

Vitamin C (Ascorbic Acid)

Deficiency, collagen pathology, clinical consequences, and the limits of excess supplementation

Nutrition • Collagen biosynthesis • Scurvy

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Learning outcomes

After this lecture, learners should be able to:

- Explain why humans require a dietary supply of vitamin C.
- Trace impaired procollagen hydroxylation to vascular, skeletal, and repair defects.
- Recognize the clinicopathologic pattern of scurvy and susceptible populations.
- Evaluate textbook evidence on purported benefits and harms of high-dose vitamin C.

Vitamin C within the vitamin classification

Storage characteristics influence nutritional vulnerability.

Water-soluble vitamin C

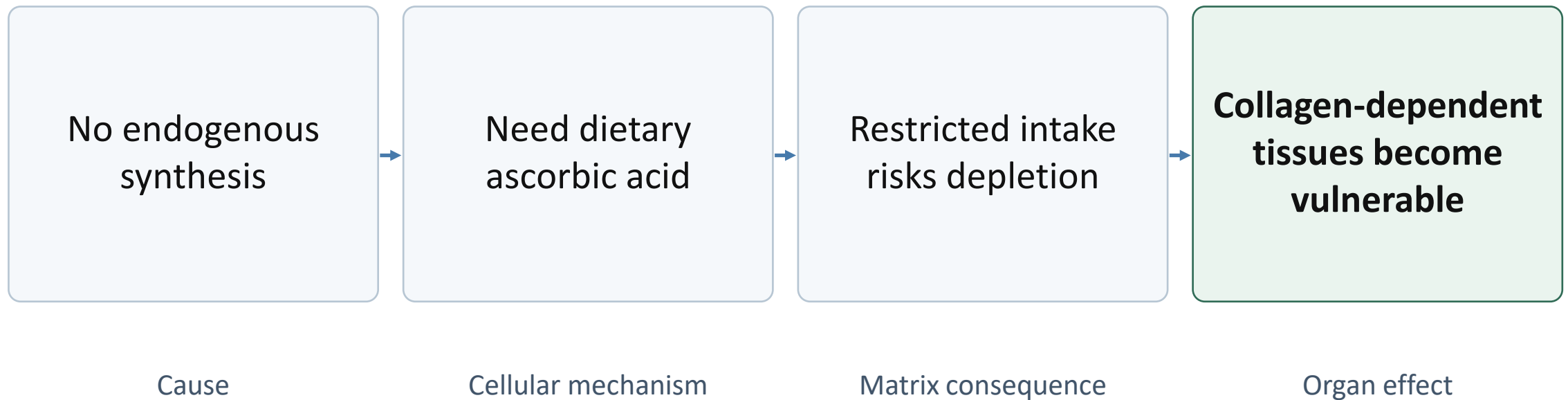
- Must be supplied through the human diet
- Member of the water-soluble vitamin group
- Deficiency produces scurvy

Fat-soluble vitamins

- Vitamins A, D, E, and K
- More readily stored in the body
- May be poorly absorbed in fat malabsorption

Dietary dependence is obligatory

Humans cannot synthesize ascorbic acid endogenously.



Food sources have different contributions

Several classes of dietary sources.

Fruits

Abundant sources of
ascorbic acid

Vegetables

Abundant sources of
ascorbic acid

Animal products

Present in milk and some
liver and fish products

Why ordinary diets usually suffice

Deficiency is uncommon when dietary diversity is maintained.

- Vitamin C is abundant in many fruits and vegetables.
- Even several animal-derived foods can contribute some vitamin C.
- That most diets, except highly restricted ones, supply enough.

Primary versus secondary vitamin deficiency

Nutritional disease can arise at more than one point.

Primary

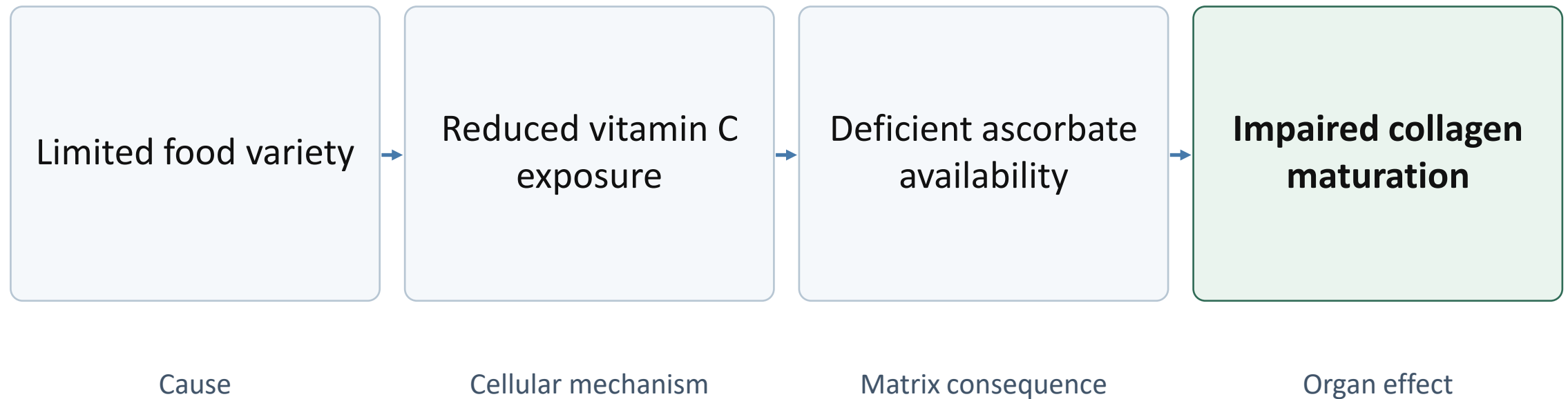
- Dietary intake is inadequate
- Particularly relevant to severely restricted diets
- Directly limits the nutrient available for tissues

Secondary

- Problems can involve absorption or transport
- Storage or metabolic handling can be disturbed
- Risk assessment extends beyond reported intake

Restricted eating creates a preventable pathway

A dietary pattern can initiate the entire deficiency phenotype.



Risk groups identified by Robbins

Scurvy persists in certain high-resource settings.

Older individuals

May have erratic or inadequate eating patterns

Living alone

Restricted food intake may go unrecognized

Alcohol use disorder

Often accompanied by nutritionally inadequate eating

Dietary context is more informative than wealth

Economic setting does not exclude micronutrient deficiency.

- Scurvy is no longer portrayed as a major global problem.
- Cases still occur in affluent populations with marked dietary restriction.
- Individual food patterns deserve more attention than national resource level.

Dialysis and unusual diets are clinical clues

Additional settings in which scurvy occurs.

Dialysis context

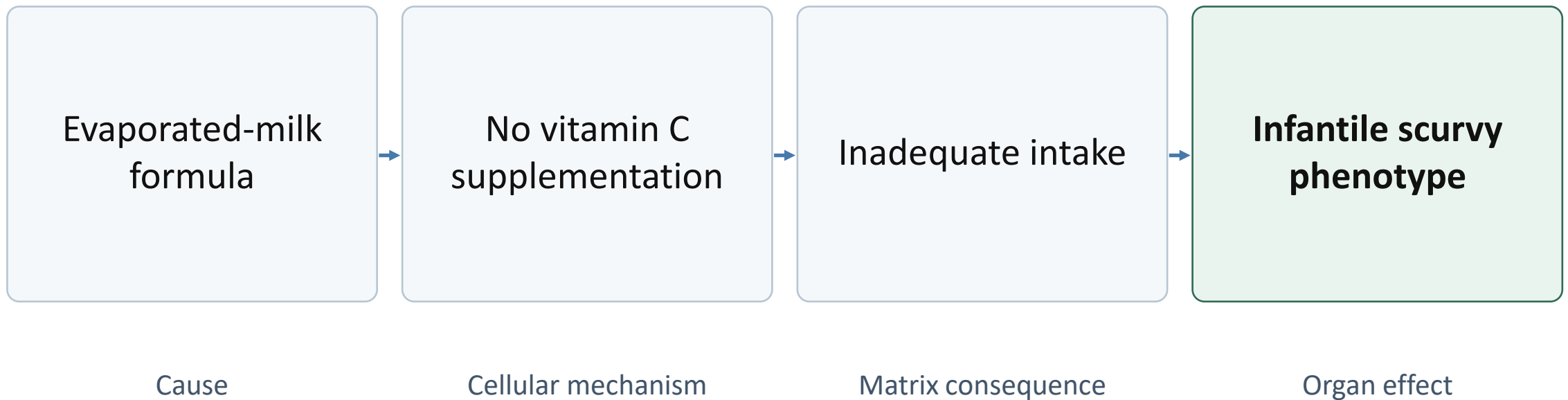
- Reported during peritoneal dialysis
- Reported during hemodialysis
- Do not assume adequate vitamin status without assessment

Restrictive food practices

- “Food faddists” are specifically mentioned
- Unbalanced exclusions may compromise intake
- Clarify the actual foods consumed

Infant feeding can create deficiency

A specific feeding-related setting.



Historical prevention illustrates causality

A dietary intervention preceded recognition of the molecule.

- Royal Navy sailors received lime and lemon juice during long sea voyages.
- The practice sought to prevent scurvy in nutritionally constrained settings.
- Ascorbic acid itself was identified and synthesized in 1932.

The three major functional themes

Keep established biochemical roles separate from proposed clinical effects.

Collagen

Hydroxylation and
mechanical integrity

Catecholamines

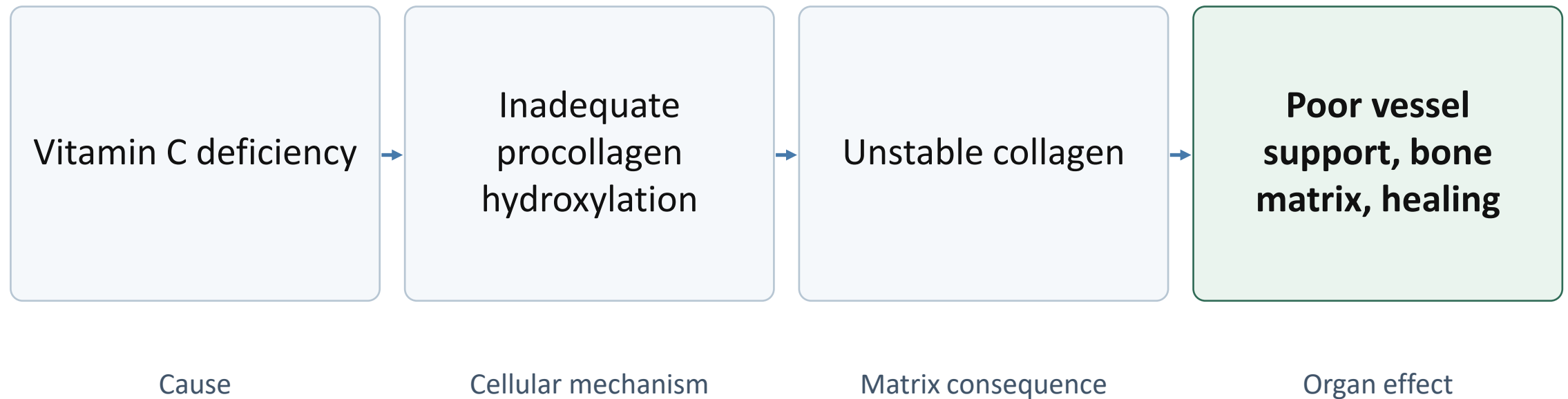
Hydroxylation during
norepinephrine synthesis

Redox biology

Antioxidant and immune-
modulating roles
proposed; Trials
disappointing

Collagen pathology connects molecular and clinical findings

The central causal chain of scurvy.



Procollagen hydroxylation is the established key function

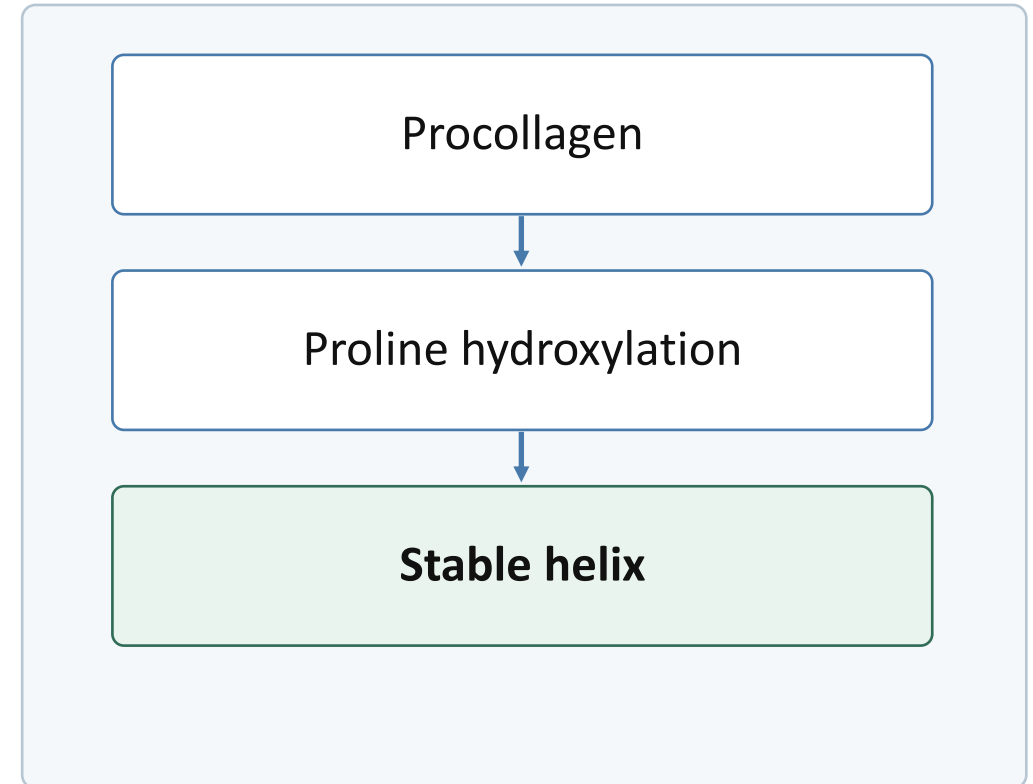
Vitamin C supports the enzymes that modify procollagen.

- Prolyl hydroxylases act on proline residues.
- Lysyl hydroxylases act on lysine residues.
- Vitamin C as required for their activation.

Proline modification stabilizes the collagen helix

The molecular target explains a tissue-wide defect.

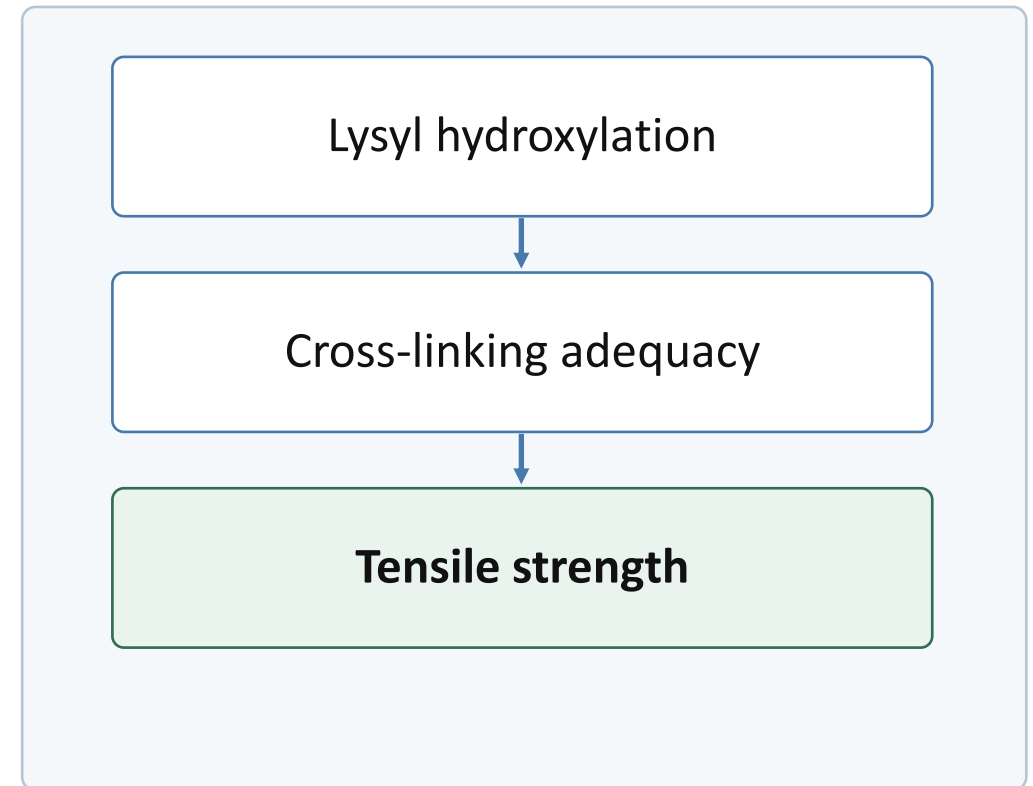
- Procollagen requires adequate residue hydroxylation to acquire a stable helical configuration.
- When hydroxylation is insufficient, ordered helix formation is compromised.
- Collagen-rich tissues experience the consequences of defective maturation.



Lysine modification contributes to collagen strength

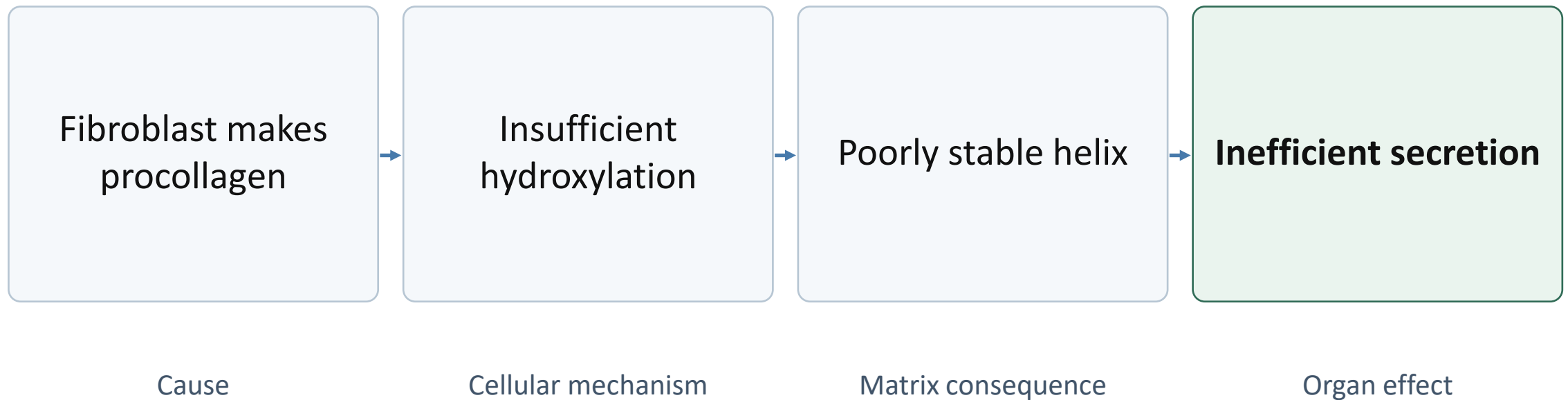
Collagen maturation affects mechanical performance.

- Vitamin C–dependent lysyl hydroxylase activity modifies procollagen.
- Inadequate hydroxylation is associated with poorly cross-linked secreted collagen.
- Weak cross-linking reduces the tissue's ability to withstand stress.



Defective procollagen is inefficiently secreted

The problem begins before mature extracellular fibrils form.



Normal versus vitamin C–deficient collagen maturation

A change in processing becomes a change in material properties.

Adequate vitamin C

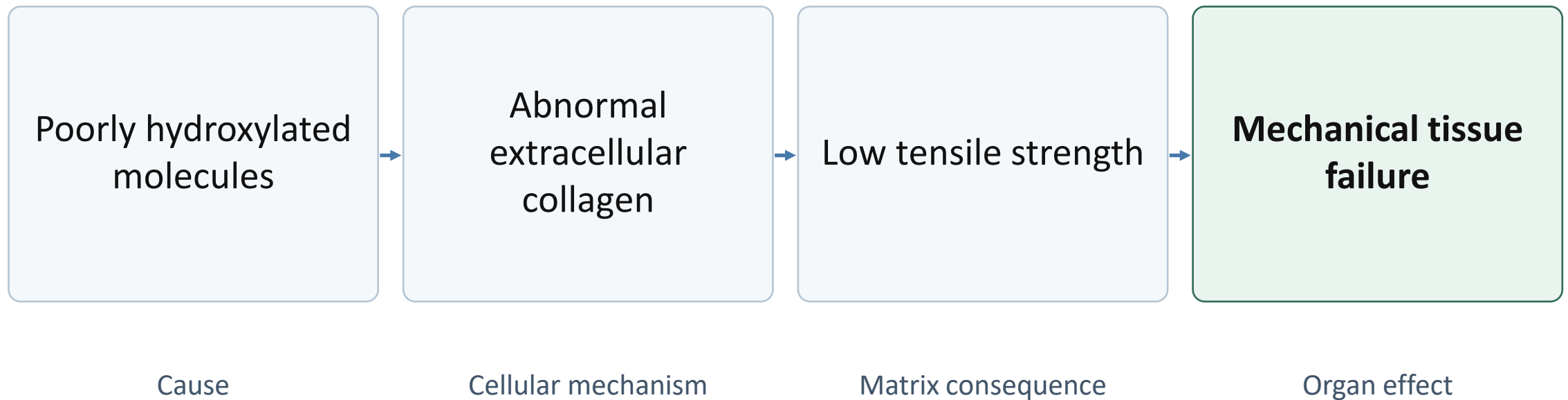
- Hydroxylases function
- Procollagen becomes structurally stable
- Matrix collagen develops tensile strength

Vitamin C deficiency

- Procollagen inadequately hydroxylated
- Helix stability and secretion suffer
- Secreted collagen is poorly cross-linked

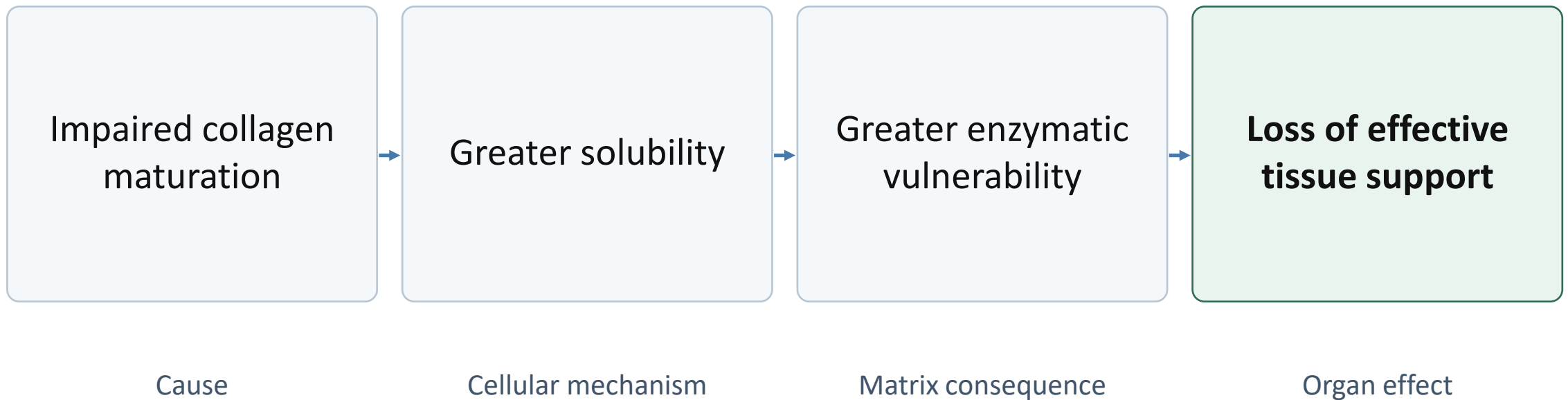
Secreted abnormal collagen is fragile

Defects persist even when molecules leave the cell.



Weak collagen is prone to degradation

The extracellular matrix cannot reliably retain integrity.



Tensile strength is the clinically relevant property

Collagen normally helps structures resist pulling forces.

- Collagen is more than an extracellular filler; It confers mechanical support.
- When its mature structure is abnormal, minor physiological stresses matter more.
- Weak blood vessels and impaired repair become predictable consequences.

A matrix defect becomes multisystem disease

Different tissues express the same primary collagen abnormality.

Microvasculature

Loss of connective-tissue support → hemorrhages

Wound beds

Poor collagen deposition
→ healing defects

Growing skeleton

Impaired osteoid formation → bone disease

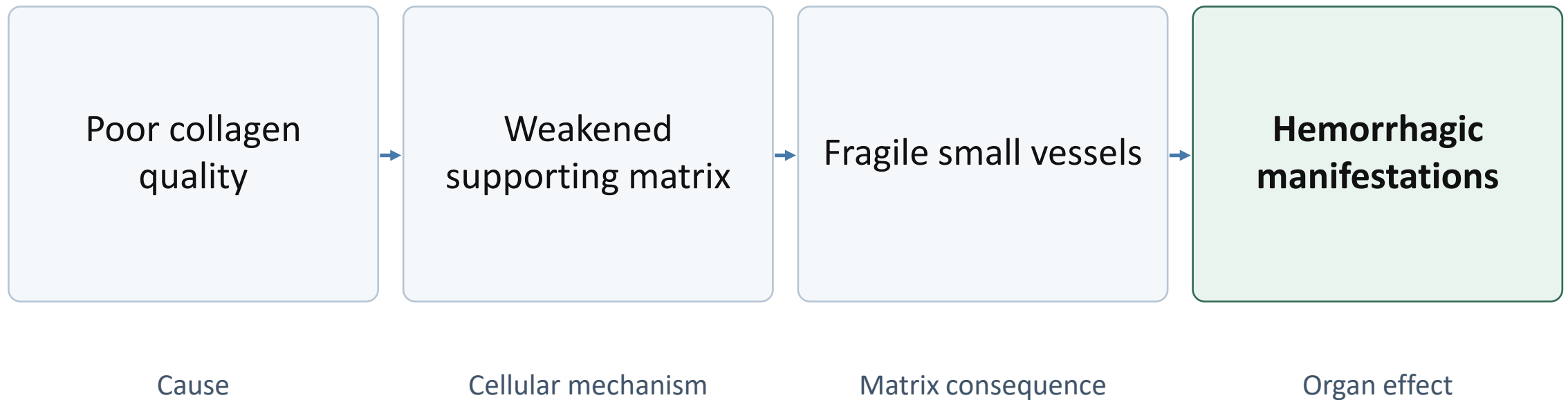
Hydroxyproline helps explain collagen sensitivity

Collagen is especially affected by deficiency.

- Collagen has an exceptionally high hydroxyproline content.
- Its normal structural assembly therefore relies strongly on hydroxylation.
- This helps explain the pronounced effects of vitamin C deficiency on vessels.

Vascular fragility causes hemorrhage

The defect lies in connective-tissue support of small vessels.



Hemorrhagic lesions need a mechanistic interpretation

The clinical endpoint of bleeding has multiple possible origins.

Scurvy-related fragility

- Structural weakness in collagen-containing tissues
- Vessels are poorly supported
- May produce purpura or other bleeding

Other bleeding mechanisms

- Platelet problems may disrupt hemostasis
- Coagulation abnormalities may impair clot formation
- Scurvy is not established by bruising alone

Tissue map of scurvy-related bleeding

Figure 9.27 links several anatomic sites to deficient collagen.

Gums

Poor vessel support and
gingival bleeding

Skin

Connective-tissue vessel
fragility

Periosteum and joints

Hemorrhagic effects
around skeletal tissues

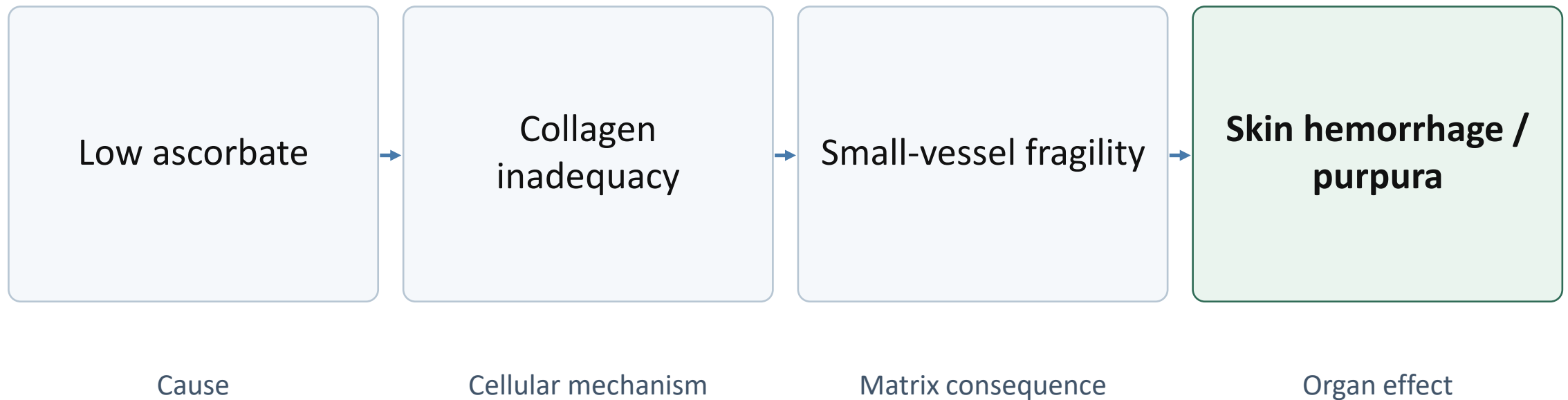
Gingival hemorrhage is a local expression of matrix failure

The gum is a clinically accessible connective-tissue surface.

- Vitamin C deficiency produces weak collagen-dependent vessel support.
- Gingival bleeding fits the generalized hemorrhagic mechanism.
- Assess the dietary context rather than treating the gingival finding in isolation.

Cutaneous purpura reflects loss of microvascular support

An apparently dermatologic feature can originate in nutrient deficiency.



Periosteal and joint manifestations follow the same defect

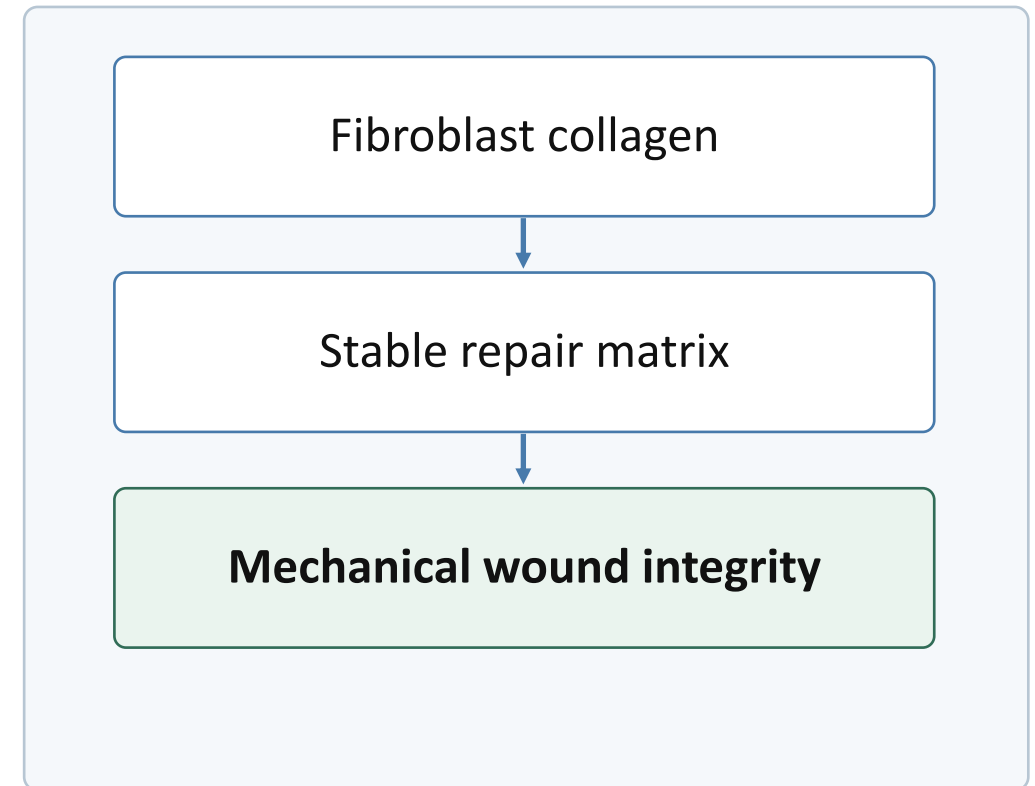
Connective tissues around the skeleton are vulnerable.

- Figure 9.27 identifies periosteum and joints among affected sites.
- Hemorrhage can accompany deficient tissue support in these locations.
- This connects bone-related symptoms with the systemic vascular phenotype.

Wound healing depends on viable collagen deposition

Repair needs newly assembled extracellular matrix.

- Fibroblasts must produce and secrete sufficiently stable collagen.
- The resulting matrix must resist degradation and mechanical stress.
- Vitamin C deficiency therefore produces defective wound healing.



Repair under adequate versus deficient vitamin C

The contrast follows directly from collagen chemistry.

Adequate status

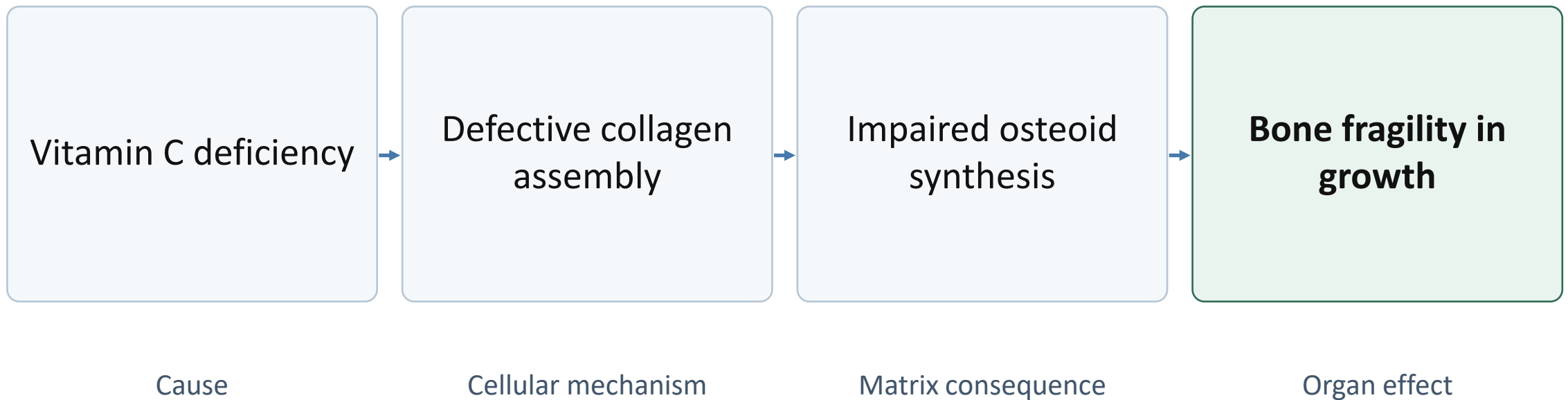
- Procollagen hydroxylated
- New matrix becomes mechanically competent
- Healing tissue gains strength

Deficient status

- Unstable procollagen
- Poor extracellular matrix quality
- Repair is mechanically inadequate

Growing bone depends on osteoid production

The skeletal consequence is most prominent in children.



Osteoid is a collagen-dependent matrix

Bone pathology is not limited to mineral metabolism.

- Figure 9.27 connects ascorbic-acid deficiency to impaired osteoid synthesis.
- Poor matrix formation can lead to osteopenia and fracture.
- This mechanism differs from the mineralization defect emphasized in vitamin D deficiency.

Vitamin C versus vitamin D skeletal defects

Two vitamin deficiencies disrupt different steps of bone formation.

Vitamin C deficiency

- Defective collagen maturation
- Impaired osteoid synthesis
- Bone weakness from abnormal matrix

Vitamin D deficiency

- Impaired calcium–phosphate homeostasis
- Inadequate mineralization of matrix
- Rickets or osteomalacia

Why children show prominent bone disease

Growing skeletons require continuous matrix production.

- Bone growth relies on newly synthesized extracellular matrix.
- Defective osteoid production has conspicuous consequences during growth.
- Bone disease in growing children as a defining scurvy feature.

Interpret bone, bleeding, and healing as a single syndrome

Clinical findings are mechanistically linked, not independent.

Bone disease

Impaired osteoid synthesis

Hemorrhage

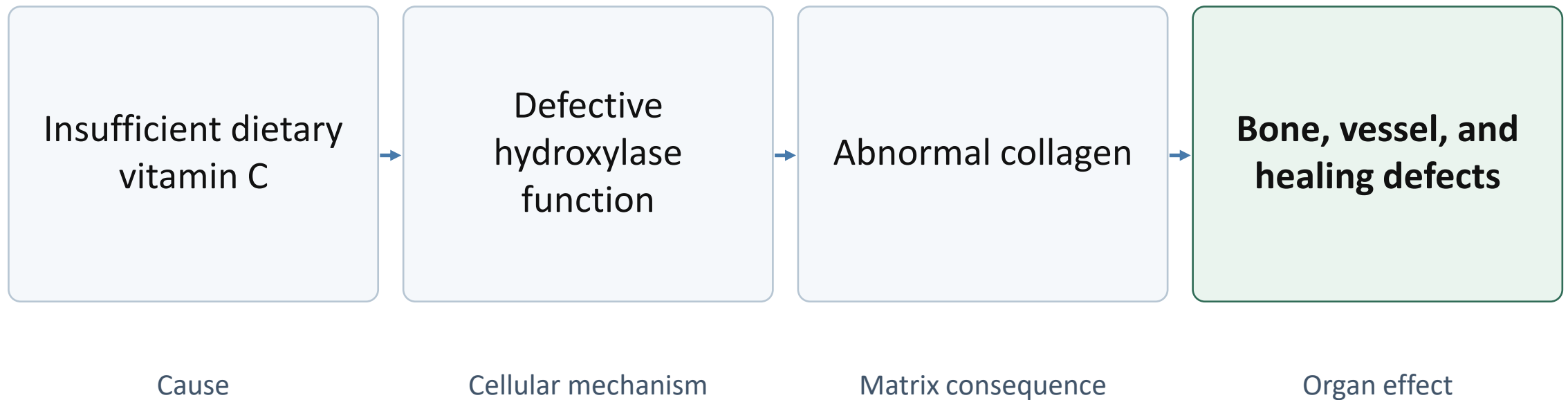
Poor collagen support of
vessels

Repair failure

Inadequate extracellular
matrix integrity

Scurvy is a deficiency-to-phenotype cascade

The disease can be reconstructed from its biochemical lesion.



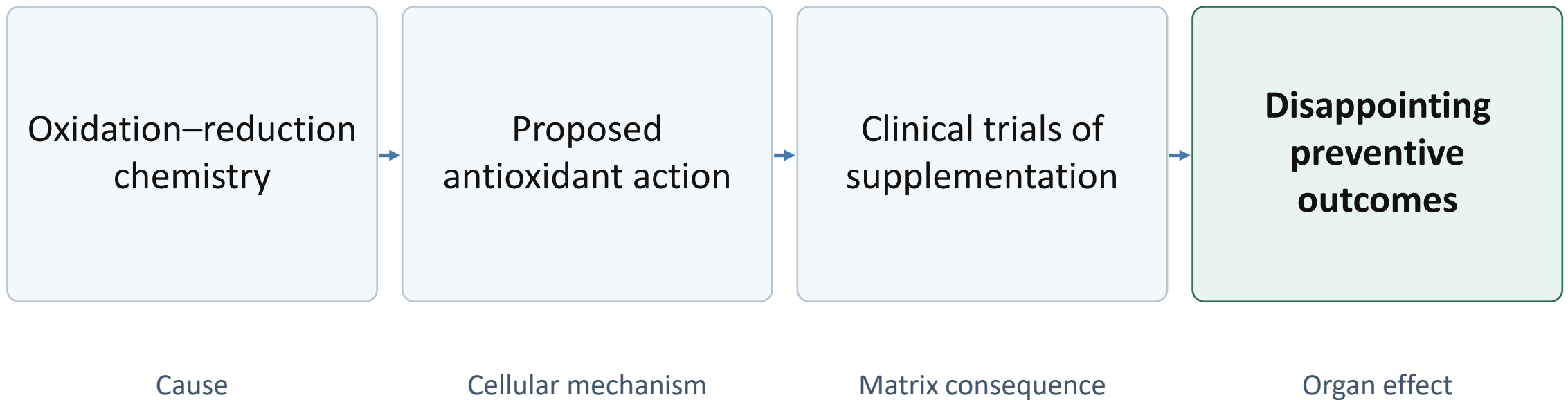
Norepinephrine synthesis is a second established role

Ascorbate participates in catecholamine production.

- Conversion of dopamine to norepinephrine includes hydroxylation.
- Vitamin C as a requirement for that step.
- Collagen dysfunction nevertheless dominates the textbook scurvy phenotype.

Separate biochemical activity from proven clinical benefit

A plausible mechanism does not guarantee an effective intervention.



Antioxidant effects are not equivalent to disease prevention

Robbins treats large clinical claims cautiously.

- Vitamin C has been promoted for antioxidant protection against oxidants.
- Generally disappointing clinical trials based on this rationale.
- Molecular plausibility should not be presented as demonstrated clinical efficacy.

Immune modulation remains distinct from the scurvy mechanism

Biochemical hypotheses and trial results must not be conflated.

- Immune modulation is described as a proposed function of vitamin C.
- Robbins does not claim strong clinical outcomes from large-dose supplementation.
- The established indication of avoiding deficiency should remain distinct.

Deficiency prevention versus megadose claims

These are fundamentally different questions.

Avoiding deficiency

- Maintain a dietary supply
- Support collagen maturation
- Prevent scurvy

Taking megadoses

- Far above normal dietary supply
- Sought for unrelated disease prevention
- Controlled trials have generally disappointed

Common cold: Claimed protection is not established

The textbook distinguishes public perception from trial evidence.

- Controlled clinical studies do not support broad claims that megadoses prevent colds.
- Robbins also does not endorse a clinically important symptom benefit.
- Do not confuse possible small symptom effects with proven prevention.

Cancer prevention: Large-dose trials were negative

Avoid turning an antioxidant hypothesis into a preventive claim.

- No identified protection against cancer development.
- The cited negative conclusion concerns large-dose vitamin C trials.
- This does not negate vitamin C's essential dietary role.

Cardiovascular prevention: Absence of demonstrated benefit

The benefit–risk argument needs outcome evidence.

- Large-dose randomized trials discussed by Robbins were not protective.
- Vitamin C biochemistry alone is insufficient to infer cardiovascular benefit.
- Deficiency prevention and cardiovascular primary prevention are separate endpoints.

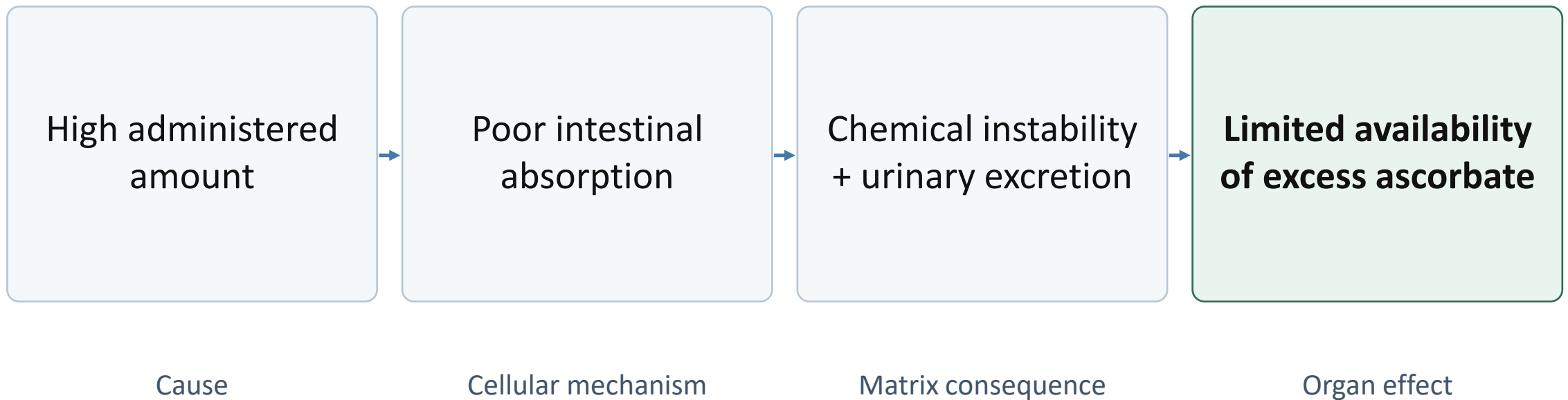
Ocular disease prevention: Negative trial findings

Proposed redox protection has not translated as expected.

- No demonstrated protection against cataracts.
- It similarly reports no prevention of macular degeneration.
- The conclusion refers to high-dose vitamin C trial claims.

Why excess intake has limited physiological availability

Three limiting factors.



Three potential high-dose toxicities

Rare but clinically important concerns.

Iron overload

Possible through increased iron absorption

G6PD deficiency

Hemolytic anemia is a concern

Kidneys

Calcium oxalate stone formation

Iron overload is a potential excess-related hazard

The risk relates to increased iron uptake.

- Possible iron overload in the setting of high vitamin C doses.
- The stated mechanism is increased iron absorption.
- The point is a safety caveat, not an assertion that routine dietary vitamin C causes overload.

G6PD deficiency alters the safety context

A metabolic vulnerability may matter at high exposure.

- Hemolytic anemia in people with G6PD deficiency as a potential toxicity.
- The concern is linked to high-dose vitamin C, not ordinary food consumption.
- Risk descriptions should retain this population-specific qualification.

Calcium oxalate stones are a potential complication

Excess does not become harmless merely because the vitamin is water-soluble.

- Calcium oxalate kidney stones among rare high-dose toxicities.
- Rapid urinary excretion limits availability of excess intake.
- A mechanistic safety discussion should not invent an incidence or a dose threshold.

Dietary adequacy and pharmacologic excess are not interchangeable

Teach the dose-context distinction without inventing cutoffs.

Adequate diet

- Supports normal vitamin-dependent reactions
- Prevents deficiency pathology
- Most ordinary diets provide enough

Very high doses

- Not shown to prevent listed chronic diseases
- Excess availability is constrained
- Rare toxicities remain possible

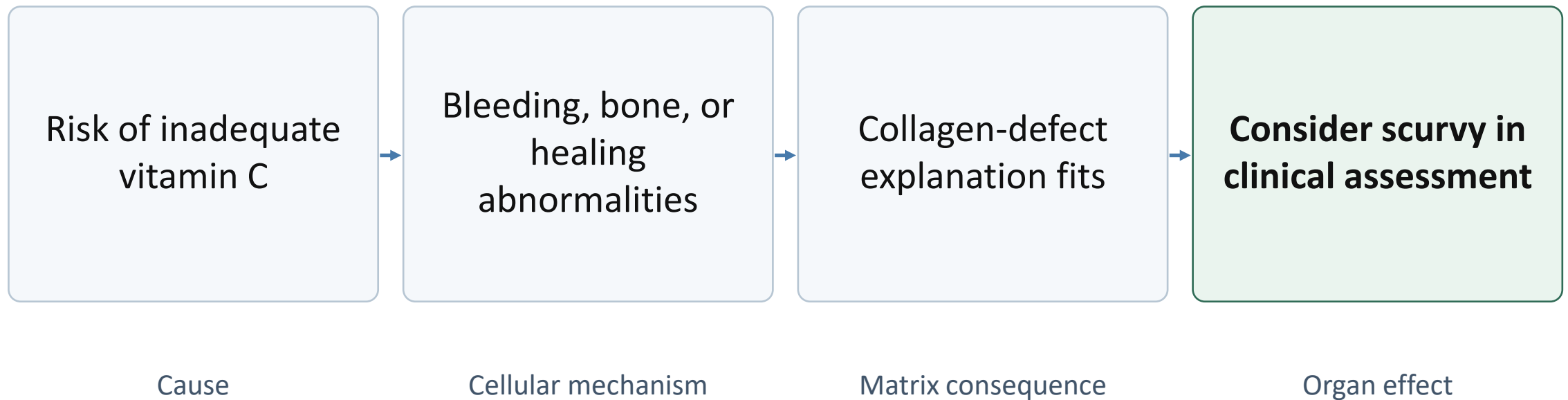
Clinical recognition starts with dietary history

A mechanistic phenotype gains meaning from exposure history.

- Ask whether the diet excludes common vitamin C food sources.
- Consider older age, social isolation, alcohol use disorder, dialysis, or atypical infant feeding.
- Interpret bleeding or poor healing in that nutritional setting.

A diagnostic reasoning pathway for suspected scurvy

Use the source-described pattern without inventing test thresholds.



A bleeding phenotype does not determine its cause

Discriminate tissue fragility from other hemostatic failures.

Clues favoring scurvy

- Constrained dietary vitamin C
- Gingival/skin bleeding with repair defects
- Skeletal manifestations, especially in children

What still needs evaluation

- Alternative vascular disorders
- Platelet-related causes of bleeding
- Other coagulation disturbances

Case: An older adult with bleeding gums

Hypothetical teaching vignette

Clinical context

- An older person living alone reports a highly restricted diet.
- There is recurrent gingival bleeding and unusually poor wound healing.
- Question: Which shared tissue-level defect best connects the two findings?

Reasoning target

Explain the finding using
the vitamin C → collagen
→ tissue consequence
pathway.

Answer is in speaker notes

Case: An infant receiving restricted formula

Hypothetical teaching vignette

Clinical context

- An infant receives evaporated-milk-based feeding without added vitamin C.
- Bone-related symptoms and bleeding are observed.
- Question: Why can both skeletal and vascular tissues be involved?

Reasoning target

Explain the finding using the vitamin C → collagen → tissue consequence pathway.

Answer is in speaker notes

Case: Hemorrhage in a dialysis patient

Hypothetical teaching vignette

Clinical context

- A patient receiving dialysis has an unusual dietary pattern.
- Skin hemorrhages and poor healing raise concern for nutrient deficiency.
- Question: Which source-listed exposure prompts nutritional assessment?

Reasoning target

Explain the finding using
the vitamin C → collagen
→ tissue consequence
pathway.

Answer is in speaker notes

Case: A request for high-dose vitamin C

Hypothetical teaching vignette

Clinical context

- A healthy adult requests megadose supplementation to prevent cancer.
- They invoke antioxidant activity as the main rationale.
- Question: What conclusion is supported by Robbins?

Reasoning target

Explain the finding using
the vitamin C → collagen
→ tissue consequence
pathway.

Answer is in speaker notes

Case: G6PD deficiency and vitamin C excess

Hypothetical teaching vignette

Clinical context

- A person with known G6PD deficiency asks about very high vitamin C doses.
- They believe a water-soluble nutrient cannot cause harm.
- Question: Which source-specific safety issue warrants discussion?

Reasoning target

Explain the finding using the vitamin C → collagen → tissue consequence pathway.

Answer is in speaker notes

Scurvy can be understood at three levels

Link the lesion from molecule to patient.

Molecular

Inadequate prolyl and lysyl
hydroxylation

Tissue

Unstable matrix with low
tensile strength

Clinical

Hemorrhage, healing
defects, and growing-bone
disease

Final clinical synthesis

The highest-yield causal relations are these:

- Vitamin C is essential in the human diet because humans cannot synthesize it.
- Deficiency prevents normal collagen maturation, secretion, and matrix strength.
- Scurvy combines vascular bleeding, defective repair, and skeletal disease in growing children.
- High-dose supplementation has not demonstrated the broad preventive benefits claimed for it.

Source and figure provenance

The lecture is based on the supplied primary Robbins source.

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Chapter 9: Environmental and Nutritional Diseases — “Vitamin C (Ascorbic Acid).”
- Figure 9.27, “Causes and consequences of impaired collagen formation due to vitamin C deficiency” (not reproduced).
- Additional context: Table 9.9 and the chapter section “Vitamin Deficiencies.”