Vitamin D and Phosphate Interactions in Health and Disease

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Abstract

Vitamin D plays an essential role in calcium and inorganic phosphate (Pi) homeostasis, maintaining their optimal levels to assure adequate bone mineralization. Vitamin D, as calcitriol ($1,25(OH)_2D$), not only increases intestinal calcium and phosphate absorption but also facilitates their renal reabsorption, leading to elevated serum calcium and phosphate levels. The interaction of $1,25(OH)_2D$ with its receptor (VDR) increases the efficiency of intestinal absorption of calcium to 30–40% and phosphate to nearly 80%. Serum phosphate levels can also influence $1,25(OH)_2D$ and fibroblast growth factor 23 (FGF23) levels, i.e., higher phosphate concentrations suppress vitamin D activation and stimulate parathyroid hormone (PTH) release, while a high FGF23 serum level leads to reduced vitamin D synthesis. In the vitamin D-deficient state, the intestinal calcium absorption decreases and the secretion of PTH increases, which in turn causes the stimulation of $1,25(OH)_2D$ production, resulting in excessive urinary phosphate loss. Maintenance of phosphate homeostasis is essential as hyperphosphatemia is a risk factor of cardiovascular calcification, chronic kidney diseases (CKD), and premature aging, while hypophosphatemia is usually associated with rickets and osteomalacia. This chapter elaborates on the possible interactions between vitamin D and phosphate in health and disease.

Keywords

Vitamin D · PTH · FGF23 · Klotho · Phosphate · Kidney · Intestine · Bone

5.1 Introduction

Vitamin D research has more than 100 years of history since McCollum and Davis's discovered the "growth-promoting fat-soluble vitamin" that was found in cod liver oil [20]. The effect of this growth-promoting factor in the treatment of rickets was so effective that cod liver oil was regarded as a panacea and gave a powerful impetus to further research on vitamin D throughout the world [71]. In the last 20 years, it has been shown that vitamin D's biological activities extend far beyond its involvement in calcium

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metabolism. Along with proven efficacy in pathological conditions and diseases such as rickets, bone loss, and osteomalacia, some novel effects of vitamin D on very diverse physiological processes have been well established [8, 39]. Vitamin D deficiency remains a critical health issue worldwide, and it has been estimated that around one billion people suffer from various vitamin D-related disorders [35].

The biological effects of $1,25(OH)_2D$ can be divided into two types: skeletal (primarily related to calcemic and phosphatemic activities) and non-skeletal, typically not associated with mineral metabolism [15]. The homeostasis of serum phosphate mediated by vitamin D is of paramount importance for adequate bone mineralization, muscle contraction, nerve conduction, and many other vital functions [26]. This brief chapter reviews our understanding of vitamin D-mediated regulation of phosphate homeostasis in health and diseases.

5.2 Physiological Regulation of Phosphate Homeostasis

Phosphorus is the sixth most abundant chemical element in the body [34]. In nature it mainly exists as phosphates, the form most suitable for living organisms [14]. In mammals, the phosphate group is primarily concentrated (~85%) in bones and teeth as hydroxyapatite. The remaining ~15% are distributed in the other tissues as intracellular ortho- and pyrophosphate groups, either free ("inorganic") or as a part of nucleotides, coenzymes, and high-energy phosphate compounds. (referred to as "organophosphates"). Inorganic phosphates exist in two forms: monovalent dihydrogen phosphate ($H_2PO_4^-$) and divalent hydrogen phosphate (HPO_4^{2-}). In the cytosol dihydrogen phosphate is contributing bulk amounts (62% of all cytosolic phosphates).

The extracellular fluid contains only <1% of the whole pool of body's inorganic phosphates [27, 33]. Interestingly, compared to the cytosol, the proportion $H_2PO_4^-$/ HPO_4^{2-} is inverted, so that the major component is now hydrogen phosphate (61% of all phosphates). In general, a 70-kilogram adult with 25% body fat content would have total body phosphorus of approximately 630 g (~21 mol) [34].

Due to its unique chemical structure, various phosphate groups (especially as nucleoside triphosphates) are key players in cellular energy metabolism, in genetic information storage, in signaling pathways, and as phospholipid components of the cell membranes [37]. Inorganic phosphates, together with bicarbonate and protein buffer systems, constitute the basis of the acid-base homeostasis of the body [42].

A healthy adult consumes 1000 mg on average of dietary phosphate per day (Fig. 5.1). Of this amount 700 mg. is absorbed in the small intestine through passive and active pathways [97]. The unabsorbed phosphate is excreted in the feces. Approximately 150 mg. phosphate is secreted into the gut in the saliva, intestinal and pancreatic secretions, while some of it is reabsorbed [47]. Although dietary phosphate intake differs from day to day, principally, phosphate homeostasis is adjusted by intestinal absorption, renal reabsorption, and skeletal resorption. The average serum phosphate concentration in healthy adults is 2.5–4.9 mg/dl [67].

The kidneys filter about 9000 mg. of phosphate daily, 80–90% of which is reabsorbed mainly in the proximal tubule [68]. At least three distinct cotransporters are involved for phosphate transcellular reabsorption in the proximal tubule, namely NaPi-IIa (SLC34A1), NaPi-IIc (SLC34A3), and PiT-2 (SLC20A2) [7] (Fig. 5.2). Phosphate reabsorption is coupled with sodium-dependent (Na^+) transport. Type NaPi II cotransporters are capable of transporting both $H_2PO_4^-$ and HPO_4^{2-} across brush border membrane (BBM) of the proximal tubules [90]. In contrast, in the small intestine, phosphate is absorbed by both transcellular (active) and paracellular (passive) processes, with the active transport being mainly mediated by NaPi-IIb [55].

Given the generally acknowledged role of phosphate in almost every molecular and cellular function, altered phosphate balance can lead to untoward effects. The serum phosphate homeostasis is firmly regulated by endocrine

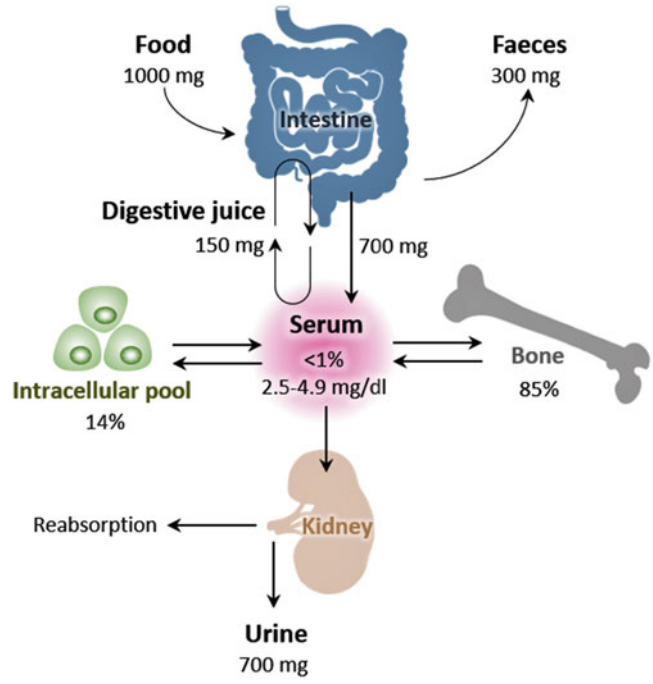

Fig. 5.1 Phosphate flows and balances in the human body [66, 83]

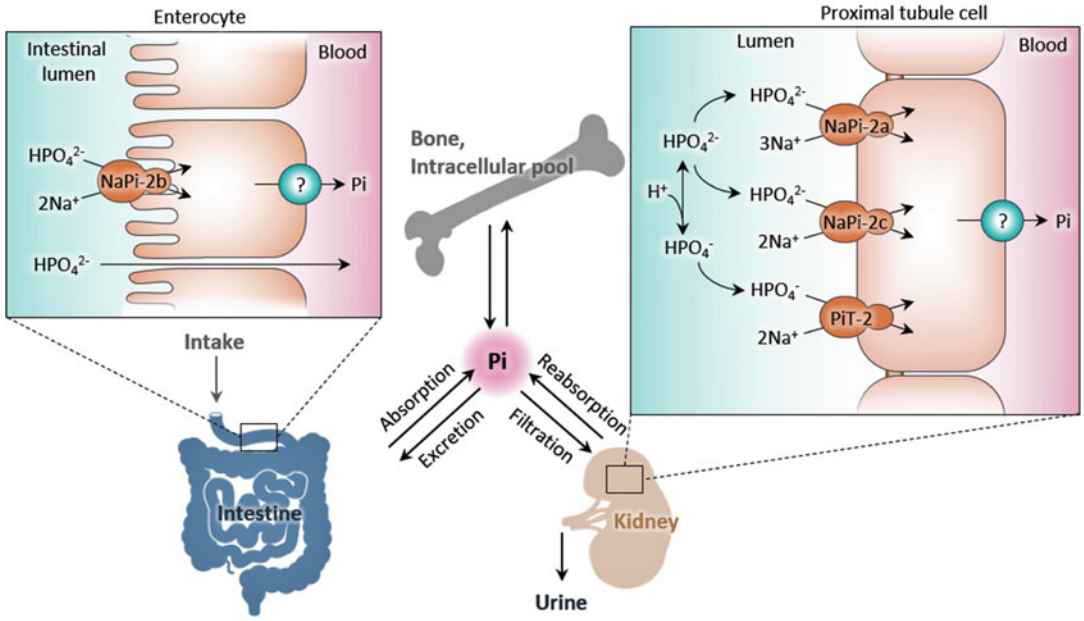

Fig. 5.2 Main transcellular phosphate traffic mechanisms

communication among parathyroid hormone (PTH), calcitriol ($1,25(OH)_2D$), and fibroblast growth factor 23 (FGF-23) [5, 11].

5.2.1 Parathyroid Hormone (PTH)

PTH, a polypeptide containing 84 amino acids with MW 9500 Da, is secreted by chief cells of parathyroid glands [92]. Extracellular calcium concentration is the main modulator of PTH secretion [60]. PTH stimulates calcium resorption from bone tissue, increases calcium reabsorption in the renal tubules, facilitates hydroxylation of 25(OH)D to $1,25(OH)_2D$ in the kidneys, and induces renal excretion of phosphate [50, 69].

In bone tissue, PTH at a permissive level of $1,25(OH)_2D$ promotes calcium resorption by activating osteoclasts [93]. In the intestine, PTH increases the reabsorption of calcium and phosphate by enhancing $1,25(OH)_2D$ synthesis [69]. High serum PTH levels and hypophosphatemia lead to activation of vitamin D-activating enzyme 1α-hydroxylase [57]. $1,25(OH)_2D$ facilitates absorption of calcium and phosphate for bone mineralization and homeostatic metabolism, preventing low serum levels of these elements [43]. PTH also stimulates the synthesis of vitamin D in the kidneys [52].

The effect of PTH on the renal tubules leads to decreased phosphate reabsorption and its increased renal excretion due to the lowered NaPi cotransporters. In general increased PTH secretion results in a decrease in serum phosphate levels [30]. The main role of $1,25(OH)_2D$ is to determine the availability of calcium and phosphate to form new bone and prevent the development of hypocalcemia and hypophosphatemia [3, 30]. This hormone increases intestinal phosphate absorption elevating its serum concentration.

Secretion PTH by the parathyroid glands is mainly triggered by low extracellular calcium by acting on Ca-sensing receptors (CaSR) [85]. Stimulation of CaSR (they belong to the class of G-protein-coupled receptors) activates multiple heterotrimeric G-proteins, in turn passing the signal to mitogen-activated protein kinase (MAPK) pathways. This cascade of reactions ultimately leads to the suppression of PTH secretion by a negative feedback loop. It has been shown that $1,25(OH)_2D$ upregulates the transcription of the gene encoding the CaSR in the parathyroid gland [13]. Additionally, a low level of calcium indirectly induces parathyroid hyperplasia [23]. However, there is also evidence of the opposite effect of stimulation of parathyroid cell proliferation in response to a high calcium concentration [81].

Interestingly, high serum phosphate levels (hyperphosphatemia) also increase PTH secretion independently of shifts in extracellular calcium [41, 86]. The further secretion of PTH is directly suppressed by $1,25(OH)_2D$, acting on VDR of parathyroid glands [79].

5.2.2 Vitamin D (Calcitriol)

From a biological point of view, vitamin D is a steroid hormone, as it is synthesized in the body and has a highly specific receptor (VDR). Most vitamin D (90–95%) is formed in the skin under the influence of UVB light, and only a minor fraction of it is obtained from dietary sources [8].

Vitamin D is stored mainly in the liver with a half-life of approximately 14 days. When a larger amount of vitamin D is absorbed, its excess is stored mainly in adipose tissue [1]. Furthermore, vitamin D in association with the vitamin D-binding protein (VBP) is transferred to the liver, where it is hydroxylated to form 25 (OH)D, which subsequently undergoes 1-α-hydroxylation in the renal tubules, turning into $1,25(OH)_2D$. This biologically active form of vitamin D is under control by serum PTH, phosphate, and FGF23 concentrations. The synthesis of $1,25(OH)_2D$ is stimulated by low serum phosphate levels and high PTH concentrations [78].

Vitamin D promotes the intestinal absorption of calcium and phosphate, significantly increases their renal reabsorption, and also inhibits the PTH secretion [40] (Fig. 5.3). Thus the major effects of $1,25(OH)_2D$ are to augment the intestinal absorption of both calcium and phosphate for proper bone mineral matrix formation [40]. In the intestine and kidneys, $1,25(OH)_2D$ increases the

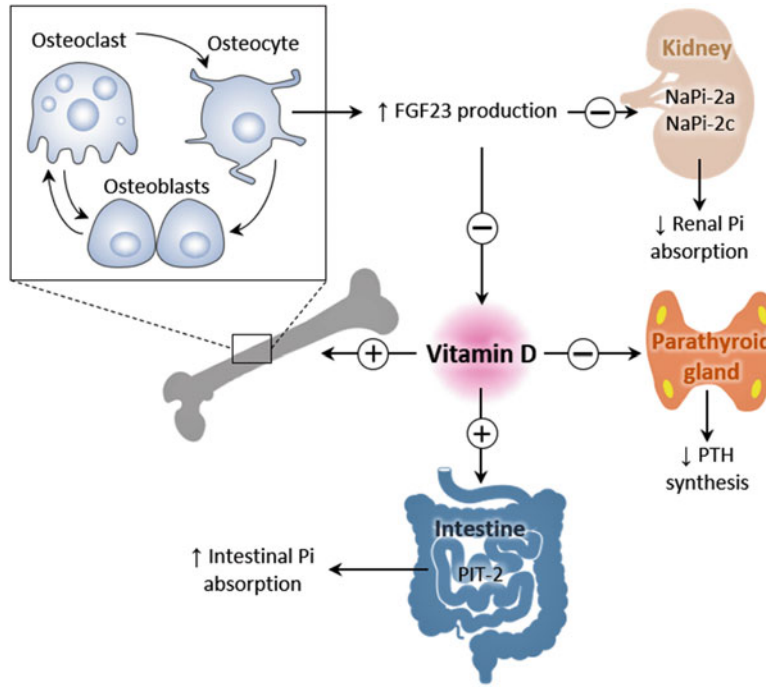

Fig. 5.3 Possible regulation of phosphate homeostasis by vitamin D

formation of calcium-binding proteins (calbidins), which promote transmembrane calcium transport to control homeostasis [2]. In bone, 1,25$(OH)_2$D potentiates the effects of PTH, stimulates bone resorption by osteoclasts, and promotes maturation of monocytes into osteoclasts [70, 84]. In parathyroid glands, 1,25 $(OH)_2$D binds to the VDR, resulting in the suppression of PTH production [96]. The optimal level of serum phosphate is maintained by the interaction of hormones; lowering serum phosphate level by PTH and FGF23, while, increasing serum phosphate level by elevating its absorption in the intestine (1,25$(OH)_2$D) and its resorption from bones (PTH, 1.25$(OH)_2$D) [37]. PTH directly activates osteoclasts and causes phosphate resorption, and indirectly enhances intestinal phosphate absorption by stimulating 1,25 $(OH)_2$D production [44].

Activation of the VDR is a potent and rapid modulator of FGF23 expression, thus forming a "classical" endocrine negative feedback loop between FGF23 and vitamin D [17]. In addition, 1,25$(OH)_2$D is a potent suppressor of PTH gene expression [9].

5.2.3 Fibroblast Growth Factor 23 (FGF23)

FGF23, secreted in bone (osteocytes, osteoblasts, and odontoblasts), is an around 32 kDa glycoprotein, which can be converted in its inactive form through cleavage by a proconvertase-type enzyme into two smaller fragments: 18 kDa (amino fragment) and 12 kDa (carboxy fragment) [32].

FGF23, like PTH, reduces renal phosphate reabsorption, which leads to a drop-in plasma phosphate levels [18]. This hormone also suppresses the secretion of PTH and inhibits the 1α-hydroxylase activity of the kidneys, thus reducing the synthesis of 1,25$(OH)_2$D [46, 51]. FGF23 acts by stimulating its receptors, for the normal function of which a cofactor is needed, i.e. the Klotho protein, synthesized, mostly in the kidneys [87]. The transmembrane Klotho protein is essential for FGF23 to exert its phosphaturic effects in the kidney [72–74, 89].

A decrease in serum phosphate under the FGF23 is achieved by inhibiting phosphate reabsorption in the renal tubules, as well as by

stimulating PTH secretion and suppressing 1,25 $(OH)_2D$ synthesis [12, 51, 56, 72, 91]. In contrast, calcitonin, is another hormone produced by the thyroid gland, slightly lowers serum calcium due to inhibition of renal and intestinal calcium reabsorption, reducing calcium and phosphate resorption from bones [36]. Plasma calcium is regulated by a complex system involving PTH and $1,25(OH)_2D$ on the intestine, bones, and kidneys. As mentioned, parathyroid gland cells respond to serum calcium concentration via CaSR. A high level of calcium in extracellular fluid stimulates CaSR receptors and activates cellular mechanisms, which ultimately leads to inhibition of PTH release [6].

Imbalance of calcium and phosphate is manifested as a shift in the calcium, phosphate levels in serum and the levels of serum hormones [PTH and 25(?H)D], as well as the development of bone pathology and cardiovascular calcification with soft anomalies [76, 88]. The exact etiology and pathogenesis of serum phosphate derangements (hyperphosphatemia and hypophosphatemia) will need further studies.

5.3 Hyperphosphatemia

Renal failure is the most common cause of hyperphosphatemia [80]. The decline in estimated glomerular filtration rate disrupts phosphate homeostasis: when it falls below 30 mL/min/1.73 m^2, the reabsorption of phosphate is maximally suppressed and fractional excretion markedly reduced. As a result, the serum level of phosphate increases [16, 21]. A primary increase in tubular reabsorption of phosphate is less common and can be observed in hypoparathyroidism, acromegaly, and tumoral calcification [38].

Excessive phosphate can be released from the intracellular compartment, which is observed in acute tumor lysis syndrome, rhabdomyolysis, hemolysis, hyperthermia, profound catabolic stress, and acute leukemia. Tumor lysis syndrome is commonly observed in malignant hematological patients, particularly non-Hodgkin's lymphoma and acute leukemia, following chemotherapy [4]. Risk factors for developing the syndrome include impaired renal function, increased levels of lactate dehydrogenase, and hyperuricemia [95]. The latter is caused by the disturbances in FGF23-mediated phosphate regulation in the proximal tubule of the kidney [10]. Increased intestinal phosphate absorption is mainly caused either by the use of phosphate-containing oral laxative, or by vitamin D overdoses [59].

5.4 Hypophosphatemia

Hypophosphatemia may be a consequence of the decreased intestinal absorption, internal redistribution, and increased urinary loss of phosphate [31]. The acute shift of phosphate from the extracellular to the intracellular compartment is most often caused by respiratory alkalosis and refeeding syndrome in hospitalized patients [19, 54]. Respiratory alkalosis causes an increase in intracellular pH, which stimulates phosphofructokinase, leading to severe hypophosphatemia with plasma phosphate of >0.32 mmol/L [82]. The intracellular shift of phosphate is also observed in the treatment of diabetic ketoacidosis and hungry bone syndrome, which occurs after parathyroidectomy performed for patients with long-standing hyperparathyroidism [31]. At the same time, in the postoperative period, serum calcium and phosphate concentrations significantly decrease.

Low phosphate intake rarely causes hypophosphatemia, probably because the phosphate content in the diet almost always exceeds the phosphate loss through the gastrointestinal tract, and the kidneys can reabsorb nearly all of the filtered phosphate [24]. Excessive urinary loss of phosphate is observed in both primary and secondary hyperparathyroidism caused by impaired vitamin D metabolism, Fanconi syndrome, diuretics, and tumor-induced osteomalacia (TIO) [31, 48]. TIO is a rare paraneoplastic syndrome characterized by hypophosphatemia, phosphaturia, decreased $1,25(OH)_2D$ level, normal 25(OH)D levels, and osteomalacia [29]. Overproduction of FGF23 caused by TIO reduces tubular phosphate reabsorption and $1,25(OH)_2D$ production [58].

5.5 Genetic Disorders Associated with Hypophosphatemia

Several inherited abnormalities are characterized by phosphate-wasting syndromes, commonly mediated by FGF23. These diseases, resulted by impaired FGF23 metabolism, include autosomal dominant hypophosphatemic rickets (ADHR), X-linked hypophosphatemic rickets (XLHR), and autosomal recessive hypophosphatemic rickets (ARHR) [94].

ADHR (OMIM 193100) is produced by *FGF23* gain-of-function mutation, which causes the resistance of the mutant FGF23 to proteolytic degradation [22]. ADHR manifests as a defect in renal phosphate transport, associated with decreased 1,25(OH)2D levels, while the PTH levels remain normal. ADHR is characterized by hypophosphatemia, renal phosphate loss, short stature, and bone disorders [25].

ARHR (OMIM 241520) is caused by mutations in the *DMP1* gene (located on chromosome locus 4q21). Patients with ARHR suffer from decreased renal phosphate reabsorption and typically display hyperphosphaturia, hypophosphatemia, reduced $1,25(OH)_2D$ concentration, with PTH values remaining normal [28, 49].

XLHR (OMIM 307800) appears as a result of mutations inactivating *PHEX* (phosphate-regulating gene with homologies to endopeptidases located on the X-chromosome). The *PHEX* gene encodes a zinc-dependent metalloproteinase, and is strongly expressed in osteoblasts, osteocytes, and odontoblasts [53]. The XLHR symptoms include growth retardation, hypophosphatemia, osteomalacia, and defective renal phosphate reabsorption. The diseased state is resistant to phosphate and vitamin D therapy [63].

5.6 Conclusions

Serum phosphate levels are tightly regulated by hormonal and metabolic factors mainly related to the triad "vitamin D-PTH-FGF23" as well as dietary phosphate. Experimental studies have convincingly shown that disorders and disturbances in phosphate regulation can lead to serious systemic complications [45, 61, 62, 64, 65, 75, 77]. Particular attention should be placed on the central activity of vitamin D in phosphate metabolism, as 1,25(OH)2D both, directly and indirectly, impact serum phosphate levels. However, despite the well-studied pivotal roles of vitamin D in phosphate homeostasis, many aspects remain unclear. For instance, what are the underlying mechanisms by which vitamin D acts on renal phosphate reabsorption, and how exactly do calcium and vitamin D modulate FGF23 production? A better understanding of these processes and interactions would help to develop more efficient strategies for the treatment of phosphate-related disorders.

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