

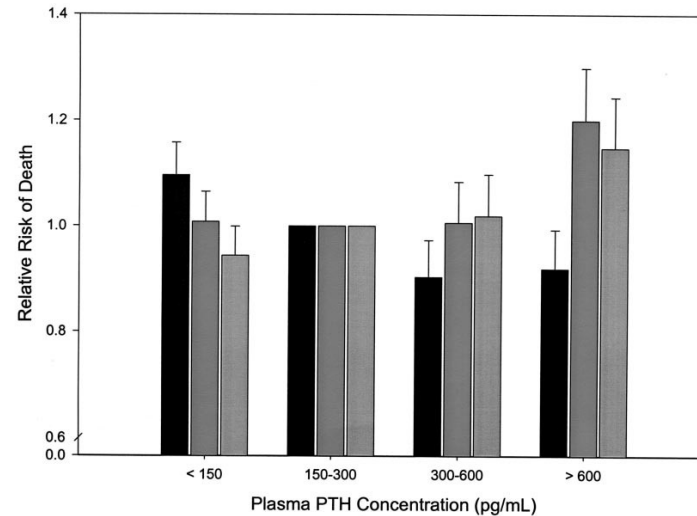
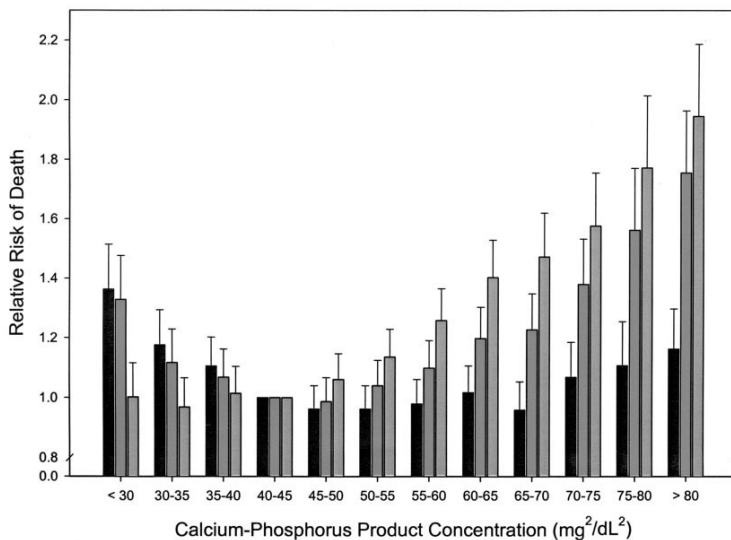
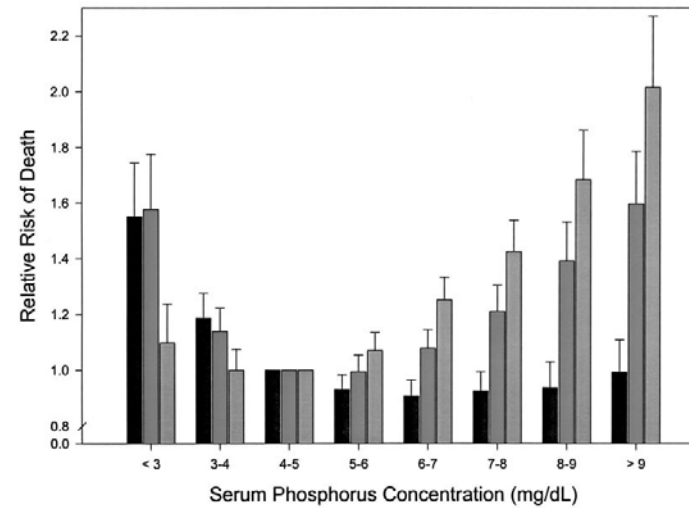
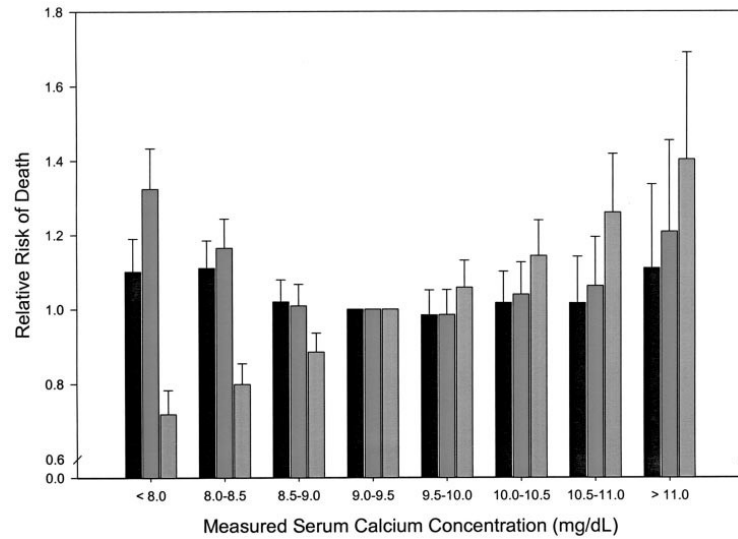


22 Mayıs 2010 Cumartesi

**HEMODİYALİZ HASTALARINDA
SERUM
FIBROBLAST GROWTH FACTOR-23
DÜZEYİ, SOL VENTRİKÜL KÜTLESİ
VE MİYOKARD PERFORMANS
İNDEKSİYLE BAĞIMSIZ OLARAK
İLİŞKİLİDİR**

**Dr. Alper KIRKPANTUR
TC SB Dışkapı YB EA Hastanesi
Nefroloji Kliniği**

Mineral Metabolism, Mortality, and Morbidity in Maintenance Hemodialysis



FIBROBLAST BÜYÜME FAKTÖRÜ-23

- Otozomal dominant hipofosfatemik rickets ve tümörle indüklenen osteomalazide etken:
 - Renal P kaybı ve hipofosfatemisi (Npt2a and Npt2c'nin azalmış ekspresyon ve endositozu),
 - Uygunsuz düşük veya normal düzeyde (1,25(OH)2D3)
 - Rickets/osteomalazi.

Consortium ADHR. Nat Genet 2000; 26: 345-348

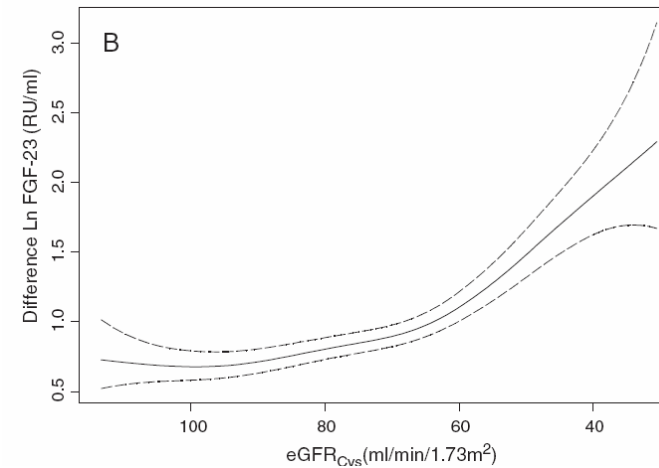
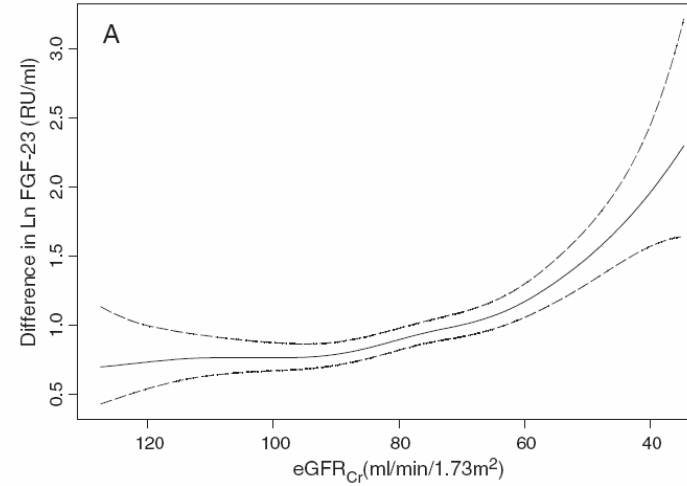
Shimada T, et al. Proc
Natl Acad Sci U S A 2001; 98: 6500-6505

BÖBREK HASTALIĞI VE FGF-23

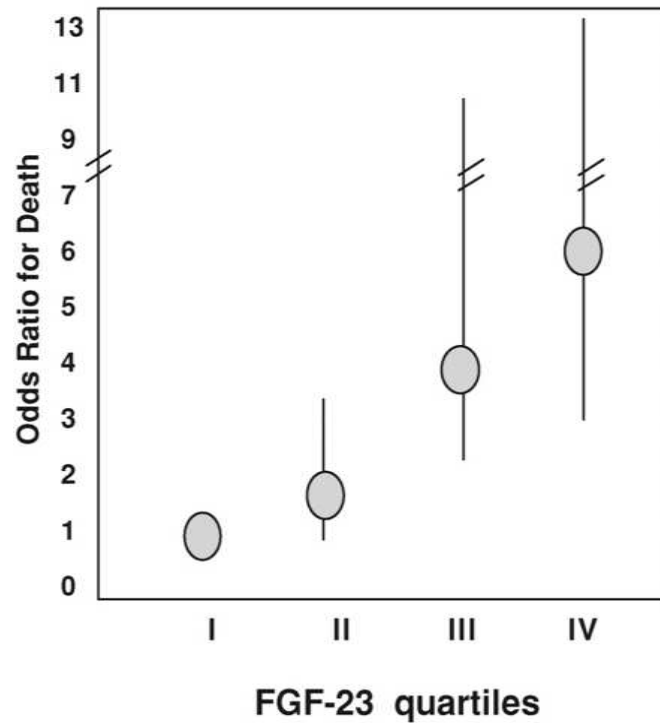
- KBH lı bireylerde serum FGF-23 düzeyi progressif olarak artar.
- ESRD'de ise normalin 100 ile 1000 katı arasında bulunur.

Nephrol Dial Transplant (2010) 25: 993–997
doi: 10.1093/ndt/gfp699

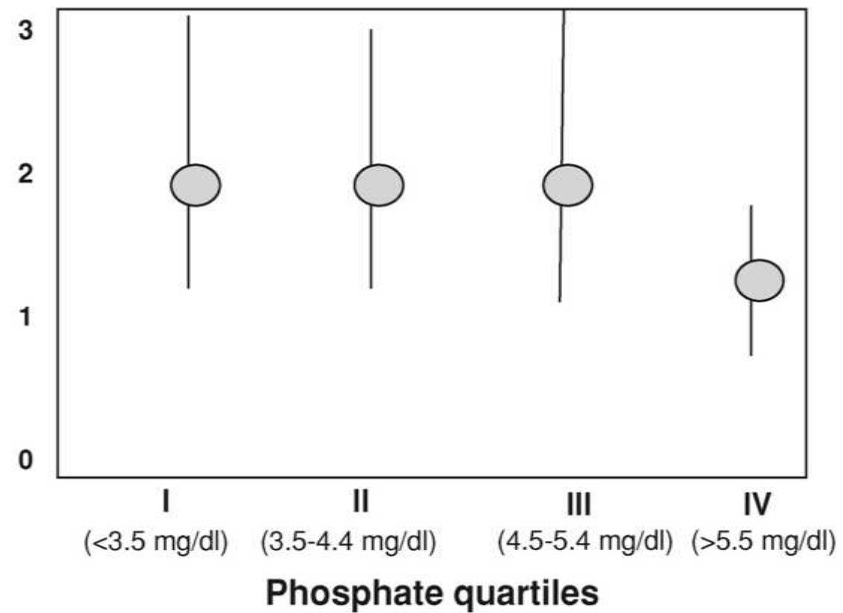
FGF-23 in chronic kidney disease



MORTALITE VE FGF-23 KUARTILLERI



Odds Ratio for Death associated with 1 unit increase in the log-transformed FGF-23 level within phosphate quartiles



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

TEİ İNDEKSİ

- Chuwa Tei
- Sistolik ve diyastolik fonksiyonu beraber değerlendirir.
- $(IRT+ICT)/ET$
- Pek çok kardiyak hastalıkta hassas
- Tei indeksi, LV fonk invazif ölçümleri ile korrele.

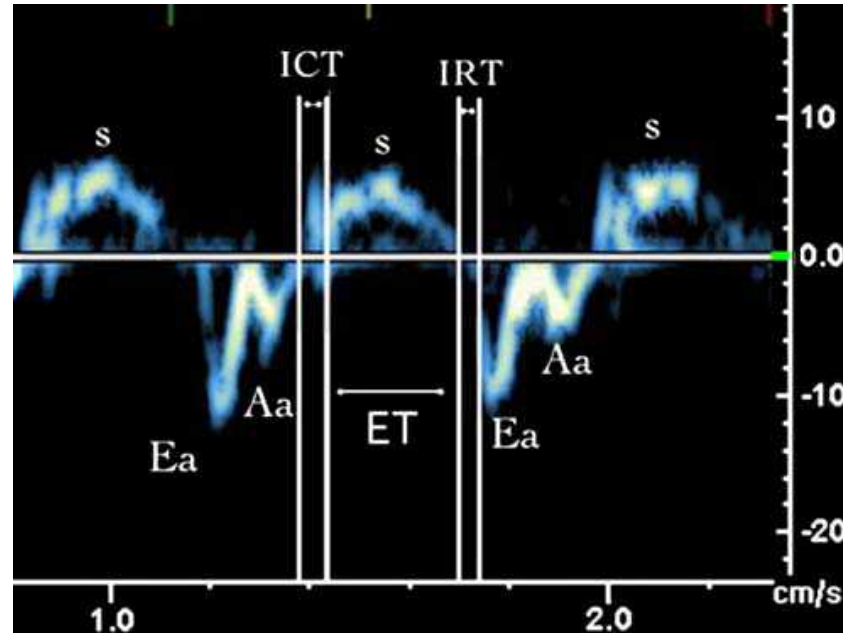


Fig. 1 Time intervals measured from pulsed tissue Doppler (*ICT* tissue isovolumetric contraction time, *ET* ejection time, *IRT* tissue isovolumetric relaxation time). TDE-Tei index is calculated as $(ICT + IRT)/ET$

Tei C et al.

J Am Soc Echocardiogr 1997;10:169-178

Pediatr Nephrol (2008) 23:1803–1808

DOI 10.1007/s00467-008-0873-3

TEI INDEKSI VE DIYALİZ

Influence of Preload Reduction on Tei Index and Other Doppler Echocardiographic Parameters of Left Ventricular Function

Silvio Henrique Barberato e Roberto Pecoits Filho
Pontifícia Universidade Católica do Paraná - Curitiba, PR - Brazil

Centro de Ciências Biológicas e da Saúde

Pediatr Nephrol (2008) 23:1803–1808
DOI 10.1007/s00467-008-0873-3

ORIGINAL ARTICLE

Preload dependence of Doppler tissue imaging-derived indices in adolescents

Predictors of Congestive Heart Failure in Patients on Maintenance Hemodialysis

Shigenori Ito, MD; Sumiko Murai, MD*; Masato Sugiura, MD;
Takayuki Yoshida, MD; Tatsuya Fukutomi, MD**

Circ J 2007; 71: 1424–1429

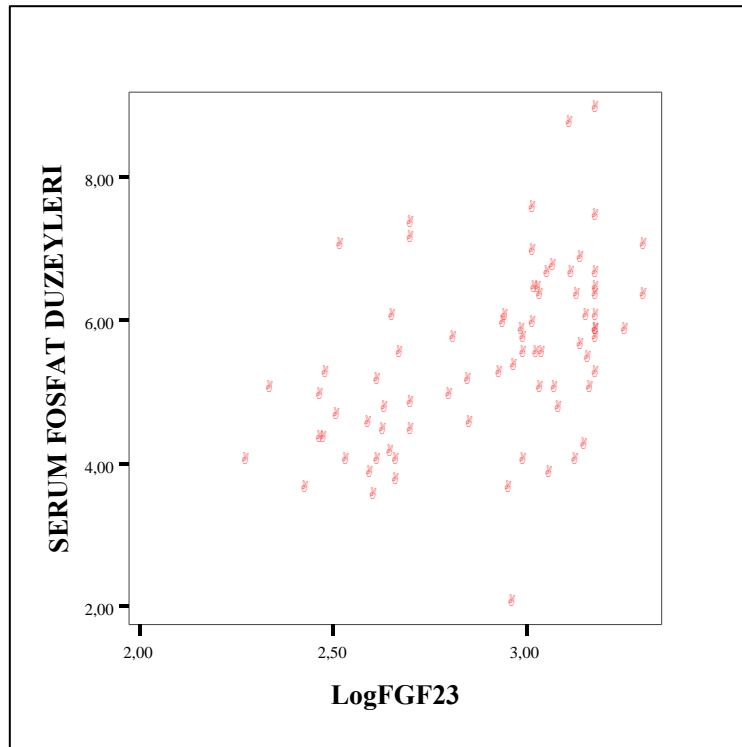
HİPOTEZ

- ◉ İdame hemodiyaliz hastalarında plazma FGF-23 konsantrasyonları ile
 - Sol ventrikül kitle indeksi(LVMI) ve
 - Miyokardiyal performans indeksi (Tei indeksi) arasındaki ilişkiyi test etmektir.

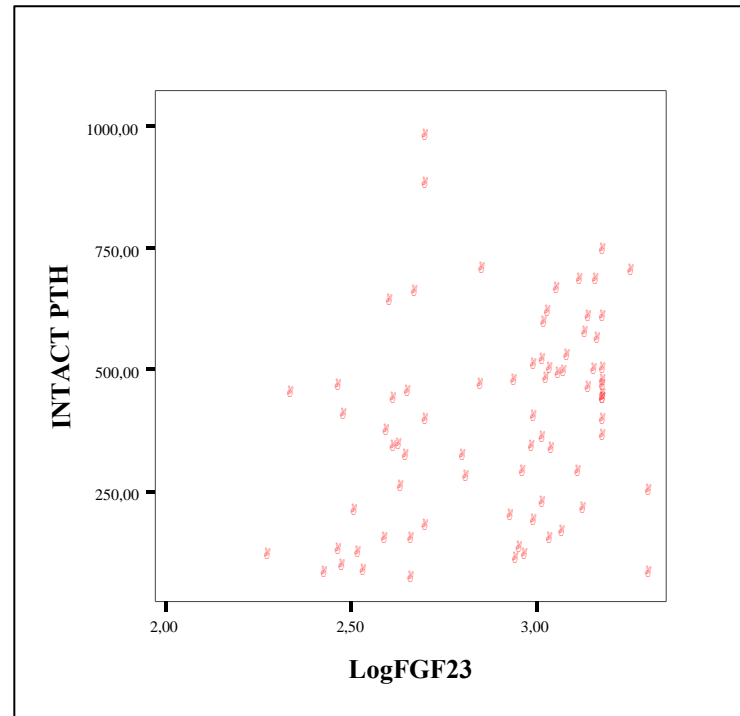
MATERYAL-METODOLOJİ

- Kesitsel çalışma düzeni
- Plazma FGF-23 düzeyleri (C-terminal human enzyme-linked immunosorbent assay kit= Immutopics®)
- Ekokardiyografi
- 128 idame hemodiyaliz hastası
 - 65 kadın ve 63 erkek hasta,
 - Ortalama yaş: 55.5 ± 13 yıl,
 - Ortalama hemodiyaliz süresi: 52 ± 10 ay,
 - Tüm hastalar 3/hf hemodiyaliz programında.

LOG FGF-23, P VE İNTEGRAL PTH



$r=0.469$, $p<0.0001$



$r=0.374$, $p=0.001$

FGF-23 KUARTİLLERİ VE EKOKARDİYOĞRAFİK PARAMETRELER

Parameter	FGF-23 Quartile 1 (<454 RU/ml)	FGF-23 Quartile 2 (454- 1023 RU/ml)	FGF-23 Quartile 3 (>1023 RU/ml)	P value
n	41	44	43	
Septal Thickness (cm)	1.34±0.21	1.45±0.18	1.59±0.19	0.004 *
Posterior wall thickness (cm)	1.11±0.22	1.23±0.17	1.36±0.18	0.009 *
LVEDD (cm)	4.17±0.69	4.49±0.72	4.81±0.75	0.010 *
LVESD (cm)	3.27±0.99	3.35±0.84	3.57±0.72	0.230
EF (%)	60.9±9.17	62±11	62±10.1	0.960
FS	30.6±6.7	31.4±6.3	32.1±6.1	0.680
LVMI (g/m²)	94±15	103±14	111±18	0.040 *
LVH (%)	19 (46%)	31 (70%)	41 (95%)	0.002 *
MPI	0.30±0.09	0.40±0.10	0.53±0.14	0.008 *

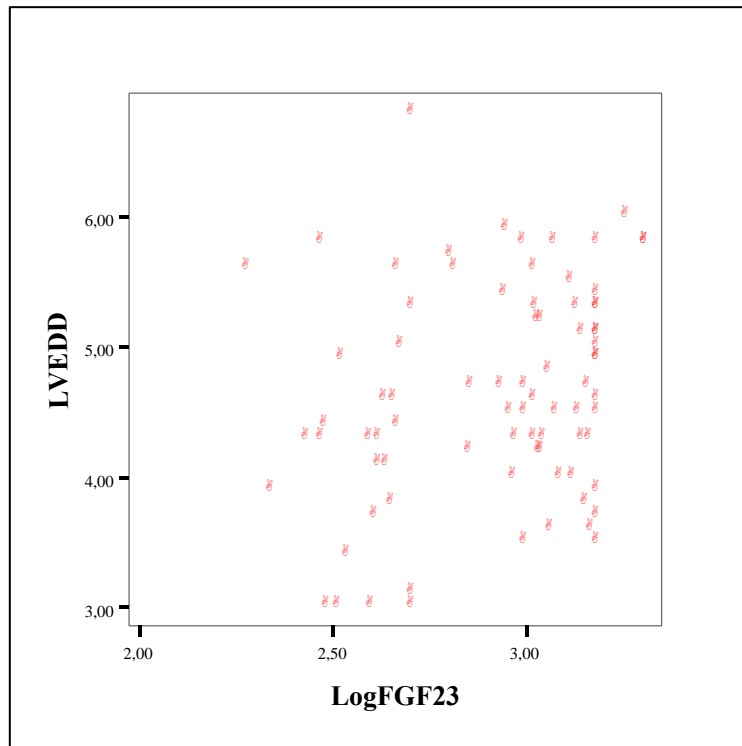
FGF-23

- Koroner arter hastalığı olanlarda
 - 3.00 ± 0.22 vs 2.82 ± 0.26 , $p=0.002$
- Aort kapak kalsifikasyonu olanlarda
 - 3.06 ± 0.19 vs 2.83 ± 0.26 , $p=0.0001$

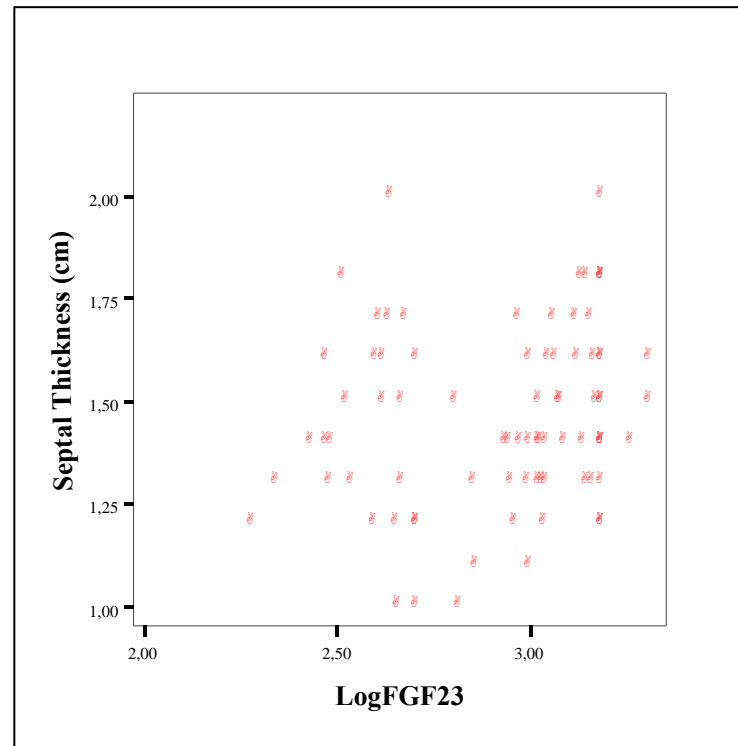
olmayanlara kıyasla daha yüksek

log-FGF 23 değerleri mevcuttu.

LOG FGF-23, LVEDD VE SEPTAL KALINLIK KORELASYONLARI



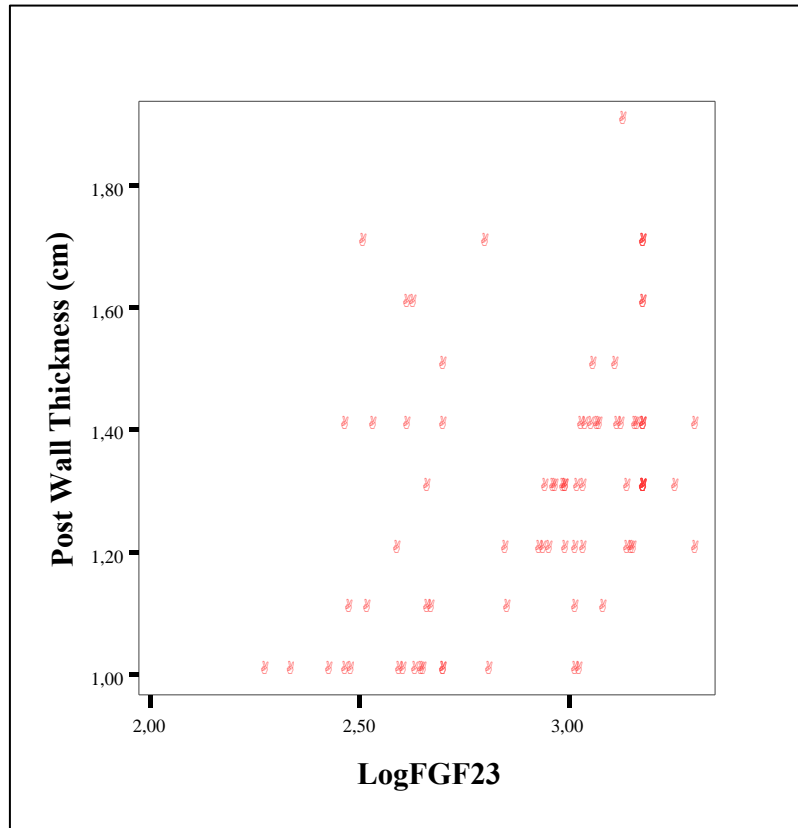
$r=0.242, p=0.029$



$r=0.221, p=0.048$



LOG FGF-23 VE ARKA DUVAR KALINLIK KORELASYONU



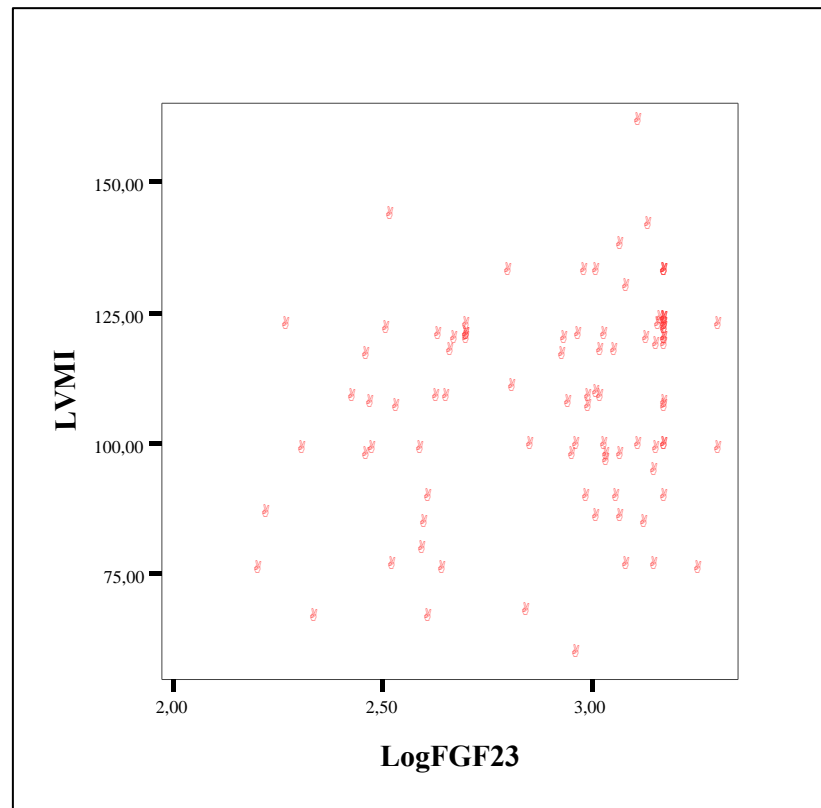
$r=0.452, p=0.0001$



MPI VE PLAZMA FGF-23 DÜZEYLERİ

- MPI>0.45 olan hastaların plazma FGF-23 düzeyleri; MPI<0.45 olanlara göre daha yüksek idi.
- **1145±378 ve 657±419 RU/ml, p=0.0001.**

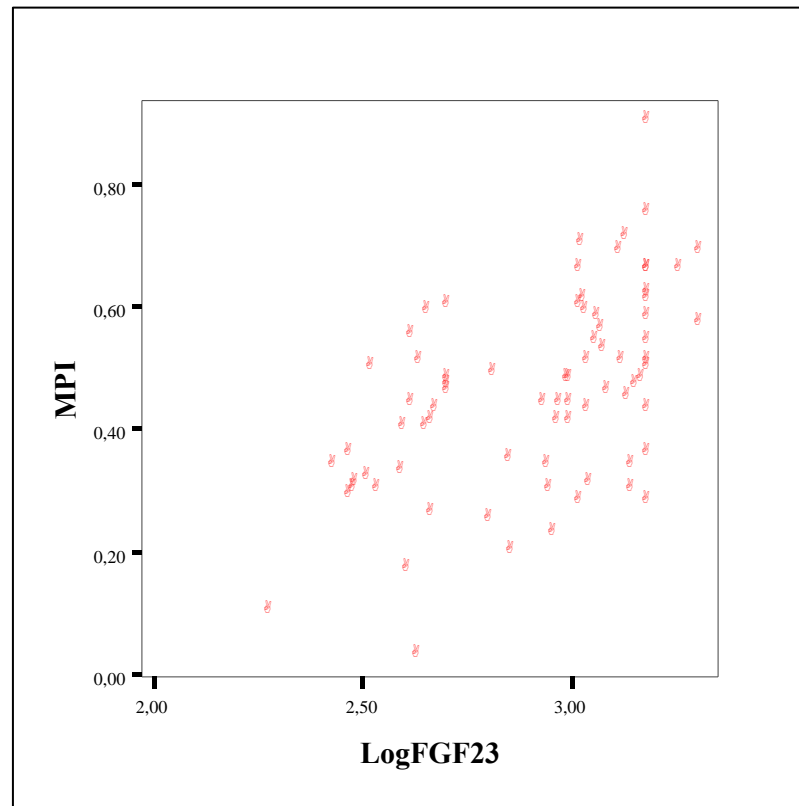
LOG FGF-23 VE LVMI



$r=0.281, p=0,007$



LOG FGF-23 VE MPI



$r=0.555$, $p=0,0001$



LVMI: TEK VE ÇOK DEĞİŞKENLİ ANALİZ

○ Tek değişkenli analize göre:

- BMI (8% ↑, 1-kg/m² p<0.0001)
- HT (19% ↑, +/- p=0.007)
- P (11% ↑, 1 mg/dl p=0.01)
- Log FGF-23 (34% ↑, 1-SD artış ile; P=0.001)
- DM(10% ↑,; +/- P=0.03)

○ Çok değişkenli modelde:

- BMI (5.2% ↑, 1-kg/m² p=0.001)
- Log FGF-23 (30% ↑, 1-SD p=0.002)
- D vitamini kullanımı sonuçları etkilememiştir.

MPI: TEK DEĞİŞKENLİ ANALİZ

- KAH 17% ↑ p=0.003,
(Var veya yok)
- P 6% ↑ p=0.01
(1 mg/dl ↑)
- Log FGF-23 38% ↑ p=0.001
(1 SD ↑)

Table 3: The percentage increase (with 95% Confident interval) in mean MPI (myocardial performance index) per 1- SD increase in Log FGF-23 concentration adjusted for serum phosphate levels and presence of coronary artery disease.

Parameter	Model 1	p	Model 2	p	Model 3	p
Log FGF-23	38% (18-43%)	0.001	35%	0.001	28.5%	0.020
Presence of CAD*			15% (8-23)	0.009	14% (8-18)	0.012
Serum P levels §					3% (1.4-7)	0.019

* CAD; Coronary artery disease,

§ P; Phosphate.

FGF-23

The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE

Fibroblast Growth Factor 23 and Mortality among Patients Undergoing Hemodialysis

Orlando M. Gutiérrez, M.D., M.M.Sc., Michael Mannstadt, M.D., Tamara Isakova, M.D., Jose Alejandro Rauh-Hain, M.D., Hector Tamez, M.D., Anand Shah, M.D., Kelsey Smith, B.A., Hang Lee, Ph.D., Ravi Thadhani, M.D., M.P.H., Harald Jüppner, M.D., and Myles Wolf, M.D., M.M.Sc.

Nephrol Dial Transplant (2009) 24: 2792-2796
doi: 10.1093/ndt/gfp191
Advance Access publication 25 April 2009

High levels of serum fibroblast growth factor (FGF)-23 are associated with increased mortality in long haemodialysis patients

Guillaume Jean, Jean-Claude Terrat, Thierry Vanel, Jean-Marc Hurot, Christie Lorriaux, Brice Mayor and Charles Chazot

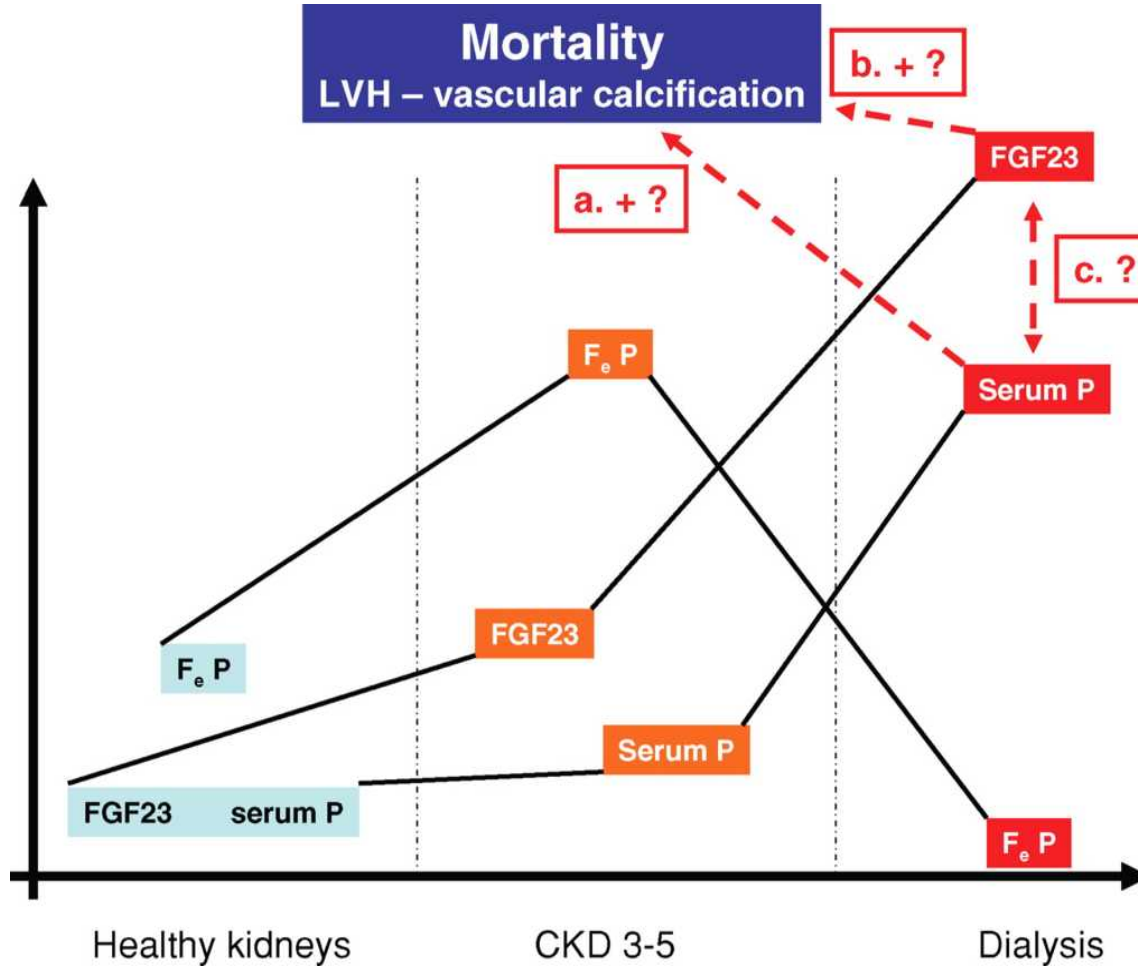
NDT
Nephrology Dialysis Transplantation

Relation between serum fibroblast growth factor-23 level and mortality in incident dialysis patients: are gender and cardiovascular disease confounding the relationship?

Hannes Olauson¹, Abdul Rashid Qureshi¹, Tetsu Miyamoto¹, Peter Barany¹, Olof Heimbürger¹, Bengt Lindholm¹, Peter Stenvinkel¹ and Tobias E. Larsson^{1,2}

DIYALİZDE MORTALİTE

FGF-23, SERUM P DÜZEYİNDEN BAĞIMSIZ OLARAK, FOSFAT YÜKÜNÜN OLUŞTURDUĞU KVS HASARININ BİYOMARKER'İ OLARAK DEĞERLENDİRİLMEKTEDİR



Ketteler, M. et al. Nephrol. Dial. Transplant. 2009 24:2618-2620

Fibroblast Growth Factor 23 and Left Ventricular Hypertrophy in Chronic Kidney Disease

Orlando M. Gutiérrez, James L. Januzzi, Tamara Isakova, Karen Laliberte, Kelsey Smith, Gina Collerone, Ammar Sarwar, Udo Hoffmann, Erin Coglianesse, Robert Christenson, Thomas J. Wang, Christopher deFilippi and Myles Wolf
Circulation 2009;119:2545-2552; originally published online May 4, 2009;

Table 3. Coronary Artery Calcification Scores and Echocardiographic Characteristics by Tertile of FGF-23

	FGF-23 Tertile 1 (<75 RU/mL)	FGF-23 Tertile 2 (75–150 RU/mL)	FGF-23 Tertile 3 (>150 RU/mL)	P for Trend
n	69	71	72	
CAC score	32 (0–270)	121 (0–302)	117 (14–384)	0.2*
CAC \geq 100 U, %	33	53	55	0.04*
LVMI, g/m ^{2.71}	35 \pm 8	40 \pm 12	42 \pm 15	<0.001
LVH, %	7	21	25	0.006

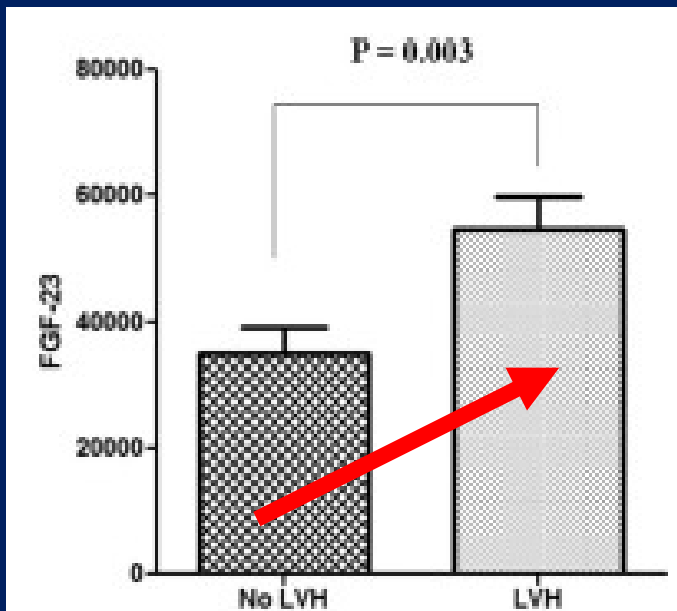
CAC indicates coronary artery calcification. Results are expressed as frequencies, mean \pm SD, or median (interquartile range) as appropriate.

*Test for trend includes only patients with CKD.

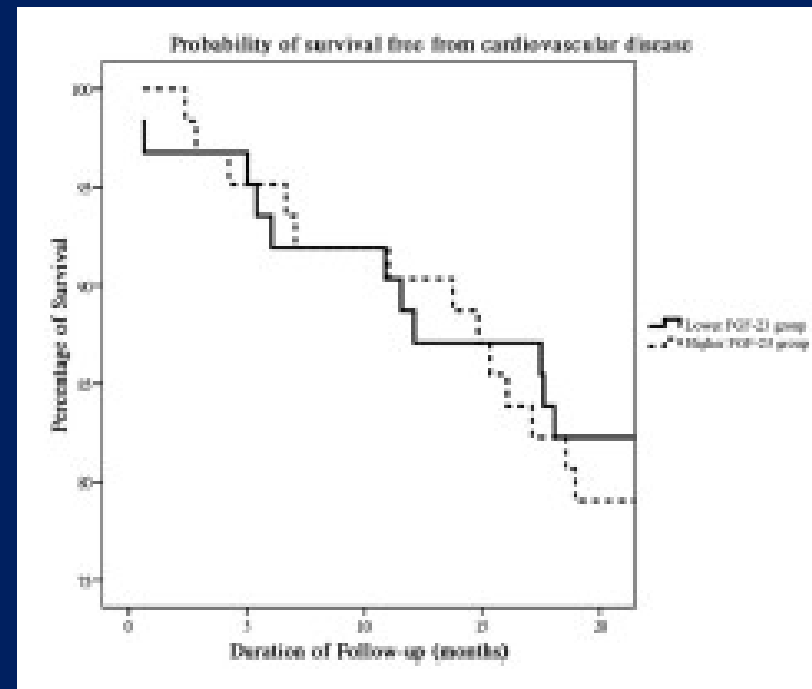
etry as a function of FGF-23 in the CKD patients. Whereas log FGF-23 was not significantly associated with risk of eccentric LVH, log FGF-23 was significantly associated with increased risk of concentric LVH in univariable (OR, 2.4; 95% CI, 1.1 to 5.1) and multivariable-adjusted (OR 3.4; 95% CI, 1.2 to 9.9) analyses.

Fibroblast Growth Factor 23: A Possible Cause of Left Ventricular Hypertrophy in Hemodialysis Patients

Heng Jung Hsu, MD and Mai-Szu Wu, MD



Left ventricle status
FIGURE 1. Serum fibroblast growth factor 23 (FGF23) level in hemodialysis patients with LVH ($54,615 \pm 38,318$ RU/mL) and without LVH ($33,070 \pm 33,763$ RU/mL). The difference was significant ($P = 0.003$).

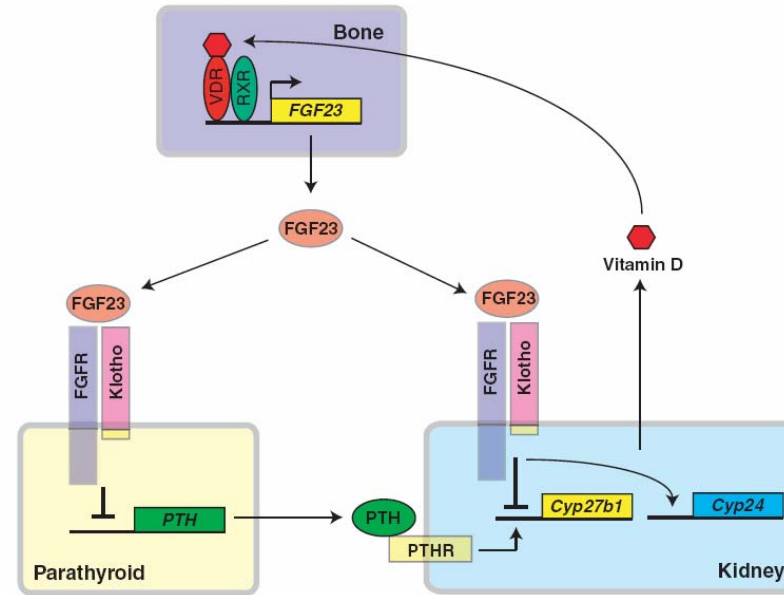


[Am J Med Sci 2009;337(2):116-122.]

FGF-23 VE ÇALIŞMA BULGULARIMIZ: NEDEN? NASIL?

○ FGF-23
kardiyovasküler
sistemi direkt olarak
etkileyebilir:

- Ancak Klotho ne kardiyak miyositlerde ne de koroner damarlarda eksprese edilmiyor.
- Dolayısıyla, FGF-23 endokrin bir paternde kardiyovasküler dokuları hedefleyemez.



Nephrol Dial Transplant (2009) 24: 1705–1708
doi: 10.1093/ndt/gfp069
Advance Access publication 18 February 2009

Editorial Comments

Klotho in chronic kidney disease—What's new?

Makoto Kuro-o

NDT
Nephrology Dialysis Transplantation

YA DA..

- Suprafizyolojik düzeyde FGF-23,
 - Spesifik olmadan,
 - Klotho'dan bağımsız bir şekilde,
 - FGF reseptörünü uyarabilir.

ÇÜNKÜ

FGF reseptörleri olan, FGFR1 ve FGFR4, bariz biçimde kardiyak miyositlerde, koroner arter ile venlerin tunica media kısmında eksprese edilmektedirler.

Volume 45(7): 1005-1010, 1997
The Journal of Histochemistry & Cytochemistry

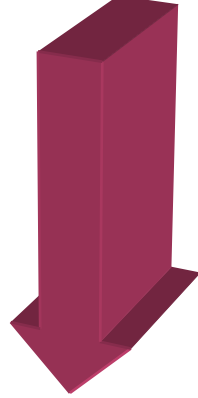
ARTICLE

Differential Expression of the Fibroblast Growth Factor Receptor (FGFR) Multigene Family in Normal Human Adult Tissues

Sian E. Hughes

Division of Histopathology, United Medical and Dental Schools, St Thomas's Campus, London, United Kingdom

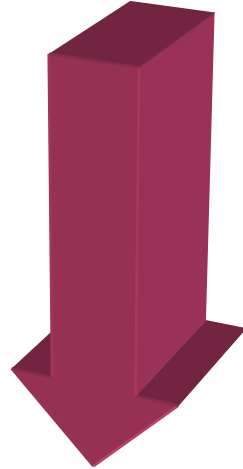
FGF RESEPTÖR AKTİVASYONU



Int J Artif Organs 2000;23:817-823
Biochem Cell Biol 1997;75:669-85
Cardiovasc Res 2003;57:8-19

FGF-2

MYOFİBROBLAST VE FİBROBLAST PROLİFERASYONU



J Clin Invest 1990;85:507-14
Circ Res 1997;81:679-87
J Clin Invest 1999;104:709-19

FGF-2

**Fibroblast growth factor-2 mediates
pressure-induced hypertrophic response**

MİYOKARDİYAL HİPERTROFİ VE FİBROSİS

FGF-23 İÇİN KANITLANMALI

!!!!



PRO...

Table 1. Circulating FGF-23 is associated with left ventricular hypertrophy (LVH) in a large, community-based cohort (PIVUS study)

	Left ventricular hypertrophy (LVH)		
	Model A	Model B	Model C
<i>Whole PIVUS cohort (n=795)</i>			
Continuous models			
1-SD increase	1.28** (1.09–1.51)	1.28* (1.05–1.55)	1.30** (1.09–1.54)
Multi-category models			
Tertile 1	Referent	Referent	Referent
Tertile 2	1.14 (0.76–1.72)	1.00 (0.62–1.63)	1.13 (0.74–1.71)
Tertile 3	1.71** (1.15–2.54)	1.63* (1.03–2.58)	1.70* (1.13–2.56)
<i>Subjects with eGFR <60 mL/min/1.73 m² (n=164)</i>			
Continuous models			
1-SD increase	1.86*** (1.30–2.67)	2.10*** (1.38–3.22)	1.78** (1.22–2.61)
Multi-category models			
Tertile 1	Referent	Referent	Referent
Tertile 2	1.05 (0.38–2.92)	0.84 (0.26–2.73)	1.09 (0.37–3.18)
Tertile 3	4.15** (1.74–9.92)	4.61** (1.61–13.17)	3.64** (1.42–9.34)

Associations are shown for all subjects ($n = 795$) and for individuals with $eGFR < 60$ ml/min/1.73 m² ($n = 164$). Values shown are odds ratios (95% confidence interval). (A) Crude model; (B) adjusted for gender, systolic blood pressure, diastolic blood pressure, BMI, diabetes and hypertension; (C) adjusted for gender, serum phosphate, calcium, 25(OH)D₃, PTH and eGFR. FGF-23 concentrations according to tertiles were <36 pg/mL, 36–48 pg/mL and >48 pg/mL, respectively. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; reproduced with permission from [59].

Mirza MA, Larsson A, Melhus H *et al.* Serum intact FGF23 associate with left ventricular mass, hypertrophy and geometry in an elderly population. *Atherosclerosis* 2009 Dec; 207: 546–551

CON.....

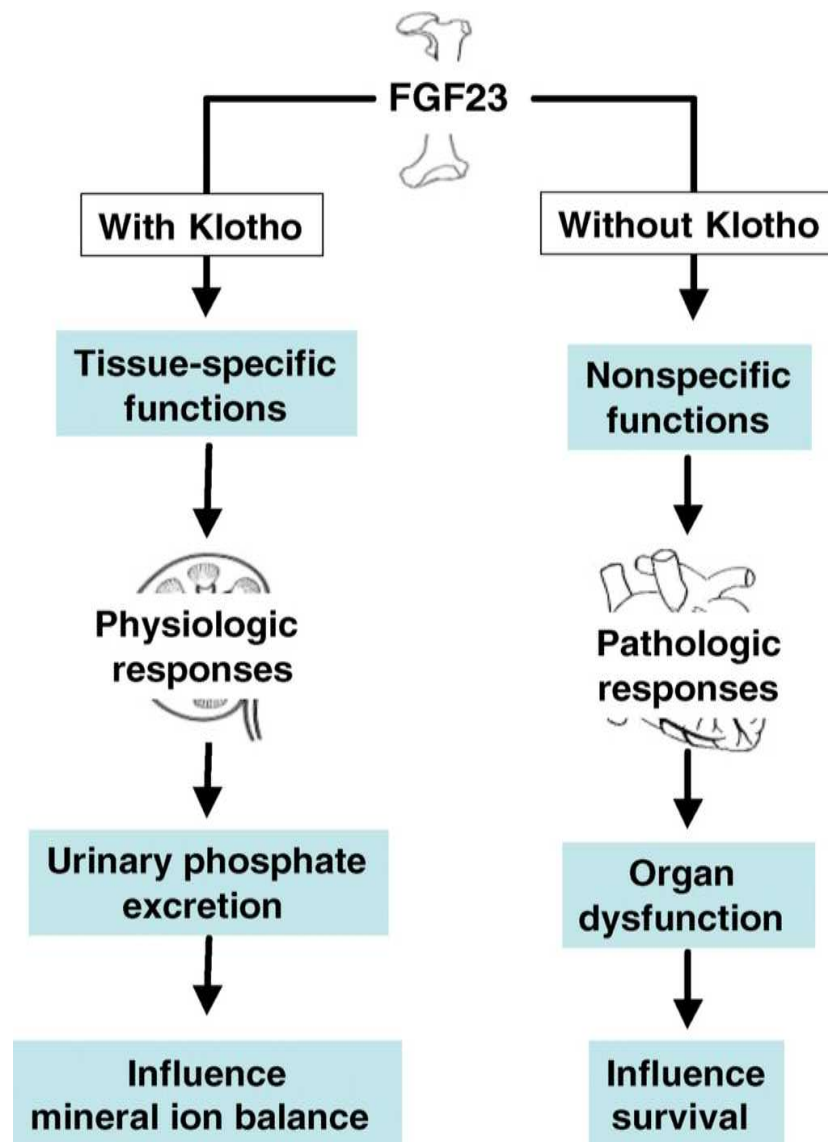
- Klotho-null mice: Belirgin derecede yüksek FGF-23 değerlerine rağmen artan serum fosfat ve 1,25(OH)2D3 düzeylerini indiremiyorlar..

Nature 2006; 444:770-774;18.

YANI BU MODEL EN AZINDAN BÖBREKTE İŞLEMİYOR.

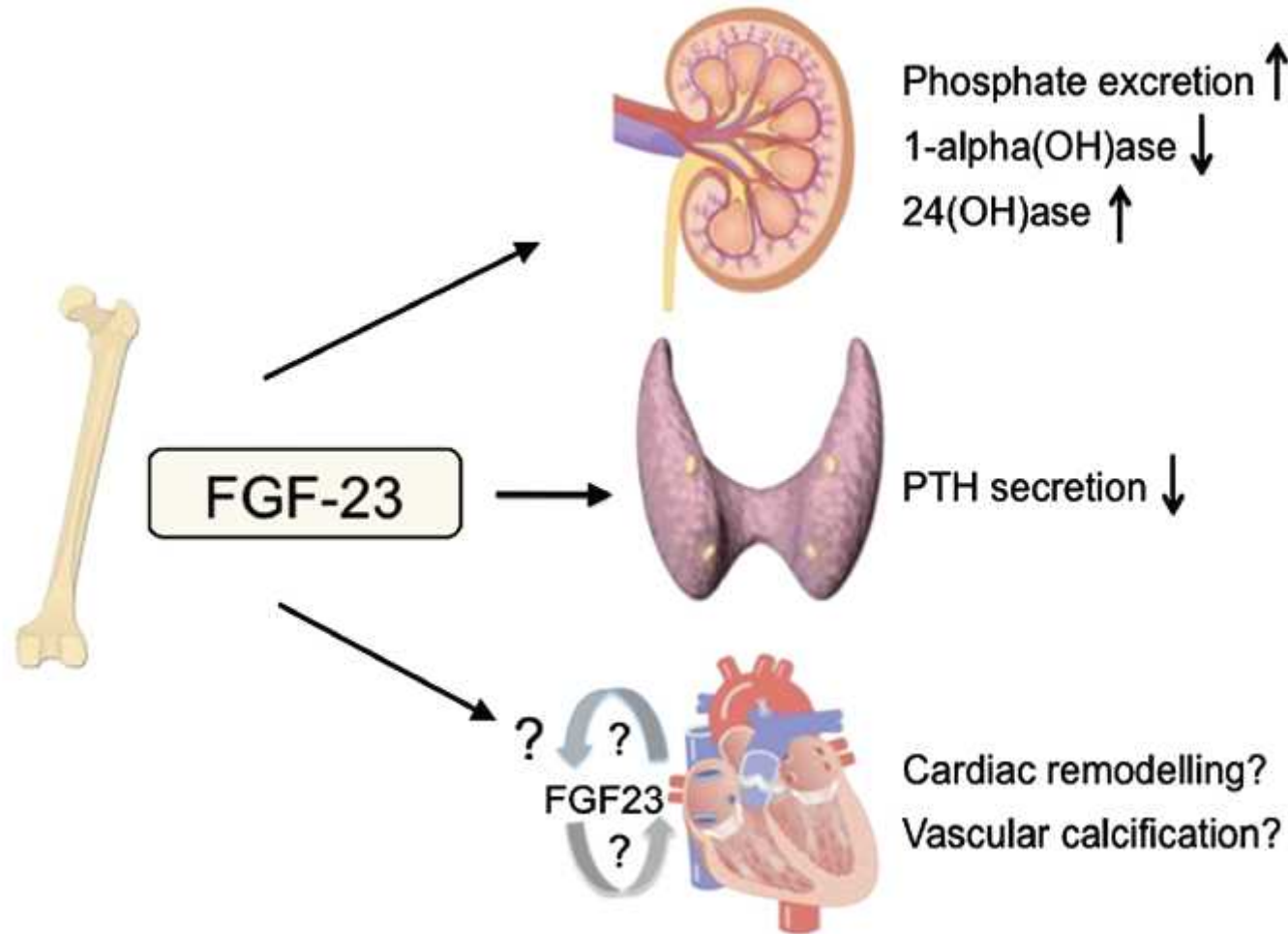
- X-e bağlı hipofosfatemik rickets ve tümörle indüklenen osteomalazi hastalarında dolaşımda yüksek oranda FGF-23 bulunduğu ve KBH olmadıkları halde, **KVH riski artmamaktadır.**

Larsson TB. Nephrol Dial Transplant 2010; 25: 1376-1381.



**Razzaque, M. S. Nephrol. Dial. Transplant. 2009
24:4-7**

Nephrol Dial Transplant (2010): Editorial Review



CONCLUSION: FRIEND OR FOE?

FGF-23

