

Clinical Manifestations of Chronic Diabetes

Vascular, renal, ocular, neural, and infectious complications

Clinicopathologic consequences of sustained hyperglycemia

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

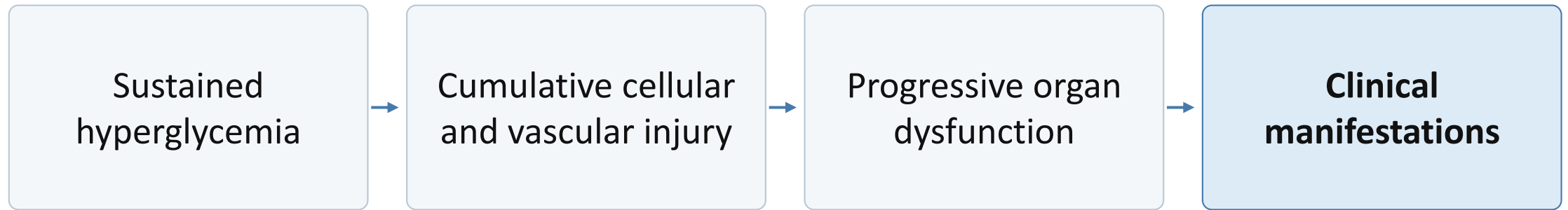
Learning objectives

- Explain why cumulative glycemic exposure is central to late diabetic morbidity.
- Differentiate macrovascular events from microvascular organ damage.
- Relate characteristic kidney, eye, and nerve lesions to clinical manifestations.
- Explain how impaired host defense and vascular injury compound infection risk.

Chronic injury dominates the long-term burden

- Long-term complications, rather than acute metabolic crises, account for most diabetes-related morbidity and mortality.
- The major targets are blood vessels, renal tissue, retina, peripheral nerves, and host-defense mechanisms.
- An apparently stable metabolic state does not exclude progressive tissue injury.

Time and glycemic exposure determine severity



Complications often become clinically evident 15–20 years after hyperglycemia begins; Timing varies among individuals.

Clinical latency does not imply absent injury

- The interval before symptomatic disease is often prolonged.
- Structural changes can accumulate before overt renal, retinal, or neurologic symptoms develop.
- The apparent onset of a complication may occur well after the pathological process has started.

Macrovascular versus microvascular disease

Feature	Macrovascular injury	Microvascular injury
Primary vessels	Large and medium arteries	Capillaries and small vessels
Characteristic process	Accelerated atherosclerosis	Basement-membrane and tissue injury
Clinical targets	Heart, brain, limbs, renal arteries	Kidney, retina, peripheral nerves
Typical consequence	Infarction or ischemia	Leakage, fibrosis, organ dysfunction

The multisystem complication map

Chronic diabetes

ARTERIAL SYSTEM

MI · stroke · limb ischemia

KIDNEY

Albuminuria · renal failure

EYE

Retinopathy · visual loss

NERVES

Distal · autonomic · focal
deficits

HOST DEFENSE

Skin and systemic infections

Why complications occur in both major diabetes types

- Type 1 diabetes produces absolute insulin deficiency through autoimmune β -cell destruction.
- Type 2 diabetes combines insulin resistance with β -cell dysfunction.
- Despite different upstream mechanisms, persistent hyperglycemia produces overlapping late vascular complications.

Hyperglycemia is necessary context, not the whole story

Glucose exposure

Long duration and high degree of hyperglycemia promote tissue damage.

Insulin resistance

Contributes to endothelial dysfunction and atherogenic dyslipidemia.

Comorbidity

Hypertension and obesity further increase vascular stress.

Four implicated metabolic injury routes

Advanced glycation

AGE formation and receptor signaling

Protein kinase C

DAG-driven signaling alterations

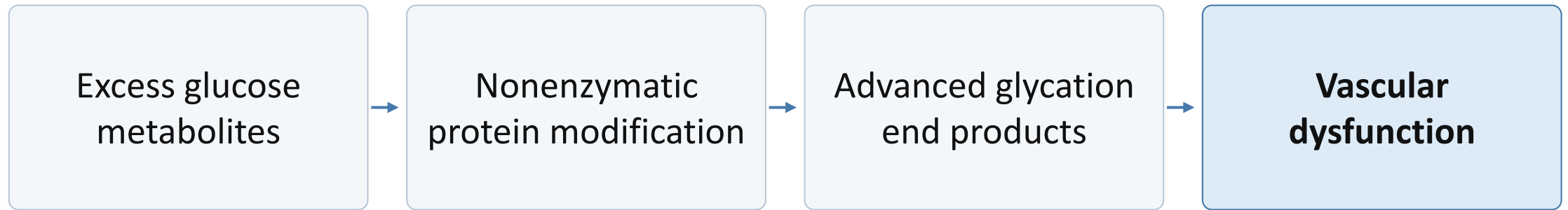
Polyol pathway

Sorbitol and oxidative stress

Hexosamine flux

Altered glucose-metabolite handling

AGE generation alters vascular biology



AGEs arise within and outside cells and can act through RAGE, the receptor for AGEs.

AGE–RAGE signaling links glucose to inflammation

Inflammatory signaling

RAGE in macrophages, T cells, and endothelium amplifies injurious responses.

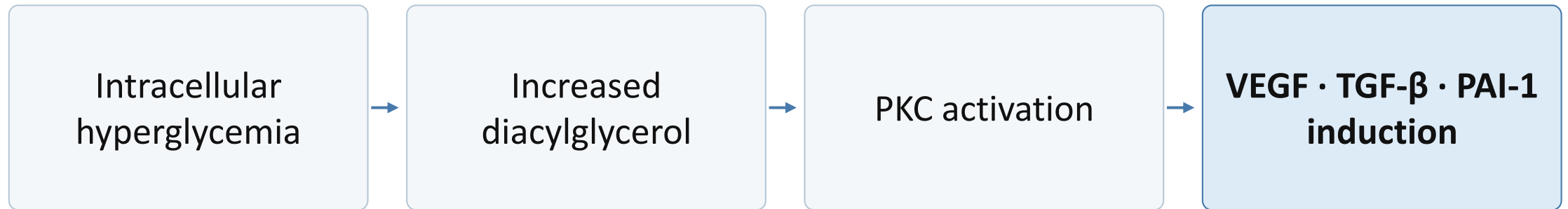
Matrix remodeling

TGF- β signaling promotes excess basement-membrane material.

Vascular dysfunction

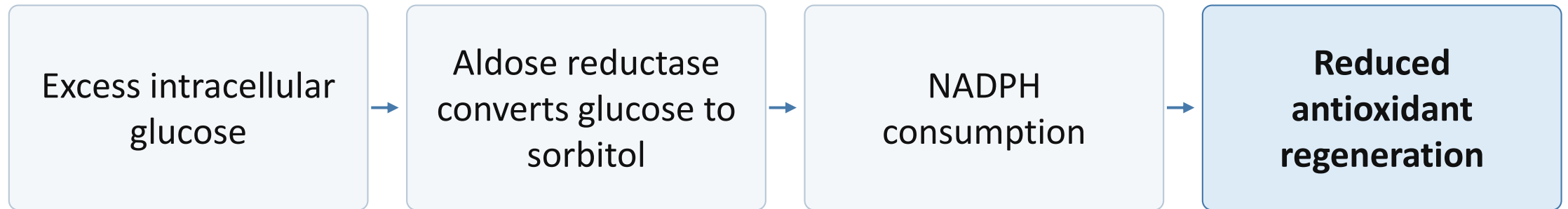
Reactive oxygen species, procoagulant activity, and smooth-muscle proliferation increase.

Protein kinase C alters the vascular milieu



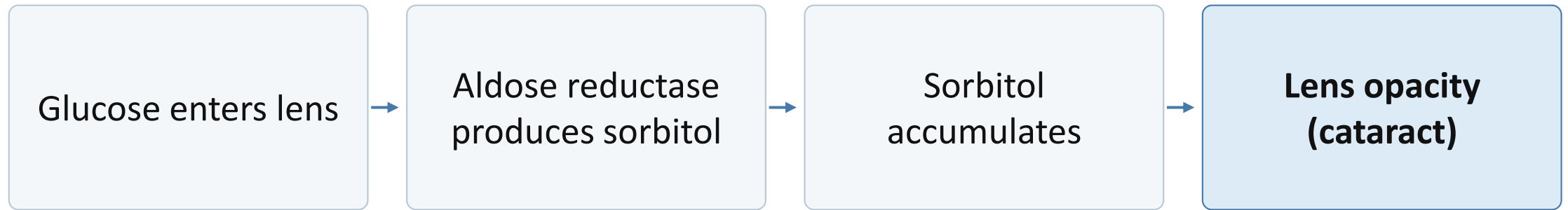
PKC effects overlap with AGE–RAGE signaling in diabetic microangiopathy.

The polyol pathway consumes reducing capacity



GSH regeneration requires NADPH; Less GSH increases susceptibility to oxidative injury.

Sorbitol links hyperglycemia to lens damage

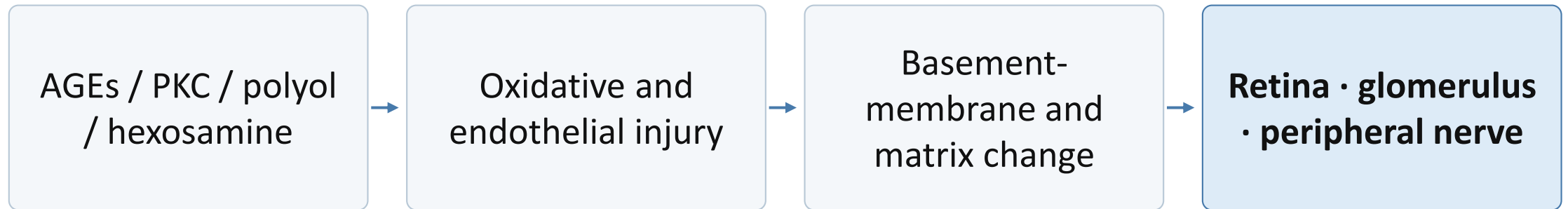


Conceptual simplification of the polyol contribution to diabetic cataract; Not a specimen illustration.

The hexosamine pathway: A proposed contributor

- Increased glucose flux diverts glycolytic intermediates through the hexosamine pathway.
- This mechanism has been proposed to enhance cell injury and oxidative stress.
- It may contribute to insulin resistance and vascular complications; Do not treat it as the sole mechanism.

Different mechanisms converge on the microvasculature



This is a conceptual synthesis; The four pathways are interacting and not a proven linear sequence.

HbA1c summarizes cumulative glucose exposure

- HbA1c is produced by nonenzymatic glucose addition to erythrocyte hemoglobin.
- It provides a longer-term measure of glycemic exposure than a single plasma glucose value.
- Prospective studies support attenuation of late end-organ damage through effective glycemic control.

Glycemic control and risk reduction are related

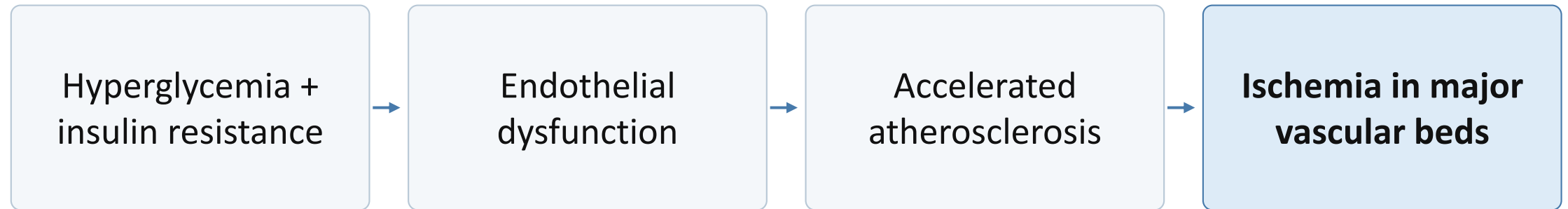
Supported causal relationship

Greater degree and duration of hyperglycemia are associated with more severe chronic injury.

Clinical implication

Reducing sustained hyperglycemia can attenuate, although not necessarily eliminate, late complications.

Macrovascular disease is accelerated atherosclerosis



The microscopic morphology of plaques resembles nondiabetic atherosclerosis; Their accelerated occurrence is key.

The principal large-vessel territories

Coronary

Atherosclerotic coronary disease → myocardial infarction.

Cerebrovascular

Large-vessel disease → cerebrovascular accidents and ischemic injury.

Peripheral

Lower-limb arterial disease → ischemia and risk of gangrene.

Coronary disease carries major mortality risk

2–4×

Higher incidence of coronary artery disease

4×

Higher risk of cardiovascular death

These comparisons against age-matched individuals without diabetes.

Myocardial infarction as a diabetic complication

- Coronary atherosclerosis underlies a major proportion of diabetes-associated mortality.
- Diabetes combines adverse vascular biology with common cardiovascular risk factors.
- A myocardial infarction is a macrovascular manifestation, not a defining microangiopathic lesion.

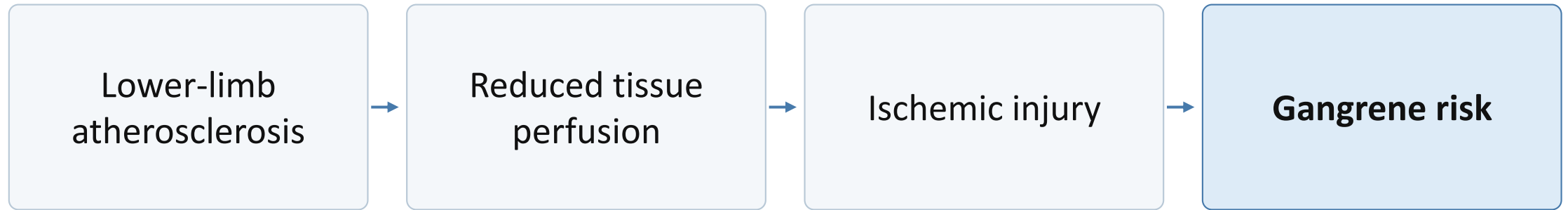
Diabetes modifies the sex pattern of infarction

- Myocardial infarction occurs nearly as often in females with diabetes as in males with diabetes.
- This differs from the lower incidence in reproductive-age females without diabetes.
- The comparison emphasizes that diabetes markedly changes the cardiovascular risk profile.

Cerebrovascular accidents belong to the vascular spectrum

- Brain vascular events are major causes of death and disability in longstanding diabetes.
- Accelerated atherosclerosis is an important substrate for large-vessel cerebrovascular injury.
- A focal neurologic deficit should not be attributed automatically to diabetic neuropathy.

Peripheral artery injury creates threatened limbs



Ischemia may coexist with sensory neuropathy and infection.

Renal arteries and glomeruli can both be affected

Macrovascular renal injury

Atherosclerosis of larger renal arteries contributes to renal vascular insufficiency.

Microvascular renal injury

Glomerular and arteriolar disease is especially important for diabetic nephropathy.

Hypertension compounds cardiovascular damage

~75%

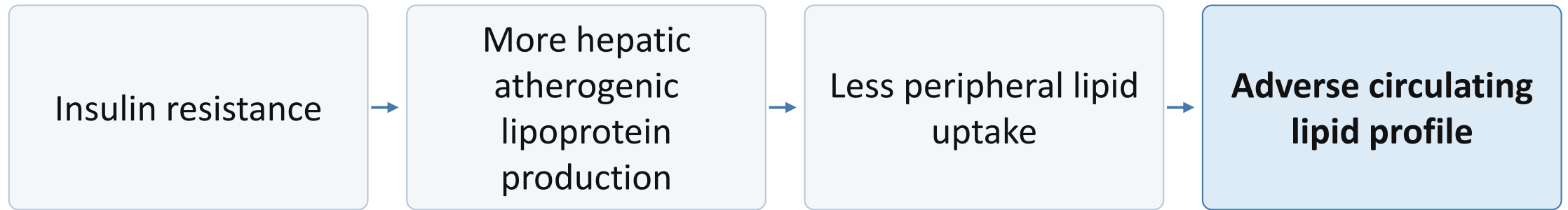
Hypertension reported among people with type 2 diabetes

High blood pressure potentiates hyperglycemia- and insulin-resistance-associated endothelial dysfunction and atherosclerosis.

Diabetic dyslipidemia is atherogenic

Lipid component	Typical direction in diabetes	Relevance
Triglycerides	Increased	Atherogenic metabolic profile
LDL cholesterol	Increased	Atherosclerotic burden
HDL cholesterol	Decreased	Reduced protective lipoprotein fraction

Insulin resistance contributes to dyslipidemia



This as a likely contributor, not an exclusive explanation.

Clinical vascular risk is cumulative

Hyperglycemia

Directly damages the vasculature over time.

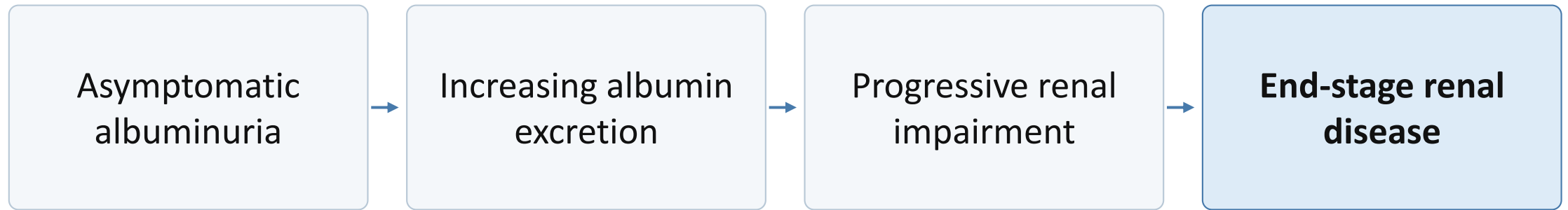
Hypertension

Adds hemodynamic stress to already impaired endothelium.

Dyslipidemia

Favors accelerated atheromatous disease.

Diabetic nephropathy has a broad clinical spectrum



This is a schematic spectrum, not a guaranteed progression in every patient.

Albuminuria can precede symptomatic kidney disease

- The earliest recognized clinical manifestation is low-grade urinary albumin excretion.
- The textbook uses “moderately increased albuminuria” instead of the older “microalbuminuria.”
- A lack of symptoms should not be interpreted as absence of renal microvascular injury.

Interpreting the albuminuria terminology

Older terminology	Preferred wording in source	24-hour urinary albumin
Microalbuminuria	Moderately increased albuminuria	>30 and <300 mg/day
Macroalbuminuria	Severely increased albuminuria	>300 mg/day

Diabetic nephropathy is clinically consequential

30–40%

Patients with diabetes developing clinical evidence of
nephropathy

The source identifies diabetic nephropathy as a leading cause of end-stage renal disease in the United States.

The progression to overt nephropathy differs by type

~80%

T1D, without specific intervention

20–40%

T2D, without specific intervention

Textbook estimates for overt nephropathy developing over 10–15 years; These are historical source estimates, not individualized predictions.

Hypertension and albuminuria often appear together

- Overt diabetic nephropathy is often accompanied by hypertension.
- Glomerular injury, arteriolar disease, and renal ischemia contribute to functional decline.
- The kidney is affected by both systemic vascular risk and intrarenal microvascular damage.

Glomerular basement-membrane thickening



Basement-membrane thickening is a structural hallmark; No authentic electron micrograph was provided.

Microangiopathy can cause leakage despite thickening

Morphologic finding

Capillary basement membranes thicken in diabetic microangiopathy.

Functional paradox

Capillaries nevertheless become more permeable to plasma proteins.

Diffuse mesangial sclerosis

- The mesangial matrix expands diffusely and is PAS-positive in tissue sections.
- Greater mesangial expansion correlates with increasing proteinuria.
- Progression may produce nodular mesangial deposits.

Nodular sclerosis: Kimmelstiel–Wilson lesions

- Rounded, frequently laminated PAS-positive nodules form in the glomerular mesangium.
- This distinctive pattern occurs with widespread background diffuse mesangial sclerosis.
- The nodular process is often associated with advanced renal dysfunction.

Renal arteriolar hyalinosis

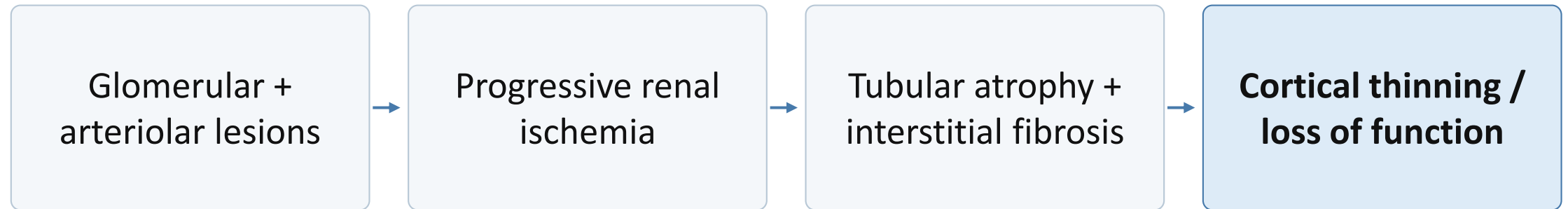
Afferent arteriole

Hyaline wall change contributes to altered glomerular perfusion.

Efferent arteriole

Hyalinosis is also prominent here and is particularly characteristic of diabetes.

How nephron injury culminates in renal failure



Process schematic derived from the morphology section; Not a direct clinical timeline.

Pyelonephritis is a parallel renal threat

- Acute and chronic pyelonephritis are more frequent and severe in patients with diabetes.
- Infection primarily affects the interstitium and tubules rather than beginning as glomerulosclerosis.
- Papillary necrosis is an important associated destructive complication.

Renal vascular injury versus renal infection

Feature	Diabetic nephropathy	Pyelonephritis
Principal injury	Glomeruli, microvessels, renal parenchyma	Infection-related interstitial and tubular inflammation
Common consequence	Albuminuria and chronic renal decline	Acute or chronic infectious injury
Characteristic context	Glomerulosclerosis / arteriolar hyalinosis	Greater susceptibility and severity in diabetes

The eye has three major diabetes-associated pathways

Retina

Microvascular retinopathy threatens central visual function.

Lens

Hyperglycemia promotes opacification and cataract.

Optic nerve

Glaucoma-related pressure injury contributes to impairment.

Diabetic retinopathy: A major cause of visual loss

60–80%

Estimated to develop some form of diabetic retinopathy

Diabetic retinopathy as a leading cause of adult blindness in the United States.

Retinopathy has nonproliferative and proliferative forms

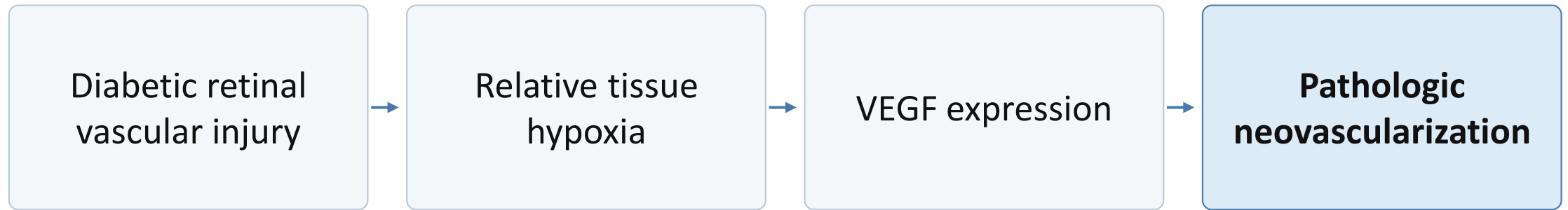
Background / nonproliferative

Earlier retinal vasculopathy without the defining new-vessel growth of proliferative disease.

Proliferative

Retinal hypoxia—associated VEGF signaling drives pathologic neovascularization.

Retinal hypoxia drives VEGF release

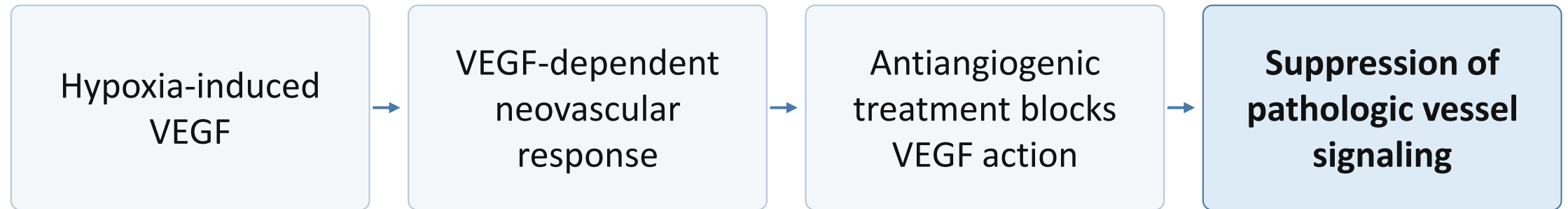


VEGF: Vascular endothelial growth factor; This diagram represents the proliferative pathway.

Why neovascularization matters to vision

- New vessel formation reflects maladaptive responses to retinal hypoxia.
- It is a characteristic advanced retinopathy mechanism highlighted by Robbins.
- The clinical endpoint is progressive visual impairment and potentially blindness.

Anti-VEGF treatment targets a causal mediator



Therapeutic mechanism only; No regimen, dose, or treatment-selection criteria implied.

Cataracts and glaucoma are not retinopathy

Condition	Primary tissue/process	Clinical outcome
Cataract	Lens opacity associated with hyperglycemia	Visual impairment
Glaucoma	Elevated intraocular pressure and optic nerve injury	Visual impairment
Retinopathy	Retinal microvascular injury $\pm$ neovascularization	Visual impairment or blindness

Neuropathy can affect several neural compartments

Distal peripheral nerves

Most frequent presentation;
Sensorimotor polyneuropathy.

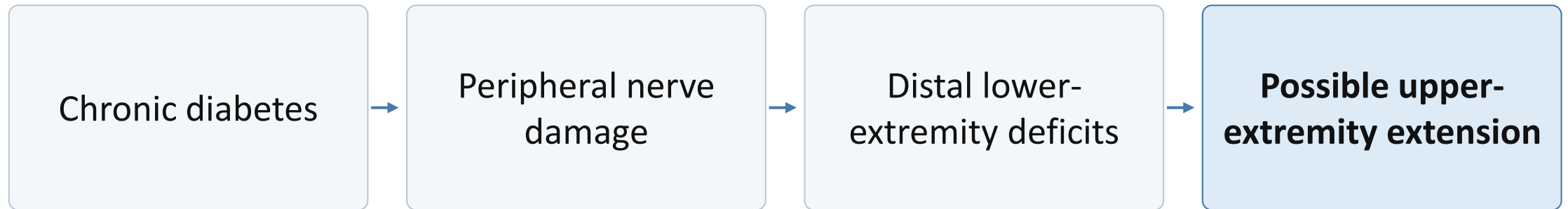
Autonomic nerves

Bowel, bladder, and sexual-function disturbances.

Individual nerves

Mononeuropathy with a localized motor or cranial-nerve deficit.

Distal symmetric polyneuropathy is the usual pattern



The usual distribution becomes a stocking-and-glove pattern over time.

The stocking-and-glove pattern has clinical meaning

- Distal symptoms commonly begin in the feet and lower legs.
- Upper-extremity involvement may develop later, producing a glove-and-stockings distribution.
- The pattern is typically bilateral and symmetric, unlike isolated focal mononeuropathy.

Neuropathy affects both sensory and motor function

Sensory involvement

Distal sensory deficits may interfere with detection of minor injuries.

Motor involvement

Peripheral sensorimotor injury may impair motor function and mobility.

Autonomic neuropathy causes visceral dysfunction

Gastrointestinal

Disturbances of bowel function.

Urinary

Bladder dysfunction.

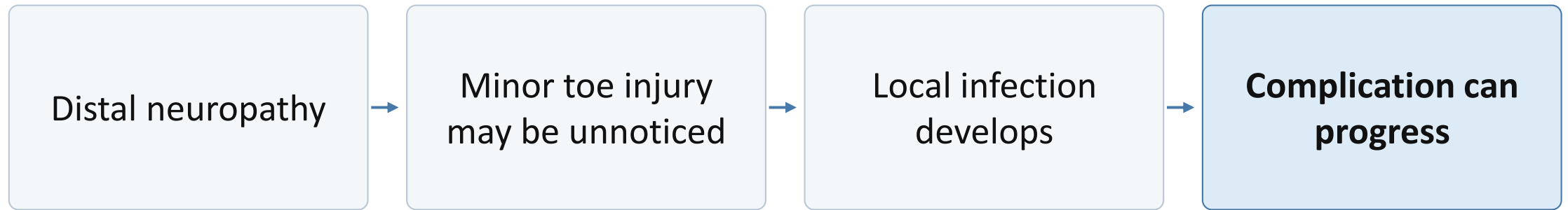
Genitourinary

Erectile dysfunction in some patients.

Mononeuropathy creates focal clinical deficits

Presentation	Pattern	Interpretation
Footdrop	Focal lower-limb motor deficit	Possible diabetic mononeuropathy
Wristdrop	Focal upper-limb motor deficit	Possible diabetic mononeuropathy
Cranial nerve palsy	Isolated cranial deficit	Possible diabetic mononeuropathy

Sensory loss changes the significance of a minor wound



Clinical conceptual sequence; Diabetic vascular compromise worsens local host defense.

Diabetes increases susceptibility to several infections

Skin and soft tissue

Local infection may initiate a severe limb complication.

Respiratory

Pneumonia and tuberculosis are emphasized in the source.

Urinary tract

Pyelonephritis is more common and often more severe.

Neutrophil dysfunction contributes to infection risk

Chemotaxis

Abnormal migration toward infection

Adhesion

Impaired endothelial interaction

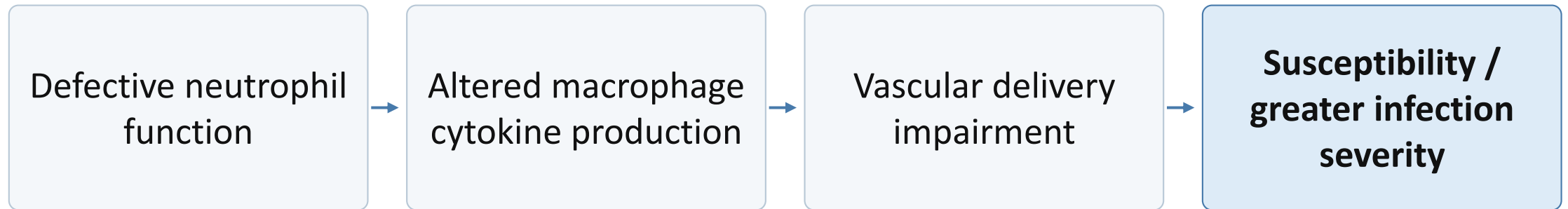
Phagocytosis

Reduced microbial ingestion

Killing

Impaired microbicidal activity

Host-defense impairment is multifactorial

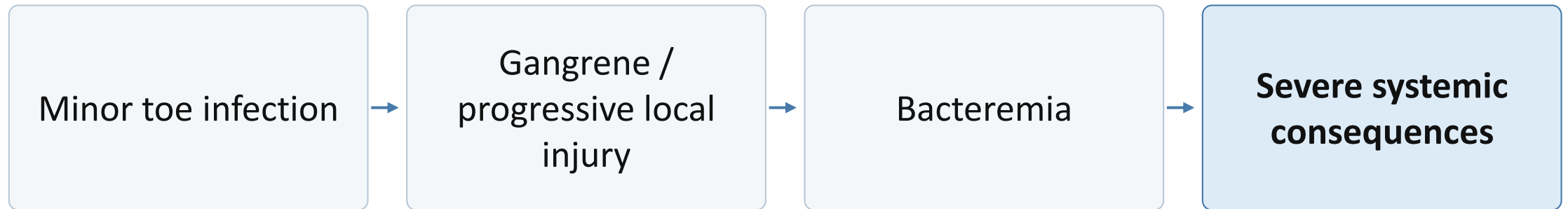


Multiple parallel contributing processes are shown in a linear layout for clarity; Not a strict biochemical sequence.

Vascular compromise limits immune-cell delivery

- Compromised vascular supply restricts access of defensive cells and soluble immune components.
- A local infection may become difficult to contain when circulation is impaired.
- Vascular injury and leukocyte functional impairment reinforce one another.

A diabetic toe infection can become systemic



Adapted from the illustrative clinical cascade; Not a deterministic patient trajectory.

The diabetic limb problem is a three-way interaction

NEUROPATHY	VASCULAR INJURY	INFECTION
Impaired injury detection	Reduced tissue perfusion	Defective local defense

All three factors may contribute to the escalation of a minor foot lesion.

Case: Painless toe wound with spreading infection

A person with long-standing diabetes does not notice a small toe injury. Local infection progresses while the foot shows evidence of poor perfusion.

- Which two chronic complications explain the vulnerability?
- How can infection progress beyond the initial lesion?

Clinicopathologic interpretation

Distal neuropathy reduces awareness of injury; Arterial compromise and impaired leukocyte responses hinder containment.

Case: Asymptomatic urinary albumin excretion

A person with long-standing diabetes feels well but has persistently increased urinary albumin excretion and newly documented hypertension.

- Why can kidney damage be clinically silent at first?
- What tissue lesions explain the albumin leak?

Clinicopathologic interpretation

Early diabetic nephropathy can manifest through albuminuria before symptoms; Glomerular microangiopathy and mesangial changes alter permeability.

Case: Deteriorating sight in longstanding diabetes

A patient with years of hyperglycemia develops progressive visual impairment and retinal neovascularization is documented.

- What drives the new vessel formation?
- What treatment target is linked to this mechanism?

Clinicopathologic interpretation

Retinal hypoxia induces VEGF; Antiangiogenic agents can block VEGF-dependent signaling.

Case: Focal weakness versus distal neuropathy

Two people with diabetes present differently: One has bilateral distal foot sensory loss; Another develops sudden unilateral footdrop.

- Which presentation fits distal symmetric polyneuropathy?
- Which presentation suggests mononeuropathy?

Clinicopathologic interpretation

Bilateral distal loss fits polyneuropathy; An abrupt focal deficit is compatible with mononeuropathy, although alternative causes need clinical assessment.

Clinical clues localize diabetic complications

Clue	Probable organ system	Pathologic framework
Myocardial infarction / stroke	Large arteries	Accelerated atherosclerosis
Urinary albumin	Renal glomeruli	Microangiopathy / glomerulosclerosis
Retinal neovascularization	Retina	Hypoxia / VEGF signaling
Distal symmetric sensory loss	Peripheral nerves	Diabetic polyneuropathy
Recurrent severe infection	Immune system / tissue perfusion	Cellular and vascular host-defense defects

Clinical complications need simultaneous assessment

- Vascular events, kidney injury, eye disease, neuropathy, and infection susceptibility coexist in the same chronic disease.
- Recognition of one manifestation should increase attention to other end-organ compartments.
- Clinical features should be interpreted with exposure duration and concomitant vascular risks.

Long-term glycemic management has organ-level consequences

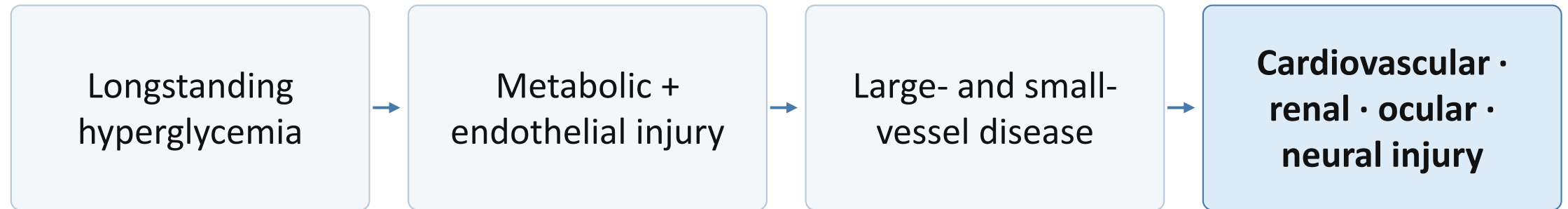
Reduction of chronic exposure

Effective control of hyperglycemia attenuates development of late end-organ injury.

Limits of glucose-only thinking

Insulin resistance, blood pressure, dyslipidemia, and obesity also affect complication risk.

Integrated mechanistic synthesis



Host-defense dysfunction and infection can amplify morbidity at any point.

Summary: Five clinical domains

Vascular

Myocardial infarction, stroke, limb ischemia.

Renal

Albuminuria progressing to glomerulosclerosis and renal failure.

Ocular

Retinopathy, cataracts, glaucoma, visual loss.

Neural

Distal symmetric, autonomic, or focal neuropathy.

Infectious

Impaired leukocytes plus compromised vascular delivery.

References and interpretation

- Primary teaching source: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed. (2026), Chapter 24, pp. 1006–1011.
- Core scope: “Clinical Manifestations of Chronic Diabetes”; mechanistic and morphologic context from adjacent diabetes sections.
- Numerical estimates are textbook-reported and should not be assumed to represent current population-specific risk.
- All diagrams are native PowerPoint schematics; no textbook photomicrographs are reproduced.