DİYALİZ HASTALARINDA HİPOKALSEMİ VE HİPERFOSFATEMİNİN DÜZELTİLMESİ

Doç. Dr. Aydın ÜNAL

Erciyes Üniversitesi Tıp Fakültesi

Nefroloji Bilim Dalı

SUNUM PLANI

- SHP patogenezi
- Hedef Ca, P, PTH düzeyleri
- Diyette fosfor kısıtlaması
- Fosfor bağlayıcılar
- Hipokalsemi tedavisi
- 2013 KDIGO önerileri

KRONİK BÖBREK HASTALIĞI-MİNERAL VE KEMİK HASTALIĞI

RENAL OSTEODİSTROFİ TİPLERİ

- Osteitis fibrosa
- Adinamik kemik hastalığı
- Osteomalazi
- Karışık renal osteodistrofi

OSTEİTİS FİBROSA

- **Sekonder hiperparatirodizm (SHP)** nedeniyle gelişen yüksek döngülü bir kemik hastalığı
- Osteoklastik ve osteoblastik aktivite ↑
- Kronik böbrek hastalığının erken safhalarında başlar (GFR < 60 mL/dk)

OSTEİTİS FİBROSA

Sekonder Hiperparatiroidi Patogenezi

Fosfat retansiyonu

Hipokalsemi

Vitamin D3 metabolizmasında bozukluklar

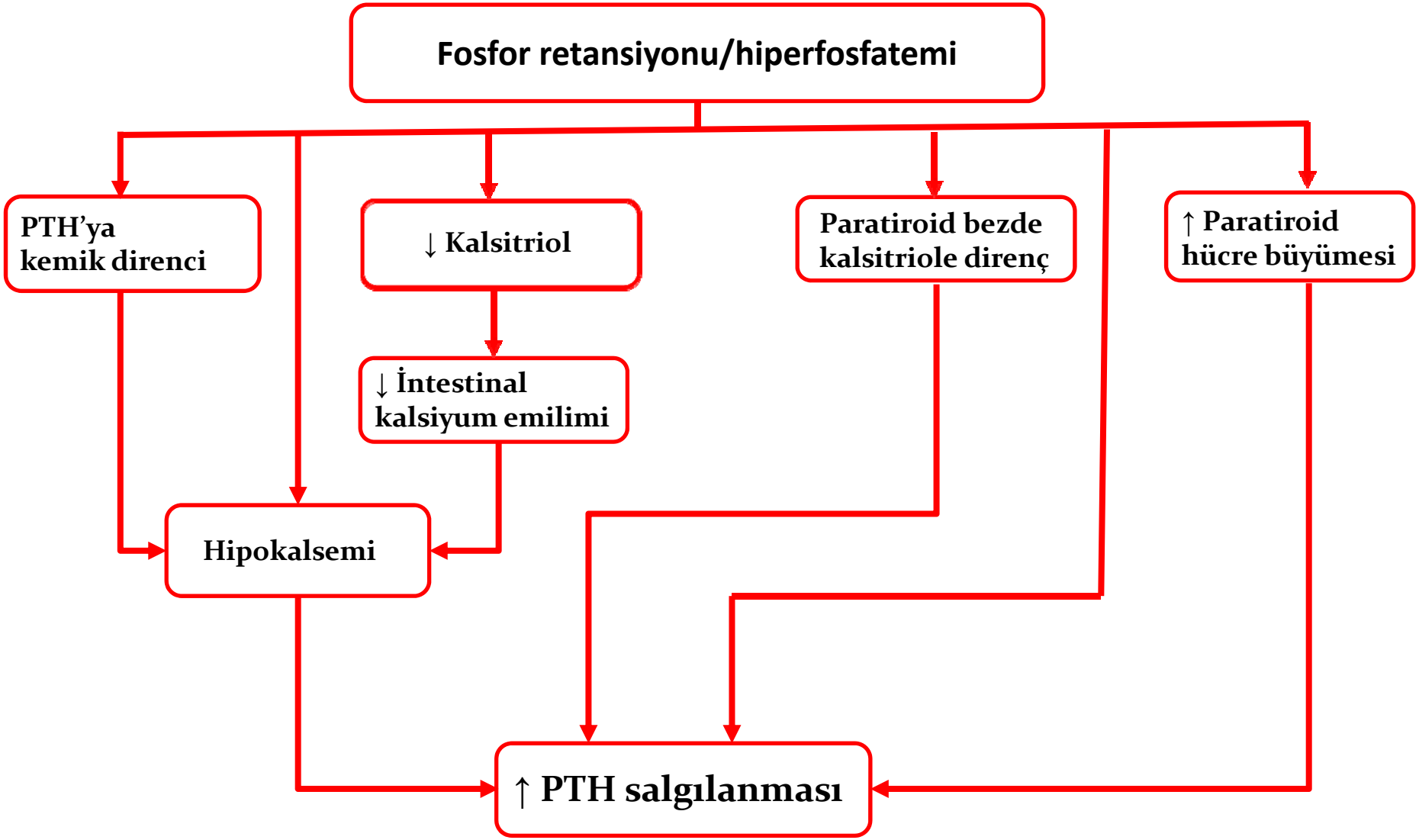
FOSFOR RETANSİYONU

- KBH'nın erken dönemlerinde başlar
- GFR azalması nedeniyle **filtre edilen fosfor yükünde azalma** nedeniyledir
- Fosfor retansiyonu sonucu;

  1. PTH↑
  2. Fibroblast büyüme faktörü (FGF)-23↑
- ↑PTH ve ↑FGF-23 ⇨ Fosfatüride artış ⇨

  Serum fosfor düzeyi normal aralıkta sürdürülür (~GFR 20 mL/dk)

FOSFOR RETANSİYONU


Fosfor retansiyonu/hiperfosfatemi
PTH'ya kemik direnci
↓ Kalsitriol
Paratiroid bezde kalsitriole direnç
↑ Paratiroid hücre büyümesi
↓ İntestinal kalsiyum emilimi
Hipokalsemi
↑ PTH salgılanması

FİBROBLAST BÜYÜME FAKTÖRÜ 23 (FGF-23)

- Kemikte osteosit ve osteoblastlar tarafından üretilen bir hormon (fosfatinin)
- GFR'deki azalmaya parelel olarak dolaşımdaki düzeyleri yükselmeye devam eder
- FGF reseptörüne bağlanarak etki gösterir
- Kofaktörü Klotho
- NPT2a'yı inhibe ederek idrarla fosfor atılımını ↑
- 1 alfa hidroksilaz inhibisyonu

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.

N ENGL J MED 359;6 WWW.NEJM.ORG AUGUST 7, 2008

- HD’ye yeni başlayan 10044 hastada yapılan prospektif bir çalışma
- Hastaların bazal FGF23 düzeyleri ölçülmüş ve 1 yıllık takibe alınmış
- 200 hasta ölmüş ve bu hastaların kontrol grubu olarak yaşayan 200 hasta alınmış
- Bazal FGF23 değerlerine göre hastalar 4 çeyreğe bölünmüş
- Kontrol grubu alınırken bazal fosfor değerleri de dikkate alınmış

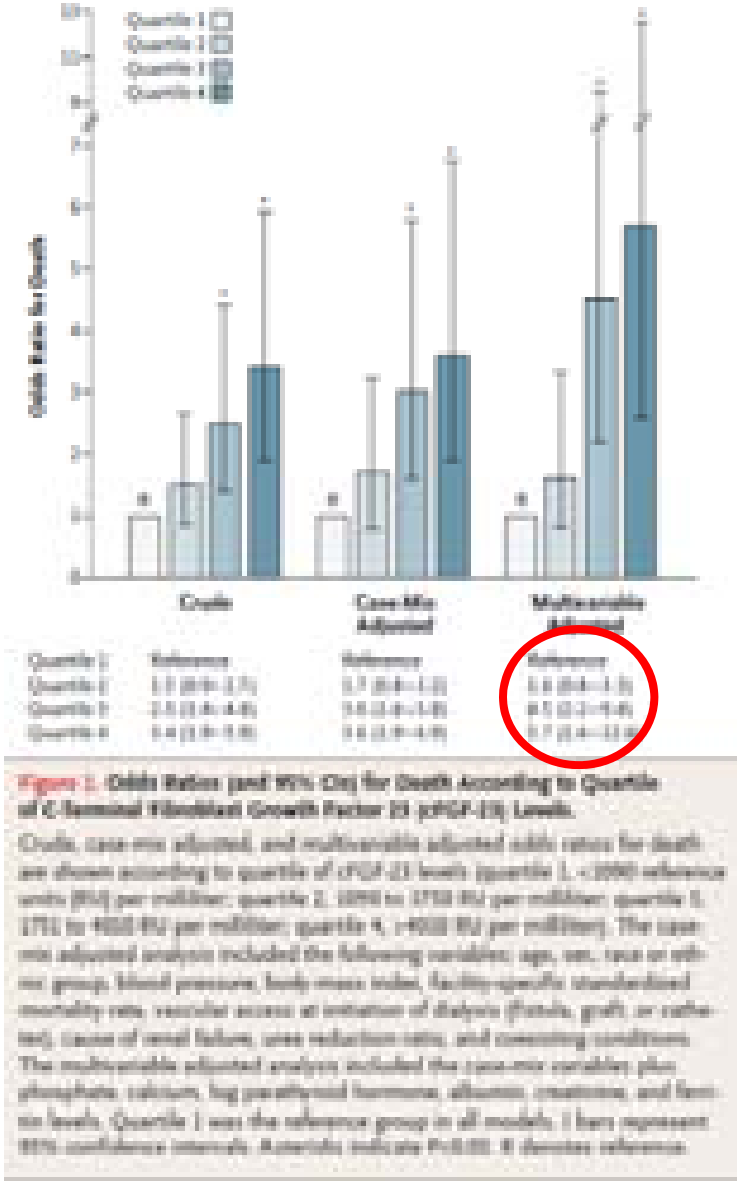


Figure 2. Odds Ratios (and 95% CIs) for Death According to Quartile of C-Terminal Fibroblast Growth Factor 23 (cFGF-23) Levels.

Crude, case-mix adjusted, and multivariable adjusted odds ratios for death are shown according to quartile of cFGF-23 levels (quartile 1, <2090 reference units [RU] per milliliter; quartile 2, 2090 to 3750 RU per milliliter; quartile 3, 3751 to 9000 RU per milliliter; quartile 4, >9000 RU per milliliter). The case-mix adjusted analysis included the following variables: age, sex, race or ethnic group, blood pressure, body mass index, facility-specific standardized mortality rate, vascular access at initiation of dialysis (fistula, graft, or catheter), cause of renal failure, urea reduction ratio, and coexisting conditions. The multivariable adjusted analysis included the case-mix variables plus phosphate, calcium, log parathyroid hormone, albumin, creatinine, and ferritin levels. Quartile 1 was the reference group in all models. I bars represent 95% confidence intervals. Asterisks indicate P<0.05. R denotes reference.

- Median FGF-23 değerleri ölen hastalarda anlamlı olarak daha yüksek
- Logaritması alınmış FGF-23 değerlerinde her bir ünite artış mortalite riskinde %18 artış ile ilişkili
- Bazal fosfor değerlerine göre hastalar çeyrek dilimlere ayrılmış ve P >5.5 mg/dL olan grupta mortalite riski, 3.5-4.5 mg/dL olan (referans) gruba kıyasla %20 daha yüksek

Fibroblast Growth Factor 23 and Risks of Mortality and End-Stage Renal Disease in Patients With Chronic Kidney Disease

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Huilong Xie, PhD
Wei Yang, PhD
Dawei Xie, PhD
Amanda Hyre Anderson, PhD, MPH
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Jiang He, MD, PhD
Stanley Schwartz, MD
Joan Lo, MD
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James Sondheimer, MD
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James Lash, MD
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John W. Kusek, PhD
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Myles Wolf, MD, MMSc
for the Chronic Renal Insufficiency Cohort (CRIC) Study Group

Context A high level of the phosphate-regulating hormone fibroblast growth factor 23 (FGF-23) is associated with mortality in patients with end-stage renal disease, but little is known about its relationship with adverse outcomes in the much larger population of patients with earlier stages of chronic kidney disease.

Objective To evaluate FGF-23 as a risk factor for adverse outcomes in patients with chronic kidney disease.

Design, Setting, and Participants A prospective study of 3879 participants with chronic kidney disease stages 2 through 4 who enrolled in the Chronic Renal Insufficiency Cohort between June 2003 and September 2008.

Main Outcome Measures All-cause mortality and end-stage renal disease.

Results At study enrollment, the mean (SD) estimated glomerular filtration rate (GFR) was 42.8 (13.5) mL/min/1.73 m^2, and the median FGF-23 level was 145.5 RU/mL (interquartile range [IQR], 96-239 reference unit [RU]/mL). During a median follow-up of 3.5 years (IQR, 2.5-4.4 years), 266 participants died (20.3/1000 person-years) and 410 reached end-stage renal disease (33.0/1000 person-years). In adjusted analyses, higher levels of FGF-23 were independently associated with a greater risk of death (hazard ratio [HR], per SD of natural log-transformed FGF-23, 1.5; 95% confidence interval [CI], 1.3-1.7). Mortality risk increased by quartile of FGF-23: the HR was 1.3 (95% CI, 0.8-2.2) for the second quartile, 2.0 (95% CI, 1.2-3.3) for the third quartile, and 3.0 (95% CI, 1.8-5.1) for the fourth quartile. Elevated fibroblast growth factor 23 was independently associated with significantly higher risk of end-stage renal disease among participants with an estimated GFR between 30 and 44 mL/min/1.73 m^2 (HR, 1.3 per SD of FGF-23 natural log-transformed FGF-23; 95% CI, 1.04-1.6) and 45 mL/min/1.73 m^2 or higher (HR, 1.7; 95% CI, 1.1-2.4), but not less than 30 mL/min/1.73 m^2.

Conclusion Elevated FGF-23 is an independent risk factor for end-stage renal disease in patients with relatively preserved kidney function and for mortality across the spectrum of chronic kidney disease.

JAMA, 2011;305(23):2432-2439 www.jama.com

HİPOKALSEMİ

- Nedenleri

  * Kalsitriol ↓

  * Fosfor retansiyonu

  * Kemikte PTH'nın kalsemik etkilerine direnç

- PTH sekresyonunun en önemli uyaranıdır

1,25 (OH)2 VİTAMİN D AZLIĞI

√ Böbrek parankim kaybı (1 α hidroksilaz ↓)

√ Hiperfosfatemi

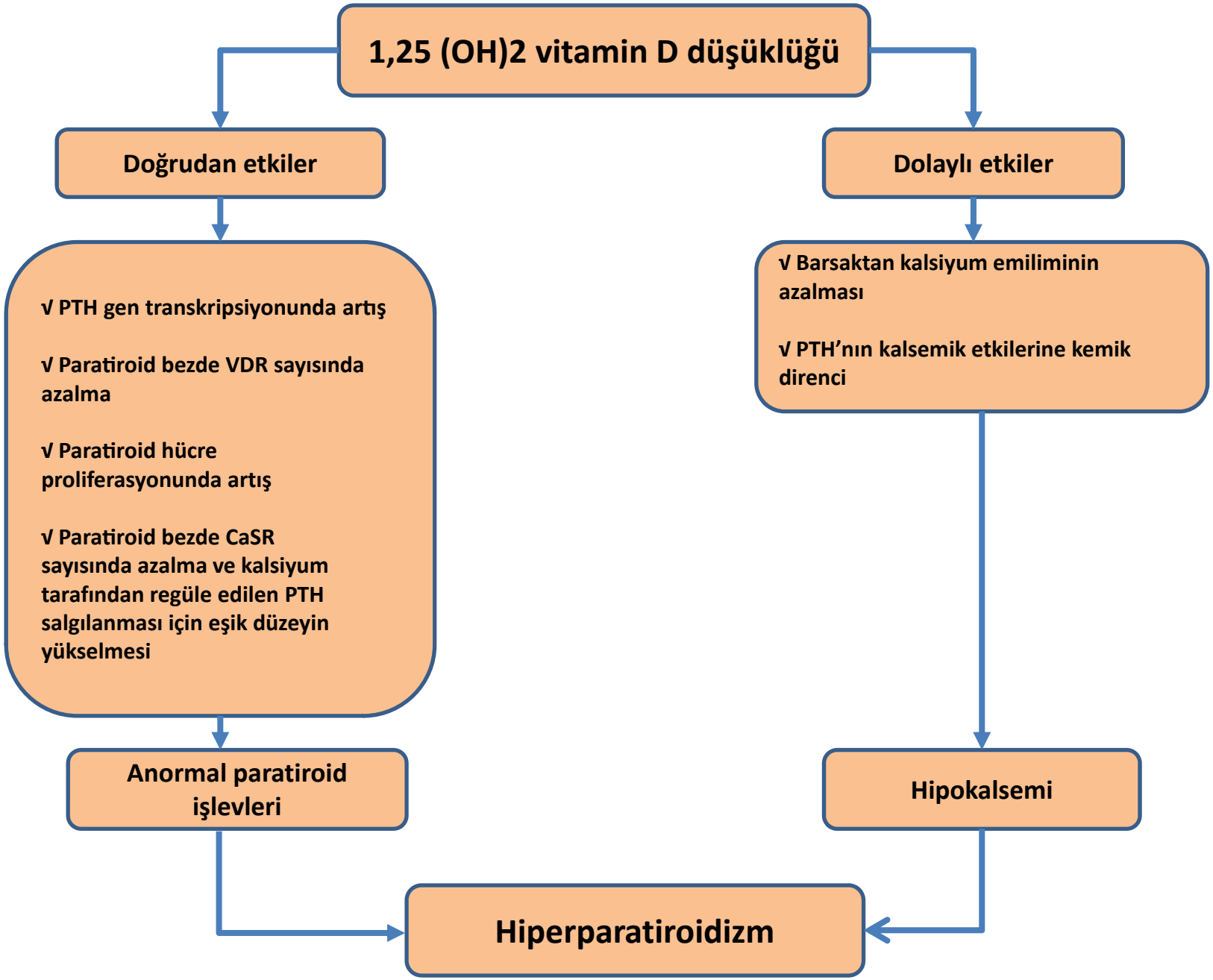
√ FGF-23 artışı

√ 25 OH vit D düşüklüğü

√ Artmış C-PTH fragmanları

√ Üremik toksinler…

1,25 (OH)2 vit D yapımı progresif bir şekilde↓


1,25 (OH)2 vitamin D düşüklüğü
Doğrudan etkiler
Dolaylı etkiler
√ PTH gen transkripsiyonunda artış
√ Paratiroid bezde VDR sayısında azalma
√ Paratiroid hücre proliferasyonunda artış
√ Paratiroid bezde CaSR sayısında azalma ve kalsiyum tarafından regüle edilen PTH salgılanması için eşik düzeyin yükselmesi
√ Barsaktan kalsiyum emiliminin azalması
√ PTH'nın kalsemik etkilerine kemik direnci
Anormal paratiroid işlevleri
Hipokalsemi
Hiperparatiroidizm

DİYALİZ HASTALARINDA HEDEF DEĞERLER

	Kalsiyum (mg/dL)	Fosfor (mg/dL)	Ca x P (mg2/dL2)	iPTH (pg/mL)
K/DOQI 2003	8.4-9.5	3.5-5.5	< 55	150-300
KDIGO 2009	Normal aralık	Normal aralık	-	Üst sınırın 2-9 katı
NICE 2013		3.4-5.3		

Kılavuzlarda tedavi hedefleri gözlemsel çalışmalara dayanıyor

Aslında klinik sonlanım noktaları açısından net hedef değerleri mevcut değil

Serum Levels of Phosphorus, Parathyroid Hormone, and Calcium and Risks of Death and Cardiovascular Disease in Individuals With Chronic Kidney Disease

A Systematic Review and Meta-analysis

Suvasini C. Palmer, MB ChB, PhD
Andrew Hayen, PhD
Petra Macaskill, PhD
Fabio Pellegrini, MSc
Jonathan C. Craig, MB ChB, PhD
Graham J. Elder, MB BS, PhD
Giovanni F. M. Strippoli, MD, PhD

CLINICAL PRACTICE GUIDELINES are a powerful influence on management strategies for common conditions. When evidence that treating risk factors reduces disease and improves health outcomes is provided by large and well-conducted randomized controlled trials, guidelines can appropriately summarize the relevant data and widely disseminate recommendations for best practice. However, when practice guidelines promote therapeutic strategies without sufficient evidence of effectiveness or harms, overtreatment and widespread inappropriate use of medications, services, or devices may occur. Accordingly, guidelines may recommend health interventions that do not actually improve population outcomes or the quality of care, resources

Context Clinical practice guidelines on the management of mineral and bone disorders due to chronic kidney disease recommend specific treatment target levels for serum phosphorus, parathyroid hormone, and calcium.

Objective To assess the quality of evidence for the association between levels of serum phosphorus, parathyroid hormone, and calcium and risks of death, cardiovascular mortality, and nonfatal cardiovascular events in individuals with chronic kidney disease.

Data Sources The databases of MEDLINE (1948 to December 2010) and EMBASE (1947 to December 2010) were searched without language restriction. Hand searches also were conducted of the reference lists of primary studies, review articles, and clinical guidelines along with full-text review of any citation that appeared relevant.

Study Selection Of 8380 citations identified in the original search, 47 cohort studies (N = 327 644 patients) met the inclusion criteria.

Data Extraction The characteristics of study design, participants, exposures, and covariates together with the outcomes of all-cause mortality, cardiovascular mortality, and nonfatal cardiovascular events at different levels of serum phosphorus, parathyroid hormone, and calcium were analyzed within studies. Data were summarized across studies (when possible) using random-effects meta-regression.

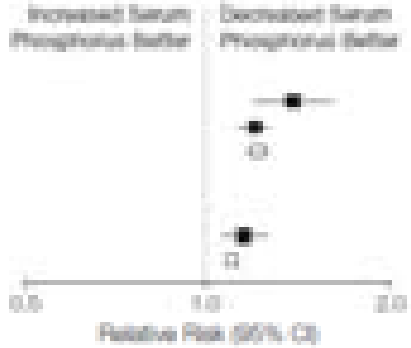
Data Synthesis The risk of death increased 18% for every 1-mg/dL increase in serum phosphorus (relative risk [RR], 1.18 [95% confidence interval (CI), 1.12-1.25]). There was no significant association between all-cause mortality and serum level of parathyroid hormone (RR per 100-pg/mL increase, 1.01 [95% CI, 1.00-1.02]) or serum level of calcium (RR per 1-mg/dL increase, 1.08 [95% CI, 1.00-1.16]). Data for the association between serum level of phosphorus, parathyroid hormone, and calcium and cardiovascular death were each available in only 1 adequately adjusted cohort study. Lack of adjustment for confounding variables was not a major limitation of the available studies.

Conclusions The evidentiary basis for a strong, consistent, and independent association between serum levels of calcium and parathyroid hormone and the risk of death and cardiovascular events in chronic kidney disease is poor. There appears to be an association between higher serum levels of phosphorus and mortality in this population.

JAMA. 2011;306(11):1119-1127

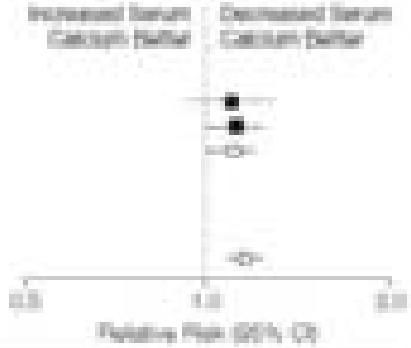
- Referans değer P için 3.5mg/dL, Ca için 8.4 mg/dL, PTH için 200 pg/mL olarak alınmış
- Ca ve P düzeyindeki her 1 mg/dL'lik artış için RR hesaplanmış
- PTH düzeyindeki her 100 pg/mL'lik artış için RR hesaplanmış

Phosphorus	No. of Cohorts	No. of Participants	Relative Risk (95% CI) Per Unit Increase
All-cause mortality			
Adequate adjustment	3	4071	1.30 (1.16-1.[illegible])
Partial adjustment	10	87 694	1.16 (1.09-1.23)
All studies combined	13	92 345	1.18 (1.12-1.25)
Cardiovascular mortality			
Adequate adjustment	1	17 326	Not estimable
Partial adjustment	2	5981	1.14 (1.05-1.24)
All studies combined	3	23 307	1.10 (1.06-1.13)



Parathyroid hormone	No. of Cohorts	No. of Participants	Relative Risk (95% CI)
All-cause mortality			
Adequate adjustment	1	17 326	Not estimable
Partial adjustment	3	83 732	1.21 (0.99-1.[illegible])
All studies combined	4	101 058	1.10 (1.00-1.[illegible])
Cardiovascular mortality			
Adequate adjustment	1	17 326	Not estimable
Partial adjustment	1	5981	Not estimable
All studies combined	2	22 307	1.05 (0.99-1.[illegible])

Calcium	No. of Cohorts	No. of Participants	Relative Risk (95% CI)
All-cause mortality			
Adequate adjustment	2	22 307	1.07 (0.91-1.26)
Partial adjustment	6	83 799	1.09 (0.99-1.21)
All studies combined	8	106 106	1.08 (1.00-1.[illegible])
Cardiovascular mortality			
Adequate adjustment	1	17 326	Not estimable
Partial adjustment	1	5981	Not estimable
All studies combined	2	22 307	1.15 (1.06-1.25)



Risks of all-cause mortality, cardiovascular mortality, and nonfatal cardiovascular events are shown per 1-mg/dL increase in serum levels of phosphorus, 100-pg/mL increase in serum parathyroid hormone, and 1-mg/dL increase in serum calcium. Summary estimates are not reported when only a single cohort contributed data. CI indicates confidence interval.

Association of Serum Phosphate with Vascular and Valvular Calcification in Moderate CKD

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ABSTRACT

Within the normal range, higher serum phosphate concentrations are associated with cardiovascular events and mortality in individuals with chronic kidney disease (CKD) and in those with normal kidney function. Experimental models suggest that phosphate has a direct calcifying effect on vascular smooth muscle. We examined associations of serum phosphate concentrations with vascular and valvular calcification in 439 participants from the Multi-Ethnic Study of Atherosclerosis who had moderate CKD and no clinical cardiovascular disease. Serum phosphate concentrations were within the normal range (2.5 to 4.5 mg/dl) in 95% of study participants. The prevalence of calcification in the coronary arteries, descending thoracic aorta, aortic valve, and mitral valve was 67, 49, 25, and 20%, respectively, measured by electron-beam or multi-detector row computed tomography. After adjustment for demographics and estimated GFR, each 1-mg/dl increment in serum phosphate concentration was associated with a 21% ($P = 0.002$), 33% ($P = 0.001$), 25% ($P = 0.16$), and 62% ($P = 0.007$) greater prevalence of coronary artery, thoracic, aortic valve, and mitral valve calcification, respectively. Adjustment for traditional risk factors for atherosclerosis, parathyroid hormone, or 1,25-dihydroxyvitamin D levels did not alter these associations. In conclusion, higher serum phosphate concentrations, although still within the normal range, are associated with a greater prevalence of vascular and valvular calcification in people with moderate CKD. It remains to be determined whether lowering phosphate concentrations will impact calcification risk in the setting of kidney disease.

J Am Soc Nephrol 20: 381–387, 2009. doi: 10.1681/ASN.2008040349

- Multi-Ethnic Study of Atherosclerosis (MESA) çalışmasından eGFR < 60 olan 439 hasta
- %95'nin P düzeyi normal (2.5-4.5 mg/dL)
- Serum fosforunda her 1 mg/dL'lik artış

  * Koroner arter kalsifikasyonunda %21

  * Torasik aorta kalsifikasyonunda %33

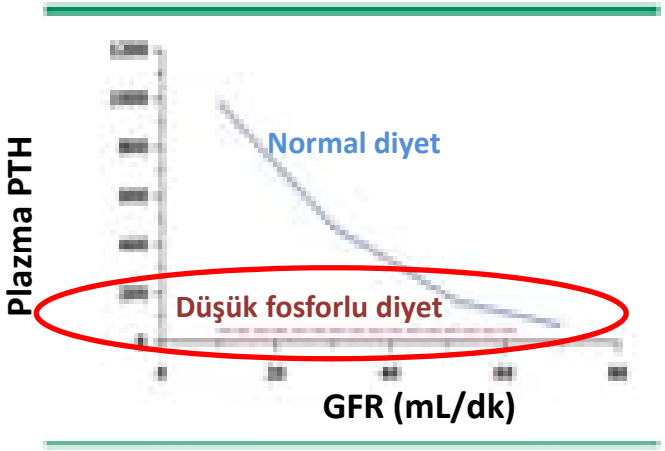
  * Aort kapağı kalsifikasyonunda %25

  * Mitral kapak kalsifikasyonunda %62 artış ile ilişkili
- PTH ve 1.25 (OH)2 D vit düzeyleri ise VC gelişimini etkilemiyor

HİPERFOSFATEMİ TEDAVİSİ

- Diyette fosfor alımının kısıtlanması
- Bağırsaklardan fosfor emiliminin azaltılması
- Diyaliz dozunun artırılması
- Paratirodektomi

DİYETTE FOSFOR KISITLAMASI



Slatopolsky E, Çağlar Ş, Pennell JP, et al.
J Clin Invest 1971;50:492-9

Nephrol Dial Transplant (2013) 28: 161–169
doi: 10.1093/ndt/gfs405
Advance Access publication 28 September 2012

Responsiveness of FGF-23 and mineral metabolism to altered dietary phosphate intake in chronic kidney disease (CKD): results of a randomized trial

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Abstract

Background. High fibroblast growth factor-23 (FGF-23) levels are associated with adverse outcomes. We studied the responsiveness of FGF-23 and mineral metabolism to altered dietary phosphate intake in chronic kidney disease (CKD) and healthy control patients.

Methods. Thirty patients were enrolled: 18 normophosphatemic CKD subjects and 12 healthy controls. The study duration was 21 days with three 7-day dietary interventions; a high phosphate (HP, 2000 mg/day), low phosphate (750 mg/day) and low phosphate plus phosphate binder (aluminum hydroxide, 500 mg thrice daily with meals), with comparable macronutrient content, administered in random sequence. Baseline and weekly fasting morning measurements of FGF-23, serum phosphate (sPO_4), 1,25-hydroxyvitamin D (1,25 D) and 24-h urinary calcium (uCa) and phosphate (uPO_4) were collected.

Results. FGF-23 levels were higher in subjects versus controls (72 pg/mL versus 30 pg/mL) at baseline, while sPO_4 remained in the normal range throughout the study. The absolute changes of uPO_4 and uCa for CKD and controls vary according to diet. The absolute changes of FGF-23 and sPO_4 suggest that the effect of the diets might also depend on the CKD status (P-values interaction effect = 0.08 and 0.07, respectively); nonetheless, these changes are evident as a function of dietary interventions, irrespective of CKD status (P-values diet effect = 0.006 and <0.001, respectively).

Conclusions. FGF-23 levels appear to be responsive to changes in diet in both CKD patients and controls.

DİYETTE FOSFOR KISITLAMASI

- Hiperfosfatemi tedavisinde ilk yapılması gereken yaklaşımdır
- Günlük 800-1000 mg fosfor alımı
- P alımını kısıtlamak ≈ Protein alımını kısıtlamak
- Diyaliz hastasında protein alımını kısıtlamak ≈ malnütrisyon ≈ mortalite ↑
- Protein kısıtlamasından ziyade protein alımının artırılması

DİYETTE FOSFOR KISITLAMASI

- Diyette gereksiz fosfor alımından kaçınılmalı
  * Süt ve süt ürünleri
  * Kuru baklagiller (fasulye, nohut, mercimek, bezelye…)
  * Kuru yemişler (fındık, fıstık…)
  * İşlenmiş gıdalar/çikolata
  * Kola…
- Yüksek biyolojik değeri olan protein kaynaklarının alımı artırılmalı
  * Et ve et ürünleri
  * Yumurta

DİYALİZ HASTALARINDA FOSFOR DENGESİ

Diyetle P alımı
1000 mg/gün
7000 mg/hafta

Emilim
%60

Uzaklaştırılması gereken fosfor
4200 mg/hafta

HD ile uzaklaştırma
3 x 700-800 mg
2100-2400 mg/hafta

PD ile uzaklaştırma
7 x 300-325 mg
2100-2275 mg/hafta

Fosfor bağlayıcı ajanların
~ fosfor bağlama kapasiteleri
CC → 1 g = 40 mg
CA → 1 g = 45 mg
Sevelamer → 1 g = 36 mg
Al → 1 g = 25 mg
Lantanyum → 1 g = 93 mg

Fosfor dengesi
+ ~ 1800-1900 mg/hafta

Nötral fosfor dengesi için
fosfor bağlayıcılar zorunlu
1800-1900/7 = 250-275 mg/gün

FOSFOR BAĞLAYICILAR

1. Alüminyum tuzları
2. Kalsiyum tuzları
3. Kalsiyum veya alüminyum içermeyen fosfor bağlayıcılar

FOSFOR BAĞLAYICILAR-Al Tuzları

- Alüminyum hidroksit/sukralfat (sülfatlı sükroz-alüminyum hidroksit)
- Adinamik kemik hastalığı/osteomalazi/ demans/ hipokrom mikrositer anemi
- Ciddi hiperfosfatemisi olan hastalarda bir defa mahsus çok kısa süreli (~3-4 hafta) verilebilir
- <u>Bu hastaların çoğu paratirodektomi adayıdırlar</u>

FOSFOR BAĞLAYICILAR-Ca Tuzları

- Kalsiyum karbonat/kalsiyum asetat
- Kalsiyumun yaklaşık %20-30'u bağırsaklardan emilir ve hiperkalsemiye neden olabilir
- D vitamini sterollerinin kullanımı riski ↑↑
- Diyalizat kalsiyumun içeriğinin azaltılması ile bu risk ↓

FOSFOR BAĞLAYICILAR-Ca Tuzları

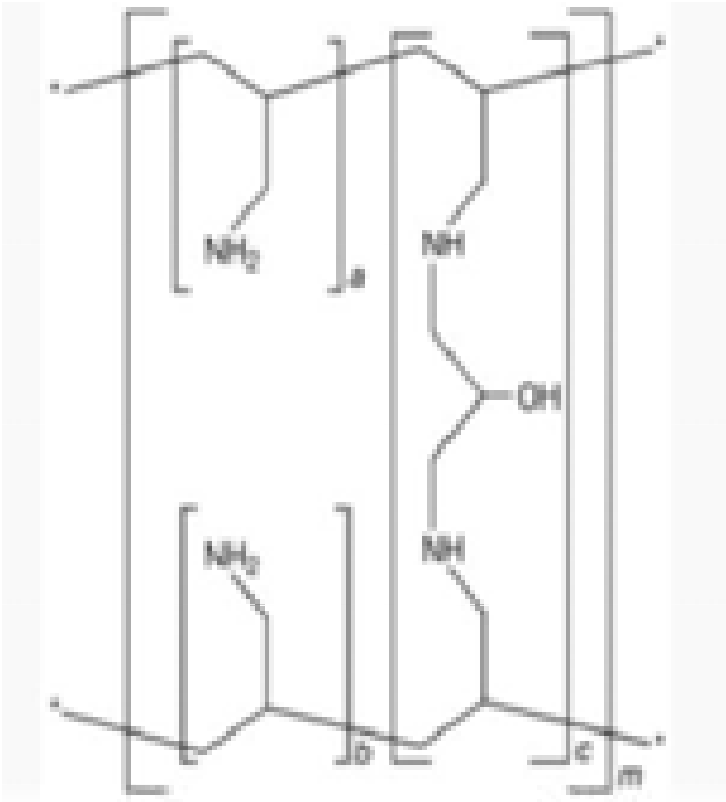
- Kalsiyum bazlı fosfor bağlayıcılarla elemental Ca alımı 1500 mg/günü aşmamalı
- 1000 mg Ca asetat → 250 mg elemental Ca
- 1000 mg Ca karbonat → 400 mg elemental Ca

FOSFOR BAĞLAYICILAR-Ca Tuzları

- Düzeltilmiş Ca > 10.2 mg/dL ise kullanılmamalı
- iPTH < 150 pg/mL ise kullanılmamalı
- Düzeltilmiş Ca düzeyleri 8.4-9.5 mg/dL arasında tutulmalı ve 10.2 sınırı aşılmamalı
- Düzeltilmiş Ca x P çarpımı 55 altı olmalı

FOSFOR BAĞLAYICILAR-Sevelamer

- Sevelamer hidroklorit/karbonat
- Ca ve Al içermeyen barsaktan emilmeyen bir molekül
- İyon değişimi yoluyla fosfora bağlanan bir katyonik polimer
- Safra asitlerine bağlanır ve fekal safra asit atılımı ↑ (LDL↓)



Sevelamer

FOSFOR BAĞLAYICILAR-Lantanyum

- Atom ağırlığı 57 olan ve doğada nadir bulunan bir element
- Oral yolla alındığı zaman emilimi son derece az
- Lantanyum karbonat bağırsaklarda fosfora bağlanarak emilimini önler
- Fosfor düşürücü etkisi kanıtlanmıştır
- Vücutta birikimi/sistemik toksisitesi var mı?

Clinical Practice

Nephron Clin Pract 2008;110:c15–c23
DOI: [illegible]

Received: December [illegible], 2007
Accepted: June [illegible], 2008
Published online: Sep [illegible], 2008

Long-Term Efficacy and Safety Profile of Lanthanum Carbonate: Results for up to 6 Years of Treatment

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Jonathan T.C. Kwan[d] Ghodsat A. Siami[e]
on behalf of the SPD405-309 Lanthanum Study Group

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Key Words
Lanthanum carbonate · Hyperphosphatemia · Clinical trial

Abstract
Background/Aims: Lanthanum carbonate (LC, FOSRENOL®) is an effective phosphate binder for which tolerability and a safety profile have been reported in haemodialysis patients. Patients from previous studies entered a 2-year extension, enabling assessment of efficacy and safety for up to 6 years of LC monotherapy. **Methods:** Patients from four previous trials entered this study. **Results:** Ninety-three patients started the extension, with 22 entering a sixth year of LC treatment. Two-thirds of all patients received LC doses of 2,250 or 3,000 mg/day. Reductions in serum phosphate and calcium × phosphate product were maintained for up to 6 years. There were no new or unexpected adverse events (AEs) and no increase in the incidence of events with increasing treatment exposure. Over the complete duration of therapy, treatment-related AEs occurred in 26.8% of patients and were primarily gastrointestinal in nature. No clinically relevant changes in liver function tests were observed and there was no evidence of adverse effects on the bone or the central nervous system. **Conclusions:** LC monotherapy was effective and well tolerated for up to 6 years with no evidence of safety concerns or increased frequency of AEs.

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Introduction

Hyperphosphatemia is a common complication in patients with chronic kidney disease (CKD) stage 5 on haemodialysis. Although dialysis and dietary restrictions are capable of reducing serum phosphate to a limited extent, the majority of patients will require additional treatment with phosphate binders to reduce serum phosphate concentrations to the target range of 1.13–1.77 mmol/l (3.5–5.5 mg/dl), as recommended in the 2003 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [1].

Lanthanum carbonate (FOSRENOL®, Shire Pharmaceuticals) is a highly effective phosphate binder. Preclinical studies have shown that lanthanum binds phosphate equally well at all relevant pH levels throughout the gastrointestinal tract [2, 3]. In short-term, placebo-controlled clinical trials, lanthanum carbonate was signifi-

Phosphate binders for preventing and treating bone disease in chronic kidney disease patients (Review)

Navaneethan SD, Palmer SC, Vecchio M, Craig JC, Elder GJ, Strippoli GFM

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 1

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Phosphate binders for preventing and treating bone disease in chronic kidney disease patients (Review)
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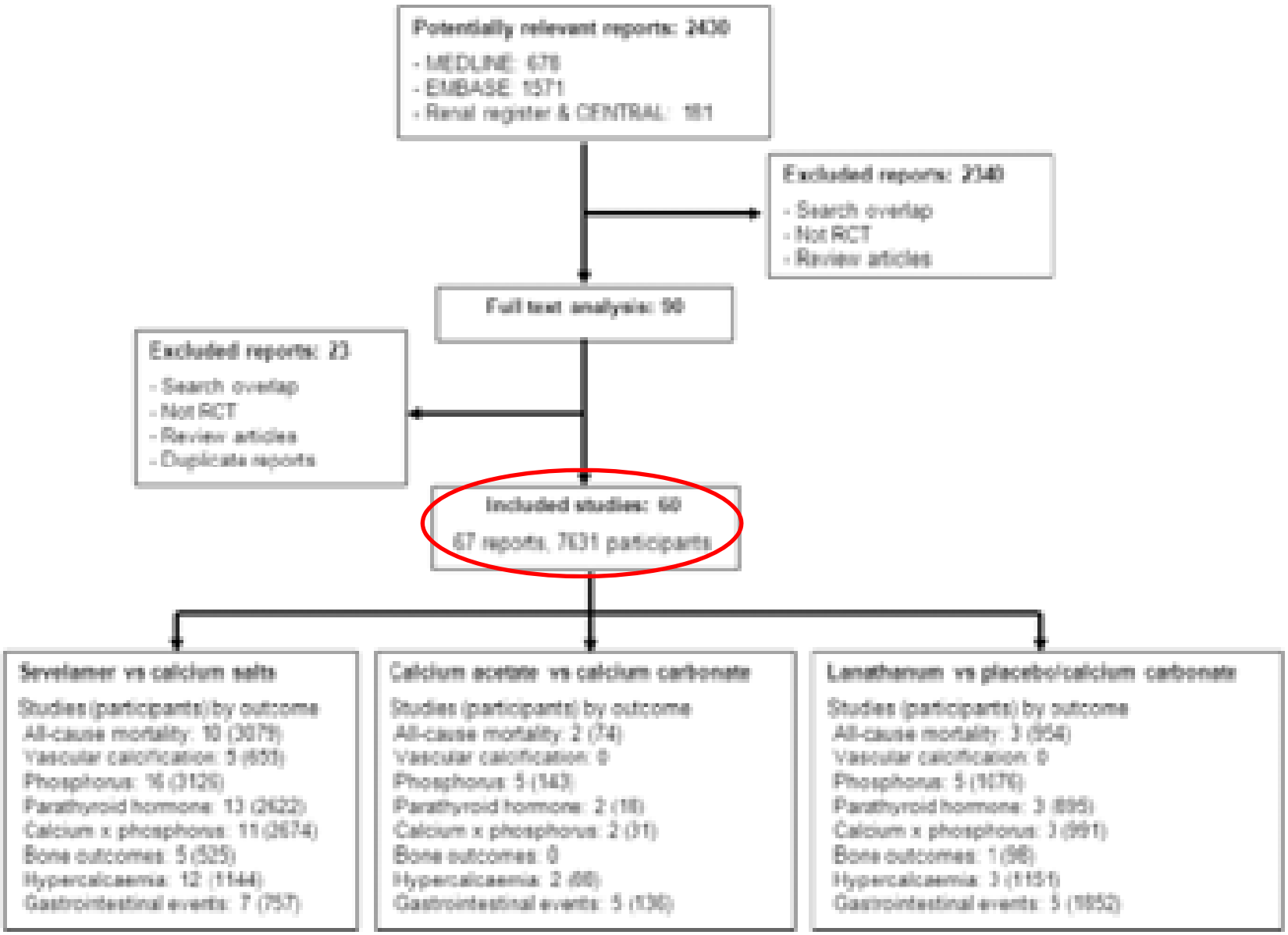
- Amaç: Çeşitli fosfor bağlayıcıların
  * Fosfor düşürücü etkileri
  * Biyokimyasal sonlanım noktaları (PTH, Ca, Ca x P)
  * Kemik döngüsü ve mineralizasyonu
  * Klinik sonlanım noktaları (mortalite, KV olaylar)
  * Vasküler kalsifikasyon üzerine etkileri karşılaştırılmış
- Meta analize randomize kontrollü (veya benzeri) çalışmalar dahil edilmiş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- EMBASE: 1571
- Renal register & CENTRAL: 181
Excluded reports: 2340
- Search overlap
- Not RCT
- Review articles
Full text analysis: 90
Excluded reports: 23
- Search overlap
- Not RCT
- Review articles
- Duplicate reports
Included studies: 60
67 reports, 7631 participants
Sevelamer vs calcium salts
Studies (participants) by outcome
All-cause mortality: 10 (3079)
Vascular calcification: 5 (653)
Phosphorus: 16 (3126)
Parathyroid hormone: 13 (2622)
Calcium x phosphorus: 11 (2674)
Bone outcomes: 5 (525)
Hypercalcaemia: 12 (1144)
Gastrointestinal events: 7 (757)
Calcium acetate vs calcium carbonate
Studies (participants) by outcome
All-cause mortality: 2 (74)
Vascular calcification: 0
Phosphorus: 5 (143)
Parathyroid hormone: 2 (18)
Calcium x phosphorus: 2 (31)
Bone outcomes: 0
Hypercalcaemia: 2 (68)
Gastrointestinal events: 5 (136)
Lanthanum vs placebo/calcium carbonate
Studies (participants) by outcome
All-cause mortality: 3 (954)
Vascular calcification: 0
Phosphorus: 5 (1176)
Parathyroid hormone: 3 (895)
Calcium x phosphorus: 3 (991)
Bone outcomes: 1 (98)
Hypercalcaemia: 3 (1151)
Gastrointestinal events: 5 (1852)

Sevelamer x Kalsiyum Tuzları

- Vasküler kalsifikasyon

  * 3 çalışmada sevelamer VC progresyonunu ↓

  * 2 çalışmada fark Ø
- Sevelamer ile kemiğin trabeküler ve kortikal yapısı üzerine olumlu etkiler (+)
- Kemik döngüsü, remodeling veya mineralizasyonu fark Ø
- Tüm nedenlere bağlı mortalite açısından fark Ø

Sevelamer x Kalsiyum Tuzları

- Sevelamer ile Ca düzeyleri ve hiperkalsemi gelişimi anlamlı ↓
- Total kolesterol düzeyleri sevelamer ile anlamlı ↓
- Fosfor ve PTH düzeyleri Ca tuzları ile anlamlı ↓
- Serum Ca x P çarpımı, ALP açısından fark Ø

- GİS yan etkileri sevelamer ile anlamlı ↑

Kalsiyum Karbonat x Kalsiyum Asetat

- Mortalite açısından fark Ø
- Serum Ca, P, Ca X P çarpımı, PTH, bikarbonat, ALP ve total kolesterol düzeyleri açısından fark Ø

- Hiperkalsemi gelişimi ve GİS yan etkileri açısından fark Ø

Lantanyum x Kalsiyum Tuzları

- Düşük döngülü kemik hastalığı gelişimi lantanyum ile daha ↓
- Serum Ca düzeyleri ve hiperkalsemi gelişimi lantanyum ile daha ↓
- Ca x P çarpımı lantanyum ile daha ↓
- Mortalite açısından fark Ø
- Serum P, PTH düzeyleri açısından fark Ø

- GİS yan etkiler açısından fark Ø

HANGİ FOSFOR BAĞLAYICIYI KULLANALIM?

- Hiperkalsemi
- Ciddi hiperfosfatemi
- Düşük PTH düzeyi (<100-150 pg/mL) ve/veya adinamik kemik hastalığı
- Vasküler kalsifikasyonlar

varsa sevelamer

yoksa Ca bazlı fosfor bağlayıcılar

HANGİ FOSFOR BAĞLAYICIYI KULLANALIM?

- P < 5.5 ve Ca < 9.5 → Ca bazlı fosfor bağlayıcı
- P < 5.5 ve Ca > 9.5 → VK varsa sevelamer, yoksa fosfor bağlayıcıya ara verilebilir
- P > 5.5 ve Ca > 9.5 → Sevelamer
- P > 5.5 ve Ca < 9.5 → Ca bazlı fosfor bağlayıcı → hala P > 5.5 ise sevelamer eklenebilir

PARATİROİDEKTOMİ

- Medikal olarak (fosfor bağlayıcılar/D vit) kontrol edilemeyen hiperfosfatemik hiperparatirodizmli hastalarda endikedir
- Ciddi hiperfosfatemi D vit kullanımı için engel (metastatik kalsifikasyon riski)
- Hiperfosfatemik/hiperkalsemik SHP;

sinakalset + sevelamer ⇨ Paratiroidektomi

HİPOKALSEMİ TEDAVİSİ

- PTH sekresyonu için güçlü bir uyaran → düzeltilmeli
- Kalsiyum karbonat (yemek aralarında)
- Aktif D vitamini (sıklıkla gerekir)
- Tedavi sırasında serum Ca ve PTH düzeyleri izlenmeli ve hedef düzeyler arasında tutulmalı
- Ciddi hipokalsemi genellikle diyalize yeni başlayan hastalarda veya paratiroidektomi sonrası
- Diyaliz ile asidozun düzelmesi sonucu iyonize Ca düşmesi ile semptomatik !!

HİPOKALSEMİ TEDAVİSİ

- 1 ampül (10ml) Ca (calcium picken® = Ca-glukonat/levülinat) ~ 95 mg elemental Ca içerir
- Semptomatik hipokalsemide 1 amp, 5 ml/dk geçmeyen bir hızda IV olarak yavaşça uygulanır.
- Aç kemik sendromunda Ca < 7.2 mg/dL ve/veya hipokalsemi semptomları varsa

  * 1-2 mg/kg/saat elemental Ca IV başlanmalı

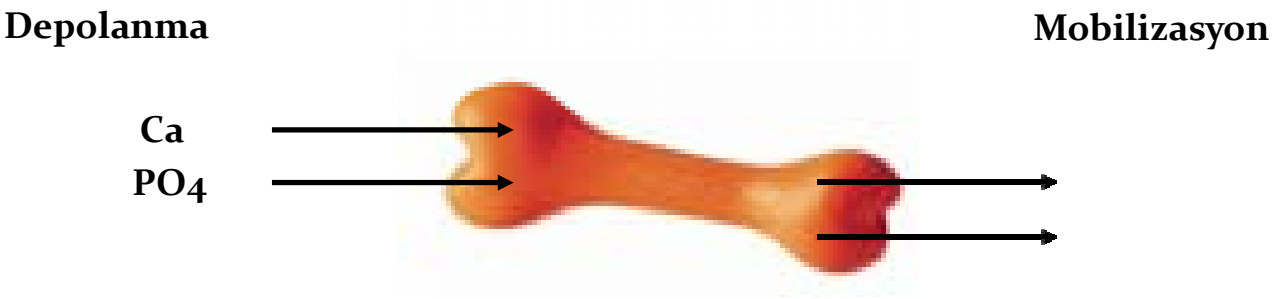
  * Yakın Ca takibi yapılarak normal aralığa getirmek için doz ayarlaması yapılmalı

  * IV (veya PO) Kalsitriol

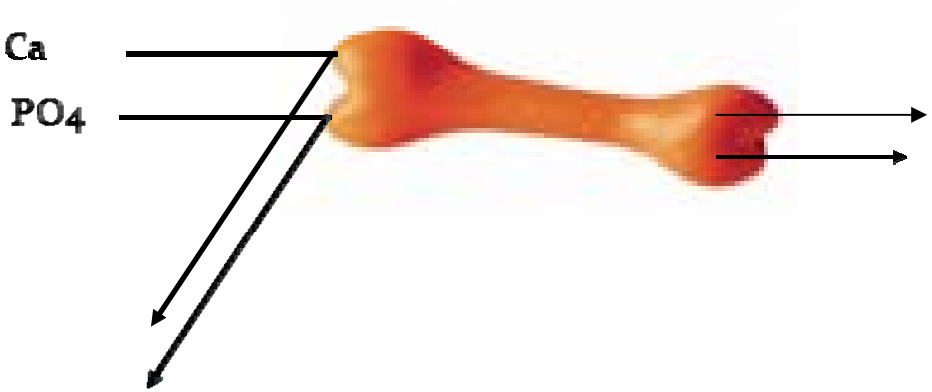
ADİNAMİK KEMİK HASTALIĞI

- Düşük döngülü kemik hastalığının morfolojik sonucudur
- Kemik yapım ve yıkım hızı ve kemik kütlesi ↓
- PTH sıklıkla düşük (<100 pg/mL)
- Ca ve P normal/↑
- VC, mortalite ve kırık riski ↑↑

Normal Kemik Döngüsü



Düşük Kemik Döngüsü
(Adinamik Kemik)



KDIGO-2013 ÖNERİLERİ

- GFR 45 mL/dk'nin altına indiğinde serum Ca, P, PTH ve ALP değerleri en az bir kez ölçülmeli
- GFR 45 mL/dk'nin altında olan hastalarda **serum fosfor düzeyleri normal aralıkta** tutulmalı
- GFR 45 mL/dk'nin altında olan hastalarda **optimal PTH düzeyi bilinmemektedir**; iPTH düzeyi normal limitlerin üst sınırını aşan hastaların hiperfosfatemi, hipokalsemi ve vit D eksikliği yönünden ilk değerlendirilmesi yapılmalıdır

ÖZET

- SHP patogenezinde temel olarak fosfor retansiyonu/hiperfosfatemi, hipokalsemi ve azalmış 1,25 (OH)2 vit D düzeyleri rol oynar
- P artışı artmış mortalite ve VC ile yakından ilişkilidir
- Hiperfosfateminin düzeltilmesi için diyette fosfor alımı kısıtlanmalı ve fosfor bağlayıcılar kullanılmalı

ÖZET

- Hiperkalsemi/ciddi hiperfosfatemi/VC varlığı/düşük PTH düzeyleri söz konusu ise sevelamer, diğer durumlarda kalsiyum bazlı fosfor bağlayıcılar kullanılabilir
- Serum Ca, P ve PTH düzeyleri ile ilgili tedavi hususunda klinik bulgular ve en önemlisi SUT kuralları da göz önünde tutulmalı

TEŞEKKÜRLER...