

Morphology of Chronic Complications of Diabetes

Pancreas · vasculature · kidney · eye · nervous system

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Learning objectives

- Distinguish the structural lesions of diabetic macroangiopathy and microangiopathy.
- Recognize the pancreatic changes characteristic of type 1 and type 2 diabetes.
- Describe the glomerular, vascular and infectious components of diabetic renal pathology.
- Link retinal, lens and neural complications to their morphologic basis.

Chronic complications: Anatomic map

Affected site	Characteristic lesion	Functional consequence
Large and medium arteries	Accelerated atherosclerosis	Ischemic myocardial, cerebral and limb injury
Capillaries / microvessels	Diffuse basement-membrane thickening	Nephropathy, retinopathy, some neuropathies
Kidney	Glomerulosclerosis, arteriosclerosis, pyelonephritis	Progressive loss of renal function
Pancreatic islets	Insulinitis / islet loss or amyloid deposition	Corresponding islet dysfunction

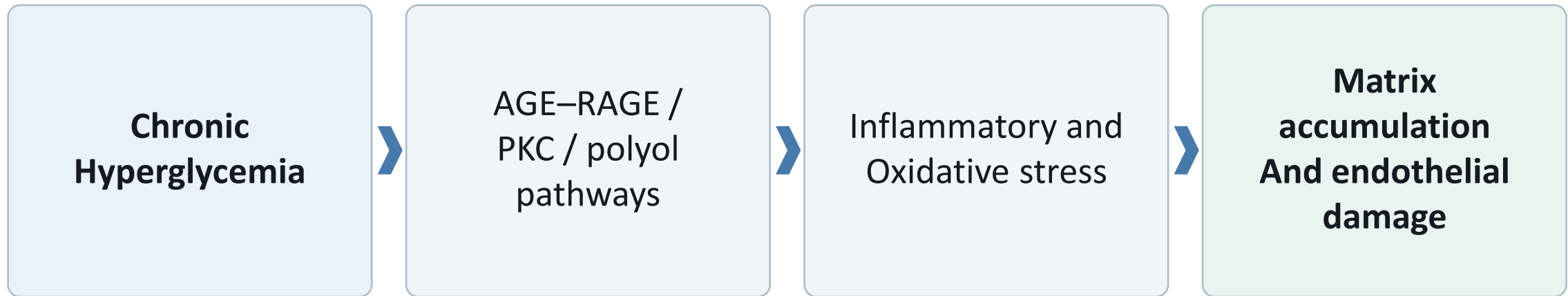
Diabetic tissue injury affects both major types

- Chronic morphologic complications arise in both type 1 and type 2 diabetes.
- Some pancreatic islet changes are more distinctive for a particular diabetes type.
- Systemic consequences reflect vascular injury affecting multiple organs.
- Distribution and severity depend on long-standing metabolic and vascular stress.

Macrovascular versus microvascular disease

Dimension	Macrovascular	Microvascular
Principal level	Aorta; Large and medium muscular arteries	Capillaries and other small vessels
Signature lesion	Atherosclerotic plaque	Thickened basement membranes
Major organs	Heart, brain, lower limbs, renal arteries	Glomeruli, retina, peripheral nerves
Important distinction	Plaque morphology resembles ordinary atherosclerosis	Thick basement membranes remain abnormally permeable

Persistent hyperglycemia connects metabolism to structure

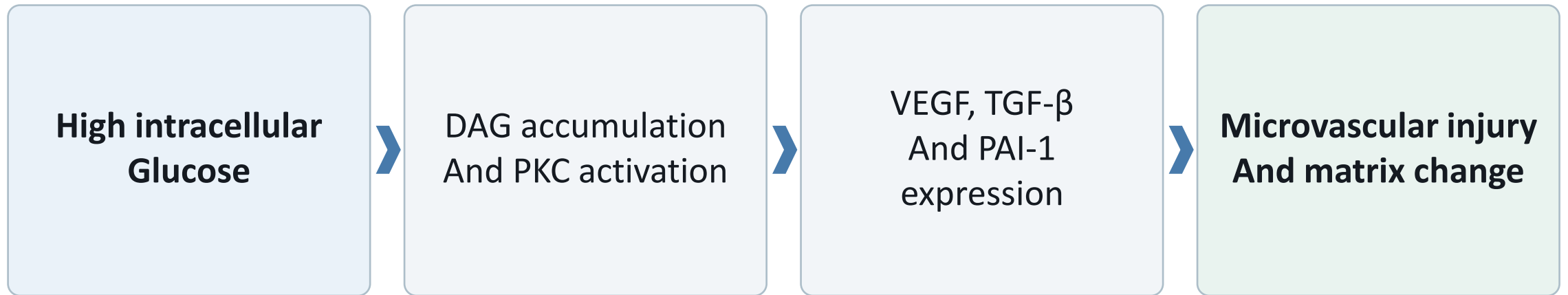


Other influences include insulin resistance and associated cardiometabolic abnormalities.

AGE-related vascular remodeling

- Advanced glycation end products (AGEs) accumulate more rapidly in hyperglycemia.
- AGE interaction with RAGE promotes inflammatory and vascular cell responses.
- TGF- β -associated signaling increases deposition of basement-membrane material.
- VEGF-associated responses are relevant to retinal vascular injury.

Protein kinase C signaling in diabetic angiopathy



AGE and PKC pathways have overlapping downstream effects.

Polyol pathway and oxidative stress

- Aldose reductase converts excess intracellular glucose to sorbitol.
- This reaction consumes NADPH, needed to regenerate reduced glutathione.
- Impaired antioxidant defenses increase susceptibility to oxidative stress.
- Sorbitol accumulation contributes to diabetes-associated lens opacity.

Metabolic mechanisms relevant to morphology

Mechanism	Immediate cellular effect	Morphologic implication
AGE formation / RAGE	Inflammation, growth-factor release	Microvascular matrix thickening
Excess PKC activity	VEGF, TGF- β and PAI-1 signaling	Endothelial and matrix responses
Polyol pathway	NADPH consumption; Oxidative stress	Cellular injury; Lens cataract
Hexosamine pathway	Abnormal metabolic flux	Proposed vascular and metabolic injury

Pancreatic islets: Lesions to recognize

Setting	Dominant pancreatic morphology
Type 1 diabetes	Reduced islet number/size; T-cell-rich insulitis may be present
Type 2 diabetes	Subtle islet-cell loss; Islet amyloid deposition and occasional fibrosis
Infants of diabetic mothers	Increased number and size of pancreatic islets
Normal aging	Islet amyloid may also be found without diabetes

Type 1 diabetes: Islet loss

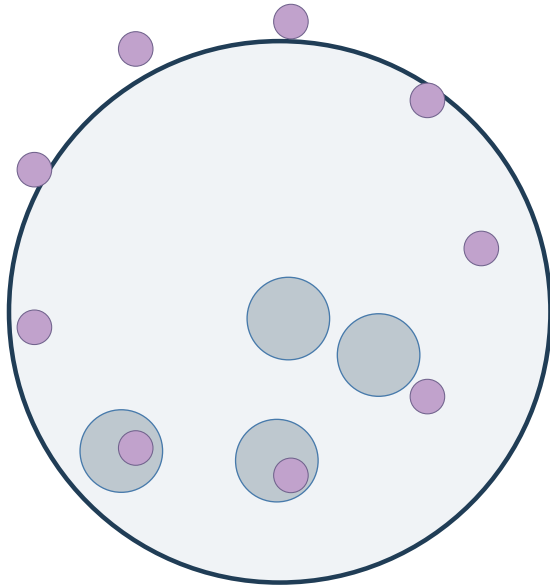
- Reduction in islet number and size is common, especially in rapidly progressive type 1 diabetes.
- Residual islets may be small and difficult to identify.
- Loss of endocrine parenchyma reflects the autoimmune β -cell destructive process.
- Islet depletion is not expected to appear identically at every disease stage.

Insulitis: Cellular composition

- Insulitis consists predominantly of T lymphocytes infiltrating pancreatic islets.
- The source notes that lymphocytic infiltrates may be found at clinical presentation.
- Insulitis reflects immune-mediated islet damage rather than amyloid deposition.
- The inflammatory infiltrate is a separate lesion from amyloid deposition in type 2 diabetes.

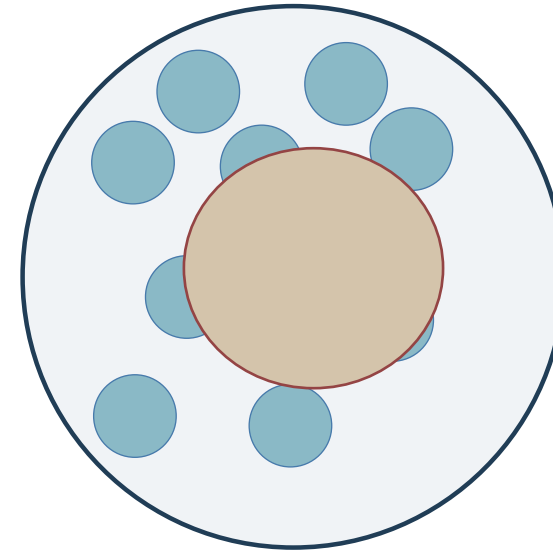
Pancreatic islets: Source-grounded schematic

Type 1 diabetes



Islet loss and lymphocytic insulinitis

Type 2 diabetes



Islet amyloid; Possible fibrosis

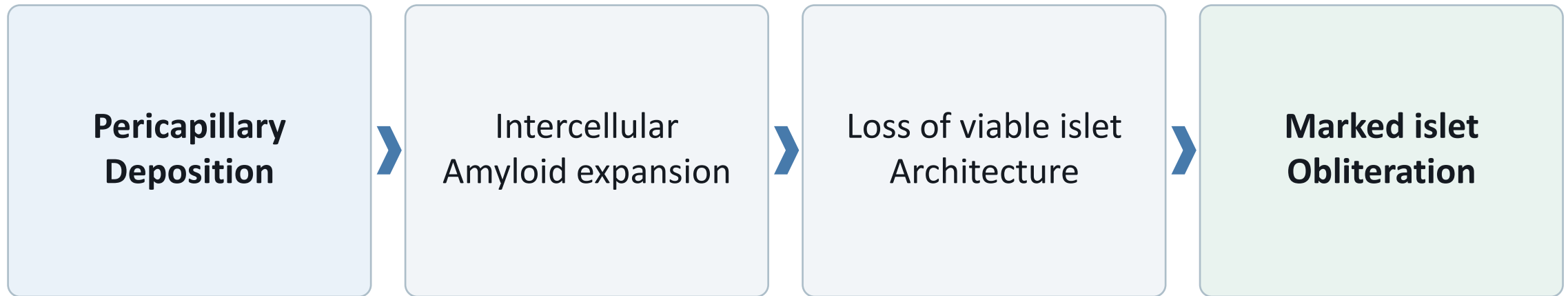
Type 2 diabetes: Subtle loss of islet cells

- A modest decrease in islet cell mass may occur in type 2 diabetes.
- The decrease can be too subtle for routine morphologic assessment.
- Morphometric studies may be required to demonstrate the reduction.
- In contrast to type 1 diabetes, prominent insulitis is not a defining lesion.

Islet amyloid in type 2 diabetes

- Amyloid initially appears around islet capillaries and between endocrine cells.
- With progression, deposits can replace much of the islet parenchyma.
- Advanced islets may become nearly obliterated by amyloid.
- Islet fibrosis may accompany these changes.

Islet amyloid: Spatial progression



This schematic shows the described morphologic distribution, not a quantified time course.

Islet amyloid is not unique to diabetes

- Amyloid deposits can be encountered in older people without diabetes.
- Their presence therefore requires clinicopathologic interpretation.
- A small amyloid deposit is not equivalent to complete islet loss.
- The important teaching distinction is extent and setting, not amyloid alone.

Type 1 versus type 2: Pancreatic morphology

Feature	Type 1	Type 2
Islet number/size	Often conspicuously reduced	May be subtly reduced
Inflammatory infiltrate	T-lymphocytic insulitis may be seen	Not the characteristic lesion
Amyloid	Not the distinguishing finding	Often deposited within islets
Fibrosis	Not emphasized as a defining lesion	Can accompany advanced amyloid

Fetal islet response in diabetic pregnancy

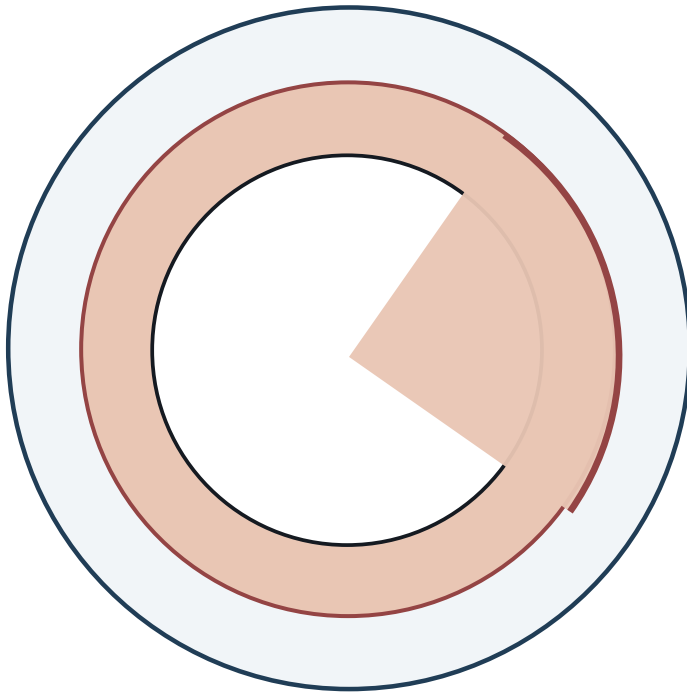
- Islet number and size can increase in newborns of mothers with diabetes.
- Maternal hyperglycemia stimulates the fetal endocrine pancreatic response.
- This observation concerns the infant pancreas, not chronic adult diabetic microangiopathy.
- It illustrates how one metabolic exposure can yield different morphology by developmental context.

Macroangiopathy: Accelerated atherosclerosis

- The hallmark is accelerated atherosclerosis in the aorta and large and medium arteries.
- Persistent hyperglycemia and insulin resistance contribute to endothelial dysfunction.
- The microscopic architecture of plaques is not distinct from nondiabetic atherosclerosis.
- Greater plaque burden raises the risk of major ischemic complications.

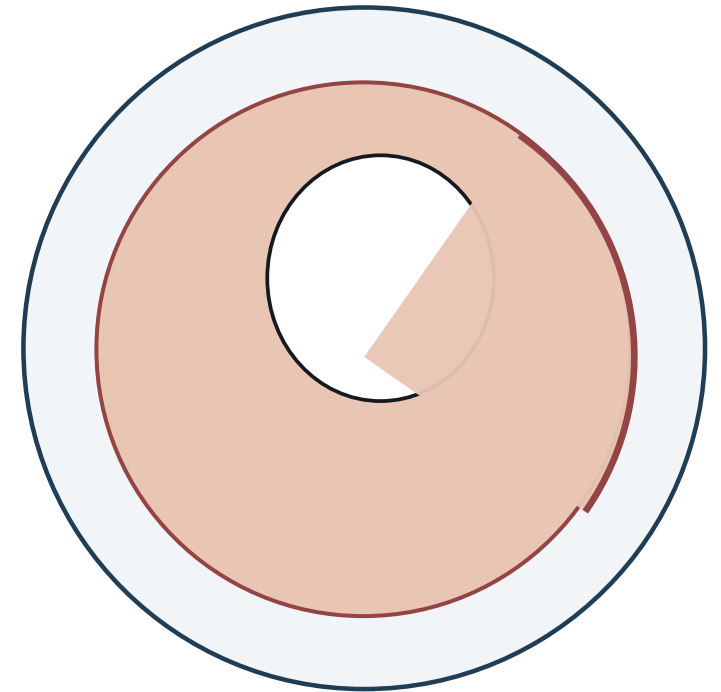
Atherosclerosis: Morphology versus burden

Conventional plaque morphology



Atherosclerotic intimal plaque

Accelerated occurrence in diabetes

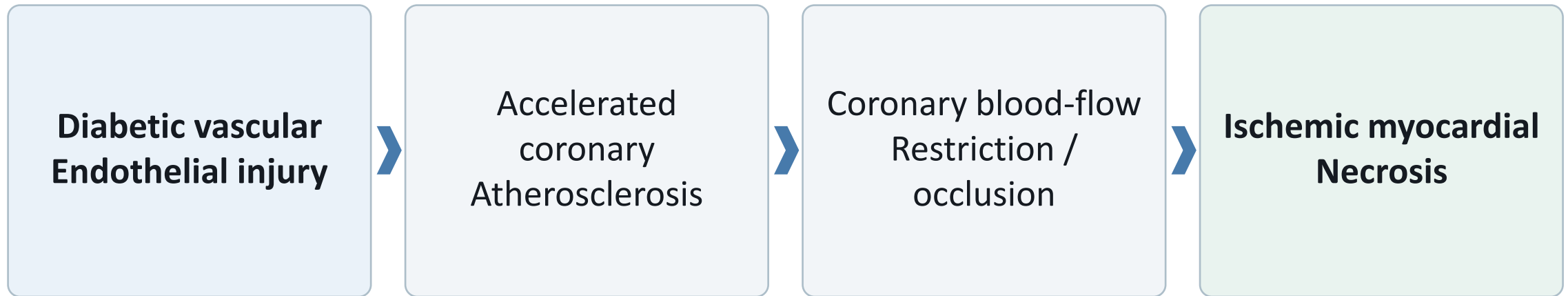


Greater plaque burden → ischemia

Endothelial dysfunction precedes ischemic outcomes

- Metabolic injury affects the vascular endothelium throughout the circulation.
- Endothelial dysfunction creates a milieu favoring atherogenesis.
- Large-vessel lesions then produce organ-specific ischemic events.
- Plaque appearance alone cannot reliably identify whether a patient has diabetes.

Coronary disease: Morphologic cause of myocardial infarction



Myocardial infarction is emphasized as the commonest cause of death section.

Peripheral arterial disease and gangrene

- Advanced atherosclerotic narrowing compromises perfusion of the lower limbs.
- Critical ischemia can progress to tissue necrosis and gangrene.
- Coexisting neuropathy and susceptibility to infection worsen limb complications.
- Gangrene is a tissue endpoint, not a specific histologic form of diabetic vasculopathy.

Diabetes also affects the cerebral circulation

- Accelerated large-vessel disease can contribute to cerebral infarction.
- The systemic complication map also includes cerebrovascular hemorrhage.
- Hypertension and atherosclerosis modify the pattern of vascular injury.
- These outcomes are consequences of vascular pathology, not primary islet lesions.

Renal arteries versus intrarenal microcirculation

Vascular level	Morphologic effect	Renal importance
Large renal arteries	Atherosclerotic narrowing	May contribute to ischemic injury
Glomerular capillaries	GBM thickening, mesangial sclerosis	Major determinant of diabetic nephropathy
Afferent / efferent arterioles	Hyaline arteriolosclerosis	Additional reduction in perfusion
Interstitial vasculature	Microangiopathic change	Contributes to chronic renal damage

Macrovascular lesions: Diagnostic interpretation

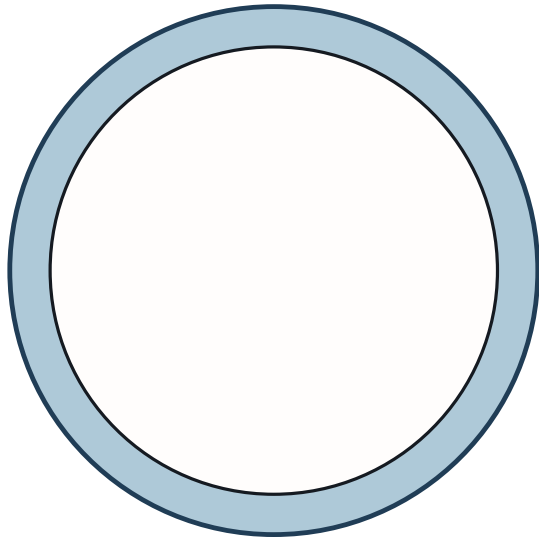
- Atherosclerosis itself is not histologically specific for diabetes.
- Clinical context establishes whether diabetes contributes to accelerated disease.
- Vascular territories must be assessed according to the organ affected.
- Renal dysfunction in diabetes may reflect far more than renal-artery plaque.

Diabetic microangiopathy: Defining lesion

- Diffuse basement-membrane thickening is among the most consistent microscopic findings.
- The lesion is prominent in capillaries of several organs.
- Some nonvascular basement membranes are also thickened.
- Despite thickening, permeability to plasma proteins increases.

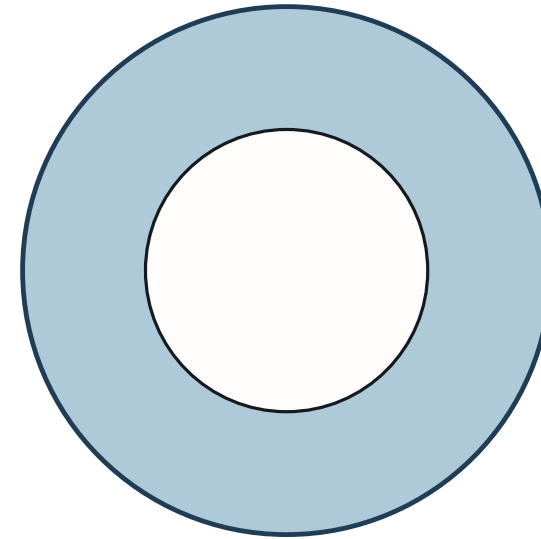
Basement-membrane thickening is not protection

Normal capillary



Thin basement membrane

Diabetic microangiopathy



Thick basement membrane
With abnormal permeability

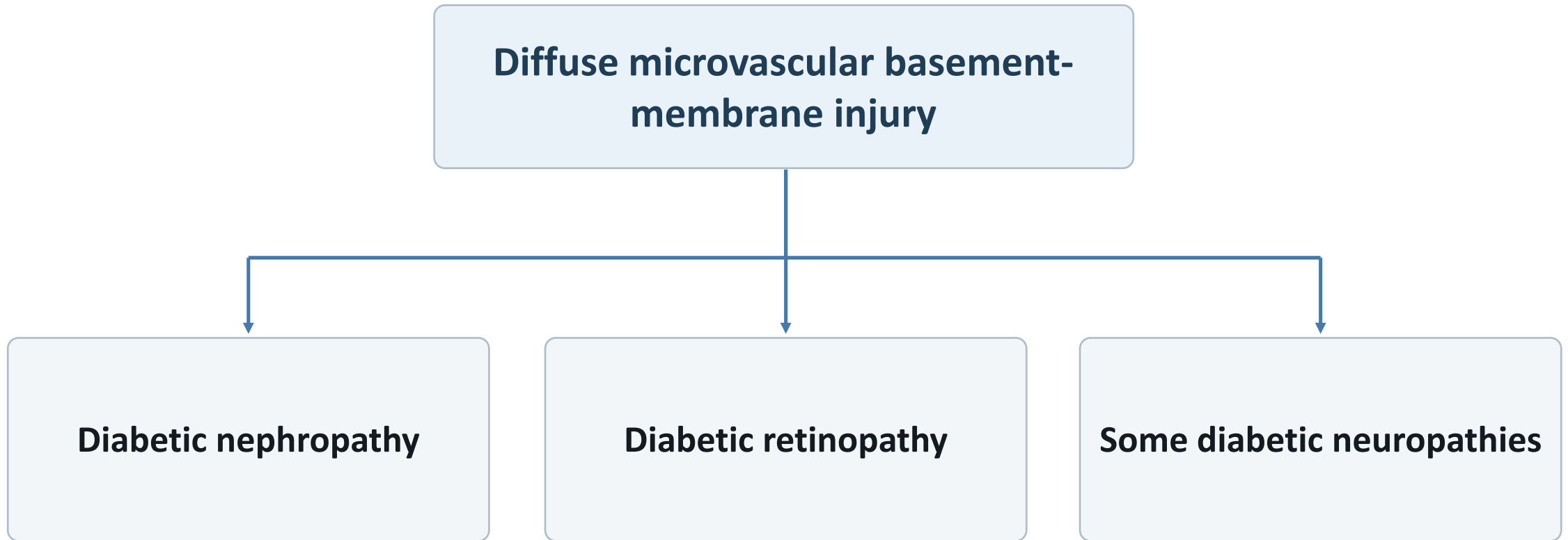
Where basement membranes thicken

Capillary locations	Additional basement-membrane sites
Skin and skeletal muscle	Peripheral nerves
Retina	Renal tubules
Renal glomeruli	Bowman capsule
Renal medulla	Placenta

Why a thicker capillary may still leak

- Diabetic basement-membrane thickening is not equivalent to a normal functional barrier.
- Capillaries remain abnormally permeable to plasma proteins.
- Matrix accumulation and endothelial dysfunction coexist.
- The morphologic lesion helps explain chronic microvascular organ damage.

Microangiopathy gives rise to three major syndromes



Three parallel organ consequences of a shared microangiopathic process.

Diabetic nephropathy: Three lesion families

Glomeruli	Renal vessels	Renal interstitium
GBM thickening	Atherosclerosis of renal arteries	Acute or chronic pyelonephritis
Diffuse mesangial sclerosis	Hyaline arteriolosclerosis	Papillary necrosis
Nodular glomerulosclerosis	Afferent and efferent injury	Tubular atrophy and fibrosis

Diabetic nephropathy is not one lesion

- Glomerular matrix injury is central to diabetic nephropathy.
- Arterial and arteriolar disease create additional perfusion deficits.
- Inflammatory infection-related injury can coexist in renal parenchyma.
- The relative contribution of each compartment varies across kidneys.

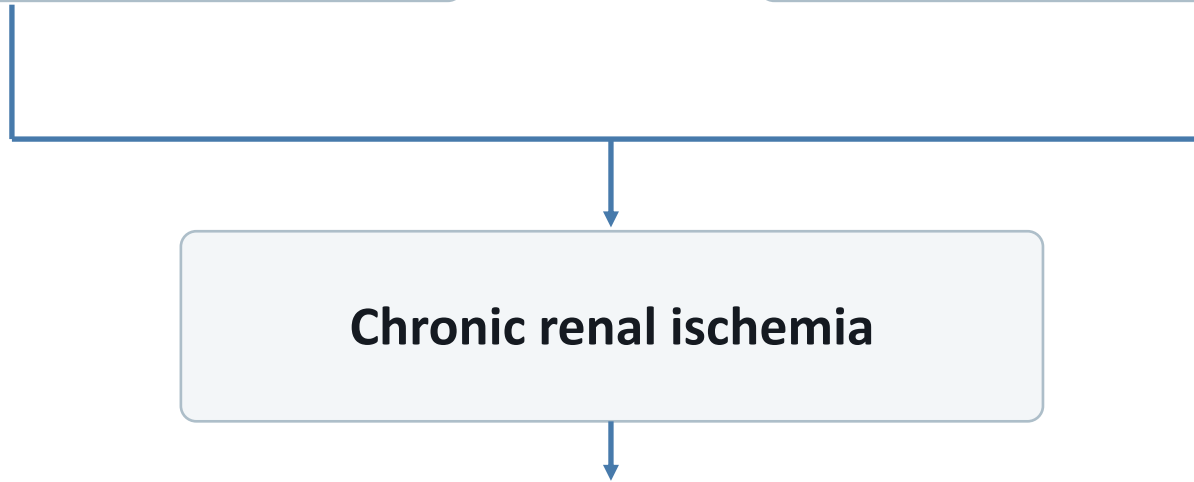
Renal tissue injury: A compartmental map

Glomerular matrix expansion

Arteriolar hyalinosis

Chronic renal ischemia

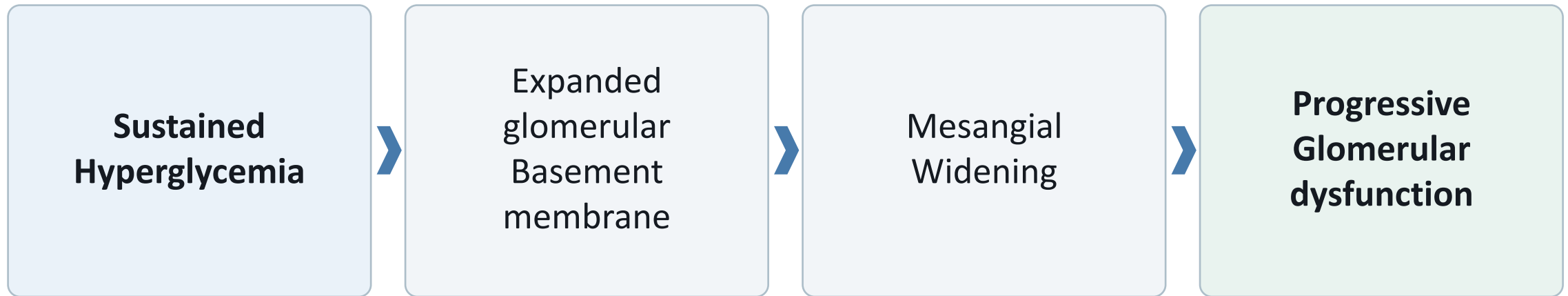
Tubular atrophy and interstitial fibrosis



Glomerular basement-membrane thickening

- The glomerular capillary basement membrane (GBM) thickens diffusely.
- This is a major manifestation of diabetic microangiopathy.
- Electron microscopy best demonstrates the increased GBM thickness.
- Thickened GBM commonly accompanies mesangial expansion.

GBM thickening: Early structural evolution



The source describes measurable GBM thickening early in type 1 diabetes.

Electron microscopy: What is assessed

- Measure or evaluate thickening of the glomerular capillary basement membrane.
- Interpret the capillary lumen, basement membrane and urinary space in correct orientation.
- Conventional light microscopy may not show early ultrastructural change adequately.
- Early ultrastructural change can precede advanced nodular glomerulosclerosis.

Tubular basement membranes are also thickened

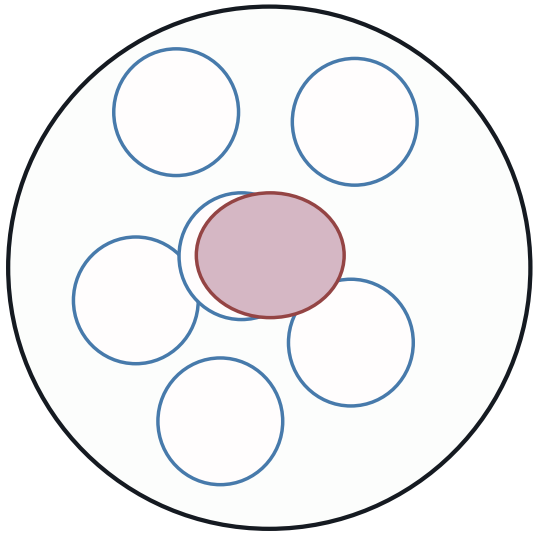
- Progressive GBM change is accompanied by thickening of tubular basement membranes.
- Both glomerular and tubular compartments are affected by the diabetic process.
- PAS highlights basement-membrane material on renal tissue sections.
- Tubular involvement should be considered in addition to the glomerular lesions.

Diffuse mesangial sclerosis: Defining feature

- There is a diffuse increase in mesangial matrix throughout affected glomeruli.
- Expanded mesangial areas stain positively with periodic acid–Schiff (PAS).
- The lesion reduces the proportion of normal patent capillary architecture.
- Diffuse mesangial expansion correlates with worsening renal function.

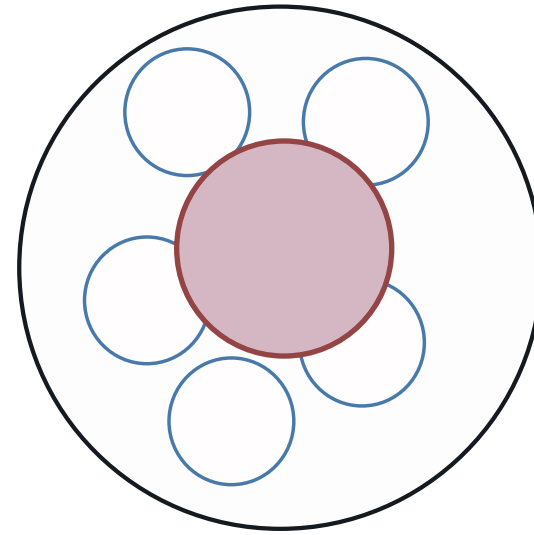
Diffuse versus nodular mesangial matrix

Diffuse mesangial sclerosis



PAS-positive expanded mesangial matrix

Nodular glomerulosclerosis

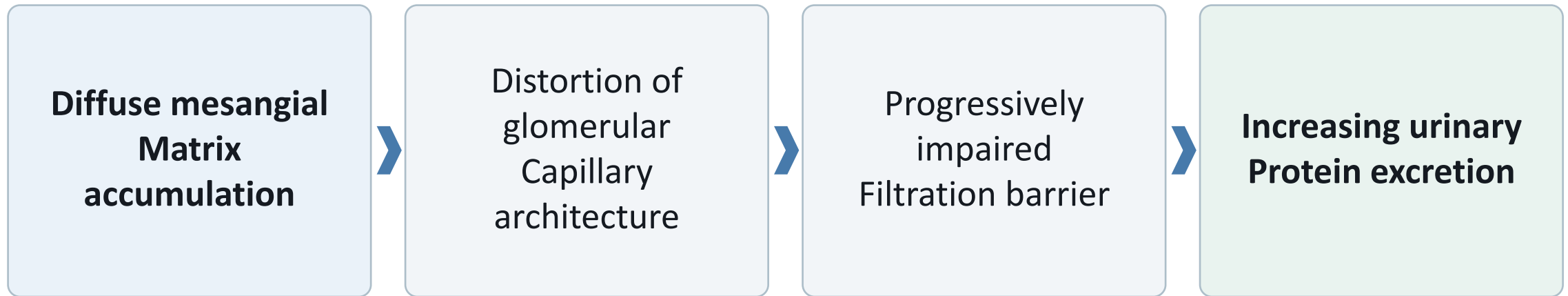


Ovoid PAS-positive mesangial nodule

PAS stain highlights renal matrix lesions

- PAS positivity brings basement-membrane and mesangial matrix material into relief.
- Diffuse mesangial sclerosis increases matrix across the tuft.
- Nodules are also PAS-positive but localized to mesangial regions.
- The stain demonstrates morphology; A diagnosis requires contextual interpretation.

Mesangial expansion and proteinuria



The source associates mesangial expansion with increasing proteinuria.

From diffuse matrix increase to nodules

- With disease progression, mesangial matrix deposits can become nodular.
- The background glomerulus often retains diffuse sclerosis.
- Nodularity is superimposed on, rather than a replacement for, diffuse injury.
- Not every glomerular lobule is affected by a nodule to the same degree.

Kimmelstiel–Wilson nodules

- Nodular glomerulosclerosis is also called intercapillary glomerulosclerosis.
- It is characterized by ovoid or spherical, often laminated, PAS-positive mesangial nodules.
- Nodules are commonly situated at the periphery of glomerular lobules.
- Adjacent glomerular capillary loops may remain patent or become markedly dilated.

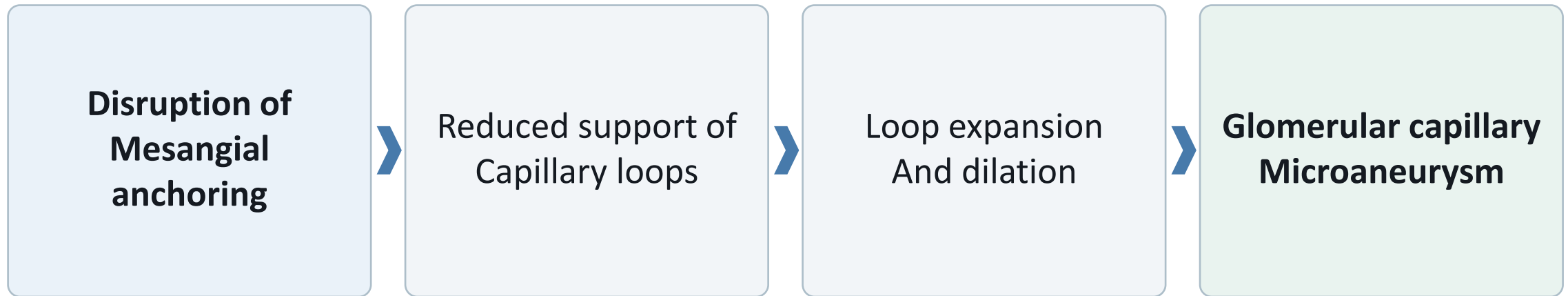
Where the nodules sit

- Nodules lie within the mesangial cores of affected glomerular lobules.
- They must be distinguished spatially from the peripheral capillary lumina.
- Some lobules may show striking nodular change while others remain diffusely sclerotic.
- Appreciating this distribution is essential for recognizing nodular mesangial sclerosis.

Mesangiolysis and microaneurysm formation

- Mesangiolysis disrupts anchoring interactions between mesangial stalks and capillaries.
- Loss of structural support can permit glomerular capillary microaneurysm formation.
- The nodules may therefore coexist with dilated peripheral capillary loops.
- This mechanism links altered mesangial structure with capillary geometry.

How mesangiolytic changes a capillary loop



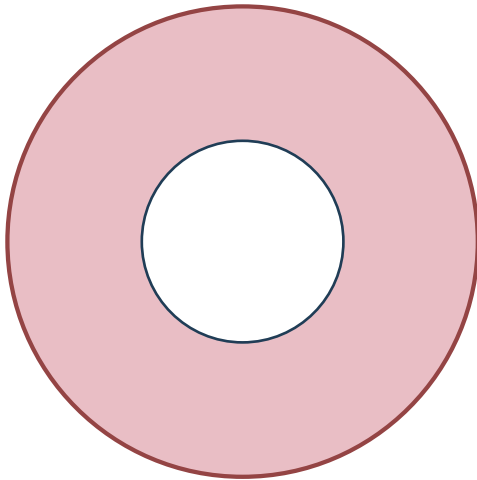
Mechanism describes a structural possibility, not a mandatory feature of every nodule.

Fibrin caps and capsular drops

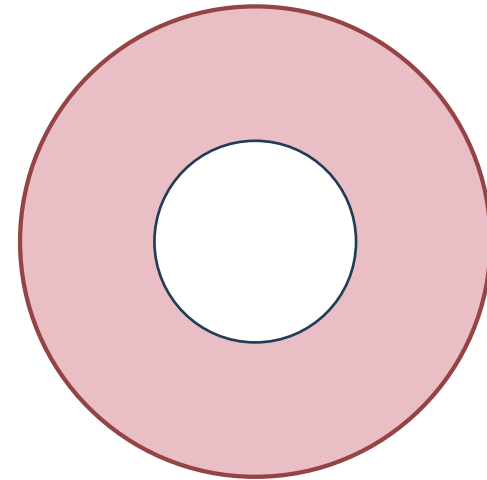
- Hyaline deposits can accumulate within glomerular capillary loops (“fibrin caps”).
- Other deposits adhere to the Bowman capsule (“capsular drops”).
- These lesions may accompany nodular glomerulosclerosis.
- The terms describe their histologic location, not separate kidney diseases.

Hyaline change can affect both glomerular arterioles

Afferent arteriole



Efferent arteriole



Hyaline wall thickening narrows the lumen

Efferent hyalinosis is especially suggestive of diabetes

Afferent and efferent arteriolar hyalinosis

- Diabetic renal hyaline arteriosclerosis affects afferent as well as efferent arterioles.
- Efferent-arteriolar hyalinosis is particularly unusual outside diabetes.
- Progressive hyaline deposition narrows arteriolar lumina.
- The resulting ischemia adds to glomerular damage.

Vascular and glomerular damage contract the kidney

**Glomerulosclerosis
And arteriolar
hyalinosis**



Chronic renal
Ischemia



Tubular atrophy
Interstitial fibrosis

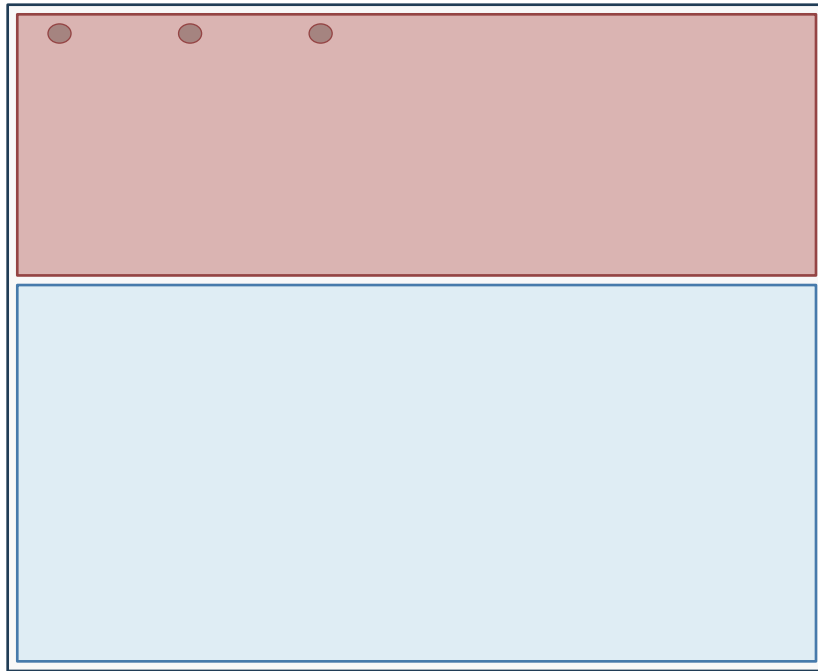


**Reduced cortical
Thickness and renal
size**

The characteristic late morphology integrates multiple renal compartments.

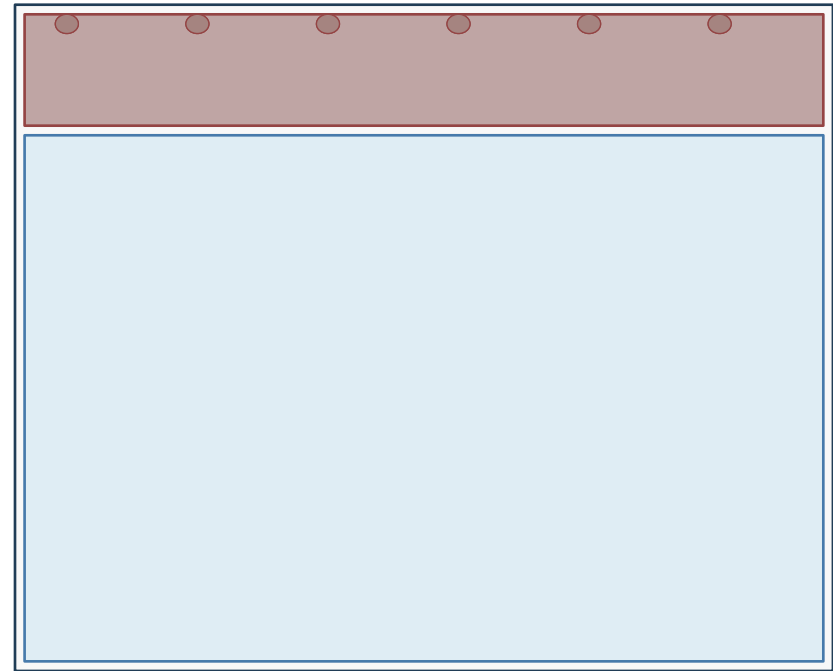
End-stage diabetic nephrosclerosis: Schematic

Relatively preserved cortex



Broad cortical compartment

Advanced diabetic nephrosclerosis



Thinned cortical compartment

Gross nephrosclerosis in long-standing diabetes

- Advanced diabetic kidneys may become contracted.
- The renal surface can develop diffuse granular change.
- Cortical tissue becomes markedly thinned.
- Irregular scars can be superimposed when pyelonephritis is present.

Renal morphology: Light microscopy to gross anatomy

Level	Signature finding	Interpretation
Electron microscopy	Thickened glomerular capillary basement membrane	Early microangiopathic change
Light microscopy / PAS	Diffuse mesangial matrix and/or nodules	Progressive glomerulosclerosis
Arterioles	Hyaline thickening; Afferent and efferent involvement	Compromised microvascular perfusion
Gross kidney	Granular surface, cortical thinning, contraction	Advanced chronic parenchymal scarring

Pyelonephritis complicates diabetes

- Both acute and chronic pyelonephritis are more frequent and severe in diabetes.
- The process generally begins within the renal interstitium.
- Inflammation can extend to and injure renal tubules.
- Infection-related scarring may coexist with diabetic glomerulosclerosis.

Papillary necrosis in diabetic pyelonephritis

- Renal papillary necrosis is a particularly important complication of acute pyelonephritis.
- The lesion reflects necrotizing injury to the renal papilla.
- It is encountered more often in patients with diabetes than without diabetes.
- It belongs to the infectious/necrotizing spectrum rather than glomerular nodular sclerosis.

Glomerular injury versus pyelonephritis

Glomerulosclerosis	Pyelonephritis
Glomerulus and its capillary matrix are central.	Tubulointerstitial inflammation is central.
GBM thickening; PAS-positive mesangial matrix.	Inflammation can spread into tubules.
Diffuse or nodular sclerosis may develop.	Acute or chronic patterns; Papillary necrosis.
Associated with proteinuria and chronic kidney dysfunction.	Adds infection-related damage and scarring.

Interpreting mixed diabetic renal disease

- A kidney can show simultaneous glomerular, vascular and interstitial lesions.
- An arteriolar lesion need not explain all observed glomerular injury.
- Conversely, glomerular matrix disease need not explain every cortical scar.
- A compartment-based description is more informative than a single undifferentiated label.

Diabetic ocular complications: Three anatomic targets

Structure	Morphologic or anatomic change	Consequence
Lens	Acquired lens opacification	Cataract / blurred vision
Anterior chamber / optic nerve	Raised intraocular pressure; Optic-nerve damage	Glaucomatous visual impairment
Retinal microvasculature	Retinal vasculopathy; Possible neovascularization	Progressive retinopathy

Cataracts: Loss of lens transparency

- Diabetes-associated hyperglycemia promotes acquired lens opacification.
- Sorbitol accumulation is one contributor described in the metabolic context.
- A cataract is a structural optical complication rather than a retinal capillary lesion.
- It should be differentiated anatomically from glaucoma and retinopathy.

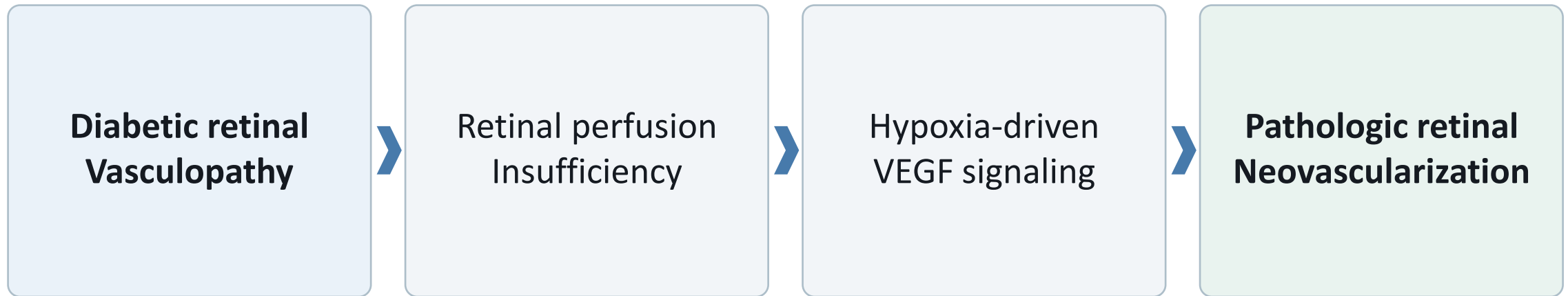
Glaucoma: Pressure-related optic-nerve injury

- Long-standing diabetes is associated with increased risk of glaucoma.
- Glaucoma involves elevated intraocular pressure and consequent optic-nerve damage.
- The relevant structural injury is not an islet or glomerular lesion.
- Visual loss in diabetes may arise by more than one ocular pathway.

Background versus proliferative retinopathy

Background / preproliferative	Proliferative
Retinal vascular injury without defining new-vessel proliferation.	New-vessel growth becomes the prominent distinguishing feature.
Reflects chronic diabetic retinal microangiopathy.	Can be driven by hypoxia-induced VEGF expression.
Potential for progression remains.	Fragile new vessels threaten visual function.

Retinal hypoxia to neovascularization



This mechanistic context is stated in the neighboring Robbins clinical-complications section.

Peripheral nerves: Another microvascular target

- Diabetic neuropathy is common, particularly in long-standing diabetes.
- The source identifies peripheral nerves among sites of basement-membrane thickening.
- Some neuropathic injury is associated with diabetic microangiopathy.
- The nervous-system phenotype is elaborated in the neighboring clinical section.

Diabetic neuropathy: Clinical-anatomic patterns

- Distal symmetric sensorimotor neuropathy commonly begins in the lower limbs.
- More advanced disease may produce a stocking-and-glove distribution.
- Autonomic neuropathy can disturb visceral function.
- Some patients develop focal mononeuropathies, including cranial-nerve palsies.

Neuropathy, ischemia and infected foot lesions

Neuropathy → unrecognized injury

Peripheral arterial insufficiency

Impaired wound defense

Infection, tissue necrosis and gangrene



Application: Recognize a diabetic glomerular pattern

A long-standing diabetic patient has proteinuria. Renal histology shows diffuse PAS-positive mesangial expansion, rounded peripheral mesangial nodules, and hyaline change in both glomerular arterioles.

Which three morphologic lesions should be named?

Application: Renal pattern — interpretation

The glomerulus contains diffuse mesangial sclerosis and nodular (Kimmelstiel–Wilson) sclerosis. Both afferent and efferent arterioles exhibit hyalinosis.

Morphologic synthesis: Diabetic glomerulosclerosis with arteriolar hyalinosis.

Application: Distinguish tissue compartments

A kidney from a patient with diabetes has nodular glomerular sclerosis together with cortical depressions attributed to previous pyelonephritis.

Are these two morphologic findings synonymous?

Application: Separate coexisting renal lesions

Nodular matrix expansion belongs to glomerulosclerosis. Irregular pyelonephritic scarring reflects a tubulointerstitial inflammatory process. Both can coexist.

Answer: Separate lesions in distinct renal compartments.

Application: Ocular mechanism

A diabetic patient develops retinal vascular complications with abnormal new-vessel growth. The associated vascular response is linked to retinal ischemia.

Which named growth factor connects retinal hypoxia to neovascularization?

Application: Ocular mechanism — answer

Retinal ischemia leads to hypoxia-induced VEGF signaling. VEGF is implicated in the development of proliferative retinal neovascularization.

Answer: Vascular endothelial growth factor (VEGF).

Integrating the morphologic phenotypes

Anatomic system	Dominant structural change	High-value recognition cue
Pancreatic islet	Insulitis / islet depletion / amyloid	Differentiate type 1 from type 2 patterns
Large vessels	Accelerated atherosclerosis	Plaque morphology itself is not unique
Microvasculature	Diffuse basement-membrane thickening	A thick wall can still be leaky
Kidney	Diffuse / nodular mesangial sclerosis	Kimmelstiel–Wilson nodule and efferent hyalinosis
Eye / nerves	Retinal neovascular response; Neural damage	Organ-specific consequences of chronic injury

Core morphology to retain

- Macroangiopathy is accelerated ordinary atherosclerosis; Microangiopathy is basement-membrane thickening with dysfunction.
- The renal hallmark combines GBM thickening, diffuse mesangial sclerosis and sometimes Kimmelstiel–Wilson nodules.
- Efferent as well as afferent arteriolar hyalinosis is an important diabetic renal clue.
- Infectious papillary necrosis, retinal neovascularization, lens opacity and neuropathy involve distinct compartments.

Principal source and figure provenance

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026), The Endocrine System, chronic diabetic complications section.

Course diagrams are original PowerPoint schematics, not clinical or histologic specimens.

Source figures 24.34–24.39 were used as conceptual references only; their original artwork was not reproduced.