Impact of Serum Phosphorus on Hemoglobin: A Literature Review

In depth review

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ABSTRACT
Phosphorus is a macroelement found in the body, mostly in the bones as crystals of hydroxyapatite. Higher levels are found in patients affected by chronic kidney disease (CKD). Since the early stage of CKD phosphorous excretion is impaired, but the increase of PTH and FGF23 maintains its level in the normal range. In the last decades, the role of FGF23 in erythropoiesis was studied, and now it is well known for its role in anemia genesis in patients affected by conservative CKD. Both Hyperphosphatemia and anemia are two manifestations of CKD, but many studies showed a direct association between serum phosphorous and anemia. Phosphorus can be considered as the common point of more pathogenetic ways, independent of renal function: the overproduction of FGF23, the worsening of vascular disease, and the toxic impairment of erythropoiesis, including the induction of hemolysis.

KEYWORDS: Phosphorus, Hemoglobin, Anemia, Chronic Kidney Disease, FGF23

Introduction

Phosphorus is a macroelement found in the body; 85% of it is deposited in the bone as crystals of hydroxyapatite, 14% in the intracellular compartment as a component of nucleic acids, plasma membranes and involved in all cellular energetic processes, and only 1% is extracellular [1].

Of the latter, 70% is organic phosphorous and 30% is inorganic phosphorous. Inorganic phosphorous can be protein-bound, complexed with sodium, calcium, and magnesium, or circulating as mono- or di-hydrogen forms. About 800 mg of phosphorous is introduced with the food, and the kidneys filter across the glomerulus about 90% of the daily phosphate load. The residual 10% is excreted by the gastrointestinal system.

Chronic Kidney disease (CKD) impairs phosphorus excretion due to the reduction of the skillful nephron mass. As a consequence of this, parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23) are over-secreted from the early stages of CKD, to prevent an increase in serum phosphorous concentration [2].

Both PTH and FGF23 increase phosphorus urinary excretion but, conversely to FGF23, PTH is related to serum calcium due to the relative activation of calcium-sensing receptor (CaSR). Indeed, PTH limits calcium gastrointestinal absorption because it reduces 1,25-dihydroxy vitamin D levels. This negative feedback tray maintains serum calcium and phosphorus within normal ranges in individuals with normal kidney function. The progression of renal disease causes the failure of this equilibrium and hypocalcemia, hyperphosphatemia, and tertiary hyperparathyroidism may occur.

Cernaro V. et al. [2] highlighted in their review as the secretion of FGF23 starts to increase when the glomerular filtration rate (GFR) drops below 90 ml/min/m^2. Anemia was not manifested with this eGFR because anemia has a multi-etiological pathogenesis, and the only increase of FGF23 is not able per se to cause anemia.

In the last decades, the role of FGF23 in erythropoiesis was well studied. It was known that circulating FGF23 is related to anemia in patients affected by conservative CKD. This information suggests that high serum phosphorus and low hemoglobin level are related via FGF23 [3, 4].

It has always been known that in patients with CKD anemia was mostly caused by inefficient EPO production in the kidneys, but the pathogenetic role of FGF-23 serum levels should be highlighted. FGF-23 is inversely related to GFR and is positively associated with the development of anemia. Among the pathways through which FGF23 impacts hemoglobin level we found the direct reduction of EPO secretion from the kidney and the block of erythroid progeny in the G2 phase of the cell cycle. Thus, an increased FGF23 value impairs the differentiation of the erythroid line and their apoptosis.

Furthermore, through the hepatic pro-inflammation molecules secretion, FGF23 promotes hepcidin synthesis, reducing iron availability.

Impaired nephron mass and renal function are related to weak production of erythropoietin (EPO) and, consequently, to the development of anemia. The mainly involved pathways include low blood iron levels, chronic inflammation, increased bleeding risk, EPO resistance, or relative EPO deficiency [5].

The impact of CKD and other electrolytes is studied [6]. The relationships among hyperphosphatemia, anemia, and vascular aging were also demonstrated in patients with normal renal function [7]. Indeed, similarly to the use of calcium-based phosphate binders, in hyperphosphatemia conditions serum phosphorous links serum calcium and precipitates, increasing vascular calcification.

Phosphate Balance and Anemia

It is known that both hyperphosphatemia and anemia share often CKD as a common cause.

Tran L. and colleagues [7] showed an association between anemia and serum phosphate also in a sample of patients without CKD. In detail, they conducted a large observational study on 155.974 individuals dividing the whole sample into tertiles based on phosphorous level: they showed an adjOR of 1.26 to develop moderate anemia and 1.35 to develop mild anemia in the higher tertile compared to middle tertile.

Indeed, differences in eGFR between mild-anemia and moderate-anemia groups (85.0 ml/min/1.73m^2 and 80.2 ml/min/1.73m^2, respectively) had, although statistically significant, little clinical impact. The sensitivity analysis conducted by dividing into subgroups for ethnicity and gender showed similar observations.

Although the impact of serum phosphorus on hemoglobin has not been fully investigated, except for cross-sectional design with conflicting results [8], the association between iPTH and anemia was largely studied. Indeed, in 1988 Bogin and colleagues [9] reported that a tenfold increase in intact PTH significantly worsened the median of fragility (MOF) of erythrocytes (0.411 ± 0.006 vs 0.454 ± 0.007, $p < 0.01$).

Circulating PTH-protein fragments that may accumulate in CKD and C-terminus or N-terminus detection was not accurate due to cross-reaction with these fragments. For this reason, the intact PTH was detected, through a two-site antibody test to detect full-length (1-84, or active) PTH molecules.

Zingraff et al. [10] and Ureña et al. [11] showed an increasing hemoglobin level after parathyroidectomy, posing the hypothesis of an impact of PTH level on anemia and EPO resistance. According to Zingraff, a probable pathogenetic pathway could be found in PTH-caused marrow fibrosis because they detected a relationship between the amount of fibrosis and increased hemoglobin levels. Analyzing the Urena et al. study, they evaluated both the impact of iPTH and the impact of serum phosphorous on the hemoglobin. In detail, iPTH was correlated with hemoglobin level with an R of -0.54 ($p<0.001$), and adjOR of serum phosphorous, including age and iPTH among the covariates, was -0.22 (95%CI -0.38/-0.05).

Based on these findings, the management of hyperphosphatemia would reduce hyperparathyroidism incidence and, consequently, it could increase hemoglobin levels. Furthermore, hyperphosphatemia and hyperparathyroidism induce hemolysis and bone marrow fibrosis [8, 10], the management of hyperphosphatemia and hyperparathyroidism could reduce the direct impact on hemoglobin levels.

Other mechanisms that could explain the impact of hyperphosphatemia on anemia are represented by the polyamines' overproduction and consequent erythropoiesis inhibition and the association between erythrocytes' ATP and phosphorus level, with lactate overproduction and consequent lysis [12, 13].

Phosphate Balance and Anemia in CKD

Limits of many studies were the observational design, the absence of longitudinal evaluation, and the absence of FGF23 level measurement.

As highlighted in introduction, overproduction of FGF23 is associated with iron deficiency, and this data is confirmed by several studies [14, 15].

Patients with CKD, especially patients in end-stage renal disease (ERSD), loss about 1-3 g/year of iron, due to uremia-related platelet dysfunction [16], but transferrin saturation was not always related to anemia. For this reason, we suppose that other pathogenic pathways links phosphorus as a common marker.

In a study of Amnuay K. et al. [17], multivariate analysis including transferrin saturation showed a negative association between phosphorous and anemia of about -0.22g/dl each mg/dl of phosphorous increase (95%CI: -0.38 to -0.049). Like all electrolytes, even phosphate has a "curved shaped risk", and hemolysis is demonstrated also in hypophosphatemia. This is the possible reason for the low linear slope detected in their study.

Griveas et al. [18] reported in an observational study conducted on 2018 that simultaneous reduction of serum phosphorous (from 6.54 ± 1.27 to 5.05 ± 1.01 mg/dl, $p < 0.05$) and an increase of hematocrit (35.9% vs 37.41%, $p = 0.10$) in six months on dialysis-dependent CKD patients treated with sucroferric oxyhydroxide, without significant differences in serum iron or transferrin saturation.

Similarly, animal experimental study [19] on rats affected by chronic kidney disease and treated with ferric citrate showed an increase of hemoglobin (12.5 vs 13.1 g/dl) and a reduction of serum phosphate (12.2 vs 8.7 mg/dl). Hepatic biopsy did not show significant differences among groups.

As highlighted by several studies on phosphorus binders, the impact of serum phosphorous on hemoglobin is carried out also through an increased erythropoiesis-stimulating agents (ESA) resistance. In fact, the Matsushima et al. [20] detected in their observation study an increased use of ESA in patients treated with sucroferric oxyhydroxide without reduction of serum phosphorus whereas Ikee and colleagues [21] showed a reduction of ESA resistance was also independently related to another iron free phosphorus-binder (Sevelamer carbonate).

Furthermore, Diskin et al. [22] demonstrated that patients with hyperphosphatemia needed higher ESA doses than patients with normal serum phosphorous. Similarly, Kamyar et al. [23] evaluated the relationship between phosphorus and ESA doses in a cohort of 49.215 patients. They showed a significant correlation between phosphorus and ESA dose both in univariate model (Rho: 0.18, $p = 0.005$) and in a multivariate model (OR: 0.92, 95% CI: 0.90–0.94) comparing "ESA hyporesponsive" to "most ESA responsive" patients.

No significant differences between hemoglobin and a low reduction of ESA doses were detected by Gubenšek J. et al. [24] in a sample of dialysis dependent patients with little reduction of serum phosphorous.

No association between serum phosphate and hemoglobin was directly computed in this study but we may postulate, based on presented data, that a better phosphorus control could reduce the demand of ESA, with consequent decrease in costs and adverse events. Opposite data were presented in literature. In details, conversely by aforementioned data, Yokoyama et al. conducted a randomized trial on hemodialyzed patients [8] testing the effects of ferric citrate. They detected unvaried hemoglobin levels despite significantly lower ESA resistance simultaneously to a phosphorus increase. Analyzing the sample features, these results could be due to the specific limits of inclusion patients: patients undergoing renal replacement therapy, low range of hemoglobin (9-12 g/dl), and the upper limit of serum phosphorus (7 mg/dl in serum assessment before the dialytic treatment).

Koibuchi et al. showed in their longitudinal analysis a negative association between hemoglobin and ferritin levels, conversely to the positive association of iron deposits with phosphate. Although this study did not directly evaluate the association between phosphorous and hemoglobin, we can suppose that higher serum phosphorous was related with lower hemoglobin levels.

Although the associations among serum phosphate, FGF23, and hemoglobin, no clear relationship between phosphorus and hepcidin was shown. In fact, only a few small observational studies showed this association [25] and the results are not consistent across other studies [26]. However, a trend toward reduced hepcidin levels was noted in patients who took lanthanum based phosphorous binders [27].

Phosphorus, vascular disease and anemia

The impact of high serum phosphorous on vascular disease is clear both in patients affected by moderate CKD [13] and in patients without CKD [28]. Hyperphosphatemia, indeed, causes calcium phosphate precipitation and cellular apoptosis due to the overactivation of Na/Pi co-transporters and a Pit-1 cotransporter with consequent mitochondrial impairment.

Instrumental investigation seems to agree this hypothesis. In fact, unitary phosphate increase seems to be related to retinal venular disorder and anomalous flowmetry as venous congestion [29]. Furthermore, also cardiac doppler imaging shown an altered diastolic function associated with hyperphosphatemia and high calcium-phosphate product [30].

This impact was studied in non-diabetic end-stage renal disease (ESRD) patients by Ishimura et al. [31, 32]. They observed, in a cohort of 421 subjects, that hyperphosphatemia has an impact on vascular calcifications in non-diabetic but not in diabetic ESRD patients. Different electrolytes impact in different subgroups is known. For example, whereas hemoglobin level was lower in hyperkalemic group than normokalemic group in a conservative CKD patients [33], differences on hemoglobin were not detected in dialysis dependent patients of the same ward [34].

According to this finding, as reported by Razzaque [35] in their observational study, lower diameter of vascular calcifications was related in patients with lower phosphate levels, independently of serum calcium concentration.

Also Locatelli et al. [36] strengthened the hypothesis of an impact of phosphorus level on the vascular calcification. Indeed, in their observational study, they showed a reduction of vascular calcification risk in patients treated with various types of phosphate binders such as lanthanum-carbonate or aluminum-based phosphate-binders.

Besides increased vascular calcification, serum phosphorous is related to cell-toxicity and myocardial hypertrophy, leading to a rapid decline in kidney function both in animal experimental models and in human observational studies [37, 41]. A pathogenetic pathway to explain this action of phosphorus was proposed by Smith et al. [42]. According to them, the deposition of calcium phosphate nanocrystals in the extracellular fluid link to a partially phosphorylated glycoprotein called fetuin-A. This linkage is known as fetuin-A-containing calciprotein particle (CCP), and it modulates the expression and secretion of tumor necrosis factor (TNF)-α and interleukin (IL)-1β in murine macrophages as well as the expression of type I and type II class A scavenger receptor (SR-AI/II) needed to clear phosphate crystals. The apoptotic reaction induced by phosphorus deposition occurs ubiquitously in the whole organism, including erythropoietic cellular line.

According to this, a cross-sectional study by Dijk et al. [43] and Michel et al. [44] showed an independent and significant linear association between hemoglobin and vascular disease, as well as a role of vascular stiffness on local hemolysis and anemia, respectively. A no less important aspect was the Quality of Life (QoL). In this sense, Wouters HJCM et al. [45] conducted a prospective observational study on 138.670 subjects, among which 5510 presented anemia. They showed that anemia is frequently related to lower QoL, mostly in patients older than 60 years.

Conclusions

Regarding the correlation between anemia and hyperphosphatemia, we currently do not have sufficient studies available in literature. Unfortunately, this limit seems to be related to the lack of research in the field of hemodialysis and the dosage of FGF23 in clinical practice. The measurement of FGF23 would make it possible to start several observational and longitudinal studies useful for understanding the correlation mechanism between hyperphosphatemia and anemia. Although large specifically designed studies are needed to confirm this hypothesis, based on this literature analysis, we can hypothesize that hyperphosphatemia may worse anemia through various ways, independently by renal function: the overproduction of FGF23, the worsening of vascular disease and the toxic impairment of erythropoiesis as well as inducing hemolysis (Figure 1).

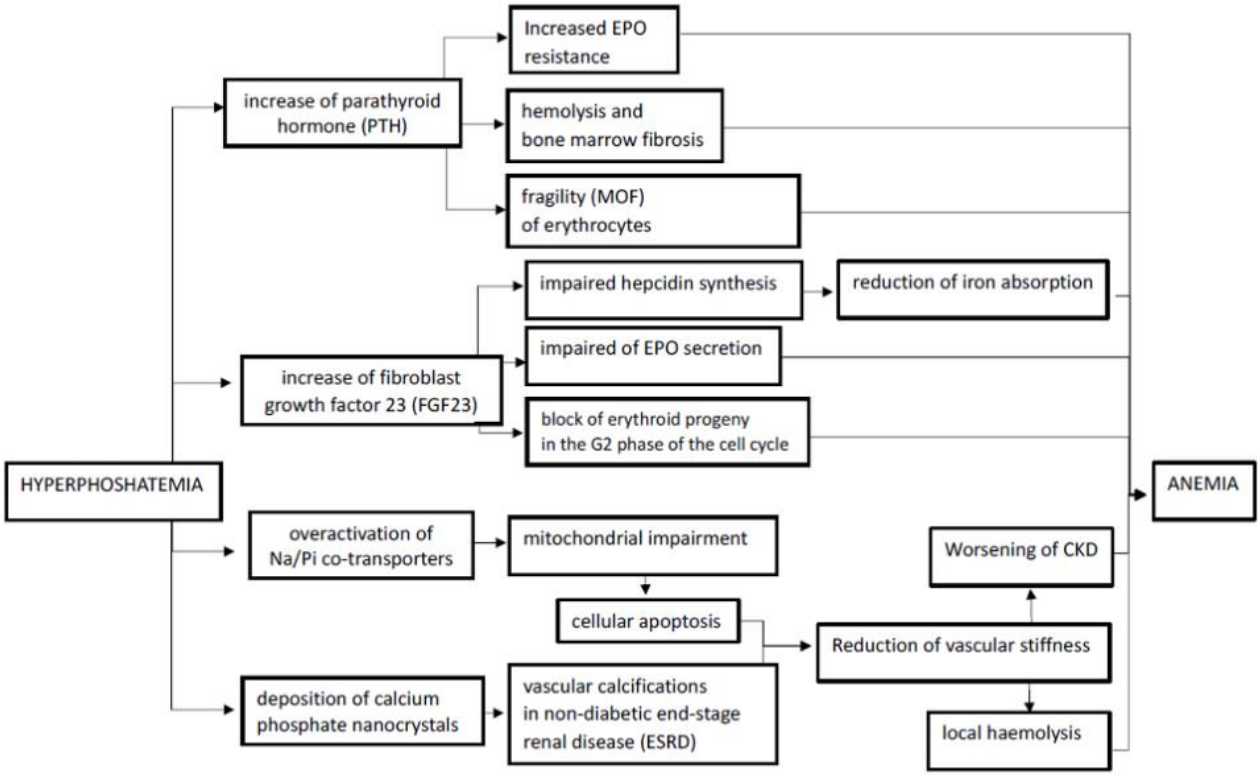

Figure 1. Pathogenic ways related to hyperphosphatemia causing anemia.

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