

Renal Osteodystrophy

Bone remodeling, mineralization, and renal endocrine dysfunction

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

Define

State the skeletal scope of renal osteodystrophy.

Explain

Trace kidney–bone endocrine and acid–base disruptions.

Recognize

Distinguish high-, low-, and mixed-turnover lesions.

Apply

Relate bone pathology to fractures and impaired growth.

Renal osteodystrophy: A skeletal spectrum

- Collective skeletal changes associated with chronic renal disease.
- Includes skeletal disease occurring in patients receiving dialysis.
- Represents multiple overlapping abnormalities, not one histologic lesion.

Conceptual scope

Chronic renal disease

Altered mineral / endocrine balance

Abnormal skeletal remodeling

Why the skeleton is affected in chronic kidney disease

Loss of renal excretory and endocrine functions



Disturbed phosphate, calcium, vitamin D, and acid–base balance



Altered PTH signaling and osteoclast/osteoblast behavior



Bone loss, defective mineralization, or abnormal turnover

Four skeletal manifestations

Osteopenia / osteoporosis

Decreased quantity of normally mineralized bone.

Osteomalacia

Insufficient mineralization of bone matrix.

Secondary hyperparathyroidism

PTH-associated increase in skeletal resorption.

Growth retardation

Skeletal consequences in immature patients.

One syndrome, several distinct bone abnormalities

Bone quantity

How much bone is present?

Bone turnover

How active are resorption and formation?

Mineralization

How effectively is osteoid calcified?

A patient can have disturbances on more than one axis.

Bone remodeling is a coupled process

Osteoclasts attach to bone and resorb matrix



Osteoblasts populate the resorbed surface



Osteoblasts synthesize osteoid



Matrix mineralization restores mature bone

Osteoblasts form the organic bone matrix

- Osteoblasts are responsible for synthesizing new osteoid.
- Bone formation follows resorption during normal remodeling.
- PTH and local signaling alter osteoblast communication with osteoclasts.

Functional link

Osteoblast

Osteoid deposition

Subsequent mineralization

Osteoclasts remove mineralized matrix

- Multinucleated osteoclasts arise from monocyte-lineage cells.
- Attachment creates a sealed resorption compartment.
- Acid and proteolytic enzymes dissolve inorganic and organic bone.

Functional link

Osteoclast attachment

Resorption pit

Matrix loss

Osteocytes couple bone to mineral homeostasis

- Osteocytes are embedded within bone matrix.
- They detect mechanical forces and regulate local remodeling.
- Osteocytes as the source of FGF-23.

Bone–kidney link

Osteocyte

FGF-23 secretion

Renal phosphate handling

RANKL stimulates osteoclast differentiation

RANKL expressed by osteoblasts / stromal cells



RANK on osteoclast precursors



NF- κ B-dependent osteoclast differentiation



Increased bone resorption

Osteoprotegerin restrains the RANKL signal

RANKL–RANK interaction

Supports osteoclast differentiation

Promotes osteoclastic resorption

OPG binding RANKL

OPG acts as a soluble decoy receptor

Blocks RANKL access to RANK

Parathyroid hormone acts indirectly on osteoclasts

PTH signaling to osteoblast lineage



Increased osteoblast/stromal RANKL



Enhanced differentiation of osteoclasts



Bone resorption and calcium mobilization

The kidney controls active vitamin D production

Renal synthesis of 1,25(OH)₂ vitamin D



Increased intestinal calcium absorption



Support of calcium homeostasis



Availability of calcium for matrix mineralization

Normal phosphaturic signaling involves FGF-23

FGF-23 released by osteocytes



Renal response involves Klotho



Promotion of urinary phosphate excretion



Regulation of phosphate balance

Normal renal–bone communication has two arms

Phosphate arm

Osteocyte-derived FGF-23

Renal Klotho-dependent response

Urinary phosphate elimination

Calcium / vitamin D arm

Renal active vitamin D production

Intestinal calcium absorption

PTH feedback and bone response

Chronic renal dysfunction disrupts both arms

Renal dysfunction



Phosphate retention and reduced active vitamin D



Hyperphosphatemia and impaired calcium absorption



Secondary hyperparathyroidism and impaired mineralization

Reduced phosphate excretion promotes retention

- Hypophosphaturia means insufficient urinary phosphate elimination.
- Impaired renal handling contributes to hyperphosphatemia.
- Phosphate retention upstream of secondary hyperparathyroidism.

Cause → consequence

Reduced phosphaturia

Phosphate retention

↑ Serum phosphate

Klotho supports renal responsiveness to FGF-23

- Klotho participates in the renal response to osteocyte-derived FGF-23.
- In renal disease, reduced Klotho expression weakens this signaling arm.
- Phosphate retention persists despite the normal phosphaturic role of FGF-23.

Disrupted signal

↓ Renal Klotho

Impaired FGF-23 action

↓ Phosphate excretion

FGF-23 is a bone-derived endocrine signal

Osteocyte



FGF-23



Kidney with Klotho-dependent signaling



Urinary phosphate excretion

Impaired FGF-23–Klotho signaling matters because...

- Bone normally communicates its phosphate status to the kidney.
- Renal Klotho reduction compromises phosphaturic signaling.
- The defect couples progressive kidney dysfunction to skeletal disease.

Mechanistic point

Bone-to-kidney signal

Reduced renal response

Systemic phosphate imbalance

Renal vitamin D synthesis declines

Progressive impairment of renal function



Reduced $1,25(\text{OH})_2$ vitamin D synthesis



Less intestinal calcium absorption



Reduced substrate for bone matrix calcification

Diminished intestinal calcium absorption

- Active vitamin D normally increases dietary calcium absorption.
- Less active vitamin D reduces intestinal calcium uptake.
- Hypocalcemia contributes to secondary PTH elevation.

Endocrine cascade

↓ Active vitamin D

↓ Gut Ca^{2+} absorption

Hypocalcemic drive

Hypocalcemia drives compensatory PTH secretion

Reduced gut calcium absorption



Hypocalcemia



Increased parathyroid stimulation



Secondary hyperparathyroidism

Secondary hyperparathyroidism is a renal response

- The stimulus arises from renal phosphate and calcium imbalance.
- Parathyroid activity increases as a secondary consequence.
- Persistent PTH excess promotes osteoclast-driven skeletal remodeling.

Distinguishing feature

Renal dysfunction

Biochemical stimulus

Secondary PTH increase

Why phosphate and calcium mechanisms converge

Pathway A

Reduced phosphate excretion

Hyperphosphatemia

Pathway B

Reduced active vitamin D

Reduced calcium absorption

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graph TD; A[Pathway A: Reduced phosphate excretion -> Hyperphosphatemia] --> C[Both pathways contribute to secondary hyperparathyroidism.]; B[Pathway B: Reduced active vitamin D -> Reduced calcium absorption] --> C;
```

Both pathways contribute to secondary hyperparathyroidism.

Tubular dysfunction causes systemic acidosis

Renal tubular dysfunction



Tubular and systemic acidosis



Altered osteoblast RANKL expression



Greater osteoclast-mediated resorption

Acidosis activates the osteoclast pathway

- Acidosis increases RANKL expression on osteoblasts.
- RANKL promotes differentiation and function of osteoclasts.
- Increased resorption produces loss of bone matrix.

Named mediator

Acidosis

↑ RANKL

↑ Osteoclast activity

Osteopenia is a quantitative bone deficit

Normal bone quantity

More preserved trabecular architecture

Normal amount of mineralized matrix

Osteopenia / osteoporosis

Reduced total skeletal bone mass

Residual matrix may be normally mineralized

Osteoporosis and osteomalacia are not synonyms

Osteoporosis

Reduced amount of bone

Mineralization of remaining bone is normal

Fragility follows reduced structural mass

Osteomalacia

Insufficient mineralization of osteoid

Bone formed during remodeling remains undermineralized

Mechanical weakness despite a different defect

Three histologic patterns in end-stage renal failure

High turnover

Resorption and formation increased

Resorption predominates

Low turnover

Adynamic bone: Both cell activities low

Osteomalacia occurs less commonly

Mixed

High- and low-turnover areas

Heterogeneous skeletal pattern

Turnover describes the pace of remodeling

High turnover

Both formation and resorption increased.

Low turnover

Osteoblast and osteoclast activity reduced.

Mixed turnover

Different regions exhibit different patterns.

Turnover is not interchangeable with mineralization or bone mass.

High-turnover osteodystrophy: Resorption dominates

Secondary hyperparathyroidism / resorptive stimuli



Higher osteoclast activity



Higher coupled osteoblast activity



Net resorption exceeds bone formation

High turnover does not mean bone gain

Cellular activity

Formation increases

Resorption increases

Net skeletal balance

Resorption predominates

Progressive reduction of structural bone may occur

High PTH favors cortical surface resorption

- Hyperparathyroidism enhances osteoclast activity.
- Subperiosteal and endosteal cortical surfaces are prominently affected.
- The process can extend into cancellous bone.

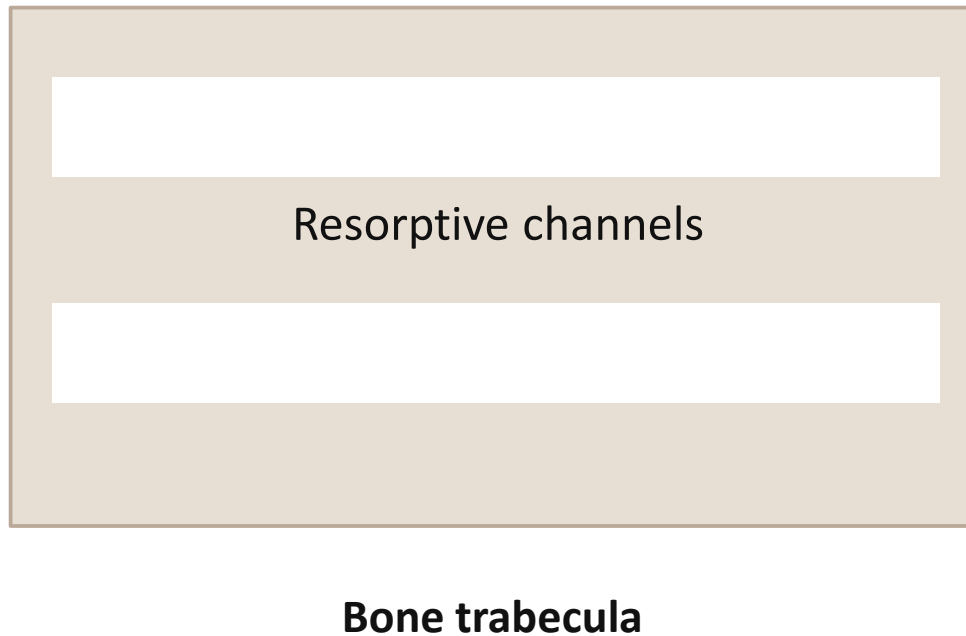
Morphologic distribution

Periosteal surface

Cortical bone

Endosteal surface

Trabecular tunneling creates dissecting osteitis



Simplified conceptual schematic — not a tissue section

- Osteoclasts may tunnel along the interior of trabeculae.
- Adjacent marrow spaces can be replaced by fibrovascular tissue.
- The resulting “railroad track” appearance is called dissecting osteitis.

Dissecting osteitis is not inflammatory osteitis

Descriptive histology term

Longitudinal osteoclastic tunneling

Railroad track-like trabecular pattern

Not implied by the name

It is not primarily an inflammatory process

The lesion reflects excessive resorption

Fibrovascular tissue follows trabecular resorption

Intense osteoclastic resorption



Disturbance of trabecular architecture



Fibrovascular marrow-space replacement



Peritrabecular fibrous change

Brown tumors reflect repair after skeletal damage

Bone loss and microfractures



Secondary hemorrhage



Macrophages and fibrovascular repair



Expansile hemorrhagic “brown tumor”

The term “brown tumor” is morphologic

- Brown pigmentation reflects hemorrhage and hemosiderin.
- The mass contains a reparative fibrovascular response.
- It is not a true neoplasm despite its tumor-like presentation.

Mechanistic triad

Hemorrhage

Hemosiderin

Reparative fibrous tissue

Severe PTH-mediated bone disease: Osteitis fibrosa cystica

- Characterized by increased bone cell activity and peritrabecular fibrosis.
- Cystic brown tumors may accompany severe disease.
- These findings in hyperparathyroidism; Secondary cases are usually milder.

Composite lesion

Resorption

Fibrosis

Cystic hemorrhagic lesions

Low-turnover osteodystrophy includes adynamic bone

Osteoclast compartment

Little resorptive activity

Reduced initiation of remodeling units

Osteoblast compartment

Little bone-forming activity

Reduced formation following resorption

Adynamic bone is a low-cell-activity state

Low osteoclastic activity



Little active resorption

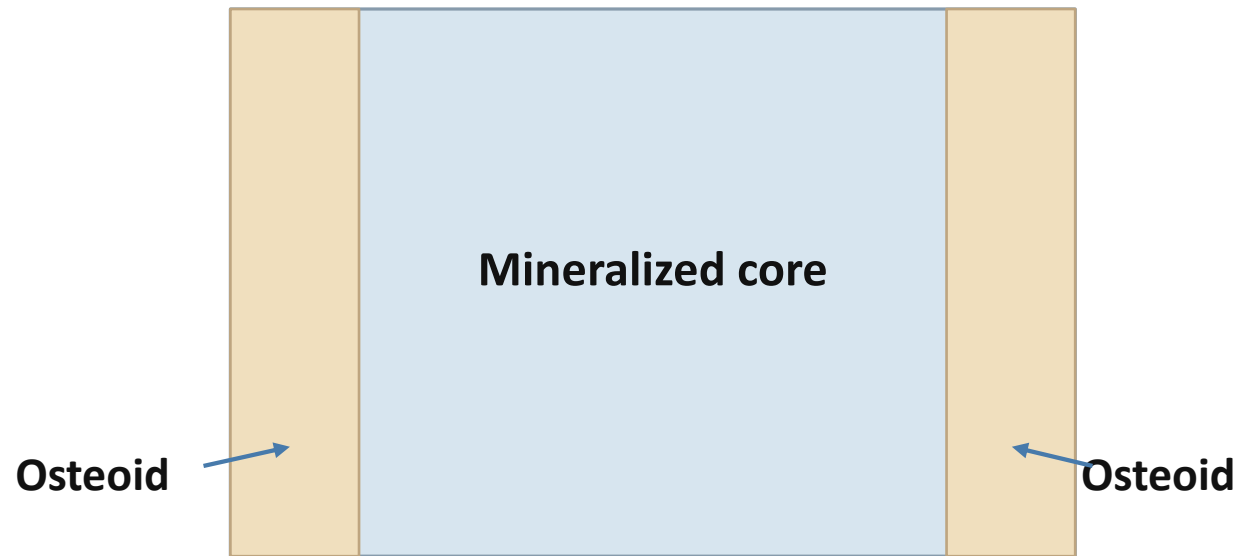


Low osteoblastic activity



Little new bone formation

Osteomalacia: Impaired calcification of osteoid



Simplified conceptual schematic — not a tissue section

- Matrix produced during bone formation remains insufficiently mineralized.
- Reduced active vitamin D and calcium availability contribute.
- Defective mineralization differs fundamentally from loss of bone quantity.

The vitamin D defect links CKD to osteomalacia

Loss of renal active vitamin D synthesis



Reduced intestinal calcium absorption



Insufficient matrix calcification



Osteomalacia

Low turnover and osteomalacia are distinct features

Adynamic bone

Low osteoclast and osteoblast activity

Turnover defect is the defining feature

Osteomalacia

Defective mineralization

Can be grouped among low-turnover lesions

Mixed-pattern disease is regionally heterogeneous

Region A

Higher remodeling activity

Prominent resorption

Region B

Lower remodeling activity

Relative cellular quiescence

Overall classification

Both present in the skeleton

Not a uniform turnover state

Compare the three renal bone patterns

Pattern	Resorption	Formation	Signature
High turnover	Increased	Increased	Resorption predominates
Adynamic / low turnover	Minimal	Minimal	Low bone-cell activity
Mixed	Variable	Variable	High + low turnover areas

Bone turnover and mineralization require separate questions

Turnover

What are osteoblasts and osteoclasts doing?

Mineralization

Is newly deposited osteoid calcifying?

Quantity

How much structural bone remains?

A single clinical label does not describe all three processes.

CKD skeletal injury affects growing bone differently

Chronic renal disease in an immature skeleton



Disturbed mineral and endocrine homeostasis



Interference with normal skeletal growth



Growth retardation

In adults, bone loss predisposes to fracture

Chronic PTH / acid–base / mineral disturbances



Resorption and/or defective mineralization



Reduced structural competence



Greater vulnerability to fractures

Deformation and joint problems are clinical sequelae

- As bone mass falls, mechanical support is reduced.
- Weak or abnormal bone can deform under habitual loads.
- Skeletal deterioration to fractures, deformation, and joint problems.

Clinicopathologic chain

Abnormal bone structure

Reduced mechanical integrity

Skeletal symptoms

Renal osteodystrophy vs primary hyperparathyroidism

Primary hyperparathyroidism

Autonomous or inappropriate PTH secretion

Bone changes principally related to PTH excess

Renal osteodystrophy

Renal mineral and endocrine dysfunction

PTH excess plus acidosis and vitamin D deficiency

Renal osteodystrophy vs isolated osteoporosis

Isolated osteoporosis

Reduced bone quantity

Remaining bone normally mineralized

Renal osteodystrophy

May include osteopenia/osteoporosis

Also includes mineralization and turnover abnormalities

Renal osteodystrophy vs osteomalacia

Osteomalacia

A specific mineralization defect

Unmineralized matrix contributes to weakness

Renal osteodystrophy

Broad CKD-associated skeletal syndrome

Osteomalacia is one possible component

Renal osteodystrophy vs Paget disease

Renal osteodystrophy

Driven by chronic renal disease

Metabolic / hormonal pathways are central

Paget disease

Disordered focal bone remodeling

Distinct triphasic histologic evolution

Integrated pathway: Renal function to skeletal loss

Pathway A

Tubular dysfunction

Systemic acidosis

↑ Osteoblast RANKL

Pathway B

Phosphate retention + ↓ vitamin D

Secondary hyperparathyroidism

↑ PTH-driven RANKL

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graph TD; subgraph Pathway_A [Pathway A]; A1[Tubular dysfunction] --- A2[Systemic acidosis] --- A3[↑ Osteoblast RANKL]; end; subgraph Pathway_B [Pathway B]; B1[Phosphate retention + ↓ vitamin D] --- B2[Secondary hyperparathyroidism] --- B3[↑ PTH-driven RANKL]; end; A3 --> C[Increased osteoclastic resorption → osteopenia]; B3 --> C;
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Increased osteoclastic resorption → osteopenia

Integrated pathway: Renal function to osteomalacia

Loss of renal active vitamin D synthesis



Reduced intestinal calcium absorption



Diminished calcification of bone matrix



Osteomalacia

Application 1: Identify a high-turnover mechanism

A teaching vignette describes chronic renal disease, secondary hyperparathyroidism, and bone with strongly increased resorption plus increased formation.

Which turnover category fits best?

Why can bone mass still decline despite increased formation?

Application 1: Mechanism-based resolution

- Classify the pattern as high-turnover osteodystrophy.
- Both osteoclastic and osteoblastic activities are increased.
- Net resorption exceeds formation, allowing progressive skeletal loss.

Reasoning sequence

↑ PTH / RANKL

↑ Resorption

Bone loss

Application 2: Recognize low-turnover disease

A conceptual bone-biopsy description in end-stage renal failure reports very little osteoclastic or osteoblastic activity.

What histologic pattern is represented?

Which two cell types define this classification?

Application 2: Distinguish adynamic bone

- The defining pattern is low-turnover (adynamic) bone.
- Both osteoclast and osteoblast activities are minimal.
- This classification is based on cell activity rather than on PTH alone.

Classification cue

Few active osteoclasts

Few active osteoblasts

Adynamic bone

Application 3: Interpret mixed renal bone disease

A teaching schematic of bone from chronic renal disease shows one region with high remodeling activity and another with low remodeling activity.

Does a single uniform turnover label capture this?

Which Robbins category accommodates heterogeneity?

Application 3: Recognize the mixed pattern

- Classify regional high- and low-turnover coexistence as mixed-pattern disease.
- The defining feature is histologic heterogeneity.
- Do not assume that every region of bone has the same turnover state.

Interpretive cue

High-turnover zone

Low-turnover zone

Mixed pattern

Mechanisms and patterns: Final synthesis

Phosphate

Poor excretion contributes to hyperphosphatemia.

Vitamin D

Deficient activation reduces gut calcium absorption.

PTH + acidosis

These promote RANKL-mediated osteoclastic resorption.

Bone response

High, low, and mixed histologic patterns can result.

References and source boundaries

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 26, pp. 1064–1073.
- Chapter 20, pp. 814–815: renal physiology and CKD manifestations.
- Figures 26.4, 26.5, 26.10, and 26.11 informed original conceptual schematics; no textbook figures were reproduced.
- Mechanism diagrams and vignettes are educational schematics, not histologic specimens or original patient data.