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REVIEW

Dysregulation of phosphate metabolism and conditions associated with phosphate toxicity

Ronald B Brown[1] and Mohammed S Razzaque[2,3]

[1]Department of Hospitality Management and Dietetics, College of Human Ecology, Kansas State University, Manhattan, KS, USA. [2]Department of Applied Oral Sciences, Forsyth Institute, Cambridge, MA, USA. [3]Division of Research & Development, VPS Healthcare, Abu Dhabi, UAE.

Phosphate homeostasis is coordinated and regulated by complex cross-organ talk through delicate hormonal networks. Parathyroid hormone (PTH), secreted in response to low serum calcium, has an important role in maintaining phosphate homeostasis by influencing renal synthesis of 1,25-dihydroxyvitamin D, thereby increasing intestinal phosphate absorption. Moreover, PTH can increase phosphate efflux from bone and contribute to renal phosphate homeostasis through phosphaturic effects. In addition, PTH can induce skeletal synthesis of another potent phosphaturic hormone, fibroblast growth factor 23 (FGF23), which is able to inhibit renal tubular phosphate reabsorption, thereby increasing urinary phosphate excretion. FGF23 can also fine-tune vitamin D homeostasis by suppressing renal expression of 1-alpha hydroxylase (1α(OH)ase). This review briefly discusses how FGF23, by forming a bone–kidney axis, regulates phosphate homeostasis, and how its dysregulation can lead to phosphate toxicity that induces widespread tissue injury. We also provide evidence to explain how phosphate toxicity related to dietary phosphorus overload may facilitate incidence of noncommunicable diseases including kidney disease, cardiovascular disease, cancers and skeletal disorders.

Introduction

All living organisms are dependent on exogenous sources of phosphorus. In humans and animals, dietary phosphorus must be acquired in sufficient amounts to avoid nutrition-related deficiencies such as rickets. In the body, exogenous phosphorus is metabolized to phosphate. Dietary phosphorus overload may contribute to dysregulation of phosphate metabolism leading to phosphate toxicity.[1] In this review, we discuss the regulation of phosphate metabolism, and how its dysregulation can lead to phosphate toxicity. We define phosphate toxicity as excessive levels of extracellular and intracellular phosphate that are harmful to cellular function. In addition, several conditions associated with phosphate toxicity such as ectopic calcification, chronic kidney disease (CKD) and tumorigenesis are discussed.

The active roles of calciotropic hormones vitamin D and parathyroid hormone (PTH) to regulate phosphate homeostasis are well known.[2,3] However, physiologic phosphate regulation cannot be fully explained by the actions of these hormones alone,[4–8] and the identification of fibroblast growth factor 23 (FGF23), which can influence both vitamin D and PTH functions, helped us gain further insights into the physiologic regulation of phosphate homeostasis. Skeletal-derived FGF23 exerts phosphate-lowering effects in the kidney via a complex endocrine network; studies have identified osteoblasts and osteocytes as the main FGF23-producing cells.[9,10] In addition to renal phosphate-lowering effects, FGF23 can lower 1,25-dihydroxyvitamin D production by suppressing the renal expression of 1-alpha hydroxylase (1α(OH)ase) and by increasing catabolism in the kidney. Studies have claimed that FGF23 may also suppress PTH synthesis.

FGF23 mediates its functions by interacting with an FGF receptor (FGFR) in a dependent manner using alpha-klotho as a cofactor. Although almost all tissues and organs express one or more isoforms of FGFRs, the restricted presence of alpha-klotho provides organ specificity to FGF23 functions.[11–14] FGF23 was initially identified in the ventrolateral thalamic nucleus of the mouse brain,[15] and its clinical importance was subsequently shown in patients with autosomal dominant hypophosphatemic rickets.[16] The *FGF23* gene has three exons separated by two introns, and the gene encodes a 32-kDa glycoprotein containing 251 amino acid residues: 24 amino acids constitute a hydrophobic signal sequence, an N terminus of 155 amino acids constitute the FGF core homology region and 72 amino acids form the C-terminal domain.[17–20] After cleavage of the 24-amino-acid signal sequence, the mature protein (25–251)-FGF23 is secreted into the circulation where three distinct forms of the FGF23 protein can be

detected: a full-length mature form (25–251)-FGF23, a shorter form (25–179)-FGF23 lacking the unique C-terminal tail of 72 amino acids and a C-terminal tail. The shorter form without a C-terminal tail arises from proteolytic cleavage at the 176RXXR179 site,[17–20] and it can also be detected in the serum. Recent studies have shown that the C terminus is not only the potential alpha-klotho-interacting site, but it also determines the functionality of the FGF23 protein. The chimeric protein containing the N terminus of FGF2 and C terminus of FGF23 could act as a phosphatonin and could reduce the renal expression of 1α(OH)ase.[19,20] It is worth mentioning that the presence of the C terminus of FGF23 in the chimeric protein paved the way for the alpha-klotho interaction. Recently, a family with sequence similarity 20, member C (Fam20C), was shown to phosphorylate FGF23. Such phosphorylation blocks O-glycosylation by polypeptide N-acetylgalactosaminyl-transferase 3. This observation suggests that the interplay between phosphorylation and O-glycosylation of FGF23 may be a critical posttranslational modification by which the activity of secreted FGF23 protein is determined.[21] Once secreted, FGF23 protein binds its receptors to exert diverse functions.

In vitro studies have shown that bioactive FGF23 protein can bind to FGFR1c, FGFR3c and FGFR4, but not to FGFR2c.[22] *In vivo* studies have suggested that FGFR1c is the main target for FGF23 in the kidney[23,24,] as loss of FGFR3 or FGFR4 activity did not affect FGF23-mediated hypophosphatemia in Hyp mice.[24] It is of relevance that Hyp mouse is the model for human X-linked hypophosphatemia related to mutations that inactivate the endopeptidases of the X chromosome (PHEX); the inactivation of PHEX leads to increased serum levels of FGF23, a phosphaturic hormone that induces excessive renal phosphate excretion and severe hypophosphatemia. Moreover, conditional deletion of FGFR1 in the kidney abolished phosphaturic effects of recombinant FGF23 administration.[25] It is of relevance that no such abolition following administration of recombinant FGF23 was noted in FGFR3 or FGFR4 knockout mice.[25] The *in vivo* functions of FGF23 are also elegantly demonstrated in genetically modified mouse models. For instance, FGF23 knockout mice develop severe hyperphosphatemia owing to increased renal reabsoption of phosphate,[26,27] whereas FGF23-overproducing transgenic mice or Hyp mice are hypophosphatemic owing to excessive urinary phosphate excretion.[28,29] Such FGF23-mediated hypophosphatemia is an alpha-klotho-dependent phenomenon, and miscommunication of FGF23 and alpha-klotho can lead to dysregulation of renal phosphate homeostasis.[1,14,30,31]

Renal Phosphate Regulation

Under normal physiologic conditions, the kidneys maintain serum phosphate balance by fine-tuning urinary phosphate excretion. Filtrated phosphate is reabsorbed in the renal proximal tubular epithelial cells using sodium-dependent phosphate (Na/Pi) cotransporters[32–34] (**Figure 1**). Although these cells contain three types of Na/Pi cotransporters, the type 2 cotransporter family that includes Na/Pi2a (encoded by the *SLC34a1* gene) and NaPi2c (encoded by the *SLC34a3* gene) is believed to be most active in renal phosphate uptake. In contrast to the type 2 cotransporter system, the type 1 cotransporter (NPT1) is mostly an anion carrier, whereas the type 3 cotransporter system comprises two transporters, PiT1

(encoded by the *SLC20a1* gene) and PiT2 (encoded by the *SLC20a2* gene), and their role in phosphate transport is an active area of research. Studies have shown that FGF23 could suppress the expression of Na/Pi2a and Na/Pi2c, leading to less renal phosphate uptake with increased urinary phosphate excretion.[25] In fact, transgenic mice overexpressing FGF23 showed severe urinary phosphate wasting owing to suppressed expression and reduced activity of renal Na/Pi2a,[28,29] whereas Fgf23 knockout mice develop severe hyperphosphatemia owing to increased renal expression and activity of Na/Pi2a.[26,27] It is of particular interest that genetically restoring FGF23 systemic actions in Fgf23 knockout mice reduced Na/Pi2a activity, resulting in reversal of hyperphosphatemia to hypophosphatemia.[29] It is important to note that the segment of the nephron on which FGF23 exerts its most potent effects is not yet clear, as alpha-klotho, the cofactor for FGF23 bioactivities, is mostly present in the distal convoluted tubule, whereas Na/Pi cotransporter activity and vitamin D metabolizing enzymes are mainly present in the proximal tubular epithelial cells.[35] Although further studies are needed to determine the exact molecular mechanisms of FGF23-mediated renal phosphate transport, miscommunication between FGF23 and alpha-klotho leads to altered phosphate balance.

Pathological conditions in CKD are mostly owing to miscommunication between bone-derived FGF23 and kidney-derived alpha-klotho, which leads to the development of phosphate toxicity. In CKD patients, reduced levels of alpha-klotho leaves FGF23 nonfunctional, thereby limiting the kidneys' ability to excrete urinary phosphate. *In vivo* studies conducted on Fgf23 knockout mice have shown that bioactive FGF23 protein could significantly reduce serum phosphate level in these mutant mice. It is of particular significance that bioactive FGF23 protein failed to exert phosphate-lowering effects in Fgf23/alpha-klotho double knockout mice,[36,37] suggesting that FGF23 loses its phosphate regulating abilities without alpha-klotho. Moreover, FGF23-induced hypophosphatemia in Hyp mice is reversed to hyperphosphatemia in the Hyp mice without alpha-klotho activity (Hyp/alpha-klotho double mutant mice), despite high serum FGF23 levels in double mutant mice.[3,36] In accordance with these animal studies, an inactivating mutation in the human alpha-klotho gene resulted in severe hyperphosphatemia, despite high serum FGF23 levels in a patient with tumoral calcinosis.[38] From the above-cited human and experimental studies, it is clear that alpha-klotho has an indispensable role in FGF23-mediated phosphate metabolism.[14,17,18,36,39,40] As mentioned, features of phosphate toxicity appear in various organs when there is a dysregulation of the FGF23-alpha-klotho system.

Phosphate Toxicity

Phosphate toxicity arising from a disproportionate accumulation of phosphate in the body has been shown to accelerate mammalian aging, produce bone deformities and reduce overall survival.[41] Genetically altered alpha-klotho-knockout mice develop phosphate toxicity as early as at 3 weeks of age, which affects weight gain and the bone maturation process, produces a generalized soft tissue atrophy and results in reduced life span.[1,14,40–46] *In vivo* studies found that phosphate toxicity in alpha-klotho ablated mice is associated with increased renal activity of NaPi2a. However, phosphate
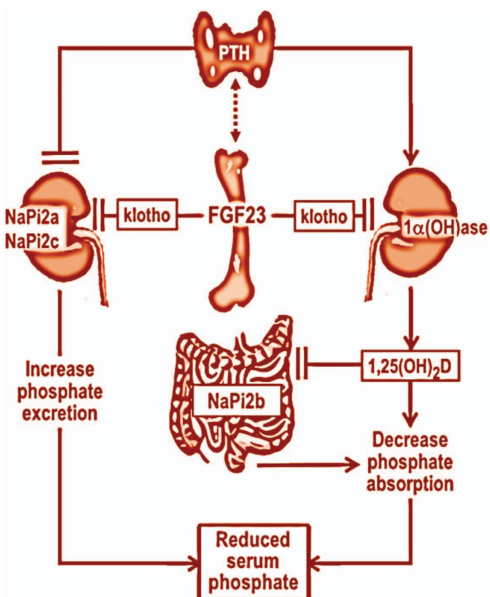
Figure 1 Simplified diagram showing multiorgan interactions in the regulation of phosphate homeostasis. Fibroblast growth factor (FGF) 23 produced in the bone cells can suppress renal Na/Pi2a and Na/Pi2c cotransporter activities to increase the urinary excretion of phosphate. Similarly, FGF23 can also suppress renal expression of 1-alpha hydroxylase (1α(OH)ase) to reduce the production of 1,25-dihydroxyvitamin D (1,25(OH)$_2$D), which can suppress intestinal NaPi2b activities to reduce phosphate absorption, resulting in decreased serum phosphate levels. Of relevance, parathyroid hormone (PTH) can induce the expression of the 1α(OH)ase, and thereby it can increase the production of 1,25(OH)$_2$D, which in turn can inhibit PTH and 1α(OH)ase expression. Such transcriptional repression feedback maintains vitamin D homeostasis. The figure is adopted with modification from our earlier publication.[1,45] (Dashed lines indicate that the interactions either might not be direct or not scientifically validated by multiple groups).

burden was lowered in hyperphosphatemic alpha-klotho-knockout mice by generating NaPi2a/alpha-klotho double-knockout mice, which resulted in prolonged survival.[41] More importantly, compared with a normal-phosphate diet (0.6%), phosphate toxicity reappeared when a high-phosphate diet (1.2%) was fed to NaPi2a/alpha-klotho mutant mice, with the appearance of premature aging-like features leading to early death.[41] These *in vivo* experimental observations clearly suggest that phosphate toxicity related to diet can contribute to the progression of the mammalian aging process, affecting both bone health and overall survival.

Phosphorous has a very strong electronegative attraction with calcium—having electronegative values on the Pauling scale of 2.1 for phosphorus and 1.0 for calcium.[47] The strength of this attraction may help explain why phosphate toxicity owing to dietary phosphorus overload can so easily impair calcium metabolism. The chemical bonding of phosphorus with calcium is most evident in the body's hydroxyapatite mineral matrix of bone. These two minerals normally unite to form bone tissue in a calcium:phosphorus ratio of approximately 2:1 by weight, averaging 2.07:1 in spongy trabecular bone tissue[48] and 2.17:1 in harder cortical bone tissue.[49] Of relevance, the mean calcium:phosphorus ratio in studies of human milk is approximately in the range of 2:1 by weight.[50]

Referring to the calcium:phosphorus ratio, the Food and Nutrition Board that set the recommended dietary allowances (RDAs) as part of the Dietary Reference Intakes[51] noted that 'there is little or no evidence for relating the two nutrients, one to the other, during most of human life (p.154).' Nevertheless, the RDA that the Board set for calcium relative to that of phosphorus is equivalent to an ample calcium:phosphorus ratio of 1.4:1 for adults and 1.7:1 for adults aged 50 years and over. However, data from NHANES III reported by Chang *et al.*[52] showed average intakes of 758 mg of calcium and 1242 mg of phosphorus for adults, which is equivalent to an average calcium:phosphorus ratio of only 0.61:1. As noted by Uribarri and Calvo,,[53] the data reported by Chang *et al.*[52] show a consistent association between increasing mortality in adult subjects and a decreasing calcium:phosphorus ratio as dietary phosphorus intake increases more than calcium intake.

In an earlier study, calcium retention increased when college women consumed 1500 mg of calcium and 800 mg of phosphorus with a calcium:phosphorus ratio of 1.88:1; however, increasing subjects' phosphorus intake to 1400 mg with a calcium:phosphorus ratio of 1.07:1 significantly reduced calcium utilization.[54] More recent research showed that decreasing the calcium:phosphorus ratio in a diet fed to young women by increasing phosphorus intake disrupted calcium metabolism, resulting in increased bone resorption as indicated by higher levels of serum PTH and urinary calcium.[55] Researchers used a calcium-adequate diet in an experimental animal model to demonstrate how lowering the calcium:phosphorus ratio by increasing the diet's phosphorus content produced defects in tooth enamel and dentin.[56] The findings of these studies imply that lowering excessive phosphorus intake rather than increasing calcium intake beyond adequate levels is required to properly balance the dietary calcium:phosphorus ratio. Unfortunately, the US adult population's average calcium intake of 758 mg reported by Chang *et al.*[52] is below RDA levels of 1000 mg and 1200 mg calcium for adults 50 years and older. Generally, the USDA Dietary Guidelines for Americans is incongruous with the latest findings on dietary phosphorus overload, with little indication for change in the 2015 Dietary Guidelines.[57] For example, a 2000-calorie eating pattern recommended by the MyPlate program of the USDA Center for Nutrition Policy & Promotion[58] averages 1884 mg of phosphorus a day—a daily overload far above the intake level where mortality effects are seen. Of particular concern, unrestricted consumption of phosphate can induce systemic complications related to phosphate toxicity (**Table 1**).

Phosphate Toxicity Associated with Ectopic Calcification

Calcium–phosphorus (CaxPi) product in serum, calculated by multiplying serum calcium and phosphorus levels, should be less than 55 mg^2 dl^{-2} in adults.[59] CaxPi product and other anions containing calcium normally account for 5% of serum calcium, whereas free ionized calcium accounts for 45% of serum calcium and the remaining serum calcium is bonded to albumin.[60] Elevated levels of serum phosphorus in hyperphosphatemia—associated with impaired kidney function, dietary phosphorus overload or both—unite with free calcium to form an additional CaxPi product. Accumulated excess CaxPi product is likely to be deposited into soft tissue causing ectopic calcification.[61] In addition, elevated serum levels of osteocalcin, a noncollagenous bone matrix protein and a marker for osteoblast function, are associated with FGF23 levels.[62] Osteocalcin is also found in calcified atherosclerotic

Table 1 Partial list of pathological events or diseases that can induce altered phosphate balance[14,40,43,102]

Hypophosphatemia
  X-linked hypophosphatemic rickets
  Vitamin D resistance/deficiency
  Severe dietary deficiency
  Sepsis
  Respiratory alkalosis
  Renal tubular defects (Fanconi syndrome)
  Renal transplantation
  Metabolic acidosis
  Hyperparathyroidism
  Hormones (insulin, glucagon and cortisol)
  Diuretics
  Diabetic ketoacidosis

Hyperphosphatemia
  Vitamin D intoxication
  Tumor lysis syndrome
  Tumor calcinosis
  Rhabdomyolysis
  Respiratory acidosis
  Phosphate enema
  Metabolic acidosis
  Magnesium deficiency
  Intravenous/oral phosphate therapy
  Hypoparathyroidism
  Hemolysis
  Chronic kidney disease
  Bowel infarction
  Bisphosphonate therapy
  Acromegaly

Please note that metabolic acidosis can induce either hypophosphatemia or hyperphosphatemia depending on clinical situations. It is believed that nonlactic metabolic acidosis associated with hypophosphatemia can be connected to impaired tubular reabsorption of bicarbonate and that phosphorus administration can improve such acidosis.[103] On the other hand, respiratory or metabolic acidosis may hydrolyze intracellular organic phosphate-containing compounds and release them into the extracellular compartment. Cell lysis disorders, such as tumor lysis syndrome, hemolytic anemia and rhabdomyolysis, may all give rise to hyperphosphatemia.[104]

plaque.[63] These associations provide evidence that rising serum calcium–phosphate product associated with hyperphosphatemia upregulates osteocalcin, which stimulates mineral deposition in soft tissue as ectopic calcification. An opposite action is seen in the protein osteopontin, which inhibits mineral deposition and regresses calcification.[64] Vascular calcification in rats reversed when they were switched to a low-phosphate diet, which the researchers suggested was associated with calcification inhibition by osteopontin.[65]

One type of soft tissue that is susceptible to ectopic calcification from the deposition of CaxPi product is the endothelium of the arterial system. Arterial calcification increases mortality risk by threefold to fourfold.[66] Calcification causes a hard or stable plaque to form in arterial vessels, which is related to arteriolosclerosis, hypertension, left ventricular hypertrophy and aortic valve disease. *In vitro* and *in vivo* experiments showed that a high phosphorus load acutely increases endothelial dysfunction by impairing vasodilation, raising the risk for cardiovascular disease.[67] High levels of serum phosphorus in healthy young adults have been associated with coronary atherosclerosis[68] and with left ventricular hypertrophy,[69] and high levels of serum phosphorus in a cohort study were associated with a 40% greater risk of heart failure.[70] A meta-analysis showed that serum phosphorus, but not serum calcium or PTH, was independently associated with mortality and risk for cardiovascular disease in CKD patients.[71]

Dietary phosphorus overload was found to raise systolic blood pressure, except from dairy products, which researchers attributed to nutrients in dairy other than phosphorus.[72]

The exact molecular mechanisms of how extracellular phosphate might exert its cytotoxicity is not yet clearly defined. Studies, however, have shown that extracellular phosphate can form insoluble nanoparticles with calcium and fetuin-A, commonly referred to as calciprotein particles (CPPs); these CPPs are highly bioactive ligands that can induce cytotoxicity, ranging from cell death to including osteogenic transformation of vascular smooth muscle cells (VSMCs). Furthermore, CPPs are detected in the circulation, both in human and animal models, particularly in patients with CKD, implicating a role in phosphate-mediated tissue injuries.[73] Calcium phosphate and other crystals may be deposited in joints causing acute inflammation and damaged cartilage.[74] Mice fed high-phosphate diets developed ectopic tumoral calcifications around joints.[75] Other types of ectopic calcifications from calcium phosphate occur in the formation of kidney stones, often in combination with calcium oxalate,[76] in bone tissue irregularities such as bone spurs or osteophytes[77] and within visceral organs and the epidermis.[61] Vascular calcification is a complex, ectopic biomineralization process, and phosphate toxicity can not only facilitate essential hydroxyapatite deposition in the calcifying vessels but also initiate the early events of apoptotic cell death, which is inflicted on both endothelial cells and VSMCs. Studies have shown higher risk for cardiovascular mortality in CKD patients undergoing hemodialysis treatment.

Phosphate Toxicity Associated with CKD

The estimated prevalence of CKD within the global population is 8–16%.[78] The role of phosphate toxicity in the pathology of CKD and beyond is published elsewhere.[1,45,73,79] A high concentration of extracellular phosphate is toxic to cells, and it leads to premature cellular aging. The kidneys regulate urinary excretion of phosphate to maintain the serum phosphate level that is circulated throughout the body. Dietary phosphate overload can lead to an increased phosphate burden, and it damages the kidneys through tubular injury and interstitial fibrosis; studies have found that subjects with high serum phosphorus had a higher risk for developing kidney diseases.[80] Glomerular filtration rate decreases as serum phosphorus increases in kidney disease, and mortality from associated cardiovascular disease in dialysis patients is 20% annually.[81] Of relevance, renal aging can accelerate systemic aging.[81]

As mentioned, increased serum calcium and phosphate levels are usually considered main contributors to vascular calcification, and the estimation of CaxPi product has long been used to predict vascular pathology in CKD patients.[82] However, recent studies have found that serum phosphate levels in patients undergoing hemodialysis treatment correlates with vascular calcification more strongly than does the CaxPi product.[83] In fact, the clinical utility of the CaxPi product has been questioned in recent studies, noting that the cause of calcification is more complicated than just the precipitation of the CaxPi product.[84] It is of clinical relevance that, in contrast to hyperphosphatemia, associations between serum calcium levels and cardiovascular events or disease outcomes of CKD patients are not yet clearly established. However, a few studies

have shown that hypercalcemia may have predictive value in determining the negative outcome of CKD patients.[85]

Although phosphate toxicity is known to promote disease progression in patients with CKD, its association with tumorigenesis is not studied in similar depth and detail. We next present evidence of this association and suggest some innovative theories of tumorigenesis. We believe that these suggestions are not based on deductive speculation, but rather on inductive theory generation grounded in reliable evidence.

Phosphate Toxicity Associated with Tumorigenesis

Hippocrates first observed that vessels attached to tumors appeared like legs on a crab. Thus, the name cancer, derived from the Latin word for crab, came into use to describe tumors.[86] Today, the elaborate vessel system of tumors is considered to be complicit with the aggressive tendency for neoplasms to grow uncontrollably and metastasize throughout the body. However, a novel theory of tumor vessel function may be induced from biological findings related to phosphate toxicity. In biology, the mycorrhiza fungal root system of plants absorbs and sequesters phosphorus from soil.[87] Evidence suggests that tumor vessels may function similarly in humans to absorb and sequester excess phosphorus from extracellular fluid. Cancer patients have been observed to retain and store phosphorus in tumors,[88] and cancer cells accumulate up to twice as much phosphorus as normal cells.[89] Just as tumorigenesis in tomato plants has been positively associated with phosphorus,[90] a cellular environment high in phosphorus in humans has been found to induce tumor neovascularization and angiogenesis, or new blood vessel formation in neoplasms.[91]

Dietary phosphorus overload has been found to stimulate tumor growth in lung tissue.[92] Increasing phosphorus levels in cultured breast cancer cells were observed to change cellular behavior and metabolism, thus supporting the role of inorganic phosphate in modulating tumor metabolism and metastasis.[93] An average daily phosphorus intake of 1395 mg in men followed up for 22 years 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.[94] Farmers of Liuchong Village in the Hubei province of China claimed that cancer cases increased in their village from drinking water contaminated by a nearby phosphate mine.[95]

Many studies have examined the association of meat and dairy intake with cancer, but a review of meta-analyses showed inconsistent findings.[96] Few studies have examined the phosphate intake from meat and dairy in association with cancer. In addition, it is difficult to isolate the effect of phosphorus in one or two foods without considering the total phosphate content of the diet. For example, subjects with high intake of dietary phosphate from meat and dairy but with overall normal phosphate intake may show less increase in cancer incidence than subjects with low intake of phosphate from meat and dairy but with a high overall phosphate intake. Comparisons of diets containing similar amounts of total phosphate at baseline should be investigated for cancer risk as the phosphate content rises from meat and dairy intake. From the above-mentioned evidence, it is likely that dietary phosphate consumption might influence tumorigenesis, possibly as a storage mechanism to help maintain phosphate

homeostasis, and further research using meaningful experimental designs is warranted to validate such speculation.

Conclusion

The endocrine communication between bone-derived FGF23 and kidney-derived alpha-klotho is essential for physiologic regulation of phosphate balance. As we have briefly discussed, dysregulation of FGF23/alpha-klotho system provokes phosphate imbalance and induces a wide range of organs/tissue damage in blood vessels, bone and kidney. Of clinical importance, phosphate toxicity induced by excessive exogenous phosphate administration in humans can be fatal.[97–99] In fact, it is becoming more evident from experimental and human observations that features of phosphate toxicity can appear after consumption of a high-phosphate diet, even when serum phosphate levels are within the normal range.[3,43,45,79] Recent survey results highlight that even future medical professionals and CKD patients undergoing hemodialysis are not adequately aware of the hidden source of phosphate in their diet, and emphasize the need for educational initiatives to raise awareness of the risk posed by dietary items with hidden phosphate ingredients.[100,101] Taking into account human and animal observations, maintaining phosphate balance through adequate dietary intake appears to be important for a healthy life and for longevity. In addition, phosphate imbalance owing to bone–kidney miscommunication can induce serious debilitating complications.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

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