Impaired cardiac and neurological function with mild hypophosphatemia during insulin therapy for diabetic ketoacidosis and marked improvement with phosphate supplementation: A case report

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Abstract
Insulin treatment for diabetic ketoacidosis occasionally results in hypophosphatemia, which is often mild and does not require treatment. However, we experienced a case in which intravenous insulin administration resulted in myocardial injury and altered consciousness despite mild hypophosphatemia. Phosphate replacement therapy resulted in a marked improvement in symptoms. As overlapping conditions that result in hypophosphatemia can cause severe complications after insulin therapy for diabetic ketoacidosis, even in patients with mild hypophosphatemia, physicians should pay more attention to changes in phosphate levels in patients undergoing treatment for diabetic ketoacidosis.

Introduction
Intravenous (i.v.) administration of insulin for diabetic ketoacidosis (DKA) occasionally results in hypophosphatemia. As insulin promotes glucose uptake into cells, this glucose movement induces hypophosphatemia as a result of massive phosphate shifts from the extracellular fluid into cells to produce adenosine triphosphate by oxidative phosphorylation. However, this does not usually require any particular treatment, because severe hypophosphatemia rarely occurs. We report a patient with impaired consciousness and myocardial injury in the recovery phase of DKA, despite only a slight decrease in serum phosphate levels. After phosphate replacement therapy, the patient showed remarkable improvements.

Case report
A 52-year-old man presented to International University of Health and Welfare, Ichikawa Hospital, Chiba, Japan, because of disturbed consciousness and abdominal pain. He had previously undergone 8 years of treatment for diabetes at a nearby clinic. He was currently taking metformin, dulaglutide (glucagon-like peptide-1 analog) once-weekly, 8 units of insulin lispro before meals, and 6 and 16 units of insulin degludec before breakfast and bedtime, respectively. The day before the visit, he did not take his insulin injection, because he skipped a meal as a result of nausea. He went to see a physician the next day, but the doctor referred him to our hospital because of disorientation. Blood chemistry and urine tests showed DKA with hyperglycemia, acidosis, increased β-hydroxybutyrate levels and undetectable C-peptide values (Table 1). A positive antigulutamic acid decarboxylase auto-antibody result led to the diagnosis of type 1A diabetes (Table 1).

On physical examination, the patient was lethargic and confused, and his Glasgow Coma Scale was 12 (E3V4M5). His blood pressure was 136/68 mmHg, pulse rate 92 b.p.m., body temperature 36.6°C, height 174.9 cm and weight 71.4 kg, with a body mass index of 23.3 kg/m². We started an isotonic saline infusion with thiamine (100 mg/day) and continuous i.v. administration of insulin. During the first 2 h, the blood glucose declined at an average rate of 74.5 mg/dL/h, which subsequently...
Table 1 | Laboratory findings on admission

| Laboratory test                          | Reference range | Initial value |
|------------------------------------------|-----------------|---------------|
| Glucose (mg/dL)                          | 75–100          | 784           |
| Hemoglobin A1c (%)                       | 46–62           | 9.9           |
| Blood pH                                 | 7.35–7.45       | 6.923         |
| Bicarbonate (mmol/L)                     | 22.0–260        | 3.7           |
| Sodium (mmol/L)                          | 135–147         | 118           |
| Potassium (mmol/L)                       | 3.3–4.8         | 6.4           |
| Chloride (mmol/L)                        | 98–108          | 76            |
| Phosphate (mg/dL)                        | 2.5–4.5         | 2.0†          |
| Blood urea nitrogen (mg/dL)              | 8–20            | 50            |
| Creatinine (mg/dL)                       | 0.7–1.2         | 2.37          |
| Albumin (g/dL)                           | 4.0–5.1         | 4.6           |
| Aspartate transaminase (IU/L)            | 8–38            | 43            |
| Creatinine kinase (IU/L)                 | 30–200          | 1,035†        |
| N-terminal-pro-B-type natriuretic peptide (pg/mL) | ≤125       | 6,029†        |
| Beta-hydroxybutyrate (µmol/L)            | ≤85             | 14,354        |
| C-peptide (ng/mL)                        | 0.6–1.8         | ≤0.03         |
| Urinary C-peptide (µg/day)               | 20.1–155        | ≤0.8†         |
| Anti-GAD65 antibody (U/mL)               | ≤1.5            | 9.1           |

Anti-GAD65 antibody, anti-glutamic acid decarboxylase 65 antibody. †Measured on day 2. ‡Measured on day 8.

>28 h after admission was 25.6 mg/dL/h (Figure 1). A total of 24 h later, his plasma glucose level decreased to 107 mg/dL; we then started potassium replacement therapy, as serum potassium levels dropped from 6.4 to 4.3 mEq/L. Although his blood pH and estimated serum osmolality improved to 7.379 and 296.9 mOsm/kg H2O, respectively, his level of consciousness was slightly worse than at the time of admission (Glasgow Coma Scale 11; E2V4M5; Figure 1). Brain magnetic resonance imaging did not show any evidence of cerebral edema (data not shown). Furthermore, ST-segment elevation was observed on an electrocardiogram monitor, and was evident in II and aVF on a 12-lead electrocardiogram, which was not initially apparent (Figure 2; days 1 and 2). High levels of creatinine kinase and N-terminal pro-B-type natriuretic peptide (Table 1), and an increased cardiothoracic ratio with a costophrenic angle blunting on a chest X-ray, as well as biochemical markers of myocardial infarction (Figure 1, lower panel), were observed. The qualitative cardiac troponin T-test was negative on day 2, turned positive on days 3–5 and became negative again on day 12 (Figure 1). On the transthoracic echocardiogram carried out on day 12, the left ventricular ejection fraction was 64.9%, and left ventricular wall motion asynchrony was not observed. He recovered without any sequela and was discharged from hospital 17 days after admission.

On publication, the local ethics committee approved this study, and the patient consented in writing to the case report.

DISCUSSION
Phosphate is a source of adenosine triphosphate, which supplies energy to cells and regulates 2,3-diphosphoglycerate levels, thereby affecting hemoglobin–oxygen affinity. Therefore, hypophosphatemia results in a deterioration of cellular function as a result of reduced energy and oxygen supply to tissues, as well as various neuromuscular symptoms. Furthermore,
cardiac dysfunction might result from profound hypophosphatemia. In the present patient, myocardial dysfunction and impaired consciousness appeared after insulin treatment for DKA with mild hypophosphatemia, and disappeared after phosphate administration. Therefore, it seems that the decrease in phosphate concentration affected the patient’s condition, which improved with phosphate supplementation. In contrast, it is necessary to consider the possibility that the glucose-lowering rate might have affected the patient’s state. However, it is unlikely that this rate caused the symptoms in the patient, as it did not exceed the general glucose-lowering pace described in the American Diabetes Association guidelines.

However, in a previous randomized controlled trial, Fisher and Kitabchi examined the efficacy of phosphate therapy, and showed that phosphate replacement did not confer any advantages during DKA therapy. Post-treatment, 2,3-diphosphoglycerate levels were higher in the treatment group than in the control group; however, the difference was not statistically significant.
significant. Conversely, in the phosphate-treated group, serum calcium levels were significantly decreased. From these results, the authors concluded that phosphate therapy for DKA treatment-associated hypophosphatemia was unnecessary. The present study was limited to 30 patients; however, significantly favorable effects of phosphate therapy might be observed in a larger sample population. Furthermore, the treatment group received a total of 204 mmol of phosphate – a dose considered too high. Even 10–50 mmol of phosphate can resolve hypophosphatemia-induced symptoms without side-effects1.

Additionally, reports show that even mild hypophosphatemia can negatively affect respiratory muscle contractility7,8. Furthermore, in patients with mild hypophosphatemia (<2.2 mg/dL), approximately 30% reportedly had rhabdomyolysis5. Therefore, the diagnosis of rhabdomyolysis induced by hypophosphatemia might be overlooked. In addition, serum phosphate concentration does not necessarily reflect intracellular phosphate levels. Libanati and Tandler9 reported that mean extranuclear phosphate concentration was sixfold less than the phosphate concentration in the nucleus. Additionally, metformin can result in severe hypophosphatemia in patients with renal failure10, as well as increase intracellular phosphate demand through activation of adenosine monophosphate-activated protein kinase, especially in hepatocytes11. The present patient was taking metformin even though he had a prerenal failure as a result of dehydration, which can lead to a rapid drop in phosphate concentration. Insulin therapy for DKA might further increase intracellular phosphate demand, resulting in severe symptoms that generally occur in cases of severe hypophosphatemia.

In conclusion, we report a patient with impaired consciousness and myocardial injury during the recovery phase of DKA despite mild hypophosphatemia. Even mild hypophosphatemia associated with insulin therapy for DKA might cause severe complications in the presence of multiple overlapping causes1. As such, physicians should consider patients' serum phosphate levels during DKA treatment.

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DISCLOSURE
The authors declare no conflict of interest.
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