CHAPTER

31

Endocrine Regulation of Phosphate Homeostasis

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OUTLINE

1. INTRODUCTION

The importance of phosphate regulation in the human body has been highlighted by research showing that phosphate dysregulation is associated with many disease conditions, including chronic kidney disease (CKD), cardiovascular disease, tumorigenesis, premature aging, and skeletal disorders.[1–8] The benefit of dietary phosphate restriction in the management of CKD is well established.[9–11] However, until recently, little attention has focused on the health and disease consequences of an oversupply of phosphorus in the diet of healthy adults. Recent epidemiological research has shown that mortality in healthy adults increases as dietary phosphate intake levels rise above 1400 mg per day.[12] Paradoxically, the United States Department of Agriculture continues to recommend dietary phosphate levels exceeding 1700–1800 mg per day for a 2000-calorie diet.[13,14] Thus, issues of phosphate homeostasis apply to the general population, not just to patients with CKD.

In this book chapter, we outline the physiological basics of phosphate homeostasis, focusing particularly on endocrine regulation of this essential micronutrient—the second most abundant mineral in the body, next to calcium. The first part discussed at the intestinal absorption and regulation of phosphate homeostasis through the bone–kidney axis, the next part explained in more detail at the interaction of specific endocrine regulators of phosphate homeostasis, and the last part elaborated some of the pathophysiological conditions associated with dysregulated phosphate homeostasis.

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2. PHOSPHATE HOMEOSTASIS

The regulation of phosphate homeostasis is biologically important because inorganic phosphorus performs many functions within the body.[15–19] Phosphate is a component of nucleic acids, DNA and RNA, and it is incorporated in the structure of phospholipids in cell membranes. As an intracellular anion, phosphate is involved in the activation and inactivation of enzymes and coenzymes. Phosphate also plays roles in cell signaling through phosphorylation, in energy metabolism as ATP, and in bone mineralization as a principal element within hydroxyapatite. Endocrine regulation of phosphate depends on a delicate balance among circulating factors like $1,25(OH)_2D_3$ (calcitriol, the active form of vitamin D), parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23). Dysregulation of these factors can induce phosphorus imbalances which can affect the functionality of almost every human system, including musculoskeletal and cardiovascular systems, ultimately leading to an increase in morbidity and mortality. Through the action of PTH, vitamin D, and FGF23, phosphate homeostasis is maintained by regulating the amount of phosphate absorbed in the intestines, reabsorbed in the kidney, and resorbed from bone (Fig. 31.1).

2.1 Intestinal Phosphate Absorption

Phosphate from dietary sources is absorbed in the small intestines, mainly through active transport by the type II sodium-dependent phosphate cotransporter, Npt2b (encoded by gene SLC34a2), and absorption is regulated by hormones and dietary conditions.[20–22] The sodium and phosphorus ions are transported by the Npt2b cotransporters, which involves voltage-dependent and electroneutral mechanisms. In addition to $1,25(OH)_2D_3$, factors that regulate the expression and function of Npt2b include FGF23, matrix extracellular phosphoglycoprotein (MEPE), epidermal growth factor (EGF), thyroid hormone, estrogens, glucocorticoids, and metabolic acidosis. Moreover, Na^+/H^+ exchange regulatory factor 1 (NHERF1) also interacts with Npt2b in the intestines under conditions of low dietary phosphorus intake.[23] A smaller amount of phosphorus is believed to be absorbed in the intestines by type III sodium-dependent phosphate cotransporters, Pit1 and Pit2, which operate by passive transport and are involved in functions of individual cells.[22] In addition, ingestion of large amounts of dietary phosphate can increase serum phosphate levels through increased absorption via a paracellular route, bypassing hormonal regulation of cotransporters.[22,24]

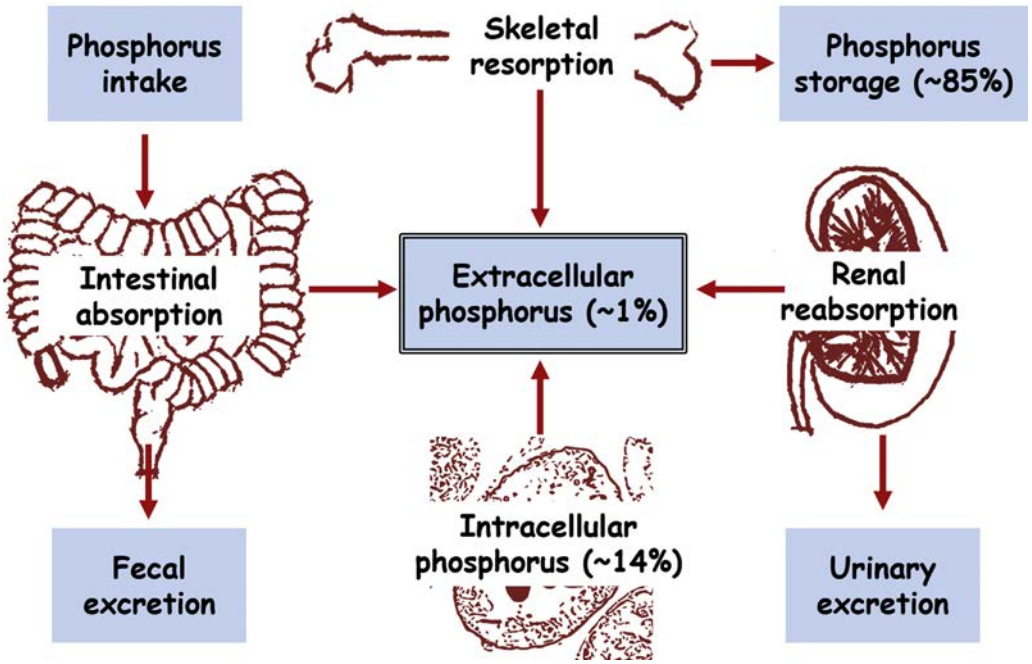

FIGURE 31.1 Total body phosphorus homeostasis is primarily maintained by a multiorgan cross-talk among parathyroid gland, intestine, kidney, and bone. Of clinical importance, since only 1% of total body phosphorus is extracellular, the serum phosphorus concentration does not truly reflect total body phosphorus content and is also a poor predictor of intracellular and storage phosphorus content.[19,120,127,133,135]

2.2 Renal Phosphate Reabsorption

Serum phosphate levels are regulated mainly through the reabsorption rate of renal phosphate within the kidney, the major organ that regulates phosphate homeostasis according to the body's requirements.[5,18,25] Renal phosphate reabsorption increases or decreases through the expression of sodium-phosphate cotransporters, Npt2a (SLC34a1) and Npt2c (SLC34a3), located in the renal proximal tubule.[26] Npt2a is electrogenic and transports three Na^+ ions coupled to phosphorus (HPO_4^{2-}) at physiologic pH, while Npt2c is electroneutral and transports two Na^+ ions for each phosphorus ion. Pit2 phosphate transporters are also located in the renal proximal tubule. It is believed that a low concentration of sodium regulated by Na^+, K^+-ATPase in the cells of the basolateral membrane facilitates phosphorus transport within the proximal tubule.[27–31] Cotransporters import phosphate from the proximal tubular lumen, translocated across the apical brush-border membrane (BBM) and exported at the basolateral membrane.[26] Although the molecules involved in phosphate translocation have not been identified, xenotropic and polytropic retrovirus receptor 1 (XPR1) appears to act as a phosphate exporter in mammalian cells, but its role as an exporter in renal cells has not yet been determined.

Hyperphosphaturia and hypophosphatemia occur in Npt2a knockout mice ($Npt2a^{-/-}$). Concentrations of serum $1,25(OH)_2D_3$ and urine calcium also increase in Npt2a knockout mice; there is a ~70% decrease in phosphate transport in the BBM, and reabsorption is supported by increased expression of Npt2c.[32–35] This evidence indicates that Npt2a in mice is a major transporter in renal phosphate reabsorption. Mutation of Npt2a in humans causes recessive Fanconi syndrome with hypophosphatemic rickets, suggesting that Npt2a plays a role in phosphate handling.[36,37] In Npt2c knockout mice, ($Npt2c^{-/-}$), hypercalciuria and higher serum concentrations of $1,25(OH)_2D_3$ occur, but hypophosphatemia or rickets does not.[34] The situation is different in humans with mutation of Npt2c, causing hereditary hypophosphatemia rickets with hypercalciuria (HHRH), which suggests that Npt2c has a more important role in phosphate homeostasis in humans than in mice.[38,39]

2.3 Skeletal Phosphate Resorption

Bone functions as a reserve for calcium and phosphate from which the body can deposit and withdraw minerals to maintain mineral ion balance.[17,40–45] Reabsorption is the process by which bone releases calcium and phosphate from the hydroxyapatite bone matrix. Osteocytes in mature bone assist in bone mineralization and phosphate homeostasis by producing factors such as FGF23 and $1,25(OH)_2D_3$. Other endocrine regulators that target bone include PTH, calcitonin, sex hormones, and osteocalcin. An endocrine communication network that regulates phosphorus homeostasis is formed between bone, kidneys, intestines, and parathyroid glands (Fig. 31.1).

3. ENDOCRINE REGULATORY FACTORS

3.1 Parathyroid Hormone

Phosphate reabsorption is decreased in the kidney by PTH, which induces phosphaturia.[26] Decreased reabsorption occurs, as levels of Npt2a and Npt2c protein are reduced in the BBM. Through endocytosis, Npt2a is delivered to lysosomes for degradation, while Npt2c is dissolved through a pathway dependent on microtubules. The basolateral and apical surfaces of the proximal tubule each contain PTH receptors. On the apical surface, PTH receptors are signaled by a protein kinase C (PKC) pathway, and a protein kinase A (PKA) pathway signals PTH receptors on the basolateral surface. PTH signaling occurs by phosphorylation of NHERF1.[46–49] Production of FGF23 is enhanced by PTH, and phosphate augments PTH production by stabilizing its mRNA.[50–54]

3.2 Vitamin D

More than 80% of required vitamin D in human is generated by ultraviolet (UV) B rays from sunlight.[55–63] As mentioned, $1,25(OH)_2D_3$ increases intestinal absorption of dietary phosphate, mainly through enhanced expression of Npt2b cotransporters. $1,25(OH)_2D_3$ is produced from circulating 25-hydroxyvitamin D [25(OH)D] through the action of 1α-hydroxylase (CYP27B1), an enzyme expressed in the renal proximal tubules. Janus kinase 3 (JAK3), produced in epithelial cells of the kidney, has also recently been found to powerfully regulate 1α-hydroxylase expression and phosphate transport.[64] Although $1,25(OH)_2D_3$ does not play a direct role in the reabsorption of renal phosphate, $1,25(OH)_2D_3$ suppresses PTH synthesis, thus indirectly preventing reduced renal phosphate

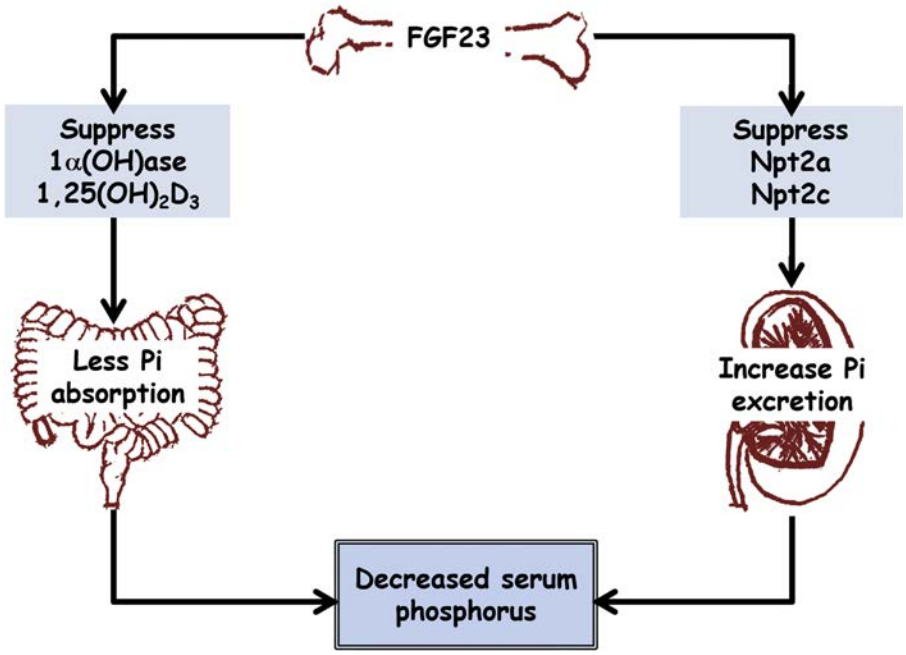

FIGURE 31.2 FGF23 produced in the bone can suppress Npt2a and Npt2c cotransporters to increase the renal excretion of phosphate. Similarly, FGF23 can also suppress the renal expression of 1α(OH)ase to reduce production of $1,25(OH)_2D_3$ to decrease intestinal phosphate absorption, resulting in reduced serum levels of phosphate.[19,132]

reabsorption caused by PTH. Rising serum phosphate levels suppress production of $1,25(OH)_2D_3$, forming a feedback loop between intestinal absorption and serum phosphate. The FGF23 production also increases as serum levels of phosphate and $1,25(OH)_2D_3$ rise.

3.3 Fibroblast Growth Factor 23 and Klotho

FGF23, produced by osteocytes and osteoblasts of bone, is a recently discovered regulatory factor in phosphorus homeostasis.[65–69] Renal phosphate wasting is caused by excessive levels of FGF23 in the serum, and the discovery of FGF23's phosphate regulatory function was made after finding that autosomal-dominant hypophosphatemic rickets (ADHR) was caused genetically by mutations in the FGF23 gene. A member of the FGF19 subfamily, the FGF23 peptide in humans contains 251 amino acids, which is cleaved proteolytically during the secretion process. FGF23 requires a transmembrane protein cofactor, Klotho, which enables the activation of FGF receptors (FGFR).[70] Ectopic calcification, high levels of $1,25(OH)_2D_3$, and hyperphosphatemia were discovered in the phenotypes of Klotho and FGF23 null mice.[71–76] Upon activation, FGF23 lowers serum phosphate levels and increases phosphate excretion in the urine by suppressing reabsorption through the action of sodium-phosphate cotransporters, mostly in the renal proximal (Fig. 31.2). Klotho is expressed in the kidney, and Klotho-activated FGF23 reduces the expression of Npt2a, possibly by phosphorylating NHERF1.[49]

Within the renal proximal tubular epithelium, recent findings imply that FGF23 activates FGFR1 as well as FGFR4, which mediates signaling involving JAK3.[49] In the distal tubular epithelium, FGF23 targets with-no-lysine kinase-4 (WNK4) which regulates solute transport.[15,49] FGF23 also downregulates synthesis of 1α-hydroxylase in the renal proximal tubules, thus suppressing $1,25(OH)_2D_3$ production. As mentioned, the release of FGF23 from bone is stimulated by increased serum levels of both phosphate and vitamin D; thus, FGF23 provides a regulatory feedback loop between the kidneys and bone.

4. DYSREGULATION OF PHOSPHATE HOMEOSTASIS

The endocrine feedback loops that regulate serum phosphate is a complex process. When endocrine regulation of phosphate homeostasis becomes dysfunctional due to phosphate burden or injury from phosphate toxicity, or due to genetic abnormalities, several associated disease conditions result. In general, dysregulated serum phosphate falls

TABLE 31.1 A List of Several Human Diseases With Abnormal Phosphate Balance Due to Dysregulation of FGF23

Diseases Associated With Increased FGF23 Activity	Cause
ADHR	*FGF23* mutation
ARHR	*DMP1* mutation
ENS	*FGFR3* mutation
McCune-Albright syndrome	*GNAS1* mutation
OGD	*FGFR1* mutation
TIO	FGF23-producing tumor
XLHR	*PHEX* mutation
Diseases Associated With Decreased FGF23 Activity	**Cause**
FTC	*GALNT3* mutation
FTC	*FGF23* mutation
FTC	*KLOTHO* mutation

Please note that the serum levels of both C-terminal and intact FGF23 are high in FTC caused by a *KLOTHO* mutation, while serum levels of C-terminal are high, the levels of intact FGF23 are low to normal in FTC caused by *GLANT3* or *FGF23* mutations.[19,132]
ADHR, autosomal dominant hypophosphatemic rickets; *ARHR*, autosomal recessive hypophosphatemic rickets/osteomalacia; *DMP1*, dentin matrix protein 1; *ENS*, epidermal nevus syndrome; *FTC*, familial tumoral calcinosis; *GALNT3*, UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase-3; *GNAS1*, guanine nucleotide-binding protein alpha-stimulating activity polypeptide 1; *OGD*, osteoglophonic dysplasia; *PHEX*, phosphate-regulating gene with homology to endopeptidases on the X chromosome; *TIO*, tumor-induced osteomalacia; *XLHR*, X-linked hypophosphatemic rickets.

within two categories: hypophosphatemia and hyperphosphatemia. However, normal serum phosphate levels do not preclude intracellular and extracellular phosphorus dysregulation and associated conditions.[4]

4.1 Genetic Disorders of Phosphate Regulation

X-linked hypophosphatemic rickets (XLHR), ADHR, and autosomal recessive hypophosphatemic rickets (ARHR) occur when the FGF23 function is excessive. High circulating levels of FGF23 result in inadequate renal phosphate reabsorption and normal to lower levels of $1,25(OH)_2D_3$. In addition to FGF23, genes that cause XLHR are phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX), ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), and dentin matrix protein 1 (DMP1) (Table 31.1).

Overexpression of FGF23 also causes hypophosphatemic rickets/osteomalacia associated with McCune-Albright syndrome, fibrous dysplasis, hypophosphatemic disease caused by intravenous administration of saccharated ferric oxide or iron polymaltose, family with sequence similarity 20, member C (FAM20C), and tumor-induced osteomalacia.[77–79] In addition to releasing FGF23, mesenchymal tumors can synthesize and release other phosphaturic factors such as FGF7, MEPE, and secreted frizzled-related protein 4 (sFRP4).[80–83] Hyperphosphatemic diseases occur when the FGF23 function is lacking due to inactivating mutations, e.g., familial tumoral calcinosis which produces elevated levels of renal phosphate reabsorption and $1,25(OH)_2D_3$, along with ectopic calcification.[84–87] In addition to FGF23 and Klotho, UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 3 (GALNT3) is the gene that causes familial tumoral calcinosis.[85,88] Klotho mutations were found to cause resistance to FGF23,[89] and mutations in GALNT3 and FGF23 impaired secretion and circulation of full-length FGF23.

4.2 Conditions Associated With Phosphate Toxicity

That excessive intake of dietary phosphate is largely absorbed and may bypass normal endocrine regulation suggests that humans, and perhaps other mammals, lack the physiological mechanisms to regulate a high-phosphorus diet. Many people, including patients with CKD[90] and future medical professionals,[91] lack awareness that a conventional Western diet, abundant in dairy, flesh foods, grains, and phosphate additives, far exceeds the recommended dietary allowances for phosphorus. Phosphate toxicity, the accumulation of excess phosphorus in the intracellular and extracellular tissues, whether from genetic disorders or excessive dietary phosphate intake, is associated with a wide variety of disease conditions.[2,92,93]

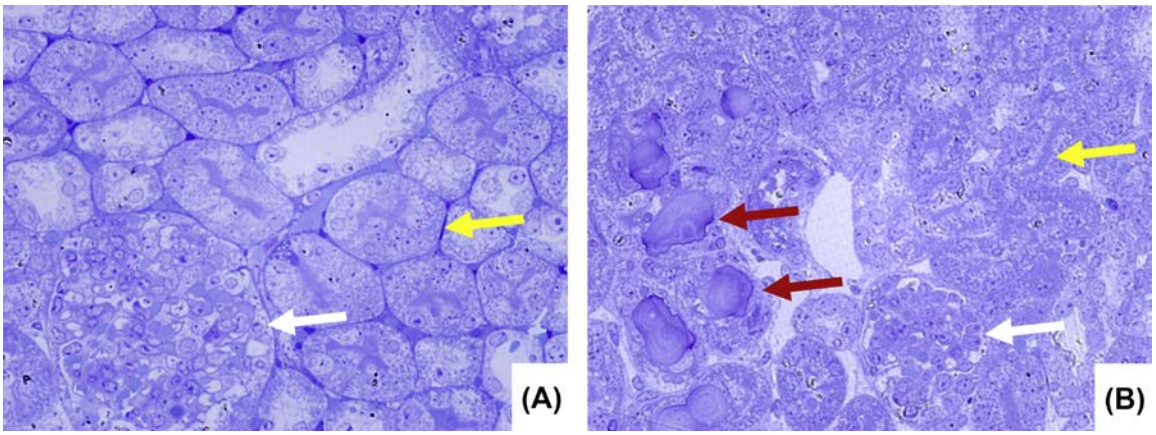

FIGURE 31.3 Ultrathin sections of kidneys of a mouse with normal serum phosphate level (A) and a mouse with high serum phosphate level (B). Please note the comparative glomerular structures (*white arrows*) and tubulointerstitial structures (*yellow arrows*) in kidneys with normal and high phosphate levels. The toluidine blue-stained kidney sections showing glomerular shrinkage, loss of tubulointerstitial uniformity, and renal calcification (*red arrows*) in kidney exposed with phosphate toxicity.[120] (Original magnification ×40).

4.2.1 Chronic Kidney Disease

High serum phosphorus concentrations have been shown to increase the risk of developing kidney disease.[94] Increased renal phosphate burden causes tubular injury and interstitial fibrosis within the kidneys.[1,95–97] As serum phosphorus increases in kidney disease patients, glomerular filtration rate decreases. Increased mortality from cardiovascular disease is also associated with CKD.[98–102] Patients with early stages or end stage renal disease are counseled to manage their condition by following phosphate-restricted diets, and patients may also be prescribed phosphate binders.[103,104]

In hyperphosphatemia, phosphorus binds with free calcium to form calcium-phosphorus (CaxPi) product, a mineral compound normally elaborated into bone hydroxyapatite.[2,92] The consequent serum reduction in free calcium stimulates release of the PTH which in turn resorbs bone to restore normal concentrations of serum calcium. This may explain how hyperphosphatemia in patients with CKD may induce secondary hyperparathyroidism, which accelerates bone resorption that may eventually lead to skeletal mineralization defects. The subsequent increase in serum concentration of CaxPi product, under continuing conditions of kidney burden that initiated hyperphosphatemia, may also be deposited into the tissue causing ectopic calcification (Fig. 31.3).

4.2.2 Vascular Calcification

The arterial system's endothelium is susceptible to ectopic calcification from CaxPi product deposition. Mortality risk is increased threefold to fourfold by arterial calcification.[105] A hard or stable plaque forms in calcified arterial vessels, which is associated with hypertension, arteriosclerosis, left ventricular hypertrophy, and aortic valve disease. Vasodilation is also impaired by a high phosphorus load, which increases cardiovascular disease risk.[106] High levels of serum phosphorus have been associated with coronary atherosclerosis,[107] left ventricular hypertrophy, [108–111] and a 40% increased risk of heart failure.[112]

4.2.3 Tumorigenesis and Premature Aging

Phosphorus is sequestered in tumors in cancer patients,[113] and cancer cells accumulate up to twice as much phosphorus as normal cells.[114] A cellular environment high in phosphorus in humans has been found to induce tumor neovascularization and angiogenesis, or new blood vessel formation in neoplasms,[115] possibly playing a role in sequestering excess phosphorus, as does the hyphae of mycorrhizae in a plant's root system.[116] Tumor growth in lung tissue has been stimulated by dietary phosphorus overload,[117] and breast cancer cells cultured with elevated phosphorus levels were observed to modulate tumor metabolism and metastasis.[118] A high daily phosphorus intake by men in the Health Professionals Follow-Up Study was associated with an increased overall risk of prostate cancer and with lethal and high-grade prostate cancer.[119] Phosphate toxicity has been found to accelerate mammalian aging, leading to early death.[5,92,120–122] In particular, renal aging plays a key role in accelerating systemic aging.[123–125]

5. CONCLUSION

Recent studies have provided convincing evidence of endocrine regulation of systemic phosphate homeostasis.[2,19,92,120,126–128] The endocrine interaction between bone-derived FGF23 and kidney-derived Klotho is essential for physiologic regulation of phosphate homeostasis. As briefly discussed, dysregulation of the FGF23–Klotho system leads to phosphate imbalance and induces a wide range of organ/tissue damage in blood vessels, bone, and kidney. Of clinical significance, phosphate toxicity induced by exogenous phosphate administration in humans can be fatal.[5] Recent studies have found that future medical professionals and CKD patients undergoing hemodialysis are not sufficiently aware of the hidden source of phosphate in their diet and highlight the need for educational initiatives to raise awareness of the risk posed by dietary items with hidden phosphate ingredients,[90,91] as maintaining phosphate balance through optimal dietary intake is important for a healthy life and for longevity.[7,120,129–134]

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