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Original article

Frequency and Prognostic Significance of Serum Lactate in Children with Diabetic Ketoacidosis

Osama A. Zaki [a], Effat H. Assar [a], Maha T. Rashwan [b], Samar D. Mohammed [a]

[a] Pediatric Department, Faculty of Medicine Benha University, Egypt. [b] Clinical Pathology Department, Faculty of Medicine Benha University, Egypt.

Corresponding to: Samar D. Mohammed. Pediatric Department, Faculty of Medicine Benha University, Egypt.

Email: samar.diaa15@gmail.com

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Abstract:

Background: Diabetic ketoacidosis (DKA) is the most common acute hyperglycemic emergency in children with diabetes mellitus. DKA is the consequence of an absolute or relative lack of insulin and concomitant elevation of counter-regulatory hormones, usually resulting in the triad of hyperglycemia, metabolic acidosis and ketosis. This study aimed to determine the frequency and prognostic significance of serum lactate in children with diabetic ketoacidosis admitted to the Pediatrics department. **Methods:** This study was a comparative cross-sectional study that included sixty participants. They were divided into 30 children with diabetic ketoacidosis and 30 age and sex matched healthy children as a control group. **Results:** There was a significant negative correlation between serum lactate and venous blood pH (p = 0.001). There was a significant positive correlation between serum lactate and CRP (p = 0.029). There was a significant negative correlation between serum lactate and recovery time (p = 0.016). **Conclusion:** Lactic acidosis is common in DKA, and is not always a finding that predicts the severity of the disease or its mortality.

Keywords: Prognostic; Significance; Serum lactate; Children; Diabetic Ketoacidosis

Introduction

Diabetic ketoacidosis (DKA) is the most common acute hyperglycemic emergency in children with diabetes mellitus. It is the consequence of an absolute or relative lack of insulin and concomitant elevation of counter-regulatory hormones, usually resulting in the triad of hyperglycemia, metabolic acidosis and ketosis (elevated levels of ketones in blood or urine; serum ketone concentration >3.0 mmol/l) (1).

The DKA occurs mostly in children with uncontrolled type 1 diabetes mellitus (T1DM; which results from the autoimmune destruction of the β-cells of the islets of Langerhans). Although any illness or physiological stress can

precipitate DKA, the most frequent causes are infections, particularly urinary tract infections and gastroenteritis (2).

During an episode of DKA, there are multiple abnormal processes going on in the body including fluid shifts, decreased perfusion and deranged pH which affects many functions and causes electrolyte abnormalities. All of these can lead to many body systems and organs being affected (3).

Lactate is produced by cells exposed to anaerobic conditions and can be used as an effective energy source in the brain and also elsewhere. The brain is thought to use lactate even in normal aerobic conditions. Glucose entering the brain via capillaries has been found not only to feed directly to neurons, but also through a unique coupling system with glial cells which is used preferentially especially during periods of intense activity. Glial cells first produce pyruvate followed by lactate via glycolysis and then lactate is transported to neighboring neurons (4).

In diabetes mellitus, insulin deficiency leads to increased gluconeogenesis, which is simultaneously accompanied by impaired glucose uptake and use in peripheral tissues resulting in hyperglycemia (5).

In T1DM and T2DM, increased hepatic gluconeogenesis results from the increased availability of gluconeogenic precursors (as lactate, glycerol and several gluconeogenic amino acids including alanine, glycine and serine). Furthermore, low insulin concentrations lead to catabolism of muscle proteins liberating amino acids that are gluconeogenic and ketogenic such as tyrosine, isoleucine and phenylalanine or purely ketogenic such as lysine and leucine (6).

Previous studies in adults have clearly shown that serum lactate levels can be used as a predictor of severity of the disease in certain critical diseases such as sepsis, burns, myocardial infarction, post-cardiac arrest, and trauma. However, there are very few studies about the significance of lactate level in patients with DKA admitted to intensive care units (7).

This study aimed to determine the frequency and prognostic significance of serum lactate in children with diabetic ketoacidosis admitted to the pediatrics department.

Patients and methods

This comparative cross-sectional study was carried out on thirty patients with diabetic ketoacidosis (patients group), compared to thirty age- and sex-matched healthy children (control group). The study was conducted in the pediatric department of Benha University Hospital and El Galaa

Military Hospital from December 2021 to May 2022.

Written informative consents were obtained from all parents of the participants. The study was approved by the ethics committee on research involving human subjects of Benha Faculty of Medicine**.** The approval number of the local ethical committee: Ms 29-1-2021

Inclusion criteria: Children meeting the following criteria were considered for enrollment: 1. Age < 18 years at enrollment. 2. Diagnosis of DKA (serum glucose concentration >200 mg/dL, ketonuria presence, venous blood pH <7.30 or serum bicarbonate concentration <15 mmol/L) (8).

Exclusion criteria: 1. Patients with underlying neurological disorders that would affect mental status testing during DKA treatment such as head trauma, meningitis or other conditions that affect the neurological function. 2. Patients who have begun DKA treatment prior to the being approached for enrollment.

All the patients and controls were checked via: History taking: A purposely-designed sheet was performed for all the participants included in this study including personal history (name, age, sex & residence), family history, perinatal history, present history (onset, course and duration of symptoms), past history, dietetic history and history of glycemic control (if not first presentation of diabetes), polyphagia, polydipsia, polyuria, loss of weight, recurrent infections, previous surgery or systemic diseases. Physical examination with stress on body weight, skin color, heart rate, respiratory rate, hydration state, body temperature and conscious level by Glasgow Coma Scale (GCS) (9). Investigations: Complete blood count, C-reactive protein, arterial blood gases (ABG), blood glucose, urine analysis, hemoglobin A1c and kidney function tests (urea, creatinine).

Measurement of Serum Lactate:

1- Spectrum diagnostics liquizyme lactate reagent for in-vitro quantitative, diagnostic determination of lactate in human plasma and CSF on both automated and manual systems (CATALOG NO. 274001).
2- Enzymatic colorimetric method (LOX/PAP) with lactate oxidase and 4-aminoantipyrine.

Assay principle: Lactate is oxidized to pyruvate and hydrogen peroxide (H2O2) by lactate oxidase (LOX). In the presence of peroxidase (POD), hydrogen peroxide reacts with 2,4,6-tribromo-3-hydroxybenzoic acid (THB) and 4-aminoantipyrine (4-AAP) to form a red quinoneimine dye.

The color intensity of the formed red quinoneimine dye is directly proportional to the lactate concentration. It is

determined by measuring the increase in absorbance at 546 nm.

System Parameters: Wavelength: 546 nm, Optical path: 1 cm, Assay type: End-point, Direction: Increase, Sample: Reagent Ratio: 1: 100, e.g.: Reagent volume: 1ml, Sample volume: 10 ul, Temperature: 37°C or 15-25°C, Zero adjustment: reagent blank, Incubation time: 5 minutes at 37°C or 10 minutes at 15-25°C, Reagent Blank Limits: low 0.00 AU/ high 0.25 AU, Sensitivity: 0.3 mg/dl (0.033 mmol/l), Linearity: 90 mg/dl (9.99 mmol/l)

Procedure: Mix and incubate for 5 minutes at 37 °C or 10 minutes at 15-25 °C. Measure absorbance of specimen (^{A}specimen) and standard (^{A}standard) against reagent blank within 30

Calculation: Lactate conc. (mg/dl) = (^{A}specimen)/ (^{A}standard) × 10

Statistical analysis

The collected data were tabulated and analyzed using SPSS version 24 software (SPSS Inc, Chicago, ILL Company). Categorical data were presented as number and percentages. Chi square test (X2) was used to analyze categorical variables. Quantitative data were expressed as mean ± standard deviation, median and range. Student "t" test was used to analyze normally distributed variables among 2 independent groups. Spearman's correlation coefficient (rho) was used to assess correlation between nonparametric variables. The accepted level of significance in this work was stated at 0.05 (p <0.05 was considered significant).

Results

There was a non-significant difference between patients and control groups regarding both age (p = 0.09) and sex (p = 0.8). However, the patients' group had significantly smaller body weights (p = 0.005) and significantly higher serum glucose concentration (p < 0.001) and serum lactate (p = 0.04) (Table 1).

There were insignificant correlations between serum lactate and age, weight or onset of symptoms (p = 0.700, 0.476 and 0.691 respectively). As well, there were insignificant correlations between serum lactate and heart rate, respiratory rate or temperature (p = 0.076, 0.203 and 0.345 respectively). There was an insignificant correlation between serum lactate and GCS (p = 0.393). Biochemically, there was a significant positive correlation between serum lactate and CRP (p = 0.029) and a significant negative correlation between serum lactate and venous PH (p = 0.001). But there was a insignificant correlation between serum lactate and serum glucose concentration (p = 0.955), ketonuria (p = 0.708) or serum bicarbonate (p = 0.078).

Similarly, there was a non-significant correlation between serum lactate and HbA1c (p = 0.988) or between lactate and urea or creatinine levels (p = 0.798 and 0.088 respectively) (Table 2).

Table 1: Comparison between the study groups regarding age, weight, sex and serum glucose and lactate

Variables		Patients		Control		T test	*p*-value
		Mean	S. D	Mean	S. D		
Age (Y's)		5.77	3.59	7.10	2.20	1.7	0.09
Weight (kg)		21.33	9.40	28.30	8.96	2.9	0.005*
Variables		Patients		Control		Total	*p*-value
		No.	%	No.	%	No. %	
Sex	**F**	18	60%	19	63.3%	37 61.7%	0.8
	M	12	40%	11	36.7%	23 38.3%	
Total		30	100%	30	100.0%	60 100.0%	
Serum glucose (mg/dL)		391.21	54.77	97.93	8.46	28.5	<0.001*
Serum Lactate (mmol/L)		8.38	4.54	6.60	1.52	2.04	0.04*

* p<0.05= significant difference

Table 2: Correlation between serum lactate and age, weight, onset, vital signs, GCS, serum glucose, ketonuria, venous blood pH, serum bicarbonate, CRP, HbA1c, and renal functions

Variables	***r***	***p*-value**
Age	0.073	0.700
Weight	0.135	0.476
Onset	0.076	0.691
Heart rate	-0.329	0.076
Respiratory rate	-0.239	0.203
Body temperature	0.179	0.345
Glasgow Coma Scale (GCS)	0.162	0.393
Serum glucose conc.	0.011	0.955
Ketonuria	0.071	0.708
Venous blood pH	-0.580	0.001*
Serum bicarbonate conc.	-0.326	0.078
CRP	0.399	0.029*
HbA1c	0.003	0.988
Urea	0.049	0.798
Creatinine	0.317	0.088

* p<0.05= significant difference

There was a significant negative correlation between serum lactate and recovery time (p = 0.016) (Figure 1).

Serum lactate levels showed non-significant difference regarding to sex of the patients (P = 0.2) (Table 3).

Table 3: Comparison between males and females regarding serum lactate**.**

Gender	N	Serum lactate (Mean±S.D)	t	*p*-value
F	37	7.05±3.17 mmol/L	1.2	0.2
M	23	8.20±3.89 mmol/L		

p<0.05= significant difference

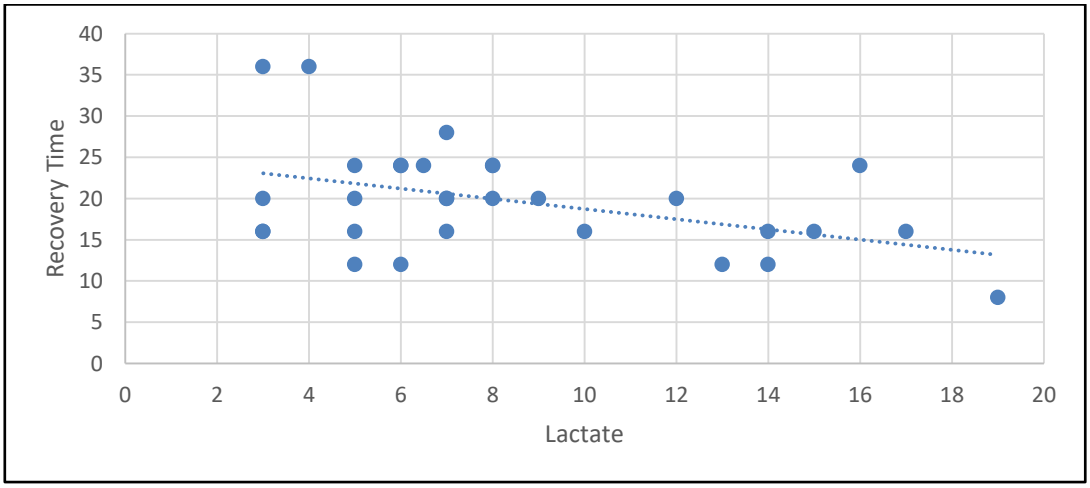

Figure 1: Correlation between lactate and recovery time

Discussion

Diabetic ketoacidosis (DKA) is a common and life-threatening complication in children with diabetes. It develops due to insulin deficiency or insulin resistance, and it is one of the reasons for their admission to the pediatric intensive care units (4).

In the current study, there was a non-significant difference between patients and control groups regarding age and sex (p = 0.09 and 0.8 respectively). Patients' weight was significantly lower than the control group (p = 0.005).

In the current study, serum glucose and serum lactate concentrations were significantly higher in the patients' group than in the control group (p < 0.001). There was a significant negative correlation between serum lactate and venous blood pH (p = 0.001). Similar results were also found by another study (7) who aimed to determine the prognostic significance of lactic acidosis in children with DKA vs diabetic patients without DKA. Significant differences were found between these two groups regarding blood glucose and CO_2.

In the current study, there were no significant correlations between serum lactate and heart rate, respiratory rate, body temperature, Glasgow Coma Scale

(GCS), serum bicarbonate, blood urea or serum creatinine levels. Also, another study (7) found that serum lactate had non-significant correlation with systolic blood pressure, diastolic blood pressure, GCS, blood bicarbonate or serum creatinine. A multivariate logistic regression analysis done by another study (10) showed that heart rate (p = 0.003), diastolic blood pressure (p = 0.001) and stage of severity (p = 0.042) were independently associated with the development of hyper-lactatemia in diabetic ketoacidosis.

In contrast to the previous results, another study (4) investigated the significance and prevalence of lactic acidosis in children with DKA presenting to the emergency department and found that the patients in the high lactate had significantly higher baseline heart rate, respiratory rate, sodium level, potassium level, pH (alkalosis) and anion gap. The patients in the high lactate group had significantly lower chloride level. Although statistically significant, these differences were small and of unclear clinical significance. Initial glucose levels were significantly higher in the patients presenting with lactic acidosis. Additionally, initial glucose levels were positively correlated with the lactate level (r = 0.20).

In the current study, there was a no significant correlation between serum lactate and serum glucose concentration or HbA1c (p = 0.955, 0.988 respectively). There was no significant correlation between serum lactate and ketonuria (p = 0.708). In disagreement with our results, another study (11) found that higher lactate levels were associated with greater hydrogen ion concentration (p < 0.0001), higher blood glucose (p = 0.009) and lower glomerular filtration rate estimated from creatinine (p = 0.025).

In the current study, there was a significant negative correlation between serum lactate and recovery time (p = 0.016). In agreement with our results, another study (12) about the incidence of hyperlactatemia in critically ill children and its association with the outcome found that the mean lactic acid levels in survivors and non survivors were 3.3±3.12 and 5.35±5.47 respectively. Hyperlactatemia was associated with death (p =0.01) and development of MODS (p =0.03) on univariate analysis. On multivariate logistic regression rising lactate and development of MODS were significantly associated with death (p =<0.05, odds ratio (OR) 9.24 (95% confidence interval 1.55-55.20).

In contrast to our results, another study (7) declared that lactate level had no significant correlation with recovery time from DKA. Also, in another study (4) there was no statistically significant difference in pediatric intensive care unit

(PICU) length of stay (LOS) between the low and high lactate groups. The mean hospital LOS was 69.1±38.3 hours. There was no statistically significant difference in hospital LOS between the low and high lactate groups. Additionally, there was no significant statistical difference between the presence of lactic acidosis and duration of intravenous insulin. Another study (10) reveled that lactate level was not significantly associated with length of hospital stay (p = 0.115) or the length of time to diabetic ketoacidosis resolution (p = 0.143).

In the current study, there was a no significant difference between the serum lactate levels and different hydration states of the patients (p = 0.4). In disagreement with our study, another study (13) showed a strong relation between systematic changes in lactic acid and associated physiological responses resulting from previous day dehydration.

Conclusion

Lactic acidosis is common in DKA and is not always a finding that predicts the severity of the disease or its mortality. Hyperlactatemia and increasing lactic acid trend in critically ill children are associated with worse outcome in PICU.

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