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Chronic Kidney Disease-mineral and Bone Disorder (CKD-MBD)

Introduction

- CKD-MBD is a systemic disorder of mineral and bone metabolism resulting from CKD that may be manifested by either one or a combination of the following:
  - Abnormalities in: Calcium, Phosphorus, PTH, Vitamin D metabolites
  - Abnormalities in: Bone turnover, Bone mineralization, Bone volume, Bone strength, Linear growth
  - Calcification of extraskeletal tissue, include the vasculature and other soft tissues
  - Each of these abnormalities is associated with high mortality rates, primarily from cardiovascular complications.

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.
- CKD-MBD assessed by bone histomorphometry. There are three key histologic descriptors:
  - Bone turnover: normal, increased, or decreased
  - Bone mineralization: normal or abnormal
  - Bone volume: normal, increased, or decrease
- This is referred to as the TMV (turnover, mineralization, and volume) system

Bone disease in patients with advanced CKD

collectively called renal osteodystroph

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

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

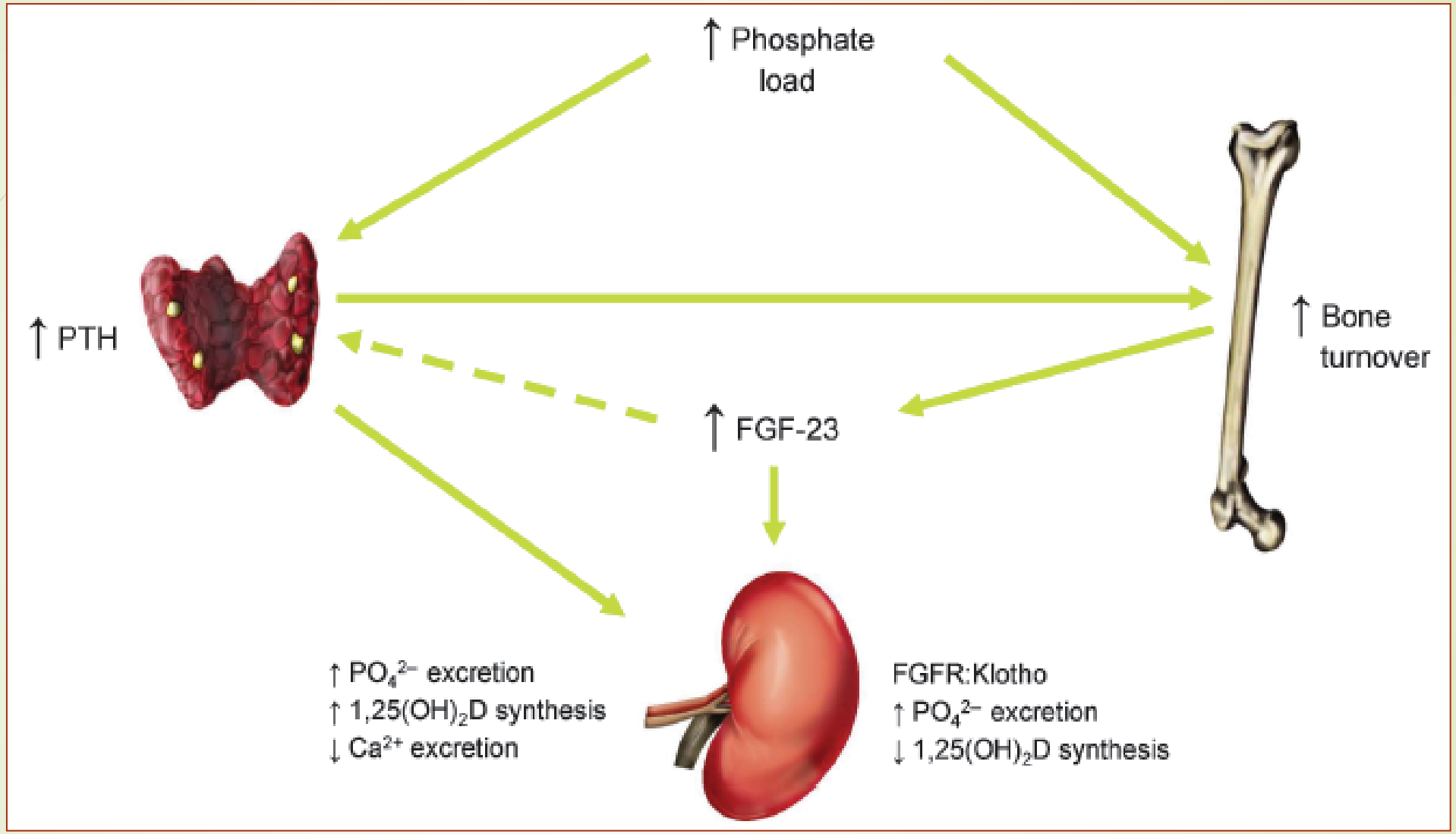
Mixed uremic osteodystrophy (MUO; hyperparathyroid bone disease with a superimposed mineralization defect

Adynamic bone (diminished bone formation and resorption)

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

Introduction

- Phosphate retention begins early in renal disease, due to the reduction in the filtered phosphate load.
- Phosphate retention is closely related to:
  1. Cardiovascular disease risk in CKD
  2. Increased FGF-23 levels
  3. Secondary hyperparathyroidism



Effect of dietary phosphorus load on phosphorus metabolism in the body.

FGF-23 appears to be the initial hormonal abnormality

- Increased FGF-23 leads to:
  1. Increased urinary phosphate excretion
  2. Suppression of $1,25(OH)_2D$
- PTH increases in response to reductions in $1,25(OH)_2D$
- PTH can correct both the hypocalcemia and the hyperphosphatemia by :
  - Increasing bone turnover & Ca- P release from bone
  - Enhancing urinary phosphate excretion.

FGF-23

- FGF-23 is also important in the renal adaptation to maintain phosphate excretion
- The fraction of the filtered phosphate that is reabsorbed, progressively reduces from the normal value of 80 -95% to as low as 15% in advanced renal failure
- Phosphate balance and a normal serum phosphate concentration are generally maintained until GFR falls below 25 -40 mL/min, at the price of elevated FGF-23 and hyperparathyroidism.

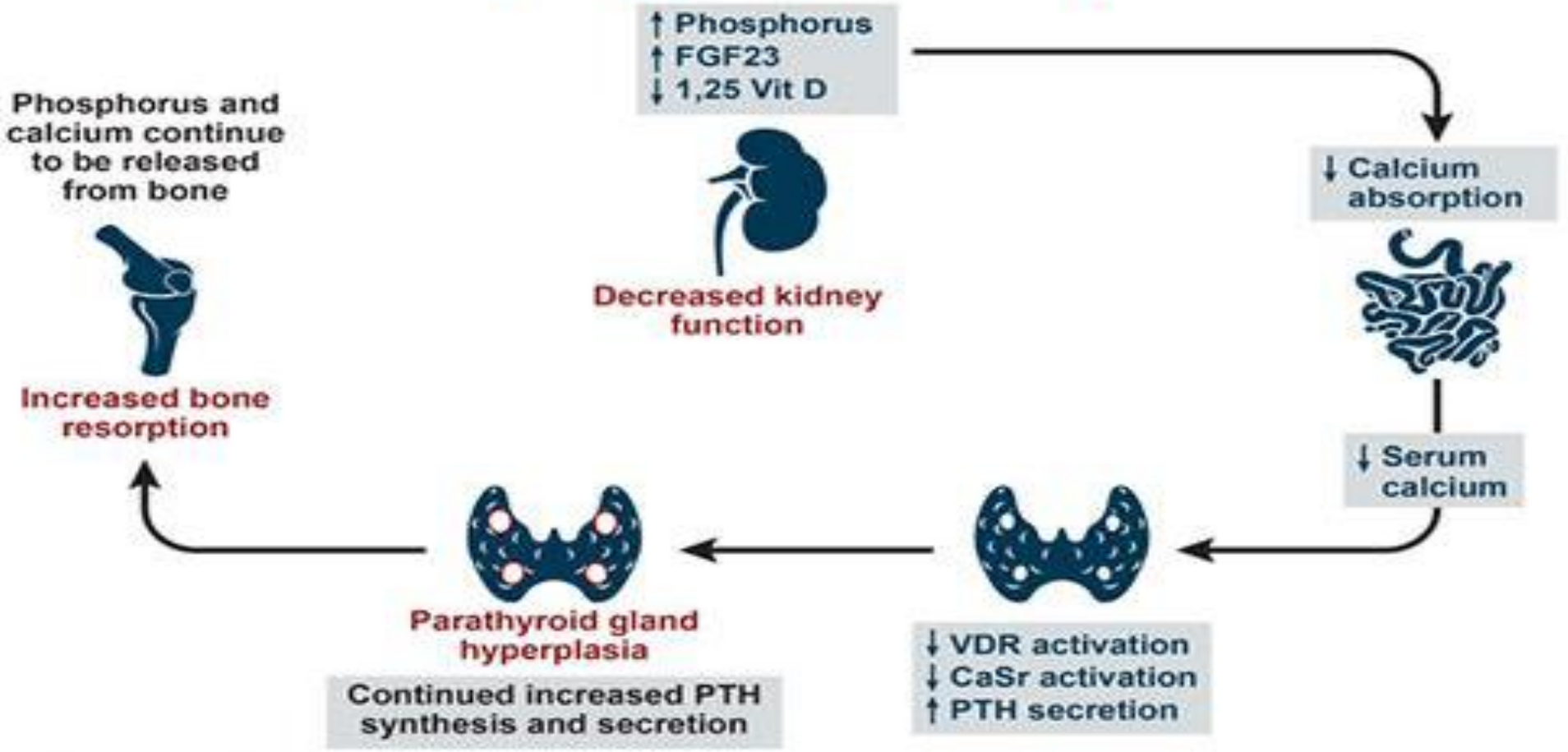
PTH effects on Phosphate

- The initial elevation in PTH secretion is appropriate since
  - 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 % to as low as 15 % of the altered phosphate.
- Hyperparathyroidism also tends to correct both
  - Hypocalcemia (by increasing bone resorption) and
  - 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

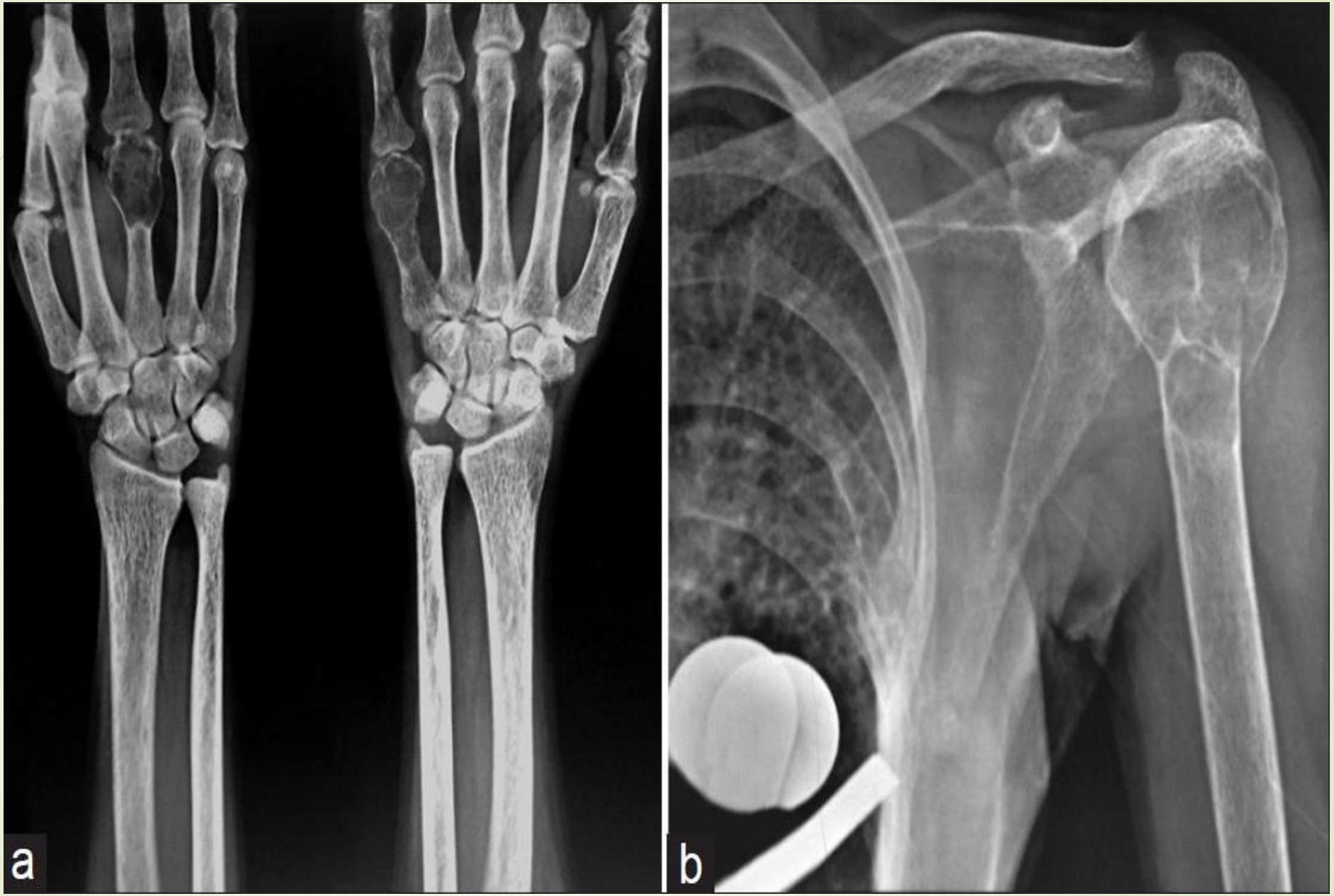
Factors Contributing to Pathogenesis of Secondary Hyperparathyroidism



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

hyperparathyroid-mediated high-turnover bone disease

- High turnover lesion, sometimes called osteitis fibrosa cystica
- Generally asymptomatic but is associated with nonspecific bone pain, proximal myopathy
- There is an increased risk of fractures
- The serum-intact PTH level is usually higher than 350 to 500 pg/mL.
- Radiologic features are :
  - Subperiosteal resorption
  - Brown tumors
  - Mottled and granular salt-and-pepper appearance to the skull.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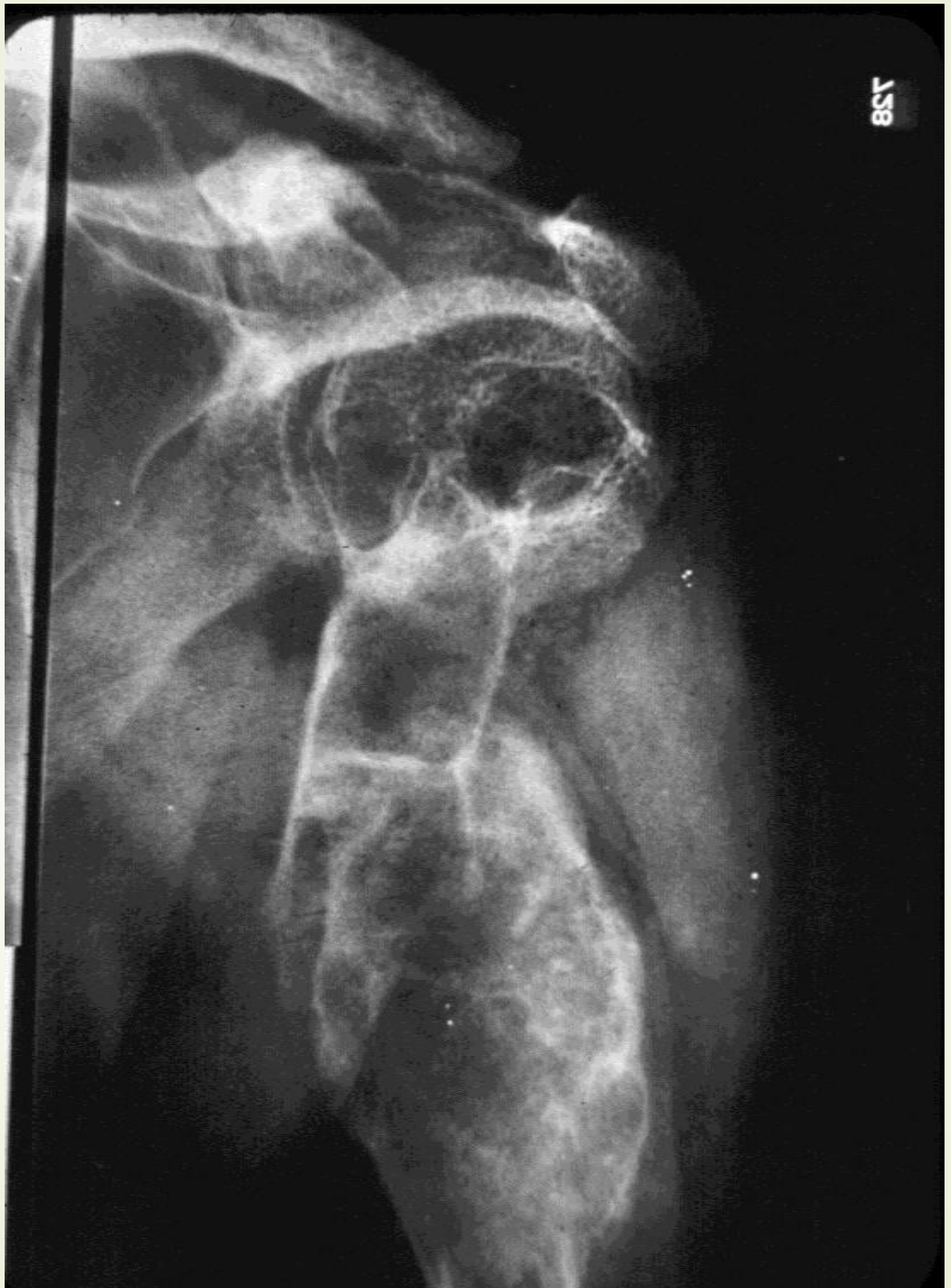
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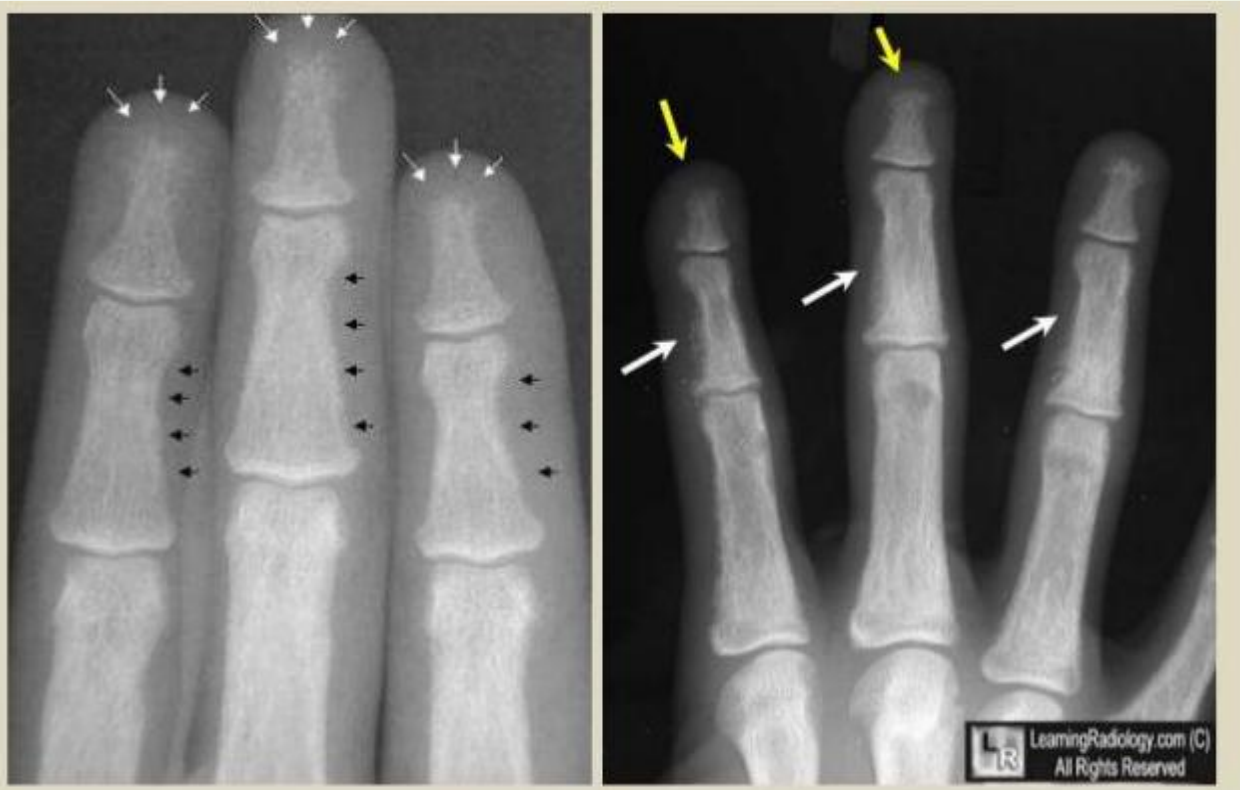
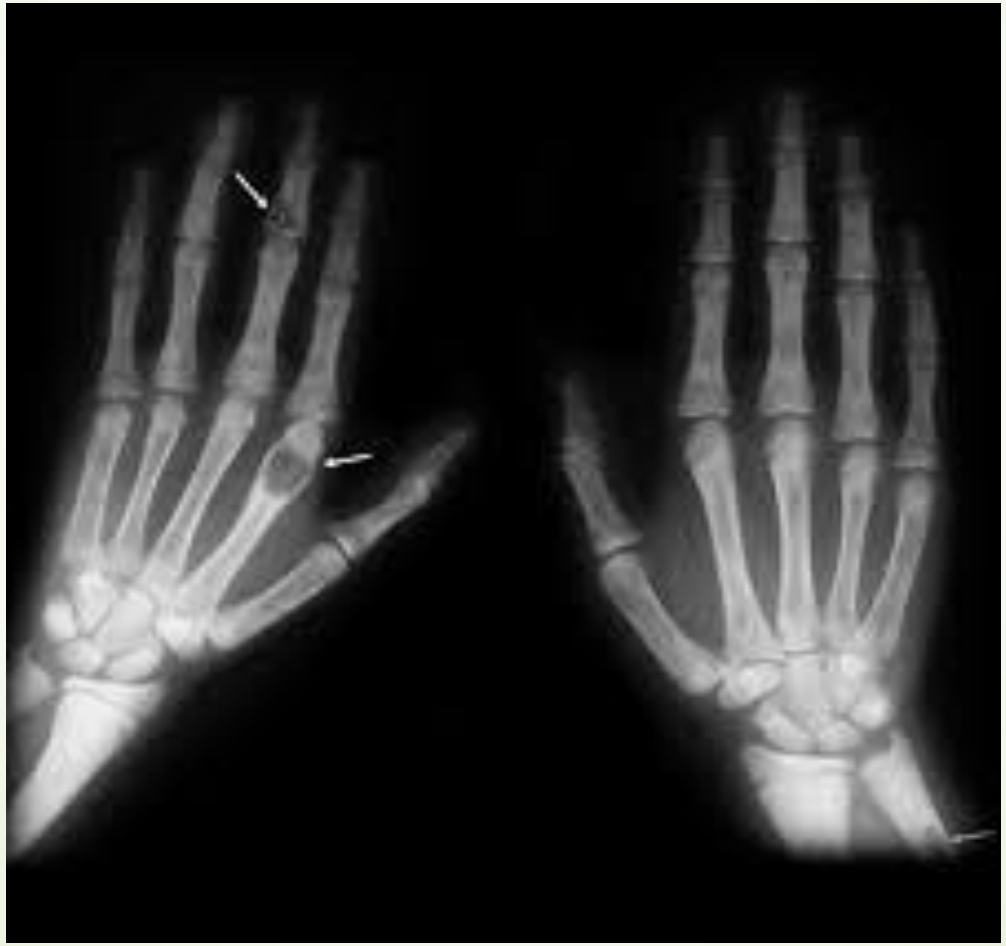
Subperiosteal bone resorption

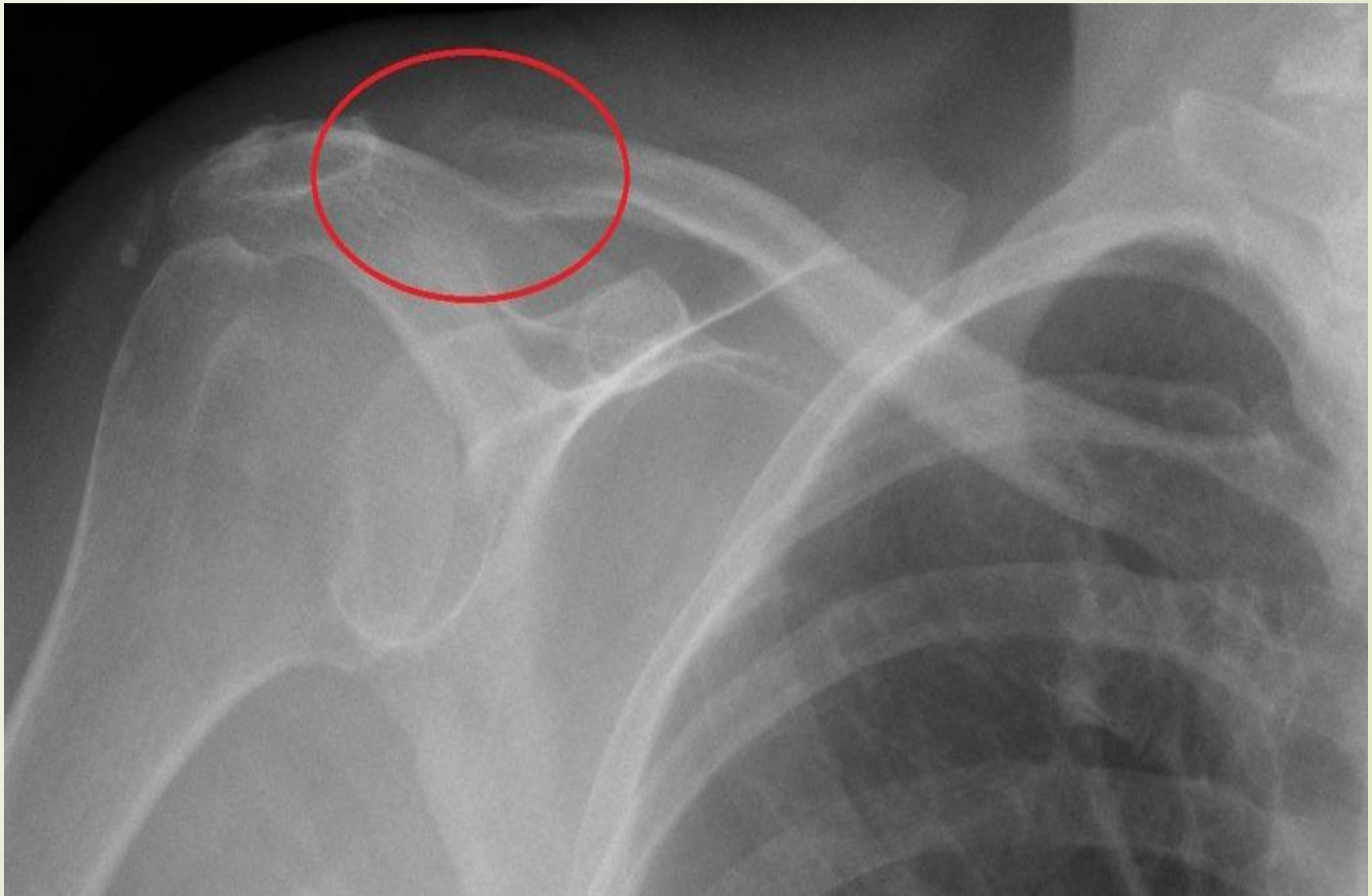


This image demonstrates subperiosteal resorption that has resulted in severe tuftal resorption . Also, note the subperiosteal and intracortical resorption.

Bone cyst



Resorption of the distal ends of long bones



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

Bone lesion associated with Hyperparathyroidism

- Histologic features include:
- Increased turnover (T) as indicated by:
  - Increased bone resorption and formation
  - Increased numbers of osteoclasts and osteoblasts
  - Increased tetracycline uptake
- Abnormal mineralization (M), as indicated by increase of woven bone, peritrabecular fibrosis and there may or may not be increased osteoid
- Generally increased volume (V)

Diagnosis of renal osteodystrophy

- 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.

Treatment of high-turnover bone disease

- Prevention and correction of the factors leading to secondary hyperparathyroidism
  - Phosphorus control:
    - Dietary restriction, phosphate binders, adequate dialysis
  - Prevention of hypocalcemia:
    - Oral calcium supplements, correction of vitamin D deficiency, dialysis
  - Suppression of PTH production and secretion:
    - Vitamin D receptor activators (VDRA), including calcitriol,

Treatment of high-turnover bone disease

- Surgical parathyroidectomy:
  - In severe cases, parathyroidectomy may be required
  - However, bone biopsy should be considered prior to surgery

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

Osteomalacia

- Osteomalacia is an abnormality of mineralization (M) that is characterized by:
  - An excess of unmineralized osteoid, manifested as wide osteoid seams and a markedly decreased mineralization rate.
  - Other features of osteomalacia include the absence of cell activity and the absence of endosteal fibrosis
  - Aluminum disease is associated with osteomalacia.
  - Serum PTH is, in general, normal or low, and hypercalcemia is common.
  - Looser zones or pseudofractures are radiologic characteristics.

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.
- Osteomalacia 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.

Adynamic bone (diminished bone formation and resorption)

Low-Turnover Bone Disease Adynamic Bone Disease(ABD)

- ABD is defined by :
  - Presence of low or absent bone formation as determined by :
    - Decreased tetracycline uptake into bone,
    - In conjunction with a paucity of boneforming osteoblasts and bone-resorbing osteoclasts (decreased T).
- ABD may also be associated with a defect in mineralization (abnormal M), resulting in the histologic lesion referred to as osteomalacia.
- Bone volume (V) is variable.
- ABD may manifest with nonspecific bone pain and fractures.
- Hypercalcemia is a common feature.
- There may be a tendency for increased extraskeletal calcification

Low-Turnover Bone Disease Adynamic Bone Disease(ABD)

- Low turnover is characterized histologically by absence of :
  - Cellular (osteoblast and osteoclast) activity
  - Osteoid formation
  - Endosteal fibrosis
- This is a disorder of decreased bone formation, accompanied by a secondary decrease in bone mineralization
- Even among CKD patients not yet on dialysis, the prevalence of ABD has reportedly increased to between 12 and 23 percent.
- In a bone biopsy study of 84 unselected patients with stage 5 CKD, ABD was the most prevalent type of renal osteodystrophy, particularly in diabetic patients.

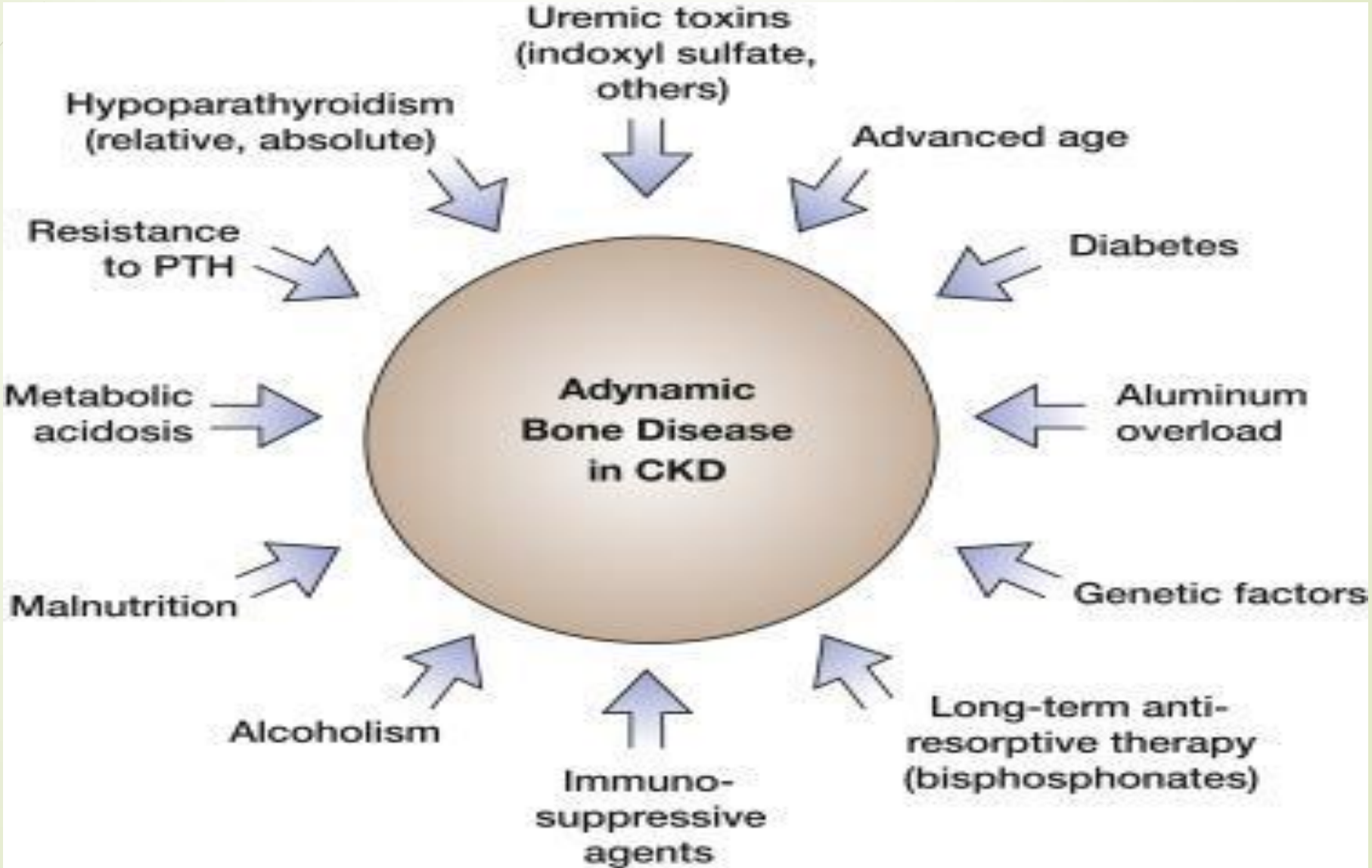
Low-Turnover Bone Disease Adynamic Bone Disease(ABD)

- PTH concentrations normal or mildly elevated (than 100 to 200 pg/mL)
- Resistance to the bone stimulatory effect of PTH in CKD
- PTH receptor downregulation is one potential mechanism to explain the bone resistance effect to PTH resulting

Low-Turnover Bone Disease Adynamic Bone Disease(ABD)

- Major risk factors for low turnover bone disease include:
  - Diabetes
  - Aging
  - Malnutrition
- Other causes of low bone formation in CKD are multifactorial and include:
  - Vitamin D deficiency
  - High serum phosphate
  - Metabolic acidosis
  - Elevated circulating cytokine levels (interleukin [IL]-I, tumor necrosis factor [TNF])
  - Low estrogen and testosterone levels

Risk factors



Adynamic bone disease

In brief….

- Low or absent bone formation
- Thin osteoid seams
- Decreased cellularity
- Minimal bone marrow fibrosis

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

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

Mixed Uremic Osteodystrophy (MUO)

- Mixed uremic osteodystrophy has features of high turnover bone disease together with evidence of a mineralization defect.
- Extensive osteoclastic and osteoblastic activity
- Increased endosteal peritrabecular fibrosis, coupled with more osteoid than expected
- Tetracycline labeling uncovers a concomitant mineralization defect


Treatment Strategies

Target Levels

	Ca (mg/dL) ▲	P (mg/dL)	PTH pmol/L	Ca Intake	Ca×P
CKD ND	Normal Lab Range	2.7- 4.6 (0.87-1.49 mmol/L)	<70 stage 3 <110 stage 4	1.4- 2 gr/d@	<55•
CKD 5D	8.4 to 9.5 (<10.2)* (2.1-2.37 mmol/L)	3.5-5.5** (1.13-1.78 mmol/L)	150-300♪	1.4- 2 gr/d@	<55•

*Values up to 10.5 have been shown not to increase mortality.

**Mortality may not be increased with serum P 3.0-7.0

@It is reasonable to keep Ca intake below 1.4 gr/day

▲Measurment of iCa is suggested by KDIGO and European studies.

♪Since iPTH>200 has been associated with CVD outcome, it is important to treat it with activated vitamin D aggressively

•All-cause mortality did not differ for the Ca x P range of 40–75mg^2/dL^2

Dietary Phosphate Restriction

- Fewer than ESRD 50% of patients meet target levels for serum phosphorus.
- Dietary phosphate restriction may reduce the serum concentration of phosphate, FGF-23, and PTH, till the relatively late stages of CKD, although not usually to normal.

Organic & Inorganic Dietary P

- The main food sources of phosphorus are
  - Protein food groups of meat
  - Poultry
  - Fish
  - Eggs
  - Dairy products
- Plants: some plant seeds, beans, peas, cereals, nuts, legumes, cocoa,
- A large whole egg contains 6 g of protein and 86 mg of P, whereas egg white from 1 large egg (3.6 g protein) contains 5 mg of P, indicating that the bulk of egg phosphorus is in the egg yolk.
- Poultry contain less P than red meat and fish

Organic & Inorganic Dietary P

- Phosphorus in plants, especially in beans, peas, cereals, and nuts, is mostly in the storage form of phytic acid or phytate, with a low absorption rate.
- Digestibility of P from animal-derived foods is higher than that of plant-based proteins.
- >90% of inorganic P from processed food may be as opposed to only 40-60% of the organic P present in natural foods

Dietary Phosphate Restriction

- Phosphate restriction should primarily include:
  - Processed foods
  - Colas
  - NOT high biologic value foods such as meat and eggs
- The average daily dietary intake of P is about 1550 mg for males and 1000 mg for females.
- Approximately 900 mg phosphorus per day is relatively acceptable.

Dietary Phosphate Restriction

- Unnecessary dietary phosphate:
  - Phosphorus-containing food additives
  - Dairy products
  - Certain vegetables
  - Many processed foods, and colas
- Patients should restrict these foods while increasing the intake of high biologic value sources of protein such as meat and eggs.

Pharmacologic Therapy

calcium-based phosphate binders

- Currently the 1st-line Rx for hyperphosphatemia
- They bind P in the intestinal lumen, & reduce its absorption.
- The main problem with these drugs is the transient episodes of hypercalcemia, requiring reduction of the dose of vitamin D analogues and adjustment of the calcium concentration of the dialysis solution.
- Ca concentration in HD or PD should be 2.5 meq/L (1.25 mmol/L) (K/DOQI 2003) or 2.5-3.0 (KDOGO 2009)

calcium-based phosphate binders

- CaCO3 dissolves only at an acid pH and many patients with advanced renal failure have achlorhydria or are taking H2-blockers.
- Calcium acetate, is soluble in both acid and alkaline environments and is a more efficient phosphate binder.
- Calcium acetate can be used in half dose of CaCO3.
- However the incidence of hypercalcemia is the same with half dose of Ca-acetate compared to CaCo3

calcium-free phosphate binders

- Sevelamer hydrochloride (Renagel)
- Sevelamer Carbonate (Renvela)
- Sevelamer is well tolerated in dialysis population and effective in reducing both serum P and Ca-P product.
- Aluminum hydroxide(Al(OH)3)

Aluminum Hydroxide Al(OH)3

- Patients showing high P levels despite high doses of calcium-based binders may receive Al(OH)3 for a limited period of time (2-4 weeks) in order to prevent hypercalcemia.
- Aluminum hydroxide is a binder more powerful than calcium-based agents, but its use has been avoided or, if used, limited because of toxic effects reported on the central nervous system, bone, and hematopoietic tissue.

Lanthanum Carbonate (Fosrenol)

- Because of high cost its use is limited to patients with hypercalcemia, or as an adjunct to a regimen supplying a maximum dose of 1500 mg of elemental calcium from calcium-based phosphate binders.
- It reduces pill burden (pills of 500, 750 and 1000 mg, with dosage of 1500 to 3000 mgr/day (max: 4500)
- Fosrenol is the largest of all pills filled in community pharmacies.
- Sometimes patients forget that fosrenol is not swallowed whole, but instead should be chewed. This has led to severe choking.
- Appears to be associated with a lower incidence of hypercalcemia and decreased PTH levels versus calcium-containing phosphate binders.
- Myalgia, muscular cramping, and peripheral edema

Nicotinamide

- Nicotinamide, a metabolite of nicotinic acid (niacin, vitamin B3)
- Inhibits the Na/Pi co-transport in the GI tract and kidneys
- May be effective in lowering P levels in dialysis patients by reducing GI tract P absorption.

Polynuclear iron (III)-oxyhydroxide phosphate (PA21)

- 154 participants were randomized to PA21 at dosages of 1.25, 5.0, 7.5, 10.0, or 12.5 g/d or sevelamer-HCl 4.8 g/d for 6 weeks
- All groups except PA21 1.25 g/d showed a significant decrease in serum P.
- The 5 g/d and 7.5 g/d dosages showed similar efficacy to 4.8 g/d of sevelamer-HCl.
- The most frequent adverse events were
  - Hypophosphatemia (18.0%) and discolored feces (11.7%) for the PA21 dose groups
  - Diarrhea, hypophosphatemia, and hypotension (each 11.5%) for sevelamer-HCl.
- The adverse events rate was similar for PA21 and sevelamer-HCl.

Wüthrich RP .Clin J Am Soc Nephrol. 2013 Feb;8(2):280-9.

Drug Preparations & Dosage

	Tab. (Suspension)	P level	dosage
Al(OH)3	300 mg (320 mg/5 ml)	Usually P >7 mg/dl	300-600 mg tid
CaCO3	500 mg		500 mg tid (max 2 g)
SevelamerHCl	800 mg	5.5-7.4 mg/dL 7.5-9.0 mg/dL ≥9.0 mg/dL	800 mg 3 tid 1200-1600 mg 3 tid 1600 mg 3 tid (Max:7200 mg/day)

Dialysis

- The average standard dialysis removes about 900 mg of P.
- Phosphate removal during dialysis is limited largely due to the intracellular location of most inorganic phosphorous.
- Full dialyzer clearance is effective in only the initial phase of the dialysis treatment.
- After this initial phase, the transfer rate for phosphate from the intracellular space to the plasma becomes the rate-limiting step for phosphate transport.
- However there several studies have shown that short daily hemodialysis improves phosphate balance.

Pohlmeier R .Kidney Int Suppl. 2001 Feb;78:S190-4

FACTORS WHICH INFLUENCE P REMOVAL IN HD

- There was a good correlation between P removal and:
  - Serum phosphate levels
  - Blood V (L) that passed the dialyzer in each session
  - AV fistula as vascular access
- No correlation was found between P removal and:
  - Membrane surface
  - KT/V
  - Dialysate flux
  - Ultra filtration or treatment duration.
- Phosphate removal was 640 ± 180 mg/session with low-flux membrane and 700 ± 170 mg/session with high-flux membrane
- On multivariate analysis, plasma phosphate and the volume of blood that passed the dialyzer in each session predicted phosphate removal

Therapeutic Strategies

- Consider patients with CKD stages 3–5D with known vascular/valvular calcification to be at the highest cardiovascular risk
- In CKD stages 3–5D & hyperphosphatemia restrict;
  - Dose of Ca-based phosphate binders
  - Dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia
- Restrict the dose of calcium-based phosphate binders in the presence of :
  - Arterial calcification
  - Adynamic bone disease
  - If serum PTH levels are persistently low

Therapeutic Strategies

- In patients with CKD stages 3–5D;
  - Avoid the long-term use of Al(OH)3 and
- In patients with CKD stage 5D:
  - Avoiding dialysate aluminum contamination to prevent aluminum intoxication
- In patients with CKD stages 3-5D:
  - Limit dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments
- In patients with CKD stage 5D:
  - Increase dialytic phosphate removal in the treatment of persistent hyperphosphatemia