D-Lactate: A Novel Contributor to Metabolic Acidosis and High Anion Gap in Diabetic Ketoacidosis

To the Editor:

Diabetic ketoacidosis (DKA), the most common and serious acute complication of diabetes, is characterized by hyperglycemia and severe high–anion-gap metabolic acidosis with ketonemia (1). In DKA, the high anion gap is attributed largely to excessive production of blood ketone bodies, and serum \( \beta \)-hydroxybutyrate quantification is recommended for the diagnosis and monitoring of DKA (2). However, even counting of all the ketone bodies, including \( \beta \)-hydroxybutyrate, does not account for the entire anion gap, suggesting that there are additional sources of anion production in DKA.

We recently demonstrated that plasma \( \beta \)-lactate concentrations were greatly increased in DKA compared with the concentrations in diabetic patients without DKA and a healthy control group (3). Nevertheless, the clinical value of \( \beta \)-lactate measurement in metabolic acidosis, especially the contribution of \( \beta \)-lactate to the metabolic acidosis and high anion gap in DKA, is not well appreciated. We report here that decreasing \( \beta \)-lactate concentrations are associated with improved clinical situations, whereas increased lactate concentrations are associated with the severity of metabolic acidosis and high anion gap in patients with DKA.

The study included 38 diabetic patients with DKA, 42 diabetic patients without DKA, and 40 healthy controls. The institutional ethics review board of the First Affiliated Hospital of Wenzhou Medical College approved the study, and written informed consent was obtained from all study participants. For patients with DKA, blood samples were collected at the time of admission to the emergency room and following medical treatment after admission, when the patient’s condition became stabilized. Plasma \( \beta \)-hydroxybutyrate was assayed by LC-MS (3). Plasma \( \beta \)-lactate concentration was determined by an enzymatic assay kit (BioVision Corporation). Other biochemical analyses were performed on automated chemistry analyzers.

Concentrations of plasma glucose [mean (SD) 450.45 (201.80) mg/dL], \( \beta \)-hydroxybutyrate [58.41 (37.38) mg/dL], and methylglyoxal [75.72 (46.25) ng/mL] were greatly increased compared with the concentrations in diabetic patients without DKA and healthy controls (all \( P < 0.001 \)). Interestingly, plasma \( \beta \)-lactate concentrations were markedly increased in diabetic patients with DKA [3.44 (1.99) mmol/L] compared to diabetic patients without DKA [0.48 (0.56) mmol/L] and healthy controls [0.32 (0.30) mmol/L] (\( P < 0.001 \)). Increased \( \beta \)-lactate concentrations were greatly reduced following treatment [3.44 (1.99) vs 0.53 (0.35) mmol/L, \( P < 0.001 \)]. The reduction of \( \beta \)-lactate concentration was consistent with the changes in and improvement of plasma glucose [450.45 (201.80) vs 170.81 (52.43) mg/dL], \( \beta \)-hydroxybutyrate [58.41 (37.38) vs 12.49 (14.89) mg/dL], bicarbonate [13.12 (6.72) vs 21.94 (3.45) mEq/L], and anion gap [20.09 (5.80) vs 8.27 (2.69) mmol/L] following treatment (all \( P < 0.001 \)). Plasma \( \beta \)-lactate concentrations were also increased in DKA, but to a lesser degree compared to \( \beta \)-lactate concentrations.

**Fig. 1.** Correlation of plasma \( \beta \)-lactate concentrations with (A), plasma bicarbonate concentrations and (B), anion gap in DKA.
concentrations of D-lactate can in-
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emic disorders such as diabetes
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Under physiologic conditions, D-lactate is present in the human body at low concentrations (4). Blood concentrations of D-lactate are increased in diabetes, and par-
ticularly in DKA in humans (3). D-lactate is generated by degrada-
tion of methylglyoxal, an intermediate glucose metabolite, through the glyoxalase system (3, 5). High concentrations of D-lactate can in-
duce severe metabolic acidosis, re-
sulting in neurological symptoms and encephalopathy. In hyperglycemic disorders such as diabetes mellitus and DKA, methylglyoxal production is greatly increased (3, 5). Consistent with our previous finding, the increased D-lactate concentration is inversely associated with bicarbonate concentration and positively correlated with the increasing anion gap. Reduction of plasma D-lactate concentrations correlated well with improvement of bicarbonate concentrations and an-
ion gap following treatment.

In conclusion, our findings suggest a large contribution of plasma D-lactate to the metabolic acidosis and high anion gap in DKA. Inclusion of the measure-
ment of plasma D-lactate concent-
trations helps to account for the
anion gap and the severity of met-
abolic acidosis in patients with DKA. Measurement of plasma D-lactate is important in predicting the severity of DKA as character-
ized by acidosis and high anion gap and monitoring DKA progression.

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