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Hypophosphatemia in cancer patients

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ABSTRACT

Dysregulation of phosphorus homeostasis resulting in hypophosphatemia is common in cancer patients and can result in serious complications and impact outcomes. Several factors, including critical illness, nutritional status, cancer type and therapy, influence the development of hypophosphatemia. Hypophosphatemia can develop as a result of phosphaturic mesenchymal tumors or as a paraneoplastic phenomenon. The clinical presentation for hypophosphatemia varies depending on the duration and severity of the hypophosphatemia and affects several organ systems. Among other serious effects, hypophosphatemia can impair tissue oxygenation and can cause hemolysis, leukocyte and platelet dysfunction, encephalopathy, seizures, arrhythmias, cardiomyopathy, rhabdomyolysis and coma. Multiple studies have demonstrated that hypophosphatemia is an adverse prognostic marker in inpatients with increased in-hospital stay, mortality and postoperative complications. The phosphate level is homeostatically regulated and maintained in a narrow range by three main hormones: parathyroid hormone, fibroblast growth factor 23 and 1,25-dihydroxyvitaminD_3. Together, these hormones regulate how the intestine, kidneys and bones traffic phosphorus. Several hematological malignancies and cancer therapies are associated with proximal tubular dysfunction (Fanconi syndrome), resulting in phosphaturia. Caution should be taken with parenteral administration of phosphate salts, because secondary complications can develop, principally due to hypocalcemia. The general approach to hypophosphatemia should target the underlying cause. Early recognition and prevention are essential and the approach to hypophosphatemia in the cancer patient, because of the nuances and complexity, should be multidisciplinary.

Keywords: electrolytes, Fanconi syndrome, hypophosphatemia, onconephrology, phosphate, phosphorus, phosphaturia

INTRODUCTION

Hypophosphatemia, defined as serum phosphorus <2.5 mg/dL, is a common occurrence in cancer patients and is associated with increased morbidity and mortality. Phosphorus is essential for the normal physiologic function of all cells and its homeostasis is frequently interrupted by cancer and cancer therapy. In the present article we review the epidemiology, clinical outcomes, physiology, pathophysiology, etiology and treatment of hypophosphatemia in the context of malignancy. Note that phosphorus as a single atom is unstable; we introduce phosphorus into our bodies in the form of phosphate . This is an important distinction because the terminology is often used interchangeably in the literature; in this review we have attempted to preserve this rhetorical precision.

EPIDEMIOLOGY AND CLINICAL OUTCOMES

Among hospitalized patients, hypophosphatemia (defined as serum phosphorus <2.5 mg/dL) is observed in up to 5% of individuals, but the rate is much higher in patients with advanced

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cancer. Based on a single-center report, the incidence of moderate hypophosphatemia (serum phosphorus <2 mg/dL) was 22.9% in ambulatory patients. In comparison, <1% of the general population is reported to have moderate hypophosphatemia [1, 2]. Of course, several factors, including the nutritional status and stage of cancer as well as therapy, influence the incidence of hypophosphatemia. The prevalence of hypophosphatemia in critically ill patients is >40%, and although it stands to reason that malignancy would raise the incidence, the epidemiology has not been well-characterized [3]. Nevertheless, in hospitalized patients, a study found that malignancy was the fourth leading etiology for severe hypophosphatemia (<1.5 mg/dL), accounting for 6% of cases [4]. Furthermore, multiple studies have demonstrated that severe hypophosphatemia (<1.5 mg/dL) is an adverse prognostic marker in hospitalized patients with increased healthcare utilization, in-hospital stays, postoperative complications, cost and mortality and lower quality of life [5–8].

The clinical presentation for hypophosphatemia varies depending on its duration and severity. In mild cases (2–2.4 mg/dL), patients may be asymptomatic. When patients have moderate or severe hypophosphatemia, symptoms may become more apparent. The effects of intracellular phosphate depletion are far-ranging and affect multiple organs, because it affects oxygen affinity to hemoglobin in red blood cells. Specifically, phosphate depletion (serum phosphorus <1 mg/dL) decreases 2,3-diphosphoglycerate levels, inhibiting oxygen release to tissues [9]. Depletion of phosphate also limits adenosine triphosphate (ATP) synthesis, which is vital for multiple intracellular functions and organ systems [10, 11]. Additional adverse hematological effects, which are rare, include inducing red blood cell rigidity and hemolysis [12]. Phosphate depletion (<1 mg/dL) can reduce the capacity for hemostasis, reducing platelet number and function. In leukocytes, it can impair chemotaxis and phagocytosis, affecting immunity [13]. Neurologically, very severe hypophosphatemia (<0.6 mg/dL) can contribute to paresthesia, altered mental status, encephalopathy, seizures and coma [14]. Depletion of ATP in the heart can result in depression of myocardial performance and tachyarrhythmias in patients with serum phosphate <1.5 mg/dL [15]. In the musculoskeletal system, chronic hypophosphatemia has been associated with increased bone resorption and osteomalacia (<1.5 mg/dL) and acute hypophosphatemia (<1.9 mg/dL) is associated with proximal myopathy, rhabdomyolysis, dysphagia and ileus [16]. In addition, hypophosphatemia with serum phosphorus <2.5 mg/dL and <1.5 mg/dL has been associated with respiratory muscle weakness in 70% and 100% of the general inpatient population, respectively, and in the critical care population, having a serum phosphorus level <2.5 mg/dL has been associated with an 18% greater risk of failure-to-wean from mechanical ventilation [17, 18].

PHYSIOLOGY OF PHOPHORUS HOMEOSTASIS

Phosphorus exists in our body in both organic and inorganic forms. Organic phosphorus is present with calcium (Ca^{2+}) as hydroxyapatite in bones and teeth (85%) and intracellular in soft tissues (14%). Besides providing structure for the body, forming the extracellular matrix of bone and teeth, phosphorus is also a significant intracellular anion and an essential component of nucleic acids, cell membranes, receptor signaling proteins, enzymes, acid buffering and energy metabolism. Inorganic phosphates exist primarily as free phosphate ions in both divalent HPO_4^{2-} and monovalent $H_2PO_4^-$ forms [19]. About 10% of inorganic phosphate is bound to plasma proteins and ~5% is bound to cations such as sodium (Na^+), Ca^{2+} and magnesium (Mg^{2+}) [20]. The serum phosphorus level is homeostatically regulated and maintained in a narrow range between 3.0 and 4.5 mg/dL (0.97–1.45 mmol/L) by three principle hormones: parathyroid hormone (PTH), phosphatonins [mainly fibroblast growth factor 23 (FGF-23) and klotho] and 1,25-dihydroxyvitamin D3 [1,25-$(OH)_2D_3$] (calcitriol). Together, these hormones regulate how the intestine, kidneys and bones traffic phosphate.

Gastrointestinal (GI) absorption

The daily requirement of phosphorus in adults is 700 mg and the average Western diet consists of ~20 mg/kg/day of phosphorus (Figure 1) [21]. Protein-rich diets, including meat, eggs, cereals and milk products, contain high amounts of phosphorus, and so does processed food [22]. Many medications contain phosphate as an excipient, which may not be reported on the package insert, but can provide a significant phosphorus burden [23, 24]. Of the total dietary intake, ~60–75% is absorbed. Absorption occurs predominantly in the jejunum. Absorption is decreased in the presence of food rich in Ca^{2+}, Mg^{2+} and aluminum. Phosphate absorption in the gut occurs through both paracellular and transcellular routes. Paracellular absorption is the predominant mechanism—the kinetics is linear, nonsaturable and dependent on the oral intake [25]. Transcellular absorption occurs through Na^+–phosphate cotransporter type 2b (NaPi-2b), present in the intestinal microvilli [26]. Its expression is upregulated by low dietary phosphate [27] and calcitriol [28] and inhibited by niacin. PTH increases intestinal absorption of phosphate indirectly by increasing the production of calcitriol in the kidneys.

KIDNEY HANDLING

Free and non-protein-bound phosphate is freely filtered at the level of the glomerulus and ~85% is reabsorbed in the proximal tubule through secondary active transport by type 2a and c Na^+–phosphate cotransporters (NaPi-2a and NaPi-2c) and Na^+-dependent phosphate transporters 1 and 2 (PiT1 and PiT2) (Figure 2) [29]. NaPi-2a is located in the brush border membrane of the proximal convoluted tubule, which is most abundant on the S1 segment [30]. NaPi-2c is located throughout the proximal convoluted tubule. PiT1 and PiT2 make minor contributions to renal phosphate reabsorption.

About 5–20% of filtered phosphate (13 mg/kg/day) is eventually excreted in the urine (Figure 1). High serum phosphorus levels cause internalization of the transporters and an increase in phosphate excretion. Renal phosphate excretion is also increased by PTH and phosphatonins (including FGF-23 and klotho) through the downregulation of NaPi-2a. Phosphate excretion is also increased by glucocorticoids [31] and estrogen [32]. In the setting of hypophosphatemia, fractional excretion of phosphate >5% (or 24-h excretion >100 mg) is diagnostic of renal phosphate wasting [33]. Excretion is decreased by growth hormone, thyroid hormone, insulin [34] and insulin-like growth factor (IGF) [35]. The remainder of phosphate excretion occurs through feces, which contain the unabsorbed phosphate in the diet and the phosphate excreted in digestive juices and enzymes [21].

REGULATION BY PTH, VITAMIN D AND PHOSPHATONINS

PTH is an 84 amino acid polypeptide hormone secreted by the chief cells of the parathyroid gland. The primary stimulus for its

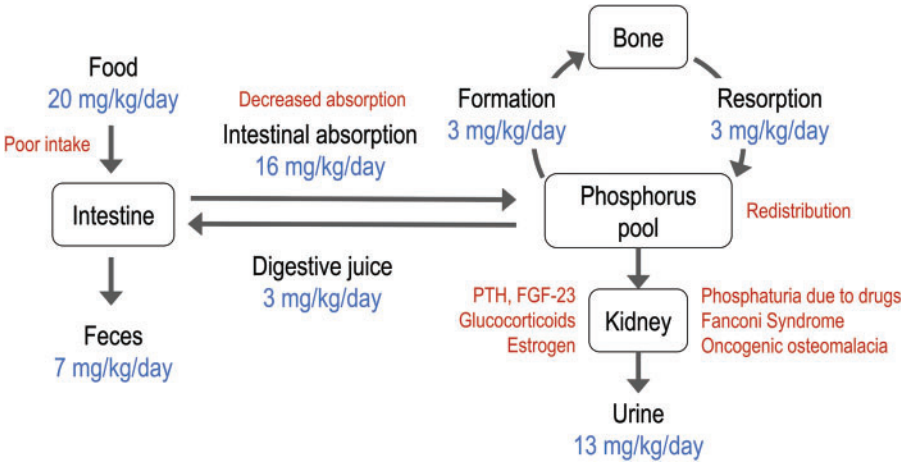

FIGURE 1: Quantitative aspects of phosphorus homeostasis in humans [21]. Factors that can cause hypophosphatemia are in red.

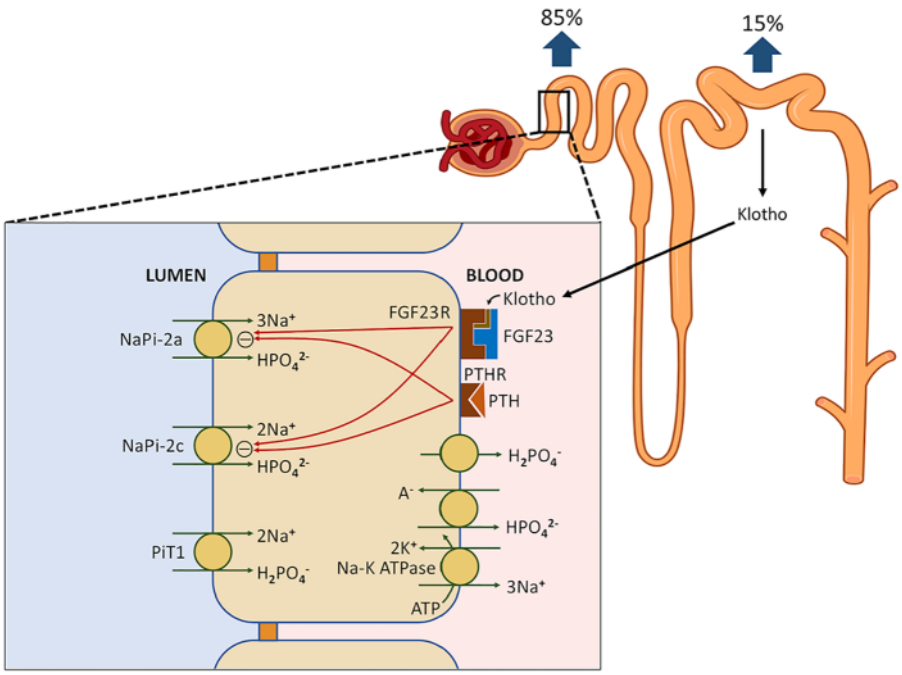

FIGURE 2: Mechanism for phosphate reabsorption in the proximal tubule in the kidney. Significant absorption occurs in the proximal tubule (85%) and ascending limb of the loop of Henle/distal convoluted tubule (15%). A^-, organic anion.

secretion is a low serum Ca^{2+} level detected by Ca^{2+}-sensing receptors. A high serum phosphorus level increases the PTH level, which acts on PTH receptor (PTHR) 1 in the proximal tubule, causing downregulation and removal of NaPi-2a, NaPi-2c and PiT-2 channels from the brush border membrane, resulting in renal phosphate loss [36, 37]. PTH upregulates 1-α-hydroxylase enzyme expression in the kidneys, resulting in an increased calcitriol level as described below. PTHR is also present in the bones, where it causes bone resorption and the release of Ca^{2+} and phosphate [38].

Vitamin D is essential for normal phosphate homeostasis and it is helpful to review the various forms and roles of its action. In the skin, ultraviolet B radiation present in sunlight converts 7-dehydrocholesterol to cholecalciferol, which gets hydroxylated to 25-hydroxy-cholecalciferol by 25-hydroxylase in the liver, and further hydroxylation occurs in the kidneys by 1-α hydroxylase enzyme to ultimately form calcitriol. This rate-limiting last step is induced by PTH, hypocalcemia and hypophosphatemia and inhibited by FGF-23, hyperphosphatemia and hypercalcemia [39, 40]. Calcitriol mainly acts on the kidneys to increase Ca^{2+} reabsorption. It may have some role in increasing intestinal phosphate absorption through NaPi-2b overexpression, especially during dietary phosphorus deficiency [28, 41].

FGF-23 is a 251 amino acid protein produced in osteocytes and osteoblasts in the bone. It was identified as the long-sought-after phosphaturic factor in tumor-induced osteomalacia and autosomal dominant hypophosphatemic rickets [18, 42, 43]. Its production is stimulated by increased dietary phosphorus intake [44, 45] and by calcitriol [46]. FGF-23, along with coreceptor klotho, acts on the proximal tubule to decrease phosphate reabsorption by downregulating NaPi-2a and NaPi-2c [42]. FGF-23 and PTH are the two main hormones that have a significant role in causing phosphate loss in urine.

ETIOLOGY OF HYPOPHOSPHATEMIA IN CANCER

Pseudohypophosphatemia

In general, the etiologies of hypophosphatemia in cancer can be classified by their mechanisms. However, it is important to be aware of pseudohypophosphatemia, defined as spuriously low serum phosphorus values that do not correspond to their actual systemic levels. Patients do not exhibit signs or symptoms of hypophosphatemia and no treatment is needed [47]. Pseudohypophosphatemia should be considered in patients receiving mannitol. It has an osmotic diuretic and a weak phosphaturic effect that can cause phosphate loss in urine, but more than that, it interferes with the colorimetric assay (DuPont aca endpoint method) for phosphorus by binding molybdate, decreasing both the rate of color development and the endpoint measurement [48]. Similarly, spurious hypophosphatemia should be in the differential of multiple myeloma (MM) and other paraproteinemias due to paraprotein's interference with the phosphate assay [49]. Moreover, pseudohypophosphatemia was observed in acute leukemia patients with extreme hyperleukocytosis and was attributed to the increased metabolic activity of the leukemic cells in the testing tube. Phosphate levels normalized when transporting the test tube to the laboratory on ice [50]. Once spurious hypophosphatemia has been excluded, the diagnostic approach outlined in Figure 3 can be applied.

Decreased intake

Patients with cancer frequently suffer from significant malnutrition marked by weight loss, loss of muscle mass and decreased activity. Treating malnutrition related to cancer and cancer therapy should be part and parcel of cancer treatment. Patients with cancer may have diminished appetite and hunger cues because of interrupted circadian rhythms or isolation. Patients with GI tumors or malignant ascites can experience early satiety, nausea and vomiting. Taste changes can frequently result from chemotherapy or radiation to the head and neck and create an aversion to food. Vulnerable patients with limited support systems may not have help with grocery shopping or preparing meals. Patients with cancer also suffer from depression, with negative symptoms resulting in anorexia.

Decreased intestinal absorption

In addition to inadequate intake, medications and chronic diarrhea contribute to poor intestinal absorption. For example, antacid and niacin can inhibit intestinal phosphate absorption. Aluminum- and Mg^{2+}-based antacids can bind to both ingested and secreted phosphate in the intestine, while niacin promotes phosphate loss by reducing intestinal NaPi-2b expression [51, 52]. Hypophosphatemia associated with chronic diarrhea is typically mild or moderate in severity. It is a consequence of both poor intestinal absorption and urinary loss secondary to vitamin D deficiency with compensatory hyperparathyroidism. Examples of cancer therapy–associated diarrhea and hypophosphatemia include tyrosine kinase inhibitors (TKIs) and antitumor agents listed in Table 1.

Transcellular shift

Refeeding syndrome is a potentially fatal metabolic disturbance due to reinstitution of nutrition in patients who have experienced a period of poor nutrition. The period of malnutrition is typically at least 5 days but can be potentiated by metabolic stress or severe illness [88]. Shifts in potassium, Mg^{2+}, acids and phosphorus can cause serious complications, including seizures, arrhythmia, heart failure and neurologic impairment. In malnutrition, hormonal and metabolic changes prevent protein breakdown of intracellular solutes, such as phosphate, and these become severely depleted. However, the serum phosphorus

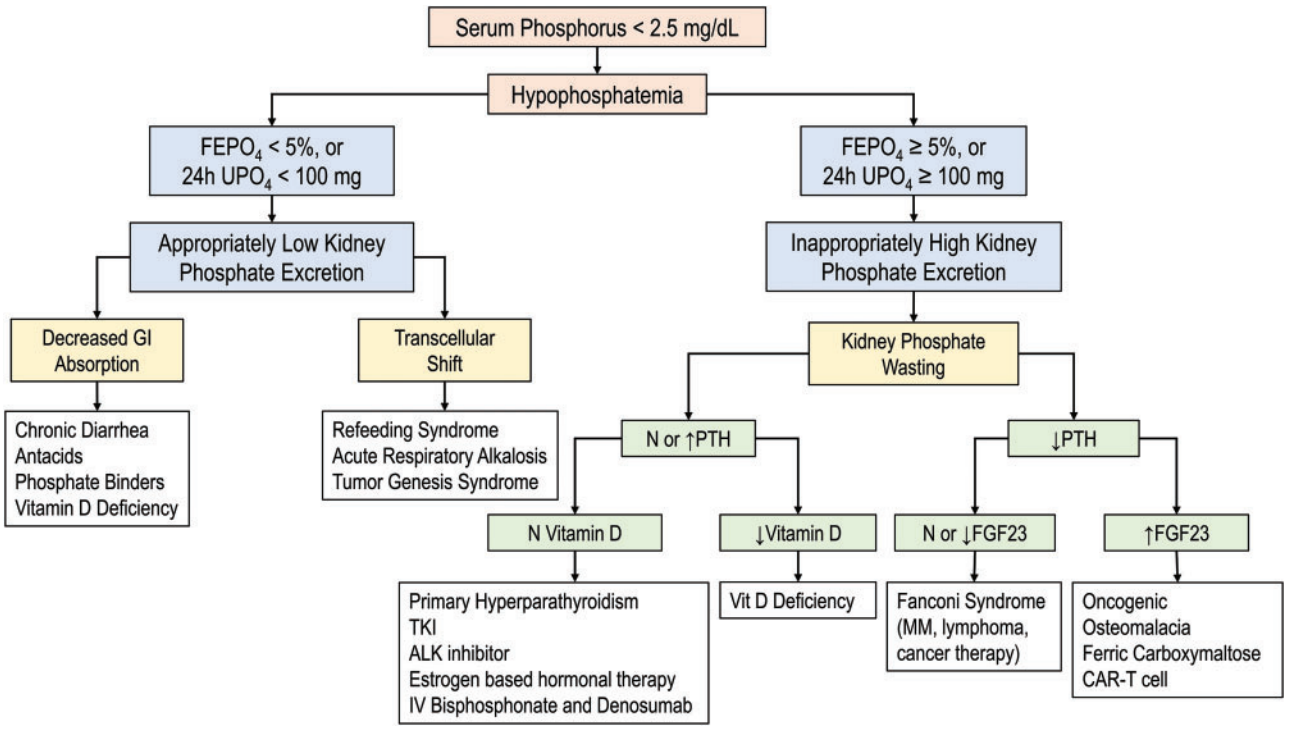

FIGURE 3: Diagnostic approach to hypophosphatemia. $FEPO_4$, fractional excretion of phosphate; 24-h UPO_4, 24-h urine PO_4; N, normal level; ↑, increased; ↓, decreased.

Table 1. Cancer therapies associated with hypophosphatemia

Medication	Incidence (%)	Hypothesized mechanism
Nitrogen mustard alkylating agent Ifosfamide	1–16 [53–55]	Proximal tubule injury [55]
Platinum based antineoplastic Cisplatin	Case reports [56–60]	Proximal tubule injury Indirectly related to hypomagnesemia and hypocalcemia with associated vitamin D resistance and PTH secretion [56–60]
Antimetabolite agent Azacitidine	66 [61]	Proximal tubule injury [61]
Nitrosourea alkylating agent Streptozocin	13 [62]	Proximal tubule injury [62]
Different classes Suramin, amrubicin, pamidronate, nivolumab, ipilimumab, imatinib, vemurafenib, capecitabine in combination with irinotecan and bevacizumab	Case reports [63–69]	Proximal tubule injury [63–69]
TKI Imatinib Sunitinib Sorafenib Regorafenib Nilotinib Dasatinib	17 [70] 6 [71] 13 [72] 7 [64] 10 [73] 7 [74]	Inhibition of PDGF receptor expressed in bone and proximal tubular cells [63,75,76] Vitamin D deficiency associated with chronic diarrhea [77] Unknown. Possibly related to inhibition of PDGF receptor expressed in bone and proximal tubular cells [63, 75, 76]
ALK inhibitor Ceritinib	3 [78]	Inhibition of IGF-1 receptor in proximal tubule [79]
mTOR inhibitor Temsirolimus Everolimus Ridaforolimus	13 32 24 [80]	Unknown. Possibly related to activation of rapamycin-insensitive protein complex 2 (mTORC2) and klotho expression [81, 82]
Estrogen-based hormonal therapy Estramustine and high-dose diethylstilbestrol diphosphate	Described in case series [83]	Downregulation of type 2a Na^+–phosphate cotransporter in proximal tubule secondary to estrogen effect [84]
ICPI Pembrolizumab, Ipilimumab and Nivolumab	17 [85]	Unknown. A case report of Fanconi syndrome [86]
CAR T cell axicabtagene ciloleucel tisagenlecleucel	37–57 [87]	Unknown. Possibly related to rising IL-6 that is associated with an increase in FGF-23 [87]

may remain normal because intracellular stores are being used and there is decreased renal excretion. During refeeding, insulin stimulates glycogen, fat and protein synthesis utilizing minerals, including phosphate, resulting in a precipitous decrease in serum phosphorus, potassium and Mg^{2+}. The National Institute for Health and Care Excellence guidelines for nutritional support have been developed to ensure adequate identification and prevention of refeeding syndrome and prescribes calibrated refeeding with the proactive replacement of vitamins and electrolytes, including phosphate [89].

There are other examples of transcellular shifts, such as respiratory alkalosis, that can induce hypophosphatemia by increasing phosphofructokinase activity, consuming more phosphate for ATP production. Hypophosphatemia may also be a complication of hematologic malignancies in a phenomenon called tumor genesis syndrome [90], where hypophosphatemia is caused by a shift of extracellular phosphorus into the rapidly replicating malignant cells that consume extracellular stores [91, 92]. This phenomenon has been described in histiocytic lymphoma, Burkitt's lymphoma and acute myelomonocytic leukemia. Similarly, patients after allogeneic stem cell transplants can develop hypophosphatemia during hematopoietic reconstitution [93].

Phosphaturia and Fanconi syndrome

Urinary phosphate wasting can be isolated as in patients with oncogenic osteomalacia, associated with bicarbonate loss as in patients with proximal renal tubular acidosis or in association with multiple solutes wasting as in Fanconi syndrome [94]. Certain hematological malignancies and cancer therapies have been associated with acquired proximal tubular dysfunction, leading to generalized impairment in reabsorption of solutes including phosphate, bicarbonate, glucose, potassium, uric acid and amino acids [95, 96].

Cancer-associated Fanconi syndrome

Fanconi syndrome occurs primarily in patients with lymphoma and monoclonal gammopathy. A few reports describe hypophosphatemia associated with Fanconi syndrome in patients with acute or relapsed adult T cell leukemia/lymphoma and Burkitt lymphoma. The etiology is attributed to infiltration of renal parenchyma by lymphomatous cells and a speculated role of human T lymphotropic virus 1, causing direct proximal tubule dysfunction [97, 98]. In patients with monoclonal gammopathy, the accumulation of light chains, mainly kappa light

chains, in the proximal tubules can alter the cells' proteolytic function, forming an intracellular crystal, or, through oxidative stress, can lead to cell dedifferentiation of the cells, apoptosis and subsequent loss of reabsorptive capacity [99, 100]. Nonetheless, Fanconi syndrome is considered a rare complication. In a single-center study, Fanconi syndrome was attributed to monoclonal gammopathy of undetermined significance in 44% of patients, MM in 31%, smoldering MM in 19% and Waldenstrom macroglobulinemia in 6% [101]. Hypophosphatemia can also be isolated with hyperphosphaturia only and without associated proximal tubule defects [102].

Cancer therapy–associated Fanconi syndrome

Ifosfamide enters proximal tubule cells through organic cation transporter 2 (OCT2) and is metabolized to chloroacetaldehyde, which induces glutathione depletion and subsequently oxidative damage [103]. The incidence of hypophosphatemia (<2.5 mg/dL) varies widely between studies, from 1 to 16% [53, 54]. Risk factors for nephrotoxicity and hypophosphatemia include a cumulative dose of ifosfamide >60 g/m^2, young age and pretreatment with cisplatin. Furthermore, hypophosphatemia might persist or even develop months after cessation of ifosfamide therapy [55]. Medications associated with hypophosphatemia in cancer patients and their hypothesized mechanisms are summarized in Table 1.

Several chemotherapeutic drugs are notable for inducing Fanconi syndrome. Azacitidine is a hypomethylating agent used for the treatment of acute myelocytic leukemia. In a study evaluating the nephrotoxicity associated with azacitidine, hypophosphatemia (<2 mg/dL) developed in 66% of patients and was attributed to proximal tubular dysfunction. This dysfunction resolved rapidly after the completion of chemotherapy [61]. Streptozocin is an alkylating agent in the nitrosourea chemotherapy class used to treat multiple malignancies, including pancreatic neuroendocrine tumors. In two studies evaluating the toxicity of streptozocin in various hematological and solid organ malignancies, the incidence of hypophosphatemia (<2.4 mg/dL) was ~13%. The phosphorus level returned to normal within a few weeks of completing the therapy [62]. Cisplatin is an alkylating agent in the platinum chemotherapy class and is used to treat multiple solid organ malignancies. Numerous reports have described cisplatin's association with various electrolyte disturbances, including hyponatremia, hypokalemia, hypomagnesemia, hypocalcemia and hypophosphatemia [104]. Solute wasting is in part related to cisplatin selective injury to S3 segment proximal tubular epithelial cells, where OCT2 plays a pivotal role in the uptake and accumulation of cisplatin in these cells [56, 57]. Another possible explanation for phosphate wasting is related to the concurrent hypomagnesemia and hypocalcemia that contribute to vitamin D resistance and stimulate PTH secretion [58, 59]. Other cancer therapies associated with hypophosphatemia attributed to proximal tubular injury/Fanconi-like syndrome based on case reports are listed in Table 1.

Oncogenic osteomalacia

Oncogenic osteomalacia, also known as tumor-induced osteomalacia (TIO), is typically the result of benign, slow-growing phosphaturic mesenchymal tumors (PMTs) and rarely manifest as a paraneoplastic feature of malignant disease [105]. These tumors secrete FGF-23 and cause hypophosphatemia through renal phosphate wasting [106]. Clinically patients present with bone pain, gait disturbances, pathological fractures, height loss and proximal muscle weakness [107]. Biochemically it is characterized by hypophosphatemia, normal or low calcitriol and elevated or inappropriately normal FGF-23. Chronic hypophosphatemia leads to osteomalacia that appears as osteopenia and pseudofractures on radiographs. The most common tumors causing TIO are the PMT mixed connective tissue variants [108]. They are usually small in size and may be located in any soft tissue or bone site throughout the body. Localization is difficult and may require an ^{18}F-fluorodeoxyglucose positron emission tomography (PET) scan or octreotide scan [109]. More recent techniques of using somatostatin analog combined with a PET–computed tomography (CT) scan (gallium-68 dotatate PET-CT scan) have shown better results in detecting the tumor [110]. A venous sampling of the FGF-23 level may be needed if multiple possible sources are detected [111]. Surgery provides definitive treatment, but excision with wide margins is necessary to ensure complete removal since recurrence rates are high with incomplete resection [112]. Postoperatively the FGF-23 level decreases rapidly, with normalization of the phosphate level by postoperative Day 5, and skeletal changes may take up to a year to normalize [113].

Targeted and novel therapies causing hypophosphatemia

TKI. Imatinib is a BCR-ABL TKI used to treat Philadelphia chromosome–positive chronic myelogenous leukemia (CML). In two clinical trials, the incidence of hypophosphatemia (<2.5 mg/dL) associated with imatinib use in CML patients was ~50%. One-third of these patients had serum phosphorus <2 mg/dL [70]. Less commonly, hypophosphatemia with levels <2 mg/dL was reported in 13 and 1.9% of metastatic renal cell carcinoma patients treated with sorafenib and sunitinib, respectively [71, 72]. The observed hypophosphatemia was attributed to possible inhibition of platelet-derived growth factor receptor (PDGFR) expressed on proximal tubular cells, with subsequent tubular dysfunction and inhibition of PDGFR expressed on osteoclasts, resulting in decreased bone resorption and secondary hyperparathyroidism [63, 75]. Other multi-TKIs that target PDGFR include regorafenib, nilotinib and dasatinib. The reported incidence for hypophosphatemia (<2 mg/dL) with these TKIs was 5.2, 15 and 7%, respectively [64, 73, 74]. Additionally, ceritinib is a TKI that inhibits anaplastic lymphoma kinase (ALK) and IGF-1 receptor. Hypophosphatemia (<2 mg/dL) developed in 3% of patients treated with ceritinib and was attributed to possible phosphaturia. The mechanism for phosphaturia could be related to the inhibition of the insulin (IGF-1) receptor in proximal tubules that promotes phosphate reabsorption [78, 79].

Mammalian target of rapamycin (mTOR) inhibitors. Hypophosphatemia is a common finding in cancer patients treated with mTOR inhibitors. The reported incidence of <2 mg/dL was 13% with temsirolimus, 4% with everolimus and 21.7% with ridaforolimus [80]. Based on an observational study, the hypophosphatemia associated with everolimus and temsirolimus use, among other biological markers, was significantly associated with tumor response and progression-free survival in patients with renal cell carcinoma [114]. The mechanism for mTOR inhibitor–associated hypophosphatemia is still not identified. Nonetheless, sirolimus, an mTOR inhibitor, has been associated with impaired proximal tubular phosphate reabsorption in kidney allograft recipients. A postulated mechanism for this observed phosphate wasting is related to

activation of rapamycin-insensitive protein complex 2 (mTORC2) and klotho expression by sirolimus [81].

Hormonal therapy. Estramustine and high-dose diethylstilbestrol diphosphate are estrogen-based medications used to treat metastatic prostate cancer and are associated with mild to moderate hypophosphatemia. Serum phosphorus levels typically decrease during the first 6 weeks of therapy then stabilize at a low normal range (2.6 ± 0.6 mg/dL). The level returns to normal upon discontinuation of treatment. The phosphaturia etiology is attributed to the estrogen effect on proximal tubules with downregulation of NaPi-2a [83, 84].

Immunotherapy. Hypophosphatemia is a commonly observed side effect after chimeric antigen receptor (CAR) T cell infusion. Fifty-one percent of patients reported developing hypophosphatemia (<2 mg/dL); however, no further evaluation was performed to identify the etiology. It is postulated that the increase in interleukin-6 (IL-6) associated with CAR T cell therapy might increase FGF-23 levels [87]. Less frequently, hypophosphatemia (<2 mg/dL) was reported in patients treated with immune checkpoint inhibitors (ICPIs), with an overall incidence of 17% [85]. The etiology is still under investigation and likely multifactorial, as only a few reports describe the association between ICPI and Fanconi syndrome [65, 86].

Supportive therapies associated with hypophosphatemia

Total parenteral nutrition (TPN). TPN is frequently utilized in cancer patients with head and neck cancer, esophageal or GI cancers and those who have undergone major abdominal surgeries or prolonged ileus or bowel obstruction. Despite the inclusion of phosphate in the TPN, the development of hypophosphatemia (<2.5 mg/dL) is common, occurring in up to 40% of patients [115]. Hypophosphatemia typically occurs early after initiating therapy related to refeeding syndrome [116]. Vigilance, anticipation and early replacement of phosphate can prevent the development of severe hypophosphatemia [117].

Intravenous (IV) iron. In a recently published systematic review, hypophosphatemia (<2.5 mg/dL) was observed in up to 92% of patients with iron deficiency anemia treated with third-generation IV iron preparation, specifically ferric carboxymaltose (FCM). Hypophosphatemia was transient; however, case reports described chronic hypophosphatemia with osteomalacia in patients with chronic anemia requiring repeated IV iron infusion [118]. The proposed mechanism is FCM blocking the cleavage of intact FGF-23 (iFGF-23) to inactive cleaved FGF-23 and subsequently the increased iFGF-23 level leads to phosphaturia [119]. Additional supportive therapies causing hypophosphatemia are listed in Table 2.

Denosumab. Denosumab blocks the receptor activator of nuclear factor κB ligand to decrease osteoclastic bone resorption in patients with osteoporosis and metastatic bone disease. This blockage leads to compensatory elevation of PTH during the first month of injection, which can contribute to hypophosphatemia by inhibiting the proximal tubule reabsorption of phosphorus [122]. About 2.1% of cancer patients with metastatic bone disease treated with denosumab developed hypophosphatemia (<2.5 mg/dL) [121].

Intravenous IV bisphosphonates. The associated hypophosphatemia with IV bisphosphonates is usually mild, transient and attributed to the elevation of PTH during the abrupt decrease in serum Ca^{2+}. The incidence varies based on the medication dose and the underlying disease. In patients with breast cancer and MM with metastatic bone disease treated with zoledronic acid and pamidronate, the reported hypophosphatemia (<2 mEq/L) incidence was 12.3 and 7.1%, respectively, while in patients with malignancy associated with hypercalcemia treated with zoledronic acid and desnosumab the reported incidence of hypophosphatemia was 2.1 and 1.1%, respectively [123].

Dialysis-related losses. Cancer patients receiving care in the intensive care unit (ICU) are at exceptionally high risk for hypophosphatemia. In addition to aspects of malignancy and its treatment contributing to diminished phosphorus stores, there are significant acid–base and electrolyte shifts that can contribute to hypophosphatemia. Furthermore, nutrition in the ICU is variable and patients may also be receiving dialytic therapy. Continuous renal replacement therapy (CRRT), in particular, is associated with hypophosphatemia, occurring in >50% of patients, and requires constant replacement [125]. Hypophosphatemia results from phosphate lost in the effluent during CRRT and can develop even if hyperphosphatemia is present at the start of therapy.

We summarized the common etiologies for hypophosphatemia in cancer patients based on the proposed mechanism in Figure 3.

Table 2. Supportive therapies associated with hypophosphatemia

Medication	Incidence (%)	Hypothesized mechanism
TPN	11–60 [115]	Transcellular shift, refeeding syndrome and unmet requirements [115, 120]
IV iron/FCM	Up to 92 [118]	Interference with FGF-23 metabolism [119]
RANKL inhibitor Denosumab	2.1 in metastatic bone disease [121]	RANK ligand-receptor inhibition will lead to compensatory elevation of PTH that can contribute to hypophosphatemia by inhibiting proximal tubule reabsorption [122]
Bisphosphonates Zoledronic acid Pamidronate	1.1–12.3 [121, 123] 7.1 [123]	Decreased proximal tubular reabsorption secondary to elevation of PTH during the abrupt decrease in serum Ca^{2+} [122] Decreased proximal tubular reabsorption secondary to elevation of PTH Proximal tubular injury [124]
CRRT	27–78 [125]	Continuous dialytic removal of phosphate [125]

Table 3. Phosphate repletion protocol [132, 133]

Phosphorus level	Route	Weight 40–60 kg	Weight 61–80 kg	Weight 81–120 kg
<1.0 mg/dL	Initial management IV	30 mmol phosphorus IV	40 mmol phosphorus IV	50 mmol phosphorus IV
1.0–1.7 mg/dL	PO if asymptomatic and enteral route feasible; otherwise IV	20 mmol phosphorus PO/IV	30 mmol phosphorus PO/IV	40 mmol phosphorus PO/IV
1.8–2.2 mg/dL	PO if asymptomatic and enteral route feasible; otherwise IV	10 mmol phosphorus PO/IV	15 mmol phosphorus PO/IV	20 mmol phosphorus PO/IV

If the patient's potassium is <4.0, use potassium phosphate; if the patient's potassium is >4.0, use sodium phosphorus. Sodium phosphate injection provides the same phosphate content as potassium phosphate. The mmol conversion is 31 (e.g. 20 mmol = 620 mg); IV infusions should be given over 3–6 h or per hospital policy. PO, oral.

MANAGEMENT

Hypophosphatemia in cancer patients should be corrected when it is first recognized and can be addressed by any member of the oncology team. In cases of severe or refractory hypophosphatemia, the involvement of nephrology should be considered. The general approach to hypophosphatemia should be to treat the underlying cause. In the case of antacids or diarrhea, for example, the agent can be discontinued and the diarrhea managed. In cases of a PMT, surgical resection usually results in resolution, but as noted, the tumors often recur. In patients with nonresectable FGF-23-secreting tumors, medical management consists of dietary phosphate and calcitriol supplementation. Hypocalcemia from phosphate therapy can give rise to secondary hyperparathyroidism, which necessitates allosteric inhibitors of calcium-sensing receptors like cinacalcet [126]. Recently an FGF-23 receptor monoclonal antibody, burosumab, has been approved for use in TIO [127, 128]. Acute conditions, such as respiratory alkalosis, should be corrected. Offending drugs like iron in bone mineralization therapy can be interrupted or replaced with alternatives while phosphorus is repleted. In critically ill patients receiving CRRT, phosphorus-containing dialysate, if available, should be considered and can be used to prevent the development proactively [129]. Decisions regarding agents specific for cancer are more difficult because, as much as possible, the general objective is to mitigate side effects while treating cancer, particularly if the offending agent is life-prolonging or curative. As a whole, hypophosphatemia, unless recurrent and life-threatening, should not be regarded as a reason to discontinue active cancer therapy, especially given the possibility of significantly improving the life expectancy of many cancer patients with the use of these agents.

Hypophosphatemia due to inadequate calorie intake, intolerance to diet or GI tract dysfunction may be addressed in part or whole with oral supplements or the implementation of enteral nutrition. Individualized recommendations containing phosphate-rich foods should be encouraged. If the dietary approach fails, then oral phosphate formulations with either Na^+ phosphate or potassium phosphate salts should be used. Typical regimens required for oral supplementation range from 2.5 to 3.5 g (15 mg/kg) in three to four divided doses, and patients may require even higher doses when there is concomitant renal phosphate wasting [130]. Skim milk, if tolerated, is also an excellent source of phosphate replacement. Vitamin D is required for intestinal absorption; therefore, often nutritional and active vitamin D is required for optimal intestinal absorption. Frequently, antimotility and bulk-forming agents to manage diarrhea are needed while replacing phosphate.

In chronic cases where patients cannot introduce phosphate through the GI tract, parenteral replacement may be necessary. The risk of complications (i.e. hypocalcemia, hypotension, arrhythmia and acute kidney injury) is much higher than with oral phosphate due to the risk of precipitating with Ca^{2+} [131]. The response to parenteral phosphate is variable and not predicted well from initial levels, but general guidance has been published from several sources (Table 3). IV phosphate replacement should be considered in any symptomatic patient or severely depleted patient <1.0 mg/dL and patients should be monitored closely for the development of arrhythmias during the infusion and the development of hypocalcemia and hyperkalemia. Oral replacement can be resumed after symptoms resolve or serum phosphate is >1.5 mg/dL. Potential long-term consequences of phosphate replacement are extrapolated from other phosphate-wasting diseases, including nephrocalcinosis, chronic kidney disease and secondary hyperparathyroidism [132].

CONCLUSIONS

Hypophosphatemia is a common disorder in cancer patients that can result from malignancy itself or from its therapy. Poor intake, transcellular shift, GI and renal loss or RRT can all contribute to this condition. Hypophosphatemia can result in significant morbidity and mortality, including prolonged hospital stays and postoperative complications. An understanding of normal phosphate physiology is essential for prevention, identification of its etiology and treatment. Management can be complex, with treatment of underlying causes and oral and parenteral supplementation, and should be multidisciplinary.

CONFLICT OF INTEREST STATEMENT

None declared.

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