

Review

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Medication-induced hypophosphatemia: a review

G. LIAMIS, H.J. MILIONIS and M. ELISAF

From the Department of Internal Medicine, School of Medicine, University of Ioannina, Ioannina, Greece

Address correspondence to H.J. Milionis, MD, Assistant Professor of Internal Medicine, Department of Internal Medicine, School of Medicine, University of Ioannina, 45110 Ioannina, Greece. email: hmilioni@uoi.gr

Summary

Hypophosphatemia (serum phosphorus concentration <2.5 mg/dl, 0.8 mmol/l), although rare in the general population, is commonly observed in hospitalized patients and may be associated with drug therapy. In fact, hypophosphatemia frequently develops in the course of treatment with drugs used in every-day clinical practice including diuretics and bisphosphonates. Proper diagnostic approach of patients with low serum phosphorus concentrations should involve a detailed medical history with

special attention to the recent use of medications. The clinical manifestations of drug-induced hypophosphatemia are usually mild but might also be severe and potentially life-threatening. This review aims at a thorough understanding of the underlying pathophysiological mechanisms and risk factors of drug therapy-related hypophosphatemia thus allowing prevention and effective intervention strategies.

Introduction

Hypophosphatemia is an electrolyte disorder occurring in a broad spectrum of patients, from asymptomatic to critically ill. Its incidence varies considerably depending on the population at risk and the definitions used in various studies. Hypophosphatemia is infrequent in the general population and is mainly encountered in hospitalized patients (ranging from 2.2 to 3.1%) or patients admitted to intensive care units (28.8–34%), as well as those with chronic alcoholism (2.5–30.4%), major trauma (up to 75%) and sepsis (65–80%).¹

Serum phosphate or phosphorus normally ranges from 2.5 to 4.5 mg/dl (0.81 – 1.45 mmol/l) in adults. Hypophosphatemia is defined as mild (2 – 2.5 mg/dl

or 0.65 – 0.81 mmol/l), moderate (1 – 2 mg/dl or 0.32 – 0.65 mmol/l), or severe (<1 mg/dl or 0.32 mmol/l).² Phosphorus is a vital component of cellular membranes, enzyme systems, nucleic acids and various nucleoproteins.³ Thus, optimal cellular function depends on the maintenance of a normal serum phosphorus concentration. Mild hypophosphatemia is generally asymptomatic. Hypophosphatemia when combined with phosphate depletion can cause a variety of signs and symptoms.^{4,5} The manifestations are closely related to the severity and chronicity of its occurrence, with the plasma phosphate concentration usually being below 1.0 mg/dl (0.32 mmol/l) in symptomatic patients.¹ It should be emphasized that serum phosphorus concentrations lower than 1 mg/dl for two or

more days can lead to serious complications, such as rhabdomyolysis, respiratory failure, acute hemolytic anemia and arrhythmias.⁶ Of note, in a retrospective study, severe hypophosphatemia was associated with a fourfold increase in mortality.⁷

Since drugs are thought to be a common cause of electrolyte abnormalities, a careful drug history is essential in patients who exhibit these disturbances. For example, in a series of 51 out of 120 patients who exhibited severe hypophosphatemia (defined as serum phosphorus ≤ 1.5 mg/dl or 0.48 mmol/l) post-operatively, medications (mainly intravenous administration of glucose, antacids, diuretics and steroids) were the most common causative factors of low serum phosphorus levels accounting for 82% of hypophosphatemia cases.⁸ Drug-related hypophosphatemia, though usually mild and asymptomatic, may be severe leading to significant morbidity or death. Consequently, a thorough understanding of the underlying pathophysiologic mechanisms of drug-induced hypophosphatemia and the associated risk factors is of vital importance.

Herein, we review the clinical information of hypophosphatemia associated with specific drug treatment and discuss the underlying pathophysiology.

Pathophysiology of hypophosphatemia

Phosphorus is the sixth most abundant element in the body. Normal total body phosphorus content in an average adult is 700 g (10 g/kg body weight), of which 85% is contained in skeleton, 14% in soft tissues, and only 1% in the extracellular fluid (Figure 1A). In plasma, phosphate is mainly present as inorganic phosphate (Pi), and this fraction is very small ($<0.2\%$ of total phosphate).³ However, body phosphate metabolism is regulated through plasma inorganic phosphate. The kidney and (to a lesser extent) small intestine are the main organs that participate in the regulation of Pi homeostasis (Figure 1B).⁹ Phosphate is plentiful in the diet. A normal diet provides ~ 1000 mg of phosphate, 65% of which is absorbed, predominantly in the proximal small intestine, even in the absence of vitamin D. On the other hand, a very low-phosphate diet and vitamin D further enhances (to 85–90%) the intestinal phosphate reabsorption.³ Phosphate is freely filtered in the glomerulus. More than 80% of the filtered load is reabsorbed in the proximal tubule and a small amount in the distal tubule. The fractional excretion of phosphate is generally in the range of 10–15%. However, renal phosphate excretion is not constant but varies directly with

dietary intake. Indeed, low dietary Pi intake induces a near complete reabsorption of filtered Pi, whereas high-phosphate diet leads to diminished renal Pi reabsorption.¹⁰

Renal and intestinal phosphate reabsorption is also mediated by multiple hormonal and non-hormonal factors. For example, parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23) decrease the absorption of phosphate in the proximal tubule, while 1,25-dihydroxyvitamin D3 increases tubular phosphate reabsorption. Moreover, intestinal absorption of phosphate is facilitated by active vitamin D.^{10–13} It should be noted that renal phosphate reabsorption is exerted by sodium-phosphate co-transporters (types I, II and III). The type II cotransporter comprises three highly homologous isoforms: types IIa and IIc, which are located in the brush-border membrane of the proximal tubules, and type IIb, which is not expressed in the kidney but is responsible for intestinal Pi absorption.^{14–16}

Hypophosphatemia results from the following processes either alone or in any combination: trans-cellular shift of Pi from the extracellular fluid into cells, increased Pi excretion via the kidneys, and decreased intestinal Pi absorption. Short-term reduction of the serum phosphorus concentration is modulated by intracellular Pi redistribution, while long-term hypophosphatemia is related to increased renal or intestinal Pi losses.³

Hypophosphatemia as a consequence of drug treatment

Hypophosphatemia-related to drug-treatment can be caused by several medications. Since hypophosphatemia can be attributed to many other causes, the diagnosis of drug-induced hypocalcemia may easily be overlooked. Furthermore, drug therapy rarely is disregarded as a contributing factor of decreased serum Pi concentration given that hypophosphatemia has often a multifactorial etiology.

In the following sections, we will present relevant information on the incidence and the pathophysiology of hypophosphatemia in association with the most commonly offending drug agents (Table 1).

Pseudohypophosphatemia

Pseudohypophosphatemia should be kept in mind in patients receiving mannitol treatment. Mannitol is a non-reabsorbable polysaccharide that acts as an osmotic diuretic. Taking into account that mannitol exerts only a weak phosphaturic effect is highly unlikely that its administration *per se* can cause

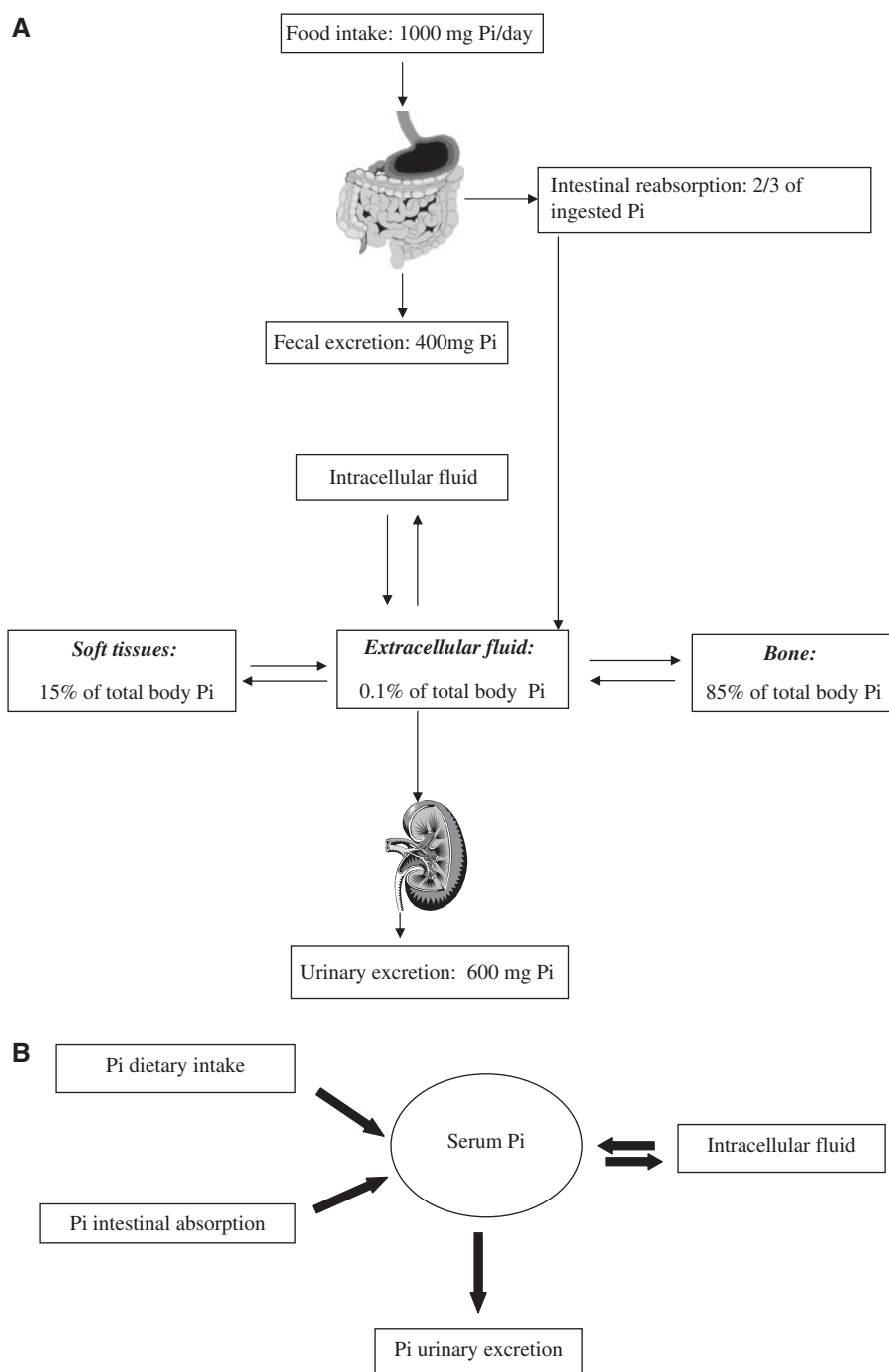


Figure 1. (A) Summary of phosphate (Pi) metabolism for a normal adult in neutral phosphate balance. (B) Major determinants of serum phosphate.

significant hypophosphatemia. Thus, it should be mostly considered as a contributing factor in patients with low serum phosphate levels.¹⁷ Nevertheless, large doses of mannitol can cause pseudohypophosphatemia by binding to the molybdate used in the colorimetric assay of phosphorus. Falsely low serum Pi values tend to occur in assays using relatively low concentrations of molybdate (Dupont aca endpoint method).^{18,19}

Hypophosphatemia due to shifts of extracellular phosphate into cells

Hypophosphatemia due to the movement of Pi from the extracellular to intracellular compartment is common. It is related to the formation of Pi-containing intermediates of glycolytic metabolism.²⁰ The source of this phosphate is the Pi in the extracellular fluid; as a result, serum phosphate

Table 1 Etiology of drug-induced hypophosphatemia

1. Pseudohypophosphatemia
Mannitol
2. Shifts of extracellular phosphate into cells
Acute respiratory alkalosis (salicylate poisoning, mechanical ventilation)
Administration of glucose, fructose, insulin therapy, parenteral nutrition
Catecholamine action: epinephrine, dopamine, salbutamol, xanthine derivatives, hypothermia
Rapid cellular proliferation (erythropoetin, GM-CSF therapy)
3. Decreased intestinal phosphate absorption
Phosphate-binding antacids
4. Increased urinary phosphate excretion
Carbonic anhydrase inhibitors
Diuretics (hydrochlorothiazide, indapamide, furosemide)
Theophylline, bronchodilators, corticosteroids
Drug-induced FS
Volume expansion (drug-induced SIADH, administration of saline)
Bisphosphonates
Estrogens, mestranol
Acyclovir
Imatinib mesylate
5. Hypophosphatemia resulting from more than one mechanism
Drug-induced metabolic acidosis (alcohol, toluene)
Alcohol
Drugs that cause vitamin D deficiency or resistance: phenytoin, phenobarbital
Acetaminophen poisoning
Intravenous iron administration

levels fall rapidly. Internal Pi redistribution because of stimulation of glycolysis takes place in several situations: respiratory alkalosis and administration of glucose, fructose, insulin, catecholamines (epinephrine, dopamine, salbutamol), xanthine derivatives, estrogen, oral contraceptives, glucagon, total parenteral nutrition insufficiently supplemented with phosphate, as well medications that cause rapid cellular proliferation (erythropoetin, other GM-CSF (granulocyte-macrophage colony-stimulating factors). Some of these mediators of redistributive hypophosphatemia deserve a more detailed analysis.

Hypophosphatemia due to acute respiratory alkalosis

It is well known that the increase in intracellular pH stimulates phosphofructokinase activity which in turn stimulates glycolysis.²⁰ Taking into consideration that for a given extracellular pH, carbon dioxide penetrates cell membrane more readily than bicarbonate, respiratory alkalosis which raises intracellular pH more than similar degrees of metabolic alkalosis may lead to a more profound effect on serum Pi concentration.²¹

Respiratory alkalosis plays a major role in the hypophosphatemia of acute *salicylate* intoxication and mechanical ventilation of patients suffering

from severe asthma or chronic obstructive pulmonary disease exacerbations.^{22,23} It should be noted that respiratory alkalosis represents the earliest acid-base abnormality of salicylate intoxication due to a direct stimulation of the respiratory center, while metabolic acidosis because of the accumulation of organic acids ensues.

Hypophosphatemia due to insulin, glucose, fructose and total parenteral nutrition

Increased *insulin* levels promote the transport of both glucose and phosphate into skeletal muscle and liver. However, in normal subjects the administration of insulin or glucose (which stimulates the beta cells of the islets of Langerhans to release insulin) leads only to a slight decrement of serum Pi levels. The risk of severe hypophosphatemia is increased in cases of underlying phosphate depletion.

Insulin therapy is associated with severe hypophosphatemia in poorly controlled diabetic patients (e.g. diabetic ketoacidosis) given that hyperglycemia induces increased renal phosphate loss via osmotic diuresis.³ Severe hypophosphatemia due to intravenous administration of glucose-containing solutions may also occur in malnourished subjects with alcoholism or anorexia nervosa.^{24–26} As compared to glucose, the rapid infusion of *fructose* by

reducing the intracellular content of Pi (except for cellular Pi sequestration) is more pernicious regarding the phosphate levels.²⁷ Finally, *total parenteral nutrition* has been associated with profound or even fatal hypophosphatemia when the hyperalimentation fluid is inadequately supplemented with phosphate.²⁸

Hypophosphatemia due to catecholamine action

Epinephrine has been characterized as a hypophosphatemic hormone in humans. Net shift of Pi from the extracellular to the intracellular compartment is the main mechanism of epinephrine-related hypophosphatemia.²⁹ Of note, increased secretion of epinephrine due to hypoglycemia explains some cases of insulin-induced hypophosphatemia. It appears that beta-adrenergic stimulation plays a pivotal role in the hypophosphatemic response to catecholamines given that the hypophosphatemic effect of epinephrine is blunted with propranolol.³⁰ In a prospective study of 82 children admitted to a pediatric intensive care unit, only the use of dopamine exhibited an independent association with hypophosphatemia among medicines known to reduce serum Pi concentration.³¹

Hypophosphatemia has also been reported with other sympathomimetic medications illustrating the potential role of catecholamines on phosphate homeostasis. In fact, it has been reported that nebulized *salbutamol* (within 20 min) as well as *theophylline* result in hypophosphatemia.^{32,33} Apart from internal Pi redistribution, sympathomimetic agents (mainly dopamine and theophylline) can cause hypophosphatemia by increasing the urinary phosphorus excretion rate.^{31,34} Finally, *therapeutic hypothermia* (32–33°C) possibly through sympathetic activation has been implicated in the development of hypophosphatemia.³⁵

Hypophosphatemia due to rapid cellular proliferation

An acute increase in hematopoietic cell production by the bone marrow is associated with phosphate uptake by the new cells, which may be of sufficient magnitude to induce hypophosphatemia. In fact, *epoetin-alfa* and *granulocyte-macrophage colony-stimulating factor* (GM-CSF) therapy have been related to hypophosphatemia.^{36,37} In a randomized, open label study of 30 anemic critically ill patients, hypophosphatemia was one of the most frequently reported adverse events of epoetin-alfa treatment affecting 15% of patients.³⁶ In a phase II study of 22 patients with Richter's syndrome or refractory lymphoproliferative disorders treated with fludarabine,

cytarabine, cyclophosphamide, cisplatin and GM-CSF, hypophosphatemia was reported in 10% of patients.³⁷

Hypophosphatemia owing to decreased intestinal phosphate absorption

Hypophosphatemia has repeatedly been associated with phosphate-binding antacids.^{38,39} In fact, absorption of phosphate can be blocked by commonly used over-the-counter aluminum-, calcium- and magnesium-containing antacids. Not only do these medications bind dietary phosphorus, but they also can remove endogenous Pi that is secreted by the small intestine during the absorptive process. Mild-to-moderate use of such phosphate binders generally poses no threat to phosphate homeostasis because dietary ingestion greatly exceeds body needs.

In a study of normal human volunteers, it took ~3 months for the combination of low phosphorus diet and antacids to diminish serum Pi levels to 1 mg/dL.³⁸ Thus, prolonged high-dose therapy with these agents is associated with increased risk of hypophosphatemia even in patients with end-stage renal disease, an entity usually characterized by phosphate retention.³⁹

Finally, hypophosphatemia related to prior antacid use is not infrequently observed in patients who undergo hepatic resection. In a retrospective study, 21 out of 35 patients (67%) exhibited hypophosphatemia after major hepatic surgery. It is noteworthy that the incidence of antacid use in the hypophosphatemic subgroup (4 out of 21; 66%) was significantly higher than the use in the non-hypophosphatemic subgroup (2 out of 14; 14%) ($P < 0.05$).⁴⁰

Hypophosphatemia due to increased urinary phosphate excretion

Hypophosphatemia can be caused by inappropriate phosphaturia. As mentioned above, PTH and FGF-23 increase the renal Pi losses by decreasing the activity of sodium-phosphate co-transporters.¹¹ Hypophosphatemia associated with increased renal phosphate clearance has also been reported in patients with hypokalemia and hypomagnesemia. In fact, studies have shown an increment in the prevalence of hypophosphatemia by six-fold and two-fold in patients with hypokalemia and hypomagnesemia,

respectively, as compared to subjects without these electrolytes disorders.⁴¹ Experimental and clinical observations have demonstrated this close link among potassium, magnesium, and phosphorus concentrations.^{42–44} Potassium depletion is associated with increased urinary excretion of magnesium, calcium and phosphorus, while magnesium depletion causes kaliuresis and potassium depletion.^{43–45} Moreover, magnesium depletion leads to renal phosphate wasting and phosphate depletion, although hypophosphatemia only rarely develops.⁴

Several drugs induce hypophosphatemia through increased renal Pi excretion. They are specifically mentioned hereafter.

Diuretics

Hypophosphatemia owing to renal losses is observed after inhibition of carbonic anhydrase with acetazolamide. *Acetazolamide* is the most effective phosphaturic diuretic because phosphorus reabsorption mainly occurs in the proximal tubules.³ *Thiazides* and *indapamide* can produce an increase in the renal clearance of inorganic phosphate and hypophosphatemia.^{46,47} The underlying mechanisms may involve a direct effect of the diuretic on distal renal tubular reabsorption of phosphate, inhibition of carbonic anhydrase as well as changes in potassium and/or magnesium homeostasis. In a series of 204 patients presenting with hyponatremia, 12.5% of patients treated with thiazide diuretics exhibited concurrent hypophosphatemia (defined as serum phosphorus <2.5 mg/dl or 0.81 mmol/l).⁴⁸

Loop diuretics have minimal effects on phosphate excretion, probably due to the fact that these drugs act on the loop of Henle where phosphate reabsorption is minimal. However, these drugs also exhibit a weak carbonic anhydrase activity, which can explain their weak phosphaturic effect.⁴⁹ In a series of 86 patients with congestive heart failure (New York Heart Association functional classes III–IV) who were all treated with furosemide, hypophosphatemia (defined as serum phosphorus <0.77 mmol/l) was diagnosed in 12.8% of patients.⁵⁰

Bisphosphonates

Mild, transient and usually asymptomatic hypophosphatemia is frequently associated with bisphosphonate therapy. For example, a single 90 mg pamidronate dose as well as a 30 mg/day for 3 days pamidronate regimen were related to a 22 and 53% incidence of hypophosphatemia, respectively.⁵¹ Furthermore, in a series of 33 patients on zoledronate, seven patients (21%) developed transient hypophosphatemia.⁵² The reduction of serum Pi concentration is caused by a significant increment of

PTH levels during the abrupt decrement of serum calcium levels.

Drugs inducing Fanconi's syndrome

Fanconi's syndrome (FS) is characterized by impaired proximal tubular reabsorption of HCO_3^- , Pi, glucose, amino acids and uric acid.⁵³ Consequently, in this setting metabolic acidosis, hypophosphatemia, hypouricemia, aminoaciduria, and/or glucosuria (in the absence of increased serum glucose levels) may be take place. It has been reported that several drugs can induce hypophosphatemia as a features of FS (Table 2).⁵⁴ Specifically, the anticancer drugs *ifosfamide*, streptozocin, azacitidine and suramin have been implicated in the development of FS and hypophosphatemia.^{54–58} Of those, a drug that may deserve emphasis is ifosfamide, a chemotherapeutic agent with considerable renal adverse events. Toxicity involves mainly proximal (reflecting partial or complete FS) and distal renal tubules (type I renal tubular acidosis and nephrogenic diabetes insipidus).^{59,60}

In a series of 593 sarcoma patients on ifosfamide the incidence of nephrotoxicity was 4.6%.⁵⁹ It has been reported that the ifosfamide metabolite, chloroacetaldehyde, may be responsible for this nephrotoxicity. It appears that chloroacetaldehyde causes kidney dysfunction, glutathione depletion and lipid peroxidation. It is known that the concurrent use of sodium 2-mercapto-ethanesulfonate (mesna), a synthetic thiol compound that detoxifies reactive ifosfamide metabolites, reduces the incidence of ifosfamide-induced hemorrhagic cystitis. However, it provides a limited protection against chloroacetaldehyde renal side effects. Clinically significant toxicity appears to occur at a total dose above 100 g/m².⁶¹ On the contrary, renal toxicity is moderate with a moderate dose of ifosfamide.⁶² Since ifosfamide-related phosphaturia is frequently observed, it should be considered as a herald of severe renal dysfunction.⁶⁰ This renal phosphate loss, though, usually reversible may be chronic lasting up to 5 years).⁶³

Clinically significant risk factors for ifosfamide-induced hypophosphatemia include the concurrent administration of another nephrotoxic agent, previous treatment with cisplatin, and the increased total dose of ifosfamide. The incidence of ifosfamide-related hypophosphatemia varies considerably. In a series of 62 children who received ifosfamide 10 (16.1%) developed hypophosphatemia. Of those, 47 (77.4%) also received *cisplatin*.⁶⁴ On the other hand, the incidence of hypophosphatemia related to moderate dose of ifosfamide may be as low as 1%.⁶²

Table 2 Medications causing hypophosphatemia by inducing FS

Anticancer drugs: ifosfamide, streptozocin, azacitidine, suramin
Antibiotics: tetracyclines, aminoglycosides
Antiviral agents: cidofovir, adefovir, tenofovir
Anticonvulsants: valproic acid
Fumaric acid

Antiviral medications including *cidofovir*, *tenofovir*, and more often, *adefovir* can induce hypophosphatemia due to FS. The incidence of adefovir-related FS and hypophosphatemia is dose-dependent. Indeed, hypophosphatemia occurred in 50% of patients after 48 weeks and in 61% of patients after 72 weeks of high dose (120 mg/day) adefovir therapy.⁶⁵ On the contrary, adefovir at a daily dose of 10 mg, which is used for the treatment of hepatitis B, did not reduce the mean serum phosphate concentration.⁵⁴

Finally, hypophosphatemia via FS has rarely been related to antibiotics (particularly *tetracyclines* and *aminoglycosides*), *valproic acid* and *fumaric acid*.^{66–69}

Miscellaneous

The administration of both large doses of *estrogens* in patients with metastatic prostatic cancer and *mestranol* in oophorectomized women have been reported to cause hypophosphatemia due to decrease in renal phosphate reabsorption.^{70–72} Experimental data suggest that renal phosphate wasting and hypophosphatemia induced by estrogen are secondary to down-regulation of NaPi-IIa in the proximal tubule.⁷³

Imatinib mesylate, a drug used in the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors, causing tubulopathy and inappropriate phosphaturia can also induce hypophosphatemia. Secondary hyperparathyroidism due to diminished calcium levels might also play a contributing role in the development of hypophosphatemia in this setting.^{74,75}

Volume expansion (e.g. via saline administration) is associated with increased renal phosphate clearance and hypophosphatemia. Experimental studies have demonstrated that volume expansion evoked an inhibition of phosphate uptake by the renal proximal tubules.⁷⁶ Furthermore, hypophosphatemia in patients with syndrome of inappropriate antidiuretic hormone secretion (SIADH) can also be attributed to volume expansion. Interestingly, hypophosphatemia is the most frequent electrolyte disorder in

patients with hyponatremia due to SIADH.⁴⁸ Taking into account that numerous drugs can induce SIADH, they should also be considered as a potential cause of hypophosphatemia.⁷⁷

Finally, increased renal phosphate excretion due to downregulation of Na–Pi-IIa co-transporter has been proposed as the possible explanation of *acyclovir*-induced hypophosphatemia.^{78,79}

Hypophosphatemia resulting from more than one mechanism

Metabolic acidosis

Metabolic acidosis induces renal wasting of phosphate disproportionate to its effect on mobilization of tissue phosphorus. The increased net loss of phosphate from cells is sometimes accompanied by a reduction in the glomerular filtration rate (GFR) resulting in elevated Pi levels during the acidotic state. Over the reparative phase of acidosis, however, cellular organic phosphates are resynthesized, causing extracellular Pi to move into cells, thus leading to hypophosphatemia.^{80,81}

Metabolic acidosis (namely, alcoholic ketoacidosis) is one of the possible underlying mechanisms of alcohol-related hypophosphatemia.⁸² It has also been reported that sniffing of toluene can cause distal tubular acidosis and hypophosphatemia.⁸³

Drugs causing vitamin D deficiency or resistance

Vitamin D insufficiency can lead to hypophosphatemia both by diminishing gastrointestinal phosphate absorption and by inducing hypocalcemia and secondary hyperparathyroidism, resulting in increased urinary phosphate excretion. It has been reported that several drugs can cause vitamin D deficiency and hypocalcemia.⁸⁴

Osteomalacia (defined as hypocalcemia, hypophosphatemia and elevated serum alkaline phosphatase levels) has been reported with prolonged therapy with anticonvulsants, such as *phenytoin* or *phenobarbital*.⁸⁵ These drugs are inducers of the cytochrome P450 (CYP450) thereby causing increased vitamin D degradation. They also decrease calcium resorption in the gut. Moreover, decreased circulating levels of calcidiol are also observed in patients treated with drugs such *carbamazepine*, *isoniazid* and *rifampin*, due to induction of P450 enzyme activity, which metabolizes calcidiol to inactive vitamin D metabolites.⁸⁴ However, to our knowledge there are currently no reports of

hypophosphatemia associated with the above mentioned agents.

Alcohol

Hypophosphatemia is often observed in alcoholic patients. In a series of 79 alcoholic patients admitted to the internal medicine department for causes related to alcohol abuse, 23 subjects (29.1%) exhibited hypophosphatemia.⁸⁶ The underlying mechanisms involved poor dietary phosphate intake, decreased intestinal Pi absorption, transcellular shift of Pi from the extracellular fluid into cells, and increased renal Pi excretion.⁸⁶

Increased gastrointestinal phosphate losses due to either use of antacids to treat recurring gastritis or diarrhea are not infrequently evident in patients who chronically abuse alcohol. Moreover, respiratory alkalosis (due to sepsis, cirrhosis or alcohol withdrawal) and hyperinsulinemia (due to administration of glucose for rehydration or refeeding) contribute to increased entry of phosphorus into the cells and hypophosphatemia.⁸⁶

Finally, inappropriate phosphaturia may play a role in the pathogenesis of hypophosphatemia. Alcohol-related phosphaturia should be ascribed to: (i) secondary hyperparathyroidism because of calcium and vitamin D malabsorption, (ii) alcoholic ketoacidosis, (iii) metabolic alkalosis which increases phosphaturia, (iv) the phosphaturic effect of ethanol per se which may be related to proximal tubular injury and (v) hypomagnesemia due to inadequate dietary intake, diarrhea, entry of magnesium into the cells during alcohol withdrawal and urinary magnesium losses induced by ethanol.

Acetaminophen overdose

Acetaminophen poisoning has repeatedly been identified as cause of hypophosphatemia. It appears that there is a correlation between the degree of hypophosphatemia and the severity of liver damage due to acetaminophen.^{87–89} The etiology of acetaminophen overdose-induced hypophosphatemia is multifactorial. Internal Pi redistribution due to hyperventilation and dextrose infusion as well as increased renal phosphate loss because of a reduction of the renal threshold for tubular phosphate reabsorption have been proposed.^{87–89}

It has been suggested that processes involved in hepatic regeneration might lead to hypophosphatemia, where as acetaminophen-related hyperphosphatemia is likely caused by renal dysfunction in the absence of hepatic regeneration.⁹⁰

Parenteral iron administration

Parenteral iron administration has been implicated as a cause of hypophosphatemia possibly by reducing renal phosphate reabsorption and inhibiting the 1- α hydroxylation of vitamin D. It has been suggested that this hypophosphatemic effect is mediated by an increase in the phosphatonin FGF-23 probably due to iron-related inhibition of enzymatic cleavage of intact FGF-23.^{91,92} Moreover, iron-related increased renal phosphate losses could be ascribed to a direct toxic effect of iron on renal tubules.^{93,94}

Treating of drug-induced hypophosphatemia

It should be emphasized that the majority of hypophosphatemic patients are asymptomatic and they do not require therapy other than the correction of the underlying cause. For instance, the offending drug should be discontinued and vitamin D should be supplemented in subjects with vitamin D insufficiency).

Phosphate supplementation is indicated in patients who are symptomatic or if risk factors for chronic phosphate depletion (e.g. renal tubular defect) are present. The safest mode of therapy is oral given that overzealous intravenous phosphate therapy for hypophosphatemia has been reported to cause a precipitous fall in serum calcium concentration resulting in tetany, hypotension, renal failure and potentially fatal arrhythmias.^{95–97} Phosphate salts are available in skim milk (~1g/l). Oral phosphate can also be administered in tablets of sodium or potassium phosphate at doses of 2.5–3.5 g daily.

Intravenous replacement of phosphorous should be reserved for patients with severe (<1 mg/dl, 0.32 mmol/l) symptomatic hypophosphatemia until the serum phosphorous exceeds 1 mg/dl and the patient can be switched to oral therapy. The serum Pi concentration should be measured every 6 h because the response to phosphate supplementation is not predictable.^{8,98,99}

Concluding remarks

Hypophosphatemia often develops in the course of treatment with drugs used in every-day clinical practice. Awareness of this undesired effect of certain pharmaceutical agents on serum phosphorous concentrations facilitates a rational clinical management of a potentially life threatening disorder, especially in patients at high-risk for the development of hypophosphatemia, such as alcoholics.

Nonetheless, patients not infrequently receive more than one drug that can negatively affect the renal handling of phosphate as for example in the case of patients with chronic obstructive pulmonary disease who receive xanthine derivatives, corticosteroids, loop diuretics, and/or beta 2-adrenergic bronchodilators and are consequently prone to develop hypophosphatemia. Reducing available phosphate may compromise any organ system, alone or in combination. The critical role phosphate plays in every cell, tissue and organ explains the systemic nature of injury caused by phosphate deficiency. Avoiding or discontinuing offending agents, when possible, is the first step in the management of mild to moderate hypophosphatemia; however, there is little question that treatment may be indicated in those with severe hypophosphatemia in order to obviate any major clinical sequelae.

Conflict of interest: None declared.

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