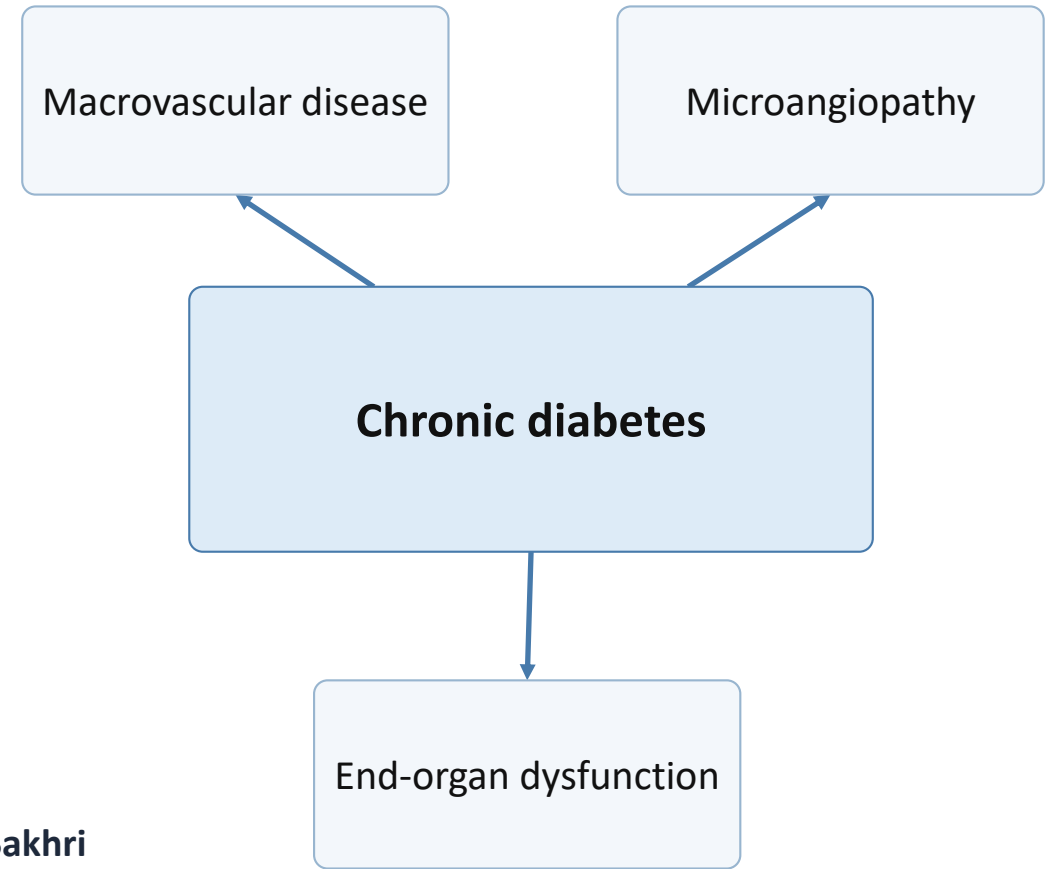


Chronic complications of diabetes

Persistent hyperglycemia drives cumulative tissue injury in both type 1 and type 2 diabetes.

- Large and medium arteries develop accelerated atherosclerosis.
- Small-vessel injury is prominent in the retina, kidneys and nerves.
- Metabolic pathways link glucose excess to inflammation, matrix accumulation and oxidative stress.



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Learning objectives

Explain chronic diabetic injury from metabolic pathways to organ damage.

- Distinguish macrovascular from microvascular complications.
- Trace AGE–RAGE, DAG–PKC, polyol and hexosamine pathways.
- Link vascular and cellular injury to renal, retinal and neural lesions.
- Interpret common clinicopathologic patterns and mechanisms.

Anatomical scale determines the dominant injury

Diabetic vascular injury affects several vessel sizes, with different consequences.

- Arteries: Accelerated atherosclerotic plaque burden.
- Arterioles and capillaries: Basement membrane and hyaline change.
- Microvascular lesions disrupt tissue exchange despite thickened basement membranes.

Large and medium arteries

Atherosclerosis

Myocardial infarction

Stroke / limb ischemia

Microvasculature

Basement membrane thickening

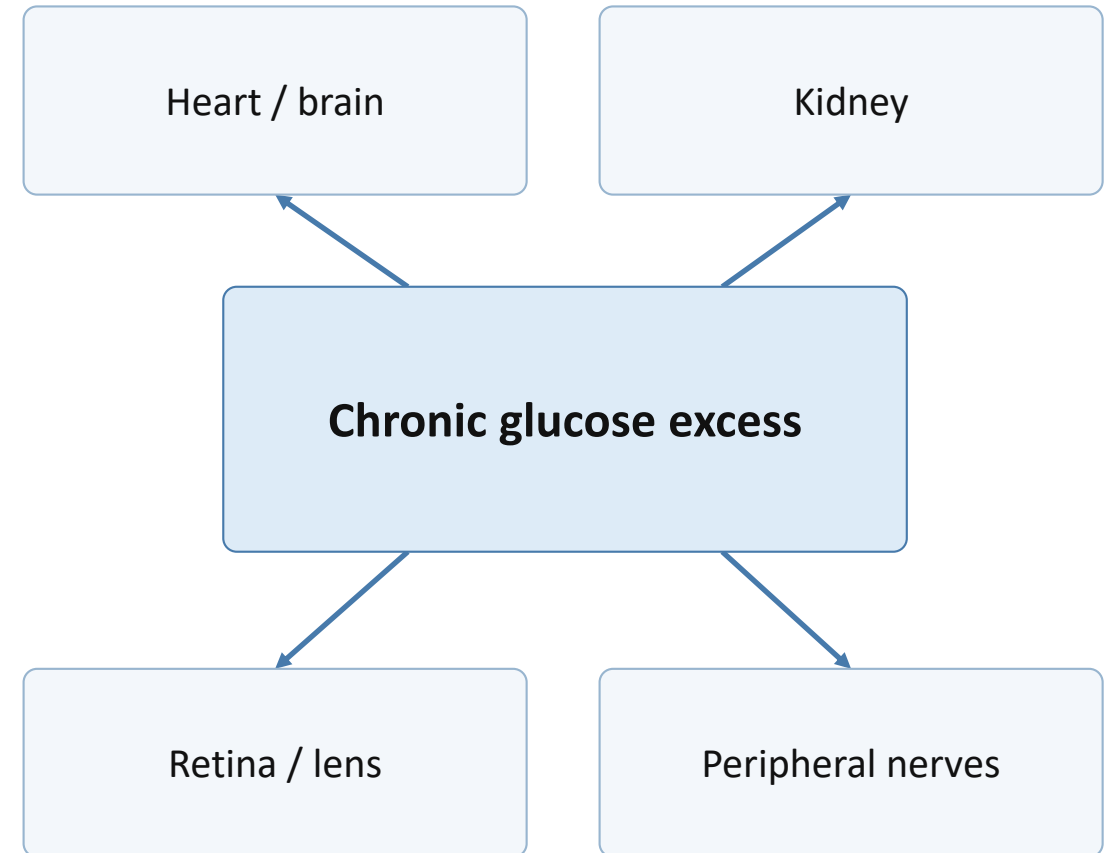
Renal / retinal injury

Some neuropathy

A multisystem disease

Organ manifestations differ, but share chronic exposure to metabolic and vascular stress.

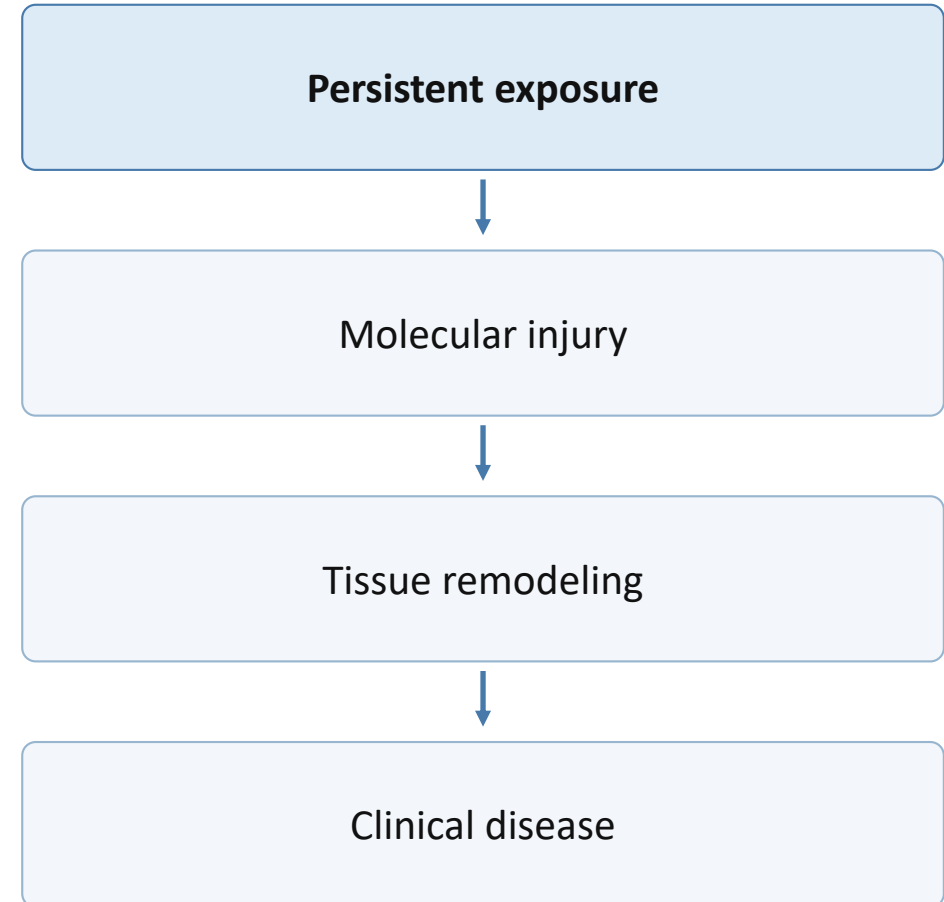
- Heart and brain: Ischemic events due to macrovascular disease.
- Kidney: Glomerular and microvascular structural damage.
- Eye: Retinal microangiopathy and lens abnormalities.
- Nerves and foot: Sensory loss compounded by ischemia and infection.



Exposure precedes overt organ dysfunction

Complications reflect cumulative disease burden, not a single glucose measurement.

- Degree and duration of hyperglycemia both matter.
- Structural changes may precede clinical symptoms.
- Intervening on glycemia attenuates end-organ damage; Risk does not disappear completely.



The same core pathways operate in both types

Type 1 and type 2 diabetes converge on sustained hyperglycemia.

- Type 1 diabetes: Absolute insulin deficiency is the central disturbance.
- Type 2 diabetes: Insulin resistance and β -cell dysfunction coexist.
- Once persistent hyperglycemia occurs, overlapping mechanisms injure vessels and organs.

Type 1 diabetes

Absolute insulin deficiency

Chronic hyperglycemia

Type 2 diabetes

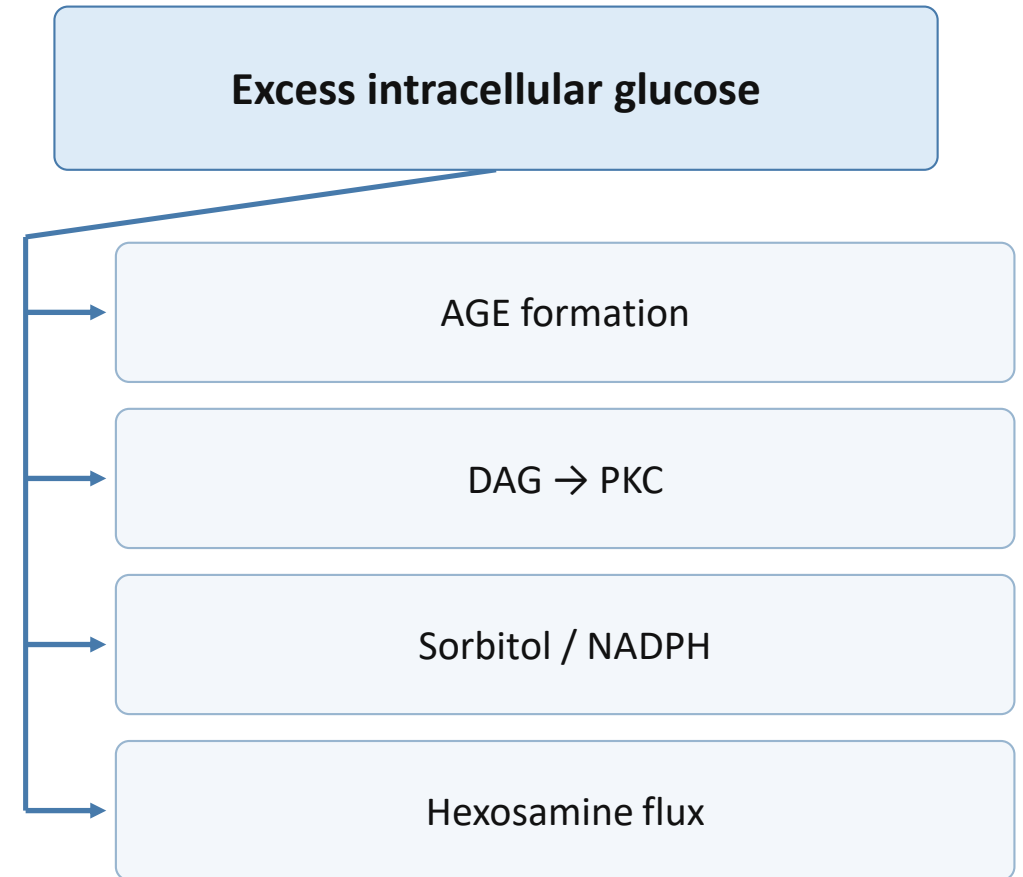
Insulin resistance + β -cell dysfunction

Chronic hyperglycemia

Glucotoxicity is not simply osmotic stress

Excess intracellular glucose alters signaling and generates injurious intermediates.

- Glycation creates reactive AGE-related products.
- Glycolytic intermediates feed DAG–PKC and hexosamine pathways.
- Polyol metabolism competes for NADPH needed by antioxidant defenses.



Four pathways organize chronic glucotoxicity

The pathways overlap but each illustrates a distinct biochemical route.

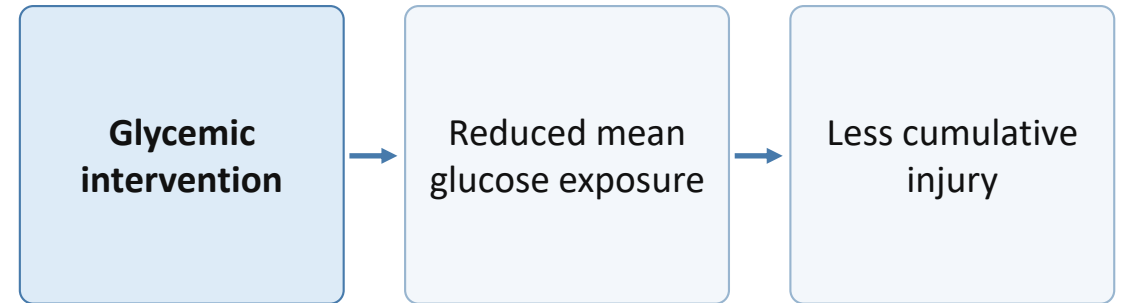
- AGE–RAGE: Extracellular/intracellular protein modification and receptor signaling.
- DAG–PKC: Altered endothelial signaling and gene expression.
- Polyol pathway: NADPH consumption, oxidative stress and sorbitol.
- Hexosamine pathway: Proposed damage from diverted glycolytic intermediates.

Pathway	Primary distinctive feature
AGE–RAGE	Protein glycation + receptor activation
PKC	DAG-mediated kinase activation
Polyol	Aldose reductase uses NADPH
Hexosamine	Increased intermediary flux

Glycemic-control evidence supports causality

Prospective randomized studies link improved control with less long-term damage.

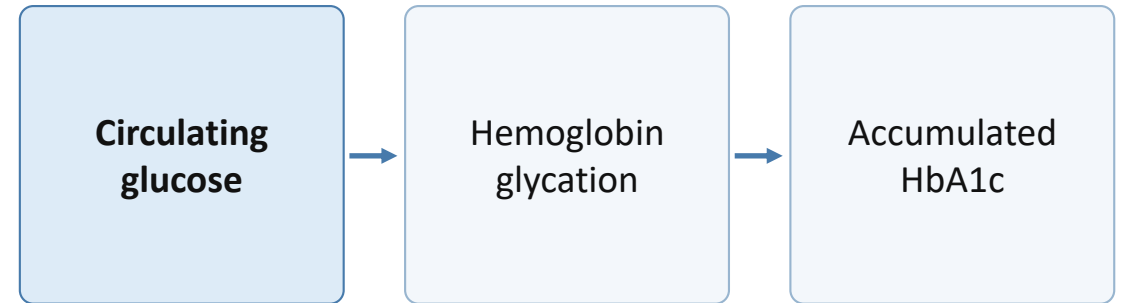
- HbA1c was used to assess mean glycemic exposure in major trials.
- Better glycemic control attenuates complication development.
- The association supports a major causal role for sustained hyperglycemia, not exclusive causation.



Why HbA1c reflects sustained glycemia

Hemoglobin undergoes nonenzymatic glycation inside circulating red cells.

- Glucose reacts covalently with hemoglobin over red-cell survival.
- Measured HbA1c reflects integrated exposure over approximately 120-day red-cell lifespan.
- A single blood glucose value captures a much shorter interval.



Spot glucose and HbA1c answer different questions

Both measurements are relevant, but describe different aspects of glycemia.

- Spot glucose: Concentration at the sampling time.
- HbA1c: Index of longer-term glycemic exposure.
- Day-to-day glucose fluctuations affect spot measurements much more strongly.

Blood glucose

Snapshot in time

Sensitive to short-term variation

HbA1c

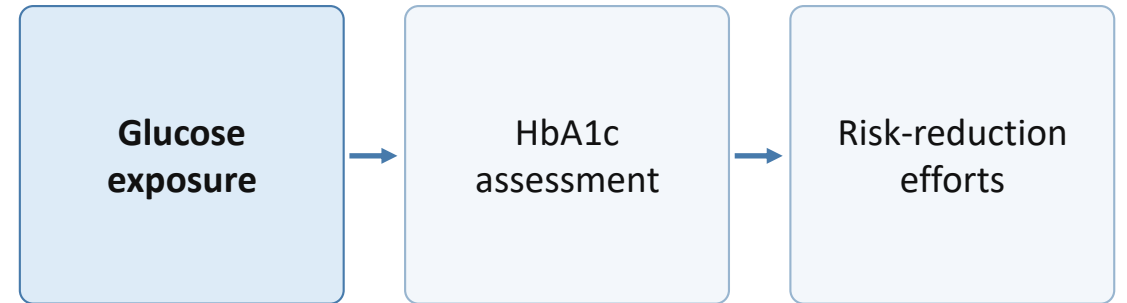
Cumulative red-cell exposure

Less sensitive to day-to-day variation

Interpreting the textbook HbA1c target

The primary source recommends an HbA1c below 7% for most people with diabetes.

- This is a general textbook treatment goal, not a diagnostic threshold.
- Complication risk relates to exposure across time.
- Individualized targets and contemporary clinical recommendations are outside this source-bound lecture.



Continuous monitoring adds a second exposure metric

Time-in-range describes the portion of monitored time glucose stays within a chosen target band.

- Continuous glucose monitoring measures changing glycemia.
- Increasing time-in-range as an emerging goal.
- It may predict complication risk better than HbA1c in some settings; The source does not establish equivalence.

HbA1c

Long-term glycemic summary

Averages fluctuations

Time-in-range

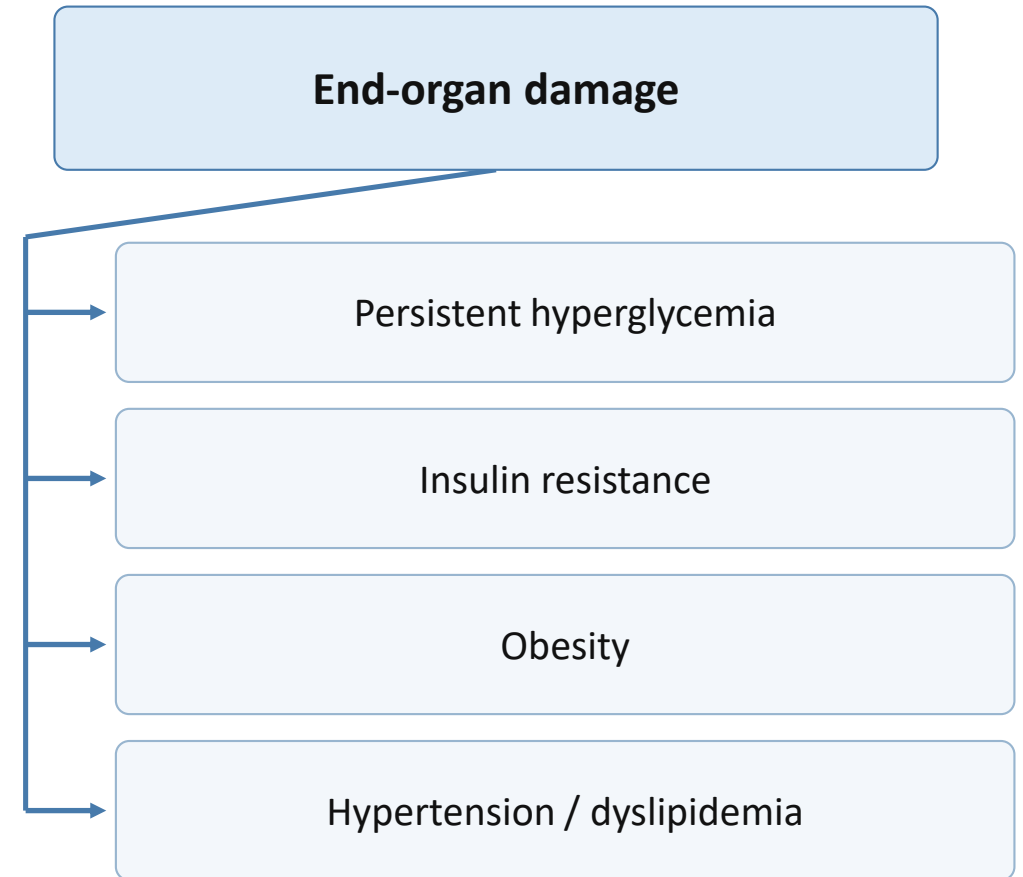
Captures duration in target band

Reflects temporal glucose patterns

Glycemic control does not explain all risk

Diabetes-associated comorbidities and metabolic disturbances modify tissue injury.

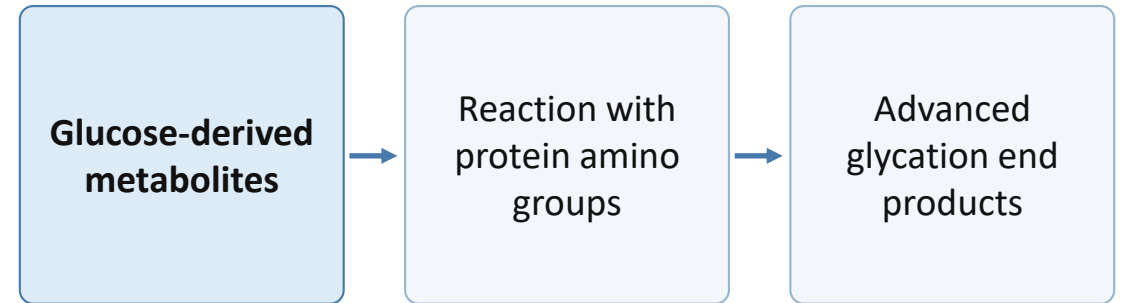
- Insulin resistance contributes independently to metabolic dysfunction.
- Obesity is a relevant comorbidity.
- Hypertension and dyslipidemia amplify vascular events in diabetes.
- A comprehensive risk model is broader than average glucose alone.



AGE formation begins with nonenzymatic chemistry

Glucose-derived dicarbonyl intermediates react with protein amino groups.

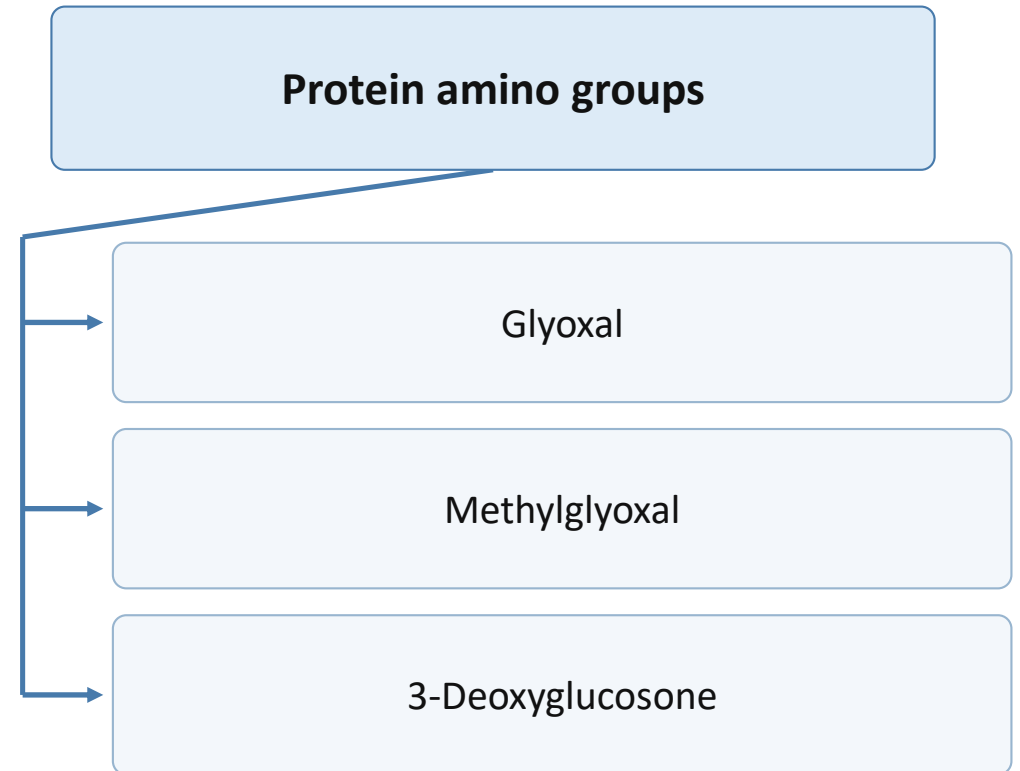
- The source names glyoxal, methylglyoxal and 3-deoxyglucosone.
- These intermediates modify intracellular and extracellular proteins.
- Persistent hyperglycemia accelerates the formation rate.



Reactive AGE precursors are chemically distinct

Different glucose-derived metabolites feed a shared class of protein modifications.

- Glyoxal is a reactive glucose-derived carbonyl compound.
- Methylglyoxal is another named precursor of AGE chemistry.
- 3-Deoxyglucosone also participates in nonenzymatic glycation.
- The lecture does not imply that all AGEs share one structure.



AGE formation has two routes to injury

Protein modification and AGE receptor signaling are conceptually separable.

- Modification changes the biochemical environment of tissue proteins.
- AGEs also act through the cell-surface receptor RAGE.
- RAGE-dependent responses especially affect the vascular and inflammatory compartments.

Protein modification

Covalent glycation

Intracellular /
extracellular proteins

Receptor route

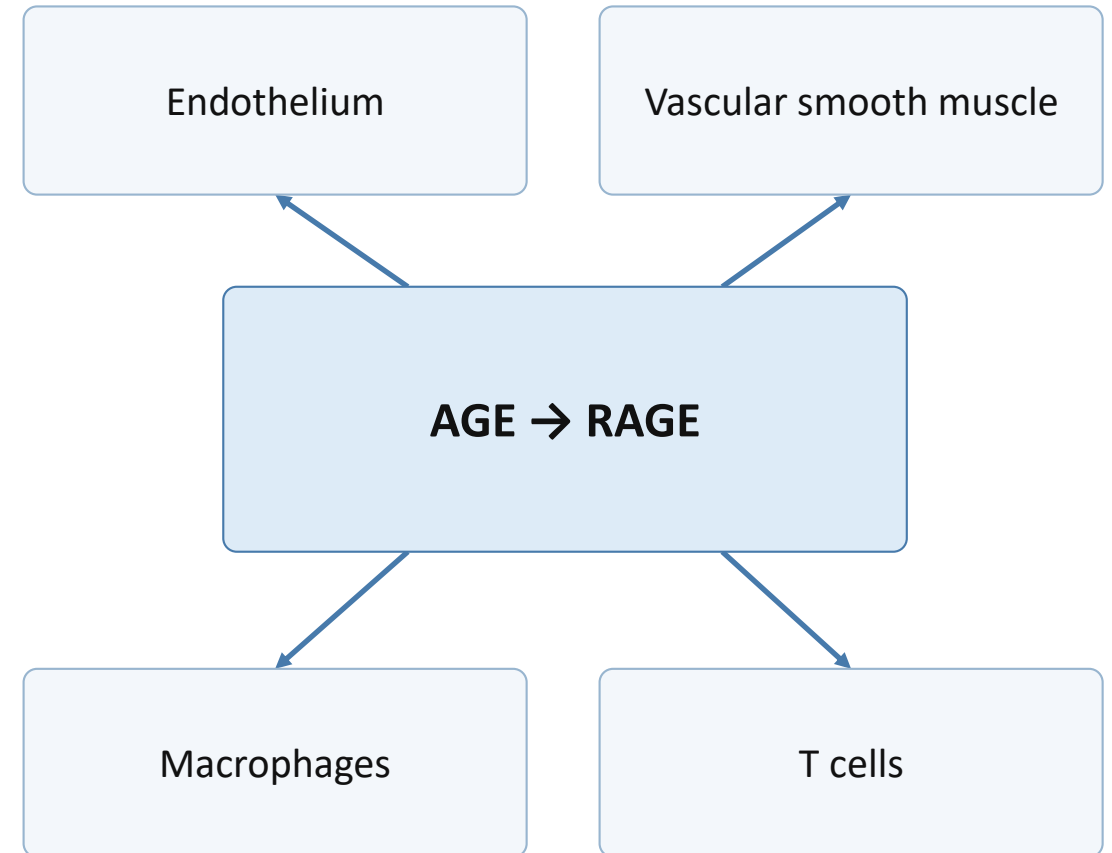
AGE ligands engage RAGE

Activation of injury
signaling

RAGE is expressed in multiple injury-relevant cells

The source identifies receptors in vascular and inflammatory populations.

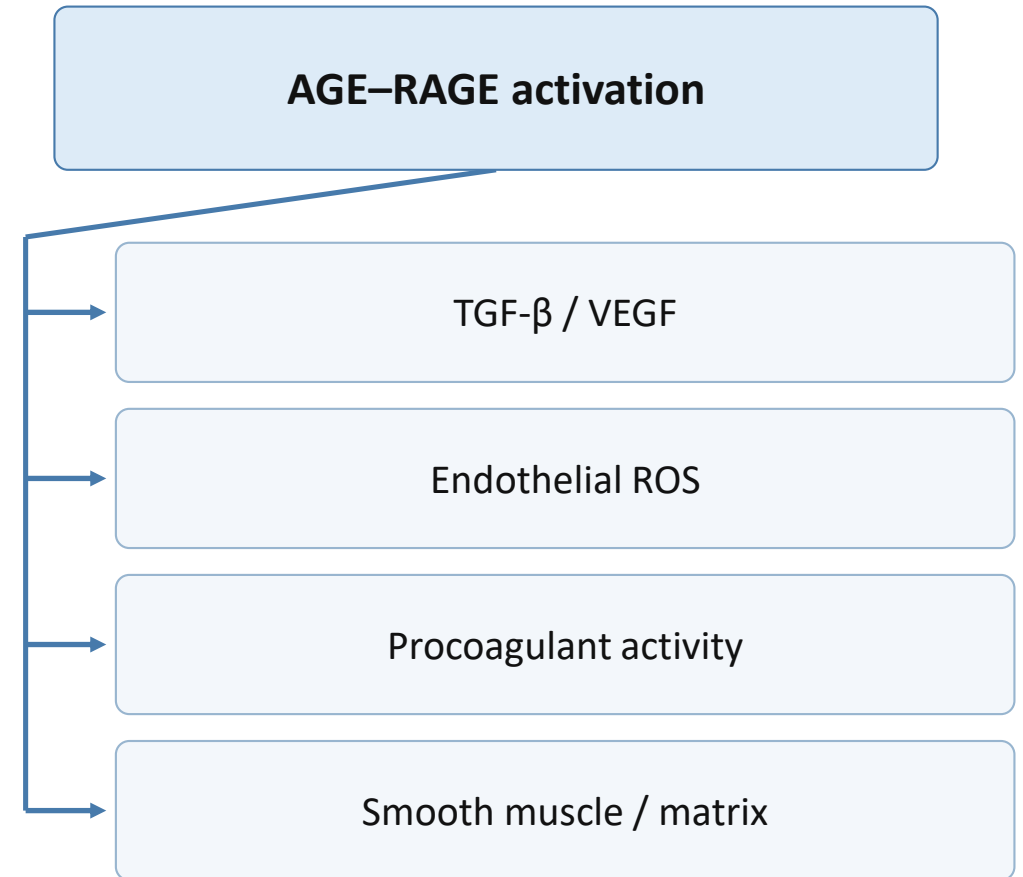
- Endothelial cells: A direct vascular signaling target.
- Vascular smooth muscle: Remodeling and proliferation.
- Macrophages and T lymphocytes: Inflammatory signaling.



AGE–RAGE initiates a vascular injury network

One receptor system can produce several mutually reinforcing consequences.

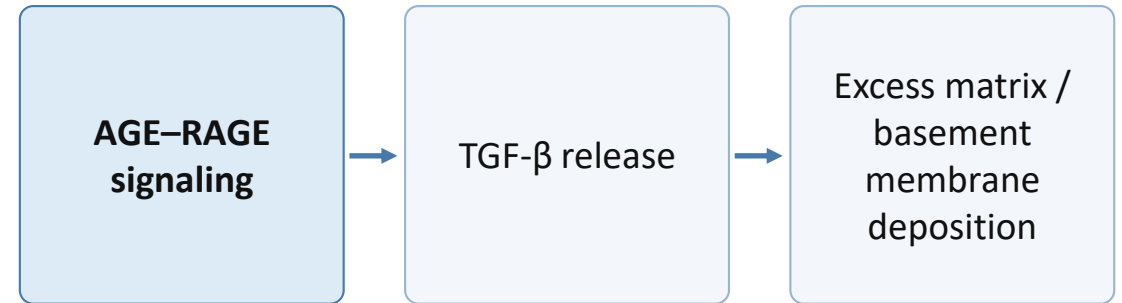
- Cytokine and growth-factor release alters vessel-wall structure.
- Endothelial reactive oxygen species intensify cell injury.
- Procoagulant activity alters the vascular interface.
- Smooth muscle proliferation and matrix synthesis promote remodeling.



TGF- β connects inflammation to basement membrane expansion

RAGE-related cytokine/growth-factor release includes transforming growth factor β .

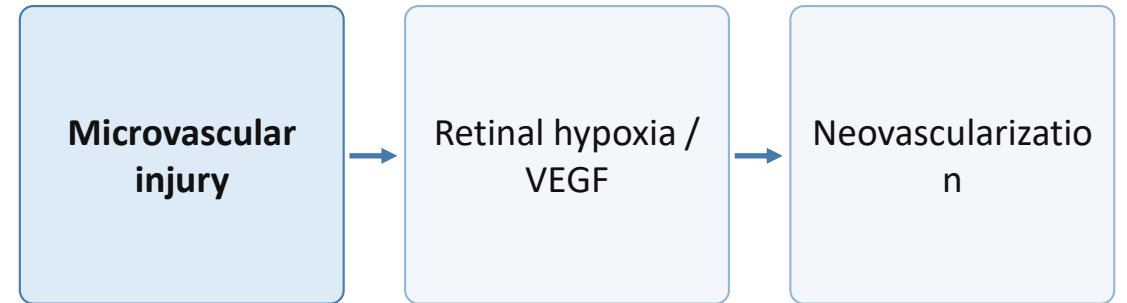
- TGF- β favors deposition of excess basement membrane material.
- Chronic matrix deposition alters microvascular architecture.
- Basement membrane thickening is a morphologic signature of diabetic microangiopathy.



VEGF connects vascular stress to retinal disease

Vascular endothelial growth factor has particular relevance to the diabetic retina.

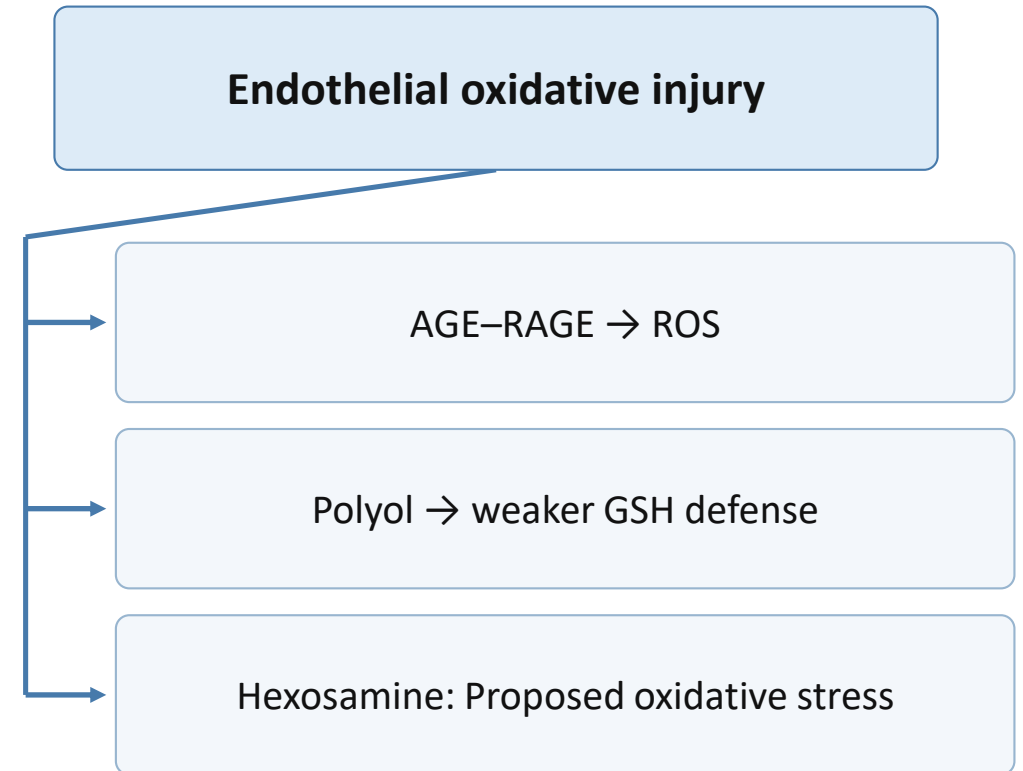
- AGE–RAGE signaling can enhance VEGF-related responses.
- Retinal hypoxia further induces VEGF expression.
- Pathologic neovascularization characterizes proliferative retinal disease.



AGE–RAGE produces endothelial oxidant stress

Reactive oxygen species are among the identified downstream effects.

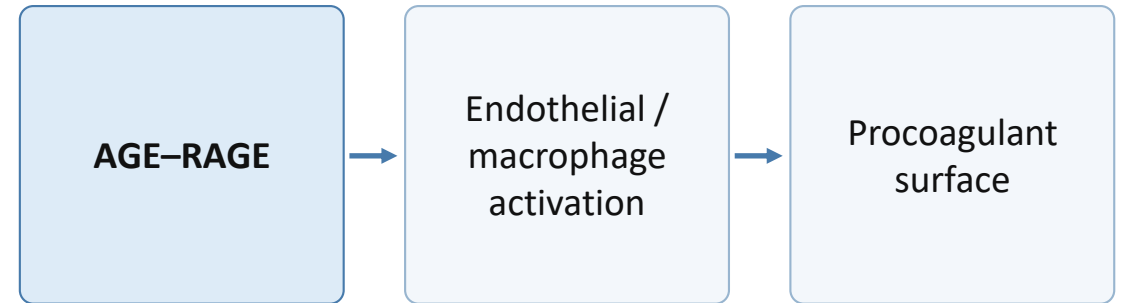
- Endothelial cells generate ROS after AGE–RAGE activation.
- Oxidants intensify dysfunction of the vascular lining.
- Other pathways also increase oxidative susceptibility, so ROS is a point of convergence.



Procoagulant effects are part of endothelial dysfunction

AGE–RAGE signaling enhances thrombogenic activity in vascular cells.

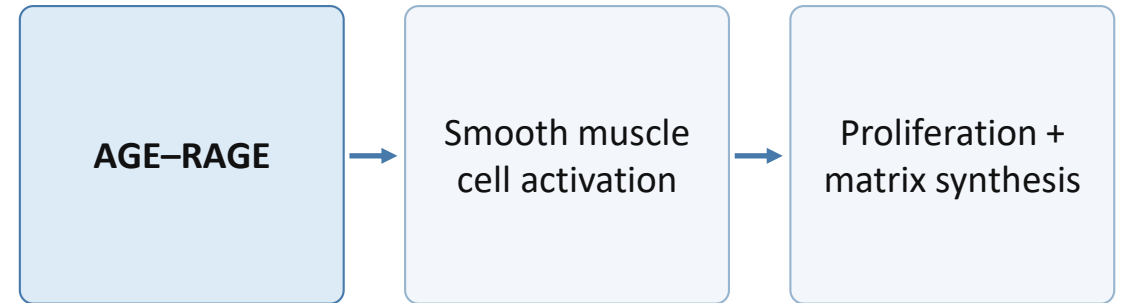
- The source identifies endothelial cells and macrophages as sites of procoagulant activation.
- A procoagulant vessel wall favors atherothrombotic complications.
- This is one component of diabetic vascular injury, not the sole cause of thrombosis.



Smooth muscle responses promote vessel-wall remodeling

AGE–RAGE influences cells beyond the endothelium.

- Vascular smooth muscle proliferation increases.
- Extracellular matrix synthesis also increases.
- Together with endothelial dysfunction, these changes contribute to vascular disease.



Experimental RAGE manipulations support mechanism

Animal studies implicate RAGE, but are not direct proof of clinical treatment benefit.

- Endothelial RAGE overexpression accelerated vessel injury in diabetic mice.
- RAGE-null mice showed attenuation of vascular damage.
- Potential RAGE antagonism is presented by the textbook as an investigational approach.

More RAGE signaling

Greater vascular injury

Experimental diabetic mice

Absent RAGE

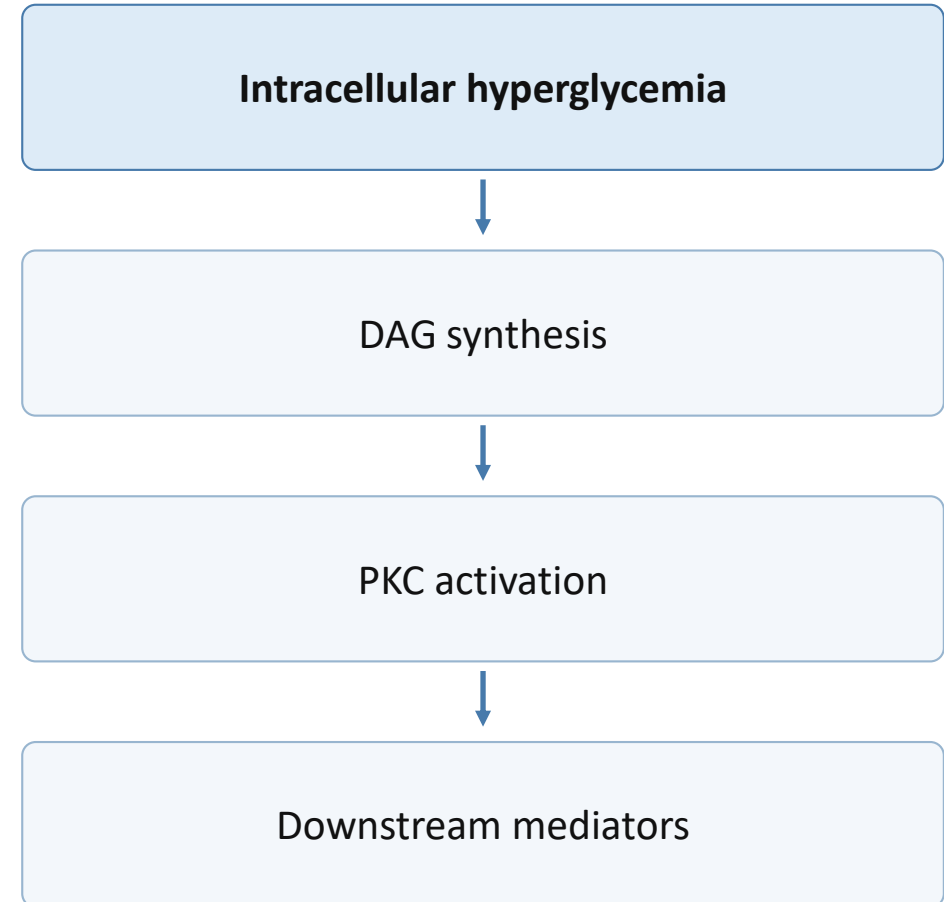
Attenuated injury

Experimental RAGE-null mice

DAG–PKC represents a signaling pathway

Hyperglycemia can induce kinase signaling without AGE receptor ligation.

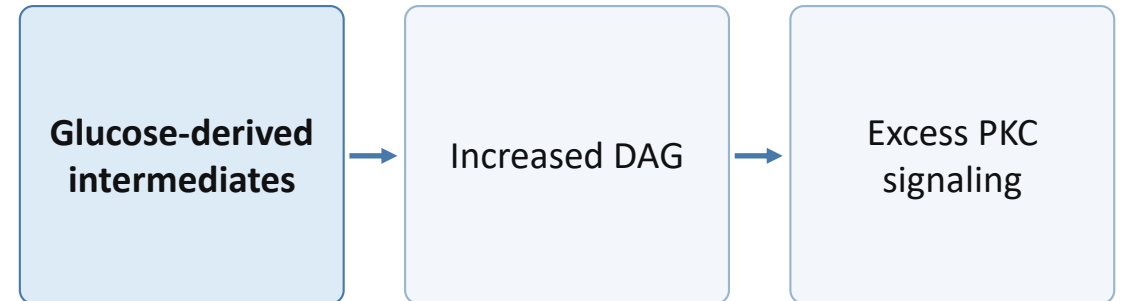
- Glycolytic intermediates feed de novo synthesis of diacylglycerol (DAG).
- DAG promotes protein kinase C (PKC) activation.
- PKC changes endothelial expression of growth and procoagulant mediators.



DAG links glucose metabolism to kinase activation

A metabolite ordinarily used in signaling becomes excessive with intracellular glucose abundance.

- Excess glycolytic intermediates increase DAG formation.
- DAG is an important second messenger in PKC-related signaling.
- The source describes excessive rather than physiologic activation.



PKC activation enhances endothelial VEGF

The molecular pathway converges on the retina-relevant growth factor.

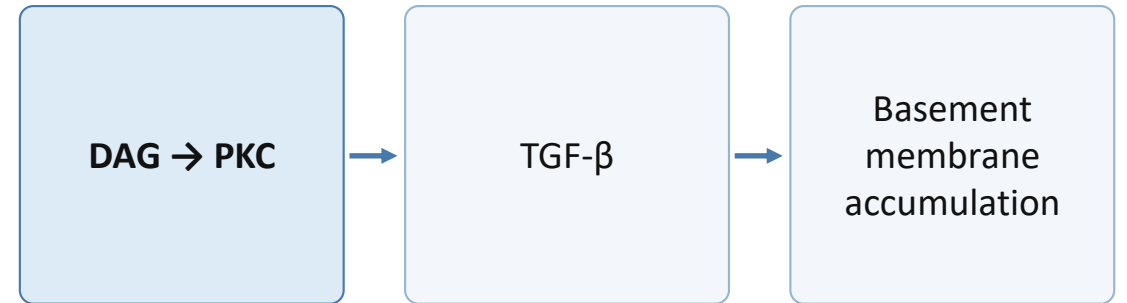
- Activated PKC promotes vascular endothelial VEGF production.
- VEGF contributes to retinal neovascular responses.
- AGE–RAGE and PKC therefore reinforce related outputs.



PKC activation also promotes TGF- β

This connects kinase dysregulation to matrix deposition.

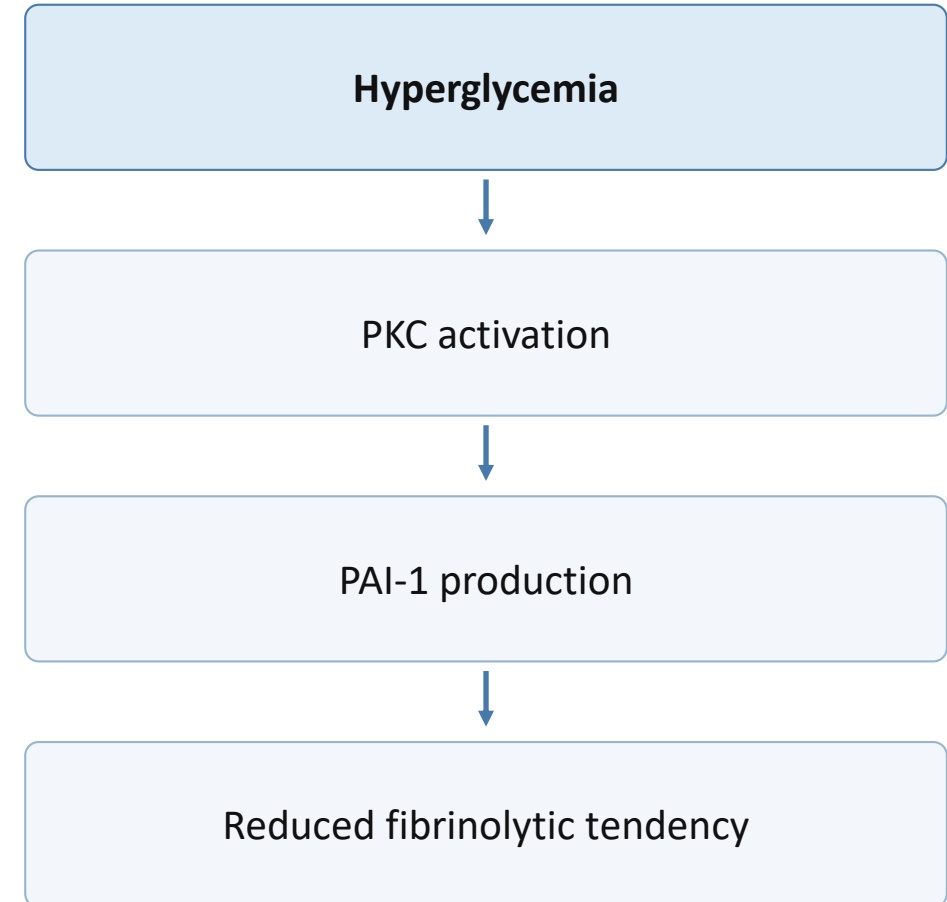
- Endothelial PKC activation increases TGF- β -related signaling.
- TGF- β supports deposition of extracellular and basement membrane material.
- Progressive matrix expansion underlies characteristic microvascular changes.



PAI-1 is a procoagulant pathway output

The source identifies plasminogen activator inhibitor-1 among PKC-induced proteins.

- Endothelial PKC signaling increases PAI-1.
- PAI-1 inhibits plasminogen activation and hence opposes fibrinolysis.
- This mechanistic interpretation helps explain a more prothrombotic vascular milieu.



AGE–RAGE and PKC share downstream effectors

Pathways should not be taught as independent silos.

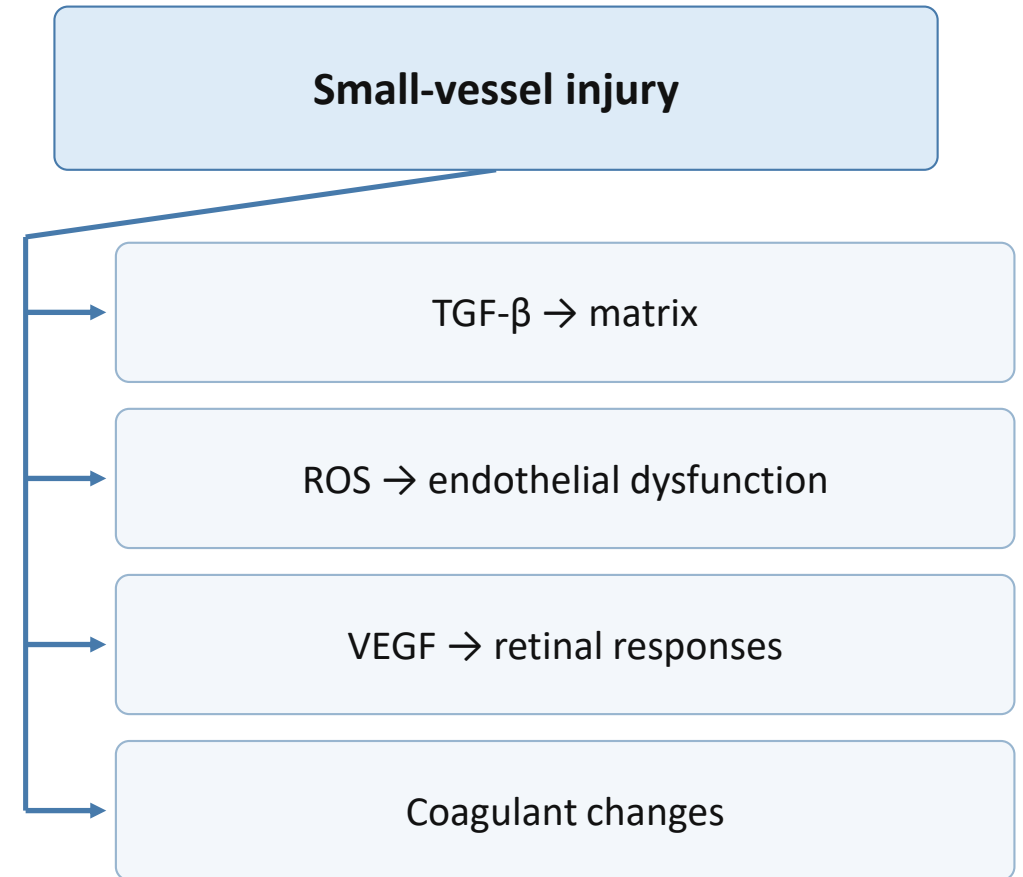
- Both can increase TGF- β -associated matrix deposition.
- Both can promote VEGF-related endothelial responses.
- Oxidant and procoagulant effects add to vessel-wall dysfunction.

Pathway	TGF- β	VEGF	Additional effects
AGE–RAGE	Yes	Yes	ROS; Procoagulant activity
PKC	Yes	Yes	PAI-1 expression

Microangiopathy reflects pathway convergence

Multiple inputs lead to a common structural phenotype.

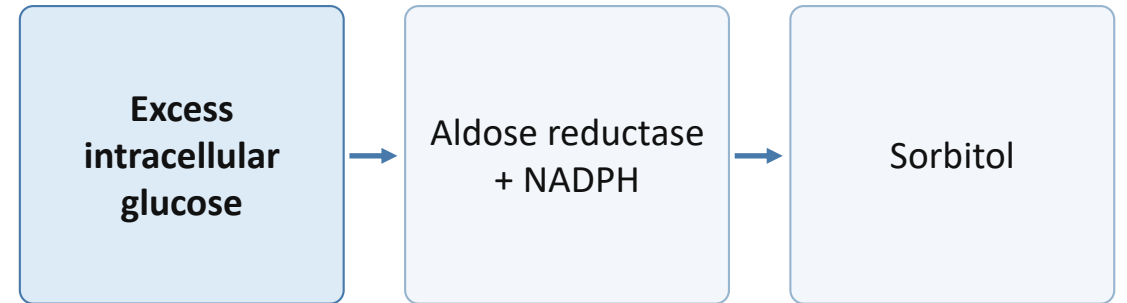
- Growth-factor signaling increases basement membrane matrix.
- Endothelial oxidant and procoagulant responses impair function.
- Persistent microvascular remodeling contributes to retina, glomerular and nerve injury.



Polyol metabolism uses an antioxidant cofactor

Some tissues take up glucose without requiring insulin to transport it.

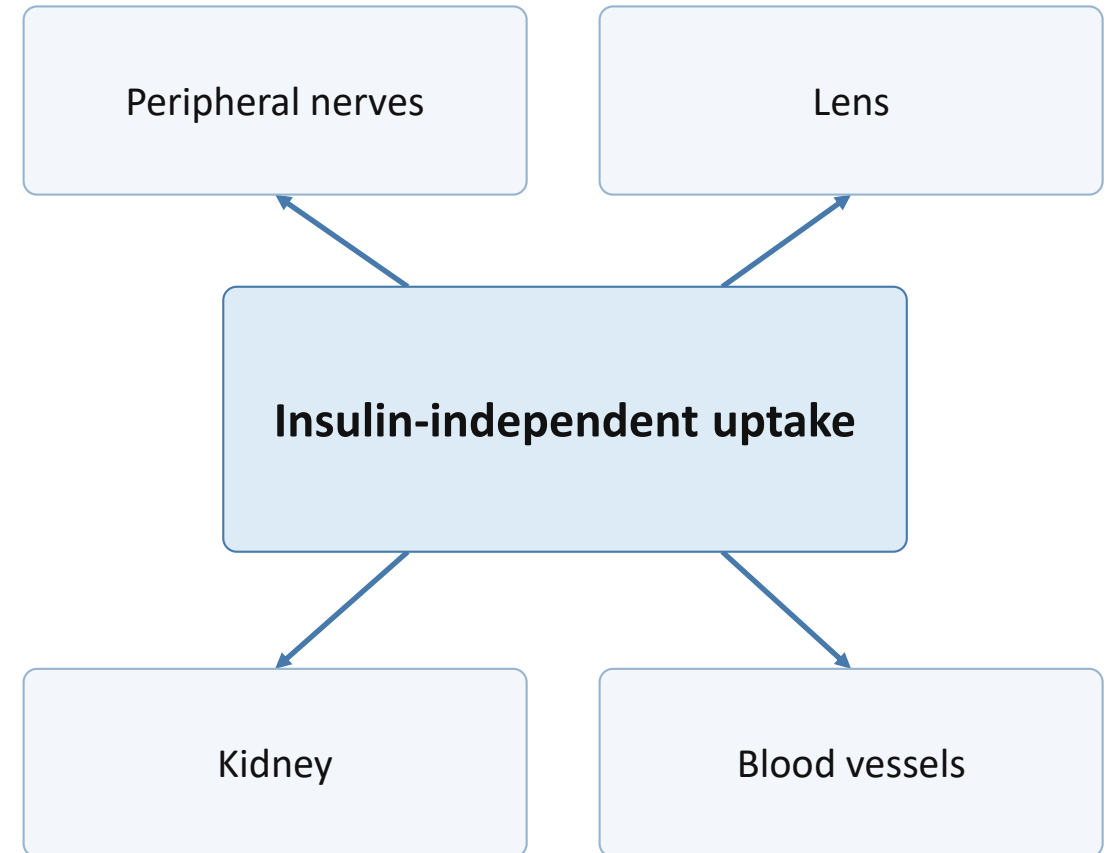
- Excess intracellular glucose becomes substrate for aldose reductase.
- Aldose reductase converts glucose into sorbitol.
- The reaction requires NADPH, which is also needed for antioxidant maintenance.



Polyol-sensitive tissues include several organs

Persistent hyperglycemia can increase intracellular glucose in insulin-independent tissues.

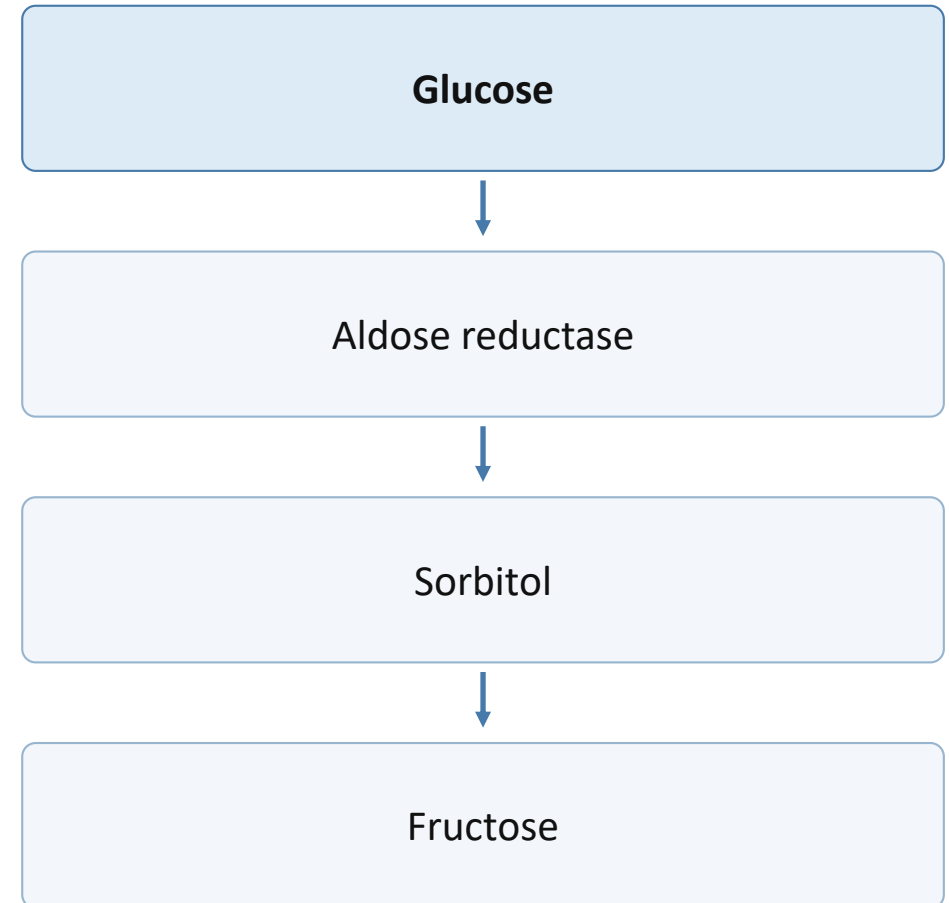
- Peripheral nerves and lenses are highlighted by the textbook.
- Kidneys and vascular tissues are additional examples.
- These compartments are susceptible to metabolic injury despite not depending on insulin for glucose entry.



Aldose reductase diverts glucose to sorbitol

The first step creates both a polyol and competition for NADPH.

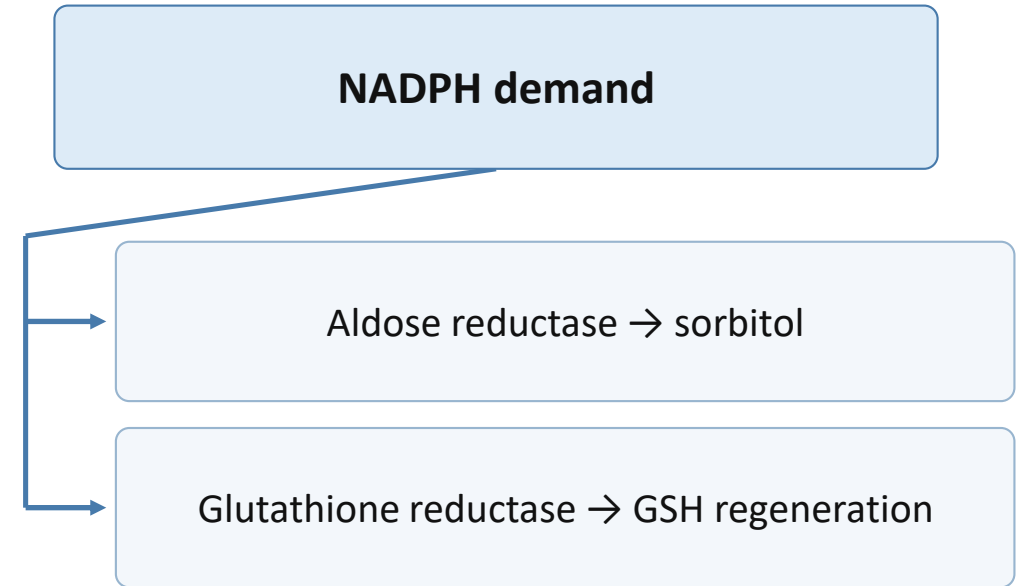
- Aldose reductase catalyzes glucose → sorbitol.
- Sorbitol can be converted further to fructose.
- The first reaction consumes reducing capacity supplied by NADPH.



NADPH availability is a metabolic bottleneck

Polyol flux and antioxidant regeneration rely on the same reduced cofactor.

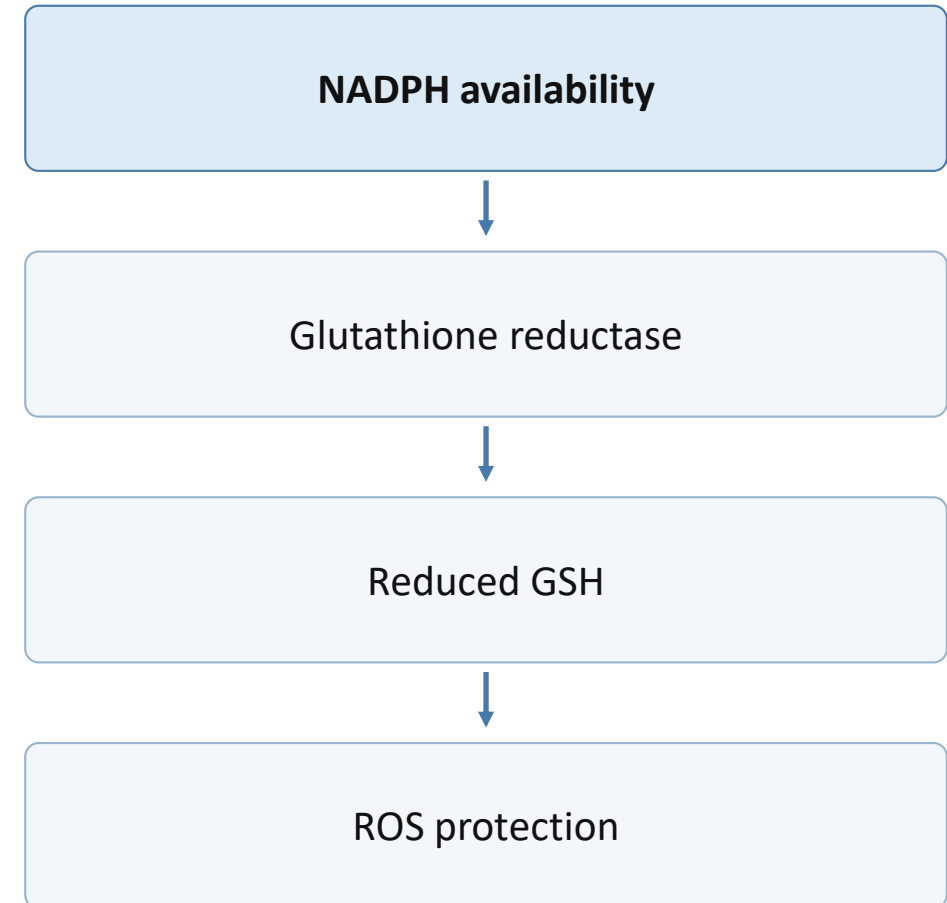
- Increased aldose reductase activity draws on NADPH.
- Glutathione reductase also uses NADPH.
- Intense polyol flux therefore compromises the regeneration of reduced glutathione.



Reduced glutathione protects against oxidants

The polyol pathway creates injury partly by reducing antioxidant capacity.

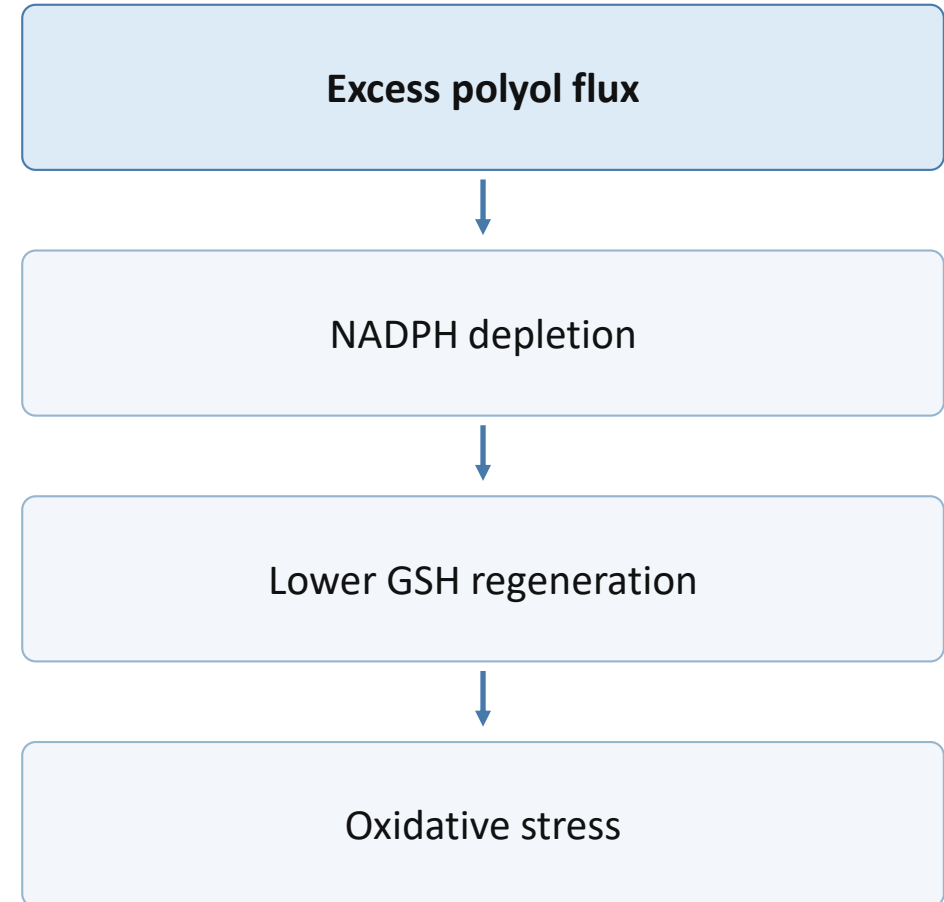
- Glutathione reductase regenerates reduced glutathione (GSH).
- GSH is an important intracellular antioxidant defense.
- Reduced NADPH availability can limit GSH regeneration.



Polyol flux can amplify oxidative stress

The critical injury is not simply the presence of sorbitol.

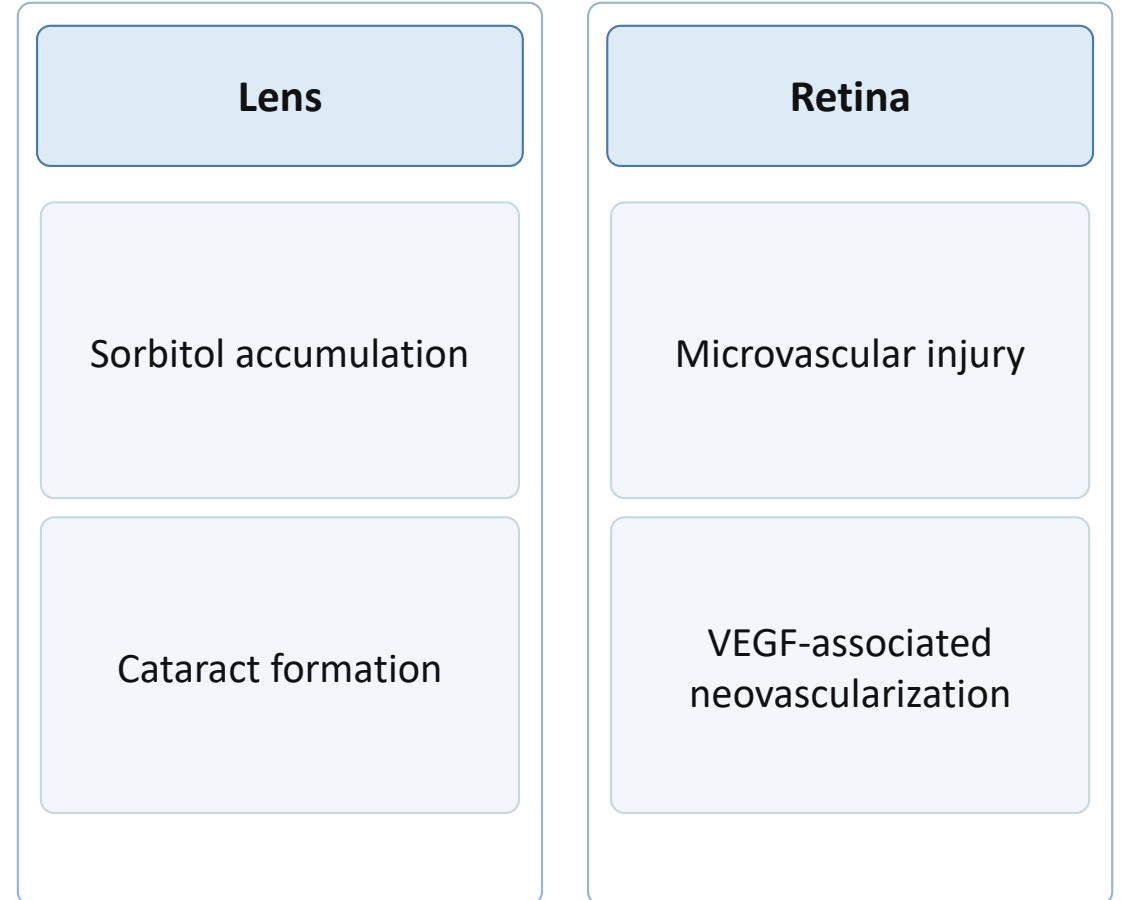
- Excess glucose increases NADPH utilization by aldose reductase.
- Lower NADPH availability compromises GSH regeneration.
- Weakened antioxidant buffering increases susceptibility to ROS damage.



Sorbitol accumulation contributes to cataracts

The lens is an important nonvascular target of glucose excess.

- Sorbitol may accumulate during sustained polyol metabolism.
- The textbook links lens sorbitol accumulation with cataract formation.
- Lens injury is distinct from microangiopathy of retinal vessels.



Polyol and AGE injury converge on oxidants

Oxidative stress can be increased by more than one route.

- AGE–RAGE signaling stimulates endothelial ROS production.
- Polyol flux reduces cellular antioxidant regeneration.
- Thus oxidant production and impaired clearance may coexist.

**Increased ROS
generation**

AGE–RAGE effects

Endothelial production

Reduced defense

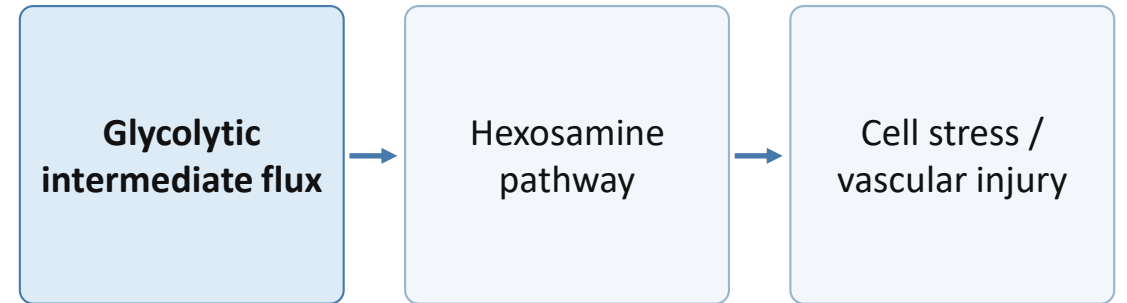
NADPH diverted

GSH regeneration
impaired

Hexosamine metabolism is a fourth proposed route

Diversion of intermediates toward hexosamine metabolism is implicated in injury.

- Hyperglycemia increases flux of glycolytic intermediates through this route.
- The source links this pathway to cell damage and oxidative stress.
- Consequences including insulin resistance and vascular complications remain mechanistic proposals.



The hexosamine mechanism has different certainty

The source explicitly frames the proposed chain as a postulate.

- Increased metabolic flux is the initiating concept.
- Oxidative injury and insulin resistance are proposed downstream effects.
- Avoid presenting a specific intermediary or quantitative impact that is not documented in this source.

Established in excerpt

Hyperglycemia increases
pathway flux

Proposed consequences

Oxidative cellular injury

Insulin resistance /
vascular complications

Metabolic routes summarized by their key intermediates

Each pathway begins with increased glucose or glycolytic flux.

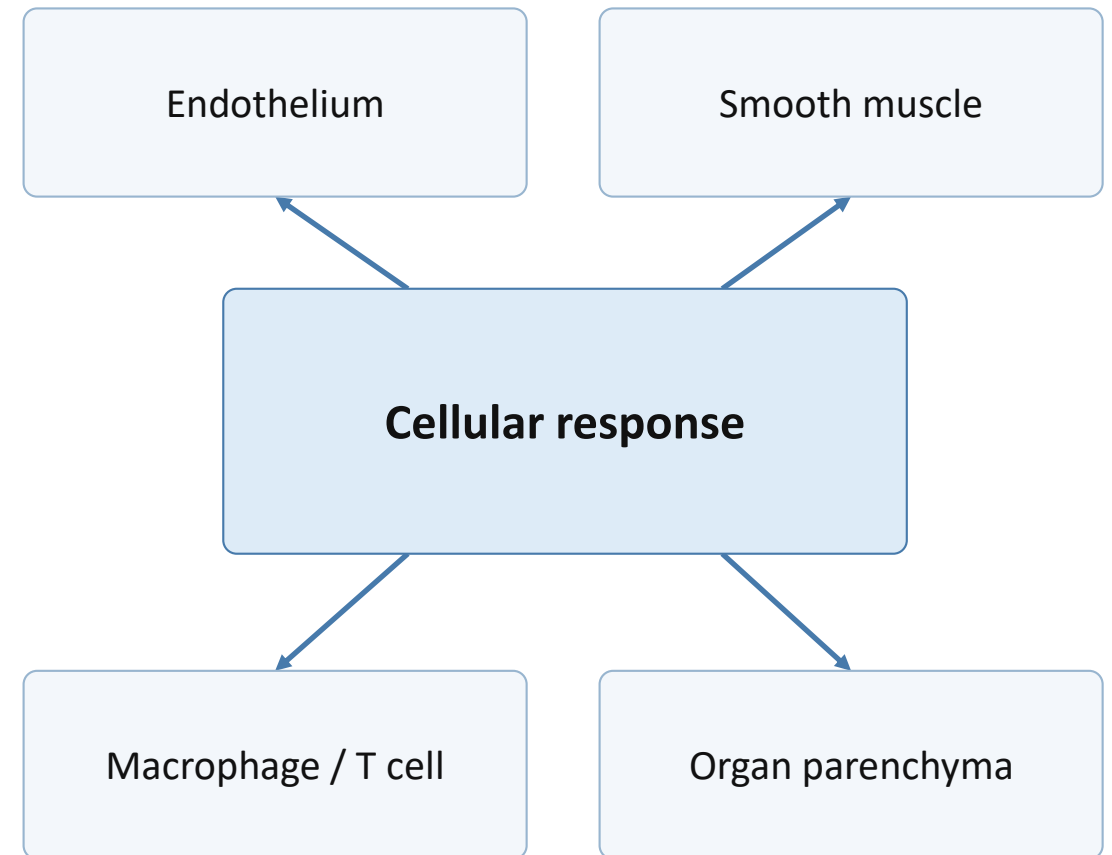
- AGE chemistry involves reactive glucose-derived metabolites.
- PKC activation follows increased DAG synthesis.
- Polyol injury features NADPH consumption and sorbitol.
- Hexosamine injury is attributed to increased pathway flux.

Pathway	Intermediate / signal	Principal injury link
AGE–RAGE	Glyoxal / methylglyoxal / AGE	Inflammation; Matrix; Oxidants
DAG–PKC	Diacylglycerol	VEGF; TGF- β ; PAI-1
Polyol	Sorbitol + NADPH use	Less GSH; Lens injury
Hexosamine	Increased pathway flux	Proposed oxidative/cellular stress

Cells translating metabolism into vascular pathology

The principal participating cells are different from those forming the final scar.

- Endothelium: Oxidative, growth-factor and procoagulant signaling.
- Smooth muscle: Increased proliferation and matrix synthesis.
- Macrophages and T cells: Inflammatory receptor responses.
- Organ parenchyma also becomes injured downstream of microvascular disturbance.



Basement membrane thickening is not protective

The diabetic capillary wall may become thicker but more permeable.

- Diffuse basement membrane thickening is an established morphologic feature.
- Capillaries paradoxically become leakier to plasma proteins.
- Structural accumulation does not imply normal microvascular barrier function.

Morphologic change

Basement membrane thickens

Excess matrix

Functional change

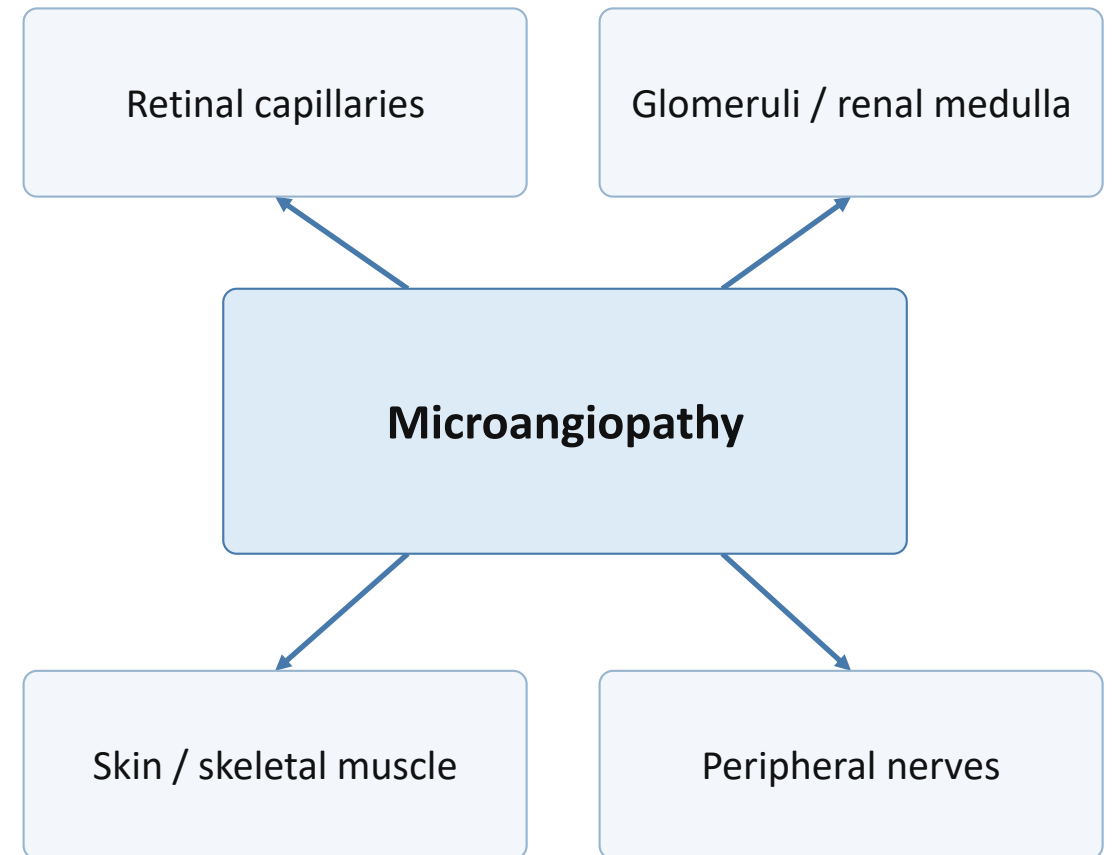
Permeability increases

Plasma proteins leak

Diabetic microangiopathy spans several tissues

Basement membrane remodeling occurs in multiple vascular and nonvascular sites.

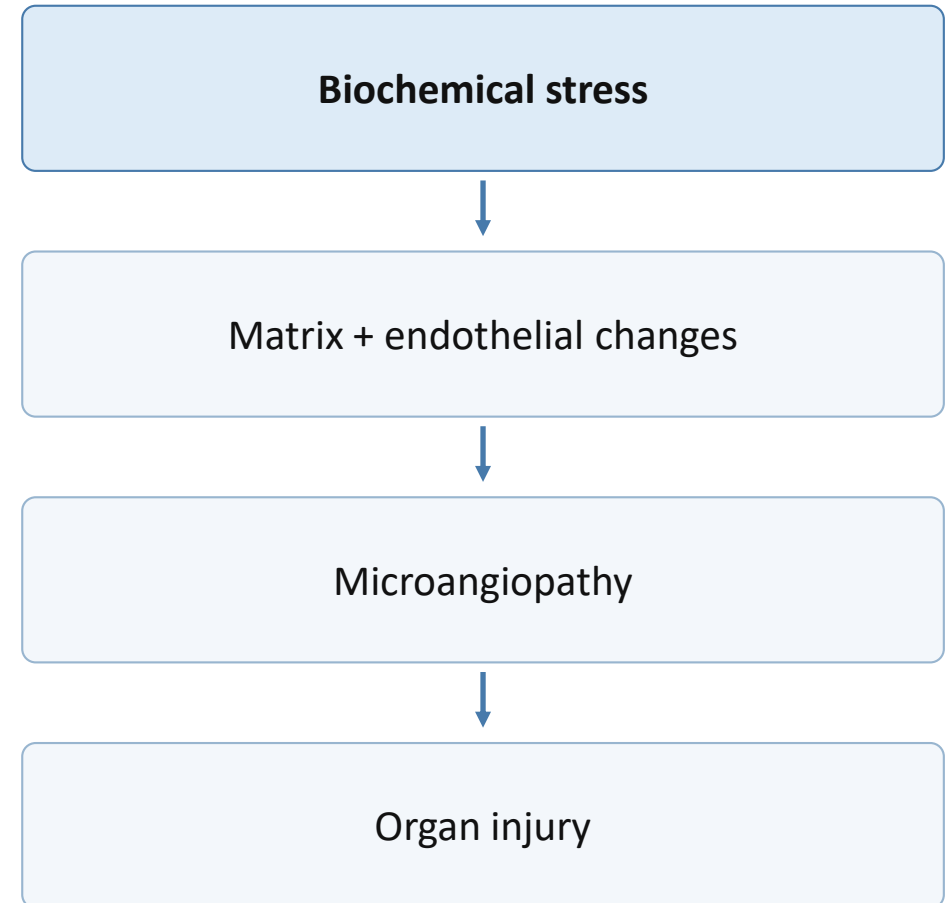
- Capillaries in skin, muscle, retina and kidney are affected.
- Nonvascular basement membranes of renal tubules and peripheral nerves may thicken.
- This distribution helps explain multisystem clinical manifestations.



How microvascular morphology follows biochemistry

Matrix growth and vascular dysfunction explain the core microscopic pattern.

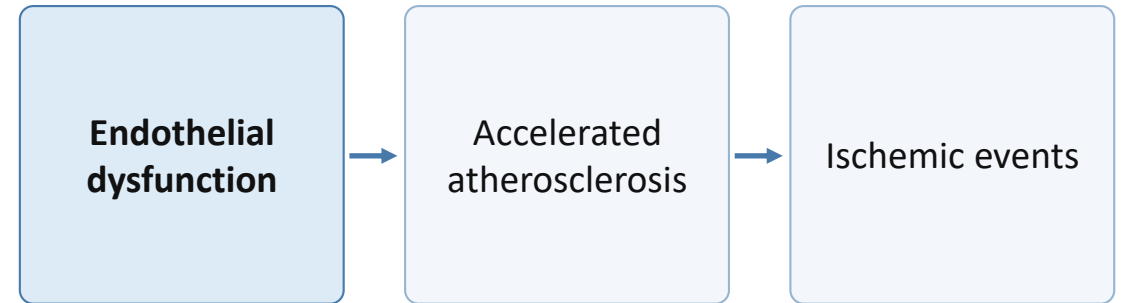
- TGF- β -related signaling promotes excess matrix production.
- Endothelial dysfunction accompanies thickened basement membranes.
- Leakiness and tissue ischemia help translate structural change into functional loss.



Macrovascular disease is accelerated atherosclerosis

Large-vessel lesions resemble conventional atherosclerotic plaques morphologically.

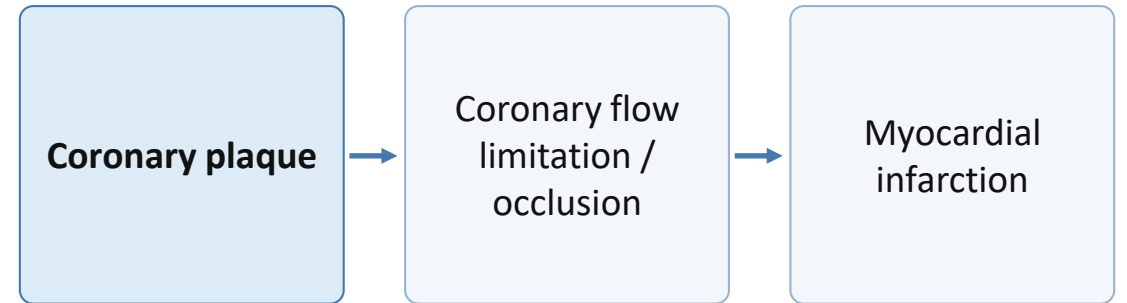
- Diabetes accelerates disease in aorta and muscular arteries.
- Persistent hyperglycemia and insulin resistance contribute to endothelial dysfunction.
- Clinical outcomes depend on the affected vascular territory.



Coronary disease is a major lethal complication

The coronary arterial bed is a critical macrovascular target.

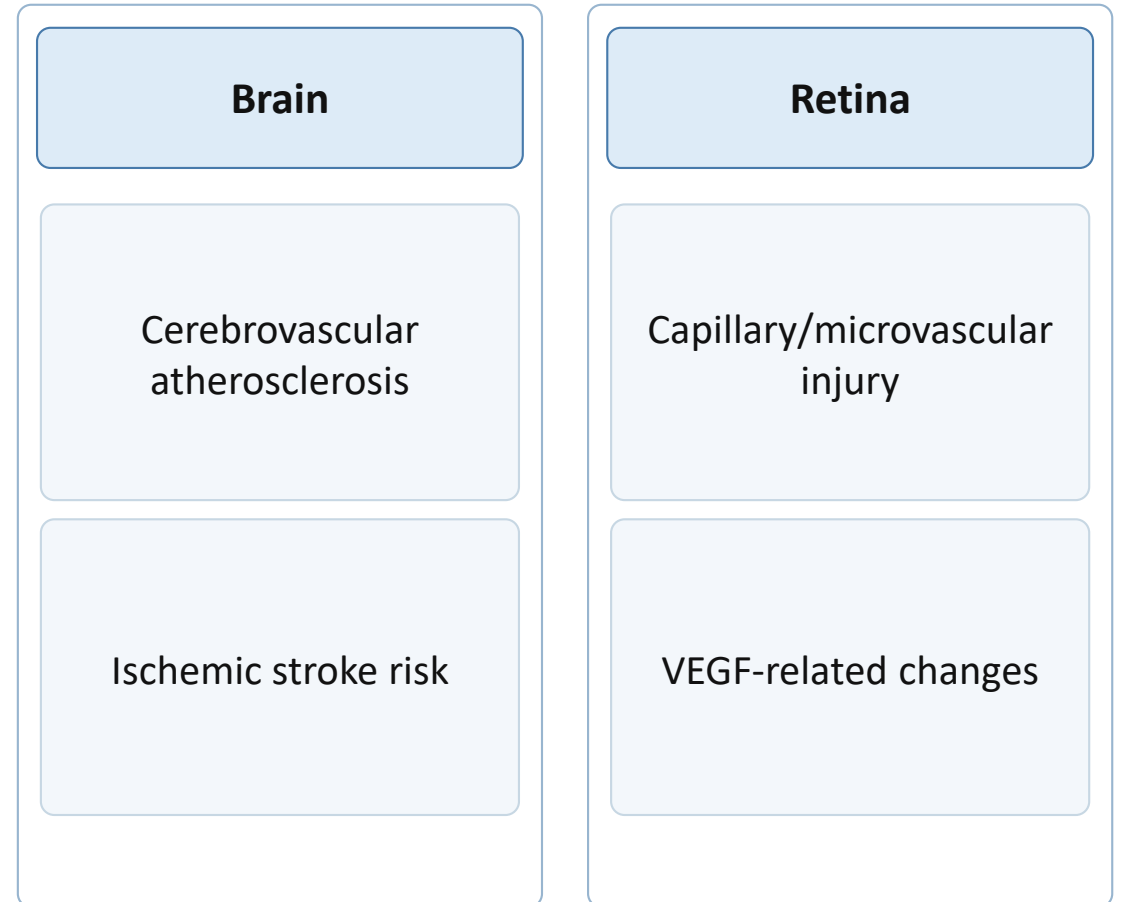
- Accelerated coronary atherosclerosis predisposes to myocardial infarction.
- Myocardial infarction as the most common cause of death in diabetes.
- Associated hypertension and dyslipidemia increase cardiovascular burden.



Cerebrovascular complications share arterial mechanisms

Macrovascular disease increases risk of ischemic brain injury.

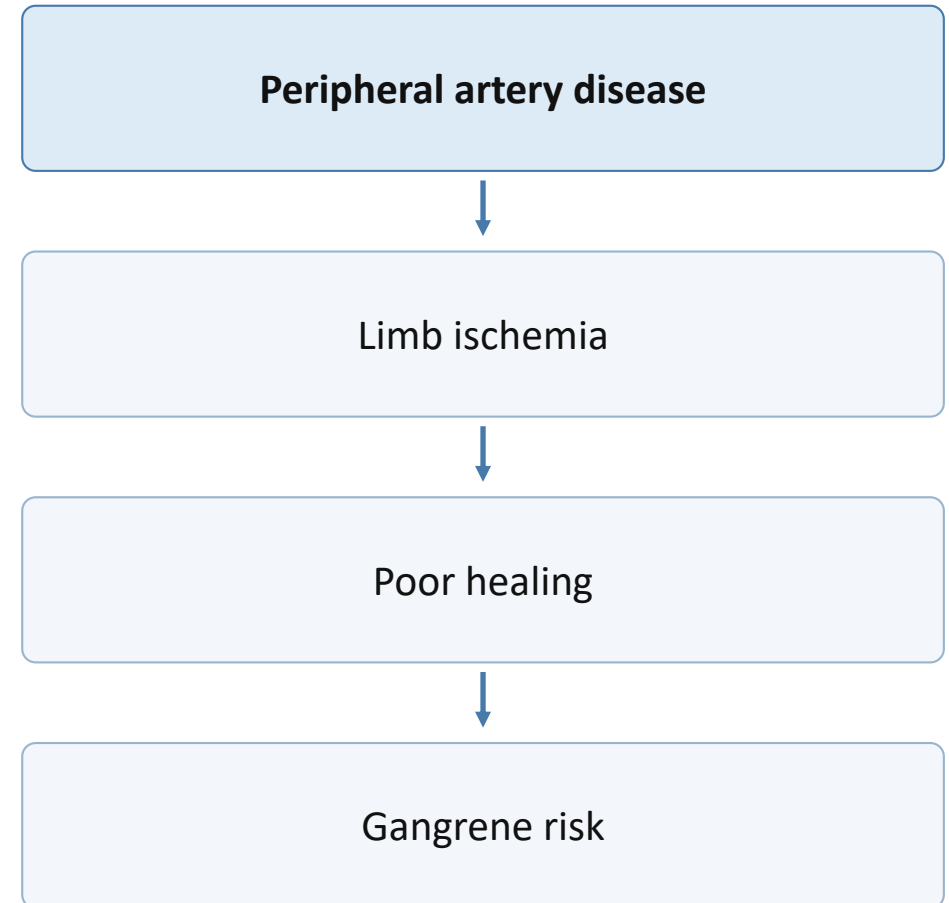
- Cerebral artery atherosclerosis contributes to ischemic stroke.
- Diabetes can coexist with hypertension, adding vascular risk.
- The mechanism is primarily large-artery disease, not identical to retinal microangiopathy.



Peripheral arterial disease threatens limb viability

Lower-extremity ischemia reflects the arterial component of diabetic foot pathology.

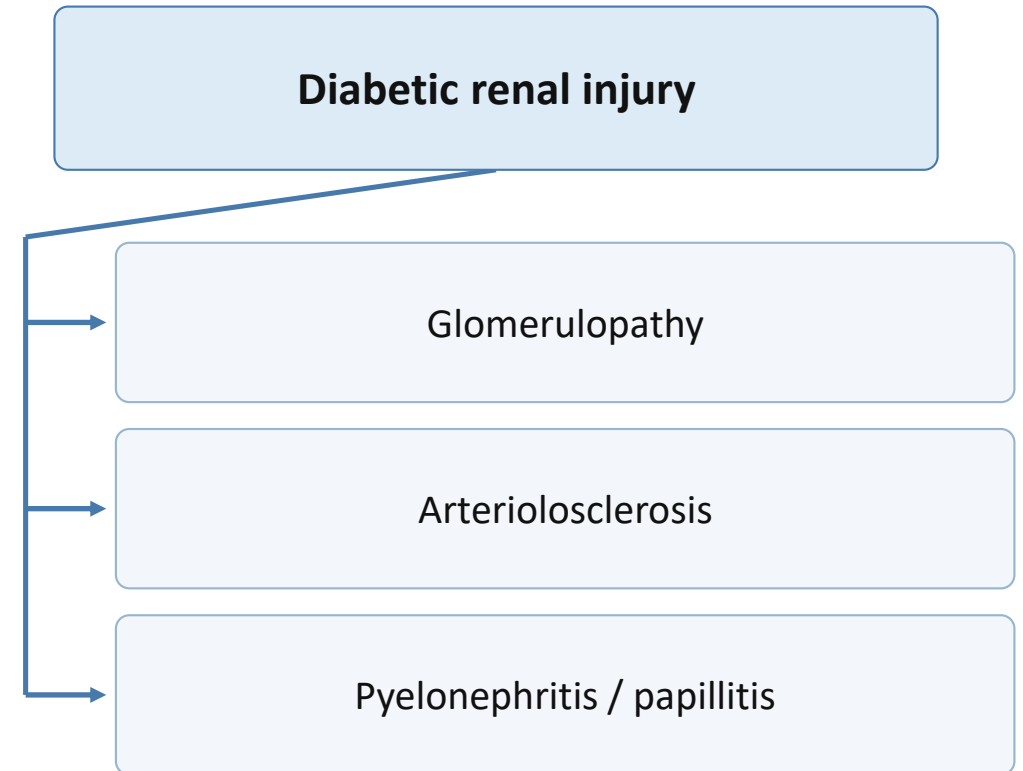
- Accelerated peripheral atherosclerosis limits perfusion.
- Tissue ischemia impairs resistance to local injury.
- When neuropathy and infection coexist, gangrene risk rises markedly.



Diabetic nephropathy includes three lesion groups

Kidney injury is more complex than glomerulosclerosis alone.

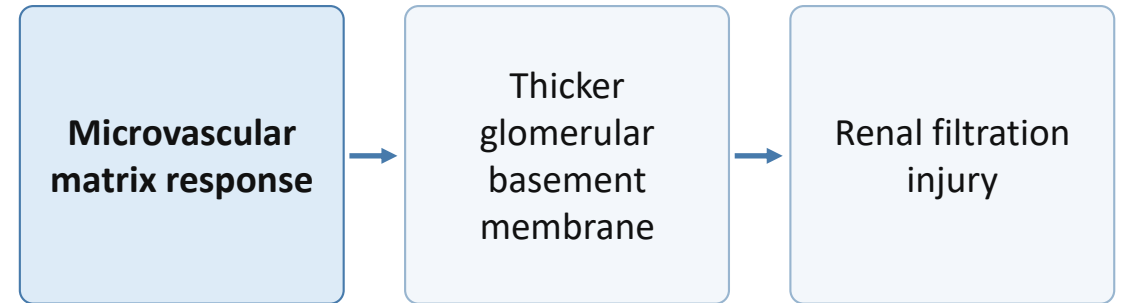
- Glomerular lesions: Basement membrane and mesangial change.
- Renal vessel lesions: Especially arteriolosclerosis.
- Infection-related injury: Pyelonephritis, sometimes papillary necrosis.



Glomerular basement membrane thickening

Glomerular capillary walls develop increased basement membrane material.

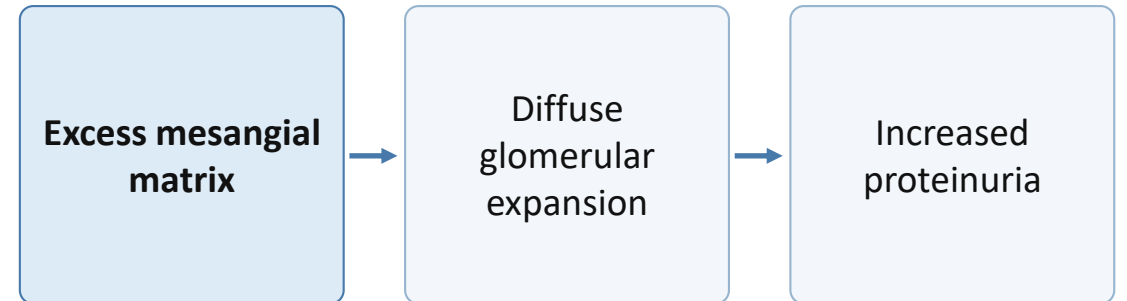
- The source describes this in virtually all cases of diabetic nephropathy.
- Electron microscopy demonstrates the structural thickening.
- Mesangial expansion and tubular basement membrane changes frequently coexist.



Diffuse mesangial sclerosis

Increased mesangial matrix is a central renal lesion.

- Mesangial expansion is diffuse rather than restricted to one nodule.
- Deposited matrix is periodic acid–Schiff (PAS) positive.
- Progressive expansion correlates with worsening renal function and proteinuria.



Nodular glomerulosclerosis

The Kimmelstiel–Wilson pattern consists of peripheral mesangial matrix nodules.

- Nodules are ovoid or spherical and PAS positive.
- Patent or dilated capillary loops may surround nodules.
- Diffuse mesangial sclerosis also occurs in uninvolved glomerular areas.

Diffuse lesion

Generalized mesangial matrix

PAS-positive expansion

Nodular lesion

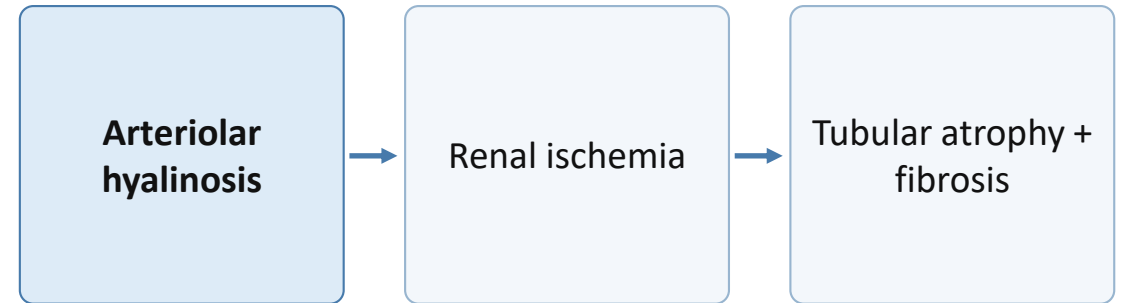
Discrete peripheral mesangial nodules

Kimmelstiel–Wilson pattern

Renal arteriolar hyalinosis has a distinctive pattern

Diabetes affects glomerular inflow and outflow arterioles.

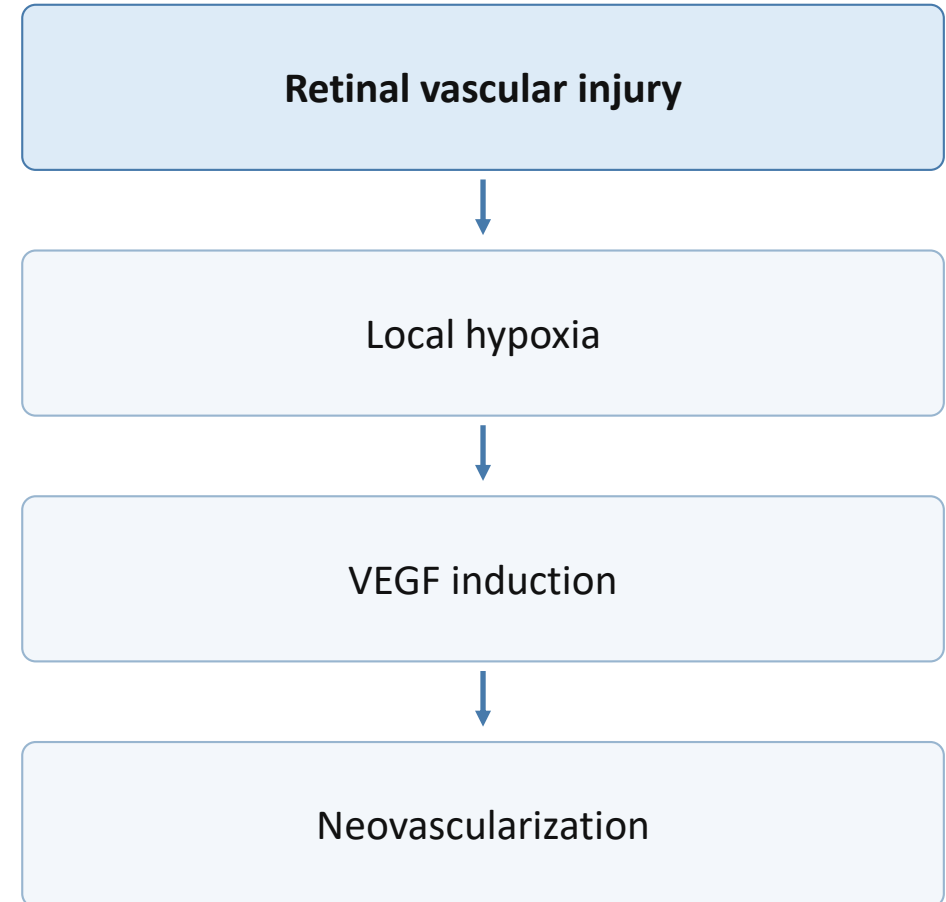
- Afferent and efferent arterioles may both show hyaline thickening.
- Efferent arteriolar hyalinosis is unusual without diabetes.
- Ischemic injury contributes to tubular atrophy and interstitial fibrosis.



Retinal disease links hypoxia to VEGF

Microvascular injury drives a hypoxic proliferative response.

- Diabetic retinopathy ranges from background to proliferative patterns.
- Hypoxia induces retinal VEGF expression.
- Pathologic new vessel formation underlies the proliferative complication.



Lens and retinal disease have different substrates

Not all diabetic eye disease is microangiopathy.

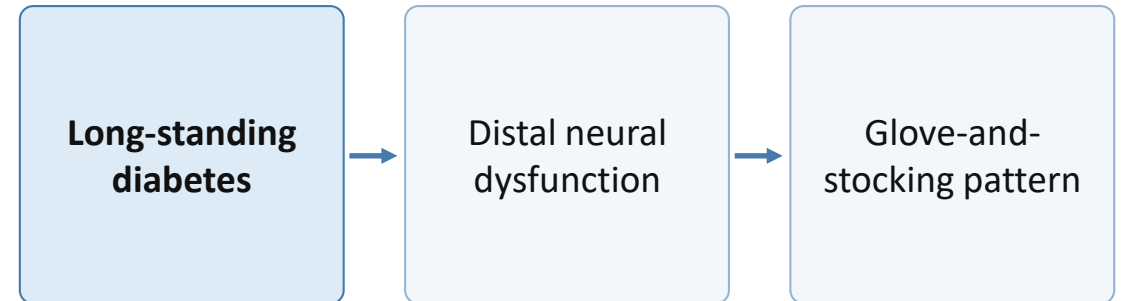
- Lens cataract: Opacification associated with glucose-related lens injury.
- Retinal disease: Microvascular dysfunction and VEGF-related vessel formation.
- Glaucoma may also coexist, but should not be equated with the polyol mechanism.

Site	Prominent process	Consequence
Lens	Polyol / sorbitol-related injury	Cataract
Retina	Microangiopathy; VEGF response	Retinopathy
Optic nerve	Glaucoma-associated damage	Visual dysfunction

Peripheral neuropathy is often length dependent

Neural injury has a characteristic sensorimotor distribution.

- Distal symmetric polyneuropathy often begins in the lower limbs.
- Later extension to hands produces a glove-and-stocking pattern.
- Microvascular compromise and intracellular glucotoxicity provide mechanistic context.



Autonomic and focal neuropathies differ

Diabetic neural complications are not limited to distal sensory loss.

- Autonomic injury may disturb bowel and bladder function.
- Erectile dysfunction is another autonomic manifestation.
- Mononeuropathies may cause focal limb weakness or cranial nerve palsies.

Autonomic neuropathy

Bowel / bladder
disturbance

Erectile dysfunction

Mononeuropathy

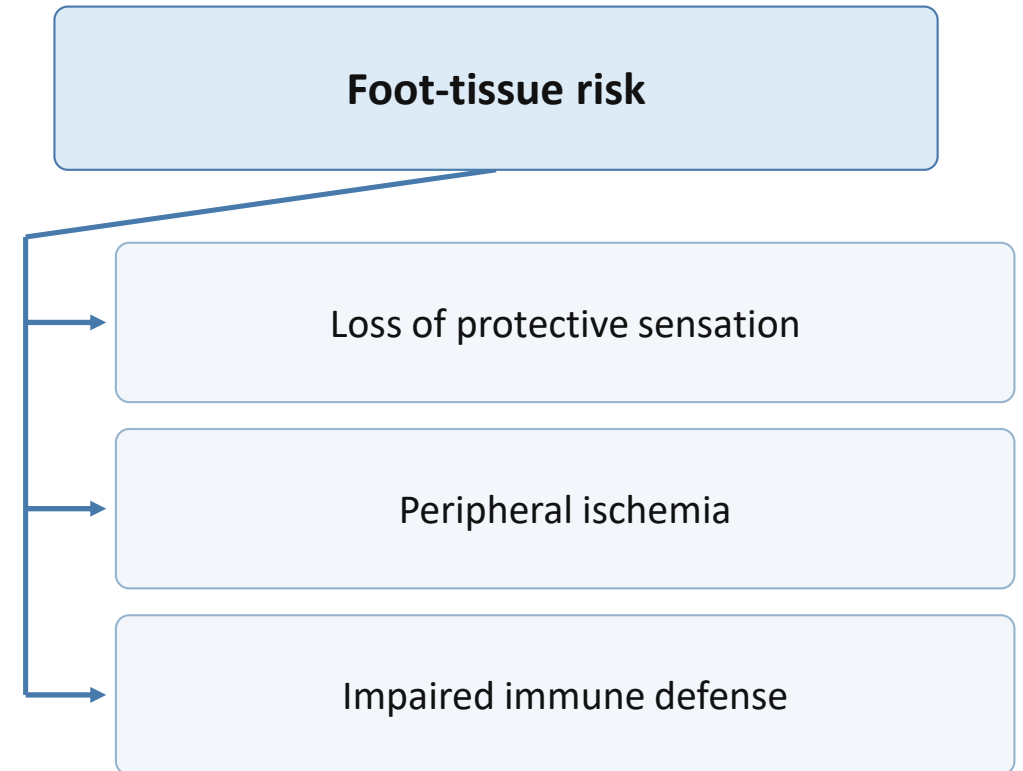
Footdrop or wristdrop

Cranial nerve palsy

The diabetic foot is a convergent clinical problem

Neuropathy, ischemia and infection together worsen tissue injury.

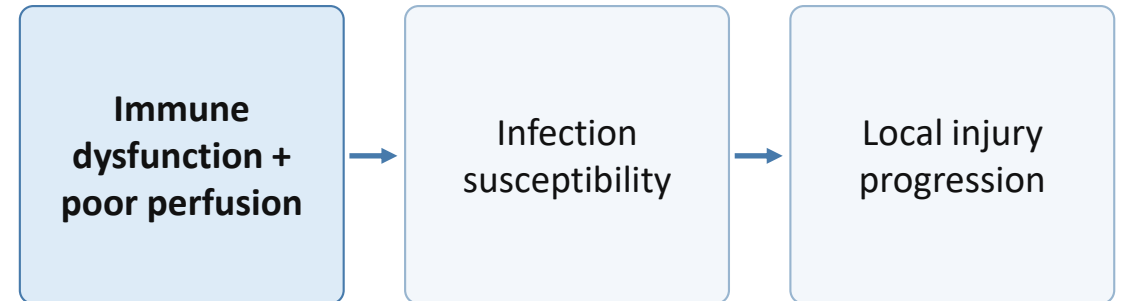
- Sensory impairment can allow a minor toe injury to go unnoticed.
- Poor perfusion limits tissue recovery and immune-cell delivery.
- Altered immune responses increase susceptibility to infection.
- Progression may include gangrene and systemic infection.



The host response to infection is impaired

Diabetes can alter leukocyte function as well as vessel perfusion.

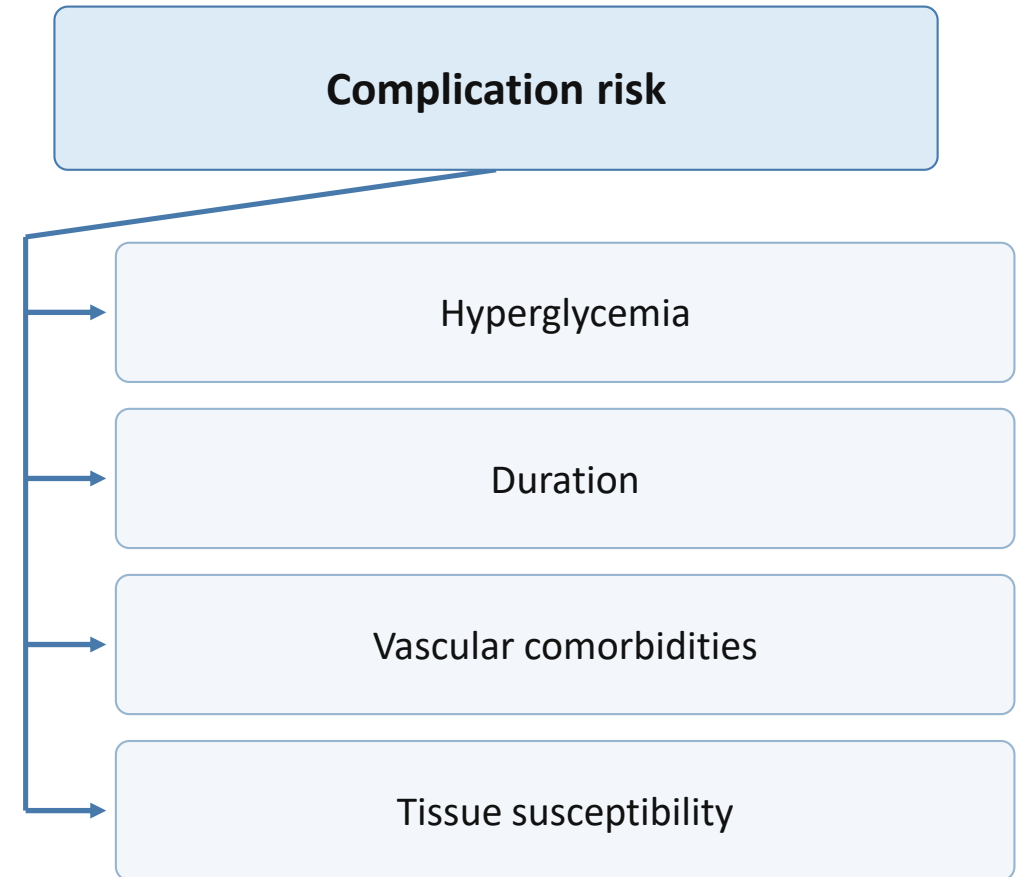
- Neutrophil chemotaxis, adherence, phagocytosis and killing may be reduced.
- Macrophage cytokine responses can be impaired.
- Vascular compromise obstructs delivery of host-defense components.



Clinical risk is multifactorial

Glycemic exposure acts alongside comorbidity and organ-specific vulnerability.

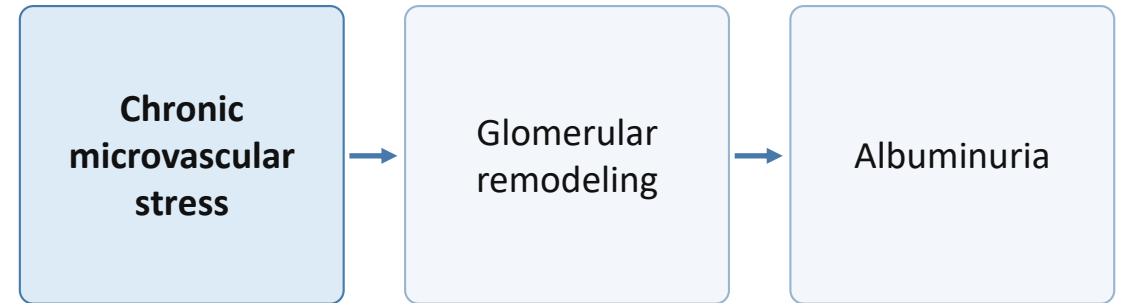
- Duration and degree of glucose elevation predict cumulative microvascular stress.
- Hypertension, dyslipidemia and insulin resistance add cardiovascular risk.
- Different tissues express different final injury patterns despite shared upstream stress.



Case: New albuminuria after years of diabetes

A patient develops persistent urinary albumin and rising blood pressure.

- Relevant structural lesion: Diabetic glomerular and mesangial injury.
- Potential vascular co-lesion: Arteriolar hyalinosis.
- Reasoning task: Connect basement membrane/matrix injury to protein leakage and renal decline.



Case: Progressive retinal vascular changes

A long-standing diabetic patient develops retinal new-vessel formation.

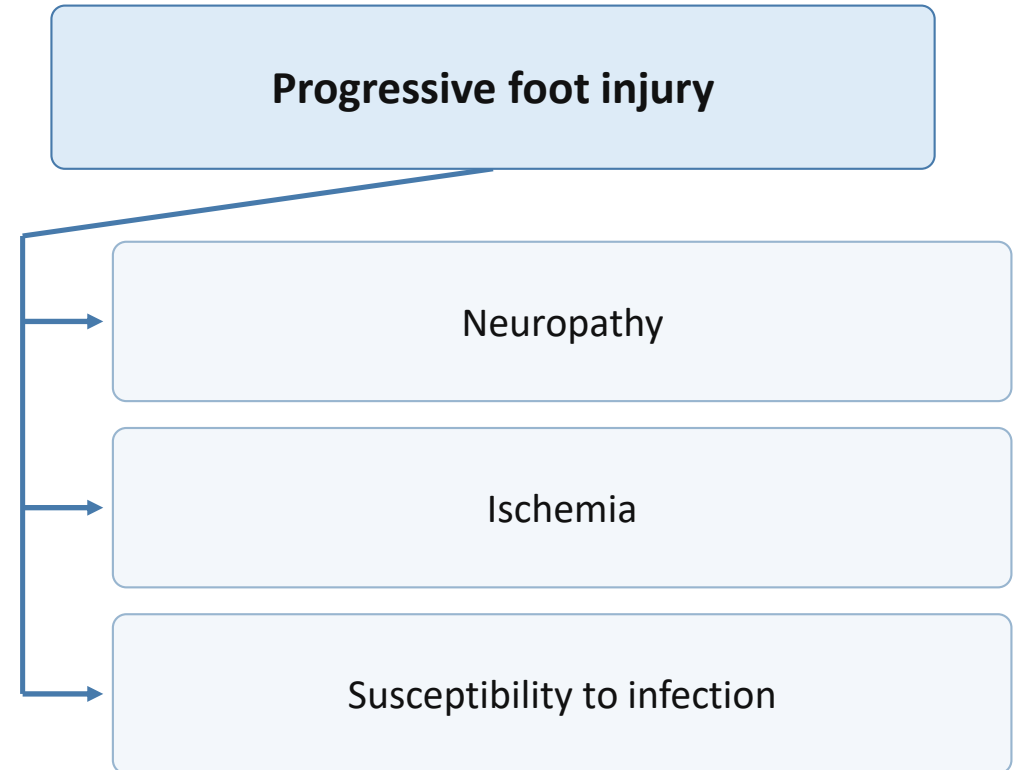
- Identify the vascular category: Microvascular disease.
- Infer hypoxia-associated VEGF upregulation as a principal mechanism.
- Explain why this differs from sorbitol-associated lens opacification.



Case: An infected toe with reduced sensation

A small unnoticed toe lesion progresses despite initial limited symptoms.

- Distal neuropathy reduces protective sensory warning.
- Atherosclerotic ischemia reduces local perfusion.
- Impaired immune function and microbial invasion can compound damage.



Mechanism-to-organ mapping

The location of injury determines the clinically visible phenotype.

- Retina: Microangiopathy and VEGF-related neovascularization.
- Kidney: Basement membrane change, mesangial sclerosis and albuminuria.
- Nerves: Metabolic and microvascular stress with peripheral/autonomic deficits.
- Large arteries: Atherosclerotic ischemic events.

Tissue	Dominant mechanism/lesion	Clinical correlate
Retina	Microvascular injury / VEGF	Retinopathy
Kidney	Matrix expansion; Arterioles	Nephropathy
Nerves	Metabolic + vascular injury	Neuropathy
Large arteries	Accelerated atherosclerosis	MI / stroke / limb ischemia

Mechanistic checkpoint

Choose the intermediate or mediator that best distinguishes each route.

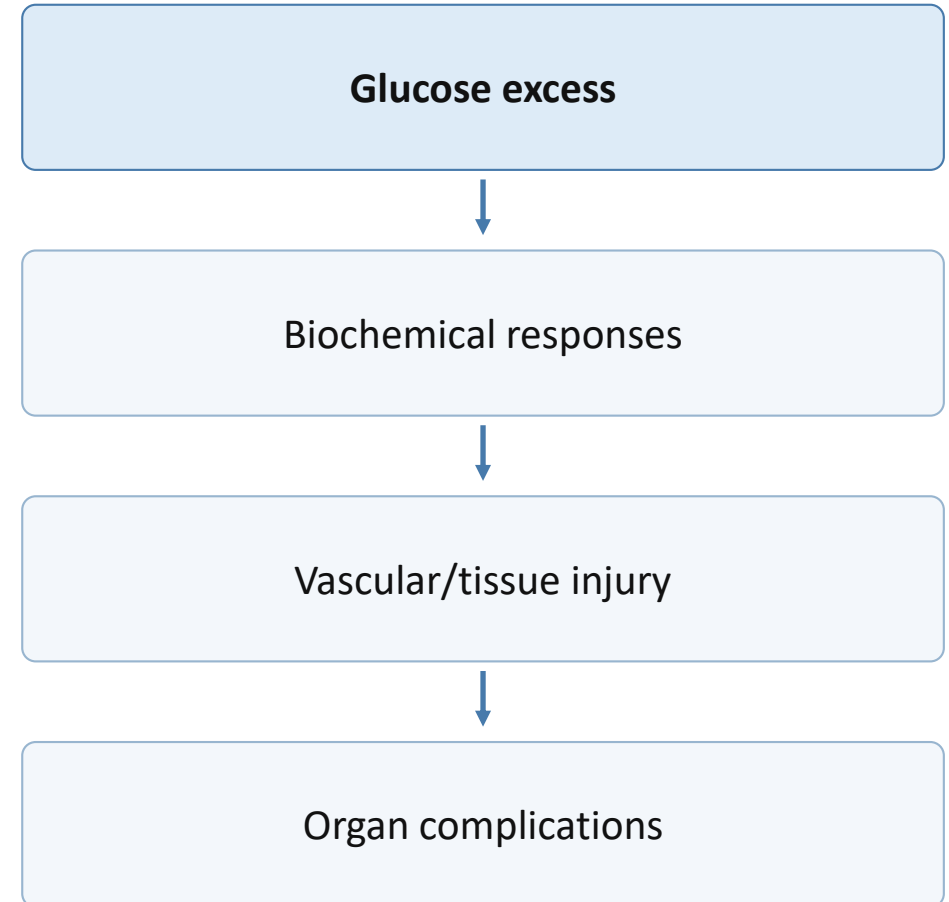
- Reactive carbonyls and RAGE → advanced glycation pathway.
- DAG and PKC → kinase signaling pathway.
- Sorbitol with NADPH use → polyol pathway.
- Diversion of glycolytic intermediates → hexosamine pathway.

Clue	Mechanistic answer
Methylglyoxal / RAGE	AGE pathway
DAG / VEGF / PAI-1	PKC pathway
Sorbitol / NADPH / GSH	Polyol / oxidative stress
Intermediate pathway flux	Hexosamine pathway

Integrated causal chain

The most useful explanation links glucose excess to altered tissue structure and function.

- Chronic glucose exposure increases injurious metabolic flux.
- Receptor, kinase and redox changes disrupt endothelial homeostasis.
- Matrix expansion, leakiness and ischemic injury follow.
- Organ-specific structural and clinical complications emerge over time.



Six take-home principles

Chronic diabetic pathology is a set of converging, cumulative injury mechanisms.

- Macrovascular = accelerated atherosclerosis; Microvascular = small-vessel injury.
- AGE–RAGE and DAG–PKC share VEGF and TGF- β outputs.
- Polyol metabolism compromises NADPH-dependent GSH regeneration.
- Hexosamine injury is a proposed mechanism; Non-glycemic risks also matter.

Primary source and scope

Source for this lecture: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed. (2026).

- Principal section: “Chronic Complications of Diabetes.”
- Morphologic context: “Morphology of Chronic Complications of Diabetes.”
- Clinical context: “Clinical Manifestations of Chronic Diabetes.”
- Conceptual schematics are original, editable teaching diagrams; no histopathology image is represented.