

Mechanisms of Progression in Glomerular Diseases

Nephron loss · maladaptive glomerular responses · interstitial scarring

Mechanistic pathology lecture

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

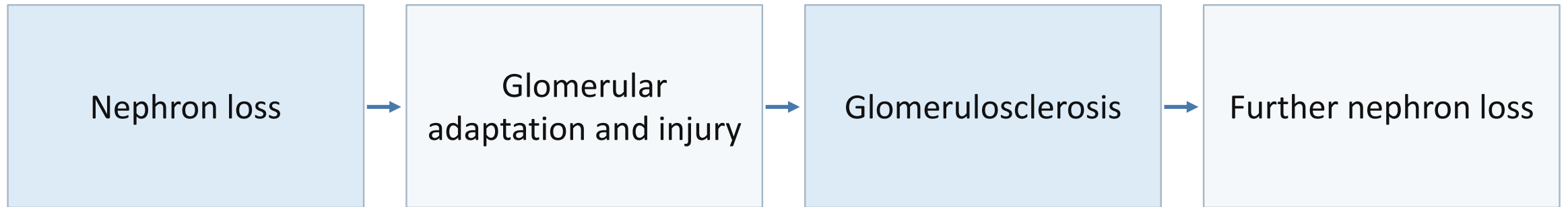
Learning objectives

- Distinguish the initiating disease from self-sustaining progression mechanisms.
- Trace nephron loss to adaptive hyperfiltration and segmental scarring.
- Explain the parallel development of proteinuria and tubulointerstitial fibrosis.
- Relate structural changes to progressive reduction in glomerular filtration.

Progression can outlast the initiating insult

- Primary immune or nonimmune injury removes functional nephrons.
- Remaining nephrons compensate, initially supporting filtration.
- The compensatory state itself can injure surviving glomeruli.
- Secondary damage may therefore persist after the original activity wanes.

Two convergent pathways to renal failure



The progressive cycle becomes partly independent of the initiating cause.

What determines the outcome of initial injury?

- Severity of the renal damage at presentation.
- Nature and persistence of the inciting antigen or insult.
- Host immune status and age.
- Genetic susceptibility and renal reserve.

The classic low-GFR progression observation

- Progression once nephron loss reduces GFR to roughly 30%–50% of normal.
- This is a historical pathophysiologic observation, not a diagnostic CKD-stage cutoff.
- The central lesson is the contribution of secondary injury once renal reserve is markedly depleted.
- Do not interpret the range as a deterministic threshold for an individual patient.

The two key chronic lesions

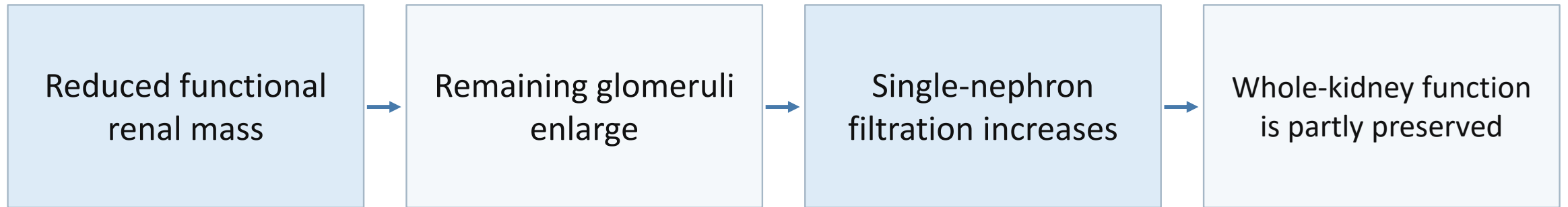
Glomerulosclerosis	Tubulointerstitial fibrosis
Glomerular capillary tufts become scarred	Tubules atrophy amid interstitial inflammation and collagenous scarring
Promotes filtration barrier failure and nephron dropout	Disrupts the tissue supporting tubular and vascular function
May appear after glomerular or nonglomerular disease	Occurs in immune as well as nonimmune kidney disorders

These lesions coexist and reinforce loss of functioning nephrons.

Nephron loss: The initiating common denominator

- Nephron destruction decreases the total functional filtering mass.
- Surviving units must accommodate increased functional demand.
- Compensation does not recreate the lost nephron population.
- An adaptive response can become a source of progressive damage.

An initially useful adaptation

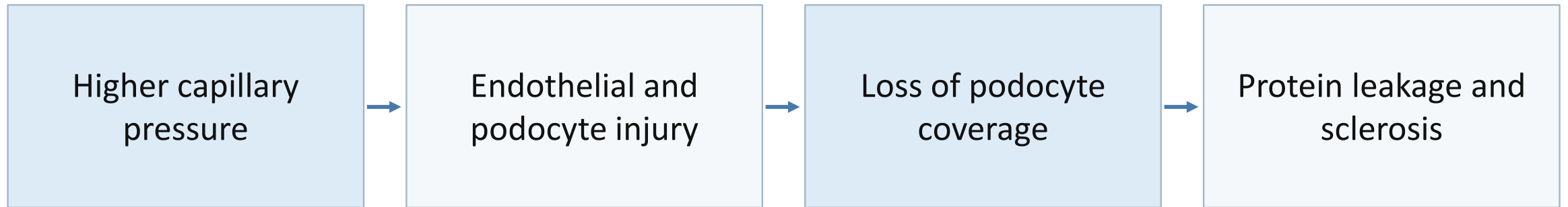


Early functional compensation can conceal structural vulnerability.

Adaptation becomes maladaptation

- Surviving glomeruli are exposed to increased blood flow.
- Their filtration and transcapillary hydraulic pressure may rise.
- Glomerular hypertension can coexist with systemic hypertension.
- Prolonged mechanical stress contributes to endothelial and podocyte injury.

Hemodynamic stress reaches the filtration barrier



An increased workload has a cost when glomerular cells cannot compensate indefinitely.

Glomerular hypertrophy: Benefit and liability

- Compensatory enlargement initially offsets loss of filtering surface.
- The enlarged tuft experiences altered flow and pressure.
- Limited podocyte replication restricts long-term adaptation.
- A mismatch develops between tuft surface area and effective podocyte coverage.

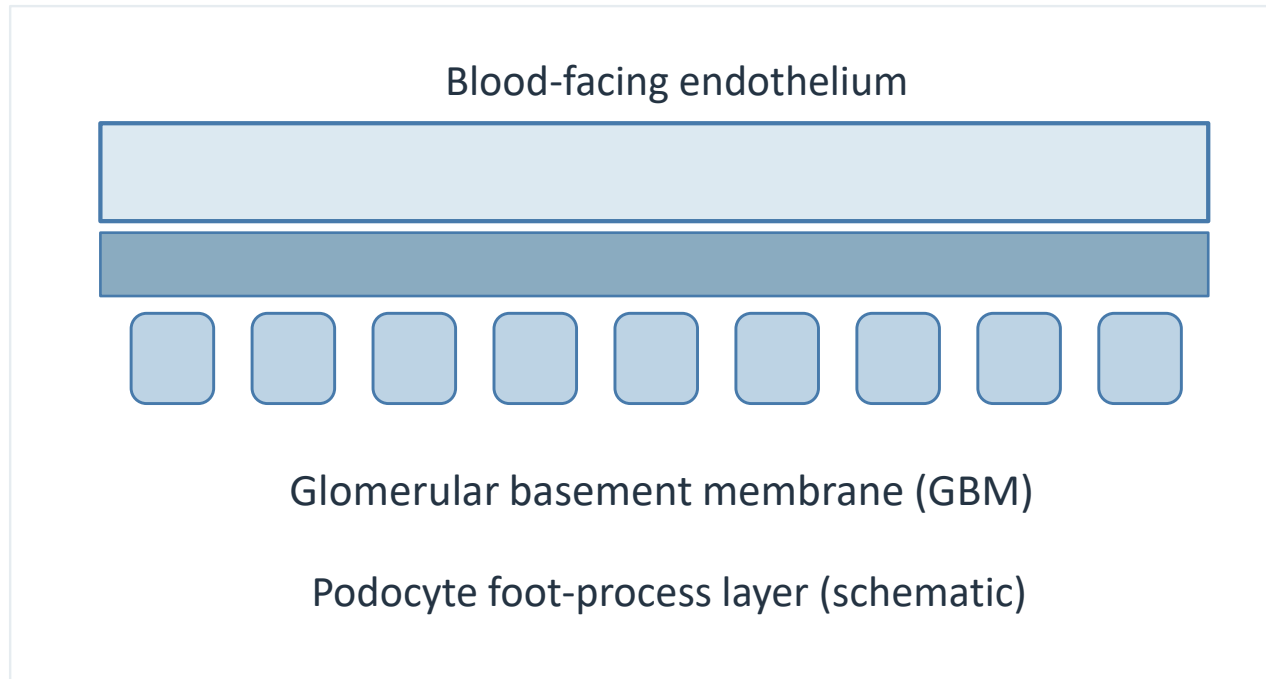
Intraglomerular $\neq$ systemic hypertension

- Intraglomerular hypertension is elevated pressure within the filtering capillary tuft.
- Systemic arterial hypertension may aggravate, but does not define, this condition.
- A patient may have injurious glomerular hemodynamics before obvious systemic hypertension.
- The two pressure disturbances can act together to accelerate damage.

Why podocytes are a limiting resource

- Podocytes form the visceral epithelial layer of the glomerular filter.
- Their foot processes and slit diaphragms support selective permeability.
- They have limited capacity for cell replacement after loss.
- Surviving podocytes can enlarge, but cannot indefinitely cover an expanding tuft.

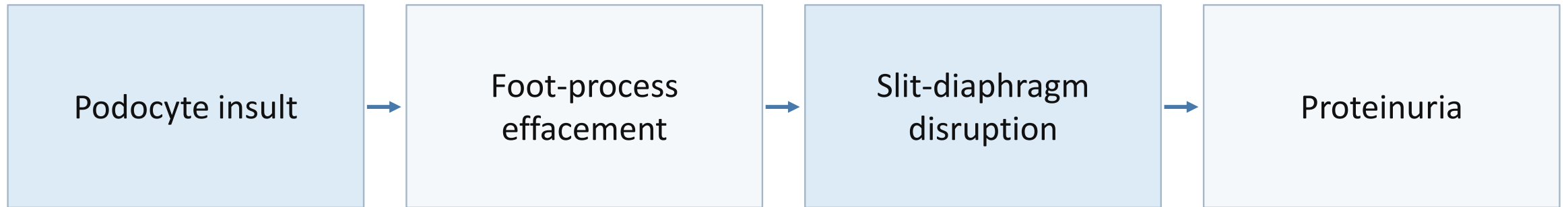
Normal filtration barrier: Conceptual layers



Schematic, not a histologic specimen

- Endothelium lies on the blood-facing side of the glomerular basement membrane.
- Podocyte processes line the urinary-facing side.
- An intact slit diaphragm contributes to protein restriction.

Podocyte injury: From structure to leakage



Barrier failure can precede established light-microscopic sclerosis.

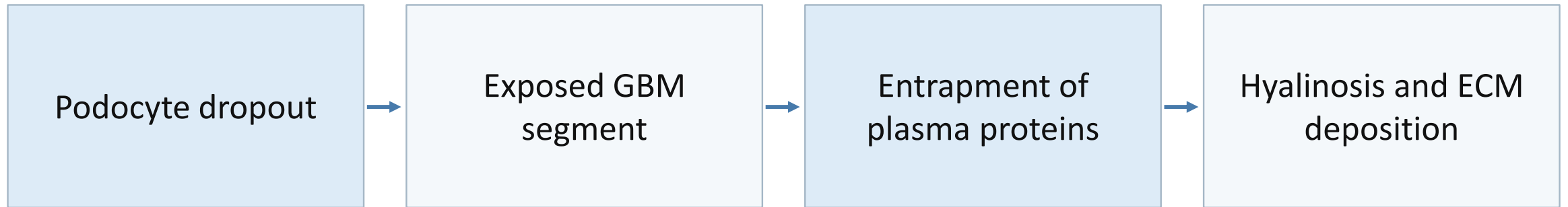
Foot-process effacement is an injury response

- Flattening and simplification replace the normal interdigitating arrangement.
- The slit-diaphragm architecture becomes disorganized.
- Protein permeability increases when barrier integrity is compromised.
- Effacement alone does not specify the initiating disease.

Detachment is more consequential than effacement

- Podocytes may lose adhesion to the underlying glomerular basement membrane.
- Some cells detach or die, leaving exposed basement membrane segments.
- Podocyte depletion can outstrip compensation by surviving cells.
- Denuded segments become foci for leakage, hyalinosis and segmental scarring.

Loss of coverage establishes a scar-prone focus



A local podocyte deficit may initiate segmental sclerosis.

The extracellular matrix is the scar substrate

- Extracellular matrix (ECM) increases within areas of chronic injury.
- Hyalinosis accompanies entrapment of circulating plasma proteins.
- Increased matrix replaces normal capillary tuft architecture.
- Progressive ECM accumulation reduces functional filtering surface.

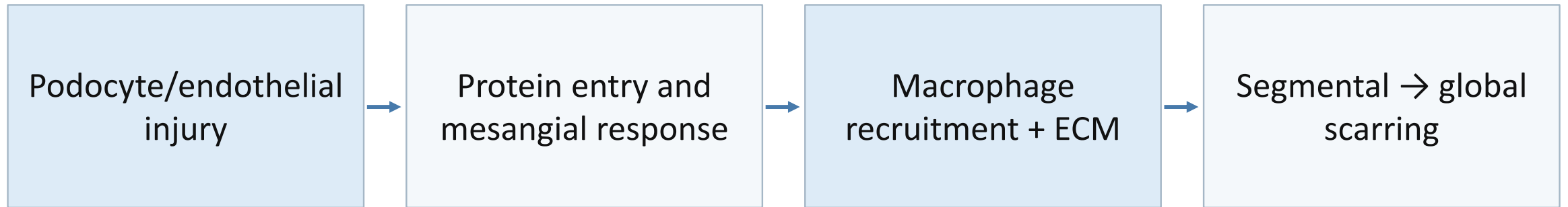
Mesangial participation in chronic remodeling

- Filtered proteins may accumulate within the mesangial matrix.
- Mesangial cell proliferation can accompany this accumulation.
- Injured and activated cells generate inflammatory and profibrotic mediators.
- Mesangial responses help convert focal injury into structural scar.

Macrophages amplify glomerular injury

- Macrophages are recruited during progressive glomerular remodeling.
- They contribute inflammatory mediators to a damaged capillary tuft.
- Their presence accompanies ECM accumulation and sclerosis in the adaptive FSGS sequence.
- The cell infiltrate is part of an amplifying injury response, not necessarily the original cause.

A progressive glomerulosclerotic lesion



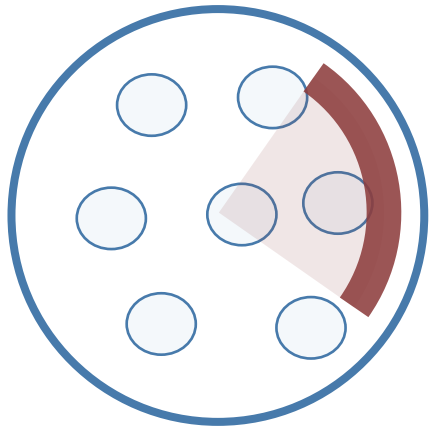
Arrows represent a simplified conceptual sequence, not an exclusive pathway.

Focal, segmental, global: Precise meanings

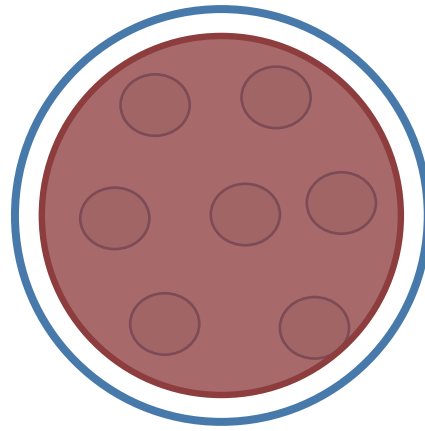
Term	Morphologic meaning
Focal	Only a subset of glomeruli is affected
Segmental	Only part of an individual glomerular tuft is scarred
Global	The entire tuft of a glomerulus is sclerotic
Diffuse	Many or most sampled glomeruli are affected

A focal segmental pattern describes distribution—not by itself the cause.

Segmental versus global sclerosis



Segmental: Part of tuft



Global: Entire tuft

Original schematic of lesion distribution

- A segmental lesion affects only a portion of a glomerular tuft.
- Advanced sclerosis may replace an entire tuft.
- These are conceptual patterns—
not substitute light micrographs.

Secondary FSGS is a shared morphologic outcome

- FSGS-like scars develop after many different renal injuries.
- The original pathology need not be a primary podocytopathy.
- Glomerulosclerosis may occur even when the initial disease is nonglomerular.
- Histologic pattern and underlying causal mechanism must be distinguished.

Primary versus adaptive FSGS

Primary diffuse podocytopathy	Adaptive FSGS
Initiating event: intrinsic or circulating-factor podocyte injury	Initiating context: insufficient effective nephron mass
Diffuse podocyte injury may cause marked proteinuria	Hemodynamic overload promotes progressive podocyte loss
Scar formation follows loss of podocyte coverage	Scar formation follows hypertrophy and glomerular hypertension

Both pathways can culminate in segmental sclerosis, but their clinical context differs.

Acquired reduction in nephron mass

- Advanced kidney disorders can progressively deplete functioning nephrons.
- Vascular disease is one setting in which loss of renal mass promotes adaptive FSGS.
- After nephron dropout, unaffected glomeruli become exposed to higher workload.
- Secondary scarring can continue despite inactivity of the original lesion.

Congenital and developmental nephron deficit

- Unilateral renal agenesis provides a classic example of reduced nephron reserve.
- Renal dysplasia can produce a comparable structural deficit.
- The solitary or relatively preserved kidney undergoes compensatory hypertrophy.
- Over time, susceptible glomeruli may develop maladaptive sclerosis.

Reflux nephropathy and progression

- Reflux-related parenchymal injury can reduce functional renal tissue.
- Surviving glomeruli experience compensatory hemodynamic load.
- Adaptive segmental glomerulosclerosis may appear in remaining viable areas.
- Ongoing nephron loss can establish a vicious cycle.

Obesity-related adaptive glomerular injury

- Effective nephron mass may be insufficient relative to increased body mass.
- Compensatory glomerular enlargement and hyperfiltration follow.
- Chronic glomerular hemodynamic stress can damage podocytes.
- This mechanism provides a nonimmune route to secondary FSGS.

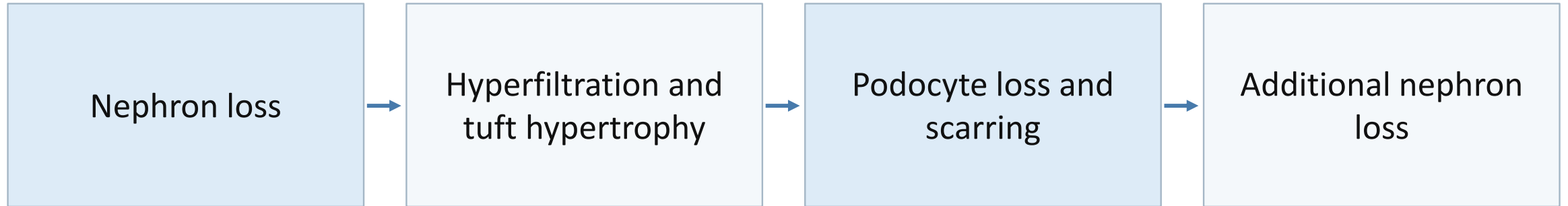
Experimental subtotal nephrectomy: The model

- After major renal mass reduction, surviving glomeruli enlarge and hyperfilter.
- Initial whole-animal renal function is partly sustained.
- Proteinuria and segmental scars subsequently appear.
- Later global sclerosis and uremia illustrate the self-amplifying cycle.

Limitations of the adaptive animal model

- Subtotal-nephrectomy models support a causal hemodynamic mechanism.
- They do not imply identical kinetics in all human glomerulopathies.
- Underlying diagnoses, comorbidities and susceptibilities remain important.
- Avoid extrapolating exact progression rates from the model.

The nephron-loss feedback loop



The output of one cycle becomes the input of the next.

Why progression can involve tubules early

- Glomerular and tubular compartments are physiologically coupled.
- Sclerosed glomeruli alter perfusion of their downstream tubular segments.
- Heavy filtrate protein loads can directly activate tubular epithelium.
- Interstitium and microvasculature are exposed to sustained secondary injury.

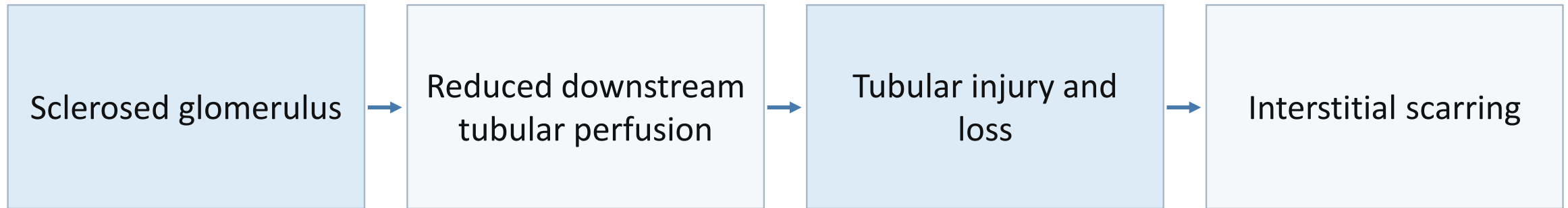
Tubulointerstitial fibrosis is not a bystander

- Tubular injury and interstitial inflammation accompany many glomerulonephritides.
- Interstitial fibrosis occurs in both immune and nonimmune disease.
- Diabetic nephropathy is a prominent nonimmune-associated example.
- The fibrosing compartment itself contributes to declining renal function.

Why tubulointerstitial damage predicts function

- The extent of interstitial injury often correlates better with functional decline than the glomerular lesion alone.
- Tubules support essential nephron function beyond filtration.
- Microvascular compromise and fibrosis affect the surviving tissue field.
- Glomerular morphology alone can underestimate overall chronic damage.

Ischemic tubular injury after glomerular scarring



A damaged upstream glomerulus can injure its associated tubule.

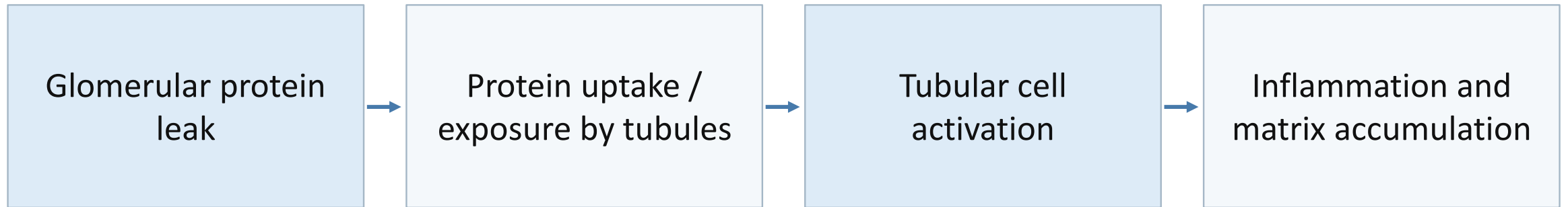
Peritubular capillaries as a vulnerable network

- Reduced peritubular capillary supply limits delivery of oxygen and nutrients.
- Microvascular insufficiency intensifies tubular ischemic stress.
- Fibrosis and tissue distortion can coexist with vascular rarefaction.
- Tubular and interstitial injury are therefore linked to renal microcirculation.

Interstitial inflammation compounds ischemia

- Acute or chronic interstitial inflammatory infiltrates can surround injured tubules.
- Inflammation may be triggered by glomerular disease and local tubular activation.
- Cell-derived signals perpetuate the fibrogenic tissue response.
- Ischemia and inflammation can operate simultaneously.

The proteinuria-to-fibrosis bridge



Proteinuria is both a marker of filtration-barrier damage and a possible mediator of tubule injury.

Proteinuria: More than a laboratory finding

- Filtered proteins increase tubular epithelial exposure to bioactive substances.
- Some filtered proteins directly injure or activate tubular cells.
- Injured cells release signals into the adjacent interstitium.
- Persistent protein leakage may therefore amplify loss of renal tissue.

Protein-associated tubular stressors

Filtered component	Potential injury mechanism
Complement products	Inflammatory and cytotoxic signaling
Cytokines and immunoglobulins	Direct tubular activation and immune signaling
Hemoglobin iron	Oxidative or toxic cellular stress
Lipid moieties / oxidized proteins	Cellular stress with inflammatory activation

These as possible contributors; Effects vary by molecular context.

Tubular activation involves adhesion molecules

- Protein-exposed tubular epithelial cells alter their activation state.
- Cell-surface adhesion molecules increase interactions with inflammatory cells.
- The response links epithelial injury to interstitial recruitment.
- Tubules become active participants in renal inflammation.

Cytokines and chemokines recruit amplifiers

- Activated tubular cells release proinflammatory cytokines.
- Chemokines promote movement of leukocytes into injured tissue.
- Ongoing leukocyte-derived mediators magnify local damage.
- This signaling helps sustain chronic interstitial inflammation.

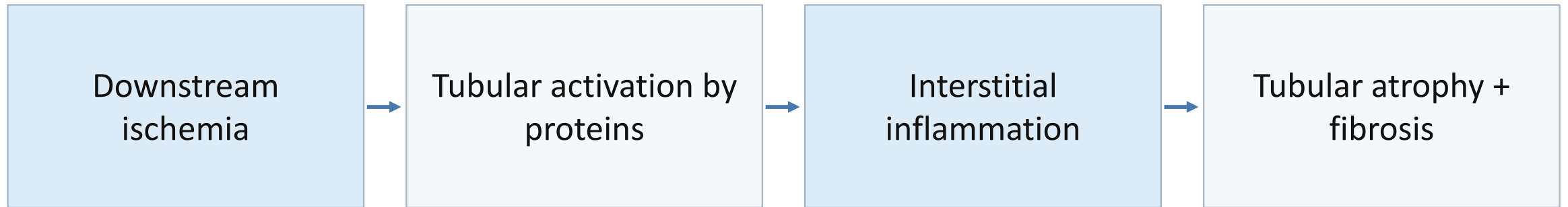
Growth-factor signaling promotes fibrosis

- Activated tubular cells also release growth factors.
- Glomerular and interstitial inflammatory cells provide additional mediators.
- Profibrotic signals favor deposition and remodeling of extracellular matrix.
- Persistent signaling converts injury into a structural scar.

TGF- β and other mediators in matrix deposition

- TGF- β , connective tissue growth factor and fibroblast growth factor as important in chronic glomerular matrix accumulation.
- Platelet-derived growth factor participates in mesangial cell proliferation.
- These pathways connect sustained injury to cell activation and ECM deposition.
- The textbook does not provide a quantitative hierarchy among these mediators.

Parallel injury routes into the interstitium



Multiple mechanisms converge on the same chronic tubulointerstitial phenotype.

Glomerular versus interstitial injury

Glomerular compartment	Tubulointerstitial compartment
Capillary tuft hypertrophy / hyperfiltration	Tubular epithelial stress and ischemia
Podocyte loss and segmental sclerosis	Interstitial inflammation and matrix deposition
Increasing protein permeability	Loss of supporting microvasculature
Reduced filtering-nephron mass	Loss of functional tubular tissue

These are coupled processes rather than competing explanations.

Chronic kidney disease: The shared endpoint

- Progressive loss may originate in glomerular, tubular or vascular compartments.
- Common chronic findings include glomerulosclerosis and interstitial fibrosis.
- Tubular atrophy and arteriosclerosis commonly accompany them.
- Surviving-nephron hyperfiltration can further intensify progressive loss.

Proteinuria and GFR report different injury dimensions

- Proteinuria reflects abnormal glomerular permeability and tubular handling.
- A falling GFR indicates reduction in aggregate filtration function.
- Proteinuria can appear before advanced structural loss.
- The two measures complement, rather than replace, morphologic assessment.

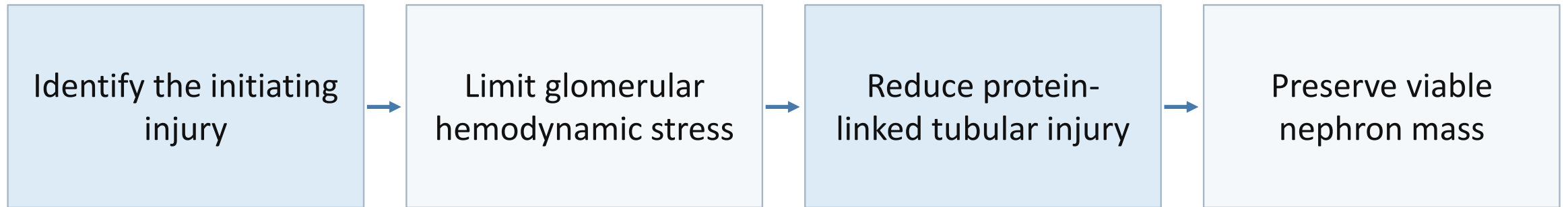
Systemic hypertension adds mechanical stress

- Elevated systemic pressure can accompany adaptive FSGS.
- Pressure effects may worsen injury to capillary endothelium and podocytes.
- Hypertension can be both an associated finding and an amplifier of renal injury.
- Its presence should trigger attention to the progressive hemodynamic cycle.

Why renin–angiotensin inhibition is mechanistic

- Inhibition of the renin–angiotensin system as an effective approach to adaptive progressive sclerosis.
- Reduced intraglomerular pressure interrupts a major injury driver.
- These agents may have additional effects on cellular injury and remodeling pathways.
- This is a pathophysiologic principle, not a patient-specific prescription.

Sites at which progression can be interrupted



The rationale for intervention follows from breaking positive feedback.

A key interpretation of biopsy chronicity

- Segmental sclerosis indicates scarring of only part of a tuft.
- Global sclerosis documents complete tuft involvement in a glomerulus.
- Tubular atrophy and interstitial fibrosis document chronic parenchymal injury.
- Pattern, distribution and clinical context matter more than any single scar.

Distinguish active disease from accumulated damage

- Active inflammatory lesions indicate ongoing tissue injury.
- Glomerulosclerosis and established interstitial fibrosis indicate accrued structural damage.
- Both processes may be present together in the same kidney.
- Declining function cannot automatically be attributed solely to current immunologic activity.

Applied case: Functioning solitary kidney

Teaching vignette (fictional): A person with a solitary kidney develops progressive proteinuria years after compensatory renal enlargement.

- What adaptive change initially protected filtration?
- Why can the same adaptation later be harmful?

Interpretation: Remaining glomeruli hypertrophy and hyperfilter; Prolonged glomerular hypertension can damage podocytes and promote secondary FSGS.

Applied case: Glomerular disease in remission

Teaching vignette (fictional): Activity of the initial immune lesion subsides, but kidney function continues to fall and chronic scarring accumulates.

- Which process can sustain progression after remission?
- What two histologic compartments require assessment?

Interpretation: Nephron-loss–driven maladaptive hyperfiltration can persist; Assess both glomerulosclerosis and tubulointerstitial fibrosis.

Applied case: Proteinuria and interstitial injury

Teaching vignette (fictional): A biopsy shows glomerular protein-leak lesions alongside tubular injury and interstitial inflammatory cells.

- Can proteinuria itself contribute to tubular disease?
- Which mediators can activated tubular cells release?

Interpretation: Yes. Filtered proteins can activate tubular cells, increasing adhesion molecules, cytokines, chemokines and growth factors.

Applied case: How to interpret segmental sclerosis

Teaching vignette (fictional): A biopsy contains a few glomeruli with scars confined to one tuft segment; Earlier clinical records document nephron loss from reflux nephropathy.

- What does “focal segmental” describe?
- Is primary idiopathic FSGS established by morphology alone?

Interpretation: It describes lesion distribution. Reflux-related reduction in nephron mass supports an adaptive secondary mechanism; Morphology alone does not establish primary FSGS.

Applied case: Mismatch between lesions and function

Teaching vignette (fictional): The number of visibly active glomerular lesions is modest, but the biopsy shows extensive tubular atrophy and interstitial fibrosis.

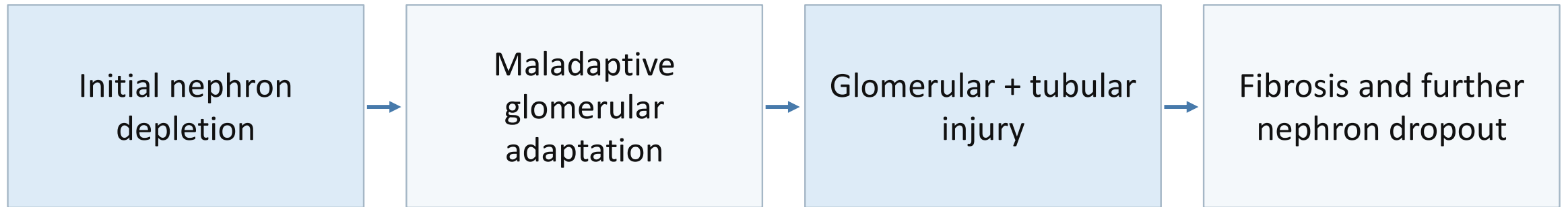
- Which compartment may better account for reduced renal function?
- What chronic injury pathways could have produced it?

Interpretation: Tubulointerstitial chronicity may correlate closely with impairment; Consider ischemia, protein-driven activation, inflammation and microvascular loss.

Integrated mechanism: From loss to scarring

- Nephron loss → adaptive glomerular hypertrophy and capillary hypertension.
- Podocyte injury and loss → proteinuria and focal tuft scarring.
- Protein exposure, hypoperfusion and inflammation injure tubules.
- Interstitial fibrosis and additional nephron loss reinforce progression.

The complete reinforcing circuit



The circuit explains a shared progression phenotype across different renal diagnoses.

High-yield distinctions

- Initiating cause is not the same as progression mechanism.
- Glomerulosclerosis is not synonymous with primary FSGS.
- Proteinuria can act as a mediator, not merely an observation.
- Tubulointerstitial chronicity is central to functional prognosis.

Five questions to retain

- What reduces the effective nephron mass?
- How do surviving glomeruli adapt?
- Why are podocytes unable to compensate indefinitely?
- How do proteinuria and ischemia injure the tubulointerstitium?
- How does the resulting scar create further nephron loss?

Textbook sources and interpretation

Primary

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Elsevier; 2026.
Chapter 20: pp. 822–823.

**Mechanistic
context**

Same chapter: Epithelial Cell Injury (pp. 822–823) and adaptive FSGS mechanisms (pp. 831–832).

Related overview

Same chapter: “Chronic Kidney Disease” (pp. 855–856).