REVIEW ARTICLE

Hypophosphatemia-induced Cardiomyopathy

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ABSTRACT

Relatively few studies have been conducted to evaluate the effect of hypophosphatemia on cardiac function. The goal of this review was to determine whether there is an association between hypophosphatemia and cardiac function and to increase awareness of hypophosphatemia-induced cardiomyopathy as a new clinical entity and a reversible cause of heart failure. We searched MEDLINE and PubMed from 1971 until March 2015 for primary studies, which reported the relationship between hypophosphatemia and cardiac function. A total of 837 articles were initially obtained. Of these articles, 826 publications were excluded according to the inclusion and exclusion criteria. In all, 11 articles were included in this review. These articles included 7 case series or case reports, 1 case-control study, 1 pretest versus posttest in a single group and 2 animal studies. In conclusion, the mechanisms of hypophosphatemia in cardiomyopathy have been reported to be a depletion of adenosine triphosphate in myocardial cells and decreased 2,3-diphosphoglycerate in erythrocytes. After correction of hypophosphatemia, left ventricular performance seems to improve in patients with severe hypophosphatemia, but not in those with mild-to-moderate hypophosphatemia. However, analyses of the relationship between cardiac function and hypophosphatemia using clinical end points have not been conducted.

Key Indexing Terms: Hypophosphatemia; Cardiomyopathy; Heart failure. **[Am J Med Sci 2016;352(3):317–323.]**

INTRODUCTION

The essential roles of phosphorus in homeostasis are energy production, nucleic acid functioning and enzyme activity. Phosphorus is also the main structural element of membranes and bones. The intracellular concentration exists mainly in the form of creatine phosphate, adenosine monophosphates and triphosphates within bones and teeth (85%), soft tissue (14%) and extracellular fluid (1%). Normal serum concentration of phosphate is 2.7-4.5 mg/dL in adults and 4.0-7.0 mg/dL in children. Most laboratories report the inorganic orthophosphate form, of which 10% is bound to protein, 5% is complexed with calcium and magnesium and 85% is in the forms of H_2PO^{4-} and HPO^{4-}. Other forms of free orthophosphate (H_3PO_4, $H_2PO_4^-$, HPO_4^{2-} and PO_4^{3-}) are present in negligible amounts under physiological pH.[1]

Total body phosphorus level is maintained through a balance of oral intake, gut absorption, kidney excretion and intracellular shifts. In the clinical setting, low serum phosphorus levels are commonly observed with refeeding syndrome, continuous insulin treatment for diabetic ketoacidosis, sepsis, alcoholism, secondary hyperparathyroidism and tumor-associated osteomalacia, and can result from either intracellular shifts or total body phosphorus depletion. Congenital causes include X-linked hypophosphatemia and autosomal-dominant hypophosphatemic rickets.

Hypophosphatemia is classified as mild, moderate or severe. The most commonly reported definition of severe hypophosphatemia is a serum level of <1.0 mg/dL (0.32 mmol/L).[2] Severe hypophosphatemia can cause ventricular arrhythmias, derangement of cardiac and respiratory functions and possibly death. As serum phosphorus level is not routinely included in the basic chemistry panel in most laboratories, the exact prevalence of hypophosphatemia is not known but is estimated to be less than 1%.[3] The clinical consequences of mild hypophosphatemia are tolerable, and treatment is recommended only for patients with moderate-to-severe hypophosphatemia.

METHODS

The effect of hypophosphatemia on cardiac function is known mainly from sporadic case reports. A comprehensive literature search of all pertinent studies published through June 2015 was undertaken by 2 investigators (N.A. and A.A.) in MEDLINE and PubMed using the key words *hypophosphatemia*, *phex*, *xlh*, *phosphorus metabolic disorders*, or *phosphates/blood*, AND *cardiac function, heart function, heart failure* or *cardiomyopathy*. Articles that discussed the relationship between hypophosphatemia and cardiac function and assessed cardiac functions with modalities (e.g., echocardiography and pulmonary artery catheter) before and after treatment of hypophosphatemia were included. All editorials, comments, letters, review articles and meta-analyses were excluded. Articles without full text and papers that were not published in English were also excluded.

Based on our extensive search of articles, the present review furthers our understanding of the mechanism of hypophosphatemia in causing cardiac disease.

RESULTS

A total of 837 articles were initially obtained. Of these articles, 820 publications were excluded according to the inclusion and exclusion criteria. The remaining 17 articles were carefully screened further. In all, 8 articles were eventually excluded; 6 did not assess cardiac functions with modalities before or after treatments of hypophosphatemia, 1 study reported the relation between hyperparathyroidism and heart failure and 1 study reported the relation between anorexia nervosa and heart failure. The remaining 11 articles were included in this review. These articles included 7 case series or case reports,[1,4-9] 1 case-control study,[10] 1 pretest versus posttest in a single group[11] and 2 animal studies.[12,13]

Clinical Manifestation

Depending on serum phosphate concentration, clinical presentations varied from asymptomatic to severe symptoms, including cardiac arrest.[14-17] Clinical presentations included muscle weakness, cardiac arrhythmia, rhabdomyolysis, paresthesia, motor neuropathy, ataxia, hallucination, seizure, hemolysis and insulin resistance.[18] Serious symptoms such as muscle weakness and cardiac arrhythmias were not usually seen until serum phosphate concentration decreases to less than 1.0 mg/dL.[10] Patients with severe hypophosphatemia were reported to have a greater incidence of ventricular arrhythmias in acute myocardial infarction and greater need for vasoactive drug titration after cardiac surgeries.[9,19] Correction of hypophosphatemia may have reversed clinical manifestations.[4,9,20] Hypophosphatemia is considered to cause reversible myocardial dysfunction, as mentioned in the first case report in 1977 and in the other articles.[1,4-13]

Pathophysiology and Clinical Studies

Phosphorus plays an important role in a number of biological processes. It is involved in the glycolytic pathway, in the generation of the high-energy phosphate bonds of adenosine triphosphate (ATP) and in the formation of 2,3-diphosphoglycerate (2,3-DPG). The mechanisms of cardiomyopathy with regard to hypophosphatemia have been described as depletion of ATP in myocardial cells and decreased 2,3-DPG in erythrocytes.

ATP is the energy source for most cellular functions. Cardiac demand for ATP is significant, constituting more than 5 kg of ATP per day or 2 metric tons per year.[21] To meet this high demand, approximately one-quarter to one-third of each ventricular cell is occupied by mitochondria, whose function is mainly to generate energy in the form of ATP to maintain cardiac contractility. Therefore, depletion of ATP can theoretically cause cardiac contractile dysfunction. The measurement of cardiac ATP is used in 31P-magnetic resonance spectroscopy that provides an index of the energetic state of the heart by means of the phosphocreatine-to-ATP ratio. However, because of low temporal and spatial resolution and low reproducibility, the use of magnetic resonance spectroscopy is currently limited to research.

Hypophosphatemia can also cause impaired oxygen delivery to the tissues owing to decreased production of ATP and 2,3-DPG. Lichtman et al[22] reported that hypophosphatemia caused by parenteral nutrition led to a 52% reduction of ATP and 45% reduction of 2,3-DPG concentrations within erythrocytes. ATP and 2,3-DPG bind to hemoglobin and decrease the cells' affinity for oxygen, leading to its release to tissues as necessary. Normal erythrocytes have nearly 3 times more 2,3-DPG than ATP. Decreased intracellular 2,3-DPG causes a leftward shift of the oxyhemoglobin dissociation curve and, consequently, tissue hypoxia. Under anaerobic conditions caused by decreased tissue oxygen supply, 1 mole of glucose yields only 2 moles of ATP, whereas under fully oxidized conditions, the same amount of glucose yields approximately 26 moles of ATP. Bersin et al[23] observed substantially reduced oxygen-hemoglobin binding and higher-than-normal 2,3-DPG concentrations in patients with severe congestive heart failure. This may be an important adaptive mechanism to maintain adequate oxygen transport. Elimination of this adaptive mechanism would necessitate an increase in cardiac output and coronary blood flow to meet the same resting metabolic demands. In the presence of limited cardiac function and impaired coronary blood flow, a decrease in 2,3-DPG could potentially exacerbate the imbalance between metabolic demands and tissue oxygen supply and lead to myocardial ischemia.

Another serum constituent crucial in phosphate metabolism is fibroblast growth factor 23 (FGF-23), the most recently identified molecule in the FGF family. Along with parathyroid hormone and vitamin D, it mobilizes sodium-phosphate cotransporters in coordination with Klotho, a transmembrane protein that has antiaging properties. Patients with severe renal disease are known to have high levels of circulating FGF-23.[24] These patients are also at risk for cardiac complications. Therefore, the influence of FGF-23 on cardiac disease has been hypothesized. In an analysis of 100 coronary care unit patients with renal insufficiency, Shibata et al[24] reported that circulating FGF-23 concentrations were positively associated with left ventricular mass and reduced left ventricular ejection fraction (LVEF), independent of renal function and other parameters related to calcium-phosphate metabolism. However, in patients with chronic kidney disease, elevated FGF-23 is associated with hyperphosphatemia, not hypophosphatemia, suggesting that elevated FGF-23 is just a bystander in patients with advanced kidney disease and cardiac diseases, and further longitudinal study is warranted.[24]

The Table summarizes the clinical observations and conclusions from 11 studies. Fuller et al[12] reported