nature REVIEWS
NEPHROLOGY

Hyperphosphataemia in CKD

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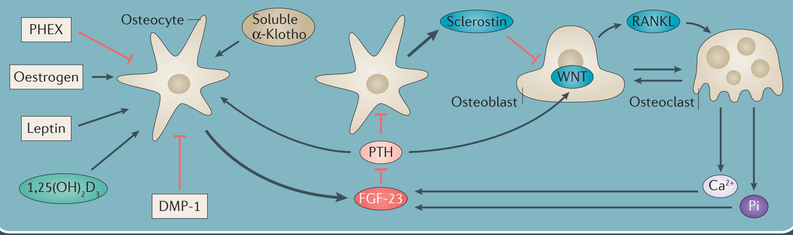
In patients with CKD renal excretion of dietary phosphate, which is consumed in the form of protein and phosphate additives, becomes increasingly difficult as nephron mass decreases. Potent compensatory mechanisms — mainly driven by PTH and FGF-23 — can prevent the occurrence of hyperphosphataemia until late in the course of the disease as it progresses towards renal failure[1,2]. Whether the maintenance of normal serum phosphate levels in CKD indicates protection against tissue phosphate accumulation is a matter of debate. Phosphate excess could have direct or indirect adverse effects.[3–5] Hyperphosphataemia, and even increases in serum phosphate levels within the normal range, are associated with worse cardiovascular and global outcomes[2,3]. Although hyperphosphataemia can be partially or fully corrected using phosphate binders, whether such correction results in improved patient outcomes remains unclear[6].

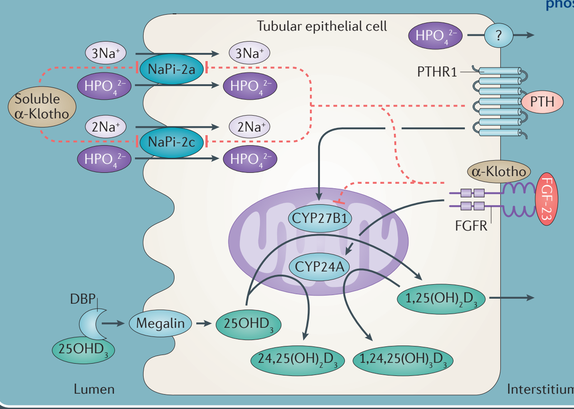
Phosphate and bone

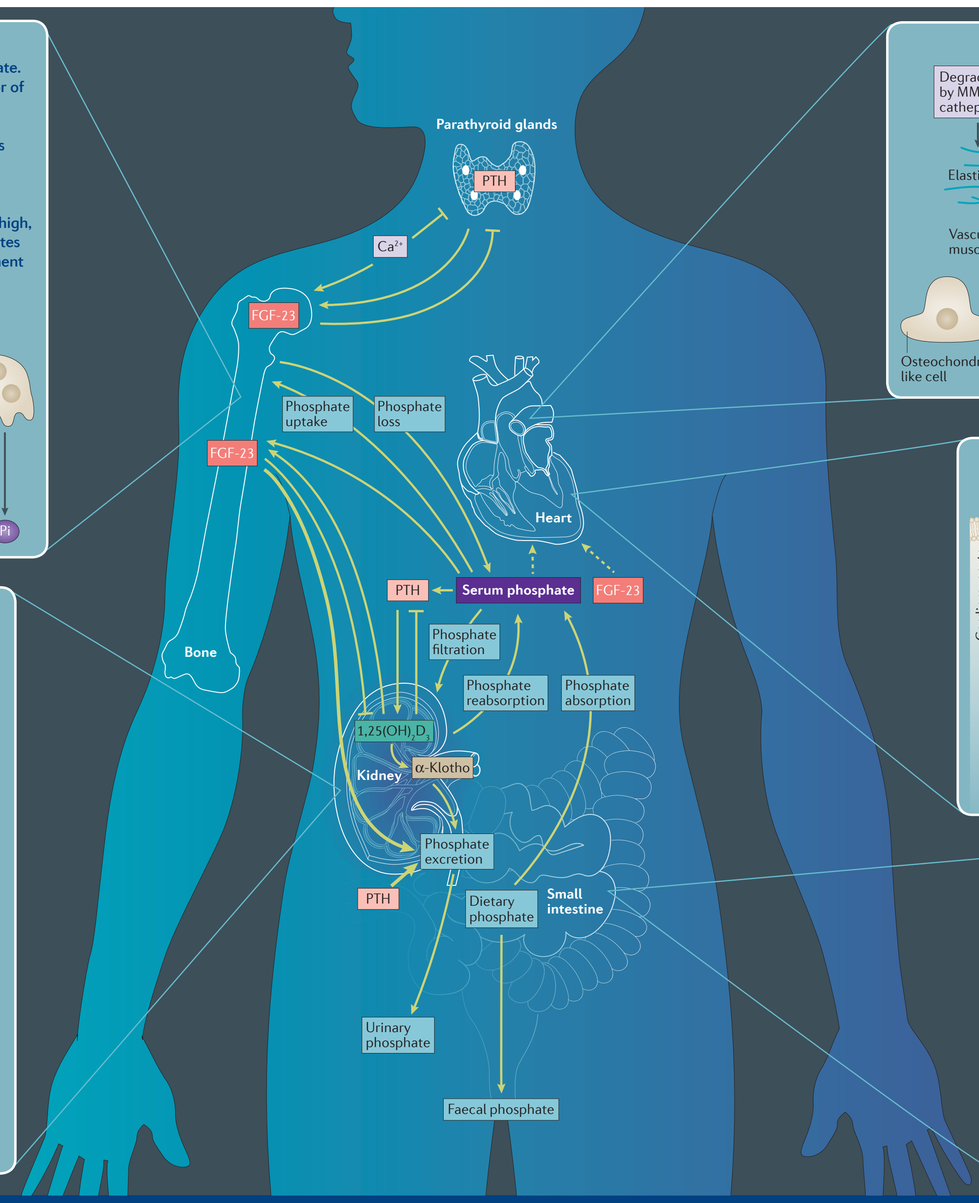
Bone is the main phosphate reservoir in the body; nonosseous soft tissues contain <20% of total body phosphate. If bone resorption outweighs bone formation, net loss of phosphate and calcium occurs[7]. PTH is a key regulator of bone formation and turnover. High PTH levels stimulate both bone formation (either directly or indirectly by suppressing the osteocytic expression of sclerostin) and resorption (by increasing osteoblastic expression of RANKL[8]). Permanent elevations of PTH favour bone resorption over formation, whereas intermittent elevations favour bone formation over resorption. Many factors modulate FGF-23 synthesis in osteocytes; phosphate, calcium, PTH, $1,25(OH)_2D_3$ and its analogues, leptin, oestrogen, soluble α-Klotho, metabolic acidosis and iron overload or deficiency stimulate FGF-23 synthesis, whereas PHEX and DMP-1 inhibit FGF-23 synthesis. Bone remodelling has also been shown to regulate the synthesis of FGF-23.[9] In CKD, serum calcium levels might be high, normal or low. Excessive loss of calcium and phosphate from bone or impaired bone uptake probably contributes to high serum levels. A reduction in renal $1,25(OH)_2D_3$ synthesis and increased PTH levels favour the development of osteitis fibrosa, a type of renal osteodystrophy. High serum calcium and phosphate levels in the setting of osteitis fibrosa or adynamic bone disease stimulate calcification of soft tissues, including the vasculature[6].



Renal phosphate handling and retention

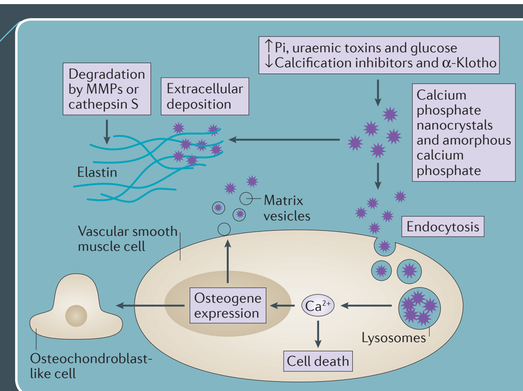
Following ultrafiltration of plasma phosphate in the glomerulus, the majority is reabsorbed in the proximal tubule via NaPi-2a and NaPi-2c on the luminal side and an unknown transporter on the basolateral side of tubular epithelial cells. In the steady state FGF-23 and PTH maintain phosphate homeostasis by adapting renal phosphate handling and urinary excretion to oral intake[1]. Binding of FGF-23 and PTH to their receptors on tubular epithelial cells activates signalling pathways that inhibit NaPi-2a and NaPi-2c. The renal action of FGF-23 requires α-Klotho, which can also directly inhibit NaPi-2a and NaPi-2c[10]. FGF-23 inhibits and PTH stimulates synthesis of $1,25(OH)_2D_3$ in the tubular epithelium. In the early stages of CKD, phosphate retention as a result of nephron loss is prevented by increases in serum FGF-23 and PTH[1,11]. As CKD progresses renal α-Klotho expression decreases, resulting in FGF-23 resistance. Increased concentrations of FGF-23 are, therefore, required to maintain phosphate excretion. In late-stage CKD, these adaptive mechanisms become insufficient and hyperphosphataemia ensues.





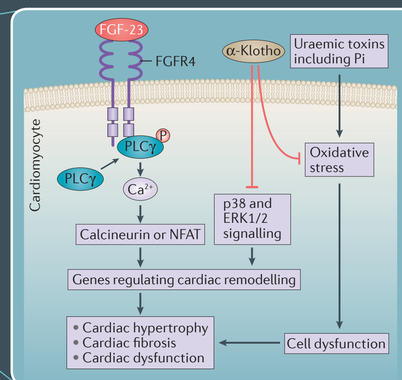
Vascular calcification

Phosphate retention in patients with CKD promotes the development and progression of vascular calcification directly via the precipitation of calcium phosphate crystals in arterial tissue, and possibly also indirectly via FGF-23 excess and α-Klotho deficiency[6,12]. Nanocrystals of calcium phosphate can accumulate in extracellular vesicles and be deposited on degraded elastin fibres or endocytosed and directed to lysosomes. Endocytosed crystals dissolve in the low pH environment of lysosomes, resulting in release of Ca^{2+} into the cytosol. The subsequent transient increase in intracellular Ca^{2+} concentration could induce cell death or osteochondrocytic transdifferentiation of vascular smooth muscle cells.



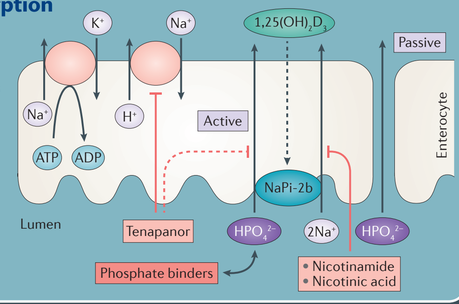
Cardiovascular dysfunction

High serum FGF-23 and reduced α-Klotho levels in association with hyperphosphataemia increase the risk of cardiac dysfunction, cardiovascular events and cardiovascular mortality in patients with CKD[3,10,13]. Circulating PTH, FGF-23 and α-Klotho independently exert direct, acute actions on the structure and function of arterial endothelial cells, smooth muscle cells and cardiomyocytes. Chronic FGF-23 excess promotes left ventricular hypertrophy by a direct, α-Klotho-independent action on cardiac muscle that involves binding to FGFR4 and activation of the PLCγ/calcineurin or NFAT pathways[14]. By contrast, α-Klotho protects against uraemic toxin-induced vascular endothelial cell dysfunction and left ventricular hypertrophy through inhibition of oxidative stress and the p38 and ERK1/2 signalling pathways[13].



Intestinal phosphate absorption

Approximately 70% of ingested phosphate is absorbed by the gut. Active phosphate transport is stimulated by $1,25(OH)_2D_3$ and involves NaPi-2b on the luminal side and a Na^+/H^+ exchanger on the basolateral side of enterocytes; passive transport occurs by diffusion via the intercellular spaces[15]. Phosphate binders reduce intestinal phosphate absorption. Inhibitors of active phosphate transport, such as tenapanor, nicotinamide and nicotinic acid are not currently used in the clinic[16,17].



Abbreviations

CKD, chronic kidney disease; CYP24A, 1,25-dihydroxyvitamin D_3 24-hydroxylase; CYP27B1, 25-hydroxyvitamin D-1α-hydroxylase; DBP, vitamin D binding protein; DMP-1, dentin matrix protein 1; ERK1/2, extracellular signal-regulated kinase 1/2; FGF-23, fibroblast growth factor 23; FGFR, FGF receptor; HPO_4^{2-}, hydrogen phosphate; MMP, matrix metalloproteinase; NaPi-2, sodium-dependent phosphate transport protein 2; NFAT, nuclear factor of activated T-cells; PHEX, phosphate-regulating neutral endopeptidase; Pi, inorganic phosphate; PLCγ, phospholipase Cγ; PTH, parathyroid hormone; PTHR1, PTH/PTH-related protein type 1 receptor; RANKL, receptor activator of NF-κB ligand; $1,24,25(OH)_3D_3$, 1,24,25-trihydroxyvitamin D_3; $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D_3; $24,25(OH)_2D_3$, 24,25-dihydroxyvitamin D_3; 25OHD-1α, 25-hydroxyvitamin D-1α; $25OHD_3$, 25-hydroxyvitamin D_3.

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