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RESEARCH: PATHOPHYSIOLOGY

Hyperlactatemia in diabetic ketoacidosis

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Abstract

Aims: The study examined the prevalence and degree of lactate elevation in diabetic ketoacidosis, and explored which biochemical abnormalities predicted L-lactate levels.

Methods: We reviewed episodes of diabetic ketoacidosis from 79 diabetes patients (one episode per patient). Separate univariate linear regression models were specified to predict lactate level from each of nine biochemical variables. Significant predictors from the univariate models were included in a final multivariate linear regression model to predict lactate levels.

Results: Mean (*SD*) lactate level was 3.05 (1.66) mmol/L; about 65% of patients had lactate levels >2 mmol/L. In the final multivariate linear regression model ($R^2 = 0.45$), higher lactate levels were associated with greater hydrogen ion concentration (standardised $\beta = .60$, $t = 4.16$, $p < 0.0001$), higher blood glucose (standardised $\beta = .28$, $t = 2.67$, $p = 0.009$) and lower glomerular filtration rate estimated from creatinine (standardised $\beta = −.23$, $t = 2.29$, $p = 0.025$). Bicarbonate, beta-hydroxybutyrate, body mass index, mean arterial pressure and calculated osmolality were not significant predictors of lactate level. There were three distinct patterns of lactate levels with treatment of diabetic ketoacidosis: group 1 = gradual decline, group 2 = initial increase and then decline and group 3 = initial decline followed by a transient peak and subsequent decline.

Conclusions: Elevated lactate level is the norm in patients with diabetic ketoacidosis. Higher blood glucose levels and higher hydrogen ion concentrations are related to greater lactate. With treatment, there are different patterns of decline in lactate levels.

KEYWORDS
blood glucose, diabetic ketoacidosis, hydrogen ion, lactate

1 | INTRODUCTION

It is frequently assumed that elevated lactate levels in diabetic ketoacidosis reflect severe illness, hypotension and peripheral circulatory failure. In the septic shock literature, elevated lactate levels are associated with increased mortality.[1,2] Infections are responsible for 25%–50% of reported cases of diabetic ketoacidosis,[3] and it is very reasonable to pursue evaluation for sepsis when lactate levels are elevated. Assumptions that elevated lactate levels in a patient with diabetic ketoacidosis are due to tissue hypoxia or sepsis and associated with increased risk of death may not be true. In an analysis of 68 patients who presented to the emergency room with diabetic ketoacidosis,

elevated L-lactate level was not associated with increased length of stay in the intensive care unit or increased mortality.[4] Additionally, a significant body of experimental and human studies show that the increase in lactate level in severe illness is most likely due to increased aerobic glycolysis and not tissue hypoxia.[5]

We have observed that mild to moderate increases in lactate levels occur in diabetic ketoacidosis. The purpose of this report is to examine the prevalence and degree of lactate elevation in cases of diabetic ketoacidosis admitted to a tertiary centre hospital over 3 years. To better understand the pathophysiological mechanisms underlying changes in lactate levels, we examined which biochemical abnormalities in diabetic ketoacidosis predict elevated lactate levels.

2 | METHODS

2.1 | Data collection

Medical records of patients with diabetic ketoacidosis admitted to the University of California, San Francisco Medical Center in 2016–2019 were reviewed for all episodes of diabetic ketoacidosis (presenting episode as well as previous ones) requiring hospital admission. The inclusion criteria for analysis were age ≥18 with type 1a or type 1b diabetes, an estimated GFR >60 ml/min/1.73 m^2 (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation), and presenting with diabetic ketoacidosis, defined by a venous pH < 7.3 and an elevated beta-hydroxybutyrate level >3 mmol/L on the first venous blood gas measured. Patients with organ transplants, or who used drugs that might affect the results, such as glucocorticoids, were excluded. Patients who might have had alcoholic ketoacidosis were excluded. Patients with type 1 diabetes who were taking medicines typically prescribed for type 2 diabetes (e.g. metformin, sodium glucose co-transporter 2 [SGLT2] inhibitors and glucagon-like peptide 1 receptor agonists) were excluded. Patients who did not have venous blood gas measured at admission and had no lactate measurement were also excluded.

Venous blood gas was used for the L-lactate determination, which was performed on a radiometer blood gas analyser (ABL90 Flex plus). The bicarbonate level was calculated from measured pCO_2 and pH using the Henderson-Hasselbalch equation $HCO_3^- = 0.23*pCO_2*10$ (pH – 6.095).[6] Beta-hydroxybutyrate determinations were made using the Stanbio enzymatic (D-3-hydroxybutyrate dehydrogenase) assay. The hydrogen ion concentration was calculated from the pH using the equation

pH = −log[H+]. The CKD-EPI equation was used to estimate the GFR from the serum creatinine.[7] Serum osmolality was calculated using the equation $(2 \times (Na + K)) + (BUN$ mmol/L) + (glucose mmol/L). Mean arterial pressure was calculated as diastolic blood pressure + 1/3(systolic blood pressure − diastolic blood pressure).

2.2 | Data analyses

Descriptive statistics, including means, standard deviations, skewness and kurtosis, were used to summarise the data. All variables were found to be normally distributed and did not require transformation prior to regression analysis.

We explored biochemical factors associated with lactate levels in two steps. First, separate univariate linear regression models were specified to predict lactate level from each of our nine biochemical variables: hydrogen ion concentration, blood glucose, creatinine (both serum creatinine and estimated glomerular filtration rate), bicarbonate concentration, beta-hydroxybutyrate concentration, body mass index, mean arterial pressure and calculated osmolality. Second, a final multivariate linear regression model was specified with lactate level as the dependent variable and all independent variables that were significant predictors in separate univariate analyses.[8] SPSS v. 19 software was used to analyse the data.

Novelty statement

What is already known?

- Previous research shows that some patients with diabetic ketoacidosis appear to have elevated lactate levels.

What has this study found?

- This study found that elevated lactate levels are the norm and not the exception in patients with diabetic ketoacidosis. The hyperlactatemia is not due to hypoxia or sepsis. Glucose levels, hydrogen ion concentrations and creatinine levels predict the degree of elevation of lactate levels.

What are the clinical implications of the study?

- In cases of elevated lactate levels, it may be unnecessary to perform extensive evaluation and empirically treat for sepsis, as elevated lactate may not be due to sepsis or to hypoperfusion and is not associated with poor outcomes.

2.3 | Ethical considerations

The collection of data for this analysis was approved by the University of California, San Francisco Committee on Human Research (Institutional Review Board Study #20-30318).

3 | RESULTS

A total of 153 individual episodes of diabetic ketoacidosis occurred in 79 patients, 40 men and 39 women. Twenty episodes in 16 patients were excluded due to various exclusion criteria. Patients' ages ranged from 18 to 89 years (median = 26) at the time of the diabetic ketoacidosis episode. The diagnosis of type 1 diabetes was based on a history of disease onset in childhood or young adulthood and treatment with insulin. Antibody testing was available in 48 of the 79 patients. Nine patients had negative antibody titres (type 1b), but their phenotype and insulin requirements were the same as patients who were antibody positive (type 1a). Mean (SD) body mass index was 22.40 (5.76) kg/m^2.

For patients having multiple episodes of ketoacidosis, only data from the first admission were used in the analysis of the biochemical factors predicting lactate levels. Each patient therefore had one record in the dataset for the biochemical analyses ($n = 79$).

Fifty-three of the 79 episodes (69%) occurred because of missed insulin doses, including a few patients who ran out of insulin. In eight episodes, no cause for the ketoacidosis was apparent. Eight episodes occurred in patients on insulin pumps. Blood cultures were available for 47 episodes (59%), and only one was positive. This patient had skin boils and had one positive culture for *Enterococcus faecalis*.

Table 1 summarises biochemical and clinical characteristics of patients with diabetic ketoacidosis. Almost all patients with diabetes ketoacidosis had elevated levels of lactate. The mean (SD) lactate level for the cohort was 3.05 (1.66) mmol/L. Fifty-one patients (64.6%) had a lactate value ≥2 mmol/L, a level that is recommended as a preferred cut-off value for septic shock criteria.[2,9] Nineteen patients (24.1%) had a lactate value ≥4 mmol/L.

Thirty-six of the 79 episodes had venous gas and lactate data after the resolution of the acidosis. Mean (SD) lactate level at the presentation of diabetic ketoacidosis for these episodes was 3.69 (0.31) mmol/L, which declined to 1.14 (0.09) after treatment ($p < 0.001$).

In univariate regression analyses, body mass index, mean arterial pressure and calculated osmolality were not significant predictors of lactate level. These were excluded from the final multivariate linear regression model. Both creatinine variables were significant predictors, but were highly correlated with each other, so only estimated glomerular filtration rate (as the more significant predictor) was included in the final model.

Table 2 presents results of the final multivariate linear regression model. Significant predictors of lactate level were hydrogen ion concentration (standardised $\beta = .60$, $t = 4.16$, $p < 0.0001$), blood glucose (standardised $\beta = .28$, $t = 2.67$, $p = 0.009$), and estimated glomerular filtration rate estimated from creatinine (standardised $\beta = -.23$, $t = 2.29$, $p = 0.025$). Bicarbonate concentration (standardised $\beta = .33$, $t = 1.78$, $p = 0.079$) and beta-hydroxybutyrate concentration (standardised $\beta = .17$, $t = 1.29$, $p = 0.201$) were not significant predictors. The overall model fit was $R^2 = 0.45$. Figure 1 shows the fitted regression lines of lactate level (mmol/L) with hydrogen ion concentration (Figure 1a), blood glucose level (mmol/L) (Figure 1b) and estimated glomerular filtration rate (ml/min/1.73 m^2) (Figure 1c). A 1.00 mmol/L increase in blood glucose was

TABLE 1 Clinical and biochemical characteristics of patients with diabetic ketoacidosis ($N = 79$)

	Mean (SD)	Range
Lactate (mmol/L)	3.05 (1.66)	0.80–7.60
Hydrogen ion concentration (H$^+$)	$7.58\ (2.19) \times 10^{-8M}$	$5.01–15.14 \times 10^{-8M}$
Blood glucose (BG) (mmol/L)	31.18 (11.17)	8.83–83.94
Venous gas pH	7.14 (0.12)	6.82–7.30
Estimated glomerular filtration rate (eGFR) (ml/min/1.73 m^2)	80.62 (33.03)	15–120
Serum creatinine (mmol/L)	103.09 (48.18)	38.01–293.49
Beta-hydroxybutyrate (mmol/L)	9.35 (2.90)	3.59–19.70
Bicarbonate (HCO$_3^-$) (mmol/L)	10.59 (4.79)	2.00–20.00
Osmolality (mOsm/kg)	314.31 (15.79)	287.71–382.20
Body mass index (BMI) (kg/m^2)	23.01 (4.44)	14.41–36.26
Mean arterial pressure (MAP) (mmHg)	96.51 (17.15)	65.00–147.33

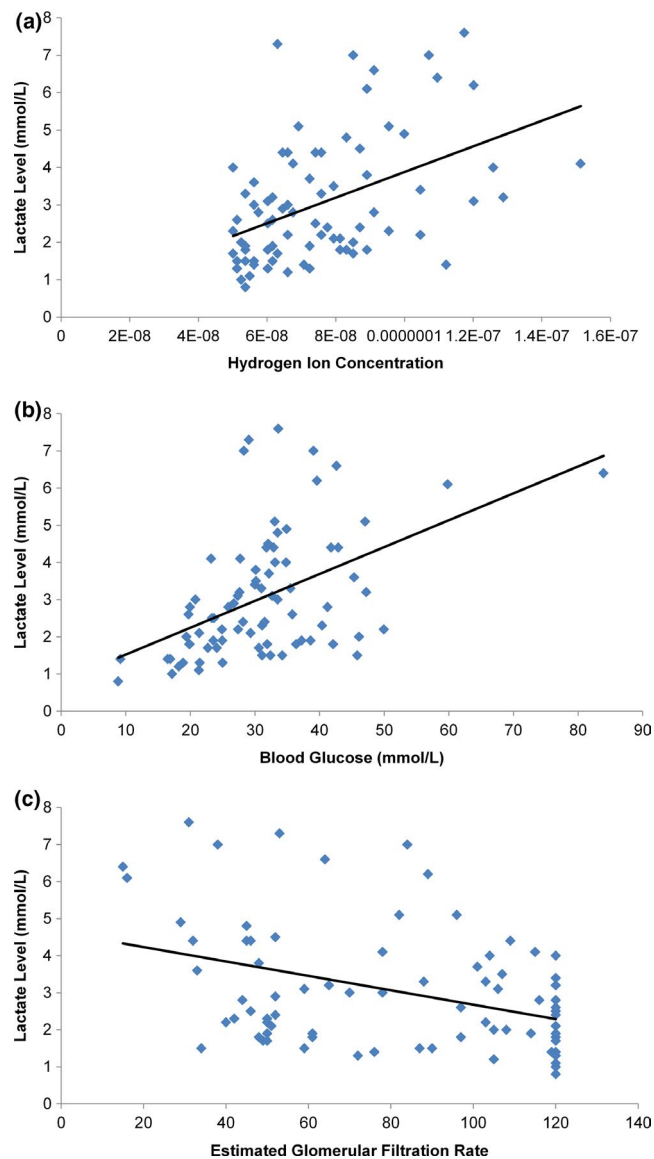| Independent variables	Unstandardised β	Standardised β	t	p Value
Hydrogen ion concentration	45104784.89	.60	4.16	<0.0001
Blood glucose	.041	.28	2.67	0.009
Glomerular filtration rate	−.012	−.23	2.29	0.025
Bicarbonate concentration	.114	.33	1.78	0.079
Beta-hydroxybutyrate concentration	.098	.17	1.29	0.201

FIGURE 1 Fitted linear regression lines of lactate level with (a) hydrogen ion concentration, (b) blood glucose level and (c) estimated glomerular filtration rate

associated with an average increase of 0.04 (95% CI: 0.01 to 0.07, $p = 0.009$) mmol/L increase in lactate, assuming other variables remain constant.

In a number of episodes of diabetic ketoacidosis, multiple blood gas measurements were recorded during treatment. Diabetes ketoacidosis episodes with three or more lactate values ($n = 27$) were reviewed to assess change over time. Several patterns of lactate levels occurred during treatment. In 10 patients, treatment of diabetic ketoacidosis caused a gradual decline in lactate levels (Figure 2a). However, in some cases ($n = 10$) there was an initial increase in lactate level and then a decline (Figure 2b). In still other patients ($n = 7$), there was an initial decline in lactate levels, followed by a transient second peak (Figure 2c).

An occasional patient with type 1 diabetes was misdiagnosed as having type 2 diabetes and prescribed metformin. There was also off-label use of SGLT2 inhibitors to control postprandial hyperglycaemia. In supplementary analyses, we reviewed the impact of metformin or SGLT2 inhibitors on the hyperlactatemia. We reviewed biochemical data of two type 1 patients with diabetic ketoacidosis who were also on metformin. The first patient's presenting glucose was 46.2 mmol/L, pH 7.19, beta-hydroxybutyrate 12.28 mmol/L and lactate 6.4 mmol/L. The second patient's presenting glucose was 37.4 mmol/L, pH 7.27, beta-hydroxybutyrate 5.04 mmol/L and lactate 3.3 mmol/L. These lactate levels were higher compared to the mean (SD) cohort value of 3.05 (1.66). Type 1 patients who use SGLT2 inhibitors to control postprandial hyperglycaemia are at higher risk for euglycemic ketoacidosis. We reviewed the biochemical data for one such patient who was taking canagliflozin. The blood glucose level was 11.6 mmol/L, pH 7.11, beta-hydroxybutyrate 6.12 mmol/L and lactate 1.8 mmol/L, a value lower than the mean cohort level.

4 | DISCUSSION

We evaluated lactate levels in all patients with type 1 diabetes who presented with diabetic ketoacidosis to determine the prevalence and degree of lactate elevation. We also examined predictors of lactate elevation as well as changes in lactate levels with treatment. We found that
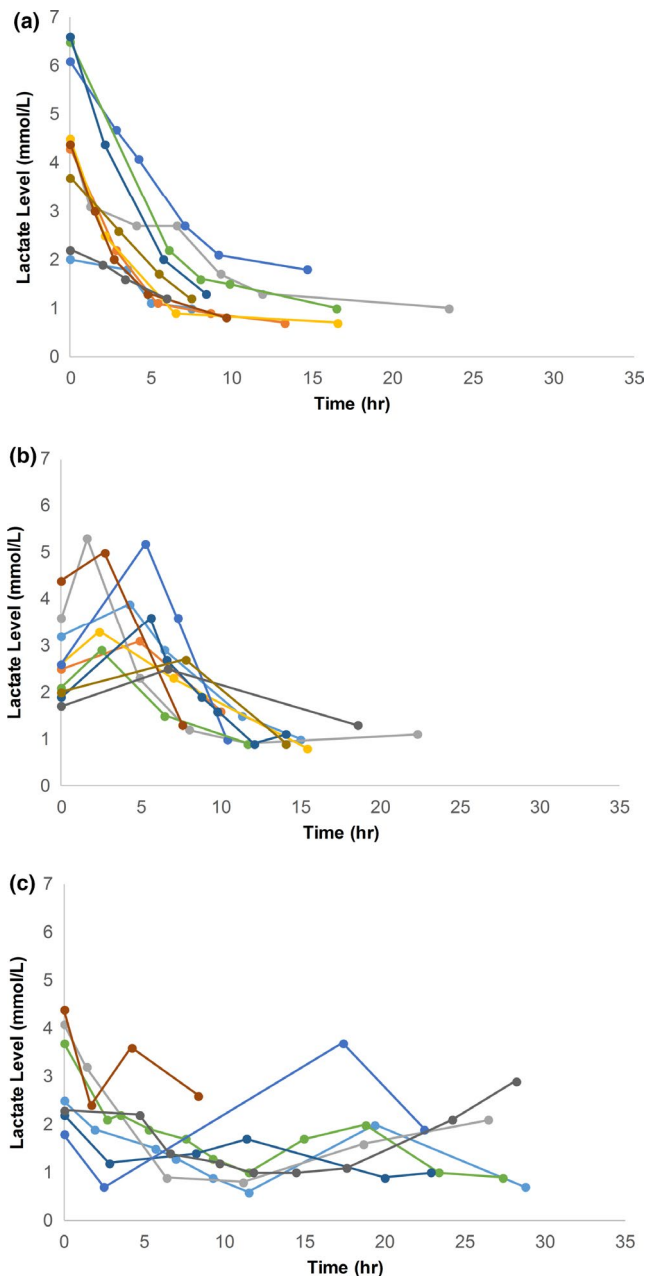
FIGURE 2 Patterns of change in lactate levels with treatment: (a) steady decline, (b) initial rise and then decline, and (c) initial decline but then an increase before declining again

elevated lactate in these patients is the norm rather than the exception. In our cohort, about 65% of patients had lactate levels of ≥2 mmol/L, and about 24% had lactate levels of ≥4 mmol/L. A previous report by Cox et al. observed that 68% had lactate levels >2.5 mmol/L with 40% having lactate levels >4 mmol/L.[4] It is unclear, however, if all patients had type 1 diabetes, or if patients were excluded because they were on metformin, which could have raised lactate levels. A paediatric cohort study reported that 63.7% of patients with diabetic ketoacidosis had lactate levels of ≥2.5 mmol/L.[10]

Infection is an important precipitating factor for diabetic ketoacidosis.[3] In our cohort of patients, in whom insulin omission is the principal cause of diabetic ketoacidosis, sepsis does not appear to predict increased lactate. Blood cultures were obtained for 47 episodes of diabetic ketoacidosis (59%) and only one was positive. In the critical care literature, lactate levels >2 mmol/L are associated with increased mortality.[2,9] A study of a Turkish cohort reported that slower decline in lactate levels over the first 2 h after admission with diabetic ketoacidosis was associated with higher 30-day mortality.[11] There were no deaths in our patient cohort.

Exploring whether biochemical abnormalities in diabetic ketoacidosis could explain the increase in lactate levels, we found that higher blood glucose and hydrogen ion concentrations, as well as a lower glomerular filtration rate, were significantly associated with higher lactate.

Why might elevated glucose levels and hydrogen ion concentrations, and a lower glomerular filtration rate, be associated with increased lactate levels? The relation between glucose and lactate most likely is attributable to the fact that lactate is the inevitable consequence of glycolysis.[12] The apparent association between hydrogen ion concentration and lactate is harder to explain. We suggest that it may reflect severity of the ketosis. It is known that the increase in hydrogen ion concentration is due to loss of ketoacid anions in the urine as Na^+ or K^+ salts. Also, the influx of acetyl-CoA units from ketones inactivates the pyruvate dehydrogenase complex and inhibits the oxidation of pyruvate. Thus, severe ketosis in uncontrolled type 1 diabetes may cause both an increase in hydrogen ion concentration and an increase in lactate levels. The terminal step in glycolysis is: Pyruvate + NADH + H^+ → Lactate + NAD^+. In other words, lactate production consumes an H^+ load that is essentially stoichiometric to lactate production, and lactate cannot contribute to the acidosis.[13] It is therefore misleading to use the term lactic acidosis to describe elevated blood lactate levels in diabetic ketoacidosis. Hyperglycaemia and acidosis lead to volume depletion and acute kidney injury in diabetic ketoacidosis.[14] Thus, it is not surprising that impaired renal function is also associated with elevated lactate levels.

We found multiple patterns of change in lactate levels with treatment. Some patients had a steady decline in lactate levels, others had an initial rise followed by a decline and still others displayed an initial decline followed by a transient increase. Gradual decline and initial increase in lactate levels have been reported previously.[15] It is now well established that lactate is an important intermediate metabolite formed and utilised under fully aerobic conditions.[16] Lactate produced by glycolysis can be used as an energy source within the same cell (intracellular lactate shuttle) or it can be exported and used by

other tissue (intercellular lactate shuttle). Not only can lactate be transformed into glucose via the Cori cycle, but it is also removed by oxidation (via pyruvate and the citric acid cycle). Carbon isotope studies suggest that lactate clearance rates range from 800 to 1800 ml/min.[17,18] Our observed patterns of change in lactate may reflect the metabolic changes that occur during the treatment of diabetic ketoacidosis and the dominance of lactate production or clearance at any given time.

We note that type 1 diabetes patients with euglycemic ketoacidosis, that is, glucose levels <16.7 mmol/L,[19] have only modest elevations in lactate levels. This aligns with our analysis that higher glucose levels are associated with higher lactate levels. We report one patient with euglycemic ketoacidosis (pH = 7.11, blood glucose = 11.6 mmol/L) with a lactate level of 1.8 mmol/L. A published report of two cases of euglycemic ketoacidosis in type 1 diabetes also noted low lactate levels (case 1, glucose = 10.6 mmol/L, lactate = 0.8 mmol/l; case 2, glucose = 5.8 mmol/L, lactate = 1.6 mmol/L).[20]

Type 1 patients taking metformin who develop diabetic ketoacidosis appear to have exaggerated hyperlactatemia. We report lactate levels of 3.3 mmol/L and 6.4 mmol/L in two type 1 patients with diabetic ketoacidosis who were taking metformin. These levels were higher than the 3.05 mean value for the cohort. We propose that this may be due to the metformin-depressing lactate clearance. There is biochemical evidence, from experiments in isolated rat hepatocytes and perfused rat liver, that metformin inhibits gluconeogenesis from lactate.[21,22] In patients with type 2 diabetes, metformin use is associated with an increase in lactate levels of 0.16 mmol/L.[23] In type 2 patients with renal failure, a metformin level of 9.9 mg/L was associated with lactate levels of ≥4 mmol/L.[24]

This study has several limitations. First, the available venous blood gases and other biochemical data were limited because the tests were obtained as part of clinical care. Therefore, other factors that could influence lactate levels, such as free fatty acid levels or acetoacetate concentrations, were not available for analyses. Measured osmolality values were not available. The osmolal gap, the difference between measured and calculated osmolality, can be elevated in diabetic ketoacidosis due to an increase in acetone.[25] Second, information on the time course of the development of ketoacidosis was not available. For example, the consumption of food and fluids, and the time of the last insulin injection, could affect the biochemical data. Third, the fact that the patient population mainly acquired diabetic ketoacidosis by omitting insulin administration might introduce a bias, as these patients tend to do better.[26,27] Fourth, because the goal of this study was to examine relations between biochemical factors and lactate levels, we did not systematically explore associations between biochemical factors and other clinical outcome measures, which is a limitation. We did find a moderate correlation between lactate level and length of intensive care unit stay ($r = 0.30$, $p = 0.008$). In a clinical outcome study in a paediatric cohort, however, elevated lactate levels were not associated with increased intensive care unit or hospital stay or with mortality.[10] Fifth, the predictor variables are physiologically connected and likely interact. In mixed model analyses, using data for all 153 episodes of diabetic ketoacidosis in the 79 patients, we found evidence indicating that bicarbonate acts as a confounder (i.e. after adding bicarbonate to the model predicting lactate, a significant change in the hydrogen ion concentration point estimate of 35% occurred), and that hydrogen ion concentration and glucose levels significantly interact with each other to affect lactate levels (interaction $p < 0.0001$). These results suggest directions for future research, but should be viewed with caution, since a dataset with a larger number of unique patients is needed to determine confounds and interactions. Sixth, although there were multiple venous blood gas measurements in a limited number of participants that enabled examination of changes in lactate levels over time, the measurements were not obtained at uniform, consistent intervals during treatment. Thus, exploration of the mechanisms underlying the patterns was somewhat limited. For example, factors that could affect lactate clearance include rapidity of initial glucose lowering, timing of insulin administration and the use of dextrose containing intravenous fluids. Further research with controlled induction and treatment of diabetic ketoacidosis is needed to fully understand the mechanisms underlying lactate changes.

5 | CONCLUSION

Hyperlactatemia is pervasive in diabetic ketoacidosis, does not appear to be due to sepsis or to hypoperfusion and is not associated with poor outcomes. These findings suggest that it may be unnecessary to perform extensive evaluation and empirically treat for sepsis simply because of elevated lactate levels.

CONFLICT OF INTEREST
None declared.

AUTHORS' CONTRIBUTIONS
UM collected the data used in the analysis. UM, AAS, KW and GAB contributed to conceptualisation of the

manuscript and initiated the first draft. UM, KW, GAB and LAS revised the manuscript. AAS, UM, GAB and LAS conducted initial and/or follow-up data analyses. UM is the guarantor of this work and takes full responsibility for the integrity of the data and accuracy of the data analyses.

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