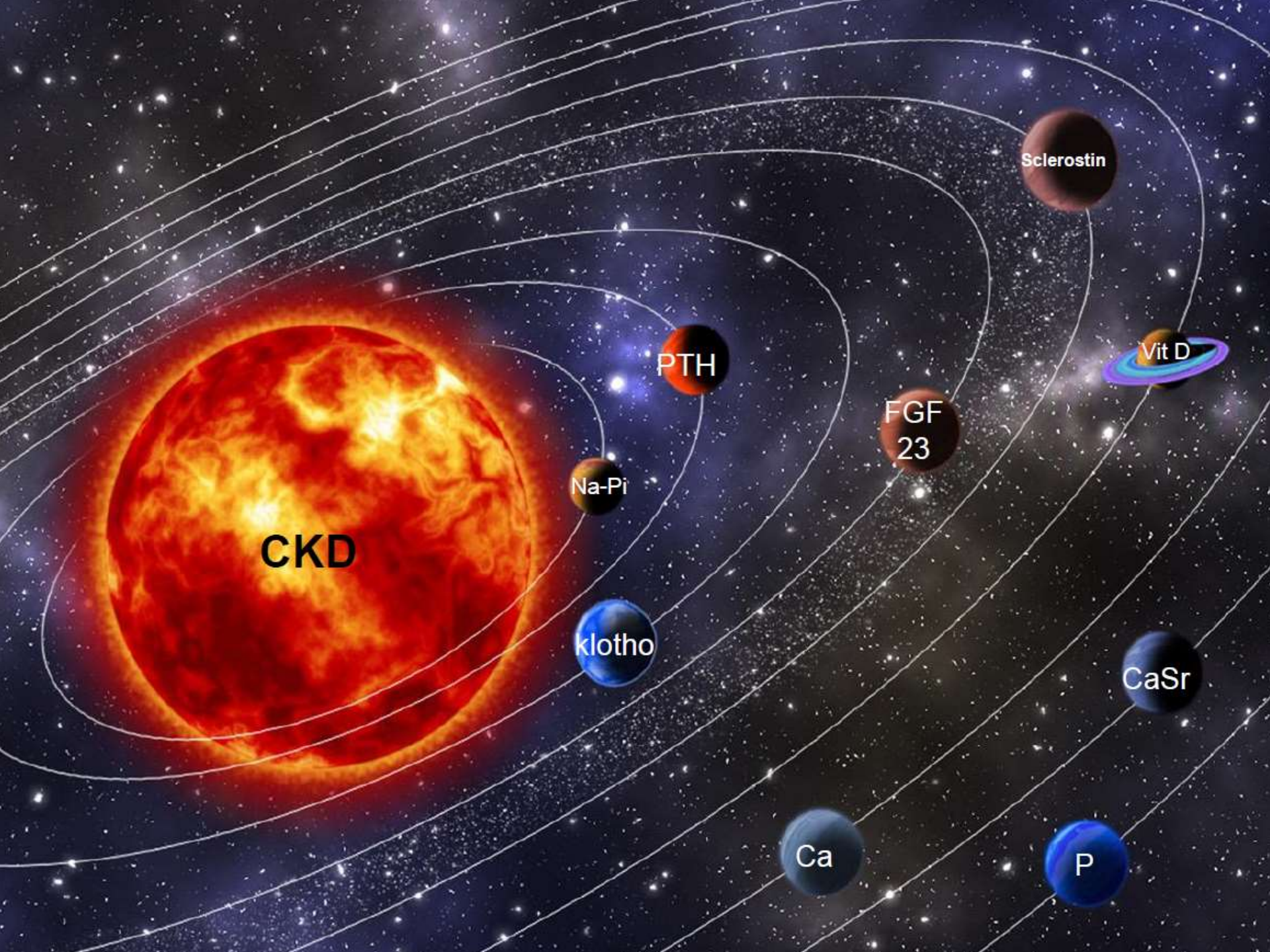
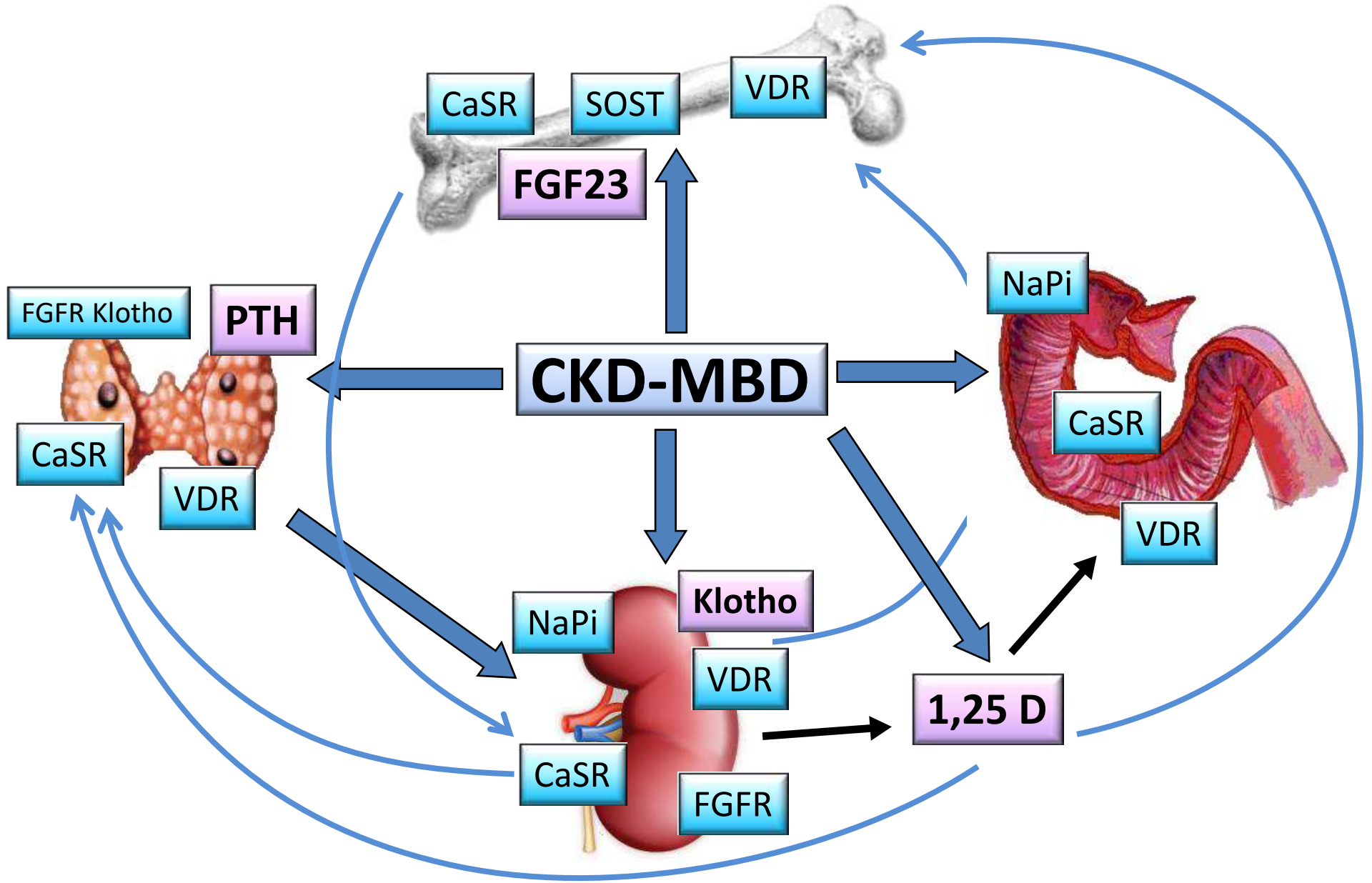
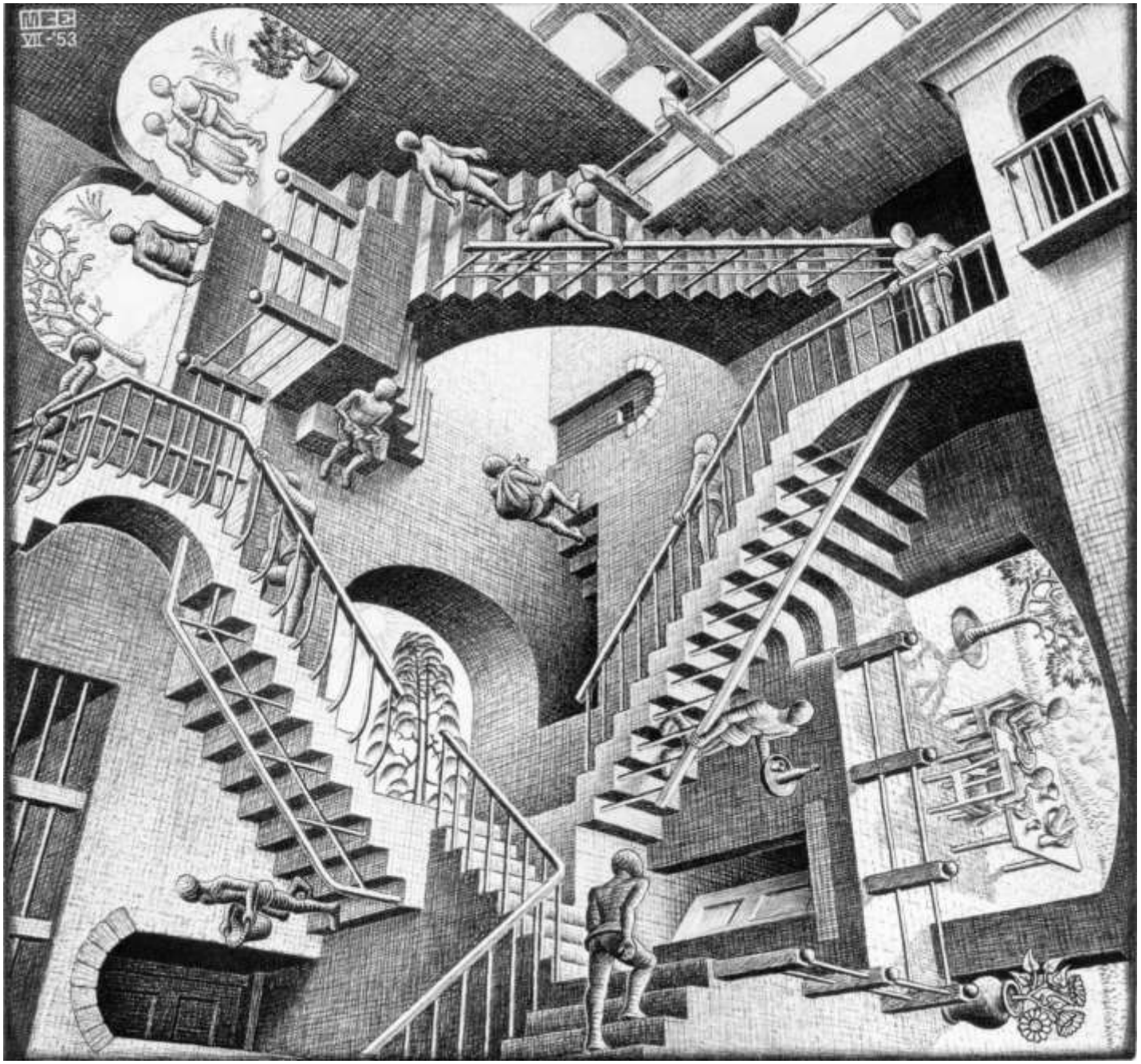
Fisiopatologia del metabolismo minerale: ruoli e interazioni di Calcio, Fosforo e PTH

Dott. G Cianciolo , Dott.ssa V Aiello


Sclerostin
Vit D
PTH
FGF
23
Na-Pi
CKD
klotho
CaSr
Ca
P

CKD-MBD


CaSR
SOST
VDR
FGF23
FGFR Klotho
PTH
CaSR
VDR
CKD-MBD
NaPi
CaSR
VDR
NaPi
Klotho
VDR
CaSR
FGFR
1,25 D


MCE
VII-'53

NEAL S. BRICKER, M.D., PETER A. F. MORRIN, M.B., B.CH., and S. WESLEY KIME, JR., M.D.
St. Louis, Missouri

The Pathologic Physiology of Chronic Bright's Disease*

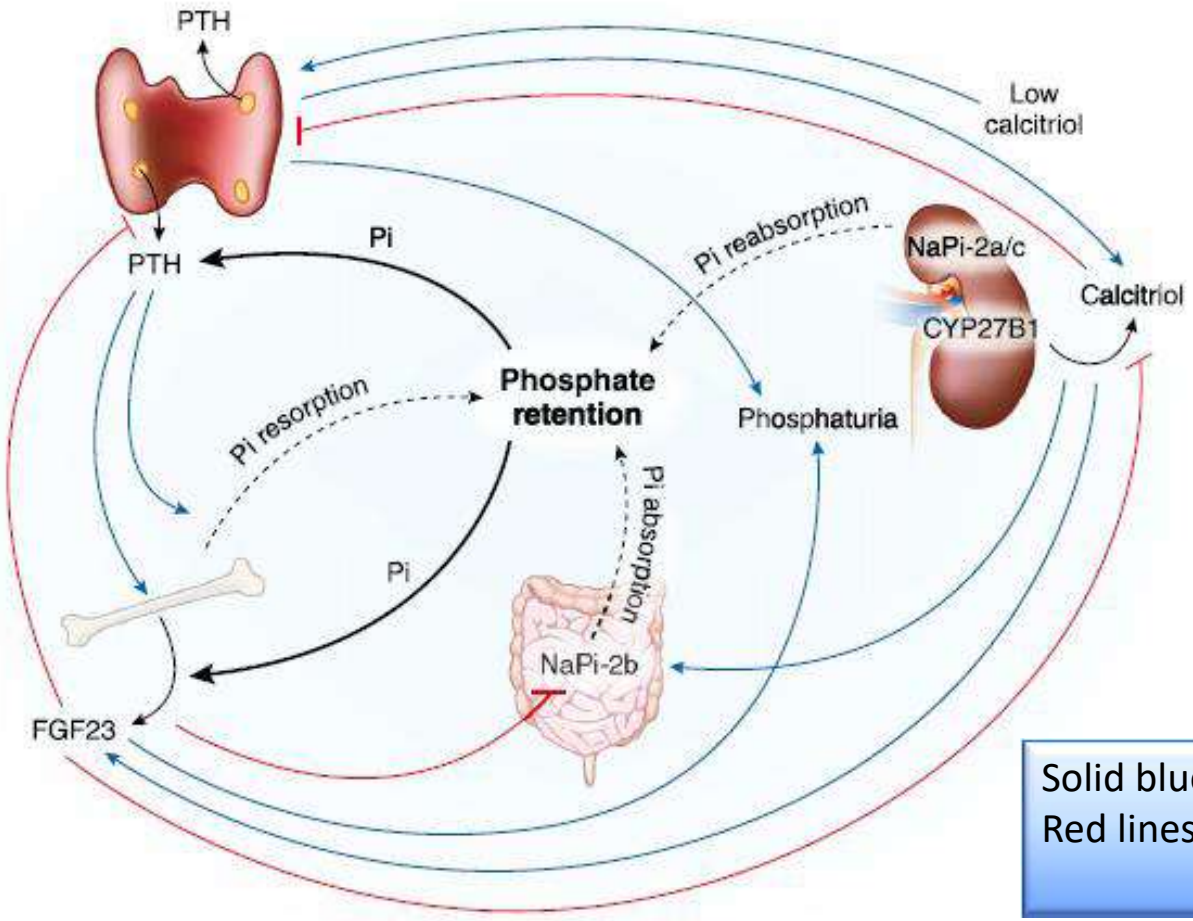
An Exposition of the "Intact Nephron Hypothesis"

"Intact nephron hypothesis" states that, although the diseased kidney consists of a diminished number of nephrons, the remaining nephrons are functionally normal.

To maintain homeostasis of any given solute, renal function of the dis eased kidney must undergo adaptive changes, wherein the excretion rate of each functioning nephron must increase progressively to compensate for damaged Nephrons.

However, a biologic price is paid for these adaptive changes As Bricker proposed in his "trade off hypothesis,"increasing nephron function to maintain solute homeostasis can result in abnormalities of the uremic state that will adversely contribute to the uremic syndrome.

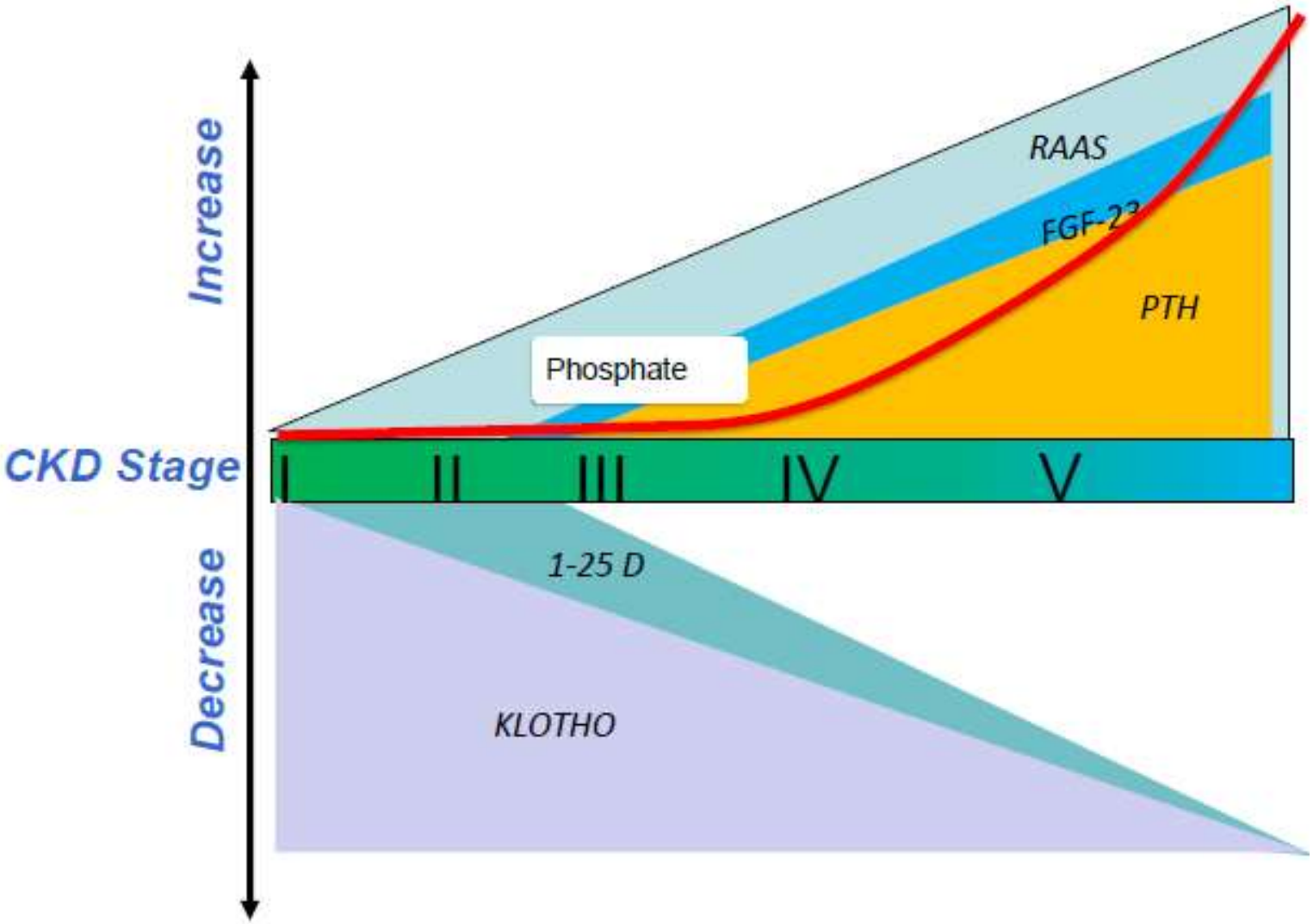
Phosphate homeostasis: A complex crosstalk between the kidney, parathyroid gland (PTG), bone, and intestine



Solid blue lines = stimulation
Red lines = inhibition

Cynthia S. Ritter and Eduardo Slatopolsky - Clin J Am Soc Nephrol, 2016

Variations in FGF23, Klotho, PTH, active vitamin D, and phosphate levels during the progression of CKD



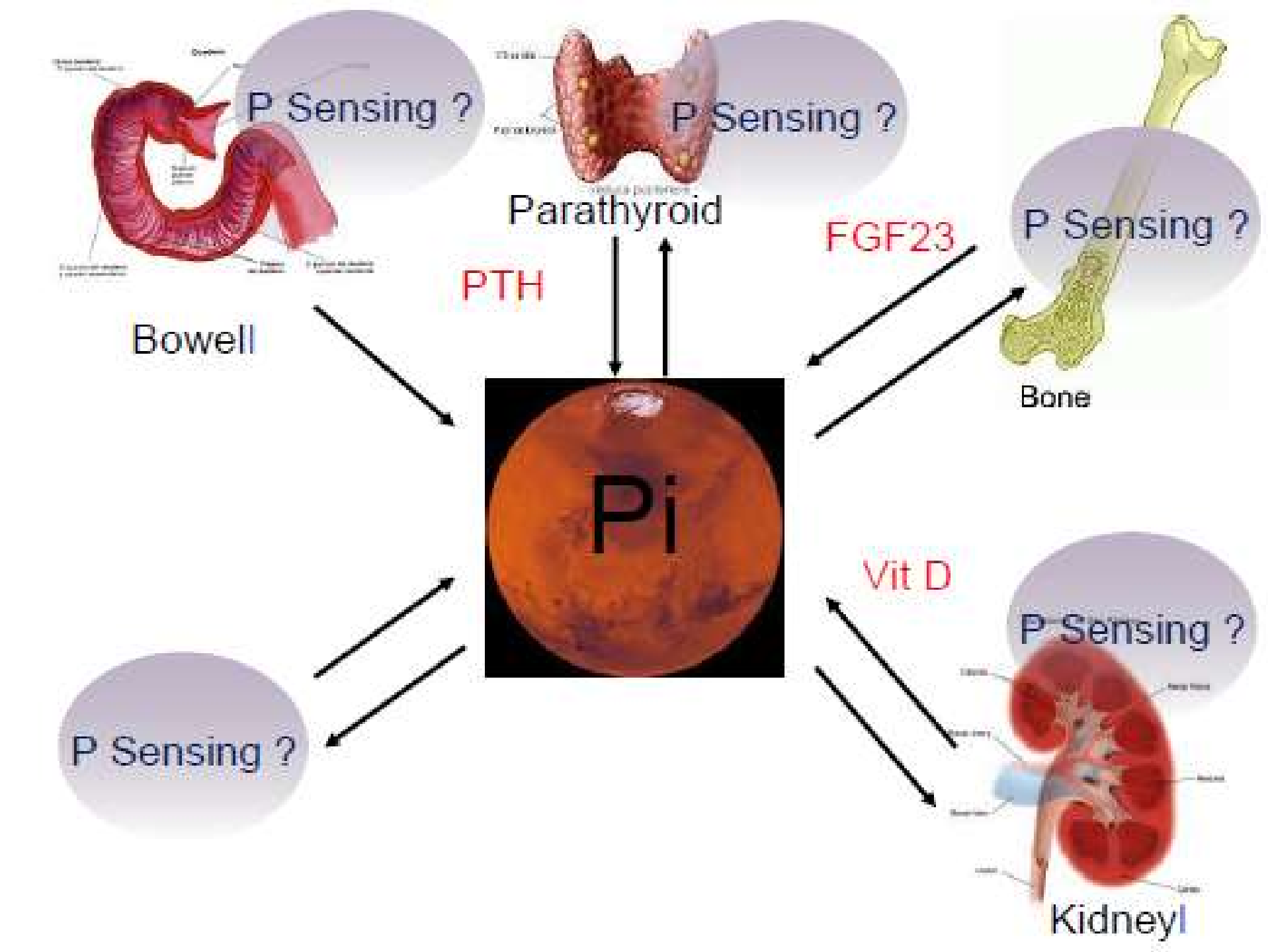
Modified from Donate Correa J et al, Cytokine & Growth Factor Reviews 2012

GUEST EDITORIAL

The Flux of Phosphate: Rapid Evolution

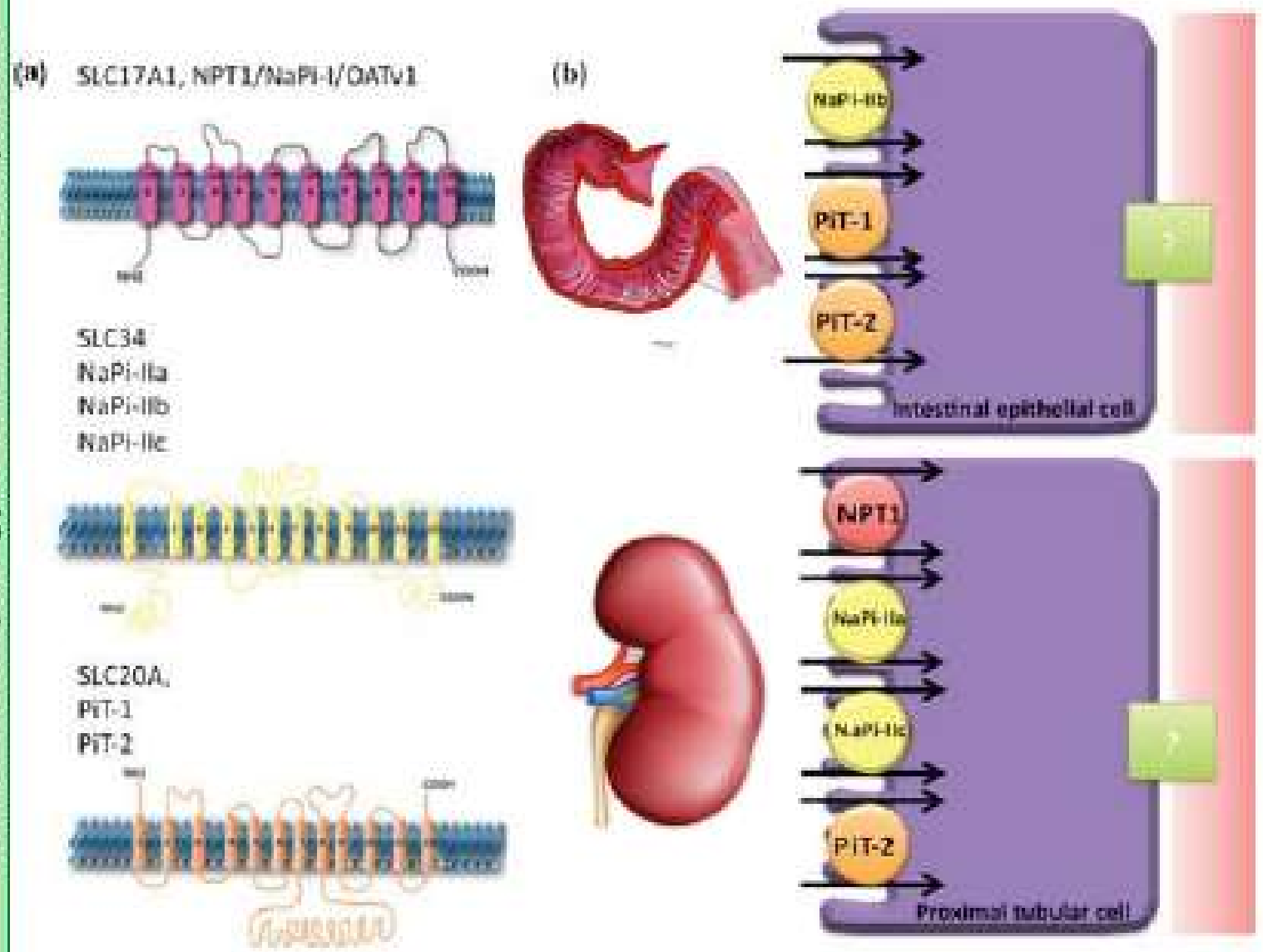
…how does the body "know" how much phosphorus to keep and how much to excrete?

Modified from Donate Correa J et al, Cytokine & Growth Factor Reviews 2012

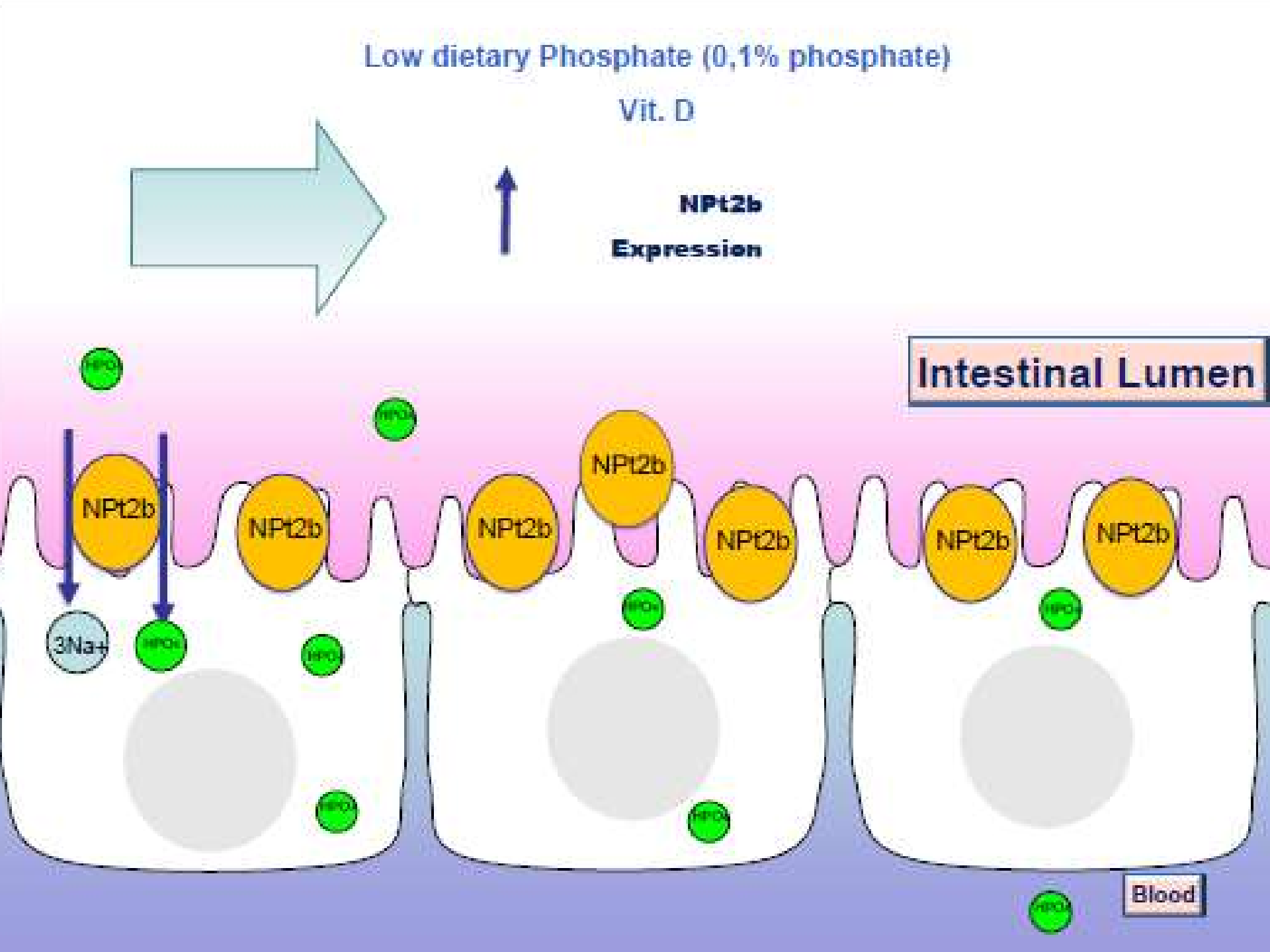

P Sensing ?
P Sensing ?
Parathyroid
P Sensing ?
FGF23
PTH
Bowell
Bone
Pi
Vit D
P Sensing ?
P Sensing ?
Kidneyl

Sodium dependent NaPi-cotransporters

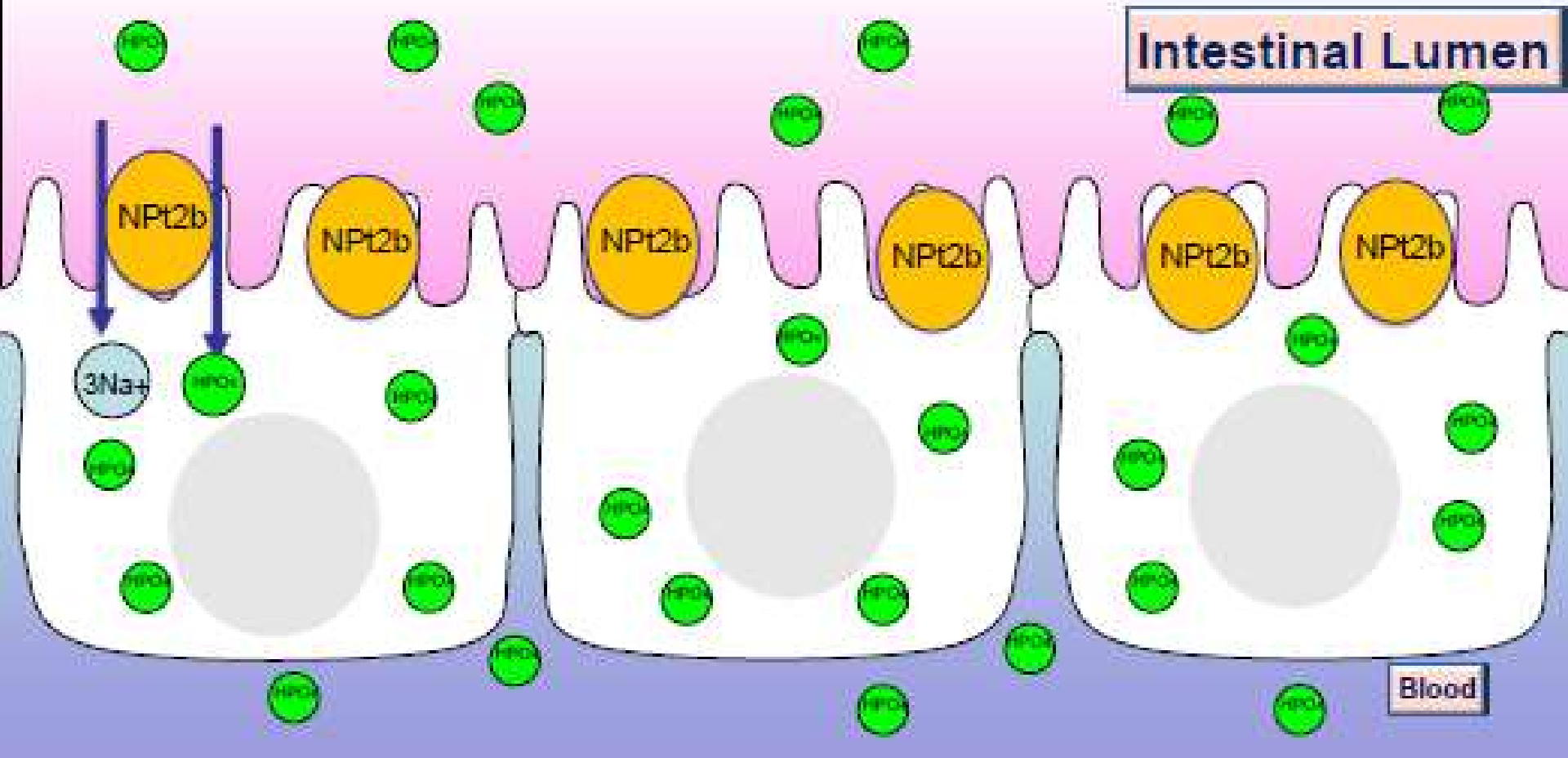
Membrane topology of the NaPi transporters



Localization of the NaPi transporters in the intestine and the kidney.


Low dietary Phosphate (0,1% phosphate)
Vit. D
NPt2b
Expression
Intestinal Lumen
NPt2b
NPt2b
NPt2b
NPt2b
NPt2b
NPt2b
NPt2b
3Na+
Blood

LOW to HIGH dietary Phosphate (0,1% phosphate)

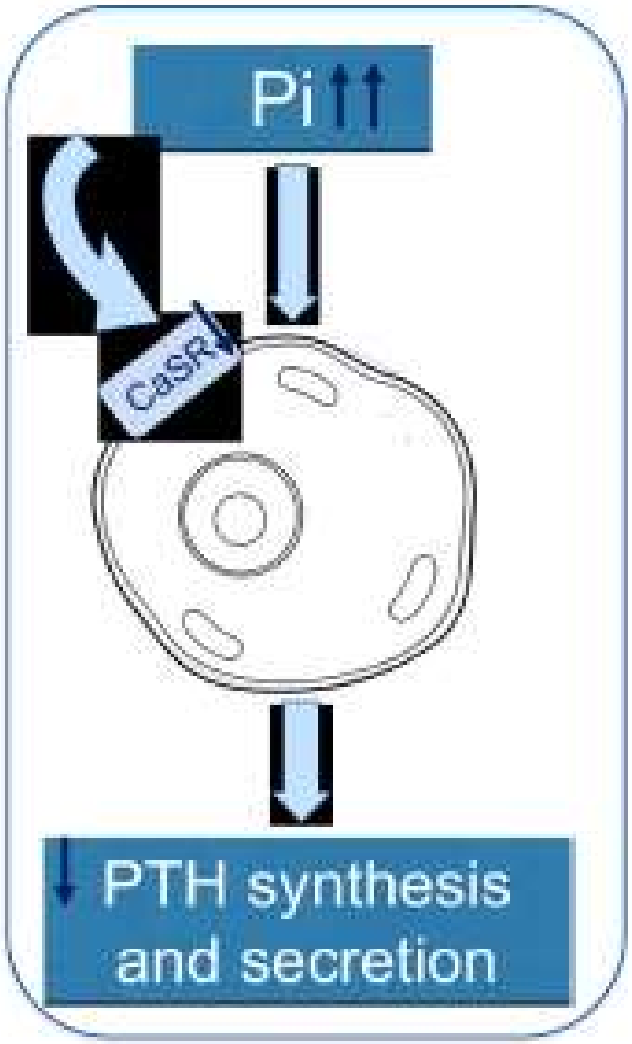


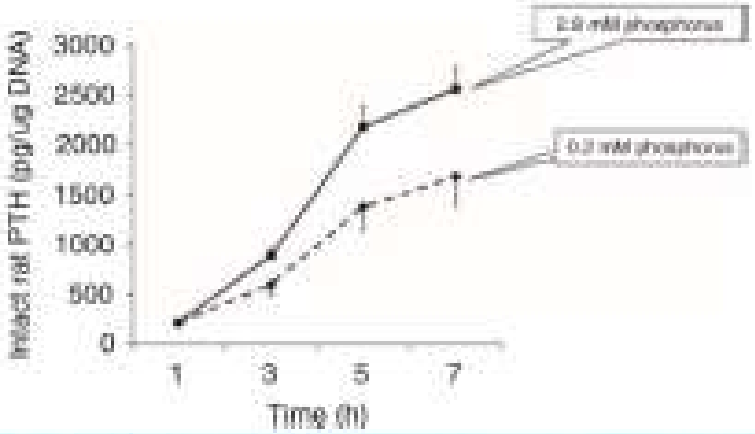
Open

The intact nephron hypothesis: the concept and its implications for phosphate management in CKD-related mineral and bone disorder

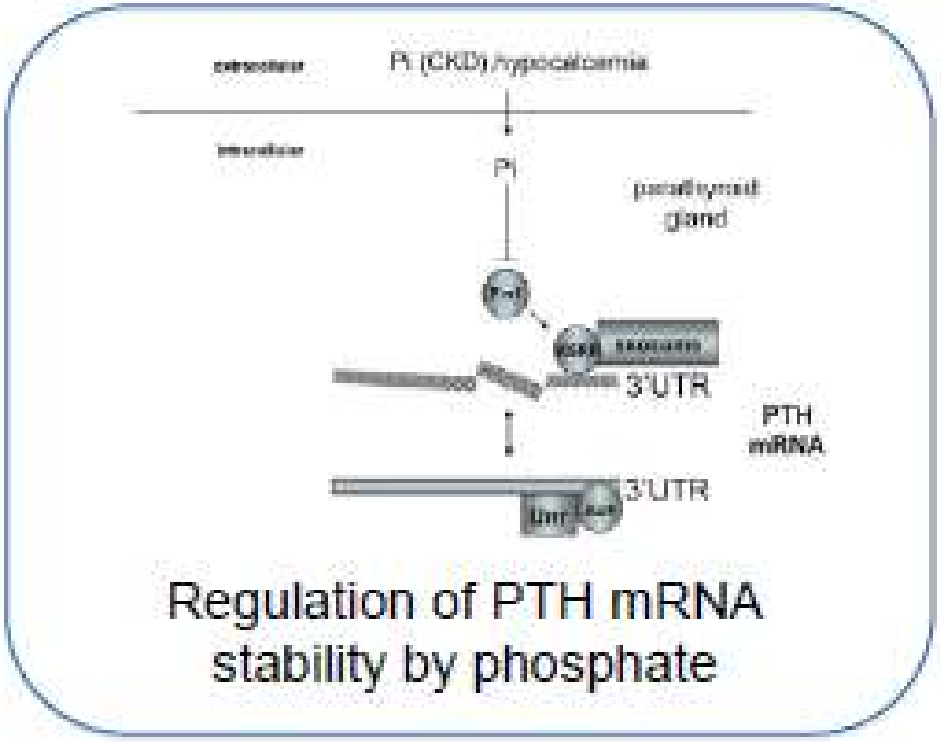
Eduardo Slatopolsky[1]

[1]Renal Division, Department of Internal Medicine, Washington University School of Medicine, St Louis, Missouri, USA



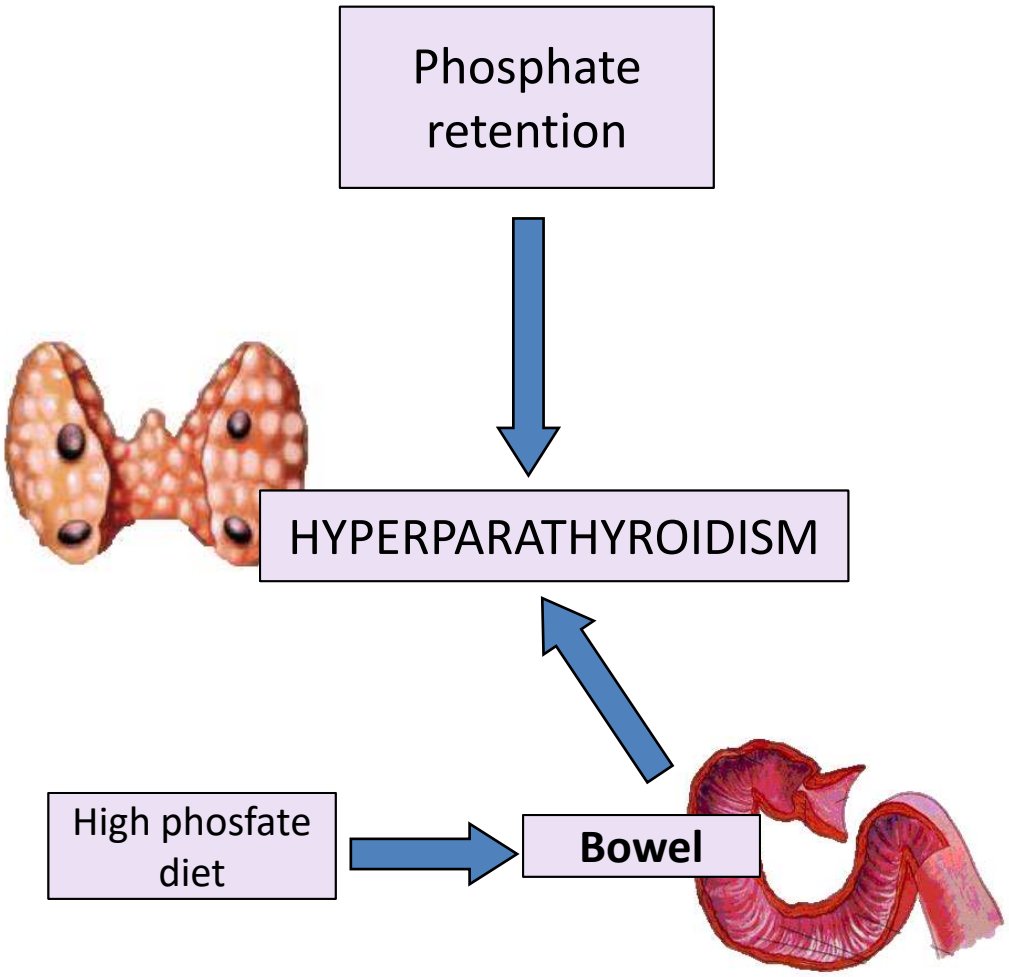


The effects of phosphorus on the secretion of parathyroid hormone in a normal rat parathyroid gland in vitro.



Regulation of PTH mRNA stability by phosphate

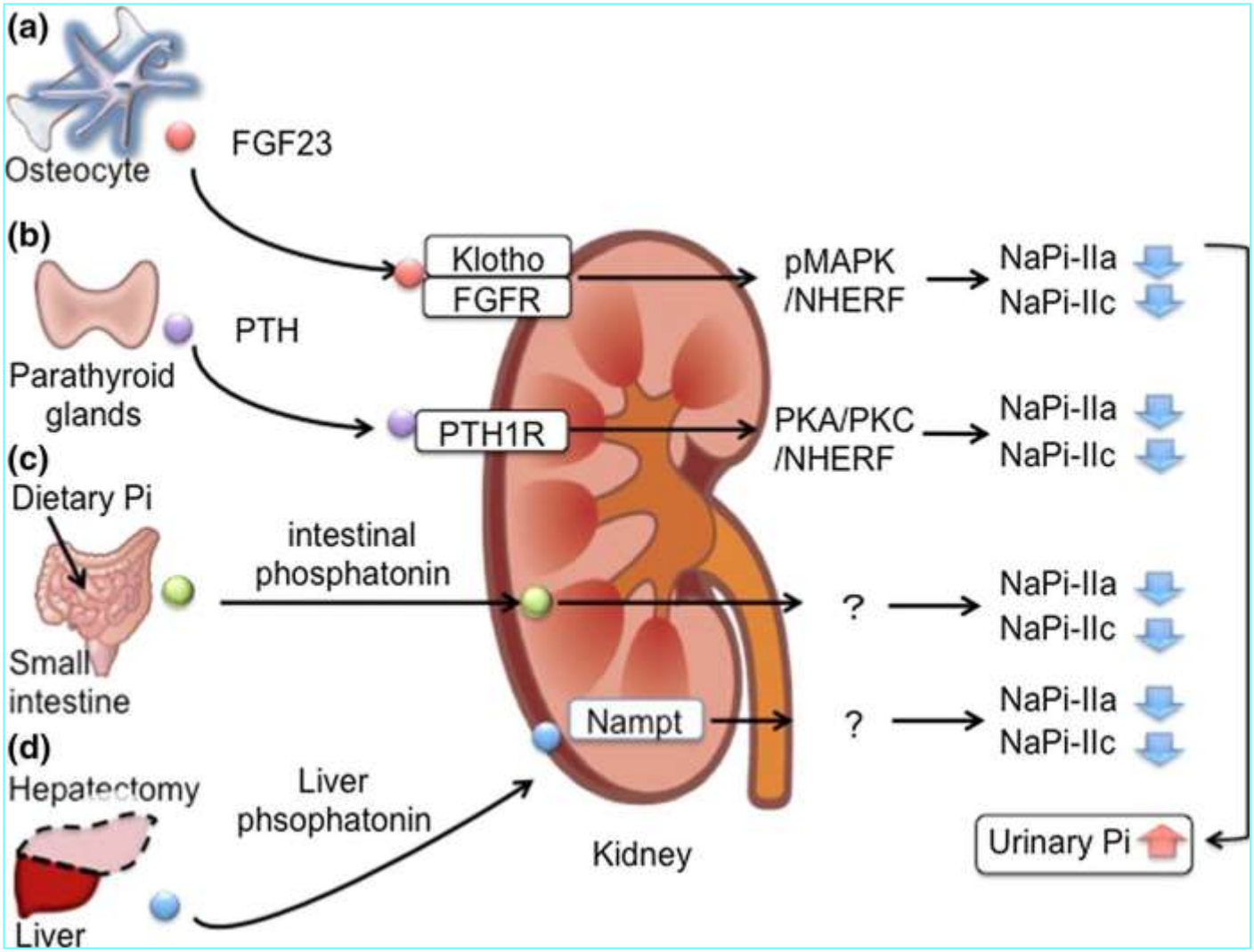
PHOSPHATE PARATHYROID INTESTINAL RENAL AXIS



'Is there an acute regulation of PTH by dietary phosphate , and if so, is it mediated by a hormone possibly derived from the gastrointestinal tract?'

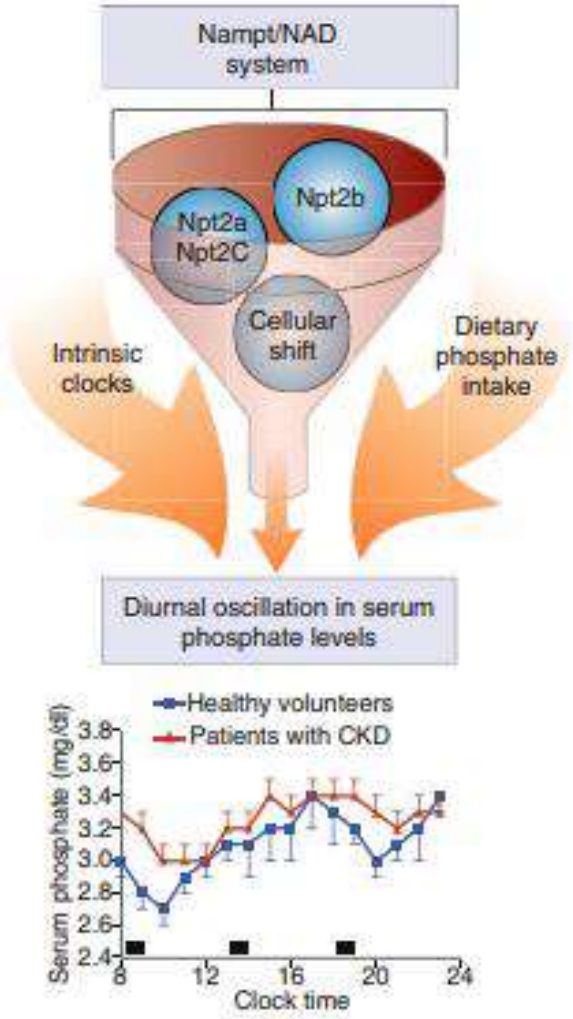
Slatopolsky Kidney International, 2011

Regulation of renal reabsorption by the inter organ communication



Sawako Tatsumi et al. J Bone Miner Metab 2016

Complex regulation of serum phosphate levels throughout the day

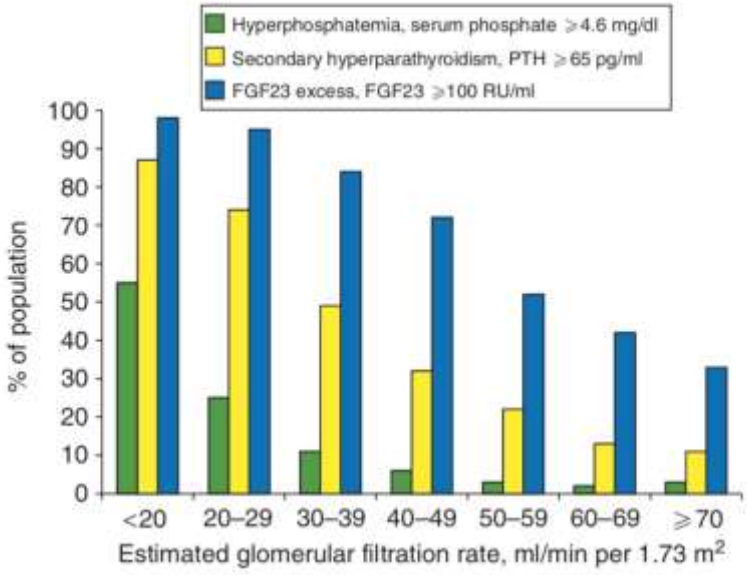


Diurnal variability of serum phosphate levels is preserved in patients with chronic kidney disease (CKD) and is likely influenced by a complex cross talk between intrinsic molecular clock networks, dietary phosphate intake, and the effects of the Nampt /nicotinamide adenine dinucleotide (NAD)þ system on renal and intestinal sodium phosphate transporters and on cellular shifts of phosphate in tissues such as the liver. Reproduced with permission from Isakova T, Xie H, Barchi Chung A, et al. Daily variability in mineral metabolites in CKD and effects of dietary calcium and calcitriol

original article http://www.kidney-international.org

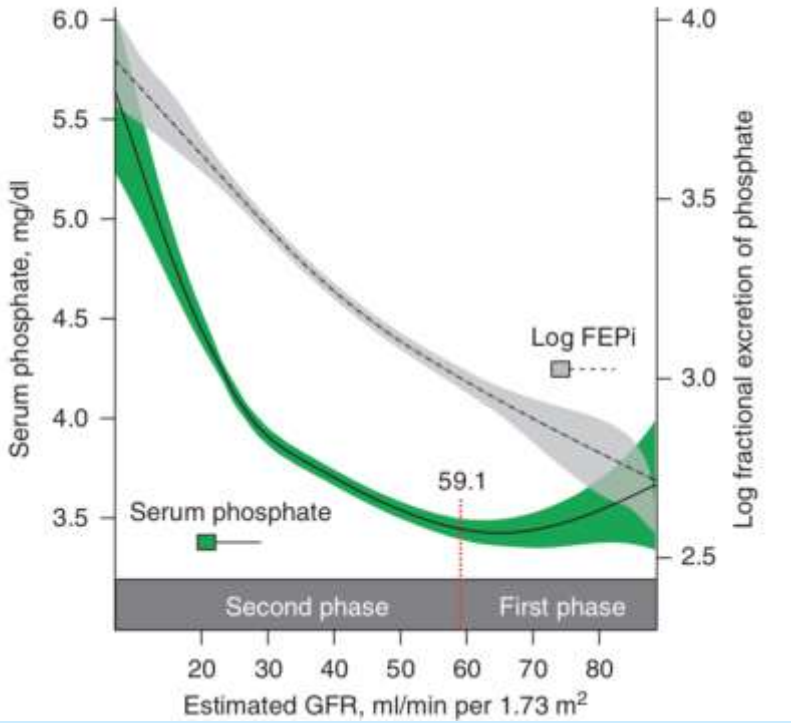
Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease

Tamara Isakova[1], Patricia Wahl[1], Gabriela S. Vargas[1], Orlando M. Gutiérrez[1], Julia Scialla[2], Huiliang Xie[3], Dina Appleby[4], Lisa Nessel[4], Keith Bellovich[5], Jing Chen[6,7], Lee Hamm[7], Crystal Gadegbeku[8], Edward Horwitz[9], Raymond R. Townsend[10], Cheryl A.M. Anderson[2], James P. Lash[11], Chi-yuan Hsu[12], Mary B. Leonard[4,13] and Myles Wolf[1], on behalf of the Chronic Renal Insufficiency Cohort (CRIC) Study Group



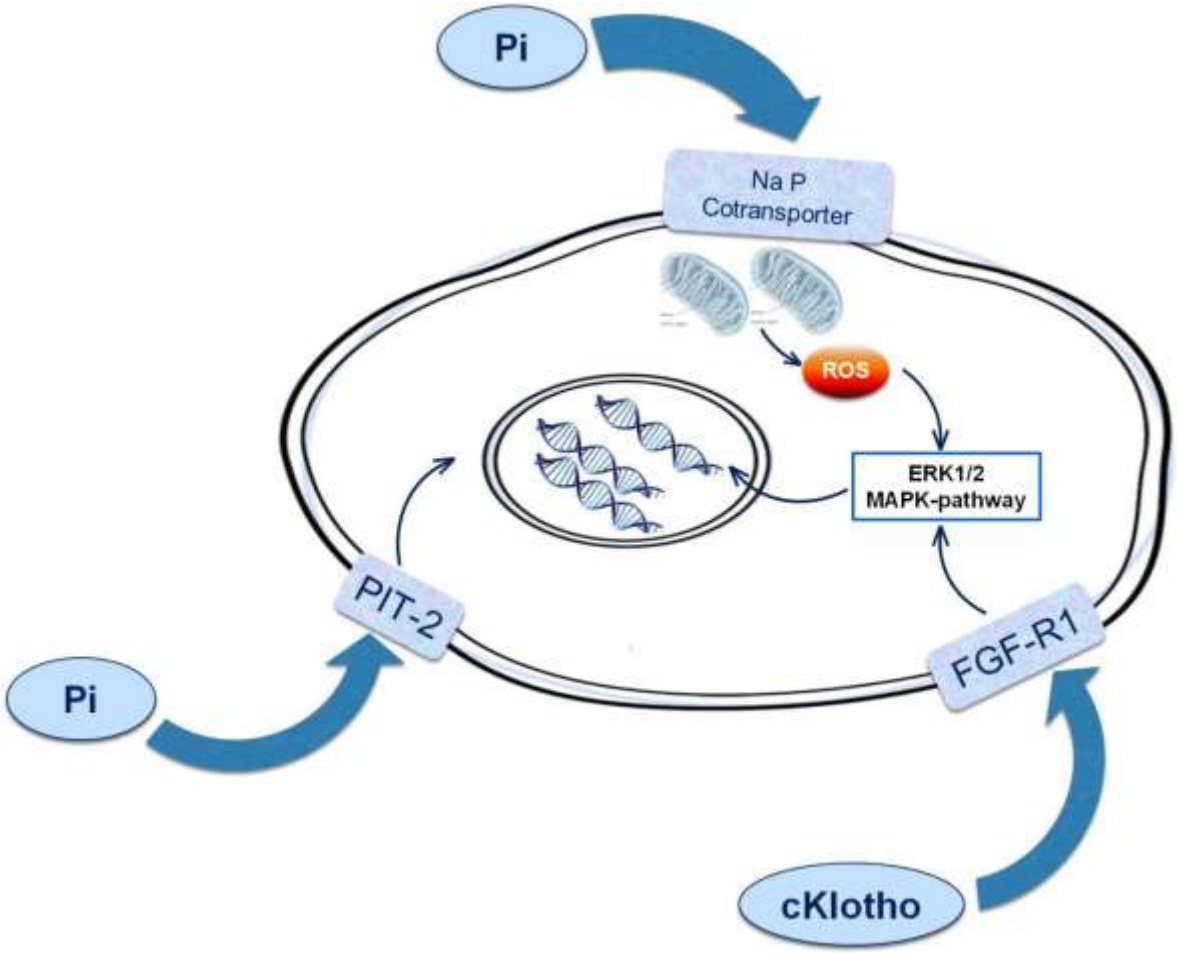
Prevalence of hyperphosphatemia, secondary hyperparathyroidism, and elevated fibroblast growth factor 23 (FGF23) in relation to estimated glomerular filtration rate (eGFR).

Cubic spline functions of the associations between serum phosphate and log fractional excretion of phosphate (FEPi) with estimated glomerular filtration rate (eGFR)



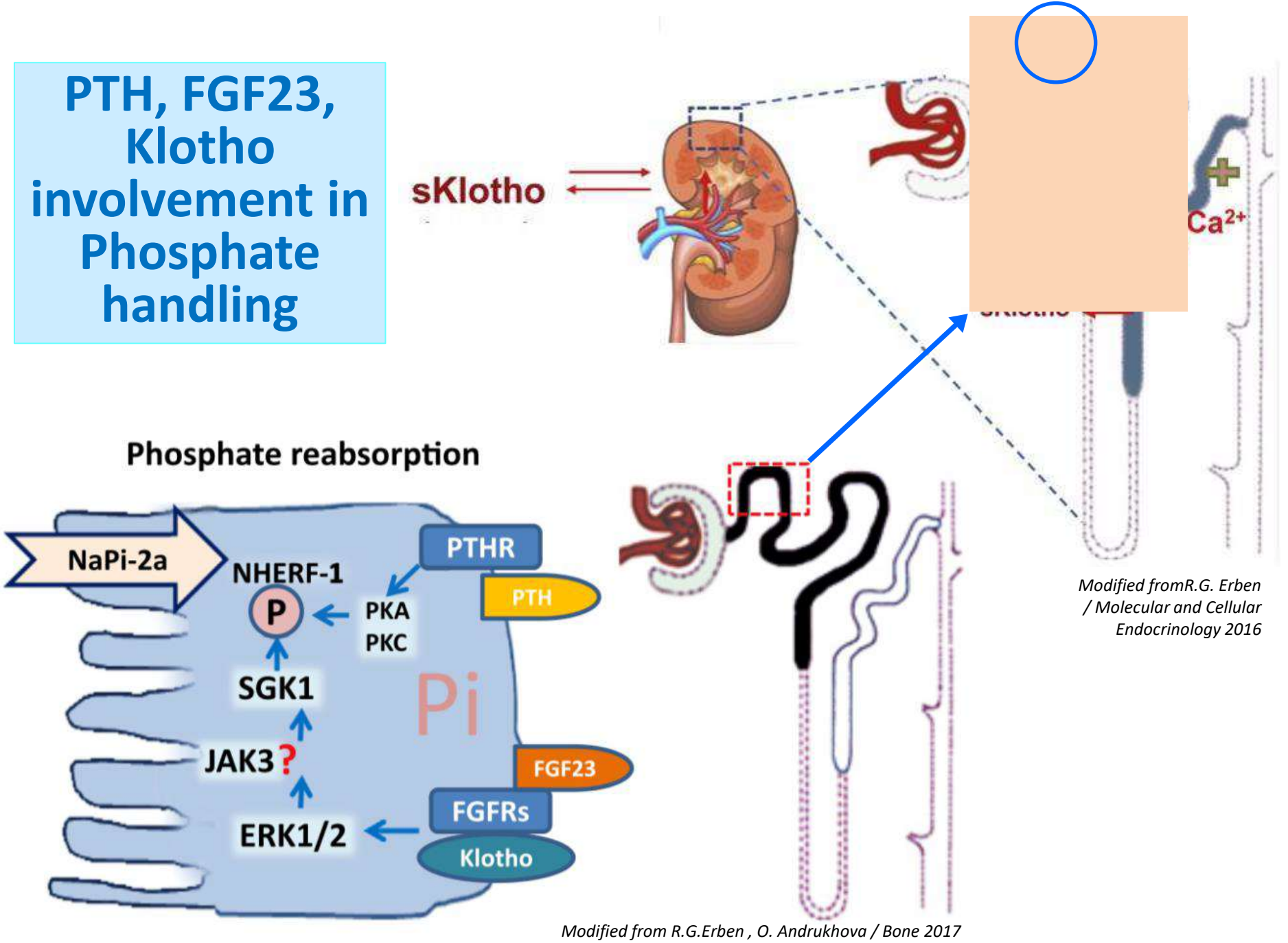
T Isakova et al. Kidney International 2011

Putative pathways involved in FGF23 expression



RC Smithet al. J Clin Invest 2012
M.Hori et al. J Bone Mineral Metabol 2016
Bon N. et al.Mol Metabolism 2018national, 2011

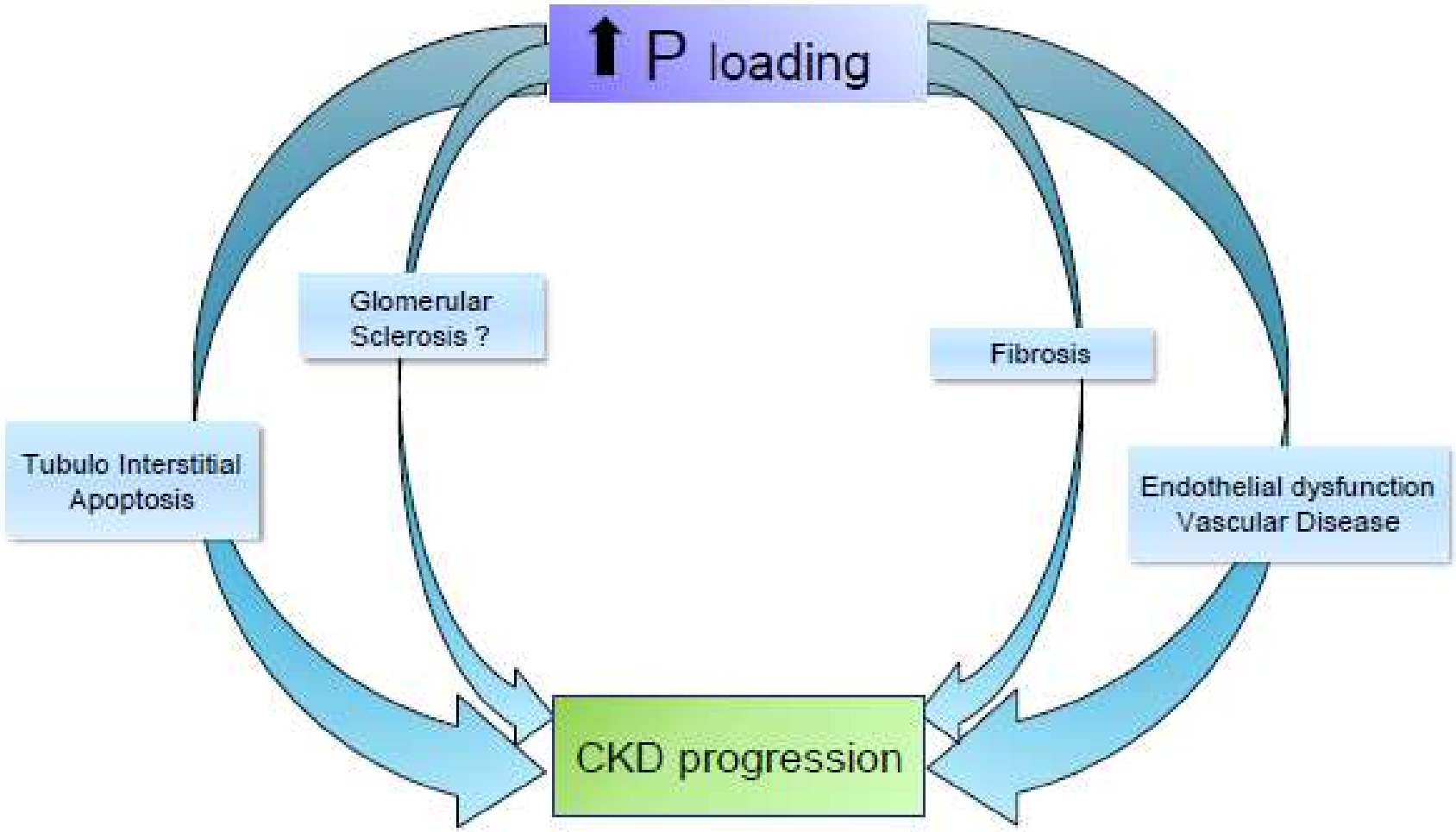
PTH, FGF23, Klotho involvement in Phosphate handling



Modified fromR.G. Erben / Molecular and Cellular Endocrinology 2016

Modified from R.G.Erben , O. Andrukhova / Bone 2017

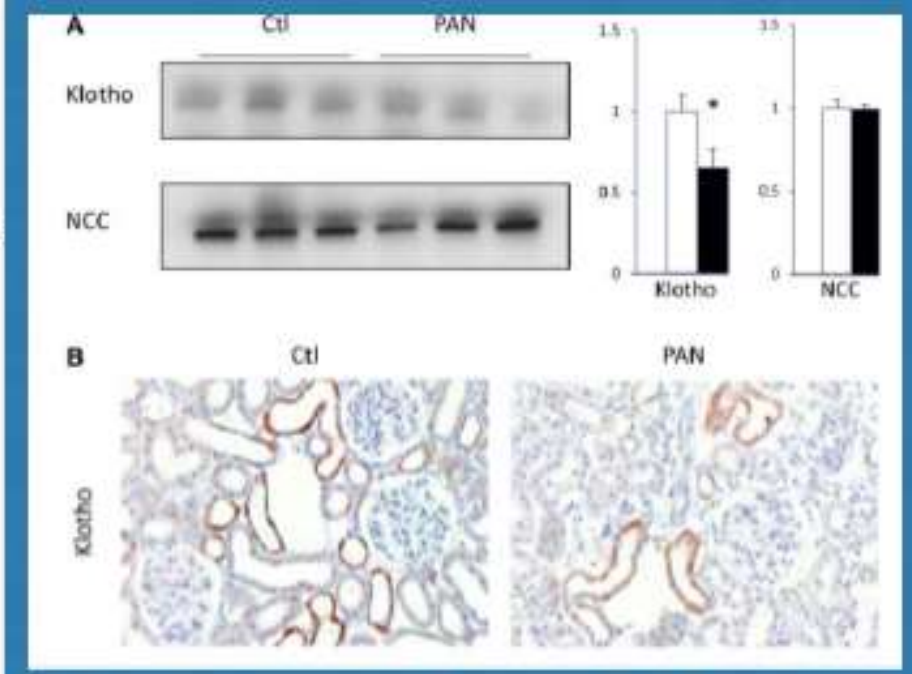
P Loading and CKD Progression



BASIC RESEARCH www.jasn.org

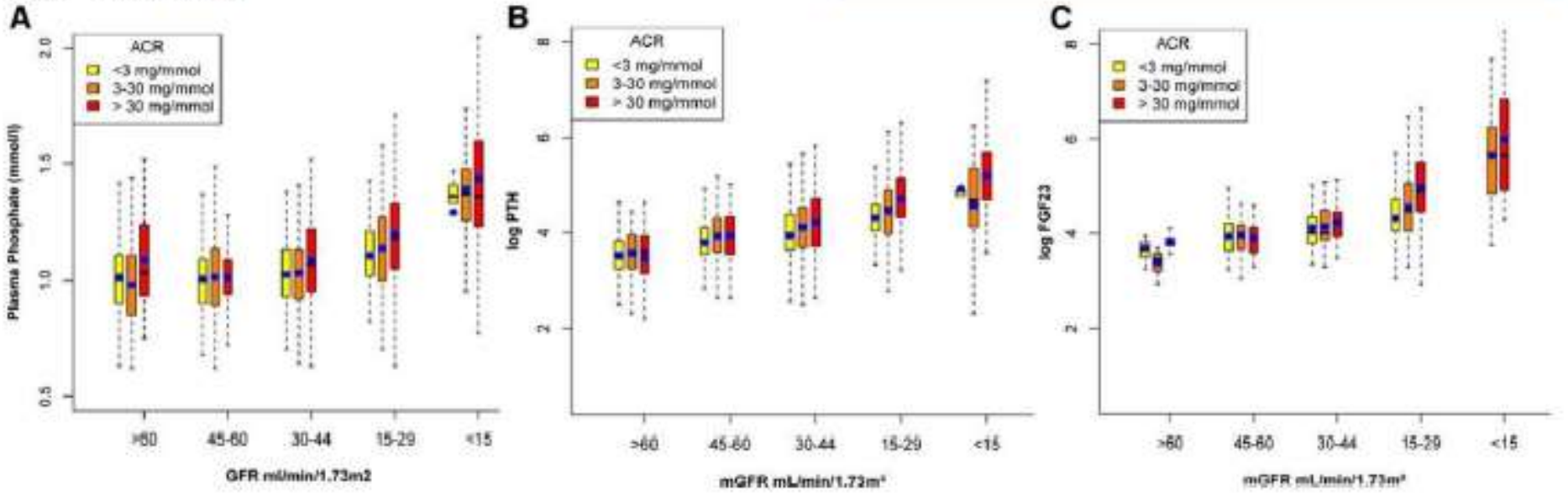
Proteinuria Increases Plasma Phosphate by Altering Its Tubular Handling

Sophie de Seigneux,*† Marie Courbebaisse,‡§ Joseph M. Rutkowski,‖ Alexandra Wilhelm-Bals,¶ Marie Metzger,** Stellor Nlandu Khodo,* Udo Hasler,* Hassib Chehade,¶ Eva Dizin,† Arezoo Daryadel,†† Bénedicte Stengel,** for the NephroTest Study Group, E. Girardin,¶ Dominique Prié,§‡‡ Carsten A. Wagner,†† Philipp E. Scherer,‖ Pierre-Yves Martin,*† Pascal Houillier,‡ and Eric Feraille*†



Klotho expression is decreased in proteinuric rats

Proteinuric patients with CKD display higher plasma phosphate, PTH, and FGF-23 levels.



ndt

Albumin downregulates Klotho in tubular cells

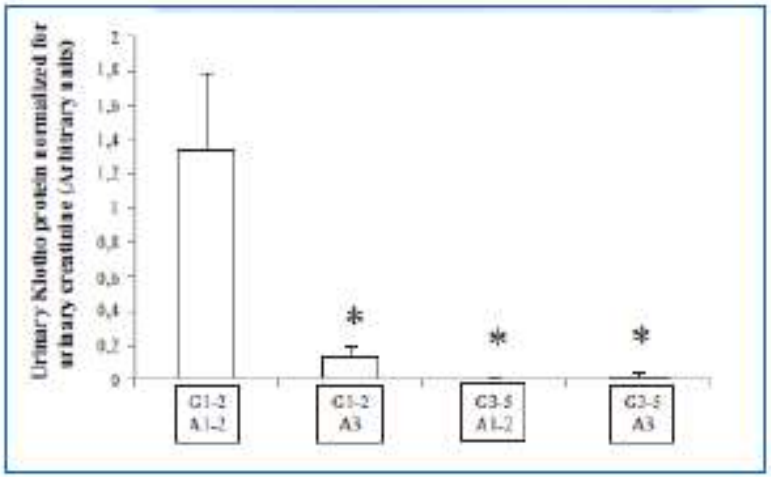
Beatriz Fernandez-Fernandez[1,2,3,*], M. Concepcion Izquierdo[1,3,3,*], Lara Valino-Rivas[1,2,3], Dimitra Nastou[4], Ana B. Sanz[1,3,5], Alberto Ortiz[1,3,5] and Maria D. Sanchez-Niño[1,3,5,5]

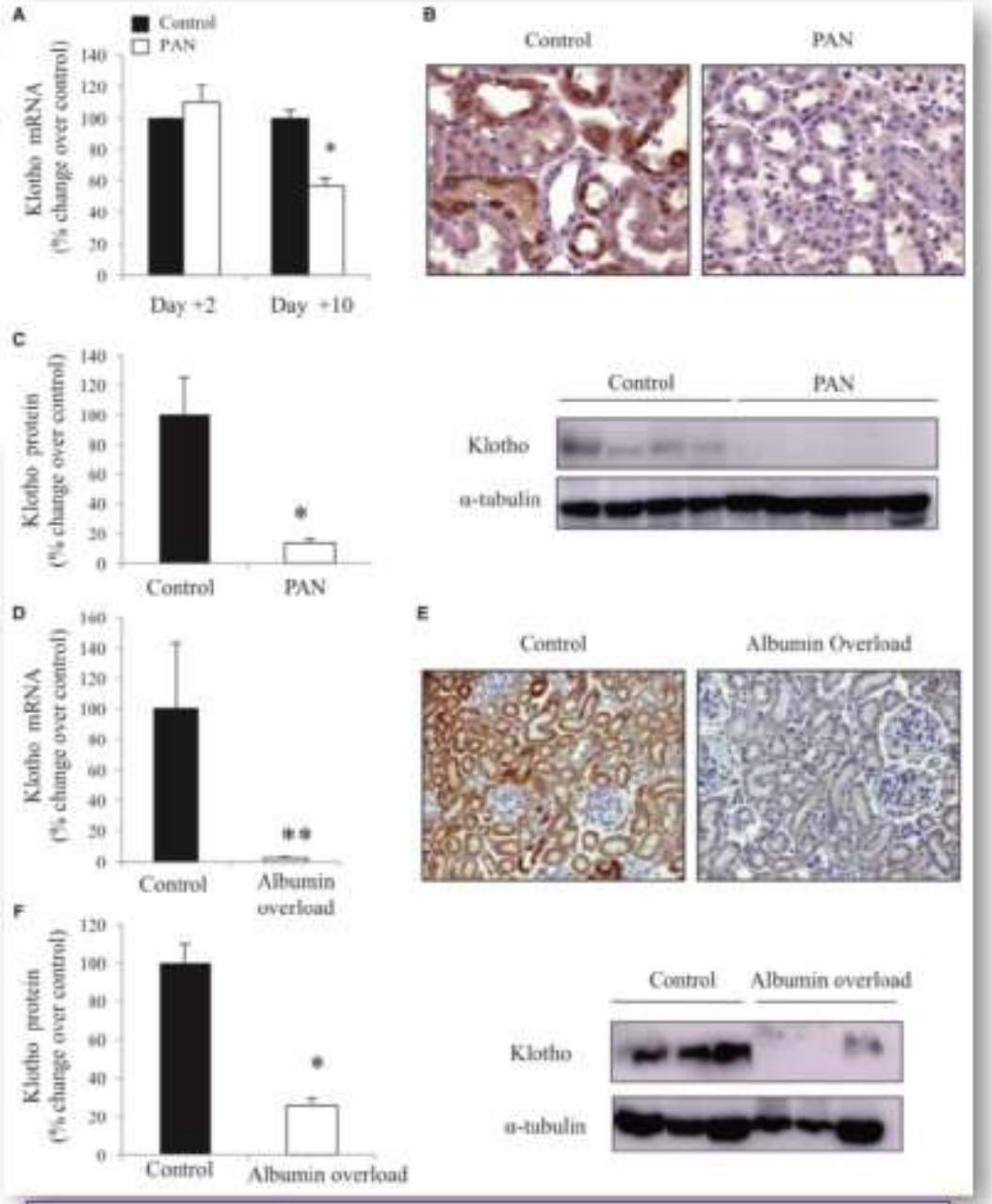
[1]Department of Nephrology, IIS-Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Madrid, Spain, [2]Fundación Gonal Hugo Alvarez de Toledo-IRSIN, Madrid, Spain and [3]REDINREN, Madrid, Spain, [4]Department of Nephrology, General Hospital of Veria, Veria, Greece and [5]Present address: Department of Pathology and Cell Biology, Columbia University, New York, NY, USA

Correspondence and offprint requests to: Maria D. Sanchez-Niño; E-mail: mdsanchez@fjd.es or Alberto Ortiz; E-mail: aortiz@fjd.es

*B.F.-F. and M.C.I. contributed equally to this work.

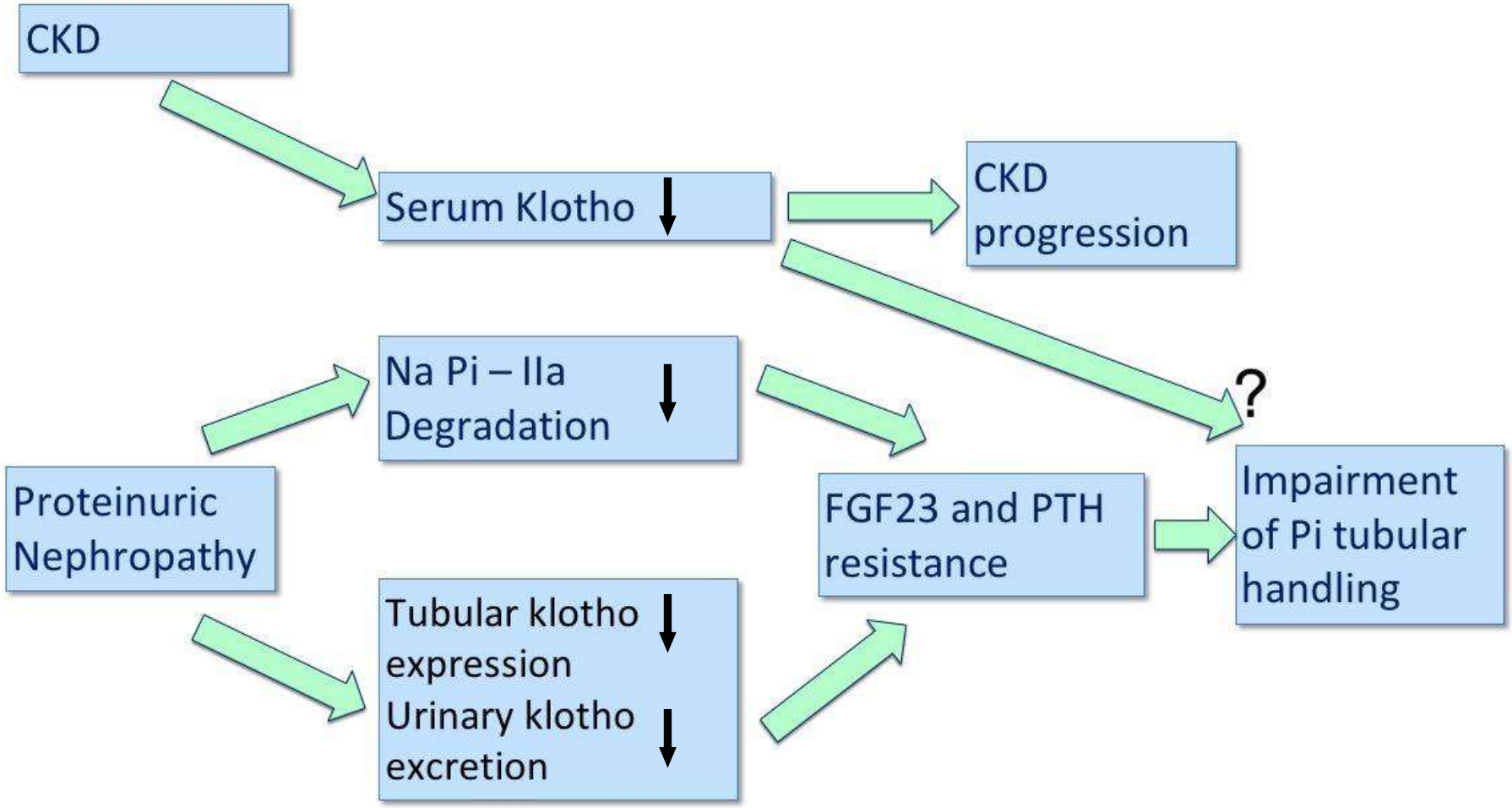
[5]A.O. and M.D.S.-N. contributed equally to this work.





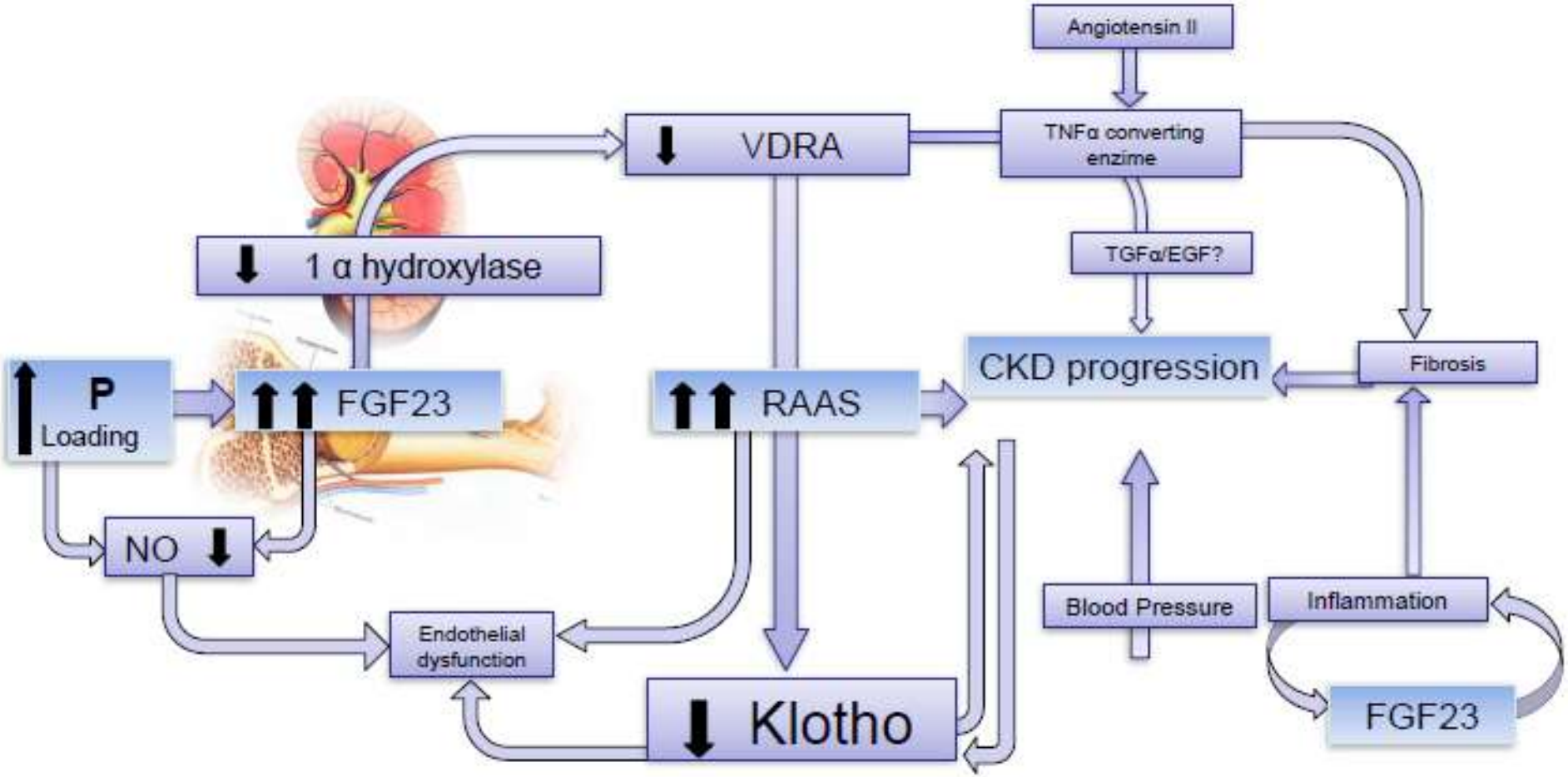
Decreased kidney Klotho expression in experimental proteinuric kidney disease

PROTEINURIA, KLOTHO AND PHOSPHATE TUBULAR HANDLING



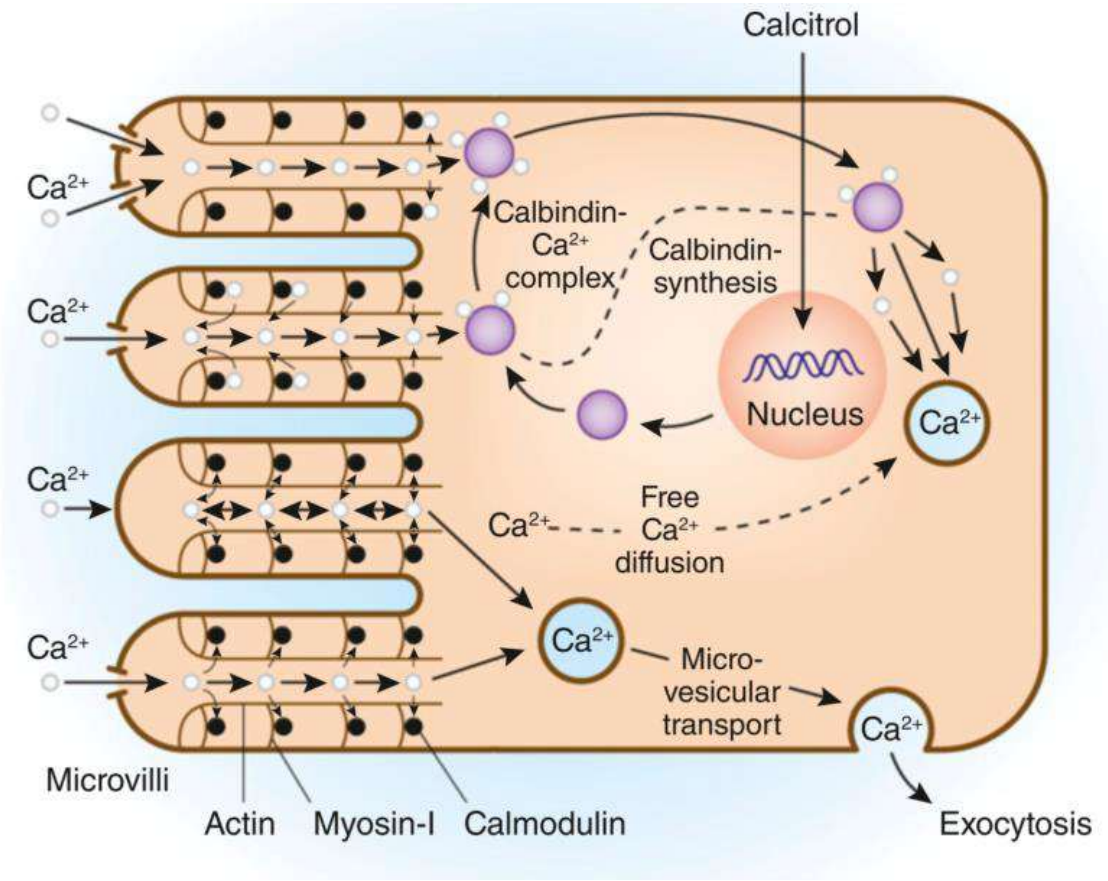
S. De Seigneux et al. JASN 2015
B. Fernandez et al.NDT 2018

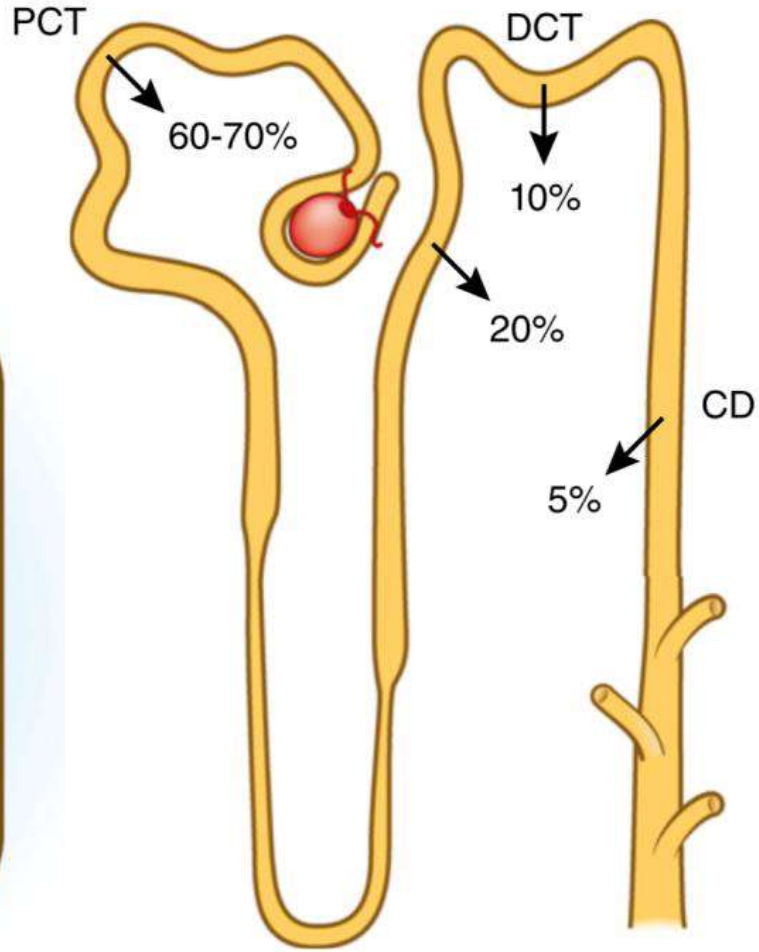
Phosphate , FGF Klotho and RAAS in CKD Progression



Scozzolino et al AJKD 2013

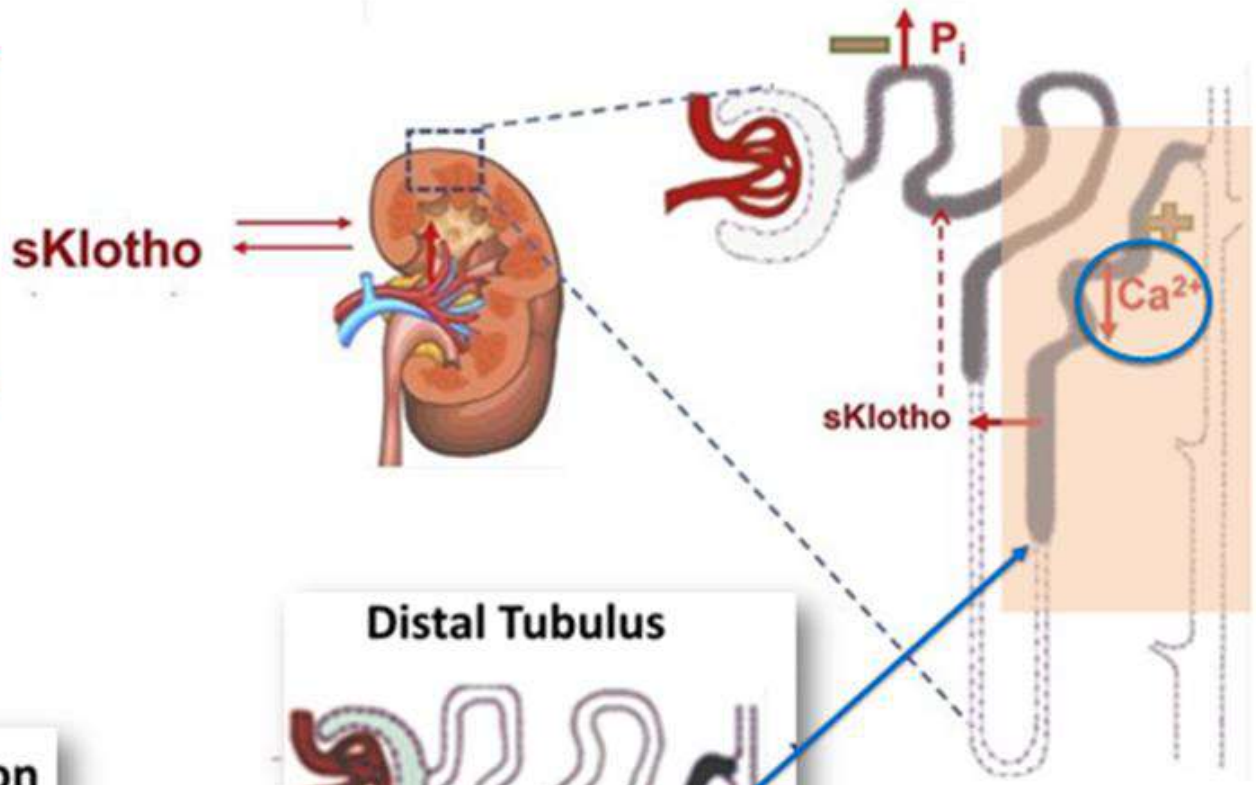
INTESTINAL AND RENAL PATHWAYS FOR CALCIUM ABSORPTION



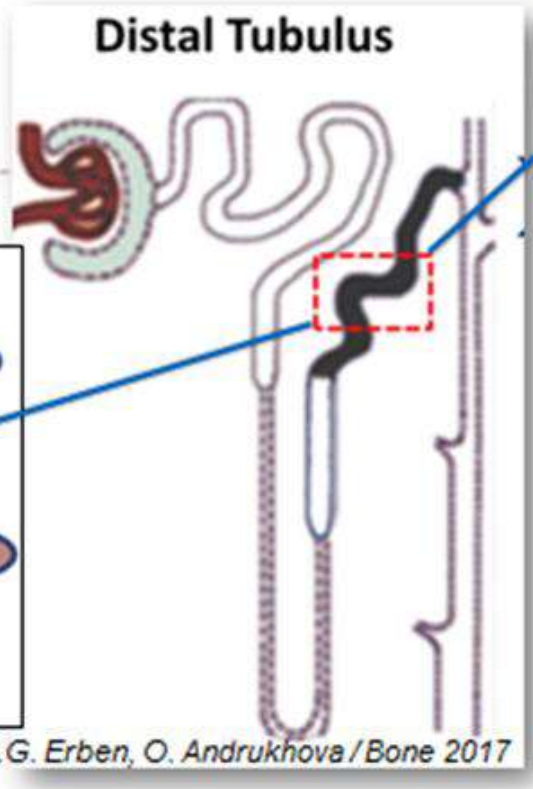


J Blaine, M Chonchol, and M Levi CJASN 2015

PTH, FGF23, Klotho evolvement in Calcium handling

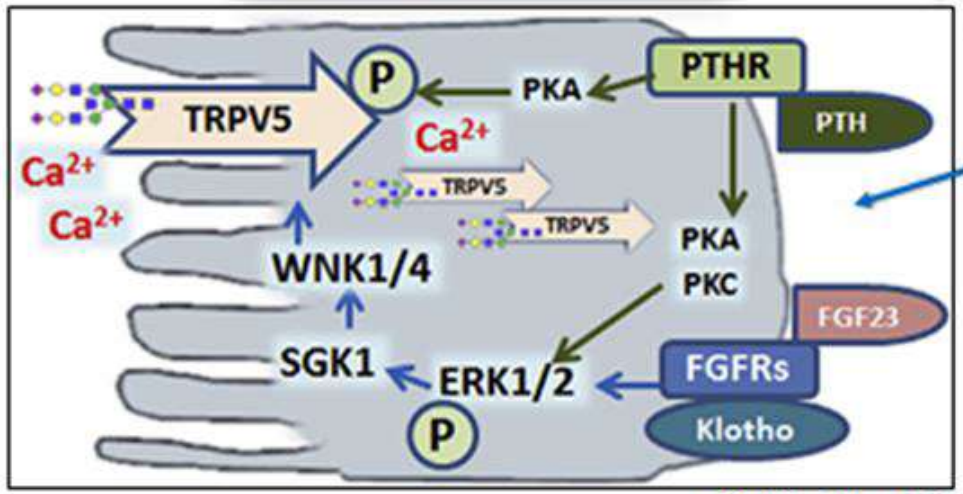


Modified from R.G. Erben / Molecular and Cellular Endocrinology 2016

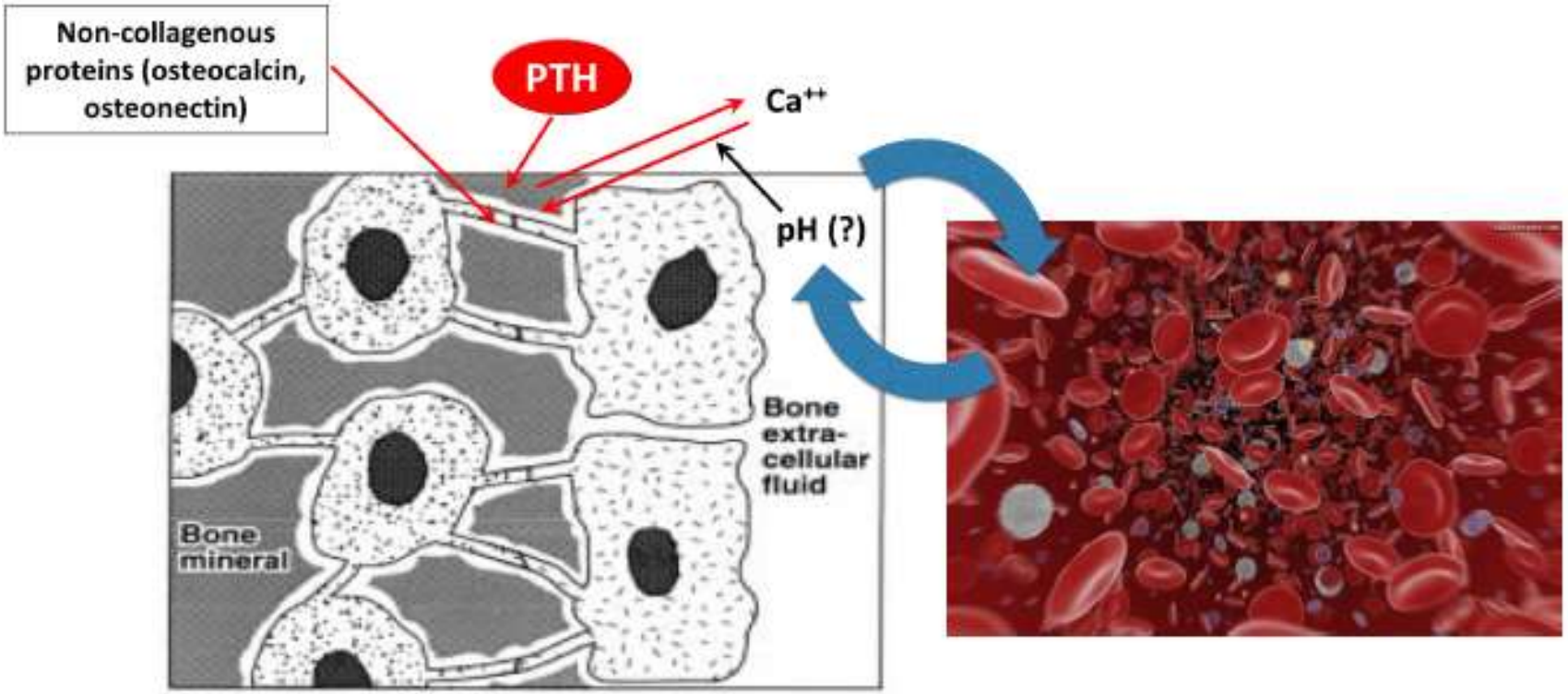


Modified from R.G. Erben, O. Andrukhova / Bone 2017

Calcium reabsorption

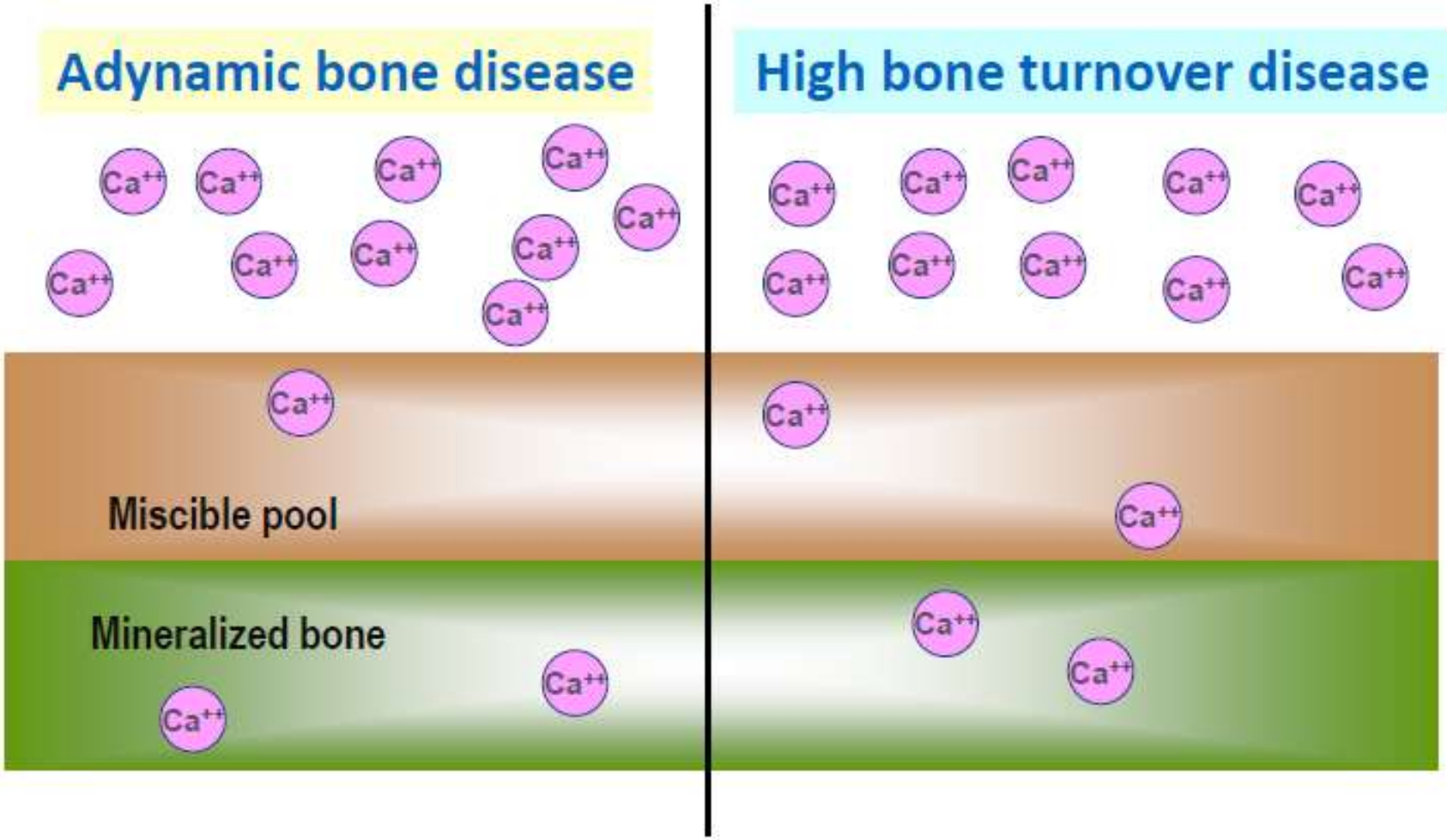


Bone cells, mineral and extracellular fluid miscible pool



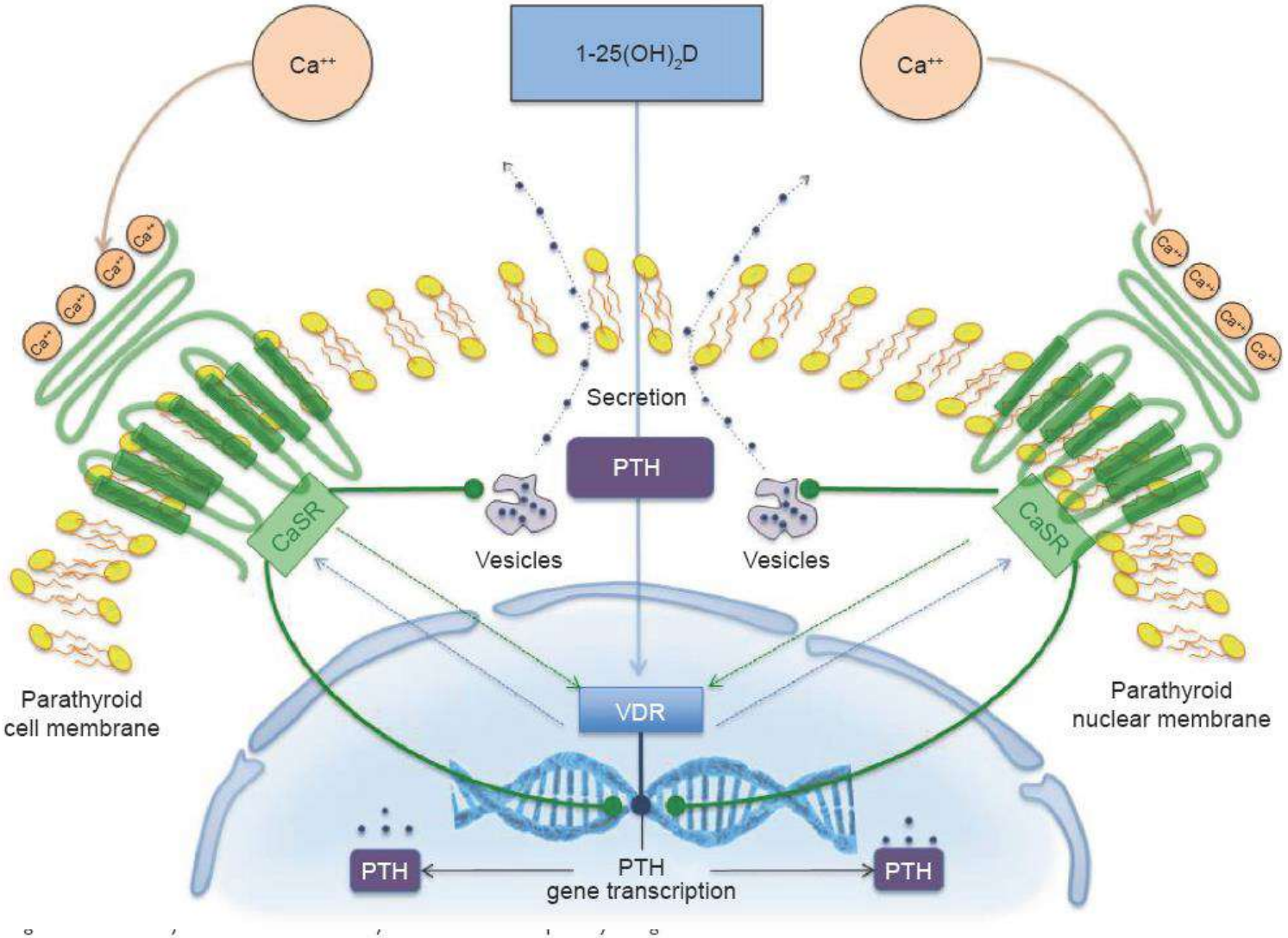
Talmage RV et al, J Musculoskelet Neuronal Interact 2003

Calcium efflux and bone accretion and retention in



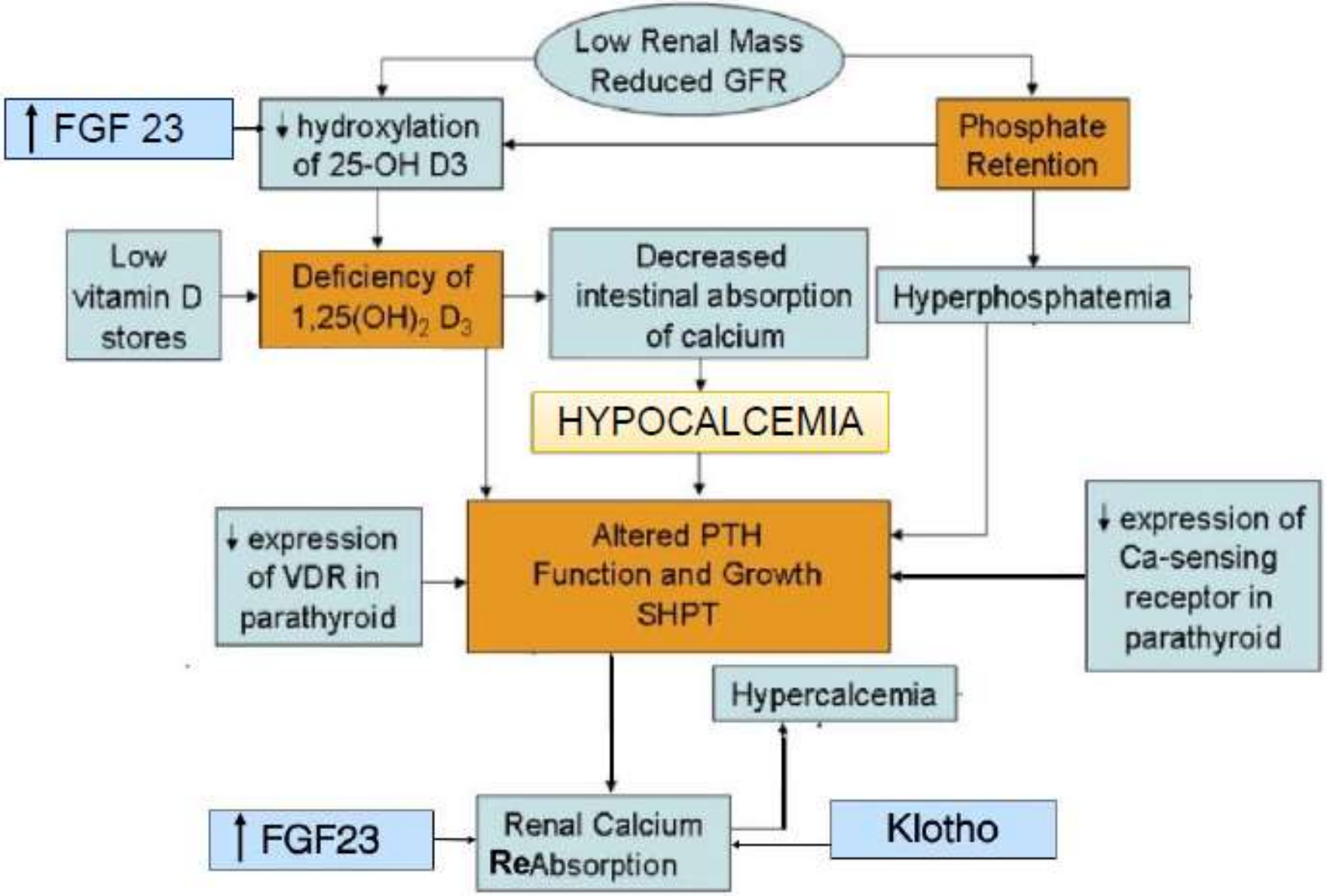
Kurz P et al, Kidney Int 1994

Regulation of PTH synthesis and secretion by CaSR and VDR in parathyroid glands

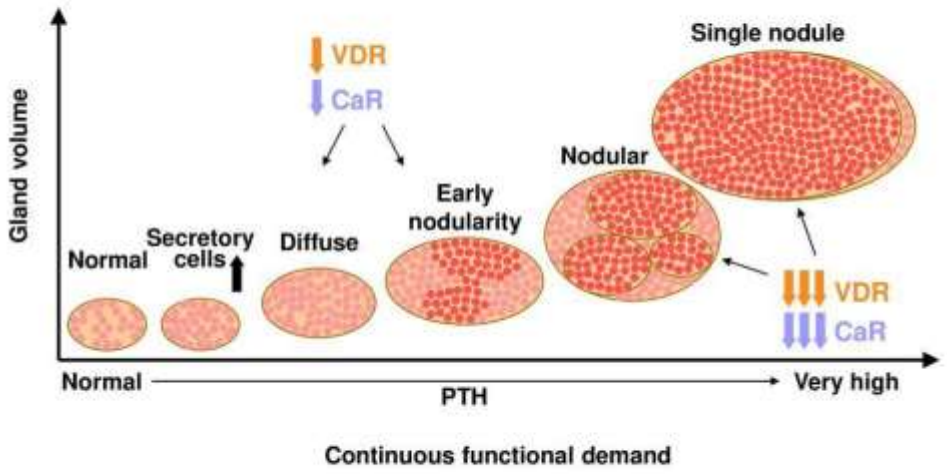


Abbreviations: Ca++, ionized calcium; CaSR, calcium-sensing receptor; PTH, parathyroid hormone; VDR, vitamin D receptor.

Cozzolino et al Therapeutics and Clinical Risk Management 2017

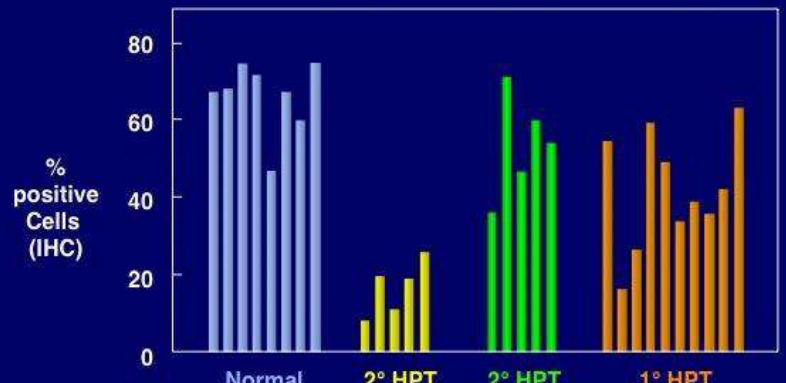

Low Renal Mass
Reduced GFR
↑ FGF 23
↓ hydroxylation of 25-OH D3
Phosphate Retention
Low vitamin D stores
Deficiency of 1,25(OH)2 D3
Decreased intestinal absorption of calcium
Hyperphosphatemia
HYPOCALCEMIA
↓ expression of VDR in parathyroid
Altered PTH Function and Growth SHPT
↓ expression of Ca-sensing receptor in parathyroid
Hypercalcemia
↑ FGF23
Renal Calcium ReAbsorption
Klotho

Progression of SHPT: parathyroid hyperplasia



Adapted, with permission, from Tominaga Y *et al. Curr Opin Nephrol Hypertens* 1996;5:336–41

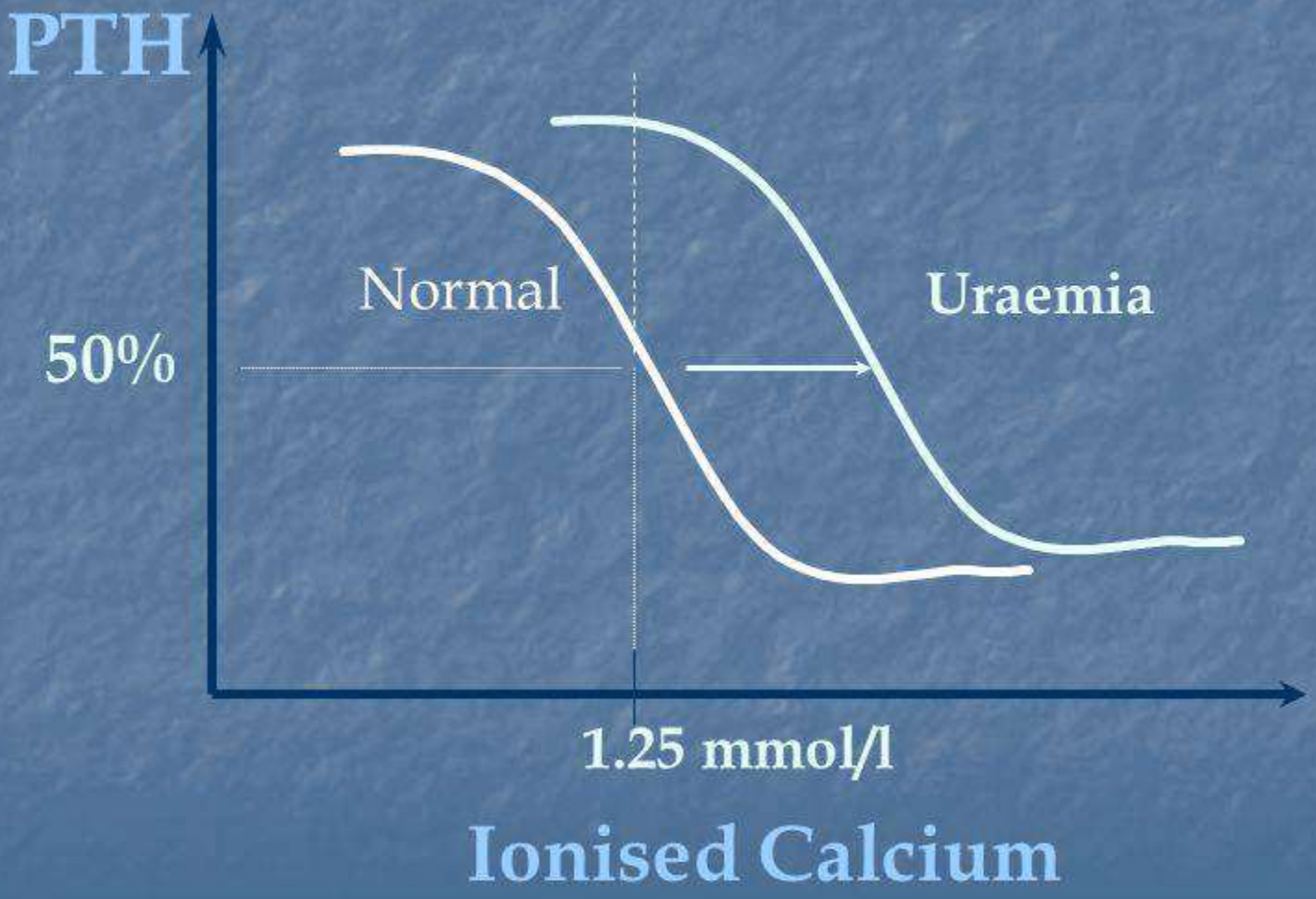
Parathyroid gland CaSR protein and mRNA expression



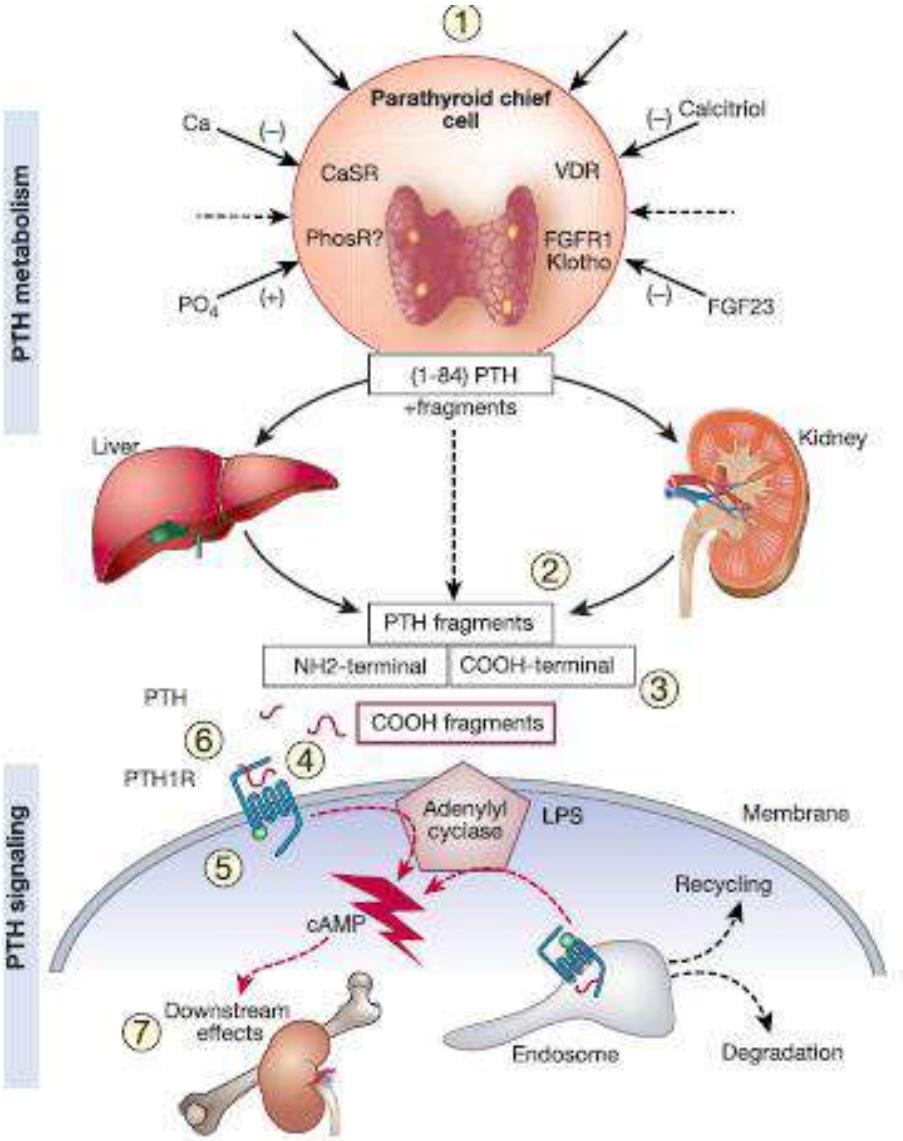
	Normal	2° HPT (nodular)	2° HPT (diffuse)	1° HPT
CaR mRNA (ISH)	52±49	21.5±7.7	22±8.4	15±0.7

Gogusev J et al, Kidney Int 1997; 51: 328-36

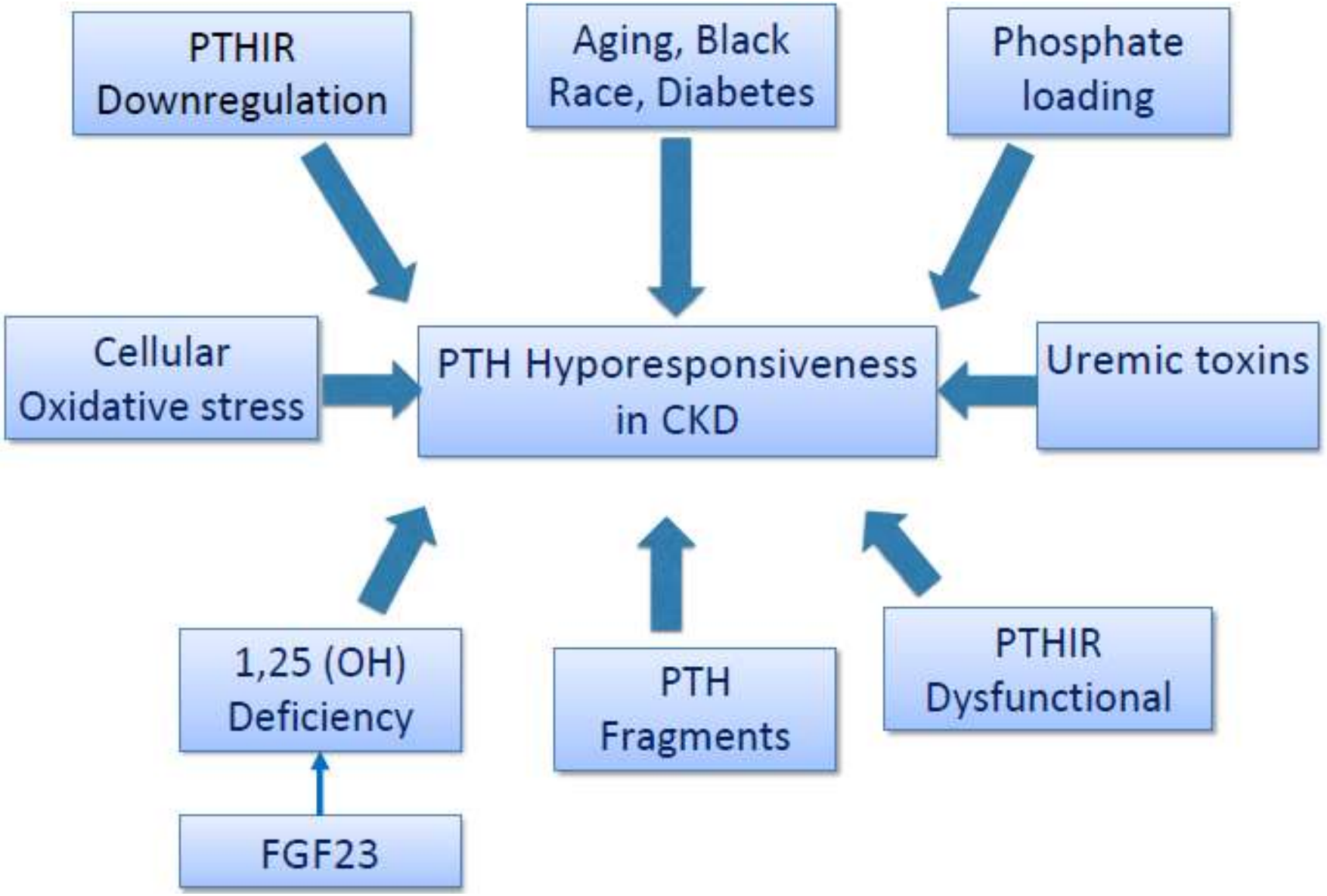
PTH - Calcium set point



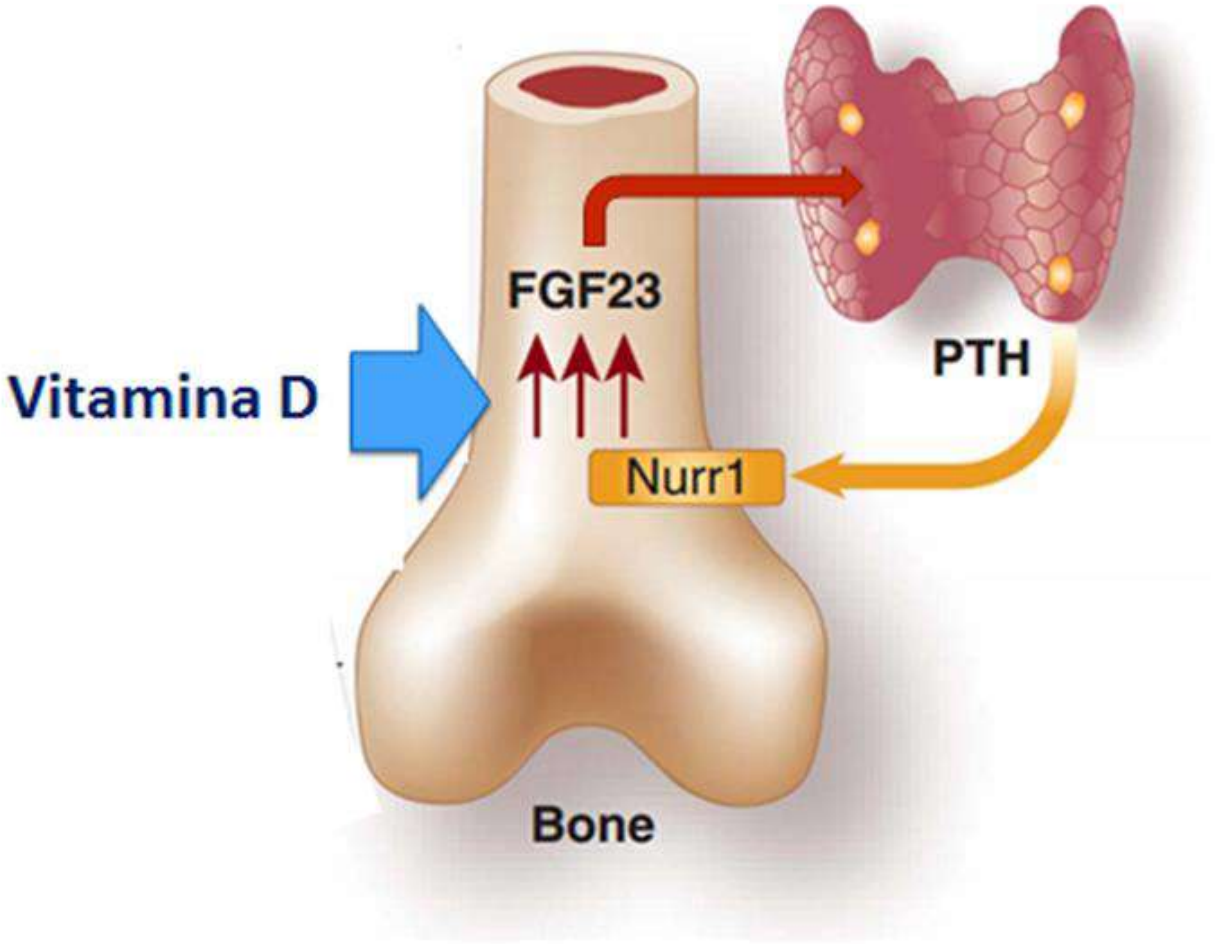
Impact of chronic kidney disease on parathyroid hormone metabolism and signaling



P Evenepoel et al, Kidney International (2016)

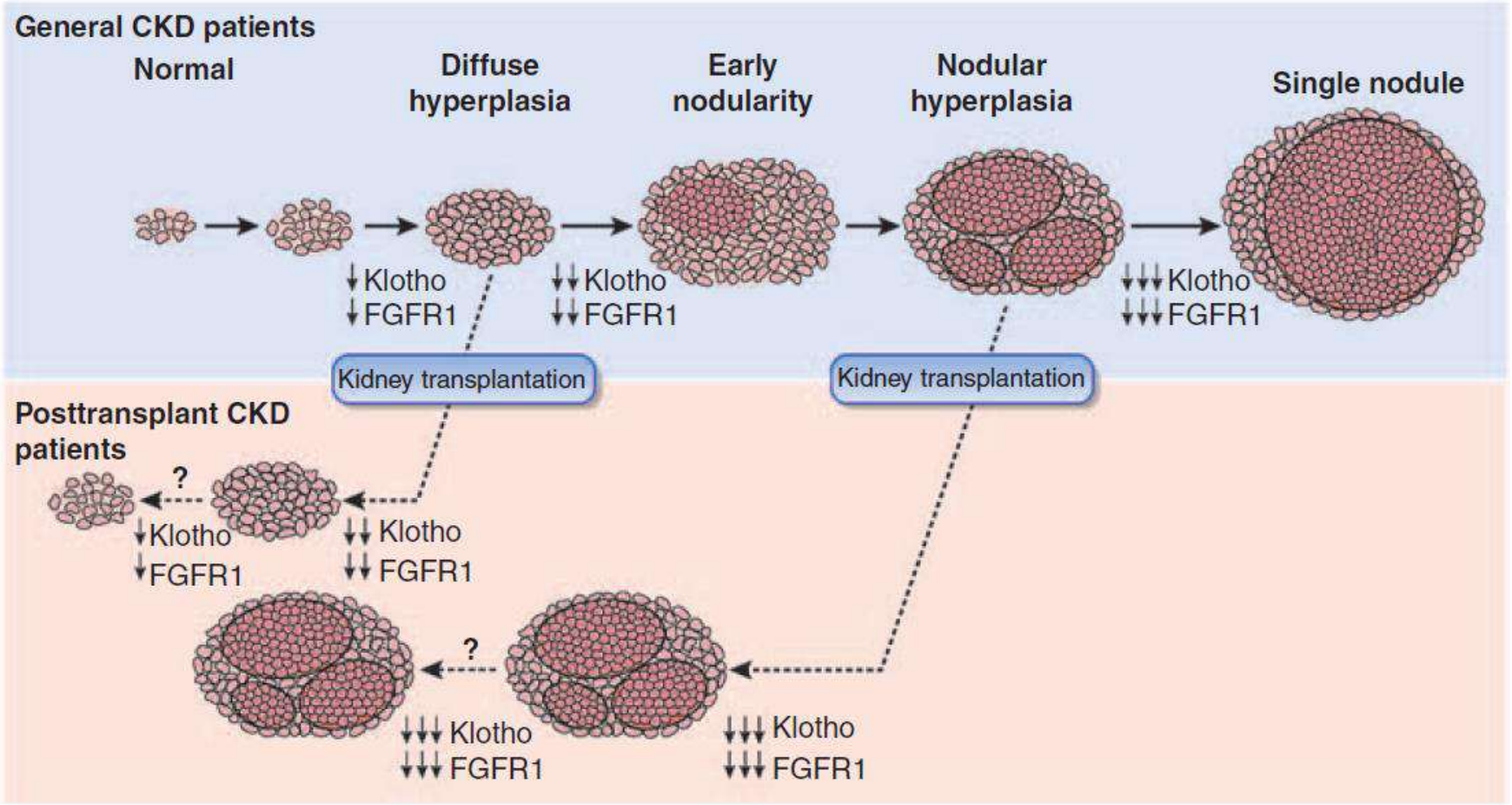

PTHIR Downregulation
Aging, Black Race, Diabetes
Phosphate loading
Cellular Oxidative stress
PTH Hyporesponsiveness in CKD
Uremic toxins
1,25 (OH) Deficiency
PTH Fragments
PTHIR Dysfunctional
FGF23

Schematic representation of currently known inducers of FGF23 production



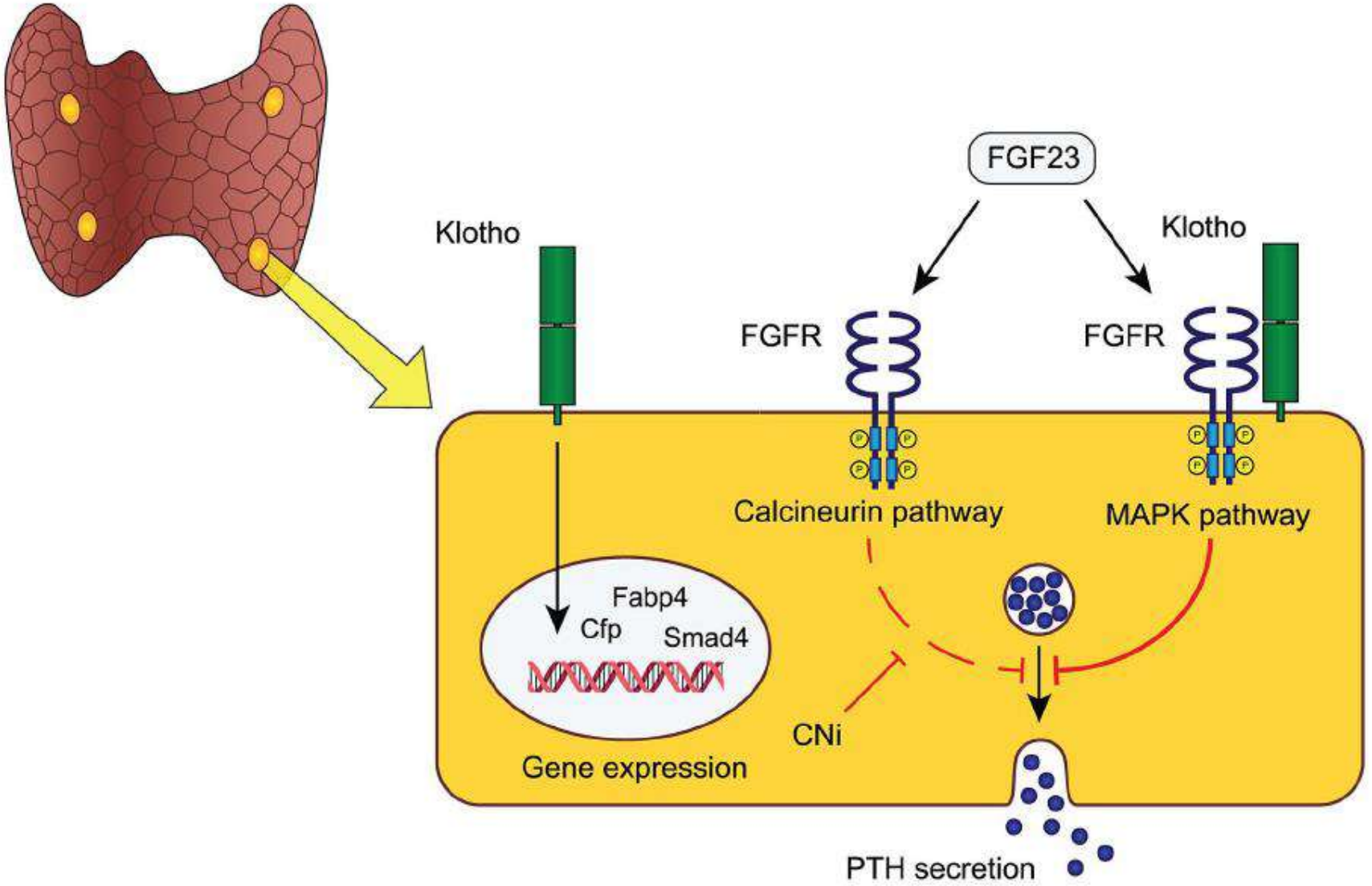
Nurr1, nuclear receptor associated protein-1

Progression of Parathyroid Hyperplasia in CKD



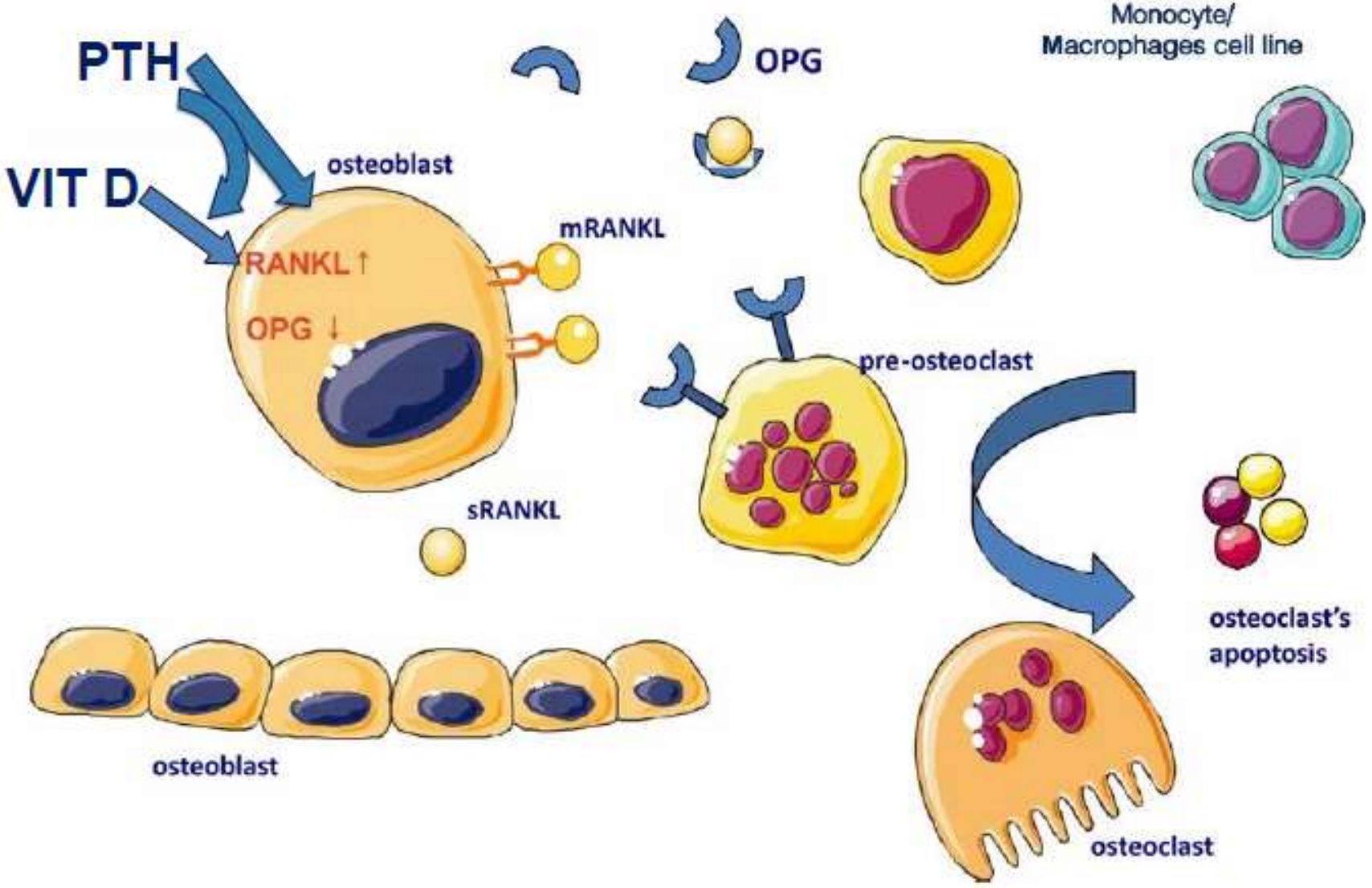
H. Komaba et al, Kidney International 2010

Proposed model of FGF23 Klotho function in parathyroid glands.



Modified from H. Olauson et al, PLOS Genetics 2013

PTH and Vitamin D modulation of RANKL/RANK/OPG system



Molecular and Cellular Endocrinology 436 (2016) 224–239

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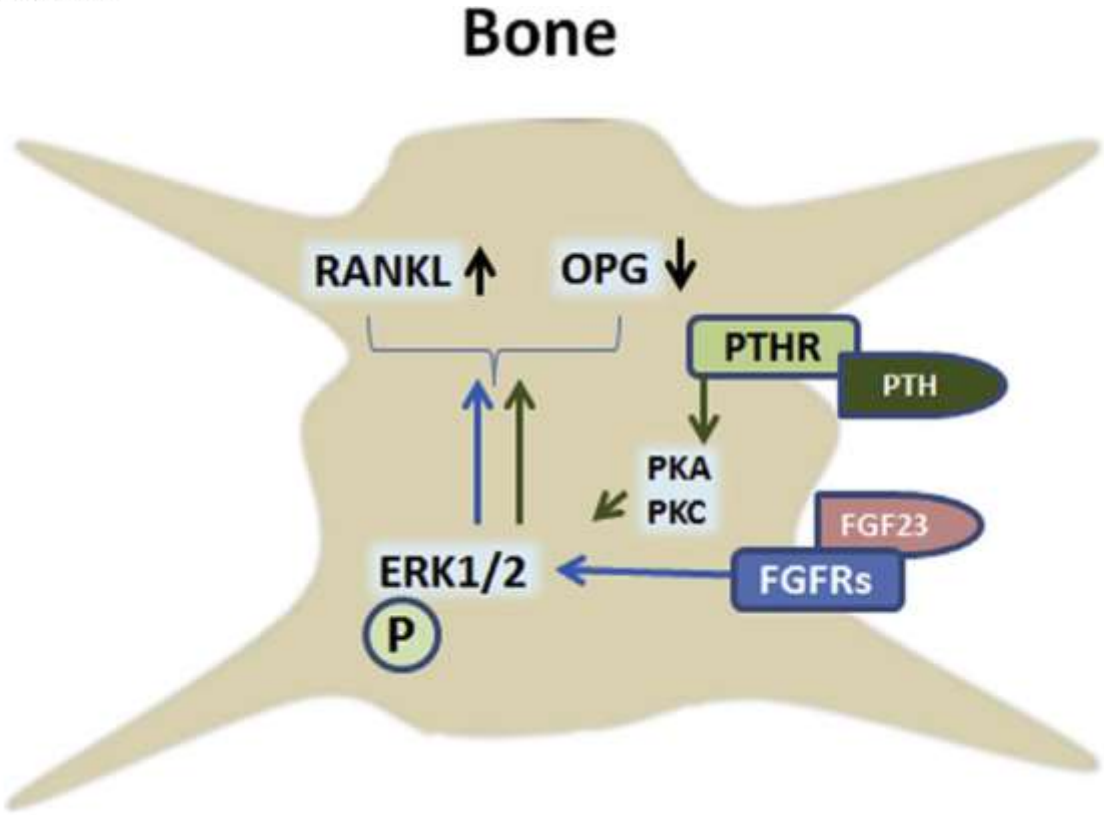
journal homepage: www.elsevier.com/locate/mce

Fgf23 and parathyroid hormone signaling interact in kidney and bone

Olena Andrukhova, Carmen Streicher, Ute Zeitz, Reinhold G. Erben*

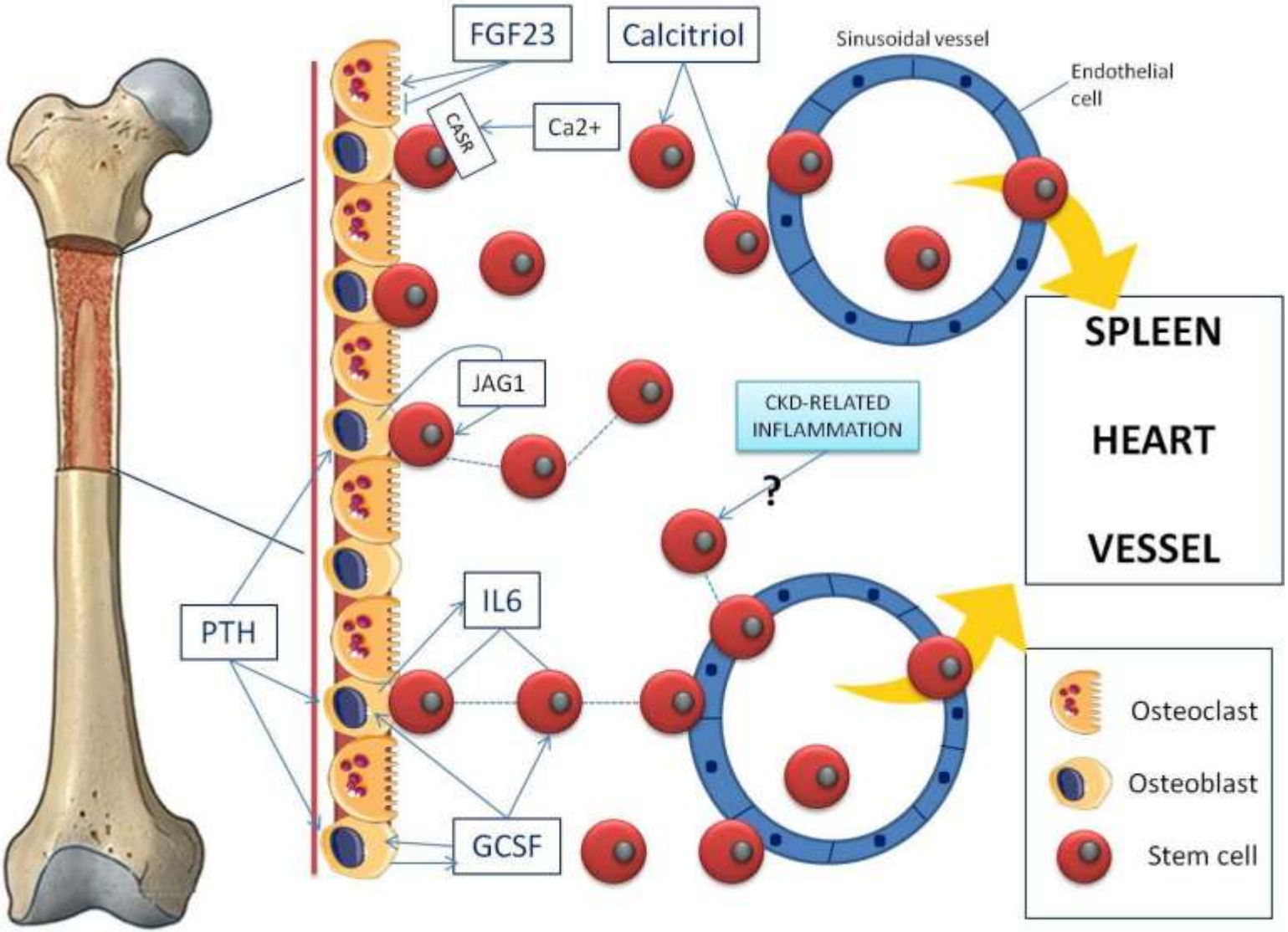
Department of Biomedical Sciences, University of Veterinary Medicine, 1210, Vienna, Austria

In osteoblasts , FGF23 and PTH signaling pathways both induce ERK1/2 phosphorylation , resulting in additive effects in the regulation of RANKL and OPG expression .



The role of PTH in stem cells renewall and mobilization

Mazzaferro S., Cianciolo G., De Pascalis A .., Guglielmo C, Urena Torres PA, Bover J, Tartaglione L, Pasquali M, La Manna G
NDT April 2018



“Arrivati a quest’ora di notte, vale a dire all’ ”Indice”, i superstiti lettori si saranno certamente resi conto che la successione dei capitoli disposta dall’autore non era che una semplice proposta: ogni lettore, infatti, se lo vuole può stabilire una sua personale sequenza”

Camilleri

Turning over renal osteodystrophy dogma: direct actions of FGF23 on osteoblast β-catenin pathway

Susan C. Schiavi[1] and Rosa M.A. Moysés[2,3]

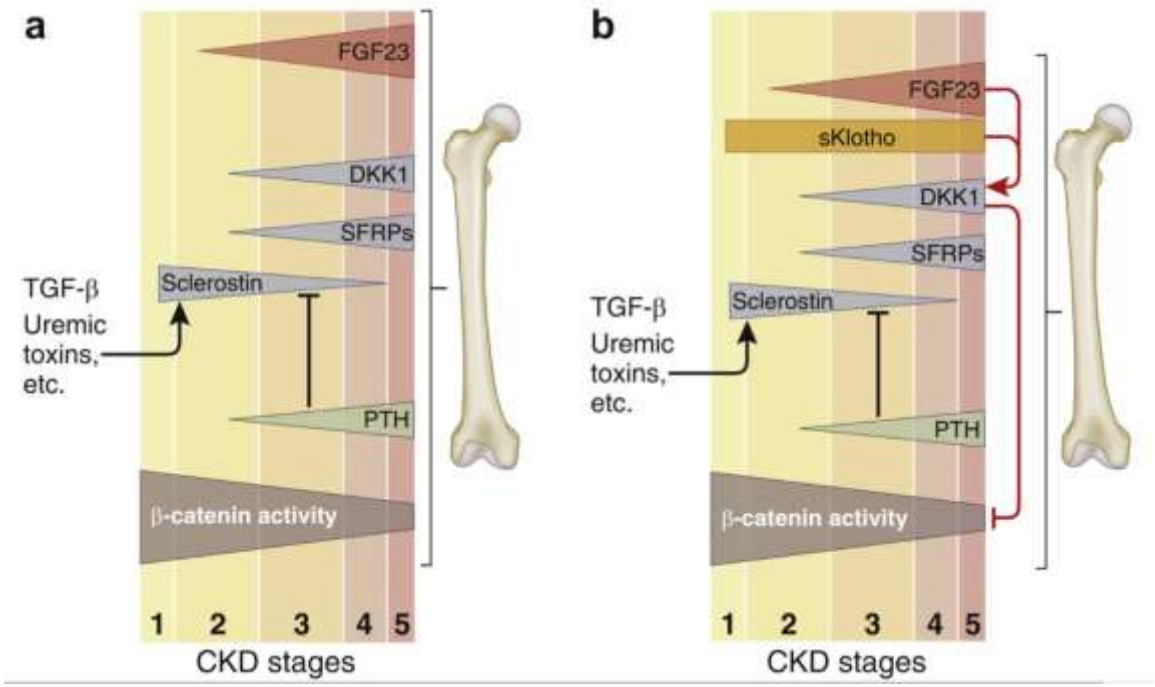
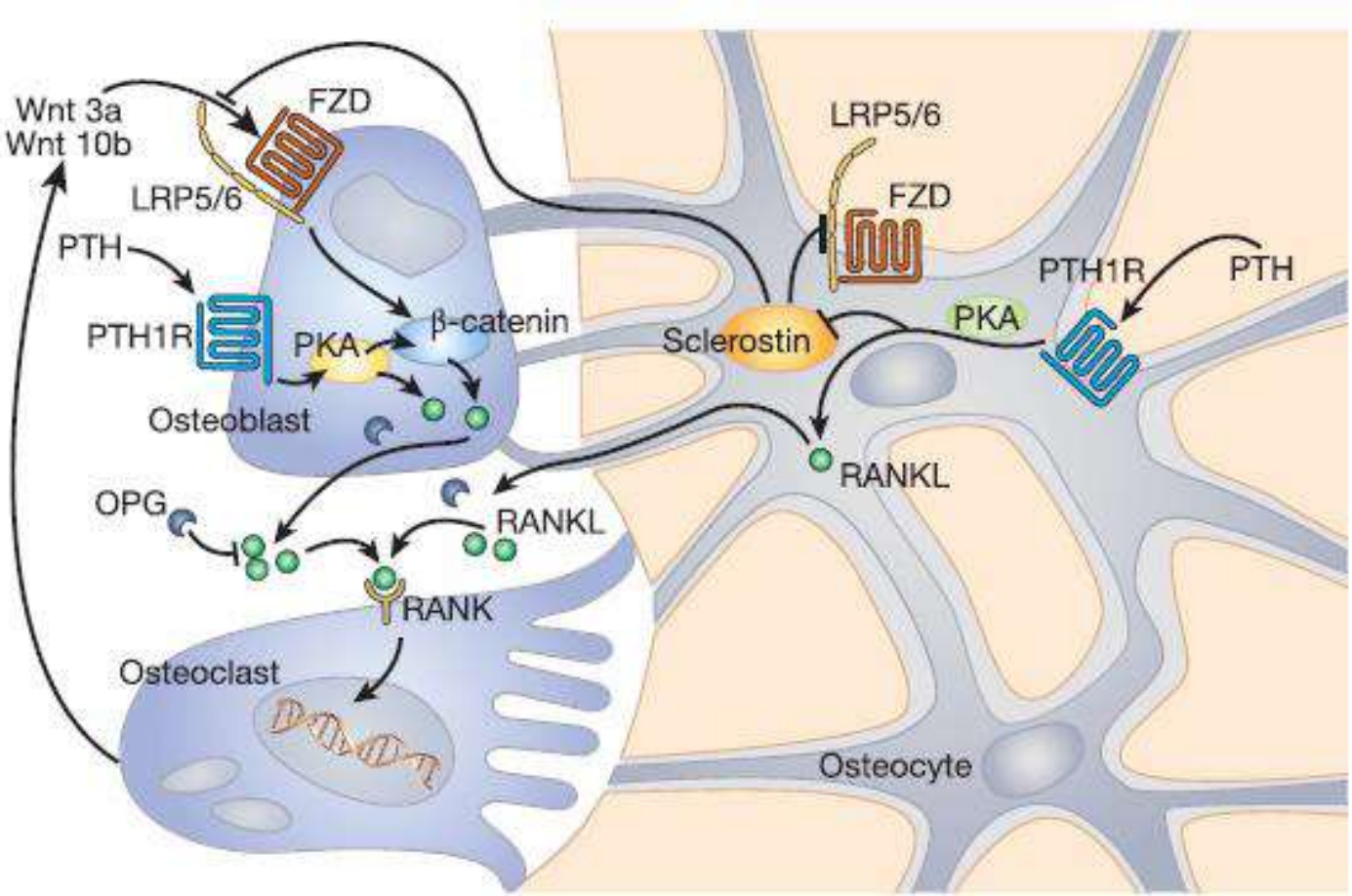


Figure 1 | Current concept of the natural history of CKD-MBD updated with the hypothesis provided by Carrilo-Lopez *et al.*[6] (**a**) Natural history of chronic kidney disease–mineral and bone disorder (CKD-MBD). In early stages of CKD, sclerostin expression is increased, leading to Wnt pathway inhibition and β-catenin phosphorylation. As CKD progresses, parathyroid hormone (PTH) rises and inhibits sclerostin. However, late in the disease, other Wnt pathway inhibitors, such as SFRPs and DKK1 are elevated. (**b**) According to Carrilo-Lopez *et al.*,[6] the combined action of high fibroblast growth factor 23 (FGF23) and maintained soluble Klotho (sKlotho) increase levels of the inactive form of β-catenin through upregulation of DKK1. TGF-β, transforming growth factor β.

Modified from H. Olauson et al, PLOS Genetics 2013

Parathyroid hormone (PTH) and bone metabolism

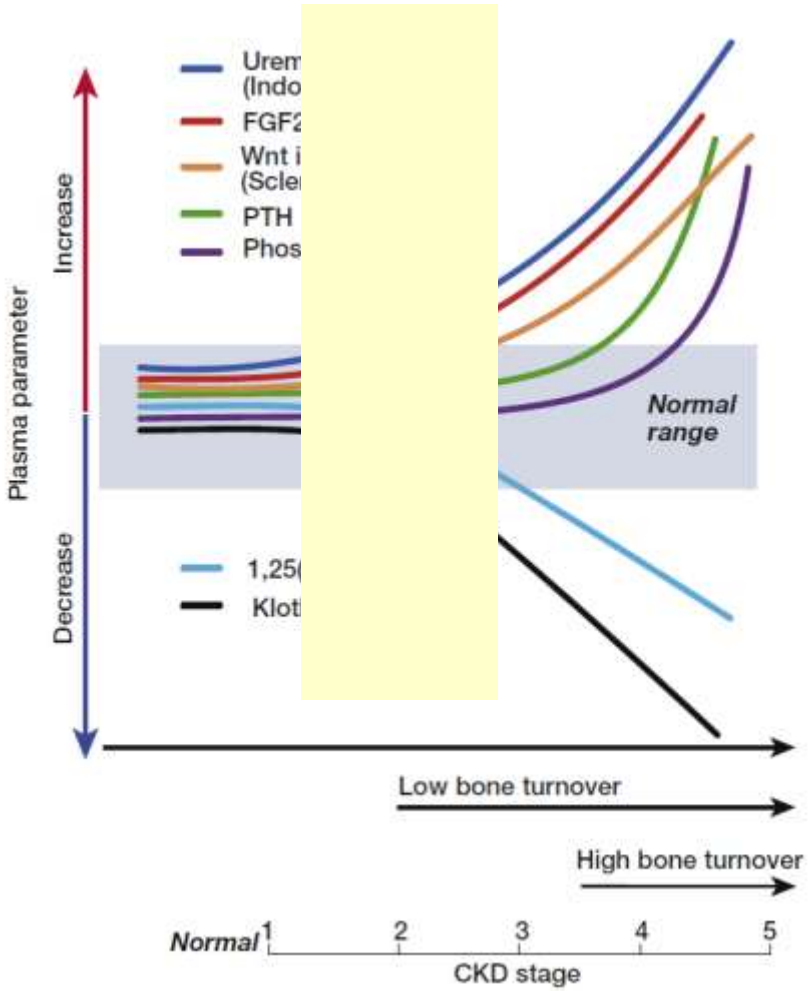


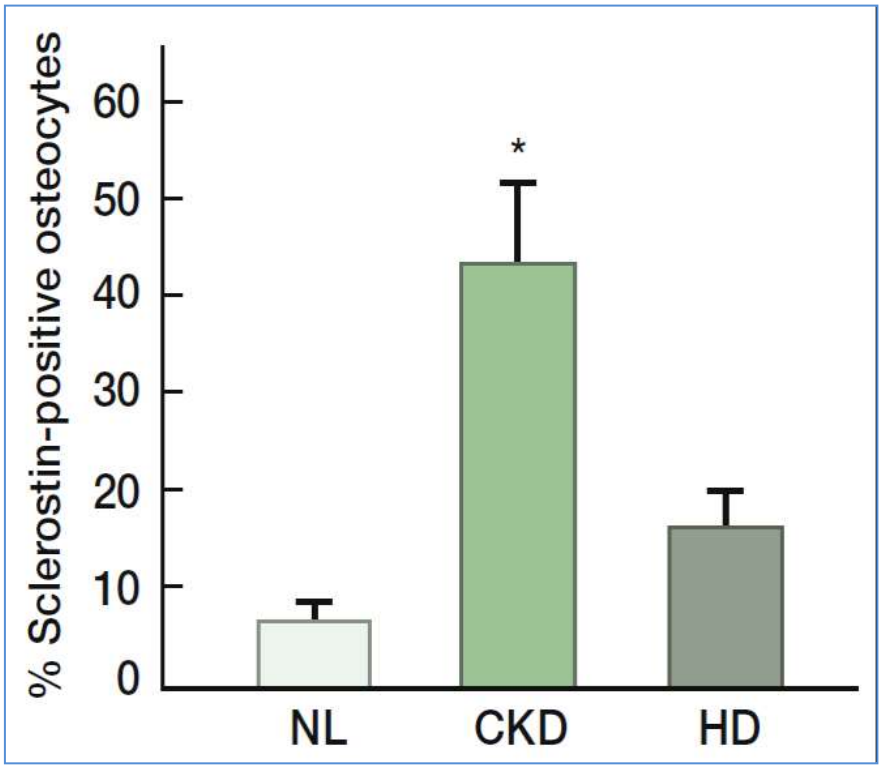
P Evenepoel et al. Kidney International 2016

Changing bone patterns with progression of chronic kidney disease

Tilman B. Drüeke[1] and Ziad A. Massy[1,2]

[1]Institut National de la Santé et de la Recherche Médicale (Inserm) Unité 1018, Centre de recherche en épidémiologie et santé des populations, Equipe 5, Villejuif; Paris-Sud University and University of Paris–Ouest, Versailles-Saint-Quentin-en-Yvelines; Paris, France; and [2]Division of Nephrology, Ambroise Paré Hospital, Assistance Publique Hôpitaux de Paris, Boulogne-Billancourt/Paris; University of Paris–Ouest, Versailles-Saint-Quentin-en-Yvelines; Paris, France

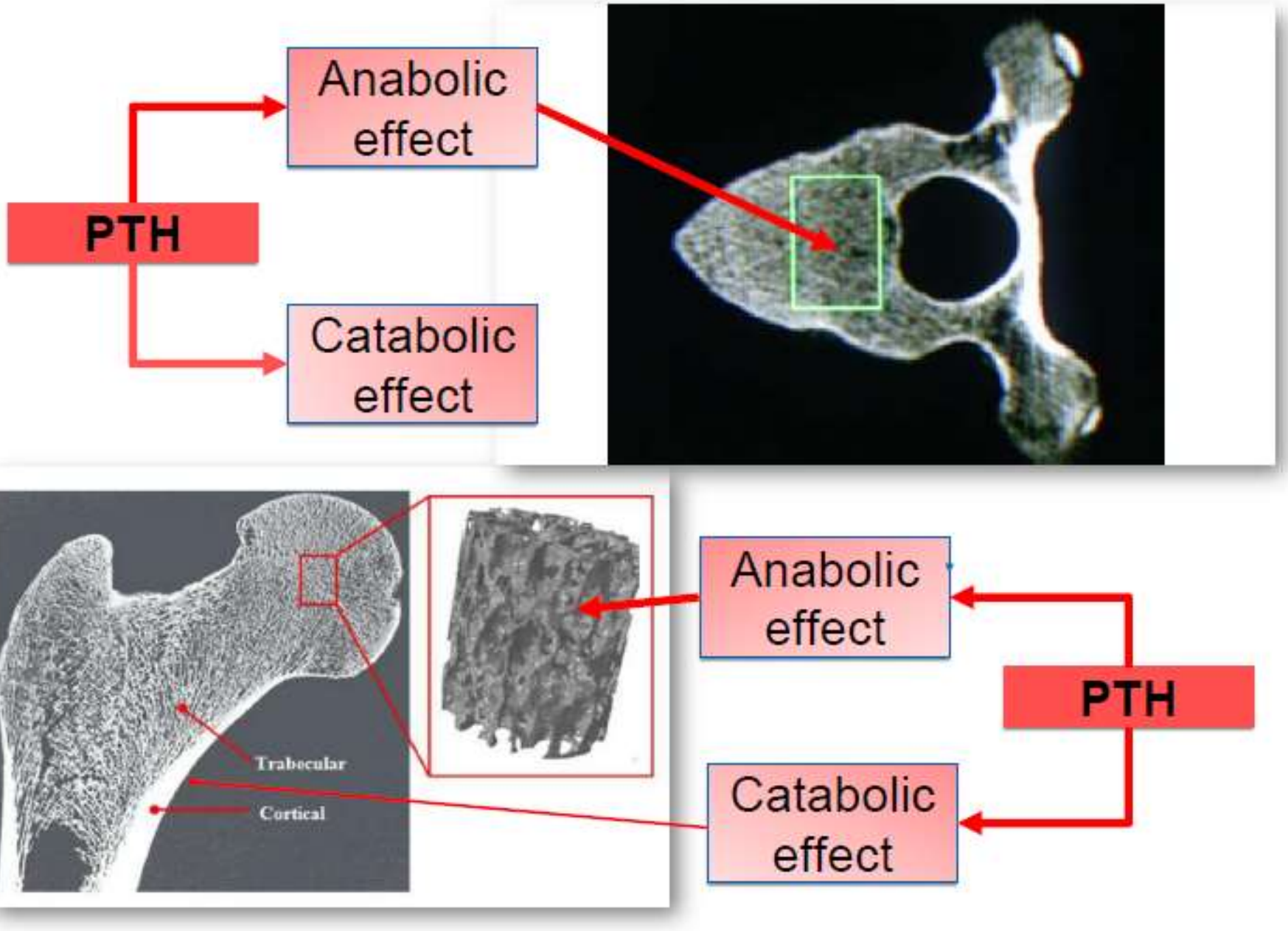




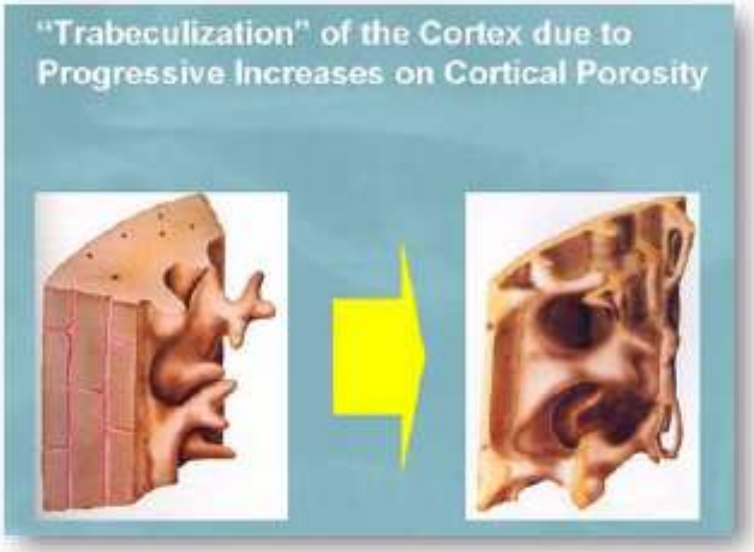
Sabbagh J Bone Min Res 2016. Bone biopsy from NL or CKD patients, showing highest Sclerostin expression in non dialysis CKD

Kidney International (2016) 89, 289-302

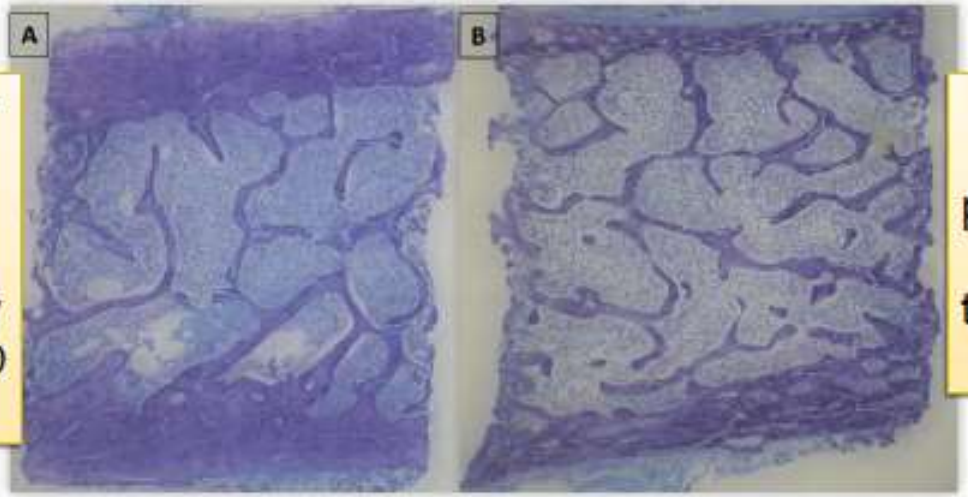
Effect of PTH on cortical and trabecular bone



Comparison of cortical compartments in bone biopsies.



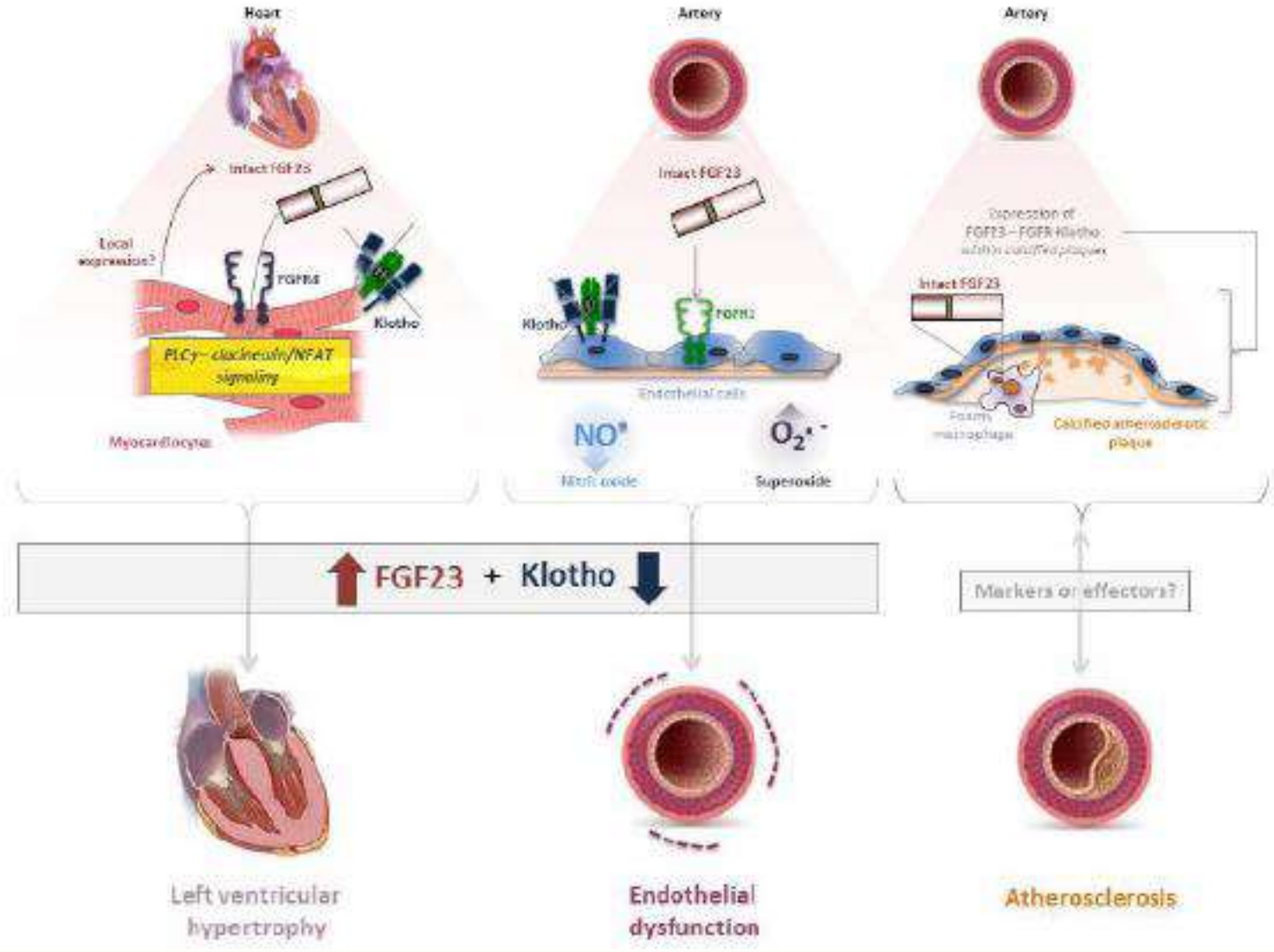
A. Bone biopsy with normal cortical thickness and cortical porosity from a non-CKD patient.



B. Bone biopsy with high porosity and low cortical thickness from a dialysis patient.

Araujo et al Bone 2016

Impact of FGF23 and Klotho on LVH, endothelial function and atherosclerosis: potential mechanisms



Cianciolo G et al Current Vascular Pharmacology, 2017

FGF23 or PTH: which comes first in CKD?

Tamara Isakova[1] and Myles S. Wolf[1]

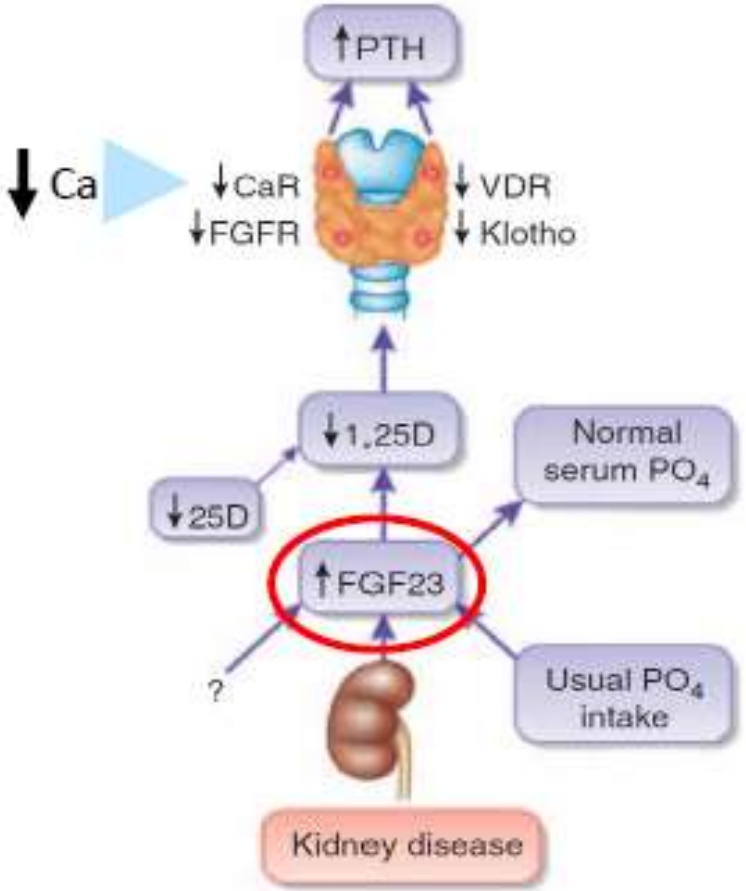
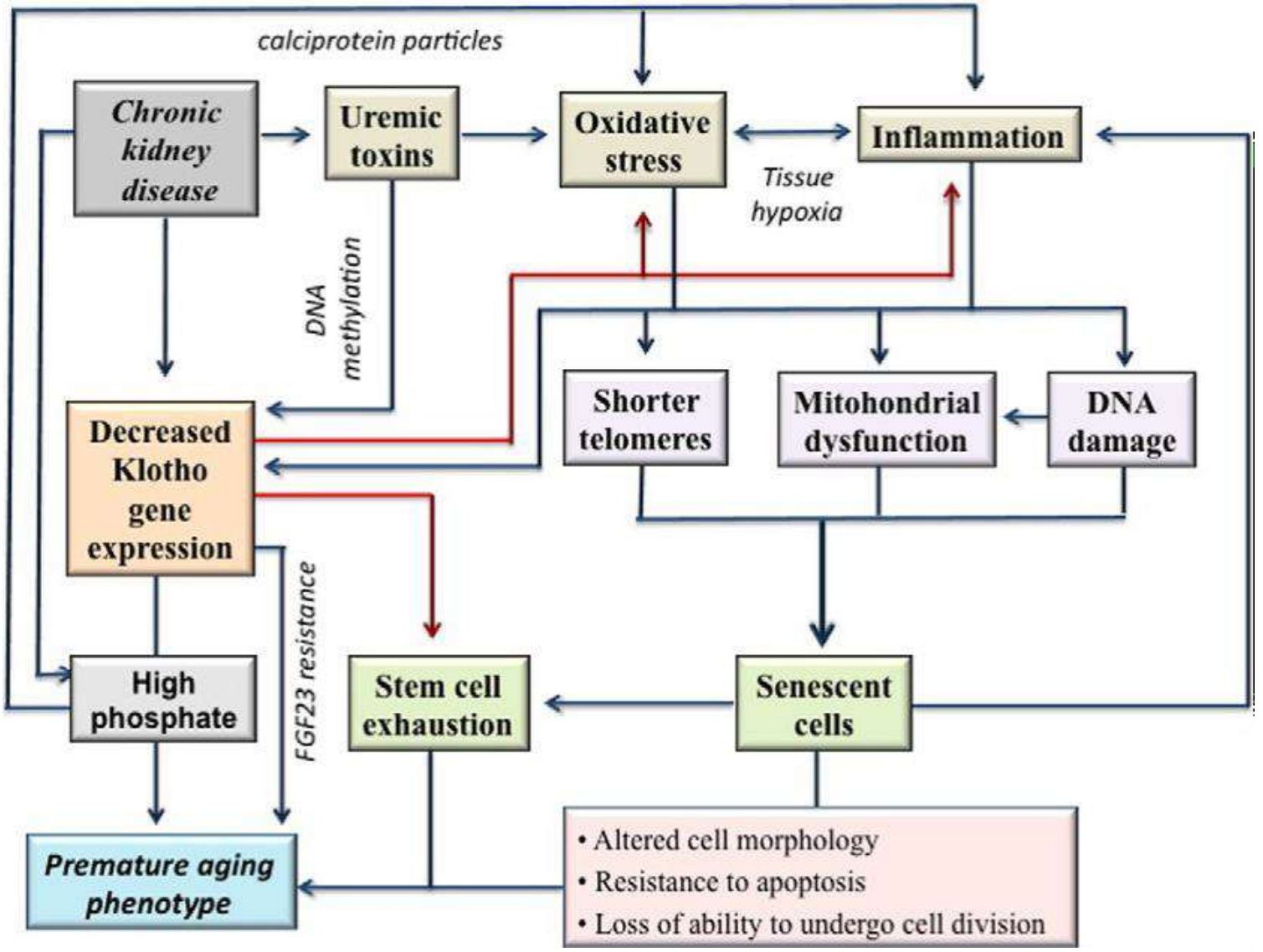


Figure 1 | Pathogenesis of disordered mineral metabolism in CKD. (**a**) Traditional view of the mechanisms that maintain secondary hyperparathyroidism in advanced chronic kidney disease. (**b**) Updated view of the mechanisms that initiate secondary hyperparathyroidism in chronic kidney disease, emphasizing the central role of FGF23. CaR, calcium sensing receptor; FGFR, fibroblast growth factor receptor; PTH, parathyroid hormone; VDR, vitamin D receptor.

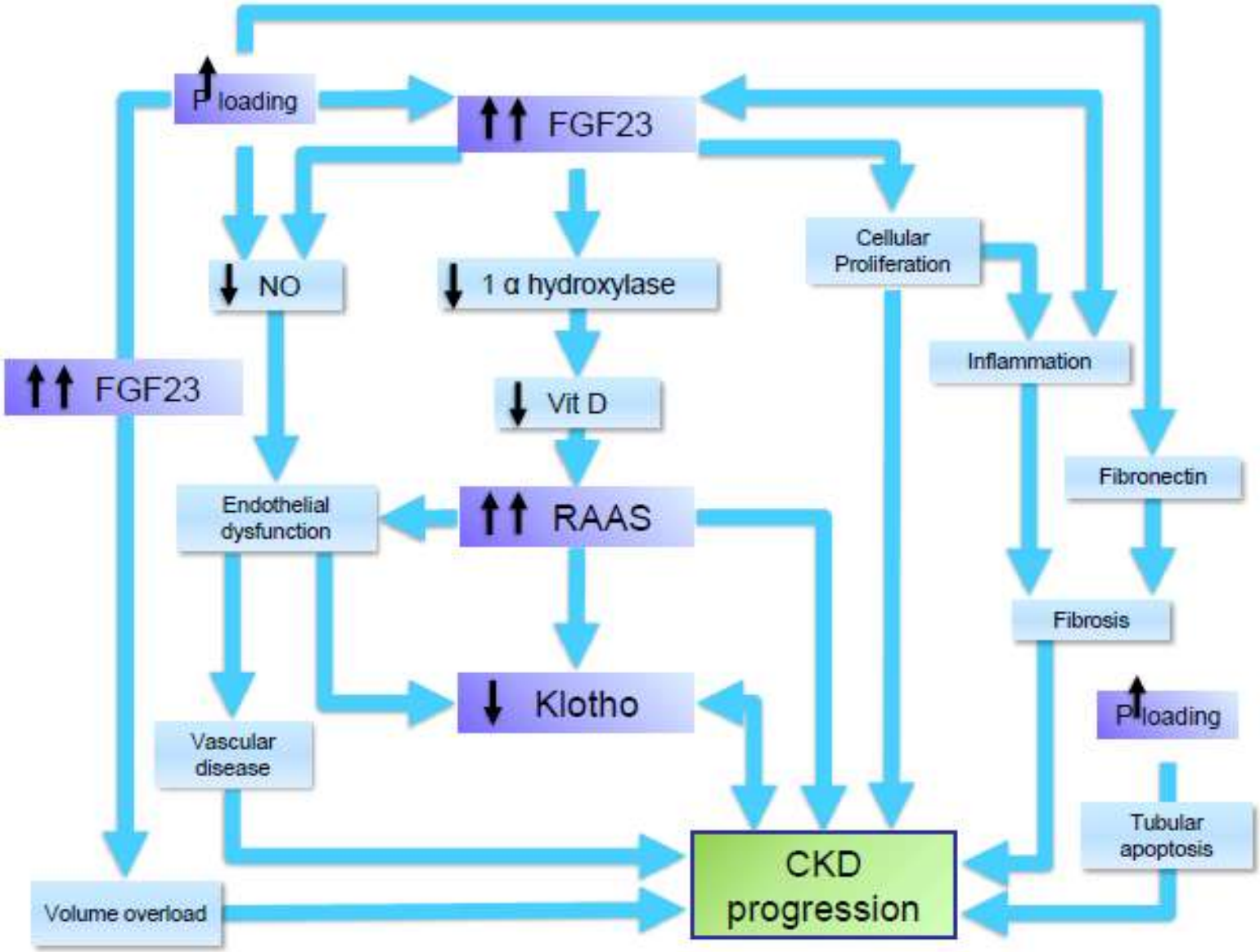
Kidney International 2013

The putative progeroid effects of the uremic mileu. The role of Phospate

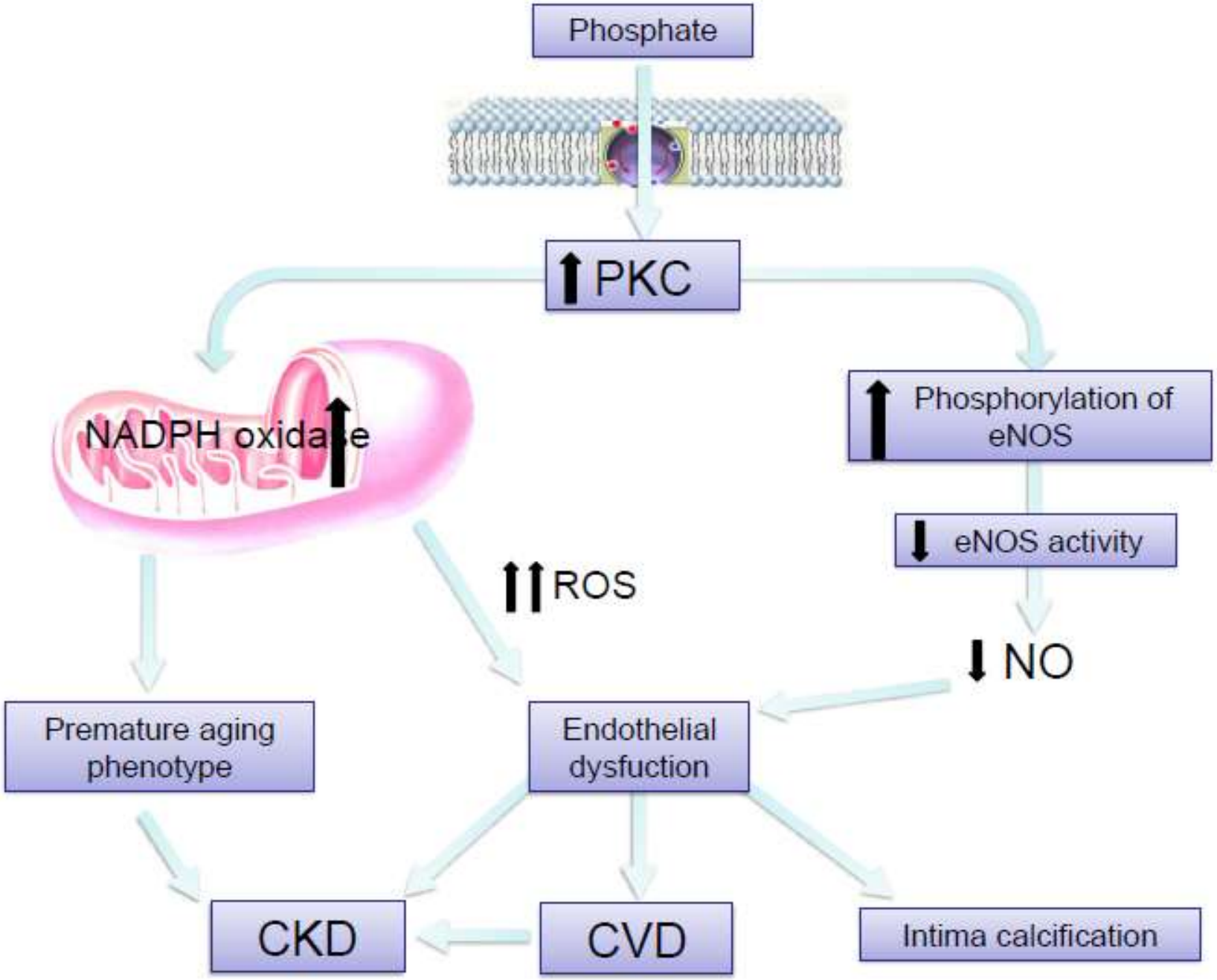


P Stenvinkel an Larsson, AJKD 2013

Phospate , FGF 23/Klotho and RAAS in CKD Progression

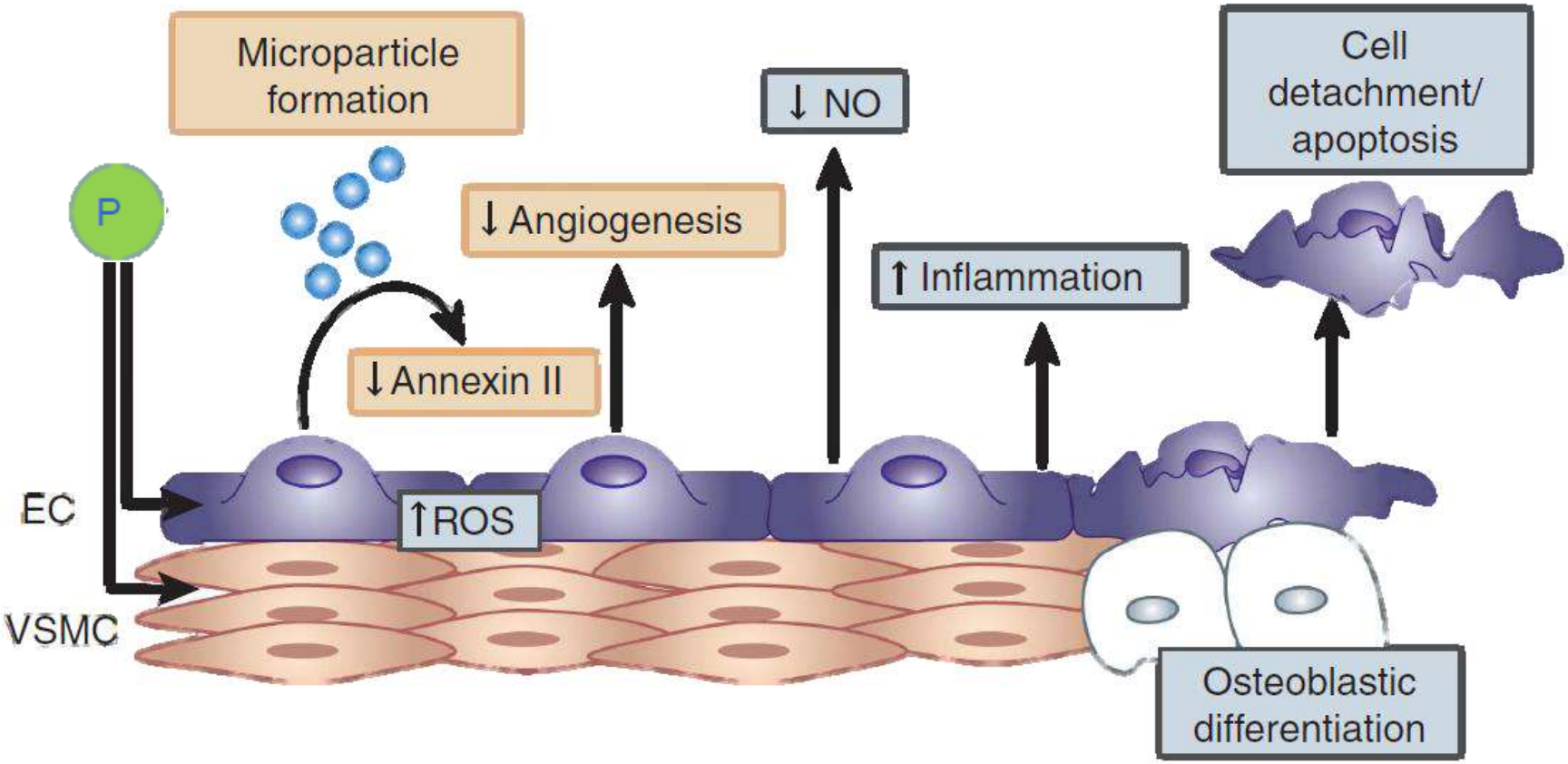


Estrapolata da Cozzolino et al, AJKD 2013



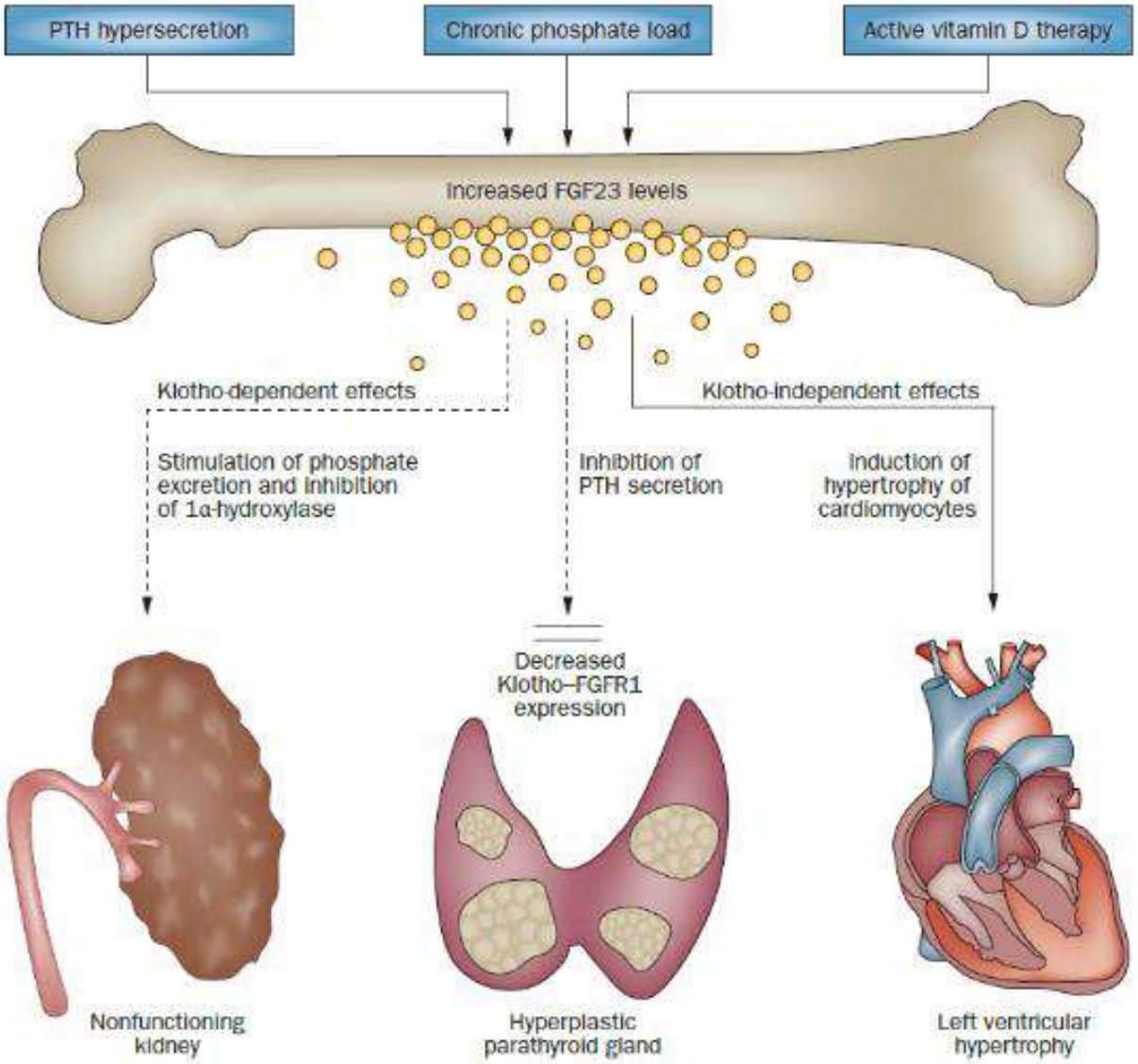
Modified from Shuto et al, JASN 2009

Putative Mecanisms by which P Influences Vascual Health and Function



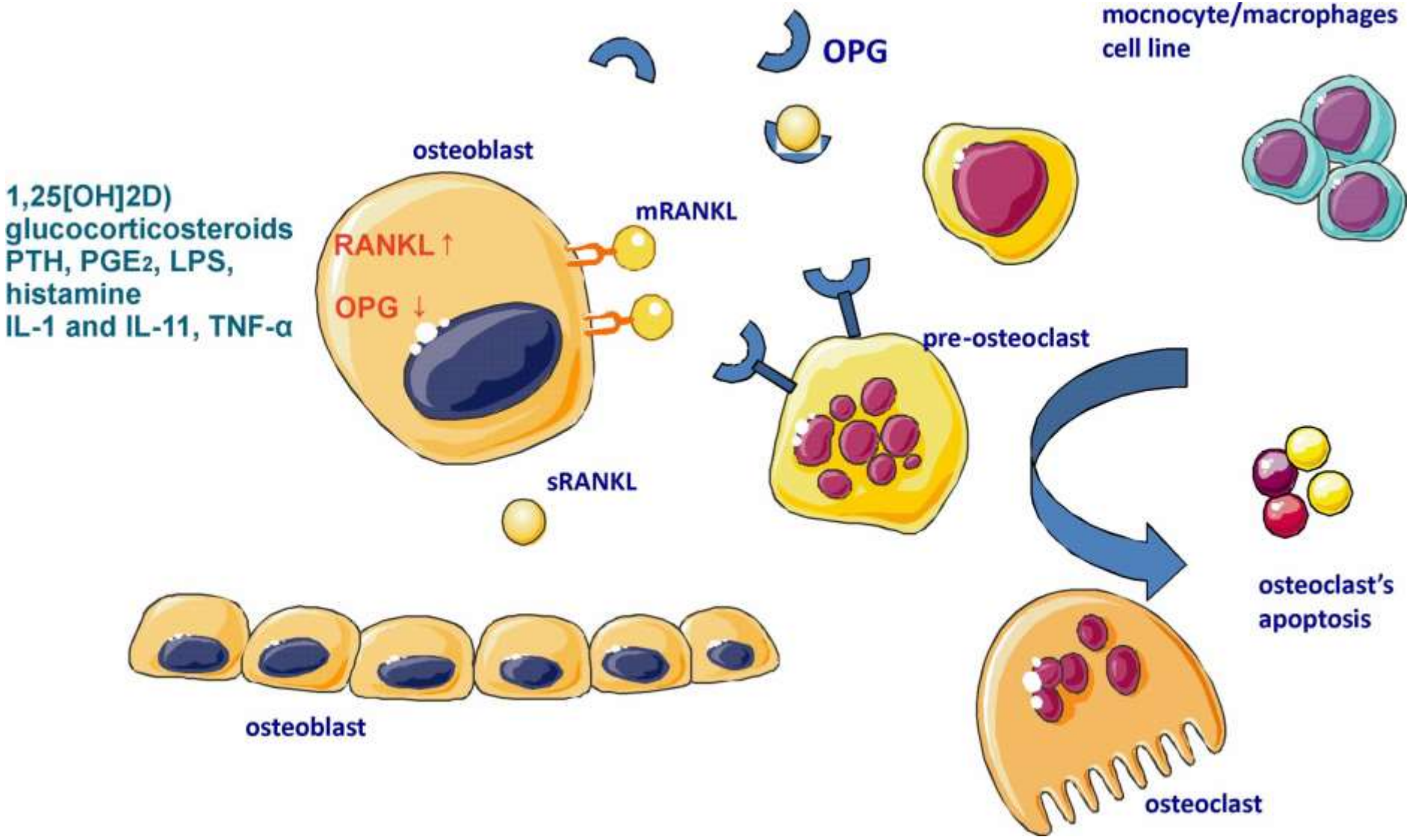
Burger et al, Kindney Int. 2013

Klotho dependent and Klotho independent Effects of FGF23 in ESRD.

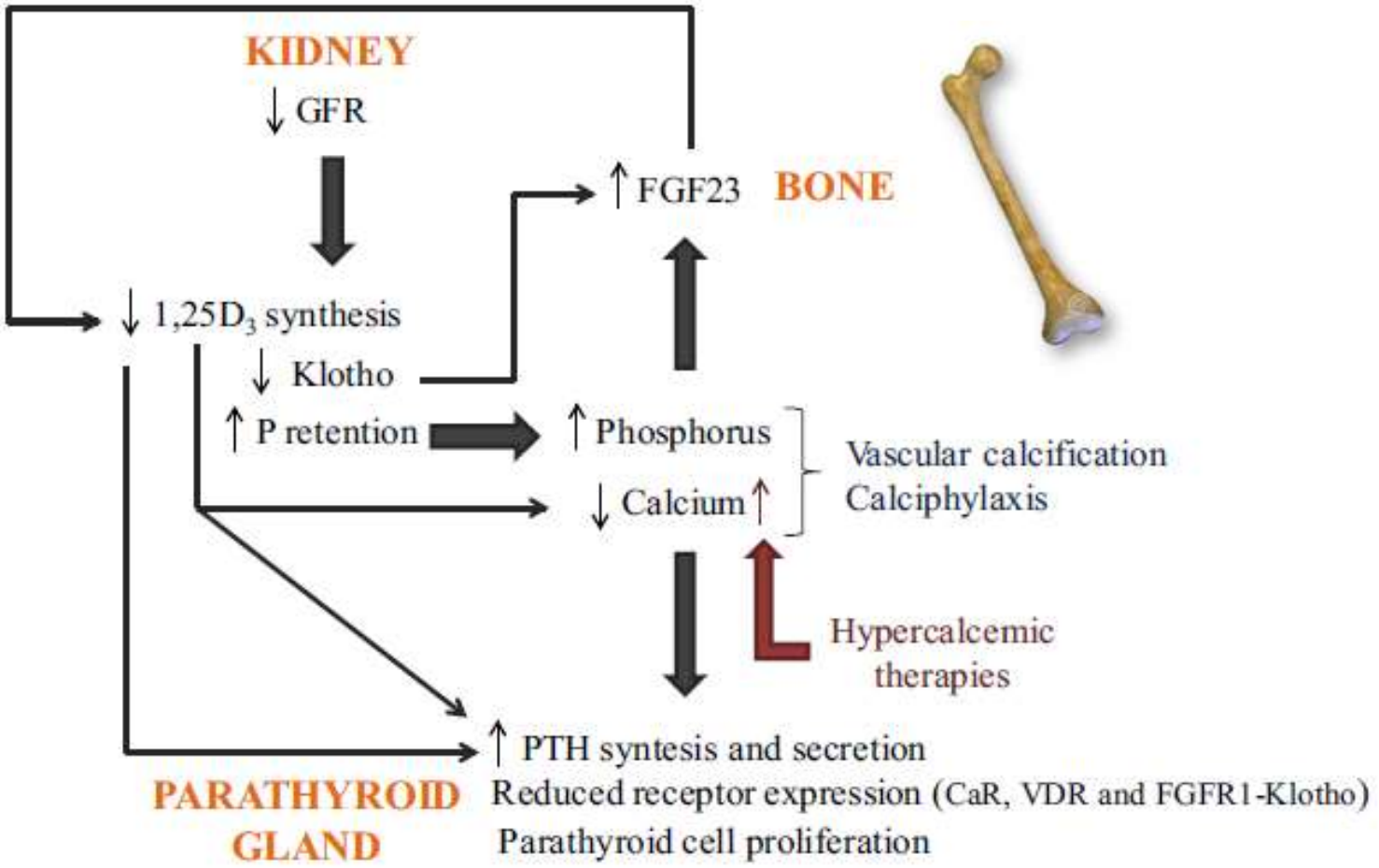


Komaba, H. and Fukagawa, M. Nat. Rev. Nephrol. 2012

- Ichiro Kaneko et al fig 2 Clin Exp Nephrol (2017) 21 (Suppl 1):S21–S26
- Pi balance in the kidney, small intestine, and salivary glands.

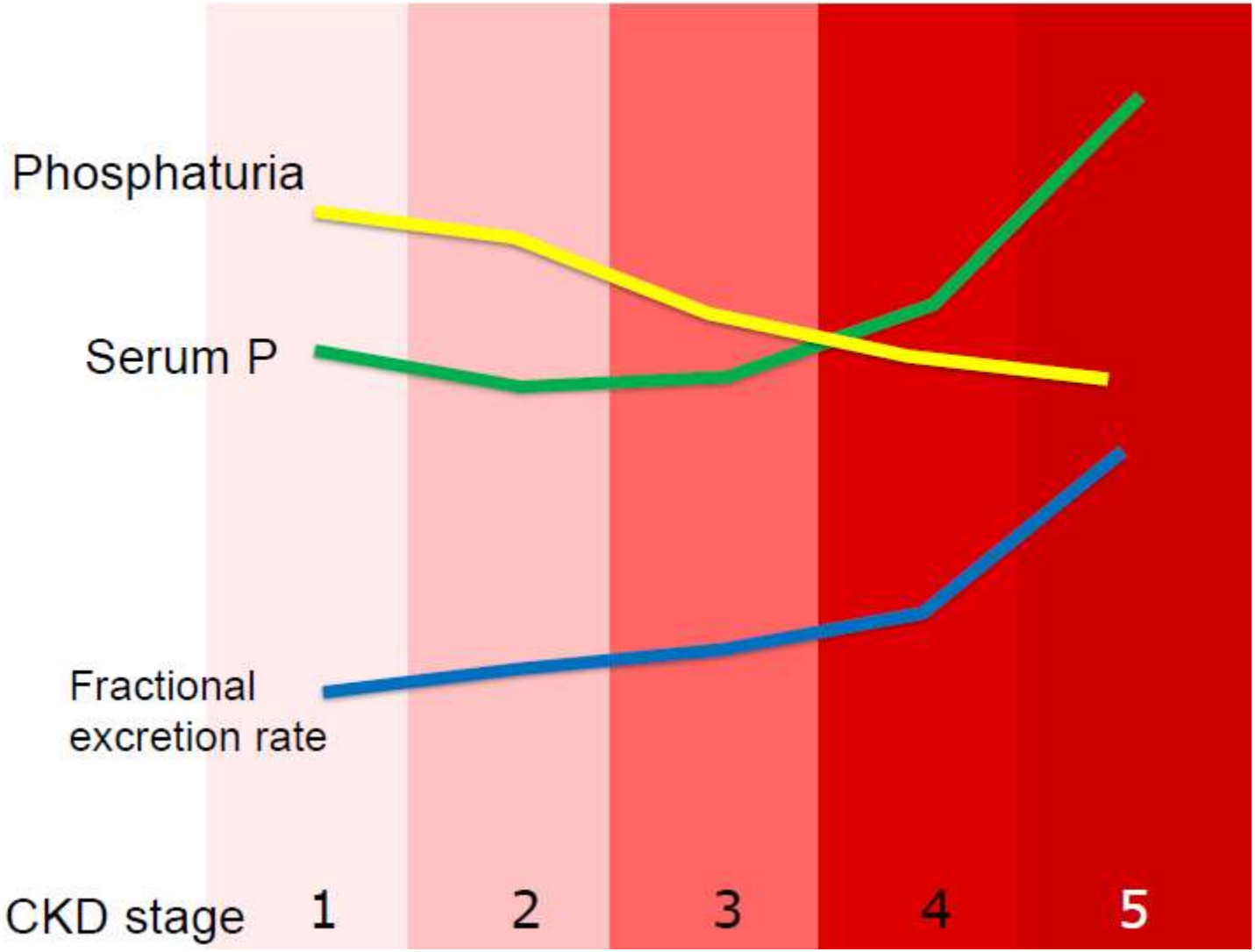

OPG
mocnocyte/macrophages
cell line
osteoblast
1,25[OH]2D)
glucocorticosteroids
PTH, PGE2, LPS,
histamine
IL-1 and IL-11, TNF-α
mRANKL
RANKL ↑
OPG ↓
pre-osteoclast
sRANKL
osteoclast's
apoptosis
osteoblast
osteoclast

Secondary Hyperparthyroidism: Pathogenesis, Diagnosis, Preventive and Therapeutic Strategies



M.Rodríguez Portillo et al Rev Endocr Metab Disord, 2017

Serum phosphate, urine phosphate and fractional excretion of phosphate for each CKD stages



Modified from L Craver, et al. Nephrol Dial Transplant, 2007

Bone: a new endocrine organ at the heart of chronic kidney disease and mineral and bone disorders

*Marc G Vervloet, Ziad A Massy, Vincent M Brandenburg, Sandro Mazzaferro, Mario A Cozzolino, Pablo Ureña-Torres, Jordi Bover, David Goldsmith, on behalf of the CKD-MBD Working Group of ERA-EDTA**

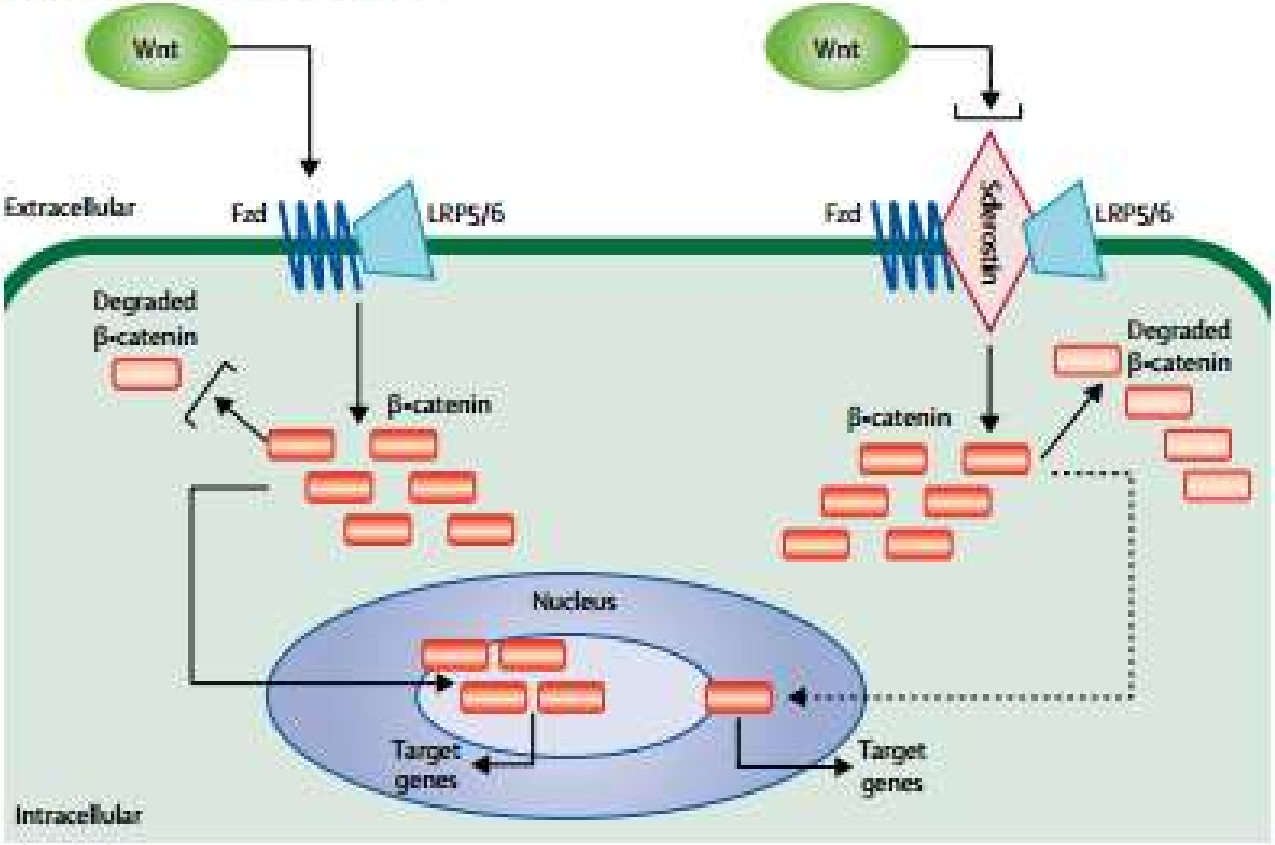
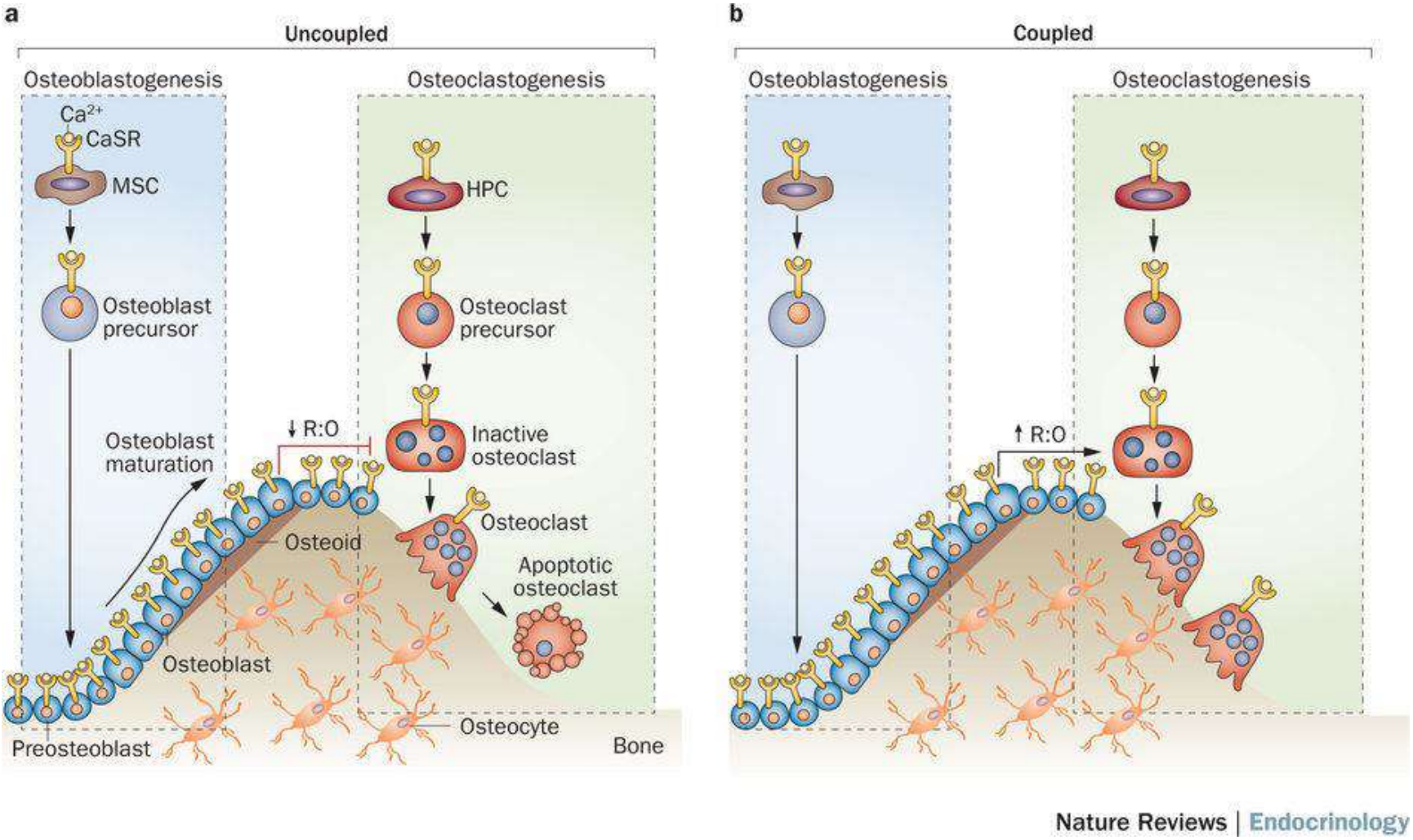


Figure 2: Inhibition of Wnt signalling

Within the canonical pathway, Wnt ligands interact with a transmembrane receptor complex including frizzled (Fzd) and LRP5/6. Activation of the receptor complex stabilises cytosolic β-catenin by blocking degradation processes. Hence, more β-catenin can enter the nucleus and assist activation of target genes. Wnt inhibitors such as sclerostin interfere with Wnt-receptor complex activation and finally reduce intranuclear β-catenin activity by stimulating phosphorylation degradation.

The Lancet 2014

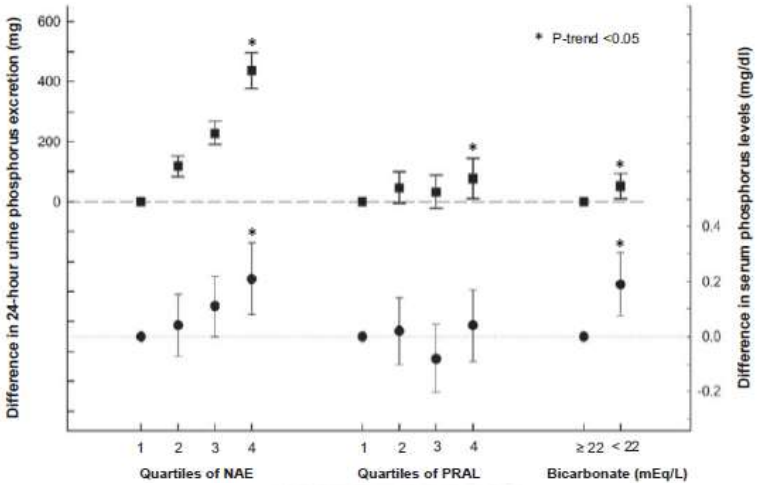
Model of CaSR action in bone formation and reabsorption



AJKD
Original Investigation

Acid Load and Phosphorus Homeostasis in CKD

Pascale Khairallah, MD,[1] Tamara Isakova, MD, MMSc,[2,3] John Asplin, MD,[4] Lee Hamm, MD,[5] Mirela Dobre, MD, MPH,[6] Mahboob Rahman, MD,[6] Kumar Sharma, MD,[7] Mary Leonard, MD, MSCE,[8] Edgar Miller III, MD, PhD,[9,10] Bernard Jaar, MD, MPH,[9,10,11] Carolyn Brecklin, MD,[12] Wei Yang, PhD,[13] Xue Wang, MS,[13] Harold Feldman, MD, MSCE,[13,14] Myles Wolf, MD, MMSc,[1] and Julia J. Scialla, MD, MHS,[1,13,15] on behalf of the Chronic Renal Insufficiency Cohort (CRIC) Study Investigators*



Acidosis and Phosporus homeostasis in CKD