

Osteopenia and Osteoporosis

Bone mass, remodeling, morphology and fracture risk

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Define osteopenia and osteoporosis and distinguish them from defective mineralization.
- Explain age-, estrogen-, nutrition-, and loading-related bone loss.
- Identify trabecular and cortical morphology and relate architecture to fractures.
- Interpret diagnostic methods and connect mechanisms to prevention and therapy.

The central pathologic lesion

- Osteopenia signifies a reduction in the quantity of bone.
- Osteoporosis is sufficiently severe loss of bone mass to increase fracture risk.
- In osteoporosis, the remaining bone is histologically normal in composition.
- Loss of structural support—not abnormal mineralization—is the defining problem.

Bone mass versus mineralization

Condition	Bone quantity	Mineralization of existing matrix
Normal bone	Maintained	Normal
Osteoporosis	Decreased	Normal
Osteomalacia	Can be variable	Defective

Why bone mass does not tell the whole story

- Bone mass reflects the cumulative balance between matrix formation and removal.
- Trabecular connectivity and cortical thickness determine structural strength.
- Architectural deterioration makes the skeleton fragile even when residual bone looks normal.
- Fracture is the consequential clinical expression of osteoporosis.

Bone-density categories in the text

Classification	Density relative to young-adult mean
Low bone mass (osteopenia)	Between 1 and 2.5 standard deviations below
Osteoporosis	At least 2.5 standard deviations below

Interpreting density thresholds

- The comparison uses a young-adult reference distribution.
- A bone-density category is a measurement classification, not a description of fracture location.
- Low bone mass and osteoporosis form a continuum of skeletal loss.
- Clinical interpretation should not ignore fracture history or competing causes of fragility.

Distribution of osteoporosis

Dimension	Localized loss	Generalized loss
Distribution	One bone or region	Multiple skeletal sites
Illustration	Immobilized limb	Postmenopausal or senile bone loss
Mechanistic emphasis	Reduced mechanical stimulation	Systemic loss of remodeling balance

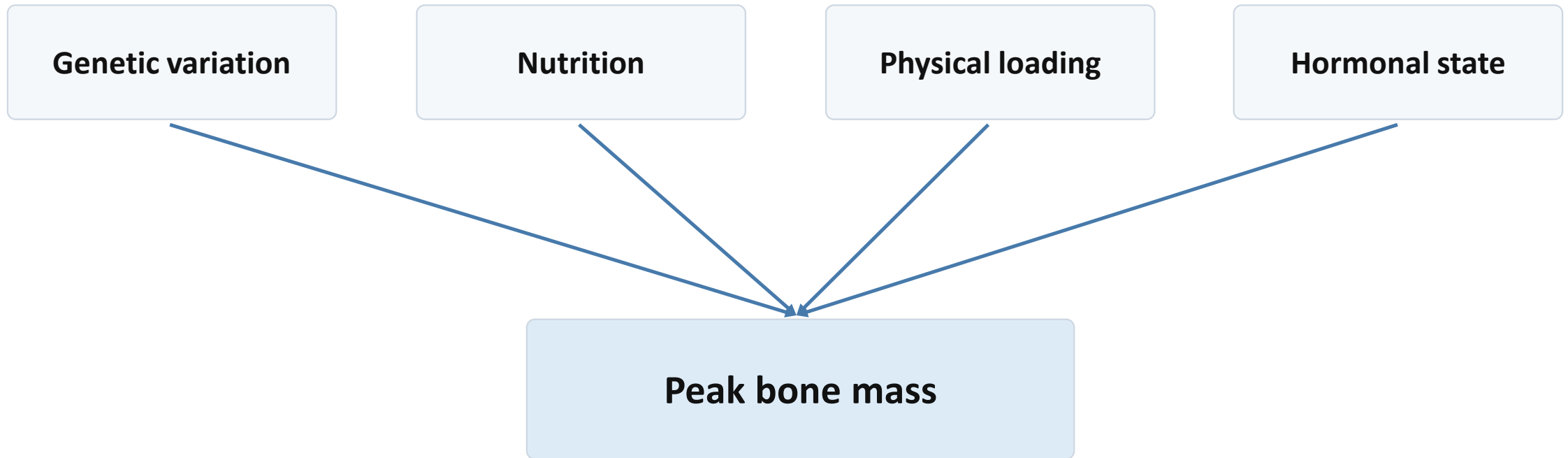
Primary and secondary generalized osteoporosis

Primary forms	Secondary forms
Idiopathic, postmenopausal, senile	Underlying endocrine, neoplastic, gastrointestinal or systemic disease
Dominant drivers: aging and estrogen deficiency	Can also follow medications or immobilization

Why peak bone mass matters

- Peak bone mass is reached in young adulthood, after skeletal growth.
- The amount accrued provides a reserve against later resorptive loss.
- Lower peak mass increases vulnerability even if later bone-loss rates are ordinary.
- Peak bone mass and subsequent loss jointly influence adult fracture susceptibility.

Determinants of peak bone mass



- Hereditary influences, physical activity, nutrition and hormones jointly set the initial skeletal reserve.
- An unfavorable combination leaves less bone to lose in later life.

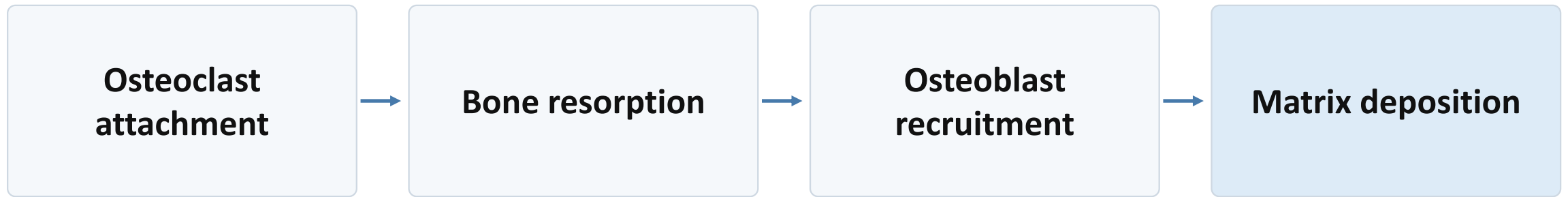
Skeletal mass changes across adult life

- After peak skeletal mass, resorption begins to exceed formation slightly.
- Average age-related loss of about 0.7% each year.
- Both sexes are affected by age-dependent skeletal mass decline.
- Menopause can superimpose an accelerated resorptive phase in women.

Bone remodeling is continuous

- Adult bone renews within coordinated basic multicellular units.
- Osteoclasts remove mineralized tissue; Osteoblasts replace matrix.
- The normal sequence couples resorption and deposition.
- An imbalance sustained over time progressively diminishes bone mass.

Sequence within a remodeling unit

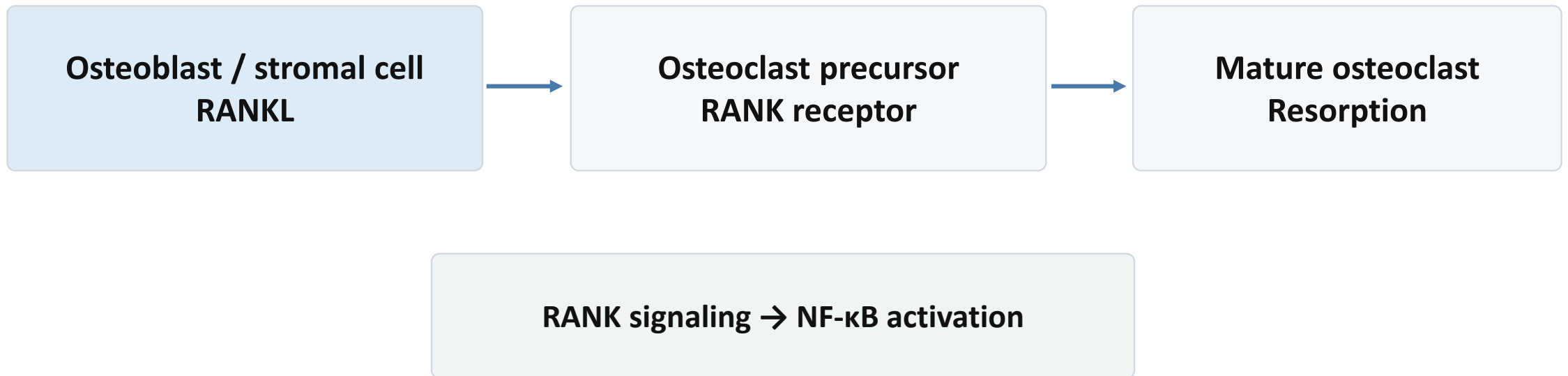


Coupled remodeling preserves the skeleton when formation replaces resorbed bone.

Bone cells: Distinct responsibilities

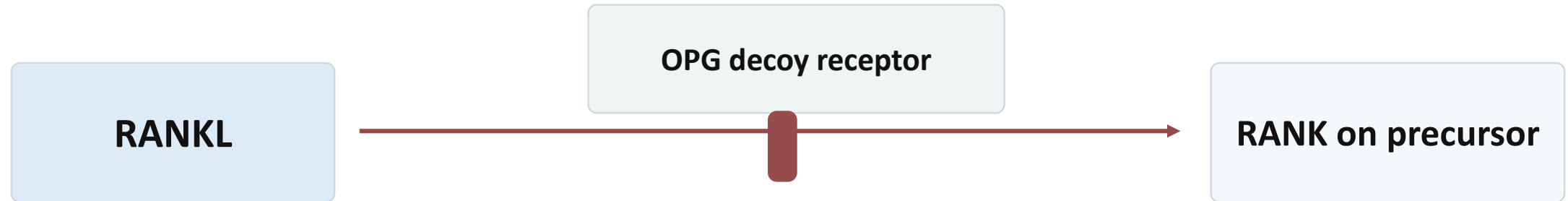
Osteoclast	Osteoblast	Osteocyte
Resorbs mineralized bone	Synthesizes new bone matrix	Senses mechanical loading
From hematopoietic lineage	From osteoprogenitor lineage	Embedded within bone
Regulated by RANK signaling	Responds to Wnt and growth signals	Controls remodeling response to load

The RANK–RANKL signal drives osteoclasts



- RANK is expressed by osteoclast precursors; RANKL is expressed by osteoblasts and marrow stromal cells.
- RANK signaling through NF-κB supports osteoclast differentiation and survival.

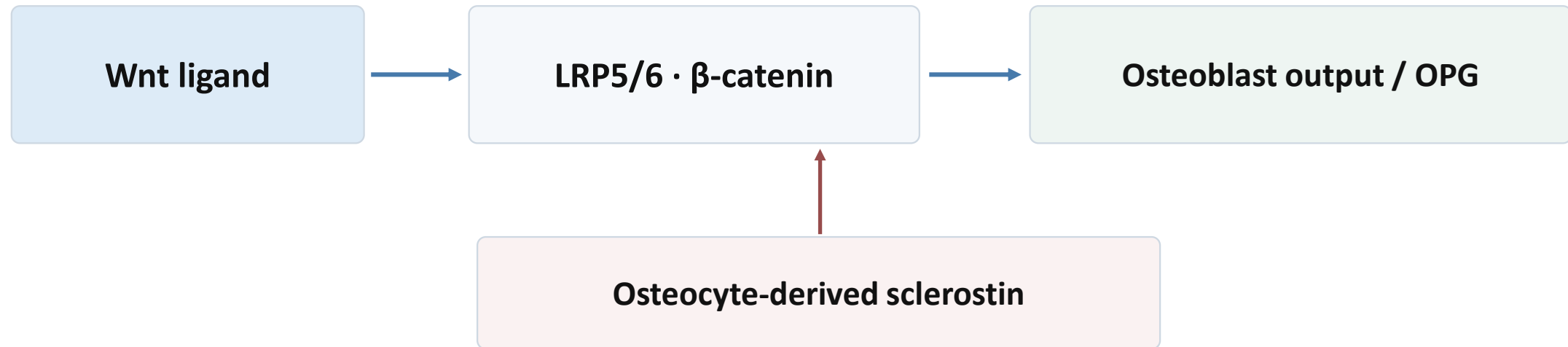
Osteoprotegerin restrains resorption



OPG sequesters RANKL; Receptor signaling is limited

- OPG is a soluble decoy receptor produced in the skeletal microenvironment.
- By binding RANKL, OPG reduces its interaction with RANK and limits osteoclastogenesis.

Wnt signaling favors bone formation



Sclerostin limits Wnt-dependent formation

- Wnt–LRP5/6–β-catenin signaling supports osteoblast function and OPG synthesis.
- Osteocyte-derived sclerostin inhibits Wnt signaling and reduces formation.

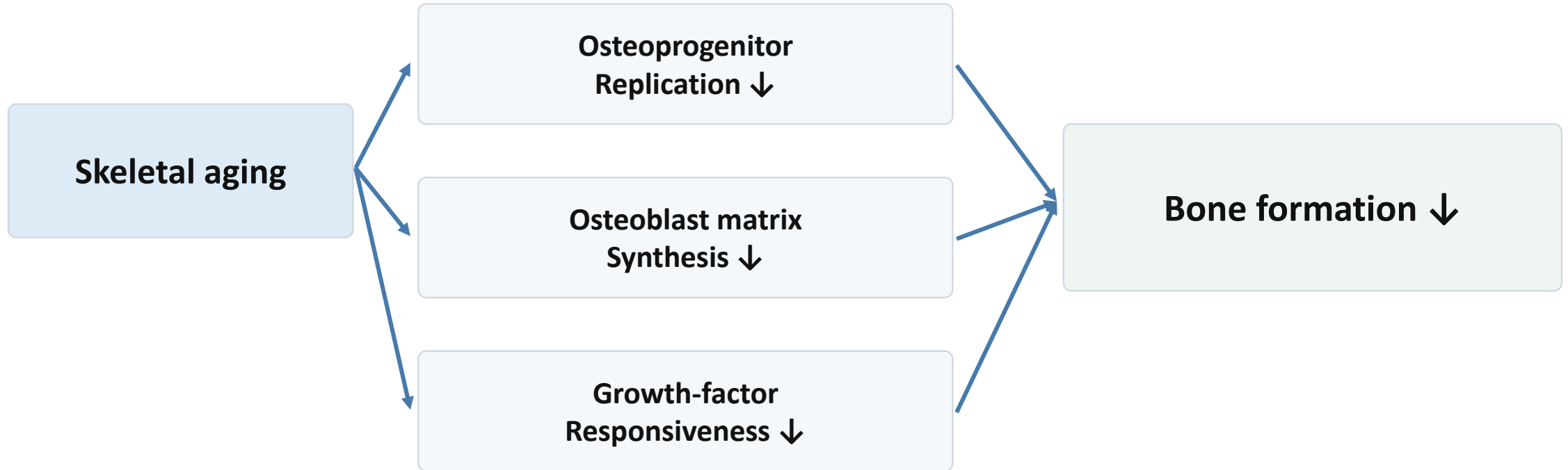
Remodeling balance integrates systemic signals

- PTH, glucocorticoids, inflammatory cytokines and sex hormones can shift remodeling.
- Local OPG, RANKL and Wnt signals mediate many of these systemic effects.
- Effects differ by the signal and the cellular compartment involved.
- Osteoporosis results from an unfavorable net balance, not a single universal cellular defect.

Two common pathogenic patterns

Postmenopausal osteoporosis	Senile osteoporosis
Estrogen decline dominates	Aging of osteoblast lineage dominates
Osteoclast-driven resorption increases	Osteoblast synthetic capacity decreases
High-turnover phenotype	Low-turnover phenotype
Cancellous bone particularly susceptible	Cortical thinning becomes prominent

Senile osteoporosis: Impaired replacement



- Older osteoblasts exhibit lower proliferation and biosynthetic activity.
- The response to growth factors is attenuated; Formation no longer fully replaces resorption.

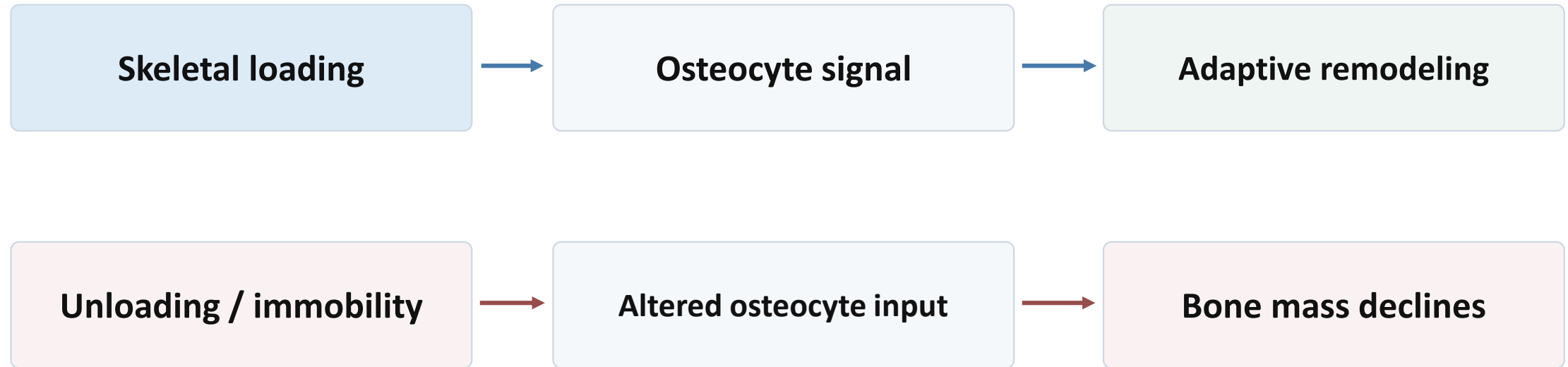
Osteoprogenitors and skeletal aging

- Replicative activity of osteoprogenitor cells declines with age.
- The pool able to differentiate into active osteoblasts becomes less productive.
- Matrix synthesis following bone resorption becomes less complete.
- Age-related bone loss can occur even without an abrupt hormonal change.

Growth-factor response falls with aging

- Osteoblasts in older adults have attenuated responses to matrix-derived growth factors.
- Paracrine coupling becomes less effective at restoring resorbed bone.
- Reduced anabolic output creates a low-turnover imbalance.
- The morphologic endpoint is decreased skeletal quantity.

Mechanical load is a remodeling signal



- Osteocytes sense loading and influence osteoblasts and osteoclasts.
- Decreased use changes local remodeling in favor of loss.

Disuse osteoporosis

- An immobilized or paralyzed limb loses bone locally.
- Decreased osteocyte loading signals reduce the stimulus for maintenance.
- Prolonged unloading can diminish skeletal mass without a systemic hormone defect.
- This illustrates the mechanostat contribution to osteoporosis.

Loading magnitude influences adaptation

- The text distinguishes magnitude of load from number of loading cycles.
- Resistance activity supplies relatively high-magnitude skeletal loading.
- Repetitive endurance activity with low skeletal loading may be a weaker density stimulus.
- Exercise effects depend on the mechanical stresses imposed on bone.

Examples of loading environments

Environment	Predicted skeletal response
Immobilized extremity	Localized bone loss
Microgravity	Generalized skeletal unloading and bone loss
Athletic high-load training	Adaptation favoring higher density

Genetics: Susceptibility is usually polygenic

- Single-gene disorders cause only a small minority of osteoporosis cases.
- Common polymorphisms influence peak bone mass and remodeling susceptibility.
- Genome-wide association signals implicate RANK, RANKL and OPG.
- The estrogen-receptor locus and HLA region also show associations.

Genetic associations are not deterministic

- RANK-axis genes encode major regulators of osteoclast activity.
- A statistical association does not imply that most osteoporosis has a single-gene cause.
- The mechanism of the HLA association is described as uncertain.
- Environmental loading and nutrition modify inherited susceptibility.

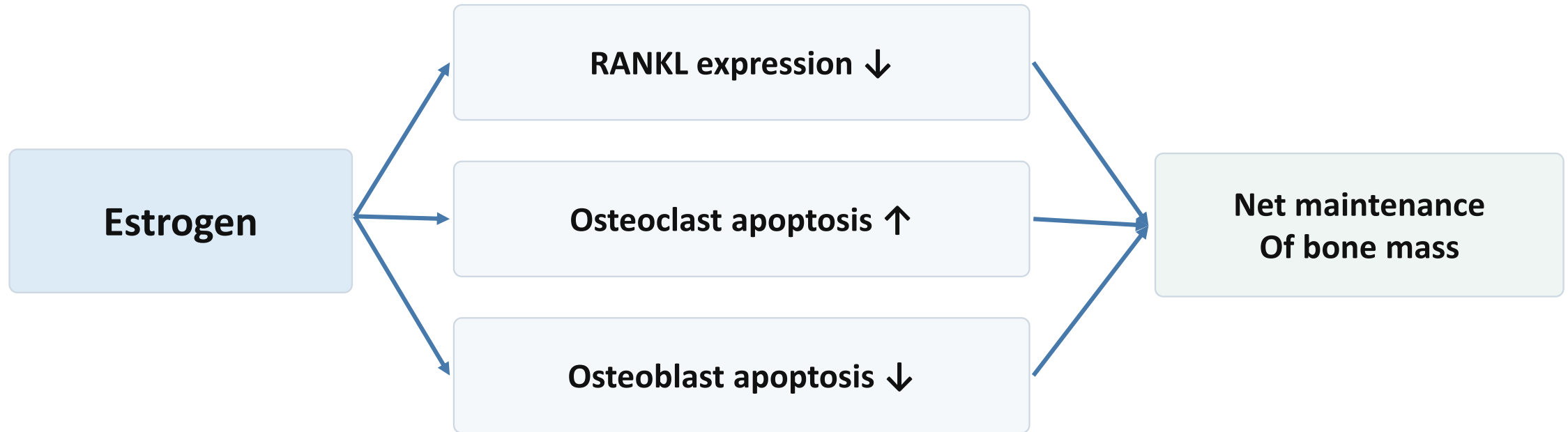
Calcium during skeletal accrual

- Inadequate calcium intake during adolescence can reduce achieved peak bone mass.
- Low peak mass increases later-life fragility vulnerability.
- The effect extends beyond the period of initial nutritional insufficiency.
- Prevention begins before the years in which fractures commonly appear.

Calcium, vitamin D and PTH with aging

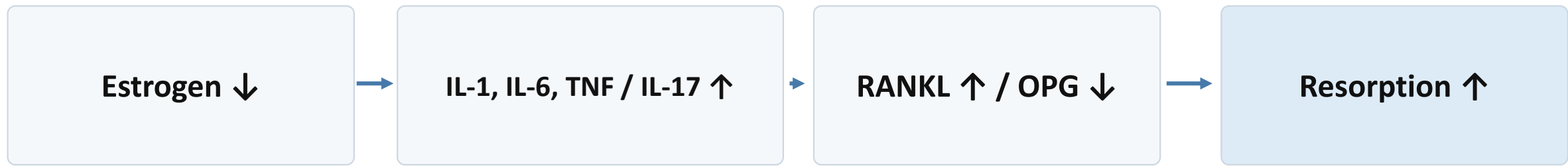
- Relative calcium deficiency can contribute to senile osteoporosis.
- Reduced vitamin D availability can coexist with aging-related bone loss.
- Compensatory PTH elevation may favor resorption.
- These influences may interact with declining osteoblast formation.

Estrogen normally favors skeletal retention



- Estrogen promotes osteoclast apoptosis and suppresses RANKL production.
- It also inhibits osteoblast apoptosis, supporting formation.

After menopause: Signaling shifts



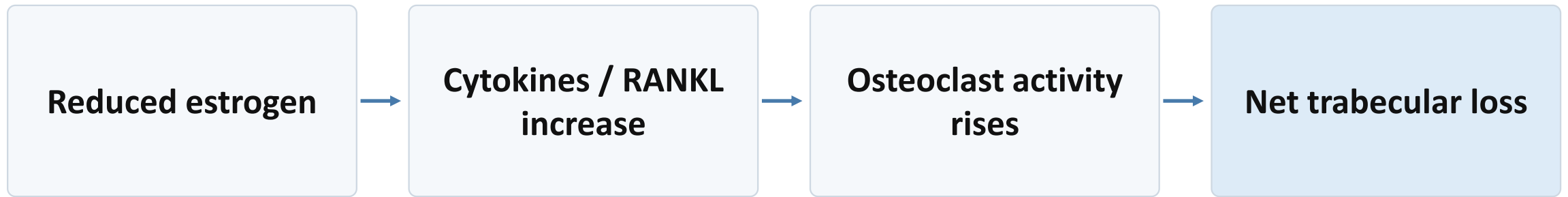
High-turnover osteoporosis: Resorption exceeds formation

- Estrogen deficiency increases osteoclast recruitment and activity.
- Resorption increases more than formation, producing high-turnover loss.

Inflammatory pathways after menopause

- Higher IL-1, IL-6 and TNF production by innate immune cells.
- Increased IL-17 production by Th17 cells also contributes.
- The upstream mechanism for these cytokine changes is not fully resolved.
- Inflammatory signaling shifts RANKL and OPG toward osteoclast activation.

From estrogen withdrawal to bone loss



This schematic summarizes the high-turnover mechanism; The cytokine drivers are multiple.

Formation rises, yet net mass falls

- Estrogen deficiency may increase both formation and resorption.
- The resorptive response is quantitatively dominant.
- The mismatch explains high-turnover postmenopausal osteoporosis.
- A rise in turnover alone does not guarantee increased bone mass.

Early postmenopausal skeletal loss

- Accelerated loss during the decade after menopause.
- Under the described circumstances, annual loss may reach 2% of cortical and 9% of cancellous bone.
- These are possible rates cited by the textbook, not universal individual trajectories.
- The marked cancellous vulnerability helps explain vertebral fragility.

Aging versus menopause: Mechanistic contrast

Feature	Age-associated pathway	Postmenopausal pathway
Dominant imbalance	Formation is reduced	Resorption rises disproportionately
Cellular driver	Osteoblast dysfunction	Increased osteoclastogenesis
Turnover label	Low turnover	High turnover
Emphasized morphology	Cortical thinning	Trabecular plate loss

Secondary osteoporosis: Why assess causes?

- Not all generalized osteoporosis is primary.
- Endocrine disease, systemic illness, neoplasia, medication exposure and immobility may contribute.
- A secondary process may coexist with age-related or postmenopausal loss.
- Recognizing the cause is essential for clinicopathologic interpretation.

Secondary causes: Endocrine disorders

Endocrine examples	Pathologic concern
Hyperparathyroidism	Resorptive effects of excess PTH
Hyperthyroidism	Altered bone turnover
Type 1 diabetes	Systemic metabolic influence on skeletal health
Adrenal and pituitary disorders	Secondary hormonal contribution

Secondary causes: Nutrition and gastrointestinal disease

Category	Examples in Robbins
Absorption / intake	Malabsorption; malnutrition
Vitamin inadequacy	Vitamin C and vitamin D deficiencies
Organ dysfunction	Hepatic insufficiency

Secondary causes: Drug exposures

Medication / exposure	How to frame it
Corticosteroids	Recognized drug-associated bone loss
Anticonvulsants	Potential secondary contributor
Anticoagulants, chemotherapy	Listed among associated drug categories
Alcohol	Listed as an acquired exposure

Secondary causes: Neoplastic and systemic

Category	Representative associated conditions
Neoplasia	Multiple myeloma; carcinomatosis
Miscellaneous	Anemia; immobilization; pulmonary disease
Hereditary skeletal disease	Osteogenesis imperfecta; homocystinuria

Clinical assessment: Potential contributors

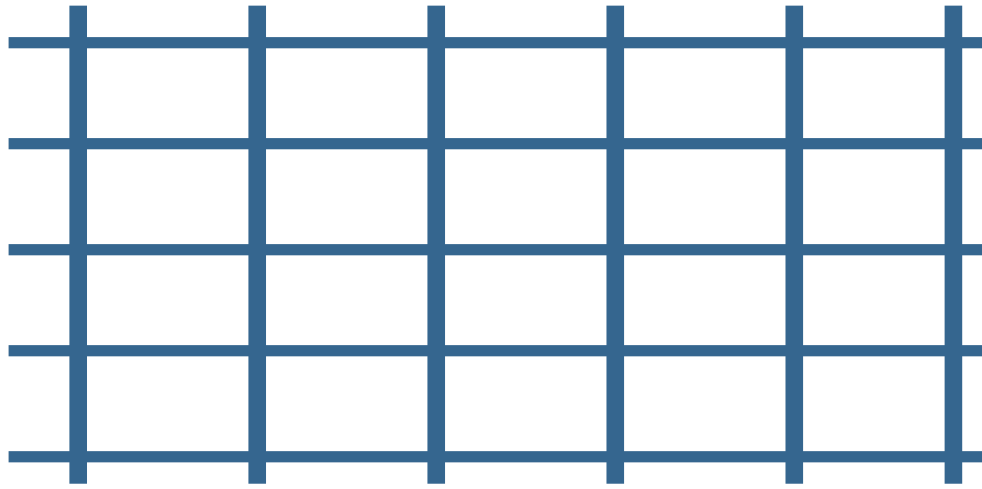
- Interpret fragility in the context of age, menopause and physical activity.
- Consider nutrition and medication exposures, particularly corticosteroids.
- Look for clues to endocrine, gastrointestinal or neoplastic disease.
- Primary and secondary categories should not be treated as mutually exclusive.

The morphologic hallmark

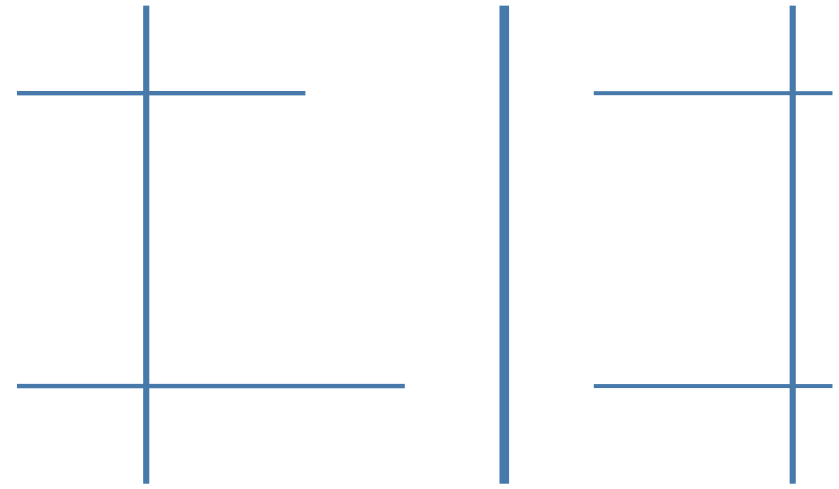
- The remaining bone tissue is histologically normal.
- The amount of trabecular and/or cortical bone is reduced.
- The architectural distribution differs with the dominant disease mechanism.
- Loss of bone quantity ultimately reduces mechanical competence.

Trabecular architecture: Normal and osteoporotic

Intact trabecular mesh



Thinned / disconnected trabeculae



Schematic — not a histologic specimen

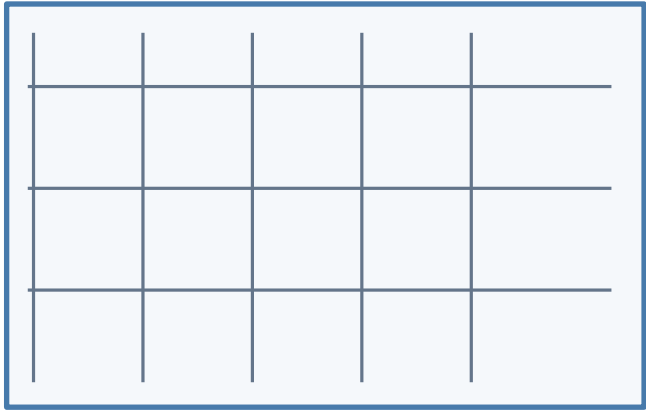
- Thinning and loss of trabecular plates diminish interconnected support.
- This is an original structural schematic, not a photomicrograph.

Trabecular perforation has a structural cost

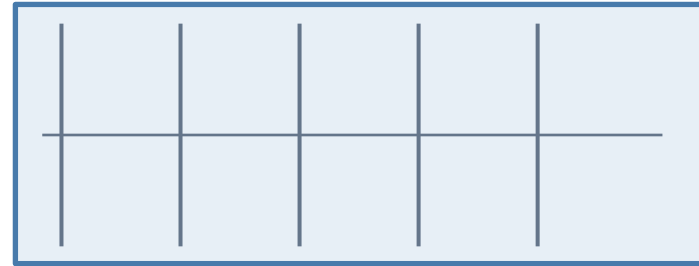
- Resorption can perforate trabecular plates.
- Trabecular struts become thinner and may disappear.
- Loss of cross-connections interrupts load-sharing pathways.
- Microfracture risk increases before obvious vertebral collapse.

Vertebral body failure under compression

Intact vertebral body



Compressed osteoporotic body



Vertical elements predominate after horizontal support is lost

Schematic — not an imaging study

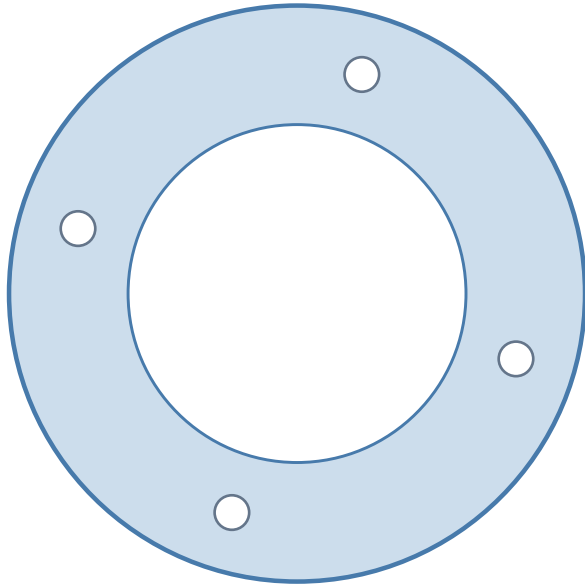
- The osteoporotic vertebral body can become shortened by compression fractures.
- The source describes loss of horizontal trabeculae with relatively prominent vertical trabeculae.

Why cancellous bone is vulnerable

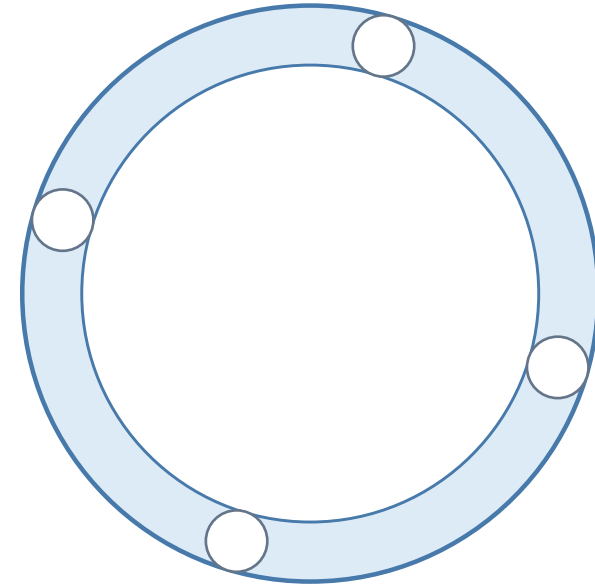
- Cancellous bone has extensive surface area exposed to remodeling.
- Postmenopausal resorption prominently affects the vertebral cancellous compartment.
- Perforation and loss of support link cellular hyperresorption to collapse.
- The resulting fragility is architecture-dependent, not merely a radiographic appearance.

Cortical bone: Thinning and enlarged canals

Relative cortical preservation



Cortical thinning / enlarged canals



Schematic cross-section — not histology

- With senile osteoporosis, cortical loss occurs at endosteal and subperiosteal surfaces.
- Haversian systems may become widened; Outer structural support is diminished.

Senile cortical remodeling changes

- Cortical thickness declines from endosteal and subperiosteal resorption.
- Haversian canals become widened by internal resorption.
- Reduced cortical cross-sectional support predisposes to mechanical failure.
- Cortical changes coexist with loss of cancellous bone in advanced disease.

Morphology: High- versus low-turnover patterns

Feature	Postmenopausal	Senile
Prominent change	Trabecular plates thin and perforate	Cortex thins; Haversian systems widen
Commonly emphasized site	Vertebral cancellous bone	Cortical compartments
Shared outcome	Less normally mineralized bone	Less normally mineralized bone

Fracture is an architectural endpoint

- Each trabecular disconnection reduces the redundancy of the load-bearing network.
- Continued loss predisposes to microfracture and collapse.
- In cortex, thinning impairs resistance to applied stresses.
- Fractures may arise with comparatively modest mechanical loads.

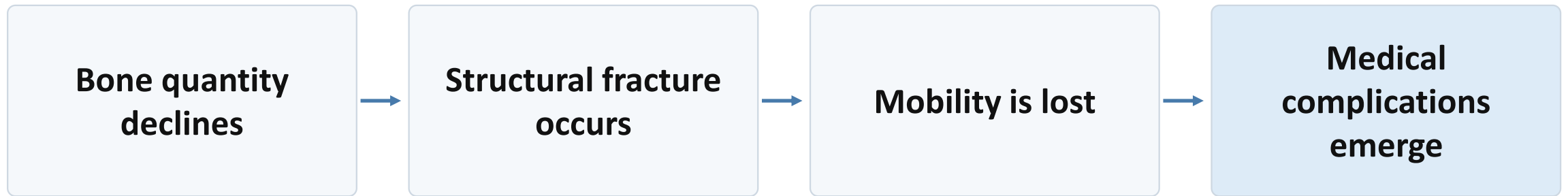
Vertebral fracture manifestations

- Thoracic and lumbar vertebrae are important fracture sites.
- Vertebral compression can cause back pain and loss of stature.
- Multiple fractures alter spinal curvature and postural mechanics.
- Kyphotic or other spinal deformities reflect repeated structural failure.

Hip and pelvic fractures: Clinical consequences

- Femoral neck and pelvic fractures can cause major loss of mobility.
- Prolonged immobilization increases risk of medical complications.
- The text highlights pneumonia and pulmonary embolism as major complications.
- Clinical severity reflects downstream effects as well as the fracture itself.

From fragility to systemic harm



The pathway is clinically important after vertebral, hip, pelvic or other major fractures.

Osteoporosis can be clinically silent

- The disease may progress without pain before a fracture.
- Symptoms depend on the site and severity of structural failure.
- Absence of symptoms does not demonstrate normal skeletal mass.
- This limits symptom-based detection in asymptomatic people.

Plain radiographs detect loss late

- Routine radiographs are insensitive to early decreases in bone mass.
- Substantial loss—approximately 30–40%—may precede reliable radiographic detection.
- Conventional images are valuable for established fractures and deformity.
- Normal-appearing radiographs do not exclude reduced bone density.

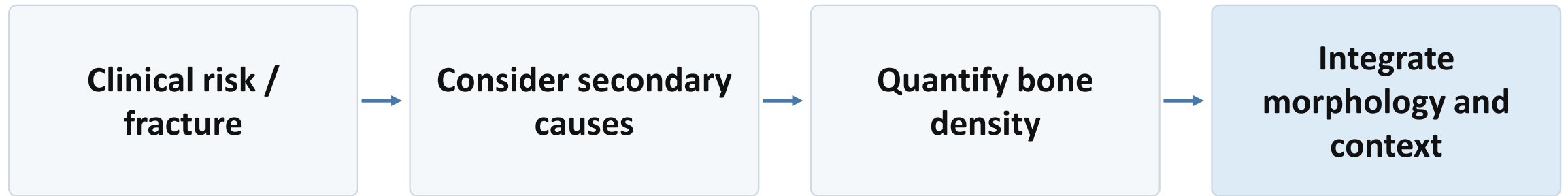
Routine biochemical results may be normal

- Serum calcium is usually normal in primary osteoporosis.
- Serum phosphorus and alkaline phosphatase are also usually normal.
- These results do not exclude loss of skeletal mass.
- Abnormal biochemical findings may redirect evaluation toward an additional disorder.

Imaging methods in the Robbins section

Method	What it contributes	Main limitation in this context
Plain radiograph	Depicts established loss and fracture	Insensitive before marked loss
Dual-energy X-ray absorptiometry (DXA)	Measures bone density	Density does not directly depict every architectural defect
Quantitative CT	Measures bone density	Requires specialized imaging

Diagnostic reasoning: Mechanism to measurement



Conceptual approach based on the chapter; This is not a formal screening or treatment guideline.

Osteoporosis and osteomalacia

Characteristic	Osteoporosis	Osteomalacia
Core defect	Reduced bone quantity	Impaired matrix mineralization
Residual bone	Normally mineralized	Undermineralized osteoid
Overlap	Both may predispose to fractures	Both may predispose to fractures

Distinguishing other skeletal fragility mechanisms

Disorder	Principal difference from osteoporosis
Osteogenesis imperfecta	Defective type I collagen and inherited skeletal fragility
Osteopetrosis	Increased bone density due to impaired resorption; bone remains fragile
Hyperparathyroidism	Excess PTH-driven resorption can itself cause secondary osteopenia

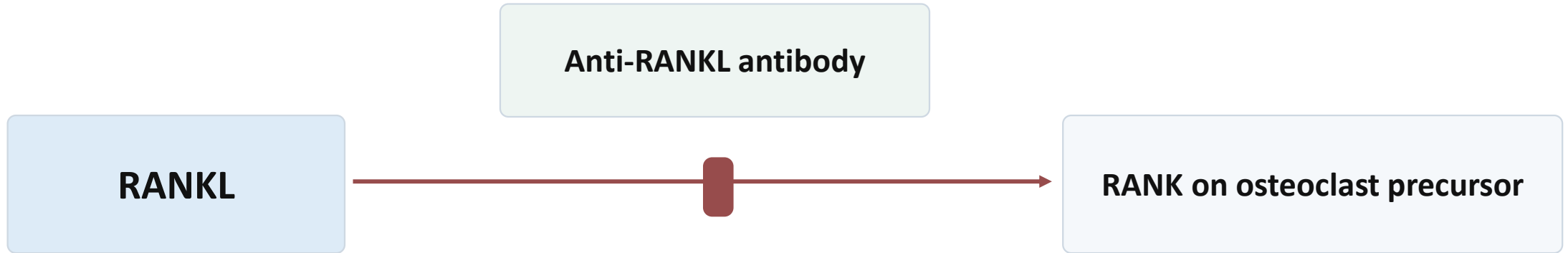
Prevention targets modifiable contributors

- Adequate calcium and vitamin D support skeletal maintenance.
- Exercise, including effective mechanical loading, can help preserve bone mass.
- Immobility and inadequate nutritional intake are modifiable drivers.
- Preventive measures address causes but do not fully reverse inherited or aging effects.

Antiresorptive therapy: Principle

- Increased osteoclast resorption is a therapeutic target.
- Bisphosphonates as major resorption-reducing agents.
- Treatment aims to reduce the imbalance responsible for progressive bone loss.
- Specific prescribing regimens are outside the pathology scope of this lecture.

Denosumab targets the RANKL pathway



Less osteoclast activation and bone resorption

- Denosumab is an antibody directed against RANKL.
- Blocking RANKL–RANK interaction inhibits osteoclast activation and resorption.

Estrogen treatment requires a risk tradeoff

- Estrogenic therapy can slow loss and reduce related fractures.
- Venous thromboembolism and stroke as important concerns.
- These complications restrict use of estrogen as osteoporosis treatment.
- The pathologic mechanism does not by itself establish the correct treatment choice.

Match intervention to the pathophysiology

Therapeutic approach	Targeted pathologic contribution
Loading / exercise	Low mechanical stimulation
Calcium and vitamin D adequacy	Nutritional contributions to low mass
Bisphosphonates	Osteoclast-mediated resorption
RANKL inhibition	Osteoclast recruitment through RANK signaling

Application: Early postmenopausal bone loss

A previously healthy woman develops low bone density during the decade following menopause. Routine serum calcium is normal.

What cellular mechanism best explains accelerated loss?

Estrogen withdrawal increases pro-resorptive cytokine/RANKL signaling and osteoclast activity; Formation rises less than resorption.

Application: Immobilized limb

A patient experiences prolonged loss of limb loading after paralysis; Regional imaging later demonstrates reduced skeletal mass.

Which bone cell senses the missing signal, and what distribution is expected?

Osteocytes sense mechanical loading; An unloaded extremity may develop localized disuse osteoporosis.

Application: Vertebral deformity

An older patient develops progressive loss of height following repeated vertebral compression fractures.

Which microscopic architectural features create vertebral vulnerability?

Trabecular thinning, perforation, lost interconnections and microfractures weaken the cancellous framework.

Application: A fragility fracture with normal chemistry

A patient with a low-trauma fracture has serum calcium, phosphate and alkaline phosphatase within laboratory reference limits.

Do these laboratory results rule out osteoporosis?

No. Routine calcium, phosphorus and alkaline phosphatase are commonly normal despite reduced bone mass.

High-yield synthesis: Lesion and cause

- Osteoporosis is quantitative loss of histologically normal, normally mineralized bone.
- Peak mass reflects genetics, loading, nutrition and hormonal status.
- Senile loss emphasizes inadequate formation; Postmenopausal loss emphasizes resorption.
- Both pathways converge on fragile skeletal architecture.

High-yield synthesis: Morphology and diagnosis

- Trabecular thinning, perforation and loss of connections weaken vertebrae.
- Cortical thinning and enlarged Haversian canals accompany age-related loss.
- Fractures cause pain, deformity, loss of mobility and systemic complications.
- DXA and quantitative CT assess density; Routine radiographs and blood chemistry can miss early disease.

Source and further reading

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 26: Bones, Joints, and Soft Tissue Tumors.
- “Osteopenia and Osteoporosis,” pp. 1070–1072, with preceding bone homeostasis/remodeling section (pp. 1065–1066).
- Conceptual diagrams in this lecture are original editable schematics, not histologic specimens or reproduced textbook figures.
- No clinical guideline updates or original chapter PDF figure verifications were incorporated.