SEMINAR ON CKD: 64th MMA: 2017

Role of Active Vitamin D in Chronic Kidney Disease

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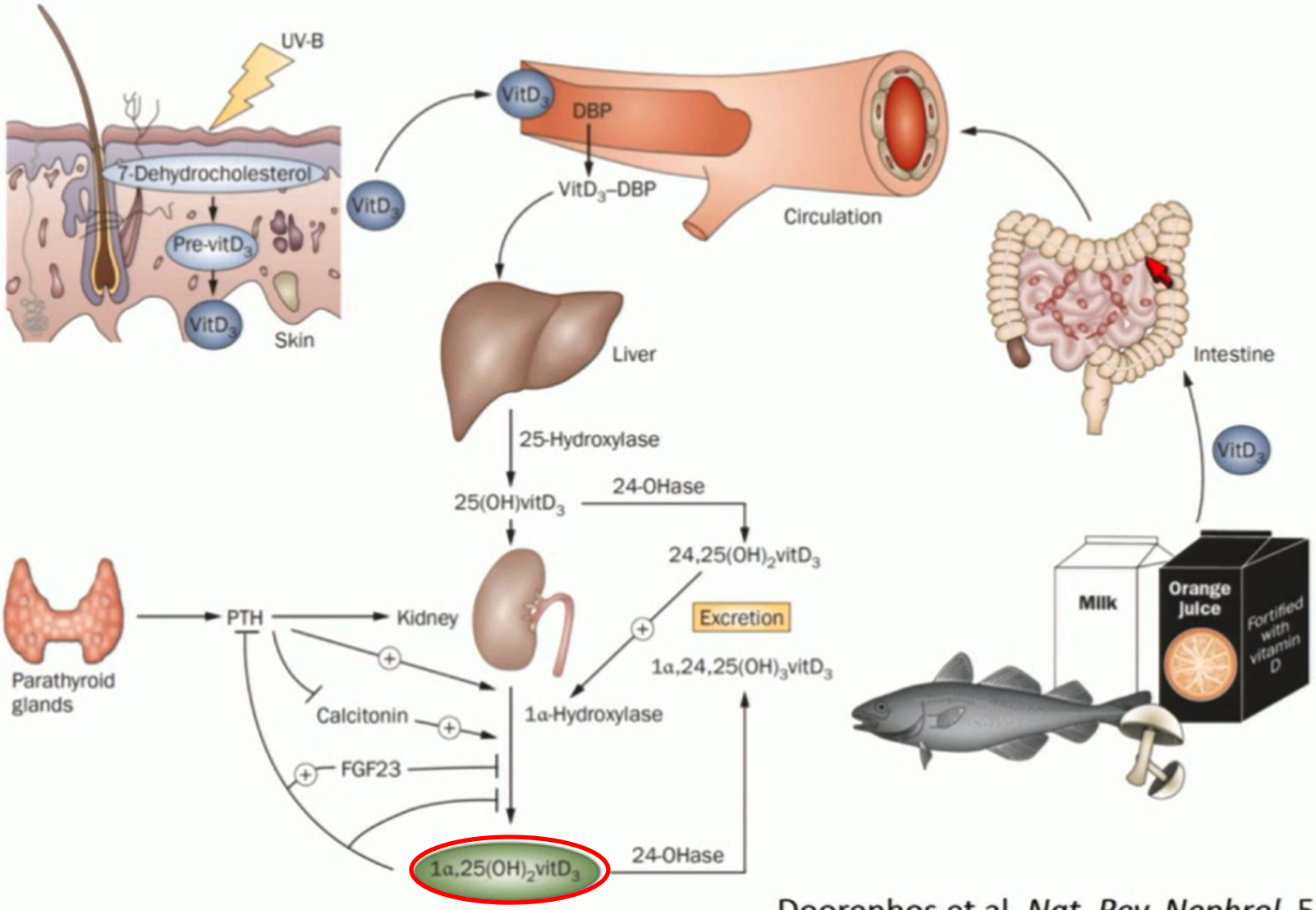
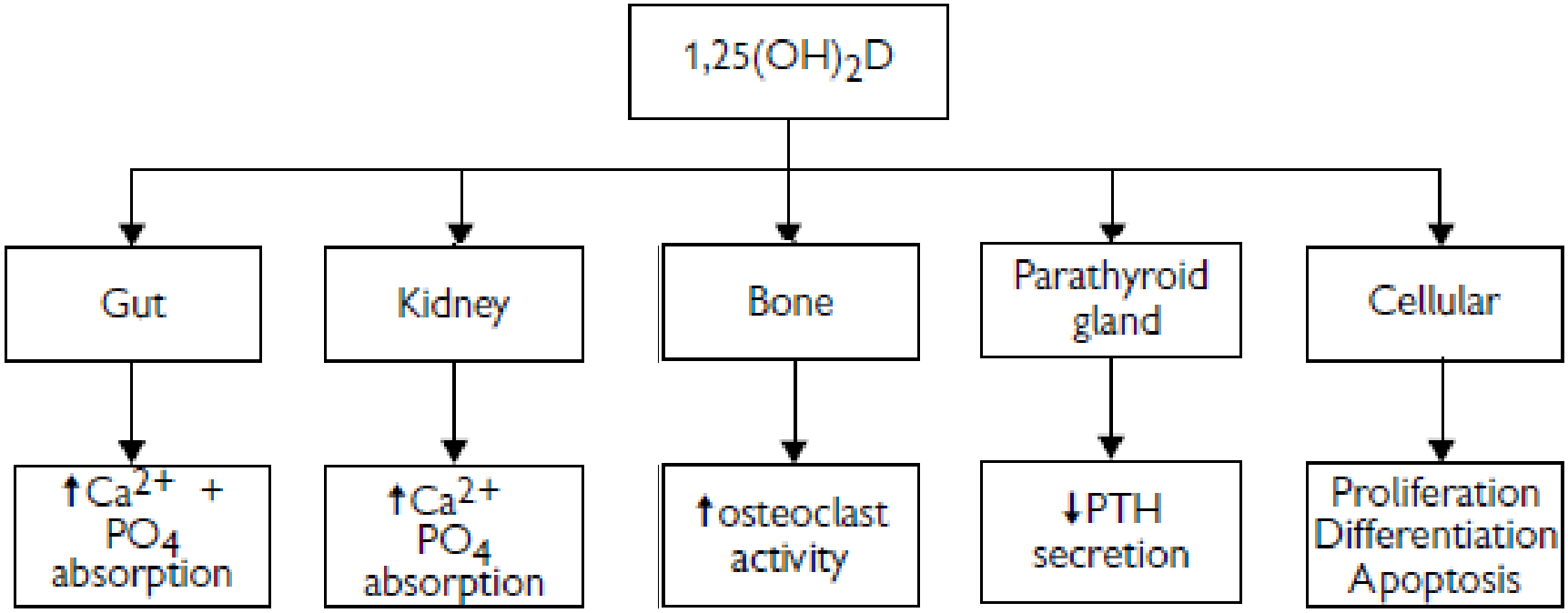
Vitamin D physiology



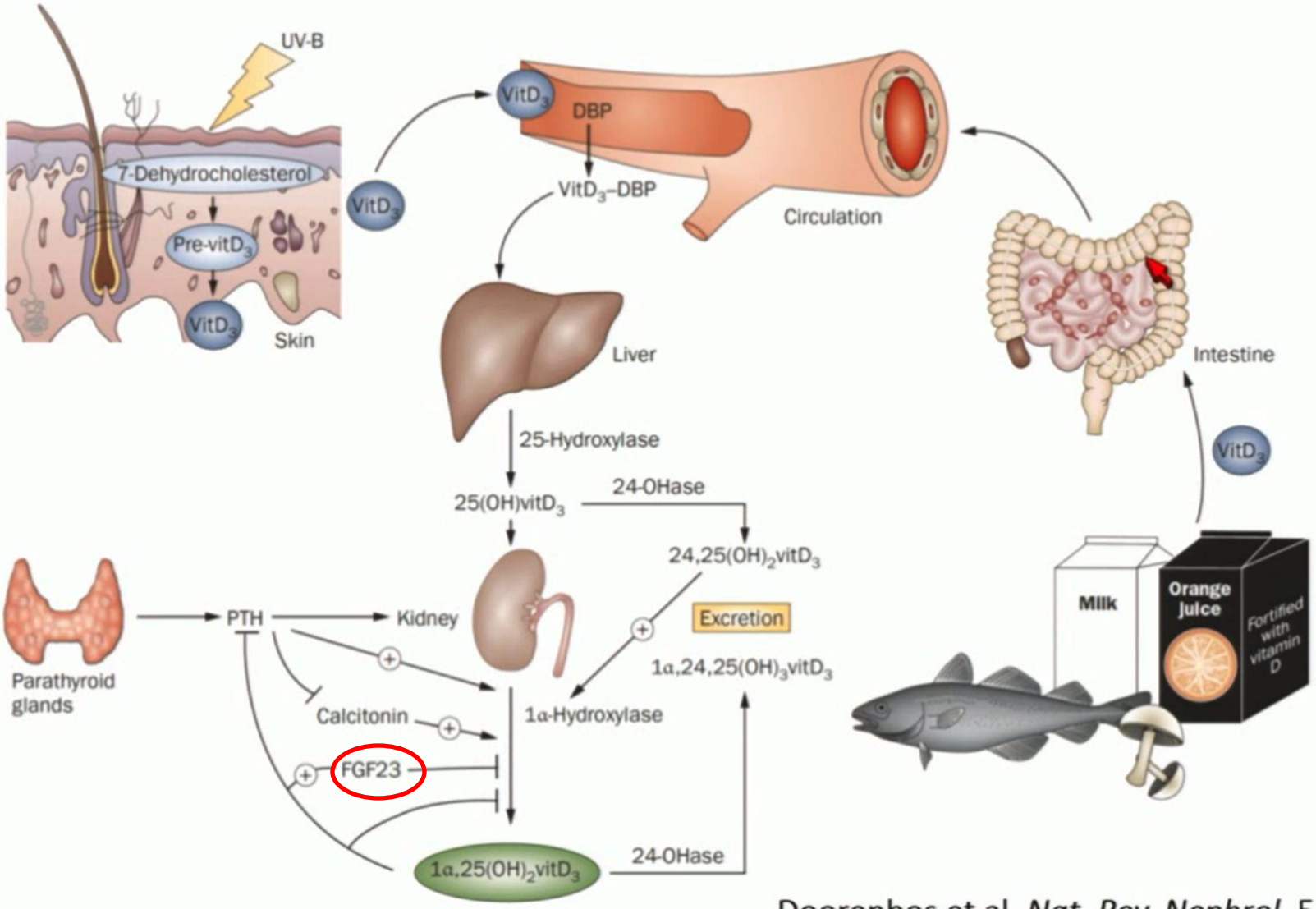
Doorenbos et al. *Nat. Rev. Nephrol.* 5, 691–700 (2009)

Vitamin D

- 1, 25(OH) 2 D exerts many important biological effects via its intracellular receptor (VDR)
- Main stimulus = PTH
- Main inhibitor = FGF23



Vitamin D physiology



Doorenbos et al. *Nat. Rev. Nephrol.* 5, 691–700 (2009)

FGF-23 (Anti-Vit D)

- Produced by osteocyte+blast when↓GFR or↑PO_4
- Action on Kidney
  - ↓↓ the 1 α –hydroxylase = ↓ 1,25$(OH)_2$ D
  - ↑ urinary PO_4 excretion

biomarker for mortality.

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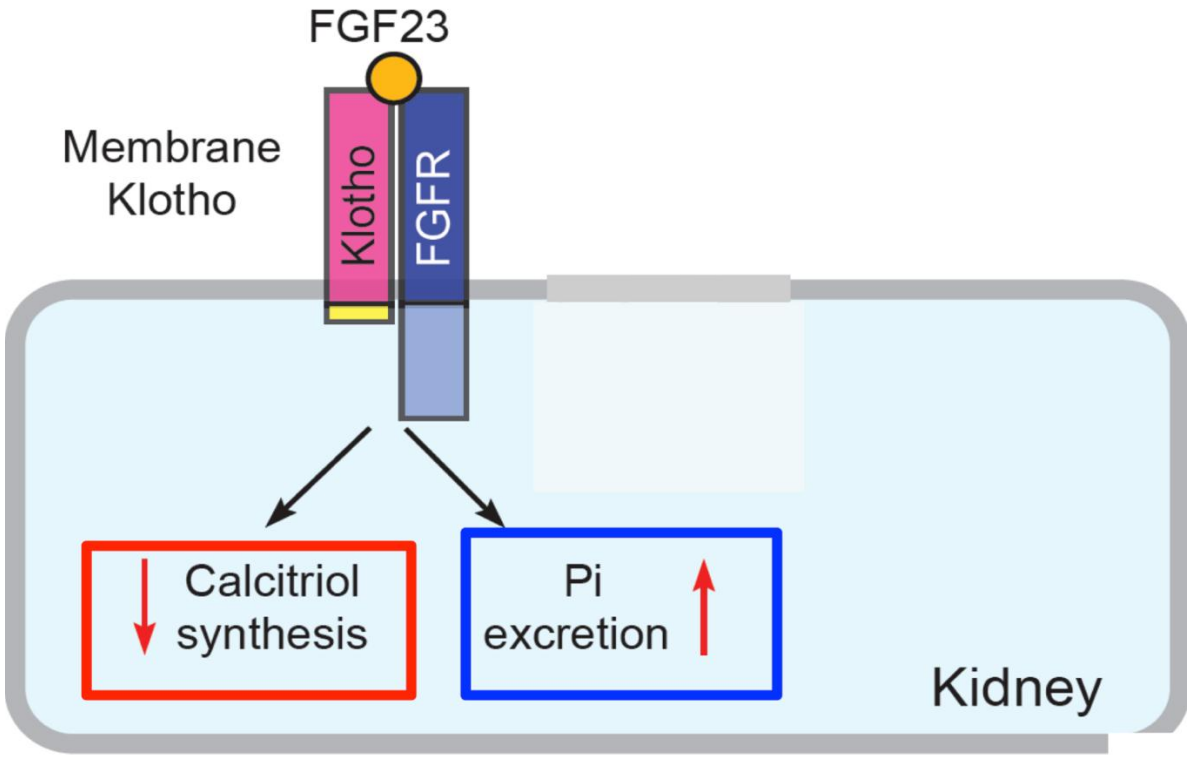
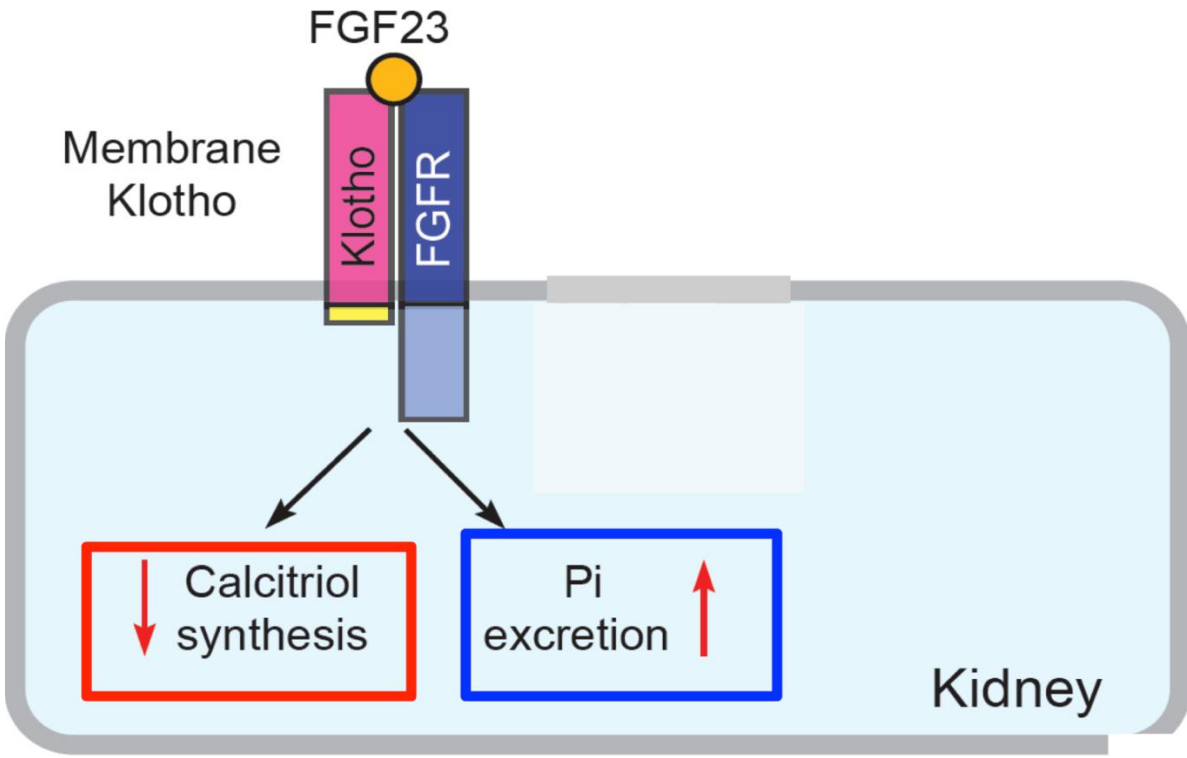


biomarker for mortality.

Klotho

- Transmembrane protein
- Forms a complex with the FGF receptor to ↑ FGF-23 affinity
- Ageing suppressor gene



THELANCETDE-D-13-00595

S2213-8587(14)70059-2

Embargo: [add date when known]

HC
Version 1
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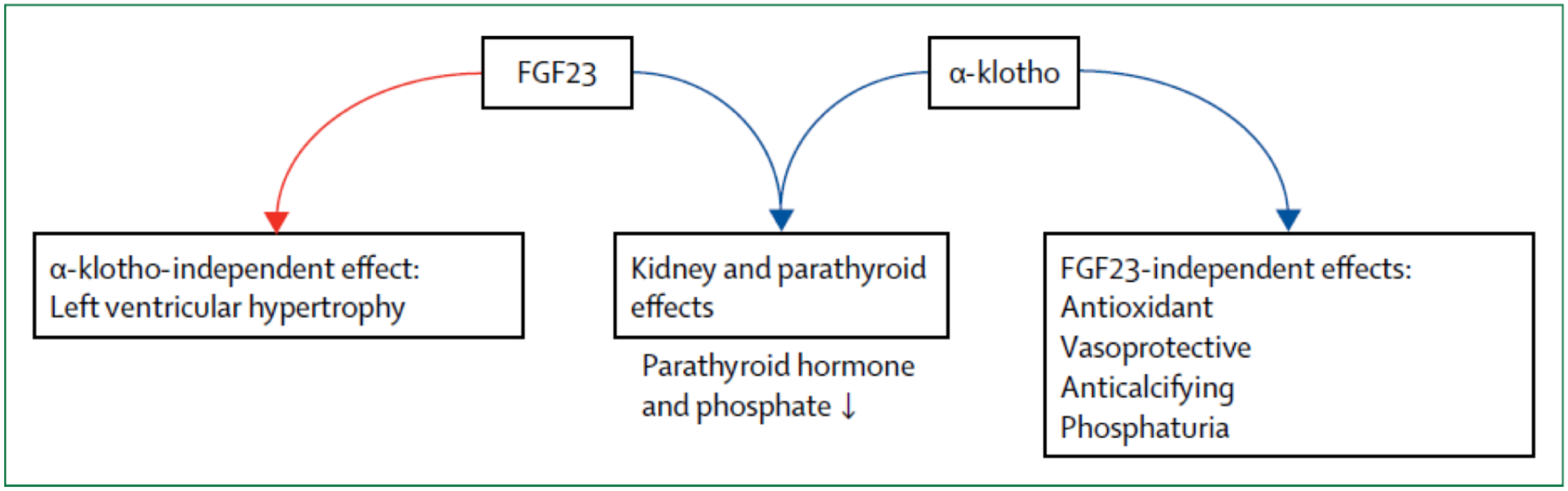
Bone: a new endocrine organ at the heart of chronic kidney disease and mineral and bone disorders

*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**



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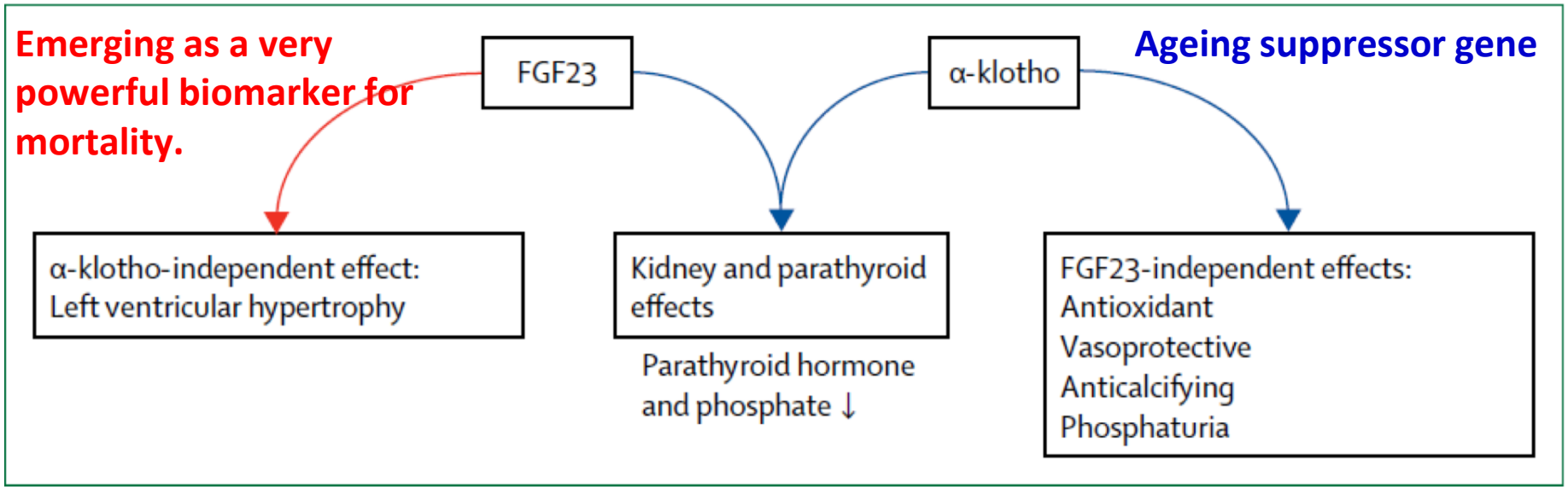
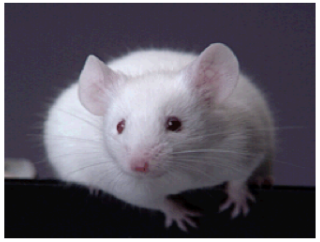
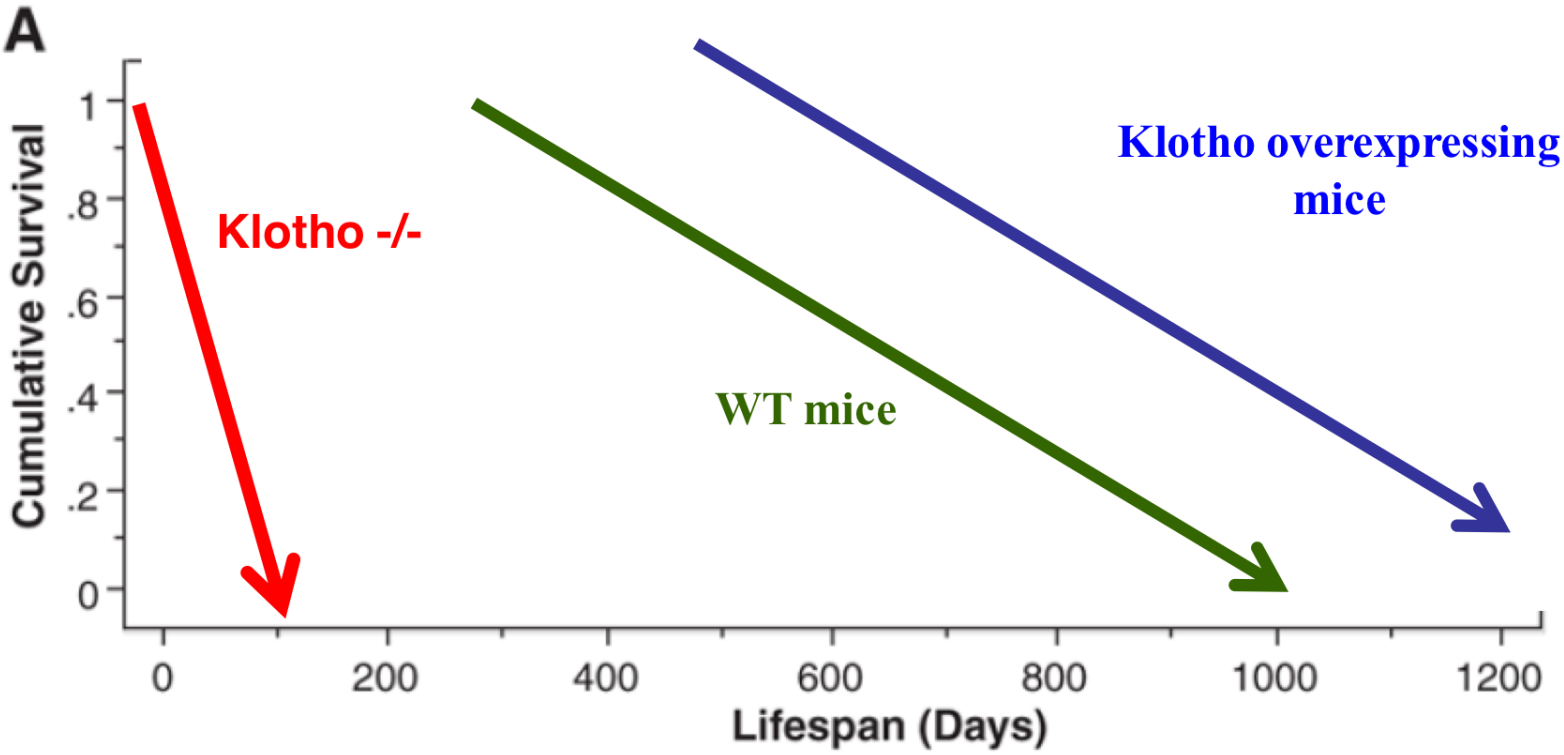


CKD-MBD

Suppression of Aging in Mice by the Hormone Klotho

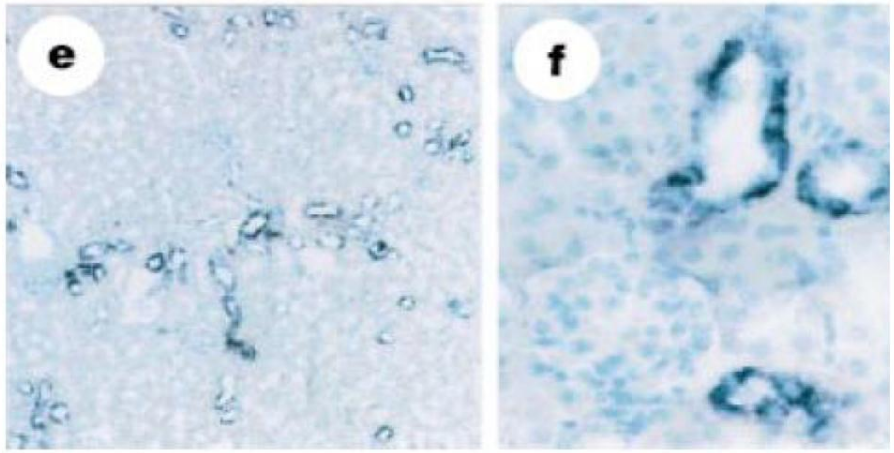


Hiroshi Kurosu[1], Masaya Yamamoto[1], Jeremy D. Clark[1], Johanne V. Pastor[1], Animesh Nandi[1], Prem Gurnani[1], Owen P. McGuinness[3], Hirotaka Chikuda[4], Masayuki Yamaguchi[4], Hiroshi Kawaguchi[4], Iichiro Shimomura[5], Yoshiharu Takayama[2], Joachim Herz[2], C. Ronald Kahn[6], Kevin P. Rosenblatt[1], and Makoto Kuro-o[1,*]

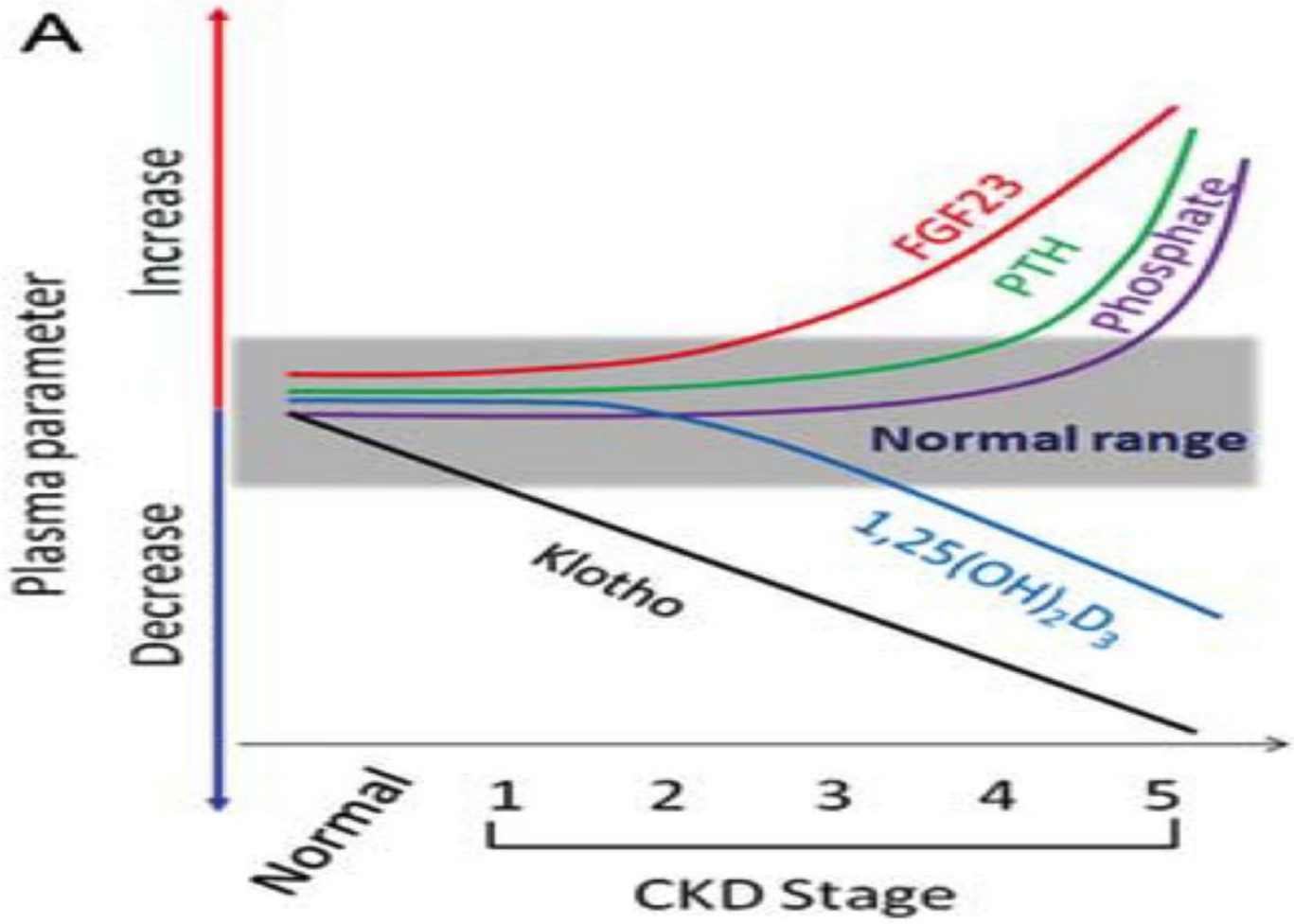


Science. 2005 September 16; 309(5742): 1829–1833.

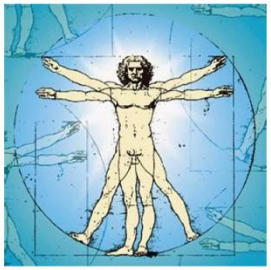
The kidney is the main site of *klotho* gene expression

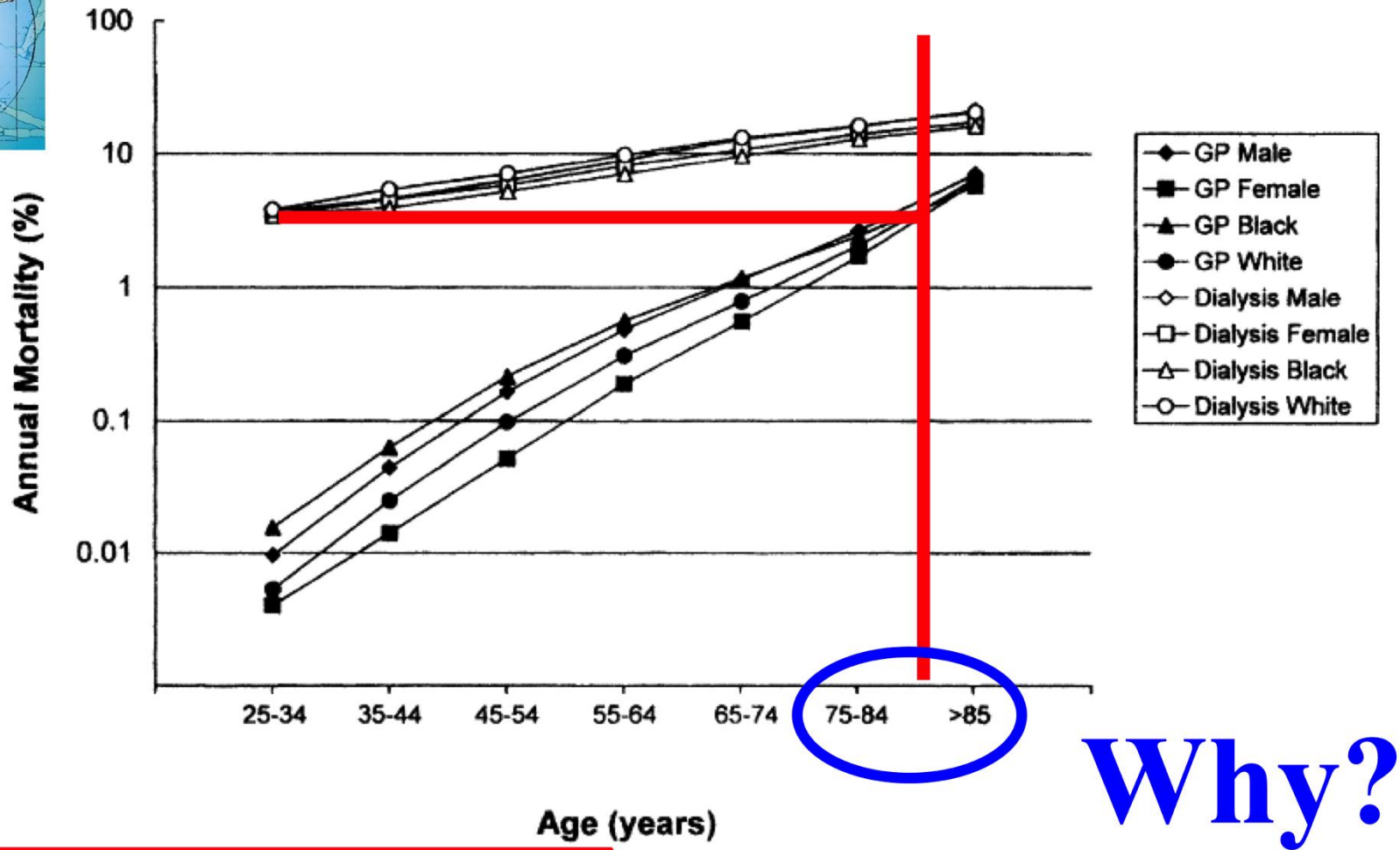


Kuro-o M. Nature. 1997


A
Plasma parameter
Increase
Decrease
FGF23
PTH
Phosphate
Normal range
1,25(OH)2D3
Klotho
Normal
1
2
3
4
5
CKD Stage

Accelerated aging in ESRD CKD patients: CVD mortality





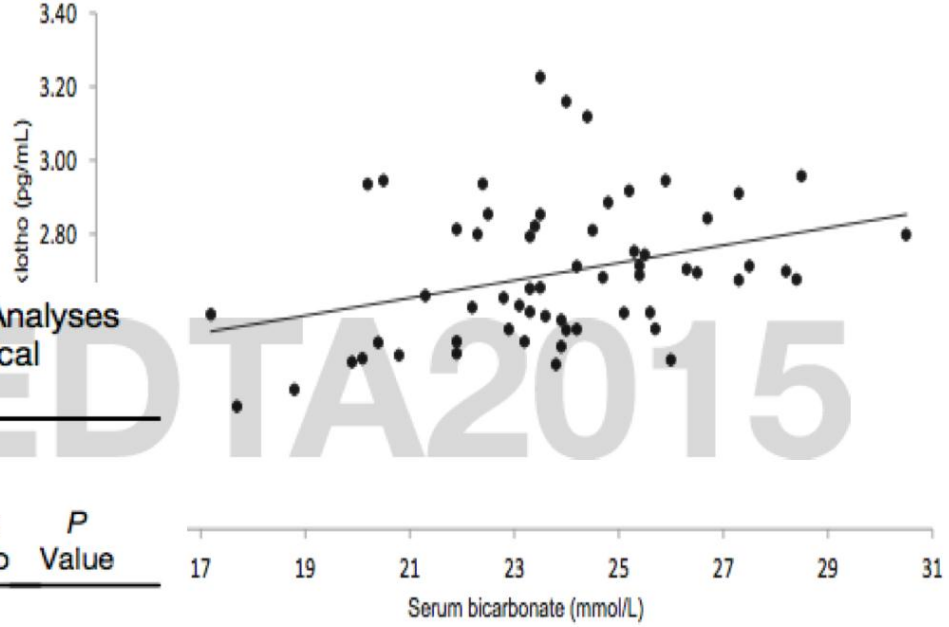
Why?

Mortality is associated to both systemic inflammation and CKD-MBD

USRDS: Levey et al. Am J Kidney Dis 1998

ERA/EDTA: de Jager DJ et al. JAMA 2009

Serum Klotho is inversely related to acidosis in st 3 CKD



between α-Klotho and serum bicarbonate ($n = 60$; $r = 0.33$; $P = .011$).

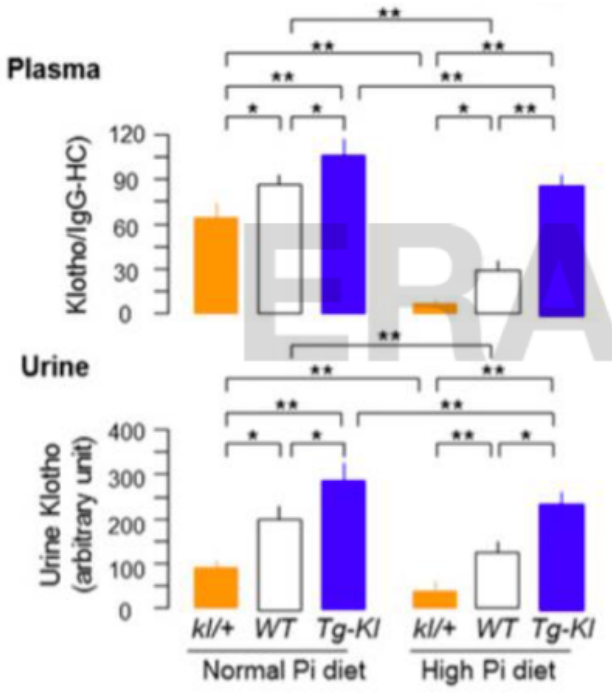
Table 2. Univariate and Multivariate Regression Analyses Between α-Klotho (Log Transformed) and Biological Parameters

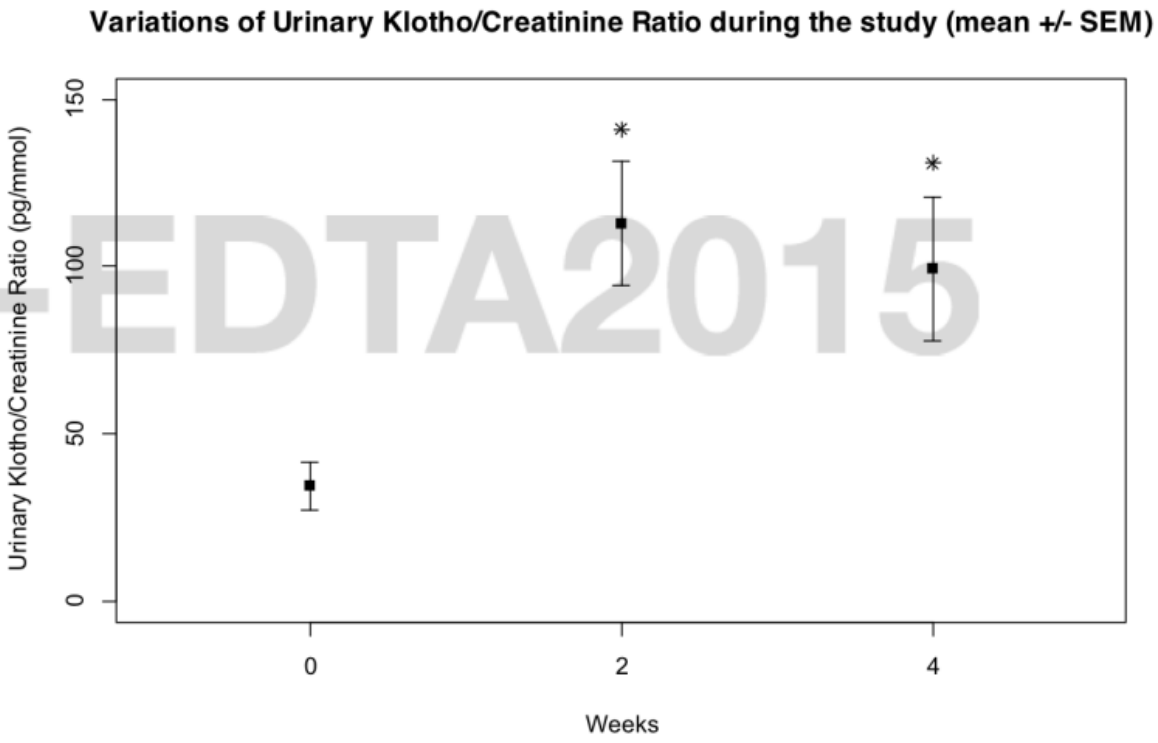
Variable	Correlation Coefficient for Difference in Log α-Klotho	*P* Value
Univariate analysis		
Serum bicarbonate (mmol/L)	0.33	.011
Proteinuria (g/d)	−0.36	.013
Serum creatinine (μmol/L)	−0.36	.007
Serum FGF23 (RU/mL)	0.23	.078
CRP (mg/L)	0.15	.412
Inulin clearance (mL/min/1.73 m^2)	0.11	.404
Multivariate analysis		
Serum bicarbonate (mmol/L)	0.428	.003
Serum creatinine (μmol/L)	−0.104	.621
Proteinuria (g/d)	−0.059	.706

CRP, C-reactive protein; FGF, fibroblast growth factor.

Hage et al. J Renal Nutr 2014;24:390-94

Sodium bicarbonate treatment restores renal Klotho production during CKD



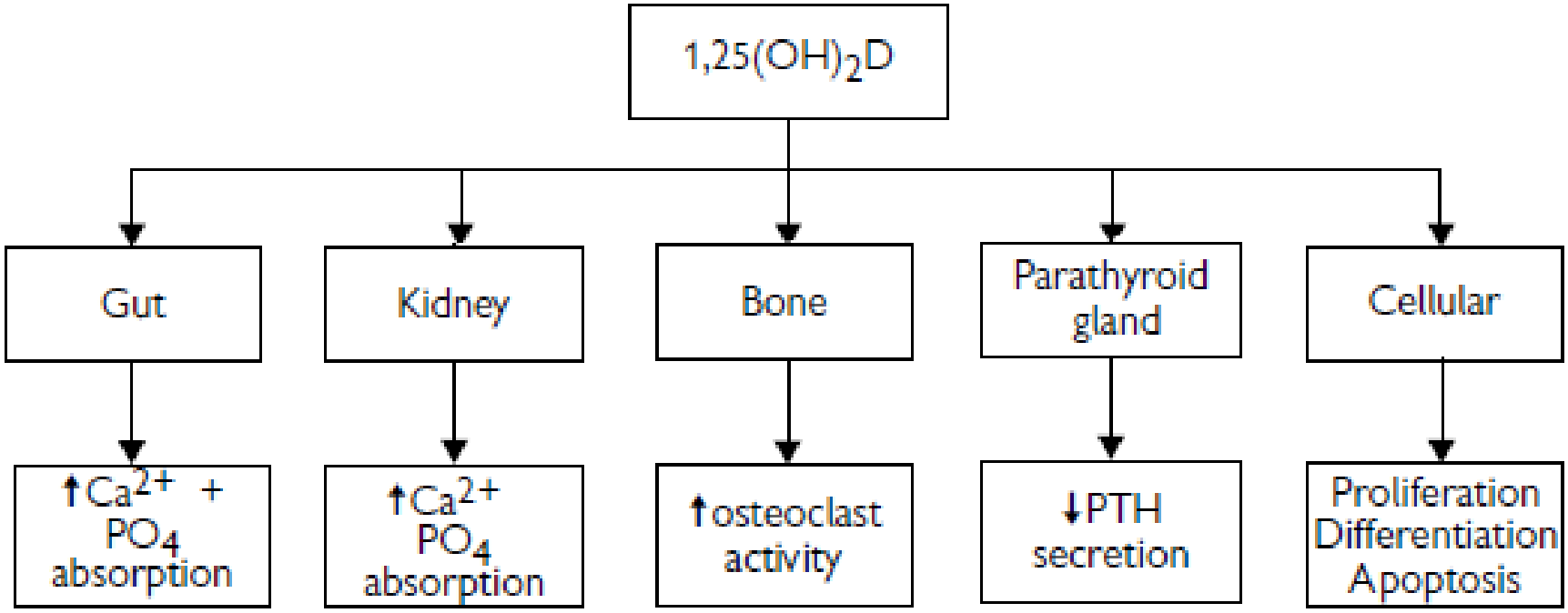


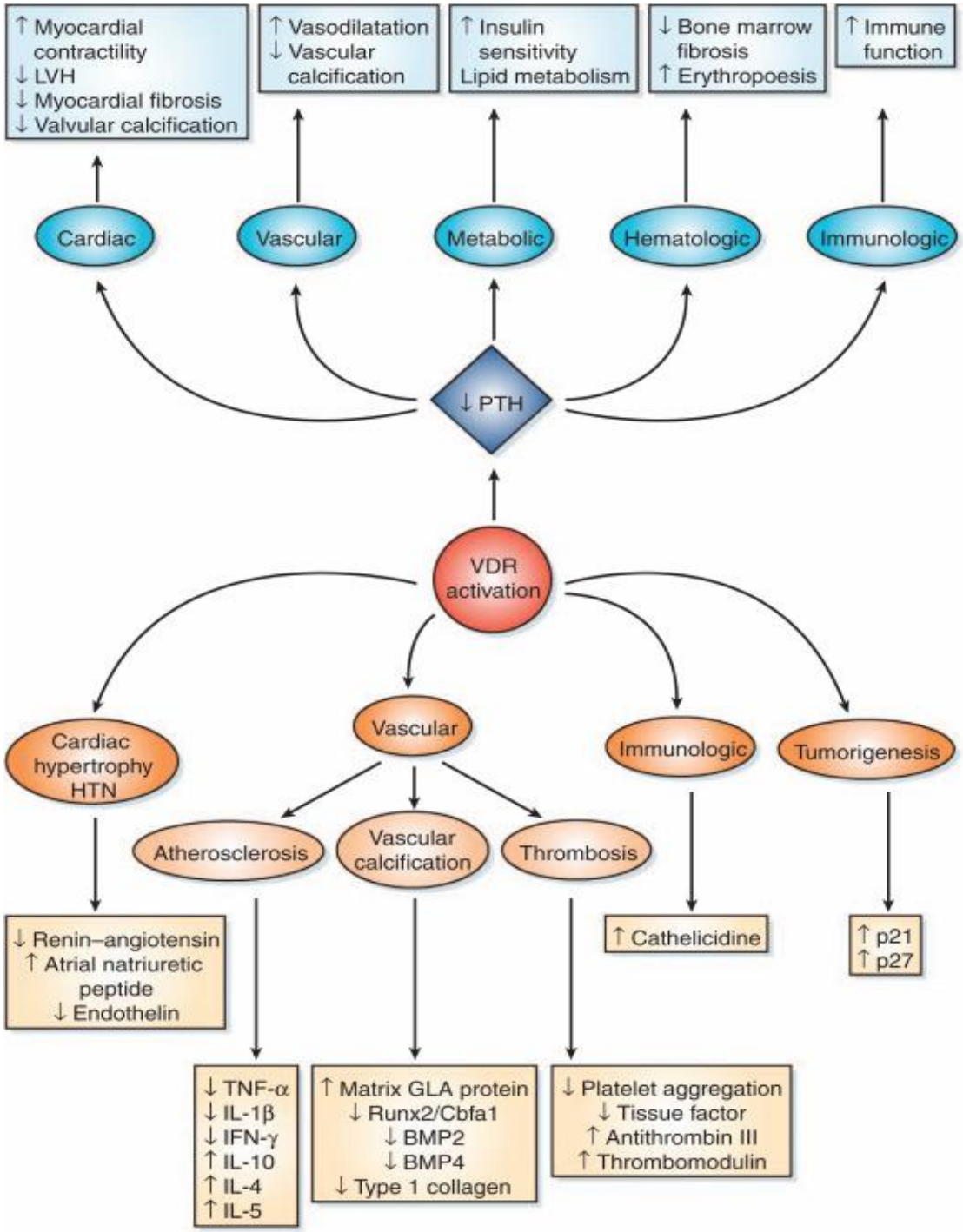
4 wk Na bicarb treatment, 3g/day, st3 CKD

Hage et al ERA-EDTA London poster 317

Vitamin D

- 1, 25(OH) 2 D exerts many important biological effects via its intracellular receptor (VDR)
- PTH = Main stimulus
- FGF23 = Main inhibitor





Kidney International 2008 73, 1355-1363DOI: (10.1038/ki.2008.35)

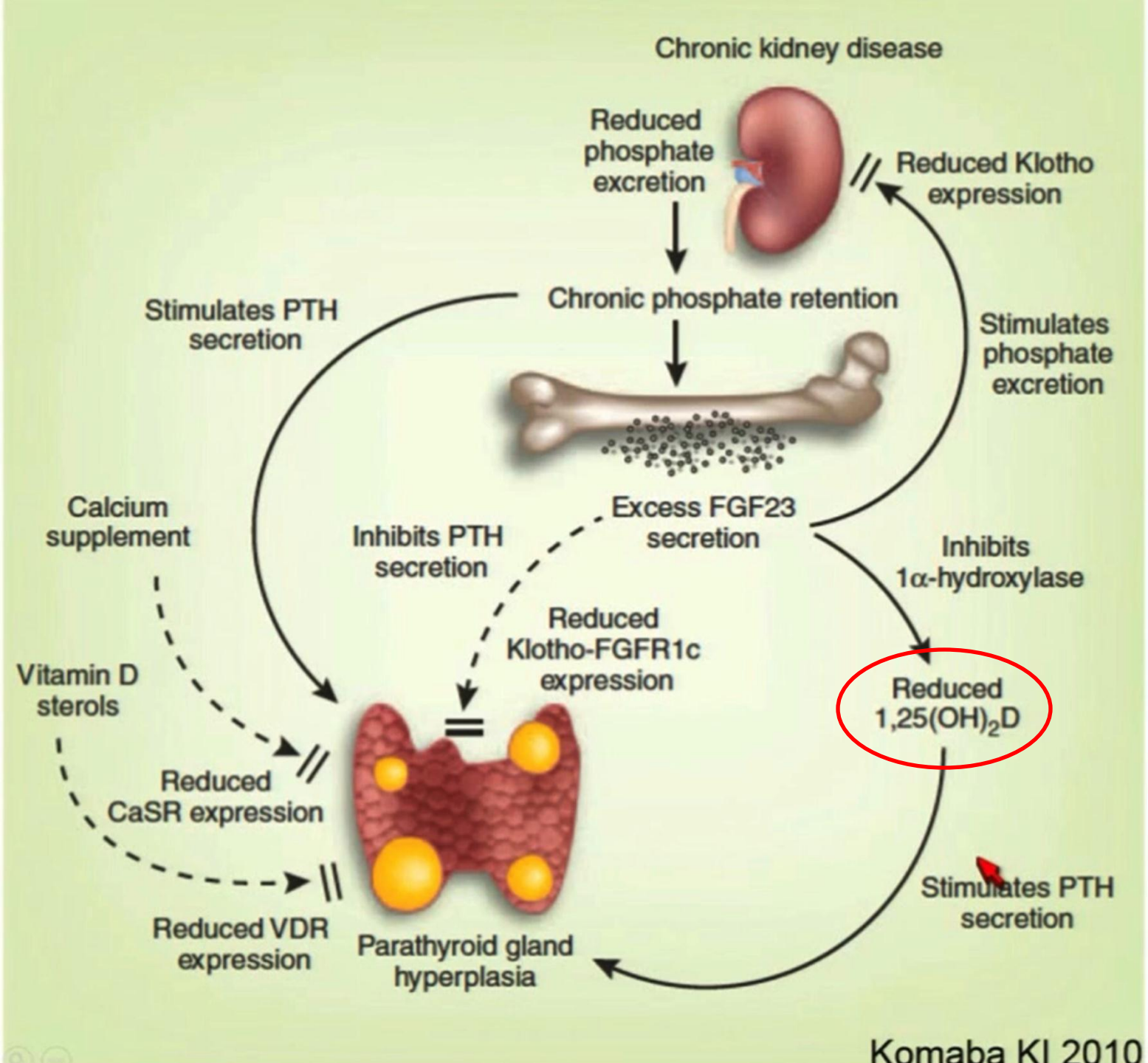
Vitamin D

- **R**oles in immunity, inflammation, vascular and cardiac function, and insulin resistance.

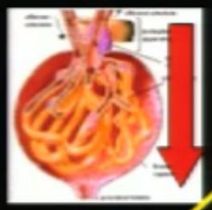
In the kidney

  - influences mesangial cell and podocyte proliferation
  - downregulates RAS (via renin inhibition)
  - prevents glomerular hypertrophy
  - decreases cytokine production, reduces inflammation, and blocks epithelial to mesenchymal transition.

- It may ameliorate proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis.

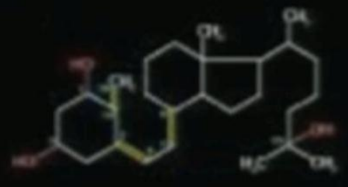

Chronic kidney disease
Reduced phosphate excretion
Reduced Klotho expression
Chronic phosphate retention
Stimulates PTH secretion
Stimulates phosphate excretion
Calcium supplement
Excess FGF23 secretion
Inhibits PTH secretion
Inhibits 1α-hydroxylase
Reduced Klotho-FGFR1c expression
Vitamin D sterols
Reduced 1,25(OH)2D
Reduced CaSR expression
Stimulates PTH secretion
Reduced VDR expression
Parathyroid gland hyperplasia
Komaba KI 2010

Pathophysiology of CKD-MBD



GFR

PO^4

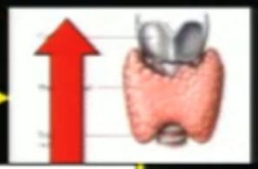


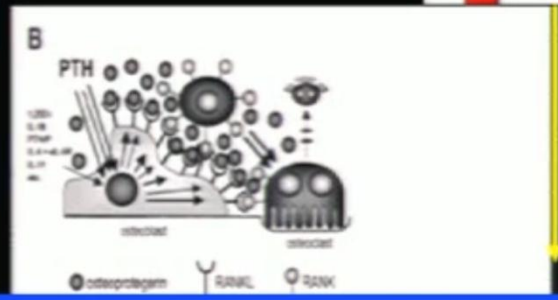
Calcitriol

Ca^2

PTH

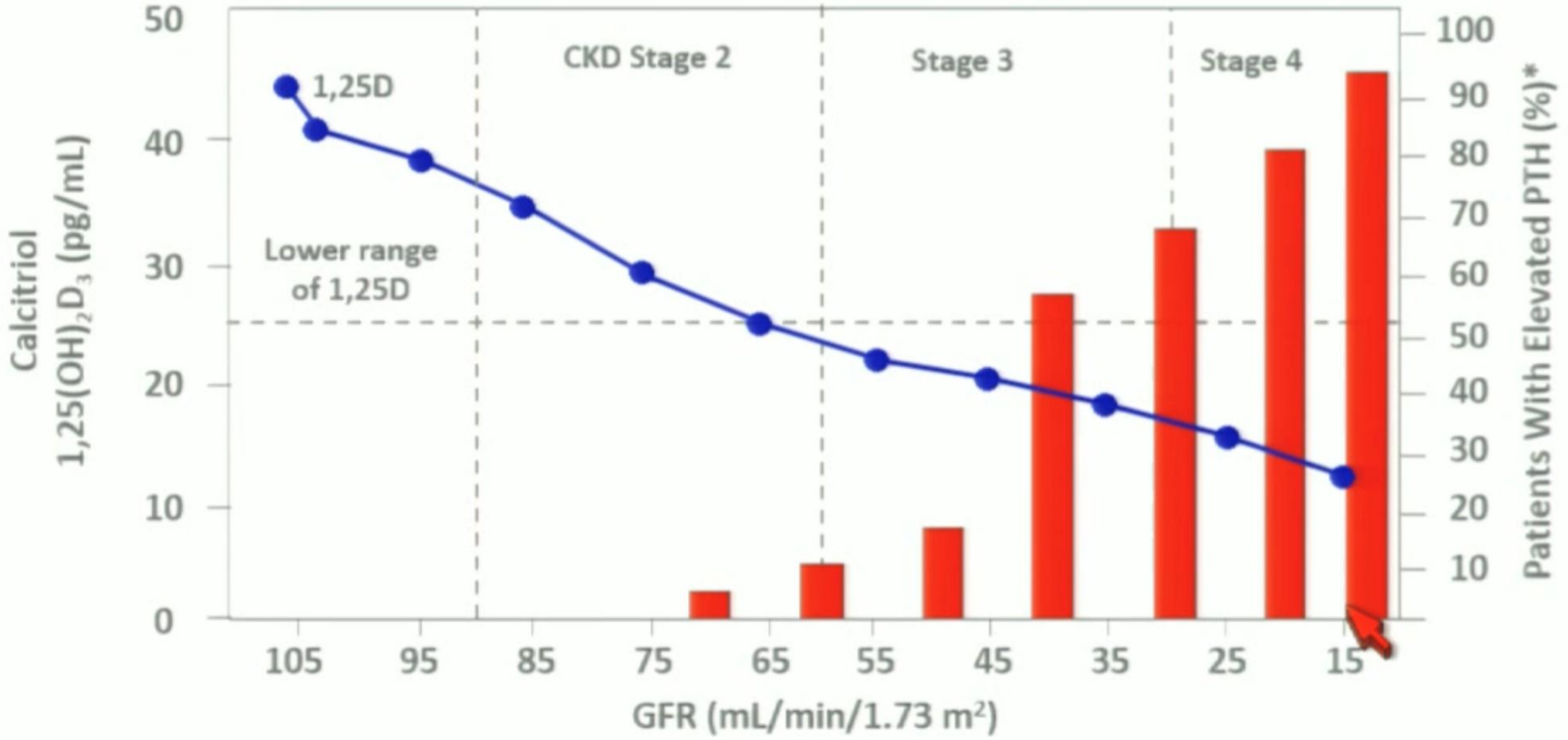
Skeletal Resistance to PTH





Hyperparathyroid bone

Calcitriol Deficiency and SHPT in CKD



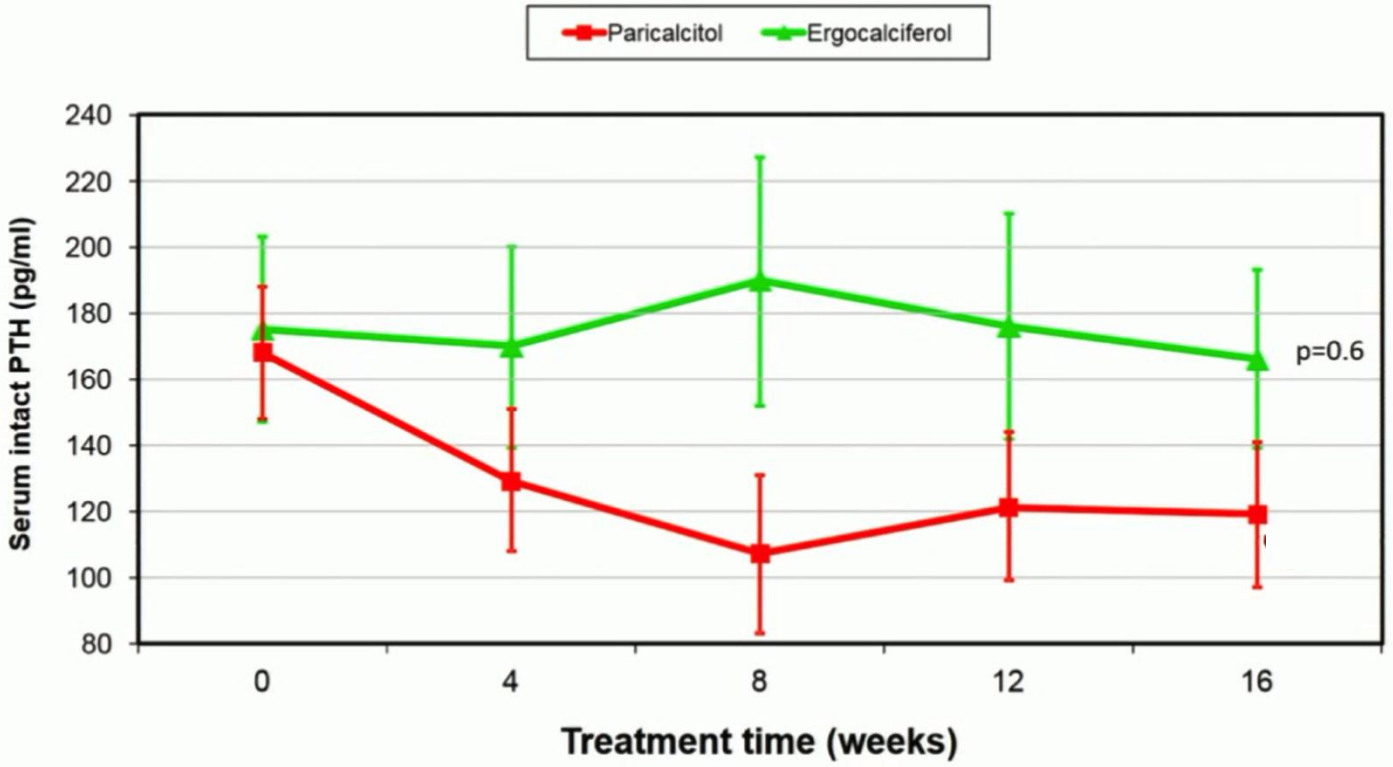
*Abnormal PTH based on Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in CKD. 2003.

Kates et al. *Am J Kidney Dis*. 1997;30:809-813; Martinez et al. *Am J Kidney Dis*. 1997;29:496-502; Martinez et al. *Nephrol Dial Transplant*. 1996;11(suppl 3):22-28; St. John et al. *Nephron*. 1992;61:422-427.

Northwestern Medicine

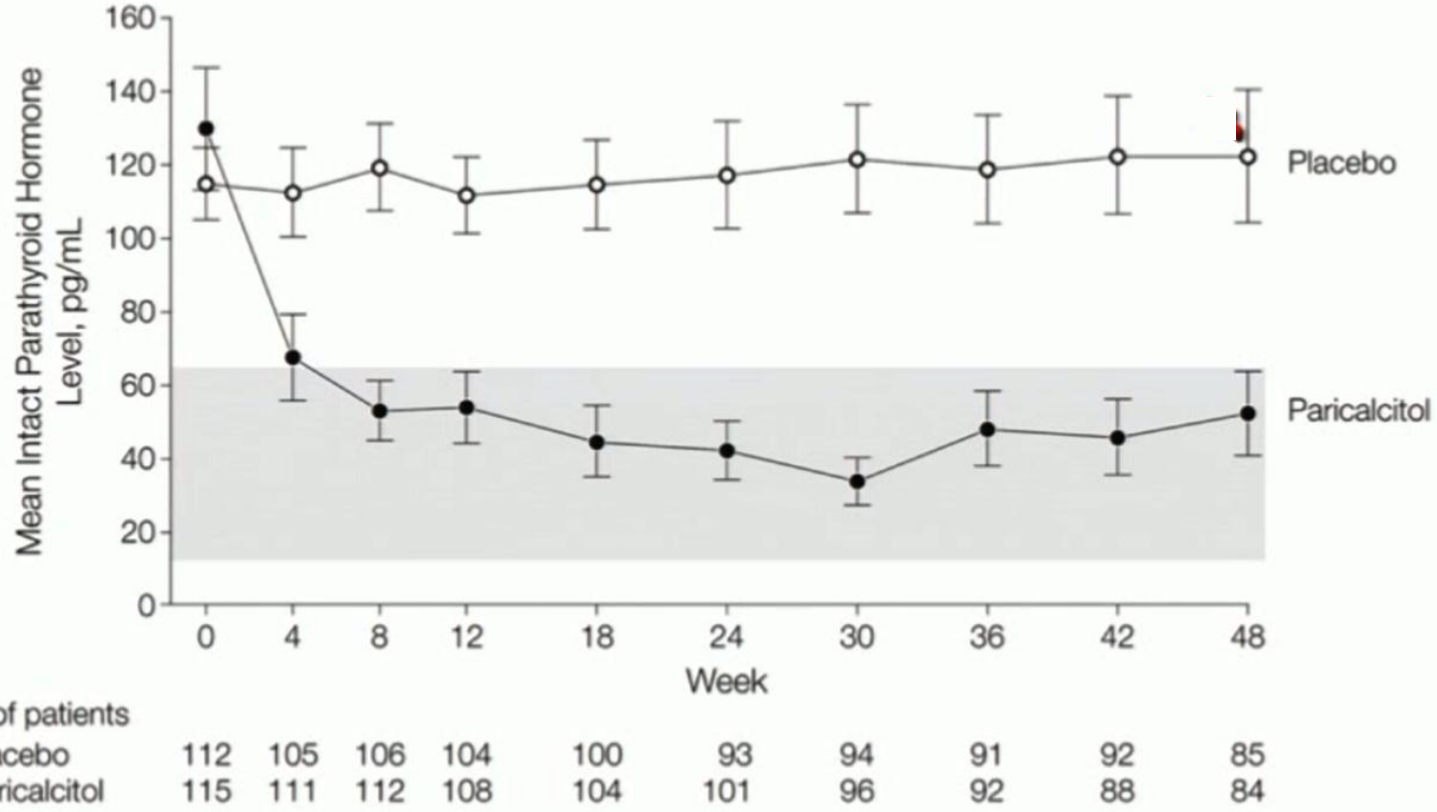
Native Vitamin D replacement

- In patients with normal kidney function
  - Replenishes 25(OH)D
- In patients with CKD
  - Replenishes 25(OH)D
    - High doses may be required
  - May not effectively increase circulating $1,25(OH)_2D$
    - Insufficient conversion by Cyp27B1
    - Enhanced catabolism by Cyp24A1 with high doses
  - How to measure therapeutic effect
    - PTH – only small part of potential biological effect, and response not specific for vitD
    - Plasma 25(OH)D level may not be indicative of biological effects



Kovesdy et al, *Am J Kidney Dis.* 2012 Jan;59(1):58-66

In the PRIMO Trial, paricalcitol decreased PTH levels



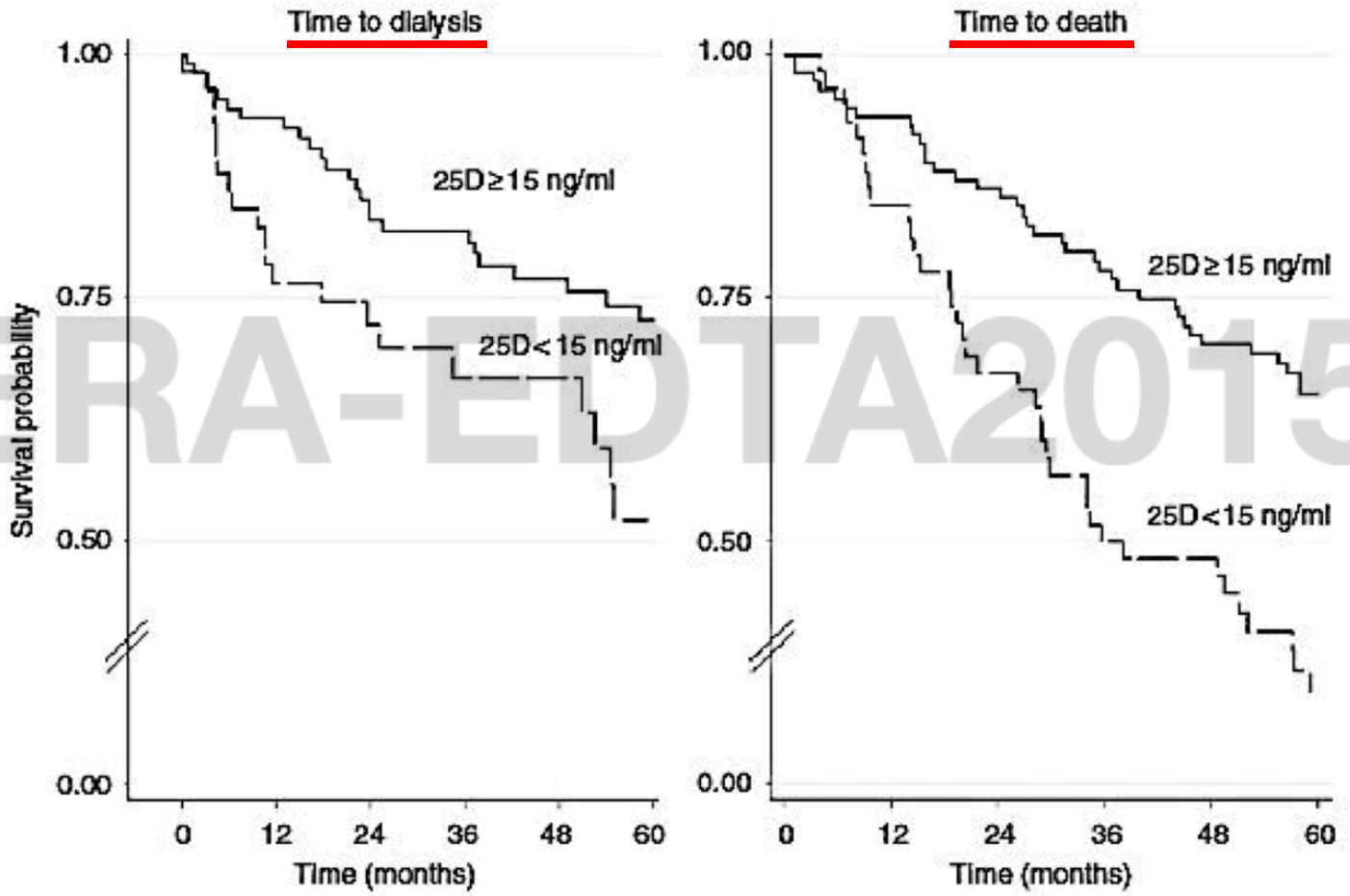
No. of patients										
Placebo	112	105	106	104	100	93	94	91	92	85
Paricalcitol	115	111	112	108	104	101	96	92	88	84

Thadhani, R. et al. JAMA 2012;307:674-684

JAMA

Vitamin D as Nephroprotective in CKD?

Vitamin D and Progression of Chronic Kidney Disease and Mortality



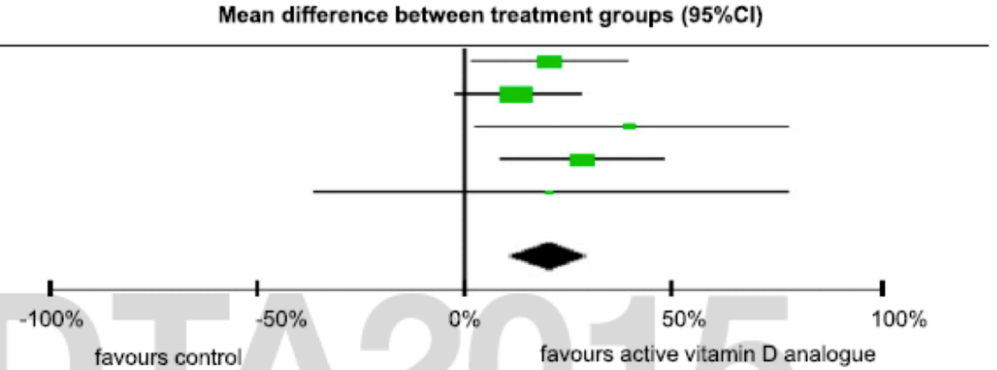
Crude renal and patient survival curves by presence of 25D deficiency (levels of 25D <15 vs 15 ng/ml or greater).

Ravani P et al. Kidney International 2008

Vitamin D effect on proteinuria in CKD

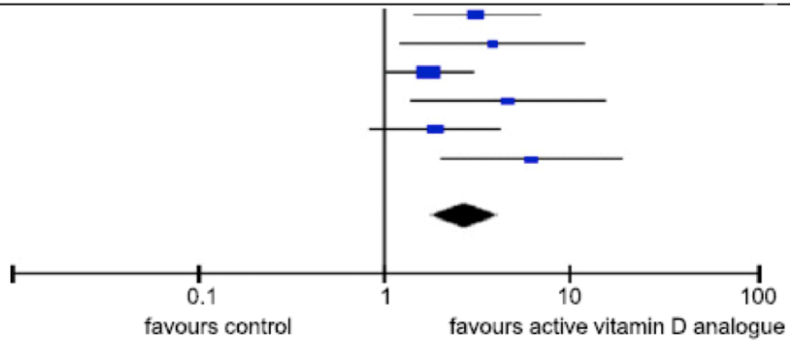
	Mean (95% CI) UP change (%)	
	control	vitamin D
Fishbane et al (2009)	+3 (-4 to +10)	-18 (-1 to -35)
De Zeeuw et al (2010)	-3 (-16 to +13)	-16 (-24 to -9)
Liu et al (2012)	+21 (-9 to +52)	-19 (-42 to +4)
Krairittichai (2012)	+10 (-3 to +23)	-19 (-33 to -5)
Thadhani et al (2012)	+12 (-30 to +54)	-9 (-51 to +33)
Overall	+6 (0 to +12)	-16 (-13 to -18)

Test for heterogeneity: I2=0%, Q=2.64, *P*=0.62
Overall effect: *P*=<0.0001



	Subjects with UP/UAE reduction / total number of subjects		Odds ratio (95%CI)
	control	vitamin D	
Agarwal et al (2005)	15 / 61	29 / 57	3.18 (1.46-6.93)
Fishbane et al (2009)	7 / 27	16 / 28	3.81 (1.22-11.92)
De Zeeuw et al (2010)	35 / 88	99 / 184	1.76 (1.05-2.95)
Liu et al (2012)	7 / 24	17 / 26	4.59 (1.39-15.15)
Thadhani et al (2012)	17 / 53	23 / 49	1.87 (0.84-4.19)
Krairittichai (2012)	5 / 45	20 / 46	6.15 (2.05-18.44)
Overall	86 / 298	204 / 390	2.78 (1.74-4.46)

Test for heterogeneity: I2=26%, Q=6.71, *P*=0.24
Overall effect: *P*<.0001

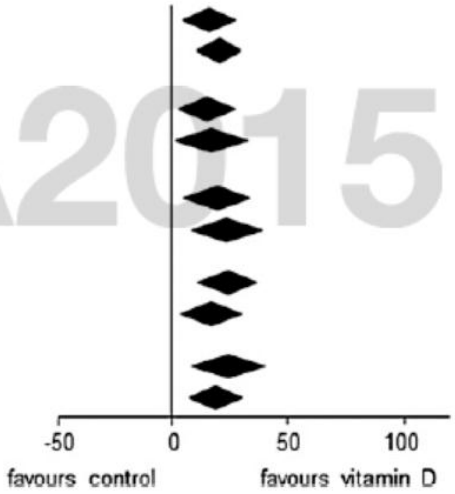


Active Vitamin D Treatment for Reduction of Residual Proteinuria: A Systematic Review

Martin H. de Borst,* Reza Hajhosseiny,†‡ Hector Tamez,† Julia Wenger,† Ravi Thadhani,† and David J.A. Goldsmith‡

Vitamin D effect on proteinuria in CKD

		Number of studies	Number of patients (vitamin D/control)	Mean difference (95% CI)	p for subgroup differences
Study drug	paricalcitol	3	264 / 171	16% (5 to 28%)	0.16
	calcitriol	2	72 / 69	31% (14 to 48%)	
Paricalcitol dose	1 ug/day	2	123 / 118	16% (3 to 28%)	0.86
	2 ug/day	2	141 / 141	17% (1 to 34%)	
Patient population	diabetic nephropathy only	2	230 / 133	20% (4 to 35%)	0.69
	not (only) diabetic nephropathy	3	106 / 107	24% (8 to 40%)	
Duration of follow-up	<24 weeks	2	77 / 75	24% (11 to 38%)	0.46
	≥ 24 weeks	3	259 / 165	17% (3 to 31%)	
Study size	number of participants <80	3	57 / 54	24% (8 to 41%)	0.61
	number of participants ≥80	3	279 / 186	19% (7 to 31%)	



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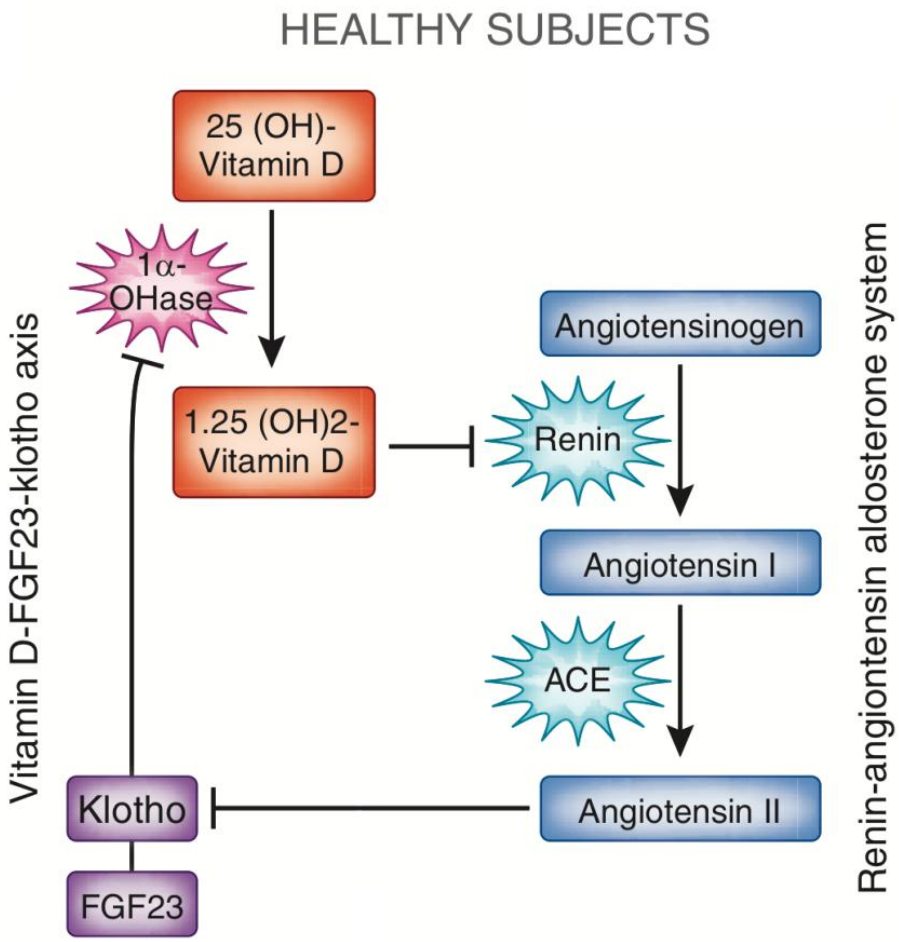
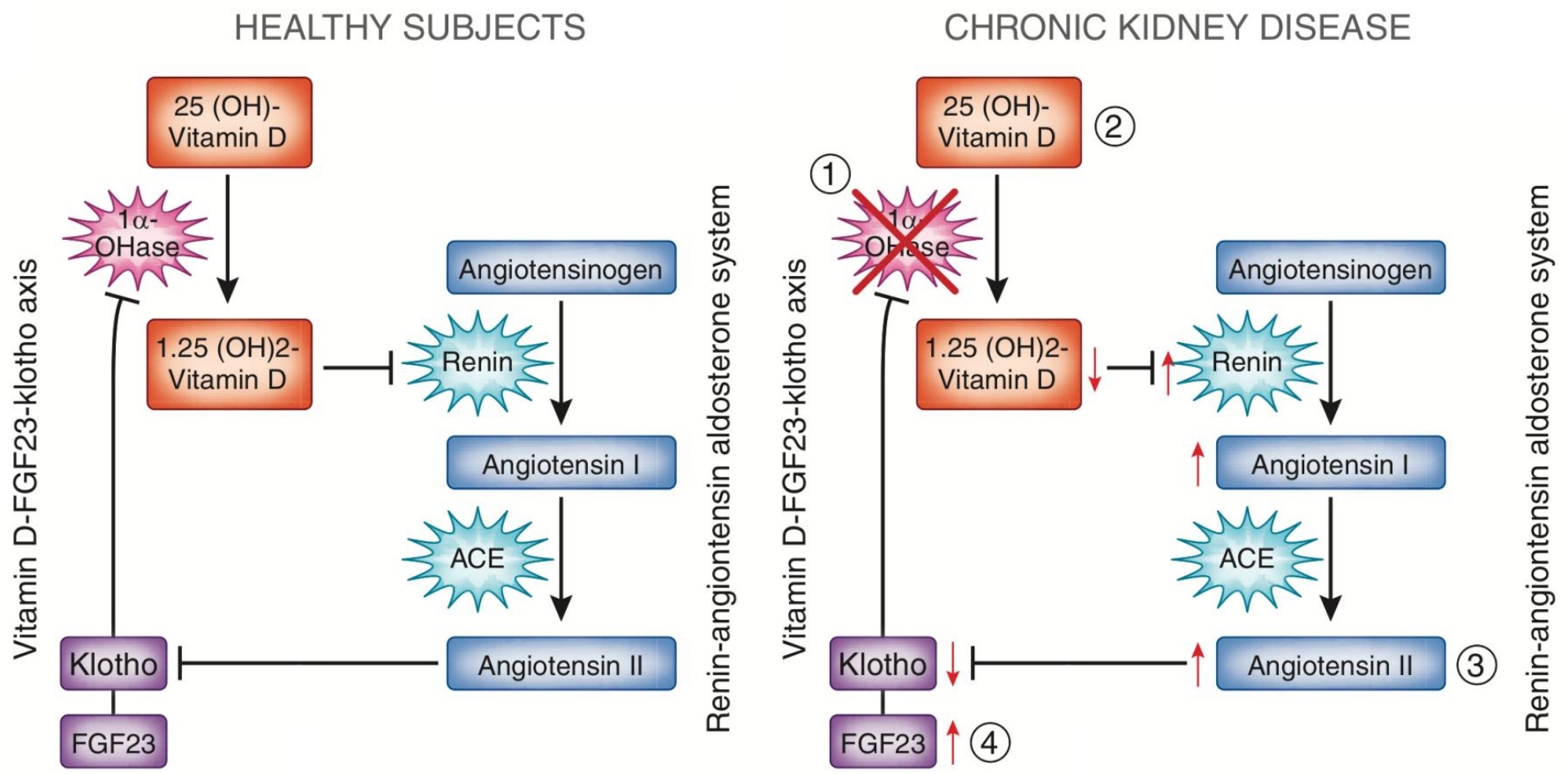

HEALTHY SUBJECTS
25 (OH)-
Vitamin D
1α-
OHase
1.25 (OH)2-
Vitamin D
Angiotensinogen
Renin
Angiotensin I
ACE
Angiotensin II
Klotho
FGF23
Vitamin D-FGF23-klotho axis
Renin-angiontensin aldosterone system


HEALTHY SUBJECTS
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Vitamin D-FGF23-klotho axis
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CHRONIC KIDNEY DISEASE
25 (OH)-Vitamin D
1α-OHase
1.25 (OH)2-Vitamin D
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Angiotensin I
ACE
Angiotensin II
Klotho
FGF23
Vitamin D-FGF23-klotho axis
Renin-angiontensin aldosterone system
①
②
③
④

Immunologic

Active Vit D Therapy in CKD (RCT)

- Lower uPCR
- Lower PTH level
- Lower CRP level
- T2DM + albuminuria + ACEI or ARB
  - ↓ uACR in paricalcitol added group
  - ↓ eGFR
  - serum creatinine without affecting iothalamate GFR measurements
  - ↓ BP
- Much further work is needed in this area

Active Vit D Therapy in CKD = Outcome

- **Use in pats on dialysis & with CKD**

  → improved survival

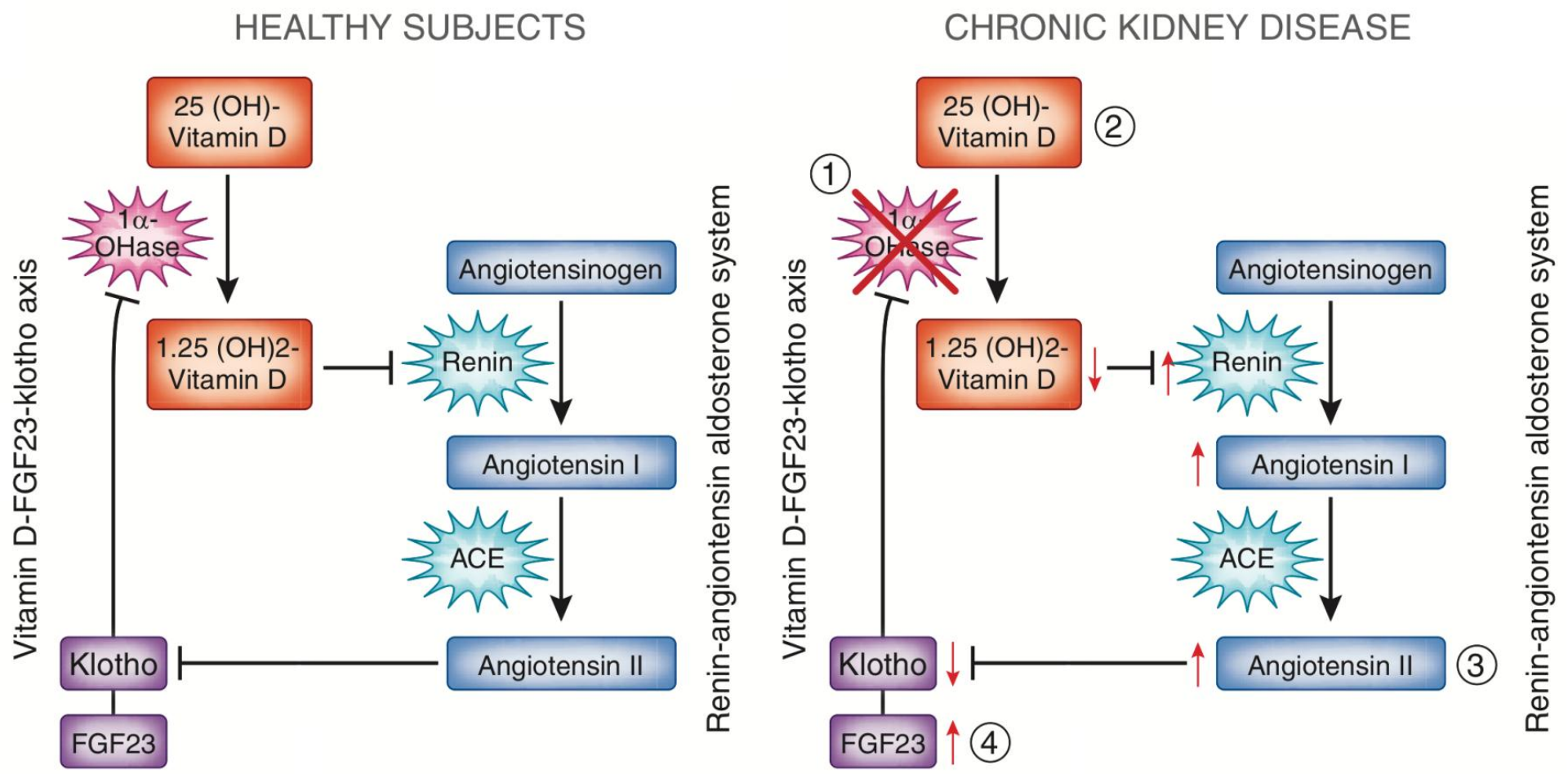
- **Active Vit D has also been associated with slower progression to ESRD**

Shoben AB, Rudser KD, de Boer IH, Young B, Kestenbaum B:

Association of oral calcitriol with improved survival in nondialyzed CKD.

J Am Soc Nephrol 19: 1613–1619, 2008

Vitamin D as Cardioprotective in CKD?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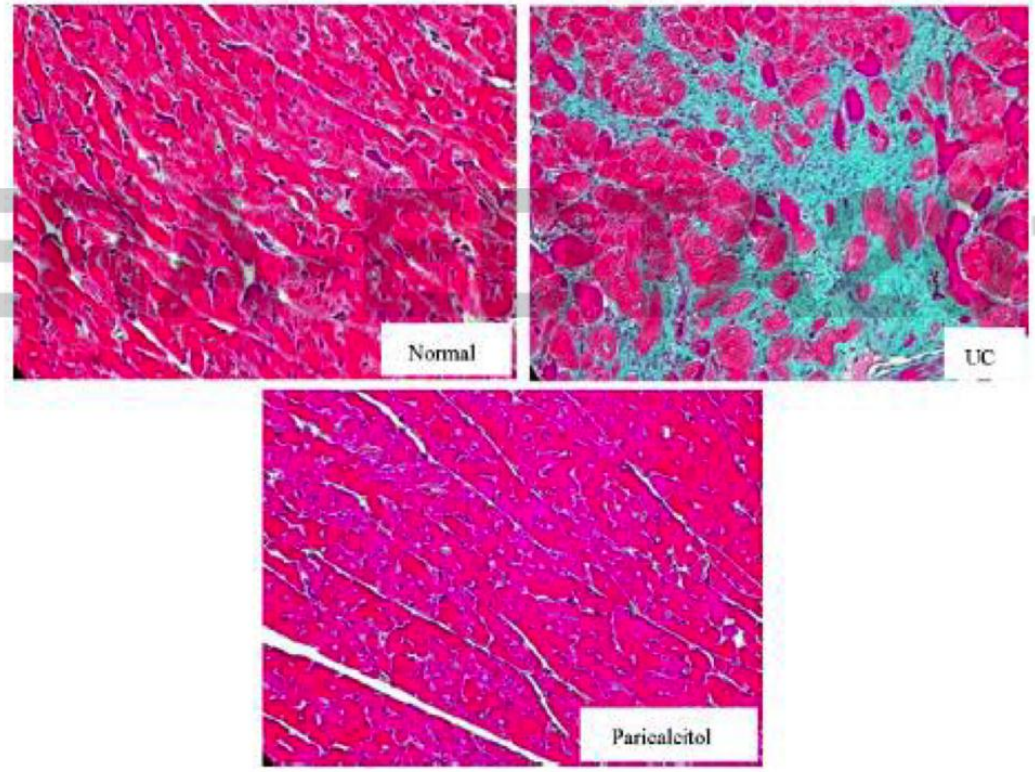
1α-OHase
1.25 (OH)2-Vitamin D
Angiotensinogen
Renin
Angiotensin I
ACE
Angiotensin II
Klotho
FGF23
Vitamin D-FGF23-klotho axis
Renin-angiontensin aldosterone system
CHRONIC KIDNEY DISEASE
25 (OH)-Vitamin D
1α-OHase
1.25 (OH)2-Vitamin D
Angiotensinogen
Renin
Angiotensin I
ACE
Angiotensin II
Klotho
FGF23
Vitamin D-FGF23-klotho axis
Renin-angiontensin aldosterone system
①
②
③
④

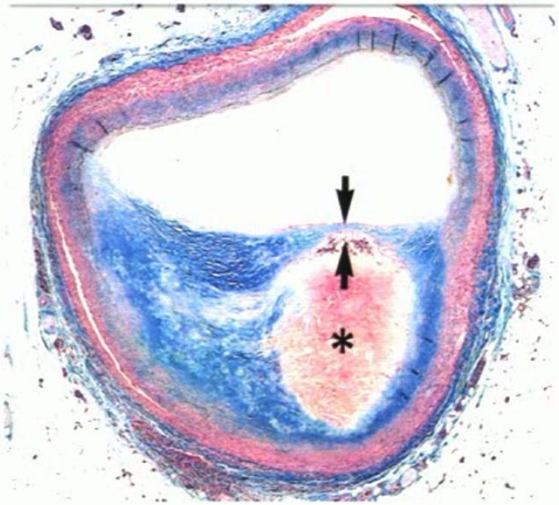
Background

5/6 Nephrectomy rats treated with Paricalcitol for 4 weeks results in reduction of cardiac fibrosis

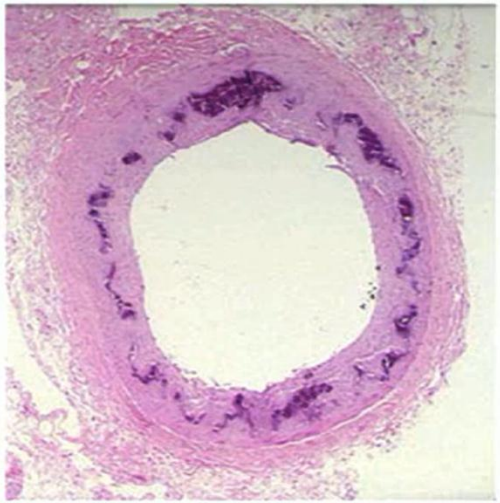


Mizobuchi M, et al. J Steroid Biochem Mol Bio 2010

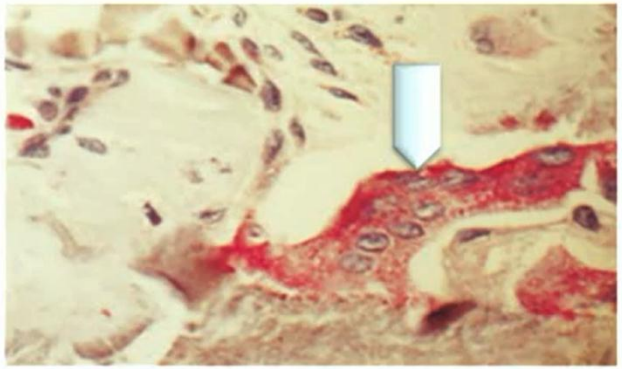
Intimal calcification



Medial calcification

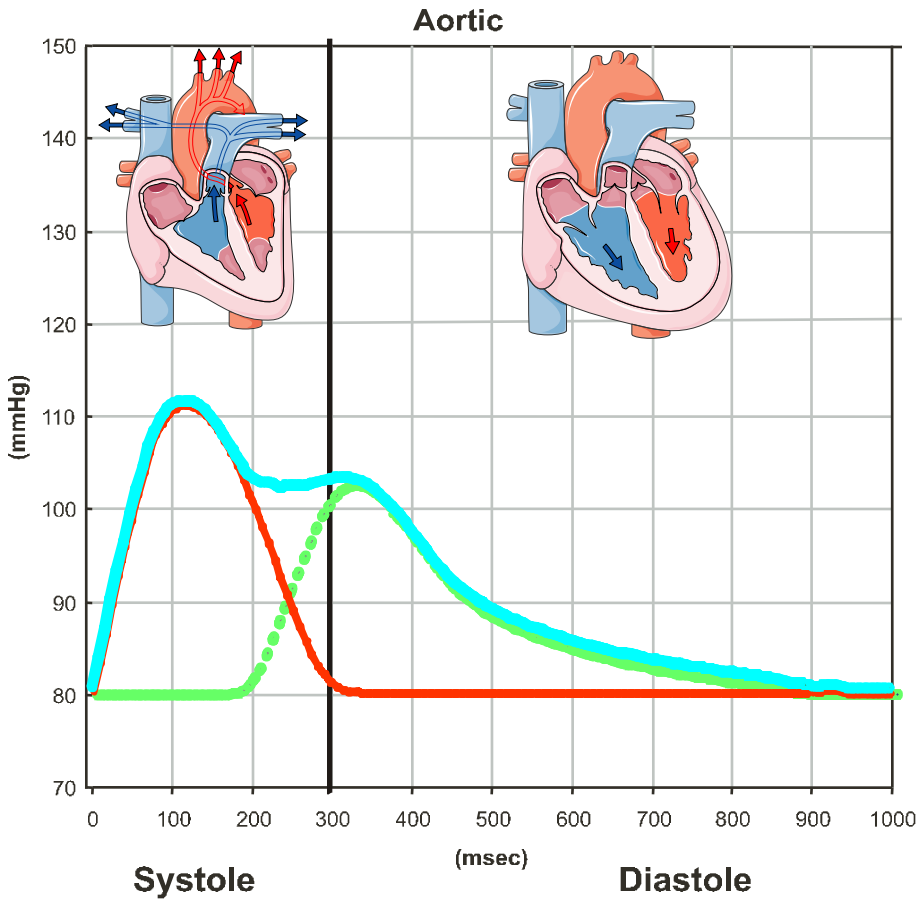


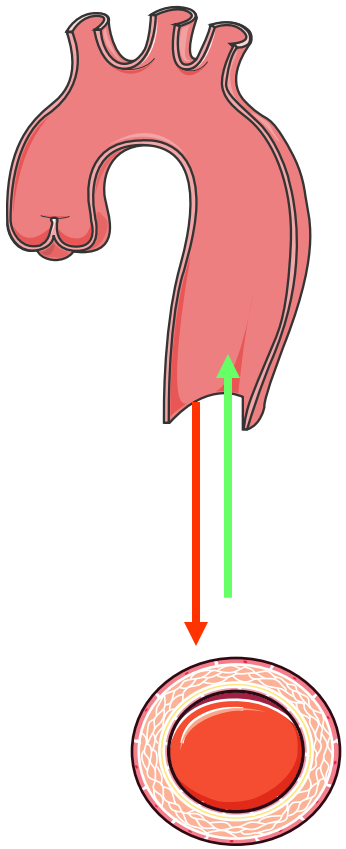
Bone formation and remodelling in atherosclerotic lesions of human carotid artery.



Jeziorska M et al Virchows Arch 1998:433:559-65

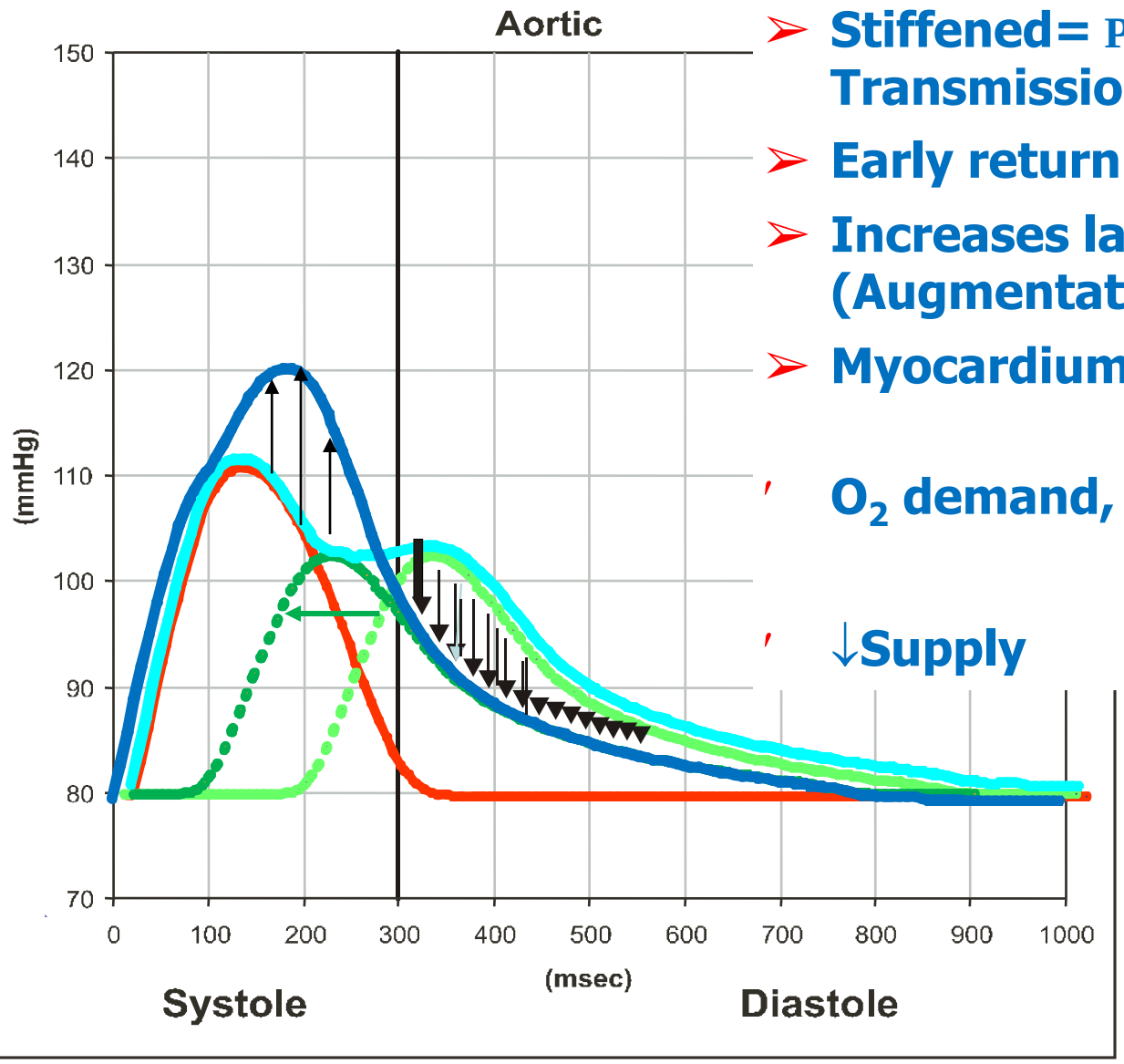
Patterns of central aortic BP in NORMAL conditions



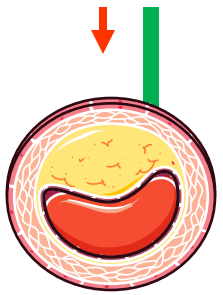


NORMAL ARTERY

Patterns of central aortic BP in PATHOLOGICAL conditions

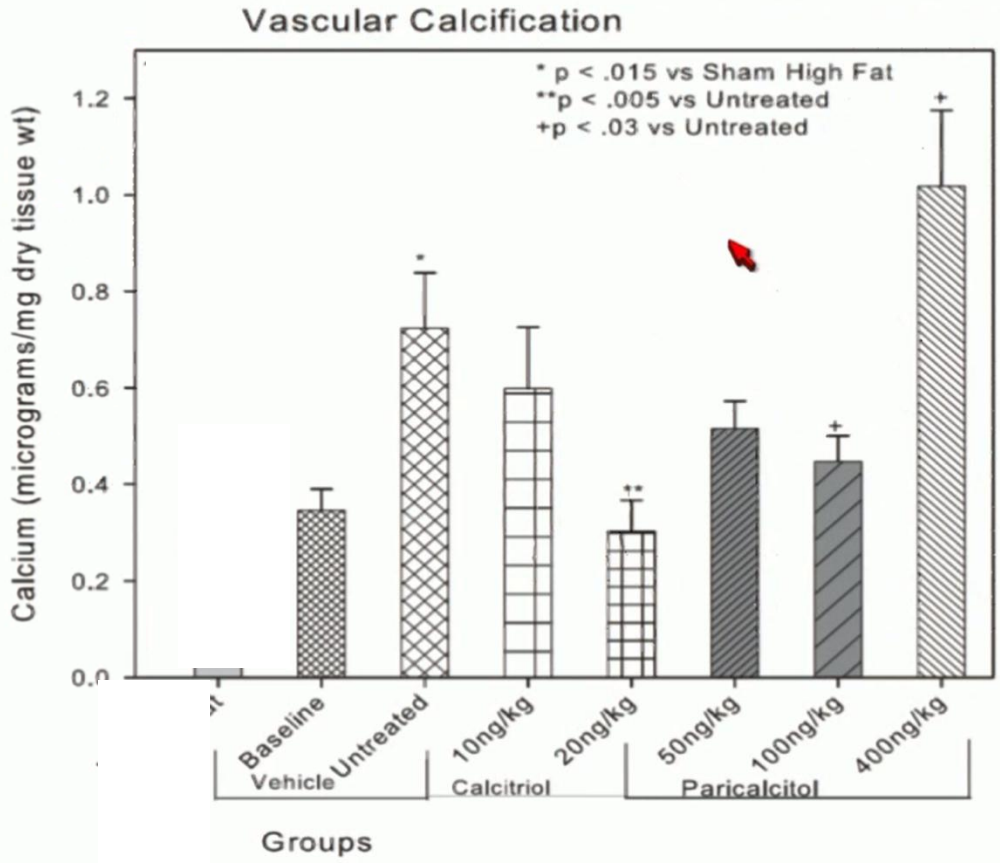


- Stiffened= PWV
  Transmission time = reduced
- Early return to heart
- Increases late systolic pressure (Augmentation)
- Myocardium = pump against increased load
  - O_2 demand, ↓SV, LVH
  - ↓Supply



HYPERTENSIVE ARTERY

Dose-dependent vascular calcification with $1,25(OH)_2$ Vitamin D



Mathew et al, *J Am Soc Nephrol.* 2008 Aug;19(8):1509-19

Disease–Mineral and Bone Disorder (CKD-MBD)

VOLUME 7 | ISSUE 1 | JULY 2017

KDIGO treatment guidelines[a] 2009

CKD stage	PTH (pg/mL)	Calcium (mmol/L)	Phosphorus (mmol/L)
3	No numerical target[a]	Normal range	Normal range
4	No numerical target[a]	Normal range	Normal range
5	No numerical target[a]	Normal range	Normal range
5D	2–9 × upper limit of normal range	Normal range	Lowered toward normal range

KDIGO treatment guidelines[a] 2017

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3	No numerical target[a]		
4	No numerical target[a]		
5	No numerical target[a]		
5D	2–9 × upper limit of normal range		

suggest avoiding hypercalcemia (2C)

Lowered toward normal range

Data support? **Safety !**

CKD-MBD: treatment

4.1.2: To lower elevated phosphate levels toward the normal range (2C)

4.1.3: To avoid hypercalcemia (2C)

4.2: ? PTH levels. For 5D ≈ 2 to 9 times upper normal limit for assay (2C)

Disease–Mineral and Bone Disorder (CKD-MBD) VOLUME 7 | ISSUE 1 | JULY 2017

CKD-MBD: treatment

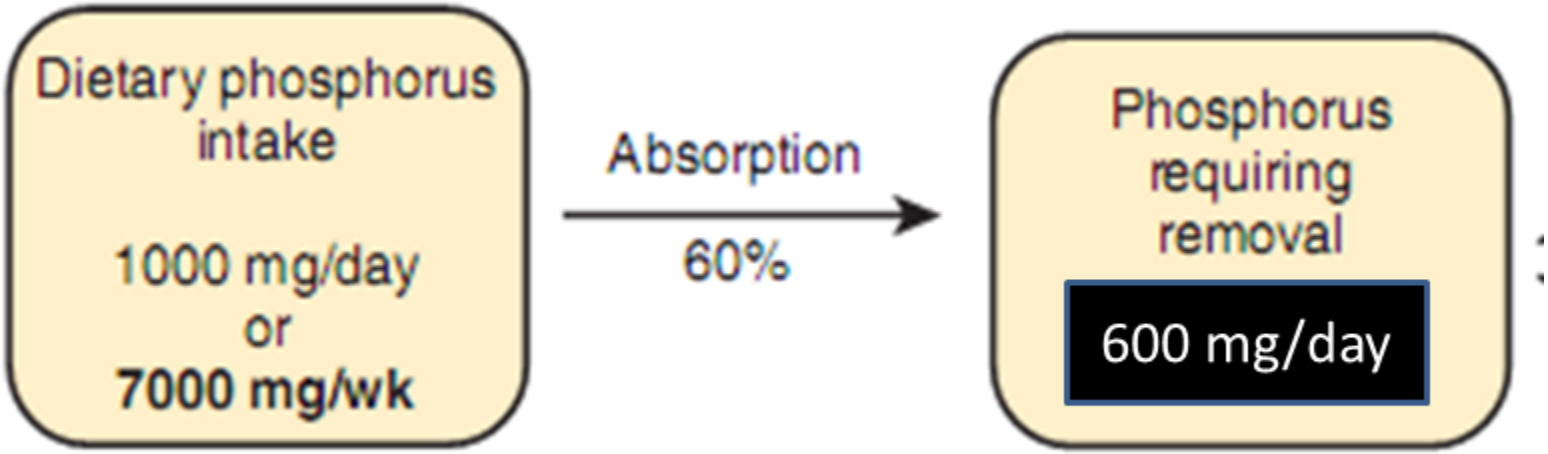
4.1.2: To lower elevated phosphate levels toward the normal range (2C)

- Dietary PO_4 restriction
- Oral phosphate binders (prevent absorption)
- Removal through adequate dialysis

CKD-MBD: treatment

4.1.2: To lower elevated phosphate levels toward the normal range (2C)

- Dietary PO_4 restriction



CKD-MBD: treatment

4.1.2: To lower elevated phosphate levels toward the normal range (2C)

- Dietary PO_4 restriction
- Oral phosphate binders (prevent absorption)

Approximate potential phosphate-binding capacities of commonly used agents:

- *Calcium carbonate: 1 g binds 40 mg*
- *Calcium acetate: 1 g binds 45 mg*
- *Sevelamer: 1 g binds 36 mg*
- *Lanthanum carbonate: 1 g binds 93 mg*
- *Aluminum hydroxide (liquid): 1 g binds 25 mg*

Ferric citrate combines with dietary phosphorus in GI tract

Excess ferric ions are reduced by bowel mucosa to ferrous iron and absorbed into systemic circulation

Sevelamer hydrochloride

-first non-calcium, non-aluminium based phosphate binder

-as effective as calcium containing binder

-similar adverse events profile to placebo

-major drawbacks are GI side effects, pills burden and cost

CKD-MBD: treatment

4.1.2: To lower elevated phosphate levels toward the normal range (2C)

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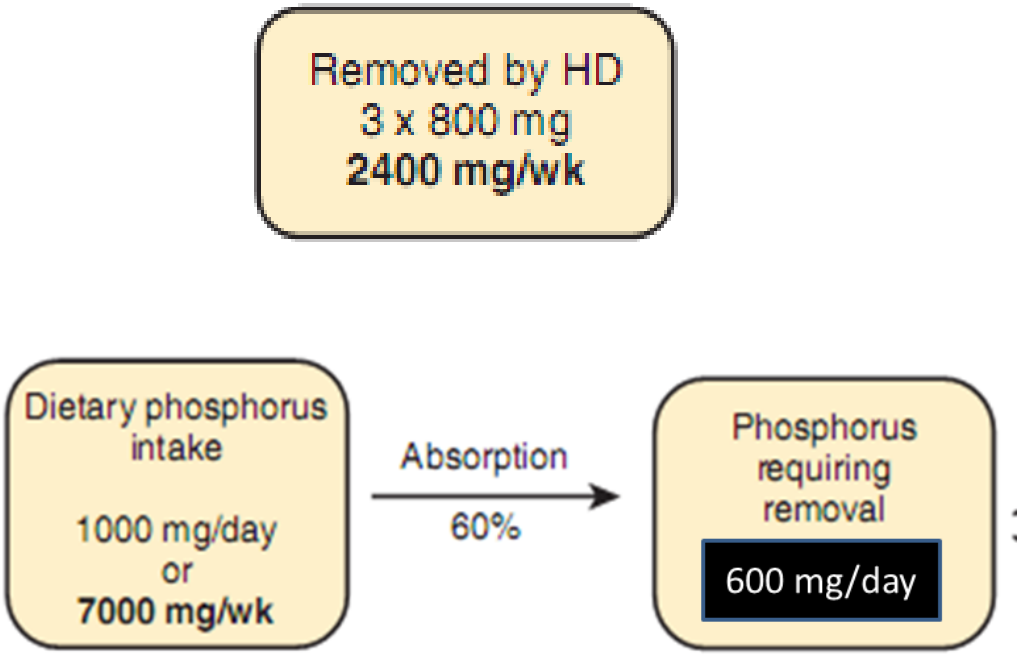


CKD-MBD: treatment

4.1.2: To lower elevated phosphate levels toward the normal range (2C)

- Dietary PO_4 restriction
- Oral phosphate binders (prevent absorption)
- Removal through adequate dialysis

4.1.3: To avoid hypercalcemia (2C)

- Appropriate Ca intake ± supplement (including Ca-containing binders)
- Appropriate vitamin D treatment.
- Appropriate dialysate concentration. [1.25 - 1.50 mmol/l,(2C)]

CKD-MBD: treatment

4.1.2: To lower elevated phosphate levels toward the normal range (2C)

- Dietary PO_4 restriction
- Oral phosphate binders (prevent absorption)
- Removal through adequate dialysis

4.1.3: To avoid hypercalcemia (2C)

- Appropriate Ca intake ± supplement (including Ca-containing binders)
- Appropriate vitamin D treatment.
- Appropriate dialysate concentration.

4.2: ? PTH levels. For 5D ≈ 2 to 9 times upper normal limit for assay (2C)

- Correct hyperphosphatemia, hypocalcemia,
- Calcitriol or vitamin D analogues (e.g. alfacalcidol, paricalcitol)
- Calcimimetic agent.

Chronic Kidney Disease: Mineral and Bone Disorder (CKD-MBD)

Effects of available treatments for CKD-BMD

	Calcium	Phosphate	PTH
Calcium-based phosphate binder	↑↑	↓↓	↓↓
Calcium-free phosphate binder	↔	↓↓	↔
Active vitamin D (alfacalcidol/calcitriol)	↑	↑	↓↓↓
Calcimimetic	↓	↓	↓↓↓
Lower dialysate calcium	↓	↔	↑
Parathyroidectomy	↓	↓	↓↓↓

What I would like to share my learning

- **Vitamin D = Classic effect / Non-classical Effects**
- **Low Vit D**

  all-cause mortality, cardiovascular events, peripheral vascular disease, hypertension, congestive heart failure, and the later need for renal replacement therapy
- **Vit D t/m = Beneficial but adverse effect**
- **PTH, FGF23 & Klotho**

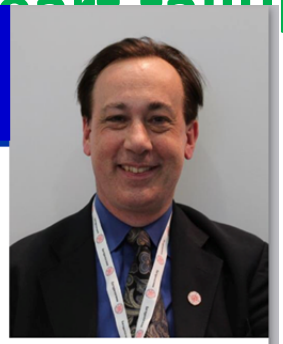
What I would like to share my learning

- Vitamin D = Classic effect / Non-classical Effects
- Low Vit D

all-cause mortality, cardiovascular events, peripheral vasc[illegible] and

- Vit
- PTH

ERA-EDTA 2015



- There are things we know that we know.
- There are things that we know we don't know
- There are things we don't know we don't know.

Thank You For Your Kind Attention

Wishing all of you in good health and happiness

Khin Maung Htay

htayrenal@gmail.com