Disturbance of inorganic phosphate metabolism in diabetes mellitus: clinical manifestations of phosphorus-depletion syndrome during recovery from diabetic ketoacidosis

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Abstract: The acute effects of intracellular phosphate depletion and hypophosphatemia on organs and tissues in and during recovery from diabetic ketoacidosis (DKA) have been reviewed. When insufficient phosphate and/or oxygen are available for high energy phosphate synthesis, cell homeostasis cannot be maintained and cell integrity may be impaired. The clinical consequences are recognized as occasional cause of morbidity and mortality. Although phosphate repletion has not been routinely recommended in the treatment of DKA, physicians should be aware of these clinical conditions and phosphate repletion in such situations should be considered.

Keywords: high energy phosphates, hypoxia, fructose 1,6-diphosphate

Introduction

The phosphorus-depletion syndrome has been known to veterinary surgeons for many decades. In the 1960s, the phosphorus-depletion syndrome was first described in Man by Bloom and Flinchum, who also reported a case of muscle weakness and osteomalacia in a patient with excessive ingestion of nonabsorbable antacids containing magnesium–aluminum hydroxides, which limit gastrointestinal absorption of phosphorus. Lotz et al presented the effects of experimental phosphorus depletion in three normal volunteers and in three patients with parathyroid dysfunction during prolonged treatment with antacids. They observed a syndrome with hypophosphatemia, increased absorption of skeletal calcium and phosphorus, and clinical symptoms such as debilitation, anorexia, weakness, and bone pain. These reports were followed by more extensive research and reviews.

Recently, we have presented the evidence of the occurrence of a paradoxical imbalance in phosphate metabolism from the early onset of diabetes mellitus and have indicated that this imbalance may lead to a reduction of high energy phosphates and tissue hypoxia. These changes take place in cells and tissues in which the entry of glucose is not controlled by insulin and occur particularly in poorly regulated, though ambulatory diabetic patients in whom long-term vascular complications are more likely.

In this article, we review the evidence suggesting the role of cellular phosphorus depletion and hypophosphatemia in the development of acute, occasionally life-threatening complications in hospitalized patients during treatment of diabetic ketoacidosis (DKA). The review is based on a search primarily using Medline (PubMed) and secondarily Embase, as well as information from reference lists.
Inorganic phosphate and ketoacidosis
DKA is associated with various degrees of intracellular phosphate depletion, partially because of a shift of phosphorus from the intracellular to the extracellular compartments and because of prolonged and excessive hyperphosphaturia. During DKA, the plasma inorganic phosphate (Pi) may be normal or even elevated despite intracellular phosphate depletion. Initial treatment with intravenous fluid and insulin allows sudden entry of plasma glucose and phosphate into the insulin-sensitive tissues for cellular phosphorylation, and plasma Pi may be drastically decreased. Riley et al demonstrated that insulin-induced hypophosphatemia is dose dependent and significant hypophosphatemia may occur within 30 minutes following administration of insulin. In the clinical situation, “refeeding” hypophosphatemia is usually first recognized at the second day of treatment and may last for a week depending on the degree of intracellular phosphate depletion and the replacement rate of intravenous fluid and insulin. In contrast to plasma Pi, the degree of intracellular phosphate cannot be clinically determined on admission because this parameter depends on the preceding dietary intake of phosphorus, the duration of the ketotic state, and the presence of associated factors, such as stress, infections, and duration of insufficient insulin intake.

Cellular phosphate depletion and associated hypophosphatemia, if severe, may give rise to signs and symptoms from many organ systems and is recognized as a cause of morbidity and mortality in DKA. When insufficient phosphate and oxygen are available for adenosine triphosphate (ATP) synthesis, cell homeostasis cannot be maintained and may result in cell lyses. Because randomized studies of patients with ketoacidosis on phosphate therapy did not affect the duration of DKA, dose of insulin required to the acidosis, abnormal muscle enzyme levels, glucose disappearance rate, or morbidity and mortality, phosphate therapy is not an essential part of the therapy for DKA in most patients. However, although phosphate repletion is not recommended as an adjuvant in the treatment of DKA, physicians should be aware of the clinical manifestations to ensure no delay in phosphate repletion in such situations.

Hematological manifestations
Phosphorus plays an important role in several aspects of cellular metabolism, including ATP synthesis, which is the source of energy for many cellular reactions, and red cell 2,3-diphosphoglycerate (2,3-DPG), which regulates the dissociation of oxygen from hemoglobin. Studies have shown low levels of 2,3-DPG and ATP in red blood cells and the fact that low levels of intraerythrocytic phosphate inhibit whereas high levels stimulate red cell glycolysis. During DKA, the effect of increased hydrogen ions on the oxyhemoglobin dissociation curve (ODC) is balanced by the diminished 2,3-DPG. However, after correction of acidosis, the low 2,3-DPG level shifts the ODC markedly to the left with a corresponding decrease in the ODC P 50 (oxygen tension at 50% oxygen saturation). In close correlation with plasma Pi concentration, it may take up to 1 week for 2,3-DPG to return to an approximately normal level, and the oxygen delivery to tissues will be impaired for the same period (Figure 1).

Neurological manifestations
Encephalopathy, confusion, seizures, hallucinations, and coma are the clinical signs that may develop during prolonged, severe hypophosphatemia following treatment of DKA. When verified, these symptoms should be promptly treated with intravenous phosphate, which often result in dramatic recovery.

Muscular manifestations
Muscular weakness is a common symptom, and myopathy, even in its more severe form as rhabdomyolysis, may occur. Among 12 consecutively admitted ketoacidotic patients, we found five with asymptomatic hypermyoglobinemia and elevated creatine kinase isoenzyme MM, characteristic of rhabdomyolysis. Patients with DKA are invariably dehydrated – often severely – and restoration of fluid and electrolytes is of first priority. In DKA, a remarkable small extraction of oxygen takes place through muscular and cutaneous tissues. Patients with DKA, in addition to dehydration, may also be in a preshock situation, which leads to a considerably increased release of catecholamine, mainly noradrenalin, and a redistribution of microcirculatory flow.
The arterioles in the cutaneous and splanchnic areas may be constricted, and blood flow will be shunted through biologically observable arteriolar–venular communications (thoroughfare channels; vascular pattern-change II) whereby blood flow bypasses the nutritive capillaries. The resulting ischemic hypoxia of glucose- and phosphate-starved muscle cells may lead to reduced ATP, resulting in membrane disruption and allowing myoglobin and creatine kinase isoenzyme MM to enter into the circulation.

**Myocardial manifestations**

Møller et al. presented two patients with severe DKA, who showed elevations of the biomarkers troponin T and creatine kinase MB and initial electrocardiographic changes.

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**Figure 1** Pattern of changes in plasma phosphate (Δ), 2,3-DPG (●), and P₅₀ at in vivo pH on the oxyhemoglobin dissociation curve (○) in a case of diabetic ketoacidosis. **Abbreviations:** 2,3-DPG, 2,3-diphosphoglycerate; Hb, hemoglobin.
compatible with myocardial infarction. However, all successive investigations including coronary arteriography were normal. The concentration of plasma Pi was not reported. Hypophosphatemia is known to be associated with low levels of cellular ATP and impairment of human myocardial performance.\textsuperscript{34,35}

**Pulmonary manifestations**

Acute respiratory failure in DKA patients with severe hypophosphatemia has been reported, and normally good results have been reported with phosphate replacement.\textsuperscript{36,37}

**Renal manifestations**

Dehydration, volume depletion, renal hypoperfusion, and decreased intracellular tubular phosphate content often occur. Therefore, signs of renal tubular cell damage, as indicated by increased urinary excretion of enzymes from the brush border membrane such as increased urinary excretion of $\beta_2$-microglobulin, $\gamma$-glutamyltransferase, leucine aminopeptidase, and N-acetyl-$\beta$-D-glucosaminidase, are common. Cases of renal tubular acidosis have also been seen.\textsuperscript{38–40}

These tubular cell disturbances may occur despite normal glomerular function.

**Gastrointestinal manifestations**

Nonspecific hyperamylasemia and abdominal pain are frequent findings during and after treatment of DKA with significantly negative correlation with plasma Pi.\textsuperscript{41–43} In a study of 12 patients with ketoacidosis, salivary, pancreatic isoamylases, and pancreas lipase were determined. Hyperamylasemia was present in six patients, of which, five showed simultaneous increases in all three specific pancreatic enzymes, and one had increased salivary isoamylases alone. In none of the patients, the clinical course or the time-concentration curves of pancreatic enzymes were consistent with acute pancreatitis.\textsuperscript{43}

**Discussion**

Despite the prevalence of hypophosphatemia, the aforementioned acute clinical consequences are not common. Some of the cited references are from the period prior to the advent of routine, low-dose insulin administration. However, as indicated, the early and severe hypophosphatemia associated with the recovery phase of DKA seems to be related to rapid uptake of glucose and Pi by the insulin-sensitive cells and tissues following the administration of insulin and correction of acidosis. In this situation, the insulin-insensitive cells may continue to be phosphate-starved and may suffer from affinity hypoxia with associated metabolic consequences. A flowchart indicating the most important factors leading to ATP deficiency in and during recovery from DKA is presented in Figure 2. Acidosis induces low red cell 2,3-DPG because of inhibition of phosphofructokinase and dehydrogenation. Through redistribution of regional microcirculation and shunt flow, ischemic hypoxia may develop, which can be curtailed by rehydration.

As insulin begins to normalize glucose metabolism in the insulin-sensitive tissues, phosphorus enters into the cells and marked hypophosphatemia may develop. Hypophosphatemia slows the abolishment of affinity hypoxia (Figure 1). The two important elements, phosphorus and oxygen, for optimal ATP synthesis may thereby be limiting factors. Following the initial treatment of DKA, the cells of many organs and tissues may release enzymes, most likely because of this inhibition of energy metabolism. The resulting ATP depletion may lead to fluxes of Na\textsuperscript{+}, K\textsuperscript{+}, and Cl\textsuperscript{−} according to their gradients across the cellular membranes and with swelling of cells. Subsequently, Ca\textsuperscript{2+} may leak into the cells, activating phospholipases and the formation of eicosanoids, affecting the cytoskeleton, and initiating oxidant formation. The precise “point of no return” is unknown, but uncontrolled Ca\textsuperscript{2+} activity in the cell probably has an important role in initiating irreversible cell damage.\textsuperscript{44}

\textbf{Figure 2} A flowchart indicating the most important factors leading to ATP deficiency in and during recovery from diabetic ketoacidosis.

\textbf{Abbreviations:} ATP, adenosine triphosphate; ODC, oxyhemoglobin dissociation curve; 2,3-DPG, 2,3-diphosphoglycerate.
Diabetic patients with clinical symptoms of phosphate depletion and severe hypophosphatemia (<1.0 mg/dL); (tetany, seizures, prolonged unconsciousness, rhabdomyolysis, respiratory failure, and ventricular tachycardia) and those with one or more defective oxygen transport mechanisms (severe anemia, chronic obstructive pulmonary disease, and congestive heart failure) should be repleted with phosphate. The symptoms and signs of phosphate depletion can vary, are nonspecific, and are usually seen in patients with multiple problems. This makes it difficult to identify phosphate depletion as the cause of the clinical manifestations.34 The response to phosphorus repletion with solutions of Pi is usually effective and safe.46 The organic phosphate, fructose 1,6-diphosphate (FDP), a key intermediate in glycolysis and the product of the major regulatory enzyme in the pathway (phosphofructokinase), has been suggested as an alternative. FDP acts as human bioenergy and can transport phosphorous into cells and, in a single report, FDP was shown to be more effective and safe than plasma Pi in restoring red cell 2,3-DPG in patients.47 Further studies on this subject are clearly needed before any conclusion can be reached.

Disclosure
The authors report no conflicts of interest in this work.

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