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 D-lactate concentrations were greatly increased in DKA compared with the concentrations in diabetic patients without DKA and healthy controls (3). Nevertheless, the clinical value of D-lactate measurement in metabolic acidosis, especially the contribution of D-lactate to the metabolic acidosis and high anion gap in DKA, is not well appreciated. We report here that decreasing D-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 methylglyoxal was assayed by LC-MS (3). Plasma D-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 D-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 D-lactate concentrations were greatly reduced following treatment [3.44 (1.99) vs 0.53 (0.35) mmol/L, $P < 0.001$]. The reduction of D-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 L-lactate concentrations were also increased in DKA, but to a lesser degree compared to D-lactate concentrations.

Fig. 1. Correlation of plasma D-lactate concentrations with (A), plasma bicarbonate concentrations and (B), anion gap in DKA.
[2.60 (1.55) vs 1.21 (0.69) mmol/L, P = 0.01]. Linear regression analyses identified a significant correlation of plasma D-lactate concentration with acidosis (bicarbonate, r = −0.575, P < 0.001) and high anion gap (r = 0.593, P < 0.001) (Fig. 1). The contribution of D-lactate to acidosis and anion gap was comparable to that of β-hydroxybutyrate. The contribution of D-lactate and β-hydroxybutyrate to the high anion gap found in DKA was statistically significant (r = 0.593, P < 0.001, and r = 0.642, P < 0.001, respectively).

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 particularly in DKA in humans (3). D-lactate is generated by degradation of methylglyoxal, an intermediate glucose metabolite, through the glyoxalase system (3, 5). High concentrations of D-lactate can induce severe metabolic acidosis, resulting 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 anion 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 measurement of plasma D-lactate concentrations helps to account for the anion gap and the severity of metabolic acidosis in patients with DKA. Measurement of plasma D-lactate is important in predicting the severity of DKA as characterized by acidosis and high anion gap and monitoring DKA progression.

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Ninety-Minute vs 3-h Performance of High-Sensitivity Cardiac Troponin Assays for Predicting Hospitalization for Acute Coronary Syndrome

To the Editor:

In patients undergoing transcoronary ablation for septal hypertrophy, concentrations of high-sensitivity cardiac troponin T (hs-cTnT)1 increase within 15 min

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