Metabolismo mineral y FGF23 / Klotho en enfermedad renal crónica pediátrica

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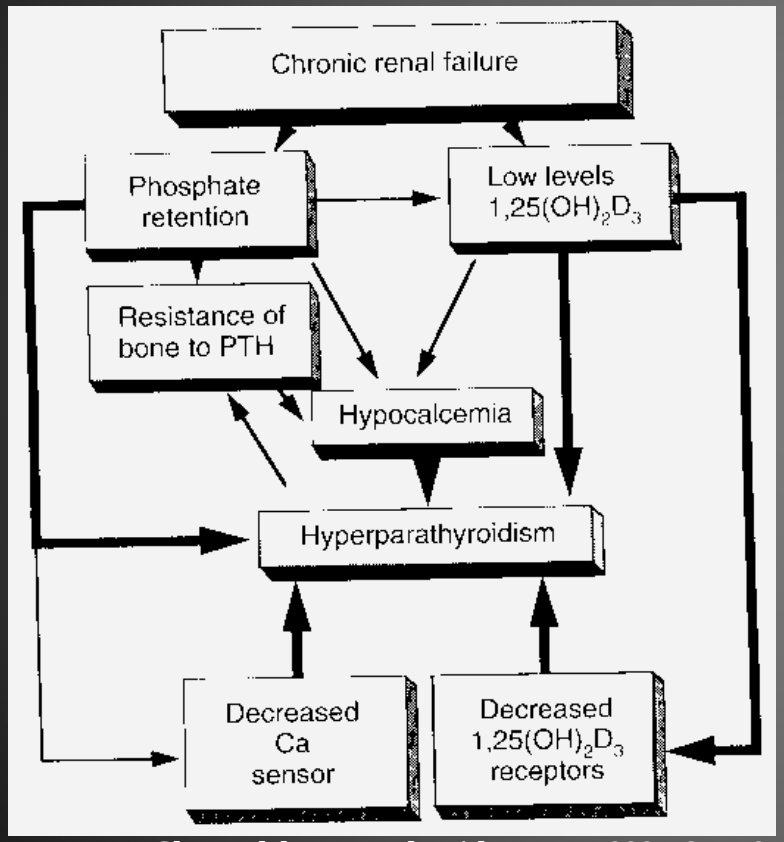
VI Congreso Argentino de Nefrología Pediátrica

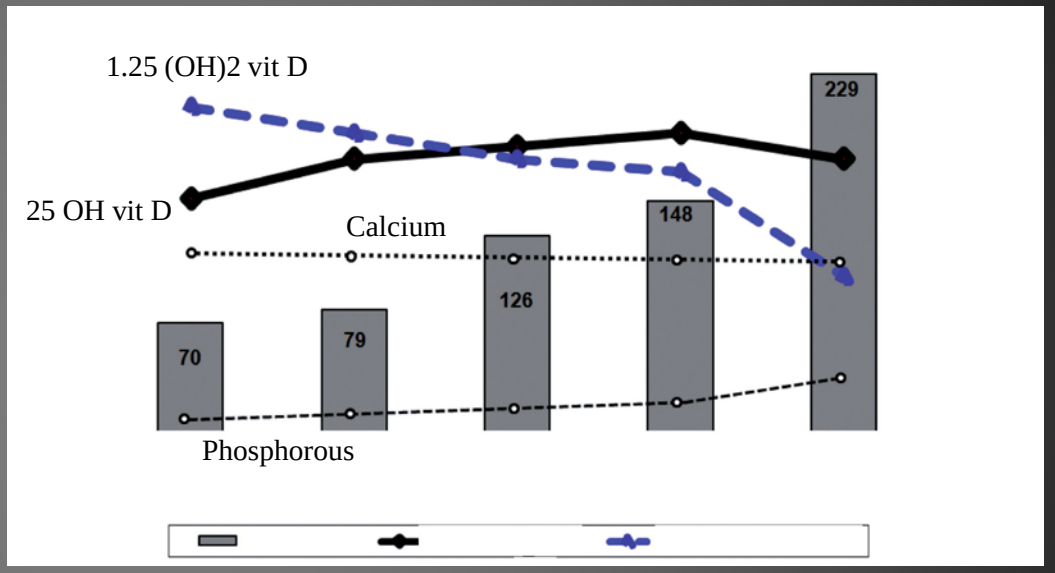
Mayo 2015

Existe un *missing factor* en EMO?



Slatopolsky E. et al: Kidney Int 1999;56:14-9

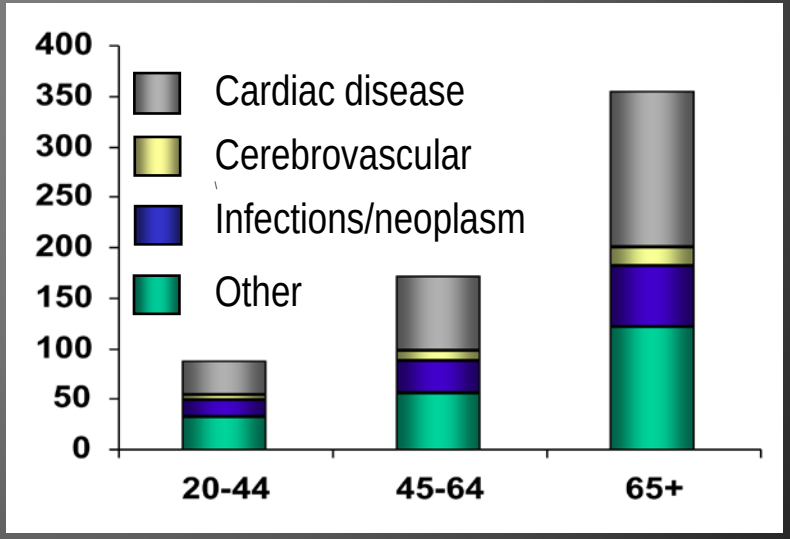
Characteristics of bone mineral metabolism in patients with stage 3-5 chronic kidney disease not on dialysis: results of the OSERCE study



Górriz J., Oserce Study, Nefrología 2013

Cardiovascular Disease is a leading cause of death in CKD

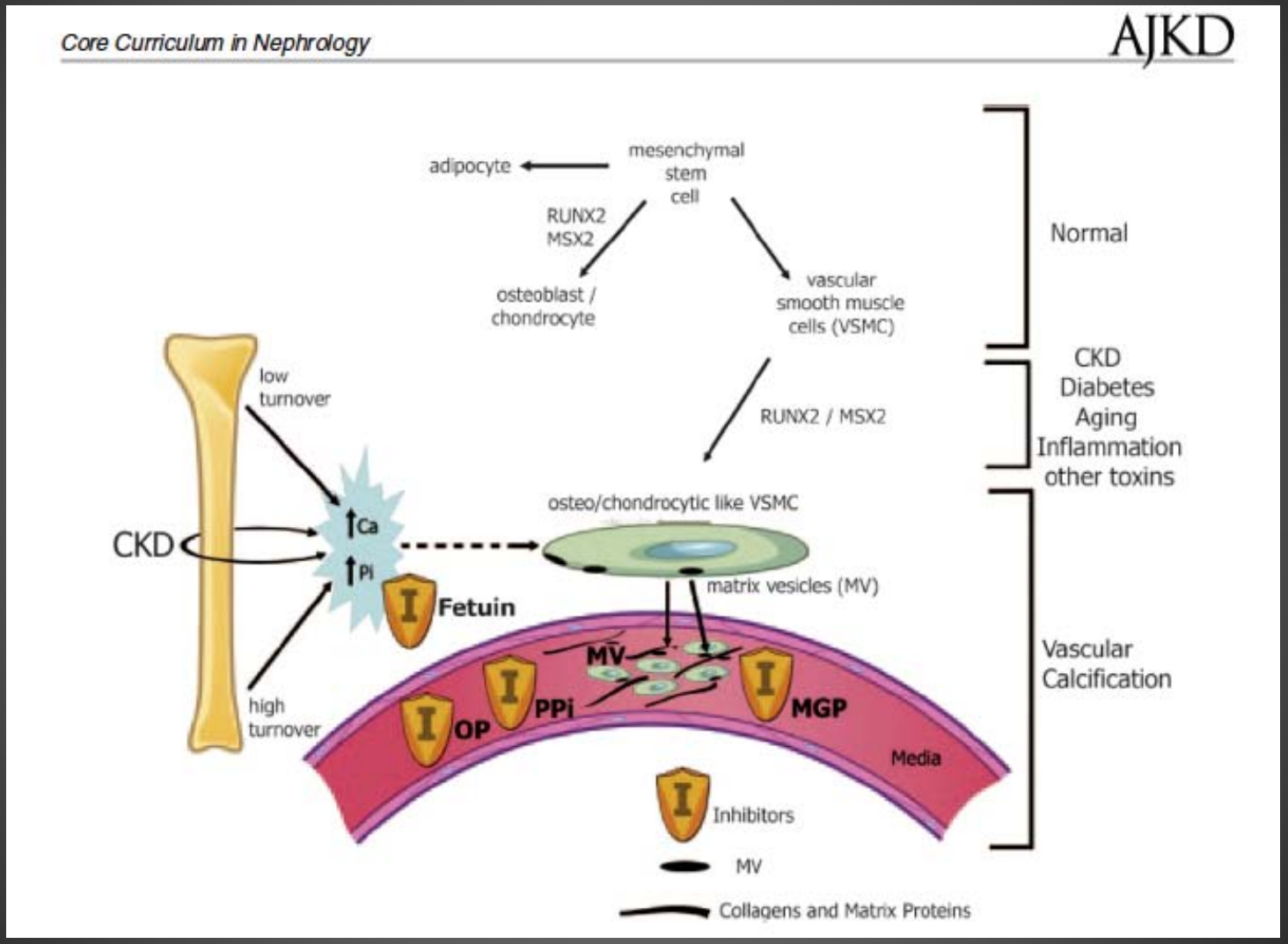
- *Mc Donald S et al., New England Journal of Medicine 2004: Long-Term Survival of Children with End-Stage Renal Disease*
- *Shroff R et al.: Pediatric Nephrology 2007: Long-term outcome of chronic dialysis in children*
- *Mitsnefes MM: Adv. Chronic Kidney Dis 2005: Cardiovascular disease in children with chronic kidney disease.*
- *Mitsnefes MM: Pediatric Nephrology 2008: Cardiovascular complications of pediatric chronic kidney disease.*
- *Monteucci M: J Am Soc Nephrol 2006: Left ventricular geometry in children with mild to moderate chronic renal insufficiency.*



Foley RN, et al. Am J Kidney Dis 1998

Slide gentileza Dr. Franz Schaefer

Osteodistrofia, del daño óseo a la enfermedad cardiovascular



CKD–Mineral and Bone Disorder: Core Curriculum 2011
Ranjani N. Moorthi, MD,1 and Sharon M. Moe, MD

EMO: de la hiperfosfemia a las fosfatoninas

- La familia de los Factores de Crecimiento de Fibroblastos comprende 22 polipéptidos agrupados en 7 subfamilias.

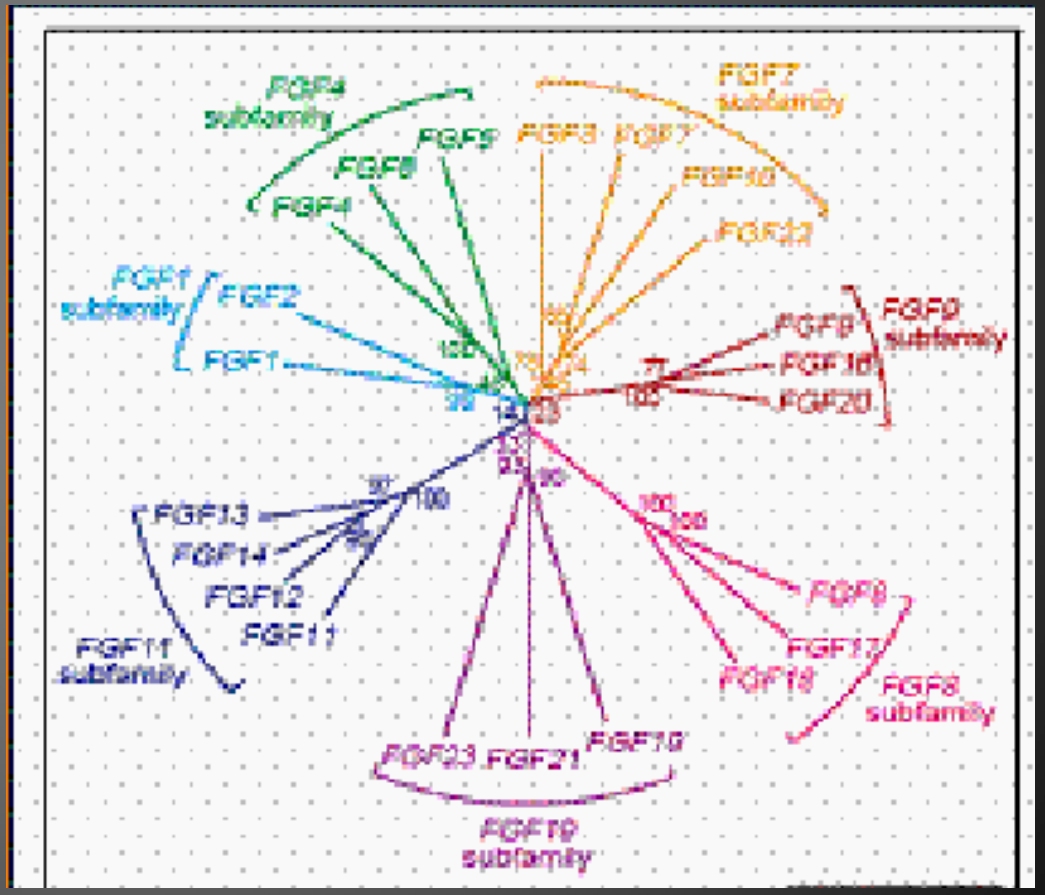
- Seis subfamilias de FGF ejercen una acción *paracrina* mediante receptores tirosina kinasa

- La subfamilia FGF19 ejerce una acción de tipo *endocrino*. Son los FGF 19, 21 y 23. Su efecto endocrino reside en su baja afinidad al heparan sulfato.

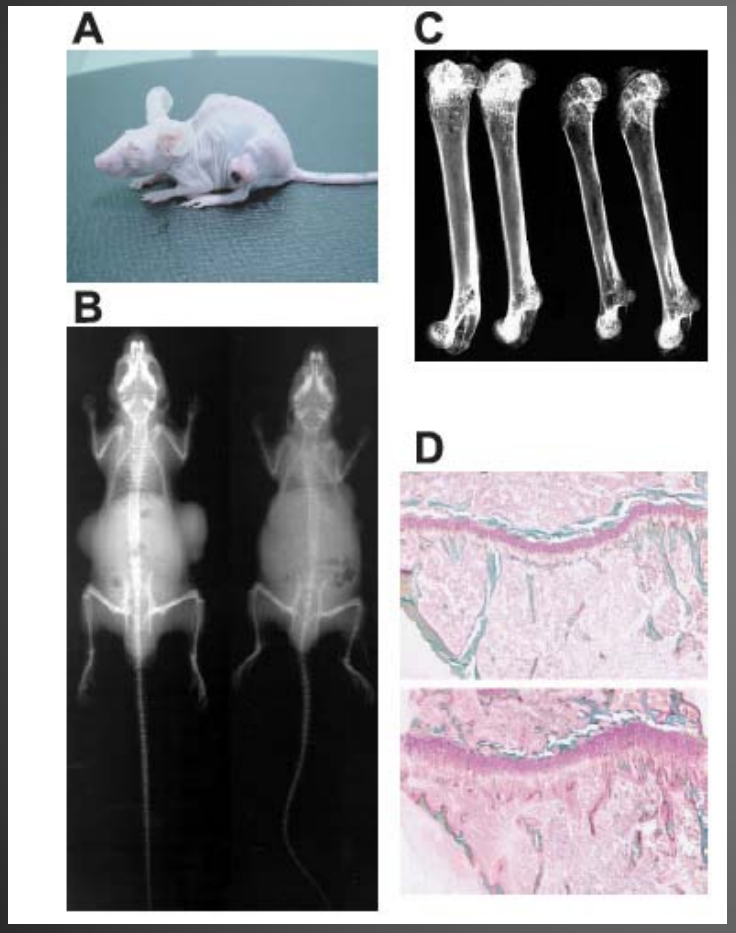
- El FGF 19 se relaciona al metabolismo de los ácidos biliares

- El FGF 21 se relaciona al metabolismo de la glucosa y lípidos

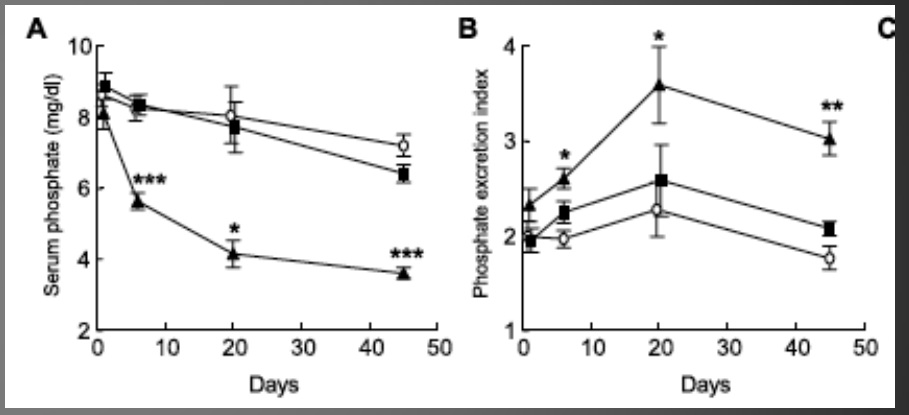
- El FGF 23 se relaciona al metabolismo del fosfato y vitamina D.



FGF23 en la EMO
Su descubrimiento

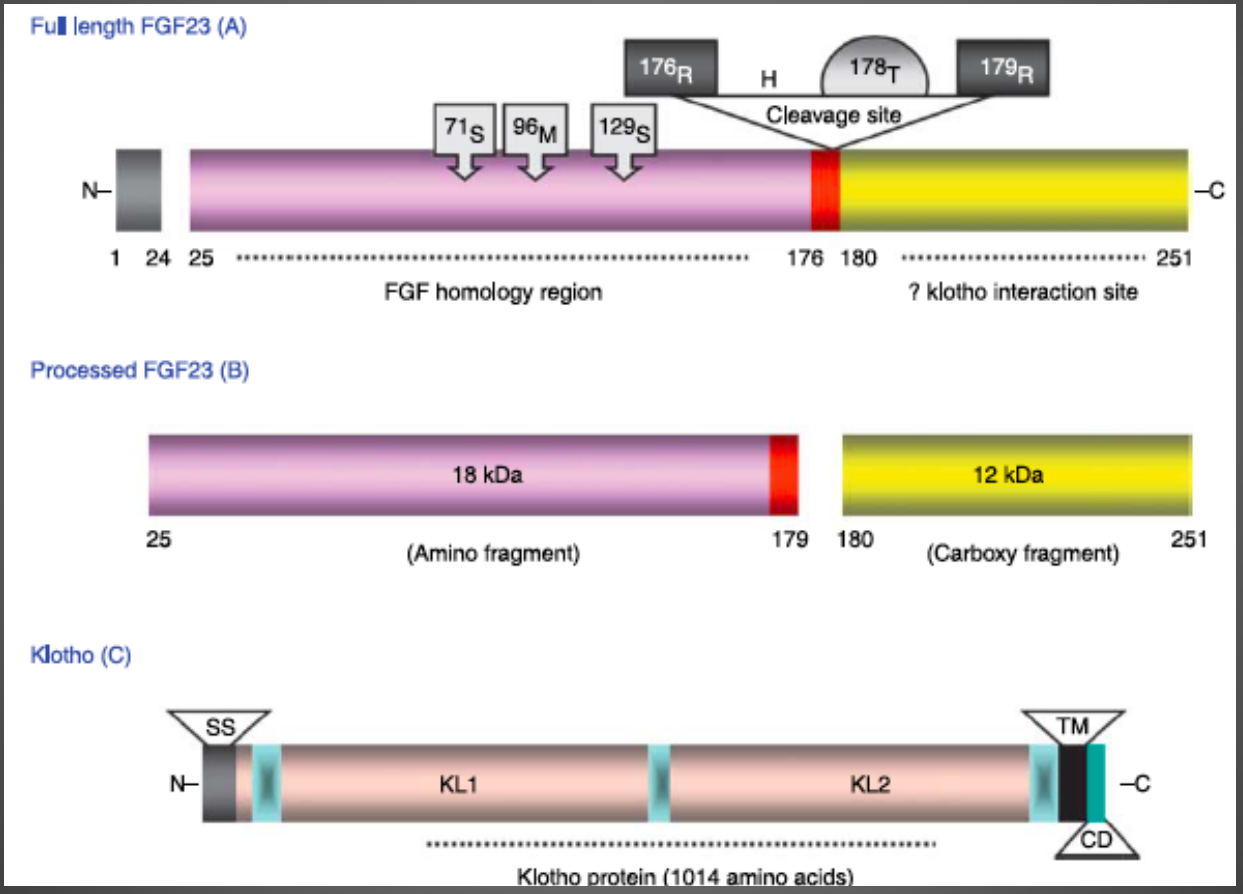


Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia



Shimada T, PNAS, 2001

FGF23 en la EMO
Su estructura



Razzaque M, Journal of Endocrinol 2007

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

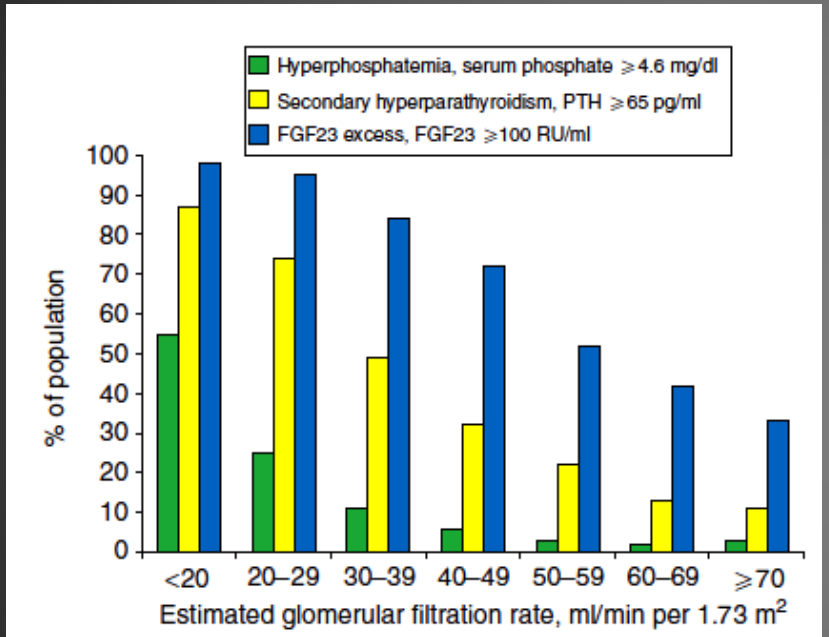
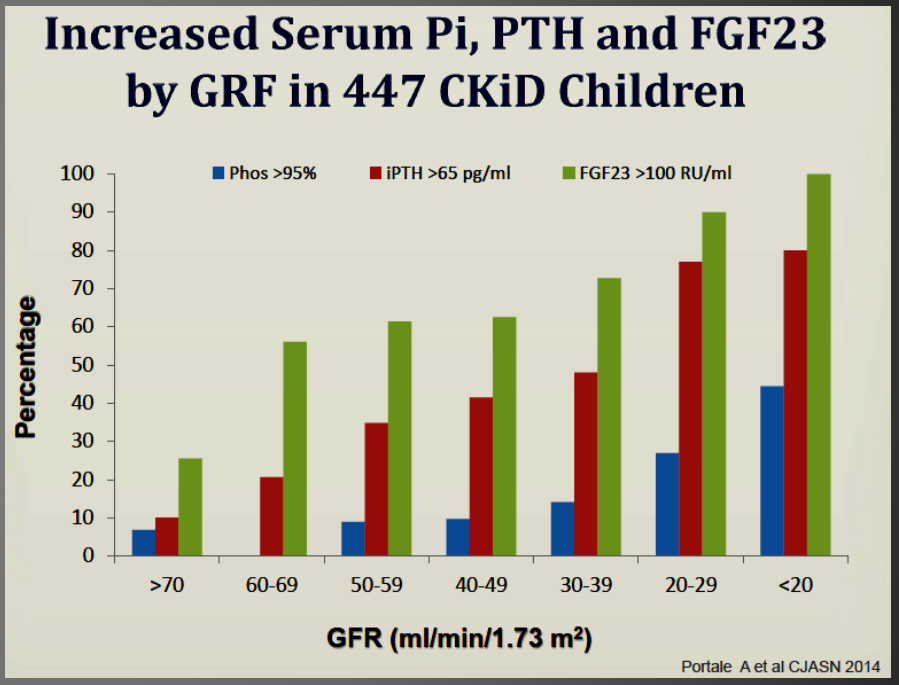


Figure 1 | Prevalence of hyperphosphatemia, secondary hyperparathyroidism, and elevated fibroblast growth factor 23 (FGF23) in relation to estimated glomerular filtration rate (eGFR). Hyperphosphatemia was defined as serum phosphate ⩾4.6 mg/dl, secondary hyperparathyroidism as parathyroid hormone (PTH) ⩾65 pg/ml, and FGF23 excess as FGF23 ⩾100 RU/ml.



Isakova T. Kidney Int **2011**

FGF23 en la EMO
Su mecanismo de accción

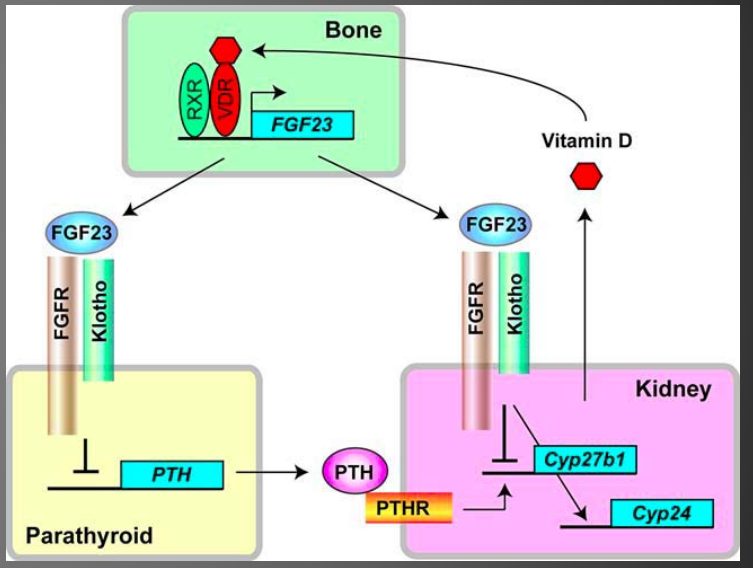
•FGF23 reduces the number of sodium-phosphate cotransporter type-2a (NaPi-2a) on the brush border membrane of proximal tubules, thereby promoting renal phosphate excretion.

•Thus, FGF23 functions as a phosphaturic hormone.

•FGF23 suppresses synthesis and promotes degradation of 1,25-dihydroxyvitamin D3 in proximal tubule. FGF23 down-regulates expression of the Cyp27b1 gene, which encodes 1α-hydroxylase,

•FGF23 up-regulates expression of the Cyp24 gene that encodes 24-hydroxylase, the enzyme that hydrolyzes and inactivates 1,25-dihydroxyvitamin D3.

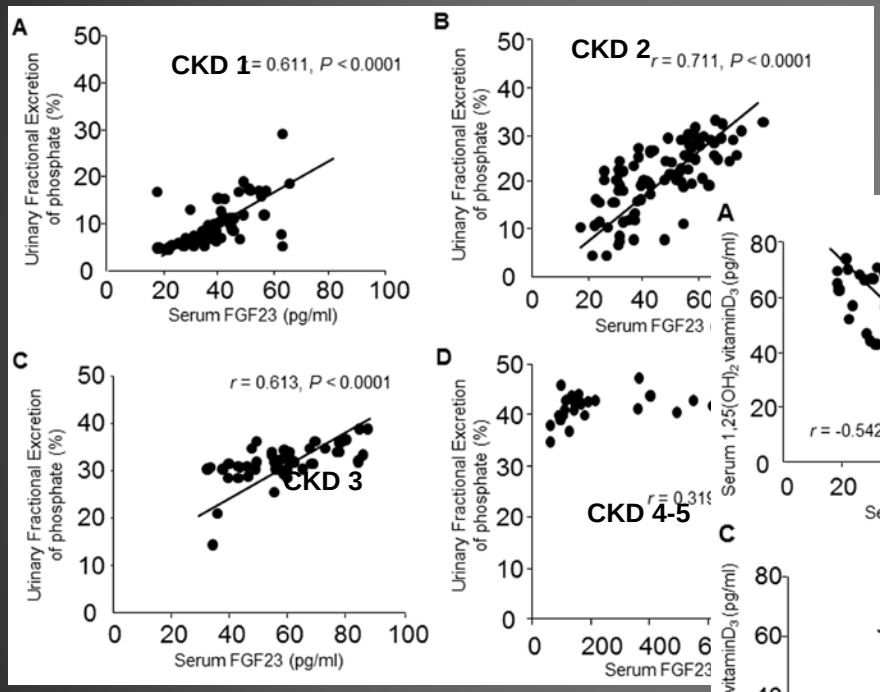
•Thus, FGF23 functions as a counterregulatory hormone for vitamin D.



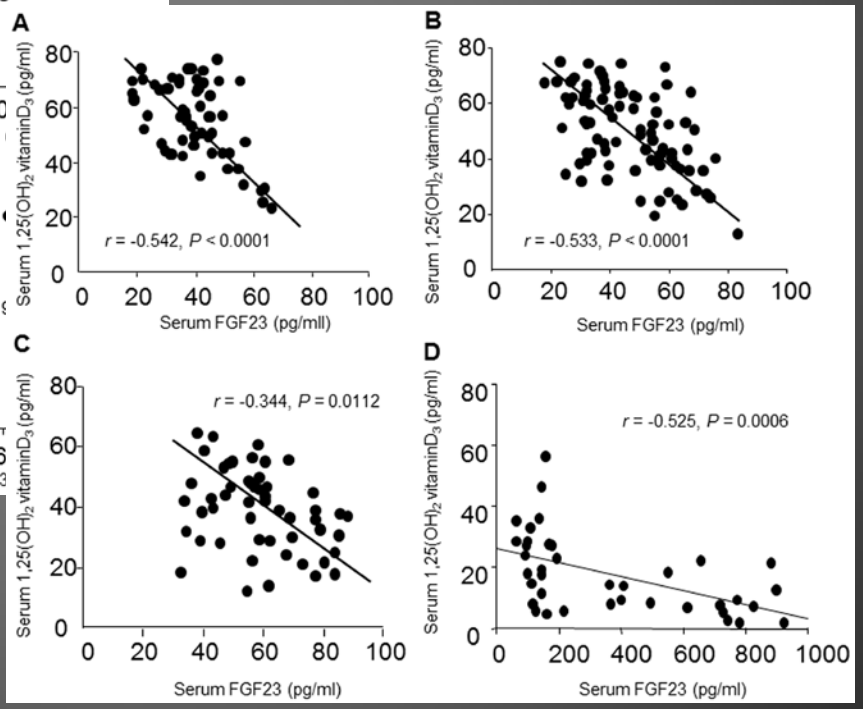
Makoto Kuro-o, Pediatr Nephrol 2010

FGF23 en la EMO
Su mecanismo de accción

fosfato



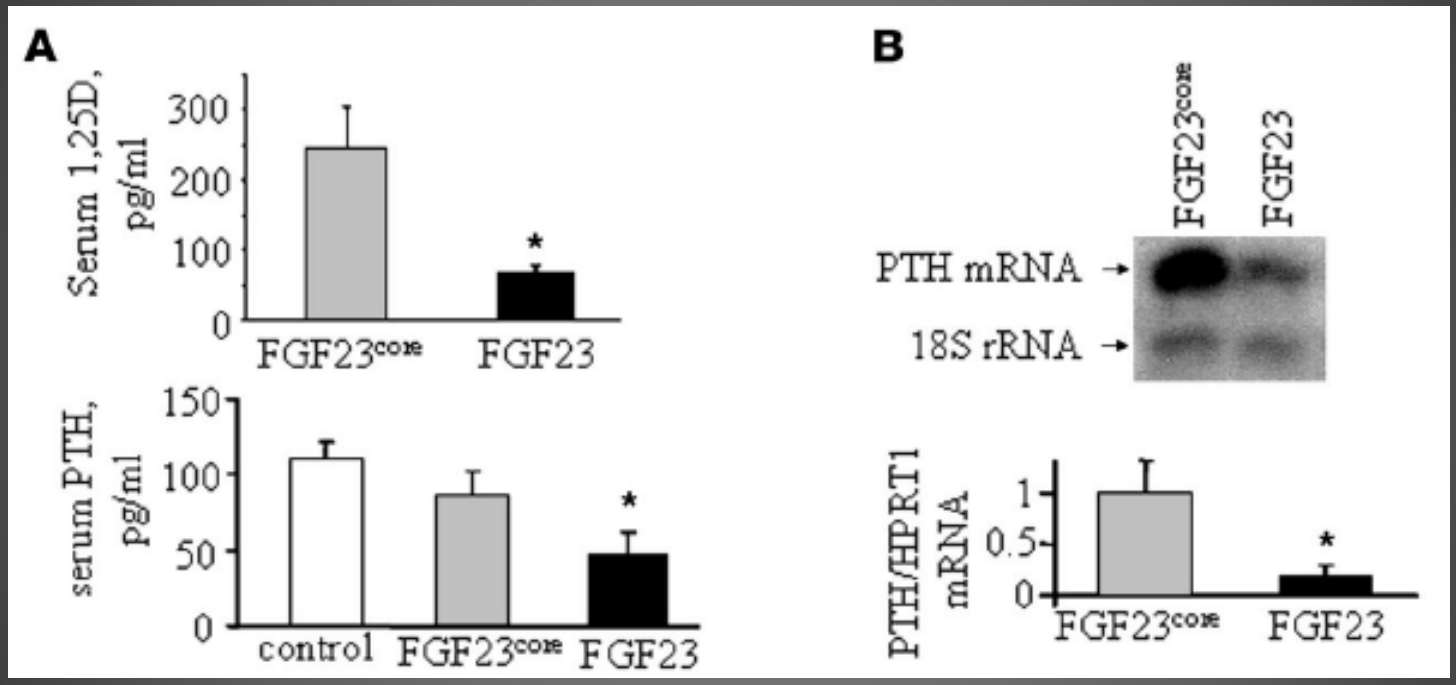
$1,25(OH)_2D$



Hirokazu Sakan, PLOS one, January 2014

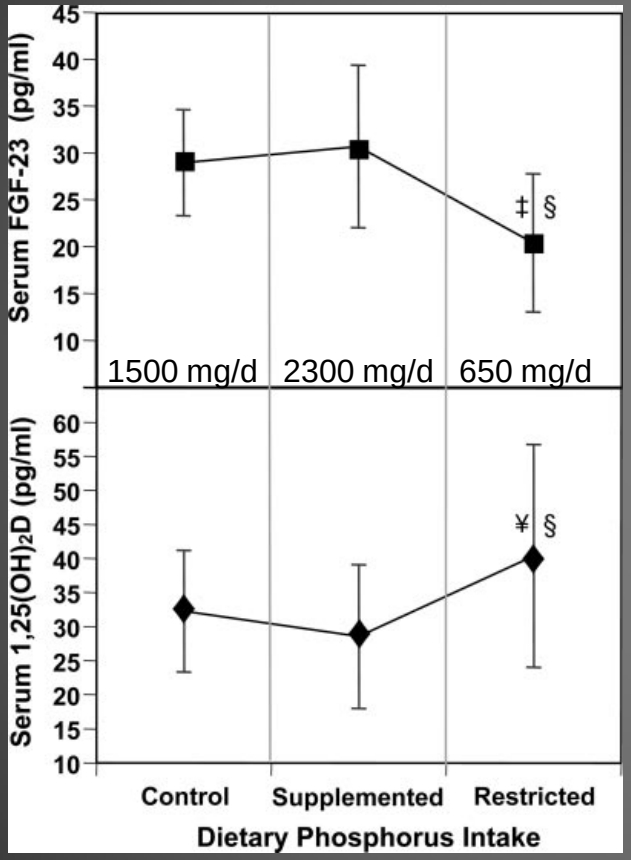
FGF23 en la EMO
Su mecanismo de accción

paratohormona

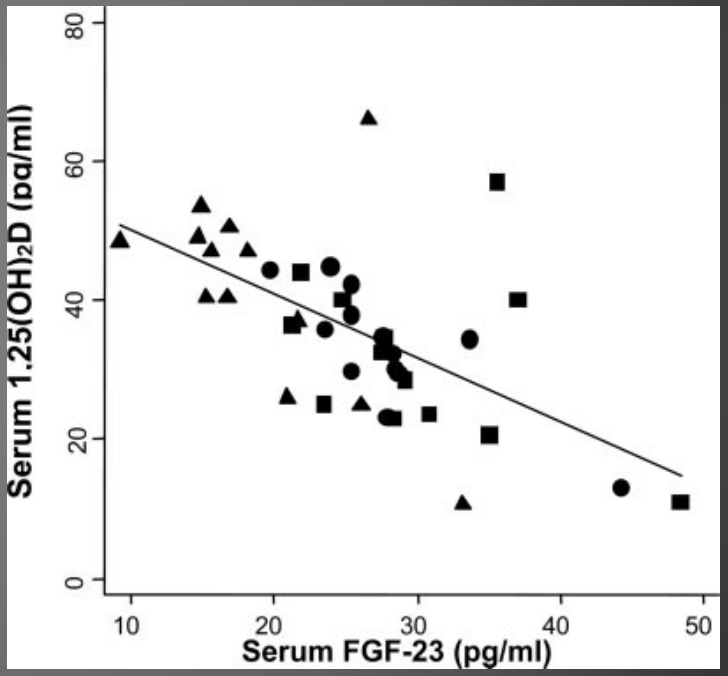


Ben-Dov et al. JCI 2013

FGF23 en la EMO
Sus mecanismos de regulación

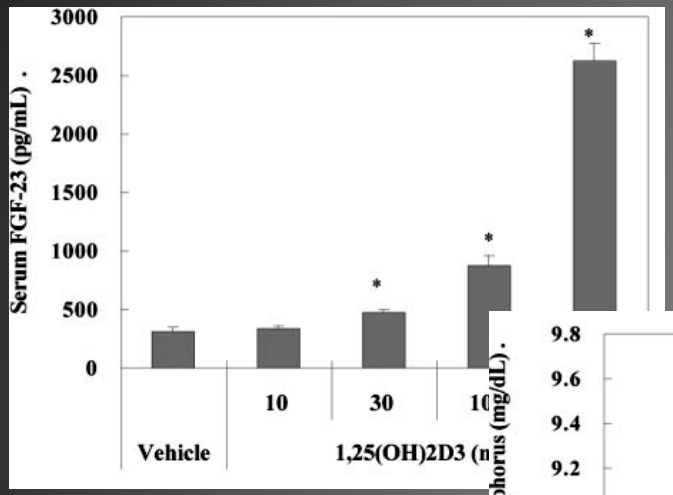


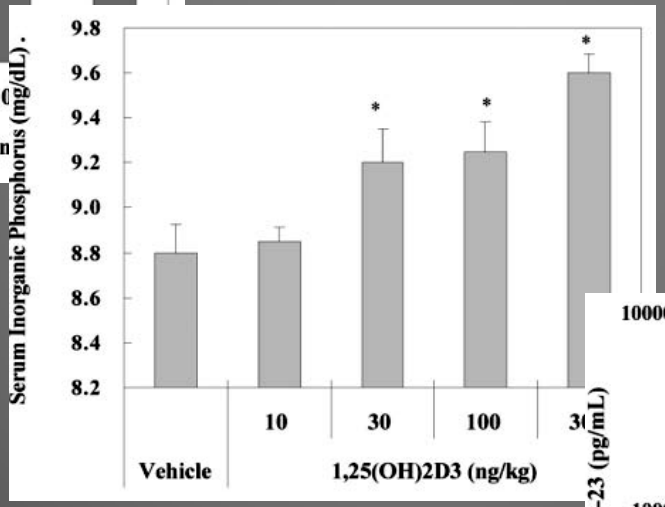
Dietary Phosphorus Regulates Serum Fibroblast Growth Factor-23 Concentrations in Healthy Men

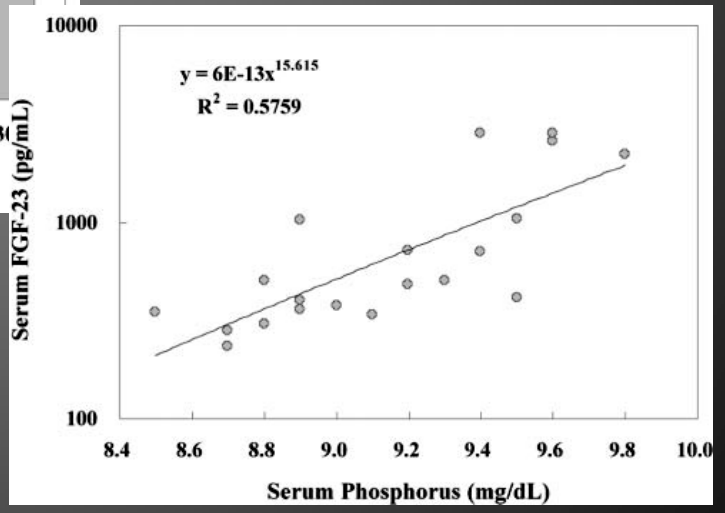


Portale A., J Clin Endocrinol Metab 2006

FGF23 en la EMO
Sus mecanismos de regulación

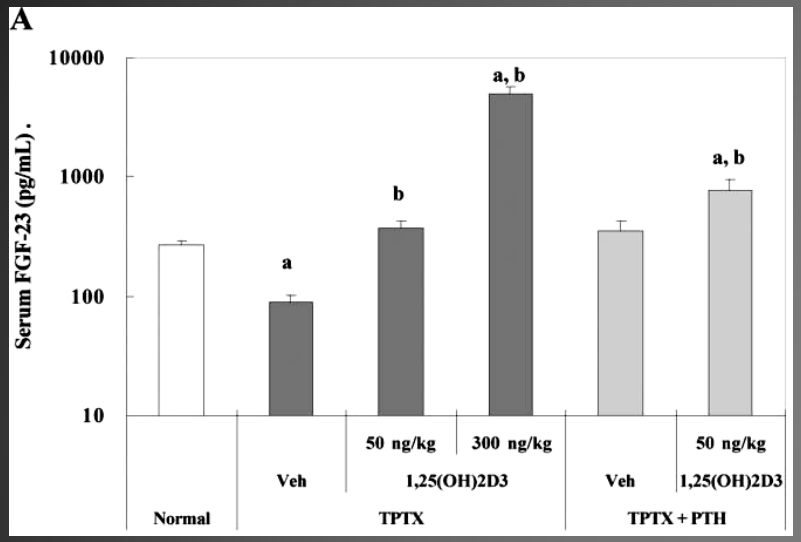


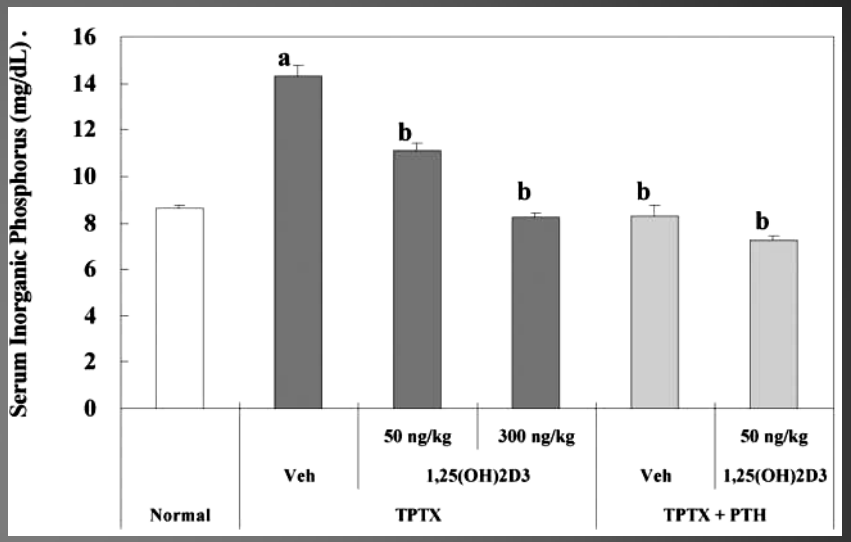


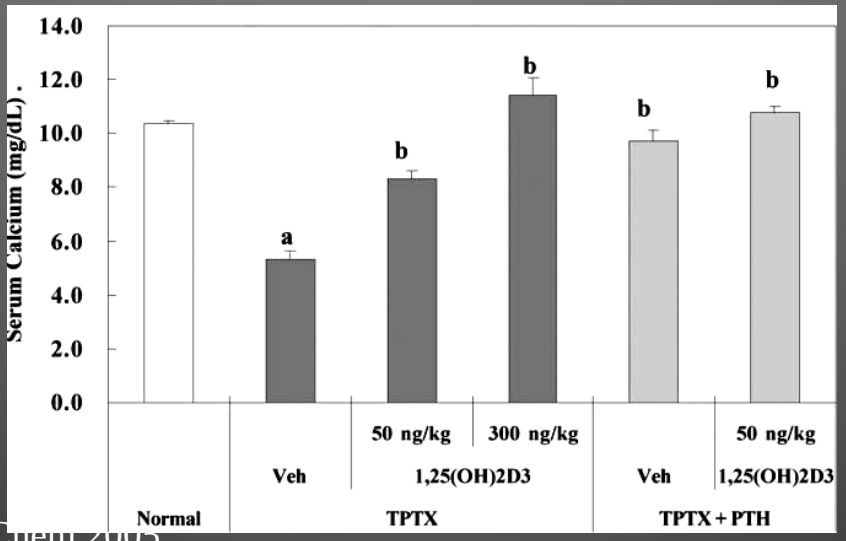


Saito H., The Journal of Biol Chem 2005

FGF23 en la EMO
Sus mecanismos de regulación



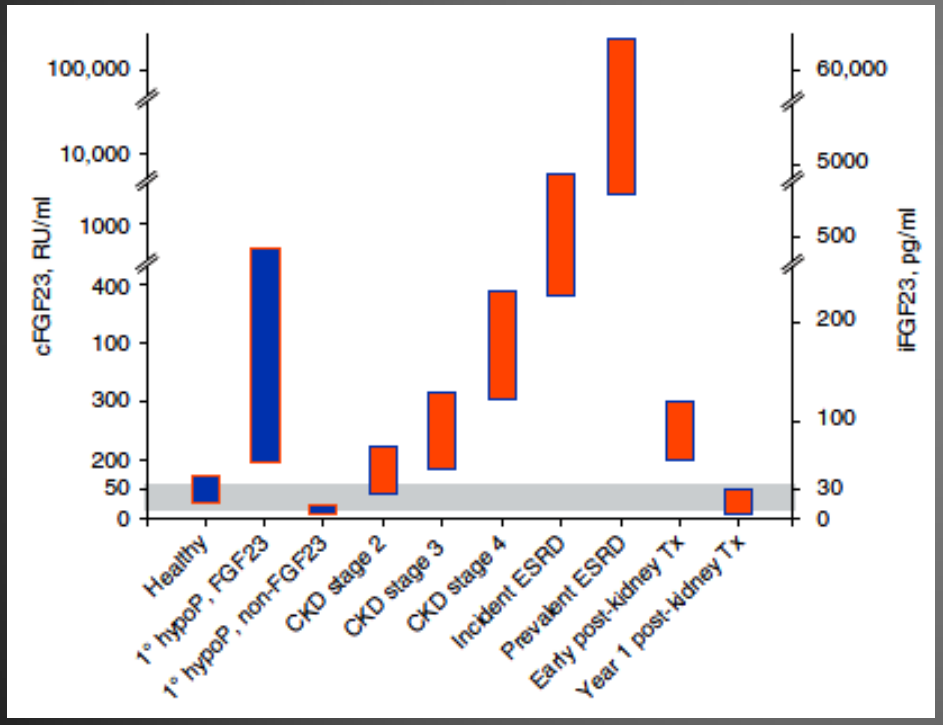




Saito H., The Journal of Biol Chem 2005

FGF23 en la EMO
A través de la enfermedad renal

Representative levels of fibroblast growth factor 23 (FGF23) in health, various states of chronic kidney disease (CKD; orange bars), and in primary hypophosphatemic disorders



Wolf M., Kidney Int **2012**

Table 1. Expected Concentration Range of FGF23 in Healthy Individuals and Across the Spectrum of CKD Based on Large-Scale FGF23 Measurements in Epidemiologic Cohorts

Population	Intact FGF23 (pg/mL)	C-Terminal FGF23 (RU/mL)
Normal renal function	20-60	25-70
CKD 2	25-80	30-150
CKD 3	40-120	50-300
CKD 4	80-500	100-1,000
CKD 5	250-1,250	400-2,000
End-stage renal disease	500-50,000	1,000-100,000

Olauson H., Seminars on Nephrology 2014

Longitudinal FGF23 and Klotho axis characterization in children treated with chronic peritoneal dialysis

	Month 1 (n:31)	Month 6 (n:25)	Month 12 (n:15)
Calcium (mg/dl) 9.4-10.3[1]	9.9 ± 1.1	9.8 ± 0.8	9.4± 0.9
Phosphorus (mg/dl) 3.6-5.8[1]	5.4 ± 1.2	5.7 ± 1.6	5.3 ± 1.3
1,25 (OH)D (pg/ml) 43±2[2]	26.7 ± 22.2	27.5 ± 21.4	NA
25(OH)D (ng/ml) >30[3]	33.7± 6.8	24.9 ±8.2	24.1 ± 5.6
Parathyroid Hormone (pg/ml) 200-300[1]	330.8 ± 273.4	349.9± 283.3	320.8 ± 205.1
FGF23 (pg/ml) Controls (45) 9.4±5.7[4]	215.1 ± 303.6	229.8 ± 252.6	194.8 ± 300.9
FGF23 log	1.98 ± 0.6	2.01 ± 0.6	1.77 ± 0.7
Klotho (pg/ml) Controls (45) 320±119.4[4]	132.1 ± 58	133.3 ±29.2	130.3 ± 34.4

Cano F., Freundlich M., y cols
Clin Kidney J, 2014
http://ckj.oxfordjournals.org/

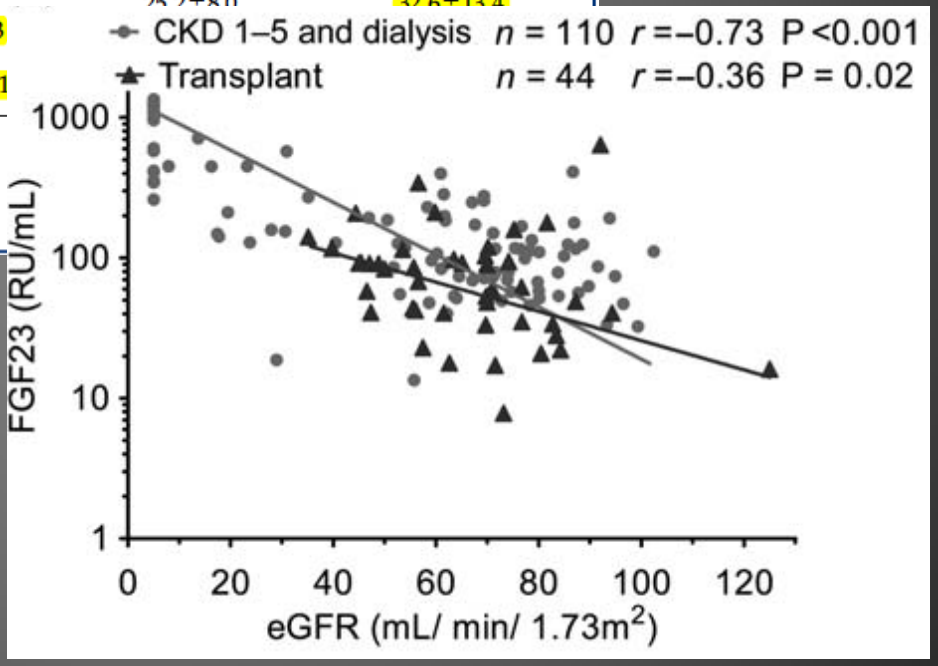
FGF23 en la EMO
A través de la enfermedad renal

Table 1. Biochemical parameters across the spectrum of CKD[a]

Biochemical Value	Stage 2 CKD (n=14)	Stage 3 CKD (n=24)	Stage 4/5 CKD (n=14)
Calcium (mg/dl)	9.5±0.4	9.2±0.5	9.3±0.9
Phosphorus (mg/dl)	4.7±0.8	4.7±1.0	6.1±1.2[b,c]
Bicarbonate (mEq/L)	22.2±3.1	21.8±5.1	19.7±2.0
Alkaline phosphatase (IU/L)	238±82	238±161	246±135
25(OH)vitamin D (μg/ml)	31.2±9.3	25.2±8.0	32.6±13.4
1,25(OH)$_2$vitamin D (pg/ml)	39.5±13.3		
PTH (pg/ml), median (interquartile range)	52 (48, 87)		
FGF-23 (RU/ml), median (interquartile range)	181 (101, 291		

FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone.
[a]Values are expressed as mean ± SD unless otherwise noted.
[b]P<0.05 above the normal range.
[c]P<0.05 from stage 2 and stage 3 CKD.

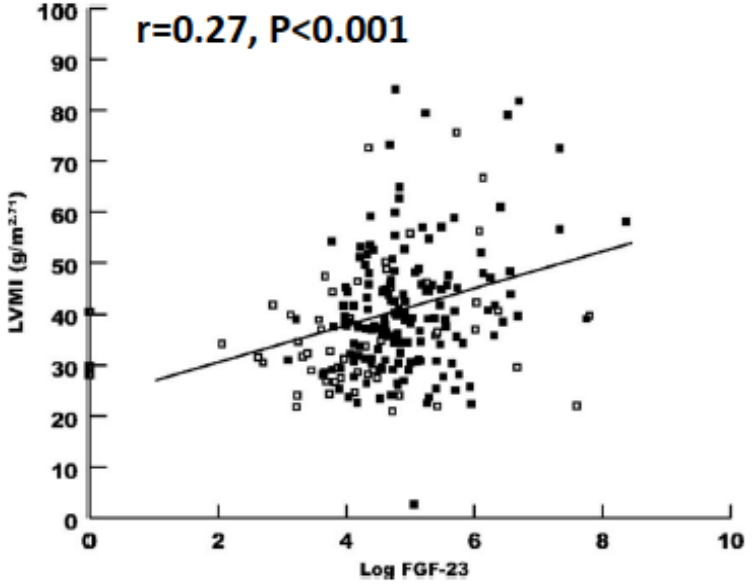
Wesseling-Perry et al.
Clin J Am Soc Nephrol 2012

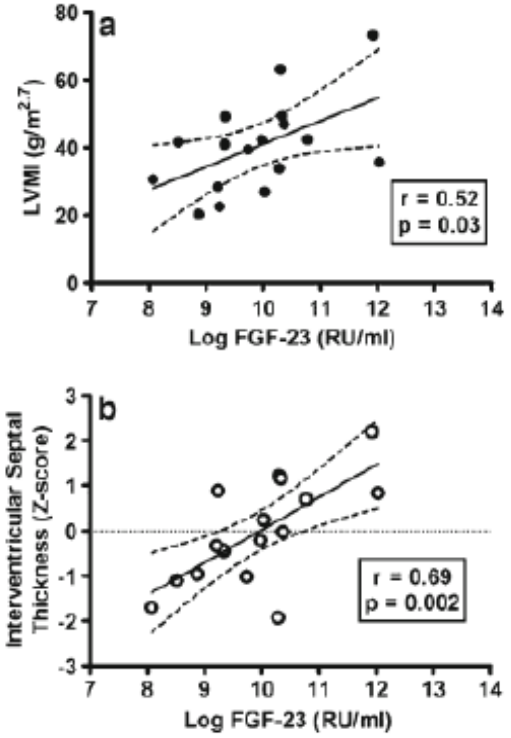


Wan M., Nephrol Dial Transplant (2013)

Efectos sistémicos del FGF23

Correlation between log FGF-23 and LVMI: Adults and Children





□ non-CKD subjects

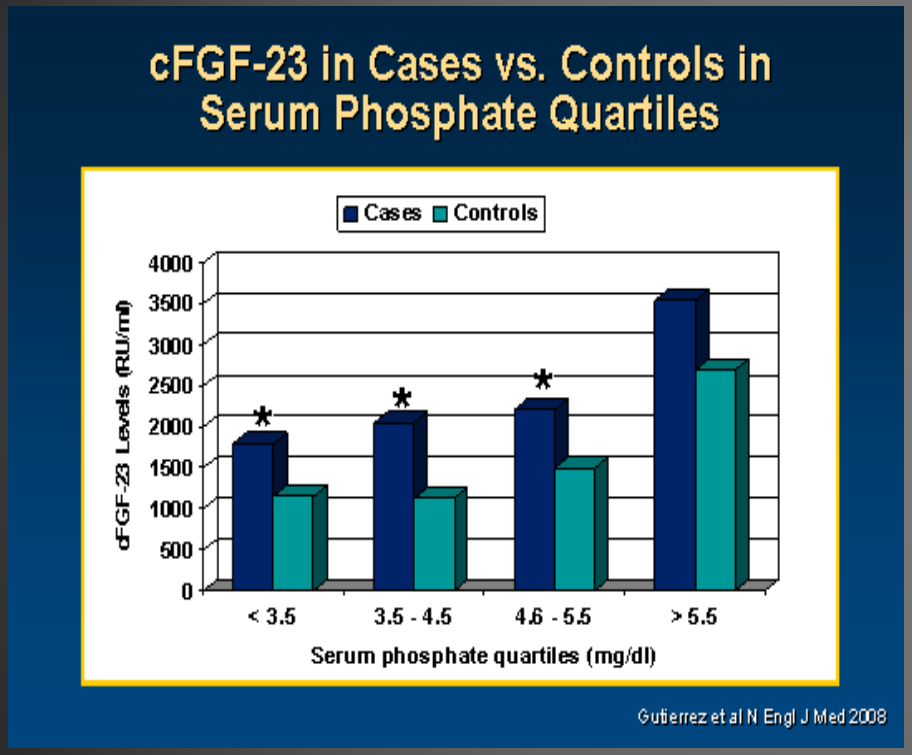
▪ subjects with CKD.

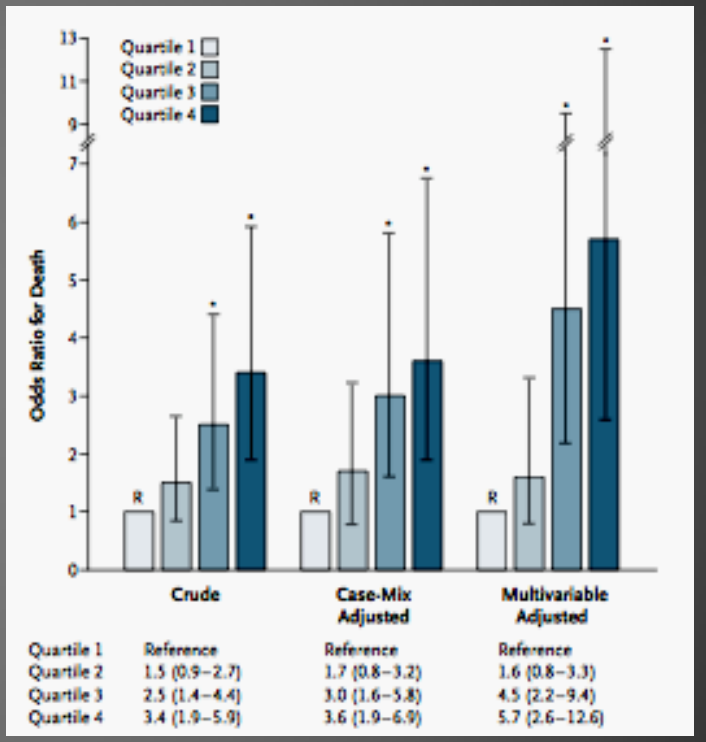
Gutiérrez O M et al. Circulation 2009;119:2545-2552

Seeherunvong W et al. Pediatr Nephrol. 2012 ;27:2129-36

Efectos sistémicos del FGF23

Figure 1. Odds Ratios (and 95% CIs) for Death According to Quartile of C-Terminal Fibroblast Growth Factor 23 (cFGF-23) Levels.

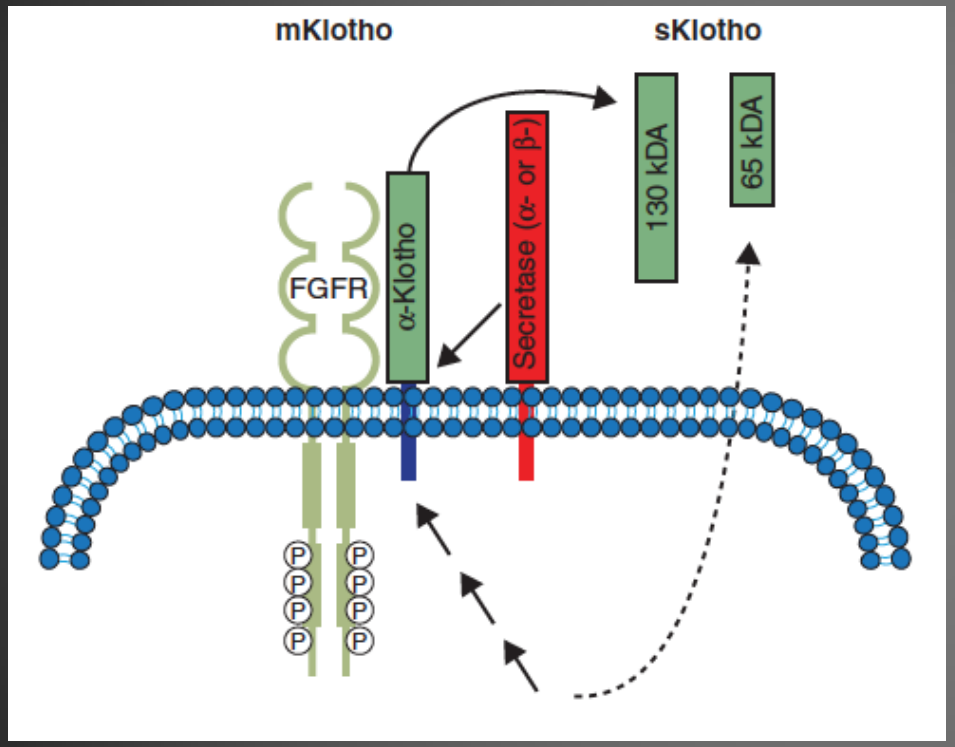




Gutierrez O.et al. N Engl J Med 2008;359:584-92

FGF23 y su Co-receptor Klotho.
(Clotho, Lakhesis, Atropos)

FGF23 y su Co-receptor Klotho



The Klotho gene encodes a single-pass type I transmembrane protein (1014 amino acids in the mouse and 1012 in humans) with a short cytoplasmic domain and an extracellular domain composed of two b-galactosidase/ glycosidase-like tandem repeats (KL1 and KL2) with b-glucuronidase and sialidase activity.

It is predominantly expressed in kidneys, brain (choroid plexus (CP), neurons sinoatrial node of the heart, endocrine (pituitary, parathyroid and pancreas) and reproductive organs (gonads and placenta).

(Kuro-o et al. 1997, Kato et al. 2000, Li et al. 2004, Takeshita et al. 2004, German et al. 2012)

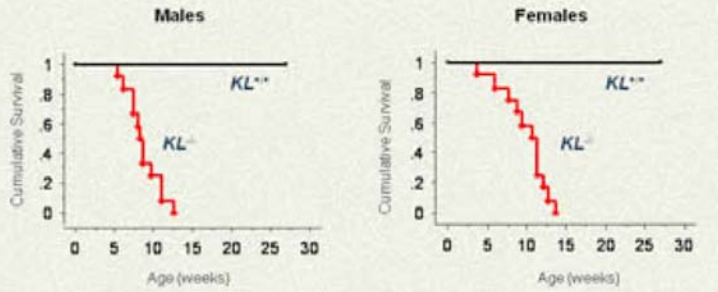
Especificidad de accion del FGF23
Rol del Klotho

Mutation of the mouse klotho gene leads to a syndrome resembling ageing

The *klotho* mouse

is one of the transgenic mouse lines that do NOT express the transgene.
Homozygotes for the transgene develop multiple aging-like phenotypes
around 4 weeks of age
due to insertional mutation.

- Short lifespan



The *klotho* mouse

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Homozygotes for the transgene develop multiple aging-like phenotypes
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- Short lifespan
- Growth retardation
- Hypogonadism
- Premature thymic involution
- Skin atrophy
- Muscle atrophy
- Vascular calcification
- Osteoporosis
- Pulmonary emphysema
- Ectopic calcification
- Motor neuron degeneration
- Hearing disorder, etc.

Gentileza Dr. Makoto Kuro-o

Especificidad de accion del FGF23
Rol del Klotho

Mutation of the mouse klotho gene leads to a syndrome resembling ageing

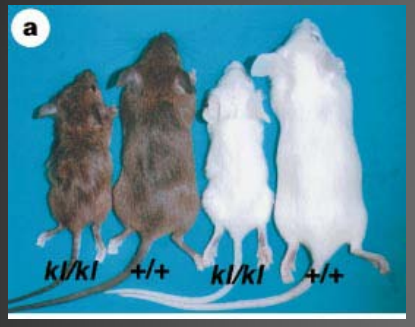
Klotho$^{-/-}$ mice and *Fgf23*$^{-/-}$ mice

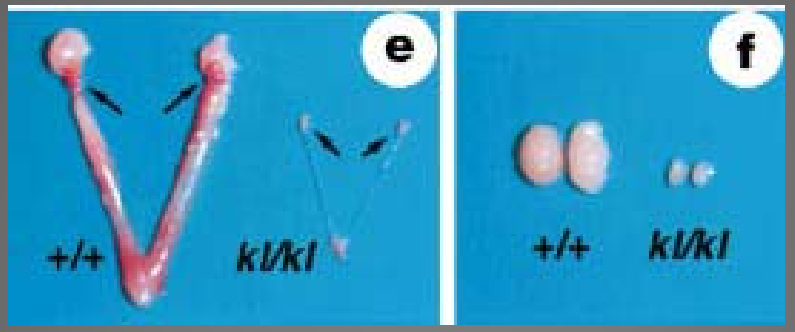
Klotho$^{-/-}$	*Fgf23*$^{-/-}$
Short lifespan	Short lifespan
Growth retardation	Growth retardation
Hypogonadism	Hypogonadism
Premature thymic involution	Premature thymic involution
Skin atrophy	Skin atrophy
Muscle atrophy	Muscle atrophy
Arteriosclerosis	Arteriosclerosis
Osteoporosis	Osteoporosis
Pulmonary emphysema	Pulmonary emphysema
Soft tissue calcification	Soft tissue calcification
Hyperphosphatemia	Hyperphosphatemia
Hypervitaminosis D	Hypervitaminosis D
Hypercalcemia	Hypercalcemia
Hypoglycemia	Hypoglycemia

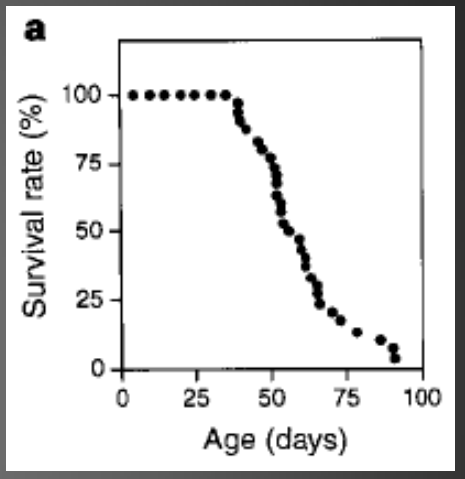
FGF23 requires Klotho to activate FGF signaling

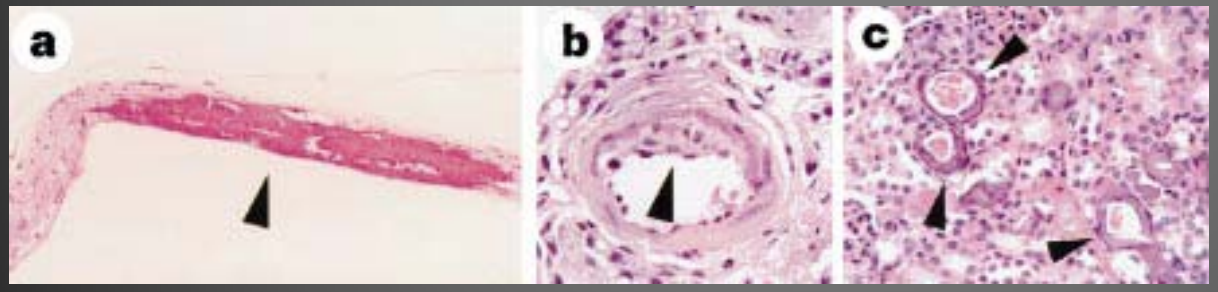
Gentileza Dr. Makoto Kuro-o

Mutation of the mouse klotho gene leads to a syndrome resembling ageing





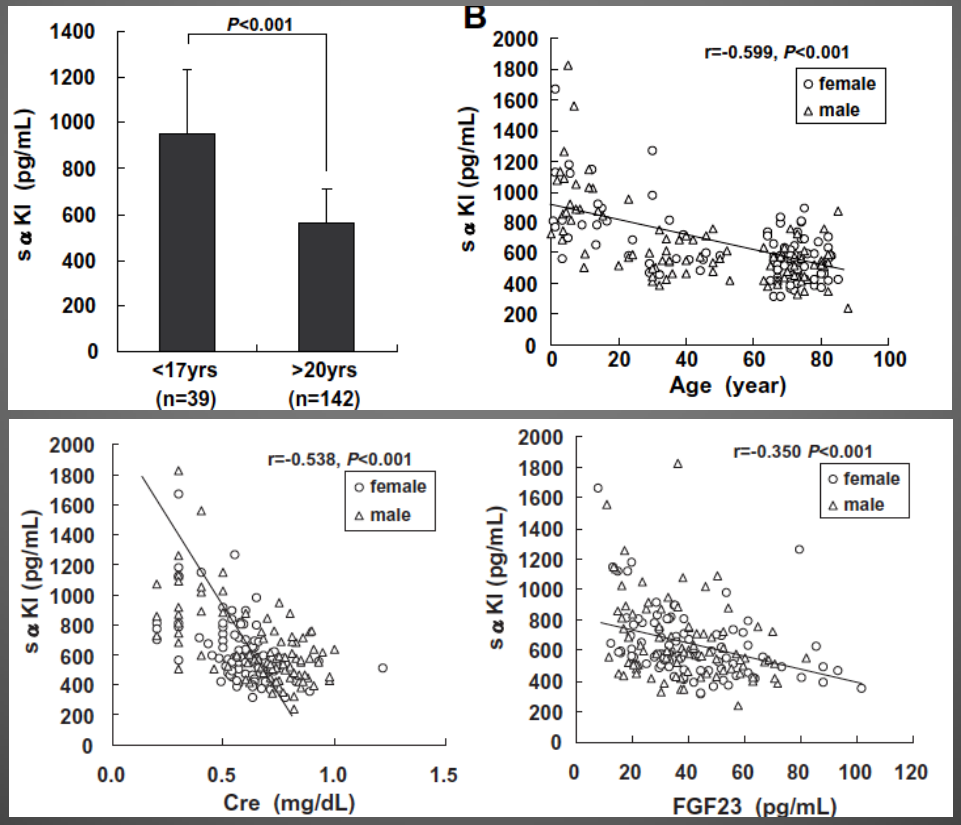




Gentileza Dr. Makoto Kuro-o

Especificidad de accion del FGF23
Klotho en la vida normal

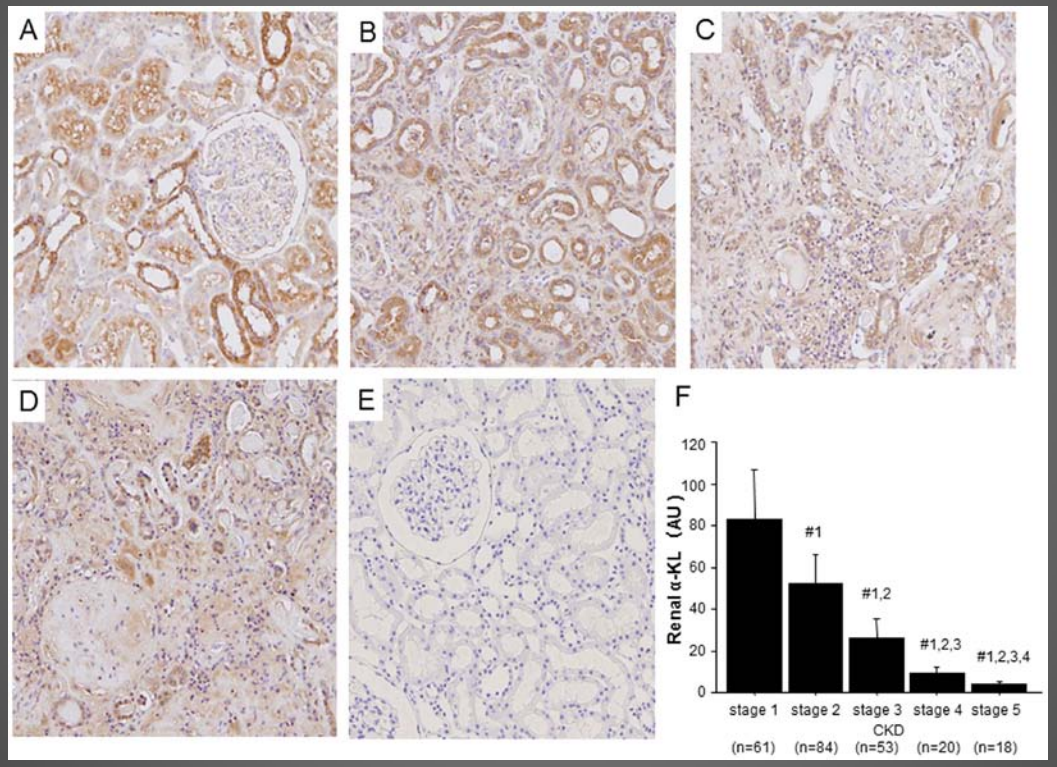
Establishment of sandwich ELISA for soluble alpha-Klotho measurement: Age-dependent change of soluble alpha-Klotho levels in healthy subjects



Yamazaki Y, Biochemical and Biophysical Research Communications 2010

Klotho en la Enfermedad Renal Crónica

Reduced Renal a-Klotho Expression in CKD Patients and Its Effect on Renal Phosphate Handling and Vitamin D Metabolism



Hirokazu Sakan, PLOS one, January 2014

Efectos sistémicos del Klotho

Left Ventricular Mass Progression despite Stable Blood Pressure and Kidney Function in Stage 3 Chronic Kidney Disease

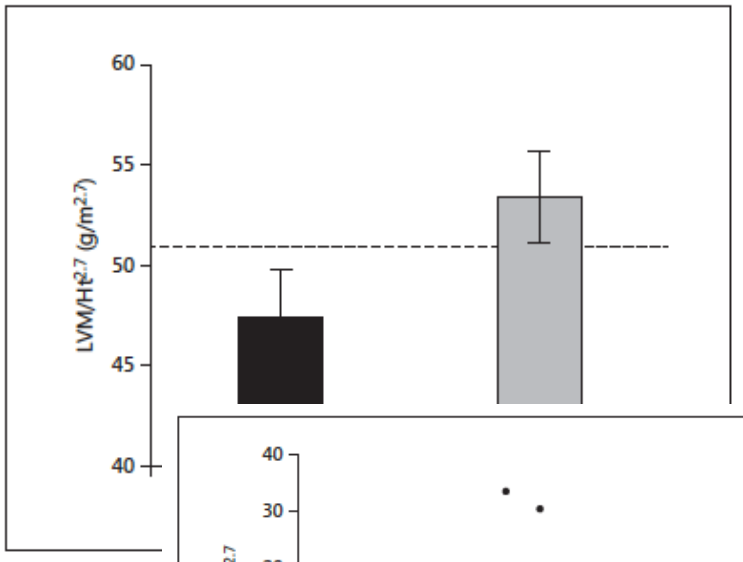


Fig. 1. Compa
12-month visi
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the threshold

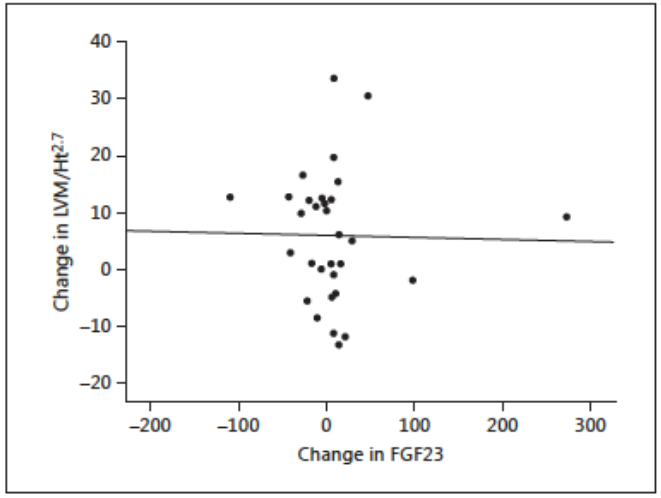


Fig. 2. Scatter plot of the change in FGF23 levels vs. the change in LVM/Ht$^{2.7}$ between the baseline and 12-month visit. The strength ($r^2 = -0.02$) and significance ($p = 0.92$) of the association were generated using Pearson's correlation.

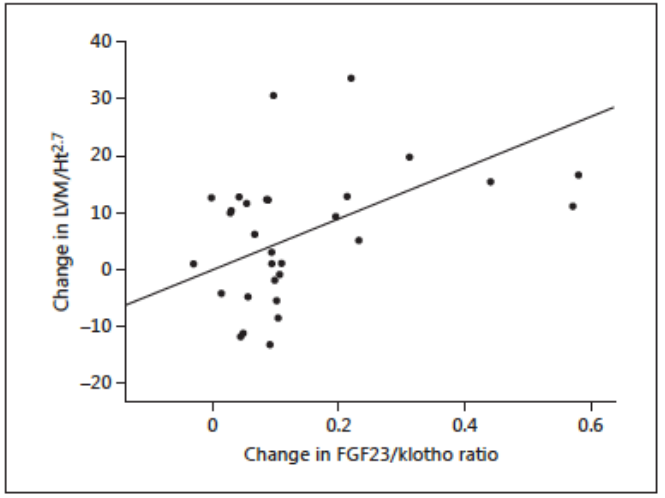


Fig. 3. Scatter plot of the change in FGF23/klotho ratio vs. the change in LVM/Ht$^{2.7}$ between the baseline and 12-month visit. The strength ($r^2 = 0.582$) and significance ($p = 0.03$) of the association were generated using Pearson's correlation.

Seifert M.,Am J Nephrol 2014

Klotho, Homeostasis del calcio, uremia y envejecimiento

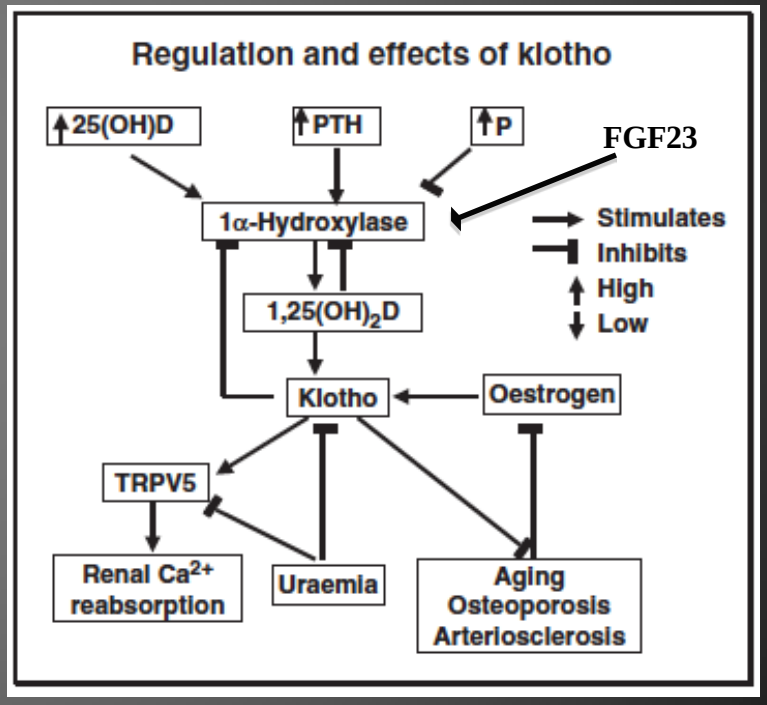
CALCIO

El envejecimiento representa un estado de cambio en la distribución del calcio, desde la masa ósea a los tejidos extraóseos, en especial los vasos sanguineos.

Funciones extracelulares: integridad de las membranas, adherencia intercelular, coagulación, mineralización ósea.
Funciones intracelulares: segundo mensajero en procesos metabólicos, motilidad celular, procesos de secresión y absorción, proliferación celular; Cofactor enzimático.

Regulación de la calcemia:

a) componente sensor de cambios en calcemia: PTH, 1,25(OH)2, Calcitonina.
b) componente efector, transportee del calcio: riñón, intestino, hueso, que responden a las hormonas del componente sensor.



El transporte activo de calcio en la membrana basolateral del túbulo distal por el Nafl /Ca2fl -exchanger, y por la Ca2fl -ATPase en riñón e intestino es regulado por 2 miembros de los canales epiteliales de calcio, "transient receptor potential superfamily" (TRP),, TRPV5 and TRPV6.

- Klotho hidroliza residuos de azucares fijando el TRPV5 en la membramna, manteniendo activo el transporte de calcio.
- Klotho y TRPV5 son positivamente regulados por 1.25vitD.
- Klotho está co-localizado junto a TRPV5 en la membrana del TCD.

Chang Q,. The betaglucuronidase klotho hydrolyzes and activates the TRPV5 channel. Science 2005

Longitudinal FGF23 and Klotho axis characterization in children treated with chronic peritoneal dialysis

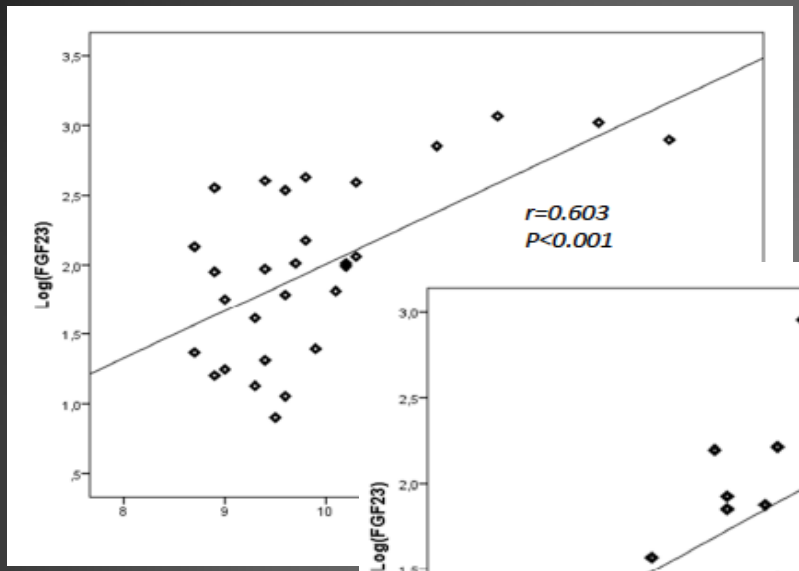
Table 2.

Nutritional and Dialytical parameters in children under chronic peritoneal dialysis at 12 months of follow-up[a]

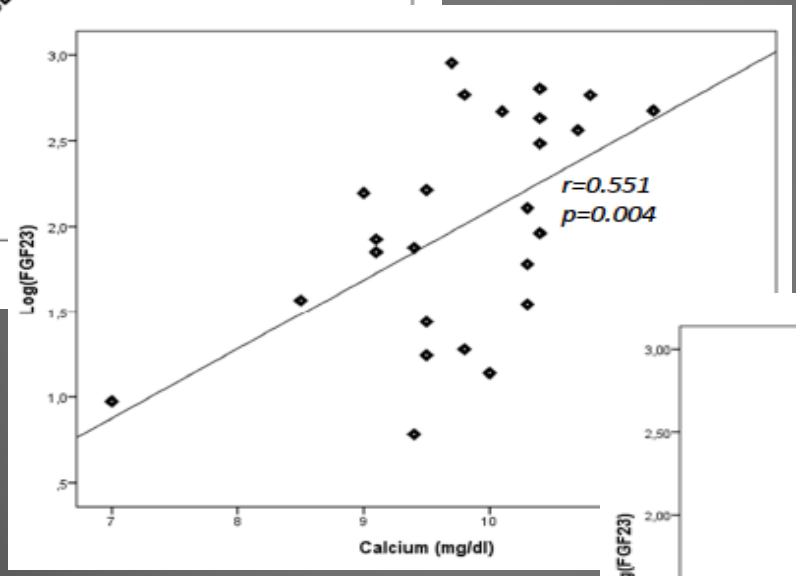
Variable	Month 1 (n:31)	Month 6 (n:25)	Month 12 (n:15)
Height/age SDS	-1,88 ± 1,18	-1,65 ± 1,07	-1,78 ± 1,15
nPNA	1.03 ± 0.3	0.97 ± 0.3	1.01 ± 0.3
Adequacy of calcium intake (%)	99.1 ± 44.5	90.7 ± 25.9	69.4 ± 27.7
Adequacy of phosphorus intake (%)	100.7 ± 70.9	91.4 ± 35.1	87± 34.2
Adequacy of protein intake (%)	117.8 ± 31.9	132.1 ± 50.2	139.2 ± 36.7
Total KtV	2.9 ± 1.4	2.9 ± 1.7	2.8 ± 1.7
Residual KtV	1.27 ± 1,5	1.02 ± 1.4	1.2 ± 1.8

Cano F., Freundlich M., y cols
Clin Kidney J, 2014
http://ckj.oxfordjournals.org/

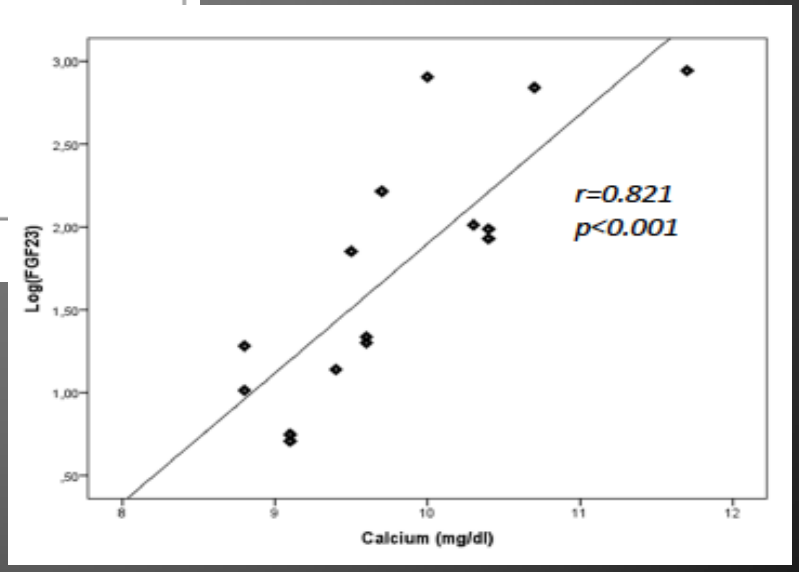
Longitudinal FGF23 and Klotho axis characterization in children treated with chronic peritoneal dialysis



Mes 1



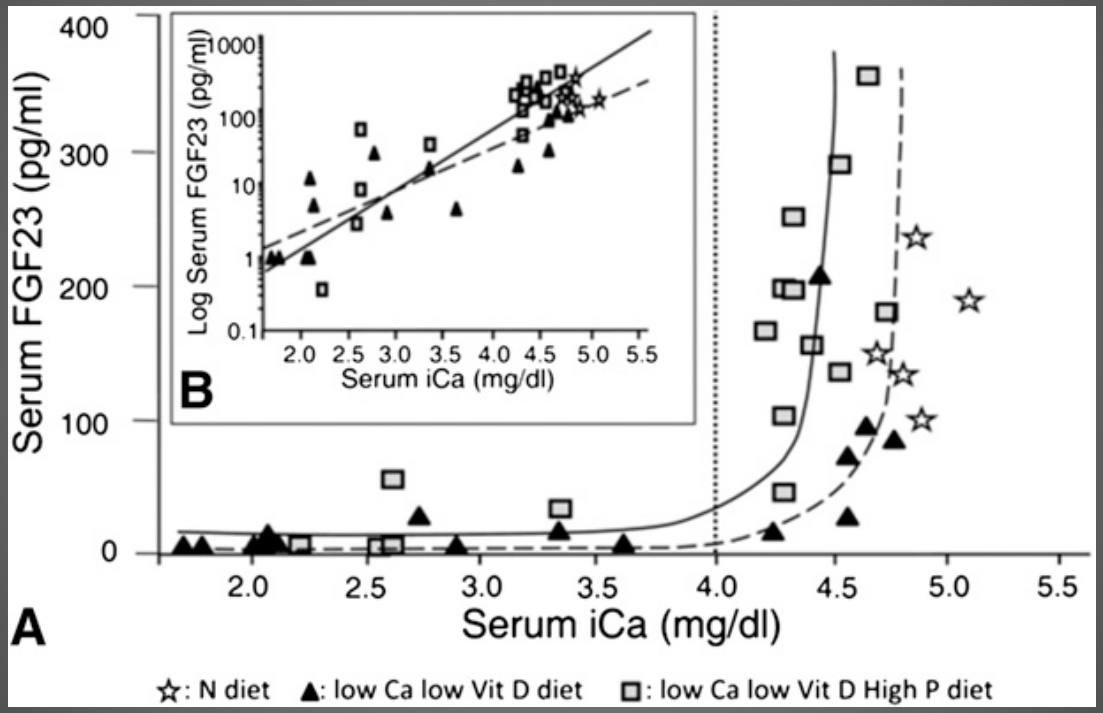
Mes 6



Mes 12

Cano F., Freundlich M., y cols
Clin Kidney J, 2014
http://ckj.oxfordjournals.org/

Calcium Deficiency Reduces Circulating Levels of FGF23 in rats

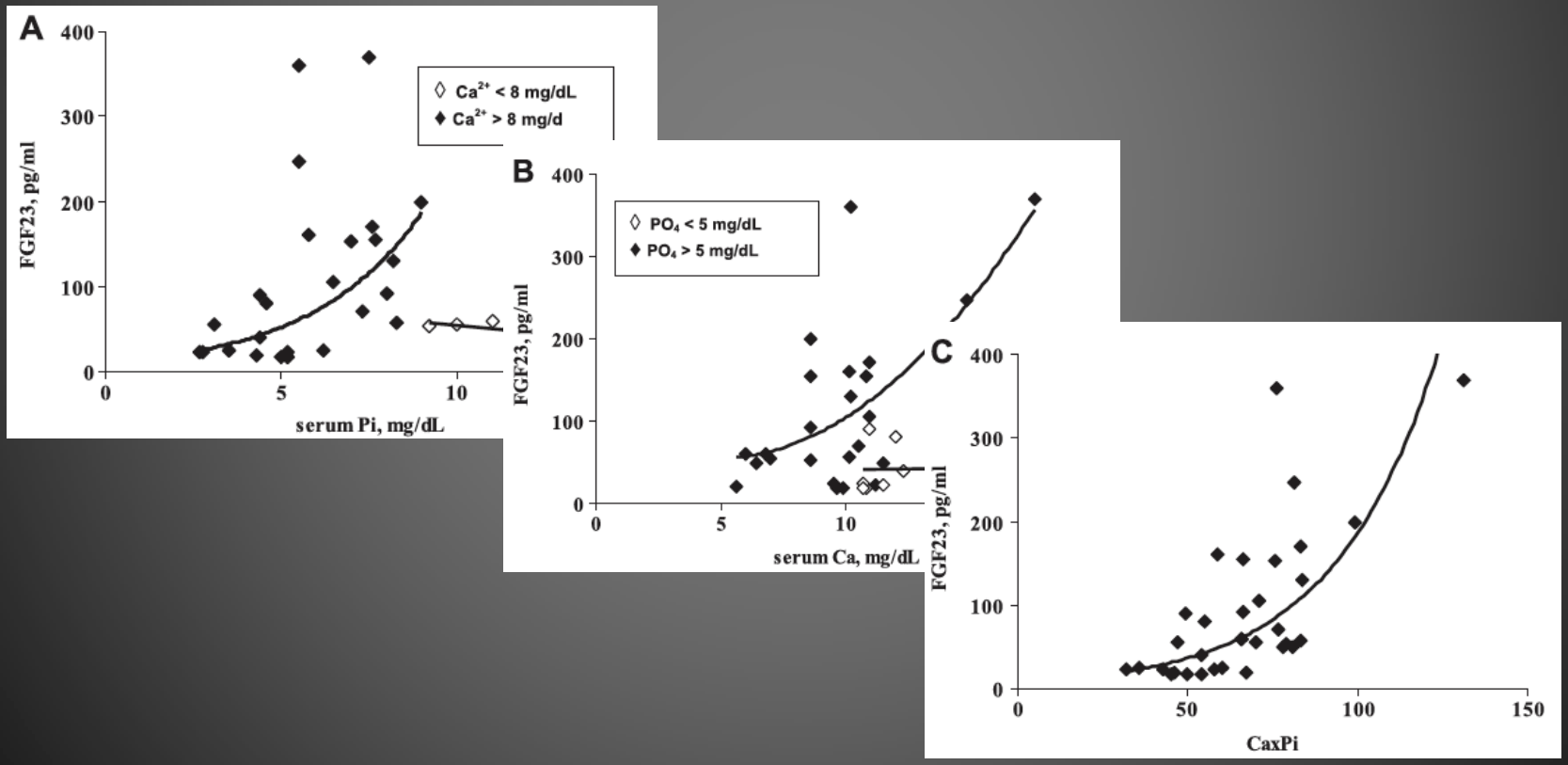


Rodriguez-Ortiz M., JASN 2012

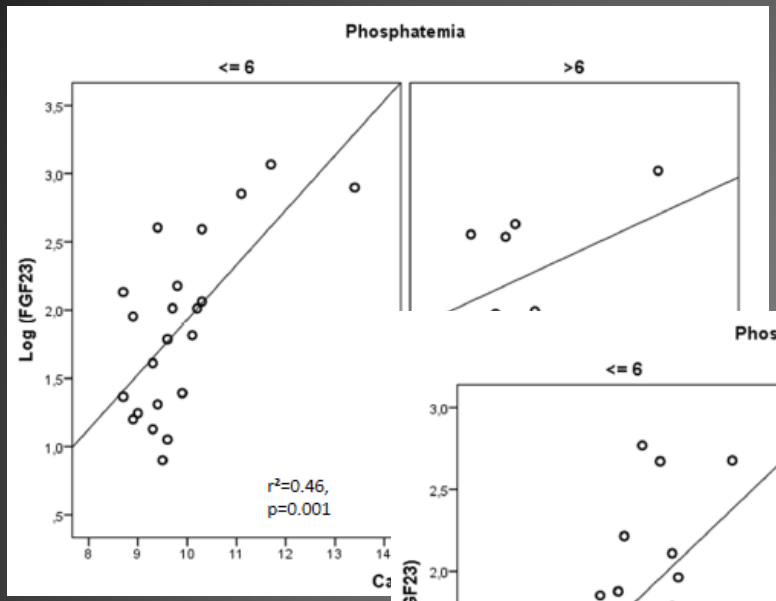
Interactions between calcium and phosphorus in the regulation of the production of fibroblast growth factor 23 in vivo

Stephen J. Quinn, Alex R. B. Thomsen, Jian L. Pang, Lakshmi Kantham, Hans Bräuner-Osborne, Martin Pollak, David Goltzman and Edward M. Brown

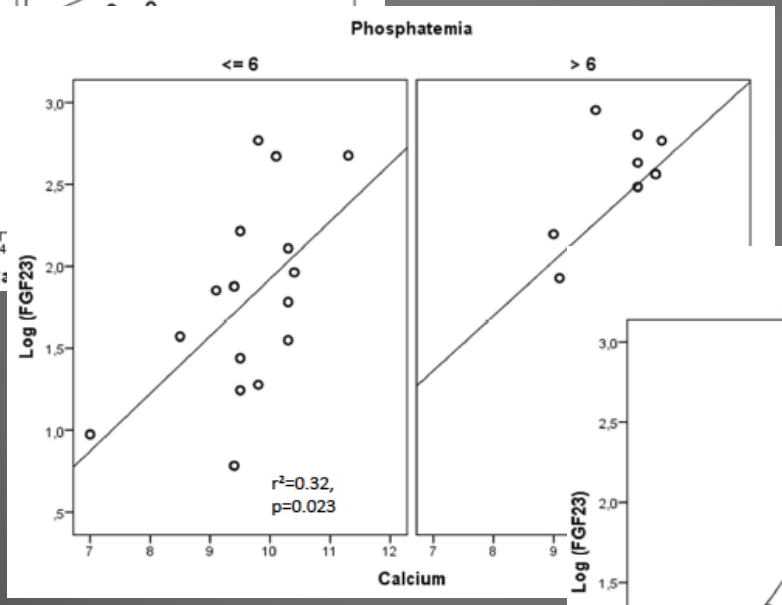
Am J Physiol Endocrinol Metab 304:E310-E320, 2013. First published 11 December 2012;



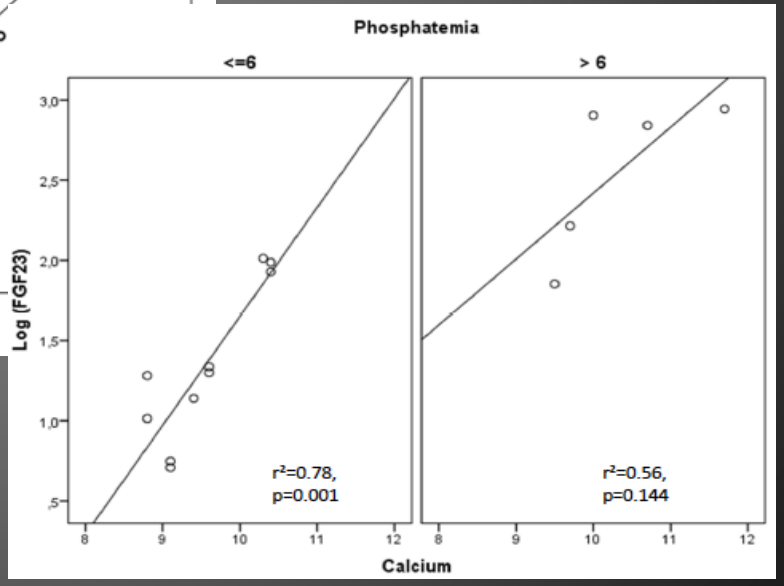
Longitudinal FGF23 and Klotho axis characterization in children treated with chronic peritoneal dialysis



Mes 1



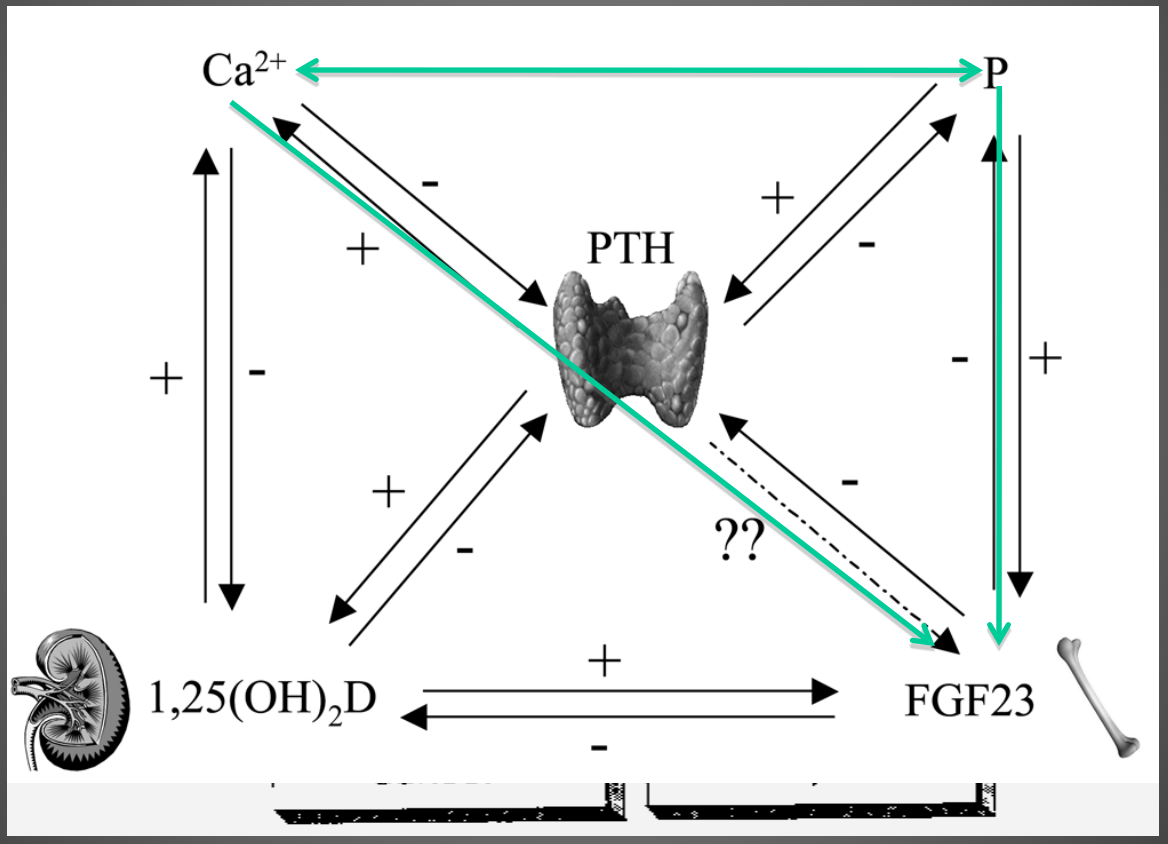
Mes 6



Mes 12

Cano F., Freundlich M., y cols
Clin Kidney J, 2014
http://ckj.oxfordjournals.org/

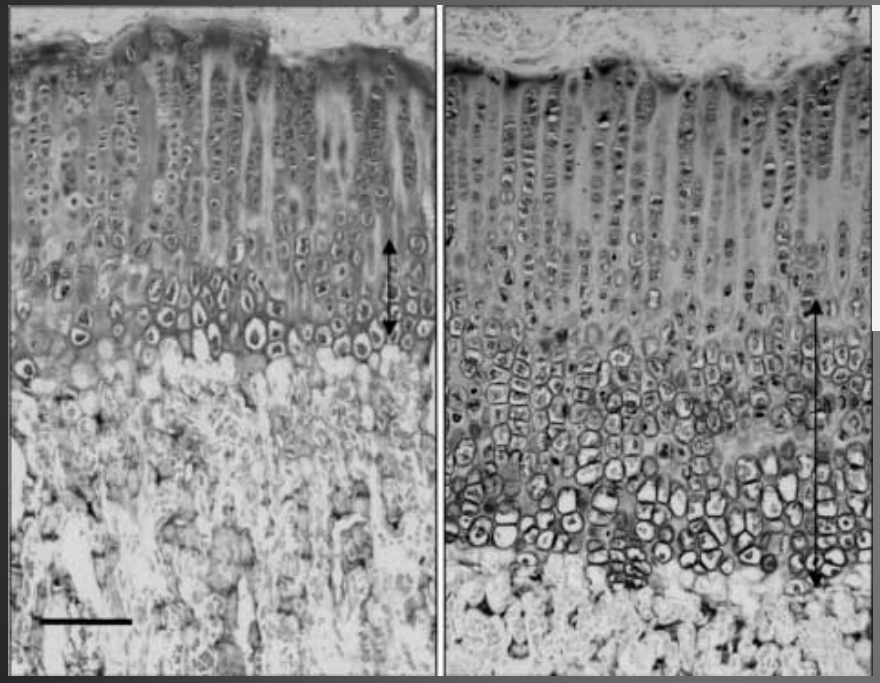
La Enfermedad Mineral Osea
En la Enfermedad Renal Crónica



Ben-Dov et al. JCI 2013


HOSPITAL LUIS CALVO MACKENNA

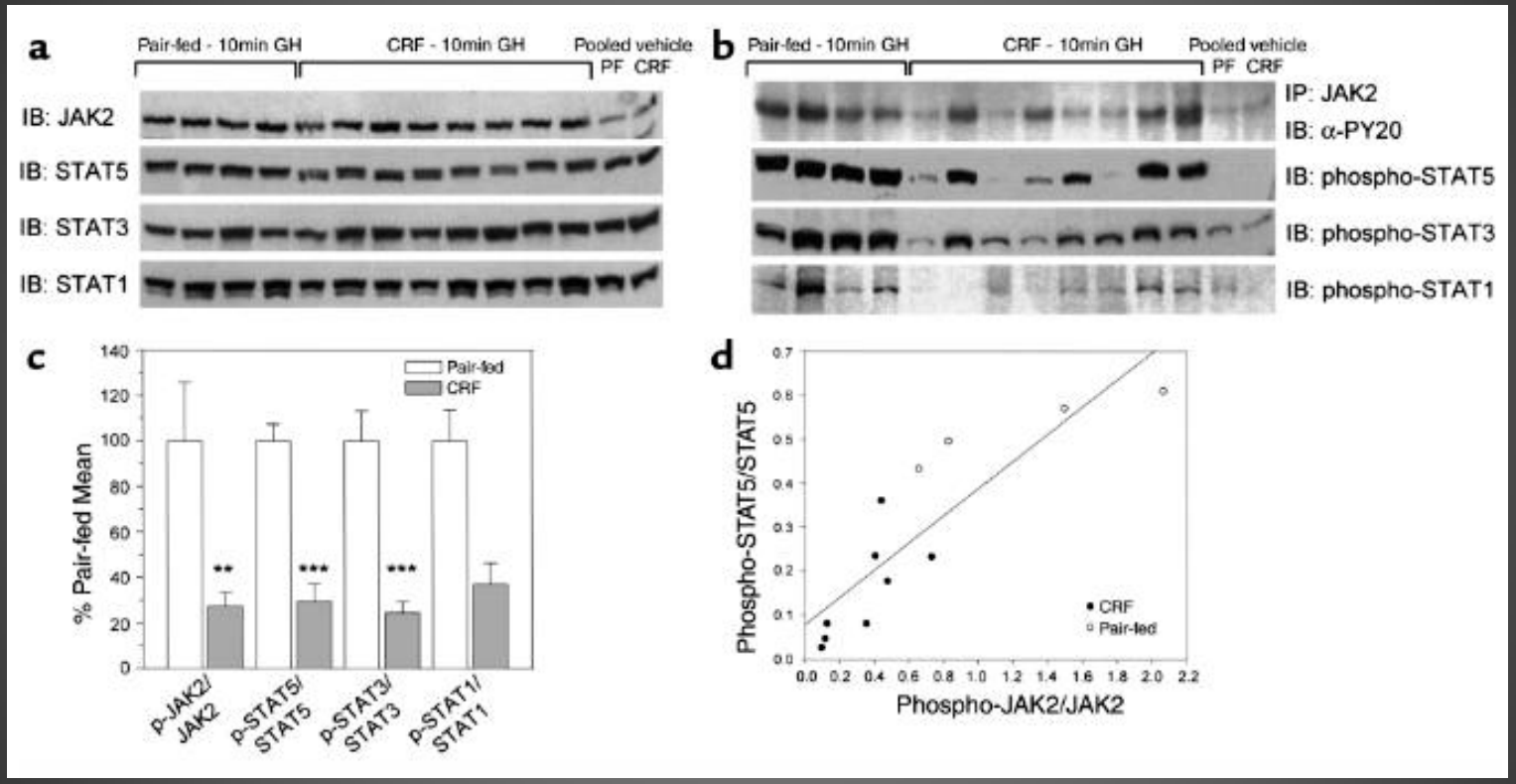
La placa de crecimiento en la insuficiencia renal crónica



	Control	Malnutrición	IRC
Volumen condrocito distal (μ^3)	16.303 ± 1.483	14.466 ± 1.521	12.080 ± 1.158*
Recambio celular por columna y día	8,0 ± 1,6	7,2 ± 1,1	5,4 ± 0,9*
Duración fase hipertrófica (h)	32,1 ± 6,7	34,8 ± 5,1	89,0 ± 15,2*
Velocidad de avance celular (μ/h)	11,3 ± 2,7	10,1 ± 2,5	7,4 ± 2,2*

Santos F., Nefrologia 2003, Pediatr Nephrol 2005

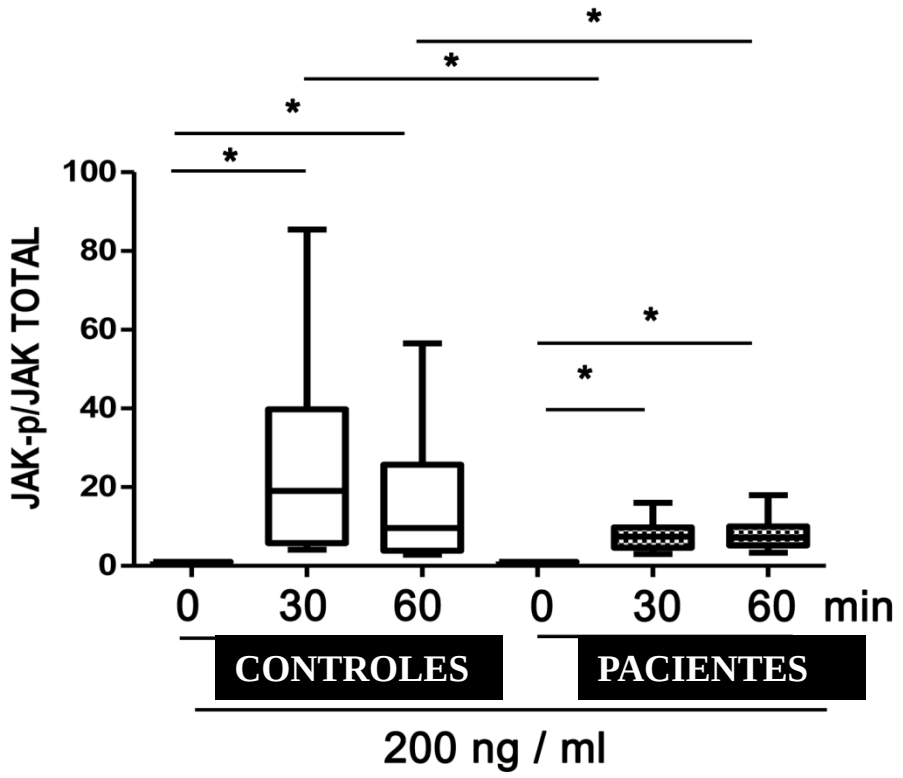
GH-mediated JAK2/STAT signal transduction is impaired in CRF



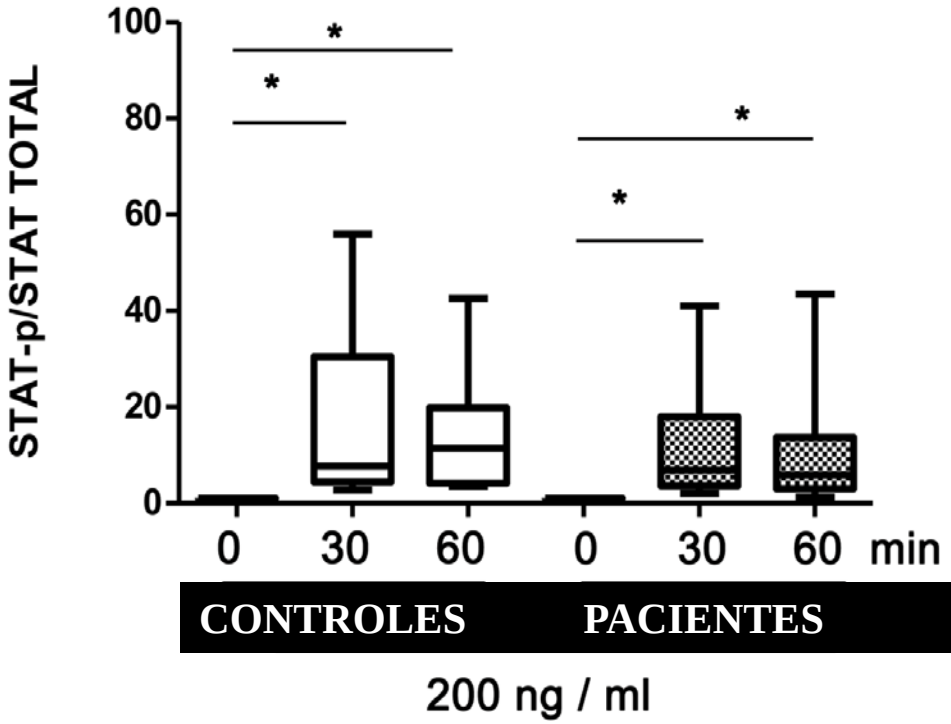
Schaeffer F, et al
J Clin Invest 2001, 108;467-75

ROL DEL EJE GH/IGF1 EN EL RETRASO DE CRECIMIENTO EN NIÑOS EN DIALISIS PERITONEAL. FONDECYT 1110226

pJAK2/JAK2 tot (cyt)



pSTAT 5b/STAT tot (cyt)



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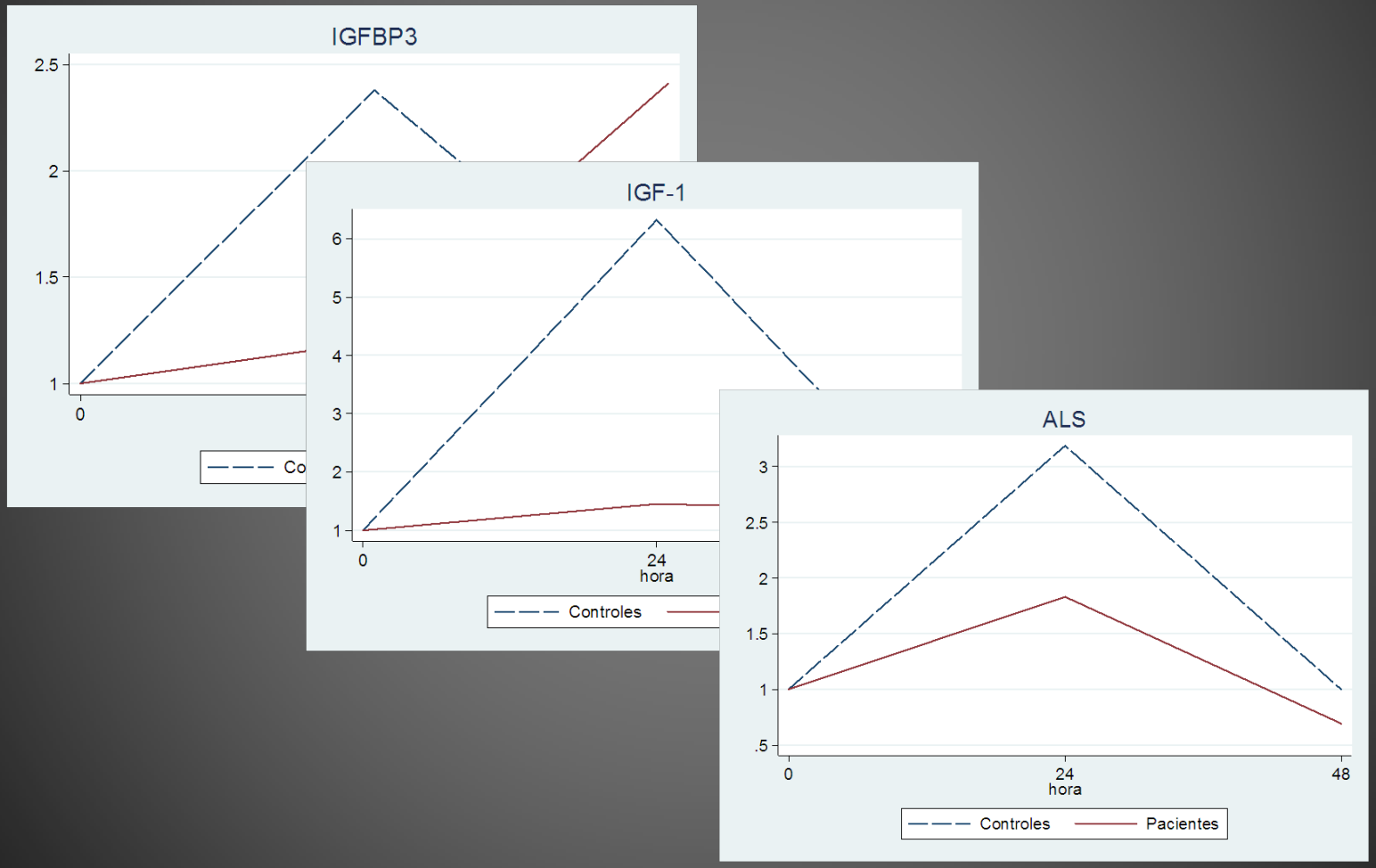
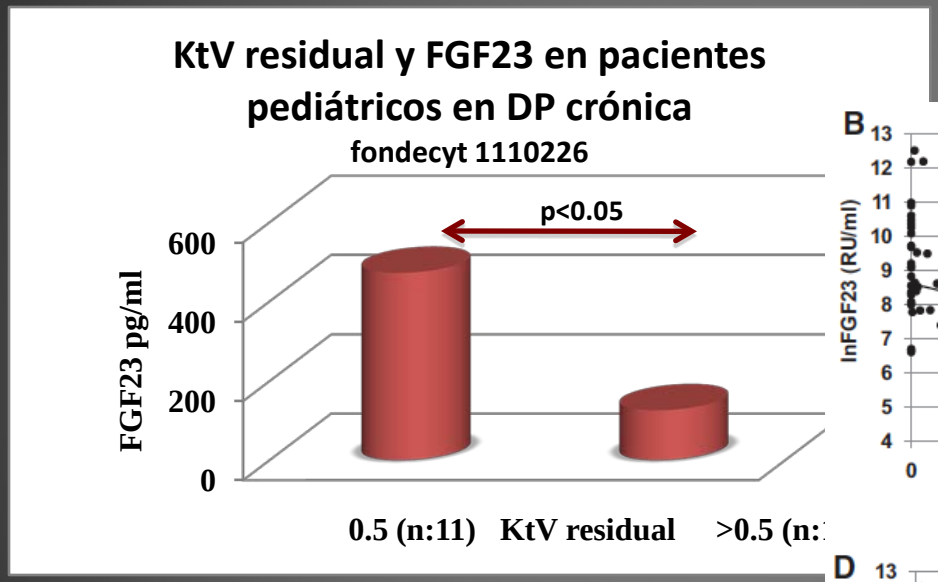
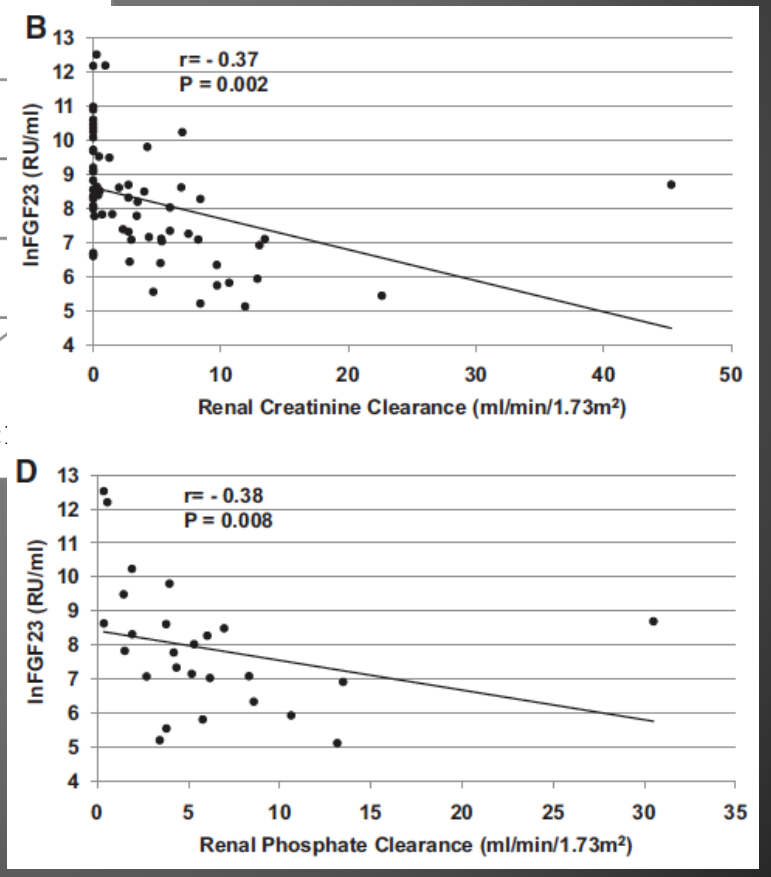


Longitudinal FGF23 and Klotho axis characterization in children treated with chronic peritoneal dialysis

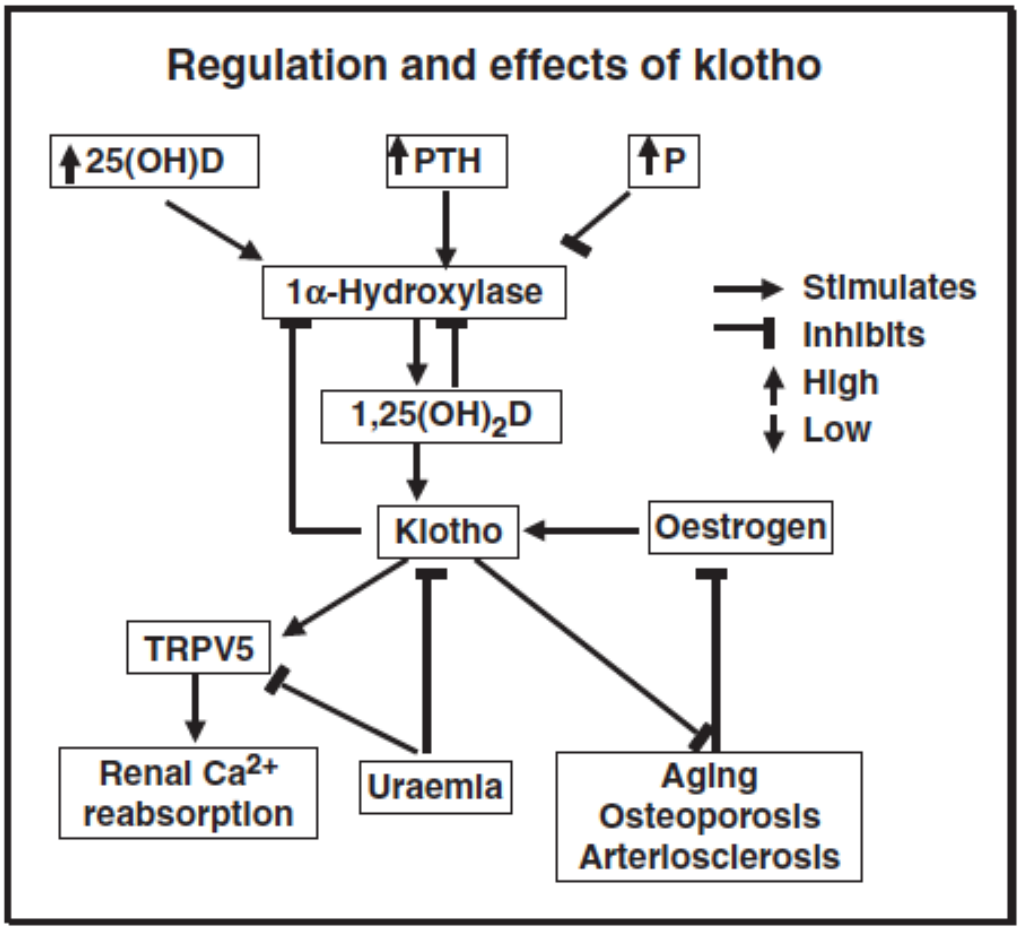


Fibroblast Growth Factor 23 in Patients Undergoing Peritoneal Dialysis



ISAKOVA T. CJASN 2011

Klotho, an important new factor for the activity of Ca^{2+} channels



Lewin E, NDT 2006

Lack of FGF23 Response to Acute Changes in Serum Calcium and PTH in Humans

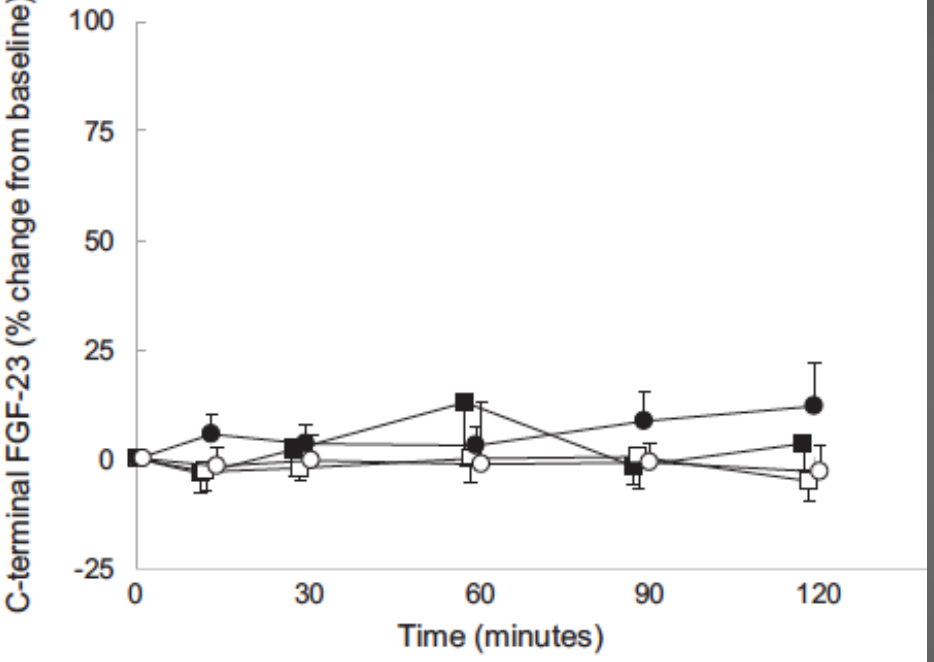


Figure 5. Percentage change in C-terminal FGF23 levels from baseline. Healthy volunteers receiving calcium, closed circles; dialysis patients receiving calcium, open circles; healthy volunteers receiving sodium citrate, closed squares; dialysis patients receiving sodium citrate, open squares.

Wesseling-Perry K. et al.
J Clin Endocrinol Metab, October 2014, 99(10):E1951–E1956