Bone Disease in CKD Patients an Update

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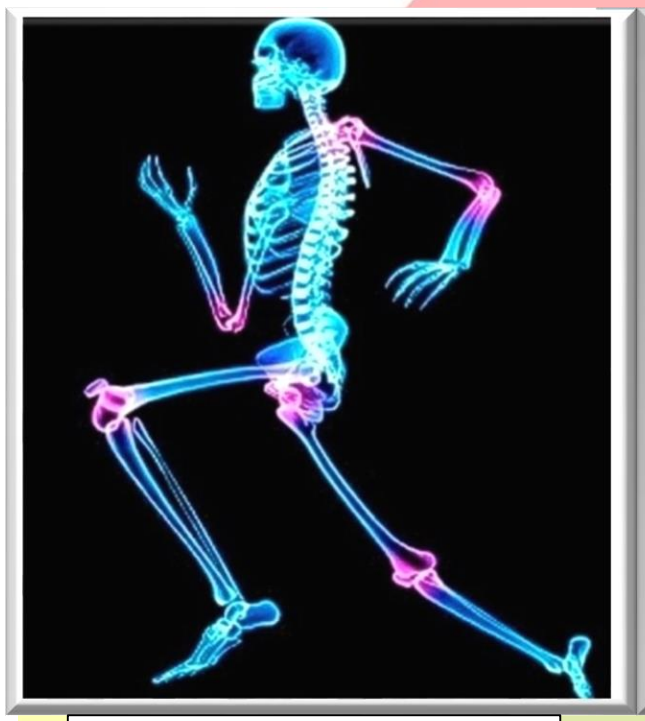
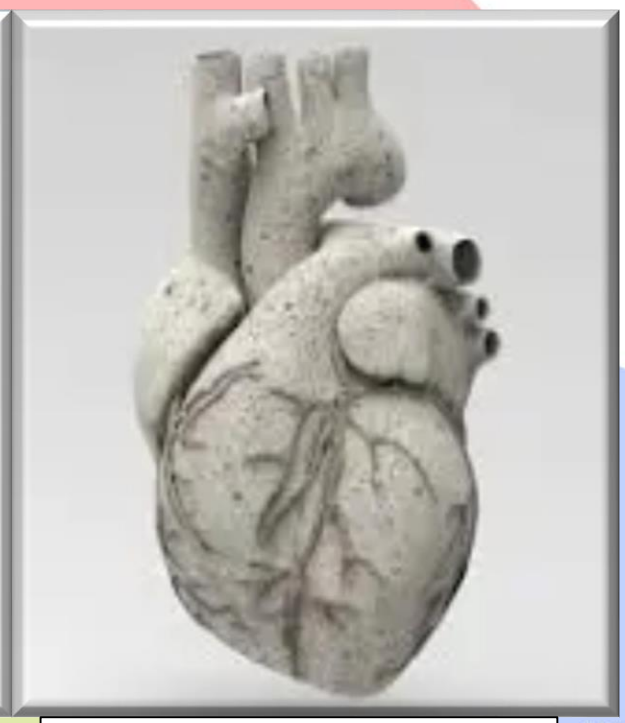
Chair, ESNT-Clinical Nephrology & CKD Chapter

CKD-MBD



Bones of Glass



Hearts of stone

alities

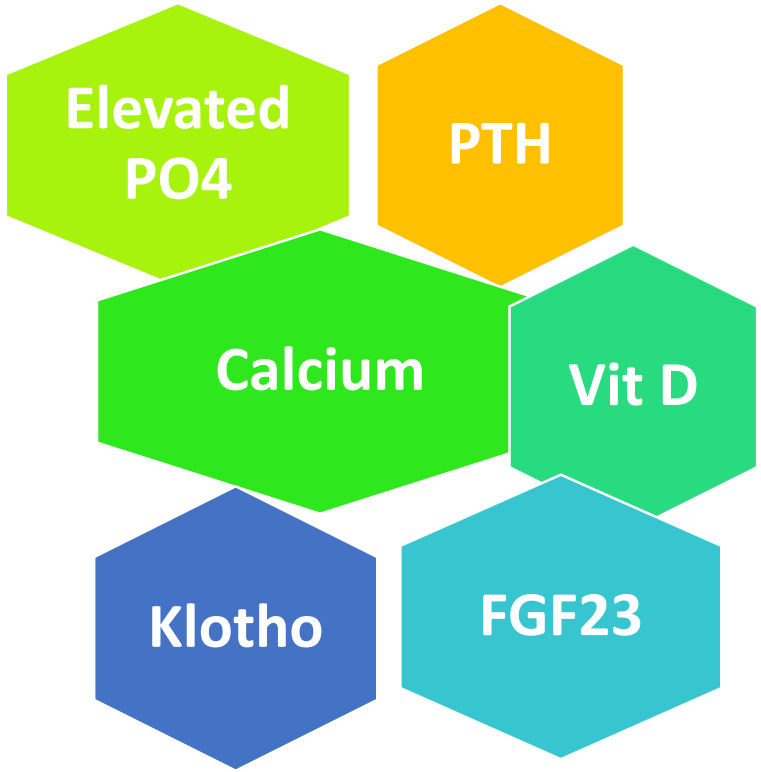
CKD-MBD

- Assessment of CKD-MBD should begin in stage 3, taking all available CKD-MBD parameters into account.

- Due to assay and biological variations, it is important to base therapeutic decisions on trends rather than on a single laboratory value, particularly with iPTH.

Systemic Mineral Disorder in CKD

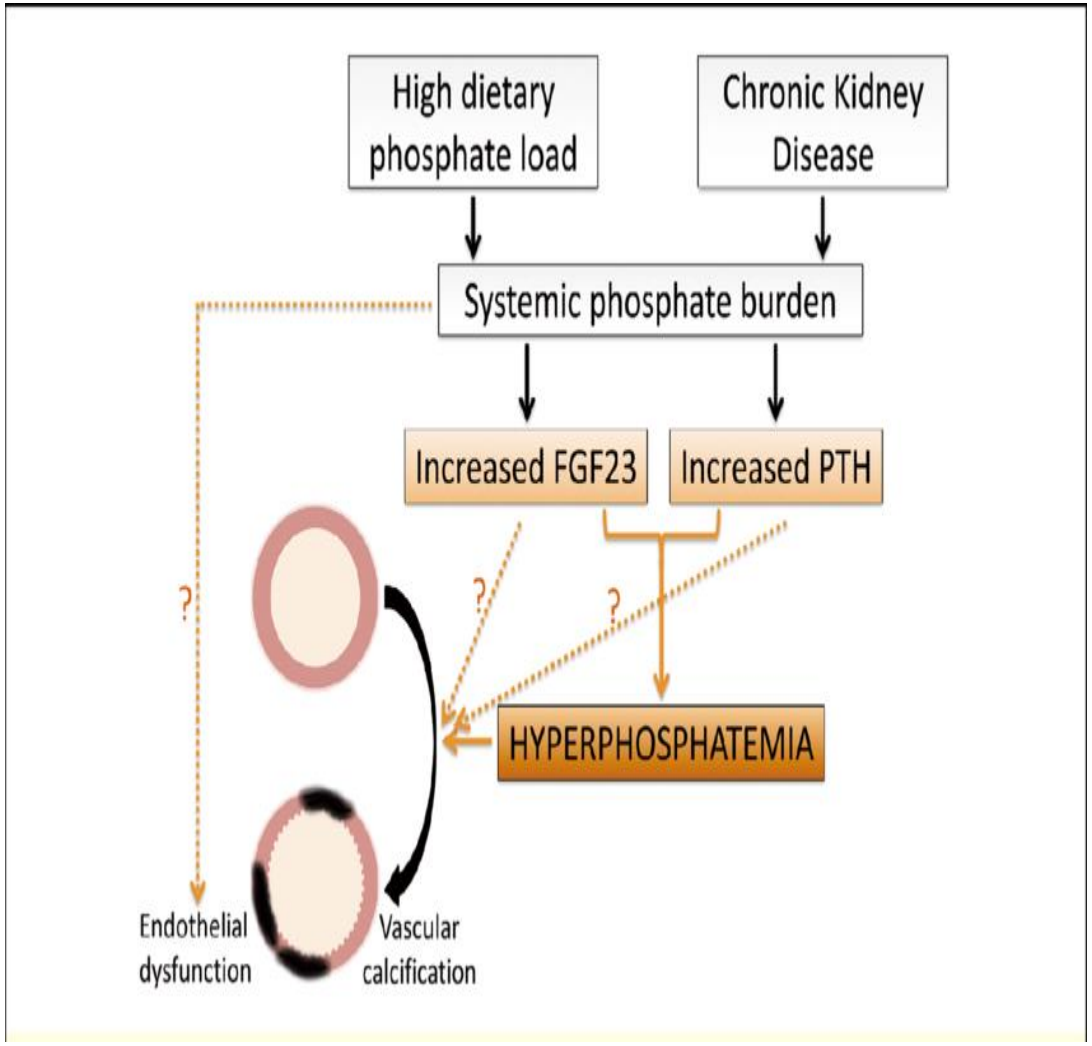
Mineral disorder in CKD encompasses a



Promoter of Calcification in CKD	Inhibitors of Calcification in CKD	Other
Osteoprotegerin	Fetuin-A	FGF-23
Osteocalcin	Matrix-Gla protein	Klotho
	Osteopontin	Vitamin D

Serum Phosphate

- Serum phosphate levels often remain within the normal range in early and intermediate stages of CKD due to compensatory increases in FGF23 and PTH.
- Elevated serum phosphate has been linked to cardiovascular morbidity and mortality.



Review > Nutrients. 2024 May 24;16(11):1599. doi: 10.3390/nu16111599.

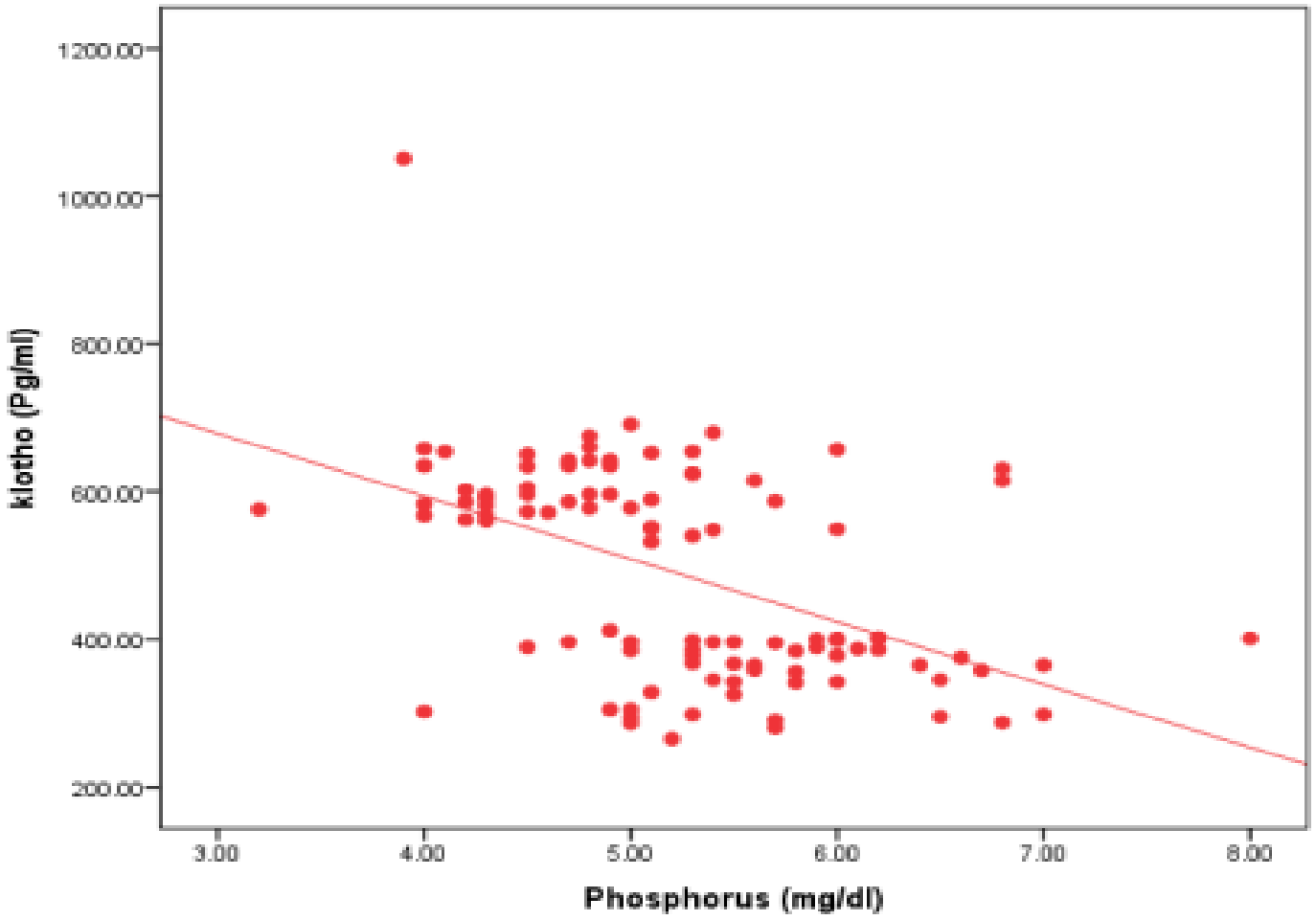
High Serum Phosphate Is Associated with Cardiovascular Mortality and Subclinical Coronary Atherosclerosis: Systematic Review and Meta-Analysis

Carolina Torrijo-Belanche [1], Belén Moreno-Franco [1 2 3], Ainara Muñoz-Cabrejas [1 2], Naiara Calvo-Galiano [2 4], José Antonio Casasnovas [2 3 4], Carmen Sayón-Orea [5 6], Pilar Guallar-Castillón [7 8 9]

Results: 25 studies met the inclusion criteria.

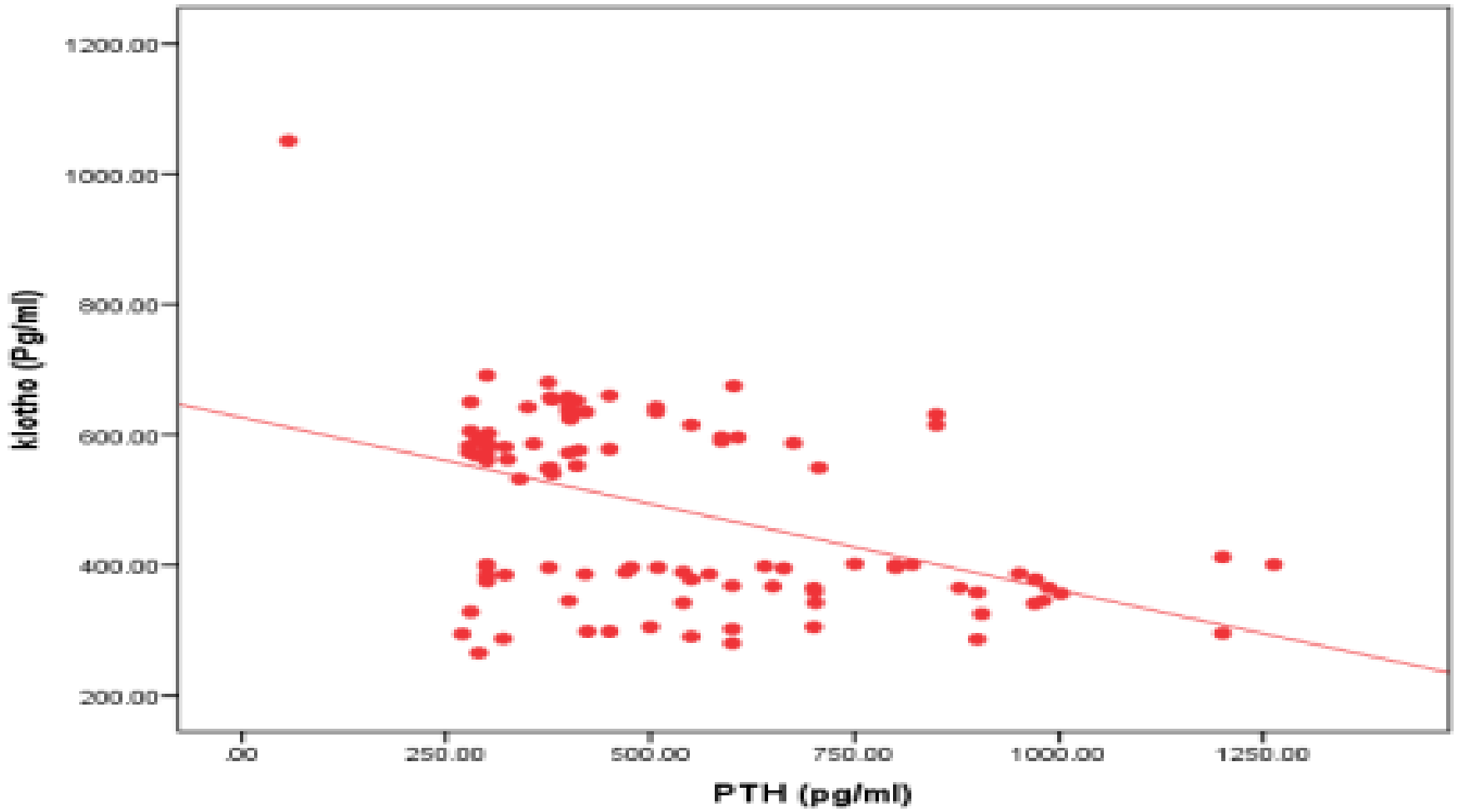
Conclusions: The highest serum phosphate concentrations were positively associated with a 44% increased risk of CVD mortality and subclinical coronary

Serum Klotho and Vascular Calcification



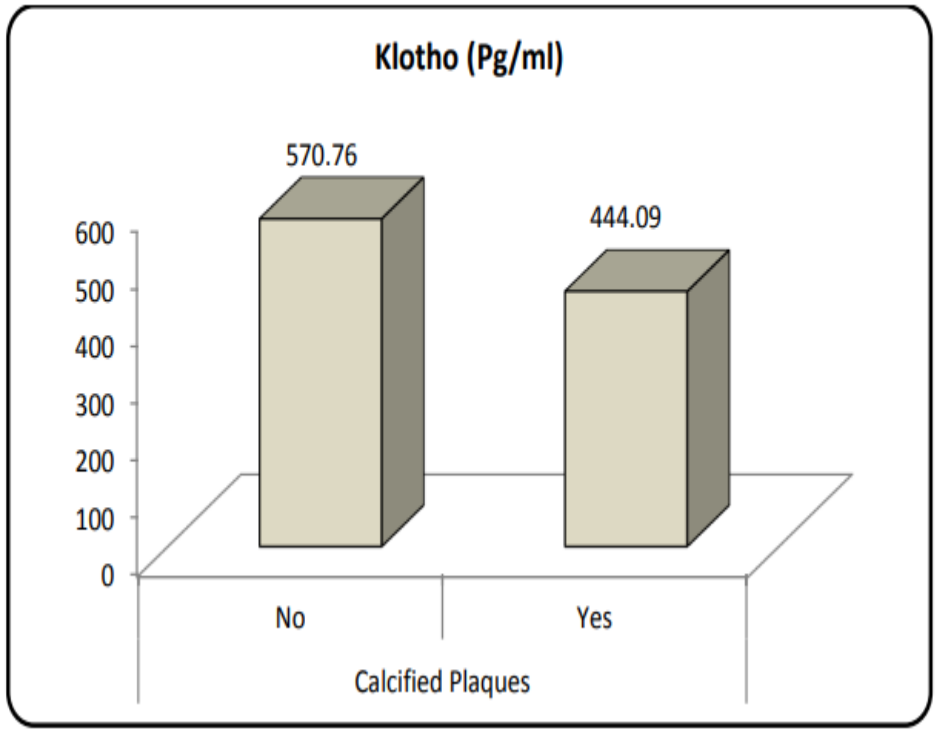
Elbaz et al., 2025 in press

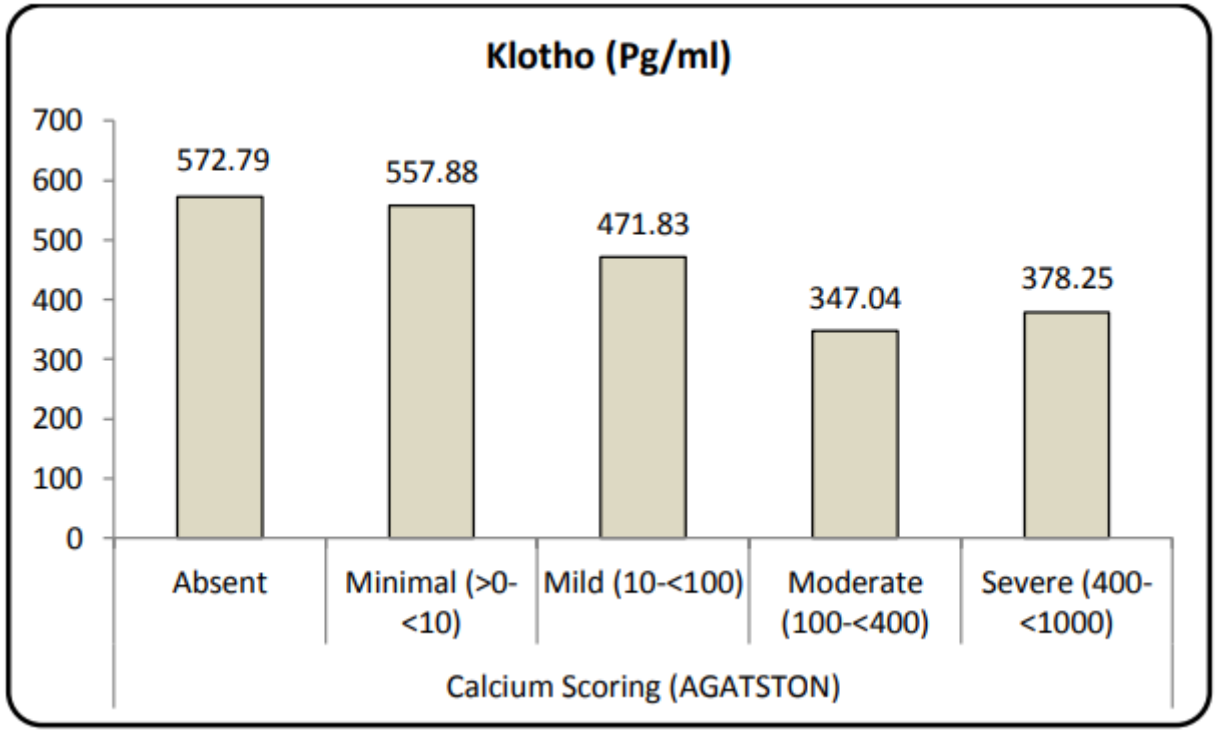
Serum Klotho and Vascular Calcification



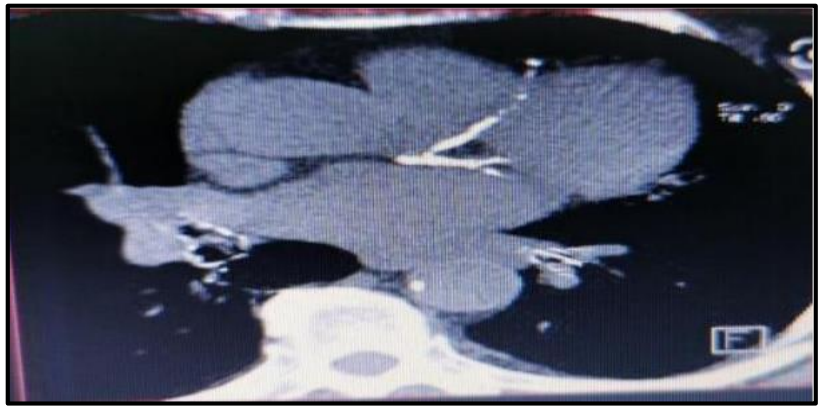
Elbaz et al., 2025 in press

Serum klotho was significantly correlated with MSCT Scan.





Serum klotho was significantly correlated with calcium scoring.



Elbaz et al., 2025 in press

Klotho and Clinical Outcomes in Chronic Kidney Disease

Setting & Participants	Analyses	Results
CRIC Chronic Renal Insufficiency Cohort Study	5-Year incidence of the following clinical outcomes:	Mean eGFR 42 mL/min/1.73 m^2 Median Klotho level 0.31 ng/ml
N = 1,088 adults with CKD	Composite kidney outcome	HR 1.05 (95% CI 0.58-1.91) Ref = lowest Klotho group
Longitudinal cohort study	HF hospitalization ASCVD events	HR 1.10 (95% CI 0.38-3.17) HR 1.19 (95% CI 0.57-2.52) Ref = lowest Klotho group
Plasma Klotho measured at baseline	All-cause mortality	HR 0.77 (95% CI 0.32-1.89) Ref = lowest Klotho group

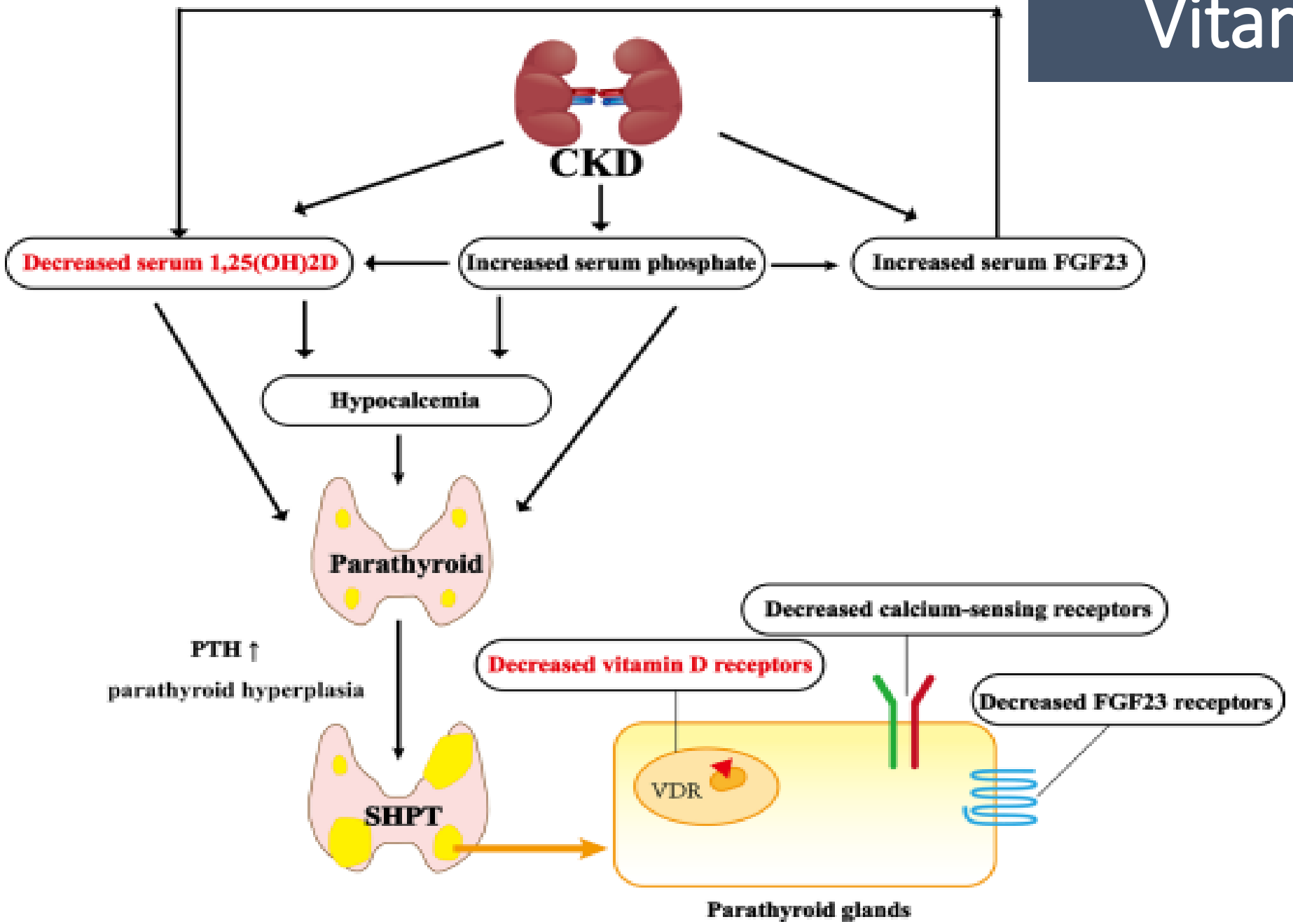
CONCLUSION: Klotho was not associated with clinical outcomes, and Klotho deficiency did not confound the association of FGF23 with mortality or heart failure hospitalization.

Daniel Edmonston, Michaela A Fuchs, Emily J Burke et al

@AJKDonline | DOI: 10.1053/j.ajkd.2024.02.008

AJKD American Journal of Kidney Diseases

Vitamin D


CKD
Decreased serum 1,25(OH)2D
Increased serum phosphate
Increased serum FGF23
Hypocalcemia
Parathyroid
PTH ↑
parathyroid hyperplasia
SHPT
Decreased calcium-sensing receptors
Decreased vitamin D receptors
Decreased FGF23 receptors
VDR
Parathyroid glands

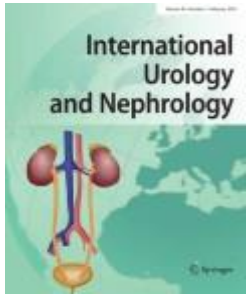
Vitamin D

NEPHROLOGY – REVIEW

Vitamin D: an important treatment for secondary hyperparathyroidism in chronic kidney disease?

Jie Yu[1] · Yulu Li[1] · Bin Zhu[2] · Jianqin Shen[3] · Liying Miao[1]

Received: 30 October 2024 / Accepted: 18 December 2024

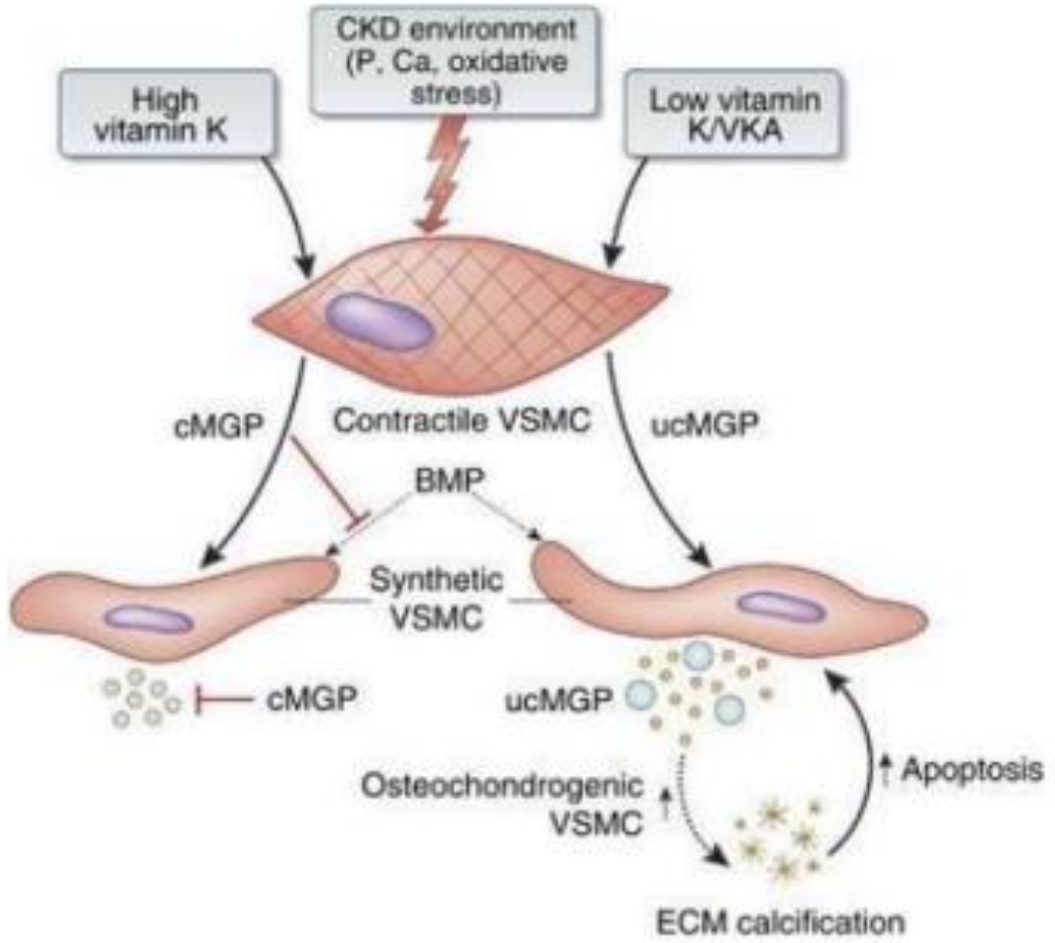


- **Vitamin D-based drugs, which inhibit PTH secretion either directly or indirectly, are commonly used to treat SHPT.**
- **Vitamin D-based drugs can also lead to a dysregulated balance between serum calcium and phosphorus, as well as other adverse reactions.**
- **New vitamin D-based drugs have been developed, and explored combinatory methods to improve treatment efficacy for the disease control.**

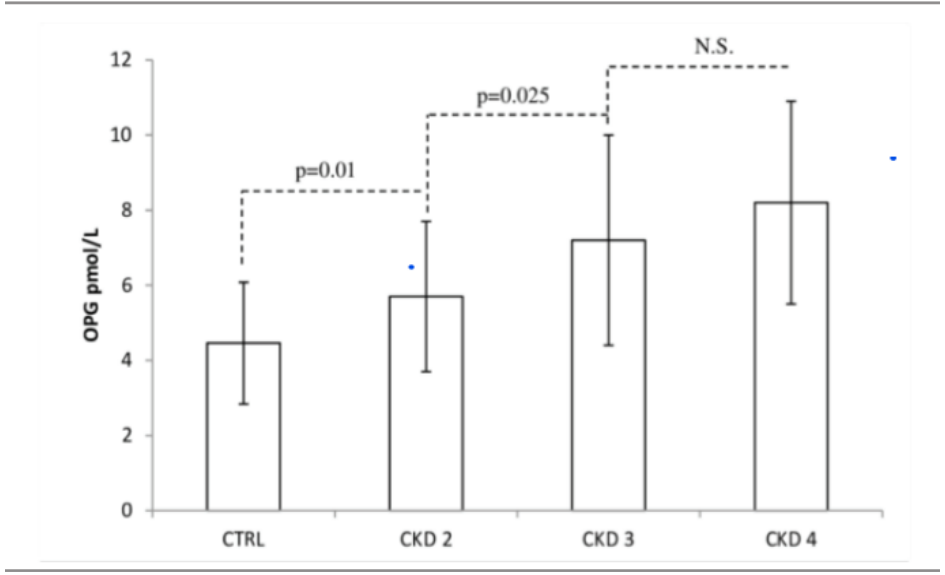
PTH

Calcification Promoters and Calcification Inhibitors

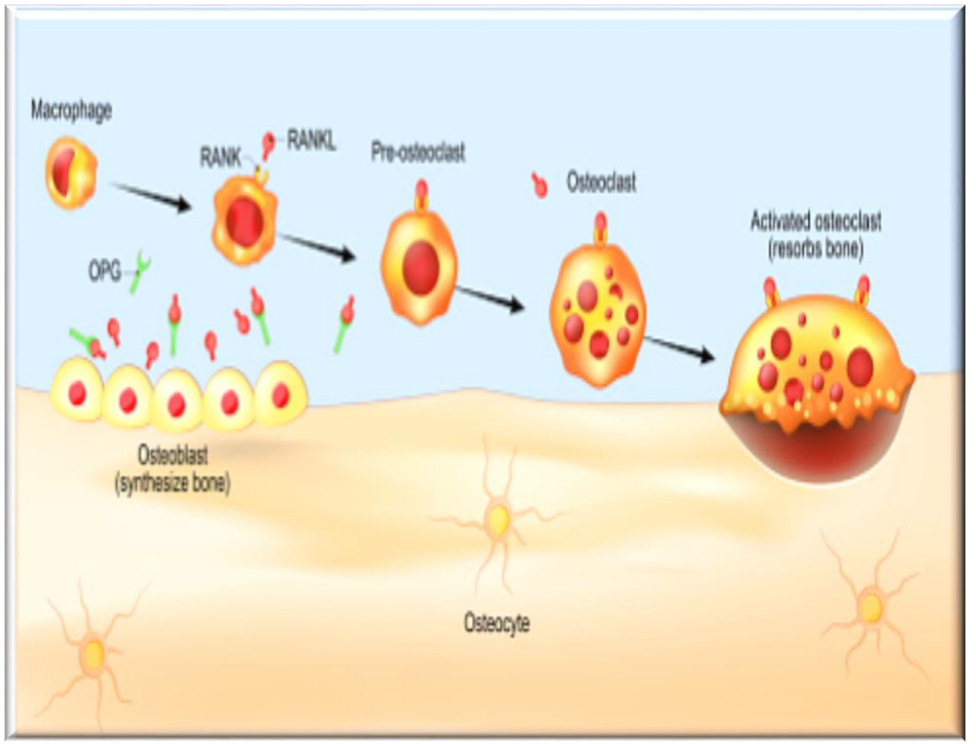
Vitamin K


CKD environment
(P, Ca, oxidative
stress)
High
vitamin K
Low vitamin
K/VKA
cMGP
Contractile VSMC
ucMGP
BMP
Synthetic
VSMC
cMGP
ucMGP
Apoptosis
Osteochondrogenic
VSMC
ECM calcification

Promoter of Calcification in CKD	Inhibitors of Calcification in CKD	Other
Osteoprotegerin	Fetuin-A	FGF-23
Osteocalcin	Matrix-Gla protein	Klotho
	Osteopontin	Vitamin D



Grskovik et al., Acta Clin Croat, Vol. 62, (Suppl. 2) 2023



ROD

Bone Metabolism Factors in CKD-MBD

Factors	Effects
Increased PTH	Bone Resorption
Decreased Vitamin D	Decreased Bone Mineralization
Increased Phosphate	Vascular Calcification
Increased FGF-23	Increased Fracture Risk
Decreased Klotho	Secondary Hyperparathyroidism

Bone biopsy in ROD
according to the (T)urnover (M)iniralization (V)olume Classification

According to histomorphometric analysis, three types of ROD have been recognized:

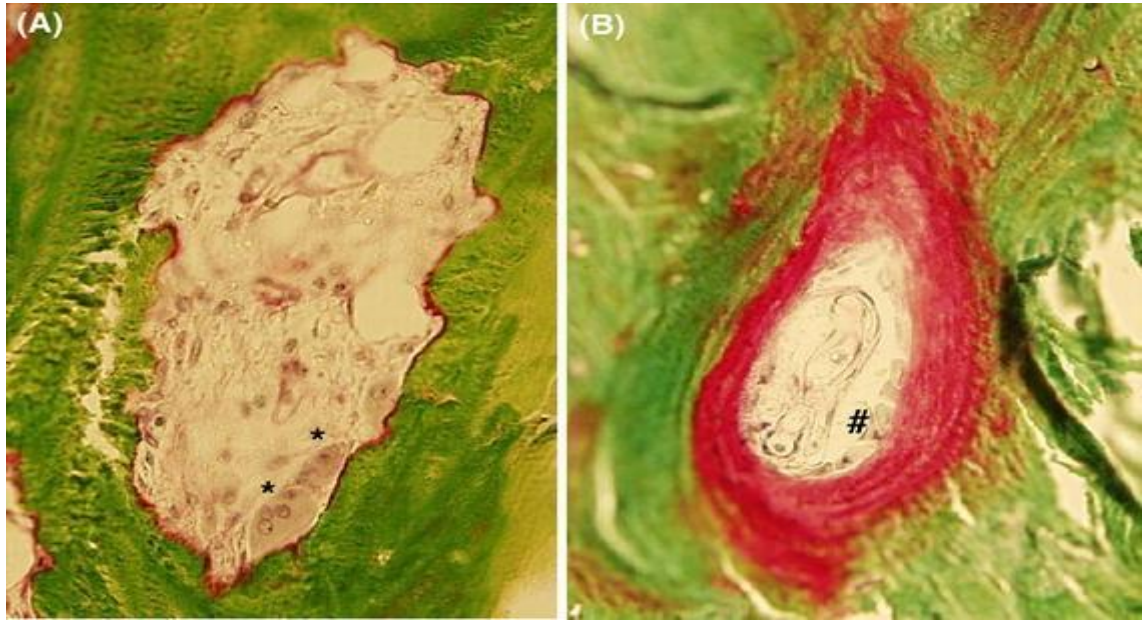
- *(a) High turnover bone disease including hyperparathyroidism or osteitis fibrosa cystica.*
- *(b) Low turnover bone disease including adynamic bone disease or osteomalacia.*
- *(c) Mixed uremic osteodystrophy characterized as high turnover bone disease in association with mineralization defects.*

Tores et al., Semin Nephrol. 2014;34:612–25

The role of bone biopsy for the diagnosis of renal osteodystrophy: a short overview and future perspectives

Review | Published: 29 July 2016

Volume 29, pages 617–626, (2016) Cite this article



a) Resorptive osteon with activated osteoclasts (*asterisk*); **b)** formative osteon with osteoid recovering bone

Osteoporosis in CKD

- Bone fragility is a prevalent complication attributable to disruptions in mineral and hormonal equilibria, leading to a **non-vertebral-fracture risk that is 4 to 6 times higher** than that of matched control individuals.

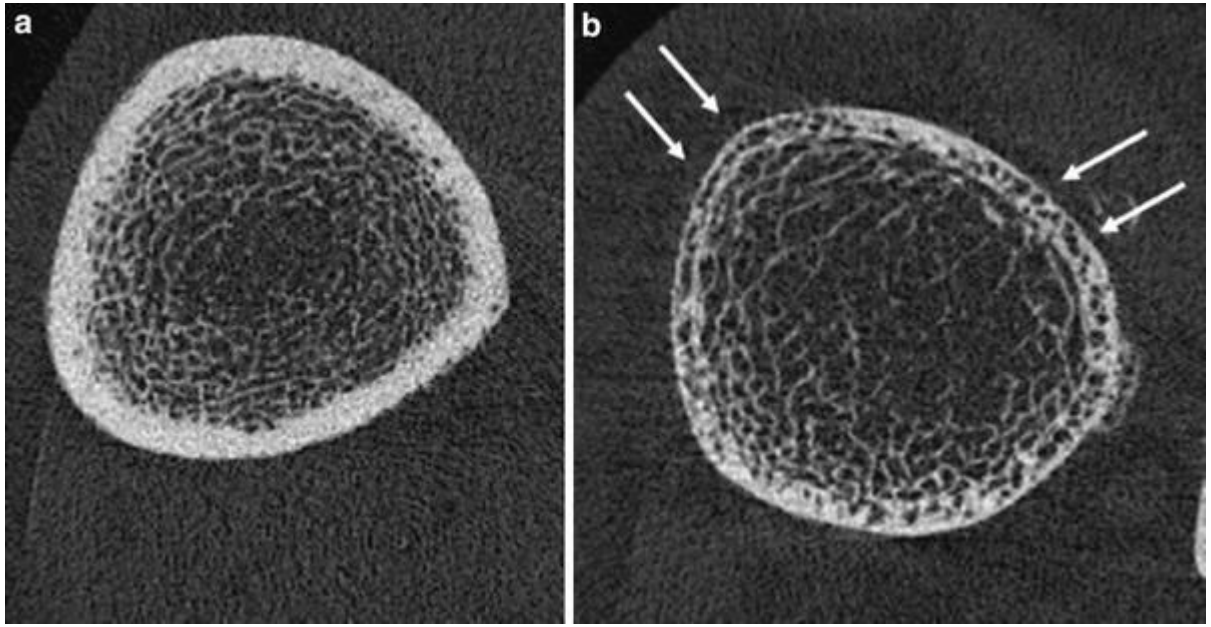
Covic and Apetrii. Volume 12, issue 4, P225-227April 2024

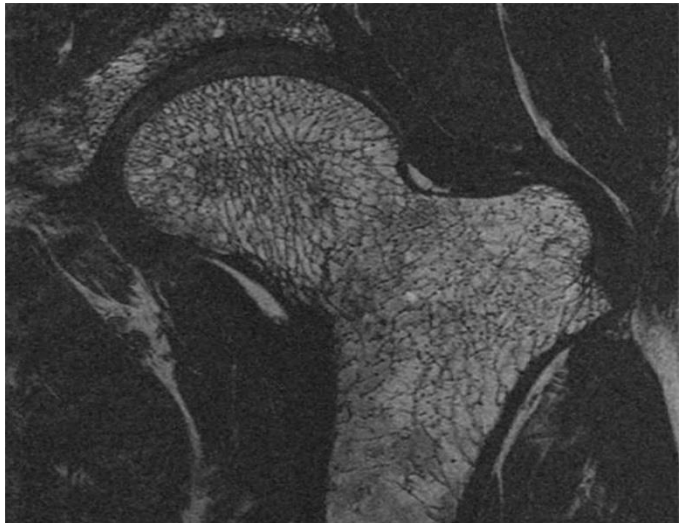
THE LANCET
Diabetes & Endocrinology

High-resolution Imaging Techniques for the Assessment of Osteoporosis

- Currently, the best suited modalities meeting these requirements *in vivo* are high-resolution peripheral quantitative imaging (HR-pQCT) and magnetic resonance imaging (MRI).

- HR-pQCT is limited to peripheral skeleton regions like the wrist and ankle, MRI can also image other sites like the proximal femur but usually with lower spatial resolution.





Boyd. Radiol. Clin.North America 2024 Sep;62(5):903-912.

Osteoporosis in CKD

- Conventional treatments, such as bisphosphonates, denosumab, and teriparatide, when tailored to CKD stages, demonstrate variable effectiveness in lowering fracture risk.

- Additionally, emerging pharmacologic agents hold promise in improving bone density, though evidence on these newer therapies remains limited.

Tariq et al., Cureus. 2024 November 17; 16(11)

Osteoporosis in CKD
Antiresorptive Medications
Bisphosphonates

- Bisphosphonates such as alendronate and risedronate have become standard therapies for osteoporosis treatment.

- High risks in patients with CKD due to renal excretion, leading to accumulation of bisphosphonates in dialysis patients treated with these drugs raising concerns of "frozen bone.“

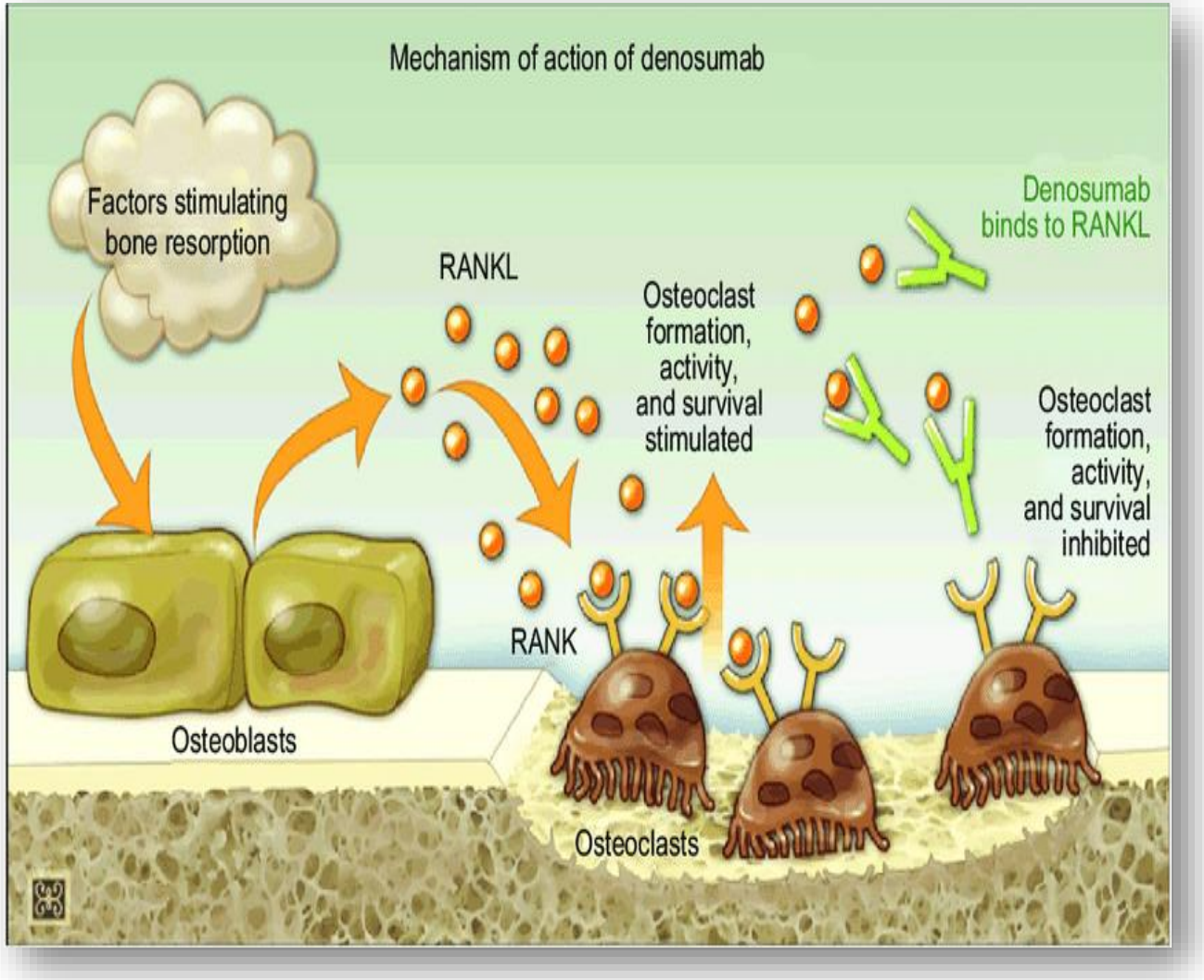
- Bisphosphonates can further suppress bone formation in CKD patients with pre-existing low bone turnover, resulting in adynamic bone disease.

Bellorin-Font et al., Nutrients. 2022;15:167.

Antiresorptive Medications
Denosumab

- **Denosumab, a monoclonal antibody targeting the nuclear factor-kappa B receptor activator.**
- **Denosumab can induce hypocalcemia, particularly in CKD patients, necessitating careful monitoring and the use of active vitamin D to maintain calcium balance.**

Gronskaya Endocrine. 2023;81:368–378.



Anabolics for Osteoporosis in CKD

- Teriparatide and abaloparatide are the two osteoanabolic drugs used to treat osteoporosis.

- Their administration is contraindicated in CKD patients with high-turnover bone disease caused by raised PTH levels.

Jah et al., Indian J Nephrol. 2024;34:254–256.

Newer Agents for Osteoporosis in CKD
Sclerostin Inhibitors

- Sclerostin, is a protein produced by osteocytes, inhibits osteoblast activity.
- Romosozumab, a monoclonal antibody targeting sclerostin, that has demonstrated promising results in promoting bone formation.
- ***Its safety in CKD needs considerations due to the cardiovascular complications.***

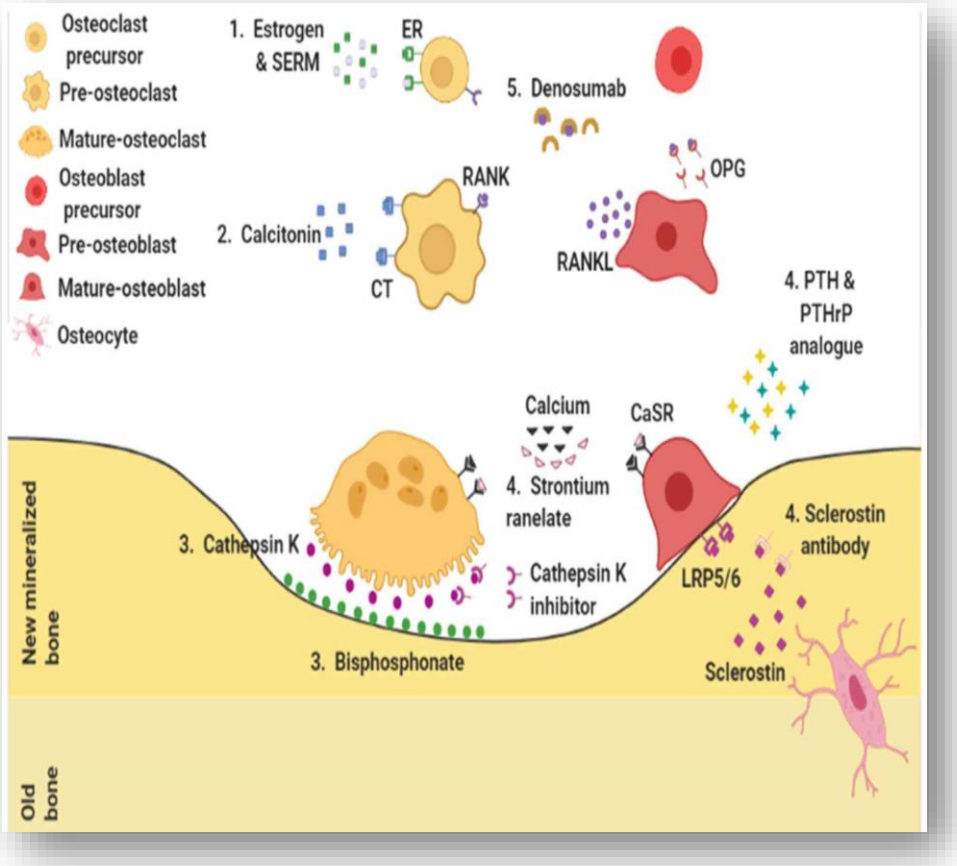
Adami et al., *JBMR Plus. 2024;8:0.*

Newer Agents for Osteoporosis in CKD
Cathepsin K Inhibitors

- Cathepsin K inhibitors, including odanacatib , are a novel class of medications for osteoporosis whose mechanism of action is to directly **inhibit bone resorption** without killing osteoclasts.

- Cathepsin K is responsible for the breakdown of collagen in the bone matrix as part of bone resorption.

- Its development was halted in 2016 due to cardiovascular safety concerns



Adami et al., JBMR Plus. 2024;8:0.

“Magnesium the Forgotten Cation”

“Magnesium the Forgotten Cation”

- Disorders of magnesium are hardly mentioned in most educational books of medicine.
- Serum Mg^{2+} concentrations are not measured routinely in hospitalized patients.
- Most magnesium abnormalities are remaining undetected.

Why ???

Lower serum magnesium is associated with vascular calcification in peritoneal dialysis patients: a cross sectional study

Amber O. Molnar, Mohan Biyani, Ian Hammond, John Paul Harmon, Susan Lavoie, Brendan McCormick, Manish M. Sood, Jessica Wagner, Elena Pena and Deborah L. Zimmerman

BMC Nephrology BMC series – open, inclusive and trusted 2017 **18**:129
https://doi.org/10.1186/s12882-017-0549-y | © The Author(s). 2017
Received: 8 December 2015 | Accepted: 3 April 2017 | Published: 6 April 2017

Blood Purification

Original Paper

Serum Magnesium and Mortality in Maintenance Hemodialysis Patie

Blood Purif 2017;43:31-36

Yu L. · Li H. · Wang S.
Author affiliations

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

November 2017 Volume 92, Issue 5, Pages 1084–1099

Dietary magnesium supplementation prevents and reverses vascular and soft tissue calcifications in uremic rats

Juan M. Diaz-Tocados[10], Alan Peralta-Ramirez[10], María E. Rodríguez-Ortiz, Ana I. Raya, Ignacio Lopez, Carmen Pineda, Carmen Herencia, Addy Montes de Oca, Noemi Vergara, Sonja Steppan, M. Victoria Pendon-Ruiz de Mier, Paula Buendía, Andrés Carmona, Julia Carracedo, Juan F. Alcalá-Díaz, Joao Frazao, Julio M. Martínez-Moreno, Antonio Canalejo, Arnold Felsenfeld, Mariano Rodriguez, Escolástico Aguilera-Tejero, Yolanda Almadén[11], Juan R. Muñoz-Castañeda[11]

- ***Lower serum magnesium is a risk factor of CV mortality in MHD patients.***

Nutrients. 2013 Aug; 5(8): 3022–3033. PMCID: PMC3775240
Published online 2013 Jul 31. doi: 10.3390/nu5083022

Magnesium and Osteoporosis: Current State of Knowledge and Future Research Directions

Sara Castiglioni,[1] Alessandra Cazzaniga,[1] Walter Albisetti,[2] and Jeanette A. M. Maier[1,*]

Author information ► Article notes ► Copyright and License information ►

- dietary **Mg^{2+}** restriction promotes osteoporosis .
- Bones of **Mg^{2+}** deficient animals are brittle and fragile, microfractures of the trabeculae can be detected and mechanical properties are severely impaired.
- **Mg^{2+}** deficiency rapidly leads to hypomagnesemia, which is in part buffered through the mobilization of surface **Mg^{2+}** from the bone.

JASN JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Magnesium and Risk of Hip Fracture among Patients Undergoing Hemodialysis

Yusuke Sakaguchi[1,2], Takayuki Hamano[1,2], Atsushi Wada[1,3], Junichi Hoshino[1,4] and Ikuto Masakane[1,5]

This Article

Published online before print November 30, 2017, doi: 10.1681/ASN.2017080849

JASN November 30, 2017 ASN.2017080849

Abstract *Free*
Figures Only

Accepted for publication October 31, 2017.

METHODS

A nation-wide cohort study in Japan

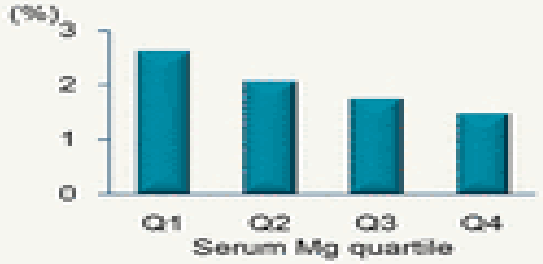
Hemodialysis patients
n = 113,683

- 2-year follow-up
- 2,305 incident hip fractures

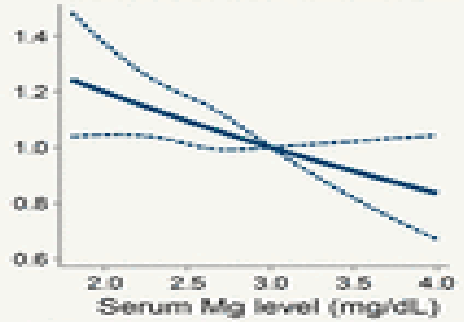
Quartile	Q1	Q2	Q3	Q4
Serum Mg (mg/dL)	-2.3	2.4-2.6	2.7-2.8	2.9-

OUTCOME: Incident hip fracture

Incidence rate of hip fracture



Adjusted odds ratio for incident hip fracture



CONCLUSION

Mild hypermagnesemia is associated with a lower risk of hip fracture among patients undergoing hemodialysis.

- **Findings provide further evidence that hypermagnesemia, at least within the clinically relevant range (≤4.0 mg/dl), decreases the risk of hip fracture.**

Conclusion

- Almost every person with CKD is at an increased risk of developing disturbances of bone and mineral metabolism (CKD-MBD).

- This presents as a disorder of mineral metabolism, as bone turnover disbalance, or as vascular and soft tissue calcifications.

- Skeletal irregularities persist even when systemic mineral parameters are normalized, adding another layer of complexity to the management of CKD-associated MBD.

Thank you