CardioRenal Medicine

Cardiorenal Med 2011;1:261–270
DOI: 10.1159/000332388
Published online: October 13, 2011

www.karger.com/crm

Review

Phosphate Metabolism in Cardiorenal Metabolic Disease

Deepashree Gupta[a] Stephen Brietzke[a] M.R. Hayden[a, b]
L. Romayne Kurukulasuriya[a] James R. Sowers[a–d]

[a]Division of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, [b]Diabetes and Cardiovascular Center, and [c]Department of Medical Physiology and Pharmacology, University of Missouri-Columbia School of Medicine, and [d]Harry S. Truman VA Medical Center, Columbia, Mo., USA

Key Words
Cardiovascular disease · Chronic kidney disease · FGF-23 · Klotho · Phosphate

Abstract
Hyperphosphatemia is a major risk factor for cardiovascular disease, abnormalities of mineral metabolism and bone disease, and the progression of renal insufficiency in patients with chronic renal disease. In early renal disease, serum phosphate levels are maintained within the 'normal laboratory range' by compensatory increases in phosphaturic hormones such as fibroblast growth factor-23 (FGF-23). An important co-factor for FGF-23 is Klotho; a deficiency in Klotho plays an important role in the pathogenesis of hyperphosphatemia, renal tubulointerstitial disease, and parathyroid and bone abnormalities. Clinical hyperphosphatemia occurs when these phosphaturic mechanisms cannot counterbalance nephron loss. Hyperphosphatemia is associated with calcific uremic arteriolopathy and uremic cardiomyopathy, which may explain, in part, the epidemiologic connections between phosphate excess and cardiovascular disease. However, no clinical trials have been conducted to establish a causal relationship, and large, randomized trials with hard endpoints are urgently needed to prove or disprove the benefits and risks of therapy. In summary, hyperphosphatemia accelerates renal tubulointerstitial disease, renal osteodystrophy, as well as cardiovascular disease, and it is an important mortality risk factor in patients with chronic kidney disease.

Stephen A. Brietzke, MD
D109 HSC Diabetes Center
One Hospital Drive
Columbia, MO 65212 (USA)
Tel. +1 573 884 0769, E-Mail brietzkes@health.missouri.edu

Introduction

Chronic kidney disease (CKD) is a condition characterized by a progressive decrease in kidney function over months or years, caused by various disease processes or natural aging. The prevalence of CKD is approaching epidemic proportions worldwide [1, 2]. More than 26 million Americans, or 13% of the total population, have CKD [3]. Most patients with CKD die prematurely, not from kidney failure, but from early onset of common diseases, such as cardiovascular disease (CVD), cancer, and infection [3–10]. There is increasing evidence suggesting that abnormalities in mineral metabolism in CKD play a major role in accelerating CVD and metabolic abnormalities associated with CKD [4–19]. Hyperphosphatemia plays a major role in promoting the comorbid conditions that are associated with CKD.

Normal Phosphate Homeostasis and Alterations in CKD

In the absence of CKD, normal serum levels of phosphorus and calcium are maintained through integrative actions of two hormones: parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D_3 (calcitriol), the principal metabolite that activates the vitamin D receptor [20–29]. There is also increasing evidence to support the existence of various factors (historically known as phosphatonins) that directly control the renal excretion of phosphorus, and elucidation of their precise role in the regulation of phosphorus metabolism is an area of active research [20, 29, 30]. These hormones and novel factors act on the primary target organs, bone, kidney, parathyroid glands and intestine to regulate systemic mineral metabolism (table 1).

One of the important phosphatonins, fibroblast growth factor-23 (FGF-23), is produced primarily by osteocytes and acts on renal proximal tubule cells to decrease the expression and/or the apical surface content of type 2a sodium-dependent phosphate co-transporters (NaPi-2a) and by decreasing the expression of the 1α-hydroxylase enzyme that converts 25-hydroxyvitamin D_3 to calcitriol [12, 23–39]. FGF-23 exerts downstream signal transduction via the FGF receptors and requires another phophatonin, the co-receptor Klotho, for optimal signaling [40]. Klotho forms a constitutive binary complex with FGF receptors and functions as an obligate coreceptor for FGF-23 [40–50]. Klotho is primarily expressed in the distal convoluted tubules where it exerts some signaling effects [44], but its major action is on proximal tubule cells [45–58]. Parathyroid tissue also expresses Klotho [59–62], where it may also act as a co-activator of FGF-23 [59]. PTH and Klotho increase FGF-23 production by osteocytes, while FGF-23 inhibits PTH secretion, thus forming an important activation pathway with negative feedback control [61, 62]. Important hormonal regulation of Klotho is also evident: increases in insulin signaling and PPAR-γ activation up-regulate and angiotensin II down-regulates Klotho expression and secretion [51, 55]. Actions of Klotho include activation of transient receptor potential calcium channels (TRPVs), especially TRVP5 and TRVP6 [53, 54]. TRVP5 is expressed in distal nephrons and mediates calcium reabsorption at that site. TRVP6 is expressed in small intestinal epithelial cells where it mediates calcium absorption. Additionally, Klotho influences potassium channel activity in the kidney by activating ROMK1, a renal outer medullary potassium channel, in distal nephrons [52]. This action of Klotho to increase ROMK1 activity promotes potassium ion secretion into the urine.

Because normal kidney function has a critical role in calcium and phosphorus homeostasis, loss of renal function has important consequences. Clinically evident derangements in serum calcium and phosphorus and the hormones that govern plasma levels are initially seen at glomerular filtration rates (GFRs) <60 ml/min and are almost always present at a

Table 1. Hormonal influences on phosphate homeostasis and their derangements in CKD

Hormone/ growth factor	Effects on normal phosphate homeostasis	Derangement in CKD	Net effect in CKD
PTH	↑ renal phosphate excretion ↑ FGF-23 expression ↑ 1α-hydroxylation of 25-OH-vitamin D (↑ calcitriol synthesis)	increased	↑ bone resorption
FGF-23	↓ proximal renal tubular NaPi-2a cotransport ↓ PTH ↓ 1α-hydroxylase activity	increased production/ decreased effect	↓ phosphaturia (due to ↓ functional nephron mass)
Klotho	↑ FGF-23 activity	decreased	↑ vascular calcification ↓ FGF-23 effects ↓ renal phosphate excretion ↑ hyperphosphatemia faster progression of renal disease
Calcitriol (1,25-OH-vitamin D)	↑ intestinal phosphate absorption	decreased	↓ intestinal phosphate absorption ↓ intestinal calcium absorption

GFR <30 ml/min [21–23]. As CKD progresses, hyperphosphatemia ensues, and CKD severity increases with progressive diminution of renal function. Far from an innocent bystander, hyperphosphatemia is known to be an important mortality risk factor in patients with CKD [9–12]. Studies have shown that increased serum FGF-23 and PTH, and decreased calcitriol levels precede the onset of clinical hyperphosphatemia during CKD progression (fig. 1) [29, 30]. In this regard, phosphaturic hormones are able to maintain normal levels of serum phosphate during the early stages of kidney disease [31–33]. As CKD progresses towards end-stage renal disease, high levels of FGF-23 and PTH are offset by deficiency in Klotho and the intrinsic capacity for phosphate excretion due to functional loss of a critical mass of nephrons.

The FGF-23 coreceptor Klotho has considerable potential as a biomarker and as a potential therapeutic target in the detection and treatment of patients with CKD. Klotho protein levels in the urine are decreased in relatively early stages (stages 1 and 2) of CKD [46, 63]. In CKD, relative deficiency in Klotho expression is associated with renal tubulointerstitial disease [45–58], hyperphosphatemia, hyperkalemia, secondary hyperparathyroidism [59–61], renal osteodystrophy [62], vascular calcification and uremic cardiomyopathy (fig. 1, 2) [63]. Accordingly, hyperphosphatemia and diminution of Klotho is associated with and possibly contributory to several of the key cardiovascular abnormalities that constitute the cardiorenal metabolic syndrome (fig. 2). In mouse models of CKD, transgenic overexpression or gene delivery of Klotho results in improvements in kidney function and reduces renal glomerular damage and tubulointerstititial fibrosis [45, 46]. Increased Klotho is associated with improved FGF-23-mediated phosphaturia. Increased Klotho expression in parathyroid glands likely amplifies the effect of FGF-23 on PTH suppression, thereby attenuating the severity of CKD-related hyperparathyroidism. In this regard, the development of strategies to increase the production or delivery of Klotho to kidneys, bone and parathyroid glands may decrease the rate of development of progressive kidney disease, renal osteodystrophy, and hyperparathyroidism in patients with CKD.

Cardiorenal Med 2011;1:261–270
DOI: 10.1159/000332388

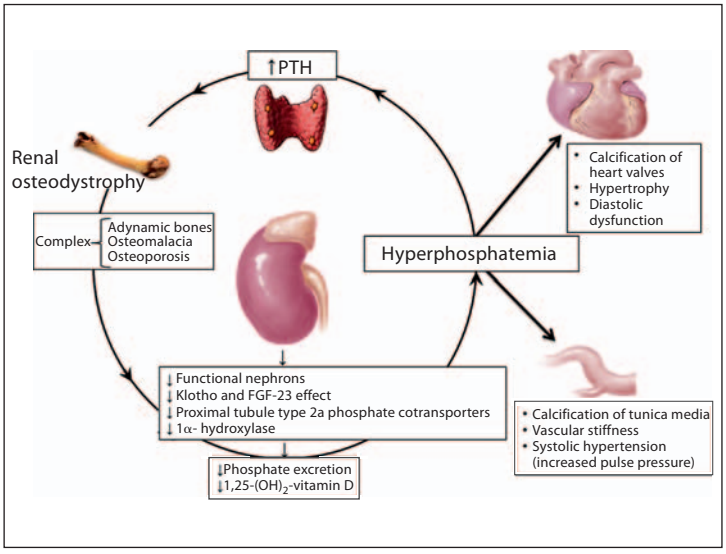

Fig. 1. Pathways involved in the pathogenesis of hyperphosphatemia in CKD. As nephron mass is lost in progressive CKD, renal capacity for phosphate excretion diminishes and renal production of Klotho decreases. Klotho normally enhances the effects of FGF-23 and PTH on phosphate excretion, and in the setting of CKD, bone production of FGF-23 and PTH secretion both increase. However, the effects of increased FGF-23 and PTH are inadequate to return phosphate excretion to normal.

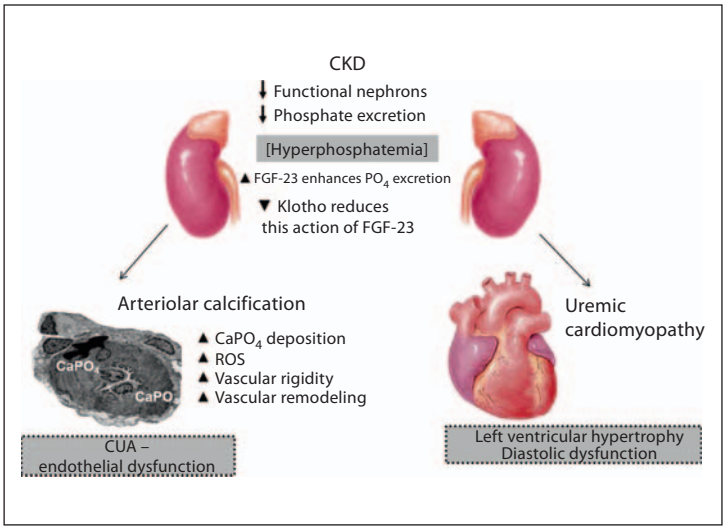

Fig. 2. Role of hyperphosphatemia and decreased Klotho in the cardiorenal metabolic syndrome. This illustration demonstrates that in CKD associated with the cardiorenal metabolic syndrome there is a decrease in the functional nephron number with subsequent hyperphosphatemia. $CaPO_4$ = Calcium phosphate.

Low Klotho levels in bone may contribute to the decreased osteoblast function and bone formation seen in CKD [62]. Thus, correcting the deficiency in Klotho might correct this impaired skeletal anabolism via direct actions and indirectly by increasing active vitamin D levels. In early renal disease, the increasing requirements for phosphate excretion per remaining nephron results in a compensatory increase in FGF-23, decreased calcitriol, increased PTH, and decreased Klotho. Thus, dietary restriction of phosphate intake and/or administration of a phosphate binder should be initiated relatively early in CKD, perhaps as soon as elevated serum or urine levels of FGF-23 or suppressed levels of Klotho are detected. There is also emerging evidence that angiotensin receptor blocker or angiotensin-converting enzyme inhibitor therapy may upregulate Klotho and help interrupt the detrimental cycle associated with hyperphosphatemia.

Renal Osteodystrophy

Since bone represents the largest reservoir of calcium and phosphate in the body, understanding the regulation of calcium-phosphate deposition and reclamation from bone is integral to appreciating the derangements in mineral homeostasis in CKD (fig. 1) [64]. The bone disease linked to CKD is termed renal osteodystrophy, and this entity comprises a complex spectrum of adynamic bone disease, osteomalacia and osteoporosis, any of which may be predominant in a given patient. Growth retardation and skeletal deformities predominate in children, whereas bone pain and muscle weakness may occur at any age and often predominate in adults. The heterogeneous skeletal and mineral disorders of CKD are now classified in aggregate as CKD mineral bone disorder [64]. The earliest recognized manifestation of this disorder occurs in early CKD (stage 2), a stage characterized by elevated FGF-23 and normal serum phosphorus, calcium, PTH and calcitriol levels [65, 66]. As CKD progresses beyond stage 2, depletion of the functional nephron mass gradually results in hyperphosphatemia and the progression of renal osteodystrophy (fig. 1).

Hyperphosphatemia is a potent stimulus for both FGF-23 production by osteocytes and PTH secretion by parathyroid glands. The synergistic phosphaturic effects of FGF-23 and PTH limits, but typically does not overcome, the decreased capacity for phosphate excretion in evolving CKD. In stage 4 and 5 CKD, when GFR falls to <30% of normal, hyperphosphatemia persists despite marked elevation in FGF-23 and PTH [67]. The combination of diminished nephron mass (limiting functional 1α-hydroxylase availability) [68], hyperphosphatemia, and elevated FGF-23 result in decreased synthesis of calcitriol by the kidney. In turn, low serum calcitriol causes decreased intestinal calcium (and phosphate) absorption. Hyperphosphatemia further decreases serum calcium through physicochemical binding and precipitation of calcium phosphate salts in soft tissue. Hypocalcemia, hyperphosphatemia, and low calcitriol levels all stimulate synthesis and secretion of PTH and gradually lead to diffuse nodular hyperplasia of the parathyroid gland [69]. This state of secondary hyperparathyroidism accelerates skeletal remodeling and osteoclastic bone resorption, and leads to net bone resorption. Hyperphosphatemia causes abnormal osteoblast-mediated bone matrix mineralization, osteoblastic transcription factor gene expression [70], and osteoclastic bone resorption [71]. In aggregate, all mineral and hormonal derangements associated with advancing CKD contribute to a mixed bone disease characterized by excessive bone resorption and defective organic bone formation and mineralization. Defective bone mineralization, high serum calcium-phosphorus double products exceeding solubility, and increased FGF-23 activity result in increased heterotopic mineralization or calcific uremic arteriolopathy (CUA), formerly known as metastatic calcification, or calciphylaxis of blood vessels and heart tissue (fig. 3) [72, 73].

Calcific Uremic Arteriolopathy

CUA is associated with multiple vascular abnormalities that include medial calcific, fibrotic, proinflammatory and prothrombogenic arterioles compatible with a calcific obliterative arteriolopathy-vasculopathy (fig. 2, 3) [74]. While vascular calcification was initially described as a passive degenerative process, it is currently understood as an active coordinated process similar to osteogenetic bone modeling and physicochemical deposition of mineral in bone [74–76]. The existing model for vascular calcification begins with differentiation of vascular smooth muscle cell(s) [VSMC(s)] into chrondrocytes, which have an osteoblast-like cellular phenotype. This mechanism is initiated with the interaction of factors (hyperphosphatemia, uremic toxins, and reactive oxygen species) and the decrease in local

Cardiorenal Med 2011;1:261–270
DOI: 10.1159/000332388

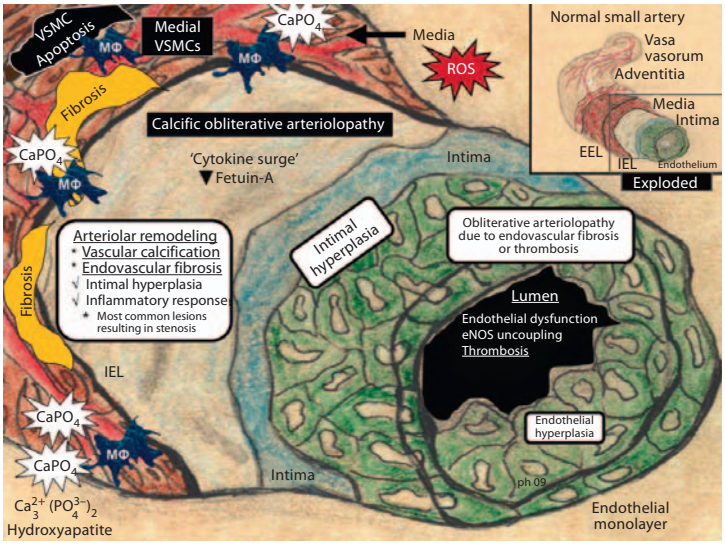

Fig. 3. Role of hyperphosphatemia in promoting calcemic arteriolopathy. Phosphate deposition is associated with the development of CUA/calciphylaxis due to arteriolar calcification, which is known to be associated with hyperphosphatemia and excessive reactive oxygen species (ROS). EEL = External elastic lamina; eNOS = endothelial nitric oxide synthase; IEL = internal elastic lamina; MΦ = macrophage (figure used with permission [74]).

vascular calcification-inhibitory proteins such as MGP (matrix Gla protein) and the systemic globulin: fetuin-A (fig. 3) [74]. Elevation in serum phosphate and the calcium-phosphate product have been closely associated with the degree of CUA [74]. Indeed, the treatment of human VSMCs with a solution containing elevated phosphate induces these cells to differentiate into osteoblast-like cells, as shown by the expression of osteoblast differentiation markers such as osteocalcin [74]. There is also evidence that FGF-23 is protective against the development of CUA, and decreased vascular action of this factor contributes to the development of this devastating disease [74, 77]. Thus decreased FGF-23 signaling, in part related to reduced Klotho activation as well as decreased MGP and fetuin-A, are important contributing factors in the pathogenesis of CUA.

Uremic Cardiomyopathy

Uremic cardiomyopathy is another pathological condition that develops in patients with hyperphosphatemia and CKD (fig. 2) [78]. In this disorder, cardiomyocytes enlarge and there is excessive myocardial fibrosis. Uremic cardiomyopathy is characterized by diastolic dysfunction similar to that seen in cardiomyopathy associated with obesity and diabetes [79, 80]. It has been estimated that almost 75% of patients have left ventricular hypertrophy at the time of initiation of dialysis, and that the presence of this abnormality is a strong independent risk factor for reduced survival in this population [78]. There is emerging evidence that the molecular pathways responsible for uremic cardiac hypertrophy involve various growth factors, including angiotensin II, which activate the mammalian target of rapamycin (mTOR) and downstream ribosomal kinase (S6-K) signaling pathways [78]. Activation of this pathway promotes mRNA translation for cardiomyocytes and collagen/fibrin protein synthesis [68–70]. Indeed, uremic cardiac hypertrophy in experimental animals is reversed with rapamycin treatment [78], thus documenting the importance of this signaling pathway in cardiomyopathy. The importance of the mTOR/S6-K signaling pathways in the pathogenesis of kidney [3, 79] and heart diseases [79, 80] associated with overnutrition and impaired insulin metabolic signaling has previously been reviewed.

Conclusion

An important evolving concept links deranged phosphate metabolism in CKD with the increased CVD morbidity and mortality as well as progression of renal insufficiency [81]. Serum PTH and FGF-23 increase in response to rising serum phosphate as renal capacity for phosphate excretion is lost and their increased levels are accompanied by increased renal osteodystrophy, hyperparathyroidism, calcemic uremic arteriopathy and uremic cardiomyopathy. Furthermore, as renal function is lost, renal production of Klotho diminishes, resulting in diminished FGF-23 ability to promote phosphaturia [82, 83]. The vascular disease and cardiomyopathy associated with hyperphosphatemia and reduced Klotho levels contribute to the development of the cardiorenal metabolic syndrome and increased CVD morbidity and mortality in association with CKD.

Acknowledgments

The authors would like to thank Brenda Hunter for her assistance in editing the manuscript.

This research was supported by the National Institutes of Health (R01 HL73101-01A and R01 HL107910-01) and Veterans Affairs Merit System 0018 (J.R.S.).

Disclosure Statement

The authors have nothing to disclose.

References

1 Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS: Prevalence of chronic kidney disease in the United States. JAMA 2007;298:2038–2047.

2 Levey AS, Atkins R, Coresh J, Cohen EP, Collins AJ, Eckardt K-U, Nahas ME, Jaber BL, Jadoul M, Levin A, Power NR, Rossert J, Wheeler DC, Lameire N, Eknoyan G: Chronic kidney disease as a global public health problem: approaches and initiatives – a position statement from Kidney Disease Improving Global Outcomes. Kidney Int 2007;72:247–259.

3 Whaley-Connell A, Bomback AS, McFarlane SI, Li S, Roberts T, Chen S-C, Collins AJ, Norris K, Bakris GL, Sowers JR, McCullough PA, Kidney Early Evaluation Program Investigators: Diabetic cardiovascular disease predicts chronic kidney disease awareness in the Kidney Early Evaluation Program. Cardiorenal Med 2011;1:45–52.

4 Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB: Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 2000;342:1478–1483.

5 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–1305.

6 Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK: Association of elevated serum PO_4, Ca × PO_4 product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 2001;12:2131–2138.

7 Raggi P, Boulay A, Chasan-Taber S, Amin N, Dillon M, Burke SK, Chertow GM: Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol 2002;39:695–701.

8 Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM: Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 2004;15:2208–2218.

9 Stevens LA, Djurdjev O, Cardew S, Cameron EC, Levin A: Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: evidence for the complexity of the association between mineral metabolism and outcomes. J Am Soc Nephrol 2004;15:770–779.

10 Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, Sherrard DJ, Andress DL: Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol 2005;16:520–528.

11 Tonelli M, Sacks F, Pfeffer M, Gao Z, Curhan G: Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. Circulation 2005;112:2627–2633.

12 Stubbs JR, Liu S, Tang W, Zhou J, Wang Y, Yao X, Quarles LD: Role of hyperphosphatemia and 1,25-dihydroxyvitamin D in vascular calcification and mortality in fibroblastic growth factor 23 null mice. J Am Soc Nephrol 2007;18:2116–2124.
13 Ohnishi M, Nakatani T, Lanske B, Razzaque MS: In vivo genetic evidence for suppressing vascular and soft-tissue calcification through the reduction of serum phosphate levels, even in the presence of high serum calcium and 1,25-dihydroxyvitamin D levels. Circ Cardiovasc Genet 2009;2:583–590.
14 Pereira MA, Jacobs DR Jr, Van Horn L, Slattery ML, Kartashov AI, Ludwig DS: Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA study. JAMA 2002;287:2081–2089.
15 Martin JE, Sheaff MT: Renal ageing. J Pathol 2007;211:198–205.
16 Ohnishi M, Razzaque MS: Dietary and genetic evidence for phosphate toxicity accelerating mammalian aging. FASEB J 2010;24:3562–3571.
17 Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, Morii H, Giachelli CM: Phosphate regulation of vascular smooth muscle cell calcification. Circ Res 2000;87:E10–E17.
18 Kalaitzidis R, Tsimihodimos V, Bairaktari E, Siamopoulos KC, Elisaf M: Disturbances of phosphate metabolism: another feature of metabolic syndrome. Am J Kidney Dis 2005;45:851–858.
19 Haap M, Heller E, Thamer C, Tschritter O, Stefan N, Fritsche A: Association of serum phosphate levels with glucose tolerance, insulin sensitivity and insulin secretion in non-diabetic subjects. Eur J Clin Nutr 2006;60:734–739.
20 Schiavi SC, Kumar R: The phosphatonin pathway: new insights in phosphate homeostasis. Kidney Int 2004;65:1–14.
21 Felsenfeld AJ, Rodriguez M, Aguilera-Tejero E: Dynamics of parathyroid hormone secretion in health and secondary hyperparathyroidism. Clin J Am Soc Nephrol 2007;2:1283–1305.
22 Quarles LD: Endocrine functions of bone in mineral metabolism regulation. J Clin Invest 2008;118:3820–3828.
23 Galitzer H, Ben-Dov IZ, Silver J, Naveh-Many T: Parathyroid cell resistance to fibroblast growth factor 23 in secondary hyperparathyroidism of chronic kidney disease. Kidney Int 2010;77:211–218.
24 Shimada T, Kakitani M, Yamazaki Y, Hasegawa H, Takeuchi Y, Fujita T, Fukumoto S, Tomizuka K, Yamashita T: Targeted ablation of FGF23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. J Clin Invest 2004;113:561–568.
25 Dusso AS, Brown AJ, Slatopolsky E: Vitamin D. Am J Physiol Renal Physiol 2005;289:F8–F28.
26 Gutiérrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Jüppner H, Wolf M: Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. J Am Soc Nephrol 2005;16:2205–2215.
27 Razzaque MS, Sitara D, Taguchi T, St-Arnaud R, Lanske B: Premature aging-like phenotype in fibroblast growth factor 23 null mice is a vitamin D-mediated process. FASEB J 2006;20:720–722.
28 Hesse M, Frohlich LF, Zeitz U, Lanske B, Erben RG: Ablation of vitamin D signaling rescues bone, mineral, and glucose homeostasis in Fgf-23 deficient mice. Matrix Biol 2007;26:75–84.
29 Gutiérrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Jüppner H, Wolf M: Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med 2008;359:584–592.
30 Engberg H, Oksuzyan A, Jeune B, Vaupel JW, Christensen K: Centenarians – a useful model for healthy aging? A 29-year follow-up of hospitalizations among 40,000 Danes born in 1905. Aging Cell 2009;8:270–276.
31 Berndt T, Kumar R: Novel mechanisms in the regulation of phosphorus homeostasis. Physiology (Bethesda) 2009;24:17–25.
32 Kendrick J, Kestenbaum B, Chonchol M: Phosphate and cardiovascular disease. Adv Chronic Kidney Dis 2011;18:113–119.
33 Hruska KA, Mathew S: The roles of the skeleton and phosphorus in the CKD mineral disorder. Adv Chronic Kidney Dis 2011;18:98–104.
34 Shimada T, Urakawa I, Isakova T, Yamazaki Y, Epstein M, Wesseling-Perry K, Wolf M, Salusky IB, Jüppner H: Circulating fibroblast growth factor 23 in patients with end-stage renal disease treated by peritoneal dialysis is intact and biologically active. J Clin Endocrinol Metab 2009;2:578–585.
35 Liu S, Tang W, Zhou J, Stubbs JR, Luo Q, Pi M, Quarles LD: Fibroblast growth factor 23 is a counter-regulatory phosphaturic hormone for vitamin D. J Am Soc Nephrol 2006;17:1305–1315.
36 Marsell R, Krajisnik T, Göransson H, Ohlsson C, Ljunggren O, Larsson TE, Jonsson KB: Gene expression analysis of kidneys from transgenic mice expressing fibroblast growth factor-23. Nephrol Dial Transplant 2008;23:827–833.
37 Kurosu H, Ogawa Y, Miyoshi M, Yamamoto M, Nandi A, Rosenblatt KP, Baum MG, Schiavi S, Hu MC, Moe OW, Kuro-o M: Regulation of fibroblast growth factor-23 signaling by klotho. J Biol Chem 2006;281:6120–6123.
38 Liu S, Gupta A, Quarles LD: Emerging role of fibroblast growth factor 23 in a bone-kidney axis regulating systemic phosphate homeostasis and extracellular matrix mineralization. Curr Opin Nephrol Hypertens 2007;16:329–335.
39 Urakawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, Fujita T, Fukumoto S, Yamashita T: Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature 2006;444:770–774.
40 Tsujikawa H, Kurotaki Y, Fujimori T, Fukuda K, Nabeshima Y: Klotho, a gene related to a syndrome resembling human premature aging, functions in a negative regulatory circuit of vitamin D endocrine system. Mol Endocrinol 2003;17:2393–2403.
41 Hu MC, Shi M, Zhang J, Pastor J, Nakatani T, Lanske B, Razzaque MS, Rosenblatt KP, Baum MG, Kuro-o M, Moe OW: Klotho: a novel phosphaturic substance acting as an autocrine enzyme in the renal proximal tubule. FASEB J 2010;24:3438–3450.

42 Kuro-o M: Klotho as a regulator of fibroblast growth factor signaling and phosphate/calcium metabolism. Curr Opin Nephrol Hypertens 2006;15:437–441.
43 Kumata C, Mizobuchi M, Ogata H, Koiwa F, Nakazawa A, Kondo F, Kadokura Y, Kinugasa E, Akizawa T: Involvement of alpha-klotho and fibroblast growth factor receptor in the development of secondary hyperparathyroidism. Am J Nephrol 2010;31:230–238.
44 Farrow EG, Davis SI, Summers LJ, White KE: Initial FGF23-mediated signaling occurs in the distal convoluted tubule. J Am Soc Nephrol 2009;20:955–960.
45 Haruna Y, Kashihara N, Satoh M, Tomita N, Namikoshi T, Sasaki T, Fjuimori T, Xie P, Kanwar YS: Amelioration of progressive renal injury by genetic manipulation of Klotho gene. Proc Natl Acad Sci USA 2007;104:2331–2336.
46 Hu MC, Shi M, Quinones H, Kuro-o M, Moe OW: Klotho deficiency is an early biomarker of renal ischemia-reperfusion injury and its replacement is protective. Kidney Int 2010;78:1240–1251.
47 Hu MC, Shi M, Zhang J, Pastor J, Nakatani T, Lanske B, Razzaque MS, Rosenblatt KP, Baum MG, Kuro-o M, Moe OW: Klotho: a novel phosphaturic substance acting as an autocrine enzyme in the renal proximal tubule. FASEB J 2010;24:3438–3450.
48 Ohnishi M, Nakatani T, Lanske B, Razzaque MS: Reversal of mineral ion homeostasis and soft-tissue calcification of klotho knockout mice by deletion of vitamin D 1α-hydroxylase. Kidney Int 2009;75:1166–1172.
49 John GB, Cheng C-Y, Kuro-o M: Role of Klotho in aging, phosphate metabolism and CKD. Am J Kidney Dis 2011;58:127–134.
50 Nakatani T, Ohnishi M, Razzaque MS: Inactivation of klotho function induces hyperphosphatemia even in presence of high serum fibroblast growth factor 23 levels in a genetically engineered hypophosphatemic (Hyp) mouse model. FASEB J 2009;23:3702–3711.
51 Chen CD, Podvin S, Gillespie E, Leeman SE, Abraham CR: Insulin stimulates the cleavage and release of the extracellular domain of Klotho by ADAM10 and ADAM17. Proc Natl Acad Sci USA 2007;104:19796–19801.
52 Cha SK, Hu MC, Kurosu H, Kuro-o M, Moe O, Huang CL: Regulation of renal outer medullary potassium channel and renal K^+ excretion by Klotho. Mol Pharmacol 2009;76:38–46.
53 Cha SK, Ortega B, Kurosu H, Rosenblatt KP, Kuro-O M, Huang CL: Removal of sialic acid involving Klotho causes cell-surface retention of TRPV5 channel via binding to galectin-1. Proc Natl Acad Sci USA 2008;105:9805–9810.
54 Chang Q, Hoefs S, van der Kemp AW, Topala CN, Bindels RJ, Hoenderop JG: The β-glucuronidase klotho hydrolyzes and activates the TRPV5 channel. Science 2005;310:490–493.
55 Mitani H, Ishizaka N, Aizawa T, Ohno M, Usui S, Suzuki T, Amaki T, Mori I, Nakamura Y, Sato M, Nangaku M, Hirata Y, Nagai R: In vivo klotho gene transfer ameliorates angiotensin II-induced renal damage. Hypertension 2002;39:838–843.
56 Sugiura H, Yoshida T, Tsuchiya K, Mitobe M, Nishimura S, Shirota S, Akiba T, Nihei H: Klotho reduces apoptosis in experimental ischaemic acute renal failure. Nephrol Dial Transplant 2005;20:2636–2645.
57 Thiery JP, Acloque H, Huang RY, Nieto MA: Epithelial-mesenchymal transitions in development and disease. Cell 2009;139:871–890.
58 Kurosu H, Yamamoto M, Clark JD, Pastor JV, Nandi A, Gurnani P, McGuinness OP, Chikuda H, Yamaguchi M, Kawaguchi H, Shimomura I, Takayama Y, Herz J, Kahn CR, Rosenblatt KP, Kuro-o M: Suppression of aging in mice by the hormone Klotho. Science 2005;309:1829–1833.
59 Ben-Dov IZ, Galitzer H, Lavi-Moshayoff V, Goetz R, Kuro-o M, Mohammadi M, Sirkis R, Naveh-Many T, Silver J: The parathyroid is a target organ for FGF23 in rats. J Clin Invest 2007;117:4003–4008.
60 Komaba H, Goto S, Fujii H, Hamada Y, Kobayashi A, Shibuya K, Tominaga Y, Otsuki N, Nibu K, Nakagawa K, Tsugawa N, Okano T, Kitazawa R, Fukagawa M: Depressed expression of Klotho and FGF receptor 1 in hyperplastic parathyroid glands from uremic patients. Kidney Int 2010;77:232–238.
61 Krajisnik T, Olauson H, Mirza MA, Hellman P, Akerström G, Westin G, Larsson TE, Björklund P: Parathyroid klotho and FGF-receptor 1 expression decline with renal function in hyperparathyroid patients with chronic kidney disease and kidney transplant recipients. Kidney Int 2010;78:1024–1032.
62 Saji F, Shiizaki K, Shimada S, Okada T, Kunimoto K, Sakaguchi T, Hatamura I, Shigematsu T: Regulation of fibroblast growth factor 23 production in bone in uremic rats. Nephron Physiol 2009;111:p59–p66.
63 Hu MC, Shi M, Zhang J, Quiñones H, Griffith C, Kuro-o M, Moe OW: Klotho deficiency causes vascular calcification in chronic kidney disease. J Am Soc Nephrol 2011;22:124–136.
64 Olgaard K: KDIGO: Clinical Guide to Bone and Mineral Metabolism in CKD. New York, National Kidney Foundation, 2006.
65 Malluche HH, Ritz E, Lange HP: Bone histology in incipient and advanced renal failure. Kidney Int 1976;9:355–362.
66 Craver L, Marco MP, Martínez I, Rue M, Borràs M, Martín ML, Sarró F, Valdivielso JM, Fernández E: Mineral metabolism parameters throughout chronic kidney disease stages 1–5-achievement of K/DOQI target ranges. Nephrol Dial Transplant 2007;22:1171–1176.
67 Slatopolsky E, Robson AM, Elkan I, Bricker NS: Control of phosphate excretion in uremic man. J Clin Invest 1968;47:1865–1874.
68 Goodman WG, Quarles LD: Development and progression of secondary hyperparathyroidism in chronic kidney disease: lessons from molecular genetics. Kidney Int 2007;74:276–288.
69 Martin DR, Ritter CS, Slatopolsky E, Brown AJ: Acute regulation of parathyroid hormone by dietary phosphate. Endocrinol Metab 2005;289:E729–E734.

70 Beck GR Jr: Inorganic phosphate as a signaling molecule in osteoblast differentiation. J Cell Biochem 2003;90:234–243.
71 Gupta A, Guo X-L, Alvarez UM, Hruska KA: Regulation of sodium-dependent phosphate transport in osteoclasts. J Clin Invest 1997;100:538–549.
72 Davies MR, Lund RJ, Mathew S, Hruska KA: Low turnover osteodystrophy and vascular calcification are amenable to skeletal anabolism in an animal model of chronic kidney disease and the metabolic syndrome. J Am Soc Nephrol 2005;16:917–928.
73 Hruska K, Mathew S: The roles of the skeleton and phosphorus in the CKD mineral bone disorder. Adv Chronic Kidney Dis 2011;18:98–104.
74 Sowers KM, Hayden MR: Calcific uremic arteriolopathy: pathophysiology, reactive oxygen species and therapeutic approaches. Oxid Med Cell Longev 2010;3:109–121.
75 Saab G, Whaley-Connell A, Khanna R, Sowers JR: Therapy for the altered mineral metabolism of chronic kidney disease: implications for vascular calcification. Ther Adv Cardiovasc Dis 2007;1:107–112.
76 Okuno S, Ishimura E, Kitatani K, Fujino Y, Kohno K, Maeno Y, Maekawa K, Yamakawa T, Imanishi Y, Inaba M, Nishizawa Y: Presence of abdominal aortic calcification is significantly associated with all-cause and cardiovascular mortality in maintenance hemodialysis patients. Am J Kidney Dis 2007;49:417–425.
77 Inaba M, Okuno S, Imanishi Y, Yamada S, Shioi A, Yamakawa T, Ishimura E, Nishizawa Y: Role of fibroblast growth factor-23 in peripheral vascular calcification in non-diabetic and diabetic hemodialysis patients. Osteoporos Int 2006; 17:1506–1513.
78 Siedlecki AM, Jin X, Muslin AJ: Uremic cardiac hypertrophy is reversed by rapamycin but not by lowering blood pressure. Kidney Int 2009;75:800–808.
79 Sowers JR, Whaley-Connell A, Hayden MR: The role of overweight and obesity in the cardiorenal syndrome. Cardiorenal Med 2011;1:5–12.
80 Pulakat L, DeMarco VG, Whaley-Connell A, Sowers JR: The impact of overnutrition on insulin metabolic signaling in the heart and the kidney. Cardiorenal Med 2011;1:102–112.
81 Foley RN: Chronic kidney disease: levels of phosphorus and patient outcomes. Nat Rev Nephrol 2011;7:428–430.
82 Torres PAU, De Brauwere DP: Three feedback loops precisely regulating serum phosphate concentration. Kidney Int 2011;80:443–445.
83 López I, Rodríguez-Ortiz ME, Almadén Y, Guerrero F, Oca AM, Pineda C, Shalhoub V, Rodríguez M, Aguilera-Tejero E: Direct and indirect effects of parathyroid hormone on circulating levels of fibroblast growth factor 23 in vivo. Kidney Int 2011;80:475–482.