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Update in FGF23 and Klotho Signaling In Kidney Disease

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GUMS

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The FGF family: biology, pathophysiology and therapy

Andrew Beenken and Moosa Mohammadi

✓ **FGF23 is a member of the FGF family that comprises 18 secreted proteins that have diverse functions in development and metabolism.**

✓ **The biological effects of all FGFs are mediated by binding to 1 of the 4 FGFR isoforms (FGFR1–4)that belong to the superfamily of receptor tyrosine kinases.**

Table 2

The physiology of FGFs

Fibroblast growth factor (FgF)	Phenotype of knockout mouse	Physiological role
FGF1	Normal[69]	Not established
FGF2	Loss of vascular tone Slight loss of cortex neurons[72–73]	Not established
FGF3	Inner ear agenesis in humans[9]	Inner ear development[9]
FGF4	Embryonic lethal[128]	Cardiac valve leaflet formation Limb development[126–128]
FGF5	Abnormally long hair[129]	Hair growth cycle regulation[129–131]
FGF6	Defective muscle regeneration[133]	Myogenesis[132,133]
FGF7	Matted hair Reduced nephron branching in kidney[137,138]	Branching morphogenesis[138]
FGF8	Embryonic lethal[162]	Brain, eye, ear and limb development[160,161]
FGF9	Postnatal death Gender reversal Lung hypoplasia[170]	Gonadal development Organogenesis[170,171]
FGF10	Failed limb and lung development[142]	Branching morphogenesis[142]
FGF16	Embryonic lethal[172]	Heart development[172]
FGF17	Abnormal brain development[163]	Cerebral and cerebellar development[163]
FGF18	Delayed long-bone ossification[164,165]	Bone development[164,165]
FGF19	Increased bile acid pool[189]	Bile acid homeostasis Lipolysis Gall bladder filling[3,6,197–201]
FGF20	No knockout model	Neurotrophic factor[175]
FGF21	No knockout model	Fasting response Glucose homeostasis Lipolysis and lipogenesis[4,208–225]
FGF22	No knockout model	Presynaptic neural organizer[143]
FGF23	Hyperphosphataemia Hypoglycaemia Immature sexual organs[185,235]	Phosphate homeostasis Vitamin D homeostasis[226–261]

www.kidney-international.org

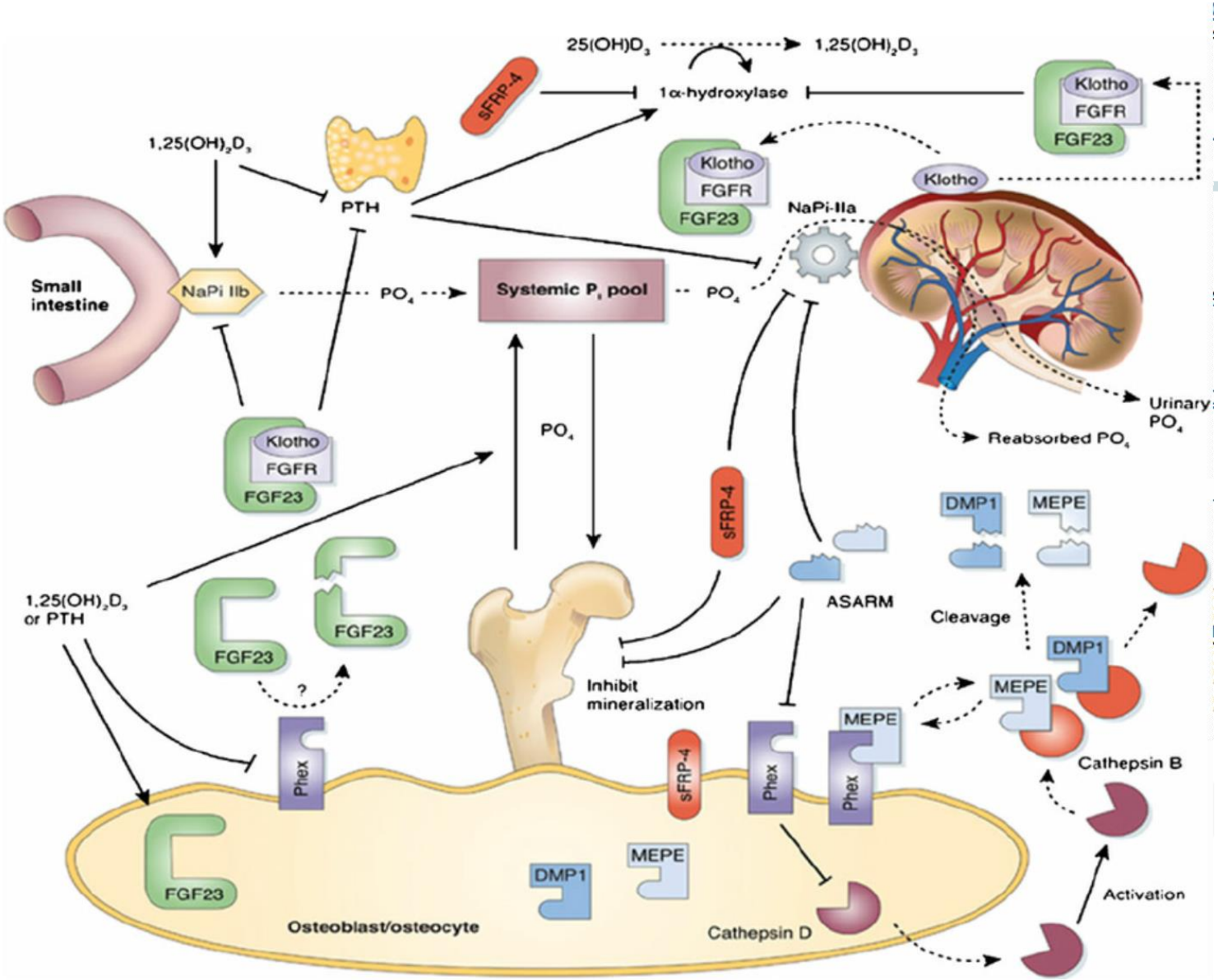
Soluble α-klotho and heparin modulate the pathologic cardiac actions of fibroblast growth factor 23 in chronic kidney disease

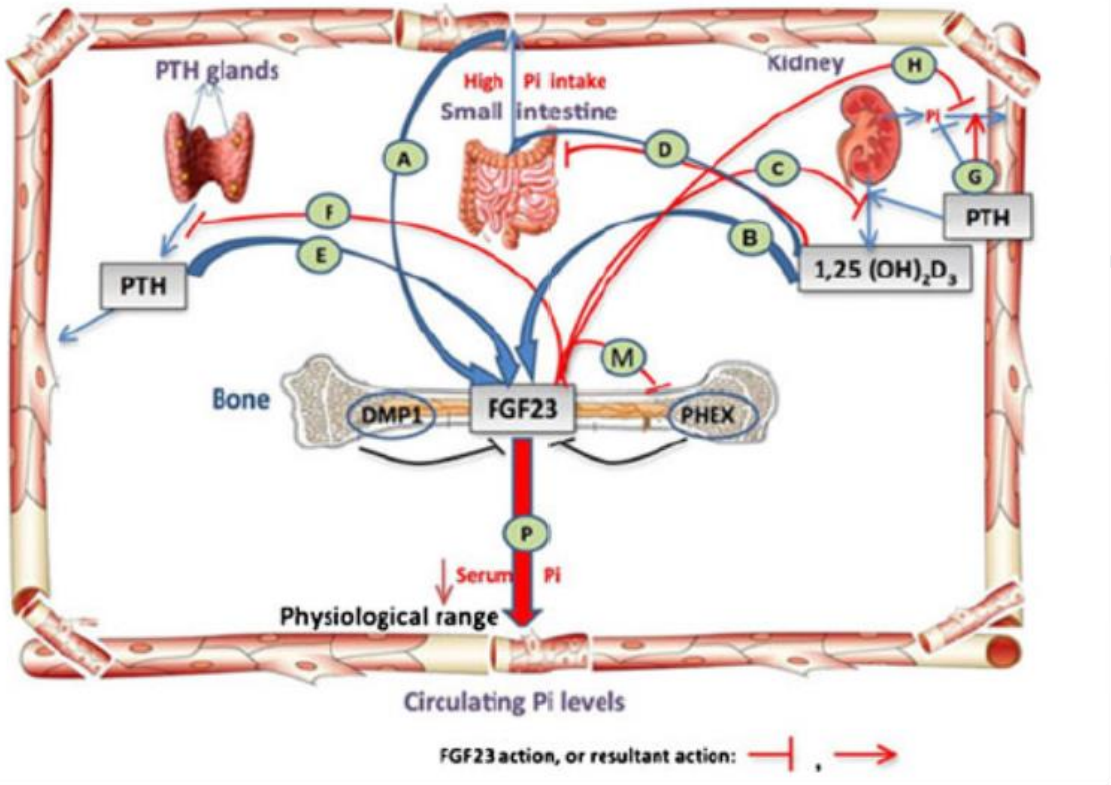
Christopher Yanucil[1], Dominik Kentrup[1,2], Isaac Campos[1], Brian Czaya[1], K
David Westbrook[1], Gunars Osis[1], Alexander Grabner[3], Adam R. Wende[4],

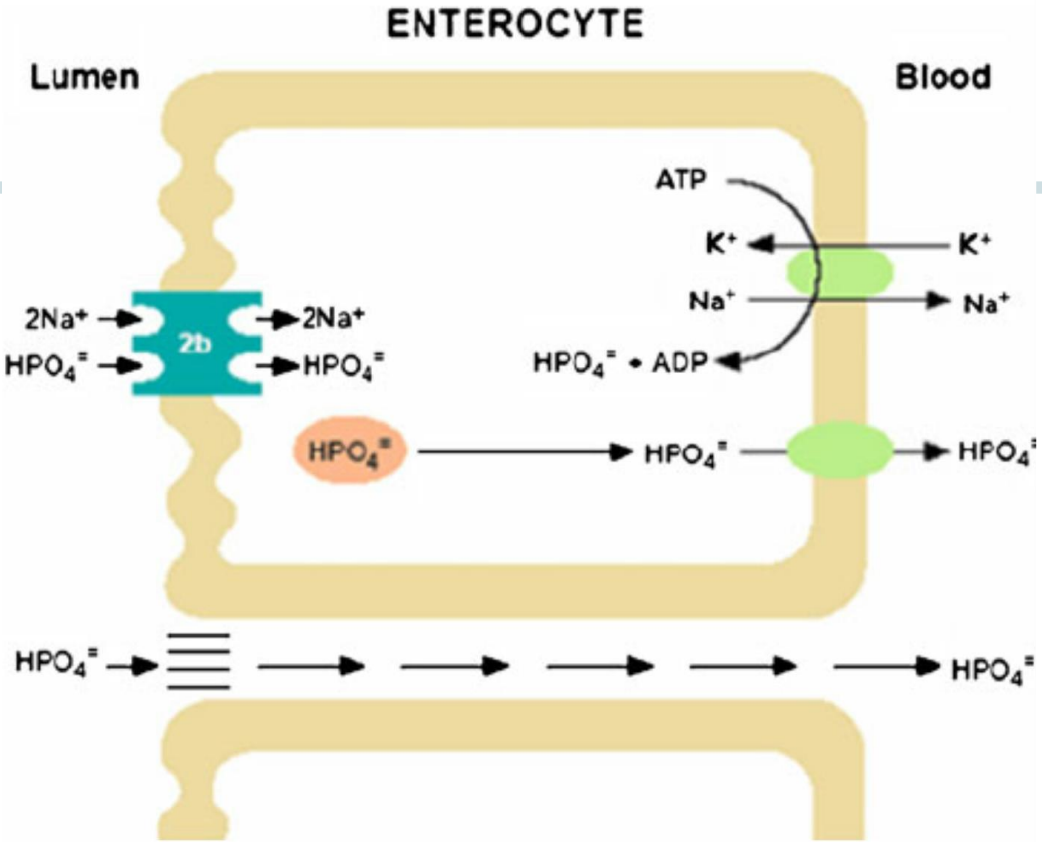
FGF 23 is a **hormone (251 aa)** that serves as a major regulator of **phosphate metabolism**.

- ✓ In response to elevations in serum phosphate levels, such as after food intake, FGF23 is secreted by the **bone** and targets the kidney via FGF receptor (**FGFR)** isoform **1c(**FGFR1c) and the **coreceptor a-klotho** , resulting in the induction of Ras/mitogen-activated protein kinase (MAPK) signaling.

- ✓ Intact FGF23 forms FGF23-FGFR-Klotho complex with FGFR and Klotho, which can inhibit expression levels of **sodium-dependent phosphate transport protein 2A** and sodium-dependent phosphate transport protein **2C** at **proximal renal** tubules, thereby promote renal phosphate excretion .





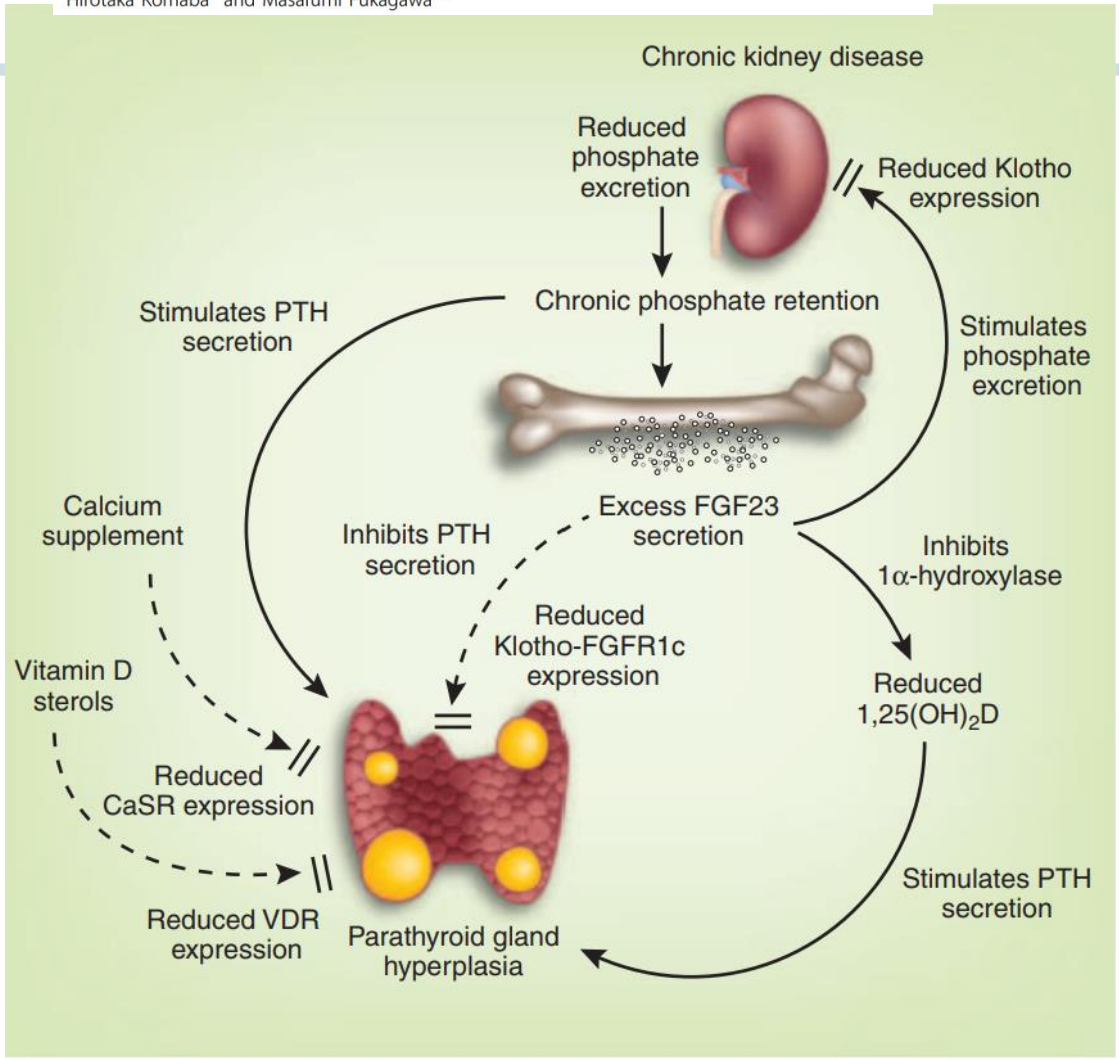


- ✓ **FGF23-FGFR-Klotho complex** also reduces intestinal absorption of dietary Pi through a vitamin D receptor (VDR)-dependent decrease in NaPi-IIb activity.
- ✓ FGF23 also ***upregulates*** **24-hydroxylase** activity that metabolize vitamin D.
- ✓ Because 1,25-dihydroxyvitamin D enhances intestinal phosphate absorption, this effect of FGF23 also leads to ***reduced phosphate*** levels231.

mini review http://www.kidney-international.org

FGF23–parathyroid interaction: implications in chronic kidney disease

Hirotaka Komaba[1] and Masafumi Fukagawa[1,2]



- ✓ FGF23 also acts on the parathyroid gland to inhibit parathyroid hormone (PTH) secretion.
- ✓ PTH increases the uptake of phosphate from bone and upregulates 1α-hydroxylase, leading to increased vitamin D activation and enhanced phosphate reabsorption in the intestine.
- ✓ Indeed, FGF23 has been shown to lower 1α-hydroxylase levels by a vitamin D receptor-independent mechanism240.
- ✓ Because the kidney is the **only organ** to excrete phosphate, reduced kidney function results in elevations of serum phosphate.
- ✓ In patients with chronic kidney disease, serum FGF23 is increased to maintain neutral phosphate balance, but this leads to suppression of renal 1,25(OH)2D production and thereby triggers the early development of secondary hyperparathyroidism.

Overview of the Klotho/FGF23 Axis

Seminars in Nephrology
Volume 33, Issue 2, March 2013, Pages 118-129

Renal and Extrarenal Actions of Klotho

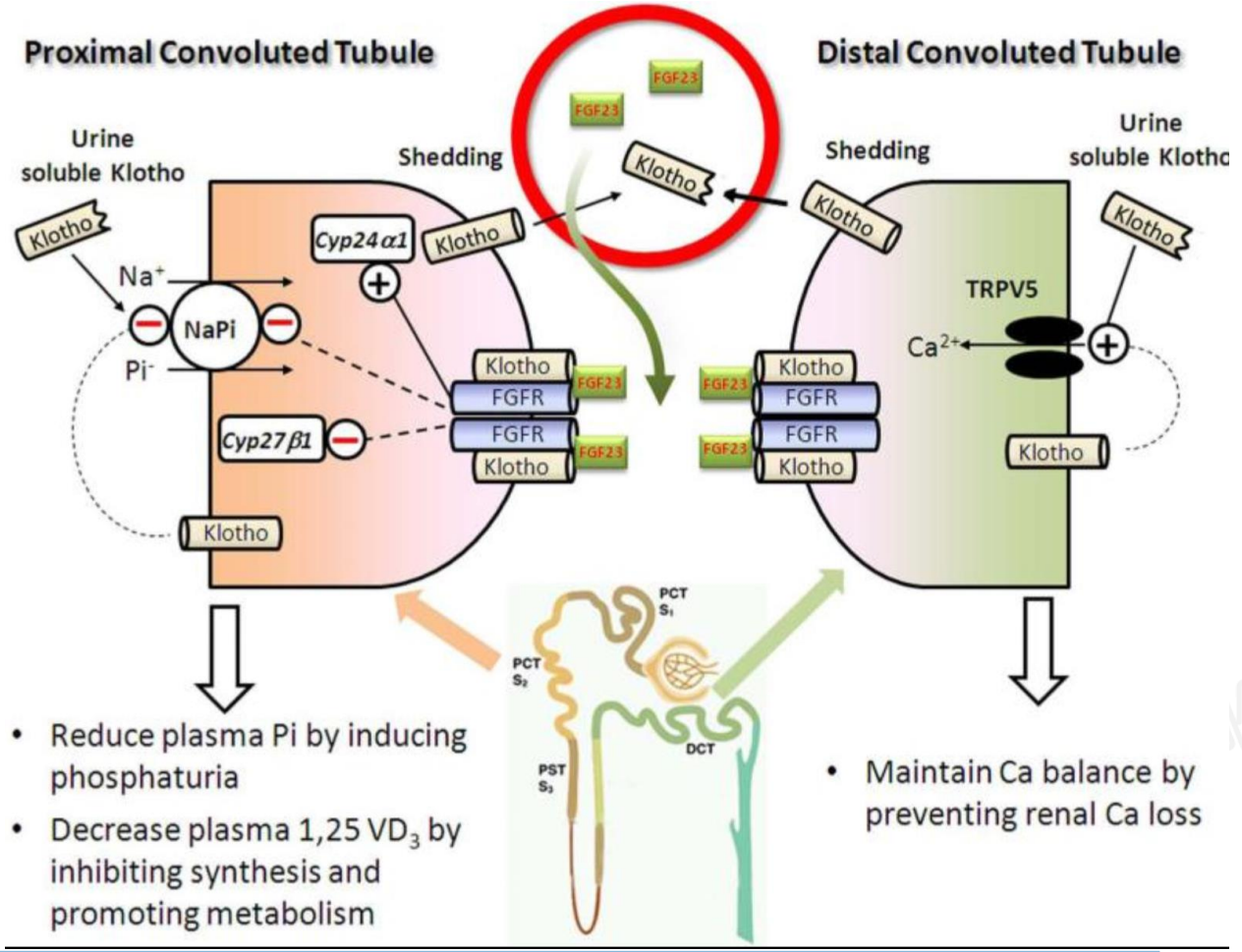
Ming Chang Hu MD, PhD, Makoto Kuro-o MD, PhD, Orson W. Moe MD

- ✓ ***Klotho protein*** is ***expressed*** in ***multiple tissues*** but is found in particularly high levels in the kidney [1]. Klotho is a single-pass transmembrane protein highly expressed in the kidney. In the kidney, Klotho is prominently expressed in the ***DCT***, but is also unequivocally found in the ***PCT*** and the IMCD.

- ✓ **Its extracellular domain** is **shed from the cell surface** and functions as an **endocrine substance** that exerts multiple renal and extrarenal functions.

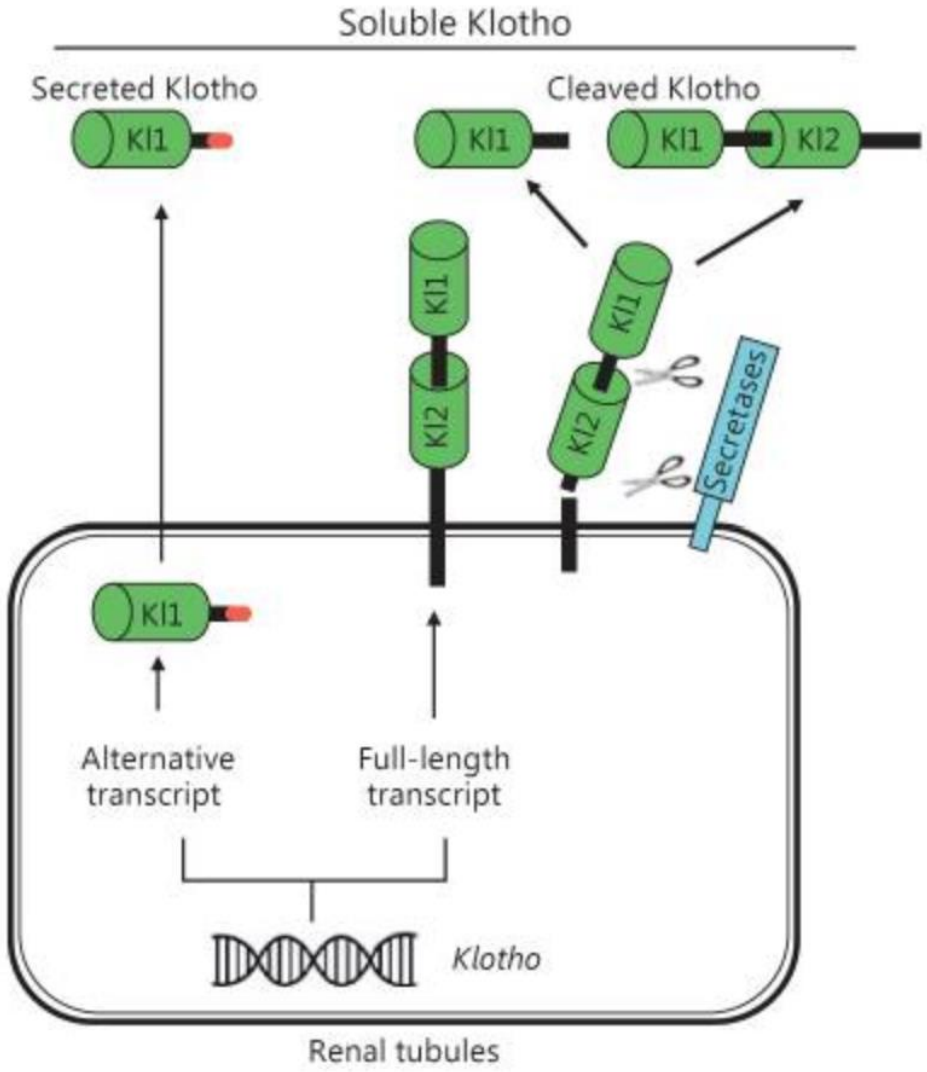
- ✓ ***Membrane Klotho functions as a coreceptor to enhance the binding of the endocrine FGF23 to FGF receptors (FGFRs) through the formation of a Klotho/FGFR/FGF23 complex, with subsequent activation of FGF signal transduction at their target organs*** .

- ✓ Klotho participates in mineral homeostasis via interplay with other calciophosphoregulatory hormones (PTH, FGF, and 1,25-$[OH]_2$ vitamin D_3) in kidney, bone, intestine, and parathyroid gland.

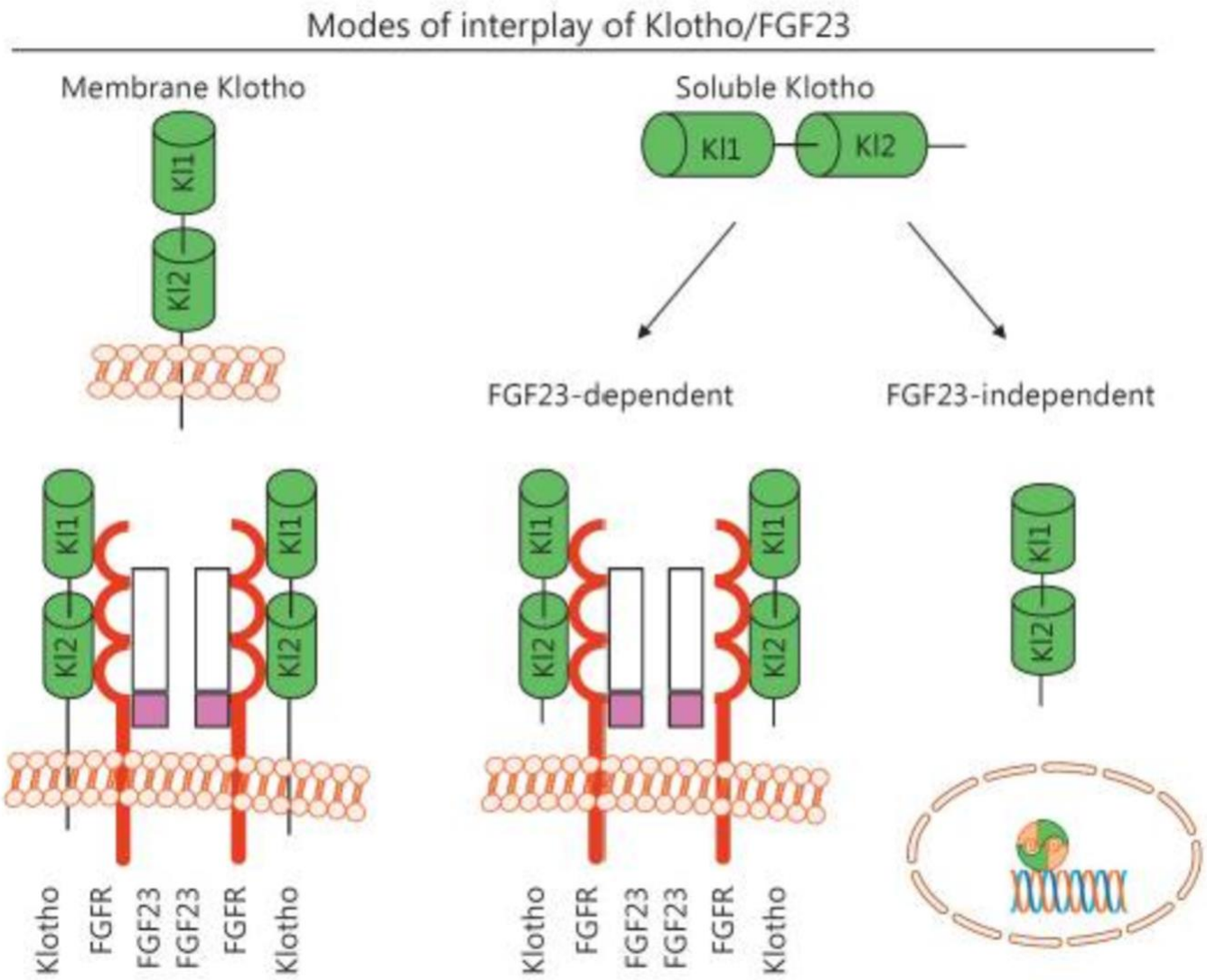


✓Source of soluble Klotho:

- ✓The kidney is the main source of circulating Klotho under physiological conditions.
- ✓Both renal proximal and distal tubules express membrane Klotho protein and also presumably produce secreted Klotho protein through alternative splicing.
- ✓The secreted Klotho only contains a Kl1 domain and is directly secreted into the blood circulation (left panel); its biological function is not completely clear yet.



- ✓ Proposed modes of **fibroblast growth factor 23 (FGF23) and Klotho action.**
- ✓ Membrane Klotho (**green**) binds to the FGF receptor (FGFR) (brown), which in turn binds to FGF23 (white and pink) to form the 2FGF23/2FGFR2/Klotho complex.
- ✓ The potential FGFRs for FGF23 include FGFR1c, FGFR3c, and FGFR4 and serve as the high-affinity receptor for FGF23 (left panel). Soluble Klotho may form a similar complex and potentially prevent high FGF23-induced side (off-target) effects (middle panel).
- ✓ Soluble Klotho also exerts its multiple biological actions in an FGF23-independent manner via a yet-to-be-identified mechanism(s) (right panel).

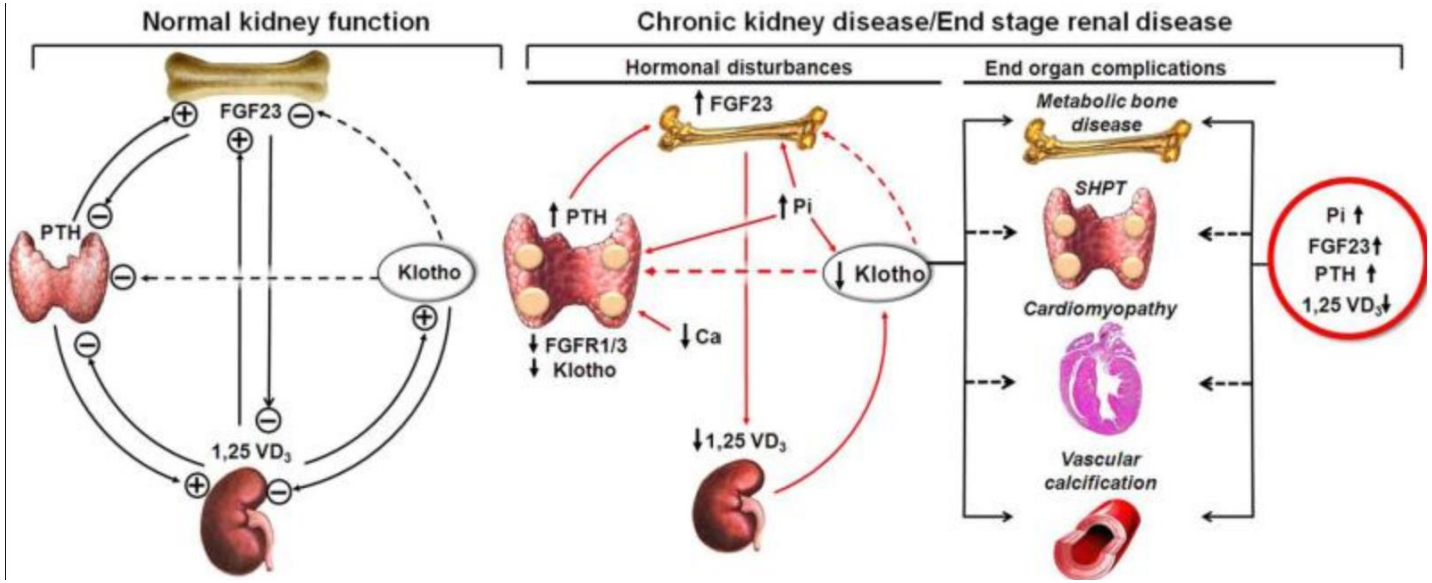


Seminars in Nephrology
Volume 33, Issue 2, March 2013, Pages 118-129

Renal and Extrarenal Actions of Klotho

Ming Chang Hu MD, PhD, Makoto Kuro-o MD, PhD, Orson W. Moe MD

- ✓ ***Physiological Role of Klotho in the Kidney***
- ✓ The kidney is not a mere excretory organ but also a hormonal source producing several active molecules such as 1,25-$(OH)_2$-vitamin D_3 (1,25 VD_3), renin, erythropoietin, and Klotho. Klotho exerts multiple actions on the kidney but only selected functions are highlighted in this article. This includes regulation of 1,25 VD_3 production and modulation of urinary phosphate (Pi), Ca, and K excretion.
- ✓ ***Physiological Role of Klotho in Extrarenal Organs***
- ✓ ***Klotho Deficiency Renders the Kidney More Susceptible to Injury***
- ✓ ***Pathophysiological Role of Klotho in the Metabolic Syndrome:***
- ✓ ***Secondary Hyperparathyroidism***
- ✓ ***Conclusions and Perspectives***
- ✓



✓ Proposed model and time profile of changes in serum Klotho, fibroblast growth factor 23 (FGF23), phosphate (Pi), and hormones relevant to mineral metabolism in relation to chronic kidney disease (CKD) progression.

- ✓ The decline in Klotho (black line) is an early event which is followed by other changes as CKD progresses.
- ✓ Low Klotho may induce FGF23 resistance causing a compensatory increase in blood FGF23 levels (red line) to maintain Pi homeostasis in CKD.
- ✓ The compensatory increase in FGF23 then suppresses 1,25-$(OH)_2$-vitamin D_3 (1,25-$(OH)_2D_3$) production (blue line).
- ✓ Low 1,25-$(OH)_2D_3$ and high blood Pi (purple line) due to progressive decline in renal function increase parathyroid hormone (PTH) (green line), which may contribute to high FGF23 in advanced CKD.

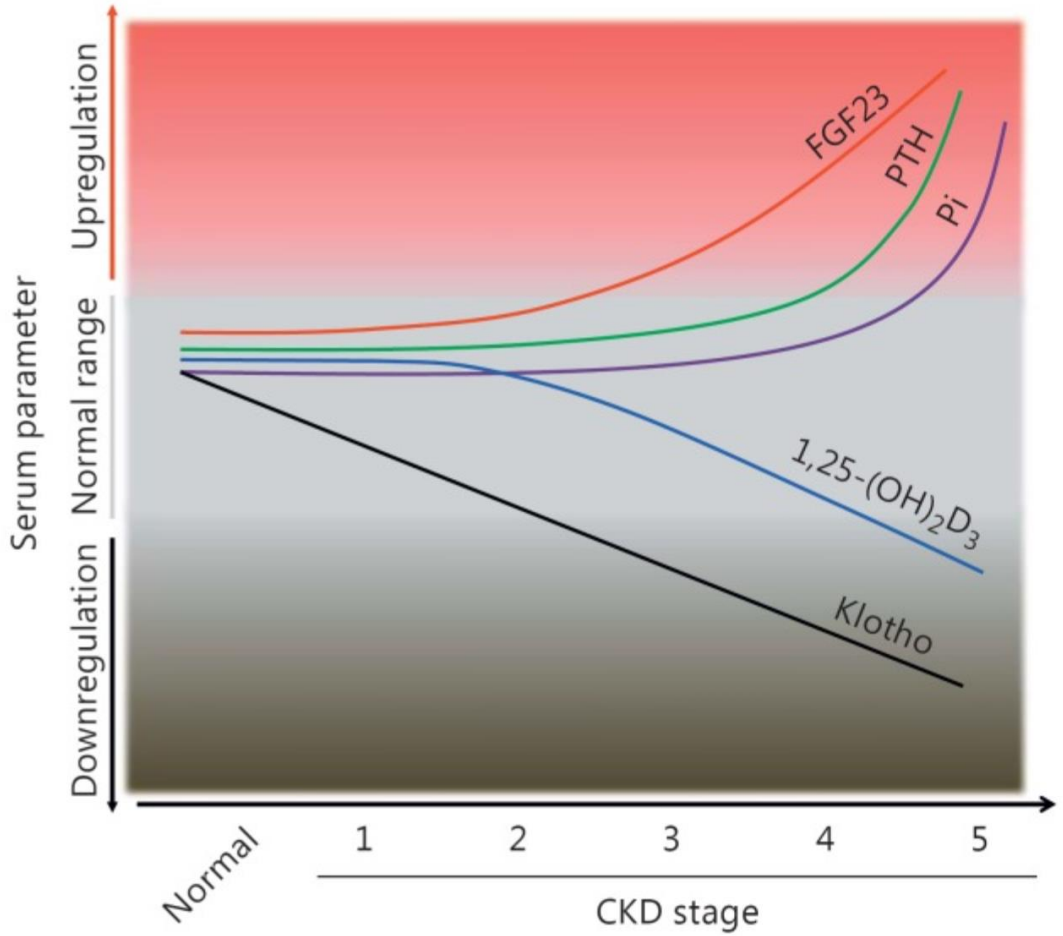
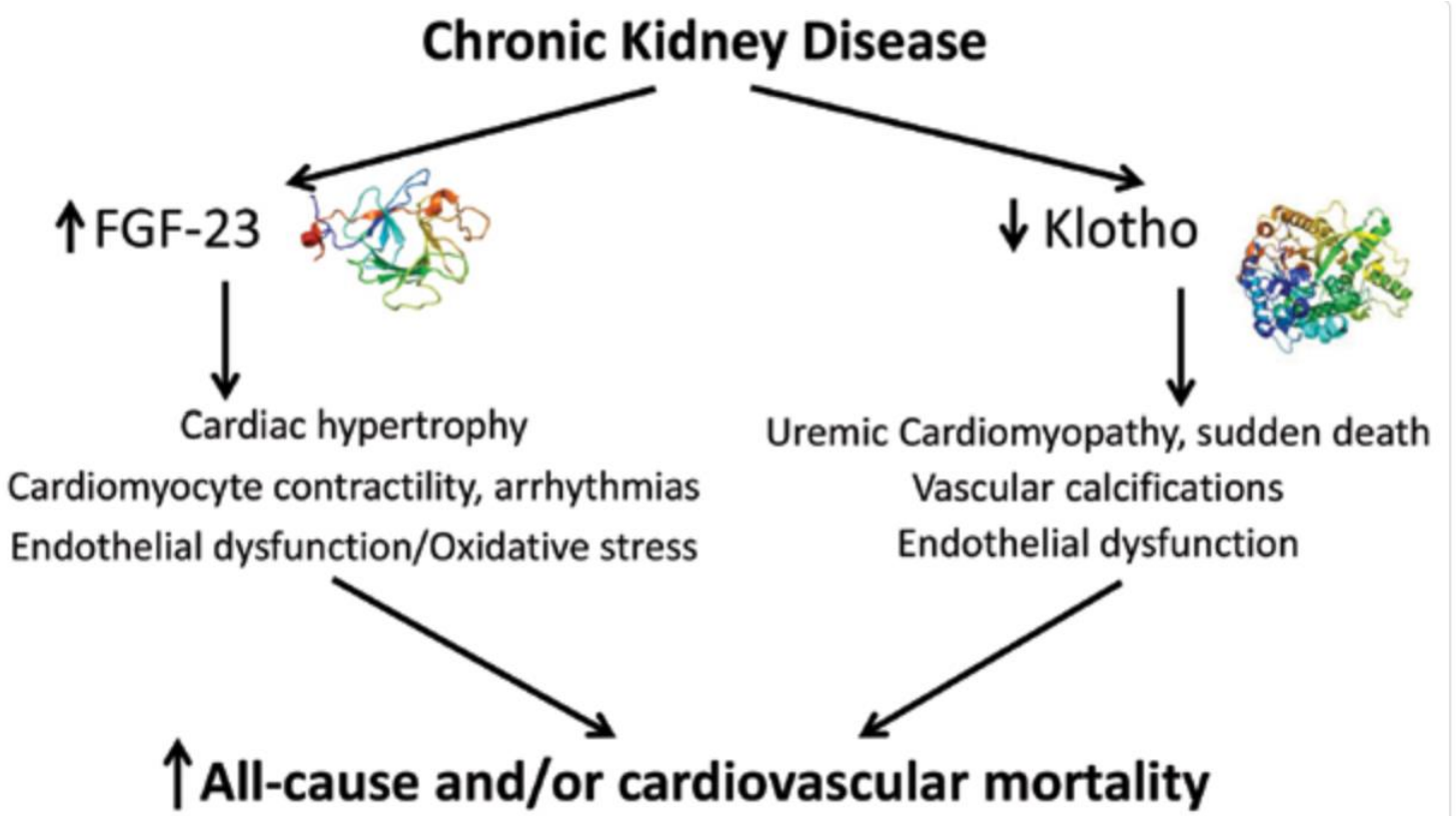


Fig. 3 Proposed model and time profile of changes in serum Klotho, fibroblast growth factor 23 (FGF23), phosphate (Pi), and hormones relevant to mineral metabolism in relation to chronic kidney disease (CKD) progression. The decline in Klotho (black line) is an early event which is followed by other changes as CKD progresses. Low Klotho may induce FGF23 resistance causing

New Insights into the Role of FGF-23 and Klotho in Cardiovascular Disease in Chronic Kidney Disease Patients.
Author(s): Evangelos Memmos and Aikaterini Papagianni*Volume 19, Issue 1, 2021.Published on: 20 April, 2020

- ✓ Moreover, **emerging data suggests** that the dysregulated FGF-23 and Klotho axis has **many effects** on the cardiovascular (**CV) system** and contributes significantly to the increased CV morbidity and mortality rates of CKD patients.
- ✓ This review examines **recent evidence** on the role of FGF-23 and Klotho in the development and progression of CV complications of uremia namely cardiac hypertrophy, uremic cardiomyopathy, and atherosclerotic and arteriosclerotic vascular lesions.
- ✓ Undoubtedly, **more studies are needed** to **further elucidate** the effects of FGF-23 and Klotho on the heart and vessels and **to gain insights** into their prognostic value as CV risk factors.
- ✓ Finally, **large prospective studies** are required to test the **hypothesis that modification of their levels** would have a **favourable impact** on the unacceptably high mortality rates of these patient populations.



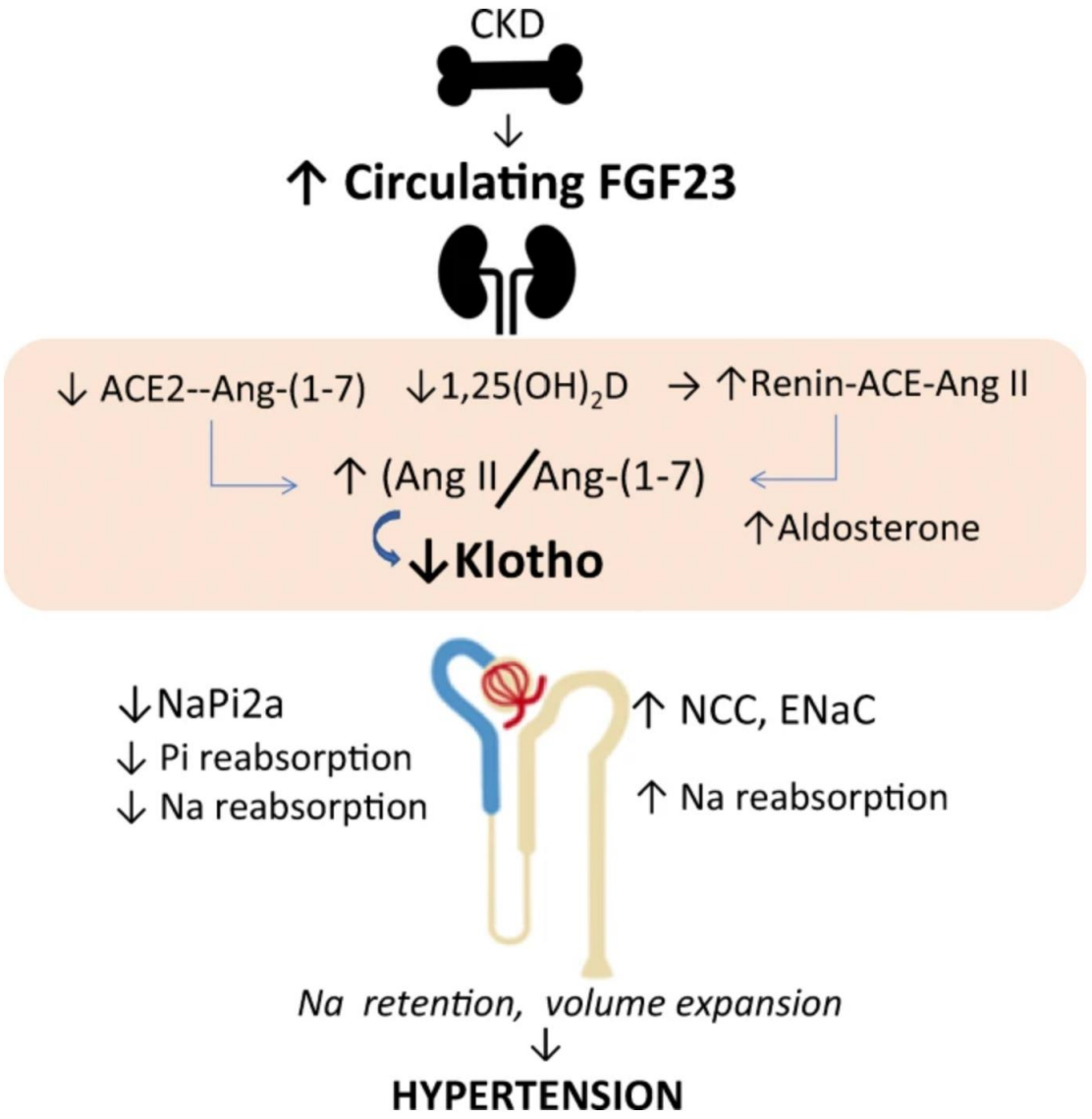
- ✓ Excess FGF23 and Klotho insufficiency links to vitamin D, the RAAS, sodium homeostasis, and hypertension in CKD. Augmented FGF23 production by the bone results in elevated circulating FGF23 levels.

- ✓ FGF23 effects in the kidney are mediated by activation of the FGFR1/Klotho complex and result in reduced 1,25(OH)2D synthesis, upregulated renin with increased ACE/Ang II, and reduced ACE2/Ang-(1-7) formation, leading to an elevated Ang II/Ang-(1-7) ratio, which contribute to sodium retention, kidney damage, and hypertension.

- ✓ In the proximal tubule (blue), FGF23 inhibits the re-uptake of phosphate by regulating the sodium phosphate transporter NaPi 2a (and NaPi 2c, not shown).

- ✓ In the distal tubule (**light brown**), FGF23 **activates the NCC** to increase reabsorption of **sodium a**nd ultimately promotes volume retention thus contributing to hypertension.

- ✓



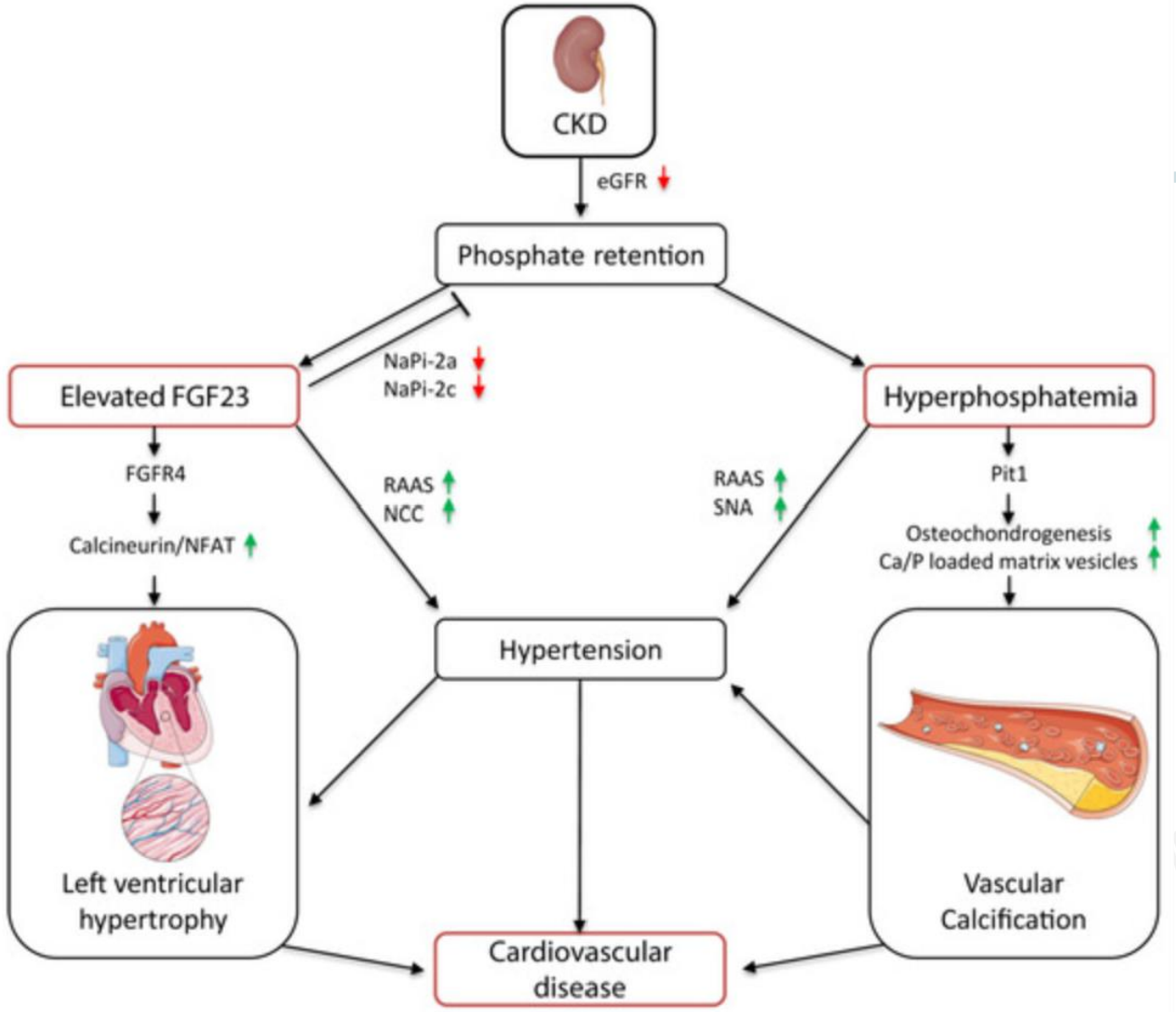
Excess FGF23 and Klotho insufficiency links to vitamin D, the RAAS, sodium homeostasis, and hypertension in CKD. Augmented FGF23 production by the bone results in elevated circulating

- ✓ **Cardiovascular pathomechanisms of elevated FGF23 and hyperphosphatemia in chronic kidney disease (CKD).**

- ✓ The phosphate excretion attenuates with declining kidney function.

- ✓ Resulting FGF23 elevation counteracts the phosphate retention by downregulating NaPi-2a/c in the kidney, but also directly promotes LVH via FGFR4–calcineruin–NFAT signaling.

- ✓ FGF23 induces hypertension by activation of the RAAS and NCC expression. Hyperphosphatemia stimulates the osteochondrogenic differentiation and release of Ca/P loaded vesicles in VSMCs via Pit-1, and thereby induces VC.



- ✓Elevated FGF23 levels can directly target cardiac myocytes, and hepatocytes, which ***do not express klotho***, thereby implying that the presence of klotho ***is not a prerequisite*** for the FGF23 responsiveness of cells.

- ✓We have shown in cell culture and in animal studies that in the absence of klotho, high levels of FGF23 can directly target cardiac myocytes specifically via ***FGFR isoform 4*** (FGFR4) and activate the phospholipase Cg (PLCg)/calcineurin/nuclear factor of activated T cell (***NFAT***) signaling cascade, thereby inducing ***cardiac hypertrophy***.

- ✓ Our studies suggest that pharmacologic ***FGFR4 blockade*** might serve as a ***novel therapeutic*** option to prevent or treat pathologic cardiac remodeling in CKD (also called ***uremic cardiomyopathy***).

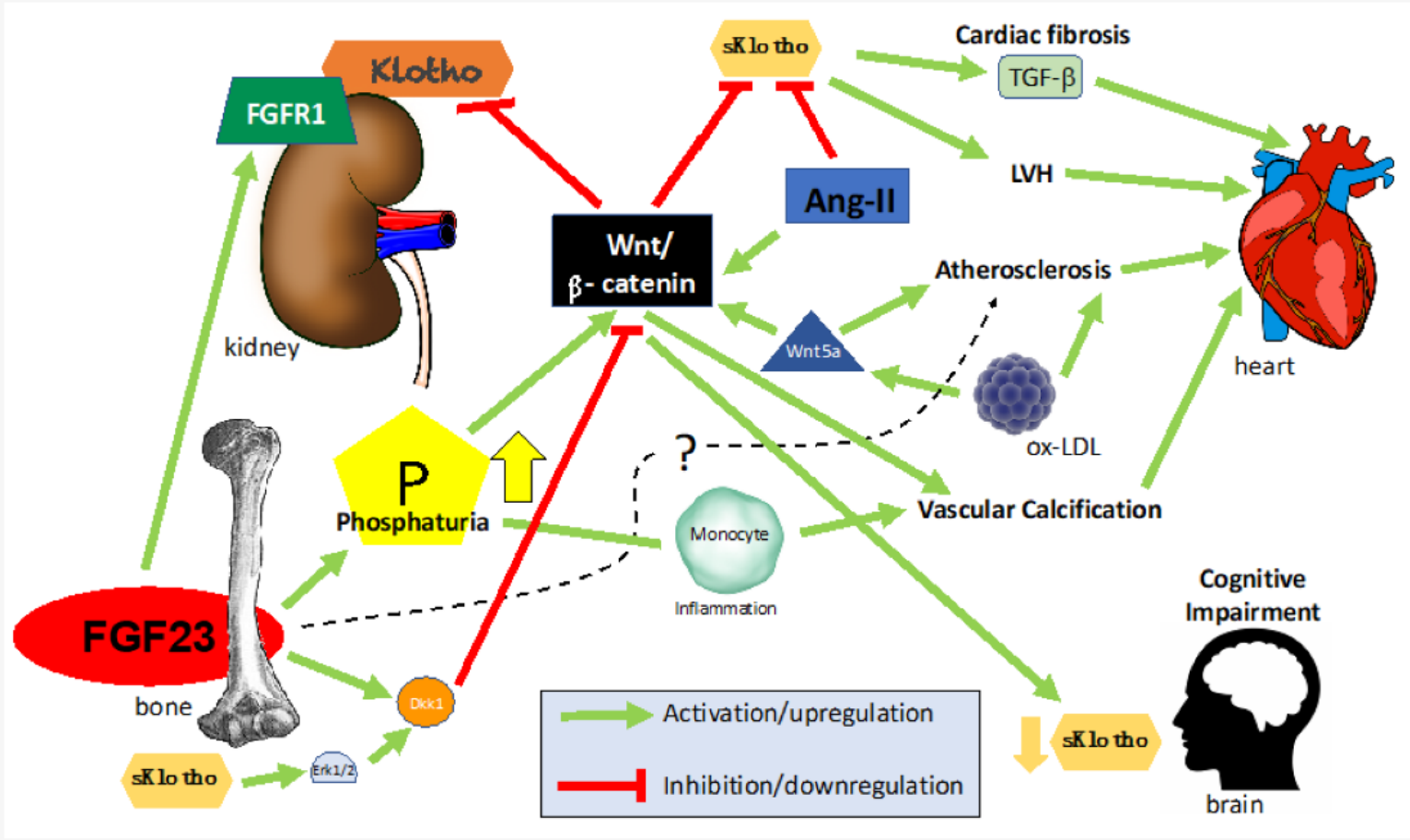
- ✓FGF23 is increased in patients with renal failure by 100–1,000-fold, partly owing to decreased renal clearance ***but also*** suggesting that it might have a compensatory role in this disease .

- ✓However, whether the increased FGF23 levels in chronic kidney disease are beneficial or harmful is still ***a matter of debate***.

- ✓ ***In any case, FGF23 levels do correlate strongly*** with disease outcome.
- ✓Increased levels of ***serum FGF23*** at the beginning of dialysis treatment predict a significant increase in 1 year mortality in patients with chronic kidney disease258.

- ✓ FGF23 serum levels are also predictive of the development of ***secondary hyperparathyroidism.***

Figure 2. Schematic representation of FGF23/Klotho interactions with the Wnt/β-catenin pathway in the bone, kidney, and heart.



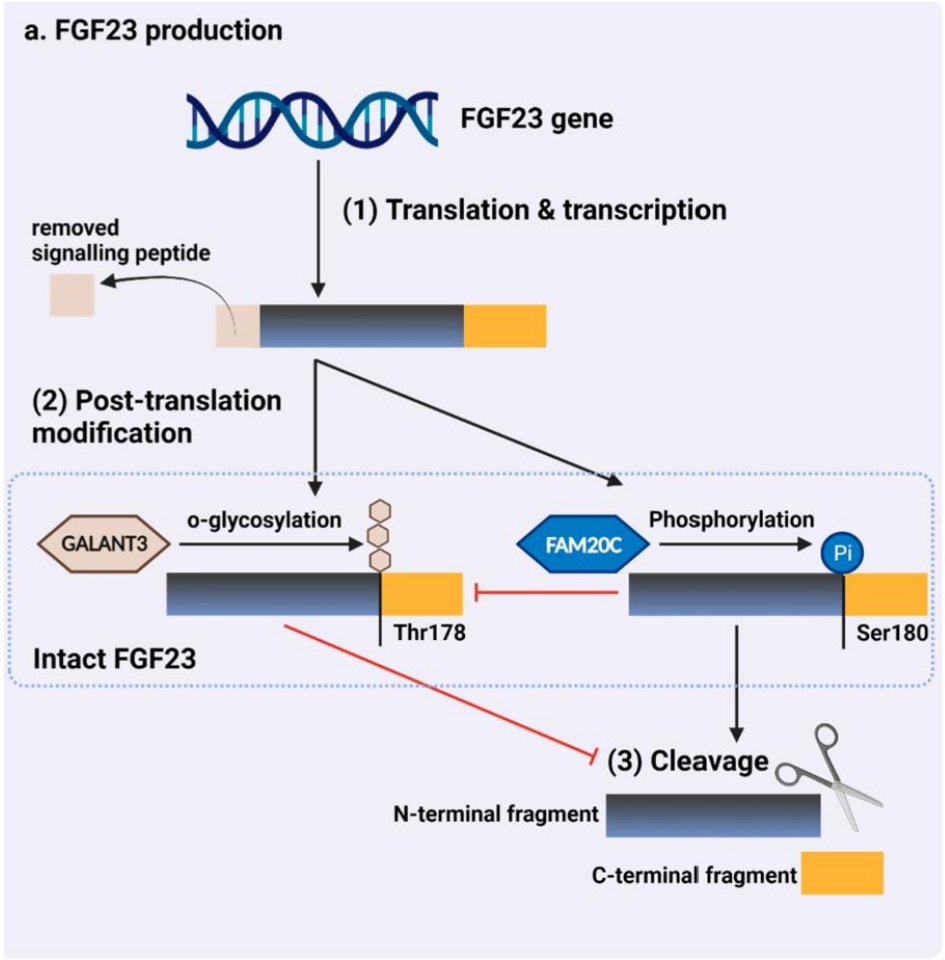
Jury still out on whether FGF23 is a direct contributor, a useful biomarker, or neither

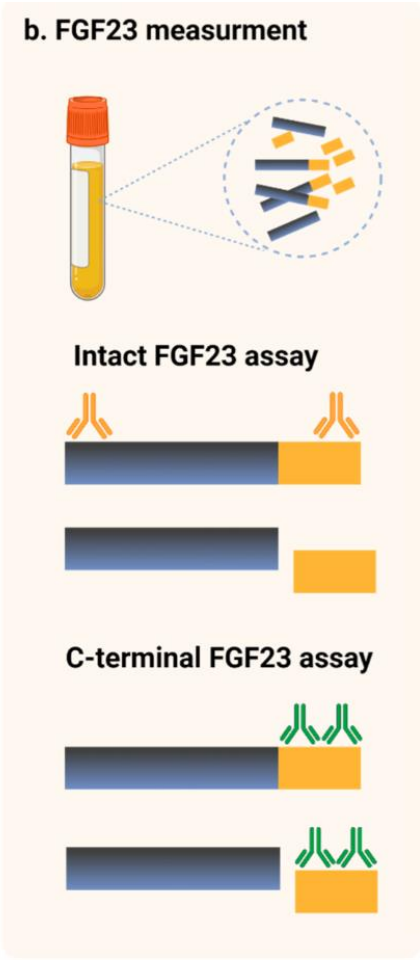
Kidney International (2021) 100, 989–993.

- ✓ ***Despite these seemingly compelling data, however, it remains unclear whether FGF23 has a causal role in adverse events and whether FGF23 serves as a useful predictor of poor outcomes or a reliable biomarker of disordered phosphate metabolism.***
- ✓ In this article, we present various arguments that plead ***against the role of FGF23*** as a causal actor in CKD associated pathologies.

Fibroblast growth factor 23, the time is right for a second wind
Kidney International (2021) 100, 986–989;

- ✓Like many novel discoveries, the recognition of a clinically relevant role of fibroblast growth factor 23 (FGF23) in nephrology was welcomed with almost untamed enthusiasm.
- ✓ ***Indeed,*** initial findings were ***stunning*** on several levels.
- ✓***First,*** the rise of circulating FGF23, as chronic kidney disease (CKD) progresses, is exponential, reaching values up to 1000-fold higher for patients with ESRD than for healthy controls.
- ✓***Second,*** etiology-based analyses of observational data from many independent cohorts of patients with varying degrees of severity of kidney failure consistently revealed an unprecedented effect size of the associations of FGF23 with clinical end points.
- ✓ Importantly, adjustment for potential confounders did not mitigate the effect size but increased it.
- ✓ ***Finally,*** an ever-increasing number of experimental studies provided, by revealing molecular mechanisms that may be involved, the biological plausibility for the clinical observations.





✓cFGF23 vs iFGF23

- ✓ Animal studies have shown that an increase in cFGF23 by C-terminal ELISA may be due to the increase in C-terminal fragments acting as an acute-phase reactant under stressful conditions because iFGF23 was not elevated [78].

- ✓ This concept in CKD patients is still uncertain and needs to be confirmed.

✓ Go to:

THANK YOU