

THE EMERGING ROLE OF THE FGF23-
KLOTHO AXIS IN RENAL REGULATION
OF PHOSPHATE HOMEOSTASIS

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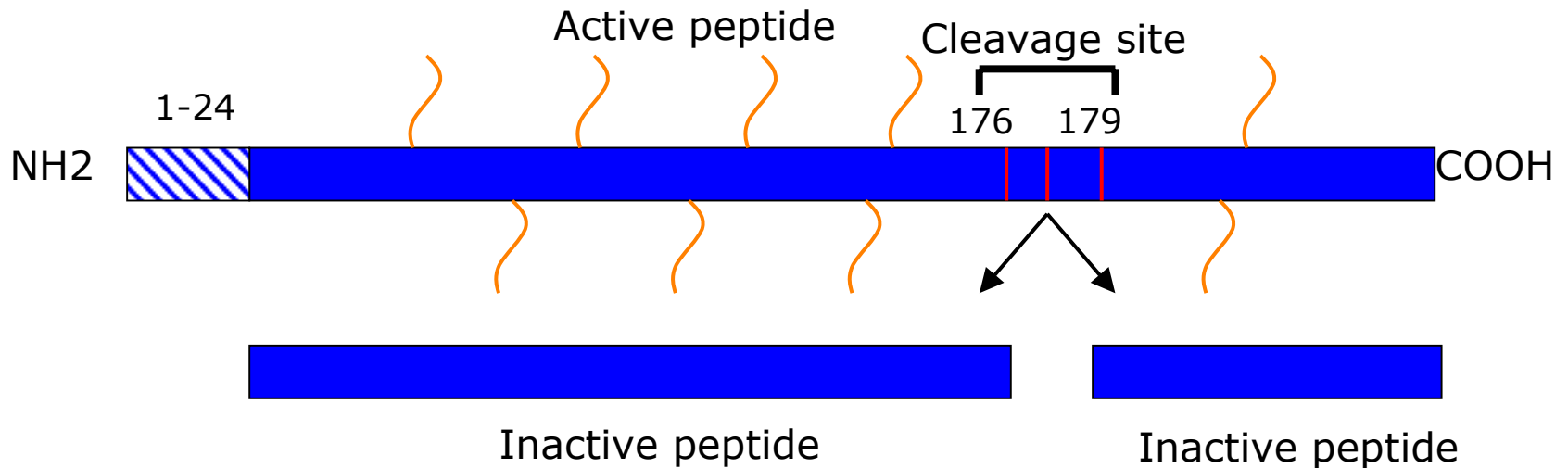
Hôpital Necker, Paris

IDENTIFICATION OF A PHOSPHATURIC FACTOR: THE FIBROBLAST GROWTH FACTOR 23

Identified in patients with Autosomal Dominant Hypophosphataemic Rickets, or tumoral osteomalacia

32 kd circulating glycosylated peptide, 251 amino acids

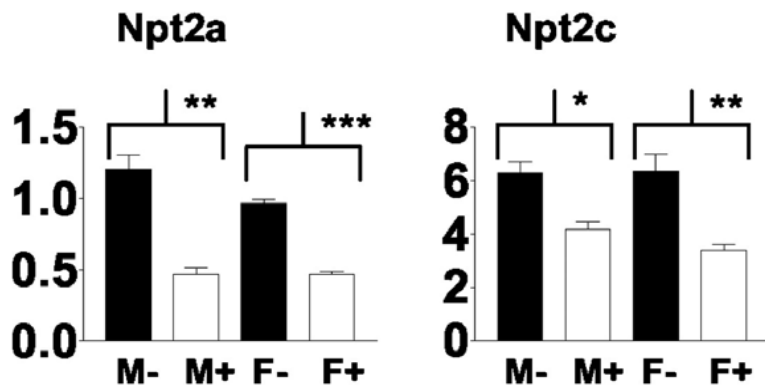
Plasma concentration in healthy subject < 50 pg/ml.



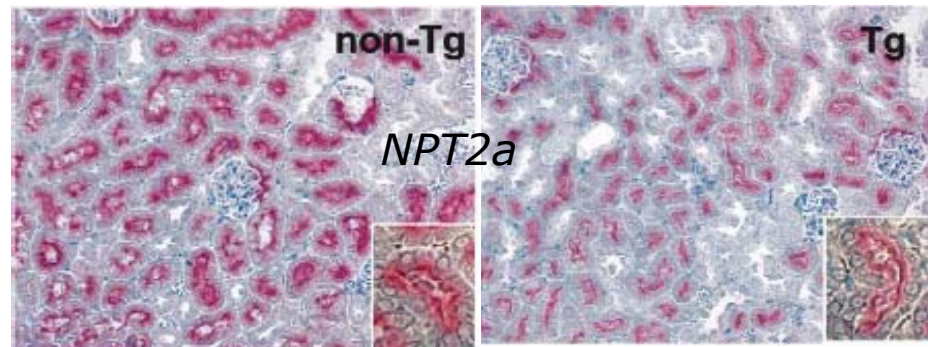
Site of synthesis: Bone (osteocytes, osteoblasts), brain, parathyroid gland, thymus, liver

EFFECT OF FGF23 ON PHOSPHATE TRANSPORT IN THE KIDNEY

Decreases renal sodium phosphate transporter mRNA and protein expression



Larsson 2004 endoc 145 3087



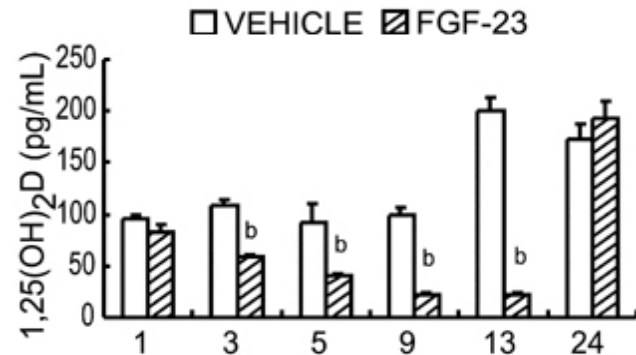
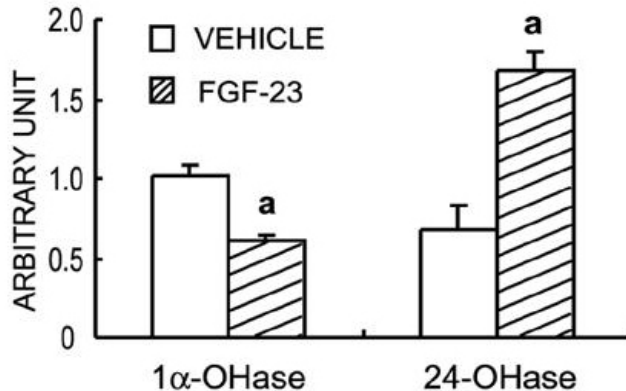
Shimada 2004 BBRC 314 409

Increases urinary phosphate excretion

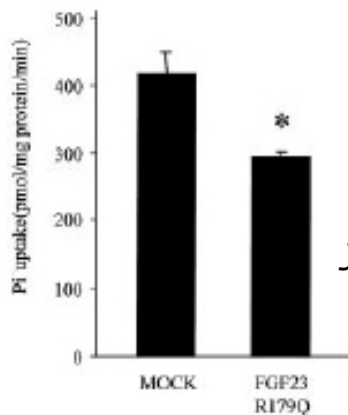
	Male (wild-type)	Male (FGF-23 transgenic)	Female (wild-type)	Female (FGF-23 transgenic)
Pi (mM)	2.75 ± 0.22	1.91 ± 0.27a	2.16 ± 0.15	1.19 ± 0.11a
FEI(Pi)	14.5 ± 2.5	34.8 ± 7.6a	14.0 ± 3.8	72.3 ± 31b

FGF23 EFFECTS ON VITAMIN D METABOLISM

Lowers 1 alpha-hydroxylase mRNA expression and stimulates 24-hydroxylase mRNA expression, decreases serum calcitriol concentration

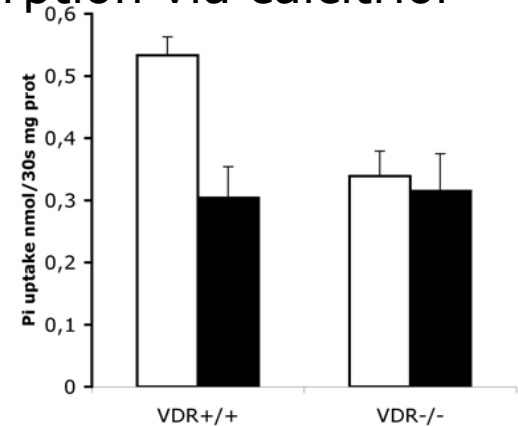


Inhibits phosphate and calcium intestinal absorption via calcitriol decrease



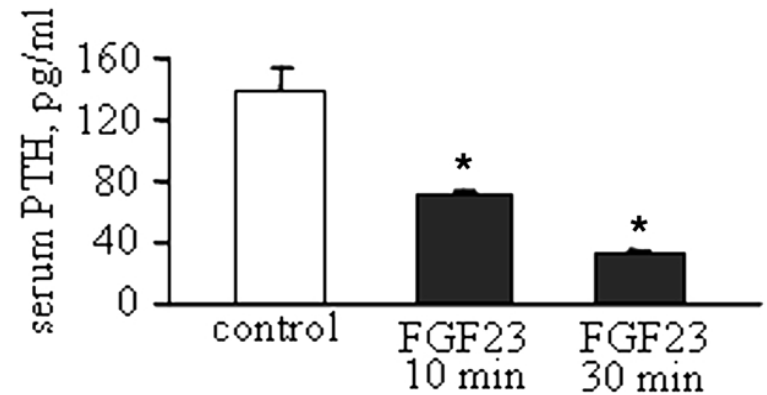
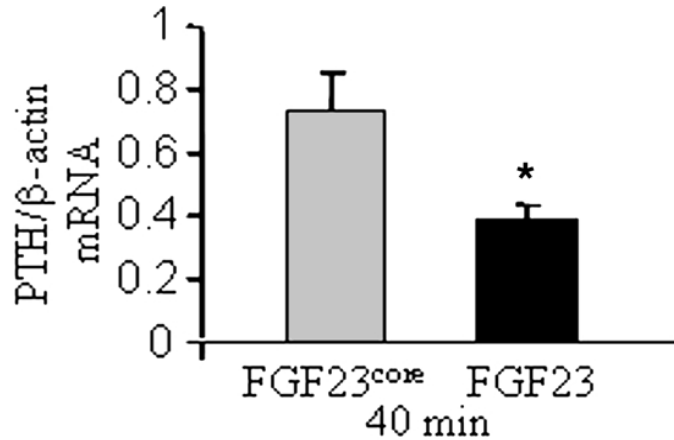
*Saito 2003
JBC 278 2206*

*Inoue Biochem.
J 2005 390 325*

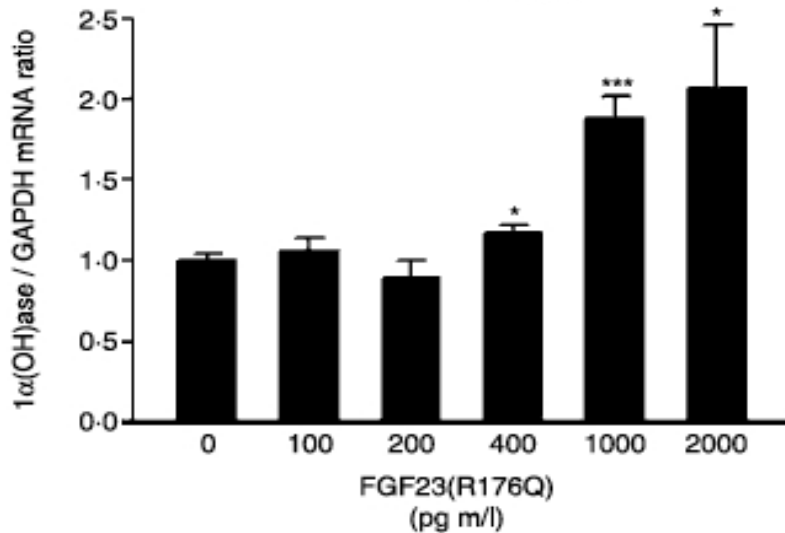


EFFECTS OF FGF23 ON PARATHYROID CELLS

FGF23 decreases PTH mRNA expression and PTH secretion



Ben-Dov, JCI 2007; 117, 12: 4003

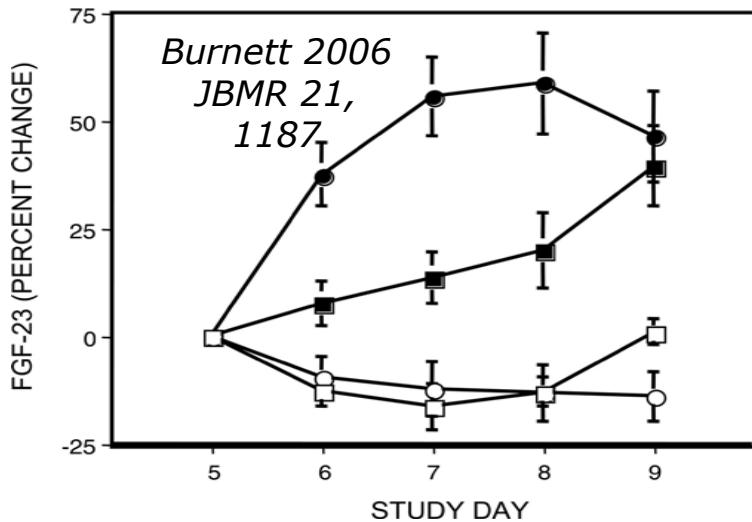
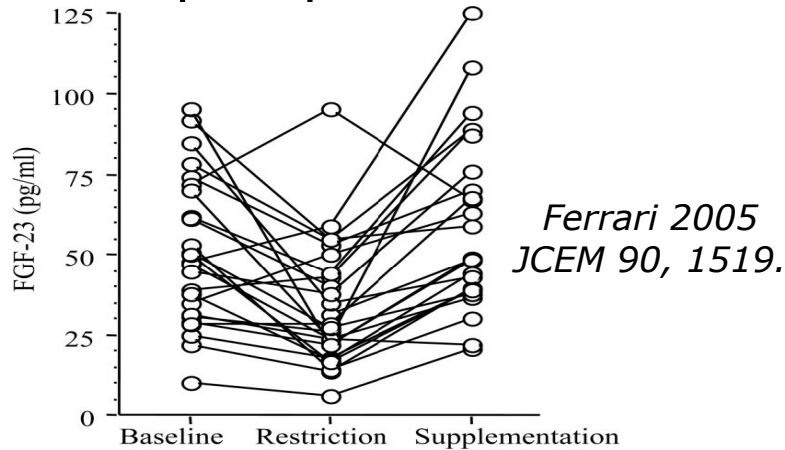


Stimulates 1α-hydroxylase mRNA expression

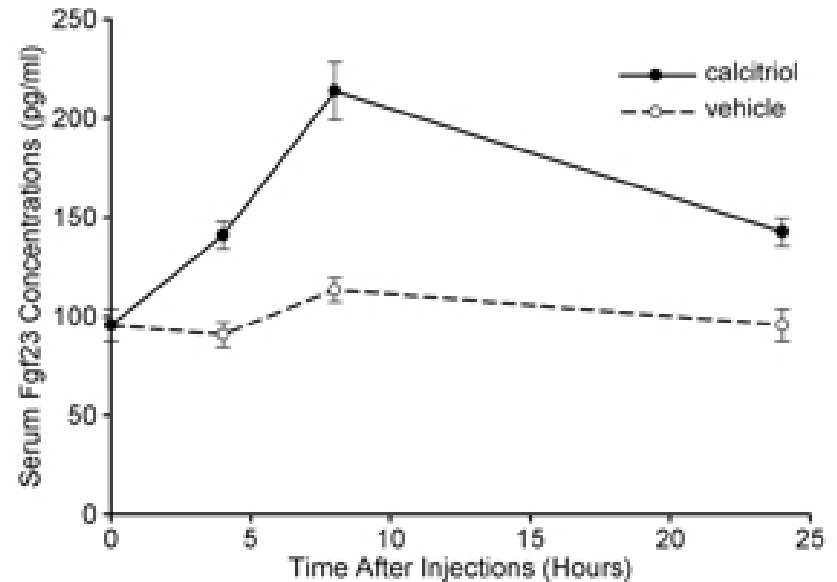
Krajisnik Journal of Endocrinology (2007) 195, 125

CONTROL OF FGF23 LEVELS

Chronic dietary phosphate and serum phosphate concentration



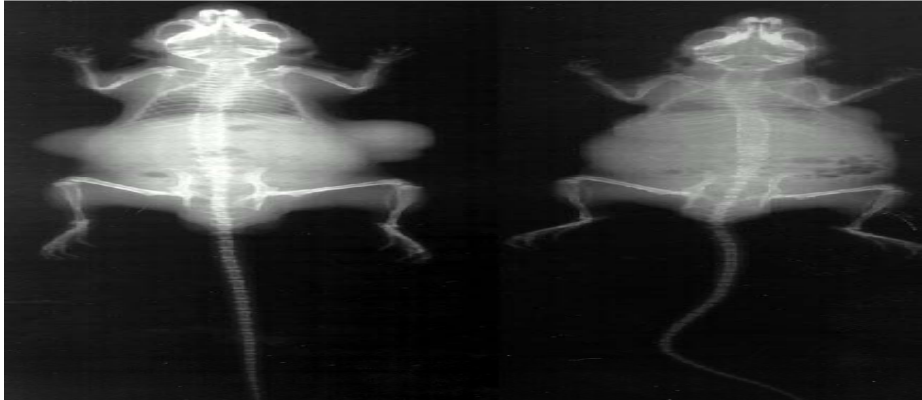
Serum calcitriol concentration



Liu 2006 JASN 17,1305

OVEREXPRESSION OF FGF23

Hypophosphataemia, bone demineralisation



control

Shimada, PNAS 2001; 98, 6500

FGF23 overexpression

FGF23 GENE DISRUPTION

Reduced life span, increased serum calcium, phosphate, calcitriol concentrations, low serum PTH, soft tissue calcifications, osteopenia, premature aging: hypogonadism, emphysema, severe muscle wasting, sparse hair, skin atrophy.

In human: familial tumoral calcinosis

RESPECTIVE ROLE OF HYPERPHOSPHATAEMIA ELEVATED CALCITRIOL IN FGF23^{-/-} PHENOTYPE

FGF23^{-/-} X 1 α (OH)ase^{-/-}

normalizes the phenotype but correction of serum phosphate and calcitriol levels (Razzaque The FASEB Journal 2006, 20: 720)

FGF23^{-/-}-mice, 2 diets

Stubbs J Am Soc Nephrol 2007, 18: 2116

Phosphate deficient diet	vitD deficient diet
Phosphate concentration NI	Hyperphosphataemia
Elevated calcitriol levels	Calcitriol levels NI
Vascular calcifications: -	Vascular calcifications: +
Rescues mortality	Improves survival

Treatment associating intestinal phosphate binders and increased phosphate urinary excretion cures soft tissue calcification in patients with Familial Tumoral Calcinosis (Garringer JCEM 2006, 91 :4037)

FGF23 RECEPTOR

23 FGF genes, 4 FGFR genes (alternative splicings->isoforms).

FGF23 binds with similar affinity to various FGFRs.

The FGFRs are largely expressed.

Activation of FGFRs causes developmental disorders and cancers.

Why are the effects of FGF23 overexpression limited to phosphate and calcitriol disorders?

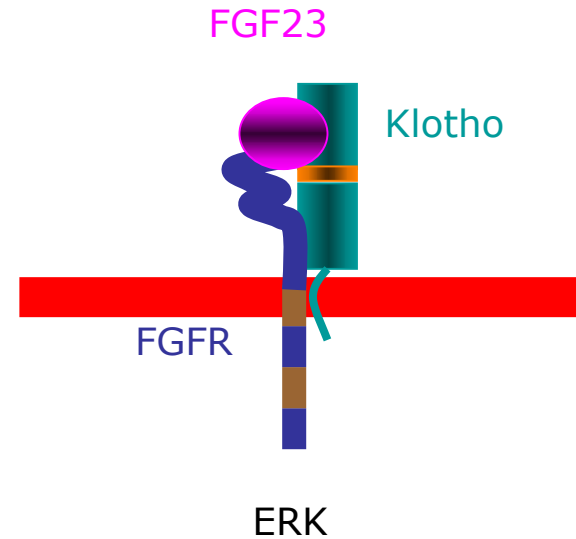
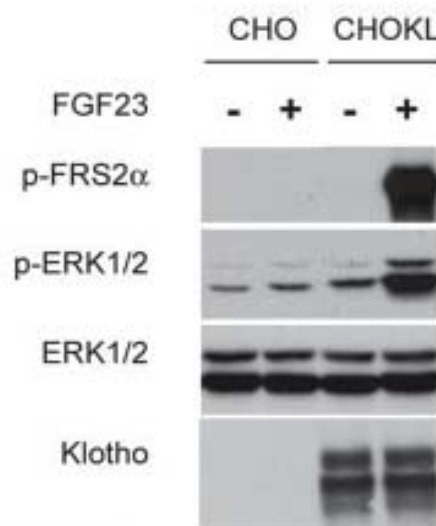
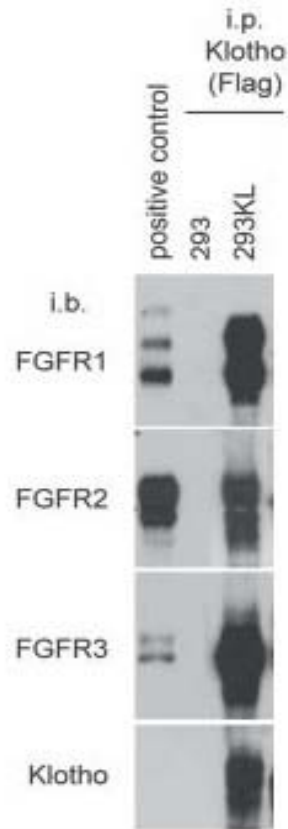
Klotho deficient or KO mice exhibit a phenotype similar to that of FGF23^{-/-} mice but serum FGF23 concentration are increased.

Can Klotho be the FGF23 receptor?

KLOTHO-FGF23 INTERACTION

Klotho binds to FGFRS

Klotho is mandatory for FGF23 signalling



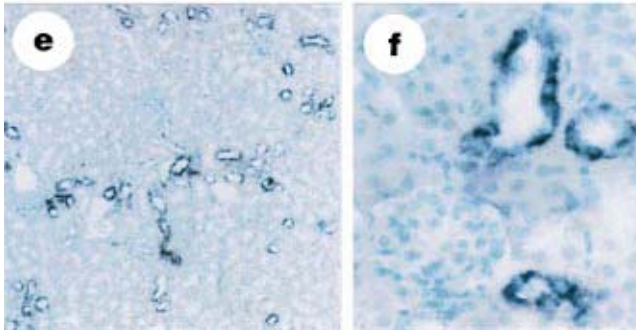
Kurosu 2006, J Biol Chem 281, 6120

KLOTHO EXPRESSION

Kuro-o, Nature
1997, 390:45

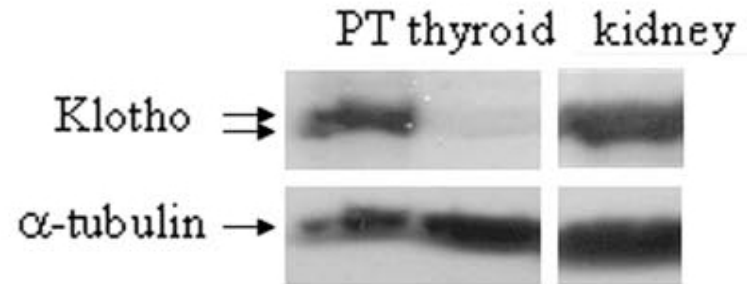


Kidney: distal convoluted tubule



Li Cell Struct Funct
2004, 29: 91

Parathyroid

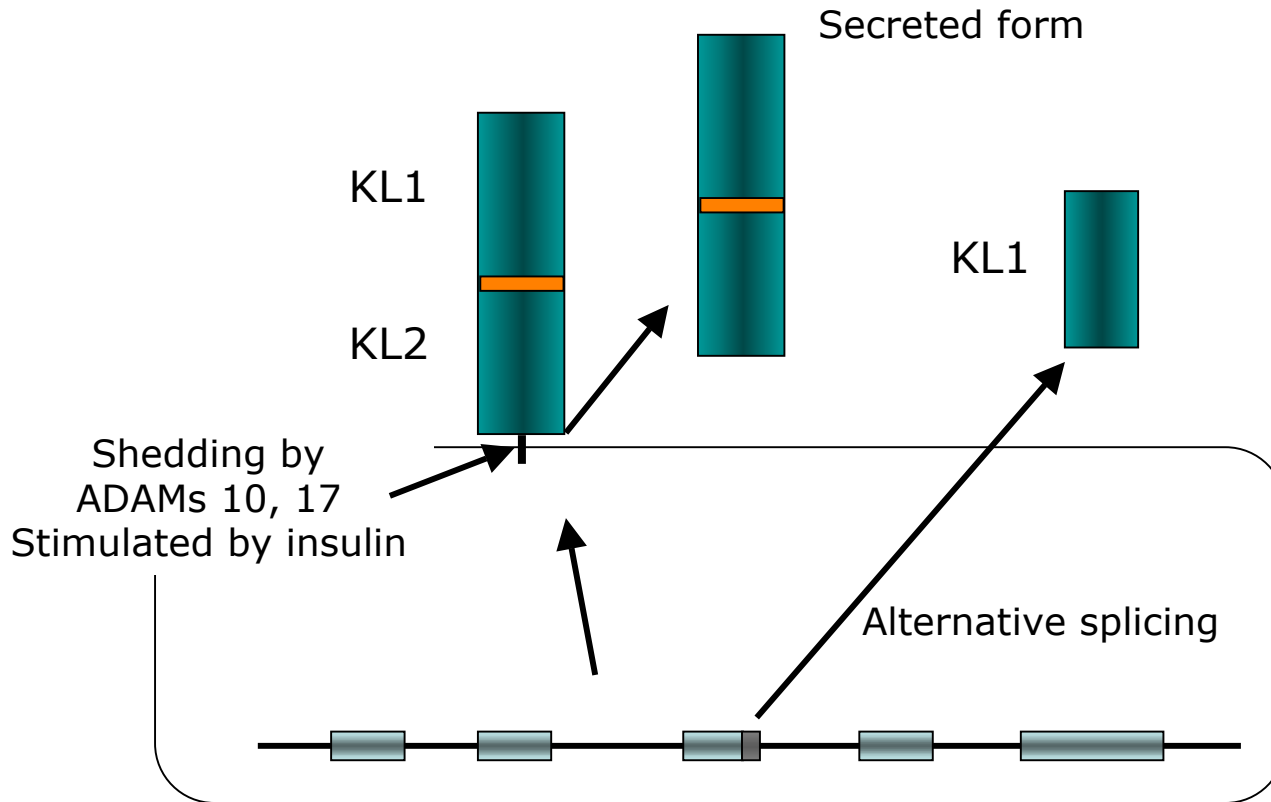


Ben-Dov, JCI
2007; 117, 12:
4003

DCT and PT glands express FGFRs

KLOTHO, STRUCTURE

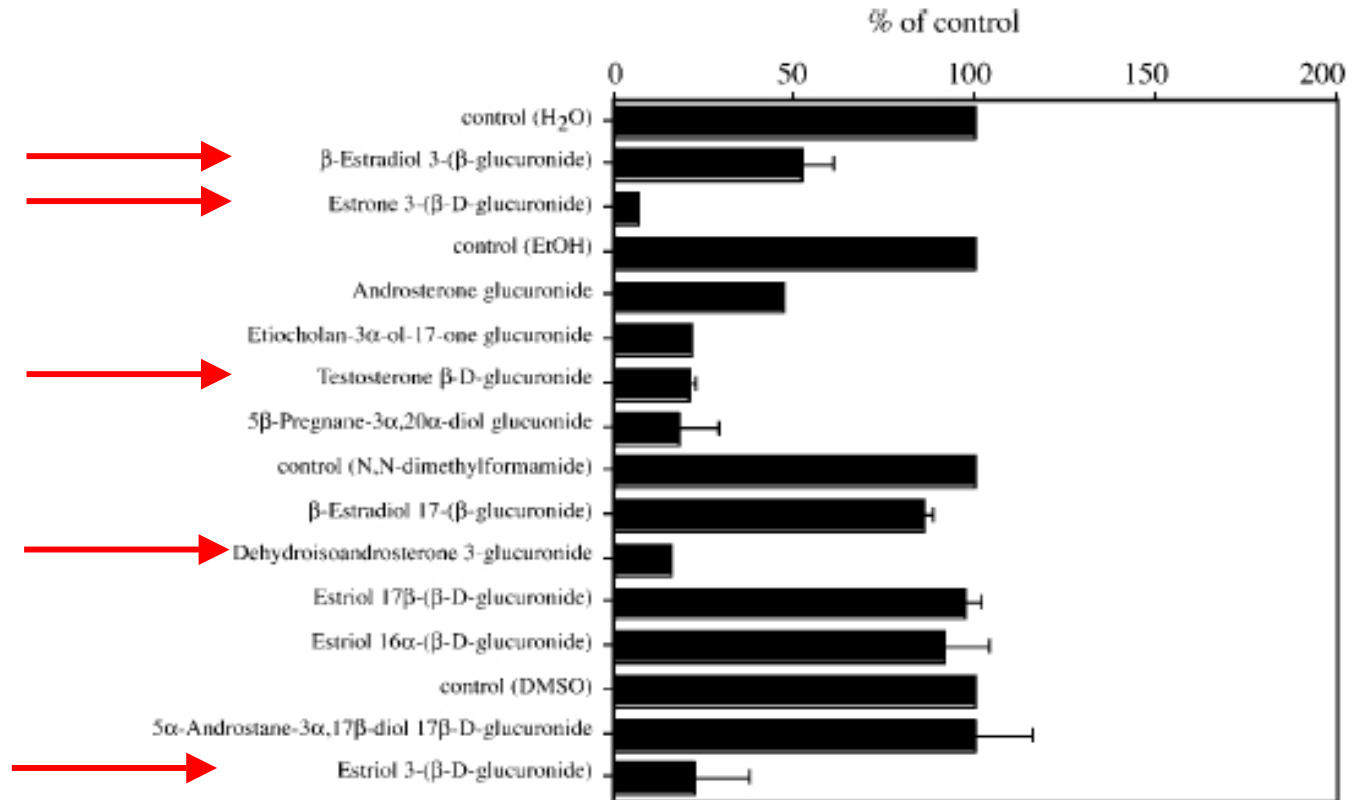
Klotho is a 1014-amino acid-long single pass transmembrane protein



KLOTHO AS AN ENZYME

Klotho exhibits β -glucuronidase activity: hydrolyses steroid glucuronides

Tohyama JBC 2004 279:9777

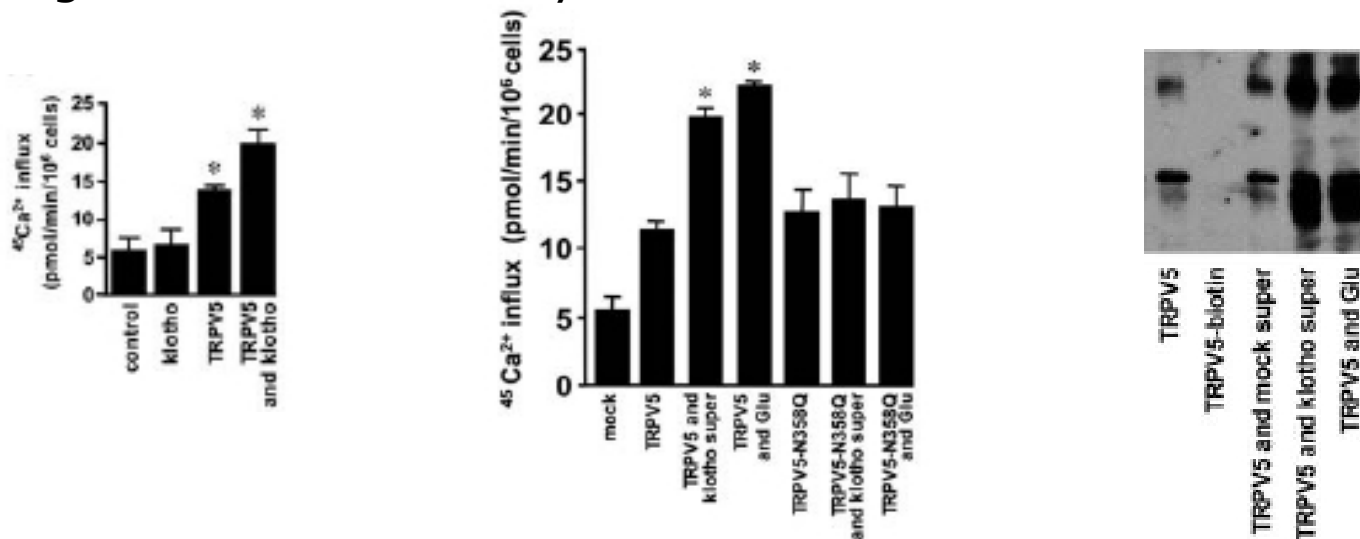


KLOTHO AND CALCIUM REABSORPTION IN THE DISTAL CONVOLUTED TUBULE

Chang science 2005, 310:490



Secreted Klotho increases membrane expression of TRPV5 via its glucuronidase activity.



KLOTHO OVEREXPRESSION

Increases life span by 20-30 % in mice

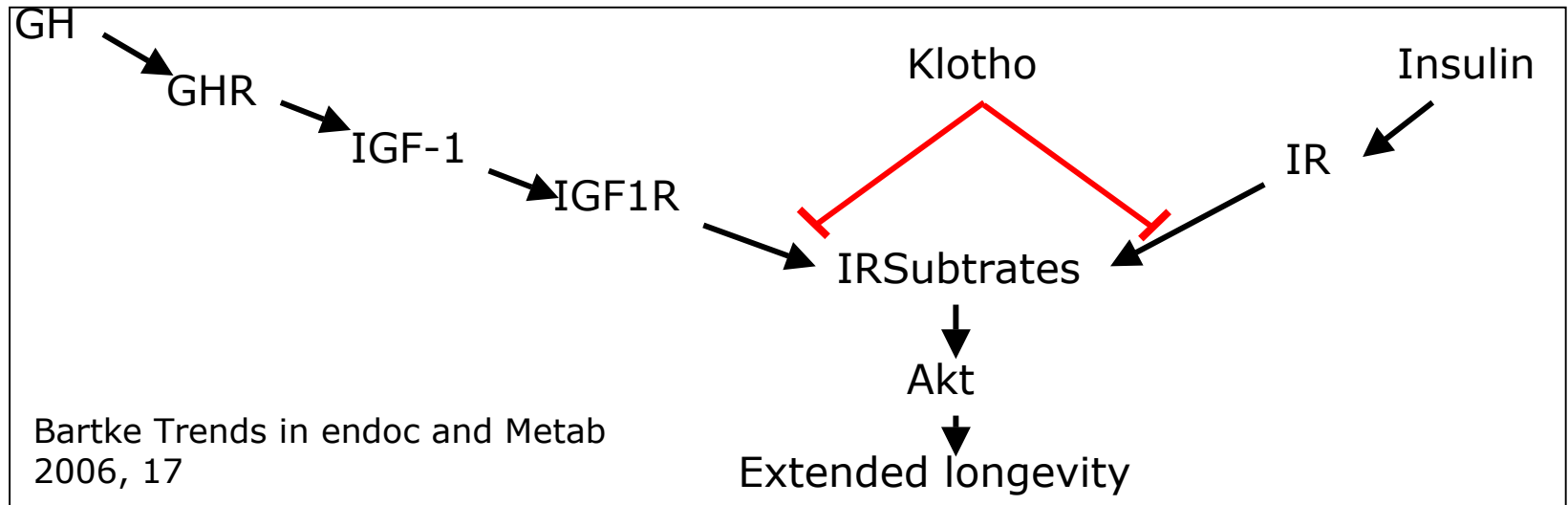
Moderate insensitivity to insulin/IGF-1

Resistance to oxydative stress (increased expression of SOD2...)

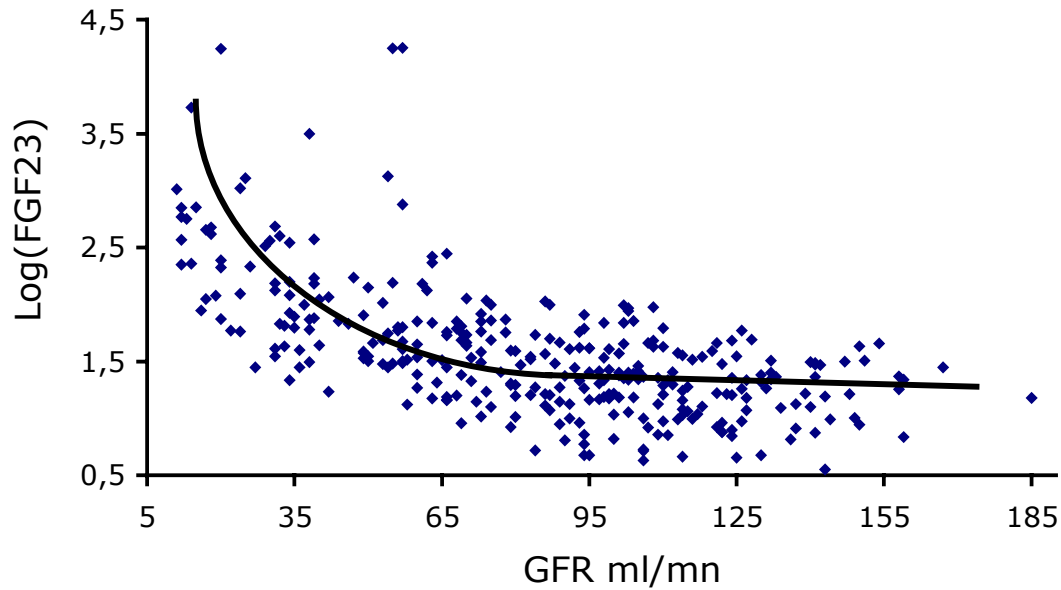
Effect on serum phosphate and calcitriol concentrations: unknown.

Expressing the transmembrane form of Klotho in adult deficient mice rescues the phenotype.

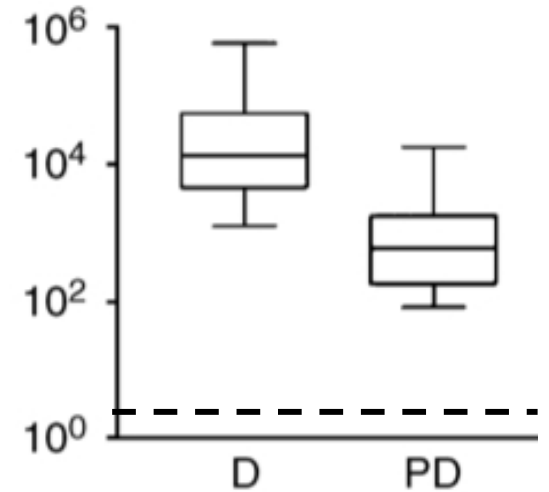
Decreasing Klotho expression in adult mice induces aging like phenotype



FGF23 CONCENTRATION INCREASES AS GFR DECLINES

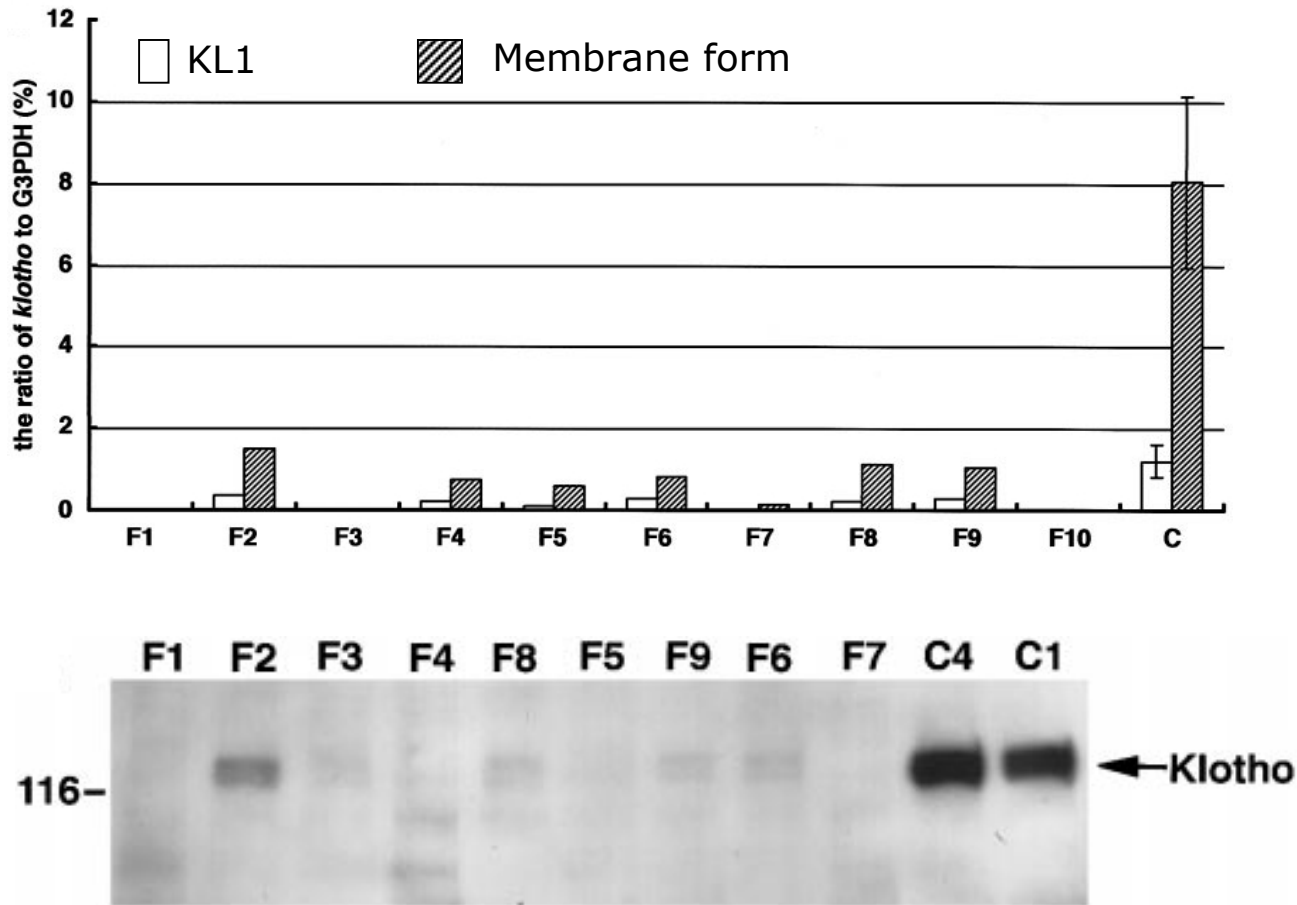


Prié personal results



Larsson 2003 KI,64:2272

RENAL EXPRESSION OF KLOTHO IN HUMAN CHRONIC RENAL FAILURE



*ARE FGF23 LEVEL ASSOCIATED WITH PTH
CONCENTRATION IN DIALYSIS PATIENTS?*

1- FGF23 decreases PTH secretion and increases Klotho expression in PT glands

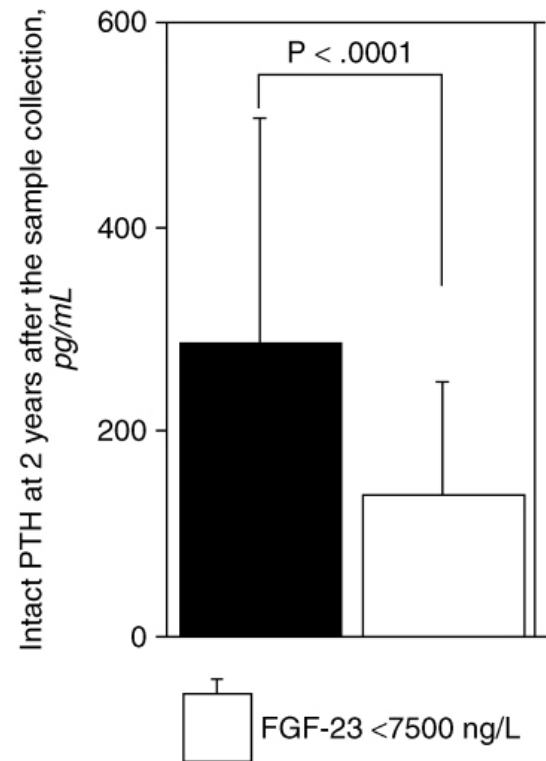
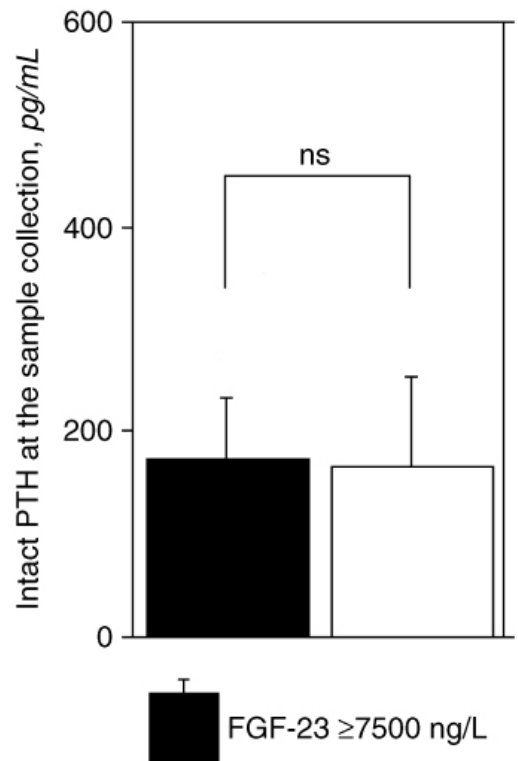
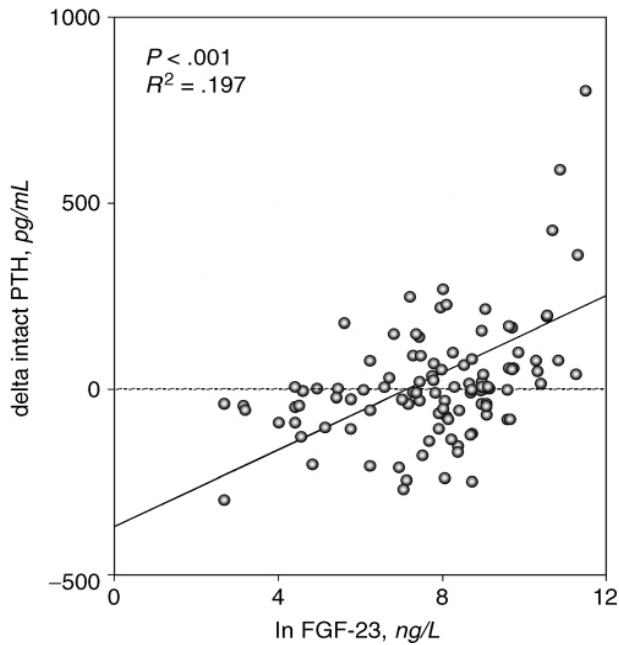
2- FGF23 concentrations are elevated in dialysis patients

3- FGF23 inhibits calcitriol synthesis

4- Klotho expression is diminished in the kidney of patients with CRF

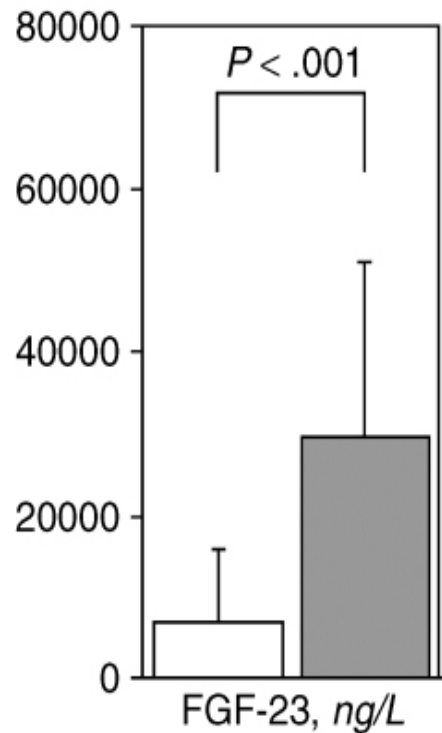
What is the result?

FGF23 LEVELS PREDICT REFRACTORY HYPERPARATHYROIDISM IN DIALYSIS PATIENTS



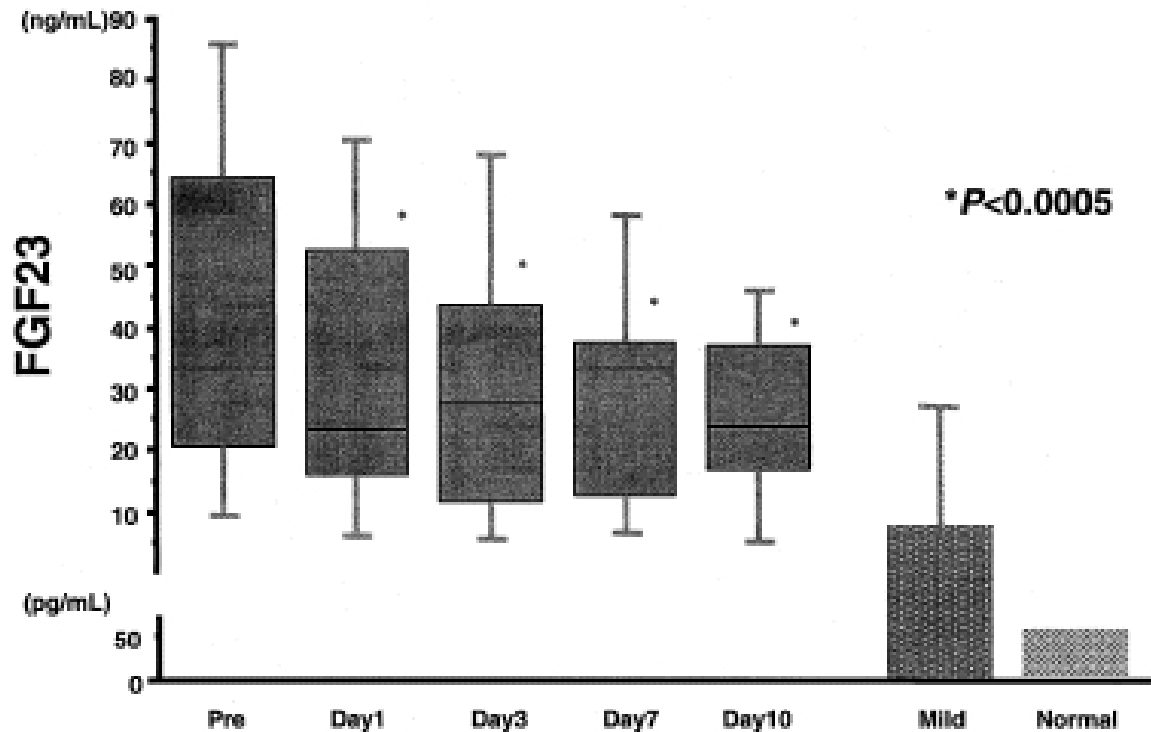
Nakanishi 2005 KI 67 1171

FGF23 LEVELS ARE ASSOCIATED WITH THE RESPONSE TO CALCITRIOL TREATMENT IN DIALYSIS PATIENTS



Response to calcitriol treatment + -

FGF23-CONCENTRATION DECREASE FOLLOWING PARATHYROIDECTOMY IN STAGE 5 CKD PATIENTS

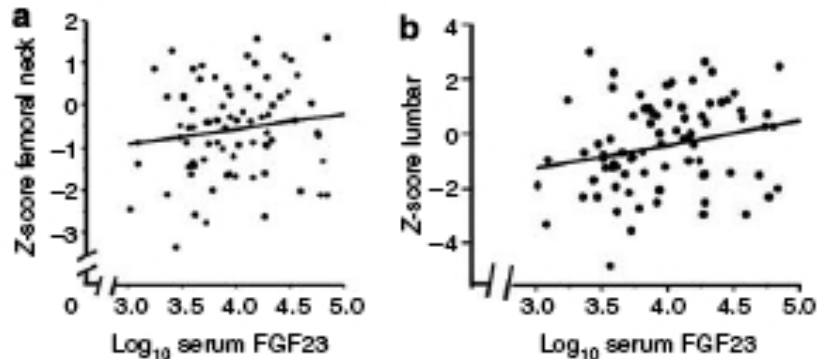


SATO 2004 AJKD 44 481.

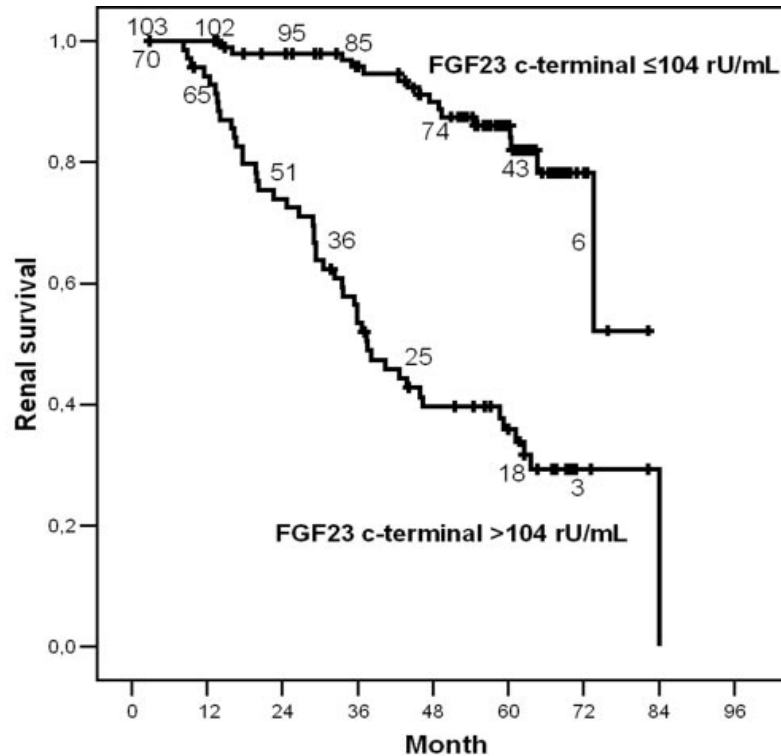
FGF23 LEVELS AND CALCIFICATIONS IN DIALYSIS PATIENTS

FGF23 concentration is an independent factor associated with hand-artery but not aorta calcification in diabetic and non diabetic dialysis patients (Inaba Osteoporos Int 2006, 17: 1506)

FGF23 levels are not correlated with bone mineral content in dialysis patients (Urena Torres, KI 2008, 73: 102)



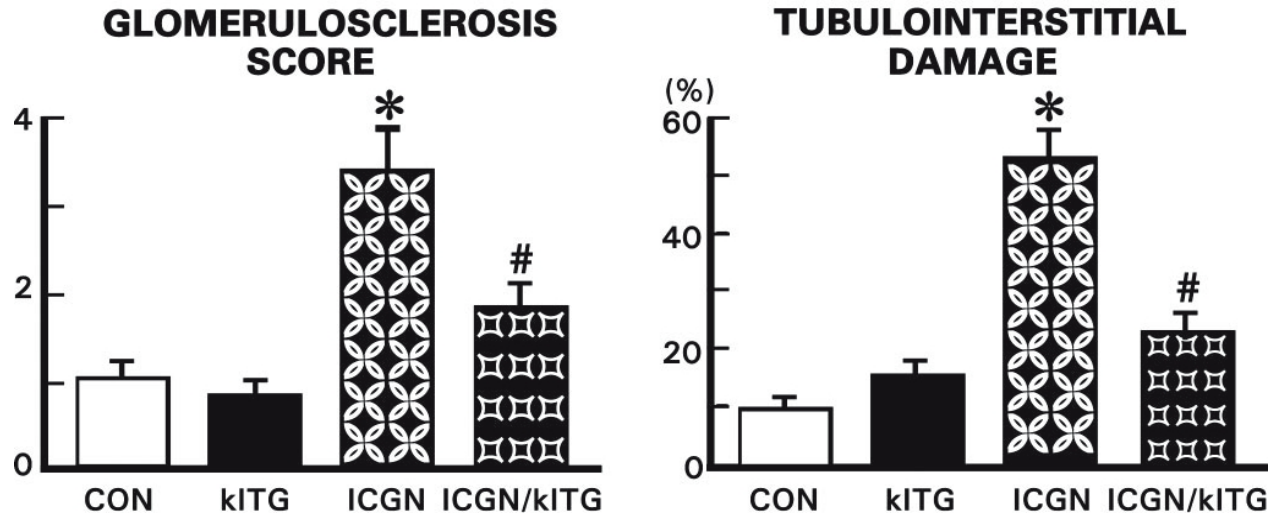
FGF23 LEVELS PREDICT PROGRESSION OF CHRONIC KIDNEY DISEASE



Predictor independent of GFR, CaXP, PTH

Fliser JASN 2007, 18: 2601

KLOTHO IMPROVES RENAL LESION IN A MOUSE GLOMERULONEPHRITIS MODEL



Improvement of renal lesions, renal function and life span.

HUMAN DISORDERS DUE TO GENETIC ALTERATIONS OF THE FGF23-KLOTHO AXIS

Increased FGF23 concentration:

Autosomal Dominant Hypophosphataemic Rickets

X-linked Hypophosphataemic Rickets

Autosomal Recessive Hypophosphatemia: ARH. Mutations in DMP1 gene.

Fibrous dysplasia, Mc Cune Albright syndrome: post zygotic mutation in GNAS gene.

Loss of function of FGF23: Familial tumoral calcinosis

Mutations in FGF23 or GALNT3 genes: Low intact FGF23 levels

Mutation in Klotho: High intact FGF23 levels

Translocation adjacent to Klotho gene: Increased Klotho and FGF23 expression, hypophosphataemia, primary hyperparathyroidism (Brownstein PNAS 2008, 105: 3455)

KLOTHO AS A PRONOSTIC MARKER

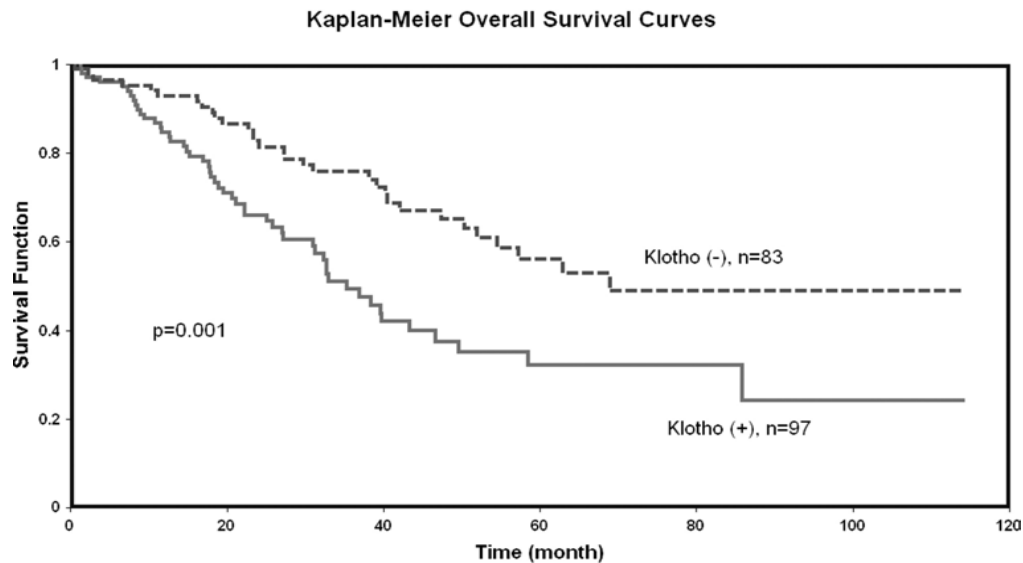
Klotho polymorphisms:

bone mineralization

survival

coronary disease

Expression of KL1 and pronostic in ovarian cancer



CONCLUSIONS

FGF23 plays a central role in phosphate homeostasis and calcitriol metabolism

Klotho is mandatory to FGF23 action

Klotho is a coreceptor and an enzyme

Disorders of the FGF23-Klotho axis alter life span