# Lactic Acidosis in Diabetic Ketoacidosis: A Marker of Severity or Alternate Substrate for Metabolism

**Javaid Ahmad Bhat, Shariq Rashid Masoodi[1], Moomin Hussain Bhat[1], Hilal Bhat[1], Peerzada Ovais Ahmad[1], Mona Sood[1]**

Department of Endocrinology, Superspeciality Hospital, GMC, [1]Department of Endocrinology, SheriKashmir Institute of Medical Sciences, Srinagar, Kashmir, India

## Abstract

**Purpose:** The lactate level is being increasingly used as a marker of severity of illness and prognosis in multitude of critical conditions. However, its role in diabetic ketoacidosis (DKA) is not well defined. **Aim:** To determine the prevalence and clinical importance along with the underlying role of metformin in lactic acidosis (LA) in patients admitted with DKA. **Methods:** A 2-year prospective and observational study involving 62 consenting in hospital DKA patients. Plasma lactate level on arrival, its clinical significance and relationship with morbidity and mortality in patients with DKA was evaluated. **Results:** The prevalence of LA (lactate ≥2.5 mmol/l) among the study cohort was found to be 55% with significant LA (≥5 mmol/l) documented in 16%. The median lactate level was 2.55 mmol/l (interquartile range, 1.70–3.20). No significant difference in the severity of LA was seen with metformin use. Lactate correlated positively with initial plasma glucose (IPG) ($P = 0.001$) and APACHE-II Score ($P = 0.002$); correlated negatively with systolic blood pressure ($P = 0.003$), pH ($P = 0.002$) and severity of DKA ($P = 0.001$). After controlling for AKI, APACHE II score and blood pressure, lactate continued to correlate positively with IPG ($P = 0.002$). No mortality or significant morbidity was documented in the entire cohort. **Conclusions:** LA has a significant presence in patients with DKA; however, it is not associated with mortality or significant morbidity. Moreover, there was no significant difference in severity of LA with metformin use. Elevated lactate levels may be an adaptation to provide alternate substrate for metabolism in the presence of hypoinsulinemic state. The study results provide rationale for large well-designed studies evaluating in-depth clinical relationship of lactate in DKA.

**Keywords:** Diabetic complications, diabetic ketoacidosis, DKA complications, lactic acidosis

## INTRODUCTION

Lactate, a product of anaerobic metabolism, is produced by most tissues in the human body, with the highest level of production from muscle.[1,2] Hepatic clearance is the major route of excretion with a small amount of additional clearance by the kidneys.[1,3] In anaerobic conditions, pyruvate is reduced to lactate-by-lactate dehydrogenase in contrast to aerobic condition, where having access to oxygen; pyruvate is converted to water and carbon dioxide in the mitochondria. The exact pathophysiology of elevated lactate in various conditions is likely multifactorial. In general, lactate elevation may be caused by increased production, decreased clearance, or a combination of both.[4]

Diabetes patients especially those in diabetic ketoacidosis (DKA) are predisposed to develop hyperlactatemia and lactic acidosis (LA) on account of having a number of risk factors including metformin use, which are known to affect plasma lactate levels. Elevated lactate is a common finding in DKA[5,6] and is generally thought to result from anaerobic glycolysis due to relative tissue hypo-perfusion and hypoxemia; however, other pathophysiological mechanisms are also thought to be responsible.[5,7]

Studies have found that lactate levels are predictive of severity of illness in several critical states including sepsis, burns, ST-elevation myocardial infarction, post-cardiac arrest, and trauma.[8–15] However, not much attention has been paid to the

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clinical significance of elevated lactate levels in DKA or its association with disease severity or morbidity in DKA. A few studies, that looked into the role and importance of lactate in DKA demonstrated that lactate does not appear to be associated with the worse outcomes[5,6] contrast to findings in other disease states.[8–15] A study involving 68 patients with DKA found that there was no correlation between lactate and morbidity in the form of duration of intensive care unit (ICU) stay or mortality,[5] thus giving credence to observation that elevated lactate may not be the marker of severity of the disease in these patients.

The role of lactate as a predictive marker of severity of illness and mortality in several critical conditions and its undetermined significance in DKA which is a relatively a common endocrine emergency given the magnitude of disease, has prompted us take up this study to determine the prevalence and significance of LA in DKA.

## Materials and Methods

The study was conducted in the Department of Endocrinology SKIMS Srinagar Kashmir, a tertiary care hospital in northern India. This was a prospective observational study of patients admitted with DKA. The study was performed in accordance with the Declaration of Helsinki statement for medical research involving human subjects. A written informed consent was obtained from all the participants/their guardians, in the language that was understandable to the patient and their attendant. The study was approved by the Institutional Ethics committee. A total of 62 consecutive patients admitted with DKA, from June 2016 to June 2018 were included in the current study. The sample size calculation was based on the primary objective, namely, to determine the prevalence of LA in patients admitted with DKA. Based on a previous study,[16] we expected to have around 100-patient DKA episodes during the study period; the prevalence of LA was presumed to be approximately 50%. Using a precision of 80% and design effect of 1.0, the sample size was calculated to be 63 participants. However, we could recruit only 62 participants. DKA and its severity were defined as per the ADA criteria. Patient demographics including age and sex, initial laboratory data including peripheral venous lactate levels, vital signs as well as comorbid diseases, use of metformin, suspected precipitants for DKA and outcomes were recorded. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated using admission laboratory values and vital signs, measured on initial contact with patient. Data were collected using a standardized data collection form. Complete clinical examination including anthropometry and evaluation of complications was done. Patients were evaluated for microvascular complications once they were out of DKA.

The blood lactate level was measured along with blood gas analysis on a blood sample drawn on initial contact with the patient that was analyzed within 15 min of venipuncture. Morbidity in the form of respiratory (acute respiratory distress syndrome, need for mechanical ventilation)

cardiac (arrhythmia, congestive cardiac failure, or cardiac arrest) cardiovascular complications (hypotension or thrombo embolic phenomenon) and or cerebral edema were recorded. Total duration of hospital stay and in-hospital mortality if any was also recorded.

We defined LA as a lactate level of ≥2.5 mmol/l[17] and lactate level ≥5 mmol/l was defined as significant as it may associated with symptoms and signs.[4] The term significant LA is used in this paper to describe lactate levels ≥5 mmol/l. Study group was subdivided on the basis of age (<20 and ≥20 years) for comparative analysis to see the clinical importance and impact of age on clinical parameters and lactate levels [Table 1]. Further, comparative analysis was done on the basis of the level of lactate concentration [Table 2]. Those with lactate level of ≤5 mmol/l were included in group I and those with lactate level of >5 mmol/l were included in group II, to determine the clinical significance of such high lactate levels (>5 mmol/l) in relation to the severity, complications and mortality in patients with DKA [Table 3].

### Statistical analysis

Data were first entered into Microsoft Excel. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 25.0 software from IBM Corporation, NY, USA. The description of quantitative (numerical) variables was performed in the form of mean ± standard deviation. The analysis of numerical variables was performed using the independent Student's t-test and one-way ANOVA with multiple range tests. The comparison of categorical data parameters was performed by using the Chi-square test. The Pearson correlation coefficient test was used to rank variables against each other either positively or inversely. A binary regression logistic analysis was performed using LA as the dependent variable to determine significant associations. A $P$ value <0.05 was considered statistically significant.

## Results

A total of 62 consecutive patients admitted with DKA were assessed in the current study. Females were affected more than the males in the ratio of 1.6:1 (61.3% vs. 38.7%). Majority (89%) of the patients were of type 1 diabetes mellitus (T1DM) while only 11% were presumed to have other types of diabetes including type 2 diabetes mellitus (T2DM). The precipitants for DKA were infection (55%), insulin withdrawal (36%), newly diagnosed diabetes (27%) and drugs like antipsychotics (2%).

LA (lactic acid level ≥2.5 mmol/l) was observed in 55% of patients and significant LA was observed in 16% of patients among the studied cohort. The median lactate level was 2.55 mmol/l (interquartile range, 1.70 –3.20).

The baseline characteristics of the patients are presented in Table 1. Patients with LA had higher initial plasma glucose (IPG) ($P$ = 0.000), lower pH ($P$ = 0.035), lower bicarbonate ($P$ = 0.014), higher frequency of severe DKA

**Table 1: Description of demographic, anthropometric, clinical, biochemical, and complications profile of DKA group further subdivided in different age groups [(age <20 years) and adults (age ≥20 years) and whole group]**

| DKA group (*n*=62) | DKA group (mean±SD) 95% CI | Subgroups based on age | | *P* |
|---|---|---|---|---|
| | | Children and Adolescents <20 years (*n*=23) (mean±SD) 95% CI | Adults ≥20 years (*n*=39) (mean±SD) 95% CI | |
| Demography and Anthropometry | | | | |
| Mean age (years) | 26.41±16.16 (22.31-30.52) | 11.78±3.59 (10.22-13.33) | 35.05±14.34 (30.40-39.70) | 0.000 |
| Sex (M: F), *n* (%) | 24:38 (39:61) | 6:17 (26:74) | 18:21 (46:54) | 0.177 |
| Clinical and biochemical characteristics | | | | |
| T1DM: Others including T2DM, *n* (%) | 55:07 (89:11) | 23 : 0 (100:0) | 32 : 7 (82:18) | 0.040* |
| Age at onset (years) | 23.29±15.87 (19.25-27.32) | 10.0±3.4 (8.53-11.46) | 31.12±15.08 (26.23-36.01) | 0.000* |
| Duration of DM (years) | 3.12±3.77 (2.17-4.08) | 1.78±2.5 (0.70-2.86) | 3.92±4.18 (2.56-5.28) | 0.030* |
| Acanthosis nigricans, *n* (%) | 9 (15) | 2 (9) | 7 (18) | 0.464 |
| Skin tags, *n* (%) | 6 (10) | 1 (4) | 5 (13) | 0.398 |
| Hospital stay (days) | 7.80±3.76 (6.85-8.76) | 7.5±3.9 (5.78-9.18) | 8.0±3.7 (6.80-9.20) | 0.602 |
| SBP (mmHg) | 105±15 (101-108) | 105±16 (98-112) | 105±14 (100-109) | 0.925 |
| DBP (mmHg) | 67±10 (65-70) | 67±11 (62-72) | 67±9 (64-70) | 0.959 |
| APACHE II score | 9.93±3.78 (8.97-10.89) | 9.30±3.4 (7.81-10.79) | 10.30±3.9 (9.02-11.59) | 0.317 |
| HbA1c (%) | 12.39±3.04 (11.62-13.17) | 12.94±3.33 (11.50-14.38) | 12.08±2.87 (11.14-13.00) | 0.283 |
| Urea (mg/dl) | 48.18±39.54 (38.14-58.23) | 33.72±22.54 (23.97-43.47) | 56.72±44.89 (42.16-71.27) | 0.026* |
| Creatinine (mg/dl) | 1.09±0.68 (0.92-1.27) | 0.81±0.50 (0.59-1.02) | 1.27±0.73 (1.03-1.50) | 0.010* |
| Initial plasma glucose (mg/dl) | 537.27±149.56 (499.29-575.26) | 546.52±120.89 (494.24-598.80) | 531.82±165.42 (478.20-585.44) | 0.712 |
| Sodium (Na) | 132.29±5.79 (130.81-133.76) | 132.9±6.0 (130.35-135.55) | 132.0±5.7 (130.05-133.74) | 0.491 |
| Potassium (K) | 4.11±0.76 (3.92-4.31) | 3.96±0.76 (3.63-4.29) | 4.20±0.76 (3.96-4.45) | 0.224 |
| PH | 7.05±0.16 (7.01-7.10) | 7.07±0.18 (6.99-7.15) | 7.05±0.15 (7.00-7.10) | 0.658 |
| Bicarbonate (HCO₃) | 6.37±3.51 (5.48-7.27) | 7.18±4.15 (5.38-8.97) | 5.90±3.03 (4.92-6.89) | 0.169 |
| Lactate at admission | 2.86±1.63 (2.45-3.28) | 3.06±2.06 (2.17-3.95) | 2.74±1.33 (2.31-3.18) | 0.468 |
| Lactate at discharge | 1.35±0.50 (1.22-1.48) | 1.38±0.66 (1.09-1.67) | 1.33±0.38 (1.21-1.46) | 0.718 |
| Precipitants of DKA | | | | |
| Infection, *n* (%) | 34 (55) | 7 (30) | 27 (70) | 0.004* |
| New onset, *n* (%) | 17 (27) | 8 (35) | 9 (23) | 0.383 |
| Insulin withdrawal, *n* (%) | 22 (36) | 12 (52) | 10 (26) | 0.054 |
| Metformin use, *n* (%) | 15 (24) | 2 (9) | 13 (33) | 0.029* |
| Severity of DKA | | | | |
| Mild, *n* (%) | 16 (26) | 9 (39) | 7 (18) | 0.079 |
| Moderate, *n* (%) | 21 (34) | 6 (26) | 15 (39) | 0.409 |
| Severe, *n* (%) | 25 (40) | 8 (35) | 17 (44) | 0.596 |
| Complications | | | | |
| Neuropathy, *n* (%) | 35 (56) | 6 (26) | 29 (74) | 0.000* |
| Nephropathy, *n* (%) | 9 (15) | 2 (9) | 7 (18) | 0.464 |
| Retinopathy, *n* (%) | 6 (10) | 1 (4) | 5 (13) | 0.398 |
| Lactic acidosis, *n* (%) | 34 (55) | 12 (52) | 22 (56) | 0.796 |
| Significant lactic acidosis, *n* (%) | 10 (16) | 5 (22) | 5 (13) | 0.478 |
| Morbidity | | | | |
| AKI, *n* (%) | 13 (21) | 2 (9) | 11 (28) | 0.106 |
| Hypotension, *n* (%) | 9 (15) | 4 (18) | 5 (13) | 0.712 |
| T1RF | 9 (15) | 2 (9) | 7 (18) | 0.464 |
| Other respiratory, cardiac and cardiovascular complications and cerebral edema. | 0 | 0 | 0 | |
| Mortality | 0 | 0 | 0 | |

Categorical data are shown as %; continuous variables are shown as mean±standard deviation. TG, Triglycerides; HDL, high density lipoproteins; LDL, low density lipoproteins; *n*, number of patients; CAD, coronary artery disease; AKI, acute kidney injury; CKD, chronic kidney disease; T1RF, type 1 respiratory failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval; *significant

(*P*=0.006) and lower systolic blood pressure (*P*=0.015) which were statistically significant [Table 2]. Comparison of patients with low-lactate (<5 mmol/l) and high-lactate (≥5 mmol/l) for different variables is given in Table 3. Although the higher

**Table 2: Comparative analysis of demographic, clinical, biochemical and complications of patients with lactate level ≥2.5 mmol/l and patients with lactate <2.5 mmol/l**

| Variables | DKA group with lactate ≥2.5 mmol/l (*n*=35) (mean±SD) 95% CI | DKA group with lactate <2.5 mmol/l (*n*=27) (mean±SD) 95% CI | *P* |
|---|---|---|---|
| Demography and Anthropometric characteristics | | | |
| Age (years) | 28.14±17.73 (22.05-34.23) | 24.18±13.87 (18.69-9.67) | 0.343 |
| BMI (kg/m²) | 18.95±4.27 (17.43-20.46) | 20.85±6.43 (18.25-23.45) | 0.179 |
| Clinical and biochemical characteristics | | | |
| T1DM: Others including T2DM, *n* (%) | 31:3 (91:9) | 24:4 (86:14) | 0.610 |
| Age at onset (years) | 25.00±17.60 (18.95-31.04) | 21.07±13.29 (15.81-6.33) | 0.338 |
| Duration of DM (years) | 3.14±3.38 (1.97-4.30) | 3.11±4.29 (1.41-4.81) | 0.974 |
| Hospital stay (days) | 7.57±3.28 (6.44-8.70) | 8.11±4.34 (6.39-9.83) | 0.579 |
| Initial plasma glucose (mg/dl) | 590±150 (538-642) | 468±117 (421-514) | 0.000* |
| SBP (mmHg) | 103±18 (98-110) | 106±9 (102-110) | 0.015* |
| DBP (mmHg) | 67±10 (63-70) | 68±9 (64-72) | 0.584 |
| APACHE II score | 10.42±4.28 (8.95-11.90) | 9.29±2.95 (8.12-10.46) | 0.245 |
| PH | 7.02±0.16 (6.96-7.07) | 7.11±0.15 (7.04-7.16) | 0.035* |
| Sodium (Na) | 131.97±5.93 (130-134) | 132.70±5.68 (130-135) | 0.626 |
| Potassium (K) | 4.21±0.84 (3.92-4.50) | 3.99±0.64 (3.73-4.24) | 0.269 |
| Bicarbonate (HCO$_3$) | 5.42±3.28 (4.30-6.55) | 7.61±3.48 (6.23-8.98) | 0.014* |
| Lactate | 3.79±1.65 (3.21-4.34) | 1.67±0.40 (1.54-1.83) | 0.000* |
| Severity of DKA | | | |
| Mild, *n* (%) | 6 (18) | 10 (36) | 0.092 |
| Moderate, *n* (%) | 9 (27) | 12 (43) | 0.191 |
| Severe, *n* (%) | 19 (66) | 6 (21) | 0.006* |
| Metformin use, *n* (%) | 5 (15) | 10 (36) | 0.135 |
| Complications | | | |
| Neuropathy, *n* (%) | 22 (65) | 13 (46) | 0.200 |
| Nephropathy, *n* (%) | 4 (12) | 5 (18) | 0.719 |
| Retinopathy, *n* (%) | 2 (6) | 4 (14) | 0.396 |
| Morbidity | | | |
| AKI, *n* (%) | 4 (14) | 9 (27) | 0.350 |
| Hypotension, *n* (%) | 7 (21) | 2 (7) | 0.166 |
| Respiratory, cardiac and cardiovascular complications and cerebral edema. | 0 | 0 | |
| Mortality | 0 | 0 | |

Categorical data are shown as %; continuous variables are shown as mean±standard deviation. CAD, coronary artery disease; AKI, acute kidney injury; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval; *Significant

lactate group tended to have higher IPG, lower bicarbonate level and longer duration of diabetes, these variables were not statistically significant between the two groups. The average hospital stay in patients with significant LA was 8.90 ± 3.72 days versus 7.59 ± 3.76 days in the rest of the cohort (*P* = 0.319). Patients in the two groups had almost similar frequency of complications and precipitants for DKA. Comparing children and adolescents (age <20 years) and adults (age >20 years) in the study group, revealed younger age group had lower urea (*P* = 0.026) and creatinine level (*P* = 0.01), where as adults had higher frequency of neuropathy (*P* = 0. 001). Infection was the most common precipitant for DKA in adult, which was statistically significant (*P* = 0.006). There were no co-morbidities (previously described) or death recorded in the studied cohort. Metformin use was documented in 24% of the study cohort with use particularly common in patients diagnosed with T2DM; however, it was also seen in patients

with T1DM who were obese and had features of insulin resistance. The comparison of various characteristics between metformin users and non-users is given in Table 4.

A statistically significant direct association between lactate levels with IPG (*r* = 0.499, *P* = 0.001) and APACHE II score (*r* = 0.490, *P* = 0.002) was found. The relationship of lactate with IPG-remained significant (*r* = 0.572, *P* = 0.002) after adjustment for severity of illness using the APACHE II score, creatinine, acute kidney injury (AKI) and hypotension. There was statistically significant inverse association between lactate levels with systolic blood pressure (SBP) (*r* = –0.326, *P* = 0.003), pH (*r* = –0.492, *P* = 0.002) and severity of DKA (*r* = –0.515, *P* = 0.001). A statistically significant association was found between IPG [odds ratio (OR) = 1.26; 95% confidence interval [CI], 1.00–1.52), APACHE-II score (OR = 1.35; 95% CI, 1.06–1.72), and development of LA. At discharge, lactic acid level was normal in all patients.

## Table 3: Comparative analysis of patients with lactate level >5 mmol/l and patients with lactate <5 mmol/l

| Variables | DKA group with lactate ≥5 mmol/l (*n*=10) (mean±SD) 95% CI | DKA group with lactate <5 mmol/l (*n*=52) (mean±SD) 95% CI | P |
|---|---|---|---|
| Age (years) | 22.30±15.47 (11.23-33.37) | 27.21±16.31 (22.67-31.75) | 0.383 |
| Duration of DM (years) | 4.60±3.59 (2.02-7.17) | 2.84±3.78 (1.79-3.90) | 0.181 |
| Hospital stay (days) | 8.90±3.72 (6.23-11.56) | 7.59±3.76 (6.54-8.64) | 0.319 |
| Initial plasma glucose (mg/dl) | 627±97 (557-695) | 520±152 (477-562) | 0.038* |
| SBP (mmHg) | 90±19 (76-103) | 108±11 (105-111) | 0.000* |
| DBP (mmHg) | 60±7 (54-65) | 69±10 (66-71) | 0.015* |
| APACHE II score | 12.80±4.34 (9.69-15.90) | 9.38±3.44 (8.4210.34) | 0.008* |
| PH | 6.94±0.13 (6.85-7.04) | 7.08±0.15 (7.03-7.12) | 0.014* |
| Bicarbonate ($HCO_3$) | 5.28±3.51 (2.76-7.79) | 6.59±3.51 (5.61-7.56) | 0.284 |
| Lactate | 6.04±1.35 (3.21-4.26) | 2.25±0.71 (2.81-4.76) | 0.000 |
| Severity of DKA | | | |
| Mild, *n* (%) | 1 (10) | 15 (29) | 0.430 |
| Moderate, *n* (%) | 1 (10) | 20 (38) | 0.143 |
| Severe DKA, *n* (%) | 8 (80) | 17 (33) | 0.007* |
| Metformin use, *n* (%) | 2 (20) | 13 (25) | 0.735 |
| Morbidity | | | |
| AKI, *n* (%) | 3 (30) | 10 (19) | 0.424 |
| Hypotension, *n* (%) | 4 (40) | 5 (10) | 0.034* |
| Respiratory, cardiac and cardiovascular complications, and cerebral edema. | 0 | 0 | |
| Mortality | 0 | 0 | |

Categorical data are shown as %; continuous variables are shown as mean±standard deviation. CAD, coronary artery disease; AKI, acute kidney injury; SBP; systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval; * Significant

## Table 4: Comparative analysis between metformin versus non-metformin users

| DKA group (*n*=62) | DKA group on metformin (*n*=15) (mean±SD) | Non-metformin users (*n*=47) (mean±SD) | P |
|---|---|---|---|
| Age | 34.80±15.76 | 23.74±15.50 | 0.02* |
| HbA1C | 12.39±2.73 | 12.40±3.17 | 0.99 |
| Urea | 44.33±24.65 | 49.41±31.25 | 0.66 |
| Creatinine | 1.17±0.90 | 1.07±0.60 | 0.63 |
| Initial plasma glucose | 488±120 | 522±156 | 0.15 |
| APACHE score | 10.00±3.20 | 9.91±3.98 | 0.94 |
| SBP | 104±10.0 | 105±16 | 0.68 |
| DBP | 66±11 | 67±10 | 0.71 |
| Hypotension | 33.3 (3) | 66.7 (6) | 0.44 |
| Lactate at admission | 2.50±1.37 | 2.97±1.70 | 0.36 |
| Lactate at discharge | 1.13±0.27 | 1.42±0.54 | 0.48 |
| Severity of DKA | | | |
| Mild | 25 (4) | 12 (75) | 0.93 |
| Moderate | 23.8 (5) | 76.2 (16) | 0.96 |
| Severe | 24 (6) | 76 (19) | 0.97 |

Categorical data are shown as %; continuous variables are shown as mean±standard deviation. CAD, coronary artery disease; AKI, acute kidney injury; SBP, systolic blood pressure; DBP, diastolic blood pressure; * significant

## DISCUSSION

LA is a high anion gap metabolic acidosis (anion gap >10) with a variable cut-off level of blood lactate concentration in different studies, ranging from ≥2.5 mmol/l in few studies[5,6,17] to >5.0 mmol/l (normal 0.4–1.2) in many other studies[18,19] in addition to the other criteria's.[20–23]

Elevated lactate is encountered in a multitude of clinical conditions and disease states, and may be due to either hypoperfusion and or hypoxemia or causes other than hypoxia/hypoperfusion. The use of lactate as a clinical prognostic marker was first suggested in 1964 by Broder and Weil when they observed in patients with undifferentiated shock that a lactate excess of >4 mmol/l was associated with poor outcomes.[24] Since then lactate levels in clinical practice are often used as a marker of illness severity and predictor of response to therapeutic interventions in different disease states especially in critical conditions. However, elevated

lactate levels in DKA or its association with disease severity have not received much attention. The present study tried to look into the role and importance of elevated lactate levels in patients with DKA, which is a relatively common finding than traditionally appreciated.[5]

The present study demonstrated the significant presence of LA in DKA which is in accordance with the available literature.[5,6,25] The prevalence of LA (lactate ≥2.5 mmol/l) among the study cohort was found to be 55% with significant LA (≥5 mmol/l) seen in 16%. Our results are similar to the results documented in the literature. A study involving 68 patients with DKA found the prevalence of LA of 68% with 40% of patients among them, having lactate levels >4 mmol/l.[5] In another study involving 92 pediatric patients with DKA, LA (≥2.5 mmol/l) was seen in 63.7% patients thus demonstrating significant presence of LA among patients with DKA.[6] In one more study, 14 patients among 32 were found to have LA with lactate levels >2.5 mmol/l and seven had lactate >4 mmol/l.[25] Taken together, these findings suggest that LA in DKA is a common finding than previously appreciated.

Several pathophysiological mechanisms are thought to be responsible for high levels of lactate in patients with DKA. Inadequate tissue perfusion and oxygenation, which is seen in patients presenting with DKA is considered to be important mechanisms responsible for elevated lactate values in patients with DKA.[26–28] In our study cohort, lactate levels were significantly associated with higher APACHE II score, lower pH and lower blood pressure including SBP and DBP. This suggests that inadequate tissue perfusion and oxygenation, which is seen with severe dehydration and hypovolemia, found commonly in DKA, may have an important role in elevating lactate levels in DKA.

However, a positive correlation of lactate with glucose as seen in our study and a negative correlation between lactate and thiamine levels in a number of studies raises the possibility that elevated lactate in DKA may not only be due to hypoperfusion, but may also be the result of an altered metabolic profile commonly seen in this condition.[5,25] In the present study, hypotension was documented only in nine patients (in four patients of significant LA group and in five patients of LA group) despite the significant prevalence of LA ($n = 34$) among the study cohort. It signifies the importance of factors other than hypotension in the occurrence of LA, although hypotension was significantly more common in the significant LA group. Metabolic derangements and hyperglycemia present in DKA are thus the factors that might contribute to the elevated lactate levels.[14,25–27] The role of metabolic derangement or altered glucose metabolism in causing elevated lactate levels in the DKA provides a plausible explanation for the absence of an adverse outcome in the face of LA. The positive correlation of IPG with lactate as seen in our patients support the possible role of hyperglycemia, in causing lactate elevation, possibly via glyoxalase pathway involving intermediate metabolite methylglyoxal formation and its subsequent conversion into

lactate.[7] This relationship of IPG with lactate demonstrated in our study is in agreement with the findings reported in literature by other investigators.

The role of metformin in pathogenesis of LA in patients with diabetes mellitus is complex, especially in the presence of other factors known to cause LA. Different studies which have studied the role of metformin have documented conflicting results as far as the risk of LA is concerned.[29,30] Metformin has been found to reduce hepatic gluconeogenesis by inhibiting mitochondrial oxidative phosphorylation, for which lactate is a substrate, thus has the potential to cause rise in LA level. Our study did not find any significant differences in severity of LA with metformin use. However, the lack of facilities for measurement of metformin concentration undermines our argument of absence of any significant role of metformin in LA. Also, it was difficult to differentiate between metformin independent LA (in which metformin cannot possibly be implicated) from other conditions associated with metformin use including metformin-induced LA and metformin-associated LA a condition in which metformin is among the factors to cause LA.

At present, only few studies have looked into the clinical significance of lactate levels in DKA or its role as a marker of severity of the disease in contrast to its role in other critical states.[8–15] Despite the high prevalence of LA in patients with DKA, our results suggest that LA is not a predictor of worse clinical outcomes in DKA as was demonstrated in other studies.[5,6] The 'alternative fuel hypothesis'[7] which postulated that lactate may be used as a substrate for gluconeogenesis in a state of relative glucose deficiency as a result of insulin deficiency, is a possible explanation why the outcome of LA in DKA could be more favorable than would be anticipated based on the relationship of elevated lactate levels with clinical outcomes in other critical conditions. This mechanism possibly provides vital tissues (e.g., heart and brain) an alternative oxidizable substrate (lactate) when glucose is unavailable as a result of the hypoinsulinemic state of DKA.[7]

Our results demonstrate that patients with significant LA had significantly lower age of onset of diabetes, lower total serum cholesterol, serum HDL cholesterol, lower pH, and severe DKA. However, the presence of significant LA was not associated with longer hospital stay or complications usually associated with DKA including respiratory failure, cardiac arrhythmia, and cerebral edema. Similarly, there was no mortality recorded during the study. These results are similar to a previous study that demonstrated a low incidence of mortality in the presence of LA in DKA.[5] These findings give credence to the suggestion that elevated lactate in DKA may not be predictive of illness severity, mortality and other comorbidities but rather an adaptation for providing alternate fuel substrate to the important organs in the presence of hypoinsulinemic state.

The novelty of this study is the demonstration of a significant presence of LA in the patients with DKA and its absence as a

predictive marker of severity of illness, significant morbidity and mortality in contrast to its role in critically ill patients of other etiologies.

## The strengths of our study included

1. Adequate sample size including both children and adults, thus helping us to study the prevalence, importance and impact of LA on different age groups.
2. Prospective nature of the study and a detailed clinical and biochemical assessment of the study cohort.

## Limitations of the study

1. Absence of mortality, morbidity and requirement of ICU care in significant number of patients in the study cohort during the study period limits the power to detect a meaningful association with the presence of LA.
2. Lack of detection of type of lactate present and elucidation of intermediate products leading to utilization of lactate as an alternate oxidizable substrate for gluconeogenesis.
3. Lack of means to demonstrate the actual contribution of lactate in acidosis during DKA.

## Conclusion

A higher lactate level among the patients with DKA is a very common and significant finding. There was no significant difference in severity of LA with metformin use. Absence of association of elevated lactate with severity of illness, DKA complications, and mortality is an important finding of this study, thus negating the possible role of lactate as a marker of severity of illness and mortality as demonstrated in multitude of other critical states. However, elevated lactate may be an adaptation to provide an alternate substrate for metabolism to the vital organs like heart, liver, and kidneys, in the presence of hypoinsulinemic state characteristic of DKA state. The study results provide rationale for large well-designed studies evaluating in-depth clinical relationship of lactate in DKA.

## Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

## Conflicts of interest

There are no conflicts of interest.

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