,17]. In an epidemic of thiamine deficiency that occurred in a World War II era Japanese prison camp, a substantial number of patients developed abdominal pain [18]. Of these, many patients with initially unrecognized thiamine deficiency had such significant abdominal pain that surgeons were prompted to perform an exploratory laparotomy. Recently, the term *gastrointestinal beriberi* was used to describe 2 patients with gastrointestinal syndromes that promptly resolved with thiamine administration [19]. The increased abdominal pain and vomiting seen in our patients with thiamine deficiency may be related to this phenomenon.

Wernicke encephalopathy is a well-defined entity among alcoholic patients with thiamine deficiency and may, in some instances, be precipitated by DKA [20]. In a case report published by Clark et al [21], a 13-year old patient with DKA developed encephalopathy that persisted after correction of her DKA and was eventually reversed with thiamine administration. Although no patients in our cohort had overt encephalopathy, we did not assess for more subtle cognitive sequelae.

Mortality from DKA has improved dramatically over the past 2 decades; however, morbidity and costs remain high [2]. In the present study, thiamine deficiency was found to be common in patients presenting with DKA, and thiamine levels correlated negatively with serum lactate. Our findings support the biologic role of thiamine in metabolism and raise the possibility that thiamine deficiency is a correctable risk factor for lactic acidosis in DKA. Prospective studies of thiamine supplementation in DKA are warranted. Thiamine supplementation is low cost and has minimal adverse effects. Future work should focus specifically on the effects of thiamine supplementation with regard to a more rapid reversal of acidosis, improvement in gastrointestinal symptoms, and reduction in hospital resource use.

Limitations of this study include its small sample size and observational nature. Trends presented in this study should be explored further in a future, well-designed randomized control trial.

5. Conclusion

In this small, prospective study, thiamine deficiency was associated with higher lactate levels in patients presenting with DKA. Patients who were thiamine deficient had more frequent gastrointestinal symptoms and an increased severity of acidosis.

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Fig. 1. Thiamine and lactate levels were transformed logarithmically because of the nonnormality of the data. Plot shows an inverse relationship between thiamine and lactate ($r = -0.56$, $P = .002$).

Fig. 2.
Plot of bicarbonate over time for patients with thiamine deficiency (blue line) and patients with normal thiamine (red line).

Table 1

Baseline demographics and data

	All	Thiamine deficient	Thiamine sufficient	P
Total (n)	32	8	24	
Age (y), median (IQR)	41.5 (27–56)	45.5 (22–61)	42 (29–52)	.82
BMI (kg/m ²), median (IQR)	25 (20–28)	25 (19–28)	26 (20–29)	.98
Male (%)	38	37.5	71	.09
Race (%)				
White	100	12.5	87.5	.10
Hispanic	100	0	100	.22
Black	100	50	50	.01
Comorbidities (%)				
Hypertension	13	3	10	.84
CAD	4	0	4	.22
Renal disease	3	0	3	.30
Myocardial infarction	1	0	1	.56
Chronic alcoholism	3	0	3	.29
Initial vitals, median (IQR)				
Heart rate (beats/min)	112 (91–125)	123 (112–132)	105 (91–123)	.025
Systolic blood pressure (mm Hg)	121 (109–155)	109 (83–161)	124 (113–152)	.39
Respiratory rate	20 (18–26)	33 (18–34)	20 (18–23)	.04
Oxygen saturation (%)	98 (95–100)	100 (98–100)	97 (95–100)	.09
Initial laboratory values, median (IQR)				
WBC ($\times 10^3/\mu\text{L}$)	11 (8–13)	11 (9–17)	10.3 (6.2–13)	.38
HCT ($\times 10^3/\mu\text{L}$)	44 (37.5–47)	40 (32–50)	44.6 (38–47.0)	.96
HCO ₃ (mEq/L)	12 (9–16)	8 (6.25–11.5)	15 (10.25–16)	.004
Nam (Eq/L)	132 (129–136)	136 (128–140)	131 (129–135)	.11
Glucose (mg/dL)	492 (412–708)	625 (415–768)	489 (405–697)	.46
Lactate (mmol/L)	2.4 (1.5–4.6)	5.8 (2.6–7.7)	1.9 (1.3–3.6)	.006
Thiamine (nmol/L)	14 (8.5–18)	6 (6–7.5)	16 (13–23.5)	.001
Creatinine (mg/dL)	1.3 (1–1.7)	1.4 (1.0–1.8)	1.3 (1.0–1.6)	.47
Severity score, median (IQR)				
APACHE II score	8 (3–12)	12 (6–14)	7 (3–11)	.24