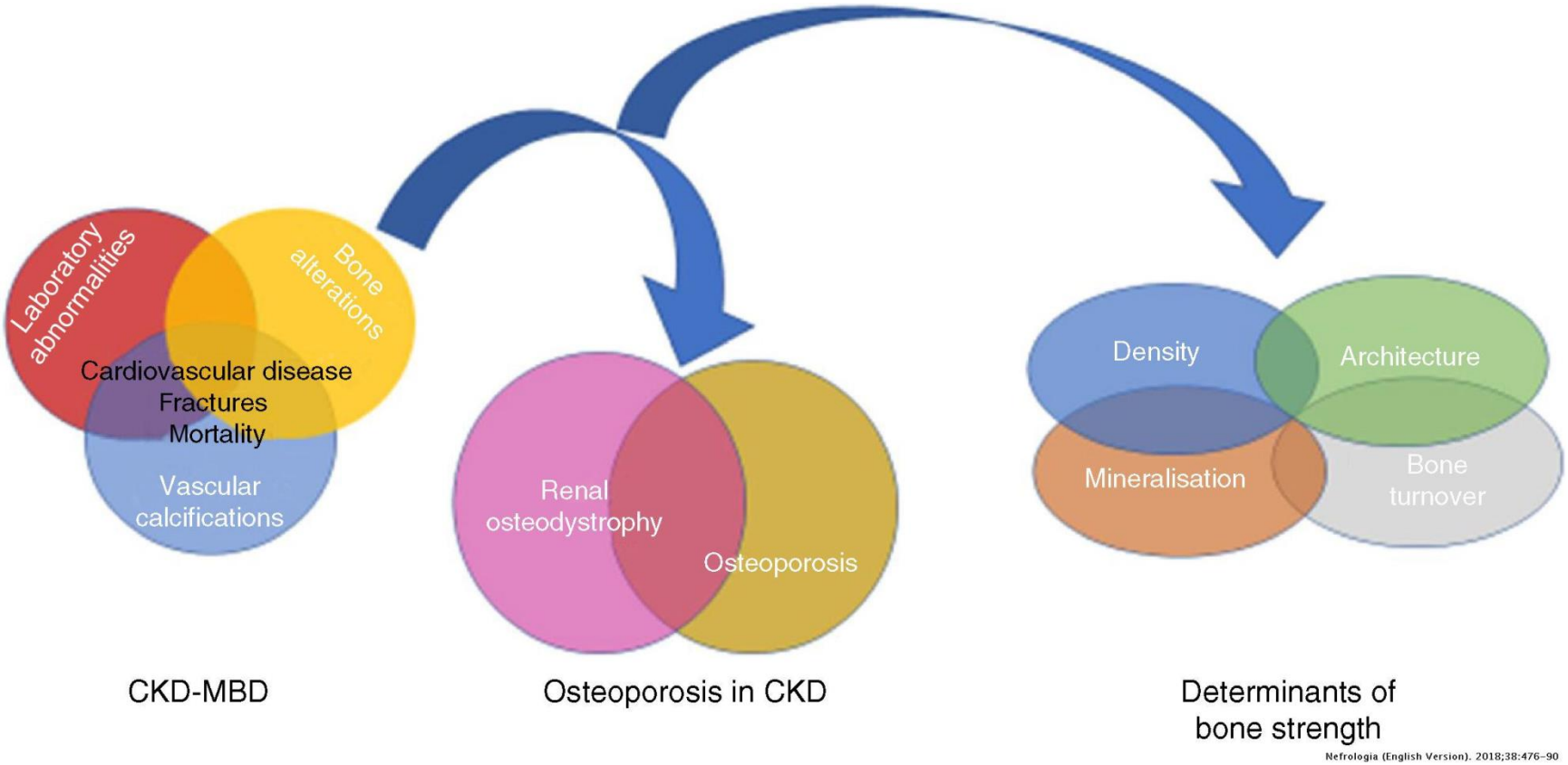
Η διαχείριση της οστικής νόσου σε ασθενή με διαβήτη και ΧΝΝ

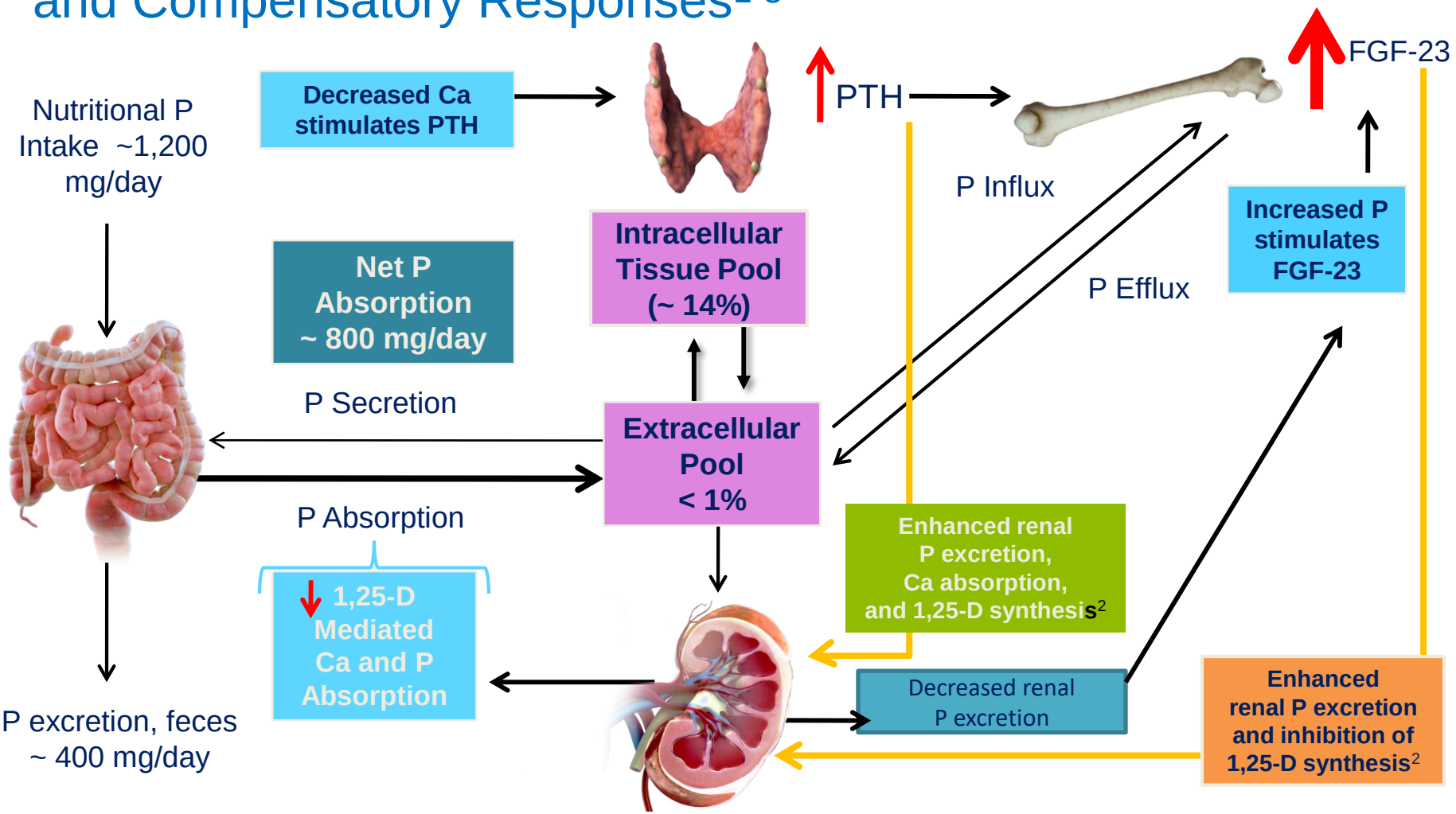
Παρασκευή Λιαβέρη
Επιμ. Β
Νεφρολογική Κλινική
Γ.Ν.Α Γ.ΓΕΝΝΗΜΑΤΑΣ

Chronic Kidney Disease-Bone Mineral Disorder (CKD-MBD)



Nefrologia (English Version). 2018;38:476-90

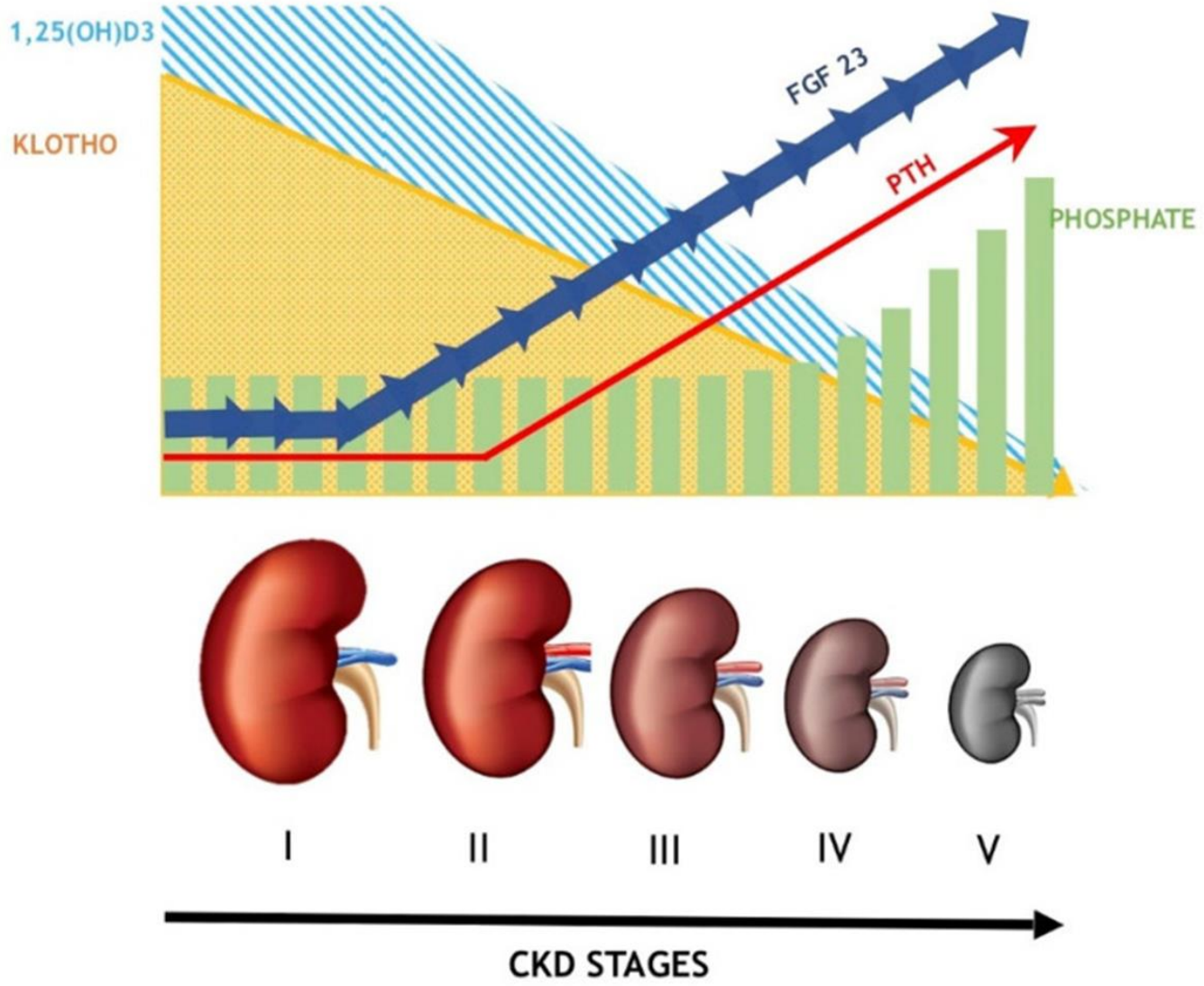
As Kidney Function Becomes Impaired, Calcium and Phosphorus Metabolism Is Disturbed, Triggering Adaptive and Compensatory Responses[1-3]



Elevated PTH and FGF-23 serve to maintain calcium and phosphorus balance in moderate CKD[2]

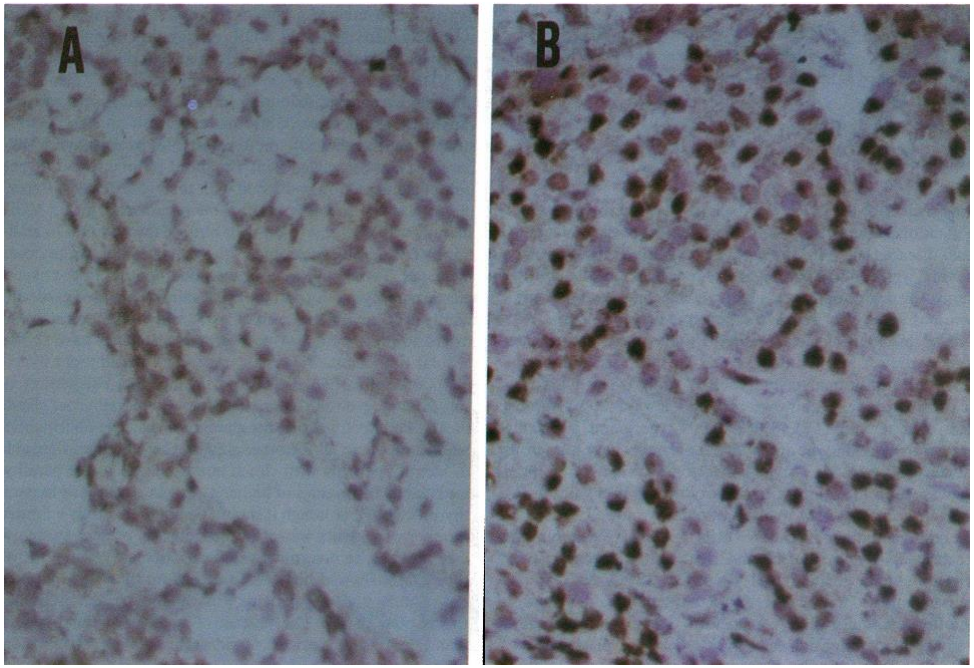
1. *Kidney Int.* 2008;74:148-157. 2. *Kidney Int.* 2009;76(suppl 114):S34-S42. 3. *J Bone Miner Res.* 2007;22:V91–V94.

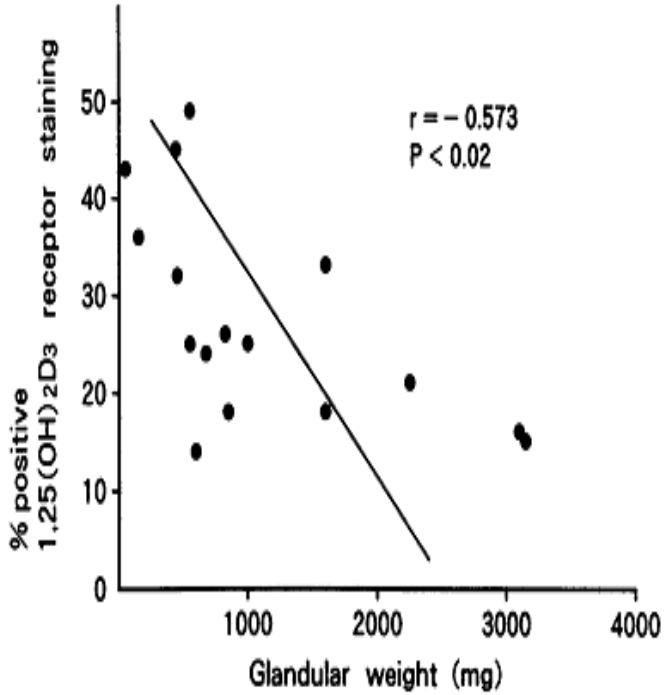
Mineral Bone Disorders in Kidney Disease Patients: The Ever-Current Topic



Int.J.Mol.Sci 2022;23:12223

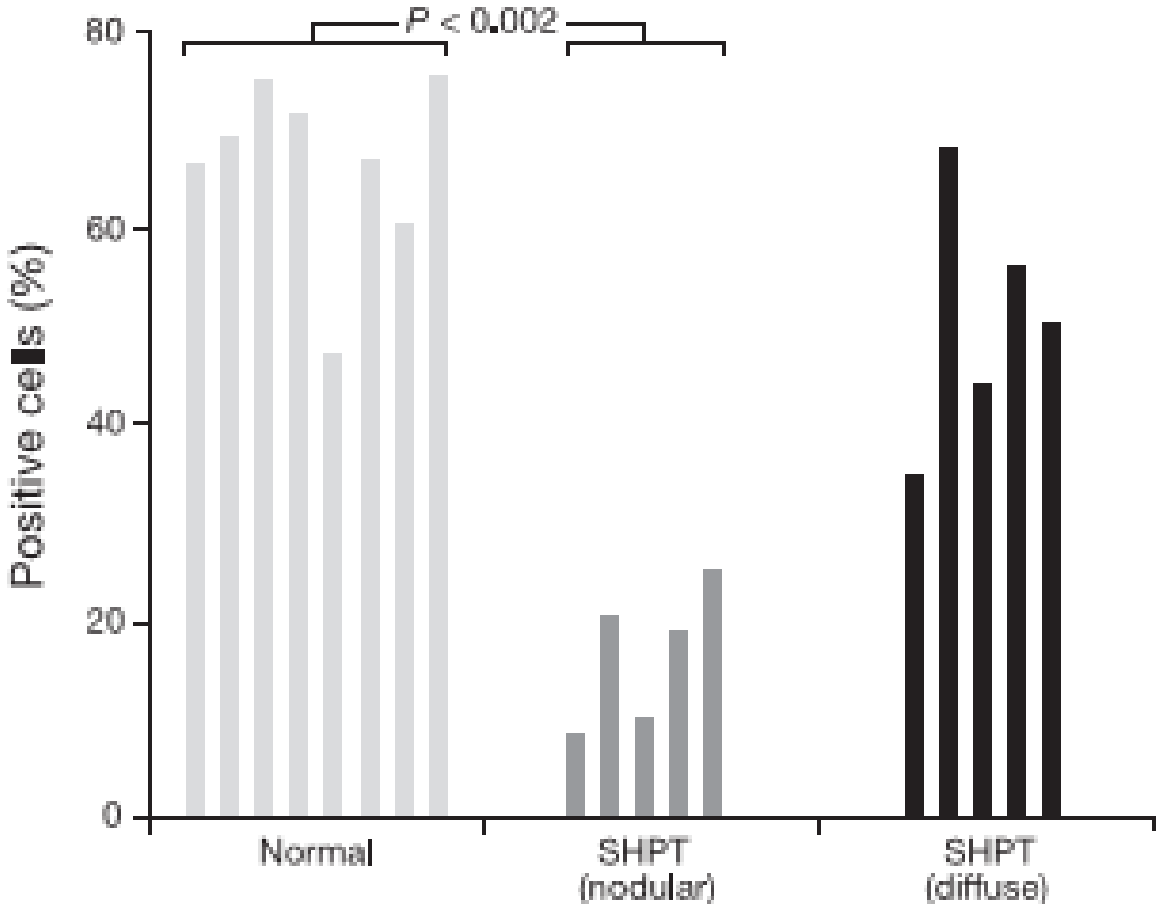
Decreased VDR density is associated with a more severe form of parathyroid hyperplasia in CKD





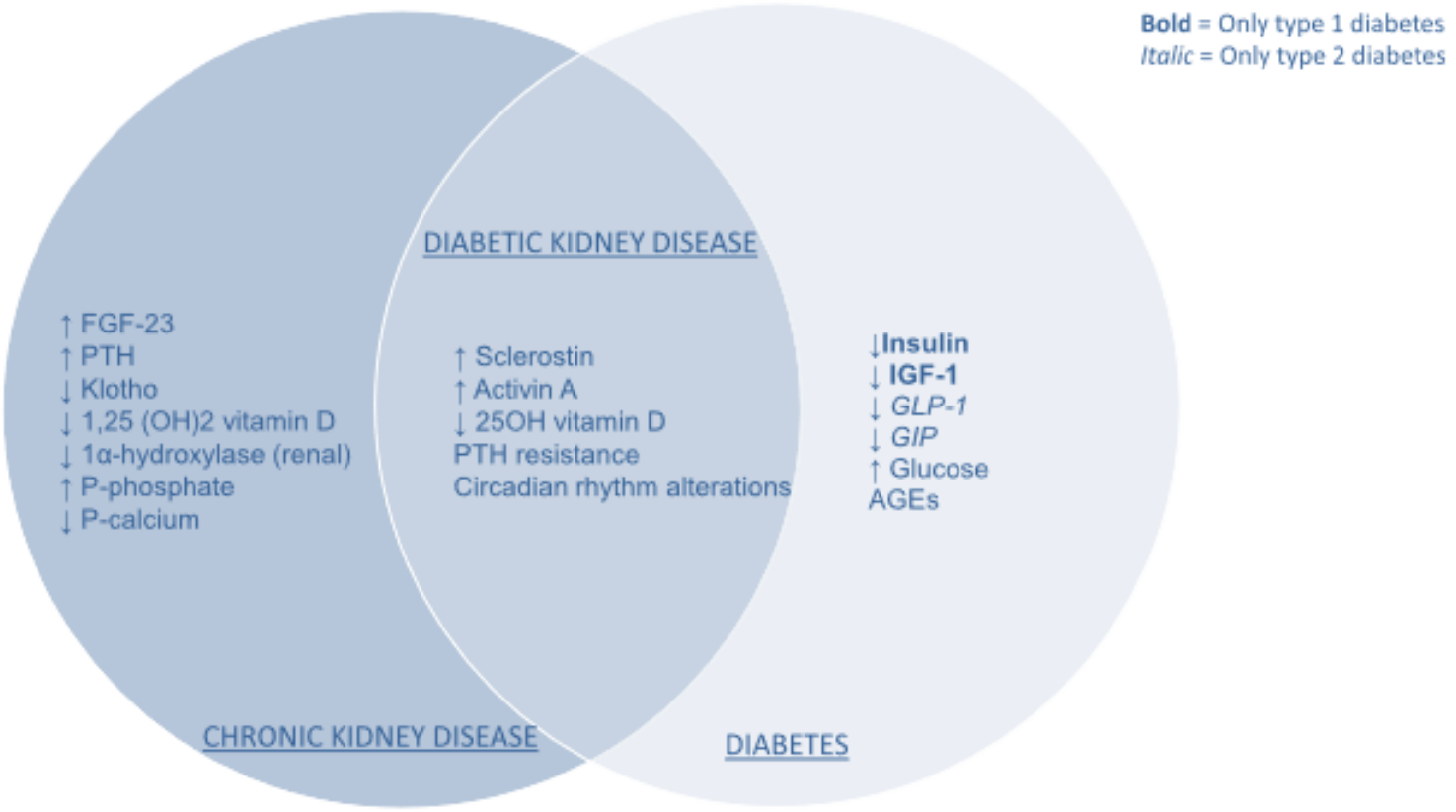
J Clin Invest 1993;92:1436-1443

Depressed expression of CaR in parathyroid gland tissue of pts with Hyperparathyroidism



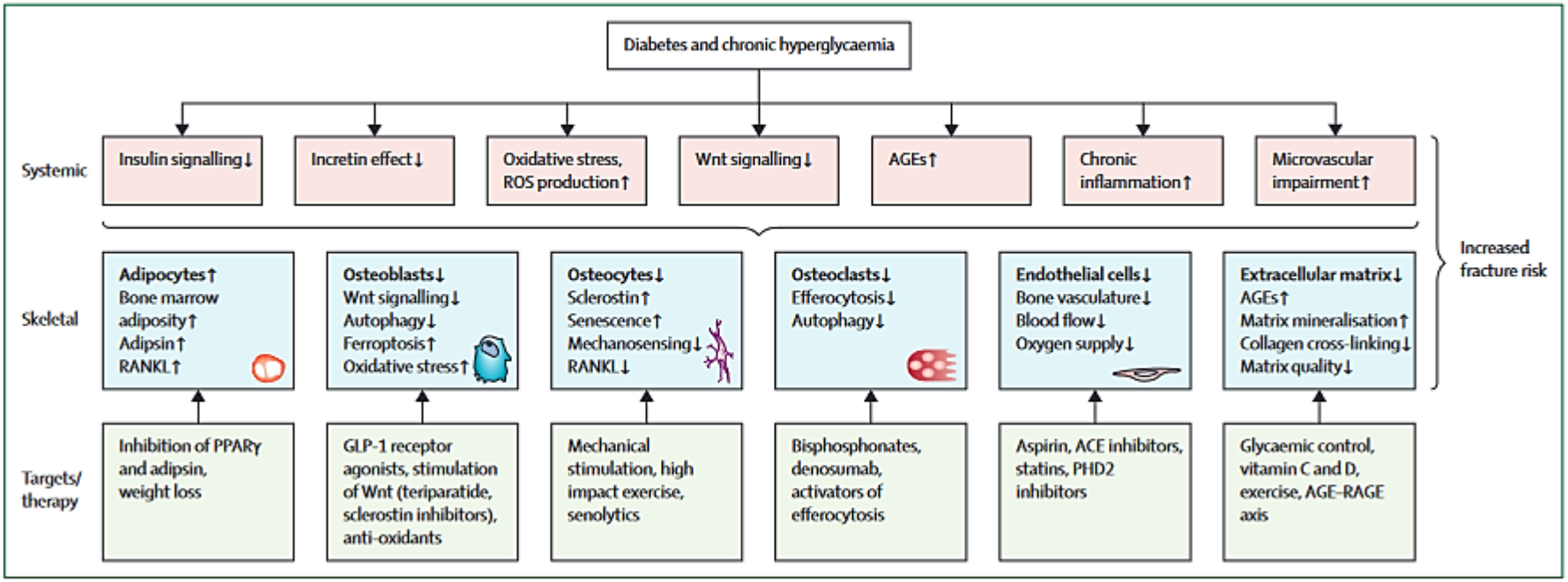
Am J Physiol Renal Physiol 2005;288:F253-F264

Understanding Bone Disease in Patients with Diabetic Kidney Disease: a Narrative Review



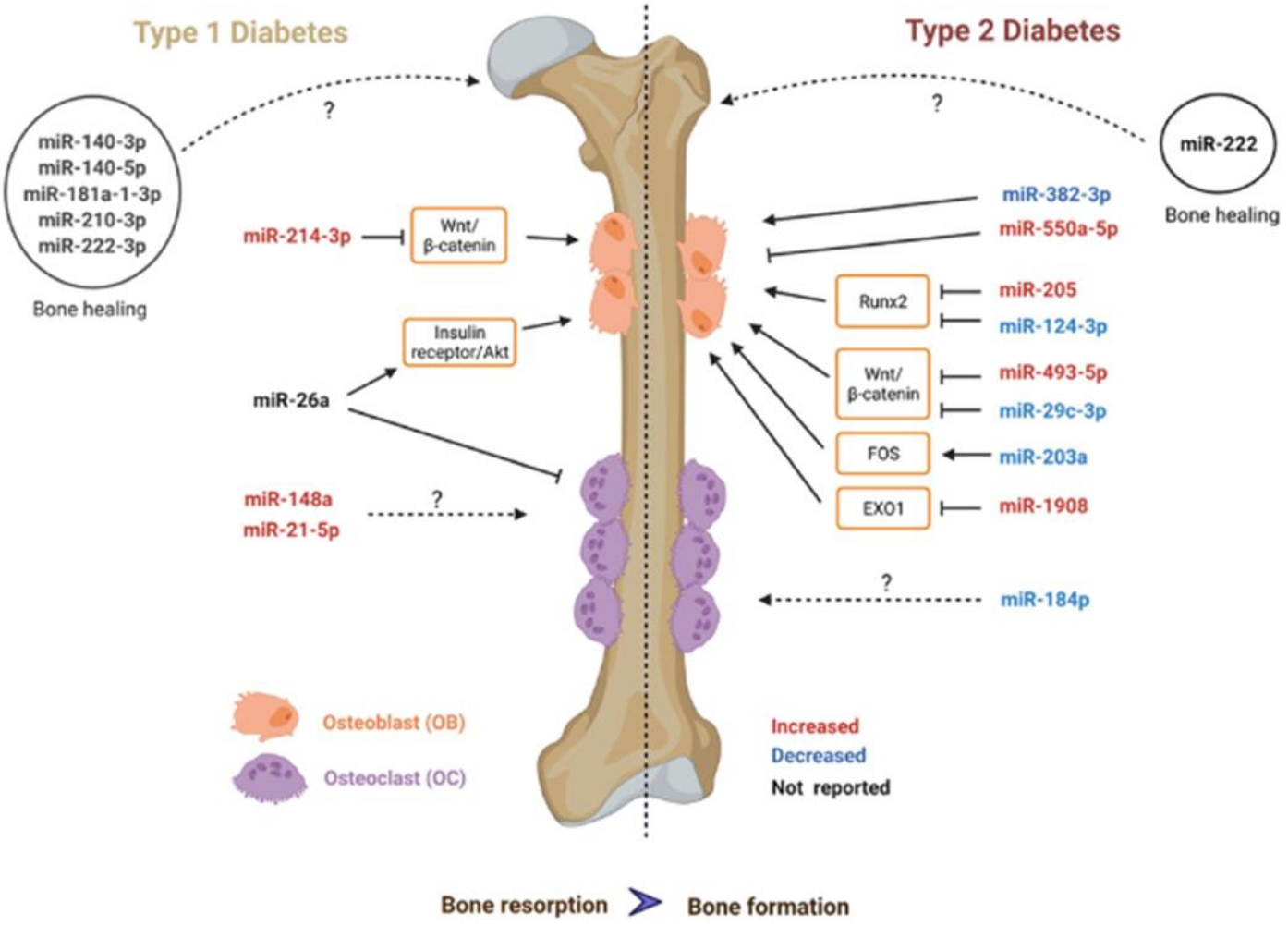
Curr Osteoporos Rep 2020;18:727–736

Bone fragility in diabetes: novel concepts and clinical implications



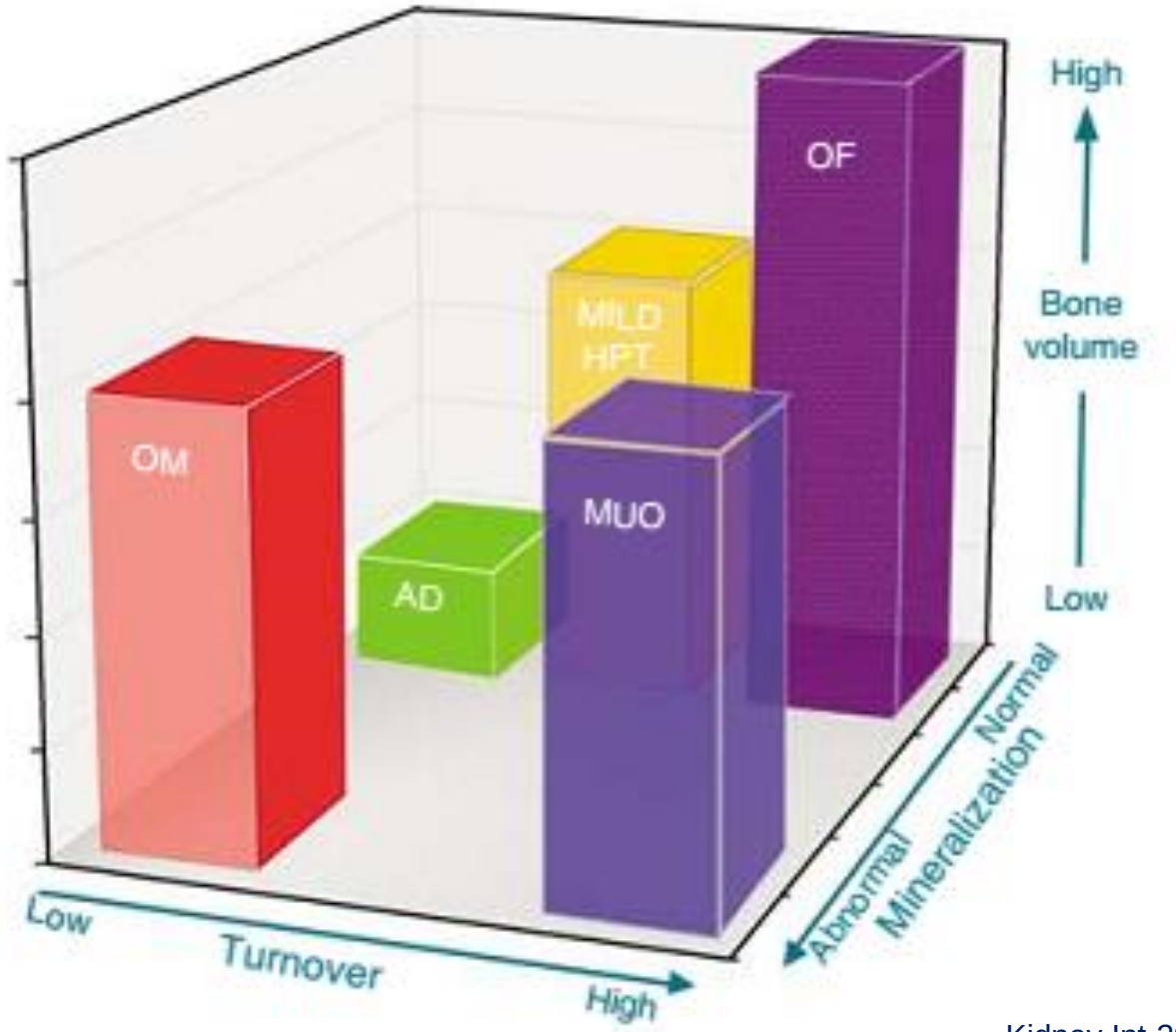
Lancet Diabetes Endocrinol 2022; 10: 207–20

MicroRNA and Diabetic Bone Disease



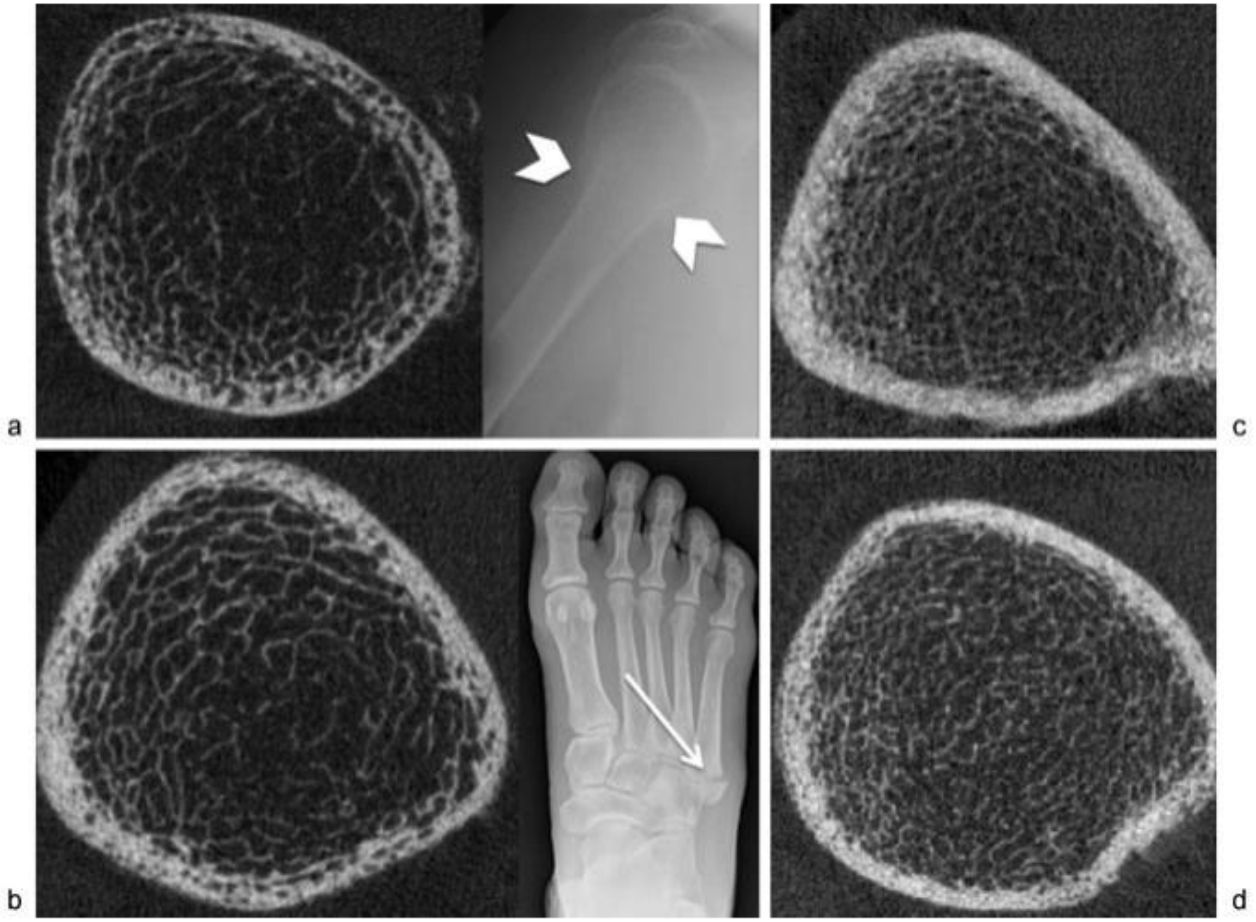
Current Osteoporosis Reports (2022) 20:194–201

Turnover-Mineralization-Volume (TMV)



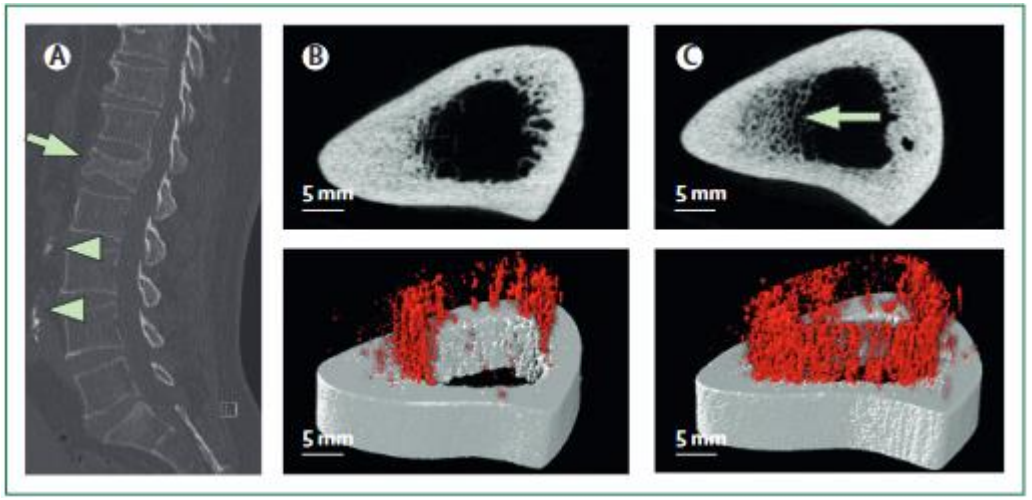
Kidney Int 2006;69:1045-1953

Diabetes and Bone



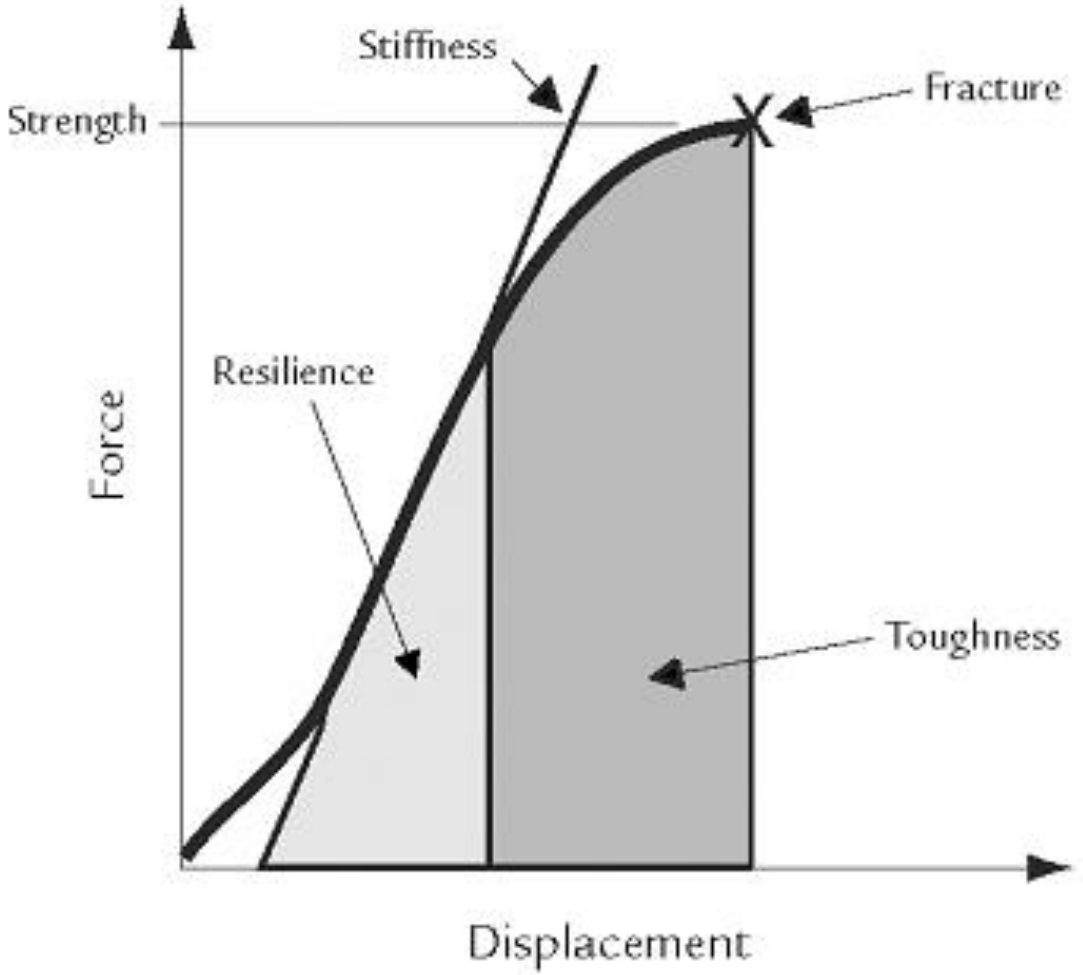
Semin Musculoskelet Radiol 2016;20:300–304

Bone fragility in diabetes: novel concepts and clinical implications



Lancet Diabetes Endocrinol 2022; 10: 207–20

Bone quality



Clinical Therapeutics 2005;27(1):1-11

Στόχοι της θεραπείας

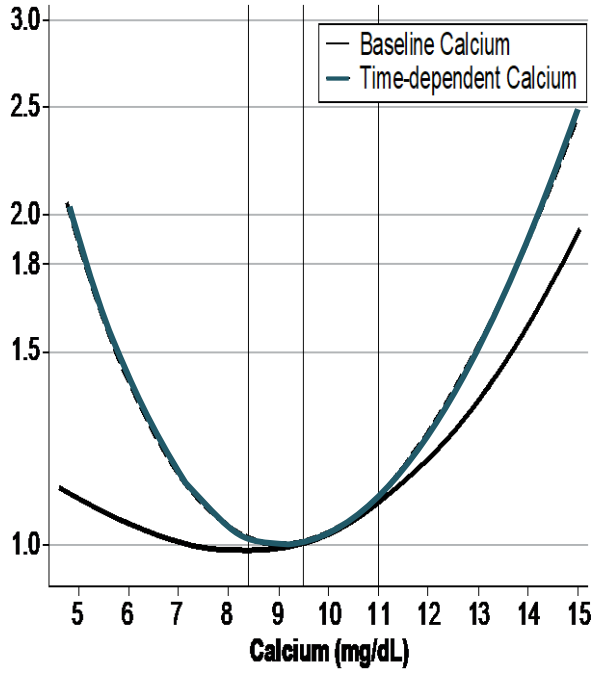
ΑΜΕΣΟΙ

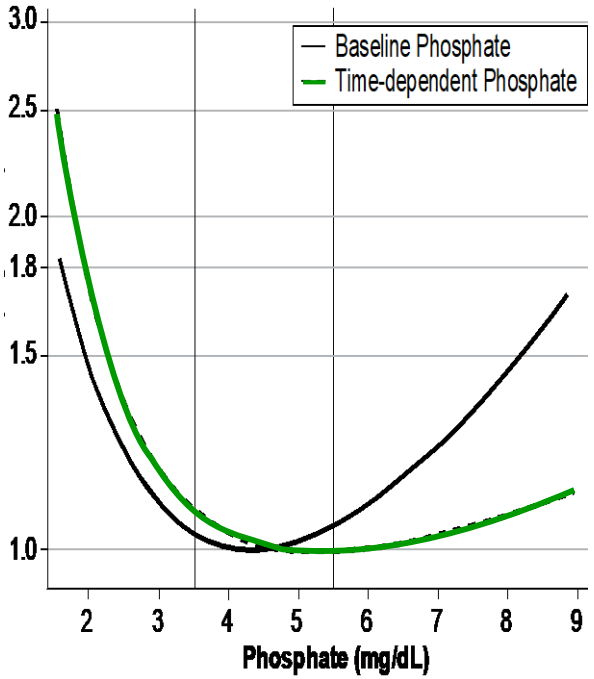
- Παραμονή της PTH σε αποδεκτά όρια
- Πρόληψη της υπερπλασίας των Παραθυρεοειδών αδένων
- Φυσιολογικά επίπεδα Ca, P
- Διατήρηση φυσιολογικού οστικού μεταβολισμού

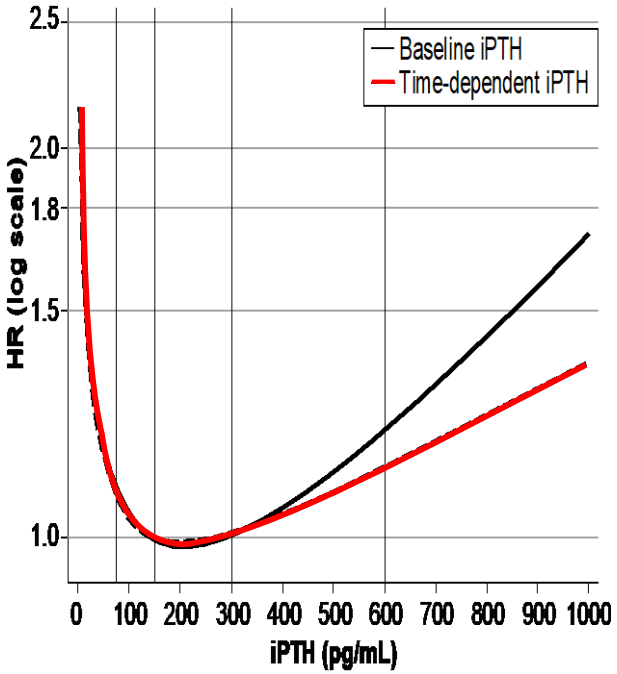
ΑΠΩΤΕΡΟΙ

- Μείωση κινδύνου εμφάνισης βαριάς οστικής νόσου
- Μείωση κινδύνου καρδιαγγειακής νοσηρότητας-θνησιμότητας που σχετίζεται με την οστική νόσο

PTH, Ca, P - MORTALITY







N=7970

Note suppressed zeros used in this graph

Nephrol Dial Transplant. 2011;26:1948-1955.

Mineral and bone metabolism markers and mortality in diabetic patients on haemodialysis

High and low levels of calcium, phosphorus, and parathyroid hormone (PTH) have been associated with a greater risk of mortality in patients with CKD and this association could differ between diabetic and non-diabetic patients on HD.

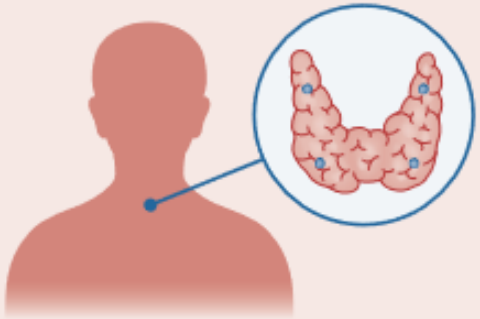
COSMOS

Current management Of Secondary hyperparathyroidism: a Multicentre Observational Study

Patients on dialysis

- With diabetes n = 1933
- Without diabetes n = 4373

Results



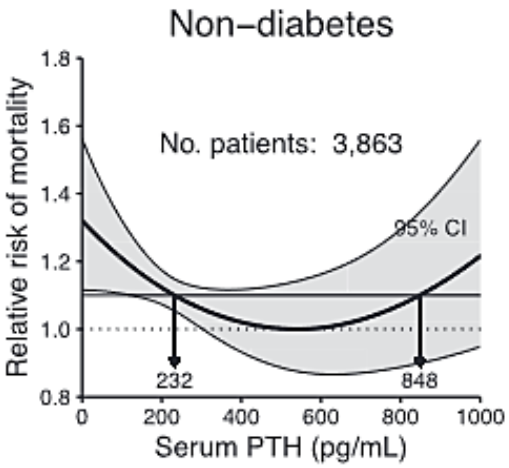
High PTH (9 × normal)

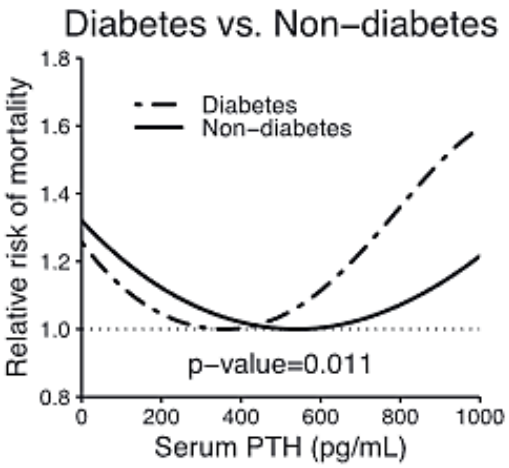
53% increase in mortality risk for patients with diabetes

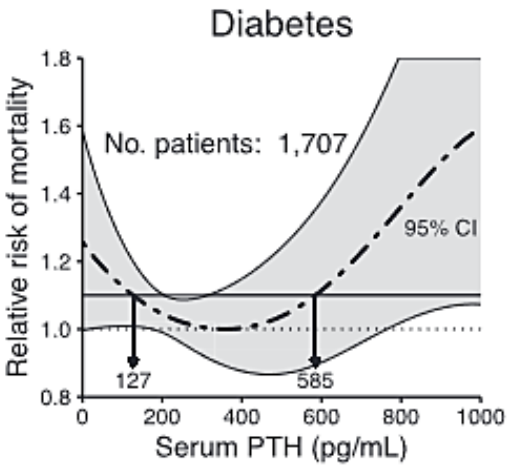
Martín-Carro, B. *et al.*
NDT (2023)
@NDTSocial

High serum PTH was associated with an increase risk of mortality in diabetic, but not in non-diabetic patients: a novel finding that should be taking into account in the diagnosis and management of CKD-MBD.

Mineral and Bone Metabolism Markers and Mortality in Diabetic Patients on Hemodialysis



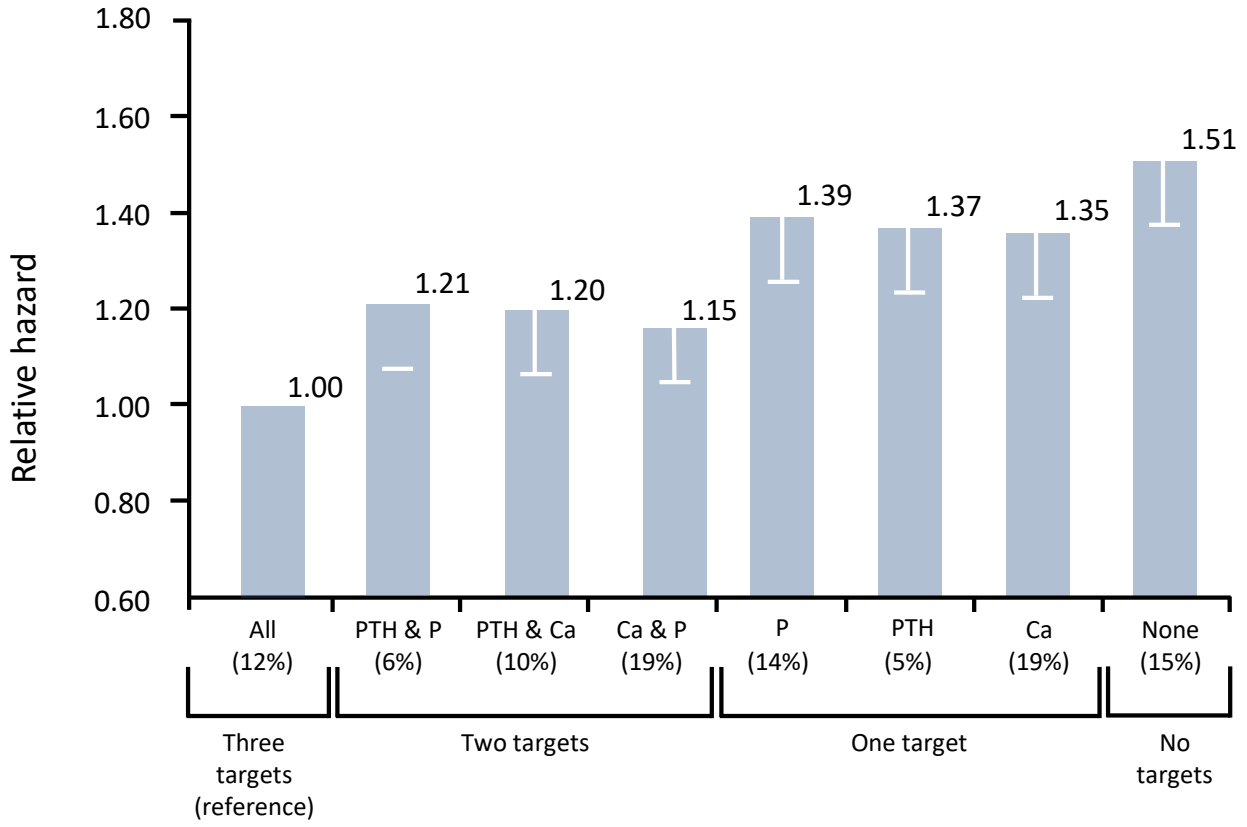




Nephrol Dial Transplant 2023;0:1–9

Evidence from observational research:

Lower mortality risk with simultaneous KDOQI™ target achievement



Groups defined by targets achieved (proportion at baseline)

Clin J Am Soc Nephrol 2008:3:1423–1429

PHOSPHATE AND CALCIUM

New 4.1.1: In patients with CKD G3a–G5D, treatments of CKD-MBD should be based on serial assessments of phosphate, calcium and PTH levels, considered together (*Not Graded).*

New 4.1.2: In patients with CKD G3a–G5D, we suggest lowering elevated phosphate levels toward the normal range (2C).

Old 4.1.1: In patients with CKD G3a–G5, we suggest maintaining serum phosphate in the normal range (2C). In patients with CKD G5D, we suggest lowering elevated phosphate levels toward the normal range (2C).

PHOSPHATE AND CALCIUM

New 4.1.3: In adult patients with CKD G3a–G5D, we suggest avoiding hypercalcemia (2C).
In children with CKD G3a–G5D, we suggest maintaining serum calcium in the age-appropriate normal range (2C).

Old 4.1.2: In patients with CKD G3a–G5D, we suggest maintaining serum calcium in the normal range (2D).

Mild and asymptomatic hypocalcemia (e.g., in the context of calcimimetic treatment) can be tolerated in order to avoid inappropriate calcium loading in adults.

MAINTAINING/LOWERING PTH

4.2.3: In patients with CKD G5D, we suggest maintaining intact PTH levels in the range of approximately 2 to 9 times the upper normal limit for the assay (2C).

We suggest that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range (2C).

MAINTAINING/LOWERING PTH

New 4.2.4: In patients with CKD G5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs (2B).

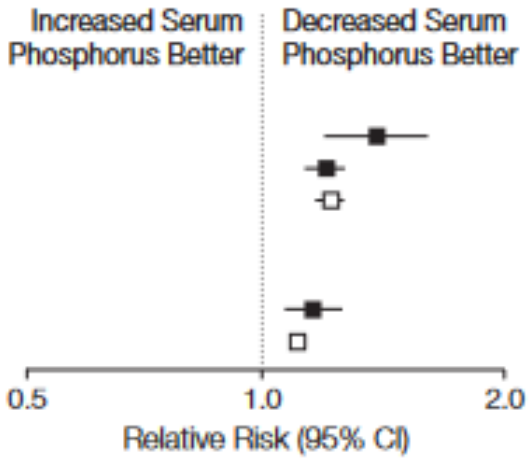
Old 4.2.4: In patients with CKD G5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH (2B).

It is reasonable that the initial drug selection for the treatment of elevated PTH be based on serum calcium and phosphorus levels and other aspects of CKD-MBD (Not Graded).

It is reasonable that calcium or non-calcium-based phosphate binder dosage be adjusted so that treatments to control PTH do not compromise levels of phosphorus and calcium (Not Graded).

Serum Levels of P, PTH and Ca and Risks of death and Cardiovascular Disease in individuals with CKD: A Systematic Review and Meta-analysis

Phosphorus	No. of Cohorts	No. of Participants	Relative Risk (95% CI) Per Unit Increase
All-cause mortality			
Adequate adjustment	3	4651	1.35 (1.16-1.57)
Partial adjustment	10	87694	1.16 (1.09-1.23)
All studies combined	13	92345	1.18 (1.12-1.25)
Cardiovascular mortality			
Adequate adjustment	1	17326	Not estimable
Partial adjustment	2	5881	1.14 (1.05-1.24)
All studies combined	3	23207	1.10 (1.06-1.13)

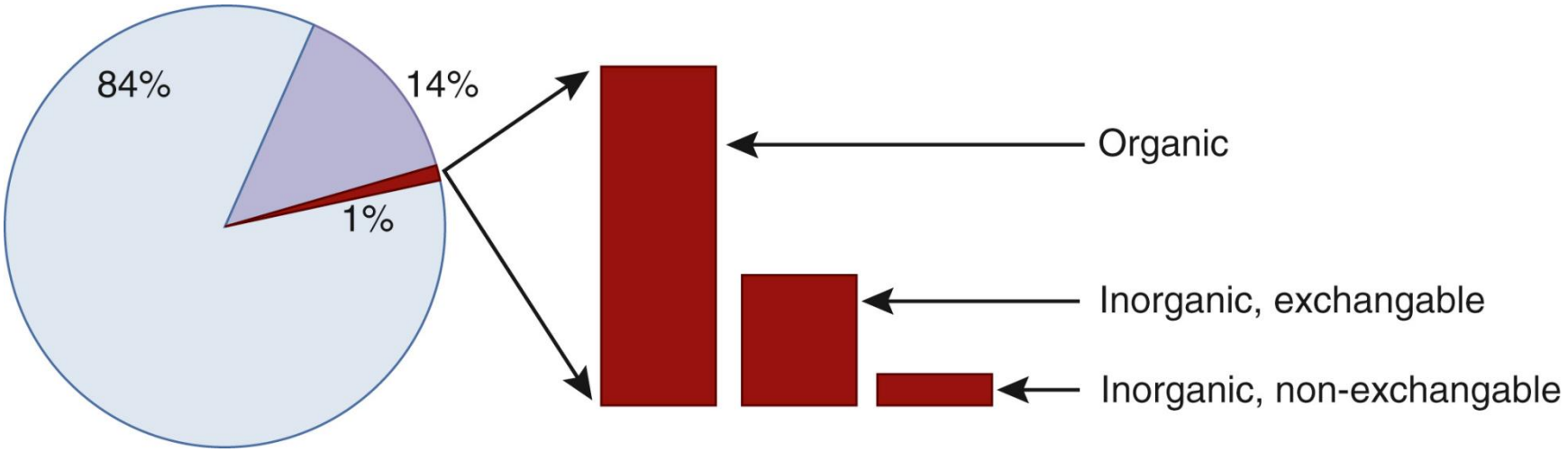


Ο σχετικός κίνδυνος θνησιμότητας για κάθε 1mg/dl αύξηση του P συνδέεται με αύξηση του κινδύνου θνησιμότητας κατά 18%.

Η αύξηση κατά 1mg/dl στη τιμή του P συνδέεται με αύξηση του κινδύνου για κάταγμα κατά 12%.

JAMA, March 16, 2011—Vol 305, No. 11

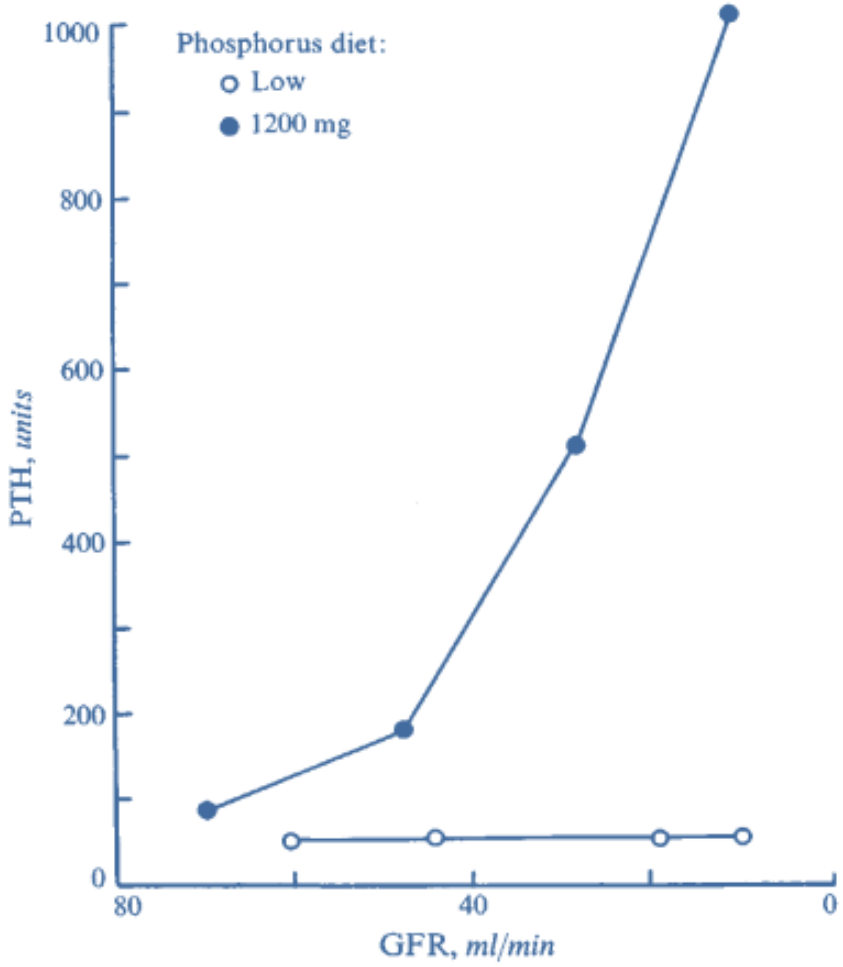
Prevention and treatment of hyperphosphatemia in chronic kidney disease

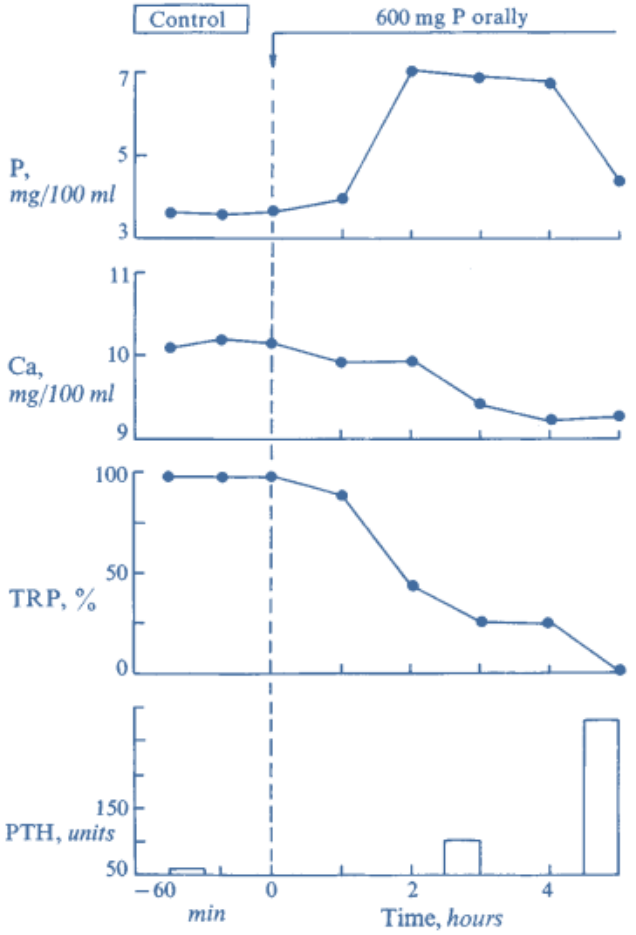


Phosphate resides in different body compartments. Bone is the largest reservoir with small amounts in plasma and interstitial fluid. Clinically the quantitative amount in each compartment is difficult to estimate except the blood compartment. It is unknown which compartment contributes most to phosphate-related toxicity

Kidney International (2018) 93, 1060–1072

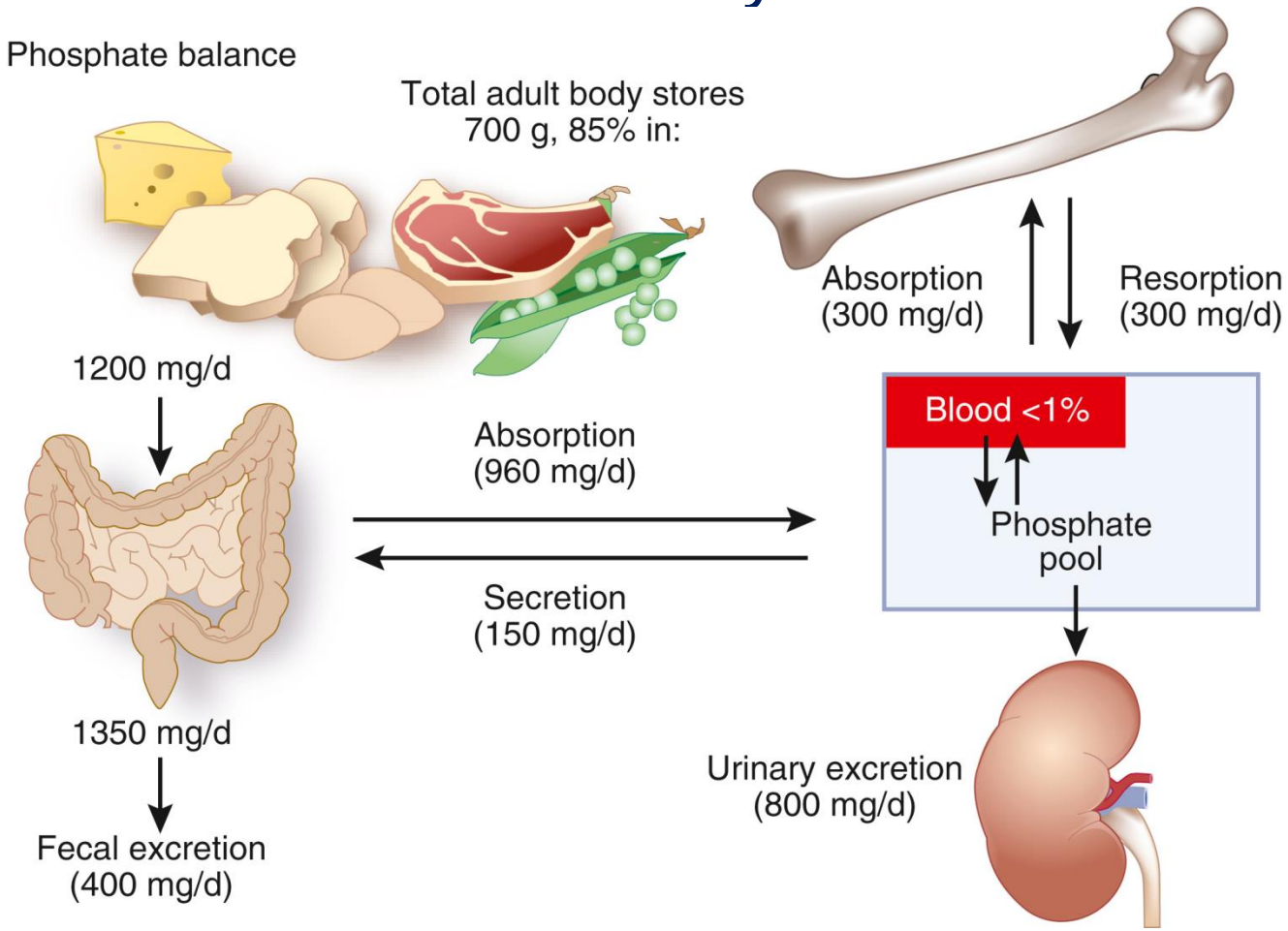
The role of phosphorus restriction in the prevention of SHPT in CKD





Kidney International 1973;4:141-145

Prevention and treatment of hyperphosphatemia in chronic kidney disease



Dietary phosphate restriction: poor adherence, effect size is modest (achieved mean reduction is approximately 0.6mg/dl over 3 months). (JAMA 2009;301:629-635)
Dietary restriction to 900mg/day (without compromising nutritional status).

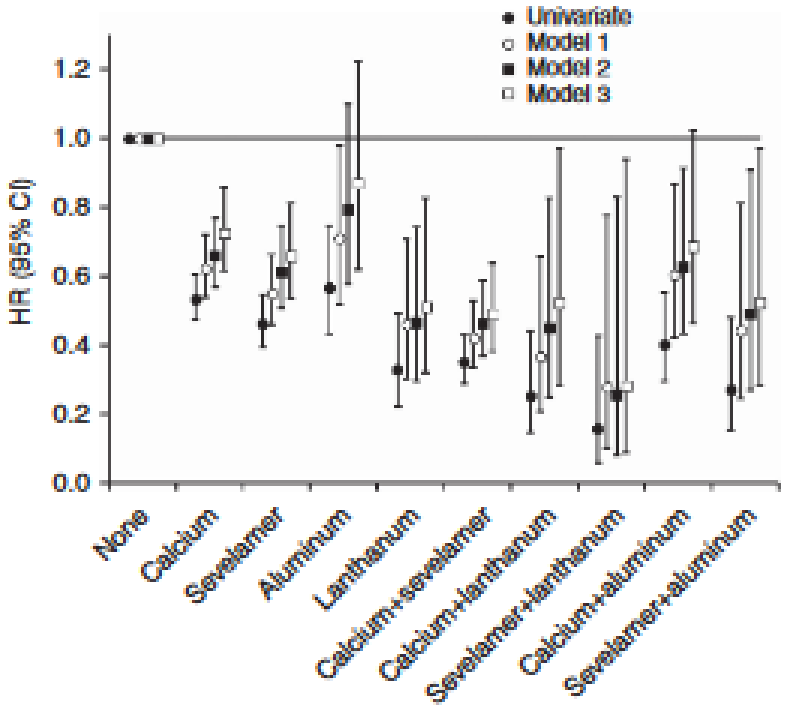
Kidney International (2018) 93, 1060–1072

Φωσφοροδεσμευτικά

- Υδροξύλιο του Αλουμινίου
- Ασβεστούχα Δεσμευτικά του P
- Σεβελαμέρη
- Ανθρακικό Λανθάνιο
- Σκευάσματα Σιδήρου

Use of phosphate-binding agents is associated with a lower risk of mortality

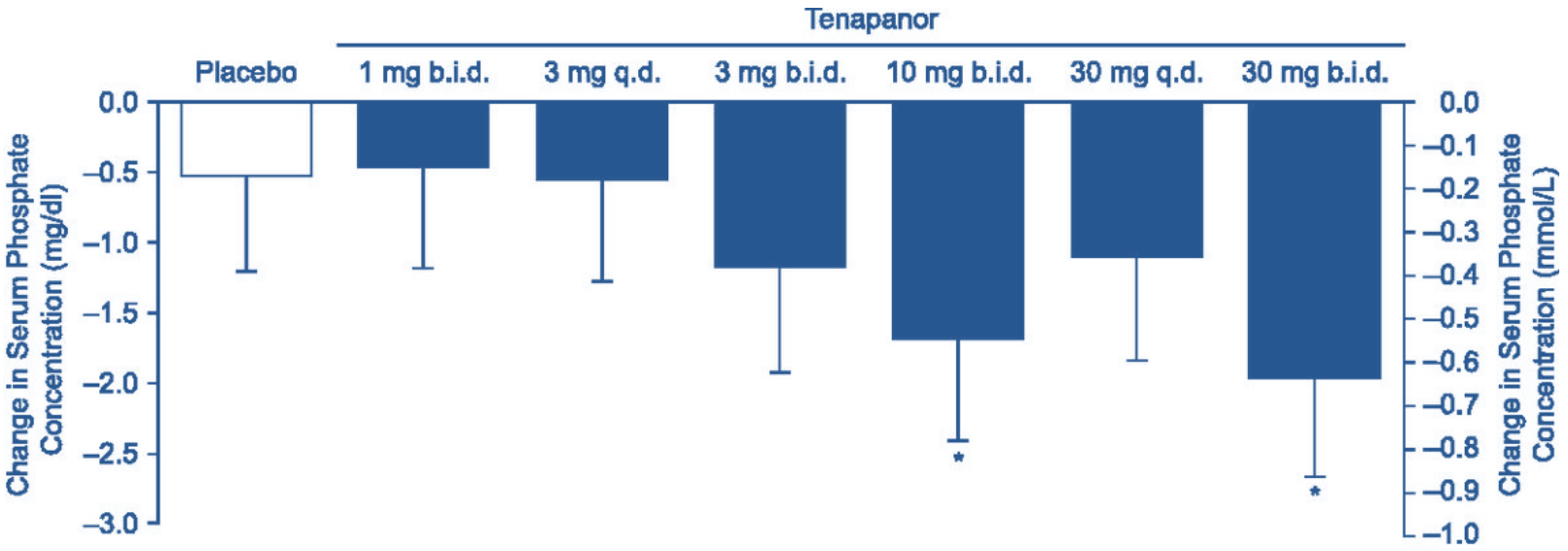
- A decrease of 8% in the relative risk of mortality was found for every 10% increase in the case-mix-adjusted facility prescription of phosphate-binding agents. All single and combined therapies with phosphate-binding agents, except aluminum salts, showed a beneficial association with survival.



Kidney International (2013) 84, 998–1008

Tenapanor (inhibitor of NHE3)

Double-blinde, placebo-controlled trial
N=162 → 115 pts on HD
1-3 weeks wash out
P:6-<10mg/dl and a 1.5mg/dl decrease
Duration= 4 weeks
Six tenapanor regimens



Serum Phosphate Concentration (mg/dl)							
Baseline[a]	7.87±1.49	7.55±1.00	7.73±1.28	7.32±1.01	7.92±1.06	7.61±0.85	7.76±1.18
Change from Baseline at EOT/ET[b]	–0.54 (–1.21, 0.13)	–0.47 (–1.18, 0.24)	–0.56 (–1.28, 0.17)	–1.18 (–1.93, –0.44)	–1.70 (–2.41, –0.99)	–1.11 (–1.85, –0.37)	–1.98 (–2.67, –1.28)
n (baseline, EOT/ET)	26, 26	23, 23	22, 22	21, 21	23, 23	21, 21	25, 24

Journal of the American Society of Nephrology 2017;28(6):1933-1942

Tenapanor-Biomarkers end points

Biomarker	Placebo, *n*=26	Tenapanor					
		1 mg Twice Daily, *n*=23	3 mg Once Daily, *n*=22	3 mg Twice Daily, *n*=21	10 mg Twice Daily, *n*=23	30 mg Once Daily, *n*=21	30 mg Twice Daily, *n*=26
Serum PTH							
Baseline serum PTH, ng/L[a]	438.8±288.8	392.3±265.4	472.0±297.6	515.8±321.5	435.8±195.5	429.3±297.3	386.1±277.1
Least squares mean change from baseline at EOT/ET, ng/L[b]	16.9	23.6	29.2	−32.9	−59.1	−71.2	−40.9
95% CI	−53.8 to 87.6	−50.5 to 97.7	−46.5 to 104.9	−111.0 to 45.2	−131.3 to 13.2	−150.7 to 8.3	−113.3 to 31.5
n (Baseline, EOT/ET)	26, 24	23, 22	22, 21	21, 20	23, 23	21, 19	25, 23
Serum FGF23							
Baseline serum FGF23, pg/ml[c]	4937 (206)	4052 (264)	3057 (255)	2601 (231)	6294 (202)	5312 (218)	4491 (347)
Ratio of geometric least squares mean between EOT/ET and baseline[d]	1.22	0.91[e]	0.89[e]	0.76[f]	0.72[f]	0.73[f]	0.81[f]
95% CI	1.00 to 1.48	0.74 to 1.11	0.72 to 1.09	0.62 to 0.93	0.59 to 0.88	0.57 to 0.92	0.66 to 0.98
n (Baseline, EOT/ET)	23, 22	21, 19	21, 20	21, 19	20, 22	18, 15	22, 21

EOT, end of treatment; ET, early termination.
[a]Mean±SD.
[b]P=0.31 (analysis of covariance; F test).
[c]Geometric mean (coefficient of variation; %).
[d]Analysis of covariance; *post hoc*.
[e]P<0.05 for ratio of geometric least squares means (EOT/ET) to placebo (analysis of covariance; t test *post hoc*).
[f]P<0.01 for ratio of geometric least squares means (EOT/ET) to placebo (analysis of covariance; t test *post hoc*).

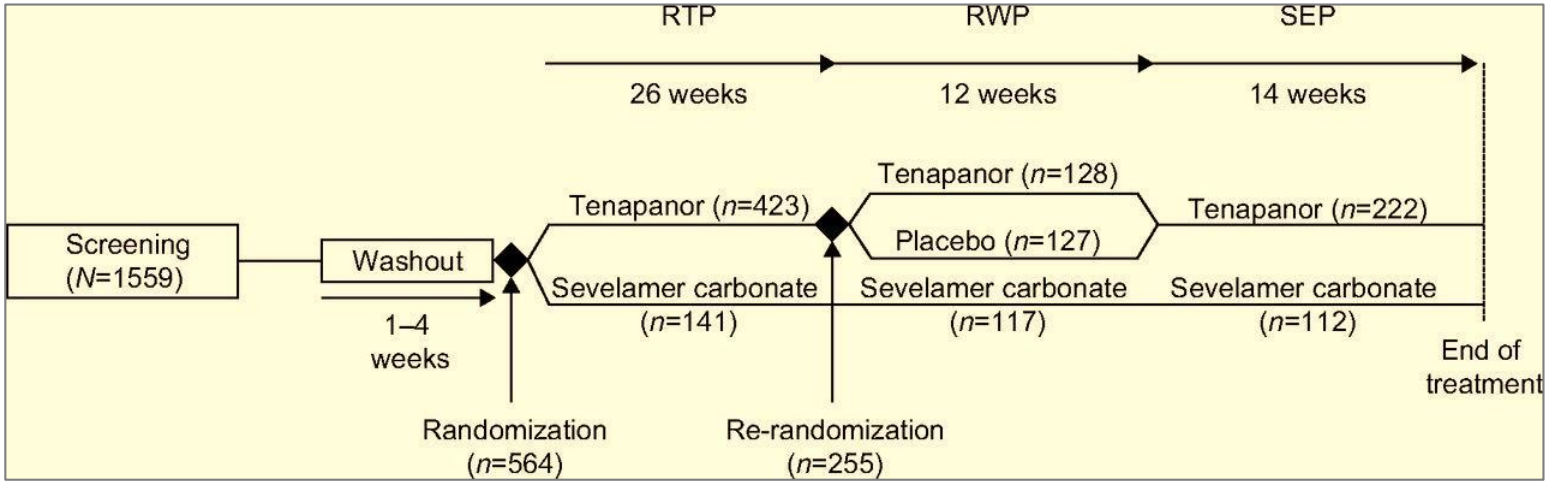
Journal of the American Society of Nephrology 2017;28(6):1933-1942

Original Investigation

Kidney360

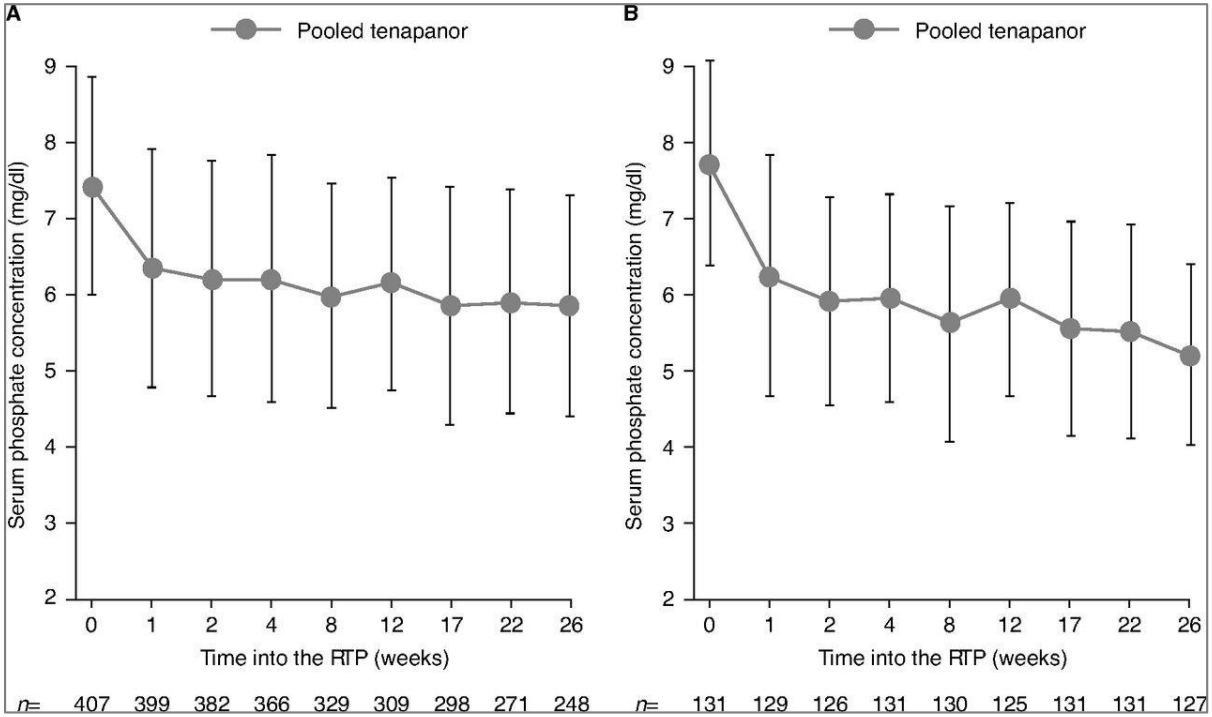
Safety and Efficacy of Tenapanor for Long-term Serum Phosphate Control in Maintenance Dialysis: A 52-Week Randomized Phase 3 Trial (PHREEDOM)

Geoffrey A. Block,[1] Anthony J. Bleyer,[2] Arnold L. Silva,[3] Daniel E. Weiner,[4] Robert I. Lynn,[5,6] Yang Yang,[7] David P. Rosenbaum,[8] and Glenn M. Chertow[9]; on behalf of the PHREEDOM Study Investigators*



Overview of study design. The safety analysis set included all participants who received at least one dose of the study drugs for the study period. RTP, randomized treatment period; RWP, randomized withdrawal period; SEP, safety extension period.

Safety and Efficacy of Tenapanor for Long-term Serum Phosphate Control in Maintenance Dialysis: A 52-Week Randomized Phase 3 Trial (PHREEDOM)



Change in serum phosphate concentration in participants receiving tenapanor during the 26-week RTP. Serum phosphate concentration in participants receiving tenapanor over the 26-week RTP for the (A) ITT analysis set and (B) the subset of participants who achieved a reduction of ≥1.2 mg/dl in serum phosphate from baseline at week 26 and continued into the randomized withdrawal period. Data are mean serum phosphate concentrations ±SD.

Wolters Kluwer

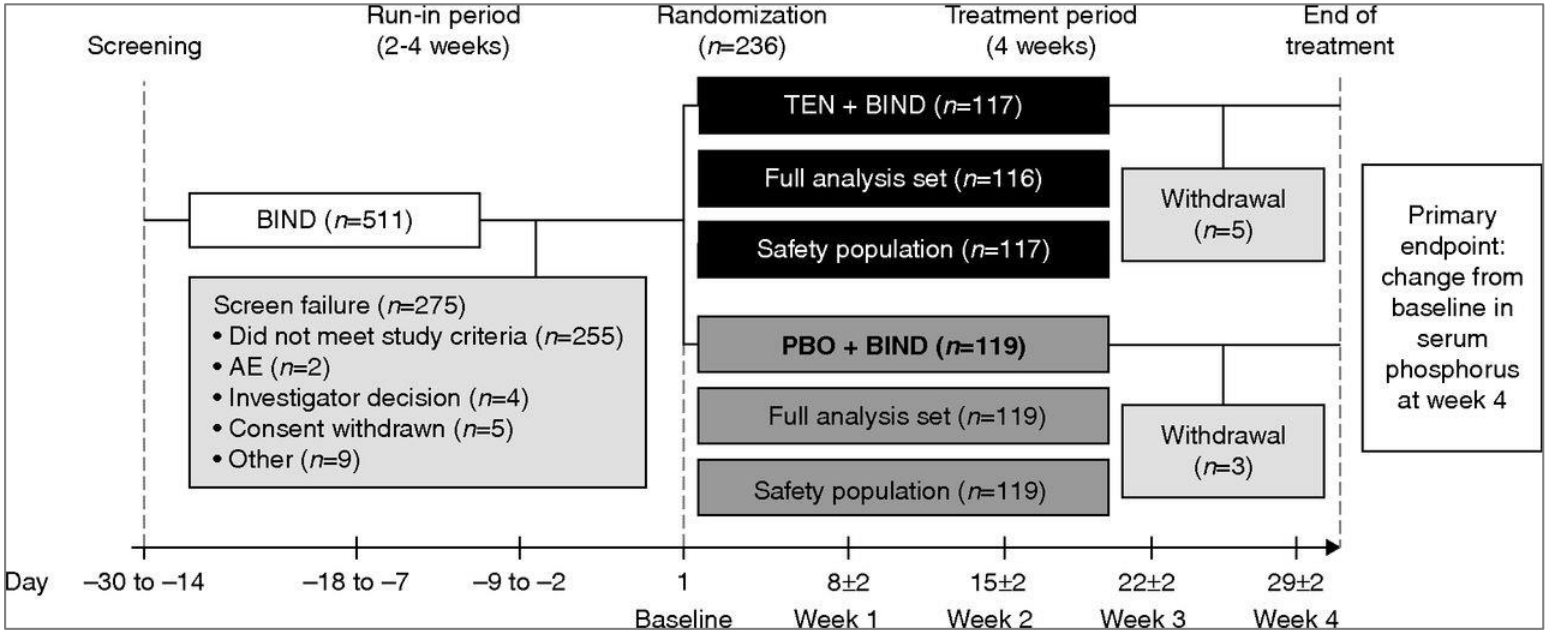
Kidney360 2021;2(10):1600-1610

Safety and Efficacy of Tenapanor for Long-term Serum Phosphate Control in Maintenance Dialysis: A 52-Week Randomized Phase 3 Trial (PHREEDOM)

Key Points

- Tenapanor is a first-in class inhibitor of NHE3 and acts *via* a nonphosphate-binding mechanism to reduce intestinal phosphate absorption.
- In the efficacy analysis set, patients randomized to tenapanor experienced a decrease in serum phosphate from 7.7 mg/dl to 5.1 mg/dl.
- Diarrhea was the only drug-related adverse event reported for more than 5% of patients and resulted in drug discontinuation in 16% of patients.

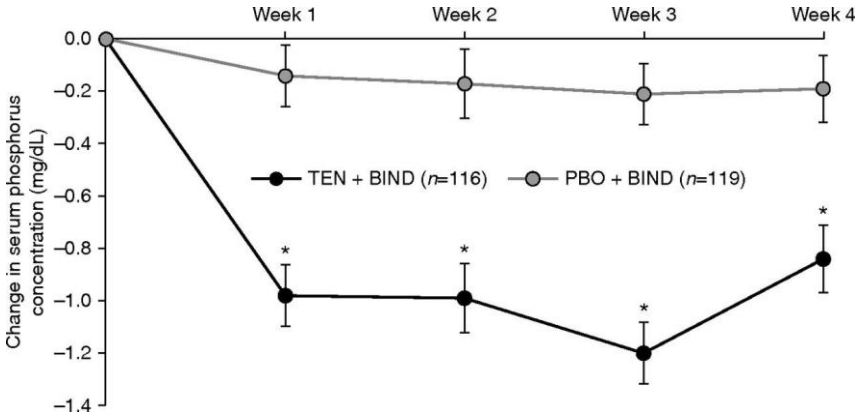
A Randomized Trial of Tenapanor and Phosphate Binders as a Dual-Mechanism Treatment for Hyperphosphatemia in Patients on Maintenance Dialysis (AMPLIFY)



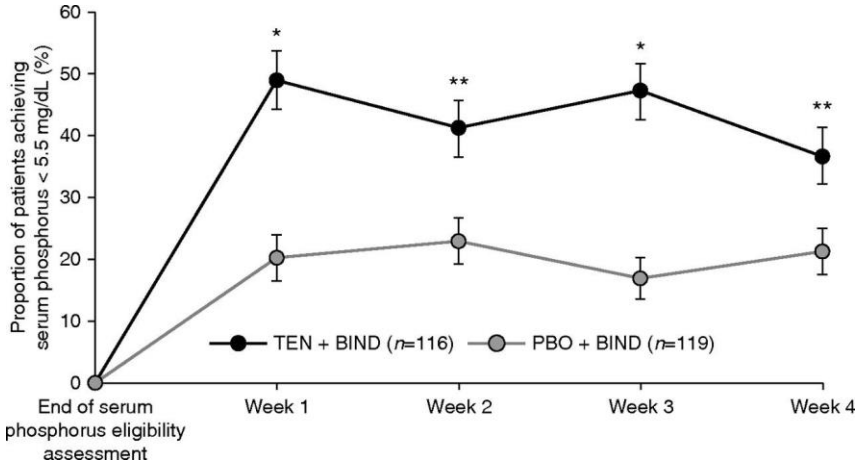
Journal of the American Society of Nephrology 2021;32(6):1465-1473

A Randomized Trial of Tenapanor and Phosphate Binders as a Dual-Mechanism Treatment for Hyperphosphatemia in Patients on Maintenance Dialysis (AMPLIFY)

Change in serum phosphorus concentration from baseline over time to week 4

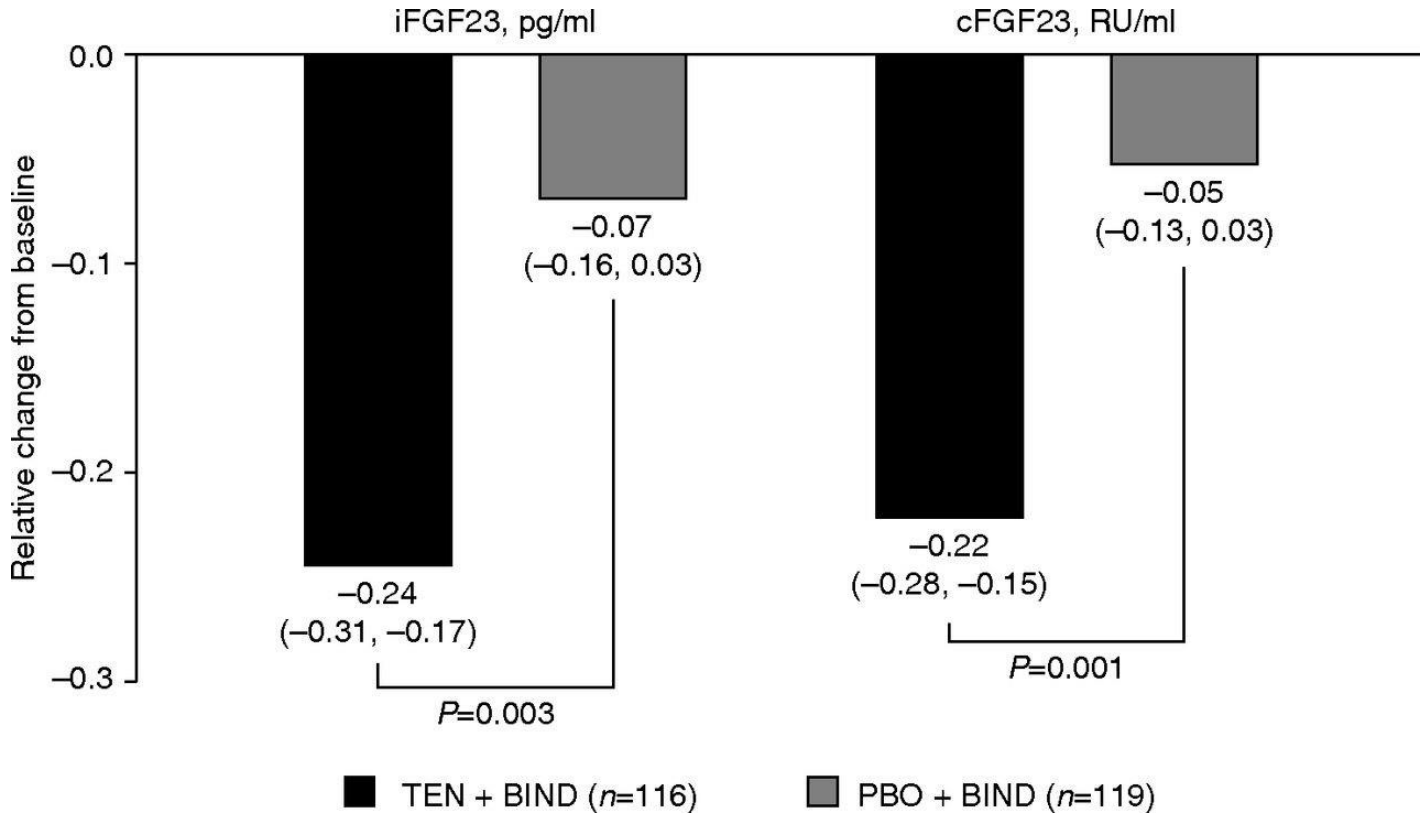


Proportion of patients achieving serum phosphorus below 5.5 mg/dl at weeks 1–4



Journal of the American Society of Nephrology 2021;32(6):1465-1473

A Randomized Trial of Tenapanor and Phosphate Binders as a Dual-Mechanism Treatment for Hyperphosphatemia in Patients on Maintenance Dialysis (AMPLIFY)



Relative change from baseline at week 4 in concentrations of iFGF23 and cFGF23

Journal of the American Society of Nephrology 2021;32(6):1465-1473

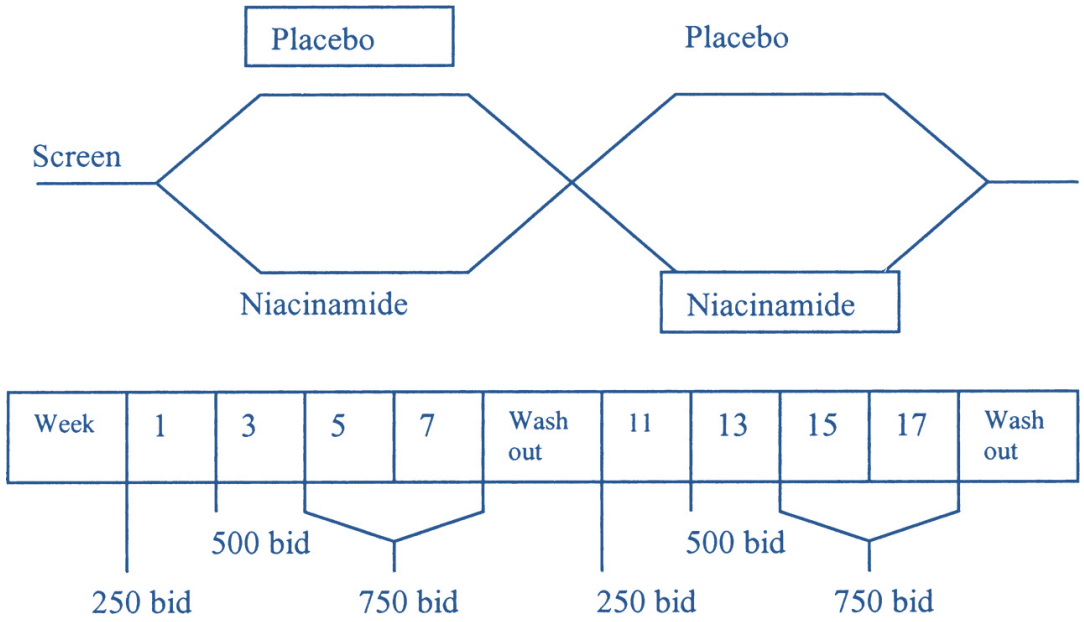
Niacinamide for Reduction of Phosphorus in Hemodialysis Patients

Niacinamide= a major form of vit. B3

Decreases P uptake by inhibiting Na/P co-transporters in renal proximal tubule (Na/Pi2a) and intestine (Na/Pi2b).

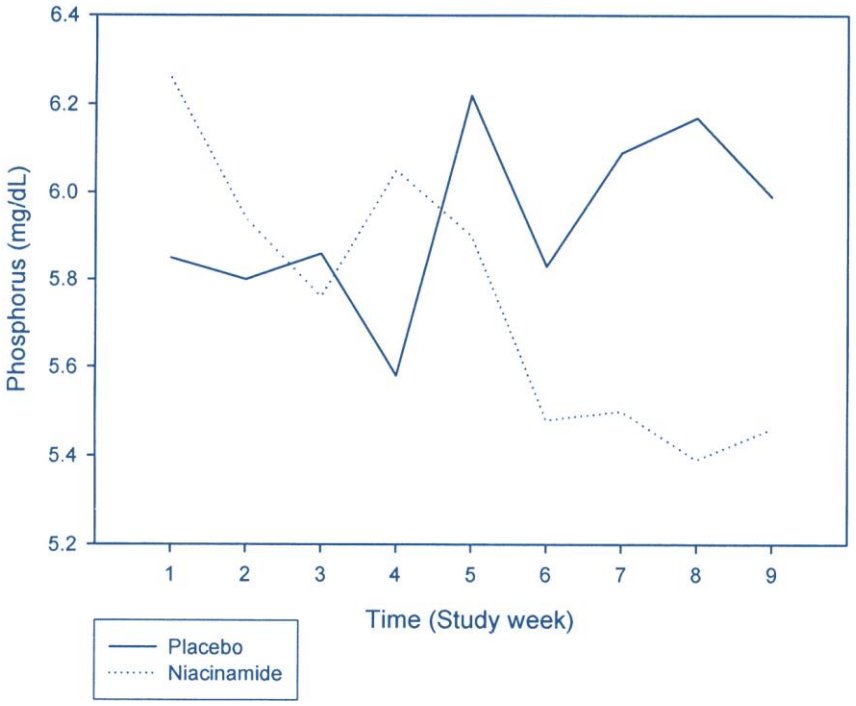
A Randomized, Double-Blind, Placebo-Controlled Trial of Niacinamide for Reduction of Phosphorus in Hemodialysis Patients:

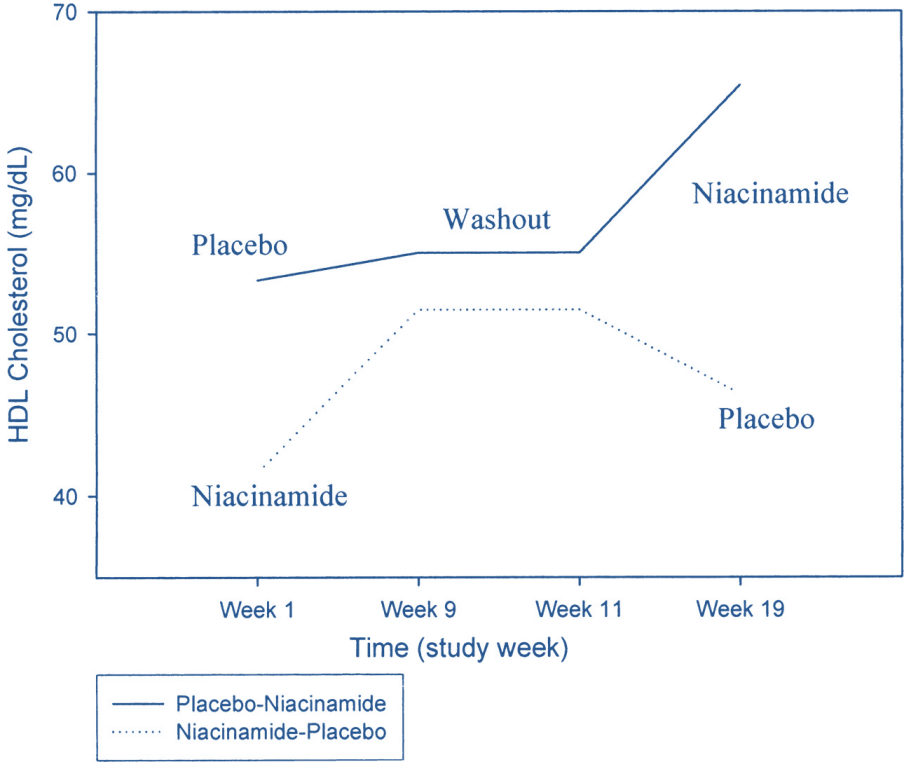
After a 2-wk screening phase, patients were randomly assigned to 8 wk of niacinamide or placebo with titration from 250 to 750 mg twice daily. A 2-wk washout preceded the switch from niacinamide to placebo or vice versa.



Clinical Journal of the American Society of Nephrology 2008;3(4):1131-1138

Niacinamide for Reduction of Phosphorus in Hemodialysis Patients





Serum phosphorus levels rose during the 8 wk of the placebo arm (solid line) but decreased significantly during treatment with niacinamide. Decrease of Ca x P from 61 to 51 (p=0.003)

HDL cholesterol levels increased significantly on niacinamide (50 to 61 mg/dl; P = 0.035).

Clinical Journal of the American Society of Nephrology 2008;3(4):1131-1138

Modified-release nicotinamide for the treatment of hyperphosphataemia in haemodialysis patients: 52-week efficacy and safety results of the phase 3 randomized controlled NOPHOS trial

Background

Modified-release nicotinamide (NAMR) was superior to placebo in reducing serum phosphate concentrations over 12 weeks in a large cohort of haemodialysis patients with hyperphosphataemia in spite of treatment with one or two phosphate binders. Here, long-term follow-up outcomes after 52 weeks of treatment are presented.

Methods

96 sites
(Germany, Poland, Austria)

Haemodialysis patients
Intake of 1 or 2 phosphate binders
Serum phosphate > 4.5 mg/dl

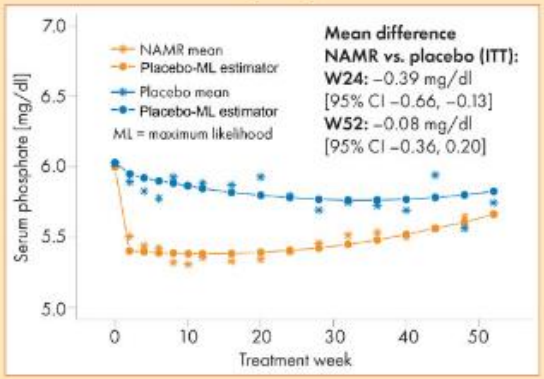
3:1

NAMR N = 539 — Add-on therapy — **Placebo** N = 183

Follow-up: 52 weeks

Results

Serum phosphate



Adverse events

NAMR was associated with an increased risk of:

- Diarrhoea
- Anaemia
- Thrombocytopenia
- Pruritus
- Herpes zoster

Conclusion

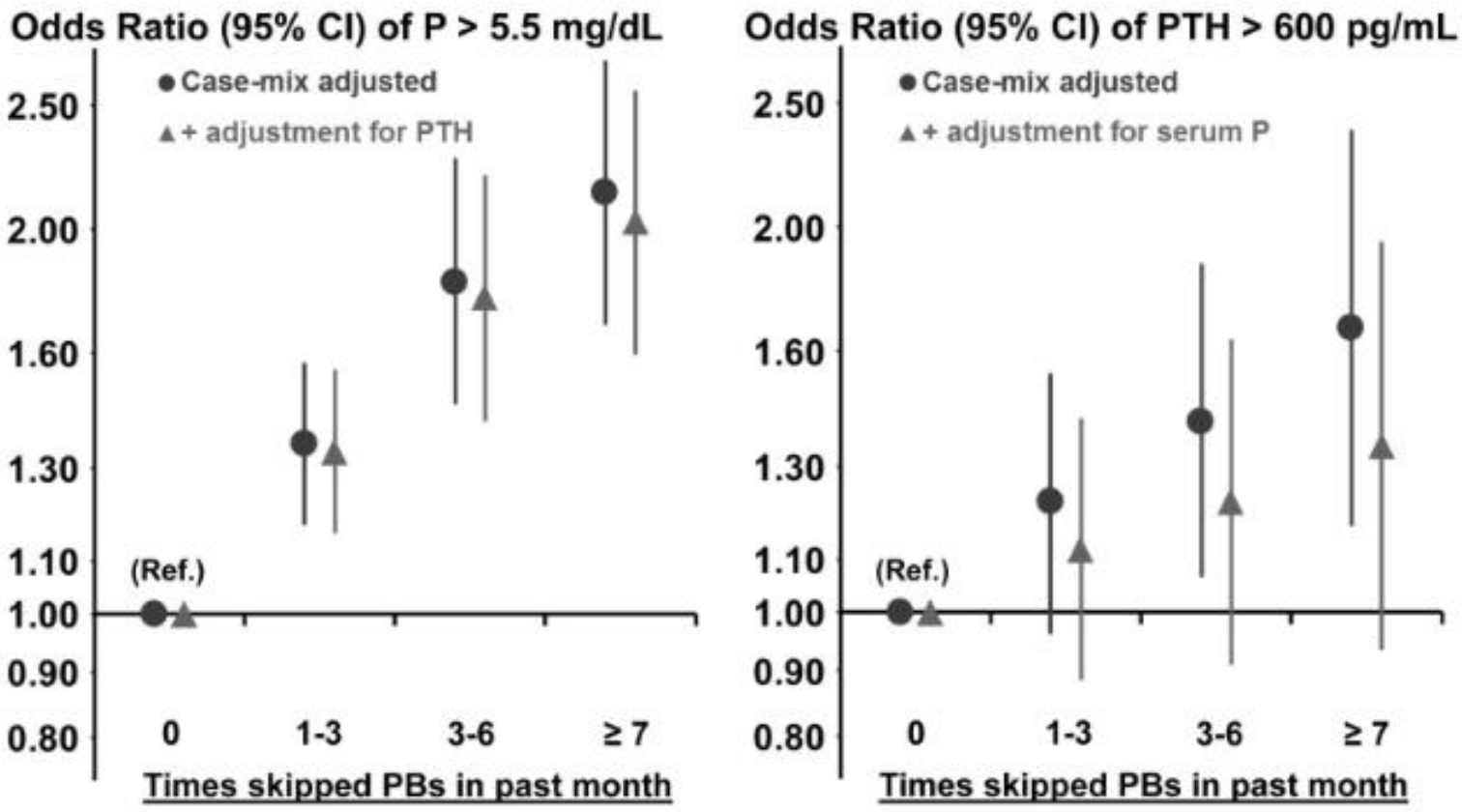
NAMR combined with phosphate binders significantly reduced serum phosphate over the first 24 weeks of treatment, but the treatment effect was not maintained up to week 52.

NEPHROLOGY DIALYSIS TRANSPLANTATION

Ketteler, M., et al. NDT (2022)
@NDTSocial

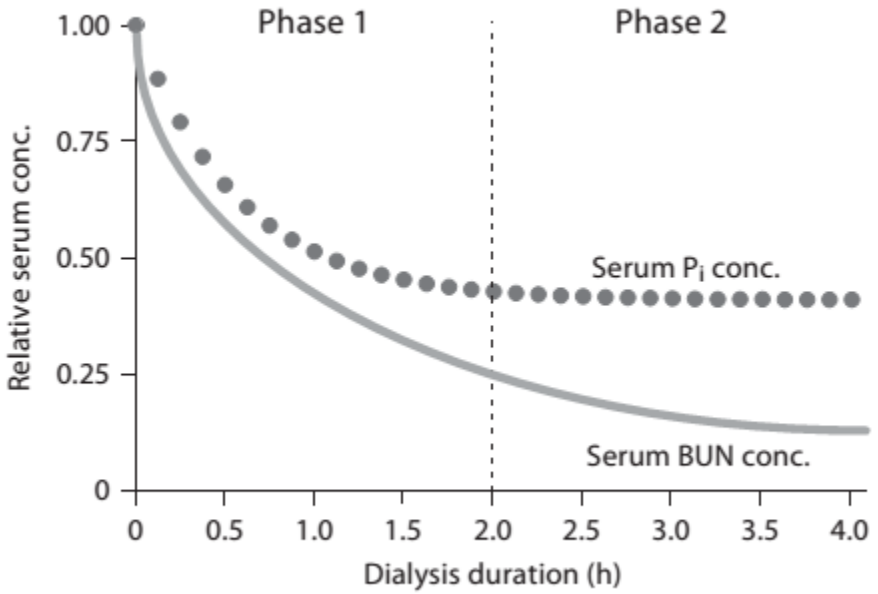
Nephrol Dial Transplant (2023) 38: 982–991

Phosphate pill burden, patient-reported non-adherence and mineral bone disorder markers: Findings from the DOPPS



Hemodial Int. 2016 January ; 20(1): 38–49

Phosphate elimination



Blood Purif 2010;29:137–144

Phosphorus Removal in Low-Flux Hemodialysis, High-Flux Hemodialysis, and Hemodiafiltration

	Mean ± SEM			*P* Value			
Variable	HDF	HFHD	LFHD	HDF *vs* HFHD	HDF *vs* LFHD	HFHD *vs* LFHD	Globa
M(P) (mmol)	38.3 ± 1.4	37.8 ± 1.6	34.0 ± 1.2	0.962	0.033*	0.062	0.023*
VB (l/procedure)	74.5 ± 2.6	74.5 ± 2.5	74.9 ± 2.5	0.999	0.955	0.966	0.952
Initial P (mmol/l)	2.0 ± 0.11	2.1 ± 0.11	1.9 ± 0.09	0.637	0.549	0.131	0.155
sp*Kt/V*	1.5 ± 0.05	1.5 ± 0.05	1.5 ± 0.04	0.540	0.998	0.505	0.455
UFR (ml/min)	10.2 ± 0.5	10.4 ± 1.2	12.6 ± 0.8	0.980	0.074	0.112	0.055

P values of the pair wise comparisons are based on the Tukey's post-hoc test.
*$p < 0.05$; Global *p* values are derived from the one-way analysis of variance with repeated measures.
HDF, hemodiafiltration; HFHD, high-flux hemodialysis; LFHD, low-flux hemodialysis; *M*(P), removed phosphorus; SEM, standard error of the mean; VB, cumulative blood flow; UFR, ultrafiltration rate.

Comment: statistically significant increase in P removal was seen only in the use of high-flux membrane (HFHD and HDF when compared with the low-flux one. It can be concluded that P removal in all 3 dialysis modes is a predominantly diffusive issue and contribution of convection to it is minor to negligible

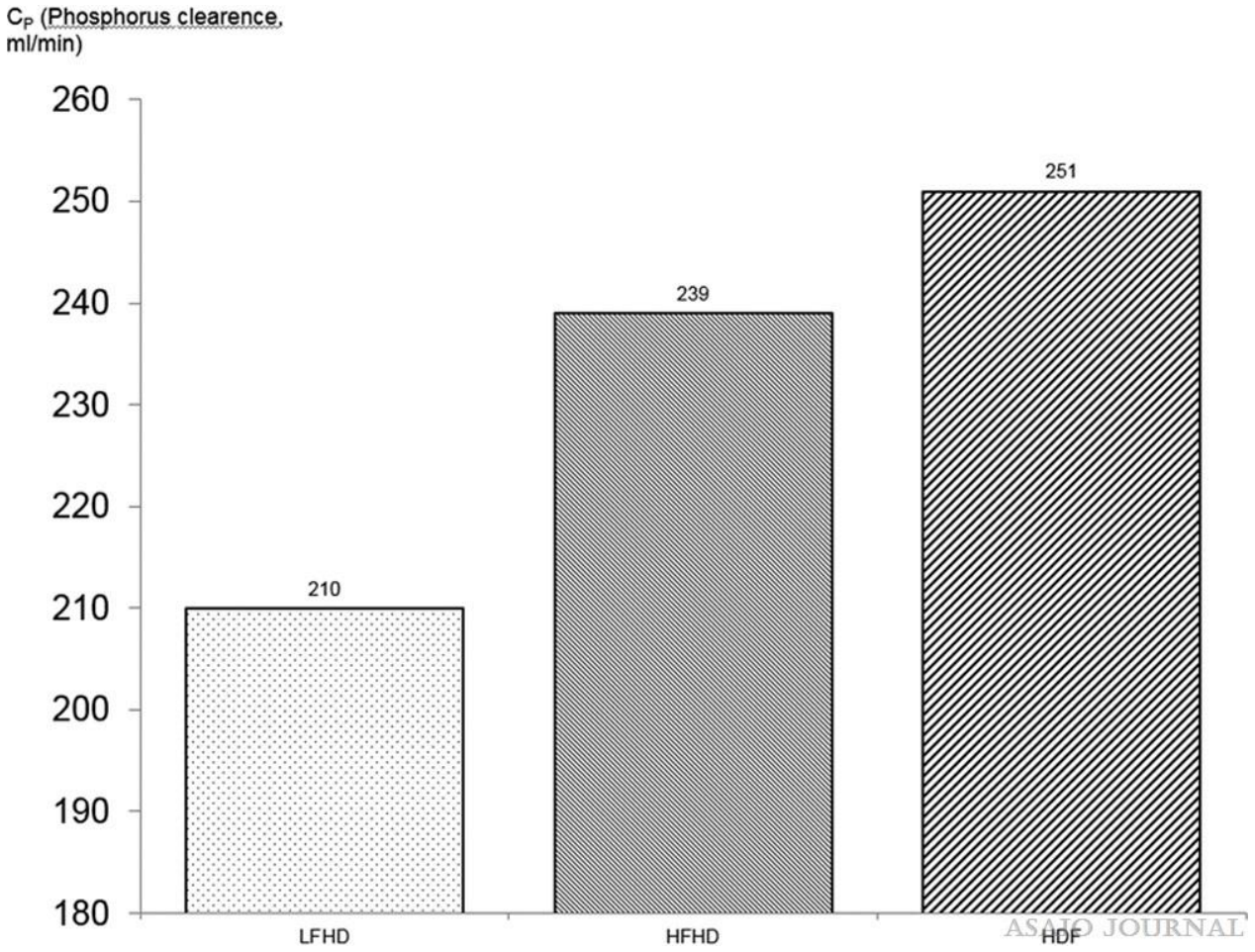
ASAIO Journal 2016;62(2):176-181

Phosphate elimination in modalities of Hemodialysis and Peritoneal Dialysis

Modality and ref.	P_i mass removal mg/week	Dialysis schedule	Flow rates ml/min	Treatment specifications
Hemodialysis				
HD high-flux [8]	2,356 ± 864	3 × 230 min	Q_B: 323 ± 22 Q_D: 500	UFV 1.8 ± 0.8 liters
HD + passive muscle activity [9]	PCM: 3,515 ± 945 TEMS: 3,591 ± 795	3 × 195–240 min	Q_B: 300–400 Q_D: 600	S-P_i 5.1 ± 0.9 mg/dl
HD – double dialyzer [10]	2,970 mg	3 × 4 h	Q_B: 350–400 Q_D: 800	F80A or F160 dialyzers S-P_i 5.3 mg/dl
Postdilution HDF [11]	3,570 ± 270 mg	3 × 4 h	Q_B: 315–345 Q_D: 500	F8 dialyzer, MSA 1.8 m^2 Q_{UF} 25–35 ml/min
Mixed-dilution HDF [12]	975 ± 272 mg/Tx (2,975 mg/week)	231 ± 18 min	Q_B: 385 ± 20 Q_D: 625 ± 16	Q_{UF} 181 ± 12 ml/min MSA 1.8 m^2
SDHD [13]	2,452 ± 720 mg	6 × 3 h	Q_B: 400 Q_D: 800	high-flux dialyzer S-P_i 4.2 mg/dl
NHD [14]	8,000 ± 2,800	6 × 6–8 h	Q_B: 150–300 Q_D: 300	high-flux dialyzer F80
	P_i mass removal mg/week	Dwell time h	Flow rates ml/min	Treatment specifications
Peritoneal dialysis				
APD, CCPD [8]	2,739 ± 1,042	18.5 ± 7.3	–	DV 13.2 ± 3.5 liters ex. 5.5 ± 1.1 S-P_i 5.0 ± 1.4 mg/dl
CAPD [8]	2,790 ± 1,022	24.0	–	DV 10.5 ± 2.1 liters ex. 4.2 ± 0.5 S-P_i 4.2 ± 0.9 mg/dl

Blood Purif 2010;29:137–144

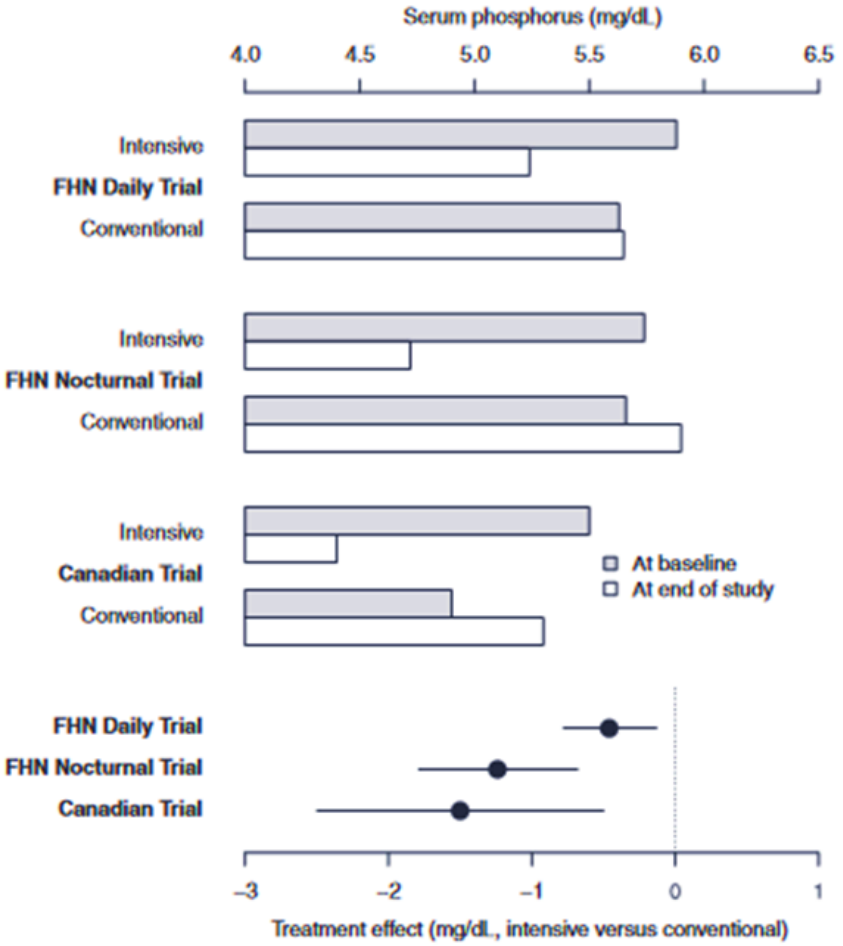
Phosphorus Removal in Low-Flux Hemodialysis, High-Flux Hemodialysis, and Hemodiafiltration

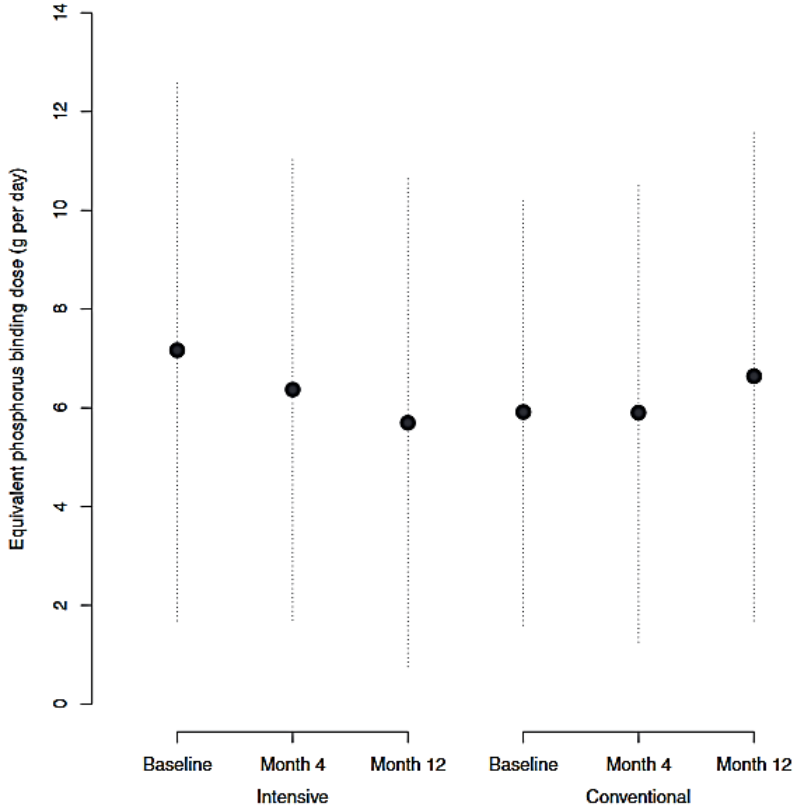


Calculated phosphorus clearance

ASAIO Journal 2016;62(2):176-181

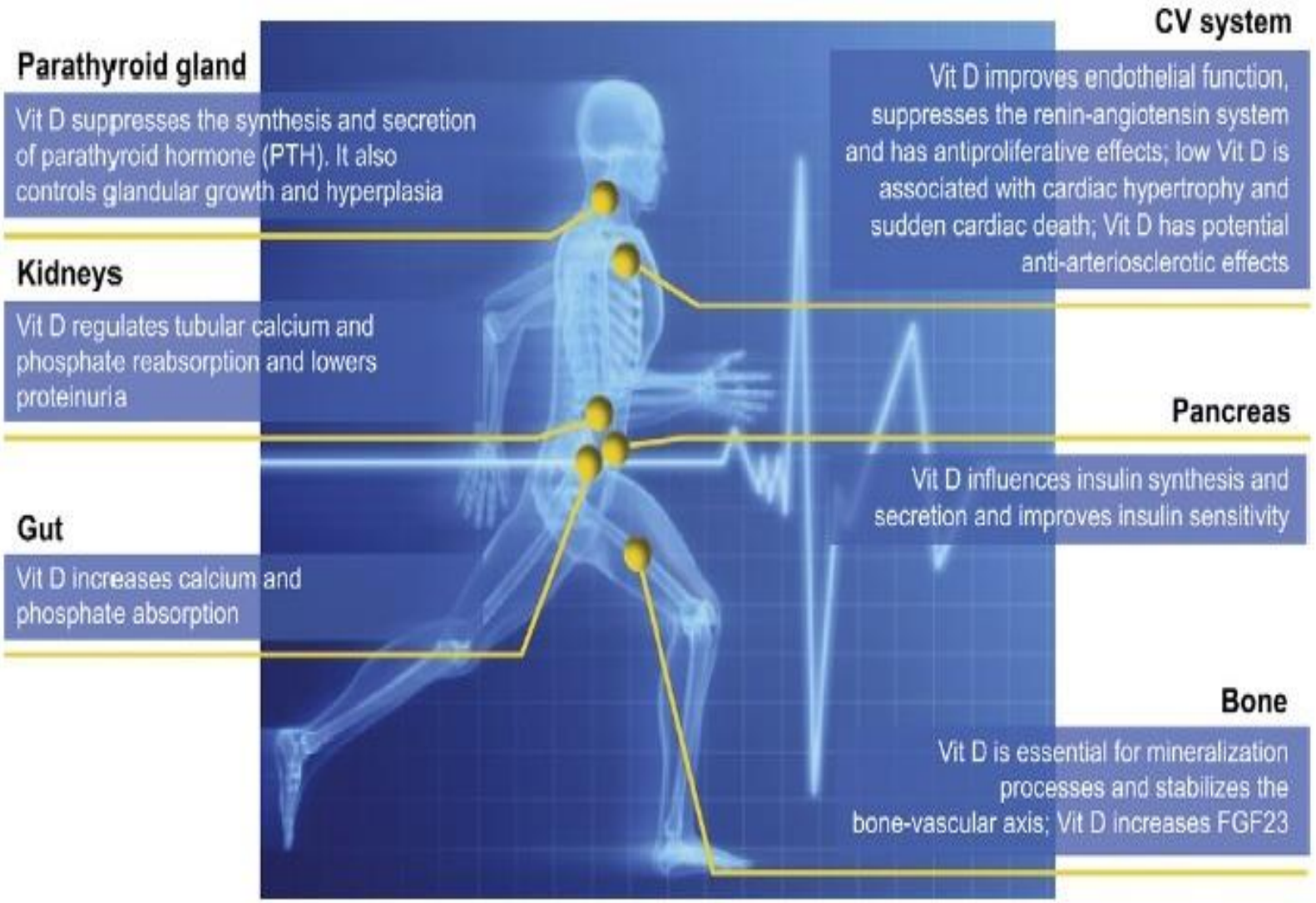
Intensive Hemodialysis, Mineral and Bone Disorder, and Phosphate Binder Use



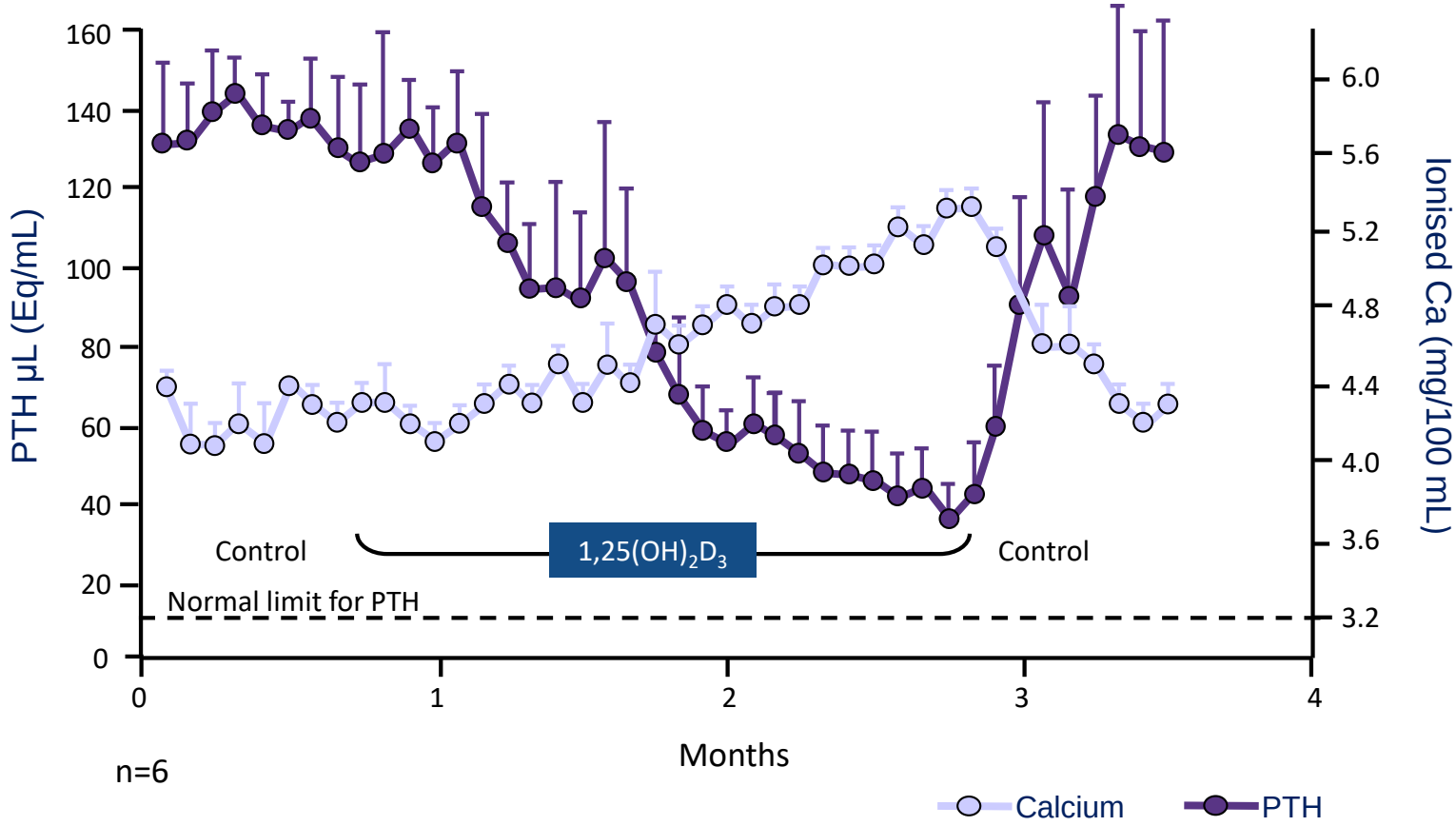


Am J Kidney Dis 2016;68(5)(suppl 1):S24-S32

Pleotropic actions of vit.D

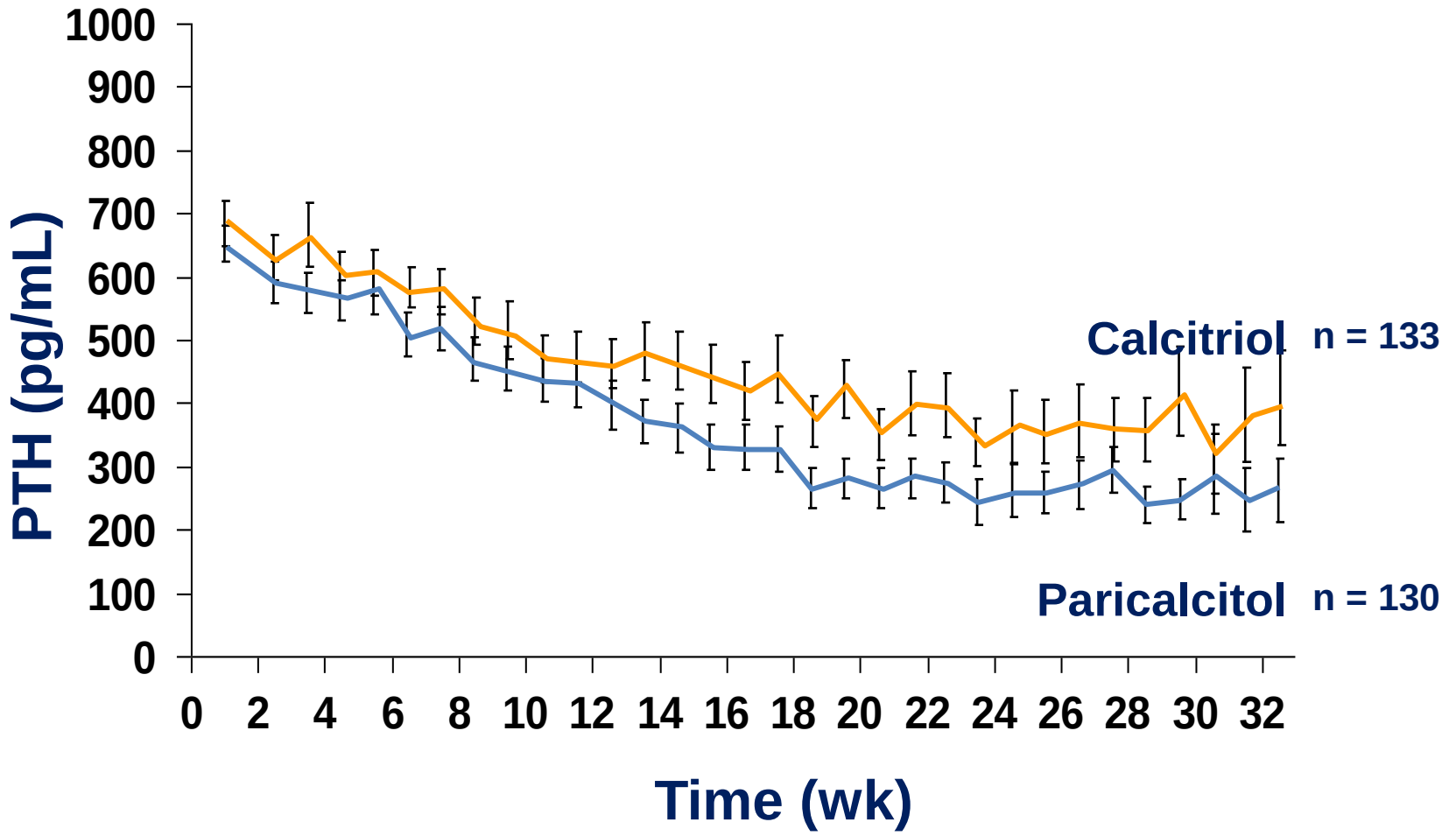


Vitamin D increases serum Ca levels



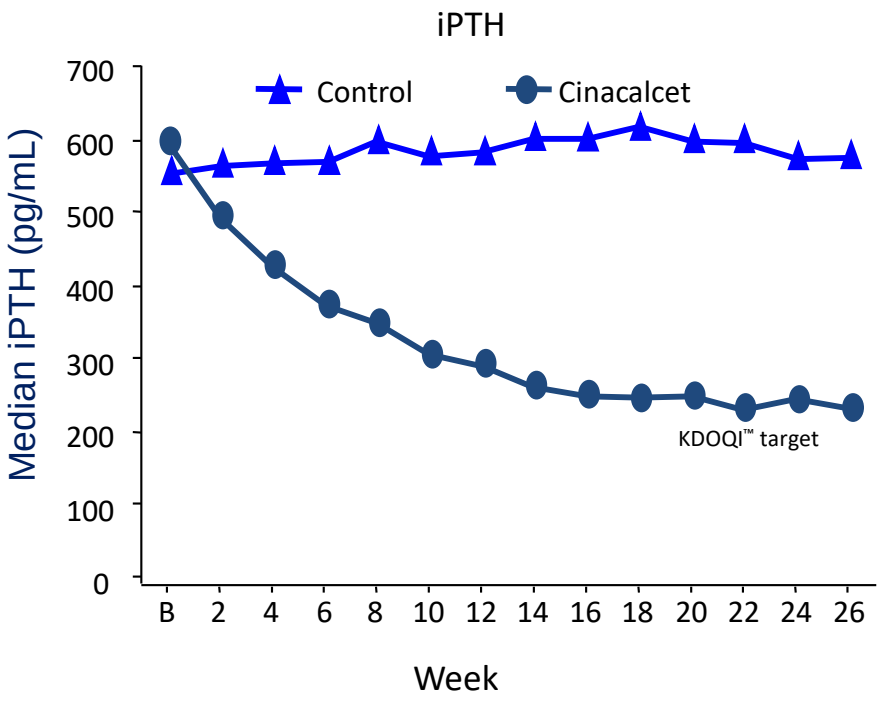
J Clin Invest 1984;74:2136–2143

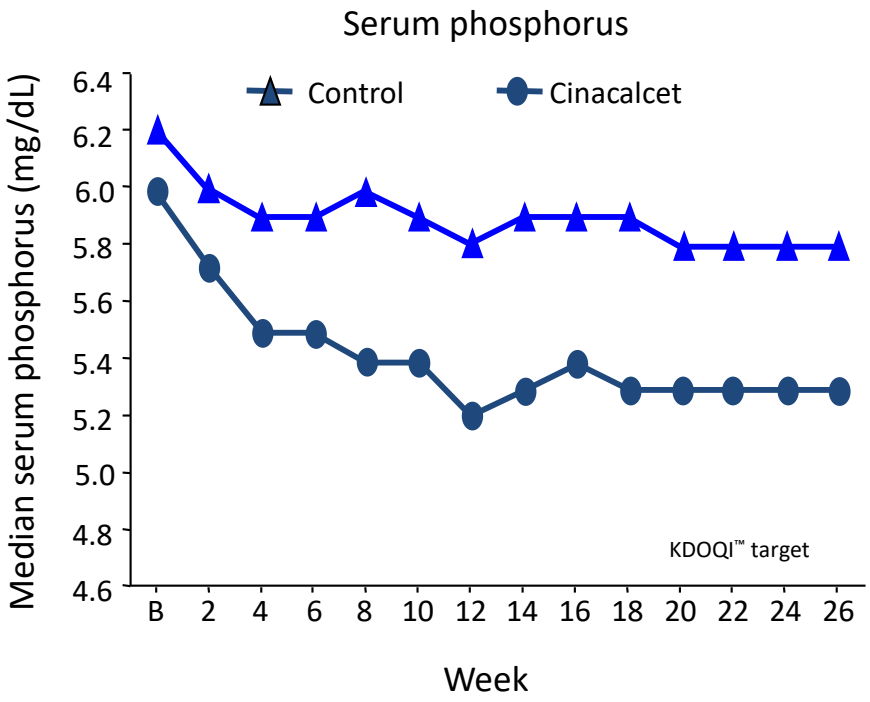
Σύγκριση της Καλσιτριόλης και Παρικαλσιτόλης στην ελάττωση των επιπέδων της PTH σε αιμοκαθαιρόμενους ασθενείς



Kidney Int. 2003;63:1483-1490

Cinacalcet improves PTH and P control simultaneously

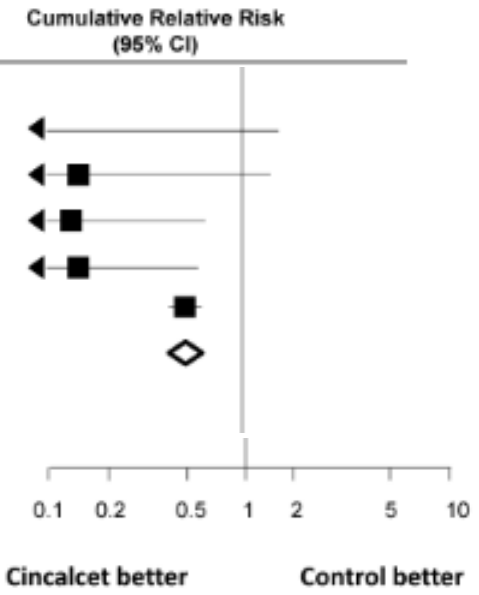




Kidney Int 2005;67:760–771

Cinacalcet in Patients with Chronic Kidney Disease: A Cumulative Meta-Analysis of Randomized Controlled Trials

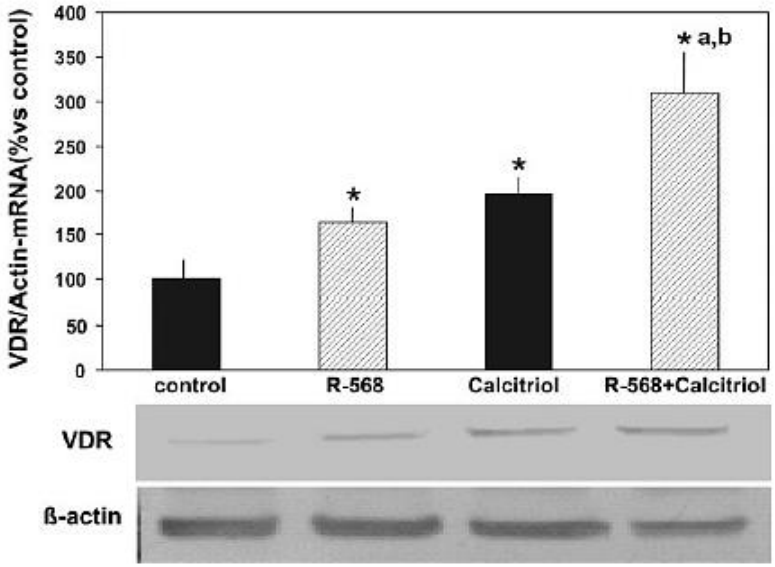
	Cumulative Events, *n/N*				Cumulative Relative Risk (95% CI)	Cumulative *P* value
	Calcimimetic		Control			
Parathyroidectomy						
Lindberg et al., 2005 (36)	1	295	3	102	0.07 (0.01 to 1.42)	0.08
ACHIEVE study., 2008 (37)	1	382	4	188	0.15 (0.02 to 1.30)	0.08
El Shafey et al., 2011 (44)	2	437	8	215	0.13 (0.03 to 0.62)	0.01
ADVANCE study., 2011 (43)	2	617	10	395	0.15 (0.04 to 0.57)	0.001
EVOLVE study., 2012 (23)	142	2565	288	2330	0.49 (0.40 to 0.59)	<0.001
Cumulative total	**142**	**2565**	**288**	**2330**	**0.49 (0.40 to 0.59)**	**<0.001**



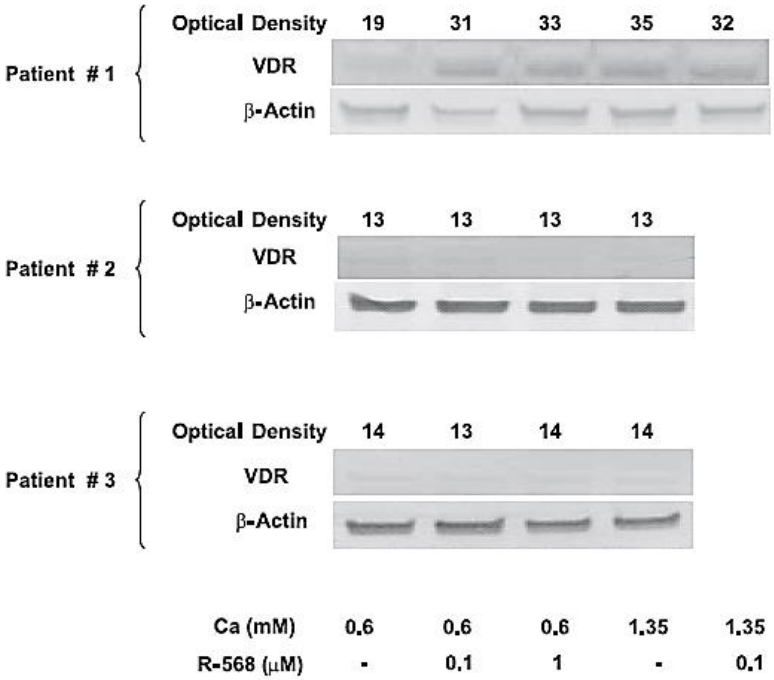
Cumulative meta-analysis of randomized trials comparing cinacalcet plus conventional therapy versus placebo or no treatment plus conventional therapy

PLoS Med. 2013 Apr; 10(4): e1001436

The calcimimetic R-568 increases vit.D receptor expression



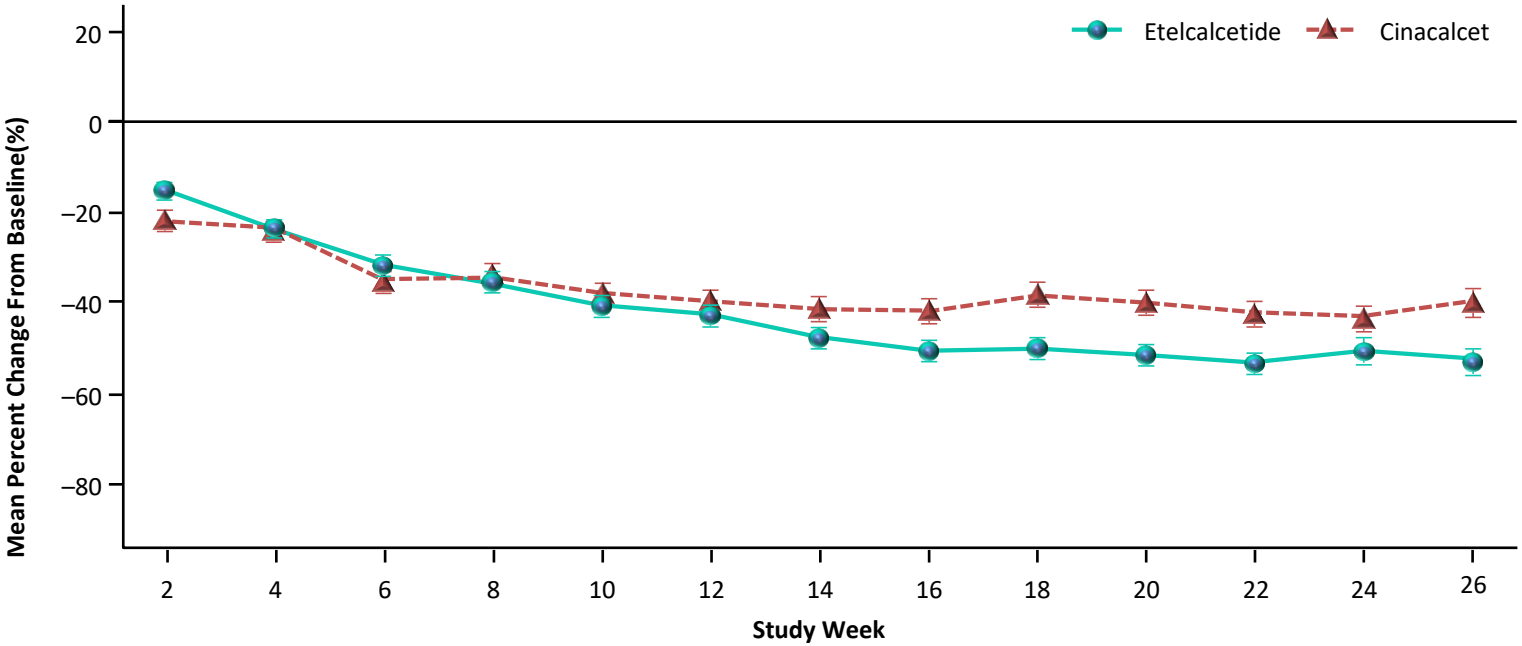
	control	R-568	Calcitriol	R-568+Calcitriol
PTH/Actin-mRNA (% vs control)	98 ± 18	51 ± 13*	89 ± 17	34 ± 11*
Plasma Ca^{2+} (mM)	1.34 ± 0.01	1.08 ± 0.06*	1.34 ± 0.03	1.26 ± 0.04
Plasma PTH (pg/ml)	22.1 ± 1.4	9.6 ± 1.9*	20.9 ± 1.5	14.1 ± 1.2*



Am J Physiol Renal Physiol 292: F1390–F1395, 2007.

Mean Percent Change From Baseline in PTH Over Time

Treatment with etelcalcetide resulted in a reduction from baseline in mean PTH compared to cinacalcet



Etelcalcetide n =	293	300	304	303	291	288	288	277	277	270	256	265	255
Cinacalcet n =	286	300	302	308	299	302	298	291	291	293	288	283	274

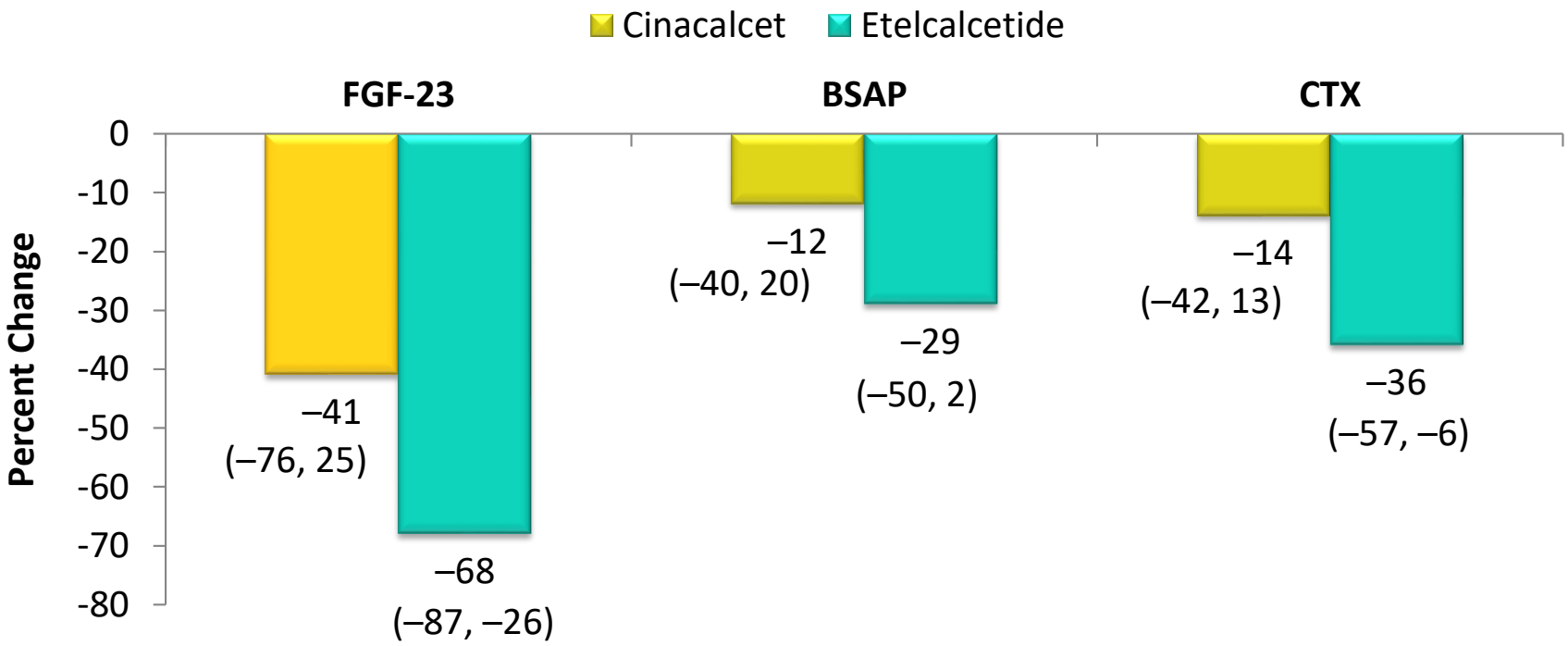
IP = investigational product; PTH = parathyroid hormone; SE = standard error.
On-treatment approach: data collected on or prior to the last on-missing dose of IP were summarized by visit. Vertical lines represent SE.

Martin KJ, et al. Poster Presented at the 2015 ASN Annual Meeting;November 3-8, 2015;San Diego, CA (# SA-PO1115).

Changes in Biomarkers: FGF-23, BSAP, and CTX

(Median Percent Change From Baseline to Week 27)

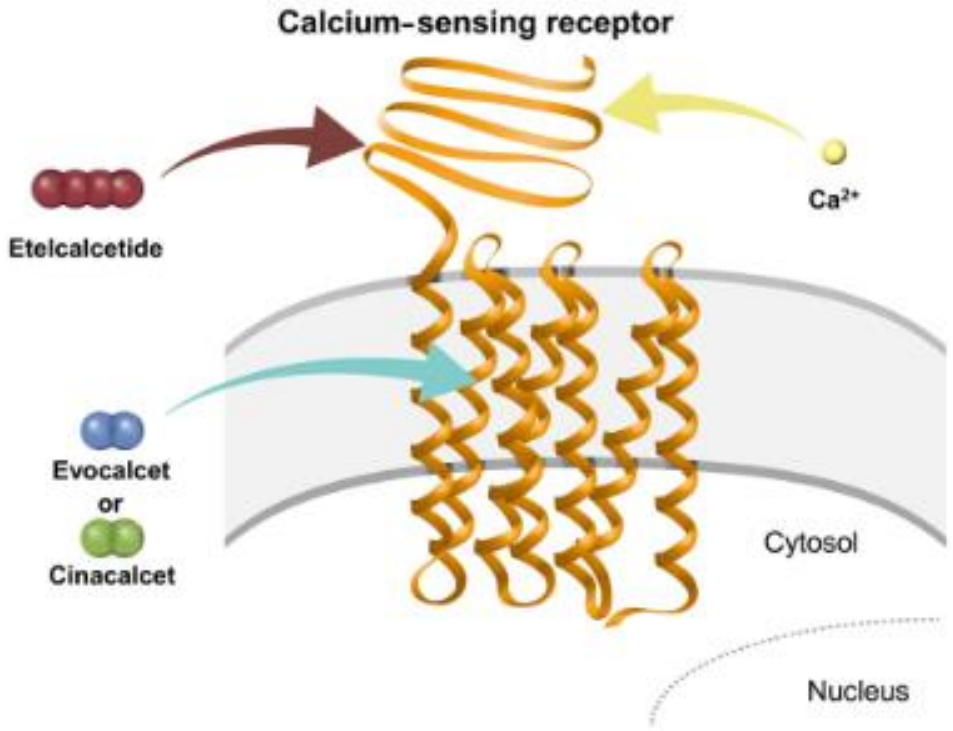
Etelcalcetide was associated with greater reductions in FGF-23, BSAP, and CTX from baseline to week 27 compared with cinacalcet



BSAP = bone-specific alkaline phosphatase; CTX = type 1 collagen C-telopeptide; FGF = fibroblast growth factor; SE = standard error.

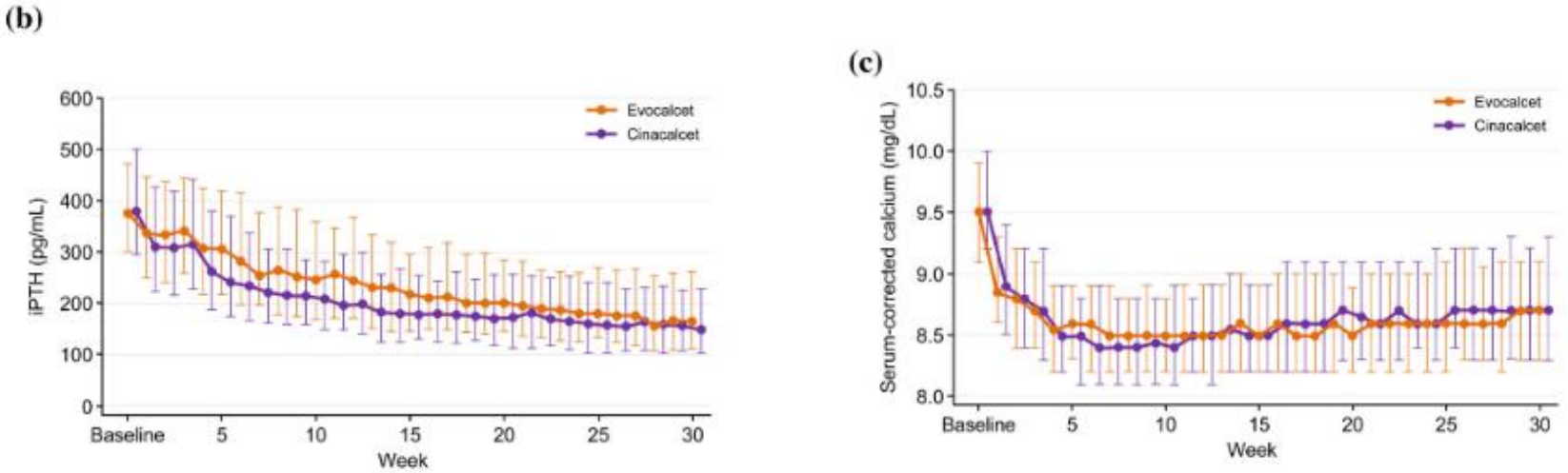
Martin KJ, et al. Poster Presented at the 2015 ASN Annual Meeting;November 3-8, 2015;San Diego, CA (# SA-PO1115).

Evocalcet: A new oral Calcimimetic for Dialysis Patients with Secondary Hyperparathyroidism



Therapeutic Apheresis and Dialysis 2020; 24(3):248–257

Evocalcet: A new oral Calcimimetic for Dialysis Patients with Secondary Hyperparathyroidism



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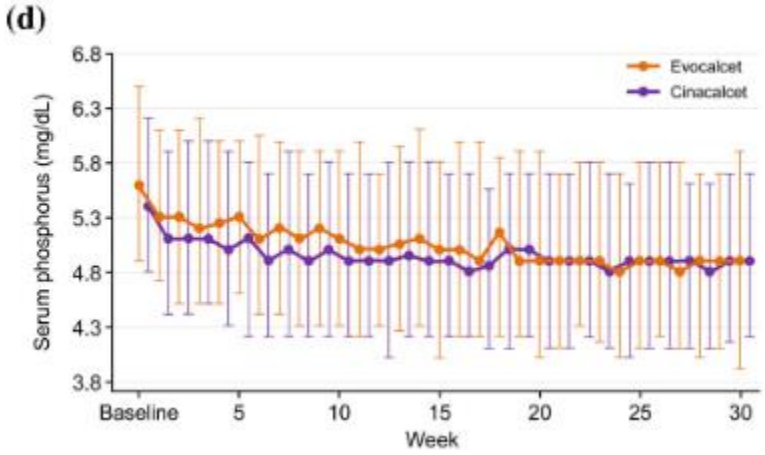
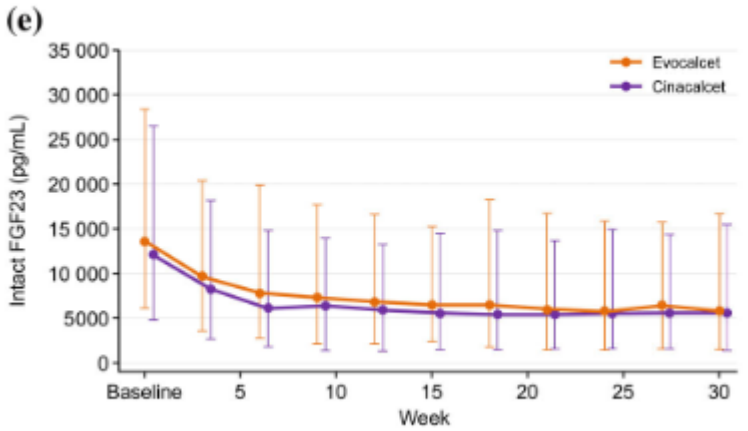
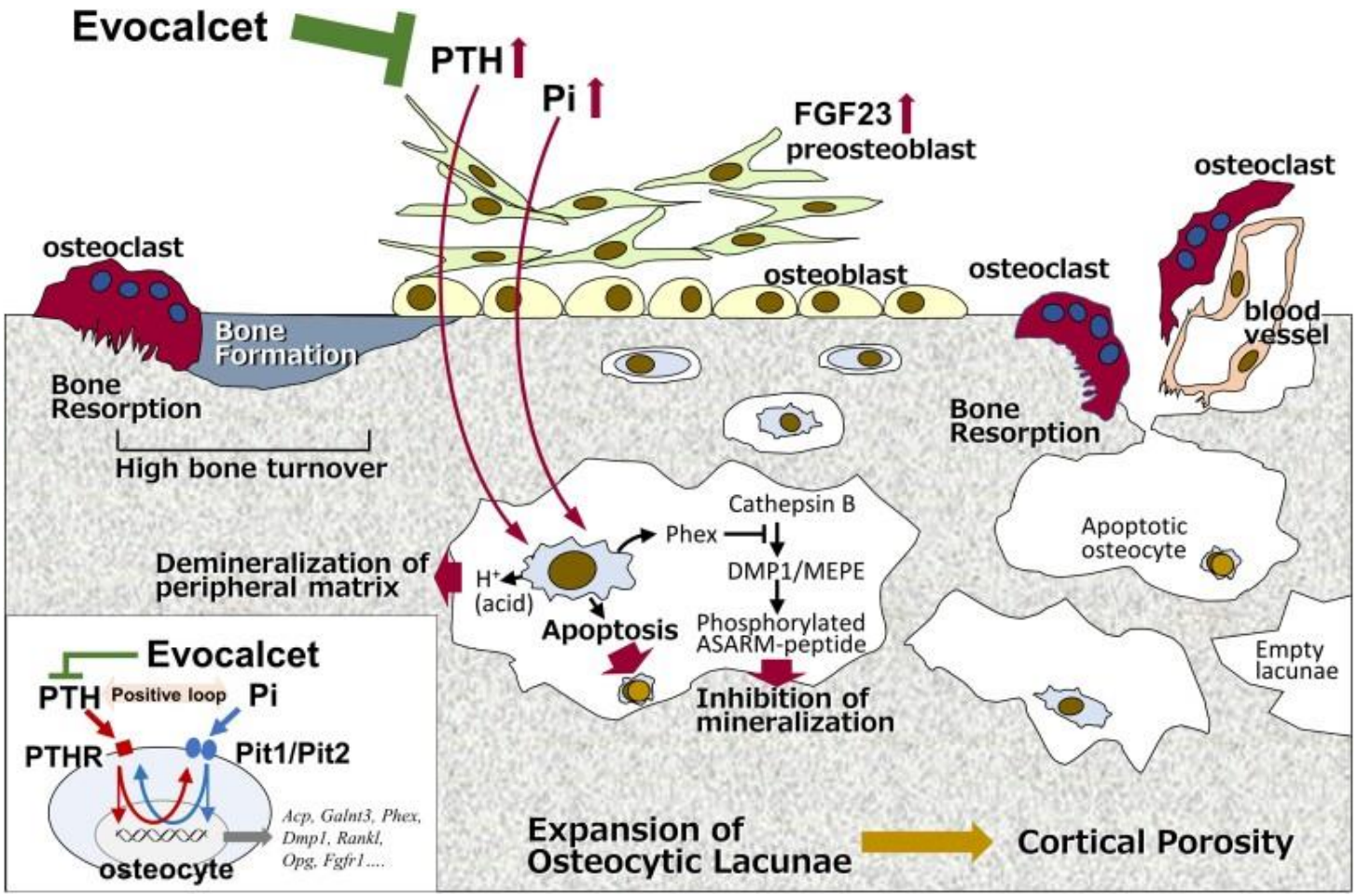




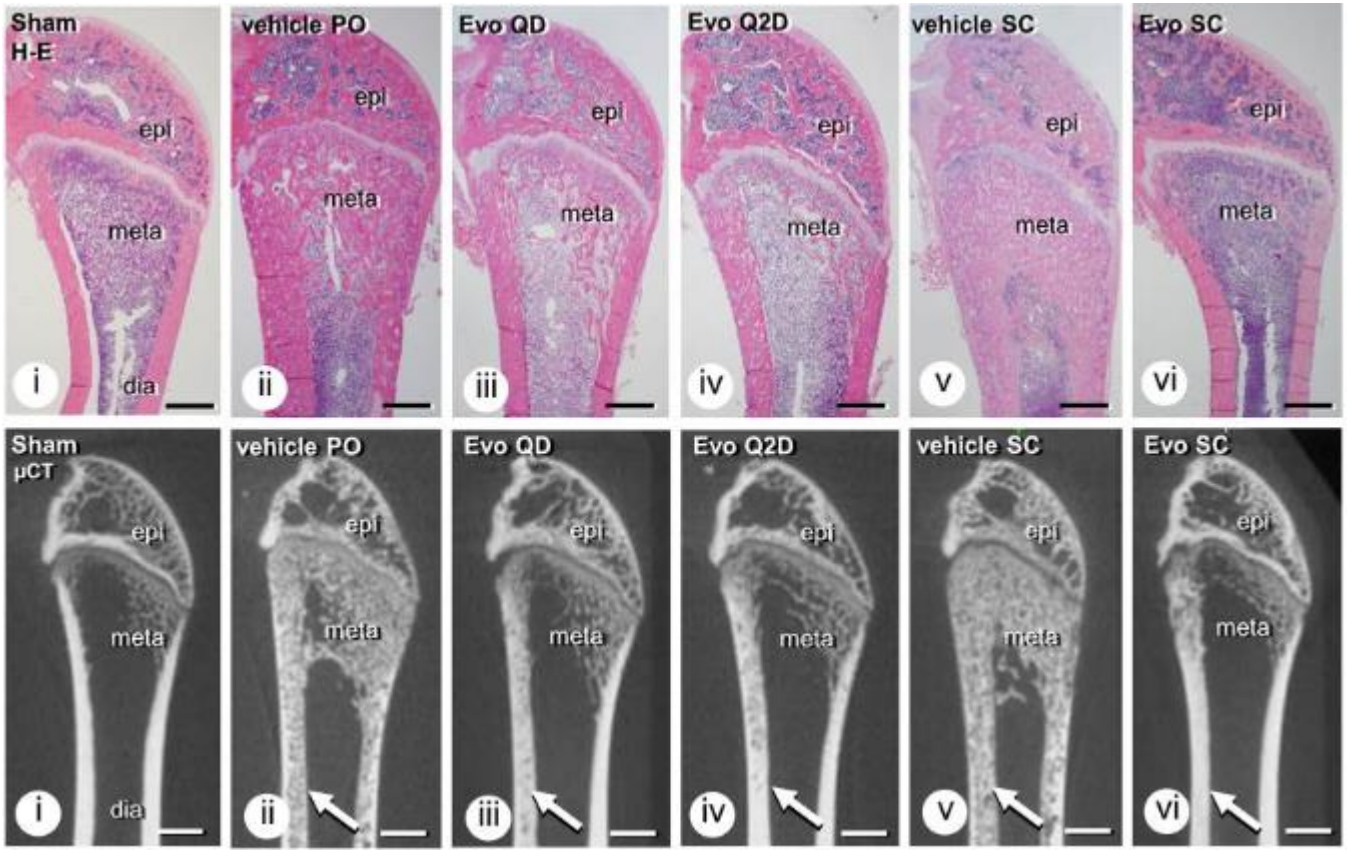
Therapeutic Apheresis and Dialysis 2020; 24(3):248–257

Evocalcet Rescues Secondary Hyperparathyroidism-driven Cortical Porosity in CKD Male Rats



Endocrinology. 2023 Apr; 164(4): bqad022

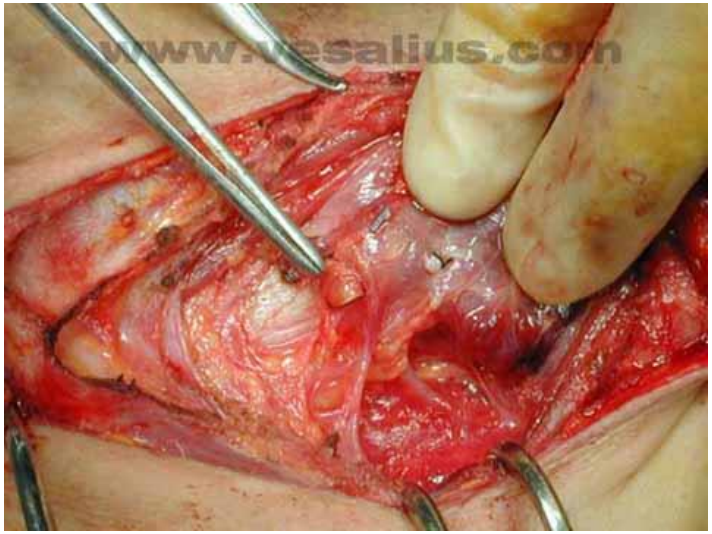
Evocalcet Rescues Secondary Hyperparathyroidism-driven Cortical Porosity in CKD Male Rats



Endocrinology. 2023 Apr; 164(4): bqad022

Ενδείξεις παραθυρεοειδεκτομής σε ασθενείς με ΧΝΝ

- Δευτεροπαθής υπερπαραθυρεοειδισμός (PTH intact > 800 pg/ ml) που συνοδεύεται από υπερασβεστιαμία ή/και υπερφωσφαταιμία χωρίς ανταπόκριση στη φαρμακευτική αγωγή.
- Επιδεινούμενες επασβεστώσεις των μαλακών μορίων ή καλσιφύλαξη με PTH intact > 600 pg/ ml.

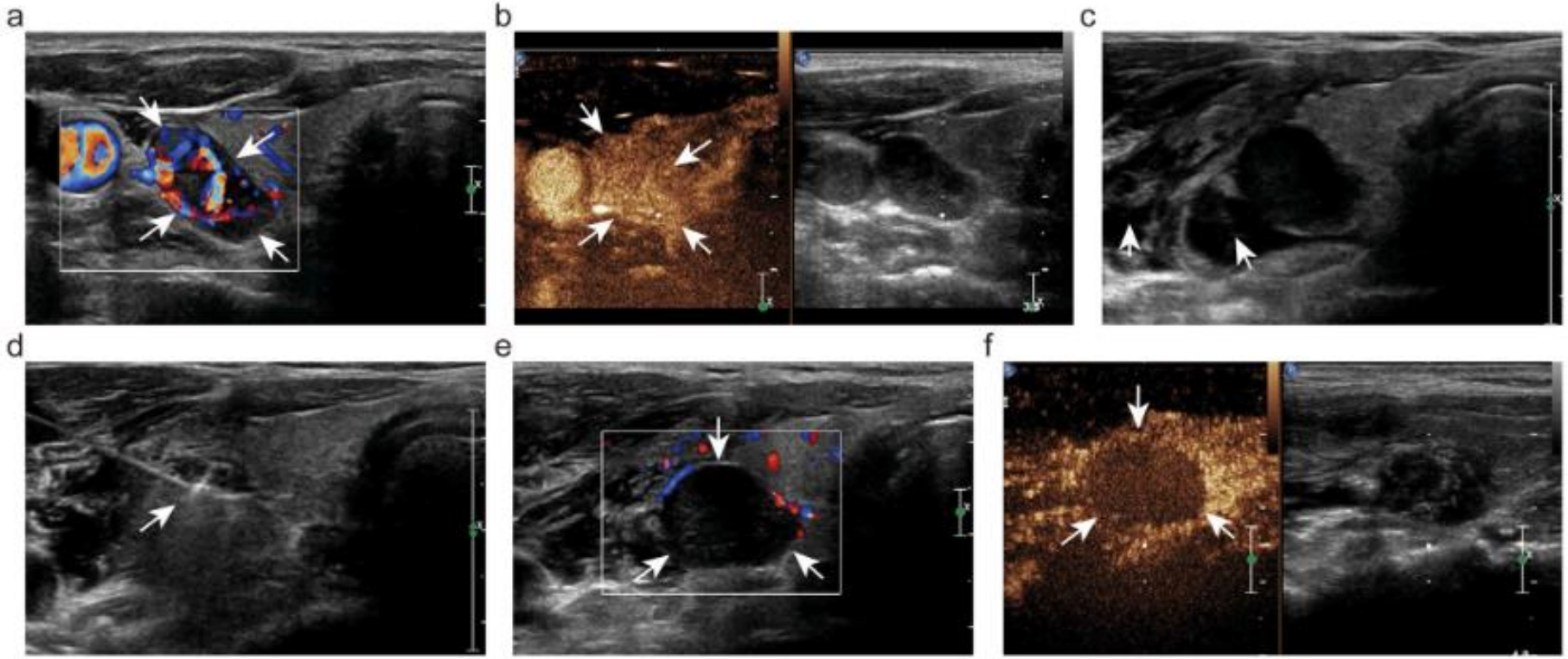


Επεμβατικές μέθοδοι θεραπείας του Δευτεροπαθούς Υπερπαραθυρεοειδισμού

- **Χειρουργική εκτομή των παραθυρεοειδών αδένων**
- **Υφολική παραθυρεοειδεκτομή**
- **Ολική παραθυρεοειδεκτομή**
- **Ολική παραθυρεοειδεκτομή και αυτομεταμόσχευση**

- **Διαδερμική καταστροφή των παραθυρεοειδών αδένων**

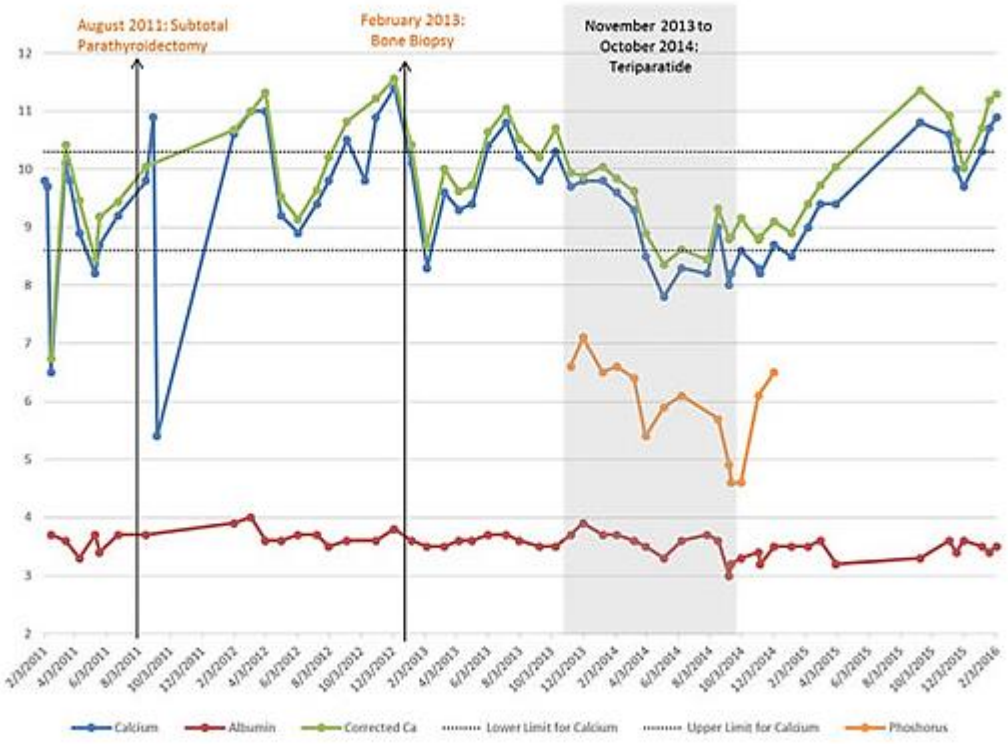
US-guided percutaneous radiofrequency ablation of secondary hyperparathyroidism



International Journal of Hyperthermia 2023;40(1): 2223370

Teriparatide Treatment for Hypercalcemia Associated With Adynamic Bone Disease

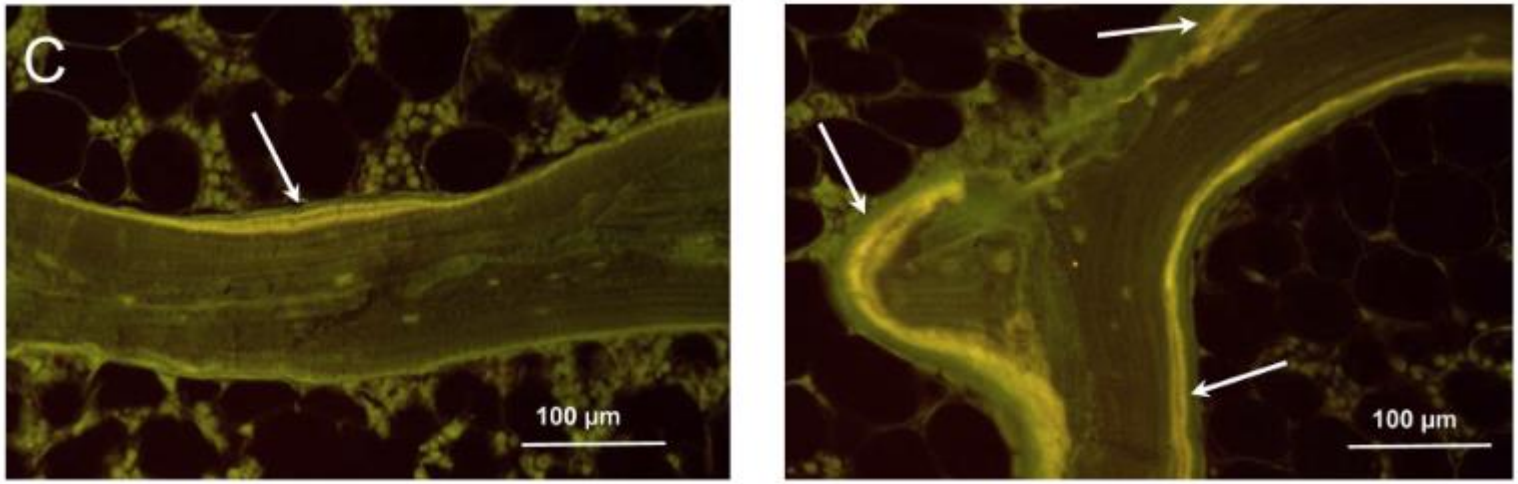
CASE REPORT



Normalization of serum calcium and phosphorus levels with use of teriparatide for adynamic bone disease

JBMR® Plus (WOA), 2019;3(7):e10176

Teriparatide and Bone Turnover and Formation in a Hemodialysis Patient With Low-Turnover Bone Disease: A Case Report



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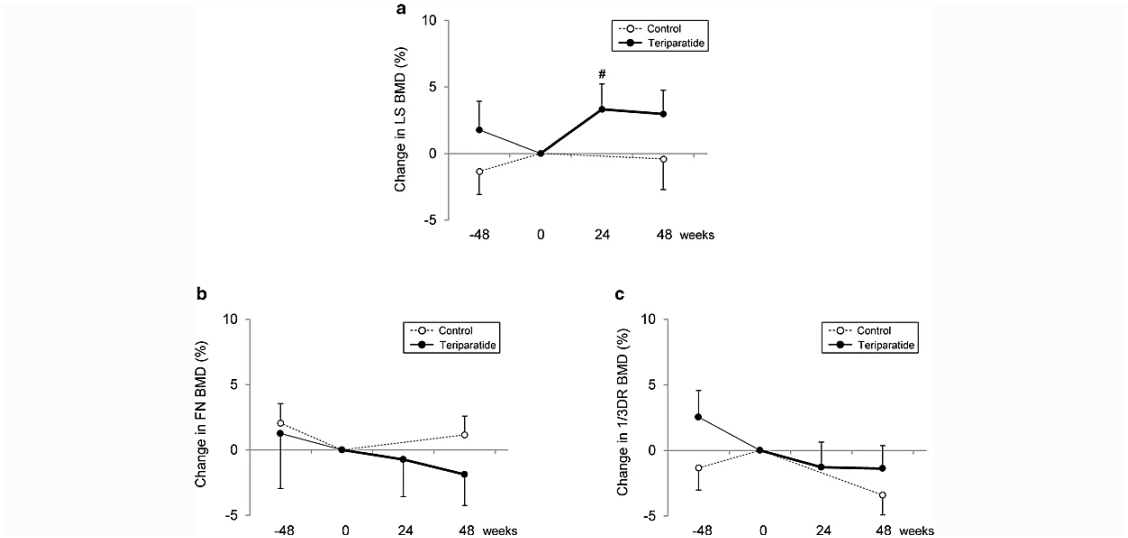
Once-weekly teriparatide in hemodialysis patients with hypoparathyroidism and low bone mass: a prospective study

N=11 pts on HD
Teriparatide once weekly 56.5μg
Duration 48 wks

↑ Osteocalcin, BAP, PINP, iPTH

↓ Ca, TRAP-5b

AE: Hypotension



Osteoporos Int 2016;27:1441–1450

Teriparatide Treatment for Hypercalcemia Associated With Adynamic Bone Disease

Summary of Studies Using Teriparatide to Treat Adynamic Bone Disease

Author, year	Bone biopsy confirmation	Intervention	Outcome	Results
Lehmann, 2009	1 of 1 patient	Teriparatide 20 μg SQ daily for 8 months	Change in bone histology	Increase in mineralized bone volume and bone turnover
Cejka, 2010	1 of 7 patients	Teriparatide 20 μg SQ daily for 6 months plus calcium and/or calcitriol	Change in BMD and CAC	Significant increase in spine but not femoral neck BMD; no change in CAC (n = 6)
Mitsopoulos, 2012	8 of 8 patients	Teriparatide 20 μg SQ thrice weekly for ~16 months	Change in BMD	No significant change in spine or femoral neck BMD
Giamalis, 2015	1 of 1 patient	Teriparatide 20 μg SQ + cholecalciferol 400 IU + alphacalcidol 0.25 μg daily + sevemelar daily	Clinical improvements	Increase in bone turnover and BMD, improved mobility and reduced pain
Palcu, 2015	1 of 1 patient	Teriparatide 20 μg SQ daily for 24 months	Clinical improvements	Increase in bone turnover and BMD, improved mobility and reduced pain
Sumida, 2016	0 of 11 patients	Teriparatide 56.5 μg once a week for 48 weeks	Change in BMD and serum bone turnover markers	11 completers had increased bone turnover and spine BMD
Fahrleitner-Pammer, 2017	1 of 1 patient	Teriparatide 20 μg SQ daily for 12 months	Clinical improvements	Increased bone turnover and volume, stable BMD

BMD = bone mineral density; CAC = coronary artery calcification score.

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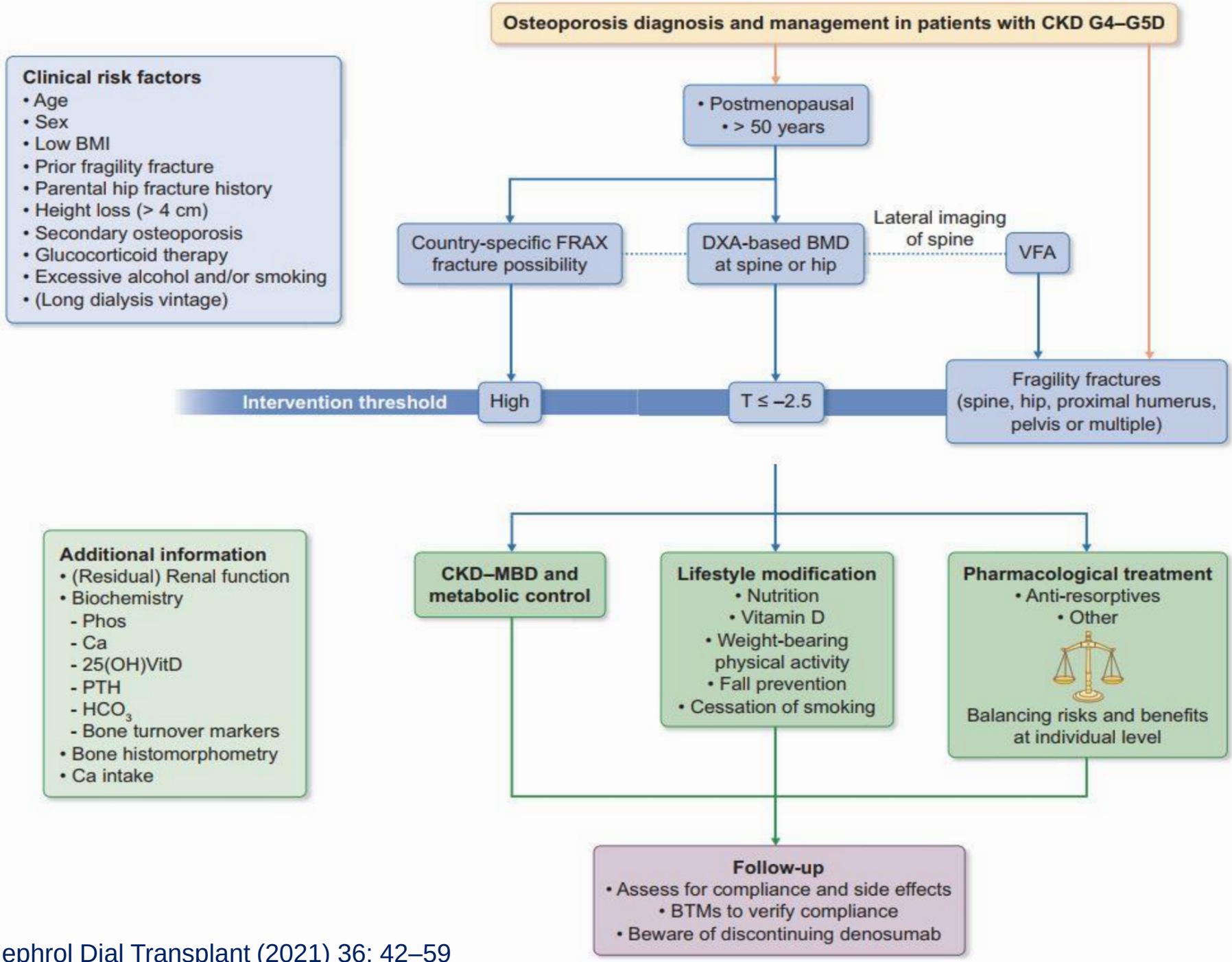
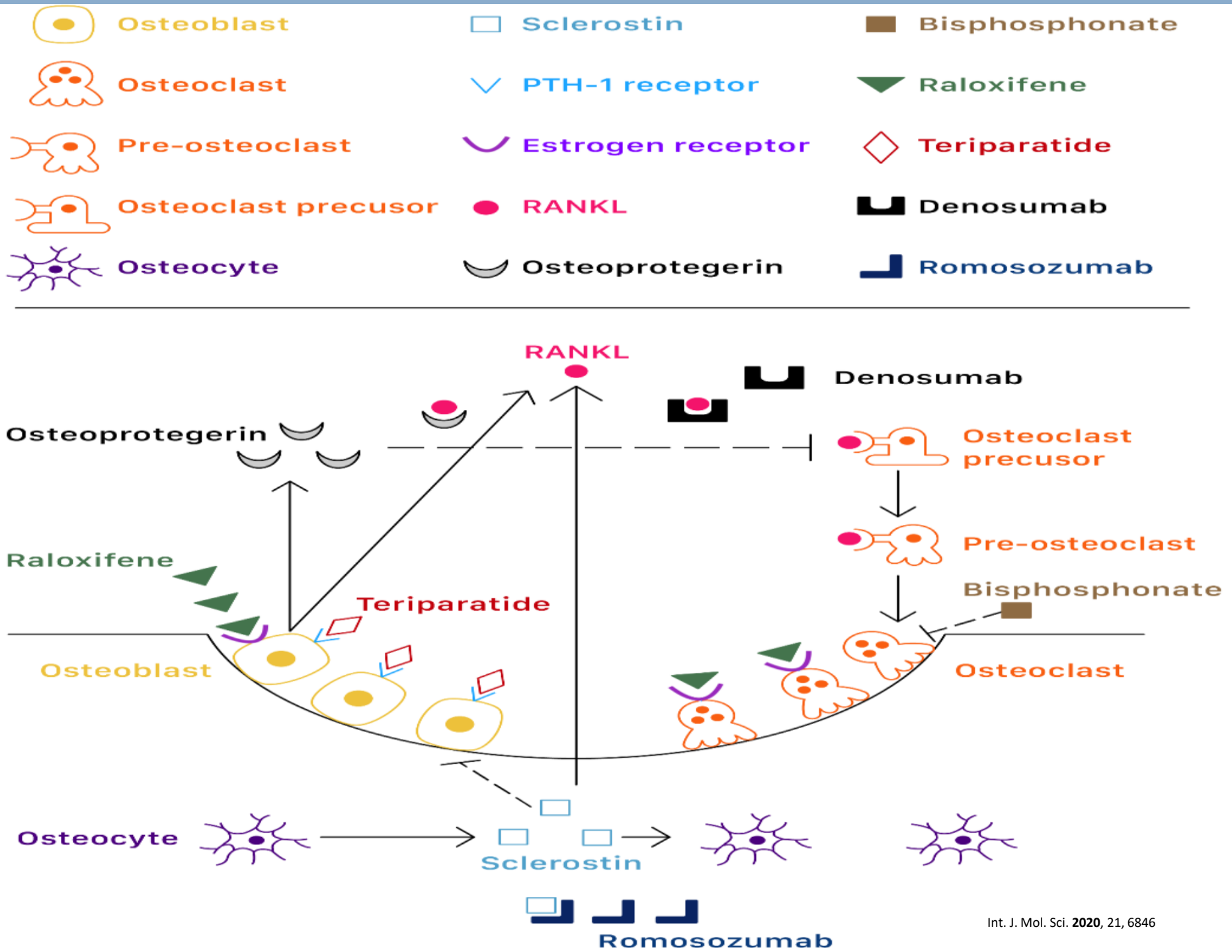
Treatment Options

New 4.3.3: In patients with CKD G3a–G5D with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy (2D).

Old 4.3.3: In patients with CKD G3a–G3b with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy (2D).



Nephrol Dial Transplant (2021) 36: 42–59

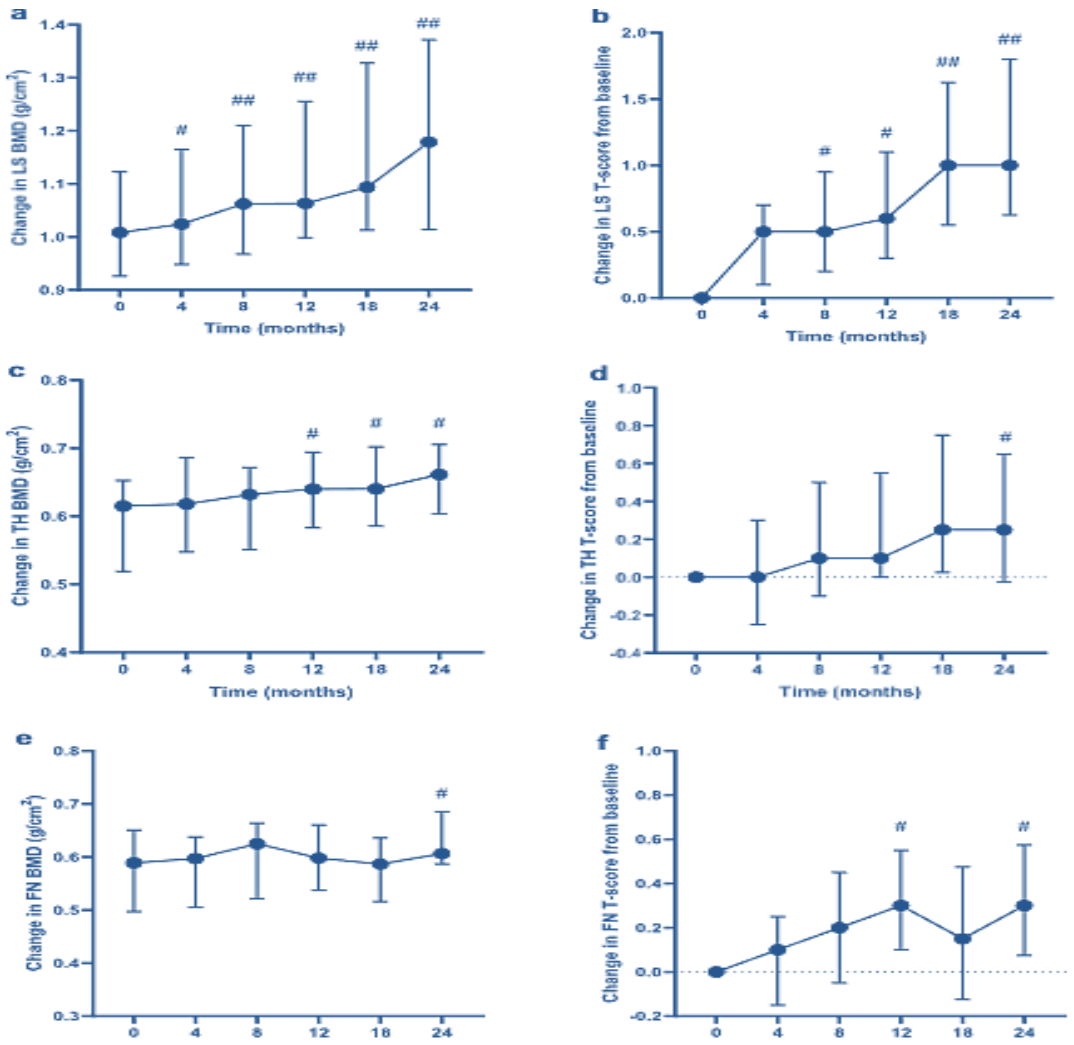


Int. J. Mol. Sci. **2020**, 21, 6846

Drugs	Renal retention	Efficacy Preclinical	*Post hoc* (postmenopausal women)	Clinical trial (advanced CKD)	Safety (postmenopausal women)	Comments
Nitrogen-containing bisphosphonates (alendronate, ibandronate, risedronate and zoledronic acid)	Yes [118, 119]	Yes [129, 157]	Fracture ↓ [120–122]	BMD (↑) [123–127]	Atypical fracture, ONJ, oesophagitis, (hypocalcemia, renal dysfunction) [131, 137–139]	Dose adjustments?
Denosumab	No [141]	Yes [145]	Fracture ↓ [142]	BMD ↑ [126, 143, 144, 147, 156]	Atypical fracture, ONJ, hypocalcaemia [138, 143]	Beware: offset of effect [150]
PTH analogues (teriparatide, abaloparatide)	No	Yes [157]	Fracture ↓ [158, 159]	BMD ↑, in patients with ABD or hypoparathyroidism [123, 160, 161]	Hypotension [160]	Dose adjustments? Therapy to be limited to a maximum of 2 years
Romosozumab	Unlikely	Yes, low PTH only [162]	No data	No data	Cardiovascular adverse events ↑ [165] (hypocalcaemia)	Beware: offset of effect

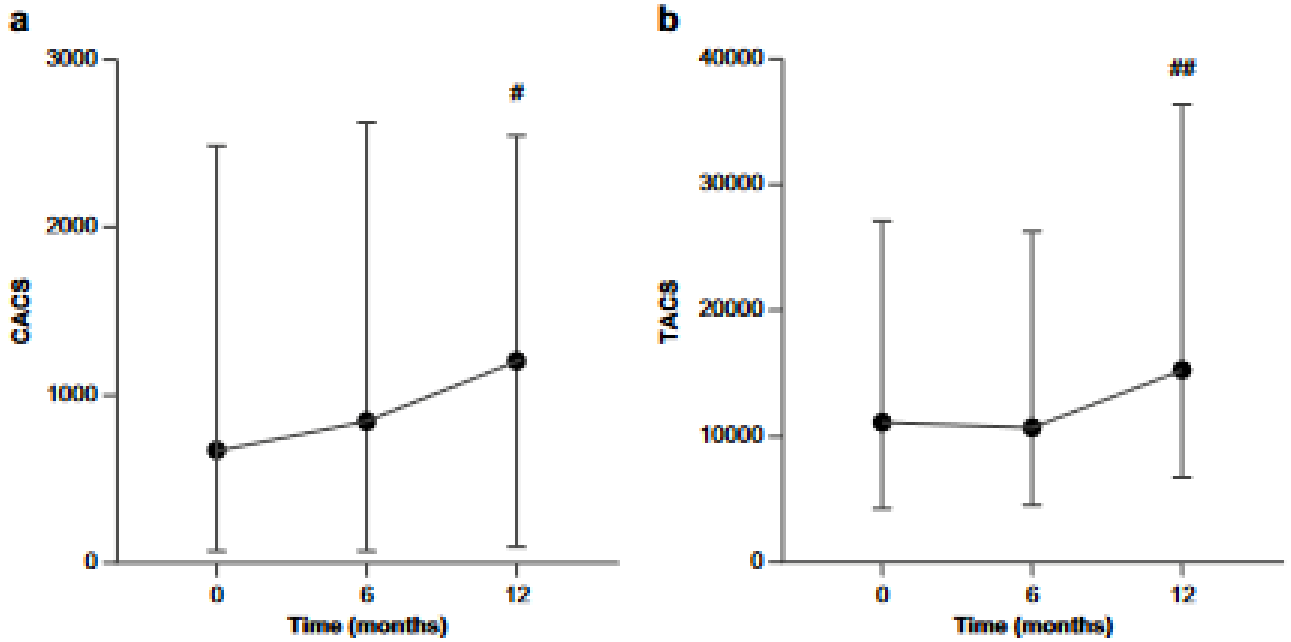
One-Year Romosozumab Treatment Followed by One-Year Denosumab Treatment for Osteoporosis in Patients on Hemodialysis: An Observational Study

Sclerostin=Glycoprotein.
It suppresses bone formation
Romosozumab acts against Sclerostin. It increases bone formation and suppresses bone resorption
N-13pts HD
ROMO 210mg/month for 1year followed by
DENO 60mg/6 months for 1 year



Calcified Tissue International 2023;112:34–44

One-Year Romosozumab Treatment Followed by One-Year Denosumab Treatment for Osteoporosis in Patients on Hemodialysis: An Observational Study



Calcified Tissue International (2023) 112:34–44

- ΧΝΝ-Διαταραχές του Μεταβολισμού των Οστών και των Μετάλλων: Συστηματική Διαταραχή
- Σακχαρώδης Διαβήτης: Διαταραχή του οστικού μεταβολισμού- Οστεοπόρωση
- Αυξημένος κίνδυνος καρδιαγγειακών συμβαμάτων και καταγμάτων-Αυξημένη νοσηρότητα και θνησιμότητα
- Θεραπευτική αντιμετώπιση σύμφωνα με τις κατευθυντήριες οδηγίες

ΕΥΧΑΡΙΣΤΩ