

Vitamin Deficiencies

Mechanisms, morphology and clinicopathologic correlations

Fat-soluble vitamins • water-soluble vitamins • deficiency patterns

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Learning objectives

- Distinguish primary deficiency from malabsorption, transport and metabolic defects.
- Connect vitamin function to tissue-specific pathology and clinical syndromes.
- Explain vitamin A deficiency, ocular injury and epithelial metaplasia.
- Explain vitamin D regulation, defective mineralization and skeletal disease.
- Recognize toxicity and interpret major clinical patterns.

Thirteen vitamins: Two physiologic groups

Solubility predicts absorption, storage and clinical vulnerability.

Fat-soluble

A, D, E and K; More readily stored in tissues.

Water-soluble

Nine vitamins: The B group and vitamin C.

Clinical implication

Fat malabsorption can simultaneously reduce several fat-soluble vitamins.

Fat-soluble versus water-soluble vitamins

Fat-soluble: A, D, E, K

- More readily stored in the body
- Require adequate intestinal fat absorption
- Several deficiency syndromes share a malabsorptive origin

Water-soluble: B vitamins and C

- Often function as coenzymes in metabolic reactions
- Includes redox, one-carbon and collagen pathways
- Clinical patterns depend on affected biochemical processes

Four mechanisms of secondary deficiency

Vitamin deficiency

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graph TD; A[Vitamin deficiency] --> B[Inadequate intake]; A --> C[Poor absorption]; A --> D[Delivery or storage]; A --> E[Metabolic conversion]; B --> B1[Primary nutritional deficiency]; C --> C1[Intestinal and fat-malabsorption disorders]; D --> D1[Impaired blood transport or tissue reserves]; E --> E1[Reduced activation to functional vitamin forms];
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Inadequate intake

Primary nutritional deficiency

Poor absorption

Intestinal and fat-malabsorption disorders

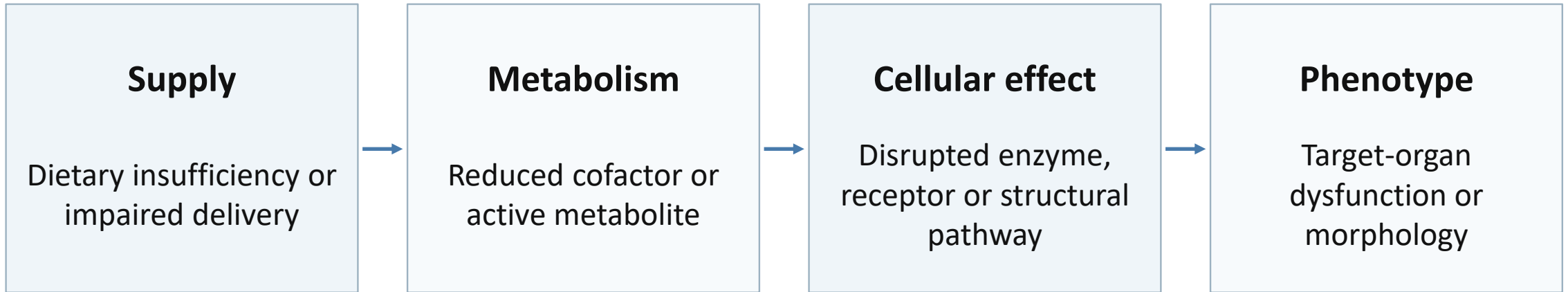
Delivery or storage

Impaired blood transport or tissue reserves

Metabolic conversion

Reduced activation to functional vitamin forms

From nutrient shortage to tissue dysfunction



- The same clinical syndrome can arise from different points in this chain.

Mixed deficiencies are clinically important

- An isolated deficiency of only one vitamin is uncommon in severe malnutrition.
- Severe acute malnutrition may involve multiple vitamin deficits.
- A single organ phenotype can coexist with broad nutritional or immune impairment.
- The cause must be sought beyond the most obvious symptom.

Endogenous synthesis is not complete protection

Contributions

- Vitamin D: Produced from skin precursor steroids
- Vitamin K and biotin: Intestinal microflora
- Niacin: Synthesized from essential amino acid tryptophan

Practical limitation

- Dietary supply remains essential for health
- Deficiency may reflect inadequate intake or altered conversion
- Synthesis does not exclude malabsorption or illness-associated deficiency

Fat-soluble vitamins: Functions and syndromes

Vitamin	Major function	Deficiency consequence
A	Vision; epithelial differentiation; immunity	Night blindness; xerophthalmia; metaplasia
D	Calcium/phosphate homeostasis; bone mineralization	Rickets; osteomalacia
E	Antioxidant defense	Spinocerebellar degeneration; hemolytic anemia
K	Carboxylation of coagulation-related proteins	Abnormal bleeding

Water-soluble vitamins: Metabolic functions

Vitamin	Biochemical role	Deficiency syndrome
B1, thiamine	Cofactor in decarboxylation	Beriberi; Wernicke–Korsakoff
B2, riboflavin	FMN/FAD in intermediary metabolism	Cheilosis, glossitis, dermatitis
B3, niacin	NAD/NADP redox reactions	Pellagra
B6, pyridoxine	Coenzyme in intermediary reactions	Neuropathy, cheilosis, dermatitis
B12, cobalamin	Folate metabolism; DNA synthesis	Megaloblastic anemia; tract degeneration

Other water-soluble vitamins: Deficiency patterns

Vitamin	Core role	Deficiency consequence
Folate	One-carbon transfer for DNA synthesis	Megaloblastic anemia; neural tube defects
Vitamin C	Redox reactions; collagen hydroxylation	Scurvy
Pantothenic acid	Component of coenzyme A	No nonexperimental syndrome recognized
Biotin	Cofactor in carboxylation	No clearly defined clinical syndrome in source table

Thiamine deficiency: Metabolic and neurologic injury

Biochemistry

- Thiamine pyrophosphate acts in decarboxylation reactions
- Energy-requiring tissues are vulnerable to disruption

Clinicopathologic patterns

- Dry beriberi: Predominant neuropathic manifestations
- Wet beriberi: Predominant cardiovascular manifestations
- Wernicke–Korsakoff syndrome: Characteristic CNS syndrome

Riboflavin deficiency: Mucocutaneous pattern

Molecular function

- Precursor of flavin mononucleotide (FMN)
- Precursor of flavin adenine dinucleotide (FAD)
- Both serve as cofactors in intermediary metabolism

Clinical findings

- Cheilosis and stomatitis
- Glossitis and dermatitis
- Corneal vascularization

Niacin deficiency: Pellagra

Niacin supplies NAD and NADP for oxidation–reduction reactions.

Dermatitis

Characteristic cutaneous
disease pattern

Diarrhea

Gastrointestinal involvement

Dementia

Neurologic and cognitive
involvement

Pyridoxine deficiency: Skin and nerve findings

Biochemical function

- Vitamin B6 derivatives participate in many intermediary reactions
- Multiple metabolic pathways depend on B6-derived coenzymes

Deficiency phenotype

- Peripheral neuropathy
- Cheilosis and glossitis
- Dermatitis

Vitamin B12 and folate: Shared and distinct patterns

Shared hematologic consequence

- Both support DNA synthesis
- Deficiency can produce megaloblastic anemia

Distinguishing consequence

- Vitamin B12 deficiency can injure posterolateral spinal cord tracts
- Folate deficiency is linked to neural tube defects
- Neurologic patterns should not be treated as interchangeable

Vitamin E and K: Two distinct failure modes

Vitamin E: Antioxidant protection

- Scavenges free radicals
- Deficiency associated with spinocerebellar degeneration
- Hemolytic anemia may occur

Vitamin K: Hemostatic function

- Cofactor for hepatic carboxylation
- Factors II, VII, IX, X; Proteins C and S
- Deficiency predisposes to abnormal bleeding

Clinical pattern recognition across vitamins

Dominant presentation	Relevant vitamin(s)	Pathologic rationale
Night blindness / dry eye	A	Visual pigment and epithelium
Rickets / osteomalacia	D	Defective mineralization
Bleeding	K or C	Coagulation vs collagen vessel integrity
Megaloblastic anemia	B12 or folate	Impaired DNA synthesis
Pellagra	Niacin	Impaired NAD/NADP-linked metabolism

Vitamin A: Three critical tissue functions

Retinoids connect vision, epithelial differentiation and immune defense.

- Retinal participates in visual pigments of rods and cones.
- Retinoic acid regulates growth and cellular differentiation.
- Deficiency disrupts mucosal epithelial integrity and increases infection vulnerability.

Vitamin A forms and their roles

Biologically active family

- Retinol: Transport/storage precursor
- Retinal: Central to visual pigment chemistry
- Retinoic acid: Nuclear receptor–mediated gene regulation

Broader chemical terminology

- Retinoids include natural and synthetic related compounds
- Structural similarity does not ensure identical biologic activity
- β -Carotene is an important dietary provitamin

Where dietary vitamin A comes from

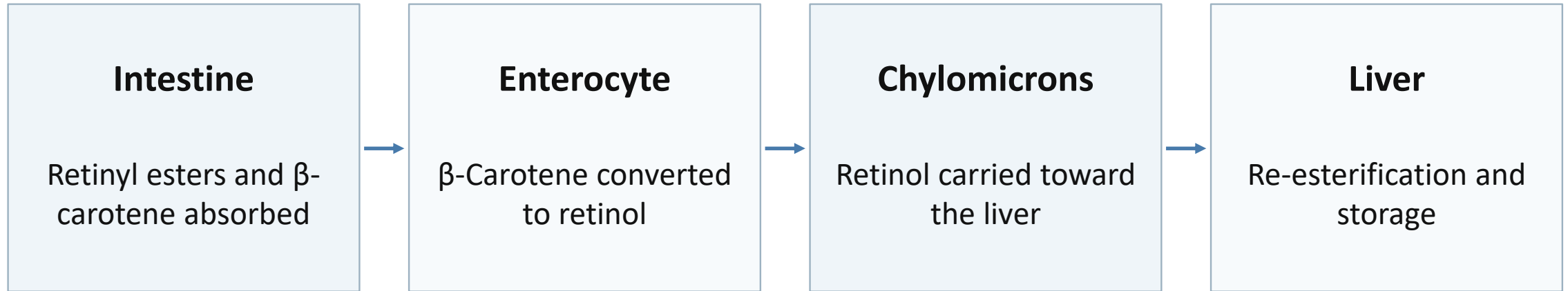
Preformed vitamin A

- Liver and fish
- Eggs, milk and butter
- Animal-derived retinyl esters

Provitamin A carotenoids

- Carrots and squash
- Spinach and other leafy green vegetables
- β -Carotene converted into vitamin A in the body

Vitamin A absorption and transport



- Requires bile, pancreatic enzymes and adequate intestinal fat handling.

Vitamin A: Hepatic storage is a buffer

Liver stores account for most of the body's vitamin A reserves.

Storage site

Predominantly perisinusoidal
stellate (Ito) cells

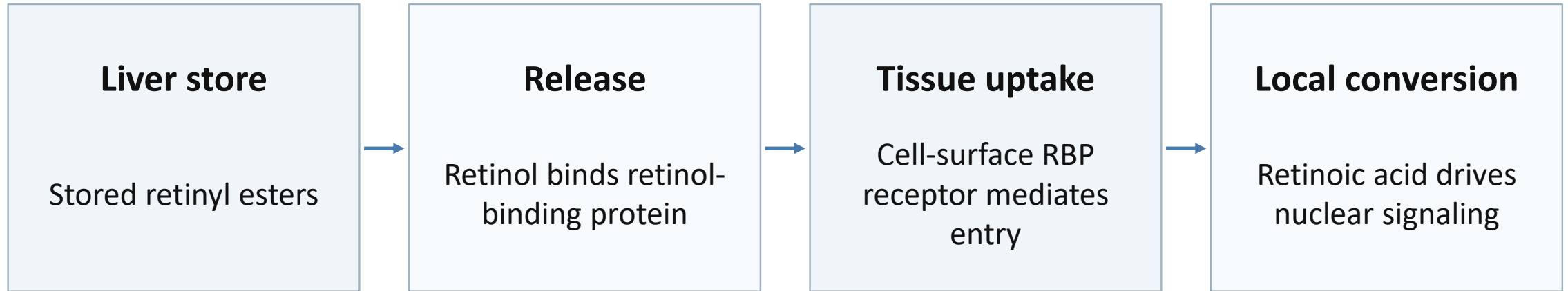
Stored form

Retinyl esters available for
mobilization

Clinical significance

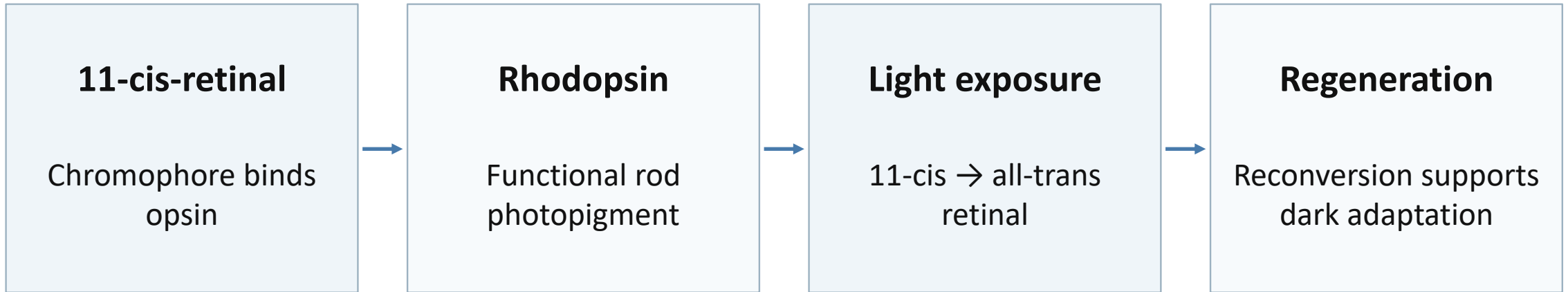
Chronic deficiency may appear
after depletion of substantial
reserves

From hepatic storage to peripheral tissues



- Low hepatic synthesis of retinol-binding protein may reduce circulating retinol.

The vitamin A visual cycle



- Insufficient retinal compromises vision in dim light before advanced ocular disease.

Rods and cones require distinct visual pigments

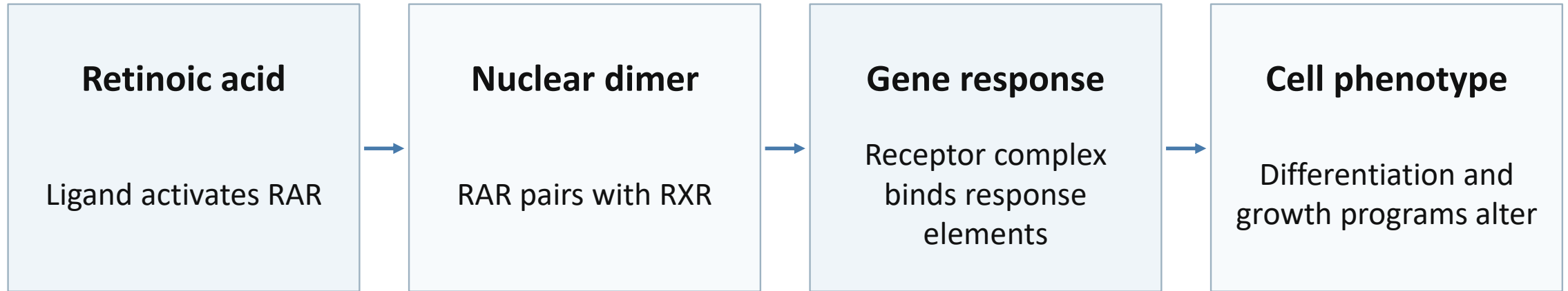
Rods

- Rhodopsin is highly light-sensitive
- Rod function is central to reduced-light vision
- Deficiency causes impaired dark adaptation

Cones

- Three iodopsin types support color discrimination
- Cones function primarily in brighter light
- Vitamin A participates in cone visual pigments

Retinoic acid controls epithelial differentiation



- Absence of proper signaling predisposes mucosal epithelium to keratinizing metaplasia.

Retinoid nuclear receptor pathways

RAR/RXR signaling

- Retinoic acid receptor heterodimerization
- Binding to regulatory DNA sequences
- Control of growth and differentiation genes

RXR and metabolism

- RXR also partners with PPAR receptors
- PPAR pathways regulate lipid metabolism
- Effects include adipogenesis and lipoprotein handling

Vitamin A supports mucosal barrier defense

A deficiency produces epithelial change and greater infection vulnerability.

Airway

Loss of normal mucociliary lining predisposes to infection

Ocular surface

Loss of mucin-secreting epithelium causes dryness

Host response

Deficiency is associated with increased susceptibility to common infections

Why vitamin A deficiency develops

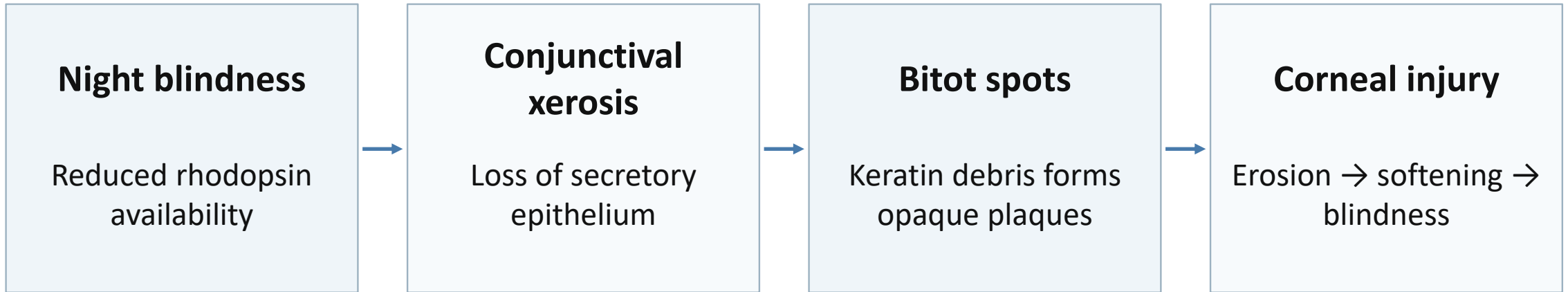
Primary and age-related

- Insufficient intake, particularly with severe malnutrition
- Infections deplete reserves in children
- Newborns have less efficient vitamin A absorption

Secondary causes

- Fat malabsorption: Celiac disease, Crohn disease or colitis
- Bariatric surgery
- Continuous mineral-oil laxative exposure

Vitamin A deficiency: Ocular progression



- Early functional impairment may precede irreversible structural damage.

Early vitamin A eye disease

Night blindness

- Impaired dim-light vision
- Reflects visual pigment deficiency
- Can precede visible ocular changes

Conjunctival xerosis

- Mucus-secreting epithelium replaced by keratinizing epithelium
- Dry conjunctival surface
- Establishes a structural basis for later lesions

Advanced ocular pathology of vitamin A deficiency

Bitot spots

- Local accumulation of keratin debris
- Small opaque plaque-like lesions
- Reflect persistent abnormal surface differentiation

Keratomalacia

- Roughening and erosion of corneal surface
- Corneal softening and tissue destruction
- May progress to permanent blindness

Squamous metaplasia extends beyond the eye

Vitamin A deficiency

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graph TD; A[Vitamin A deficiency] --> B[Upper airway]; A --> C[Urinary tract]; A --> D[Epidermis]; B --> B1[Loss of mucociliary epithelium -> infection risk]; C --> C1[Keratinized epithelium; Debris contributes to stones]; D --> D1[Follicular hyperkeratosis and papular dermatosis];
```

Upper airway

Loss of mucociliary epithelium
→ infection risk

Urinary tract

Keratinized epithelium; Debris
contributes to stones

Epidermis

Follicular hyperkeratosis and
papular dermatosis

Epithelial changes: Why morphology matters

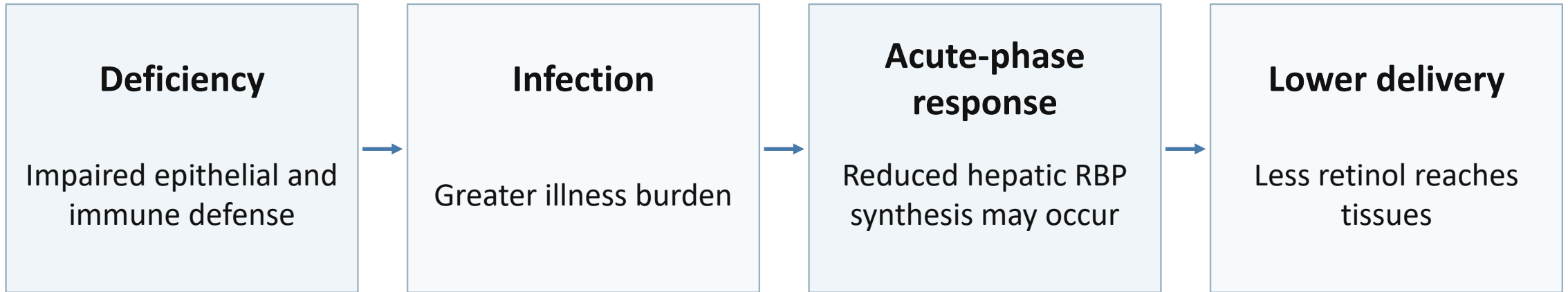
Respiratory system

- Squamous metaplasia replaces specialized mucociliary lining
- Reduced clearance predisposes to secondary pulmonary infections

Urinary and skin changes

- Desquamated keratin can contribute to urinary stones
- Follicular duct plugging and hyperkeratinization cause dermatosis

Vitamin A deficiency creates an infection–deficiency cycle



- The source describes immune effects but does not establish a complete molecular mechanism.

Integrating vitamin A deficiency findings

One vitamin deficit explains multi-organ dysfunction.

- Dark-adaptation loss reflects deficient visual pigment regeneration.
- Xerophthalmia and respiratory metaplasia reflect disordered epithelial differentiation.
- Infections are amplified by impaired barriers and immune responses.

Acute hypervitaminosis A

Exposure and mechanism

- Acute overconsumption of preformed vitamin A
- High-vitamin-A animal liver can cause toxicity

Clinical syndrome

- Headache, dizziness and vomiting
- Blurred vision and stupor
- Symptoms may resemble intracranial pressure disorders

Chronic hypervitaminosis A

Constitutional symptoms

- Weight loss and anorexia
- Nausea and vomiting
- Bone and joint pain

Skeletal effects

- Retinoic acid stimulates osteoclast production/activity
- Increased bone resorption
- Higher risk of fractures

Retinoids in clinical practice: Benefit and risk

Therapeutic contexts

- Some severe acne and psoriasis
- All-trans-retinoic acid in acute promyelocytic leukemia
- 13-cis-retinoic acid in selected neuroblastoma treatment regimens

Important caution

- Therapeutic retinoids are not identical to nutritional supplementation
- Retinoid teratogenicity requires avoidance in pregnancy
- Assess formulation and exposure before attributing toxicity

Clinical reasoning: Dim-light visual impairment

Clinical vignette

A child with restricted nutrition has difficulty seeing at dusk. Examination later reveals dry conjunctiva and focal pale plaques.

Reason through the pathology

- Which vitamin deficiency unifies the findings?
- What is the biochemical basis for night blindness?
- Which epithelial change produces the surface lesions?

Vitamin D: Mineralization depends on systemic regulation

Vitamin D protects mineral homeostasis through intestine, kidney and bone.

- Skin synthesis and diet supply precursor vitamin D.
- Hepatic and renal hydroxylation generate the active hormone.
- PTH, phosphate and FGF23 adjust activation and calcium–phosphate handling.

Vitamin D and the skeleton

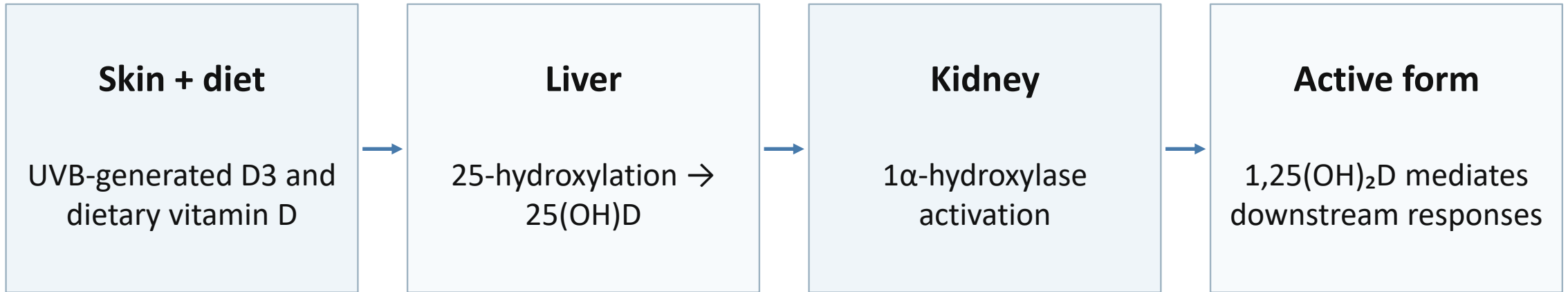
Principal physiologic objectives

- Maintain plasma calcium and phosphorus
- Support skeletal mineralization and neuromuscular function
- Prevent rickets and osteomalacia

When deficiency develops

- Reduced substrate availability for mineral deposition
- PTH compensation can preserve serum calcium
- Persistent phosphate depletion can worsen mineralization

Vitamin D: Sources and activation



- Vitamin D-binding protein transports circulating forms.

Vitamin D production: Ultraviolet exposure matters

Cutaneous source

- 7-dehydrocholesterol is the skin precursor
- UVB radiation enables production of vitamin D₃
- Higher melanin may reduce cutaneous production

Dietary source

- Fish and other dietary sources contribute
- Dietary uptake depends on fat absorption
- Reduced sunlight makes dietary contribution more important

Renal 1α -hydroxylase: Opposing regulators

Active vitamin D synthesis

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graph TD; A[Active vitamin D synthesis] --> B[PTH: Stimulation]; A --> C[Low phosphate]; A --> D[1,25(OH)2D]; A --> E[FGF23]; B --> B1[Released with hypocalcemia]; C --> C1[Upregulates hydroxylase]; D --> D1[Negative feedback inhibition]; E --> E1[Inhibits activation];
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PTH: Stimulation

Released with
hypocalcemia

Low phosphate

Upregulates hydroxylase

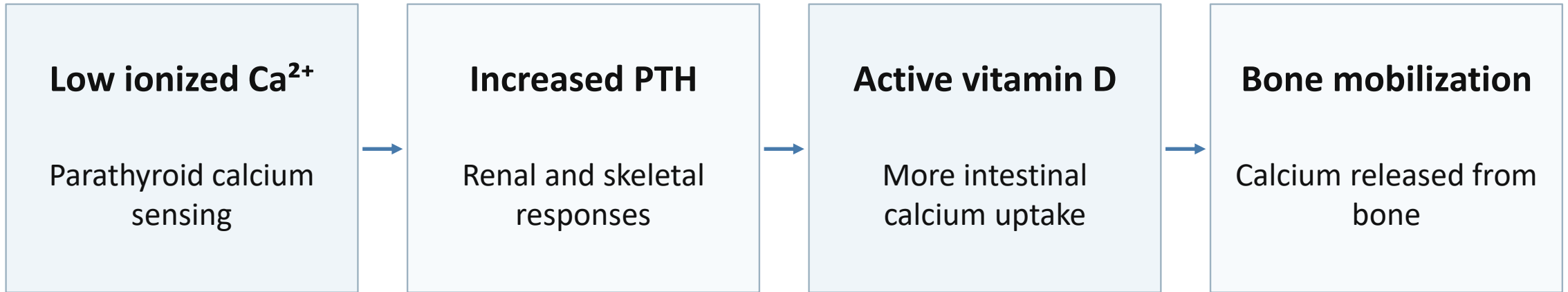
$1,25(\text{OH})_2\text{D}$

Negative feedback
inhibition

FGF23

Inhibits activation

Hypocalcemia evokes endocrine compensation



- Compensation can limit overt tetany while skeletal injury progresses.

FGF23 and vitamin D feedback

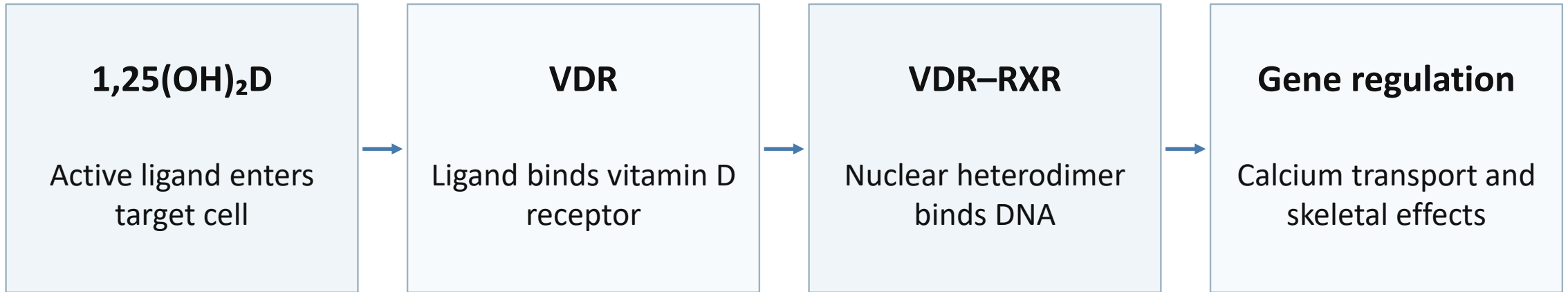
FGF23 action

- Produced by osteoblasts and osteocytes
- Inhibits renal 1α -hydroxylase expression
- Influences phosphate homeostasis

Pathologic implication

- Excess FGF23 can produce hypophosphatemia
- Rare inherited or tumor-related syndromes may lead to rickets/osteomalacia
- Not every mineralization defect is due to poor dietary intake

Vitamin D: Transcriptional signaling



- VDR is widely expressed; Not all described nonskeletal effects are proven therapeutic benefits.

Intestinal calcium transport: TRPV6

Mechanism

- Active vitamin D engages nuclear VDR–RXR
- Target-gene activation includes TRPV6
- TRPV6 supports calcium entry across enterocytes

Functional outcome

- Improved intestinal calcium absorption
- Supports circulating calcium availability
- Deficiency impairs absorption and contributes to secondary hyperparathyroidism

Renal tubular calcium transport: TRPV5

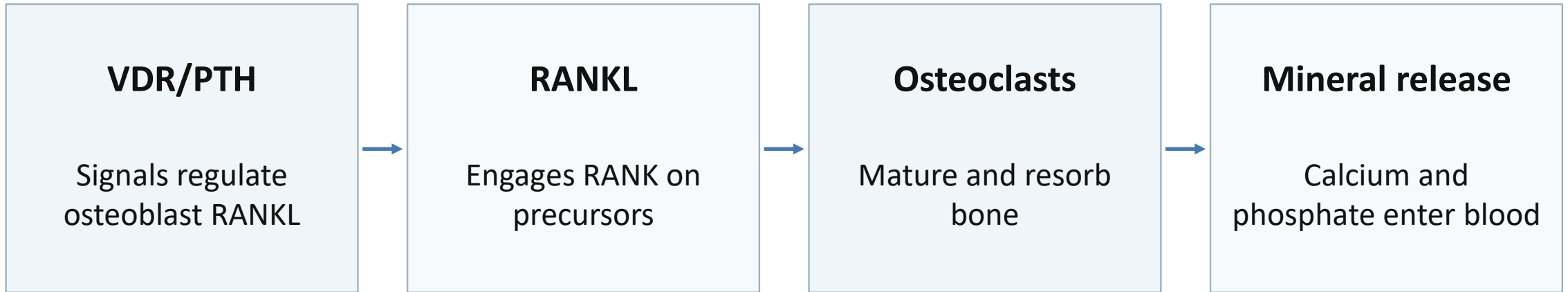
Vitamin D effect

- Active vitamin D increases TRPV5 expression
- Distal tubular calcium influx is enhanced

Coordination with PTH

- Hypocalcemia stimulates PTH release
- PTH also regulates TRPV5
- Renal conservation complements intestinal uptake

Vitamin D, RANKL and osteoclast activation



- Bone-resorptive signaling maintains extracellular calcium at a skeletal cost.

Bone mineralization: Two developmental settings

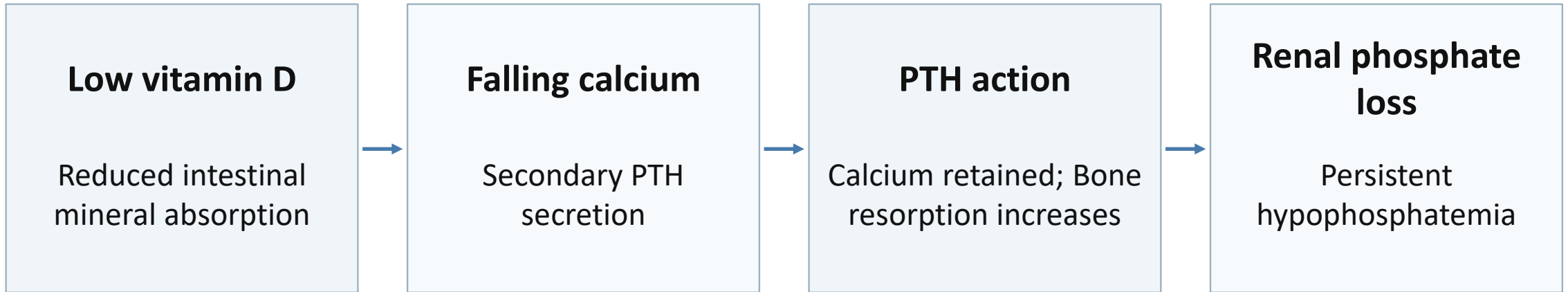
Intramembranous ossification

- Mesenchymal cells differentiate into osteoblasts
- Osteoblasts deposit collagenous osteoid
- Osteoid then becomes mineralized

Endochondral ossification

- Epiphyseal cartilage grows and provisionally mineralizes
- Cartilage is replaced with osteoid matrix
- Mineralization produces mature bone

Vitamin D deficiency: Why phosphate falls



- Inadequate phosphate contributes to defective mineralization despite calcium compensation.

Secondary hyperparathyroidism masks hypocalcemia

Calcium-preserving responses

- PTH enhances renal calcium conservation
- PTH increases bone resorption
- PTH stimulates renal vitamin D activation

The trade-off

- Phosphate wasting may persist
- Bone mineral substrate remains inadequate
- Normal calcium alone cannot exclude deficiency-related bone disease

Rickets and osteomalacia share defective mineralization

The age and location of growing skeletal tissue determine the morphology.

Rickets

Children with open growth plates; Growth-plate cartilage and osteoid affected

Osteomalacia

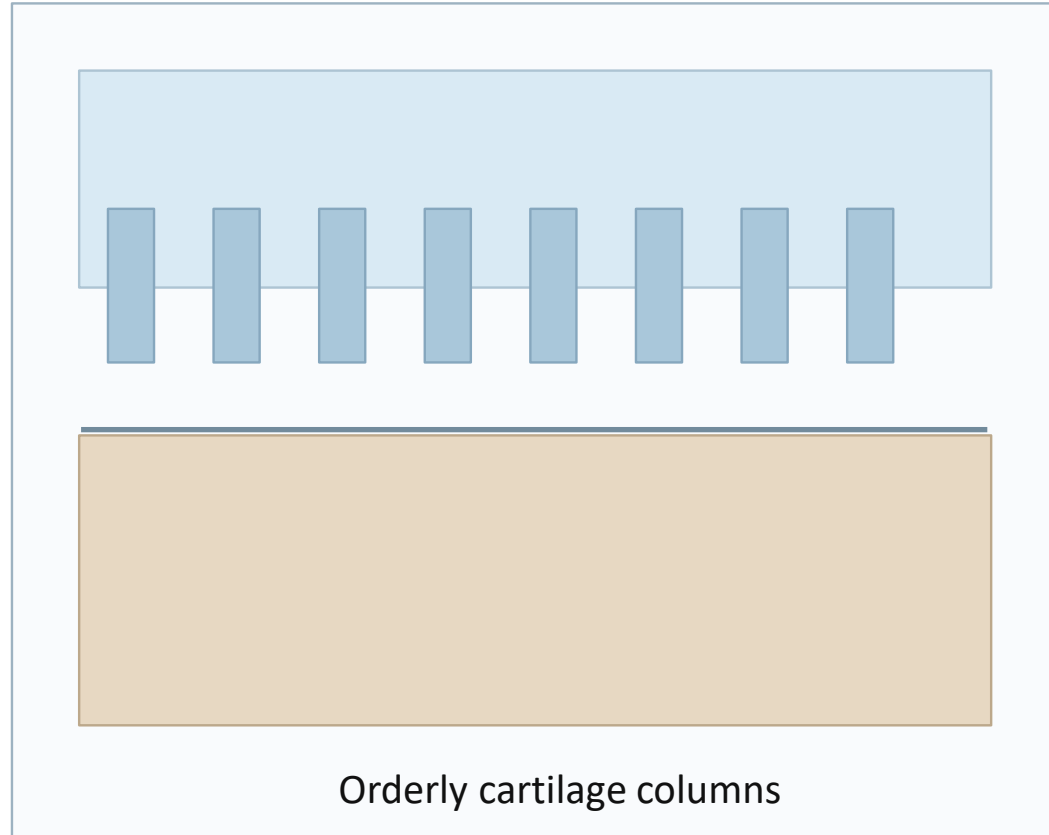
Adults; Mineralization of osteoid matrix is defective

Common mechanism

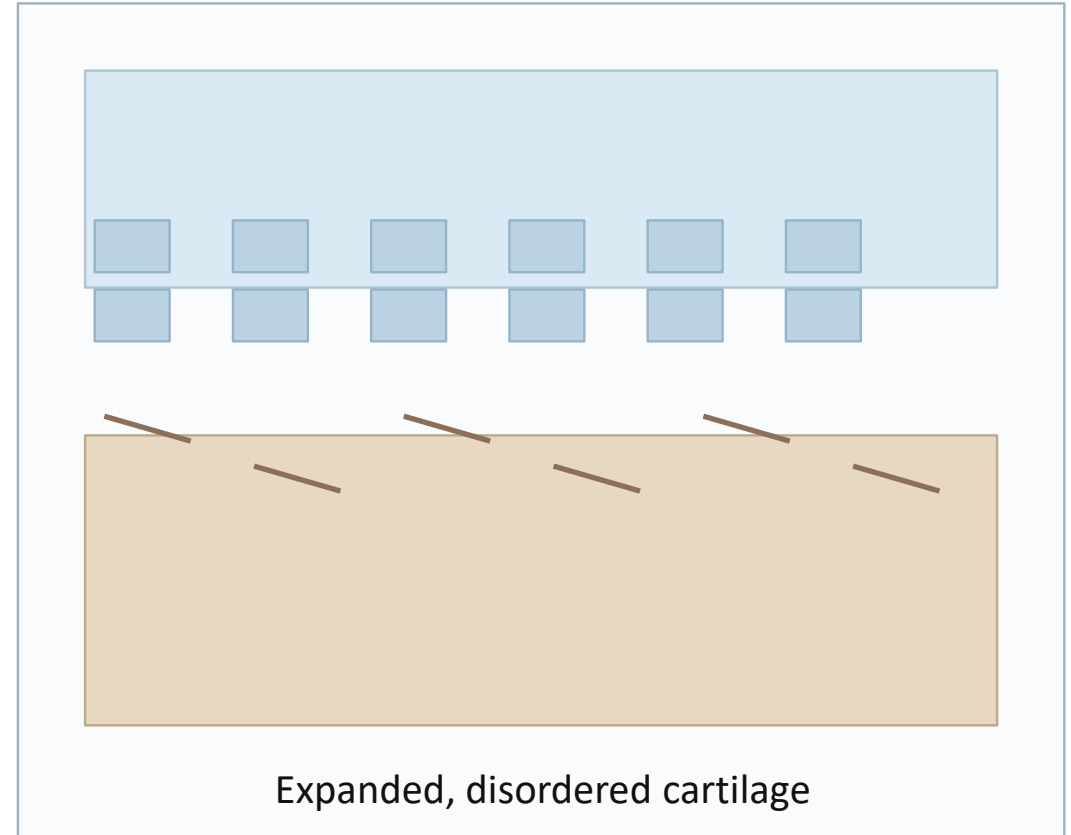
Excess unmineralized matrix due to mineralization failure

Rickets: Disrupted endochondral ossification

Normal costochondral / growth-plate organization

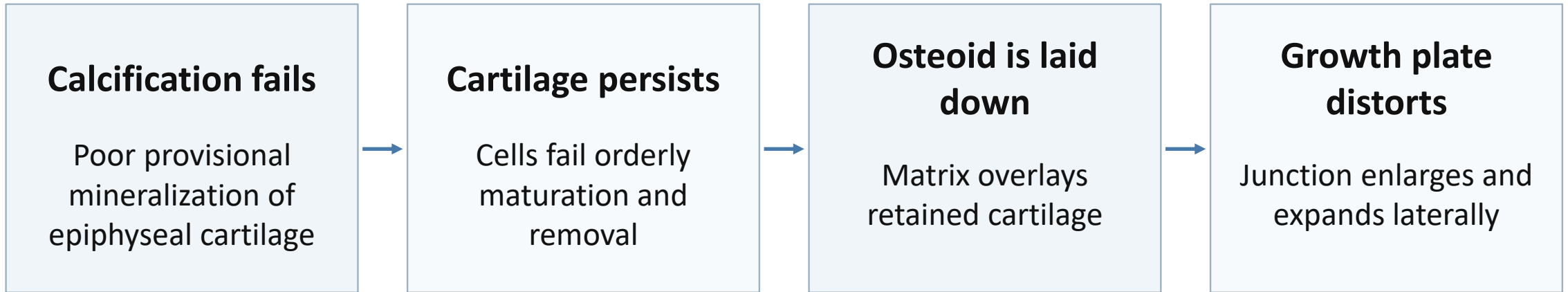


Deficient mineralization in rickets



Schematic growth-plate architecture; Not histology

Rickets: Histomorphologic sequence



- The source describes excess unmineralized matrix and disordered cartilage palisades.

Rickets: Clinically important structural effects

Developing skeleton

- Growth plates remain open
- Defective mineralization distorts cartilage–bone junctions
- Expansion occurs at osteochondral junctions

Representative phenotype

- Bowing of weight-bearing long bones
- Abnormal growth-plate architecture
- Effects differ from adult osteomalacia

Osteomalacia: Defective osteoid mineralization

Pathologic substrate

- Osteoid is deposited but insufficiently mineralized
- Unmineralized matrix accumulates
- Affects adult skeleton after growth-plate closure

Clinicopathologic association

- Bone pain may be present
- Decreased skeletal integrity reflects impaired mineralization
- Distinguish from rickets of open growth plates

Rickets versus osteomalacia

Feature	Rickets	Osteomalacia
Age-related setting	Open growth plates in children	After growth-plate closure
Primary lesion	Growth-plate cartilage and bone mineralization	Osteoid matrix mineralization
Source-described morphology	Cartilage palisade loss; widened junction	Accumulation of unmineralized osteoid
Illustrative consequence	Long-bone bowing	Skeletal pain / fragility

Who is vulnerable to vitamin D deficiency?

Reduced supply

- Limited UVB exposure
- Northern latitude or substantial skin covering
- Low dietary vitamin D and calcium

Impaired metabolism or availability

- Fat-malabsorption disorders
- Renal dysfunction affecting activation
- Phosphate depletion or rare inherited disorders

Clinical assessment: 25-hydroxyvitamin D

Why measure 25(OH)D?

- Circulating 25(OH)D represents the principal assessment analyte discussed by the source
- Evaluate biochemical status in appropriate clinical context

Textbook threshold (11th edition)

- The source lists 20–100 ng/mL as its reference interval
- Values below 20 ng/mL are described as deficiency
- Interpretation depends on clinical and laboratory context

Vitamin D outside the skeleton

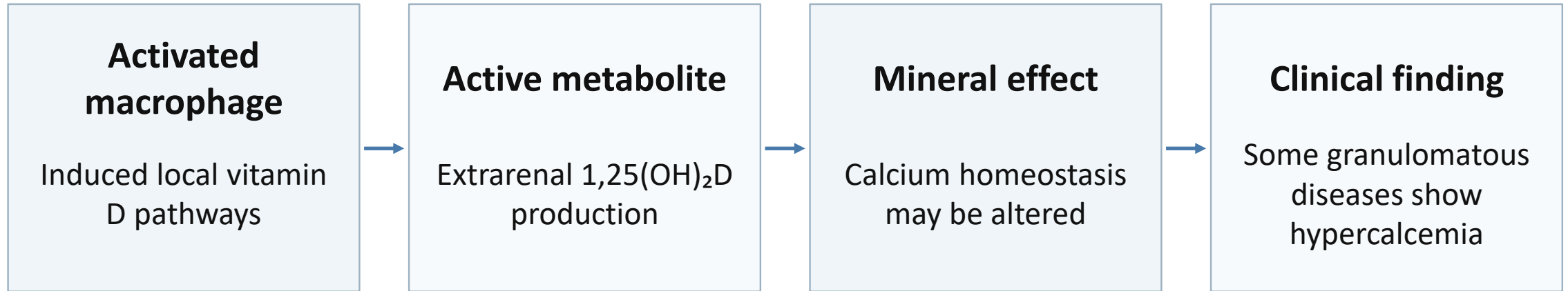
Experimental and biologic observations

- VDR is expressed in diverse tissues
- Macrophages can locally generate active vitamin D
- Antiproliferative and immunomodulatory effects are described

Limits of clinical inference

- Biologic activity does not ensure supplementation benefit
- The source reports negative trials for respiratory infections, including tuberculosis
- Avoid presenting nonskeletal effects as established clinical indications

Granulomatous inflammation and local vitamin D



- The net immunologic effect of altered macrophage vitamin D signaling remains uncertain.

Vitamin D excess: Toxicity differs from deficiency

Source of excess

- Normal prolonged sunlight is not a typical toxicity mechanism
- Oral megadoses can produce hypervitaminosis D

Consequences

- Hypercalcemia and bone pain in adults
- Metastatic soft-tissue calcification, including kidneys, in children
- Toxicity is a distinct mechanism from rickets/osteomalacia

Clinical reasoning: Impaired skeletal mineralization

Clinical vignette

A child has bowing of the legs and evidence of expanded, disorganized cartilage at developing bone ends. Sunlight exposure has been limited.

Reason through the pathology

- What pathologic process explains the skeletal change?
- Why can calcium be partially restored while phosphate remains low?
- How does this differ from adult osteomalacia?

Integrated differential: Follow the affected pathway

Clue	Most relevant deficiency	Mechanism to test
Reduced-light vision + xerosis	Vitamin A	Visual pigments + epithelial differentiation
Growth-plate distortion	Vitamin D	Impaired cartilage/osteoid mineralization
Peripheral neuropathy + dermatitis	Vitamin B6 (among others)	B6-dependent intermediary reactions
Megaloblastic anemia + tract degeneration	Vitamin B12	DNA synthesis + neural pathway injury
Mucosal bleeding from impaired coagulation	Vitamin K	Defective clotting-factor carboxylation

Diagnostic reasoning: Deficiency versus excess

Deficiency

- Dietary or absorptive compromise
- Specific dysfunctional cellular pathways
- Findings such as night blindness, rickets and bleeding

Excess

- High-dose vitamin or retinoid exposure
- Vitamin A: Neuro-ocular and skeletal manifestations
- Vitamin D: Hypercalcemia and metastatic calcification

Core clinicopathologic synthesis

Symptoms become interpretable when traced to the vitamin-dependent pathway.

- Vitamin A: Visual cycle + epithelial differentiation → ocular and barrier injury.
- Vitamin D: Endocrine calcium–phosphate regulation → rickets / osteomalacia.
- Other vitamins: Recognizable neurologic, hematologic, dermatologic and bleeding patterns.

Source and scope of this lecture

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026).
- Chapter 9, Environmental and Nutritional Diseases, pp. 397–403.
- Table 9.9: vitamins, core functions and deficiency syndromes.
- Vitamin A and vitamin D sections: mechanisms, morphology and toxicity.
- Vitamin C / scurvy is addressed in its own succeeding teaching unit.