

Diabetic Nephropathy

Mechanisms · Glomerular pathology · Vascular lesions · Clinical correlation

Pathogenesis

Morphology

Clinical consequences

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Learning objectives

OVERVIEW

- Explain how chronic hyperglycemia produces glomerular and vascular injury.
- Recognize basement membrane thickening, diffuse sclerosis, and Kimmelstiel–Wilson nodules.
- Relate arteriolar lesions and tubulointerstitial scarring to declining renal function.
- Interpret albuminuria and advanced nephropathy in clinicopathologic context.

Diabetic nephropathy: Scope and definition

INTRODUCTION

- Chronic diabetic kidney injury involves glomeruli, renal microvessels, and the tubulointerstitium.
- Renal manifestations range from albuminuria to advanced chronic kidney failure.
- The disease occurs in both type 1 and type 2 diabetes.

Diabetes mellitus



Renal microangiopathy



Glomerular injury



Chronic loss of function

Conceptual sequence — schematic

The kidney is a major diabetic target organ

INTRODUCTION

- The kidney is among the principal sites of diabetic microvascular injury.
- Renal failure is an important contributor to diabetes-associated mortality.
- Nephropathy is a leading cause of end-stage kidney disease in the United States.

Kidney injury is a systemic microvascular complication

Glomerular and microcirculatory damage predominate

Three patterns of renal injury coexist

INTRODUCTION

- Glomerular disease: Basement membrane thickening and glomerulosclerosis.
- Vascular disease: Renal atherosclerosis and hyaline arteriosclerosis.
- Infections: Pyelonephritis, sometimes with papillary necrosis.

Glomerular lesions

Renal vascular lesions

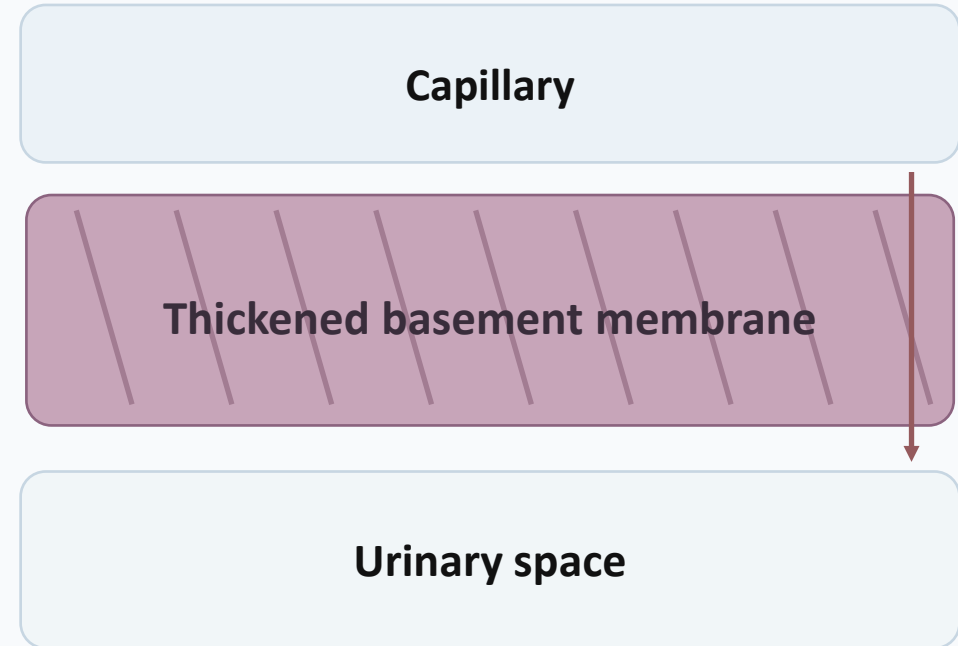
Pyelonephritis

Distinct but coexisting renal lesions

Diabetic microangiopathy provides the framework

INTRODUCTION

- Small-vessel basement membranes become diffusely thickened.
- The lesion is prominent in glomerular and medullary capillaries.
- Thickened basement membranes are nevertheless abnormally permeable to plasma proteins.



Stylized layered barrier — not an electron micrograph

Diabetes affects multiple vascular compartments

INTRODUCTION

- Large and medium arteries develop accelerated atherosclerosis.
- Microvascular disease damages the retina, kidneys, and peripheral nerves.
- Renal lesions include both glomerular microangiopathy and vascular insufficiency.

Macrovascular

Accelerated
atherosclerosis

Microvascular

Basement
membrane / small
vessel injury

Teaching comparison — schematic

Risk reflects metabolic exposure and host factors

INTRODUCTION

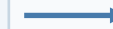
- Severity of chronic complications increases with degree and duration of hyperglycemia.
- Insulin resistance and obesity also contribute to diabetic tissue injury.
- Not every individual with diabetes develops the same renal phenotype.

**Persistent
hyperglycemia**



**Insulin resistance /
obesity**

Host susceptibility



Renal injury

Convergent pathology / interacting components

Persistent hyperglycemia drives chronic injury

PATHOGENESIS

- Glucotoxicity increases flux through several damaging metabolic pathways.
- Excess substrates produce reactive intermediates, signaling changes, and oxidative stress.
- These mechanisms converge on vascular dysfunction and extracellular matrix accumulation.



Conceptual sequence — schematic

Four metabolic pathways are implicated

PATHOGENESIS

- Formation of advanced glycation end products (AGEs).
- Excess diacylglycerol–protein kinase C (DAG–PKC) signaling.
- Polyol-associated oxidative stress and hexosamine pathway flux.

AGE–RAGE

DAG–PKC

Polyol / ROS

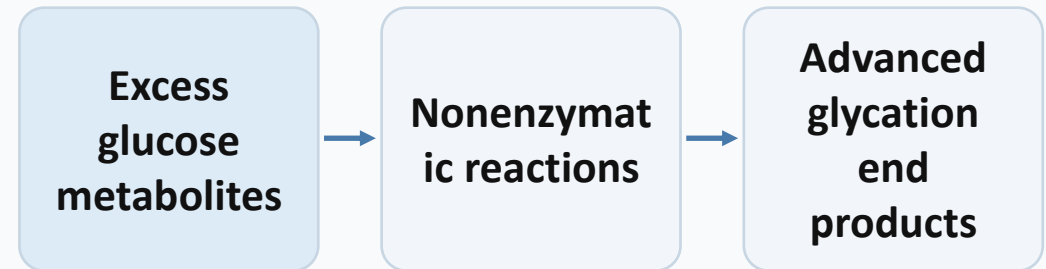
Hexosamine

Each contributes a different mechanistic or structural component

AGEs arise through nonenzymatic glycation

PATHOGENESIS

- Reactive glucose-derived metabolites modify amino groups of proteins.
- The process occurs in intracellular and extracellular compartments.
- Hyperglycemia accelerates the formation of AGEs.

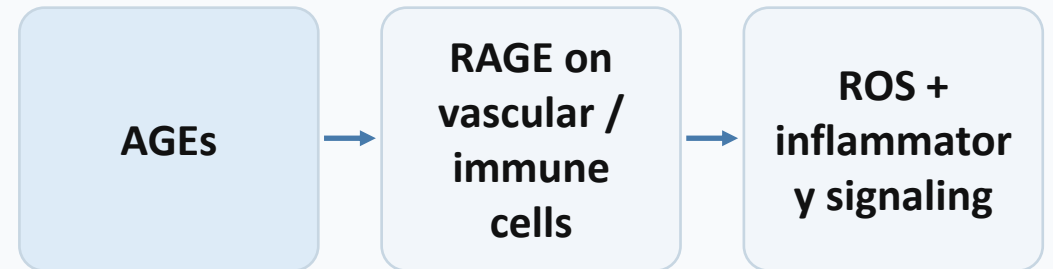


Conceptual sequence — schematic

AGE–RAGE signaling amplifies vascular injury

PATHOGENESIS

- AGEs engage the receptor for AGEs (RAGE) on several vascular and immune cell types.
- RAGE signaling promotes inflammatory and oxidative responses.
- An endothelial response contributes to diabetic microangiopathy.



Conceptual sequence — schematic

TGF- β signaling favors matrix accumulation

PATHOGENESIS

- AGE–RAGE signaling promotes release of growth factors including TGF- β .
- TGF- β enhances deposition of basement membrane and other extracellular matrix material.
- Matrix expansion is a central morphologic feature of diabetic glomerular disease.



Conceptual sequence — schematic

DAG activates the PKC signaling pathway

PATHOGENESIS

- Intracellular hyperglycemia enhances de novo DAG synthesis.
- Increased DAG drives excessive activation of protein kinase C.
- PKC modulates vascular growth factors and procoagulant signaling.

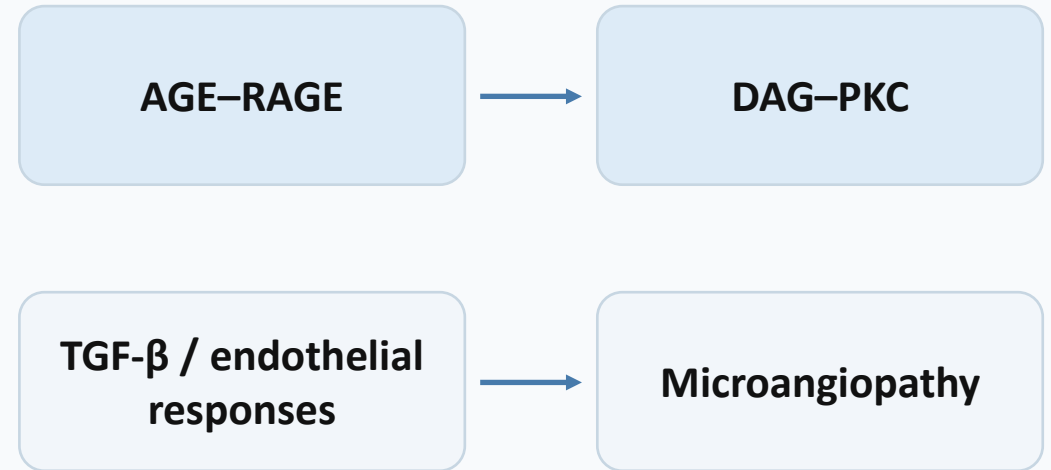


Conceptual sequence — schematic

AGE and PKC effects overlap

PATHOGENESIS

- PKC signaling promotes endothelial TGF- β and VEGF production.
- PAI-1 expression is another downstream effect.
- AGE-mediated and PKC-mediated processes share contributions to microangiopathy.

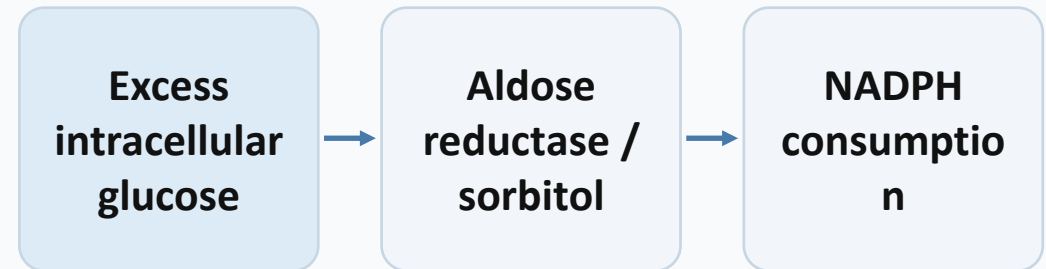


Convergent pathology / interacting components

The polyol pathway consumes cellular NADPH

PATHOGENESIS

- Aldose reductase converts excess glucose into sorbitol.
- The pathway uses NADPH, which is also needed to maintain reduced glutathione.
- Increased flux can weaken defenses against reactive oxygen species.



Conceptual sequence — schematic

Reduced glutathione is an antioxidant defense

PATHOGENESIS

- Glutathione reductase requires NADPH to replenish reduced glutathione (GSH).
- Less available NADPH can limit regeneration of GSH.
- Oxidative stress increases when reactive oxygen species are not adequately neutralized.

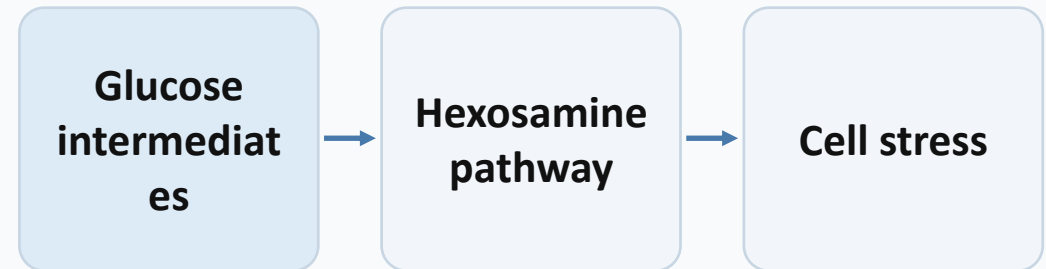


Conceptual sequence — schematic

Hexosamine flux is a proposed contributor

PATHOGENESIS

- Hyperglycemia increases availability of glycolytic intermediates.
- Some intermediates enter the hexosamine pathway.
- The textbook links enhanced flux to cellular damage and oxidative stress.



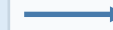
Conceptual sequence — schematic

Diverse pathways converge on renal pathology

PATHOGENESIS

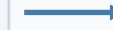
- Matrix deposition thickens glomerular and tubular basement membranes.
- Mesangial matrix expansion remodels the glomerular tuft.
- Microvascular dysfunction and ischemia compound parenchymal injury.

Matrix deposition



Mesangial expansion

Vascular narrowing



Chronic renal injury

Convergent pathology / interacting components

A thick basement membrane can still be leaky

PATHOGENESIS

- Diabetic capillary basement membranes are often markedly thickened.
- The increase in thickness does not imply restoration of barrier selectivity.
- Abnormal protein permeability helps explain urinary albumin loss.



Stylized layered barrier — not an electron micrograph

The renal injury spans four compartments

MORPHOLOGY

- Glomerular capillary walls and mesangium.
- Afferent/efferent arterioles and larger renal arteries.
- Tubules and interstitium, with superimposed infection in some patients.

Glomeruli

Arterioles

Tubules

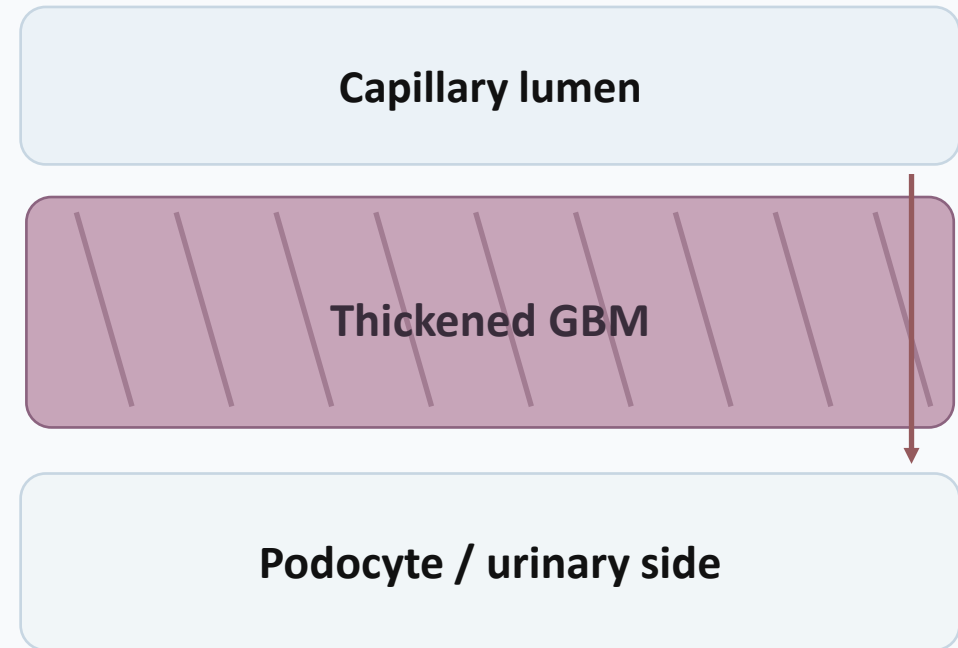
Interstitium

Each contributes a different mechanistic or structural component

GBM thickening is a fundamental lesion

MORPHOLOGY

- Glomerular capillary basement membrane thickening is widespread in nephropathy.
- It is part of the more generalized diabetic microangiopathy.
- Electron microscopy shows the change more clearly than light microscopy.



Stylized layered barrier — not an electron micrograph

GBM changes may precede clinical disease

MORPHOLOGY

- In type 1 diabetes, measurable thickening can begin early after onset.
- The source describes onset by roughly 2 years and about 30% thickening by 5 years.
- Histologic changes therefore need not parallel the first clinically recognized albuminuria.

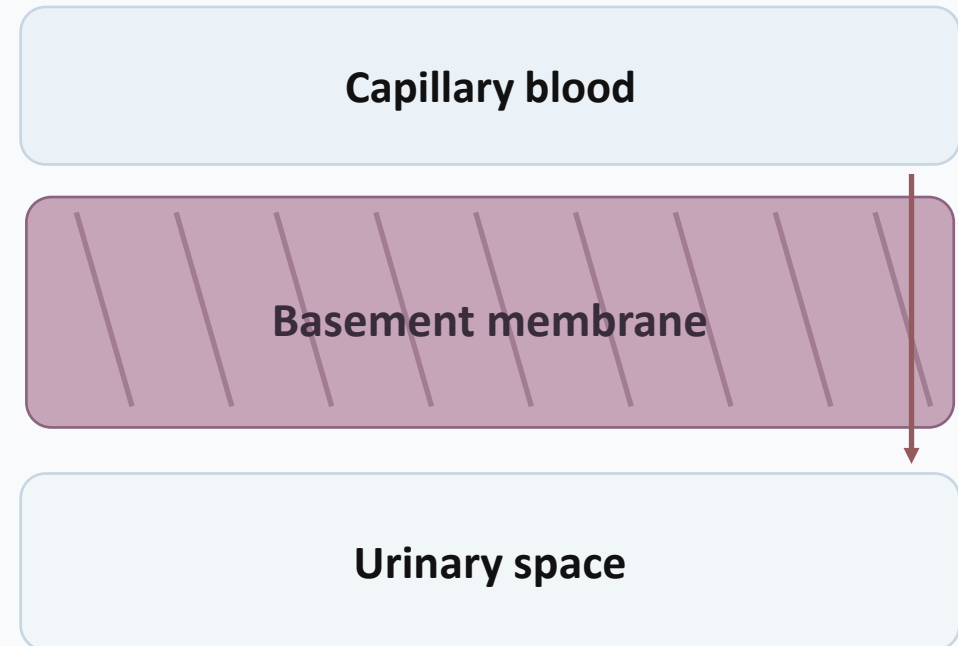


Conceptual sequence — schematic

Electron microscopy highlights wall thickening

MORPHOLOGY

- The capillary basement membrane appears expanded between endothelial and epithelial sides.
- Capillary lumina and urinary spaces provide orientation.
- An image-based diagnosis must distinguish this from a native schematic.



Stylized layered barrier — not an electron micrograph

Tubular basement membranes also thicken

MORPHOLOGY

- Diabetic microangiopathy is not limited to glomerular capillaries.
- Tubular basement membrane thickening may accompany progressive GBM changes.
- Basement membrane alteration extends across several renal structures.

Glomerular wall

Capillary GBM
thickening

Tubular wall

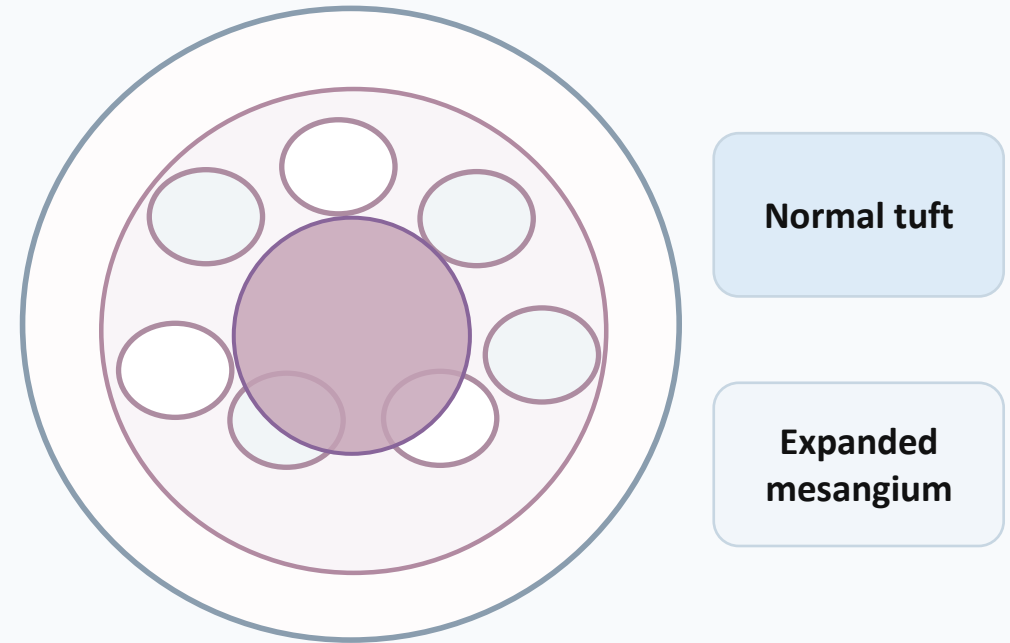
Tubular BM
thickening

Teaching comparison — schematic

Mesangial widening accompanies GBM injury

MORPHOLOGY

- Mesangial matrix gradually accumulates between capillary loops.
- Expanded mesangium alters the organization of glomerular lobules.
- Persistent expansion may lead to diffuse and nodular sclerosis.



Schematic of a glomerular tuft — not a histologic image

PAS staining highlights the excess matrix

MORPHOLOGY

- The excess diabetic mesangial matrix is PAS-positive.
- PAS accentuates basement membranes and supports assessment of mesangial expansion.
- Interpret an actual stain by identifying the pattern and location of matrix deposition.

PAS staining emphasizes carbohydrate-rich matrix

PAS-positive matrix

Mesangial expansion

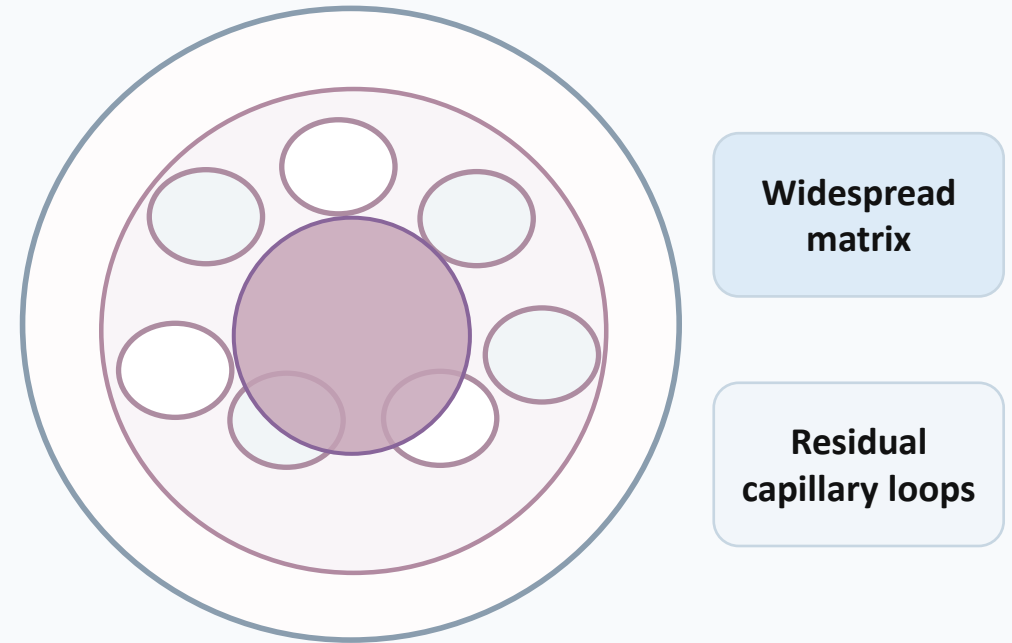
Basement membranes

Conceptual stain targets, not microscopy

Diffuse mesangial sclerosis is widespread

MORPHOLOGY

- The lesion is defined by a diffuse increase in mesangial matrix.
- Matrix deposition need not form discrete nodules.
- Diffuse mesangial sclerosis can be present in glomeruli without nodules.



Schematic of a glomerular tuft — not a histologic image

Mesangial expansion correlates with proteinuria

MORPHOLOGY

- Progressive expansion of the mesangium accompanies deterioration in renal function.
- The source specifically notes correlation with increasing proteinuria.
- This links a structural lesion to the principal clinical marker of nephropathy.



Conceptual sequence — schematic

Nodular sclerosis develops within diffuse disease

MORPHOLOGY

- Mesangial deposits can progressively develop a nodular configuration.
- The classic nodular lesion does not replace all diffuse changes.
- Adjacent lobules or glomeruli may remain diffusely sclerotic.

Diffuse pattern

Broad mesangial
expansion

Nodular pattern

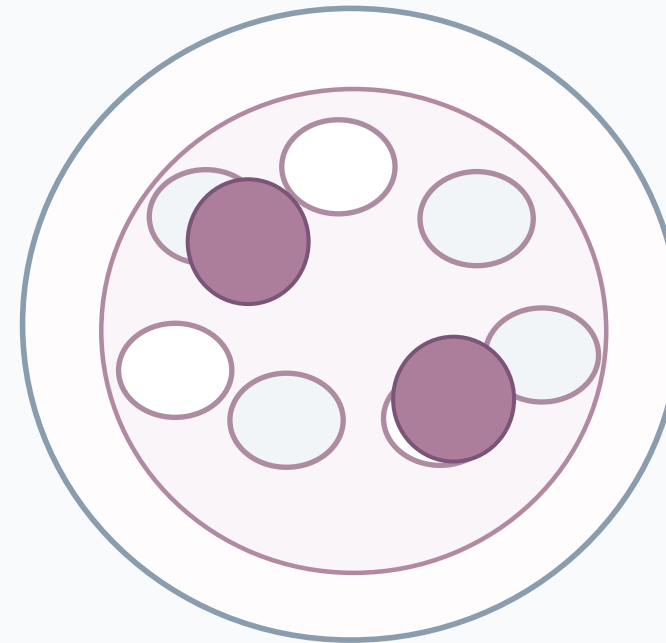
Discrete matrix
nodules

Teaching comparison — schematic

Kimmelstiel–Wilson nodules are distinctive

MORPHOLOGY

- Nodular glomerulosclerosis is also termed intercapillary glomerulosclerosis.
- Round or ovoid, often laminated nodules are PAS-positive.
- The nodules consist of mesangial matrix rather than a proliferating cellular mass.



**PAS-positive
nodules**

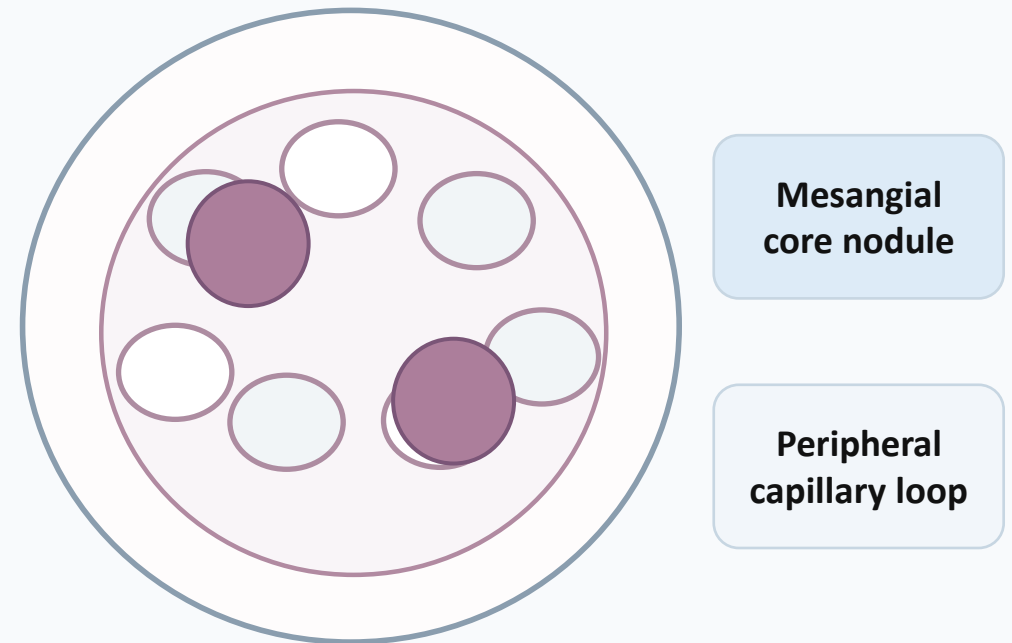
**Mesangial
matrix**

Schematic of a glomerular tuft — not a histologic image

The nodules occupy the mesangial lobules

MORPHOLOGY

- Nodules develop in the mesangial core at the glomerular periphery.
- Patent capillary loops may outline the nodules.
- Other loops can become markedly dilated.

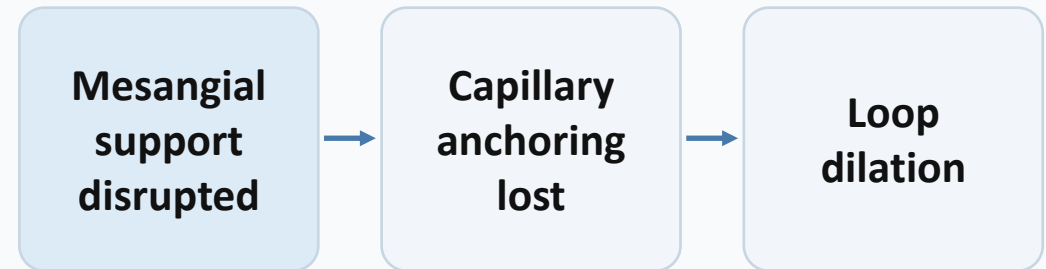


Schematic of a glomerular tuft — not a histologic image

Mesangiolytic weakens capillary anchoring

MORPHOLOGY

- Mesangiolytic denotes disruption of support between capillaries and mesangial stalks.
- Mesangiolytic features in nodular lesions.
- Loss of structural support can permit localized dilation of capillary loops.



Conceptual sequence — schematic

Capillary microaneurysms may result

MORPHOLOGY

- Localized capillary loop dilation reflects weakened mesangial support.
- Microaneurysms may accompany nodular glomerulosclerosis.
- They are a distinct feature from the extracellular matrix nodule itself.

Nodule

Excess mesangial
matrix

Microaneurysm

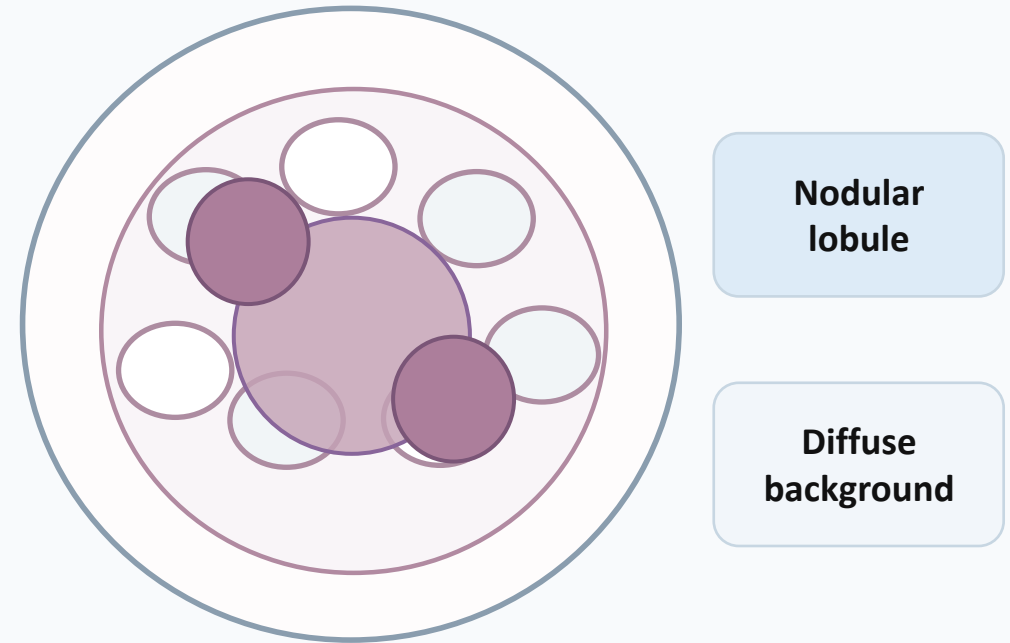
Dilated capillary
loop

Teaching comparison — schematic

Nodules coexist with diffuse mesangial lesions

MORPHOLOGY

- Nodules may involve only selected lobules within a glomerulus.
- Apparently uninvolved lobules can still show diffuse mesangial sclerosis.
- Evaluate the entire glomerular tuft rather than one isolated nodule.

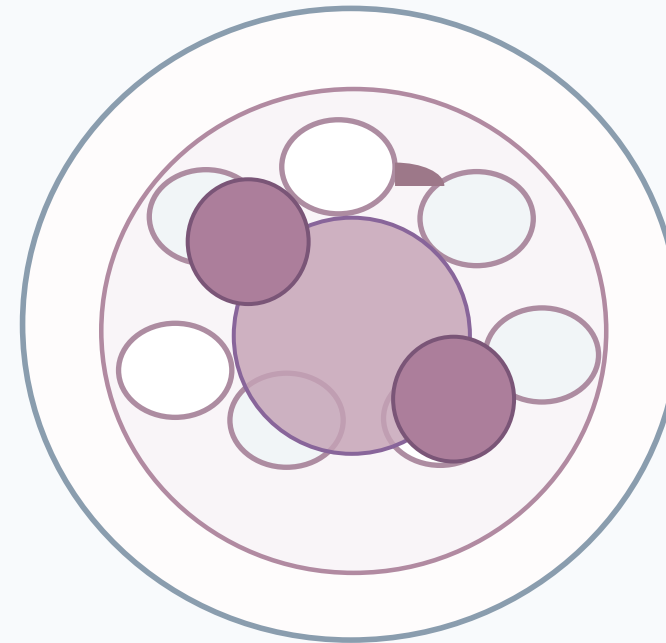


Schematic of a glomerular tuft — not a histologic image

Fibrin caps are glomerular hyaline deposits

MORPHOLOGY

- Hyaline accumulations in glomerular capillary loops.
- These deposits are traditionally called “fibrin caps.”
- They are associated findings rather than the definition of nodular sclerosis.



Schematic of a glomerular tuft — not a histologic image

Capsular drops occur along Bowman capsule

MORPHOLOGY

- Hyaline deposits may adhere to Bowman capsule.
- These lesions are called “capsular drops.”
- Distinguish the capsular location from capillary-loop fibrin caps.

Fibrin cap

Capsular drop

Capillary-loop
deposit

Bowman capsule
deposit

Teaching comparison — schematic

Diffuse and nodular patterns: A comparison

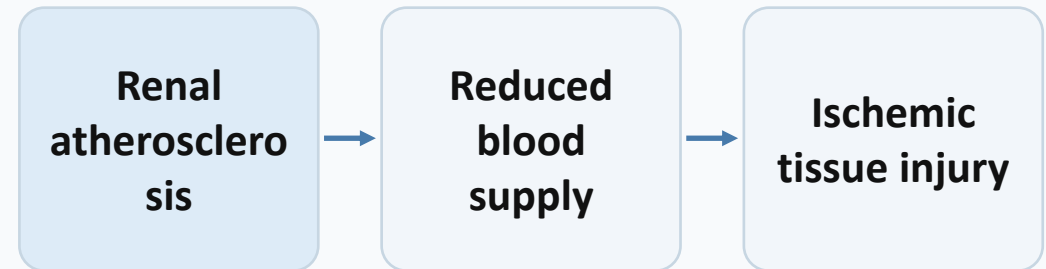
MORPHOLOGY

Feature	Diffuse mesangial sclerosis	Nodular glomerulosclerosis
Architecture	Widespread mesangial expansion	Discrete mesangial nodules
PAS	Matrix-positive	Strongly matrix-positive nodules
Background	May be present alone	Usually diffuse changes elsewhere
Support	Tuft remodeled	May show mesangiolysis

Renal atherosclerosis adds ischemic injury

VASCULAR INJURY

- Diabetes accelerates disease in large- and medium-sized renal arteries.
- Renal macrovascular narrowing adds to glomerular and arteriolar damage.
- Ischemia is therefore multifactorial in advanced diabetic kidneys.

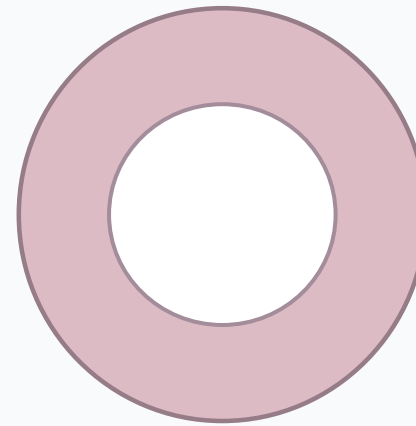


Conceptual sequence — schematic

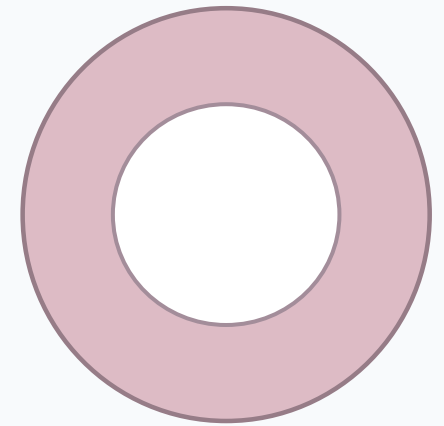
Hyaline arteriolosclerosis involves both poles

VASCULAR INJURY

- Afferent arterioles may show hyaline thickening and narrowing.
- Efferent arterioles are also affected in diabetic nephropathy.
- This combined involvement is a useful morphologic clue.



Afferent arteriole



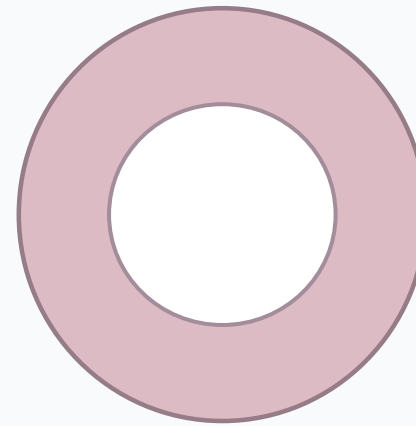
Efferent arteriole

Hyaline wall thickening with luminal narrowing — schematic

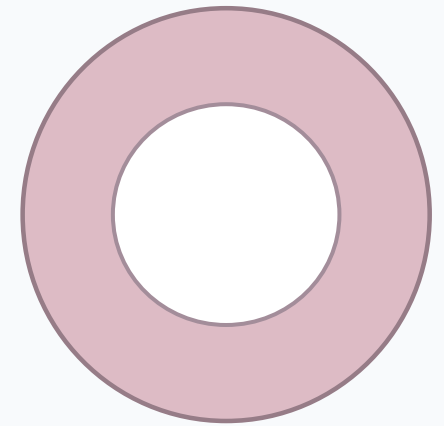
Efferent arteriolar hyalinosis is informative

VASCULAR INJURY

- That efferent arteriolar hyalinosis is rare without diabetes.
- Assess arteriolar walls along with the glomerular matrix lesions.
- No single arteriolar change substitutes for the overall morphologic pattern.



Afferent: Hyaline wall



Efferent: Hyaline wall

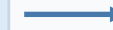
Hyaline wall thickening with luminal narrowing — schematic

Glomerular and vascular lesions compound ischemia

VASCULAR INJURY

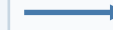
- Mesangial sclerosis compromises glomerular architecture.
- Hyaline arteriolosclerosis reduces microvascular caliber.
- Their combined effects promote chronic tubulointerstitial injury.

Glomerulosclerosis



Arteriolosclerosis

Chronic ischemia



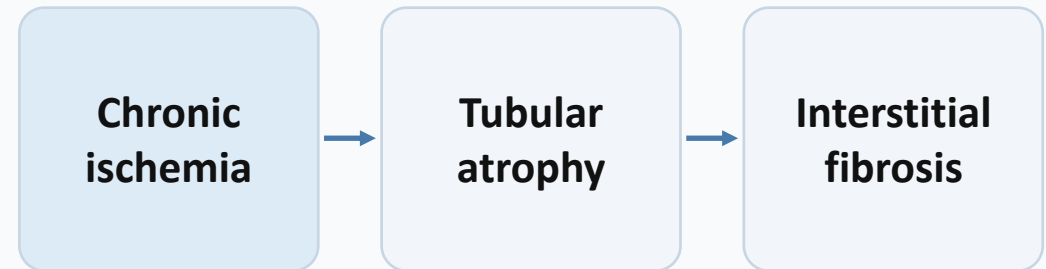
**Tubulointerstitial
injury**

Convergent pathology / interacting components

Chronic ischemia produces tubular atrophy

VASCULAR INJURY

- Ischemic injury leads to loss and shrinkage of functional tubules.
- Tubular atrophy accompanies interstitial fibrosis.
- These changes are part of advanced diabetic kidney scarring.



Conceptual sequence — schematic

The advanced kidney may become contracted

VASCULAR INJURY

- With long-standing disease, sclerosis and ischemia can reduce kidney size.
- Granular surface change and marked cortical thinning.
- Irregular depressions may reflect superimposed pyelonephritic scars.

Cortical scarring

Tubular atrophy

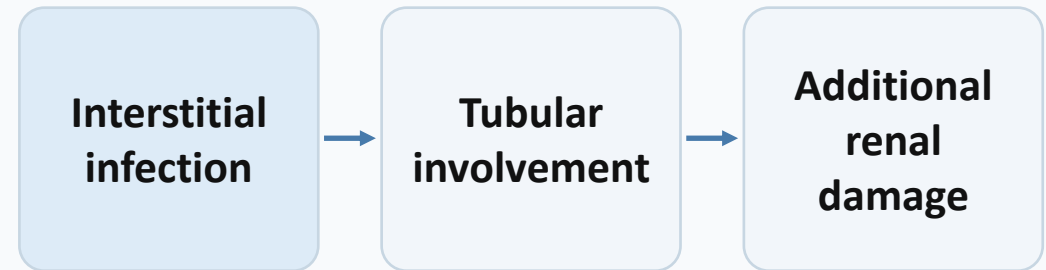
Interstitial fibrosis

Anatomic consequences — conceptual; Not gross specimen

Pyelonephritis is more severe with diabetes

INFECTION

- Acute and chronic pyelonephritis occur more commonly in diabetes.
- The source describes greater severity in affected patients.
- Pyelonephritis begins in the interstitium and can extend into tubules.



Conceptual sequence — schematic

Papillary necrosis is a notable complication

INFECTION

- Papillary necrosis is a necrotizing pattern of acute pyelonephritis.
- It is more prevalent in people with diabetes than in those without diabetes.
- This complication is separate from the characteristic glomerular sclerosing lesion.

Glomerular injury

Chronic matrix /
microvascular
lesions

Papillary necrosis

Necrotizing
inflammatory
complication

Teaching comparison — schematic

The characteristic tissue pattern is composite

INTEGRATION

- Glomerular: Thick GBM, diffuse matrix expansion, sometimes nodules.
- Vascular: Afferent and efferent hyalinosis with renal atherosclerosis.
- Chronic parenchymal: Tubular atrophy and interstitial fibrosis.

Glomerular sclerosis

Vascular hyalinosis

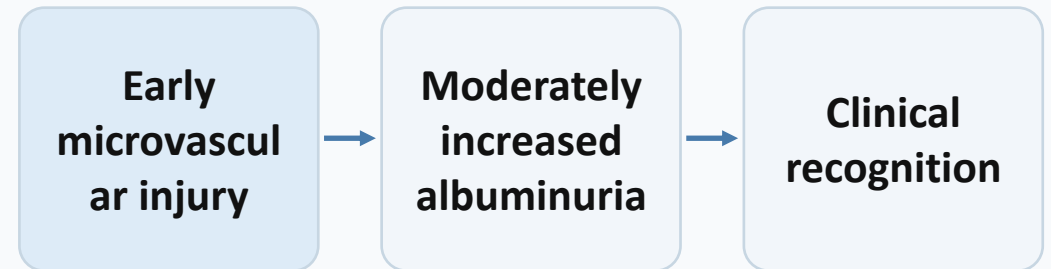
Tubulointerstitial scarring

Distinct but coexisting renal lesions

Albuminuria is an early clinical manifestation

CLINICAL COURSE

- Low-level urinary albumin excretion is an early signal of diabetic nephropathy.
- The traditional term “microalbuminuria” is replaced by “moderately increased albuminuria.”
- It is possible to have structural renal injury before symptomatic kidney disease.



Conceptual sequence — schematic

Albuminuria terminology defines severity

CLINICAL COURSE

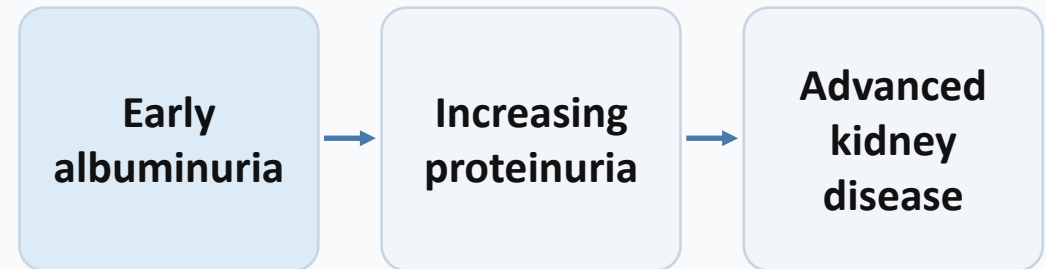
The clinical course of albuminuria is defined by the severity of albuminuria, which is defined by the amount of albumin excreted in the urine.

Textbook term	Daily urinary albumin	Former term
Moderately increased	>30 to <300 mg/day	Microalbuminuria
Severely increased	>300 mg/day	Macroalbuminuria

Progression may lead to overt proteinuria

CLINICAL COURSE

- Progressive renal injury increases albumin excretion.
- Transition from low-grade albuminuria to overt nephropathy.
- Hypertension commonly accompanies the more advanced proteinuric phase.

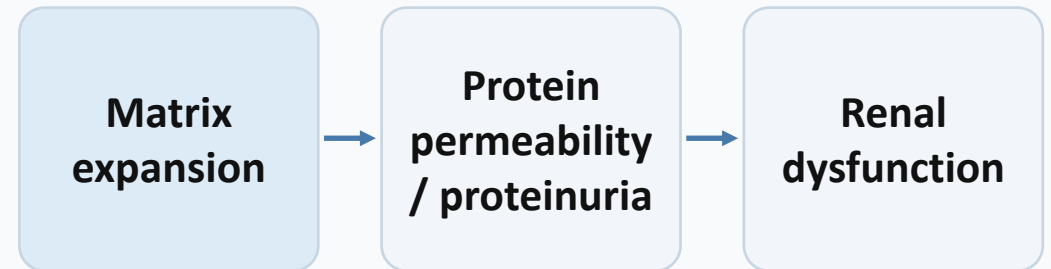


Conceptual sequence — schematic

Proteinuria links clinic and morphology

CLINICAL COURSE

- A clinical increase in proteinuria often reflects increasing mesangial matrix deposition.
- In advanced disease, glomerular and vascular abnormalities coexist.
- Interpret urine findings alongside renal function and systemic diabetic disease.



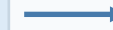
Conceptual sequence — schematic

Hypertension compounds renal vulnerability

CLINICAL COURSE

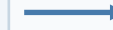
- Hypertension frequently accompanies overt diabetic nephropathy.
- It can coexist with renal arteriolar hyalinosis and glomerulosclerosis.
- The clinical phenotype reflects vascular as well as glomerular injury.

Albuminuria



Hypertension

Vascular pathology



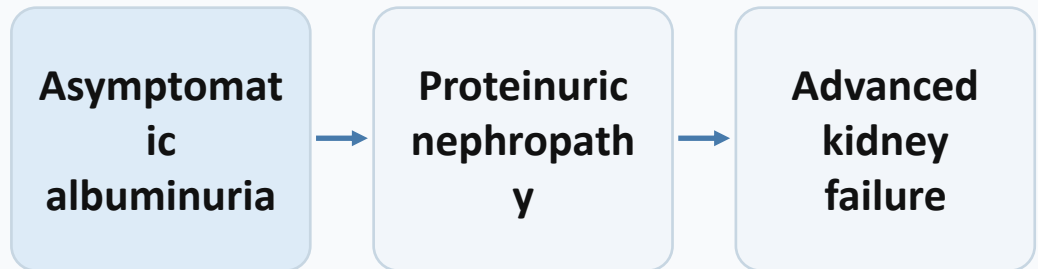
Renal impairment

Convergent pathology / interacting components

The clinical spectrum is broad

CLINICAL COURSE

- Early nephropathy may be clinically silent except for urine albumin abnormalities.
- Increasing proteinuria may precede marked loss of kidney function.
- Advanced disease may require dialysis or renal transplantation.



Conceptual sequence — schematic

Not all patients progress identically

CLINICAL COURSE

- The source places clinical evidence of nephropathy in roughly 30–40% of patients with diabetes.
- Course differs among individuals with type 1 and type 2 diabetes.
- Duration, glycemic exposure, and other risk factors influence progression.

Type 1 diabetes

Characteristic
glomerular changes

Type 2 diabetes

Characteristic
glomerular changes

Teaching comparison — schematic

Chronic complications are often delayed

CLINICAL COURSE

- Long-term complications typically accumulate after years of hyperglycemia.
- The source describes many clinical complications first appearing after 15–20 years.
- Timing is variable; Morphologic alterations can precede overt functional impairment.



Conceptual sequence — schematic

Loss of filtration becomes the final consequence

CLINICAL COURSE

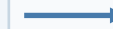
- Glomerulosclerosis reduces effective filtration surface.
- Vascular narrowing and fibrosis reduce viable renal parenchyma.
- The combined lesions may culminate in end-stage kidney disease.

Glomerular scarring



**Ischemic
parenchymal loss**

Interstitial fibrosis



Kidney failure

Convergent pathology / interacting components

Renal and cardiovascular injuries coexist

CLINICAL COURSE

- Diabetes produces both macrovascular and microvascular disease.
- Renal atherosclerosis and glomerular injury can occur in the same patient.
- Kidney findings should be understood within the systemic vascular burden.

**Macrovascular
damage**

Atherosclerotic
ischemia

**Microvascular
damage**

Glomerular
microangiopathy

Teaching comparison — schematic

Clinicopathologic patterns can be aligned

SYNTHESIS

Clinical pattern	Pathologic correlate
Albuminuria	GBM / mesangial matrix injury
Progressive kidney failure	Sclerosis + ischemia + fibrosis
Acute renal infection	Pyelonephritis ± papillary necrosis

Clinical case: Early nephropathy

APPLICATION

- A patient with long-standing diabetes has no renal symptoms but increasing low-level urinary albumin excretion.
- Which microscopic compartment is affected before overt kidney failure?
- Explain why basement membrane thickening does not prevent protein leakage.

Assess

GBM and mesangium

Reason

Microangiopathy and permeability

Clinical case: Nodular glomerular lesion

APPLICATION

- A renal biopsy in a patient with long-standing diabetes shows PAS-positive round matrix nodules within glomerular lobules.
- Name the characteristic nodular lesion.
- What additional changes should be sought in the background tufts and arterioles?

Assess

Nodular mesangial sclerosis

Seek

Diffuse sclerosis + arteriolar hyalinosis

Clinical case: Worsening kidney function

APPLICATION

- A patient with diabetes develops rising proteinuria, hypertension, and declining filtration.
- Connect glomerulosclerosis to vascular compromise and interstitial fibrosis.
- Why can kidney size decrease in advanced disease?

Glomerular matrix

Vascular hyalinosis

Chronic ischemia

Atrophy and fibrosis

Morphology exercise: Separate two deposits

APPLICATION

- A PAS-stained diabetic glomerulus shows hyaline material within capillary loops and along Bowman capsule.
- Identify the conventional name of each deposit by location.
- Distinguish both from the mesangial Kimmelstiel–Wilson nodule.

Capillary loops

Fibrin caps

Bowman capsule

Capsular drops

Four morphologic features worth recognizing

SYNTHESIS

- Thickened glomerular capillary and tubular basement membranes.
- Diffuse mesangial sclerosis with or without Kimmelstiel–Wilson nodules.
- Hyaline arteriosclerosis, including efferent arterioles.
- Tubular atrophy and interstitial fibrosis in advanced disease.

**Basement
membranes**

Mesangial matrix

Arterioles

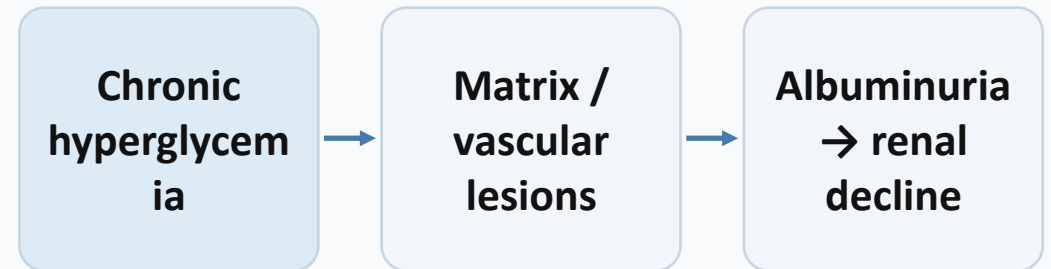
Tubulointerstitium

Each contributes a different mechanistic or structural component

One causal chain integrates the lecture

SYNTHESIS

- Chronic metabolic abnormalities damage endothelium and alter matrix production.
- Glomerular sclerosis and microvascular narrowing amplify renal damage.
- Albuminuria precedes or accompanies progressive functional decline.



Conceptual sequence — schematic

References and source boundaries

SELECTED SOURCES

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 20: The Kidney (p. 841).
- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 24: The Endocrine System (diabetic chronic complications).
- Source sections: chronic diabetic complications, microangiopathy, diabetic nephropathy, and clinical manifestations.