Renal osteodystrophy Updates on Pathogenesis and Classification

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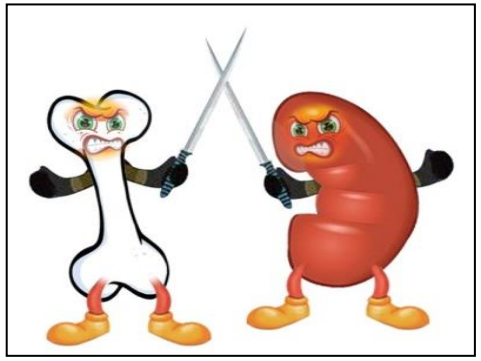
Isfahan University of Medical Sciences

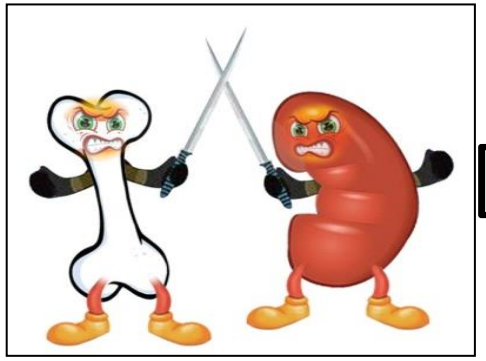
Outlines

- Introduction to Renal osteodystrophy and diagnosis.
- Bone disease in patients with advanced CKD.
  - Predominant hyperparathyroid-mediated high-turnover bone disease
  - Osteomalacia
  - Adynamic bone
  - Mixed uremic osteodystrophy



Introduction

- **Definition of CKD–MBD**
- A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:
  - Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism.
  - Abnormalities in bone turnover, mineralization, volume, linear growth, or strength.
  - Vascular or other soft-tissue calcification.
- **Definition of renal osteodystrophy**
  - Renal osteodystrophy is an alteration of bone morphology in patients with CKD.
  - It is one measure of the skeletal component of the systemic disorder of CKD–MBD that is quantifiable by histomorphometry of bone biopsy.



Diagnosis of renal osteodystrophy

- Histology and histomorphometry serve as powerful tool in assessing systemic skeletal diseases like osteoporosis.
- Histomorphometry is one of the standard method to study different cell type activities under normal and diseased condition.
- Bone histomorphometry provides qualitative and quantitative information on bone structure, bone remodelling and turnover in histological sections of mineralized (undecalcified) bone

Indications of bone biopsy

Clinical	Laboratory	Imaging	Research
Unexplained bone fracture	Discordance between PTH levels and bone-specific alkaline levels	Extremely increased or decreased BMD	
Suspicion of osteomalacia	Unexplained hypercalcemia or hypophosphatemia	Unexplained radiologic bone abnormalities	
Before surgical parathyroidectomy (suspicion of aluminum overload)	Toxicity with aluminum or with other metals	Progressively rapid cardiovascular calcifications	
Evaluation of the histologic effect of several treatments of CKD–MBD			
Before the use of bisphosponates, denosumab, and romosozumab			

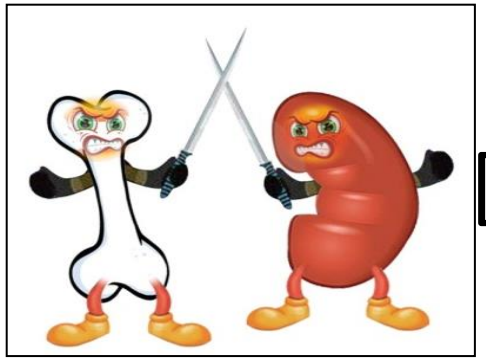
In patients with CKD G3a-G5D, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions

Principal histomorphometric parameters of bone biopsy in chronic kidney disease patients

Histomorphometric parameters	Secondary hyperparathyroidism	Osteitis fibrosa	Adynamic bone disease	Osteomalacia
Bone formation				
Osteoid volume	Normal	Normal/high	Normal/low	Low/normal/high
Osteoid thickness	Normal	Normal/high	Normal/low	Normal/very high
Osteoblast number	High	Very high	Low	Low
Bone formation rate	High	Very high	Low/very low	Low/very low
Mineralization lag time	Normal	Normal	Normal	prolonged
Bone resorption				
Osteoclast number	High	Very high	Low	Low/normal/high
Fibrosis	Absent	Present	Absent	Absent

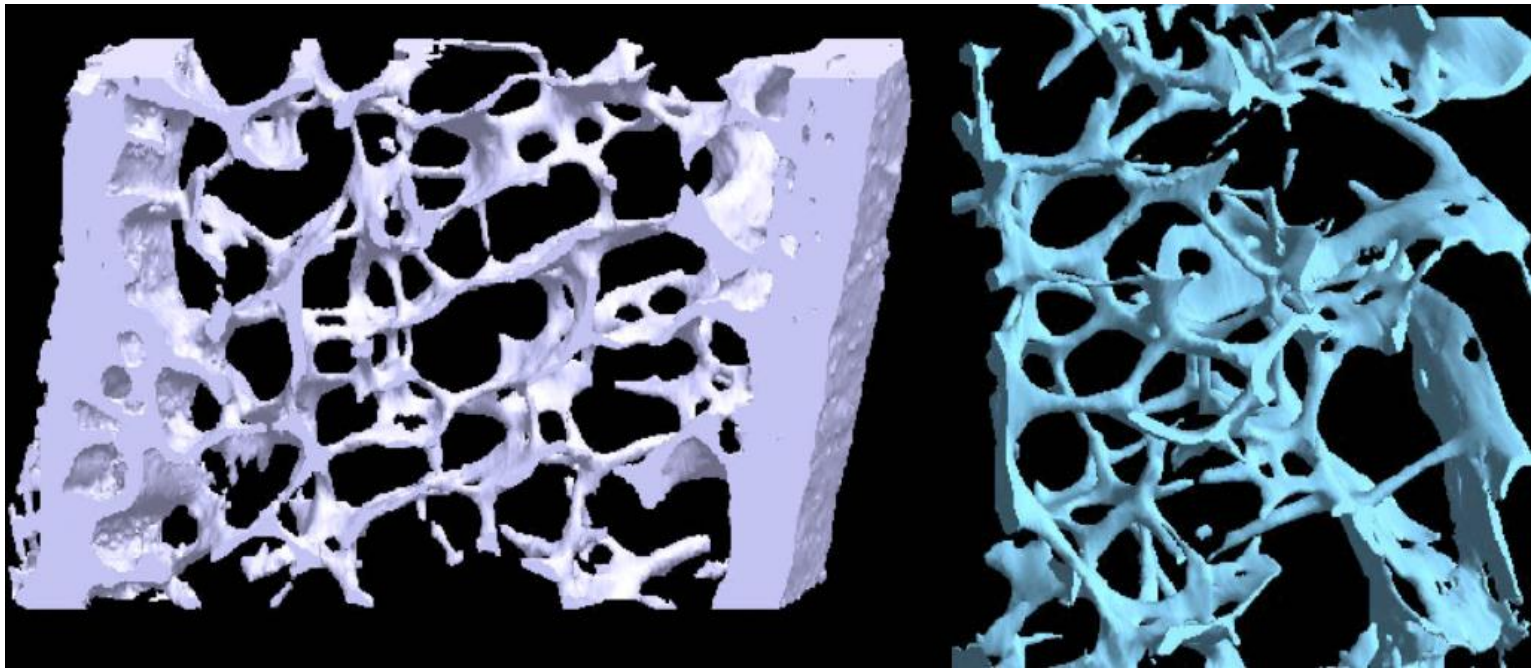
KDIGO 2017 Clinical Practice Guideline Update Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD

- In patients with CKD G3a–G5D, we suggest not routinely measuring bone-derived turnover markers of collagen synthesis (such as procollagen type I C-terminal propeptide) and breakdown (such as type I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline) .



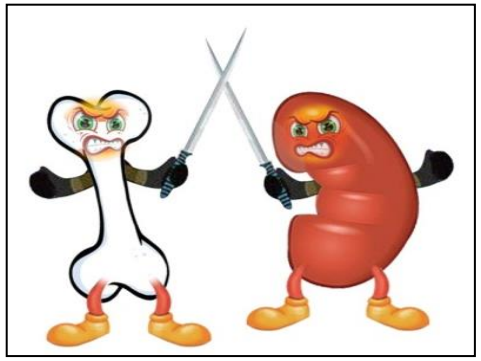
Diagnosis of renal osteodystrophy

- It can be applied either to bone histological sections or to high-resolution images produced by techniques such as microCT and microMR



Diagnosis of renal osteodystrophy

- Multiple new prospective studies have documented that lower dual-energy X-ray absorptiometry (DXA) BMD predicts incident fractures in patients with CKD G3a-G5D.
- A DXA BMD result might impact the decision to do a bone biopsy.



- Although definitive diagnosis in an individual patient requires a bone biopsy, much information about bone disease can be inferred from clinical and laboratory findings.

Bone disease in patients with advanced CKD

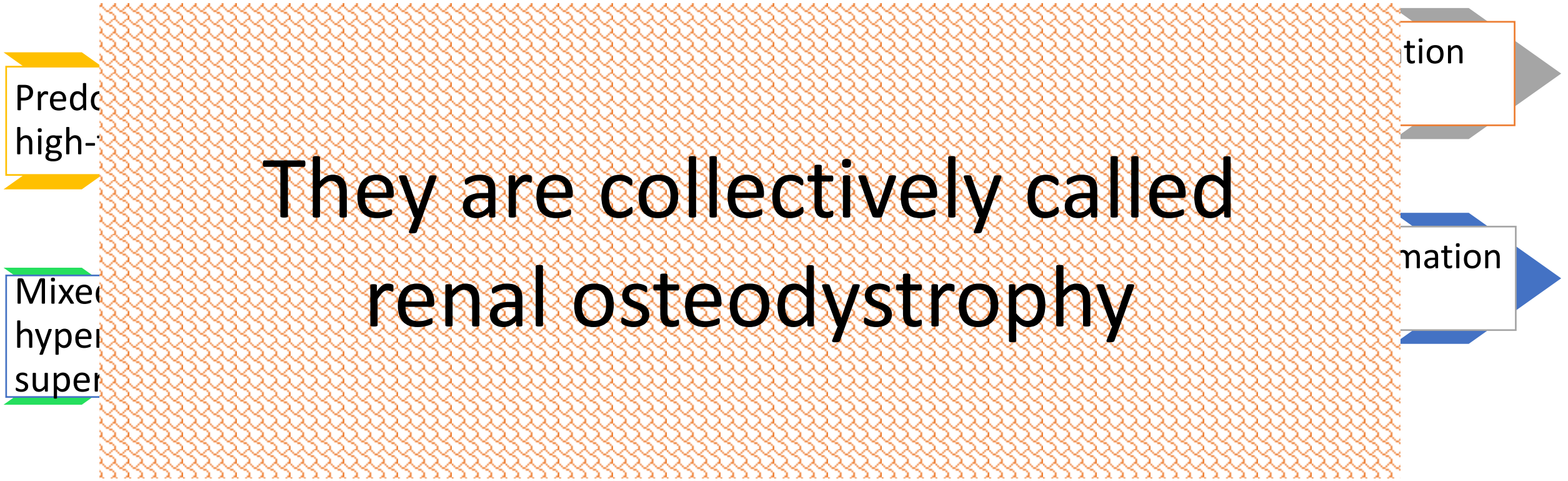
Predominant hyperparathyroid-mediated high-turnover bone disease (osteitis fibrosa)

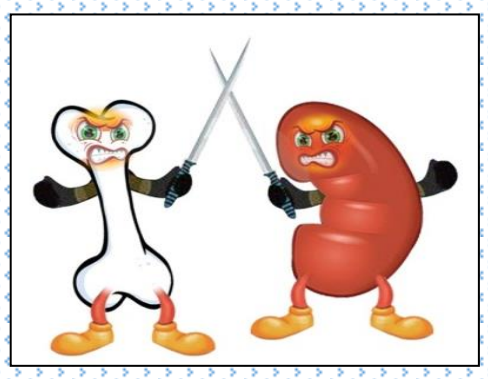
Osteomalacia (defined as a mineralization lag time >100 days)

Mixed uremic osteodystrophy (MUO; hyperparathyroid bone disease with a superimposed mineralization defect)

Adynamic bone (diminished bone formation and resorption)

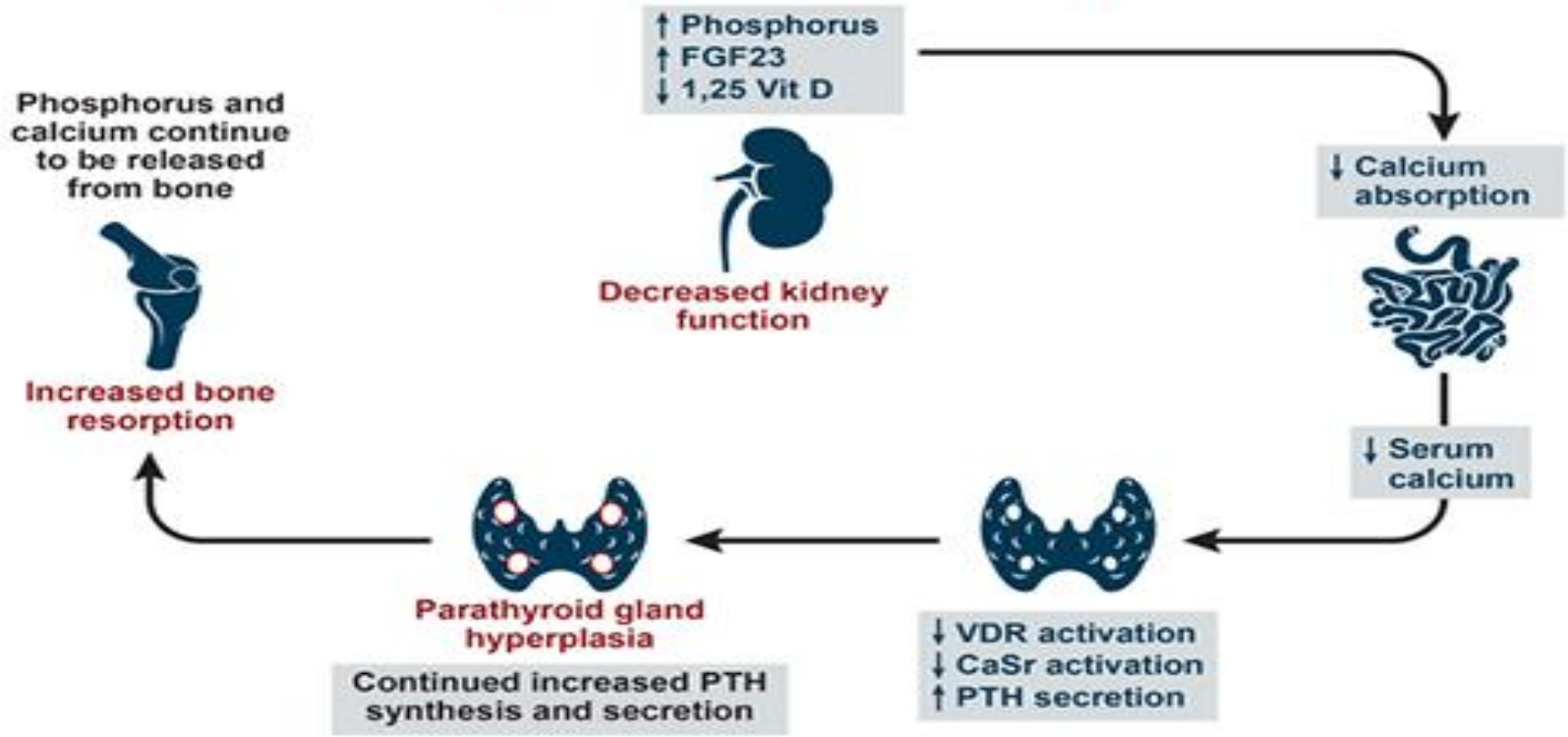
Bone disease in patients with advanced CKD





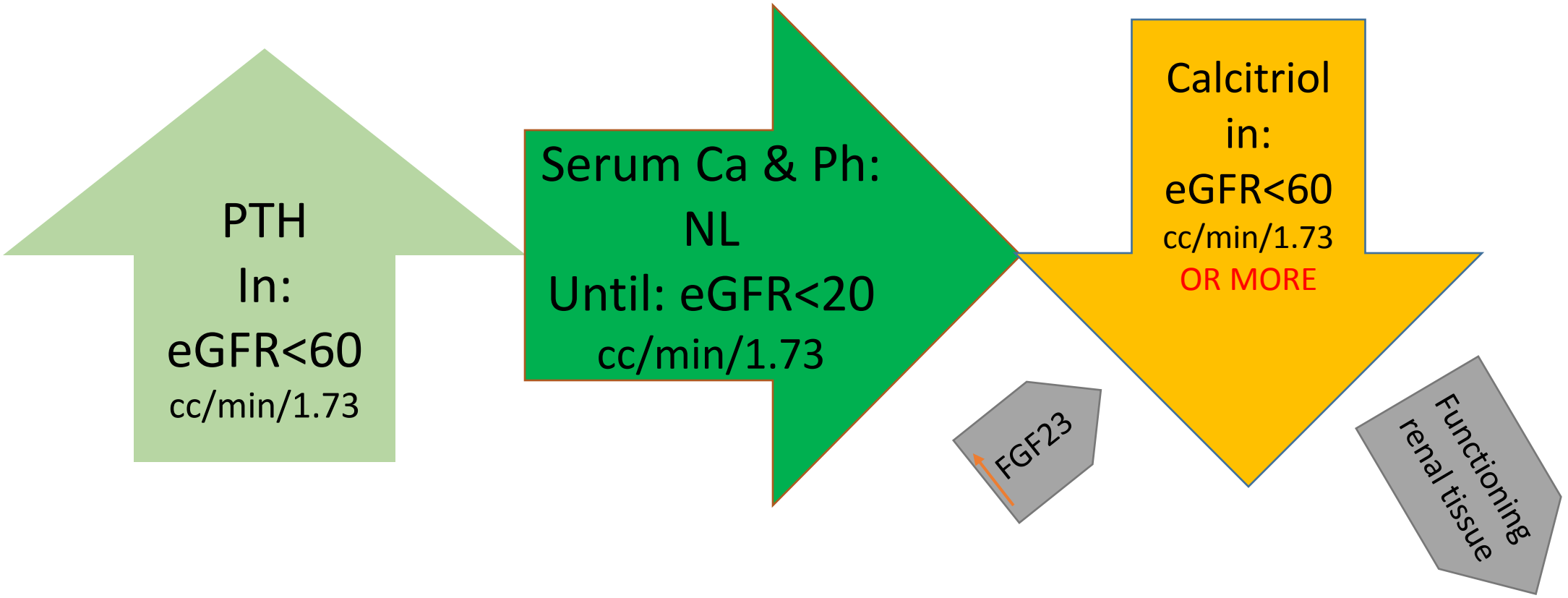
Predominant hyperparathyroid-mediated high-turnover bone disease (osteitis fibrosa)

Factors Contributing to Pathogenesis of Secondary Hyperparathyroidism



Hruska KA, et al. *Kidney Int*. 2008;74:148-157.
Rodriguez M, et al. *Am J Physiol Renal Physiol*. 2005;288:F253-F264.

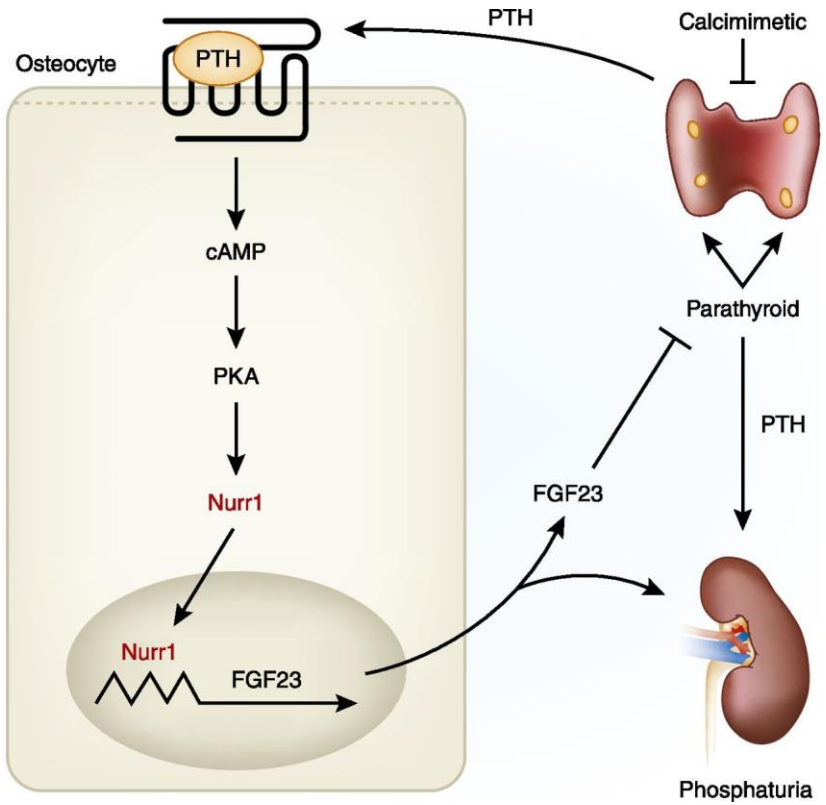
Laboratory changes in 2nd hyperparathyroidism

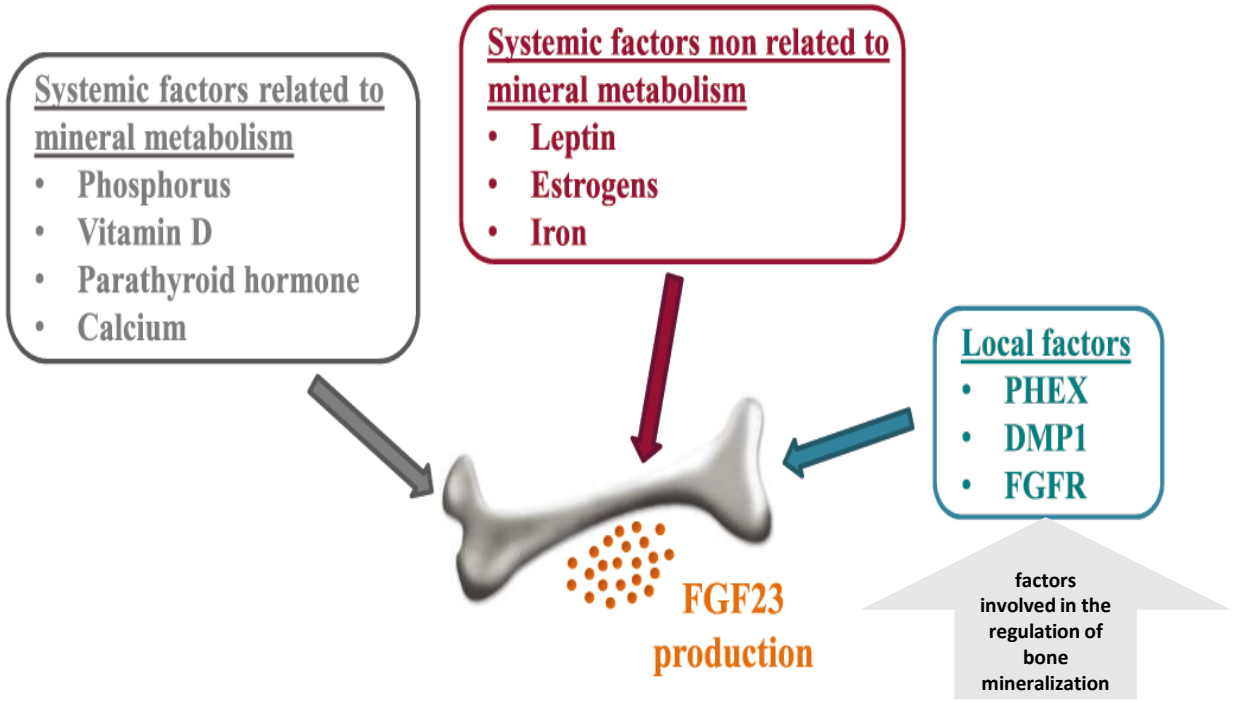


Phoosphate……

- Serum phosphate levels are not elevated in the majority of patients in the early stages of CKD, probably due to a reduction in renal tubular phosphate resorption mediated by increased levels of PTH and FGF23.
- The effects of FGF23 on phosphate excretion may become blunted by klotho deficiency, which occurs early in CKD.
- At this point, PTH may become the primary factor in maintaining serum phosphate level.

FGF23





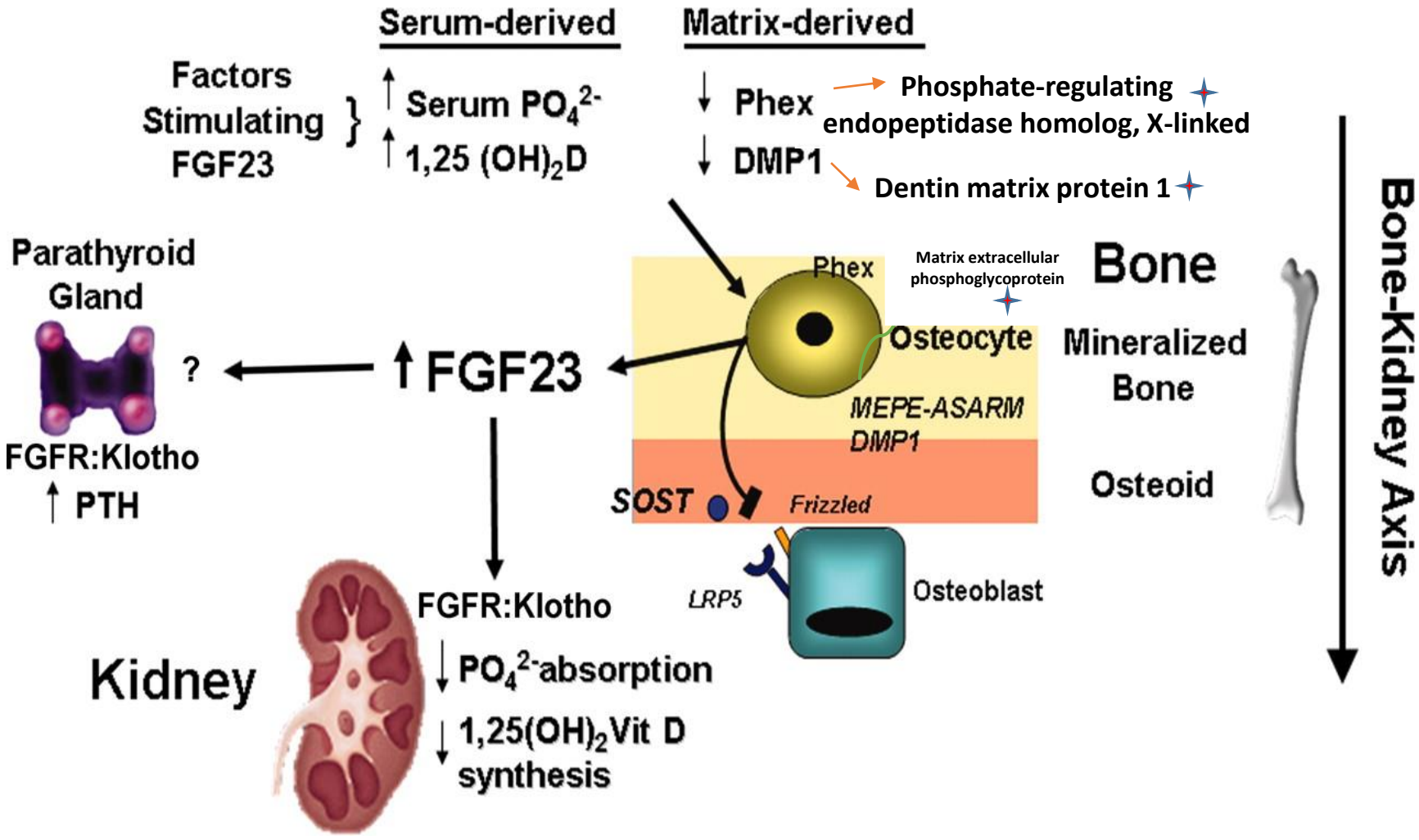
F1000Research 2015, 4(F1000 Faculty Rev):1472 Last updated: 17 JUL 2019

REVIEW

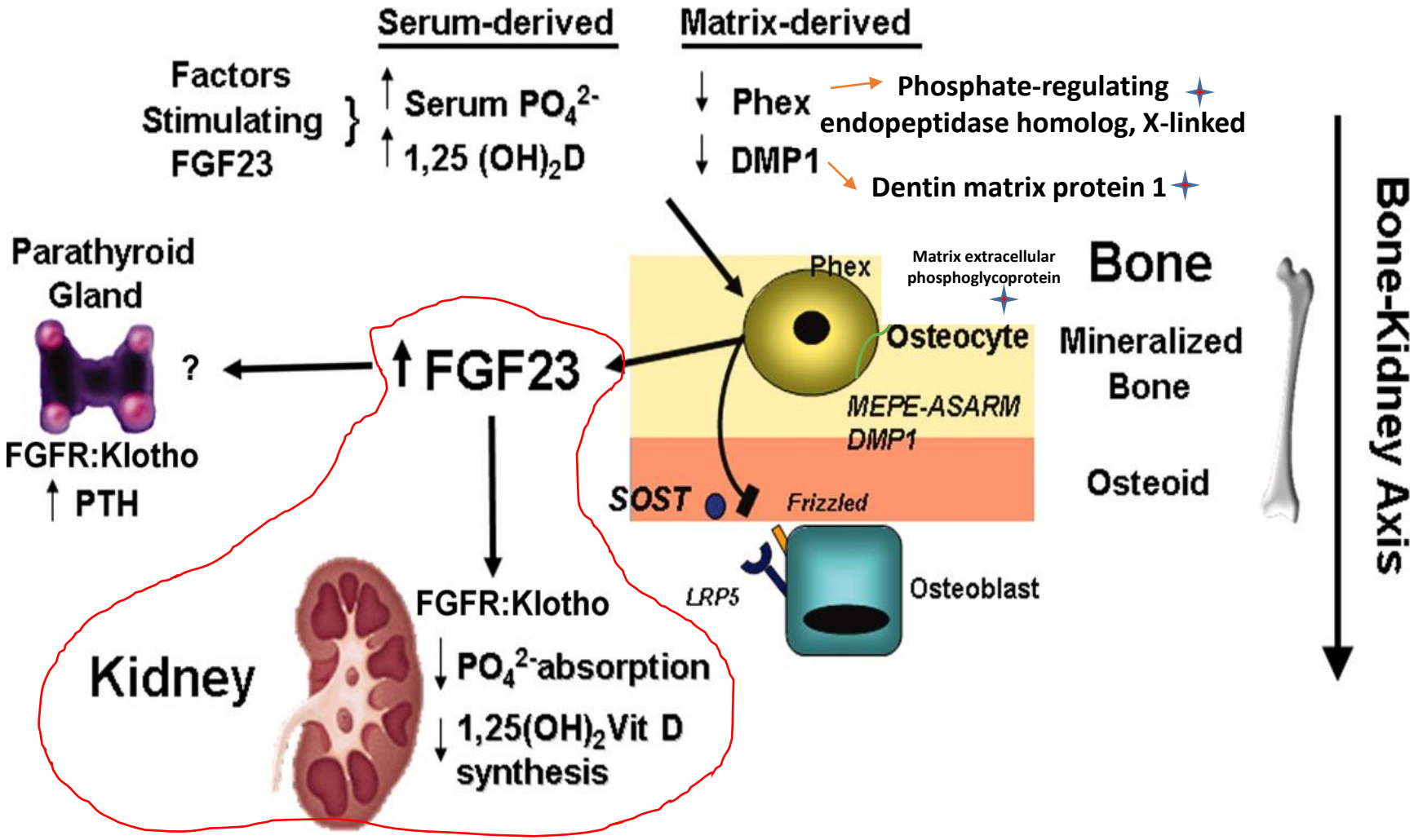
FGF23 as a calciotropic hormone [version 1; peer review: 2 approved]

María E. Rodríguez-Ortiz[1], Mariano Rodríguez[2]

What about FGF23?



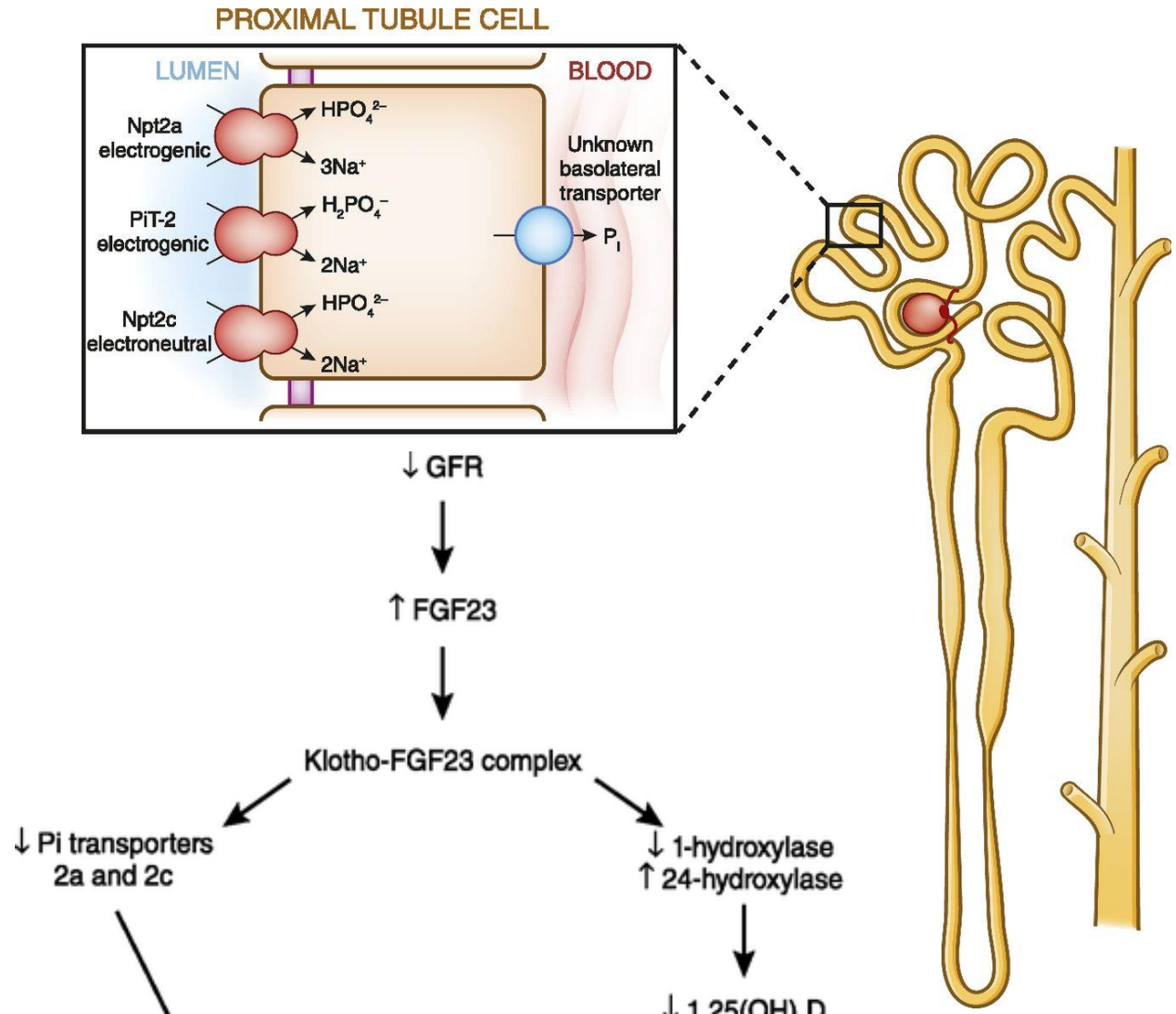
✦ Regulate bone mineralization and FGF23 expression

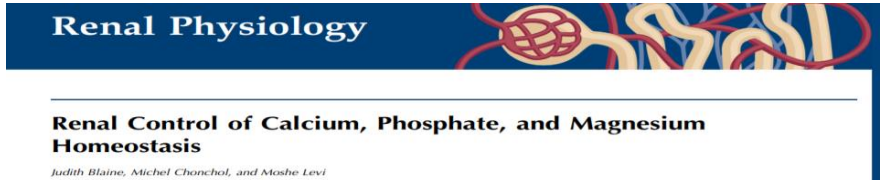


Regulate bone mineralization and FGF23 expression

FGF23

- In proximal renal tubules, FGF23 suppresses the membrane expression of the sodium-phosphate cotransporters Npt2a and Npt2c which mediate urinary reabsorption of filtered phosphate.





Clin J Am Soc Nephrol 10: 1257–1272, 2015. doi: 10.2215/CJN.09750913

Kidney International (2016) 90, 648–657

FGF23

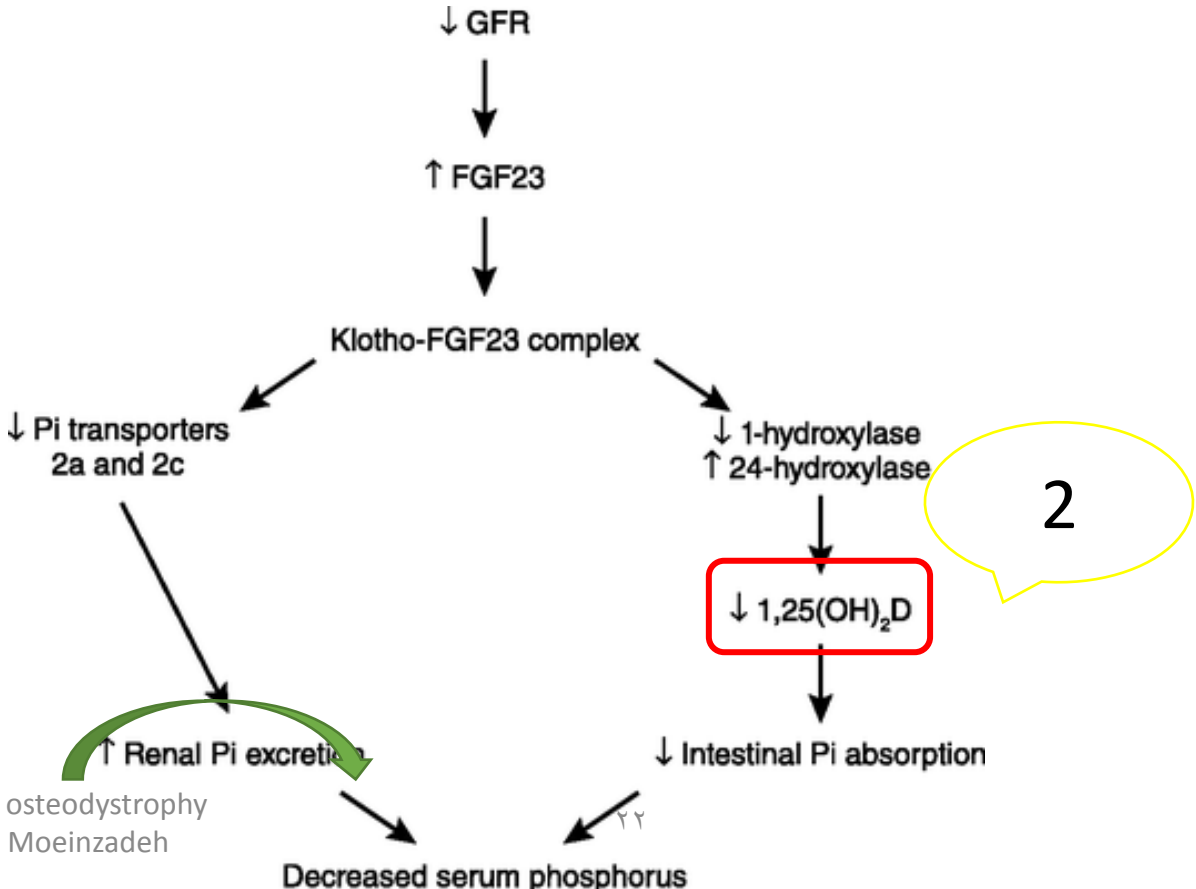
1

- Among individuals with eGFR in a normal range, the PTH may increase before FGF23, when the eGFR decreases modestly.

Fibroblast growth factor 23 and markers of mineral metabolism in individuals with preserved renal function

see commentary on page 4

Nasser A. Dhayat[1,10,11], Daniel Ackermann[1,11], Menno Pruijm[2], Belen Ponte[3], Georg Ehret[4], Idris Guessous[5,6], Alexander Benedikt Leichtle[7,11], Fred Paccaud[6], Markus Mohaupt[1], Georg-Martin Fiedler[7,11], Olivier Devuyst[8], Antoinette Pechère-Bertschi[9], Michel Burnier[2,11], Pierre-Yves Martin[3], Murielle Bochud[6], Bruno Vogt[1,11] and Daniel G. Fuster[1,10,11]



2

FGF23

- Another study found that, in patients with CKD and vitamin D deficiency, PTH levels were markedly elevated relative to those of FGF23, suggesting that FGF23 may have a lower phosphaturic role when PTH secretion is stimulated in response to vitamin D deficiency

The impact of vitamin D status on the relative increase in fibroblast growth factor 23 and parathyroid hormone in chronic kidney disease

Maarten W. Taal[1], Victoria Thurston[1], Natasha J. McIntyre[1], Richard J. Fluck[1] and Christopher W. McIntyre[1,2]

Kidney International (2014) **86**, 407–413

FGF23

- However, among CKD patients, the presence of high PTH concentrations, despite high FGF23 concentrations, suggests that the parathyroid gland becomes relatively resistant to the elevated concentrations of FGF23.
- This may be related to the markedly decreased expression of FGFR 1 and klotho protein in the hyperplastic parathyroid gland

Depressed expression of Klotho and FGF receptor 1 in hyperplastic parathyroid glands from uremic patients

Hirotaka Komaba[1], Shunsuke Goto[1], Hideki Fujii[1], Yasuhiro Hamada[1], Akira Kobayashi[2], Koji Shibuya[3], Yoshihiro Tominaga[4], Naoki Otsuki[5], Ken-ichi Nibu[5], Kimie Nakagawa[6], Naoko Tsugawa[6], Toshio Okano[6], Riko Kitazawa[7] and Masafumi Fukagawa[1,8]

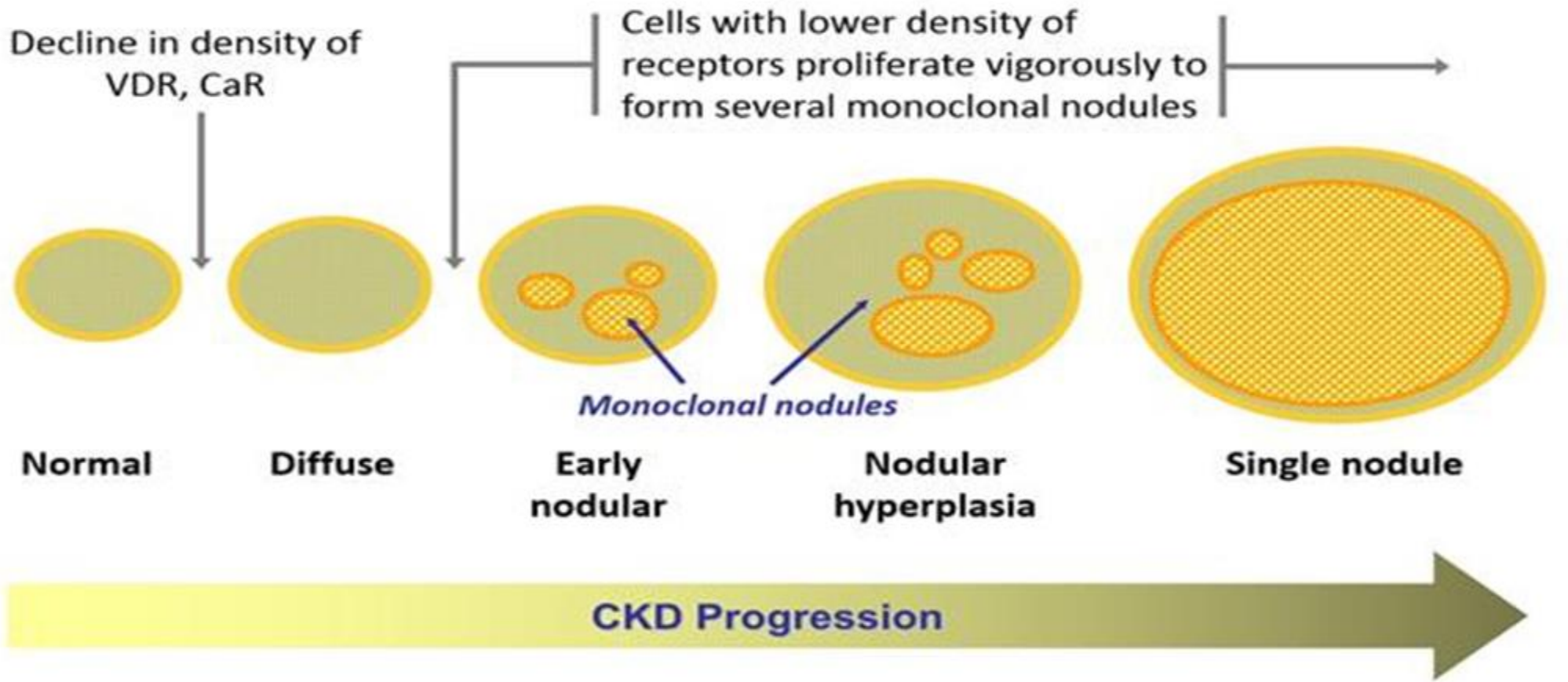
PTH effects on Phosphate

- The initial elevation in PTH secretion is appropriate since the ensuing increase in phosphate excretion lowers the plasma phosphate concentration toward normal.
- Among patients with severely reduced GFR, PTH inhibits proximal tubule phosphate reabsorption from the normal 80 to 95 percent to as low as 15 percent of the altered phosphate.
- Hyperparathyroidism also tends to correct both the hypocalcemia (by increasing bone resorption) and the calcitriol deficiency (by stimulating the 1-hydroxylation of calcidiol [25-hydroxyvitamin D] in the proximal tubule).

PTH effects on Phosphate

- In advanced stages of CKD, when the GFR drops below 30 mL/min, the compensatory increase in the levels of PTH and FGF23 becomes inadequate, and hyperphosphatemia develops.
- Moreover, since phosphate reabsorption by the renal tubules cannot be lowered below a minimum threshold, continued PTH-induced release of phosphate from bone can actually exacerbate the hyperphosphatemia.

Progression of Parathyroid Gland Hyperplasia in CKD



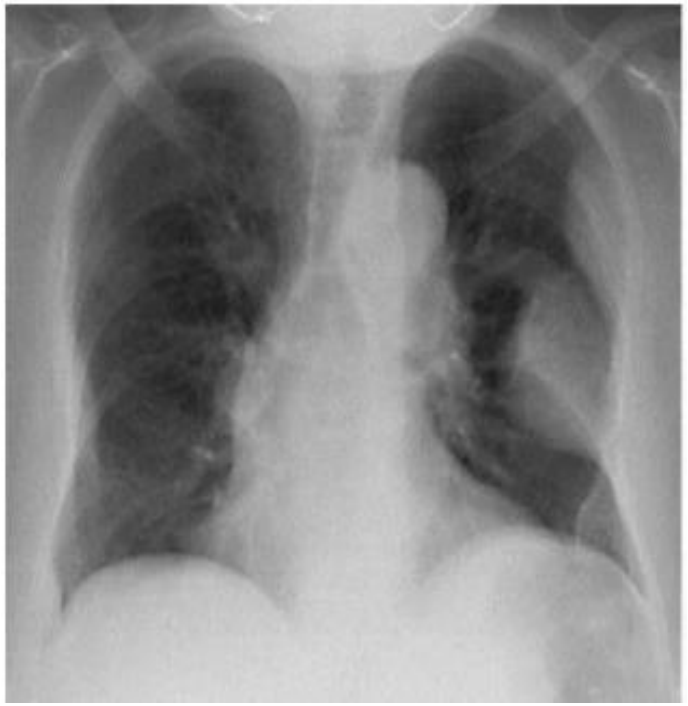
VDR= vitamin D receptor. CaR= Ca-sensing receptor.

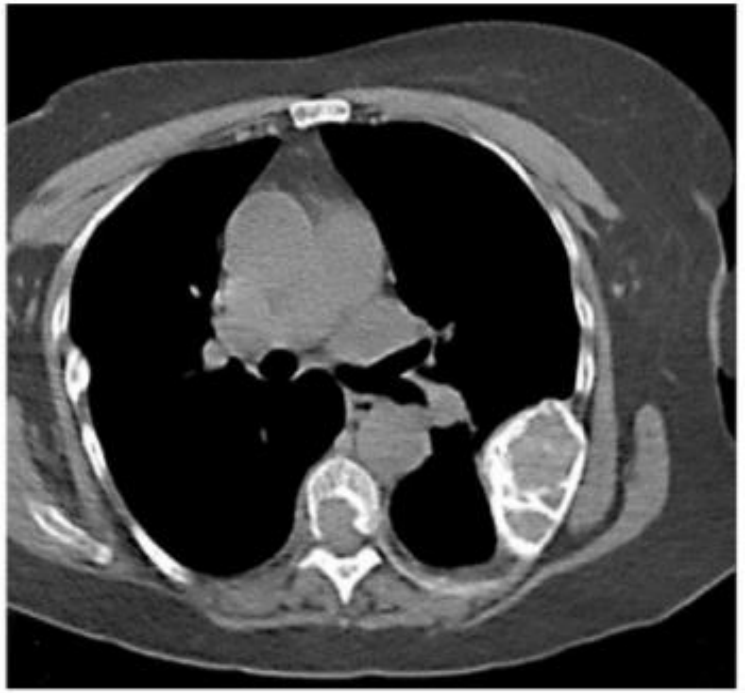
Adapted from Murayama A et al. *Endocrinology*. 99;140:2224-2231.

Case 1

- A 45 years old man with ESRD under hemodialysis (4 years) complaints of generalized pain in his musuloskletal system from 6 months ago. He received some drugs like analgesics without any improvement. His laboratory data listed below:
- Ca= 8.2mg/dL P= 6.5 mg/dL Alb= 3.5g/L PTH= 1200pg/mL
- He received Cinacalcet 30mg/d and next PTH as: 1000pg/mL.
- He had sore throat and cough within week ago and had chest X-ray due to suddenly chest pain and local pain on ribs.

Case 1





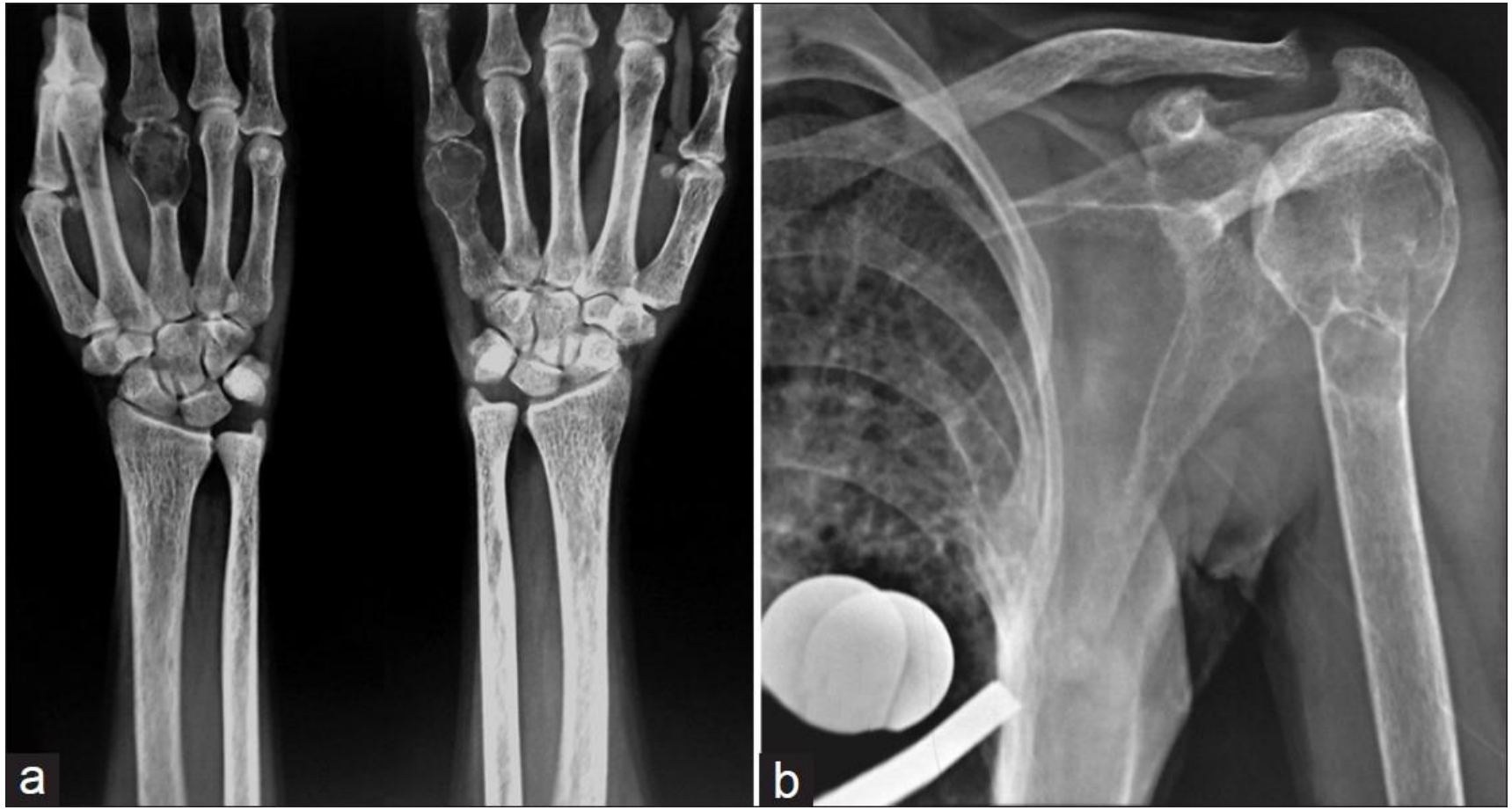
what is your diagnosis?

Osteitis fibrosa

- Osteitis fibrosa s characterized by increased bone turnover activity and defective mineralization, both demonstrated by bone biopsy.
- This disorder is generally asymptomatic but is associated with bone pain in a minority of patients.
- There is an increased risk of fractures.

Osteitis fibrosa

- Histologic examination: increased numbers of osteoblasts and osteoclasts.
- An increased rate of bone formation
- Wide osteoid seams are seen indicating that bone is turning over faster than it can be mineralized.
- Foci of marrow fibrosis are characteristically seen.
- The resultant bone architecture is distinctly abnormal and intrinsically weaker and less durable than normal bone.


a
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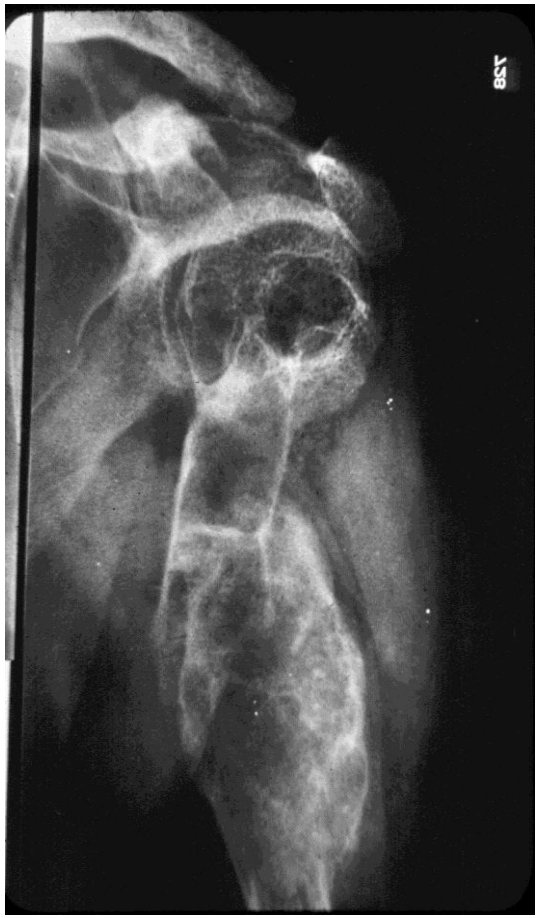
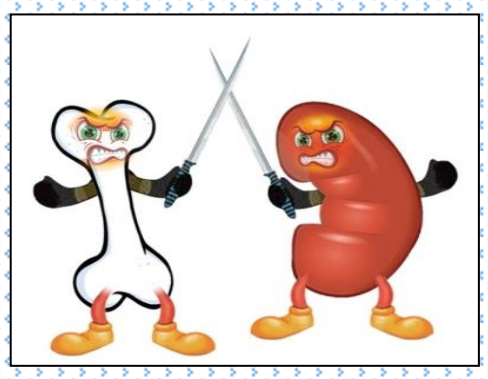


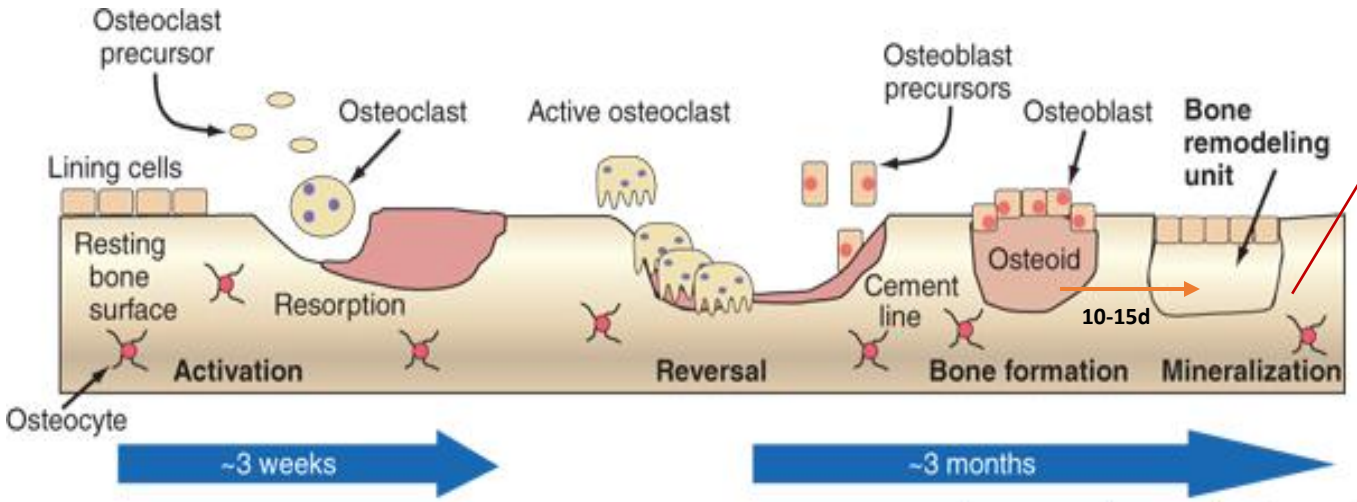


Osteomalacia (defined as a mineralization lag time >100 days)

Osteomalacia

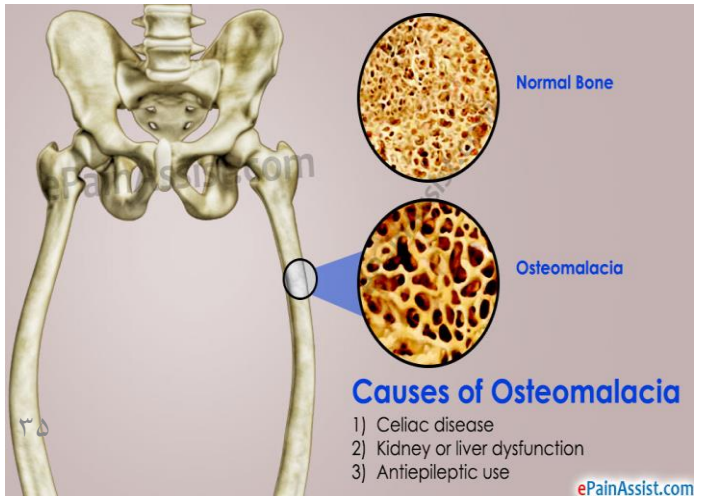
- Bone remodeling occurs continually on both trabecular and Haversian bone surfaces.
- At any given time, approximately 7 percent of the bone surface is in the process of forming new bone.
- It is the softening of the bones due to impaired bone metabolism as result of insufficient levels of phosphate, calcium, and vitamin D, or because of resorption of calcium.
- All of this leads to inadequate bone mineralization.

Bone remodeling



Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com

Amorphous calcium phosphate → hydroxyapatite



Diagnosis of osteomalacia

- DXA cannot distinguish between osteoporosis and several other metabolic bone disorders such as various types of osteomalacia, osteitis fibrosa, uremic osteodystrophy, hypophosphatasia, Paget's disease of bone, etc.
- DXA cannot tell us anything about microarchitecture of bone, tissue level dynamics, bone cellular activity, bone mineralization and bone remodeling.

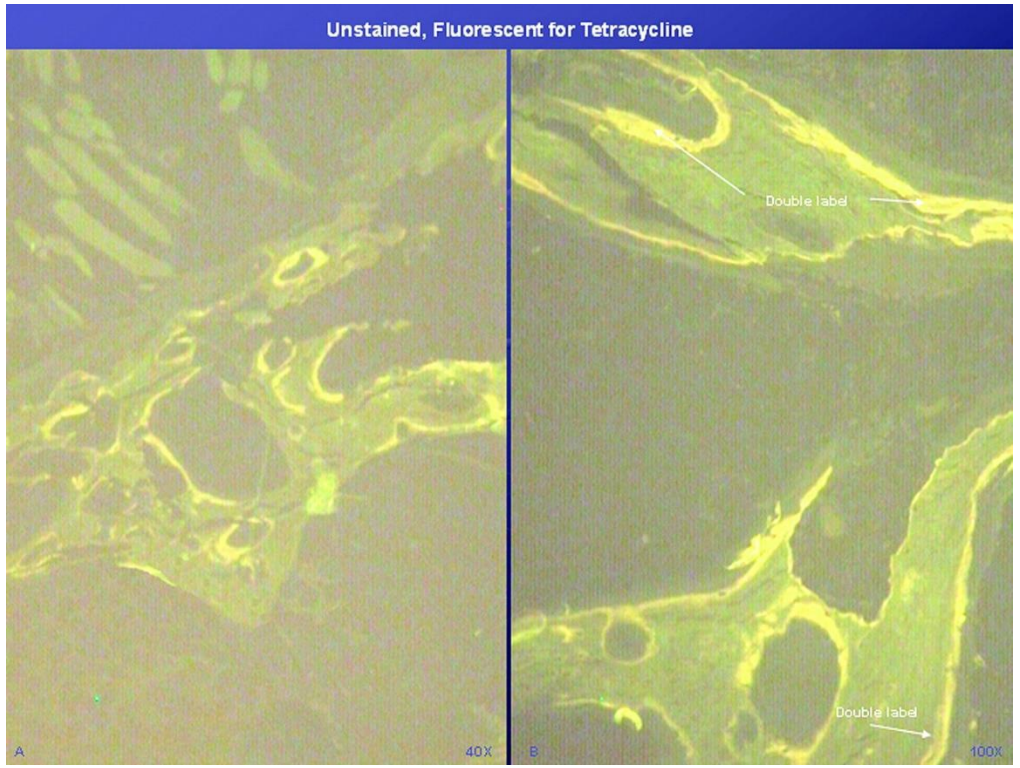
Bone Reports 8 (2018) 125–134

Bone histomorphometry in the evaluation of osteomalacia☆

Arti Bhan[a], Shijing Qiu[b], Sudhaker D. Rao[b,*]

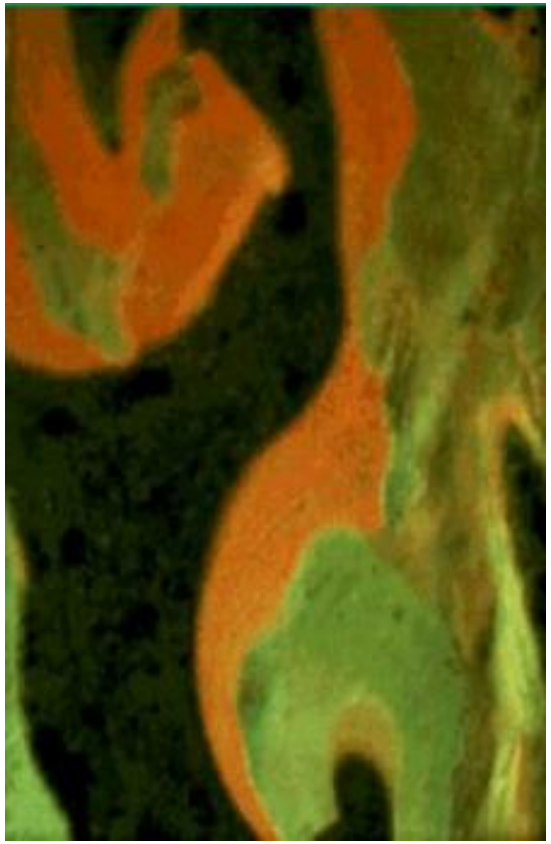
[a] Division of Endocrinology, Diabetes, and Bone & Mineral Disorders, Henry Ford Health System, Detroit, MI, 48201, United States
[b] Bone & Mineral Research Laboratory, Henry Ford Health System, Detroit, MI, 48201, United States

- The rates of bone formation and calcification can be measured by histomorphometric techniques using double tetracycline labeling
- After two courses of the antibiotic, separated by a period of days, the growth rate of the skeleton can be estimated in iliac crest biopsies by measurement of the distance between the bands of deposited tetracycline



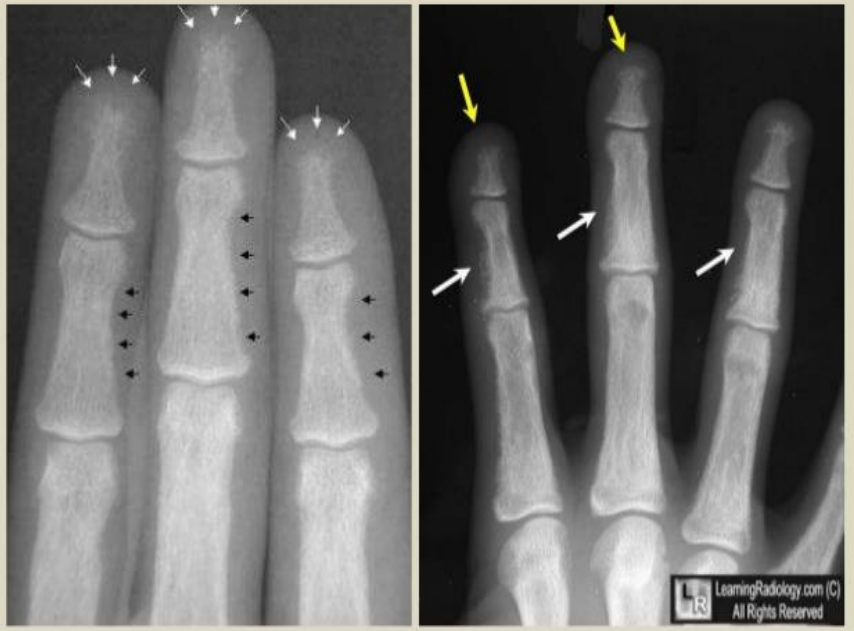
In osteomalacia:

- The distance between tetracycline bands is reduced.
- The unmineralized matrix appears as a widened osteoid seam (more than 15 microns) and the osteoid volume is more than 10 percent.



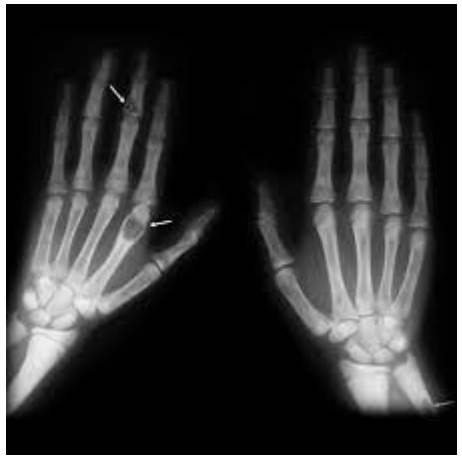
✓ Etiologies in ESRD:
-Reduced formation of 1,25-dihydroxyvitamin D,
-Metabolic acidosis
-Aluminum like in aluminum-containing antacids use.

Subperiosteal bone resorption

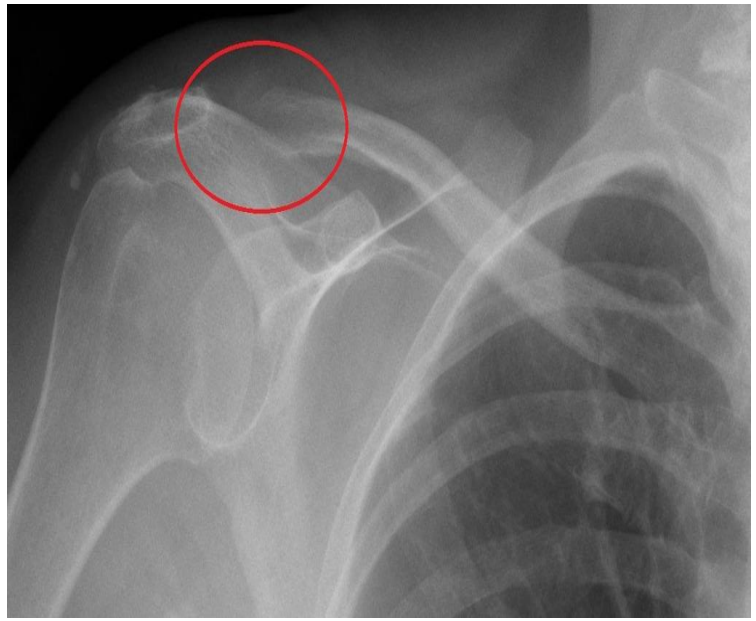


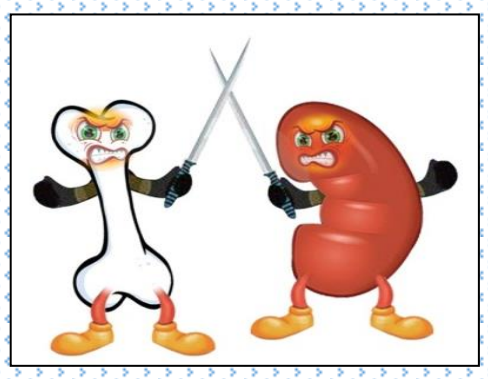
This image demonstrates subperiosteal resorption that has resulted in severe tuftal resorption . Also, note the subperiosteal and intracortical resorption.

Bone cyst



Resorption of the distal ends of long bones

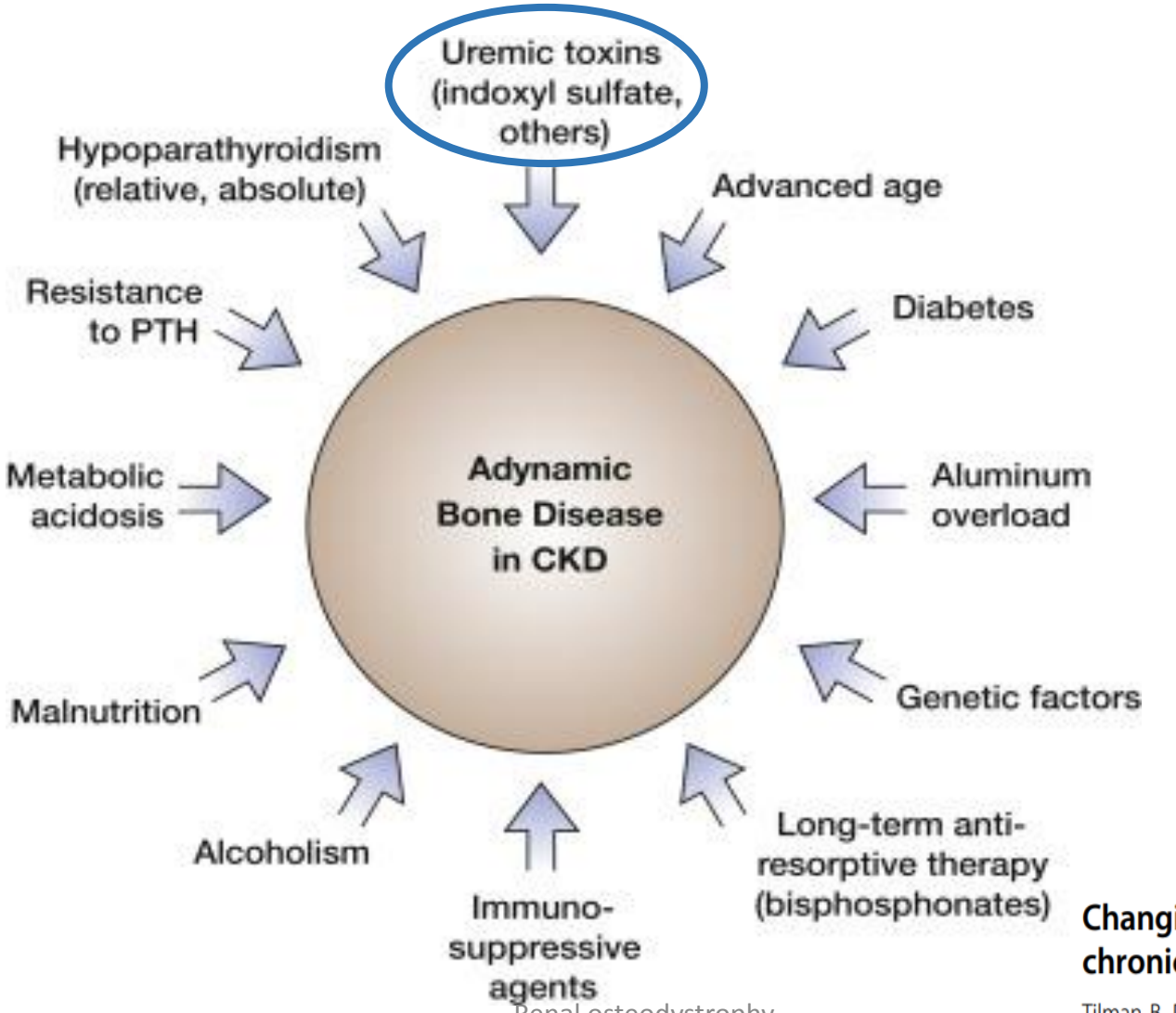




Adynamic bone (diminished bone formation and resorption)

- Even among CKD patients not yet on dialysis, the prevalence of low-turnover disease has reportedly increased to between 12 and 23 percent.
- In a bone biopsy study of 84 unselected patients with stage 5 CKD, adynamic bone disease was the most prevalent type of renal osteodystrophy, particularly in diabetic patients.

Risk factors

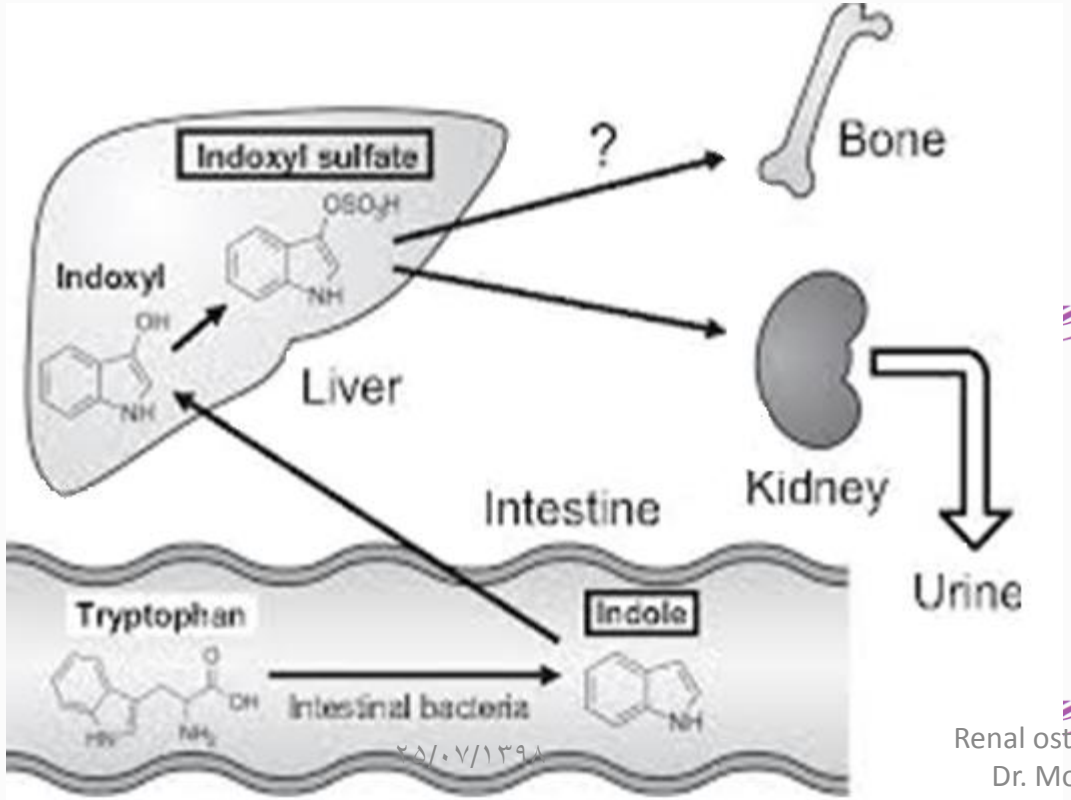


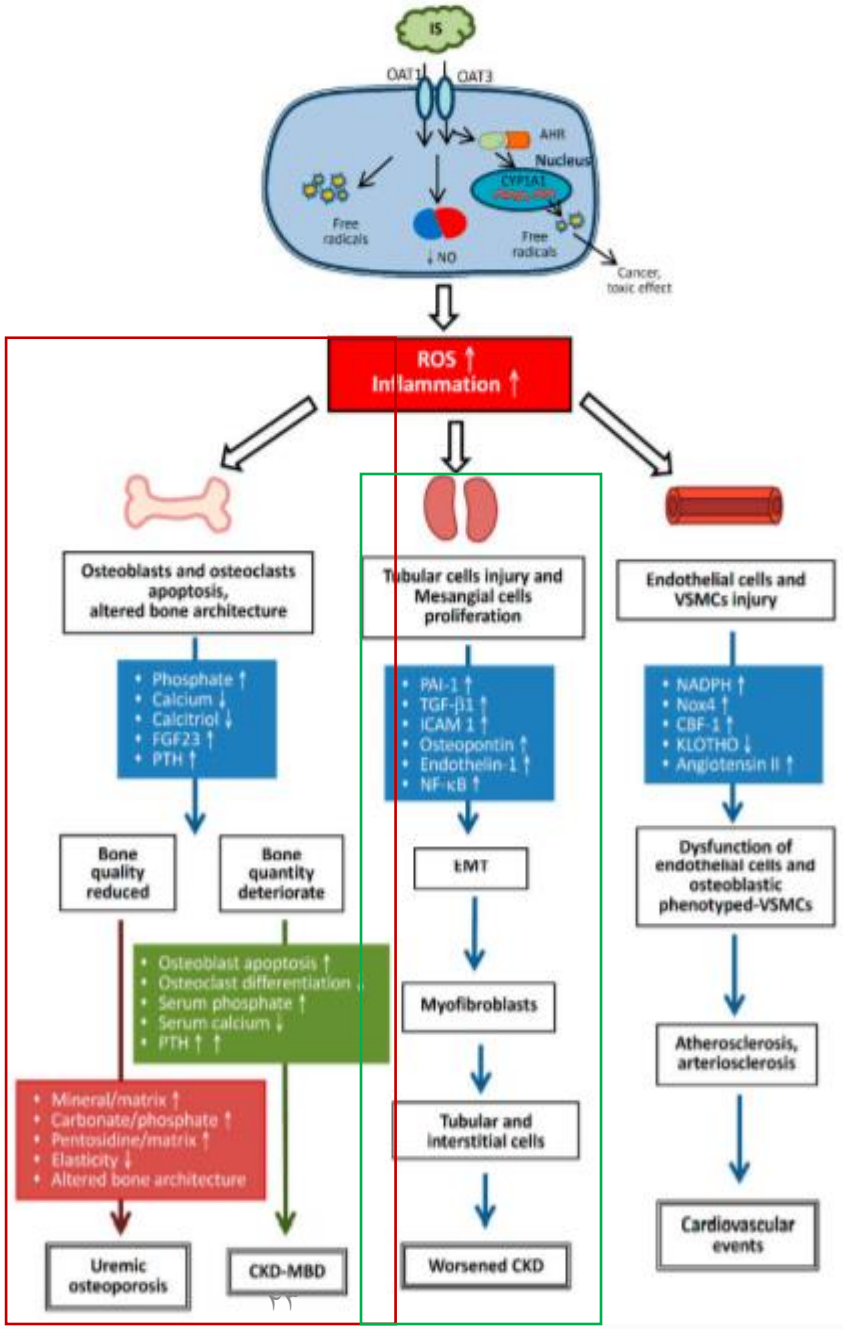
Kidney International (2016) **89,** 289–302

Changing bone patterns with progression of chronic kidney disease

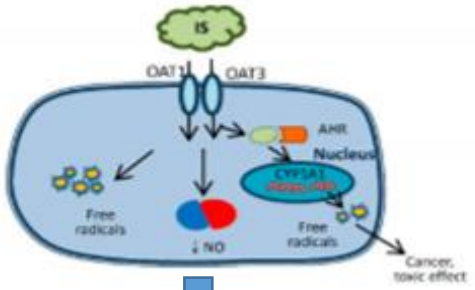
Tilman B. Drüeke[1] and Ziad A. Massy[1,2]

Indoxyl sulfate is a small solute with a molecular weight of 213 g/mol & is at least 90% bound to plasma proteins.





Indoxyl sulfate



↑ROS
↑Inflammation

Osteoblast & osteoclast apoptosis, altered bone architecture

↑Phosphate
↓Calciume
↓Calcitriol
↑FGF23
↑PTH

Bone quality: reduced

↑-Mineral/matrix
↑-Carbonate/phosphate
↑-Pentosidine/matrix
↓-Elasticity
-Bone architecture: altered

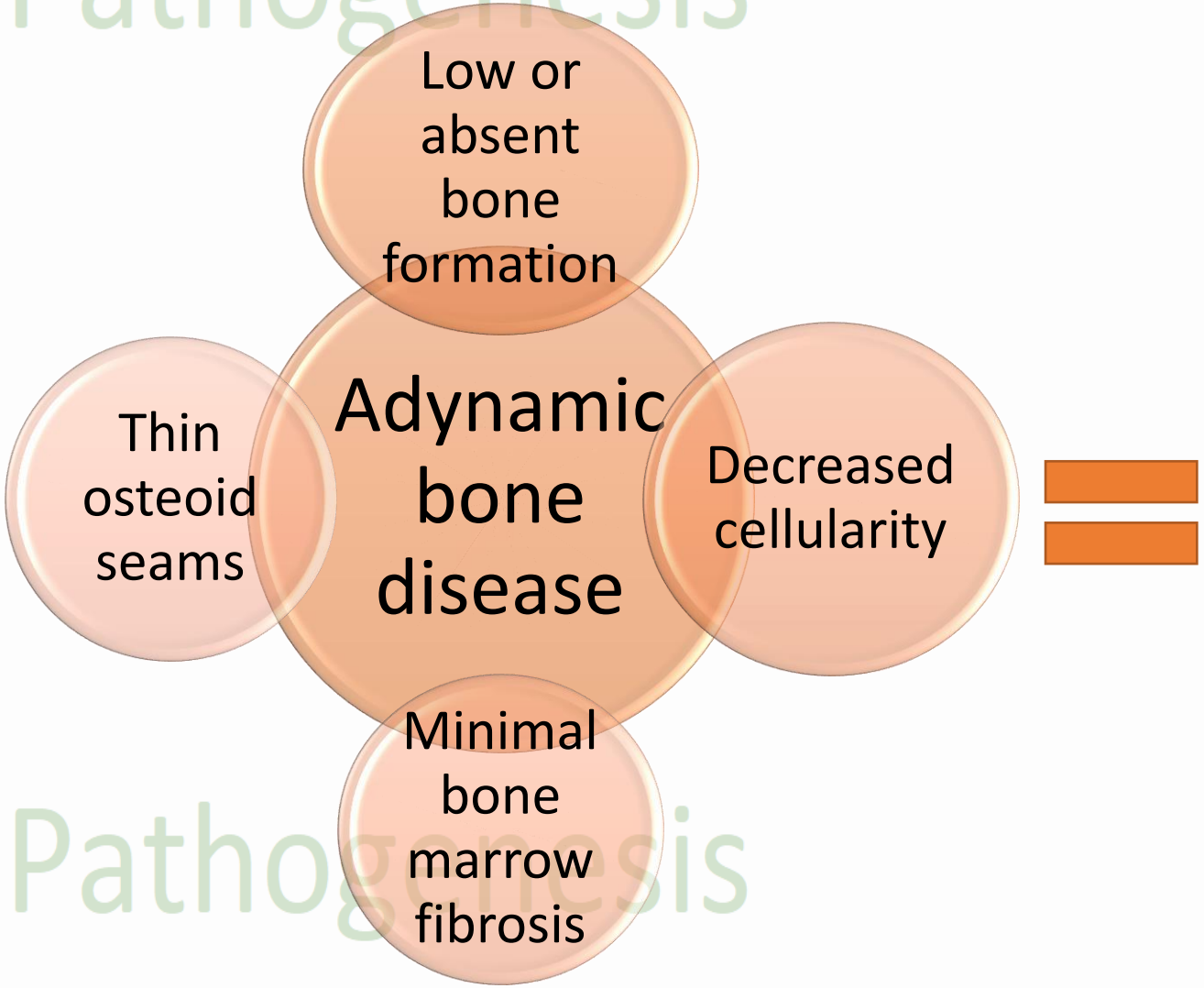
Uremic osteoporosis

Bone quantity: deteriorate

↑-Osteoblast apoptosis
↓-Osteoclast differentiation
↑-Serum phosphate
↓-Serum calcium
↑↑-PTH

CKD-MBD

In brief....

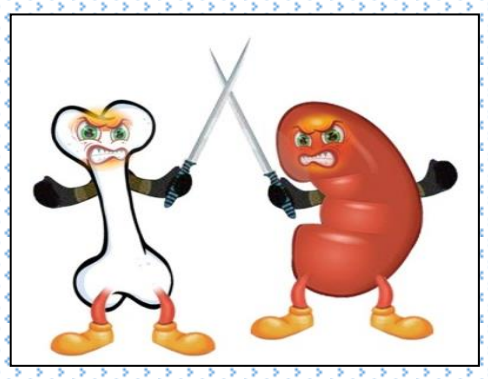


- Bone turnover is markedly reduced
- Lack of bone cell activity (both osteoblasts and osteoclasts)

Principal factor underlying adynamic bone disease

Resistance to the bone stimulatory effects of PTH may play an even larger role

the healthy population



Mixed uremic osteodystrophy (MUO; hyperparathyroid bone disease with a superimposed mineralization defect)

Definition

- Mixed uremic osteodystrophy has features of high turnover bone disease together with evidence of a mineralization defect.
- Thus, there is more osteoid than expected, and tetracycline labeling uncovers a concomitant mineralization defect.

Case 2

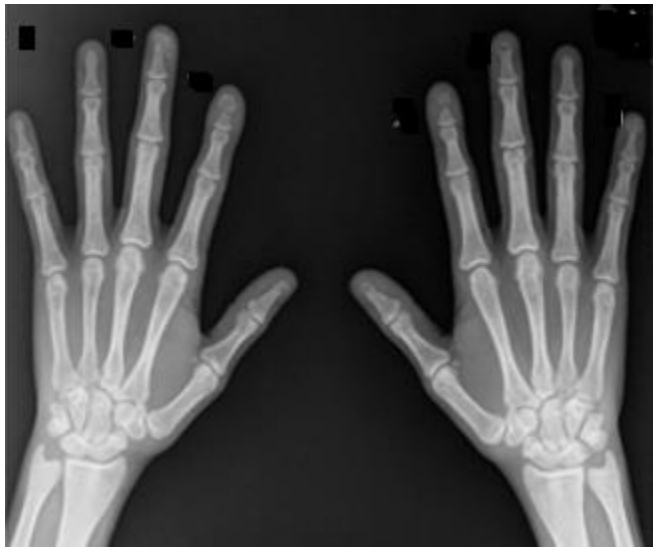
- A 28-year-old male with no known past medical history has presented with nausea, vomiting, epigastric pain and nose bleeds.
- He was a recent immigrant from Afghanistan and has not seen a physician recently.
- BUN= 213 mg/dl, Cr=19 mg/dl, K= 5.8 mmol/l , Bicarbonate=14 mmol/l and he was hypervolemic.
- Renal replacement therapy was initiated.
- His uremic symptoms including nose bleeds improved with dialysis.

Case 2

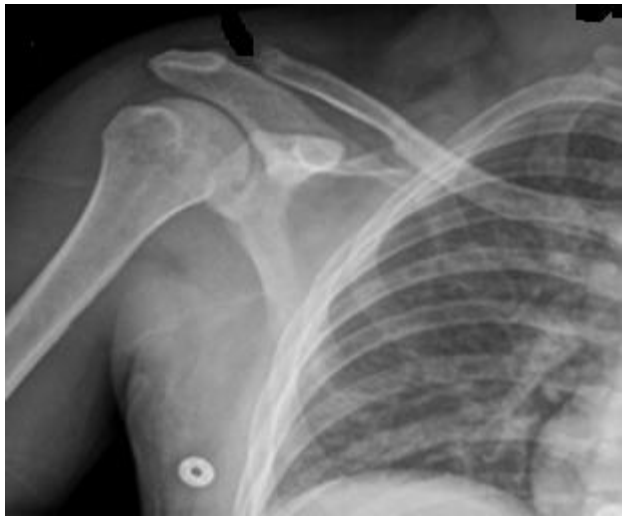
- Work up of acute kidney injury was negative for any auto-immune or glomerular processes.
- PTH =3904 pg/ml ca = 9.5 mg/dl P=10.8 mg/dl. Vitamin D= 20 ng/ml.
- He later complained of shoulder and hand pain for which radiographs were obtained.
- X-ray of the hands showed bilateral

acro-osteolysis with resorption of the

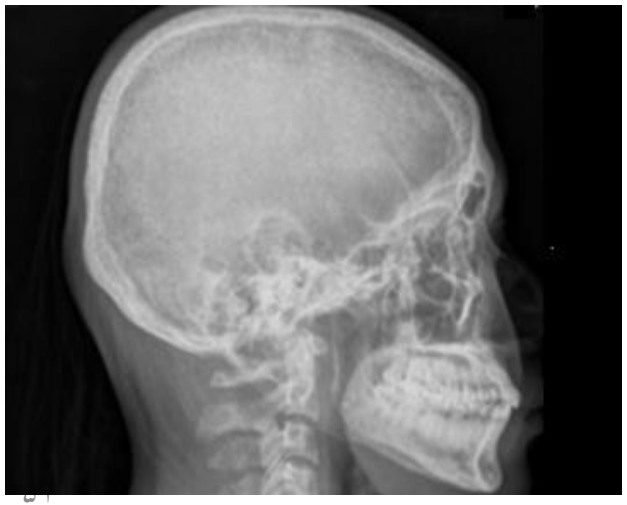
distal phalangeal tufts.



- X-ray of the right shoulder showed resorption of the distal end of the clavicle and also mild focal subchondral cystic change along the posterior lateral humeral head.



- X-ray of the skull showed abnormal bony mineralization along the patient's calvarium.



Take home messages

- Renal osteodystrophy is an alteration of bone morphology in patients with CKD.
- It is one measure of the skeletal component of the systemic disorder of CKD–MBD that is quantifiable by histomorphometry of bone biopsy.
- Although definitive diagnosis in an individual patient requires a bone biopsy, much information about bone disease can be inferred from clinical and laboratory findings.

Take home messages

- In predominant hyperparathyroid-mediated high-turnover bone disease (osteitis fibrosa) : FGF23 has phosphaturic effect and lowering level of 1,25 OH vit D that later is prominent.
- Osteomalatia is a disease with defective mineralization
- Adynamic bone disease has higher prevalence in dialysis patients with low bone turnover.

Thanks for your attention