Programme de la Réunion Annuelle du Club Des Jeunes Néphrologues

#Immunity_report

Du 15 au 17 mars 2018, Paris

#FGF23&Infection

Paris Marriott Ambassador Hotel – Paris
16 boulevard Haussmann. 75009 Paris

Dr Pablo Ureña Torres
urena.pablo@wanadoo.fr

Clinique du Landy. Service de Néphrologie et Dialyse. 23, rue du Landy. 93400 Saint Ouen, France.
Service des Explorations Fonctionnelles. Hôpital Necker-Enfant Malades, Assistance Publique-Hôpitaux de Paris.

Conflicts of Interest

Pablo A. Ureña Torres, MD

Grants/research support: Abbvie, Amgen, Astellas, GSK, Hemotech

Consultant: Abbvie, Amgen, Sanofi, Vifor Pharma FMC

Scientific advisor: Amgen

Honoraria: none

Board position: CKD-MBD Working Group ERA-EDTA

#FGF23&Infection

CLINICAL EPIDEMIOLOGY www.jasn.org

Fibroblast Growth Factor 23 and the Risk of Infection-Related Hospitalization in Older Adults

Kristen L. Nowak,* Traci M. Bartz,† Lorien Dalrymple,‡ Ian H. de Boer,§ Bryan Kestenbaum,§ Michael G. Shlipak,‖¶** Pranav S. Garimella,†† Joachim H. Ix,‡‡§§‖‖ and Michel Chonchol*

Nowak KL et al. CJASN 2017 Apr;28(4):1239-1246

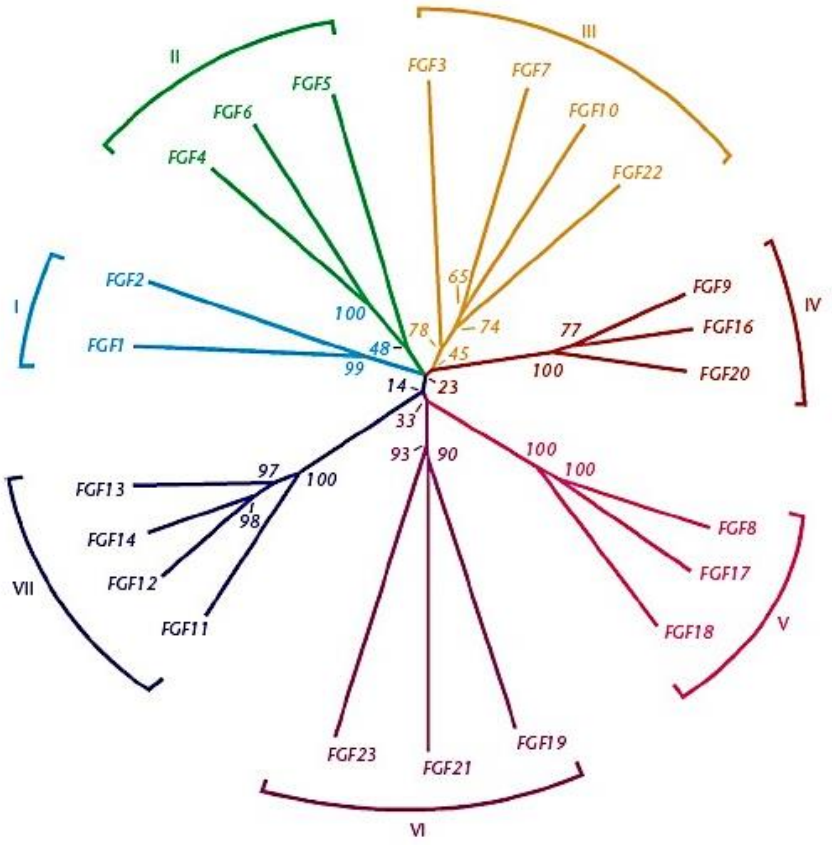
- What is FGF23 ?

- What is FGF23 ?

- HbA1c, the biomarker of diabetes mellitus control
- LDL, the biomarker of hypercholesterolemia
- PTH the biomarker of primary and secondary hyperparathyroidism
- 25OHD the biomarker of vitamin D Status

- Is FGF23 the biomarker (or surrogate biomarker) of phosphate accumulation and toxicity?

Fibroblast Growth Factors Family



FGF15 only in mouse

The mammalian FGF family comprises 22 polypeptides grouped into 7 subfamilies

Classical FGFs exert their biological activity locally as paracrine factors via binding to one of four distinct FGF receptor tyrosine kinase gene products (Fgfr1 to Fgfr4) in a process that requires heparin as a cofactor

The FGF19 subfamily members (consisting of FGF19, FGF21, and FGF23) are heparin independent resulting from unique structural features permitting them to circulate and act as endocrine factors:

- FGF19 : energy and acid bile homeostasis
- FGF21: glucose and lipid metabolism
- FGF23: phosphate and vitamin D homeostasis

Ornitz DM. Encyclopedia Life of Sciences 2007

FGF23

Gene : Chromosome 12 (12p13.3)

mRNA : 2270 bp (2.27 kb)

Protein : 251 amino acids

Molecular weight : 28 kD

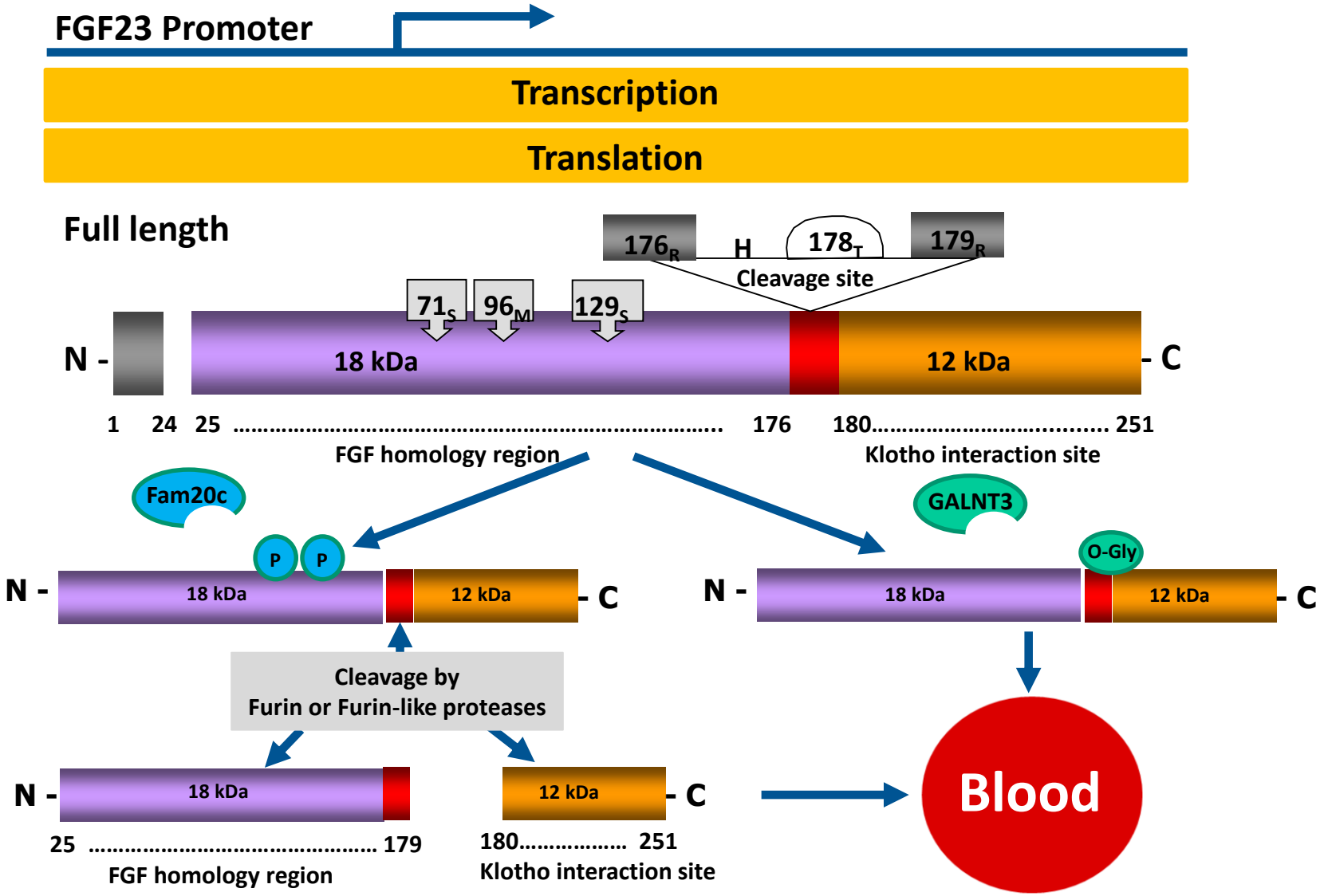
Half-life intact FGF23: 58 min

Half-life C-terminal FGF23 : > 72 h

Produced by: Bone (osteocyte, osteoblast and osteoclast cells);

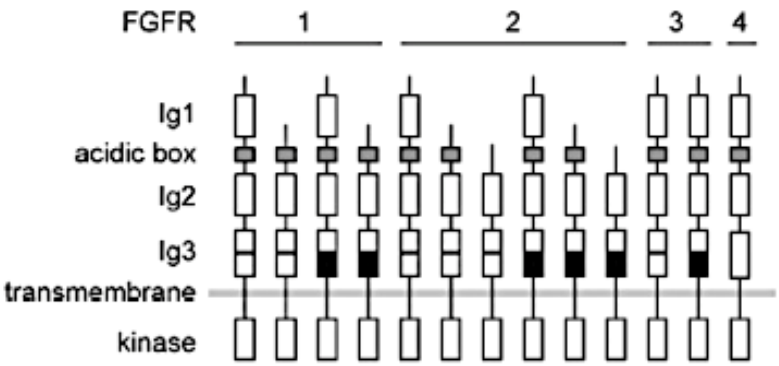
Injured kidney, Cyst in PKD, Injured Liver…

FGF23 Production and Cleavage



Razzaque MK et al. J Endocrinol 194:1-10, 2007

Mode of Action of FGF23



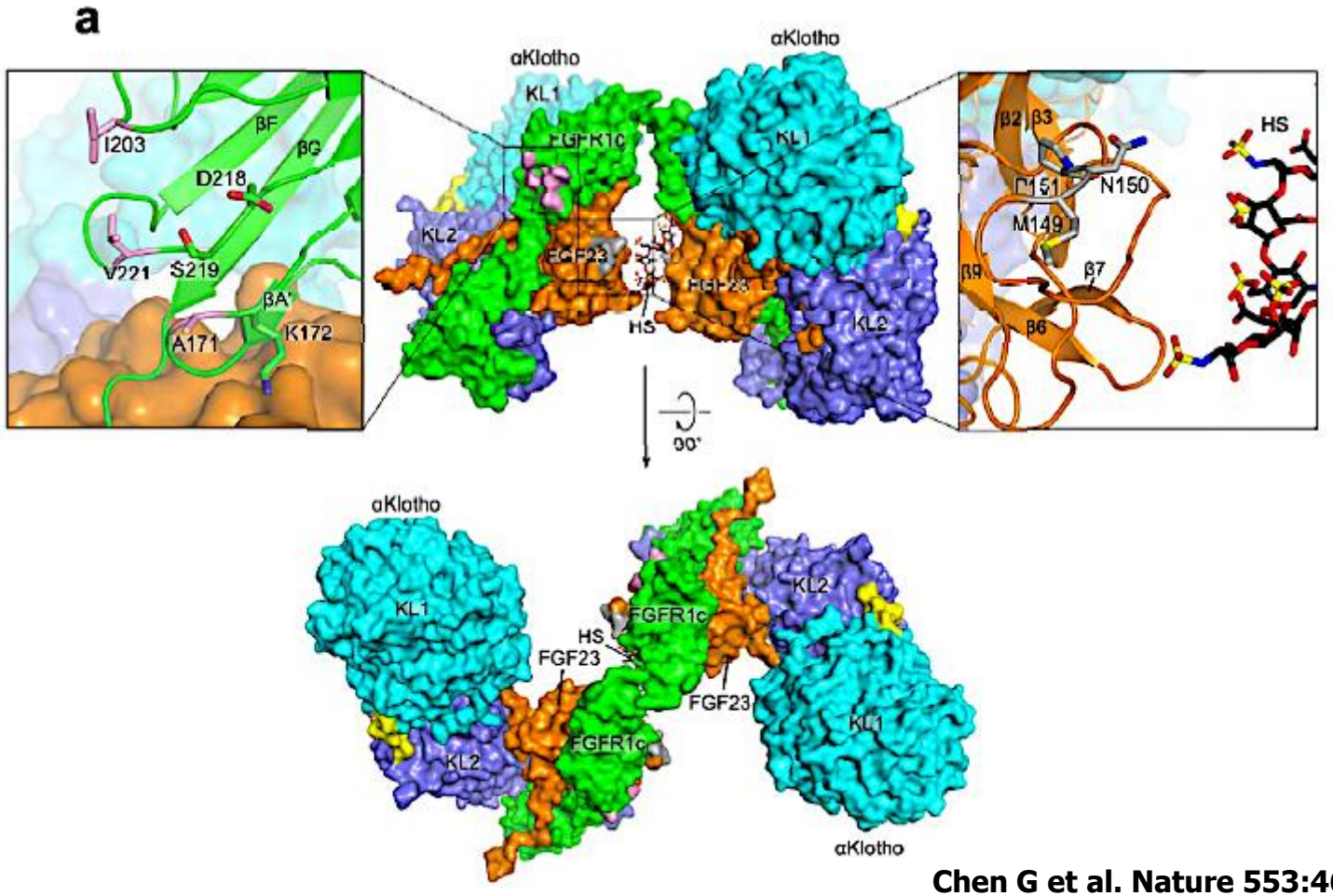
Kurosu H et al. 2006
Khachigian LM. 2006

ARTICLE

doi:10.1038/nature25451

α-Klotho is a non-enzymatic molecular scaffold for FGF23 hormone signalling

Gaozhi Chen[1,2*], Yang Liu[2*], Regina Goetz[2], Lili Fu[1,2], Seetharaman Jayaraman[3], Ming-Chang Hu[4], Orson W. Moe[4], Guang Liang[1], Xiaokun Li[1] & Moosa Mohammadi[2]



Chen G et al. Nature 553:461-468, 2018

What Are the Physiological Effects of FGF23 ?

- FGF23 binds to FGF receptors and their cofactor Klotho causing internalization of NPT2a and NPT2c, thereby resulting in less renal phosphate reabsorption: increased phosphaturia, lower phosphatemia

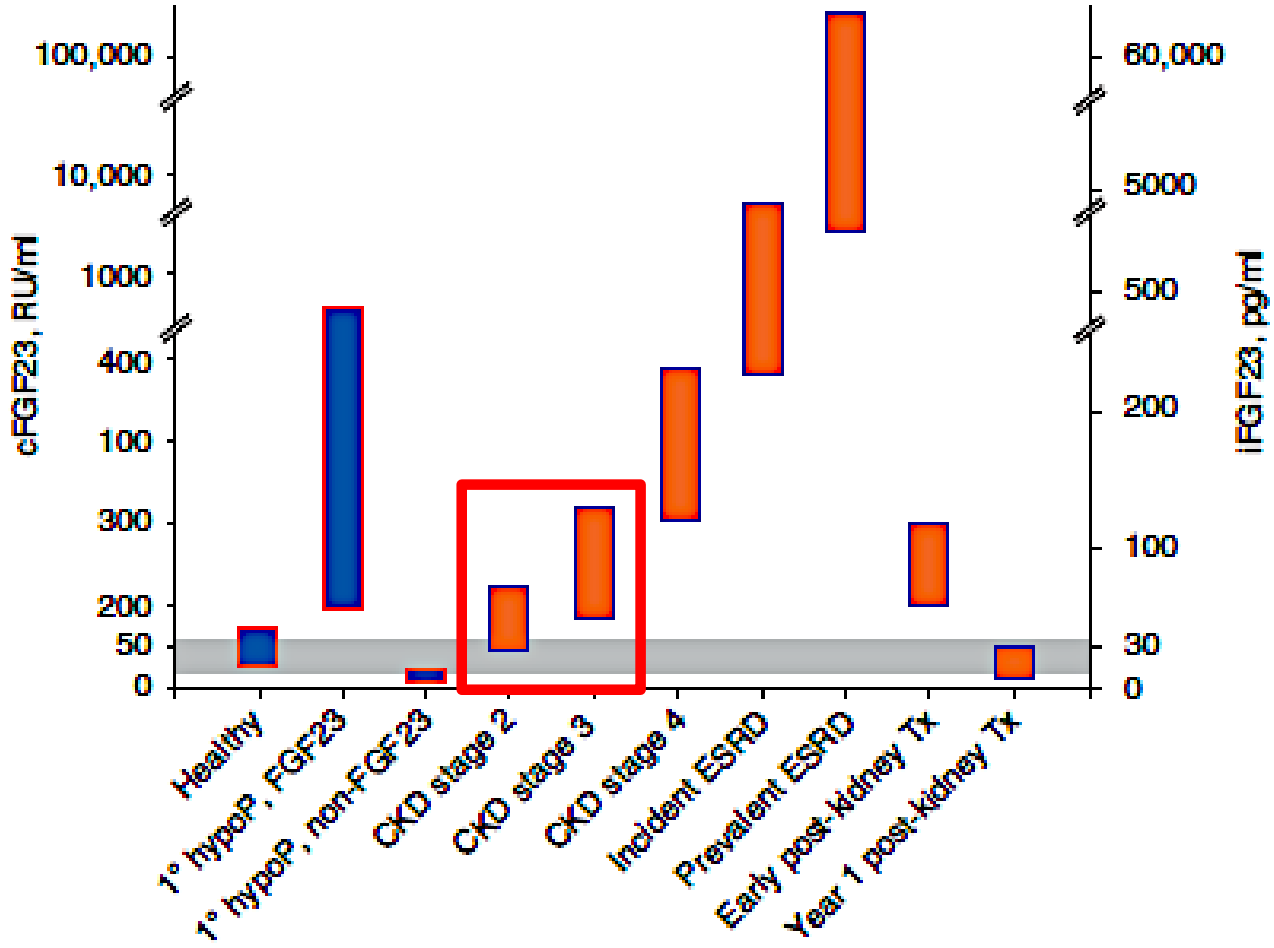
- FGF23 inhibits renal 1α-hydroxylase and the synthesis of $1,25(OH)_2D_3$. Stimulates renal expression of 24-hydroxylase and vitamin D degradation: Lowers calcitriol, decreased intestinal absorption of calcium and phosphate

- Inhibits parathyroid cell proliferation and synthesis of PTH : stimulates parathyroid 1α-hydroxylase

- Changes of Circulating FGF23

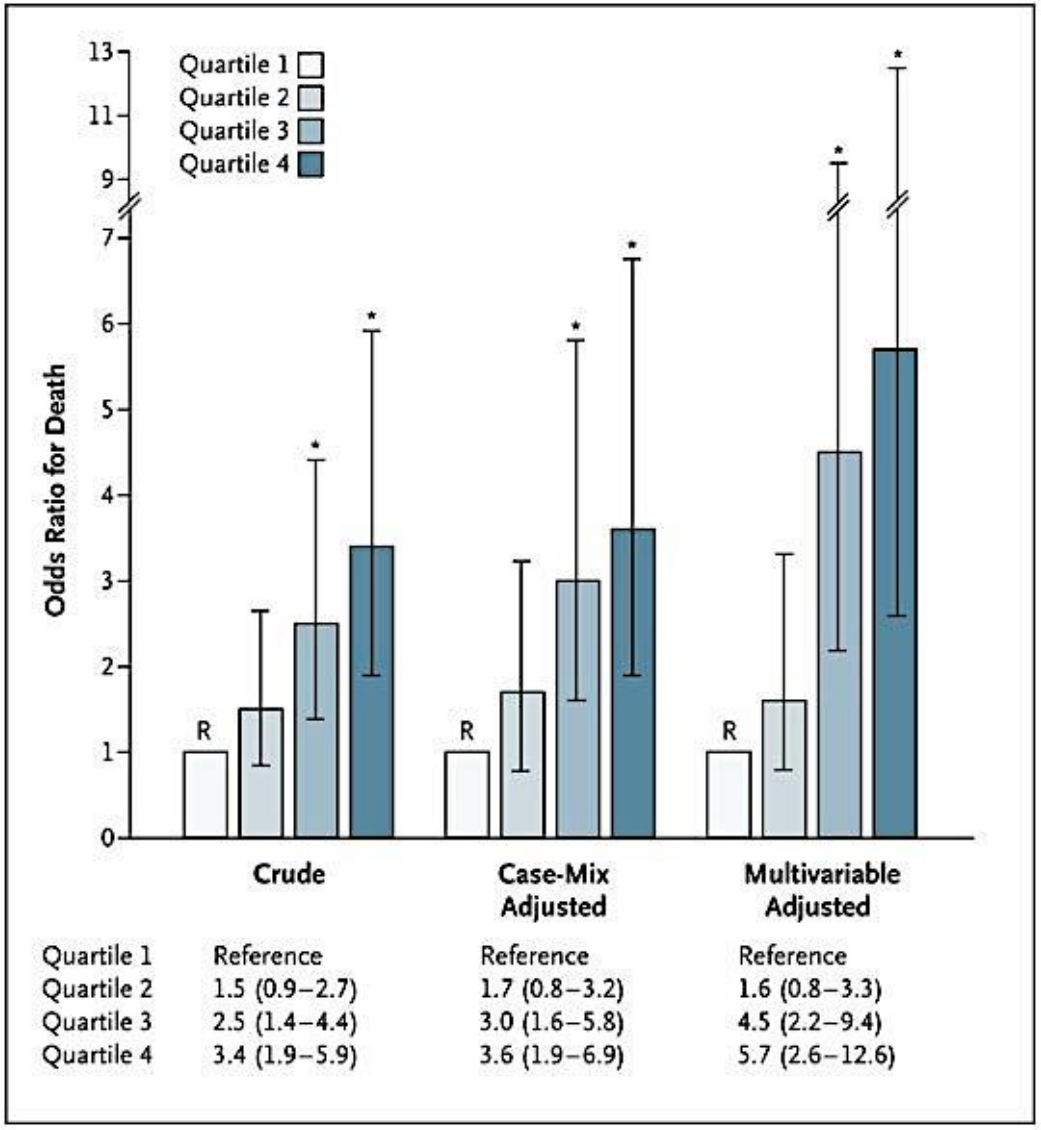
Concentration in Chronic Kidney Disease

Serum C-Terminal FGF23 Levels In Patients with Chronic Kidney Disease



Wolf M et al. Kidney Int 82:737-747, 2012

Serum C-Terminal FGF23 Levels Are Associated with the Risk of Mortality in Dialysis Patients



- Prospective Cohort Study

- In 10,044 Incident hemodialysis patients

- C-terminal FGF-23 levels

- Mortality in a nested case–control sample of 200 subjects who died and 200 who survived during the first year of hemodialysis treatment.

Gutierrez O et al.
N Engl J Med 2008;359:584-592

Serum FGF23 Levels Are Associated with the Risk of Mortality Independently of Serum Phosphate in Dialysis Patients

Table 3. Levels of cFGF-23 and Associated Risk of Death within Serum Phosphate Quartiles in the Case–Control Sample.

Phosphate Level	Median cFGF-23 Level (interquartile range)		P Value	Odds Ratio for Death (95% CI)*
	Patients Who Died (N = 200)	Patients Who Survived (N = 200)		
	reference units per milliliter			
All levels	2260 (1196–5296)	1406 (989–2741)	<0.001	1.5 (1.2–1.8)
<3.5 mg/dl	1790 (1175–3941)	1148 (927–2169)	0.008	1.8 (1.2–2.8)
3.5–4.4 mg/dl	2049 (1109–4865)	1131 (893–1629)	0.003	1.8 (1.2–2.7)
4.5–5.5 mg/dl	2207 (1186–5238)	1499 (1044–2262)	0.02	1.8 (1.1–3.0)
>5.5 mg/dl	3541 (1871–10,491)	2686 (1527–6210)	0.29	1.1 (0.7–1.6)

* The odds ratios are for a one-unit increase in the natural log-transformed cFGF-23 level in all 400 patients and in each quartile of 100 patients.

cFGF23	2369	1574 (RU/ml)

Gutierrez O et al. N Engl J Med 2008;359:584-592

Studies Demonstrating an Association between Serum FGF23 Levels and the Risk of Several Outcomes Including Mortality in Dialysis

Study	Population	Sample size	Duration of follow-up	Results
1- Gutierrez et al. (2008)	**Incident dialysis** patients	10,044	1 year	Increased levels of C-terminal associated with increased risk of mortality independently of phosphatemia
2- Jean G et al. (2009)	**Permanent dialysis** patients	219	2 years	Increased levels of C-terminal FGF23 associated with increased risk of death and CV calcifications
3- Olauson et al. (2010)	**Permanent dialysis** patients	229	5 years	Increased levels of intact FGF23 associated with increased risk of death only in men with CVD
4- Parker et al. (2010)	Patients with stable **coronary artery disease** from Heart ans Saoul Study, 22% with eGFR < 60 ml/mn/1.73 m^2 b.s.	855	Median 6.0 years	Increased levels of C-terminal FGF23 associated with increased risk of death and CV events
5- Isakova et al. (2011)	Patients with **CKD stages 2-4** from CRIC study; mean ± SD eGFR 42 ± 13 ml/mn/1.73 m^2 b.s.	3,579	Mean 3.5 years (IQR 2.5-4.4 years)	Increased levels of C-terminal FGF23 associated with increased risk of death
6- Kendrick et al. (2011)	Patients with **advanced CKD** from the HOST study; all patients had eGFR < 30 ml/mn/1.73 m^2 b.s.	1099	Mean 2.9 years (IQR 2.1-3.7 years)	Increased levels of C-terminal FGF23 associated with increased risk of death, CV events, and initiation of dialysis
7- Titan et al. (2011)	**Diabetic proteinuric patients** with advanced CKD (eGFR < 30 ml/mn/1.73 m^2 b.s.	55	4 years	Increased levels of intact FGF23 associated with increased risk of a composite (doubling of creatinine, initiation of dialysis, and death)
8- Floege et al. (2014)	**Prevalent hemodialysis** patients with **secondary hyperparathyroidism**	3883	64 months	Cinacalcet decreased c-terminal FGF23 levels and the risk of mortality (EVOLVE)

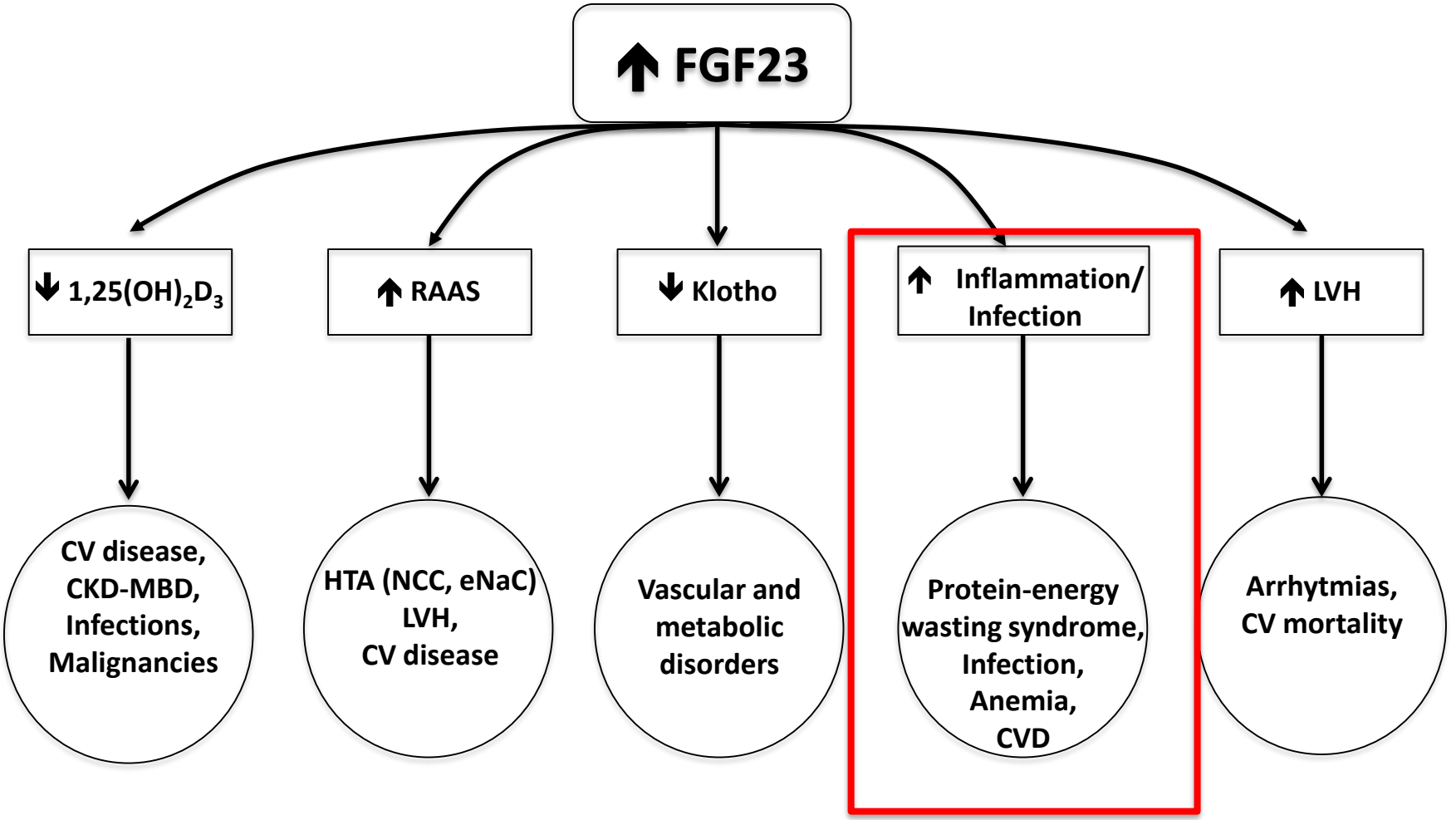
Komaba et al. Nat Rev Nephrol. 2012. Update by P Urena 2014

Studies Demonstrating an Association between Serum FGF23 Levels and the Risk of Several Outcomes Including Mortality in CKD

Study	Population	Sample size	Duration of follow-up	Results
Fliser et al. (2007)	**Non diabetic** patients with CKD stages 1-5 from MMRD study	227	Mean 53 months (IQR 3-84 months)	Increased levels of C-terminal and intact FGF23 associated with progression of CKD
Parker et al. (2010)	Patients with stable **coronary artery disease** from Heart ans Saoul Study, 22% with eGFR < 60 ml/mn/1.73 m^2 b.s.	855	Median 6.0 years	Increased levels of C-terminal FGF23 associated with increased risk of death and CV events
Seller et al. (2010)	Patients with **predialysis CKD**, mean ± SD eGFR 36 ± 23 ml/mn/1.73 m^2 b.s.	149	Mean ± SD 4.8 ± 0.9 years	Increased levels of C-terminal FGF23 associated with increased risk of CV events
Isakova et al. (2011)	Patients with **CKD stages 2-4** from CRIC study; mean ± SD eGFR 42 ± 13 ml/mn/1.73 m^2 b.s.	3,579	Mean 3.5 years (IQR 2.5-4.4 years)	Increased levels of C-terminal FGF23 associated with increased risk of death
Kendrick et al. (2011)	Patients with a**dvanced CKD** from the HOST study; all patients had eGFR < 30 ml/mn/1.73 m^2 b.s.	1099	Mean 2.9 years (IQR 2.1-3.7 years)	Increased levels of C-terminal FGF23 associated with increased risk of death, CV events, and initiation of dialysis
Titan et al. (2011)	**Diabetic proteinuric patients** with advanced CKD (eGFR < 30 ml/mn/1.73 m^2 b.s.	55	4 years	increased levels of intact FGF23 associated with increased risk of a composite (doubling of creatinine, initiation of dialysis, and death)
Semba et al. (2012)	**Community dwelling women** from the Women's Health and Aging study: mean ± SD eGFR 60 ± 16 ml/mn/1.73 m^2 b.s.	701	2 years	Among 307 individuals without CKD at baseline, increased levels of intact FGF23 associated with increased risk of incident, stage 3 CKD, and declining kidney function
Nakano et al. (2012)	Patients with **CKD stages 1-5** in Japan; mean ± SD eGFR 35 ± 19 ml/mn/1.73 m^2 b.s.	738	Median 4.4 years (IQR 4.0-4.6 years)	Increased levels of intact FGF23 associated with increased risk of renal outcomes (doubling of creatinine or initiation of dialysis)
Lundberg et al. (2012)	Patients with **IgA nephropathy** with CKD stages 1-4	180	55 months	Increased levels of C-terminal FGF23 associated with increased risk of proteinuria and progression of CKD

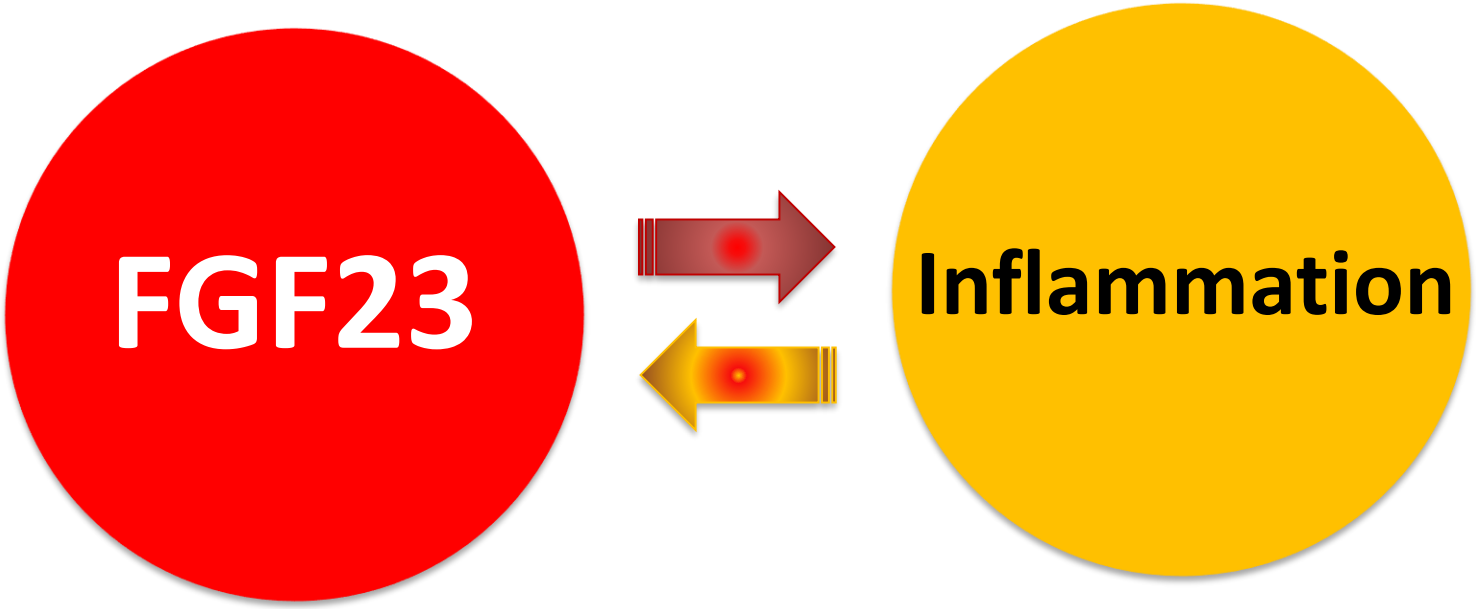
Komaba et al. Nat Rev Nephrol. 2012. Update by P Urena 2014

High FGF23 and Morbidity/Mortality



Putative mechanisms of action underlying the pathologic effects of elevated FGF23 levels

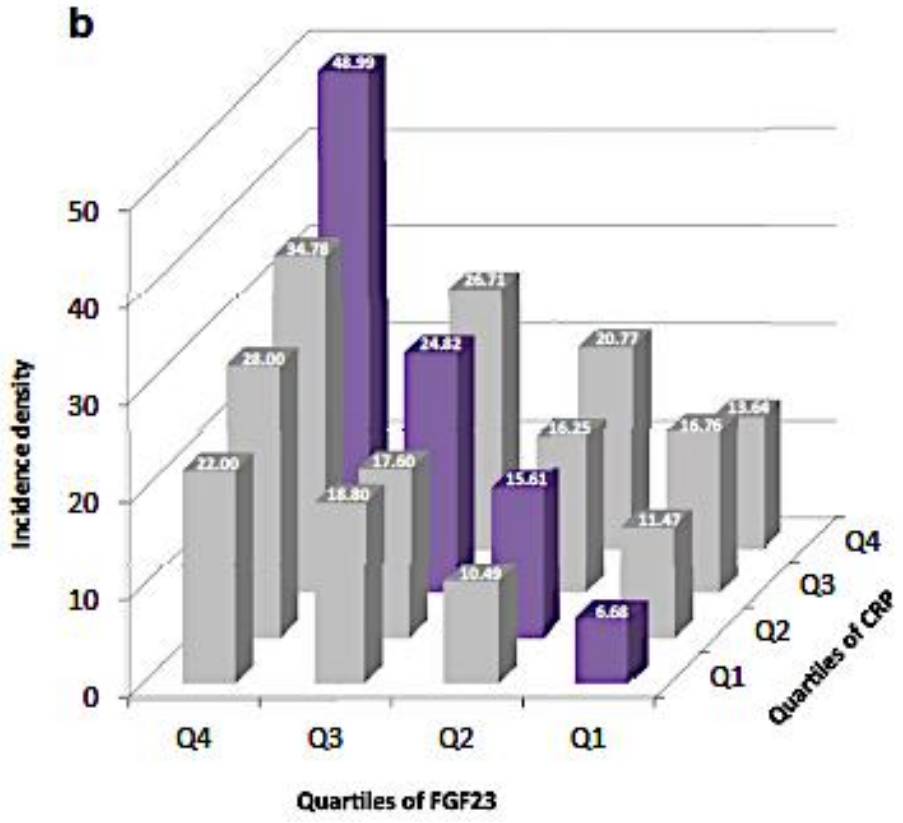
FGF23 and Inflammation

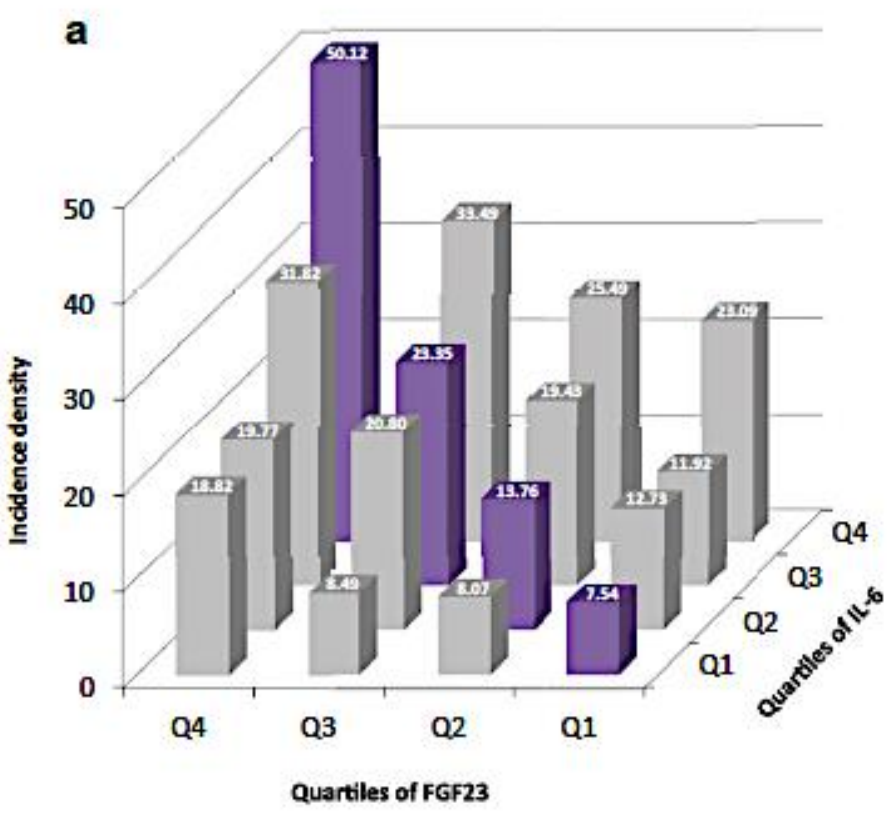


FGF23 is a pro-inflammatory molecule

Inflammation stimulates bone turnover and FGF23

FGF23 and Inflammation



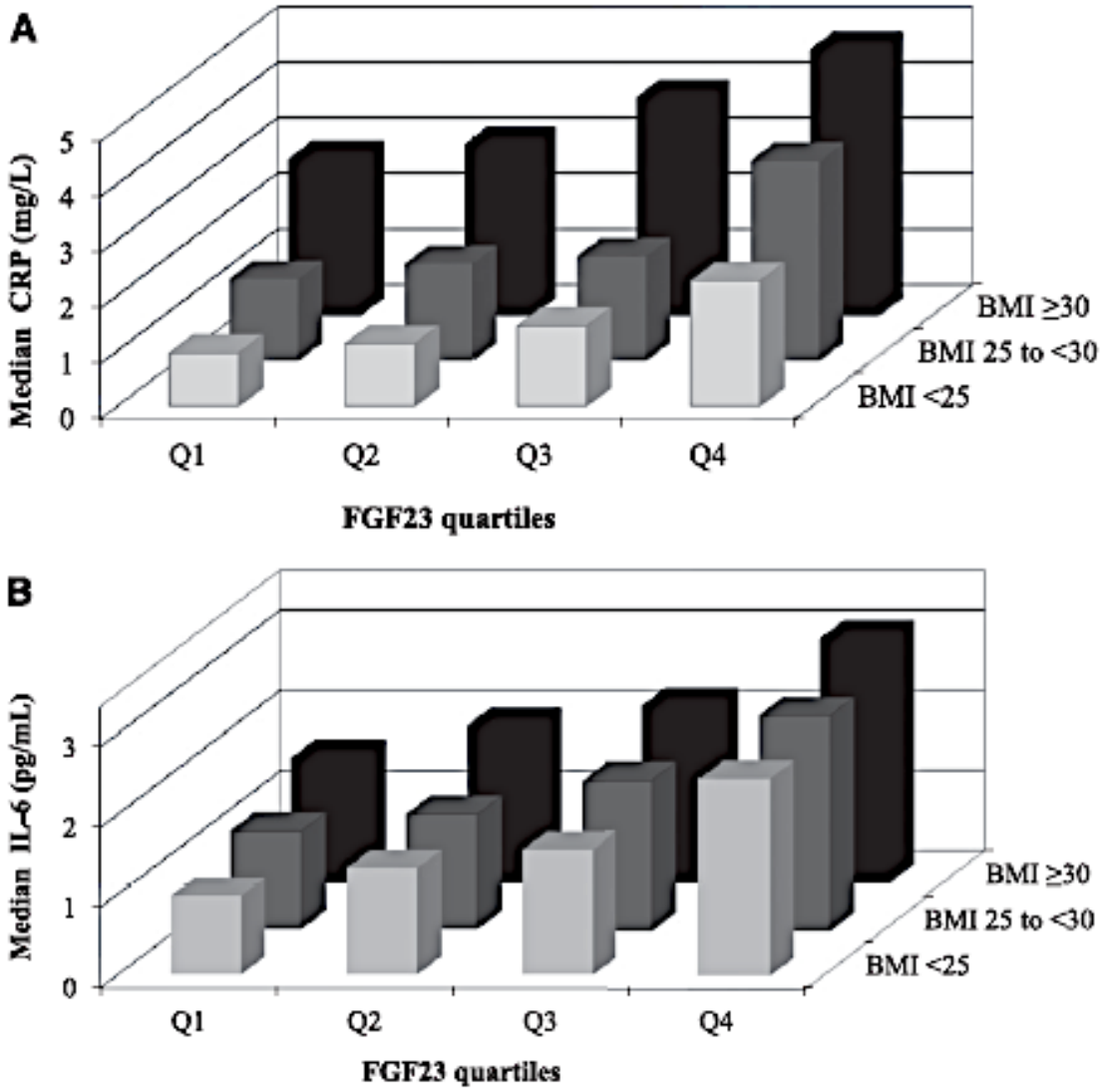


Chronic Renal Insufficiency Cohort (CRIC)
3875 Patients
58 years
CKD Stages 2-4
CKD-EPI : 44 ml/min

Munoz-Mendoza J et al. Kidney Int 91:711-719, 2017

FGF23 and Inflammation

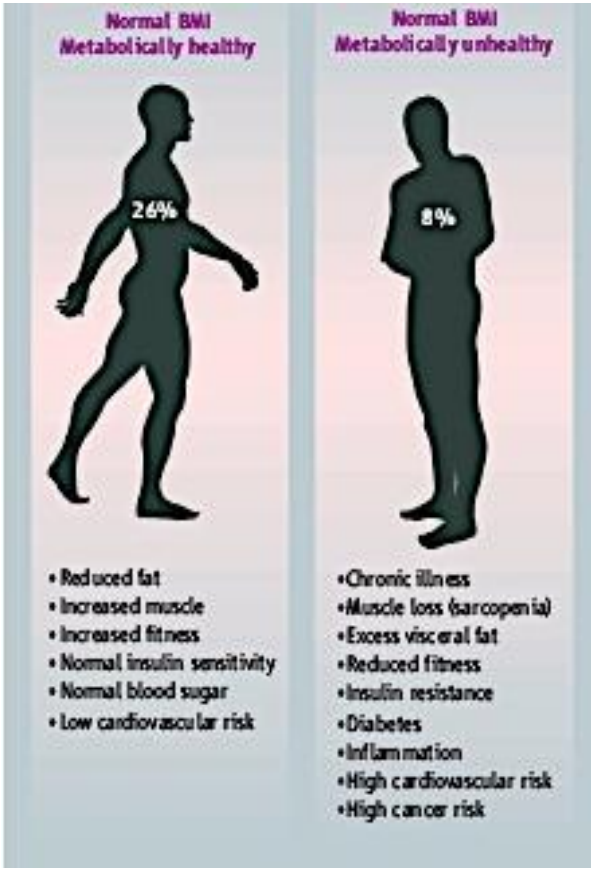
Chronic Renal Insufficiency Cohort (CRIC)
3879 Patients
58 years
CKD-EPI : 43 ml/min



Munoz-Mendoza J et al. CJASN 7:1155-1162, 2012

Nutritional Status Affects FGF23 Levels

A very thin man. Claude Ambroise Seurat (19th century).



Denutrition
FGF23 : ?

Normal
iFGF23 : 12-22 pg/ml

Obesity
iFGF23 : 22-111 pg/ml

Ahima R et al. Science, 2013

FGF23 and Inflammation

Chronic Renal Insufficiency Cohort (CRIC)
3879 Patients
58 years
CKD-EPI : 43 ml/min

<u>Severe Inflammation</u> =
Fourth quartile of
IL-6
TNFα
CRP
Fibrinogen

FGF23 positively correlates with all inflammation markers

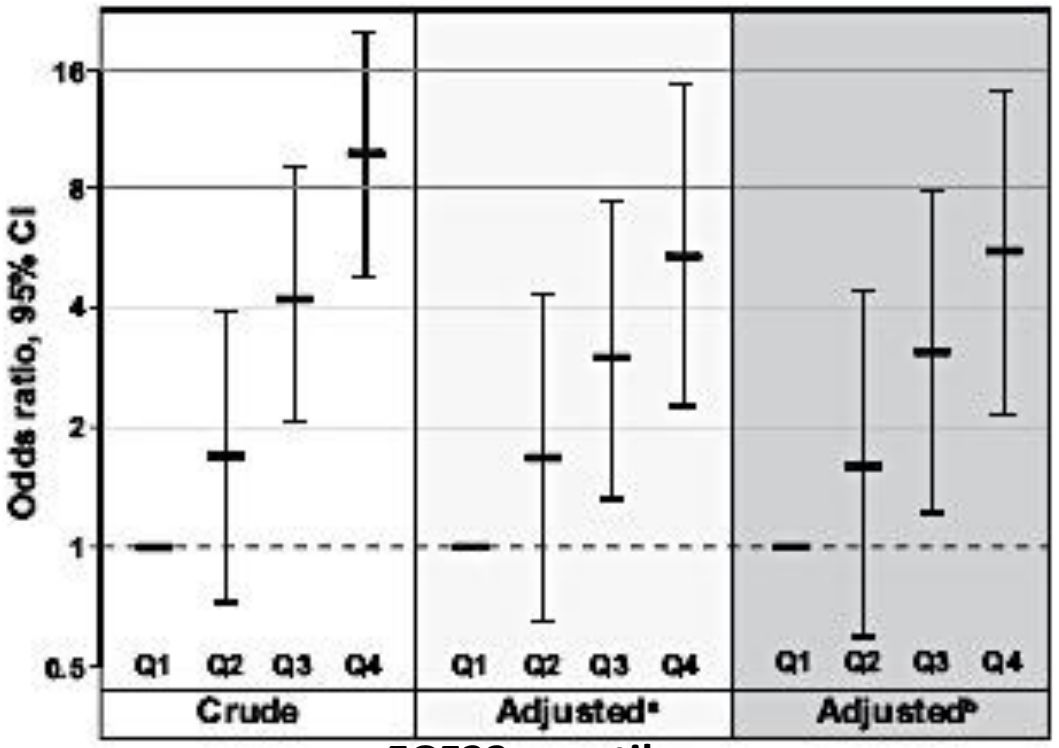
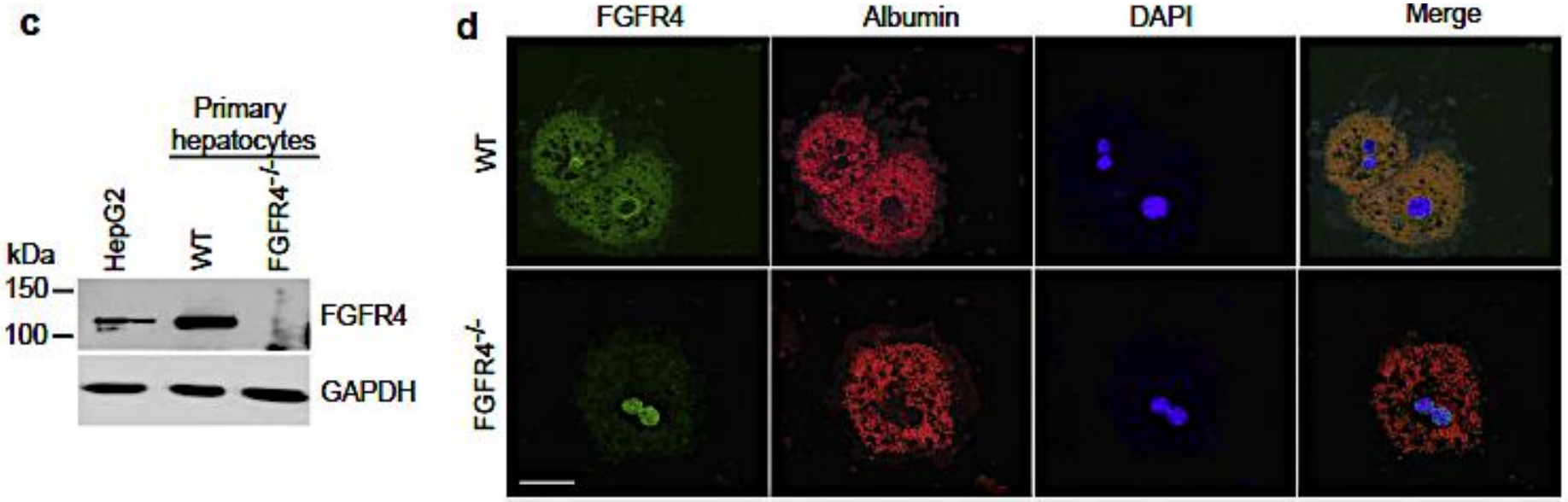


Figure 2. | Crude and multivariable-adjusted logistic regression analyses evaluating the association between fibroblast growth factor 23 (FGF23) with severe inflammation. Severe inflammation was defined as being in the highest 25th percentile of each of the IL-6, C-reactive protein, TNF-α, and fibrinogen (n=1335) distributions. Error bars indicate 95% confidence intervals. [a]Adjusted for age, sex, black race, Hispanic ethnicity, diabetes, current smoking, body mass index (BMI), use of statins, estimated GFR, and urinary albumin-to-creatinine ratio. [b]Adjusted for values in model A plus further adjustment for phosphate and parathyroid hormone. *P* for trend < 0.001 for all three models. Q1, FGF23 quartile 1 (<95.8 RU/ml); Q2, FGF23 quartile 2 (95.8–145.4 RU/ml); Q3, FGF23 quartile 3 (145.5–239.1 RU/ml); Q4, FGF23 quartile 4 (≥239.20 RU/ml).

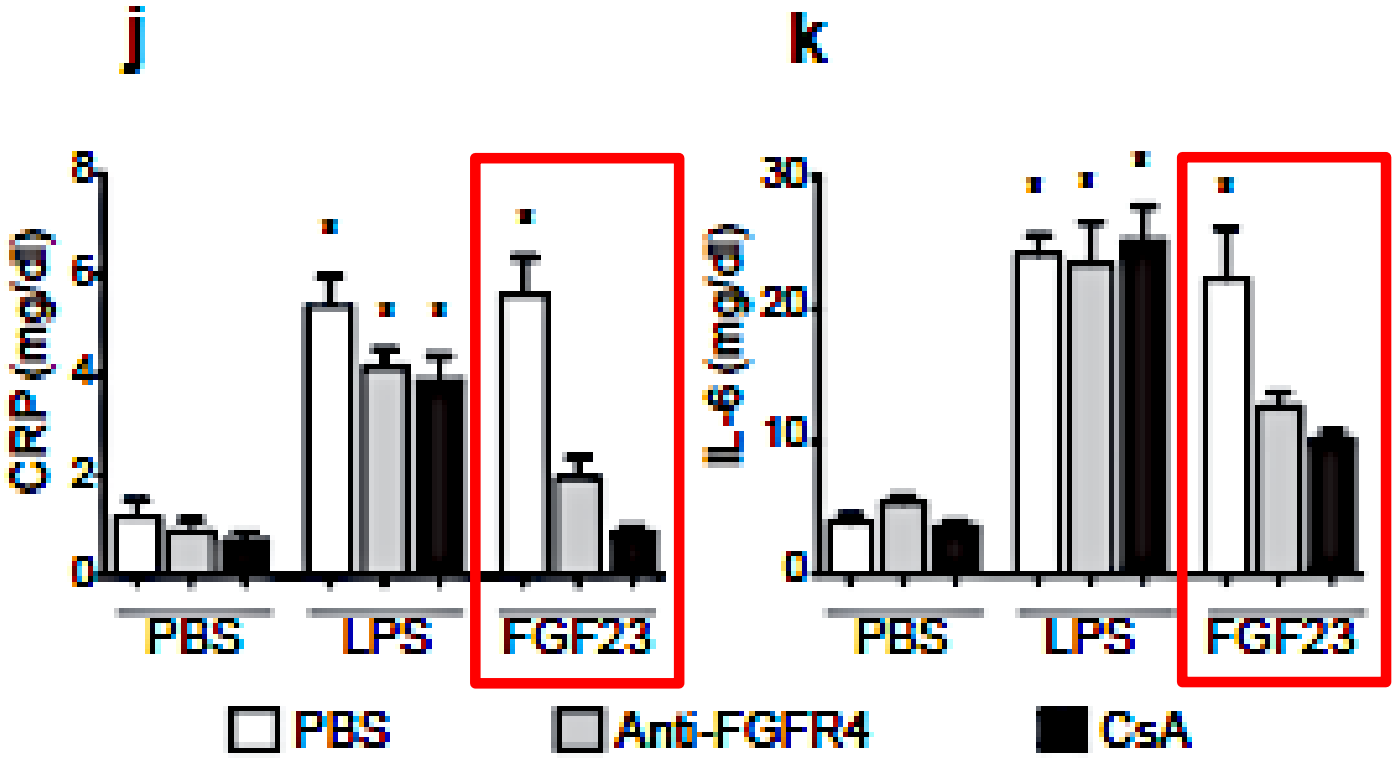
Munoz-Mendoza J et al. CJASN 7:1155-1162, 2012

Hepatocytes Express FGFR4



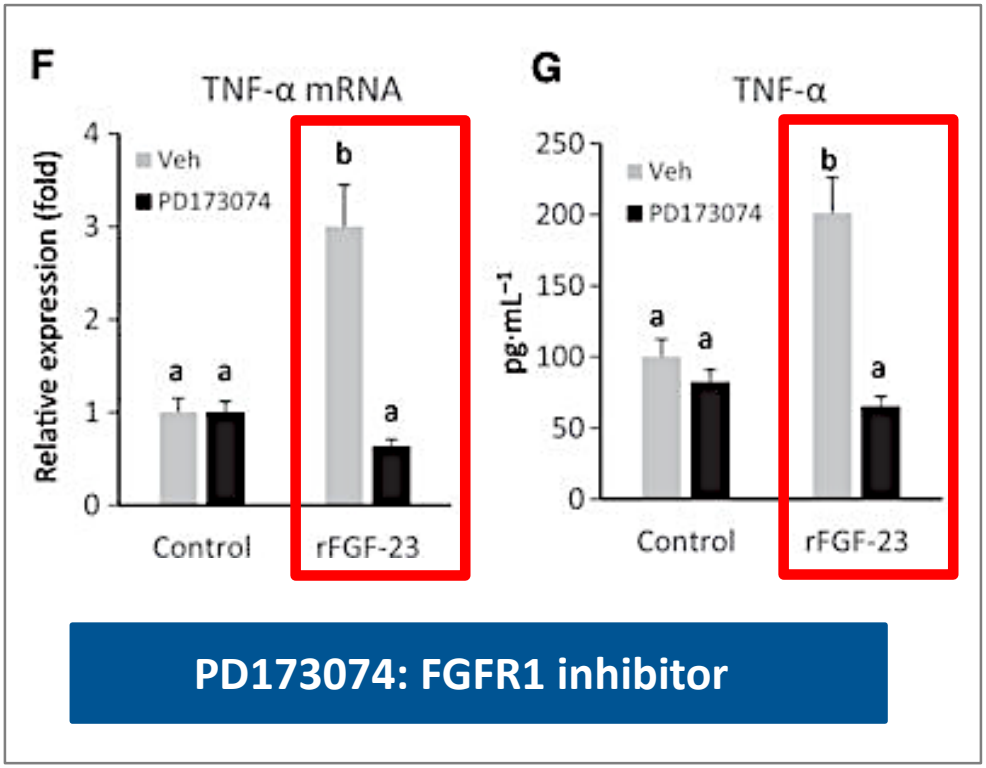
Singh S et al. Kidney Int 90:985-996, 2016

FGF23 Stimulates CRP and IL-6 in Mouse Hepatocytes

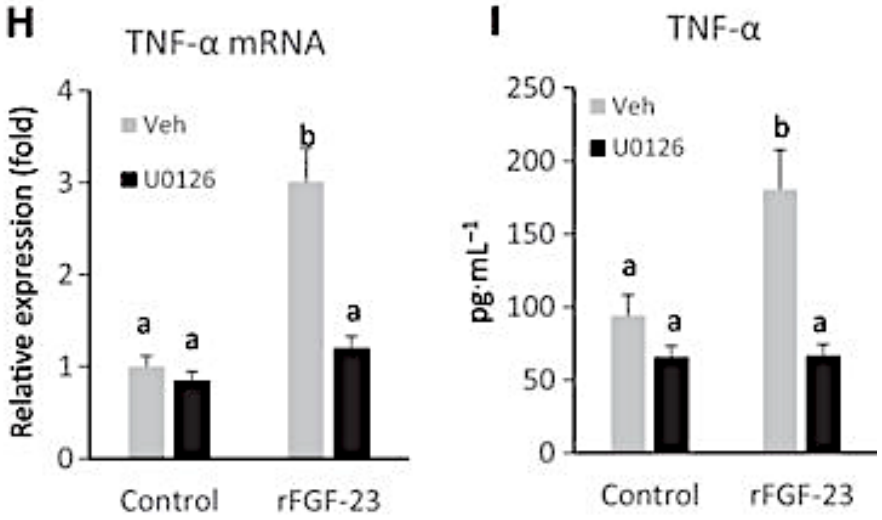


Singh S et al. Kidney Int 90:985-996, 2016

FGF23 Stimulates TNFα in Macrophages



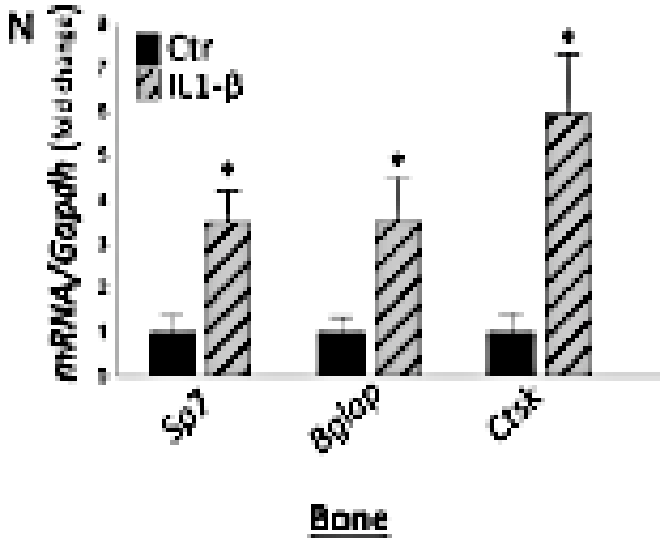
PD173074: FGFR1 inhibitor



UO126: ERK 1/2 inhibitor

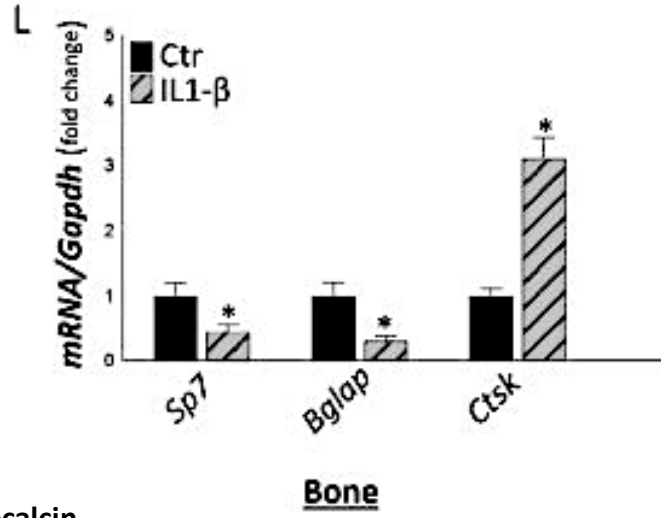
Han X et al. FEBS Letter 590:53-67, 2016

Inflammation and Bone Remodeling



Acute inflammation

6 hours post-injection of a single dose of 50 ng/g of Interleukine-1b



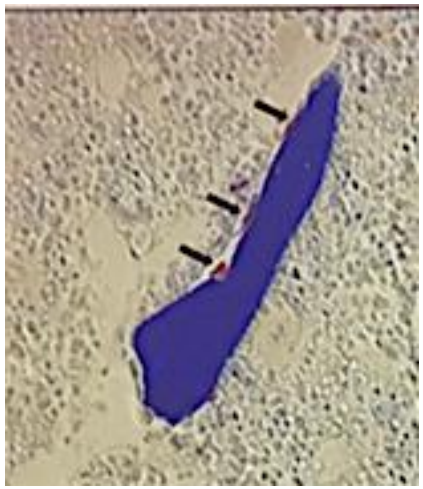
Chronic inflammation

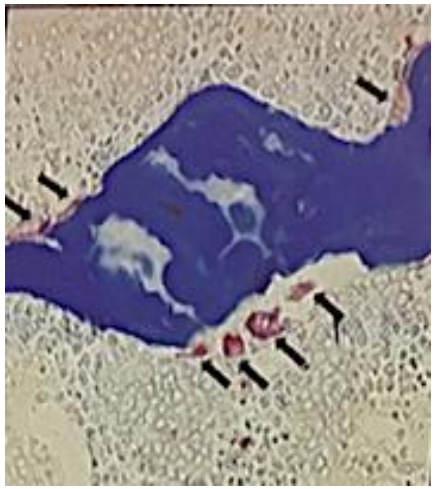
4 days post-injection of daily dose of 50 ng/g of Interleukine-1b

Sp7: Osterix
Bglap: Ostoecalcin
Ctsk: Cathepsin

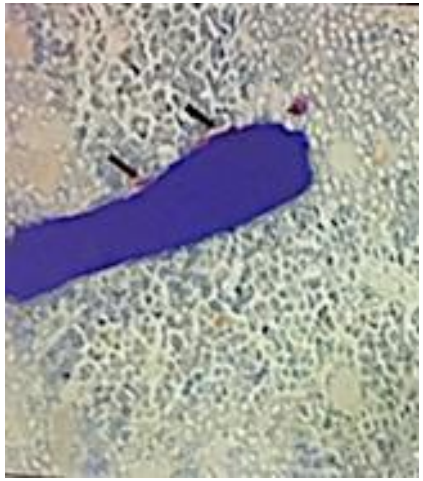
David V et al. Kidney Int 89:135-146, 2016

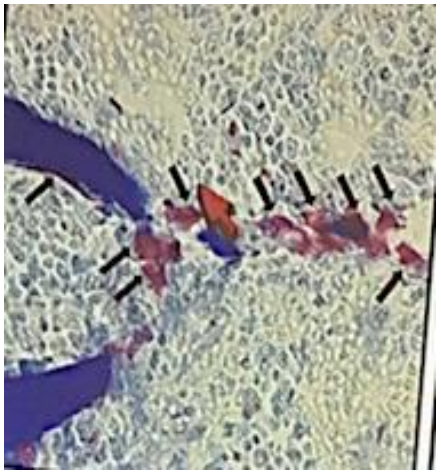
Inflammation and Bone Remodeling





Acute inflammation
6 hours post-injection of a single dose of 50 ng/g of Interleukine-1b

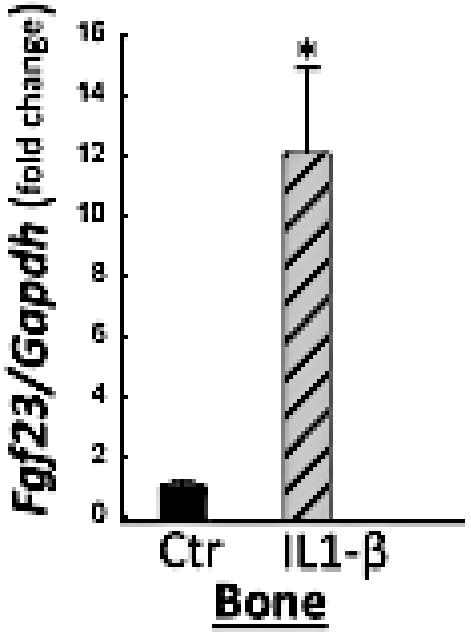


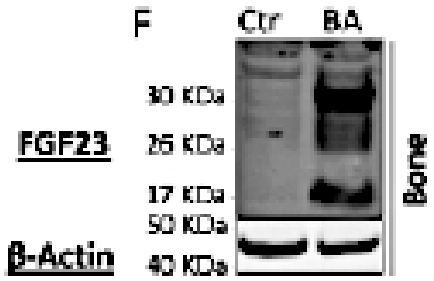


Chronic inflammation
4 days post-injection of daily dose of 50 ng/g of Interleukine-1b

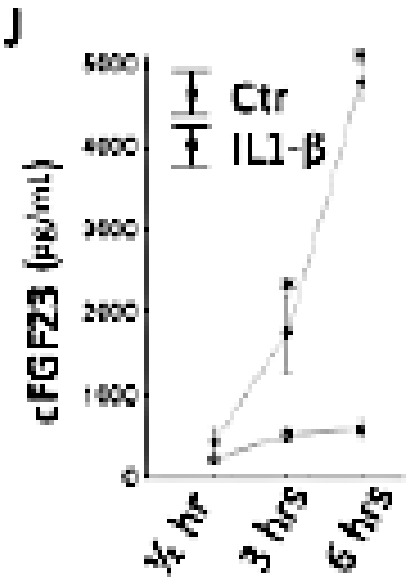
David V et al. Kidney Int 89:135-146, 2016

Acute Inflammation Stimulates FGF23 Cleavage and Increases cFGF23 Levels

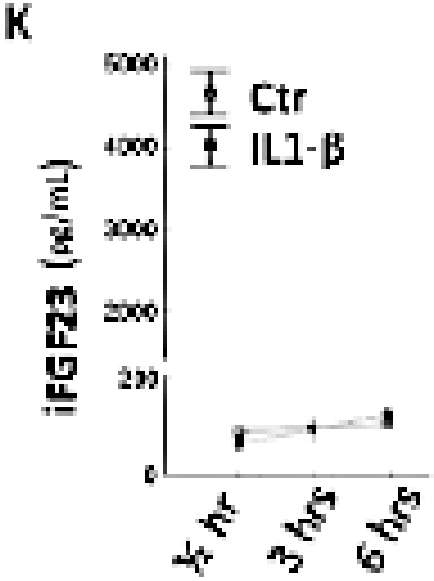




cFGF23



iFGF23

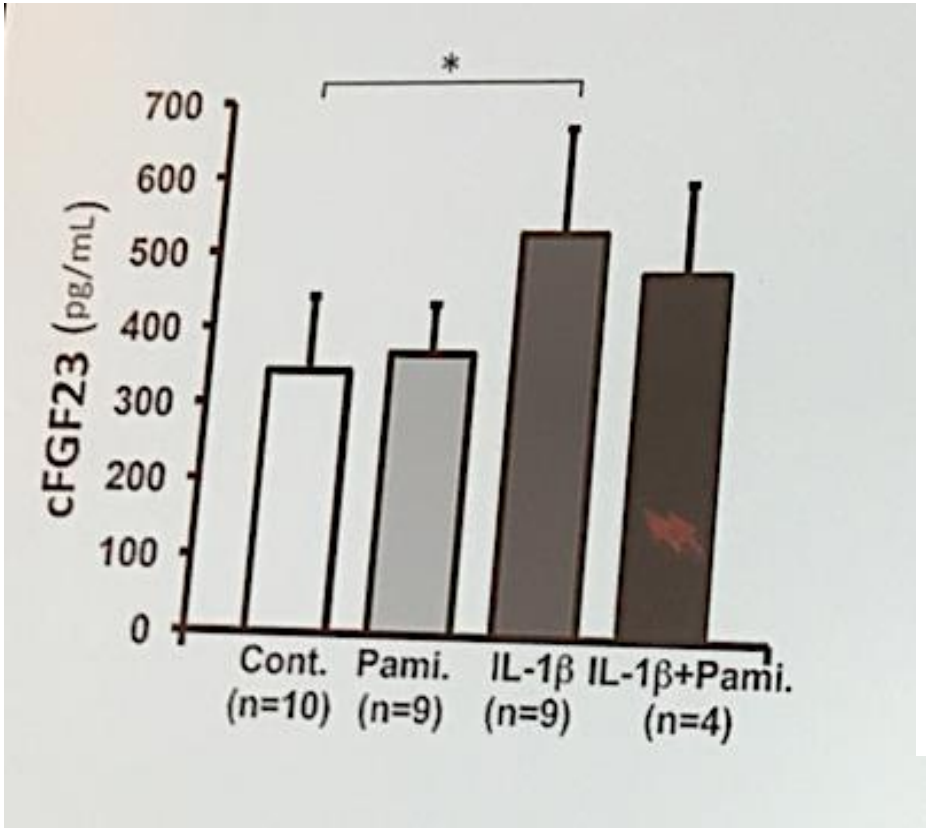


Acute inflammation
6 hours post-injection of a single dose of 50 ng/g of Interleukine-1b

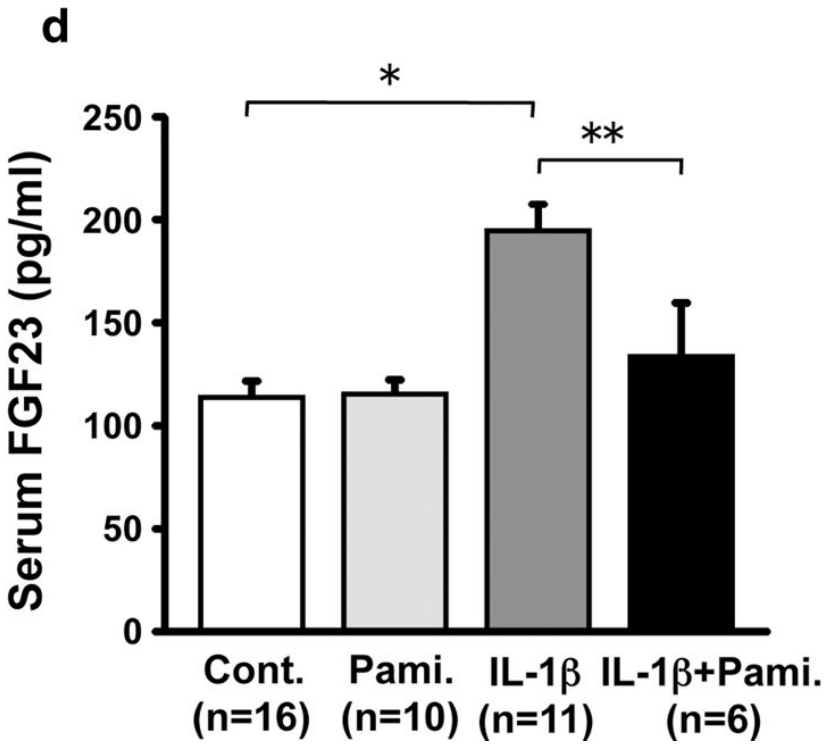
David V et al. Kidney Int 89:135-146, 2016

Inflammation and Bone Remodeling Favors FGF23 Secretion

C-Terminal FGF23

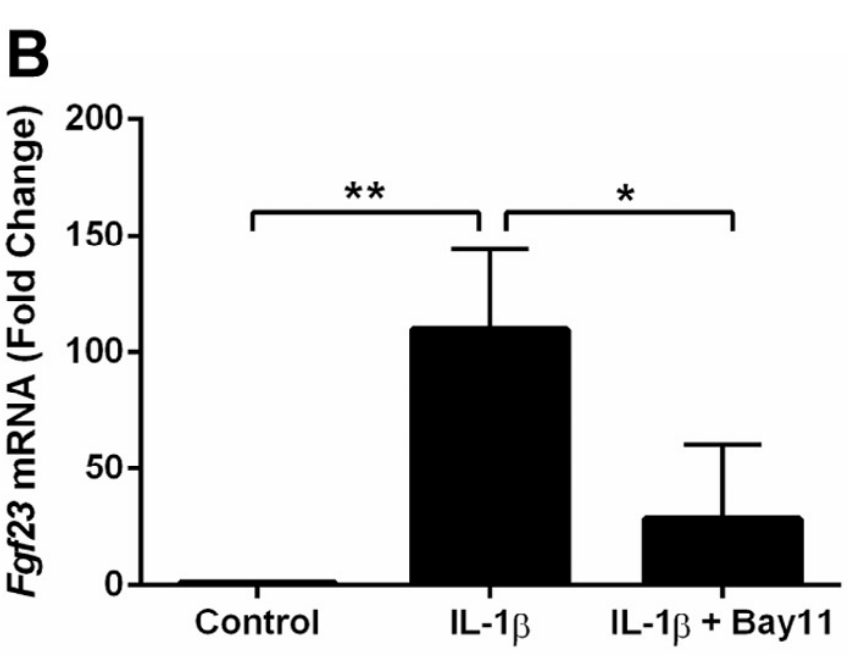


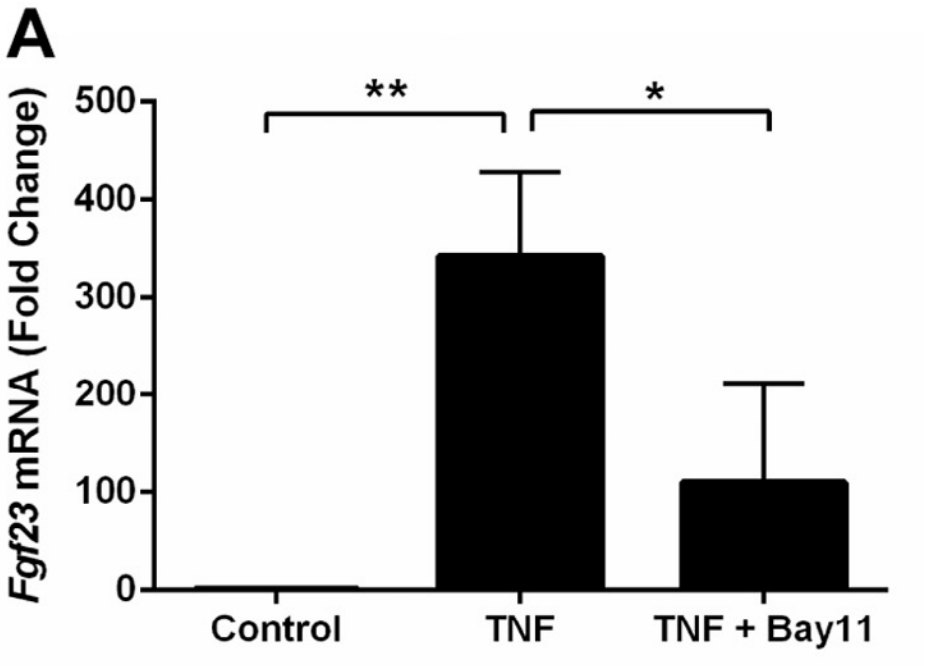
Intact FGF23



Yamazaki et al. JBMM, 2015

Pro-Inflammatory Stimuli Increase FGF23 in an Osteocyte Cell Line



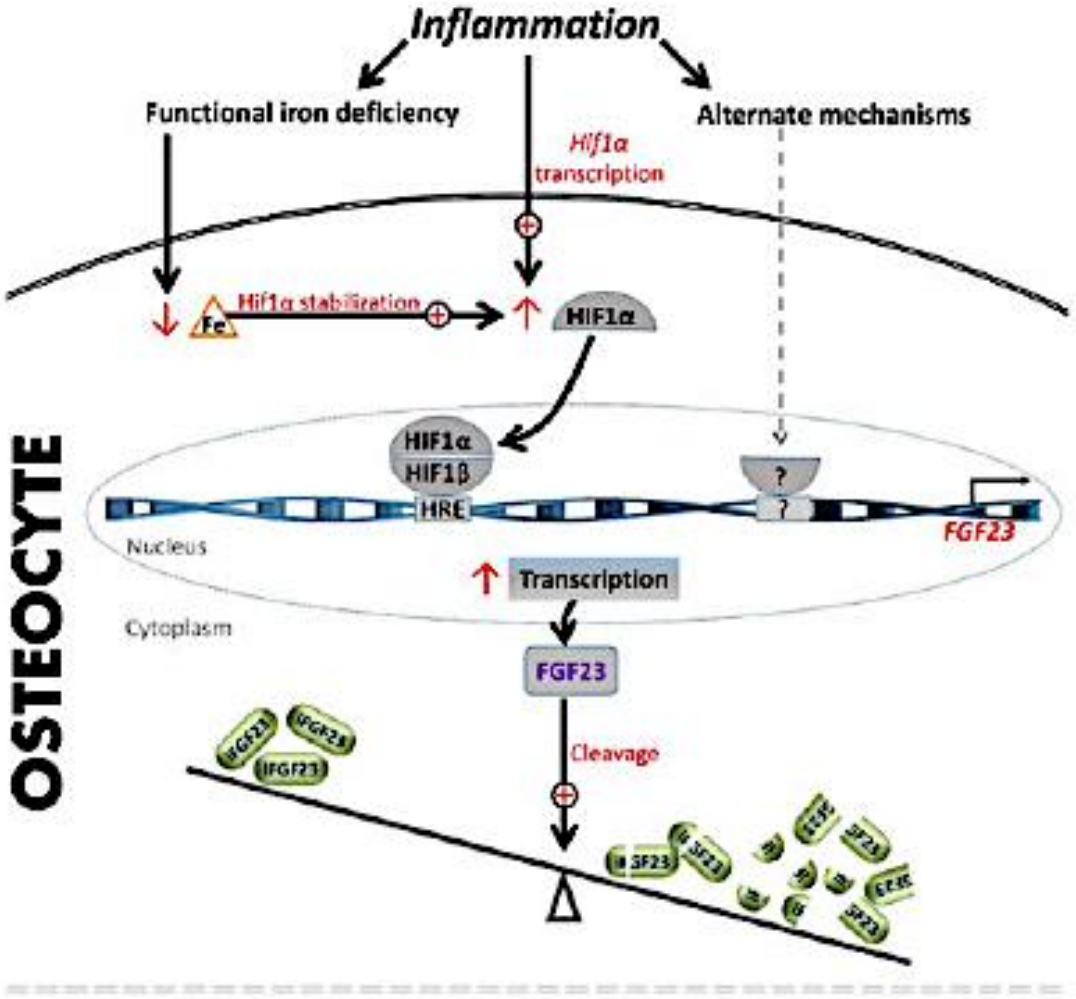


Bay 11: Nf-κB inhibitor

TNFa: Tumor Necrosis Factor-alpha

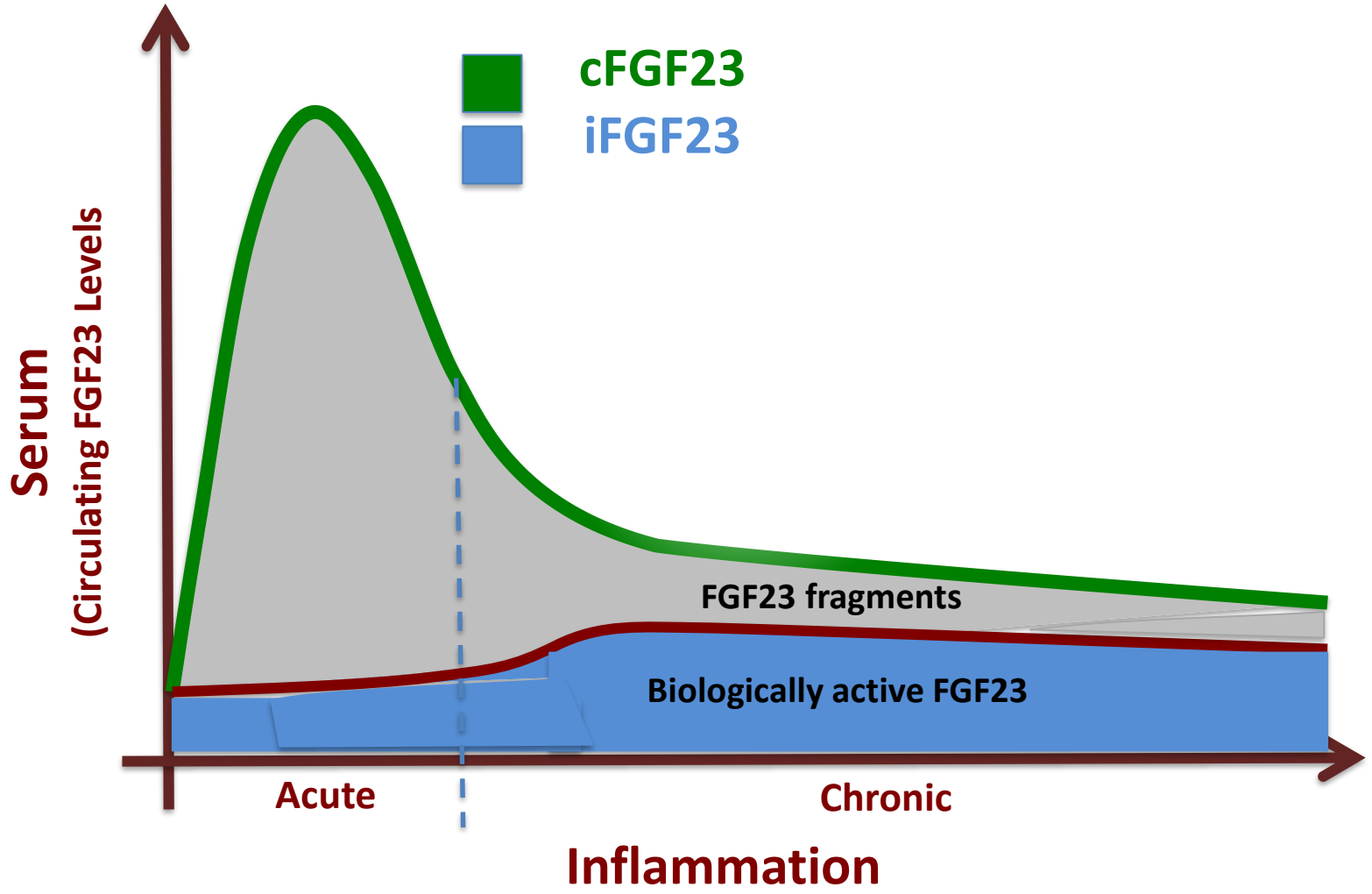
Ito et al. Mol Cell Endocrinol, 2015

Mechanisms of FGF23 Regulation by Inflammation and Iron



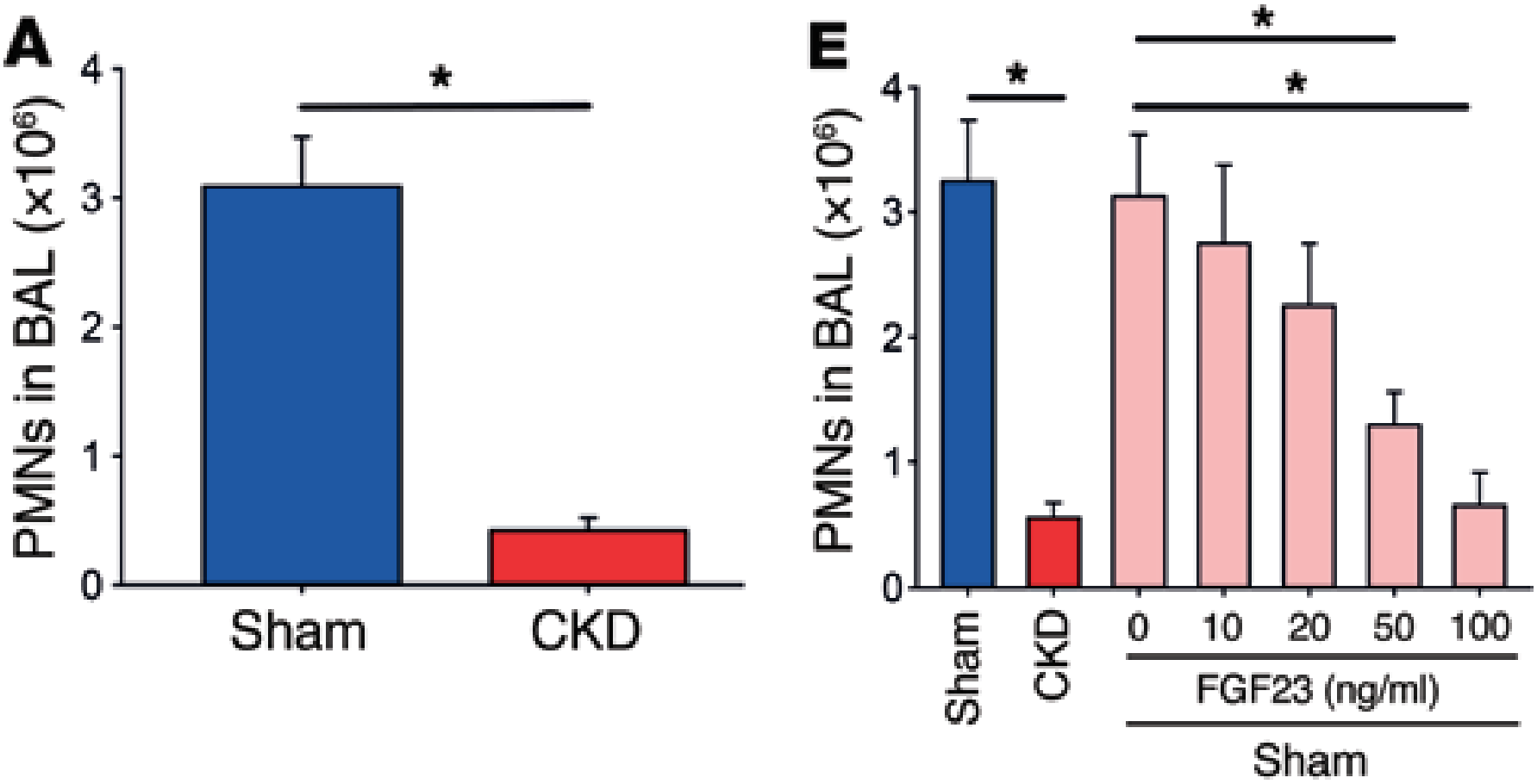
David V et al. Kidney Int 89:135-146, 2016

Inflammation Status and Circulating FGF23



David V et al. Kidney Int 89:135-146, 2016

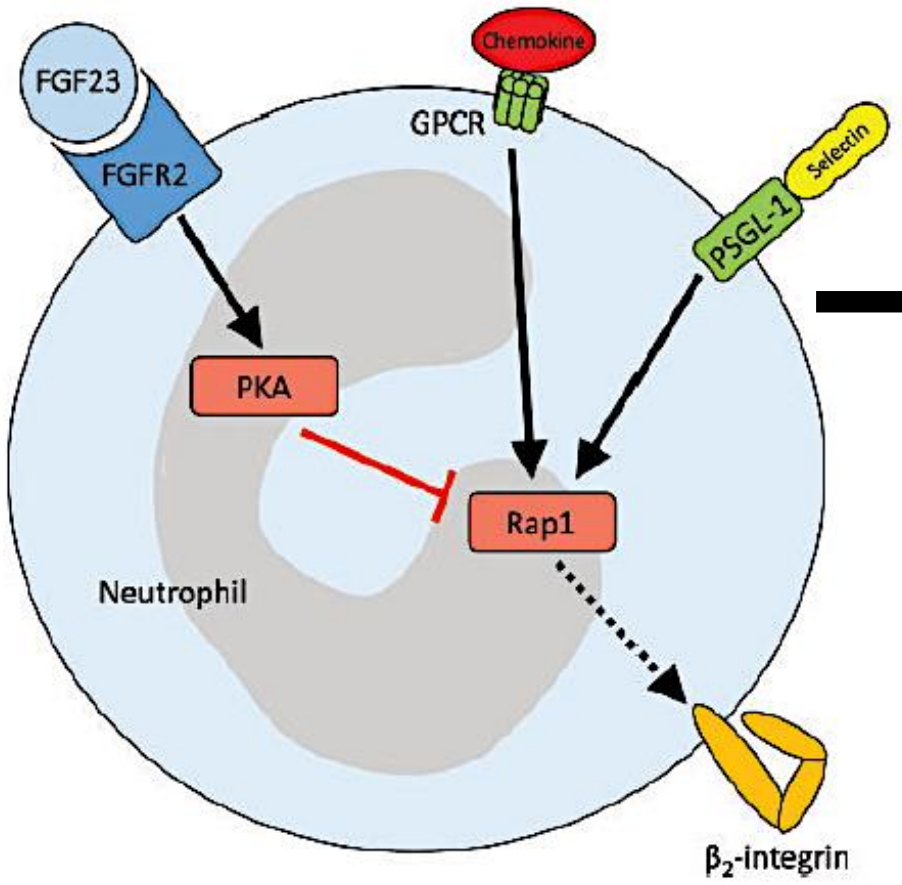
FGF23 and Infection



Neutrophil recruitment and host defense during pneumonia is decreased in CKD mice. CKD was achieved in mice by 5/6-nephrectomy, and pneumonia was induced by E. coli instillation after 10 days. (A–D) Twenty-four hours after inducing pneumonia, neutrophils were counted in the BAL.

Rossaint J et al. JCI 126:962-974, 2016

FGF23 and Infection



Reduced neutrophil migration

Decreased Anti-bacterial immunity

Molecular mechanisms of FGF23-mediated integrin deactivation in neutrophils. Chemokine and selectin engagement to G-protein coupled receptors (GPCR) or P-selectin glycoprotein ligand 1 (PSGL-1) causes activation of b2-integrins on neutrophils. FGF23 binding to its receptor FGFR2 on neutrophils activates PKA, which deactivates Rap1 and inhibits chemokine- and selectin-mediated integrin activation

Rossaint J et al. JCI 126:962-974, 2016; Rossaint J et al. NDT 32:1448-1452, 2016

#FGF23&Infection

CLINICAL EPIDEMIOLOGY www.jasn.org

Fibroblast Growth Factor 23 and the Risk of Infection-Related Hospitalization in Older Adults

Kristen L. Nowak,* Traci M. Bartz,† Lorien Dalrymple,‡ Ian H. de Boer,§ Bryan Kestenbaum,§ Michael G. Shlipak,‖¶** Pranav S. Garimella,†† Joachim H. Ix,‡‡§§‖‖ and Michel Chonchol*

Nowak KL et al. CJASN 2017 Apr;28(4):1239-1246

FGF23 and the Risk of Infection-Related First Hospitalization in Older Adults

Cardiovascular Health Study

3141 adults > 65 years old

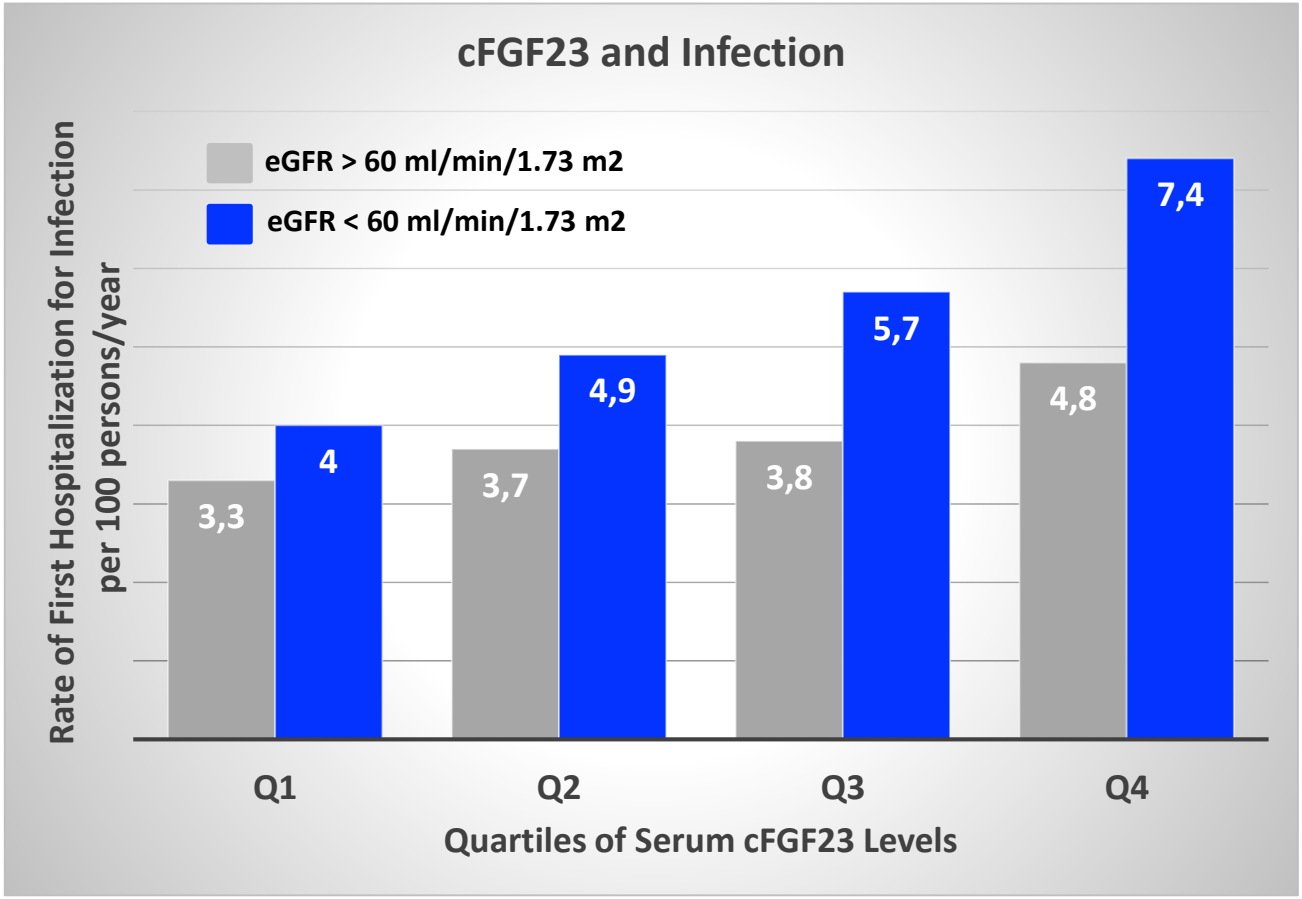
8.6 years of follow-up

37% (1164) hospitalizations

FGF23 in Q4 roughly doubles

The risk of infection

(HR 2.02; CI 1.41-2.91)



Nowak KL et al. CJASN 2017 Apr;28(4):1239-1246

Conclusions

- FGF23 is a new hormone regulating mineral and bone metabolism (phosphate and vitamin D)

- FGF23 increases very early in the evolution of CKD and is associated with increased risk of morbidity and mortality

- FGF23 is a pro-inflammatory molecule (stimulating several cytokines such as TNFa, IL-1b) and inversely inflammation stimulates FGF23 production and cleavage

- High FGF23 decreases poly-morphonuclear (PMN) recruitment, creates a state of acquired immuno-suppressive syndrome, and favors infection

Merci Beaucoup

Muchas Gracias