

Chronic Kidney Disease

A clinicopathologic framework

Progressive nephron loss · convergent renal scarring · systemic consequences

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Learning goals

- Define CKD and distinguish azotemia from clinical uremia.
- Explain why nephron loss promotes further glomerular and interstitial injury.
- Recognize the four main chronic renal lesions and relate them to causes.
- Connect loss of renal function to major systemic manifestations.

CKD is a final common pathway

Persistent nephron loss from diverse renal injuries

A clinical syndrome, not one etiologically uniform histologic disease.

Glomerular · Tubulointerstitial · Vascular injury

Clinical definition of CKD

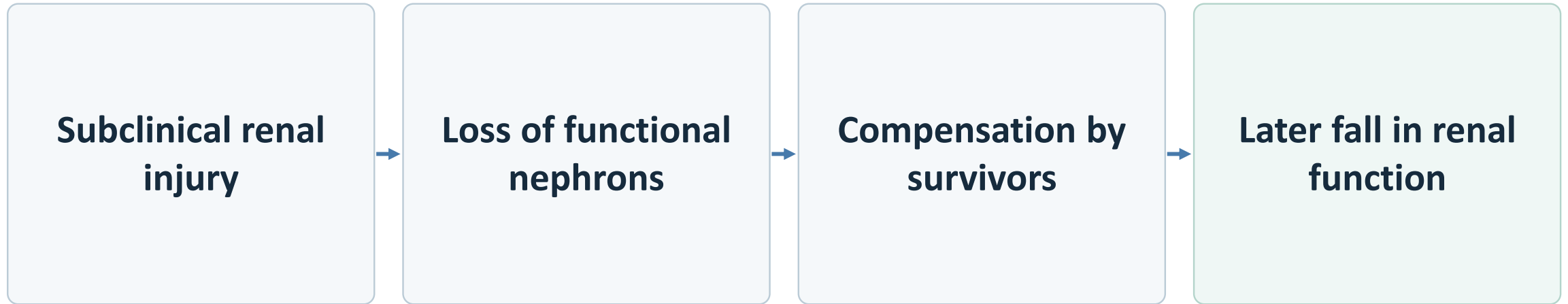
Filtration criterion

- Persistently diminished GFR
- $<60 \text{ mL/min/1.73 m}^2$
- Duration ≥ 3 months

Kidney-damage criterion

- Or persistent albuminuria
- Evidence of chronic glomerular damage
- May occur before severe filtration loss

Renal reserve delays recognition



Kidney function may remain clinically inconspicuous until considerable damage has accumulated.

Four compartments converge in advanced CKD

Glomerulus

Glomerulosclerosis

Tubules

Tubular atrophy

Interstitium

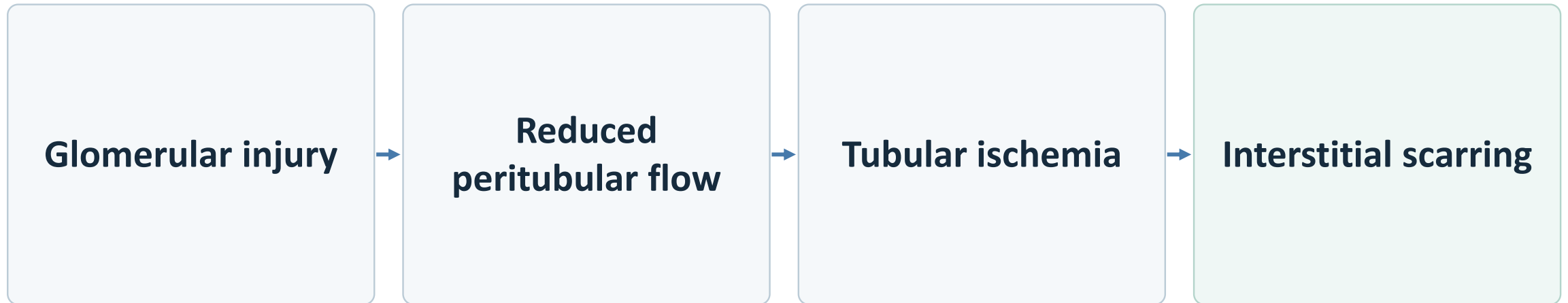
Fibrosis

Vessels

Arterio-/arteriosclerosis

Damage initiated in one compartment eventually affects the others.

Cross-talk makes CKD self-amplifying



The reciprocal pathway also matters: Tubular damage can worsen glomerular injury.

AKI and CKD: Distinguish the time course

Acute kidney injury

- Rapid decline in GFR
- Hours to days
- Acute fluid/electrolyte imbalance

Chronic kidney disease

- Persistent dysfunction
- At least 3 months
- Progressive nephron loss; Often initially silent

Azotemia is not the same as uremia

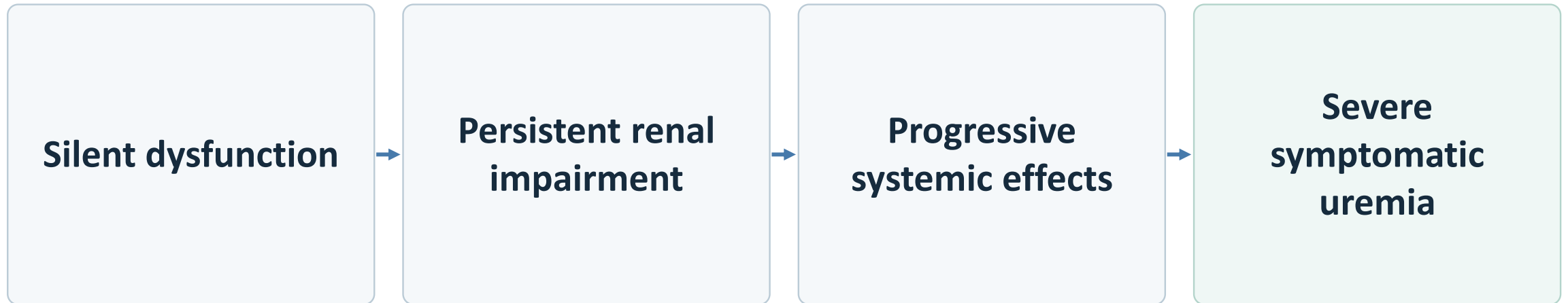
Azotemia

- Elevated BUN and creatinine
- Biochemical signal of reduced filtration
- May be prerenal, renal, or postrenal

Uremia

- Clinical syndrome of advanced renal dysfunction
- Excretory plus metabolic/endocrine effects
- May involve nerves, heart, gastrointestinal tract

The clinical continuum of CKD



Severity depends on both remaining renal function and associated complications.

The etiologic map of CKD

Metabolic

Diabetic nephropathy

Vascular

Nephrosclerosis and ischemia

Glomerular

Chronic glomerular disease

Tubulointerstitial

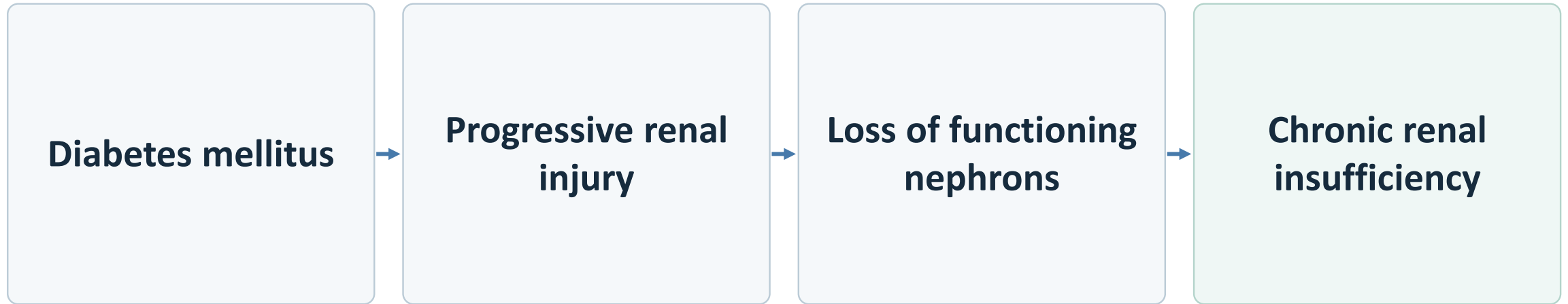
Chronic pyelonephritis / injury

Hereditary and developmental disorders can also reduce effective nephron mass.

Diabetes and vascular disease dominate

- Diabetic and vascular kidney disease as the most common CKD antecedents.
- Both may damage several renal compartments over time.
- Histologic scarring is often nonspecific by the time renal failure is advanced.

Diabetic nephropathy can culminate in CKD



Diabetic nephropathy is described as a leading cause of chronic kidney failure; Detailed diabetic lesions belong to its own chapter.

Vascular narrowing creates ischemic injury

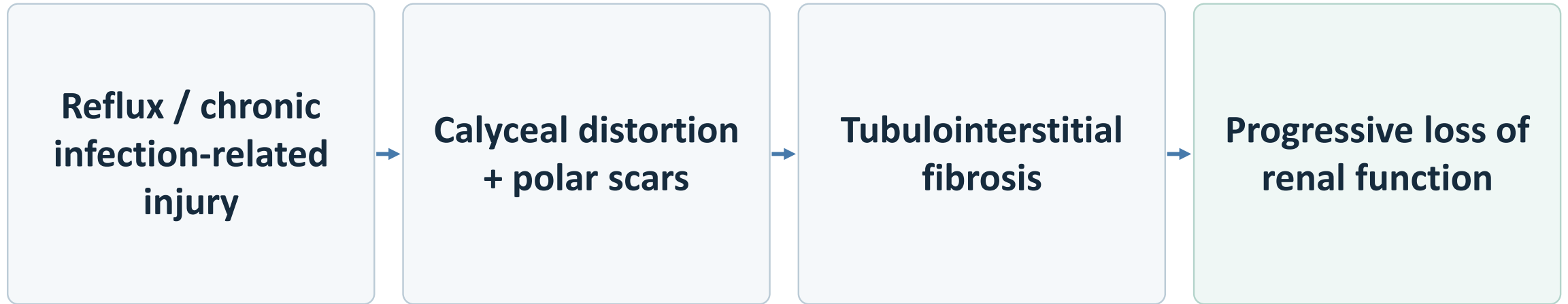


Nephrosclerosis illustrates how vascular disease ultimately becomes a pan-renal lesion.

Glomerular diseases may end in sclerosis

- Different primary or systemic glomerular insults may destroy nephron units.
- Progressive segmental and global glomerulosclerosis can follow.
- The remaining nephrons experience compensatory hemodynamic stress.

Chronic pyelonephritis produces an alternate pattern



Calyceal damage differentiates chronic pyelonephritis from many other scar-forming renal diseases.

Congenital nephron deficit can matter lifelong

Agenesis

- Unilateral renal agenesis
- Solitary kidney undergoes compensatory enlargement
- Adaptive sclerosis may develop

Hypoplasia

- True renal hypoplasia
- Reduced developmental nephron mass
- Associated with later CKD susceptibility

Cystic disorders can also cause chronic loss

- Some inherited cystic disorders progressively replace renal parenchyma.
- Autosomal dominant polycystic kidney disease is an important CKD cause.
- Acquired cystic changes may occur after end-stage kidney disease; Distinguish cause from consequence.

Primary lesion predicts initial clues

Glomerular

Proteinuria / hematuria

Tubular

Polyuria / nocturia

Interstitial

Tubular dysfunction, chronic scarring

Vascular

Hypertension / ischemic injury

These clues become less specific as multi-compartment scarring accumulates.

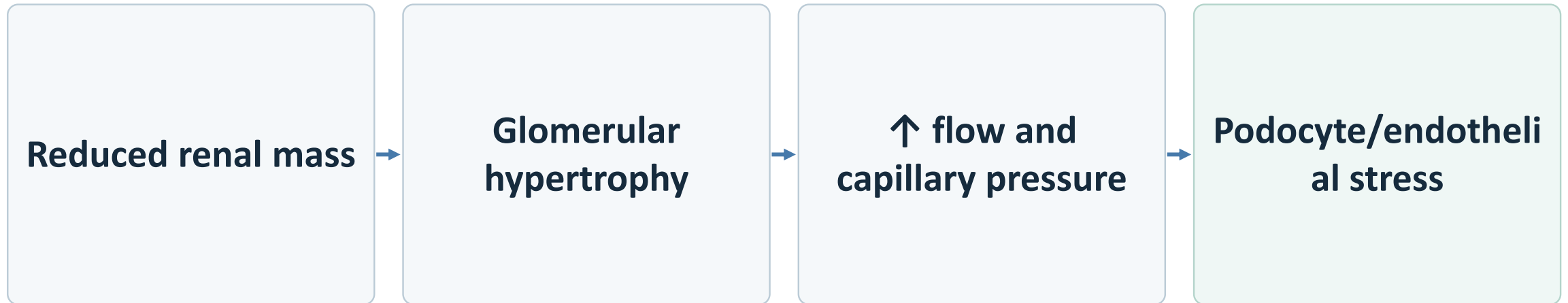
Adaptive hyperfiltration: Short-term benefit, long-term cost

Fewer nephrons → higher workload per surviving nephron

Compensatory filtration helps preserve total GFR but exposes remaining glomeruli to injury.

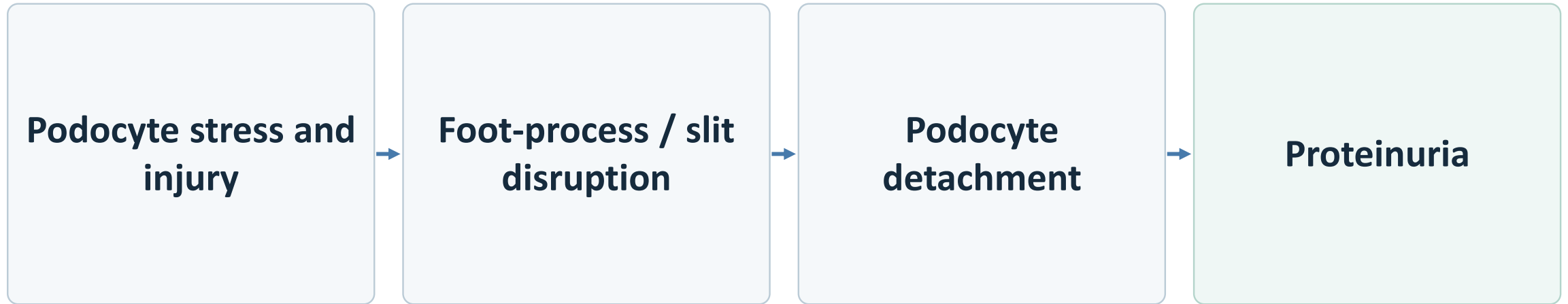
Functional adaptation does not replace lost nephron mass.

From nephron loss to glomerular hypertension



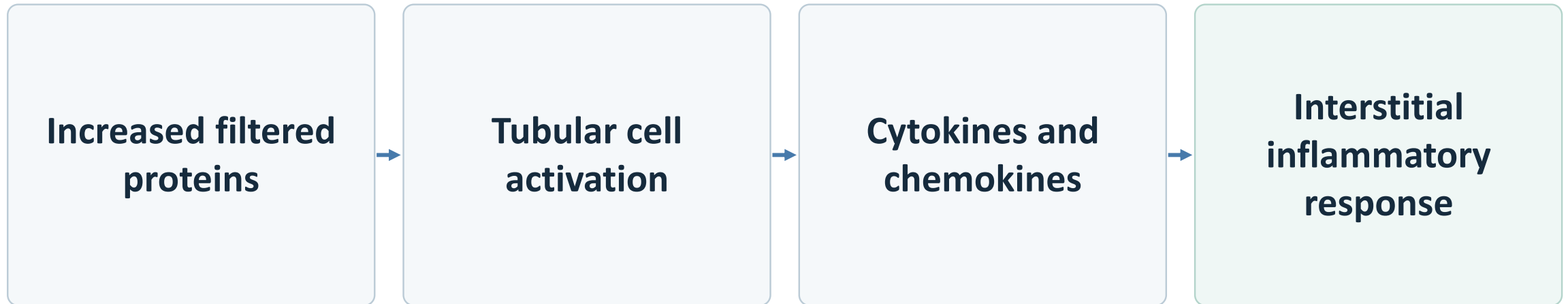
This sequence is particularly evident in adaptive FSGS after reduced nephron number.

Podocyte loss becomes a protein leak



Podocytes have limited capacity for replication; Depleted podocyte coverage is difficult to restore.

Proteinuria can injure tubules



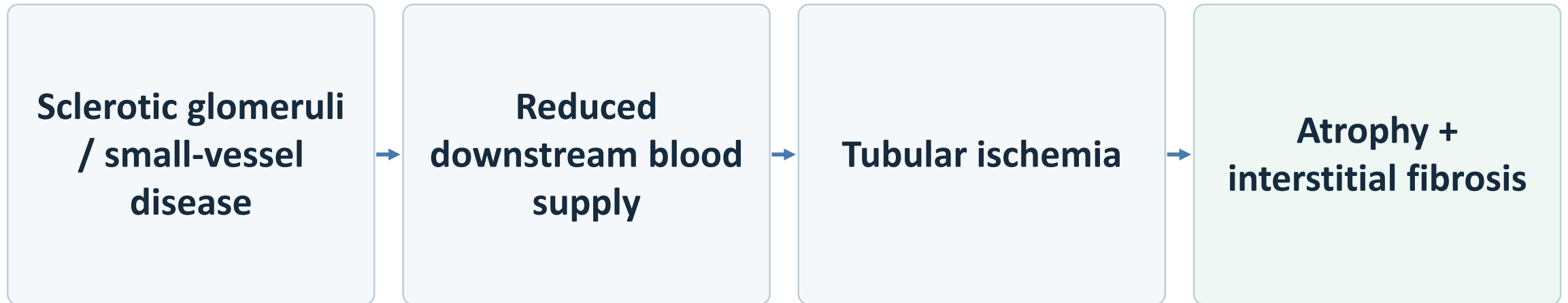
Protein is both a clinical marker of glomerular damage and a potential participant in tubular injury.

Interstitial fibrosis completes a vicious circle



Fibrosis reduces functional parenchyma, which sustains maladaptive responses in surviving nephrons.

Peritubular hypoperfusion accelerates damage



Reduced peritubular perfusion links vascular and glomerular lesions to tubular destruction.

Two pathologic engines of progression

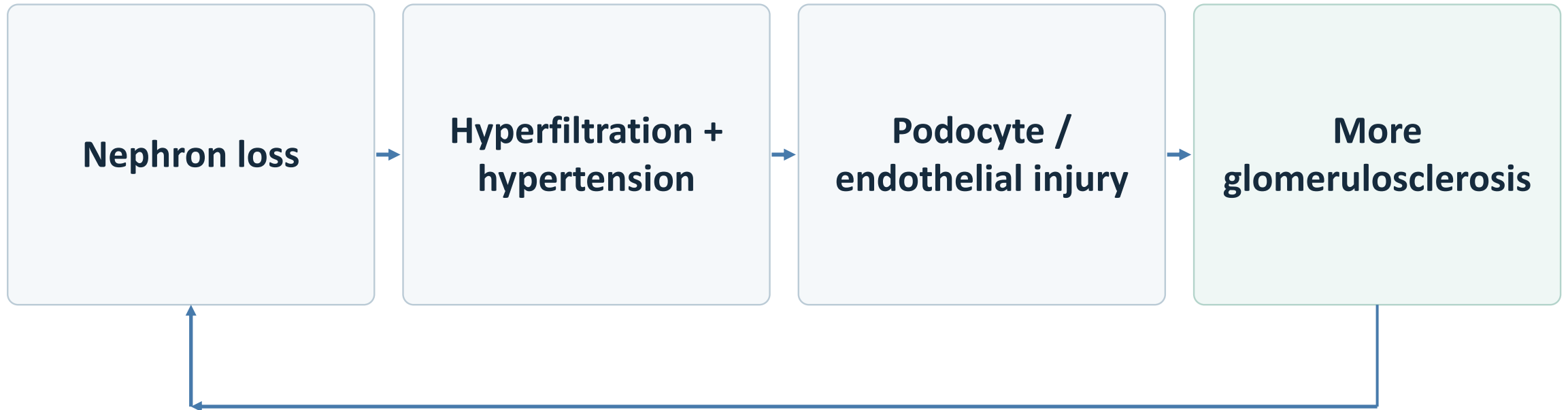
Glomerular compartment

- Glomerulosclerosis
- Segmental → global obsolescence
- Progressive decline in filtration surface

Tubulointerstitial compartment

- Tubulointerstitial fibrosis
- Tubular dropout and fibrous replacement
- Strong association with functional decline

The feed-forward cycle of chronic injury



The cycle can persist even when the initial insult is no longer active.

Why reduced nephron number has consequences

- Adaptive glomerular hypertrophy sustains filtration initially.
- Increased intraglomerular pressure contributes to protein leakage and sclerosis.
- Further nephron loss increases stress on the remaining units.
- This shared mechanism applies across otherwise different renal diseases.

Podocyte injury versus mesangial scarring

Initiating structural failure

- Podocyte injury
- Foot-process effacement or loss
- Filtration barrier permeability ↑

Established chronic lesion

- Sclerosing response
- Mesangial matrix accumulation
- Segmental then global glomerular obliteration

What drives interstitial scarring?

Ischemia

Reduced capillary supply

Inflammation

Persistent interstitial immune response

Protein stress

Tubular activation by filtered proteins

Matrix deposition

Fibroinflammatory remodeling

These are interacting processes, not four independent disease entities.

Advanced CKD has a nonspecific histologic quartet

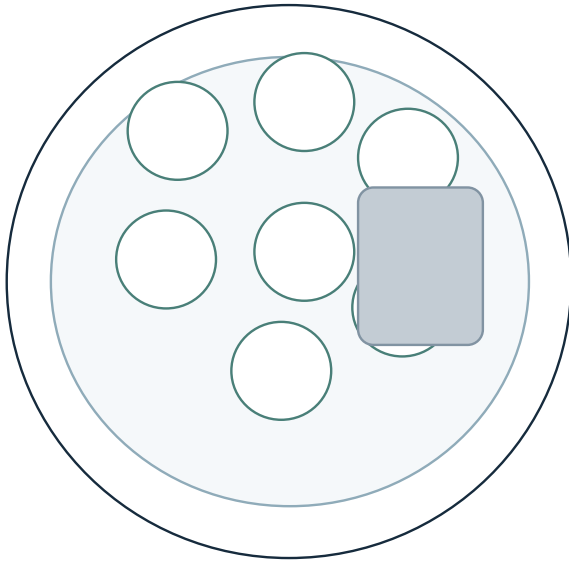
**Glomerulosclerosis · Interstitial fibrosis · Tubular atrophy
· Arteriosclerosis**

The pattern shows chronicity and loss of nephron mass; It may not identify the initiating etiology.

Interpret morphology alongside the clinical and imaging history.

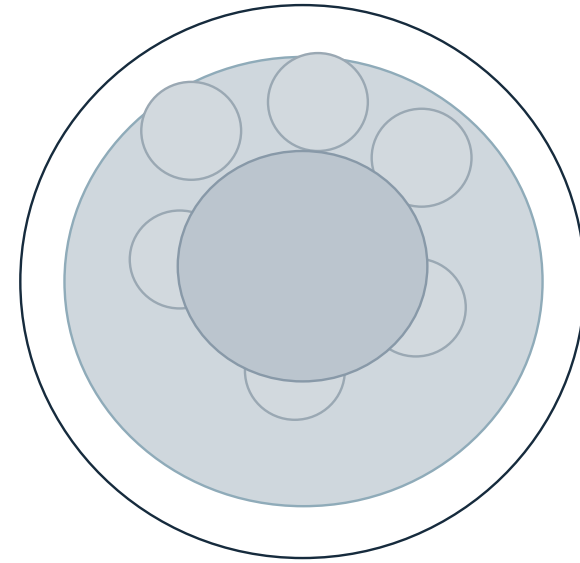
Glomerulosclerosis: Segmental versus global

Segmental glomerulosclerosis



A portion of the tuft is scarred

Global glomerulosclerosis



Entire tuft is scarred

Schematic only — capillary tuft profiles simplified; Not a photomicrograph.

Glomerular scarring can evolve

**Compensatory
enlargement**



**Epithelial/endothelial
injury**



Matrix deposition



**Segmental then
global sclerosis**

Sclerosis represents chronic structural remodeling rather than an intact filtration barrier.

What tubular atrophy implies

Tubular epithelial loss

Reduced functional epithelium

Atrophic tubules

Smaller or simplified profiles

Tubular dropout

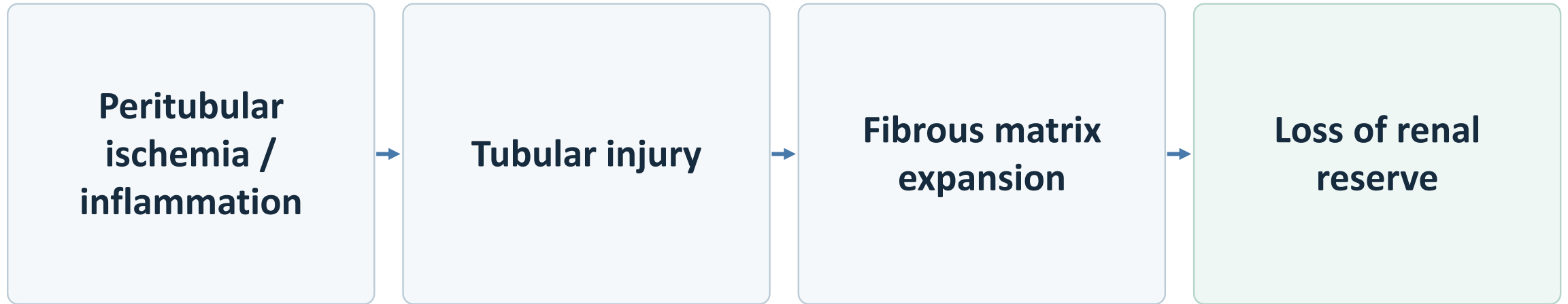
Loss of renal epithelial units

Surrounding fibrosis

Replacement of parenchyma by matrix

Atrophy is one of the reproducible endpoints of chronic kidney damage.

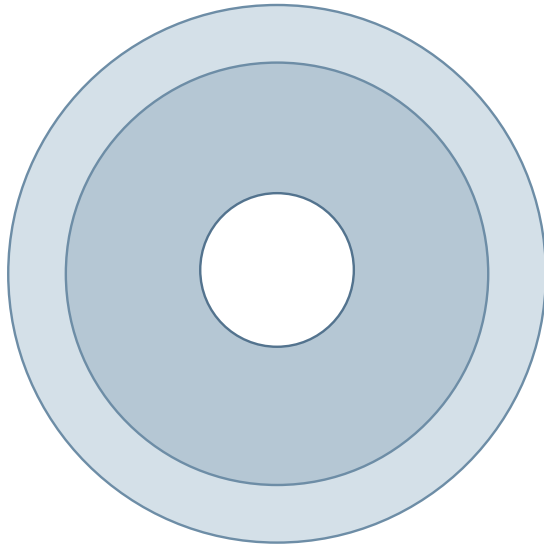
Interstitial fibrosis tracks functional injury



The extent of tubulointerstitial damage often correlates more closely with decline in function than glomerular injury.

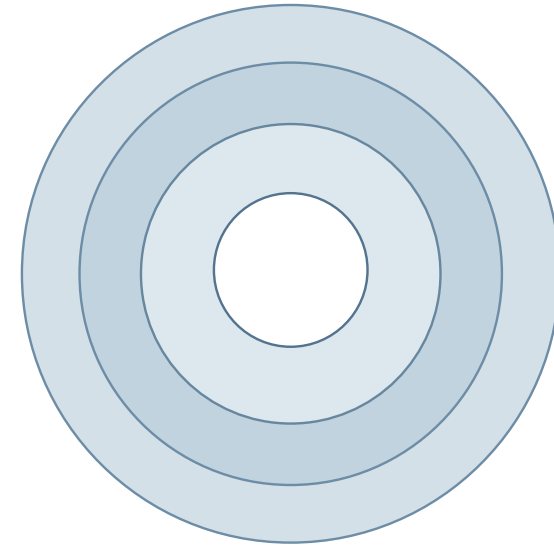
Renal vessel lesions: Hyaline and fibroelastic

Hyaline arteriosclerosis



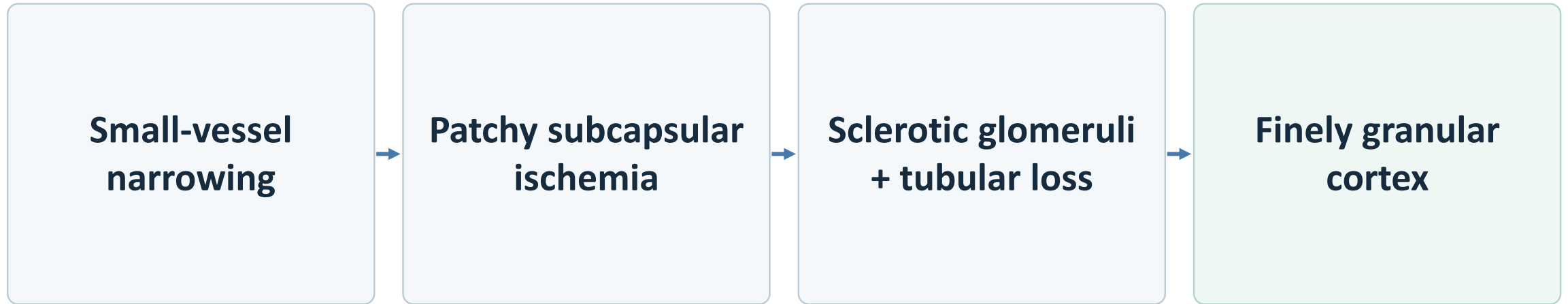
Hyaline wall thickening; Lumen narrowed

Fibroelastic arterial thickening



Arterial intimal / medial remodeling

Surface granularity reflects microscopic scars



This is a characteristic gross correlate of nephrosclerosis, not a unique sign of every CKD cause.

Fine granularity versus coarse polar scars

Vascular pattern

- Nephrosclerosis
- Fine, even cortical granularity
- Patchy cortical ischemic atrophy

Reflux / infection pattern

- Chronic pyelonephritis
- Coarse corticomedullary scars
- Blunted and distorted underlying calyces

Acquired atrophy versus true hypoplasia

Chronically damaged kidney

- Acquired chronic scarring
- Fibrosis and distorted architecture
- Often uneven cortical scarring

Underdeveloped kidney

- True congenital hypoplasia
- Reduced number of renal lobes / pyramids
- No acquired scars by definition

Anatomical diagnosis needs context

Glomerular biopsy

Sclerosis: Extent and distribution

Tubulointerstitial biopsy

Fibrosis / atrophy burden

Vascular biopsy

Wall thickening / ischemic patterns

Imaging / history

Size, scars, calyces, chronology

The shared chronic endpoint can obscure the primary renal disease.

Morphologic interpretation: Common pitfalls

- Do not infer the original cause of CKD from global sclerosis alone.
- Adaptive segmental sclerosis can complicate a primarily nonglomerular disorder.
- Coarse scars with deformed calyces suggest chronic pyelonephritis.
- Renal ischemia may produce combined glomerular, tubular, and interstitial lesions.

CKD may be silent before uremia



An absence of early symptoms does not establish normal renal structure or function.

GFR and albuminuria answer different questions

Filtration

- GFR
- Functional filtration capacity
- May decline gradually with nephron loss

Damage marker

- Albuminuria
- Persistent glomerular barrier damage
- May be present while filtration is relatively preserved

Urine findings can suggest where injury began

Albuminuria

Glomerular filter injury

Hematuria

Possible glomerular disease

Polyuria / nocturia

Tubular dysfunction

Mild proteinuria + scars

Possible tubulointerstitial injury

No single urine finding specifies the full chronic renal histologic pattern.

Acute azotemia requires another differential

Prerenal physiology

- Prerenal azotemia
- Renal hypoperfusion without primary tissue injury
- May reverse after perfusion correction

Postrenal obstruction

- Postrenal azotemia
- Obstruction distal to the kidney
- May reverse with relief of obstruction

Case: Albuminuria before severe azotemia

A patient has persistent albuminuria but preserved filtration capacity on routine assessment.

- Does the source definition permit CKD?
- Which compartment is likely generating the urinary finding?
- Why are serial measurements important?

Teaching interpretation

Yes—persistent albuminuria qualifies in the Robbins definition; It suggests filtration-barrier injury, and chronicity must be established.

Case: Solitary kidney and later proteinuria

An adult born with one kidney develops proteinuria after years of preserved renal function.

- What was initially compensatory?
- What hemodynamic stress emerges?
- What secondary glomerular lesion is plausible?

Teaching interpretation

Glomerular hypertrophy and hyperfiltration; Intraglomerular hypertension; Adaptive segmental sclerosis.

Fluid and electrolyte manifestations

Water deficit

Dehydration

Salt and water retention

Edema

Potassium handling

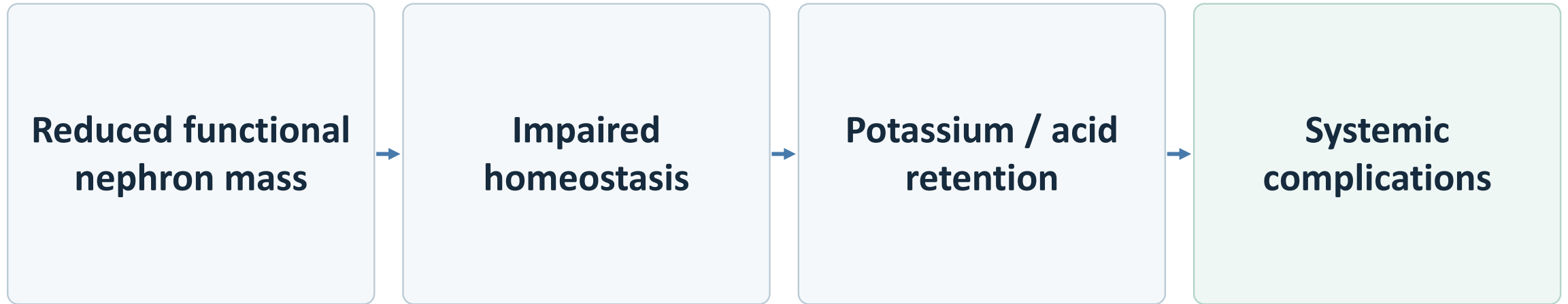
Hyperkalemia

Acid handling

Metabolic acidosis

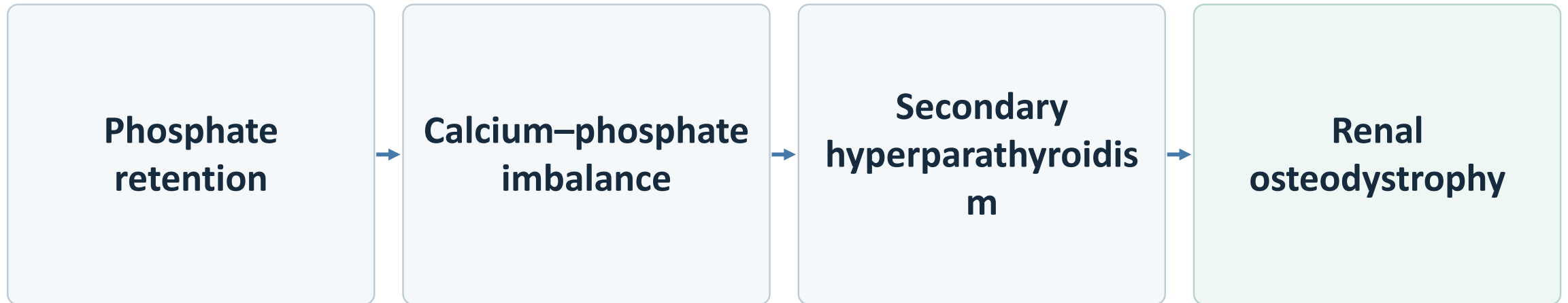
The clinical balance varies with residual tubular function and stage of disease.

Hyperkalemia and acidosis reflect excretory failure



Hyperkalemia and metabolic acidosis are major CKD manifestations listed Table 20.1.

Mineral imbalance affects bone



Robbins groups hyperphosphatemia, hypocalcemia, parathyroid changes, and skeletal disease together.

Hematologic complications of CKD

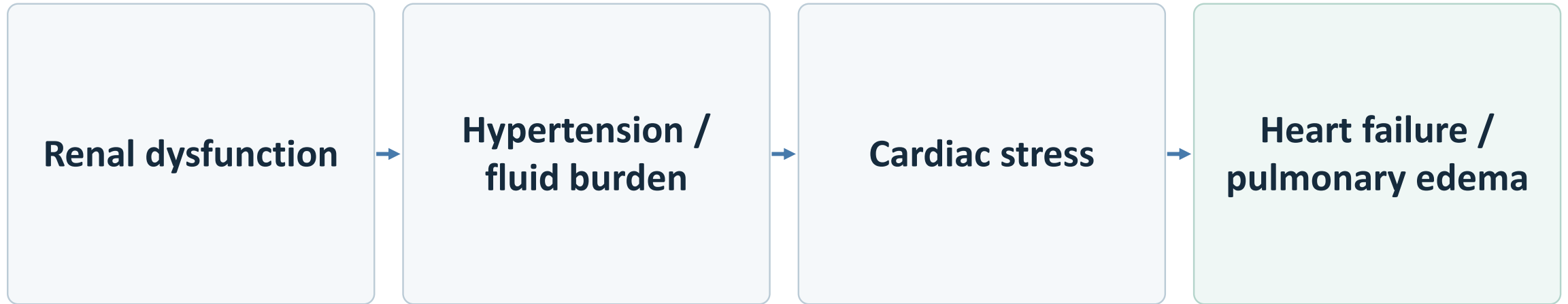
Red-cell consequence

- Anemia
- Common hematologic manifestation
- Associated with chronic renal dysfunction

Hemostatic consequence

- Abnormal bleeding
- Bleeding is listed among uremic manifestations
- Can occur despite lack of severe thrombocytopenia

Cardiovascular complications reinforce CKD burden



Cardiomyopathy and congestive heart failure are also prominent manifestations.

Uremic pericarditis is an advanced consequence

- Uremic patients may develop fibrinous pericardial inflammation.
- It reflects systemic effects of severe renal dysfunction.
- Do not interpret pericarditis as a defining finding of early CKD.

Gastrointestinal manifestations of uremia

Nausea

Systemic uremic symptoms

Vomiting

Metabolic / gastrointestinal effects

Mucosal inflammation

Esophagitis, gastritis, colitis

Bleeding

Potential gastrointestinal complication

GI symptoms should be integrated with biochemical and other systemic findings.

Neuromuscular manifestations of uremia

Myopathy

Muscular dysfunction

Neuropathy

Peripheral nerve involvement

Encephalopathy

Central nervous system dysfunction

Clinical implication

Multisystem disease, not isolated azotemia

These complications indicate consequences beyond the renal parenchyma.

The skin may signal advanced dysfunction

- Pruritus is listed among dermatologic manifestations.
- Sallow discoloration and dermatitis can occur.
- Cutaneous findings are supportive clinical clues rather than specific CKD tests.

Systemic effects: Four key domains

Cardiopulmonary

Hypertension · edema · heart failure

Hematologic

Anemia · abnormal bleeding

Mineral–bone

Hyperphosphatemia · osteodystrophy

Neurologic / GI

Neuropathy · nausea · encephalopathy

CKD is a systemic illness once renal excretory and endocrine functions fail.

APOL1 risk is ancestry-associated, not deterministic

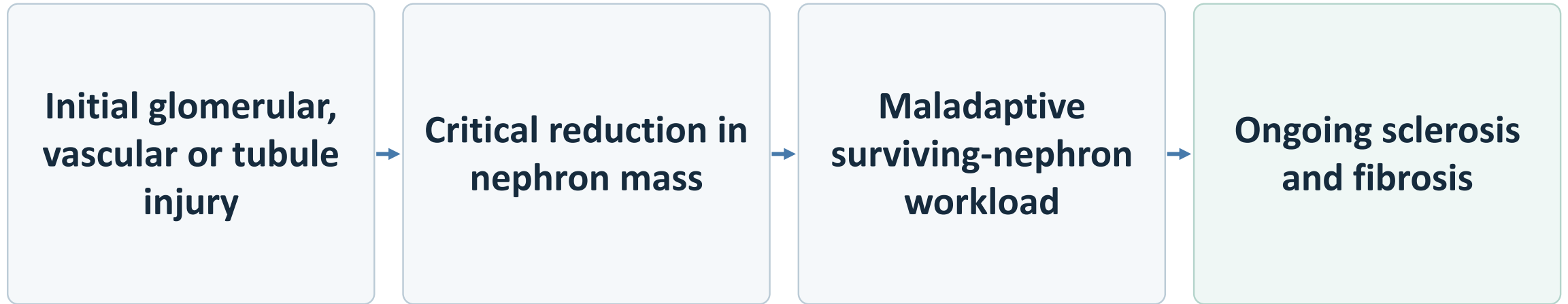
Textbook association

- Population association
- Higher CKD frequency in some groups with African ancestry
- High-risk APOL1 variants may contribute

Interpretation limit

- Individual inference
- Ancestry is not a renal diagnosis
- Genetic susceptibility does not replace cause-specific evaluation

Why CKD can progress after the initiating insult



The source emphasizes shared, secondary mechanisms once substantial nephron loss has occurred.

Renin–angiotensin system blockade: A mechanism target

- Inhibition of the renin–angiotensin system in progressive glomerulosclerosis.
- Reducing intraglomerular hypertension can interrupt maladaptive injury.
- This is a pathophysiologic principle, not an individualized prescribing algorithm.

Case: Coarse scars and nocturia

Imaging shows asymmetrically scarred kidneys with blunted calyces. The patient has nocturia and longstanding hypertension.

- Which chronic injury pattern best fits?
- Why might nocturia develop?
- Which microscopy findings would support the impression?

Teaching interpretation

Chronic pyelonephritis / reflux nephropathy; Impaired concentrating ability; Tubular atrophy, interstitial fibrosis and chronic inflammation.

Case: Fine cortical granularity and ischemic damage

A kidney has a finely granular cortical surface; Arterioles show hyaline thickening and narrowed lumens.

- Identify the dominant initiating compartment.
- Explain the cortical granularity.
- Predict the other compartments affected.

Teaching interpretation

Vascular nephrosclerosis; Patchy ischemic cortical scars; Secondary glomerulosclerosis and tubular/interstitial injury.

Case: Multisystem uremia

A patient with longstanding renal disease develops pruritus, nausea, anemia and pulmonary edema.

- Is azotemia alone sufficient to describe the syndrome?
- Which body systems are represented?
- What unifies these manifestations?

Teaching interpretation

No; This is systemic uremic illness involving dermatologic, gastrointestinal, hematologic and cardiopulmonary systems due to advanced renal dysfunction.

Integrating pathology with clinical signals

Sclerosis + proteinuria

Consider glomerular injury and adaptation

Atrophy + nocturia

Consider tubular dysfunction

Arteriolar narrowing

Consider chronic ischemia

Fibrosis + declining GFR

Chronic renal parenchymal loss

Use the full pattern; Avoid single-finding diagnosis.

Diagnostic interpretation: What CKD does and does not say

Syndrome-level conclusion

- CKD establishes
- Chronic kidney dysfunction or damage
- Risk of progressive loss of renal function
- Need to assess systemic effects

Etiologic questions remain

- CKD alone does not establish
- The initiating histologic diagnosis
- Whether injury is active or burned out
- A single universal gross appearance

Five source-grounded conclusions

- CKD is a shared outcome of chronic renal insults and nephron loss.
- Surviving glomeruli hyperfilter; Adaptive injury can accelerate sclerosis.
- Tubulointerstitial fibrosis strongly relates to loss of renal function.
- Glomerular, tubular, interstitial and vascular lesions converge.
- Severe CKD produces multisystem uremic manifestations.

Self-assessment: Locate the lesion

A progressively scarred kidney shows glomerulosclerosis, tubular atrophy, interstitial fibrosis and arterial thickening.

- Can the cause be assigned by the quartet alone?
- Which lesion may best correlate with functional decline?
- Name one route by which vascular disease causes glomerular scarring.

Teaching interpretation

No. Tubulointerstitial damage is often particularly informative. Vascular lumen narrowing causes ischemia and secondary glomerular/tubular injury.

Primary teaching sources

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 20, The Kidney.

Clinical Manifestations of Renal Diseases + Table 20.1 (pp. 814–815).

Mechanisms of Progression in Glomerular Diseases (pp. 822–823); adaptive FSGS (pp. 831–832).

Nephrosclerosis (pp. 851–852); Chronic Kidney Disease (p. 855).

Chronic pyelonephritis and developmental anomalies: adjacent chapter context.