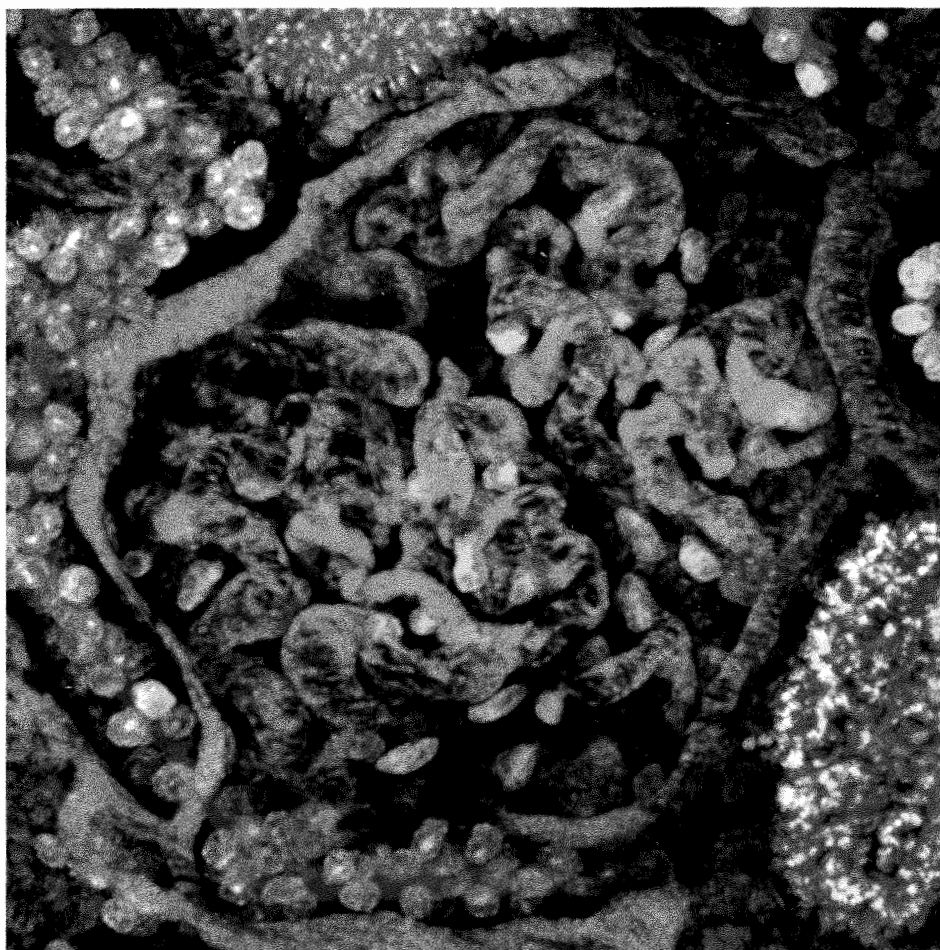


July 2007
Vol. 18, No. 7
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JASN

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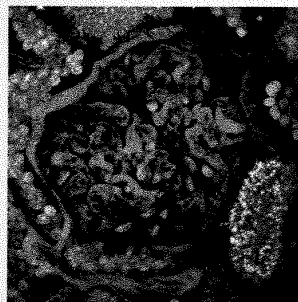
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CLINICAL COMMENTARY

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Hypophosphatemia: Clinical Consequences and Management

Steven M. Brunelli*[†] and Stanley Goldfarb*

*Renal-Electrolyte and Hypertension Division, Department of Medicine, and [†]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

ABSTRACT

Current evidence regarding the clinical consequences of hypophosphatemia is not straightforward. Given the potentially different implications of hypophosphatemia among various patient groups, this commentary touches on patients with low serum phosphate after acute hospitalization, those with chronic ambulatory hypophosphatemia, and those with hypophosphatemia in the setting of advanced renal disease. Finally, this commentary examines the evidence regarding how best to replete phosphorous in the hypophosphatemic patient.

J Am Soc Nephrol 18: 1999–2003, 2007. doi: 10.1681/ASN.2007020143

Although rare in the general population, the incidence of hypophosphatemia is high in certain subgroups of patients, such as those who are hospitalized (2.2 to 3.1%) or admitted to intensive care units (28.85 to 33.9%), and those with sepsis (65 to 80%), chronic alcoholism (2.5 to 30.4%), major trauma (75%), and chronic obstructive pulmonary disease (21.5%).¹ So what are the potential clinical consequences of hypophosphatemia, and how should one replete phosphate? Because the physiologic consequences of hypophosphatemia are likely different among different groups of patients, our commentary considers patients with hypophosphatemia in the setting of acute hospitalization, those with chronic ambulatory hypophosphatemia, and those who demonstrate hypophosphatemia in the setting of advanced kidney disease.

When first examined in the 1970s, patients who received phosphate-free hyperalimentation manifested severe hypophosphatemia (<0.3 mmol/L [1 mmol/L = 3.125 mg/dl]) and developed acute hemolytic anemia² as a result of reduced erythrocyte cell membrane deformability and life span,^{3–5} resulting

probably from intracellular ATP depletion. A similar syndrome was described in chronic alcoholics with rhabdomyolysis.⁶ In current clinical practice, instances of dramatic hypophosphatemia are rare compared with hypophosphatemia of lesser magnitude and shorter duration, and the clinical consequences of the latter circumstance are much less certain.

The association between hypophosphatemia and mortality among hospitalized patients is outlined in Table 1. Despite variations in the underlying patient cohorts, definitions of hypophosphatemia, and study designs, the results of these studies consistently demonstrated an association between hypophosphatemia and in-hospital mortality. However, none of these studies adjusted for potential confounding on the basis of demographic factors, comorbid disease state, or nutritional status, thus leaving in question the potential for causality.

Similarly, numerous studies have examined the associations between hypophosphatemia and surrogate outcomes among hospitalized patients (Table 2). Although the evidence sug-

gests an association between hypophosphatemia and markers of poor respiratory, cardiovascular, and postsurgical outcomes, these studies also fail to adjust for confounding variables. Inconsistent definitions of hypophosphatemia across studies, use of invalidated outcome surrogates, and issues of multiple comparisons further obscure conclusions. Overall evidence demonstrates an association between hypophosphatemia and poor clinical outcomes among hospitalized patients, suggesting that hypophosphatemia is an adverse prognostic marker. However, the data cannot determine potential causality.

Given the commonplace clinical overlap between the two syndromes, hypophosphatemia among patients with diabetic ketoacidosis (DKA) warrants special consideration. A randomized controlled trial demonstrated that among patients who presented with DKA, phosphate supplementation did not improve biochemical or clinical outcomes, and it was associated with lower ionized calcium.⁷ On the basis of these findings, routine repletion of phosphate in patients who present with DKA is probably not warranted.

The role of hypophosphatemia as a determinant of left ventricular function in ambulatory patients was first popular-

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr Steven Brunelli, 423 Guardian Drive, Blackley Hall, Suite 109, Philadelphia, PA 19104. Phone: 215-662-2638; Fax: 215-898-0643; E-mail: steven.brunelli@uphs.upenn.edu

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Table 1. Association between hypophosphatemia and mortality among hospitalized patients^a

Study Design	Underlying Patient Population	Definition of HP	n	Outcome Measure (HP versus Controls)	Outcome
Case-control ³⁸	Hospitalized; >65 yr old	≤0.77 mmol/L	325 HP, 326 controls	OR in-hospital mortality	2.79 (2.0 to 3.89) ^b
Retrospective cohort ³⁹	Hospitalized patients	≤0.33 mmol/L	10,197	Incidence of in-hospital mortality	18.2 versus 4.6% (P < 0.001)
Prospective cohort ³⁵	Surgical critical care	LLN	60 HP, 148 controls	Incidence of in-hospital mortality	30 versus 15.2% (P < 0.05)
Matched case-control ⁴⁰	Septic patients	≤0.32 mmol/L	26 HP, 29 controls	OR in-hospital mortality	7.98 (2.3 to 27.6) ^b

^aHP, hypophosphatemia; LLN, lower limit of normal; OR, odds ratio.^bPoint estimate (95% confidence interval).**Table 2.** Association between HP and surrogate outcome measures^a

Study Design	Underlying Patient Population	Definition of HP	n	Outcome Measure (HP versus Controls)	Outcome
Cross-sectional ⁴¹	Hospitalized general medical	≤0.8 mmol/L	23 HP, 11 controls	Prevalence of respiratory muscle weakness ^b	70 versus 0% (P < 0.001)
Prospective cohort ⁴²	Surgical critical care	Fall ≥0.05 to absolute level ≤0.21 mmol/L	21 HP, 41 controls	Duration of mechanical ventilation	10.5 ± 5.2 versus 7.1 ± 2.8 d ^d (P = 0.04)
				Duration of hospitalization	12.1 ± 7.1 versus 8.2 ± 4.6 d ^d (P = 0.01)
Crossover ⁴³	Septic shock	<0.64 mmol/L	10	LV stroke work index ^c	23.8 ± 10 versus 27.5 ± 8.5 g/m ² (P < 0.01)
				Systolic BP ^c	114 ± 14 versus 129 ± 20 mmHg (P < 0.01)
Retrospective cohort ⁴⁴	After hepatectomy	<0.48 mmol/L on POD 15	15	Incidence of postoperative complications	60 versus 16% (P < 0.001)
Retrospective cohort ⁴⁵	Hepatic lobectomy or cryosurgery	<0.8 mmol/L	21 HP, 14 control	Incidence of postoperative complications	80 versus 28% (P < 0.05)
Crossover ⁴⁶	Mechanically ventilated patients	Mean phosphate 0.55 mmol/L	8	Stimulated transdiaphragmatic pressure ^c	9.75 ± 3.8 versus 17.25 ± 6.5 cmH ₂ O (P < 0.001)
Prospective cohort ⁴⁷	Coronary care unit patients after MI	<0.83 mmol/L	38 HP, 73 controls	Incidence of ventricular tachycardia	57 versus 27% (P = 0.007)

^aLV, left ventricular; MI, myocardial infarction; POD, postoperative day.^bRespiratory muscle weakness defined as maximal inspiratory pressure <40 cmH₂O or maximal expiratory pressure <70 cm H₂O.^cMean ± SD before versus after phosphate repletion.^dMean ± SD.

ized by Darsee *et al.*⁸ in the 1970s, who reported dramatic improvement in left ventricular function in three patients with hypophosphatemia after phosphate repletion. Subsequent allegations that these data were fraudulent called into question the relationship between serum phosphate and cardiac function. A prospective cohort study in which left ventricular function was compared among groups of patients with moderate (0.45 mmol/L) and severe (0.29 mmol/L) hypophosphatemia and normophos-

phatemic control subjects was conducted later.⁹ Correction of hypophosphatemia resulted in improved left ventricular performance in severe but not in mild hypophosphatemia. However, none of the patients in any group had clinically overt heart failure at baseline. In addition, children who had X-linked hypophosphatemic rickets and in whom hypophosphatemia (mean 0.83 ± 0.16 mmol/L) was induced by withholding phosphate and vitamin D supplements demonstrated normal echocar-

diographic measurements of left ventricular performance.¹⁰ To our knowledge, no analytic studies of the relationship between cardiac function and hypophosphatemia using clinical end points have been conducted. The conflicting evidence in studies that used surrogate markers emphasizes the need for such investigations.

Given the pivotal role of phosphate in intermediary metabolism, a hypothetical basis exists to suspect the role of hypophosphatemia in glucose intolerance,

obesity, and the metabolic syndrome. One trial demonstrated that patients with chronic hypophosphatemia had a propensity for glucose intolerance in both euglycemic and hyperglycemic states as compared with normophosphatemic control subjects.¹¹ Furthermore, among patients with a family history of type 2 diabetes, serum phosphate levels were significantly negatively correlated with glucose tolerance.¹² Data also indicate significant negative correlations between serum phosphate and body mass index and waist-to-hip ratio.¹³ Among patients who entered a lifestyle modification program for cardiovascular risk reduction, serum phosphate was significantly negatively correlated with systolic BP.¹⁴ Taken together, these findings favor an association between hypophosphatemia and glucose intolerance, obesity, and other manifestations of the metabolic syndrome. Adequate data do not exist, however, to warrant phosphate repletion in patients with hypophosphatemia on the basis of improving glucose tolerance or cardiovascular risk profile.

Grounds also exist to suspect an association between hypophosphatemia and short stature and poor bone health. Chronic hypophosphatemia in general pediatric populations is exceedingly rare and usually results secondarily from vitamin D deficiency. However, the potential for confounding on the basis of deficiency of other nutrients besides vitamin D makes this disorder a poor model for the study of hypophosphatemia and growth. Among children with X-linked hypophosphatemic rickets, those who initiated treatment with supplemental phosphate and vitamin D before puberty achieved greater mean height SD scores than untreated historical control subjects.¹⁵ Similarly, initiation of treatment before 1 yr of life results in greater height than later treatment.¹⁶ Although an association between hypophosphatemia and short stature and bone health in children with X-linked hypophosphatemic rickets seems plausible, a primary role of hypophosphatemia remains in question given alterations in 1,25 (OH)₂ vitamin D levels and fibroblast growth factor 23.

It is doubtful that patients with X-linked hypophosphatemic rickets can be generalized to other groups of pediatric patients with hypophosphatemia. Nonetheless, phosphate repletion is widely recommended.

Derangements in serum phosphate are also common in patients with advanced chronic kidney and ESRD. Most often, this manifests as hyperphosphatemia; however, hypophosphatemia related to phosphate binder therapy or nutritional status is not uncommon. One study demonstrated that among patients who had chronic kidney disease and were not yet receiving renal replacement therapy, hypophosphatemia (<0.8 mmol/L) was not associated with increased mortality compared with low-normal serum phosphate (0.8 to 0.93 mmol/L).¹⁷

Multiple studies have examined the relationship between serum phosphate level and mortality among dialysis-treated patients. One large retrospective cohort study of patients who were treated by a single dialysis provider chain demonstrated a U-shaped unadjusted relationship between serum phosphate level and all-cause mortality.¹⁸ However, on adjustment for case mix, comorbid disease, and nutritional status, lower levels of serum phosphate (<0.96 mmol/L) were no longer associated with increased mortality risk.

US Renal Data System data demonstrate no increased cardiovascular events or adjusted death rates among patients in the lowest quintile of serum phosphate (≤ 1.4 mmol/L).¹⁹ Unfortunately, no distinction was made between frank hypophosphatemia and low-normal serum phosphate. Conversely, the multinational Dialysis Outcomes and Practice Patterns Study (DOPPS) found a significant adjusted relationship between hypophosphatemia (<0.8 mmol/L) and all-cause mortality.²⁰ Whether the discrepancies between the US Renal Data System and DOPPS data represent differences in the underlying dialysis populations, differences in treatment paradigms, or residual confounding is unclear.

Given that serum phosphate levels are dynamic among dialysis-treated patients, one group used time-varying

Cox proportional hazards models to examine the relationship between serum phosphate and all-cause mortality.²¹ There was a large unadjusted association between low serum phosphate (<0.96 mmol/L) and mortality (hazard ratio approximately 3.2) that was mitigated but remained statistically significant after adjustment for case mix and markers of the malnutrition-inflammation-cachexia syndrome (hazard ratio approximately 1.4). Overall, there seems to be an association between low and low-normal serum phosphate and mortality among dialysis-treated patients.

Hypophosphatemia is also very common after kidney transplantation. Initially, this was thought to result from sudden normalization of glomerular filtration in the setting of persistently high levels of parathyroid hormone, relative vitamin D deficiency, and use of glucocorticoids in the immunosuppressive regimen; however, the pathogenic role of phosphatonins has recently come into view.²² Posttransplantation hypophosphatemia coexists with histologic and radiographic changes in bone mineralization,^{23,24} and increased fracture risk.^{25,26} Whereas surrogate markers of bone and nutritional health (e.g., serum phosphate, parathyroid hormone, osteocalcin, vitamin D levels) normalize in response to phosphate supplementation,²⁷ no study has found effects on clinical outcomes.

Finally, something in general should be said about phosphate repletion. Most authors recommend oral repletion in ambulatory patients who have chronic hypophosphatemia. A typical regimen is 15 mg/kg oral phosphate, given in three to four divided doses to minimize gastrointestinal adverse effects such as diarrhea and gastric irritation.²⁸ Often cow milk can be used as a source of oral phosphate. For patients who are unable to tolerate dairy products, there are a number of commercially available preparations of oral sodium and potassium phosphate. We know of no studies that have evaluated the safety and the efficacy of oral phosphate repletion regimens. However, given the relative ease of oral repletion, and considering the absence of data that suggest harm, oral therapy is probably

Table 3. Phosphorus repletion protocol^a

Phosphorus Level	Weight 40 to 60 kg	Weight 61 to 80 kg	Weight 81 to 120 kg
<0.32 mmol/L	30 mmol Phos IV	40 mmol Phos IV	50 mmol Phos IV
0.32 to 0.54 mmol/L	20 mmol Phos IV	30 mmol Phos IV	40 mmol Phos IV
0.58 to 0.70 mmol/L	10 mmol Phos IV	15 mmol Phos IV	20 mmol Phos IV

^aReproduced with permission from Taylor et al.³⁷ IV, intravenous; Phos, phosphorus. If the patient's serum potassium is <4.0 mEq/L, then use potassium phosphorus; if the patient's serum potassium is >4.0 mEq/L, then use sodium phosphorus.

warranted for most ambulatory patients with hypophosphatemia.

Often, oral phosphate repletion is not feasible in hospitalized patients, particularly the critically ill. Given the potential physiologic benefits of phosphate repletion in these patients, considerable interest has been given to developing safe and efficacious intravenous phosphate repletion regimens.

Complications after overzealous attempts at intravenous phosphate repletion, including renal failure, hypocalcemic tetany, hypotension, hyperphosphatemia, and electrocardiographic abnormalities,^{29–31} led to the development of very conservative regimens. For many years, the standard of care was 0.32 mmol/kg intravenous phosphate administered over 12 h.³² However, after this protocol, only 58% of treated patients achieved serum phosphate levels >0.64 mmol/L by 24 h.

The lack of efficacy of traditional protocols, along with concerns of compromising intravenous lines during prolonged phosphate infusions, has led to a move toward more aggressive intravenous phosphate repletion regimens. Administration of 15 mmol of intravenous sodium phosphate over 2 h (repeated up to three times over 24 h) is well tolerated and efficacious among surgical intensive care patients with moderate hypophosphatemia (0.32 to 0.64 mmol/L), normal renal function, and normocalcemia.³³ A graded dosing scheme for intravenous phosphate repletion (0.16 mmol/kg over 4 to 6 h, 0.32 mmol/kg over 4 to 6 h, and 0.64 mmol/kg over 8 to 12 h for serum phosphate levels of 0.74 to 0.96, 0.51 to 0.70, and <0.48 mmol/L, respectively) has been efficacious among critically ill, nonobese surgical and trauma patients with normal renal function and normocalcemia.³⁴ Administration of 0.4 and 0.8 mmol/kg intravenous phosphate over 30 min to patients with moderate and severe

hypophosphatemia, respectively, is also well tolerated.³⁵ Randomized, controlled trial data suggest equal safety and efficacy of rapid (30 mmol over 2 h and 45 mmol over 3 h for serum phosphate of 0.40 to 0.65 mmol/L and <0.40 mmol/L, respectively) versus conservative phosphate infusions (equivalent doses given over 4 and 6 h, respectively).³⁶ Use of a weight- and serum phosphate-based algorithm for intravenous phosphate repletion (Table 3) resulted in significant improvement in the proportion of patients who achieved normal serum phosphate, as compared with historical control subjects who received phosphate repletion via a nonstandardized approach: 76 versus 47%, respectively.³⁷ The bulk of existing evidence suggests the overall advantage of faster, more aggressive and tailored intravenous phosphate repletion regimens.

DISCLOSURES

None.

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