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The relationship between lactate and thiamine levels in patients with diabetic ketoacidosis☆

Ari Moskowitz, MD [a], Amanda Graver, MPH [b], Tyler Giberson, BS [b], Katherine Berg, MD [c], Xiaowen Liu, PhD [b], Amy Uber, BS [b], Shiva Gautam, PhD [d], Michael W. Donnino, MD [b,c,*]

[a] Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA
[b] Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA
[c] Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Beth Israel Deaconess Medical Center, Boston, MA
[d] Department of Medicine, Division of Gastroenterology, Beth Israel Deaconess Medical Center, Boston, MA

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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.

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.

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* Corresponding author. Beth Israel Deaconess Medical Center, Boston, MA 02215. Tel.: +1 617 754 2323; fax: +1 617 754 2350.
E-mail address: amoskowi@bidmc.harvard.edu (A. Moskowitz).

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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 mEg/L or less, anion gap greater than 16 mEg/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, Research Electronic Data Capture Consortium, Nashville, TN). 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 × *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, Cambridge, MA, 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.

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 ($\times 10^3/\mu$L)	11 (8-13)	11 (9-17)	10.3 (6.2-13)	.38
HCT ($\times 10^3/\mu$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