Hypophosphatemia: An Evidenced-based Approach to its Clinical Consequences and Management

Medical Grand Rounds
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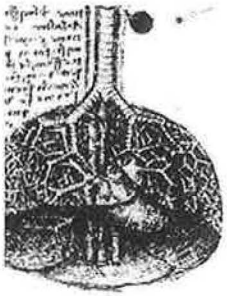


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I. Bartter's original description of phosphorus-depletion syndrome in man

Lotz and Bartter were the first to describe phosphorus-depletion syndrome in man and its association with clinical signs and symptoms (1). Given the ubiquitous nature of dietary phosphorus, it was believed by some that phosphorus depletion could not occur. They studied three normal patients, two patients with hypoparathyroidism and one with pseudohypoparathyroidism in a controlled GCRC environment. Patients were given magnesium and aluminum hydroxide in combination four times daily in order to induce phosphorus depletion. Results of a balance study in a normal female volunteer are shown in Figure 1.

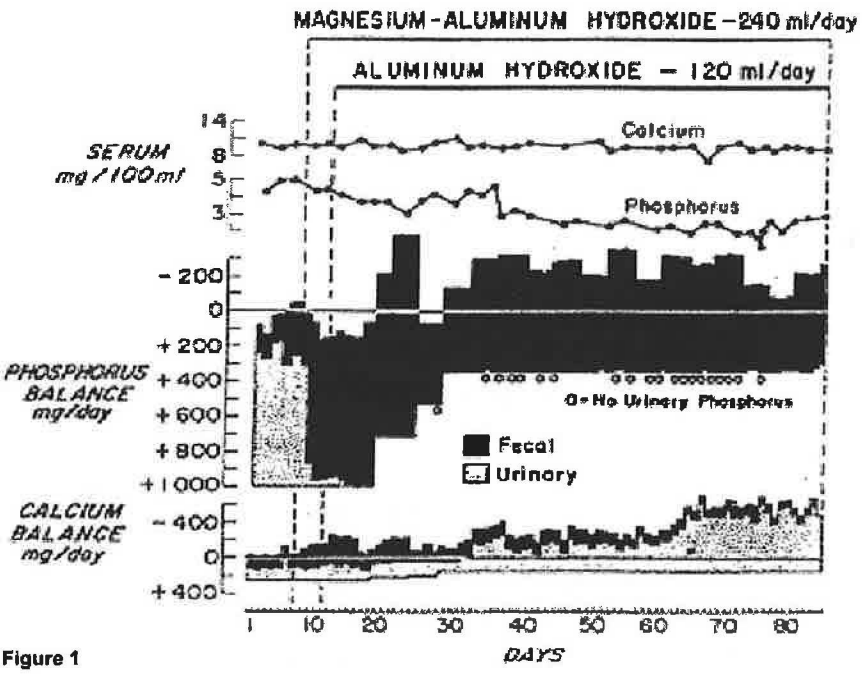


Figure 1

Urinary phosphorus declined to zero within 5-7 days. There was increased GI calcium reabsorption and hypercalciuria. After 14-21 days phosphorus balance became negative. Skeletal calcium and phosphorus resorption increased. Severe symptomatic hypophosphatemia occurred after 75 days of antacid treatment. Subjects complained of anorexia, weakness, bone pain, and malaise. Symptoms reversed several days after antacids were discontinued.

Bartter drew a variety of conclusions from the data that later would be confirmed when more sophisticated analytic tools became available. He noted that decreased urinary phosphorus excretion was not dependent on a reduced filtered load. He postulated that the mechanism leading to renal phosphorus conservation must be very sensitive given that total body phosphorus was depleted by only one gram out of a total of approximately 700 grams, and that cellular phosphorus concentration played a role in the regulatory process in kidney. It is now know that proximal tubular phosphorus reabsorption is mediated via a Na-phosphate cotransporter that is regulated by dietary phosphorus (2). Since hypercalciuria was reversed by phosphorus administration Bartter suspected that phosphorus played a direct role in renal tubular calcium reabsorption. This was confirmed in micropuncture studies by Agus (3). Intestinal calcium reabsorption was increased. This was subsequently shown to be mediated via a hypophosphatemia-induced increase in calcitriol concentration.

II. Clinical consequences of hypophosphatemia

Rhabdomyolysis

Fuller and Knochel at the Dallas VA examined the effect of chronic hypophosphatemia on muscle function and composition in dogs fed a low phosphorus diet for 4 weeks. During phosphorus depletion, average resting transmembrane electrical potential difference (Em) fell and muscle Na^+, Cl^-, and water content increased. After 4 weeks of phosphorus repletion, these values returned toward control. The authors concluded that moderate phosphorus depletion can induce reversible changes in skeletal muscle composition and transmembrane potential in dogs (4). The same group found that subclinical myopathy (induced by starvation in dogs) may set the stage for rhabdomyolysis if acute, severe hypophosphatemia is superimposed (5). A muscle biopsy from one of the dogs in the study is shown in Figure 2.

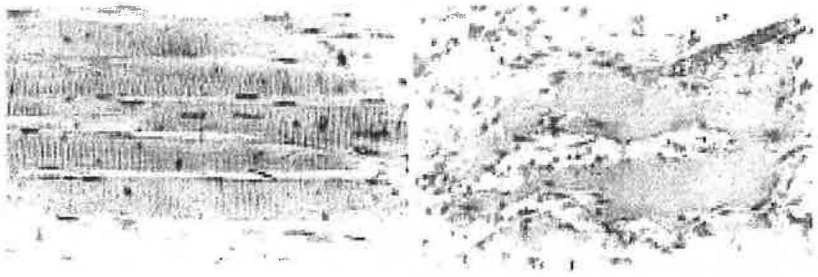


Figure 2

In another study of phosphorus depleted rats, skeletal muscle mitochondrial respiration and oxidative phosphorylation was impaired with no change in adenine nucleotide levels (6). The majority of cases of hypophosphatemia-associated rhabdomyolysis in humans were reported in alcoholics (7). Hypophosphatemia is frequently observed in alcoholic patients due to a combination of several pathophysiological mechanisms, such as increased GI phosphorus loss from diarrhea, inappropriate phosphaturia, and phosphorus shifts from the extracellular to the intracellular space (8). In hospitalized patients these factors can be compounded by alcohol withdrawal and/or alcoholic ketoacidosis. Hyperventilation with resultant respiratory alkalosis and dextrose-containing fluid infusion further adds to hypophosphatemia by stimulating phosphorus movement into cells. The resultant hypophosphatemia can further accentuate the direct toxicity of alcohol on striated muscle and worsen alcoholic myopathy (9).

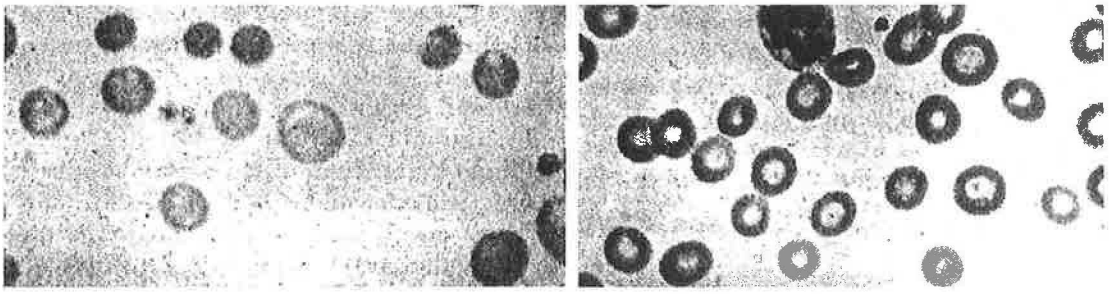
Two studies in humans, however, did not detect a relationship between hypophosphatemia and serum CPK levels (10,11). In both reports hypophosphatemia was moderate, range 0.9-2.0 mg/dL and 1.1-2.4 mg/dL, respectively. In the first of these studies, 36% of 129 patients admitted to hospital with hypophosphatemia were diagnosed with rhabdomyolysis. Hypophosphatemic rhabdomyolysis was defined as an increase in CPK concentration greater than 1½ times the upper limit of normal, with no other associated cause, that subsequently normalized. Mean serum phosphorus concentration was 1.6 mg/dL and was not significantly lower in those that either did or did not develop rhabdomyolysis. The mean CPK concentration was 872±110 IU/L (range 233 to 3,933 IU/L). Rhabdomyolysis was diagnosed on routine laboratory testing and no patient had related signs or symptoms (11). Elevated serum concentrations of sodium, chloride,

glucose, blood urea nitrogen, and uric acid, were associated with the occurrence of rhabdomyolysis in the hypophosphatemic state. The concentration differences, however, between those that developed rhabdomyolysis and those that did not were small, although statistically significant they are of questionable clinical importance.

Given the small numbers of case reports and presence of coexistent metabolic abnormalities that were also implicated as etiologies of rhabdomyolysis, it is difficult to establish a strong cause and effect relationship between hypophosphatemia and rhabdomyolysis in any individual patient. Taken together, these studies indicate that moderate hypophosphatemia is not associated with rhabdomyolysis. Severe hypophosphatemia in the setting of subclinical muscle injury may be associated with rhabdomyolysis that infrequently results in clinical sequellae.

Hemolysis

ATP is required for the maintenance of red cell biconcavity and viability in the



Hypophosphatemia **Phosphorus repleted**

Figure 3

circulation (12,13). ATP depletion is associated with the formation of microspherocytes shown in Figure 3. There are more than a dozen case reports of hypophosphatemia-associated hemolytic anemia. The majority occurred in patients with severe hypophosphatemia with one exception (14-17). A child with marked hyperphosphatemia from the administration of phosphorus-containing enemas developed hemolytic anemia during a therapeutically- induced abrupt fall in serum phosphorus concentration (58 mg/dL to 1.7 mg/dL).

In Figure 4 red cell survival studies in a patient with severe hypophosphatemia showed a shortened survival on admission. Serum phosphorus concentration was 0.1 mg/dL. Red cell deformability was also markedly reduced. Microspherocytosis was noted in the peripheral smear. Phosphorus was repleted and these abnormalities reversed. Red cell ATP levels correlated with serum phosphorus concentration and are shown in Table 1. During the first 7 days of admission red cell ATP levels were less than 15% of control values.

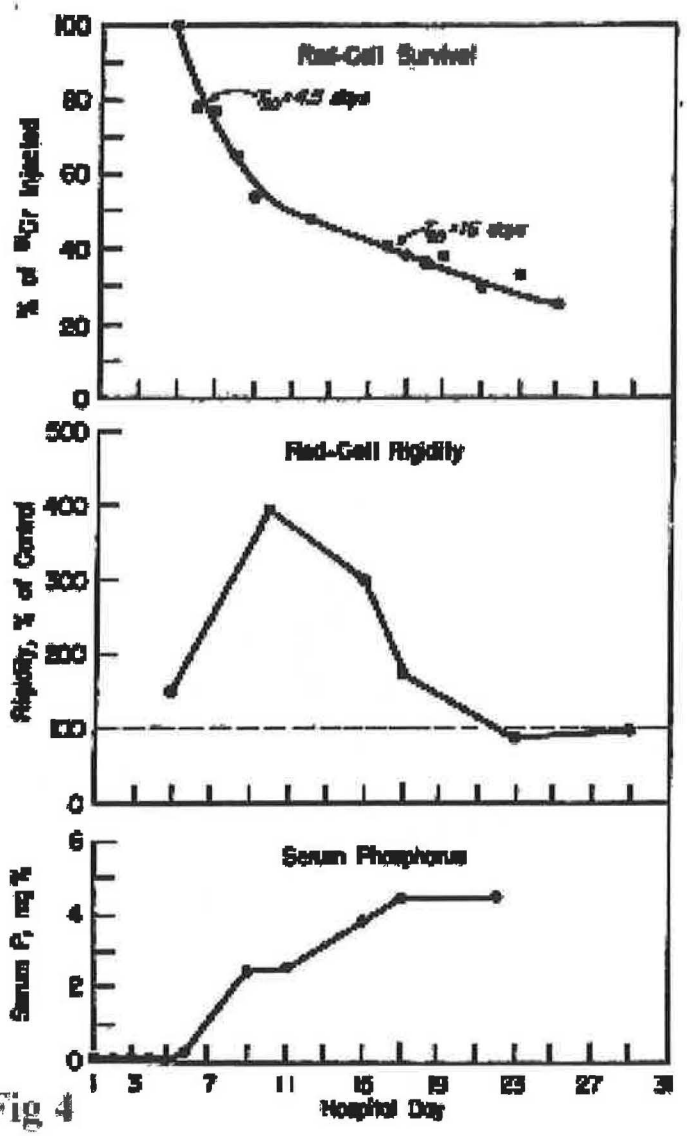


Fig 4

Hypophosphatemia can result in alterations of red cell glycolytic intermediates and oxygen transport. These alterations include marked reduction in erythrocyte ATP and 2,3-DPG levels. With the decrease in ATP and 2,3-DPG concentrations, there is an increased affinity of oxygen for hemoglobin, reflected by a drop in P50. The fall in ATP decreases red cell hexokinase activity and increases phosphofructokinase activity. As a result red cell concentrations of glucose-6-phosphate and fructose-6-phosphate are reduced and there is an accumulation of triose phosphates (18). Phosphorus depletion reduces the activity of glyceraldehyde 3-P dehydrogenase with a decrease in concentration of products distal to the enzyme (Figure 5). The degree of hemolysis is often profound with falls in hematocrit from normal values to 15-20%.

Table 1

Hospital day	µmoles/gm of Hb	% of normal
4	0.39	11
7	0.46	13
9	1.54	44
11	1.80	51
16	2.24	64
21	3.40	97
30	5.50	157

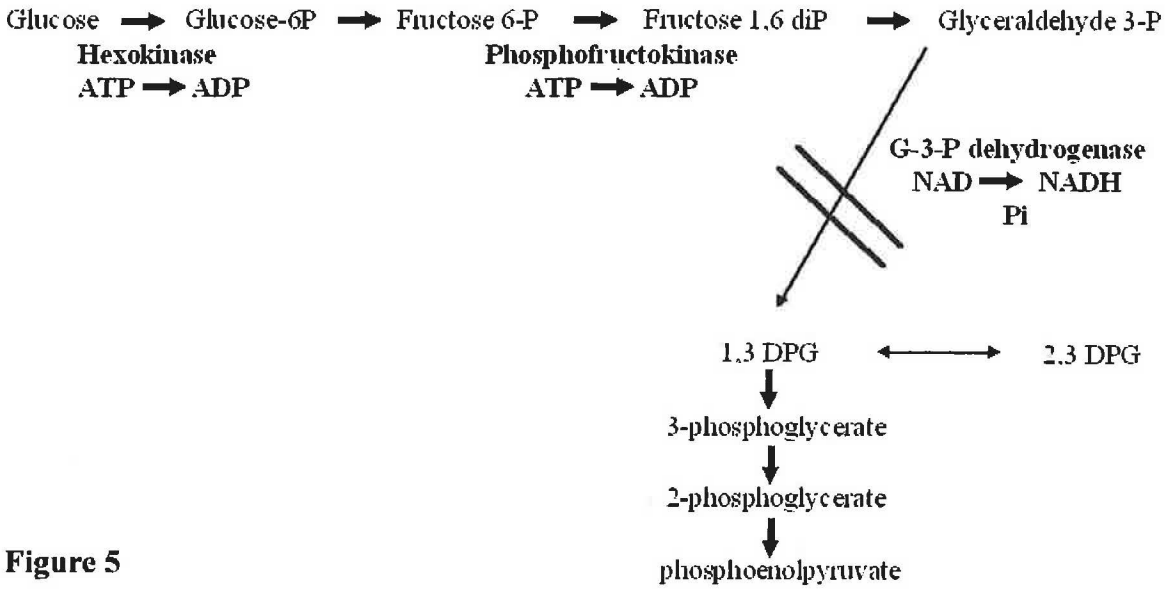


Figure 5

Leukocyte dysfunction

In animal studies hypophosphatemia also causes a reduction in leukocyte ATP content, significant reduction of neutrophil phagocytosis, intracellular killing, consumption of oxygen, and generation of superoxide during phagocytosis (19,20). The high rate of sepsis during hyperalimentation may in part result from acquired dysfunctions in chemotaxis and phagocytosis by leukocytes as a consequence of hypophosphatemia induced by refeeding (19). Although there is good evidence in animal models that hypophosphatemia impairs leukocyte function, there is no compelling evidence in animals or humans that this is associated with an increased infection risk.

Respiratory failure

Table 2

Parameter	SH group	Control group	P value
Duration ventilation (days)	2.1 (1.7)	1.1 (0.9)	0.05
Duration ICU stay (days)	2.6 (2.9)	2.1 (2.7)	NS
Hospital LOS (days)	7.8 (3.4)	5.6 (2.5)	0.05
Incidence atrial fibrillation	55 (28.4%)	116 (31.1%)	NS
Cardioactive drugs (%)			
At ICU admission	83.5%	76.1%	NS
< 4 h	26.5%	44.5%	0.05
12–24 h	16%	10.9%	0.05
> 24 h	23.5%	13.8%	0.05
> 1 drug ICU admission	42.3%	28.2%	0.05
Mortality (%)	10/194 (5.2%)	17/372 (4.6%)	NS

NS, not significant; LOS, length of stay

While infrequent, hypophosphatemia as a cause of respiratory failure and refractory weaning from the ventilator was reported on multiple occasions. The majority of these patients were severely hypophosphatemic (≤1.0 mg/dL). In these case reports weaning from the ventilator was achieved with correction of hypophosphatemia (21-28).

Storm studied 566 consecutive patients undergoing cardiac surgery shown in Table 2 (29). Severe hypophosphatemia defined as a serum phosphorus concentration < 1.5 mg/dL, was present in 34.3%. Mean serum phosphorus concentration in this group of

patients was 0.88±0.4 mg/dL. A control group had a mean serum phosphorus concentration of 2.62±0.25 mg/dL. Hypophosphatemic patients had a prolonged time on the ventilator, an increase in length of hospital stay, and use of more cardioactive drugs.

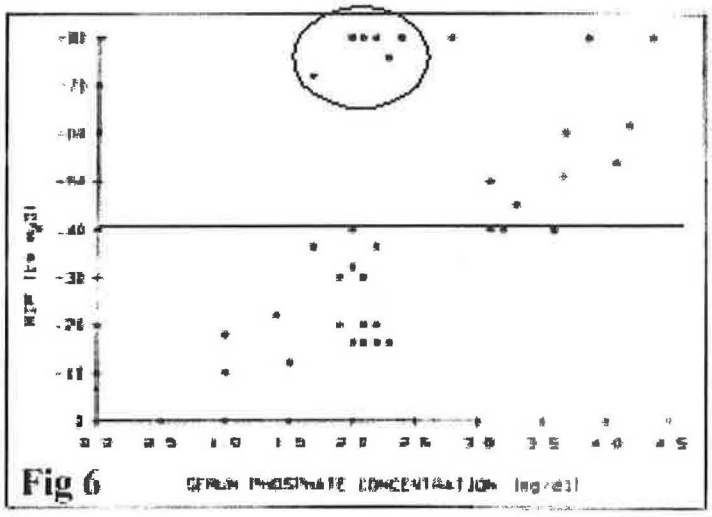


Fig 6

Gravelyn measured maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) at the bedside in hospitalized patients with serum phosphorus concentrations less than 2.5 mg/dL. These measurements were repeated daily during phosphorus repletion until serum phosphorus concentration reached the normal range. The majority of hypophosphatemic patients, but none of the control patients exhibited respiratory muscle weakness defined by low MIP (less than 40 cm H_2O) or MEP (less than 70 cm H_2O) that improved after phosphorus repletion. Mean serum phosphorus concentration of these 23 patients was 1.9±0.4 mg/dL. Twelve patients had a serum phosphorus concentration ≤2.0 mg/dL, and 4 had serum phosphorus concentrations between 1.0 and 1.5 mg/dL. There was a relationship between the decrease in MIP and the severity of hypophosphatemia (Figure 6) (30). In contrast to other reports, there was a group of patients with moderate hypophosphatemia without respiratory muscle weakness.

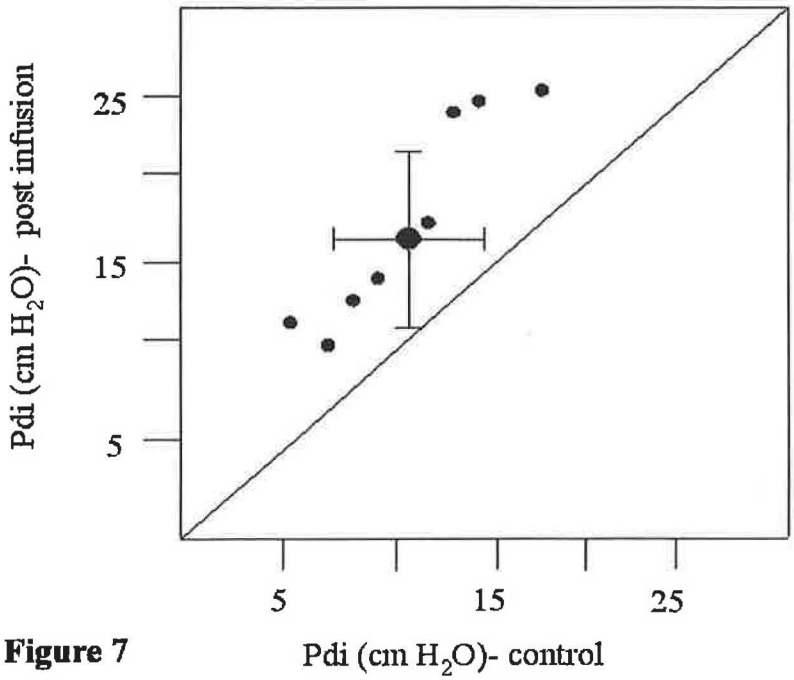


Figure 7

Hypophosphatemia also impairs the contractile properties of the diaphragm during acute respiratory failure (31). In a group of 8 patients with moderate hypophosphatemia and acute respiratory failure requiring mechanical ventilation, diaphragmatic function was evaluated pre and post phosphorus infusion. Transdiaphragmatic pressure generated at functional residual capacity during bilateral supramaximal electrical

stimulation of the phrenic nerves was measured. Transdiaphragmatic pressure increased in all 8 patients from a mean of 9.8±3.8 cm H_2O to 17.25±3.8 cm H_2O (Figure 7). The increase correlated with the change in serum phosphorus concentration. A representative pressure tracing is shown in Figure 8.

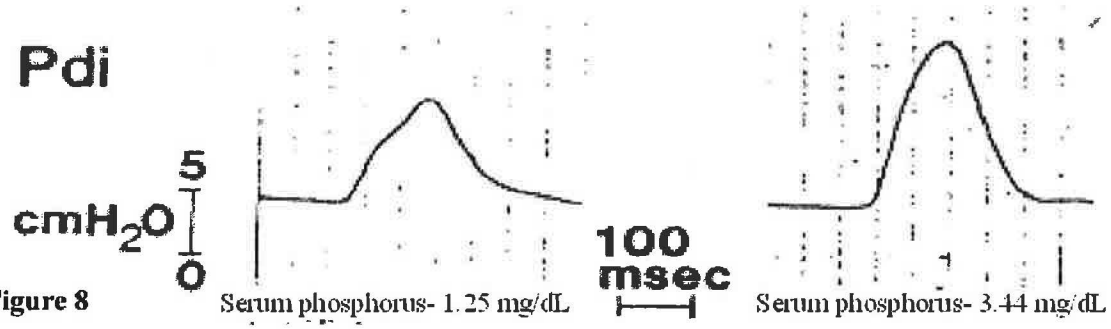


Figure 8

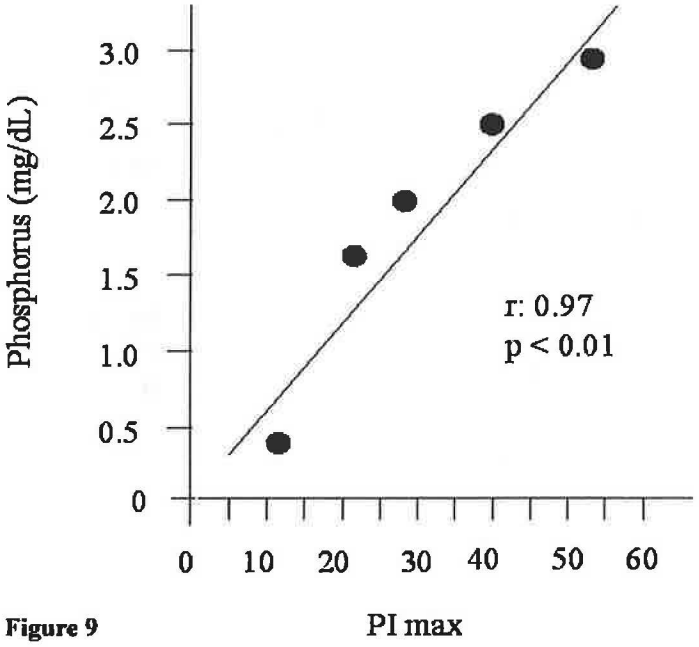


Figure 9

Agusti measured the maximal inspiratory pressure (the negative pressure generated during inspiration from functional residual capacity) in a ventilated patient with severe hypophosphatemia during phosphorus repletion (32). He found a high degree of correlation between serum phosphorus concentration and maximal inspiratory pressure (Figure 9).

Hypophosphatemia is common in patients with COPD. In one study, hypophosphatemia (serum phosphorus concentration ≤ 2.5 mg/dL) was found in 34 (21.5%) of 158 patients (33). Hypophosphatemia was not associated with severity of respiratory illness. Indices of renal phosphorus handling were compatible with an inappropriately high phosphorus excretion given the degree of hypophosphatemia (low percent tubular phosphorus reabsorption, low renal phosphate threshold $TmPO_4/GFR$ values). Prevalence of hypophosphatemia was significantly higher among COPD patients taking one or more drugs known to increase renal phosphorus excretion including: xanthine derivatives; corticosteroids; loop diuretics; and beta 2-adrenergic bronchodilators. In another study, while muscle phosphorus content of both peripheral and respiratory muscles (intercostals muscles) of COPD patients was also reduced, a relationship between muscle and serum phosphorus concentration was demonstrable only in peripheral muscle (34). COPD is a condition where serum phosphorus concentration may not be representative of cellular phosphorus stores.

In summary, diaphragmatic contractility can be improved with correction of severe, as well as moderate hypophosphatemia. One should monitor serum phosphorus concentration carefully in intubated patients and correct it into the normal range if possible.

Myocardial performance

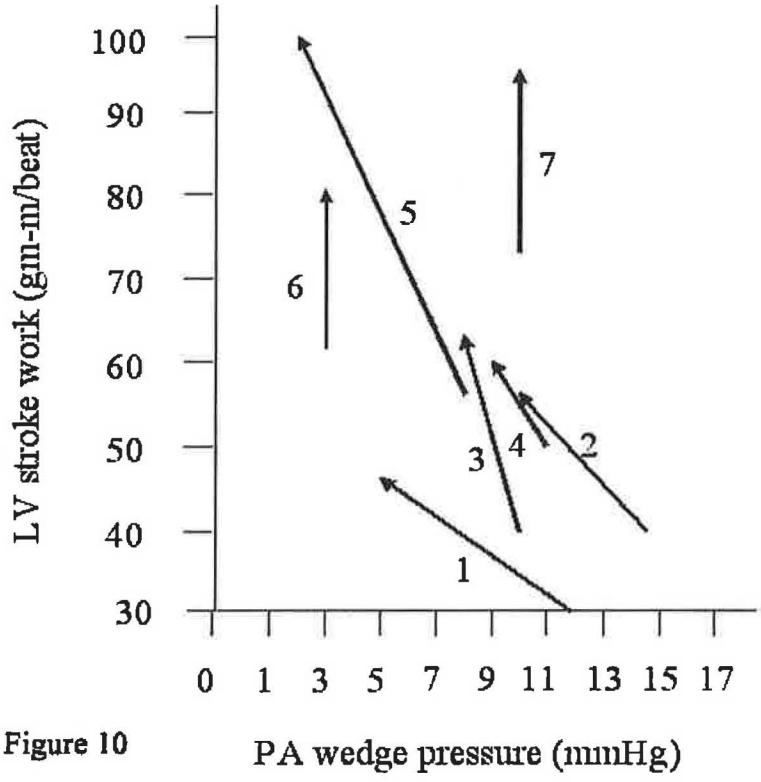


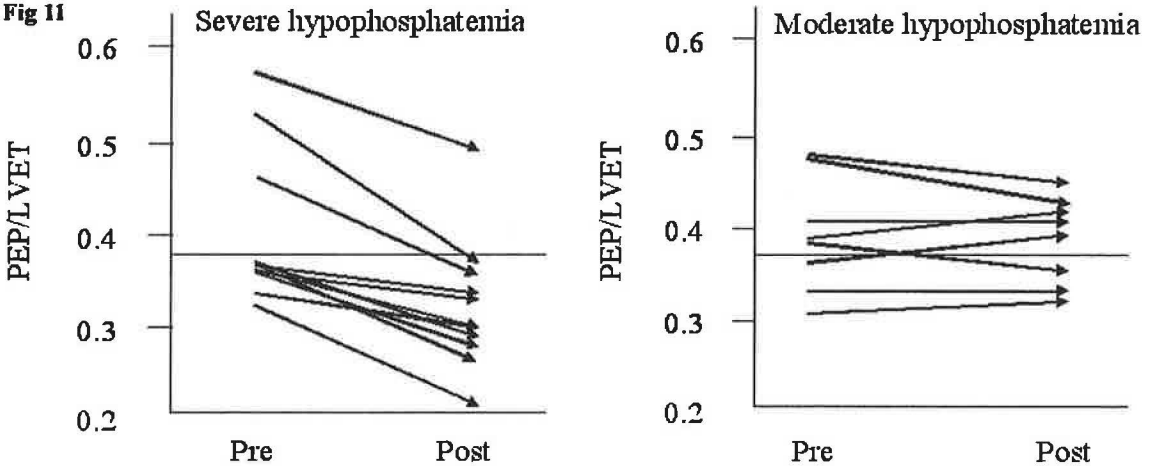
Figure 10

Several studies examined the effects of moderate and severe hypophosphatemia on cardiac function in humans. O'Connor measured cardiac output by thermodilution and calculated stroke work in seven patients with severe hypophosphatemia before, during, and after repletion with an intravenous potassium phosphate solution. All patients were critically ill and in the intensive care unit. Return of serum phosphorus concentration to normal improved myocardial stroke work, increased stroke volume, and reduced pulmonary capillary wedge pressure (35). The effect on pulmonary capillary wedge pressure is shown in Figure 10. An increase in stroke work at the same or lower pulmonary capillary wedge pressure with the same or higher afterload is indicative of increased myocardial contractility. Vered reported that chronic hypophosphatemia (serum phosphorus concentration 1.6-2.0 mg/dL) did not cause left ventricular dysfunction (36). This discrepancy may be related to the different mean serum phosphorus concentrations of patients in these two studies. While the mean serum phosphorus concentration in O'Connor's study was 0.97 mg/dL, in Vered's report it was much higher, 1.88 mg/dL. In addition, O'Connor's patients were critically ill ICU patients, while Vered examined stable outpatients.

Davis showed that improvement in left ventricular performance (Figure 11) after correction of hypophosphatemia was seen only in patients with severe hypophosphatemia (0.9±0.15 mg/dL) and not in those with moderate hypophosphatemia (1.4±0.11 mg/dL) (37). In 11 patients without clinical evidence of congestive heart failure he employed a combination of EKG, phonocardiography and carotid pulse tracings to measure myocardial contractility. These were used to determine the preejection period (PEP) which is a measure of isovolemic contraction time, and the left ventricular ejection time

(LVET) which is a measure of stroke volume. The ratio of PEP/LVET is a sensitive index of myocardial dysfunction and is highly correlated with angiographic ejection fraction. An increased ratio is an indicator of myocardial dysfunction representing either an increase in PEP or decrease in LVET.

Fig 11



0.39 ± 0.008 → 0.32 ± 0.06 (p < 0.001)
All patients improved

0.35 ± 0.12 → 0.30 ± 0.02 (NS)
3 of 8 patients improved

Two additional studies confirmed that moderate hypophosphatemia does not cause myocardial dysfunction. Vered examined 10 patients (aged 5-18 years) with X-linked hypophosphatemic rickets and mean serum phosphorus concentration of 2.6±0.5 mg/dL. He found no evidence of left ventricular dysfunction as measured by echocardiography in this human model of long-standing hypophosphatemia. The lowest serum phosphorus concentration in these patients was 1.5 mg/dL (38). Rasmussen studied 16 patients after colon or rectal surgery with glucose-induced hypophosphatemia (39). Serum phosphorus concentration declined to a mean of 1.47±0.28 mg/dL after 2 days. There was no change in stroke volume, cardiac output or mean arterial pressure (Table 3).

Table 3

	Day 1		Day 2	
	Preinfusion	Postinfusion	Preinfusion	Postinfusion
Phosphorus (mg/dL)	2.93	2.09	2.22	1.47
Stroke volume (ml)	50	50	50	49
Cardiac output (L/min)	4.12	4.3	3.85	3.63
MAP (mmHg)	93	95	93	95

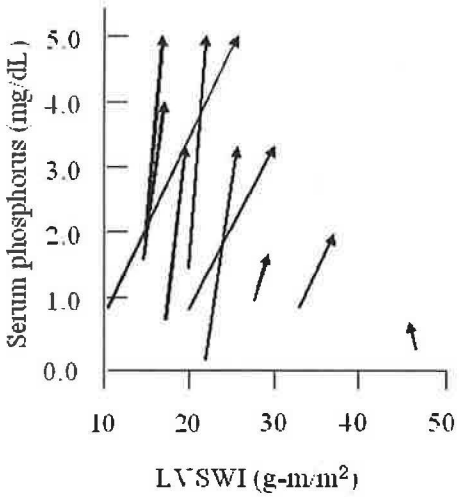
Two subsequent reports confirmed that acute severe hypophosphatemia does affect myocardial performance. Zazzo studied 8 SICU patients with mean serum phosphorus concentration of 1.00±0.38 mg/dL and noted that short-term phosphorus infusion increased cardiac index, stroke index, and left ventricular stroke work index with no change in mean arterial pressure (Table 4) (40).

Table 4

Parameter	Pre infusion	Post infusion	p value
Phosphorus (mg/dL)	1.00 ± .38	2.66 ± 1.4	< 0.01
CI (L/min m^2)	3.82 ± 1.97	4.52 ± 1.83	< 0.01
SI (ml/m^2)	36.4 ± 14.8	42.3 ± 13.8	< 0.01
LVSWI (g-m/m^2)	44.2 ± 23.9	52.4 ± 24.6	< 0.01
MAP (mmHg)	91 ± 14	91 ± 15	NS

Figure 12

Parameter	Pre infusion	Post infusion	p
Phosphorus (mg/dL)	1.05 ± .45	3.40 ± 1.4	< 0.01
CI (L/min m^2)	3.30 ± 1.00	3.60 ± 1.20	NS
LVSWI (g-m/m2)	23.8 ± 10.0	27.5 ± 8.5	< 0.01
MAP (mmHg)	70 ± 11	77 ± 11	NS



Bollaert examined 10 patients with septic shock and hypophosphatemia (41). An infusion of 20 mmoles of phosphorus was given over 1 hour. Left ventricular stroke work index increased significantly (23.8±10 g/m^2 to 27.5±8.5 g/m^2) but there was no change in cardiac index or mean arterial pressure. As can be seen in Figure 12 the greatest response was noted in three patients with severe hypophosphatemia.

Case reports of clinical congestive heart failure are rare. An initial report of three patients with antacid-induced hypophosphatemia and congestive heart failure was subsequently retracted (42).There are three additional reports of clinical congestive heart failure associated with hypophosphatemia that reversed with repletion (43-45). The best documented occurred in a 39 year old woman with alcoholic ketoacidosis and a serum phosphorus concentration of 0.5 mg/dL (45).

Two studies examined the relationship between serum phosphorus concentration and cardiac arrythmias. In the first, low serum phosphorus concentration (less than 2.6 mg/dL) was a significant predictor of ventricular tachycardia in patients with a recent myocardial infarction (46). The investigators examined 325 consecutive patients admitted to a CCU over a six month period, 111 were diagnosed with an acute myocardial infarction. In patients with a serum phosphorus concentration < 2.6 mg/dL, 57% had ventricular tachycardia in the first 24 hours. In those with a serum phosphorus concentration > 2.6 mg/dL, 27% had ventricular tachycardia. Schwartz studied 16 patients with sepsis and no evidence of cardiac disease in their first 24 hours in an ICU (47). Ten of 16 patients had 21 episodes of atrial and ventricular arrhythmias. The serum phosphorus concentration was lower in those with arrythmias, 2.28±0.5 mg/dL versus 3.19±1.0 mg/dL.

In conclusion, correction of severe hypophosphatemia increases myocardial contractility approximately 20%. The effect is variable between patients with some showing minimal to no response and others showing large responses. Moderate hypophosphatemia probably has little effect on myocardial contractility. Data remains too limited to draw any firm conclusions on the association of hypophosphatemia and serious cardiac arrhythmias.

Central nervous system

There are multiple case reports indicating an association of hypophosphatemia with neurological manifestations including altered mental status, polyneuropathy including cranial nerves, seizure, and central pontine myelinolysis (48-51). In some cases the clinical picture mimicked that of Guillain-Barré syndrome. In almost all reports of neurologic disorders associated with hypophosphatemia serum phosphorus concentrations were below 1 mg/dL. The majority of patients developed hypophosphatemia in the setting of refeeding. In three reported cases of central pontine myelinolysis all were alcoholics that developed the syndrome in the absence of changes in serum sodium concentration. A few cases of proximal muscle weakness were associated with moderate hypophosphatemia in hemodialysis patients (serum phosphorus concentrations of 2.2-3.2 mg/dL) but this may have been the result of vitamin D deficiency (52).

Some of these neurologic signs and symptoms were reported by patients in Lotz and Bartter's study including weakness, tremor, and paresthesias that reversed with cessation of antacids. It seems likely that these symptoms are the result of hypophosphatemia. Whether there is a cause and effect relationship between hypophosphatemia, a Guillain-Barré-like syndrome, and central pontine myelinolysis is less clear.

Metabolic consequences of hypophosphatemia

Hypophosphatemia is associated with impaired glucose metabolism in both hyperglycemic and euglycemic states, and this primarily reflects decreased tissue sensitivity to insulin. DeFronzo carried out insulin and glucose clamp studies in 6 stable nondiabetic outpatients with chronic hypophosphatemia versus normal controls (53). Range of serum phosphorus concentration was 1.6-2.8 mg/dL. None of the patients were

hyperglycemic and no attempts were made to correct hypophosphatemia. The amount of glucose metabolized per unit of insulin (M/I ratio) was 12.09±0.75 mg/kg/min per unit of insulin x100 in controls and 8.71±1.37 mg/kg/min per unit of insulin x100 in the hypophosphatemic group.

In patients with untreated diabetic ketoacidosis serum phosphorus concentration may be normal or slightly elevated despite the fact that renal phosphorus excretion is increased. Seldin examined the metabolism of glucose and cellular balances of electrolytes in diabetic acidosis. Phosphorus translocation from intracellular to extracellular fluid was highest initially and fell during treatment of ketoacidosis with insulin and fluids. Initial phosphaturia also decreased after correction of ketoacidosis (54).

Kono found that ketoacidosis inhibited the glycolytic enzyme phosphofructokinase in erythrocytes. As a consequence the concentration of glycolytic intermediates proximal to this step increased, while those distal, including 2,3-DPG, decreased. Although insulin administration produced hypophosphatemia within 8-12 hours, and it persisted for 24 hours or longer, in vitro studies revealed that acidemia was mainly responsible for phosphofructokinase inhibition (55).

III. Management of hypophosphatemia

Only in selected circumstances does moderate hypophosphatemia (1-2.5 mg/dL) have significant clinical consequences in humans, therefore, there is little need for aggressive intravenous phosphorus replacement. This is particularly true in situations associated with intracellular phosphorus shifts. On the other hand, there is evidence indicating improvement of respiratory parameters in ventilated patients after treatment of moderate hypophosphatemia and phosphorus should be repleted into the normal range in this setting.

The role of phosphorus replacement in the management of diabetic ketoacidosis (DKA) is controversial. In a prospective randomized study it was concluded that phosphorus repletion may accelerate regeneration of erythrocyte 2,3-DPG in patients with DKA but it had no demonstrable influence on tissue oxygenation or clinical response to low dose insulin therapy. Furthermore, with phosphorus replacement there was an exaggeration of hypocalcemia, a reason for caution in the use of such therapy (56). It should be noted that the amount of phosphorus administered to patients that developed hypocalcemia was very high.

It is generally recommended that severely hypophosphatemic patients (less than 1.0 mg/dL) be repleted with parenteral phosphorus to avoid potential detrimental consequences. Administration of radiolabeled phosphorus shows that the phosphorus space is heterogeneous. Phosphorus enters several pools at varying rates that can be altered by many factors, including simultaneous administration of glucose or insulin (57). Lentz proposed that in a given hypophosphatemic patient, rapid shifts of phosphorus among body compartments may occur during phosphorus infusion and accordingly neither the phosphorus space, the body deficit, nor response to replacement can be easily predicted. He recommended intravenous therapy for severe hypophosphatemia with an initial dose of 0.08 mmol/kg body weight (2.5 mg/kg body weight) if hypophosphatemia is recent and uncomplicated, and 0.16 mmol/kg body weight (5 mg/kg body weight) if it

is prolonged and has multiple causes. He also advised that each dose be given over 6 hours (58). Although widely quoted none of these recommendations are based on clinical data.

In addition to total dose, rate of administration has been a concern in the parenteral treatment of hypophosphatemia. Intravenous phosphorus therapy was reported to cause a precipitous fall in serum calcium concentration, hypotension and acute renal failure when given in high doses for treatment of hypercalcemia (59). The rate of administration in these case reports was 100 mmoles over three hours and 50 mmoles over one hour. In another case report hypocalcemia resulted from administration of approximately 150 mmoles of phosphorus per day in the treatment of patients with diabetic ketoacidosis (60). These doses are much higher than currently administered.

Several studies examined the safety and efficacy of short-term phosphorus infusions and are summarized in Table 5.

	Dose	N	Severity	Complications
Rosen	15 mmol/2hrs Q6H, no > 45 mol/day	11	moderate 1.5-1.9 mg/dL	none
Vannatta	9 mmol Q12hrs for 48 hrs	10	severe	1 hypocalcemia
Vannatta	0.32-0.48 mmol kg Q12 hrs for 48 hrs	10	severe	none
Kingston	0.25-0.50 mmol/kg over 4 hrs 0.5-1.0 mg/dL- 0.25 mmol/kg < 0.5 mg/dL- 0.50 mmol/kg	28	severe	none
Perreault	15-30 mmols over 3 hrs 1.27- 2.48 mg/dL- 15 mmol/kg < 1.24 mg/dL- 30 mmol/kg	27	Both	2 mild fall in Ca within nl range
Charron	1.25-2.03 mg/dL- 30 mmols 2-4 hrs < 1.25 mg/dL- 45 mmols 3-6 hrs	47 (37/10)	Both	1 hyperphosphatemia
Taylor	< 1 mg/dL- 40-60 kg 30 mmols, 61-80 kg- 40 mmols, 81-120 kg- 50 mmols 1.0-1.7 mg/dL- 40-60 kg- 20 mmols, 61-80 kg- 30 mmols, 81-120 kg- 40 mmols 1.8-2.2 mg/dL- 40-60 kg-10 mmols, 61-80 kg- 15 mmols, 81-120 kg- 20 mmols	111	Both	None reported

Ten adult patients with severe hypophosphatemia (≤1.0 mg/dL), two or more clinical reasons for hypophosphatemia, and normal renal function were studied prospectively by Vannatta (61). Patients were treated with 0.32 mmol/kg of phosphorus infused intravenously over 12 hours for up to 48 hours. They concluded that this dose was safe and efficacious. These same authors reported 10 patients with severe hypophosphatemia repleted with 9 mmoles of phosphorus every 12 hours for up to 48 hours. One patient developed symptomatic hypocalcemia. Serum phosphorus concentration increased to greater than 1 mg/dL in all patients after 36 hours, and was in the normal range in 6 of 10 patients after 48 hours (62). Rosen studied 11 patients in a surgical intensive care unit

with moderate hypophosphatemia (serum phosphorus concentration from 1.5 to 1.9 mg/dL). They administered 15 mmoles of sodium or potassium (if serum potassium concentration was <3.5 meq/L) phosphate
intravenously over two hours. The same dose could be repeated to a maximum of 45 mmol in a 24 hour period if either the 6 hour or 18-24 hour follow up postinfusion serum phosphorus concentration remained <2.0 mg/dL. All patients were successfully repleted using the described protocol without any significant adverse events (63). Perreault studied a group of patients with moderate (serum phosphorus concentration 1.27-2.48 mg/dL) and severe (<1.24 mg/dL) hypophosphatemia (64). The repletion rate varied based on severity of hypophosphatemia, 15 or 30 mmol over 3 hours, in the moderate and severe patients, respectively. Serum phosphorus concentration returned into the normal range in 81% of moderately hypophosphatemic patients and 30% of patients with severe hypophosphatemia. Serum calcium concentration declined within the normal range in two patients. Over the subsequent two days many patients required additional doses of phosphorus. Kingston safely administered 0.25-0.5 mmol/kg of phosphorus over 4 hours in a group of 31 severely hypophosphatemic patients (65). Charron reported 47 patients with moderate (1.25-2.03 mg/dL) and severe (< 1.25 mg/dL) hypophosphatemia (66). As in other studies the dose of phosphorus administered varied depending on the degree of hypophosphatemia, 30 mmoles over 2-4 hours and 45 mmoles over 3-6 hours in moderate and severe patients, respectively. Only one patient developed hyperphosphatemia. At 24 hours 21% of patients required supplemental doses. Taylor employed a much more complicated regimen in 111 patients with both moderate and severe hypophosphatemia. Phosphorus dose varied based both on the severity of hypophosphatemia and the patient's weight and was administered over 6 hours (67). Doses are shown in Table 5. Most patients were repleted into the normal range with a single dose, 78% of moderately hypophosphatemic patients and 62% of severely hypophosphatemic patients. It is important to recognize that patients with a creatinine clearance less than 25 ml/min, a serum creatinine concentration of 4.0 mg/dL, a urine output less than 30 ml/hour, and hypocalcemia were excluded. This group of patients would be at high risk for complication with a rapid repletion protocol. The authors also excluded patients receiving phosphorus-containing total parenteral nutrition. Not all studies excluded this group of patients, however, this additional source of parenteral phosphorus must be considered when contemplating a repletion regimen.

In summary, although these studies support that hypophosphatemic patients can be repleted with rapid phosphorus infusion, the use of intravenous phosphorus-containing solutions is best justified in the critically ill intubated patient where it was shown that hypophsophatemia may increase the number of days a patient is intubated and extend hospital stay. Other clinical sequellae such as severe hemolytic anemia may also warrant rapid repletion. Patients with moderate hypophosphatemia should be repleted orally unless they are on a ventilator. For those interested in reading more on this topic please consult reference 68.

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