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CASE REPORT

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[1]. However, this does not usually require any particular treatment, because severe hypophosphatemia rarely occurs[2]. 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 antiglutamic 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/m^2. 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

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Table 1 | Laboratory findings on admission

Laboratory test	Reference range	Initial value
Glucose (mg/dL)	75–100	784
Hemoglobin A1c (%)	4.6–6.2	9.9
Blood pH	7.35–7.45	6.923
Bicarbonate (mmol/L)	22.0–26.0	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 H_2O, 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 (Figure 1) indicated myocardial injury. However, the cardiologist recommended against coronary intervention due to a left ventricular ejection fraction of 60.3% and ambiguity of wall motion asynergy on a transthoracic echocardiogram. The estimated water deficit was 7,100 mL[3], and we maintained the fluid balance at +2,500 mL on the first day (Figure 1). However, as we noticed signs of congestive heart failure on the chest X-ray, we maintained it in a negative balance from the second day onwards (Figure 1).

Further testing showed a moderately decreased serum phosphate level (2.0 mg/dL; Table 1) that continued to decrease 1 h after the initial test (1.8 mg/dL; Figure 1). As the pathophysiology can only be explained by hypophosphatemia, we initiated phosphate replacement therapy (i.v. administration of neutral sodium phosphate buffer solution dissolved in isotonic saline 30 mmol/6 h). By the early morning of the second day, despite some disorientation, the patient opened his eyes in response to speech. However, he complained of nausea around 10.00 hours, and at around 13.00 hours, he could not open his eyes without a painful stimulus. The patient was unable to obey commands and was repeatedly getting entangled in the i.v. tube. We started phosphate replacement around 18.00 hours, and 1 h later, his condition recovered to a level where there was an eye-opening response to speech. His disorientation disappeared on the third day of hospitalization (Figure 1). Furthermore, there were definite improvements in the ST-segment elevation on electrocardiogram (Figure 2) 5 days after the initiation of the treatment. Improvements in the cardiothoracic ratio and 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 asynergy 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[1]. Furthermore,

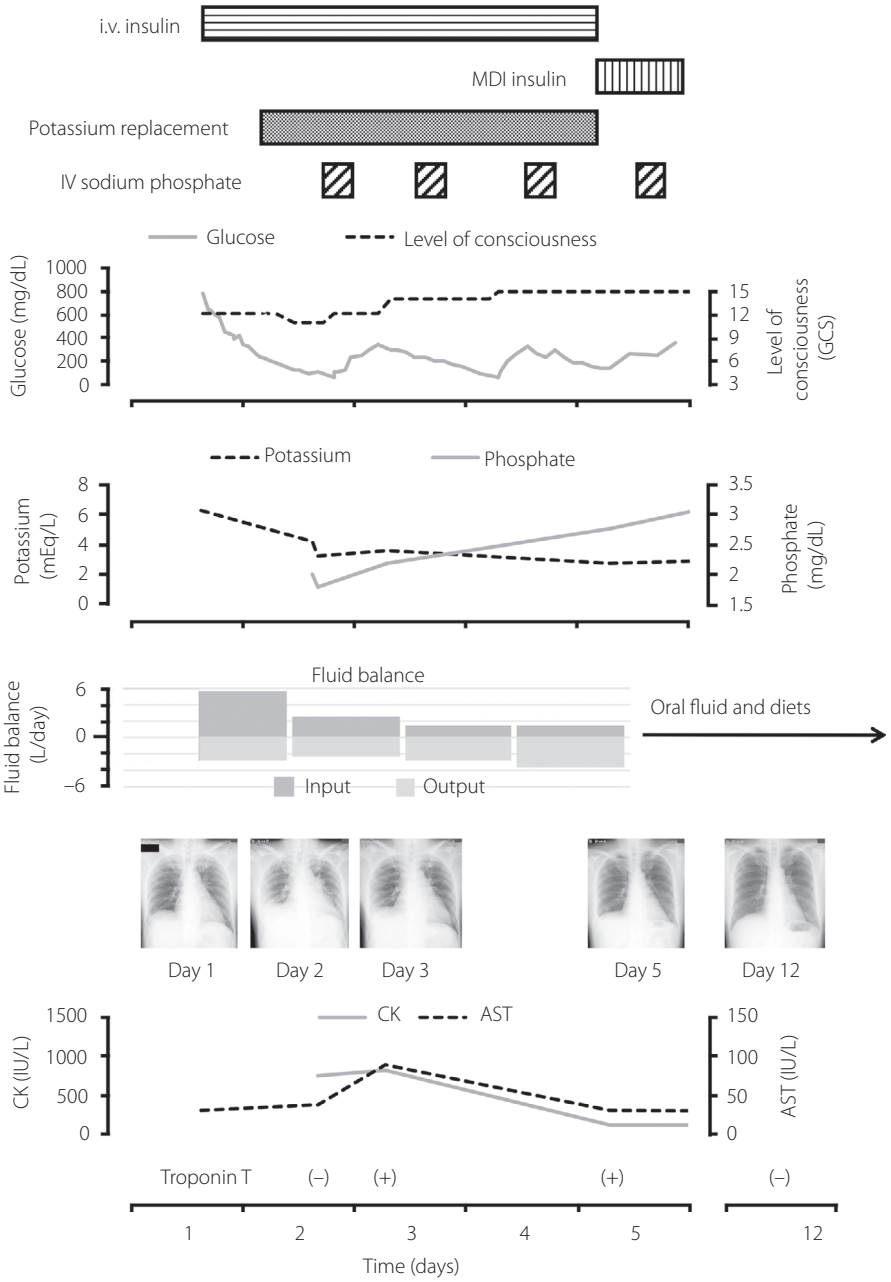

Figure 1 | Changes in laboratory test results and chest X-ray findings during treatment. The main treatments are shown in the top part of the figure. AST, aspartate aminotransferase; CK, creatinine kinase; GCS, Glasgow Coma Scale; i.v., intravenous; MDI, multiple daily injections.

cardiac dysfunction might result from profound hypophosphatemia[3]. 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[4,5].

However, in a previous randomized controlled trial, Fisher and Kitabchi[6] 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

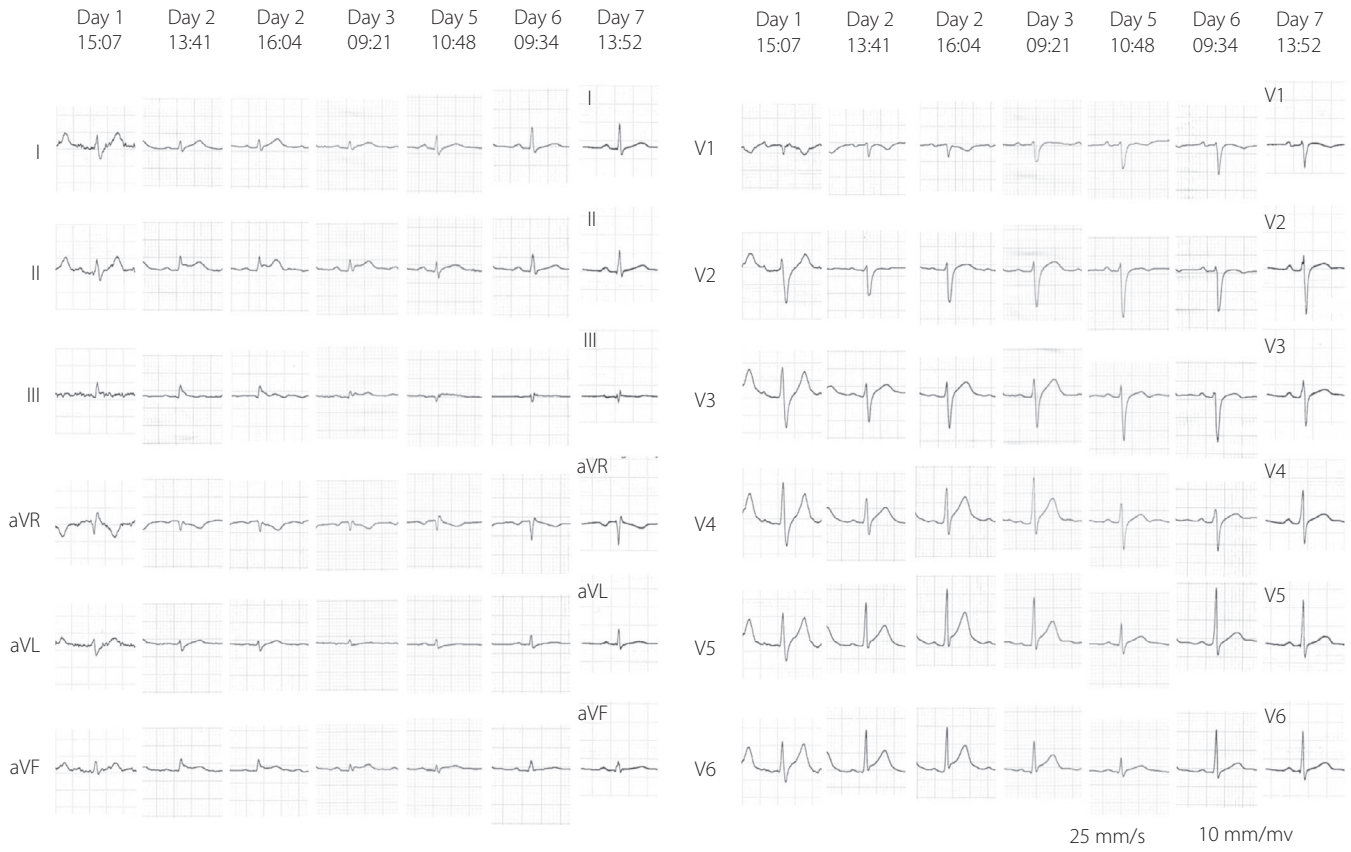

Figure 2 | Electrocardiographic changes during treatment. All electrocardiograms were recorded at the standard electrocardiogram paper speed of 25 mm/s and 10 mm/mV.

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-effects[1].

Additionally, reports show that even mild hypophosphatemia can negatively affect respiratory muscle contractility[7,8]. Furthermore, in patients with mild hypophosphatemia (<2.2 mg/dL), approximately 30% reportedly had rhabdomyolysis[1]. 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 Tandler[9] 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 failure[10], as well as increase intracellular phosphate demand through activation of adenosine monophosphate-activated protein kinase, especially in hepatocytes[11]. 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 causes[1]. 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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