

Diabetes Mellitus

Diabetic retinopathy and ocular complications

Retinal microangiopathy • Neovascularization • Clinicopathologic consequences

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Learning objectives

Recognize the microscopic lesions of diabetic retinal microangiopathy.

Distinguish intraretinal pathology from vessels that cross the internal limiting membrane.

Explain edema, vitreous hemorrhage, tractional detachment, and neovascular glaucoma mechanistically.

Link ischemia and VEGF to the rationale for retinal ablation and VEGF inhibition.

The eye: The relevant diabetic lesions

Diabetes affects the lens, iris, ciliary body, and retina.

This unit concentrates on retinal microangiopathy and its secondary effects.

Posterior-segment ischemia also drives pathology in the anterior segment.

Anterior structures

Retinal microvasculature

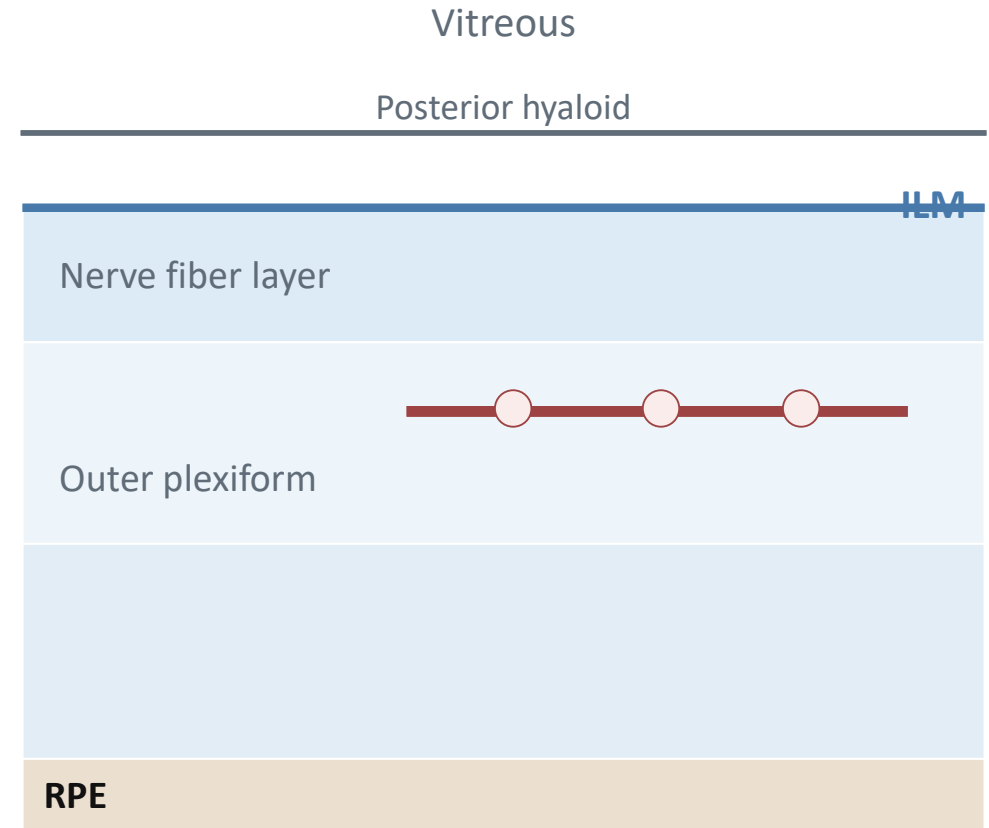
Secondary complications

Retinal architecture determines disease patterns

Retinal vessels lie within the neurosensory retina.

The internal limiting membrane (ILM) is its inner boundary toward the vitreous.

The retinal pigment epithelium (RPE) lies external to the neurosensory retina.



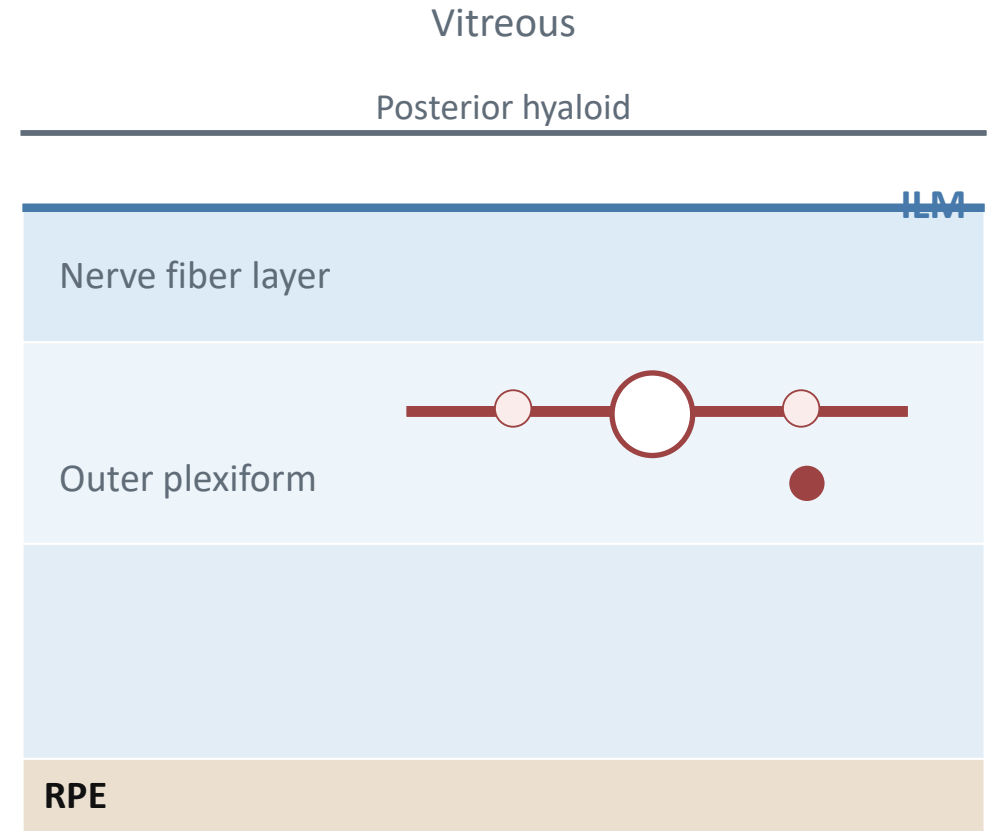
Schematic, not a histologic section

The ILM separates two pathogenetic stages

Nonproliferative vascular pathology remains within the retina, beneath the ILM.

Proliferative retinopathy is defined by new vessels crossing the ILM.

This anatomic distinction is more precise than vessel abundance alone.



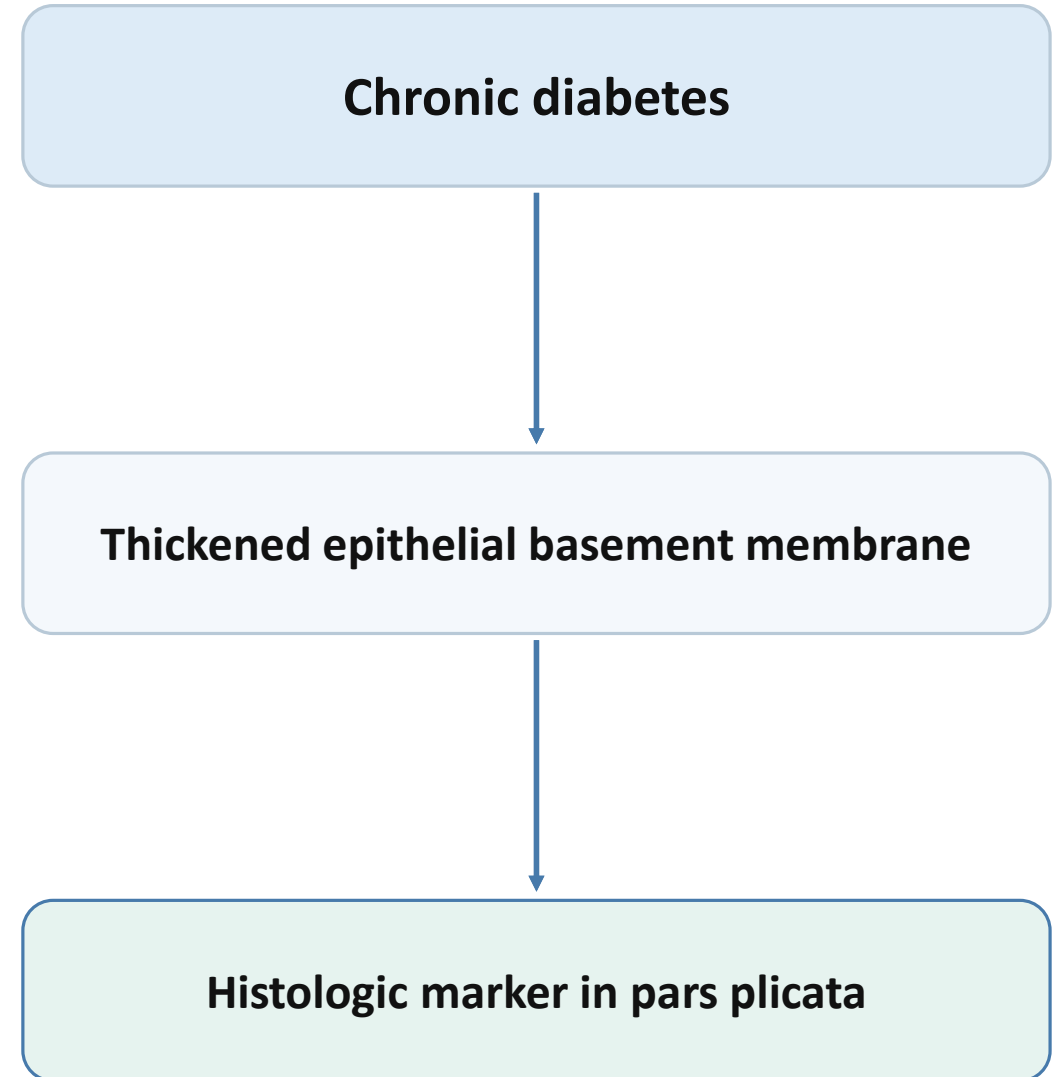
Boundary determines category

The ciliary body carries a chronic diabetic signature

The pars plicata produces aqueous humor.

The basement membrane of its epithelium can become markedly thickened in chronic diabetes.

This microscopic change with diabetic glomerular mesangial change.



Retinopathy accumulates with diabetes duration

Retinopathy in approximately 60%–80% of patients 15–20 years after diagnosis.

This is a textbook estimate, not a contemporary screening-population prediction.

Duration describes exposure; Fundus pathology establishes the ocular phenotype.

60%–80%

15–20 years after diagnosis

Robbins 11th edition estimate

Two vascular failures coexist in diabetic retina

LEAKAGE

Barrier dysfunction

Edema / exudate

CLOSURE

Micro-occlusion

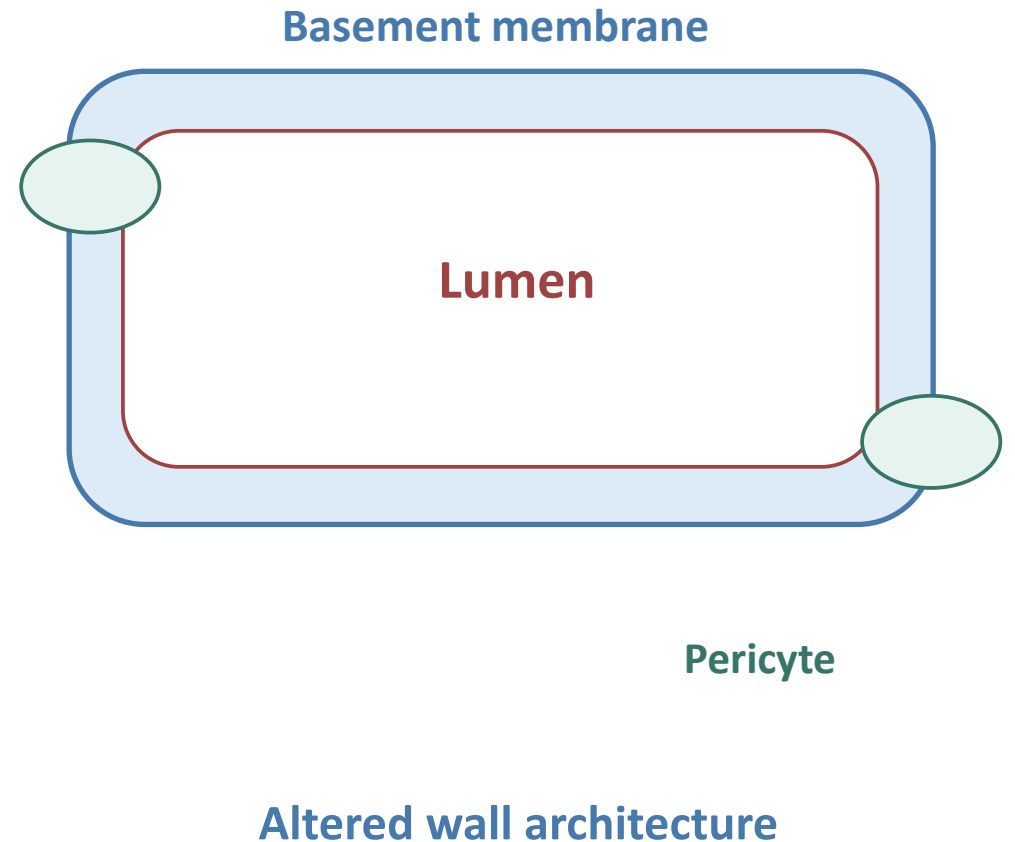
Ischemia / VEGF

The retinal vascular basement membrane thickens

Diabetic retinal vessels typically show increased basement-membrane thickness.

This is a structural manifestation of systemic diabetic microangiopathy.

Thickened basement membrane does not imply normal barrier function.

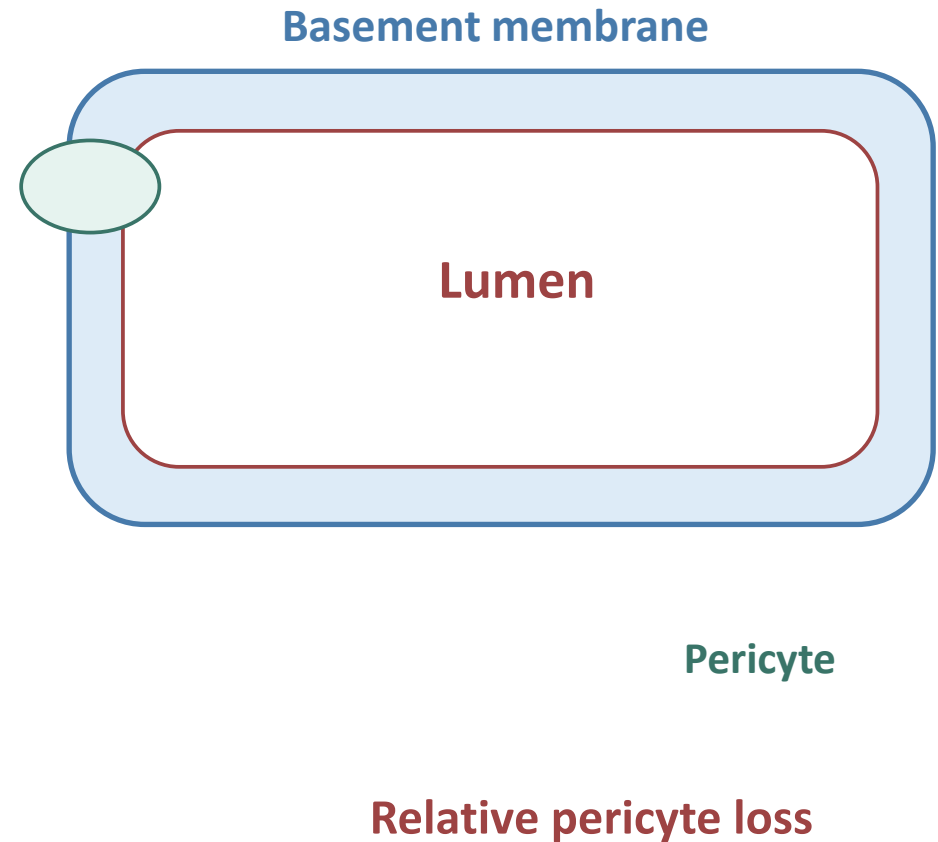


Pericytes become depleted relative to endothelium

The number of pericytes decreases relative to endothelial cells.

Pericyte loss accompanies the retinal microvascular structural lesion.

Evaluate vessel wall support together with lumen patency and leakiness.

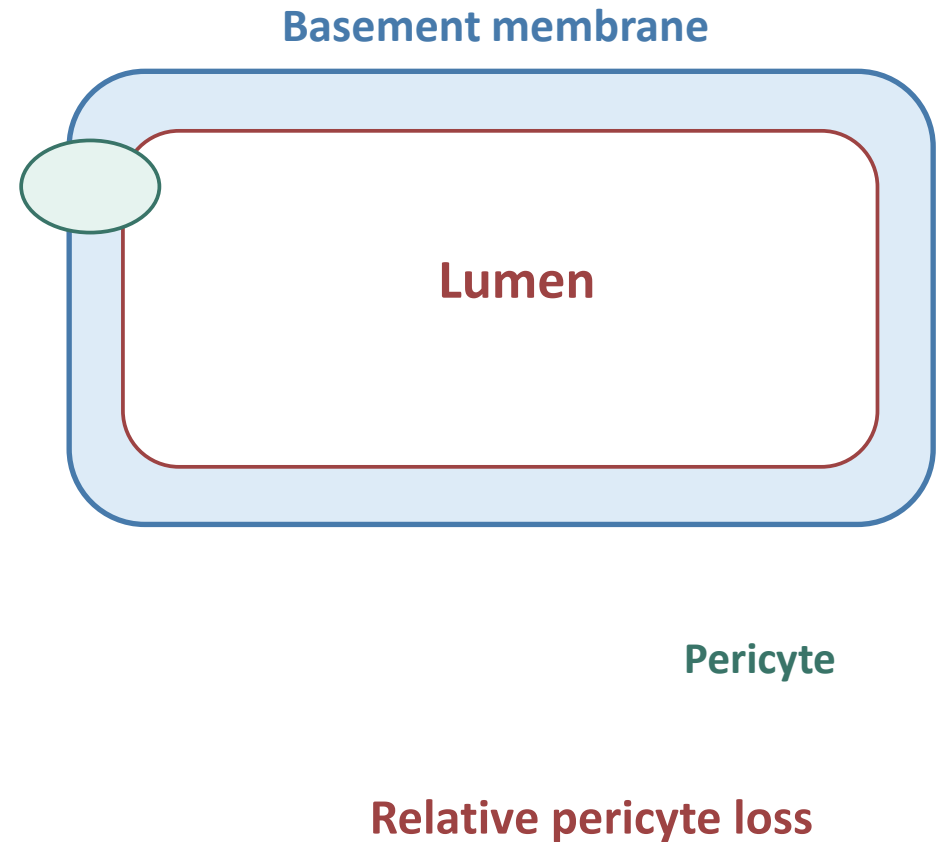


Basement-membrane change and pericyte loss coexist

The same capillary network may show thickened walls and relative pericyte depletion.

These changes are not alternative diagnostic categories.

Their downstream manifestations include microaneurysms and vascular dysfunction.

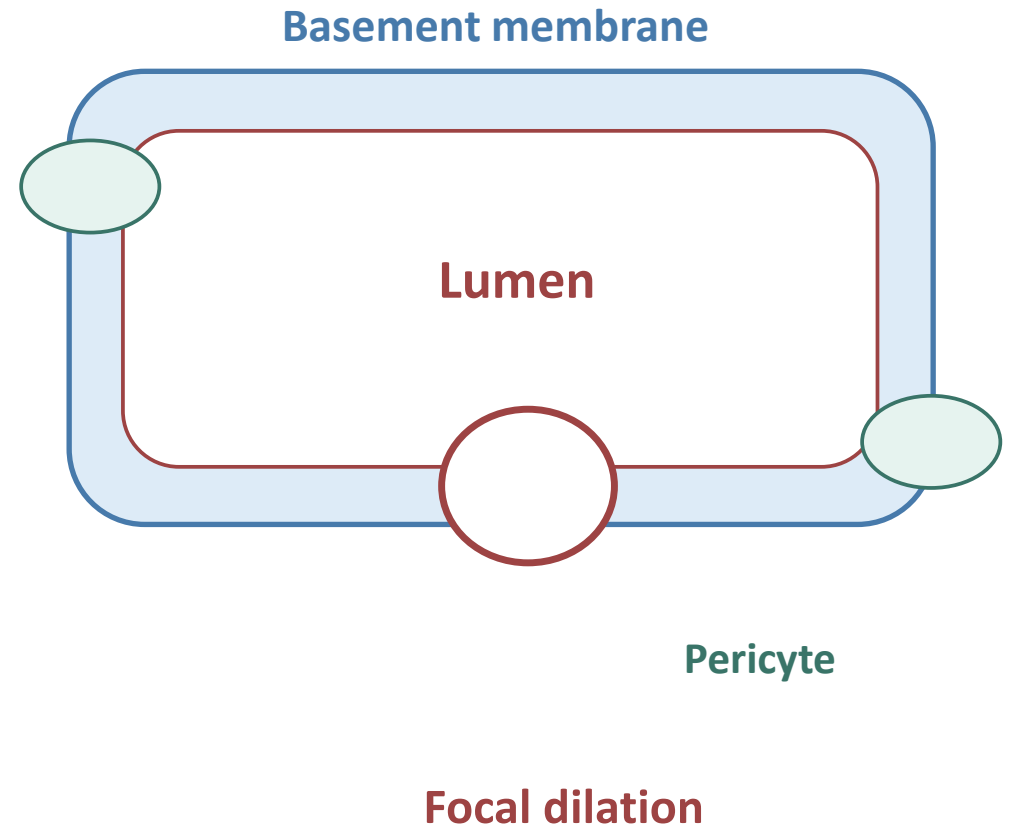


Microaneurysms are a major microangiopathic lesion

Microaneurysms are focal dilatations of retinal microvessels.

They are a prominent manifestation of diabetic retinopathy.

A capillary-level lesion may have important visible retinal consequences.



An ophthalmoscopic red dot needs interpretation

MICROANEURYSM

Focal microvascular dilation

Often below direct resolution

MICROHEMORRHAGE

Extravasated erythrocytes

Can resemble a tiny red dot

Blood–retinal barrier dysfunction causes leakage

Structural microvascular injury is associated with functional barrier breakdown.

Fluid and plasma-derived material leave abnormally permeable vessels.

Edema and exudates represent different consequences of vascular leakage.

Abnormal retinal vessel



Blood–retinal barrier failure



Fluid / solute escape



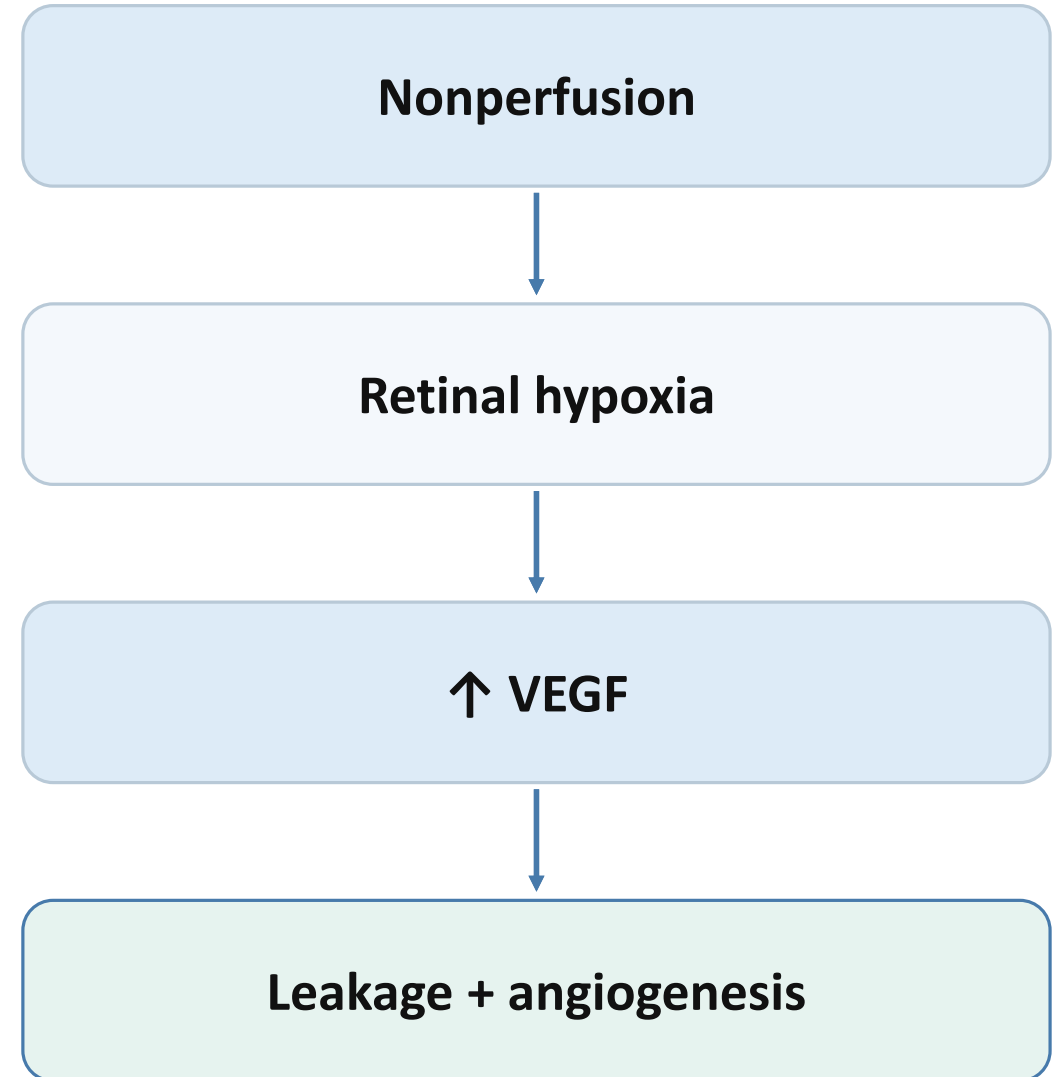
Retinal tissue changes

VEGF links ischemia with permeability

VEGF is induced by hypoxic retina.

VEGF was originally termed vascular permeability factor.

Its biological effects connect retinal ischemia, leakage, and angiogenesis.

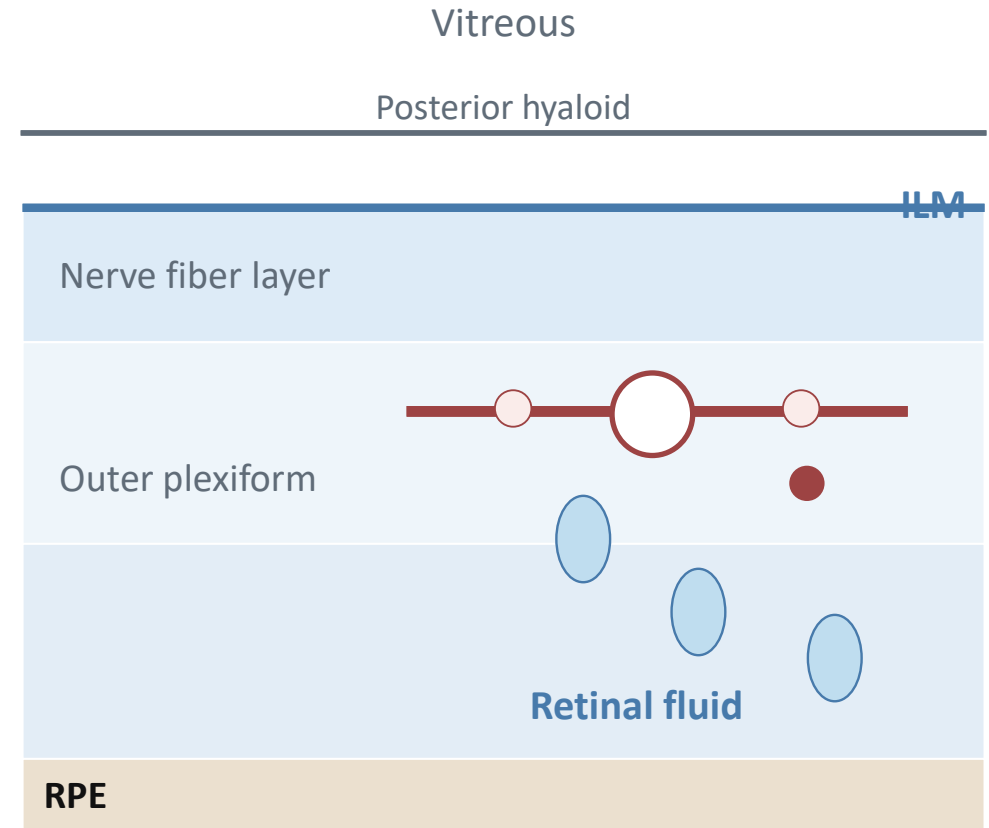


Macular edema is a major pathway to visual loss

Leakage into the retina produces tissue edema.

Edema involving the macula compromises central retinal function.

Macular edema as a common cause of visual loss in diabetes.

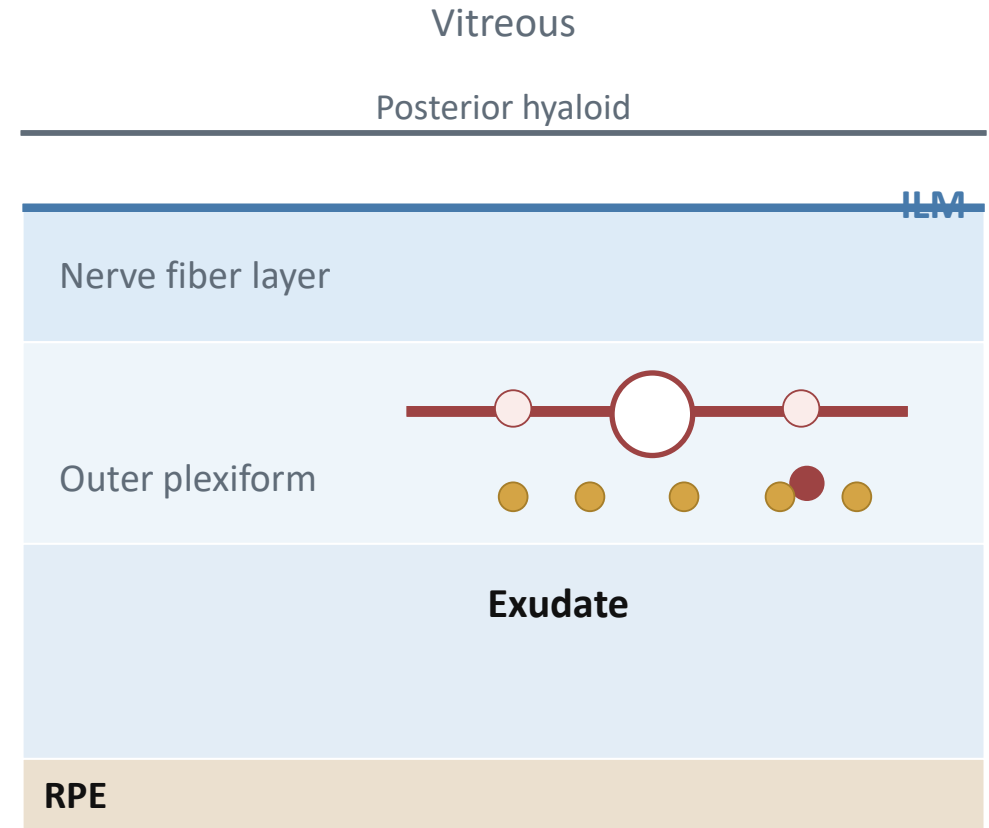


Exudates accumulate in the outer plexiform layer

Abnormal permeability produces retinal exudates.

The outer plexiform layer is a characteristic location for their accumulation.

The retinal layer explains the clinical distribution of exudate.



Retinal hemorrhage shape reflects its depth

SUPERFICIAL

Nerve fiber layer

Flame-shaped profile

DEEPER

Deeper retinal layers

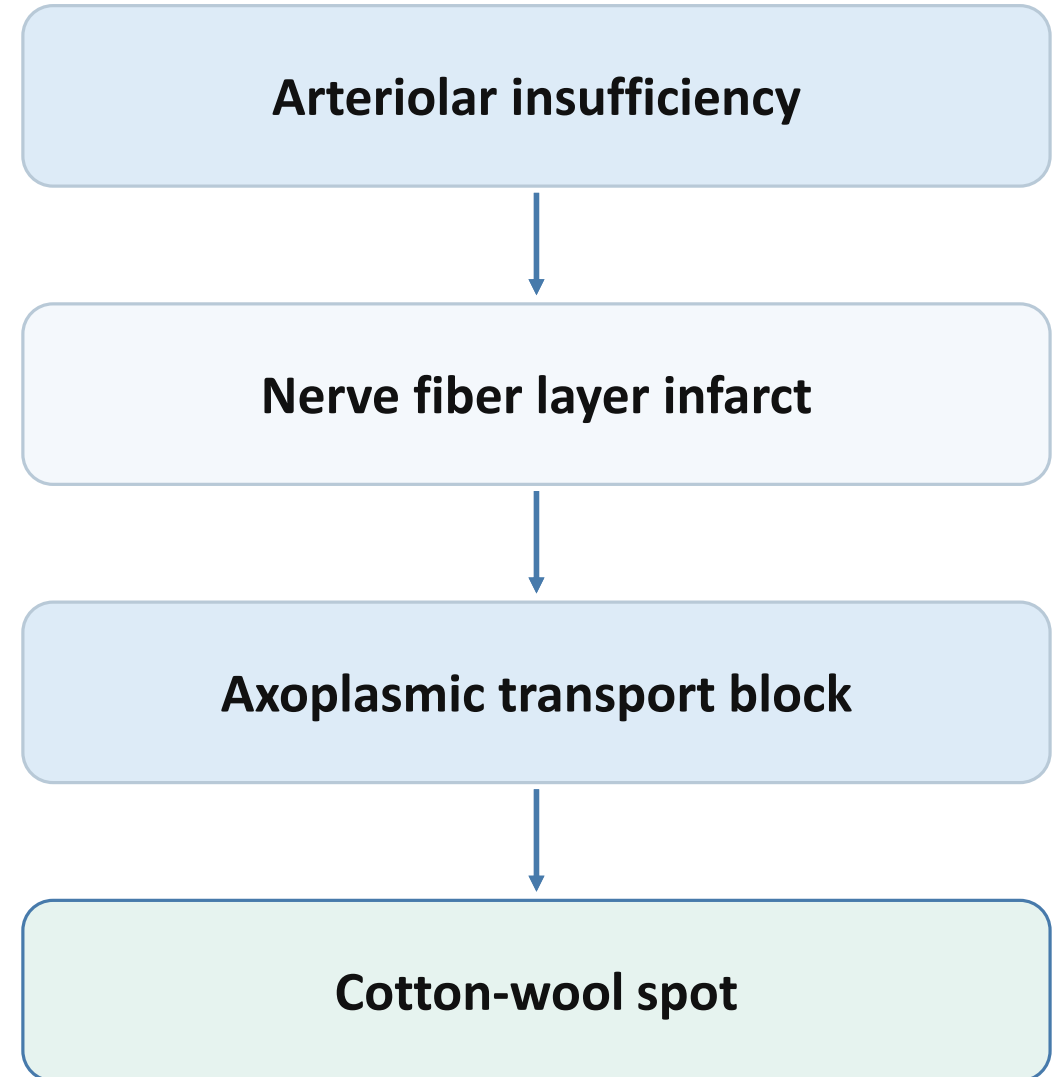
Dot/blot profile

Cotton-wool spots signal focal axonal ischemia

A cotton-wool spot is an infarct of the retinal nerve fiber layer.

Disrupted axoplasmic transport produces swollen axonal endings (cytoid bodies).

The finding is not diabetes-specific: Other occlusive retinal diseases also cause it.



Retinal micro-occlusion produces nonperfusion

Diabetic capillaries may become obstructed despite being hyperpermeable elsewhere.

A nonperfused region is deprived of effective microcirculatory delivery.

Micro-occlusion supplies the ischemic stimulus for neovascularization.

Microvascular obstruction



Local nonperfusion



Tissue hypoxia



Angiogenic response

Fluorescein can reveal two opposite abnormalities

VASCULAR INCOMPETENCE

Fluorescein leakage

Abnormally permeable vessel

VASCULAR NONPERFUSION

Absent capillary filling

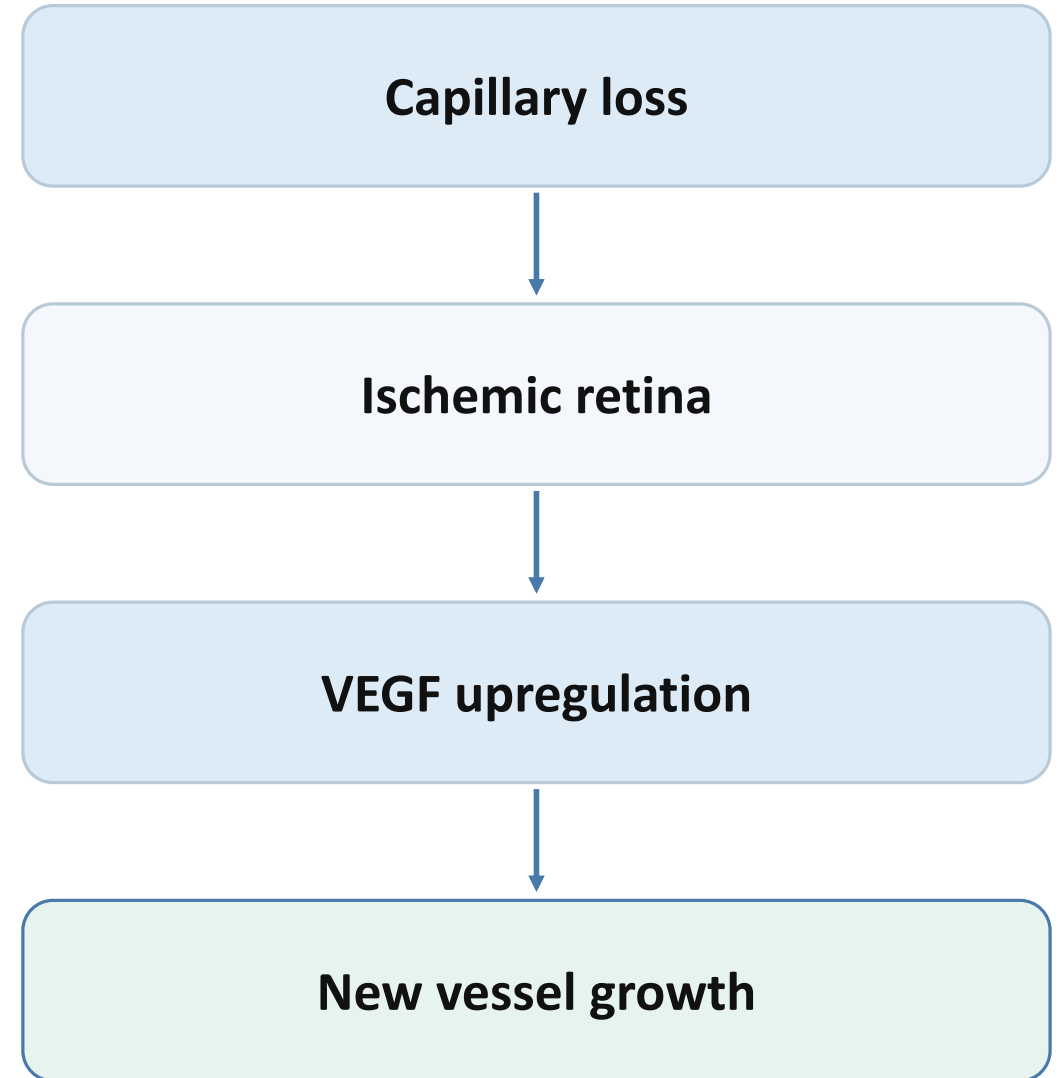
Ischemic retinal territory

Hypoxia upregulates retinal VEGF

The central driver of pathological new-vessel formation is retinal hypoxia.

Hypoxic retina increases VEGF expression.

Angiogenesis can first be intraretinal before surface neovascularization develops.



Diabetic retinopathy has two principal categories

NONPROLIFERATIVE

Intraretinal lesions

Leakage $\pm$ nonperfusion

PROLIFERATIVE

Preretinal new vessels

Fibrovascular complications

Nonproliferative retinopathy: The lesion set

Microaneurysms and microhemorrhages reflect focal vessel abnormality.

Leakage causes edema and outer plexiform exudates.

Closure causes nonperfusion and secondary ischemic change.

Wall remodeling

Leakage

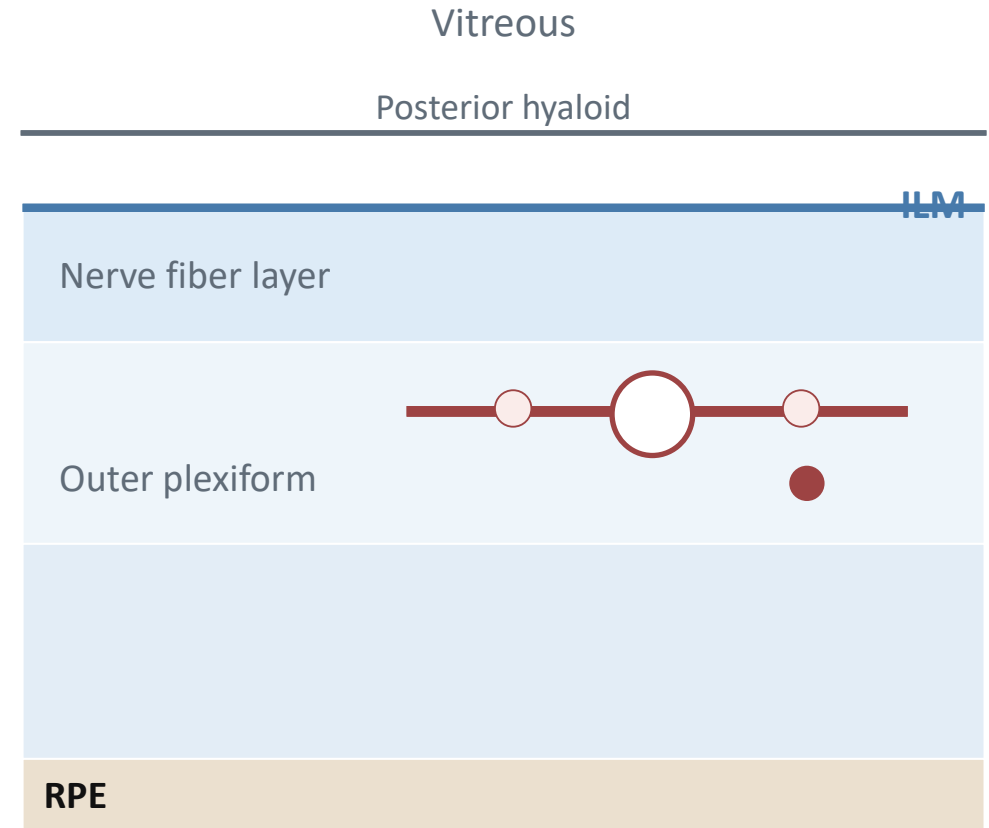
Microvascular closure

Nonproliferative disease remains beneath the ILM

Dilated vessels, leakage, and small hemorrhages lie within the retina.

Intraretinal angiogenesis does not itself meet the proliferative definition.

A clear ILM landmark prevents overcalling preretinal proliferation.

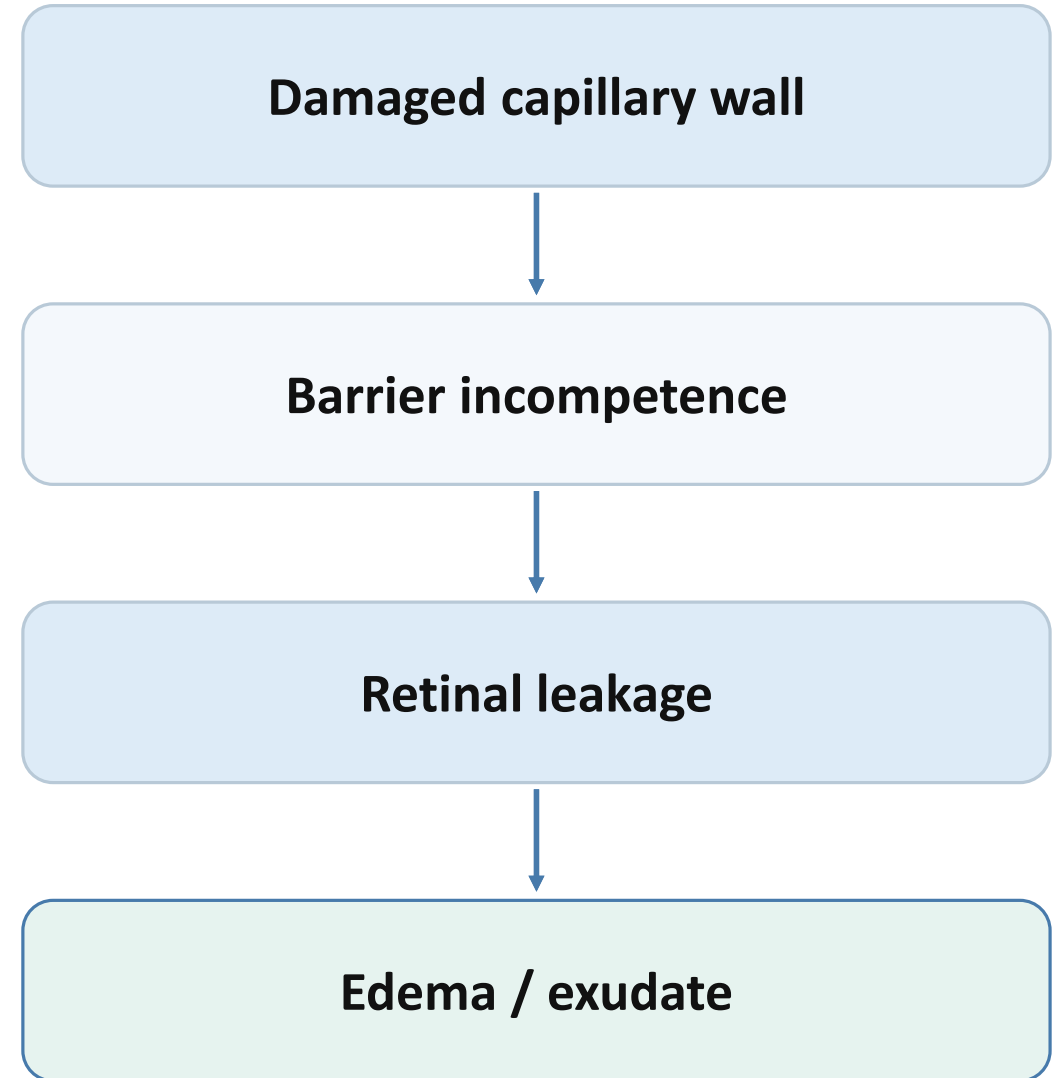


Capillary incompetence drives the exudative phenotype

Microvascular structural injury can destabilize normal retinal compartmentalization.

The resulting leak produces edema and exudative deposits.

This pathway does not require visible preretinal neovascularization.



Macular involvement determines functional importance

MACULAR EDEMA

Leakage-related visual impairment

May occur without PDR

SURFACE NEOVESSELS

Evidence of proliferative stage

Risk of hemorrhage / traction

Edema and exudate are not interchangeable

EDEMA

Fluid in retinal tissue

Disturbs retinal structure

EXUDATE

Deposited leakage products

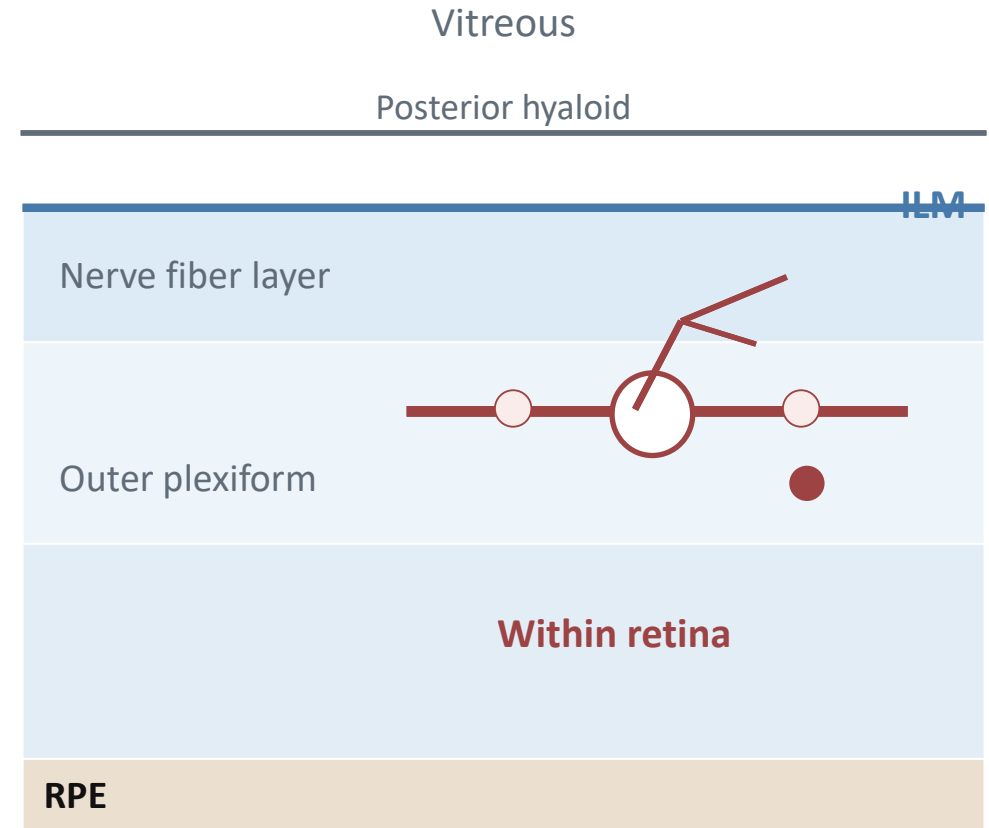
Often outer plexiform layer

Intraretinal angiogenesis precedes the ILM breach

Nonperfused retina produces a proangiogenic environment.

New vascular channels may develop within the retina.

Intraretinal angiogenesis differs anatomically from surface retinal neovascularization.



IRMA is not identical to preretinal neovascularization

INTRARETINAL MICROANGIOPATHY

Contained beneath ILM

Retinal compartment

PRERETINAL NEOVESSELS

Crosses ILM

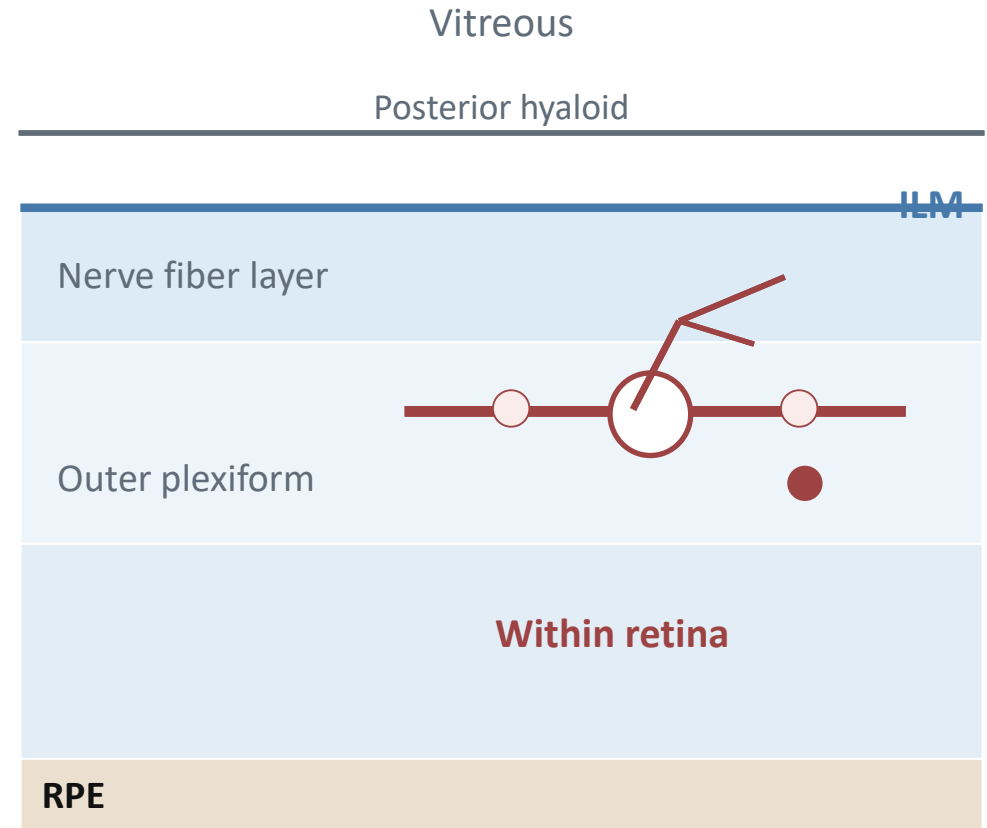
Retinal / disc surface

A classification exercise: Trace the vessel

Start by identifying the retinal surface and ILM.

If the vascular process remains entirely intraretinal, describe an intraretinal lesion.

If newly formed vessels cross the ILM, classify retinal neovascularization.

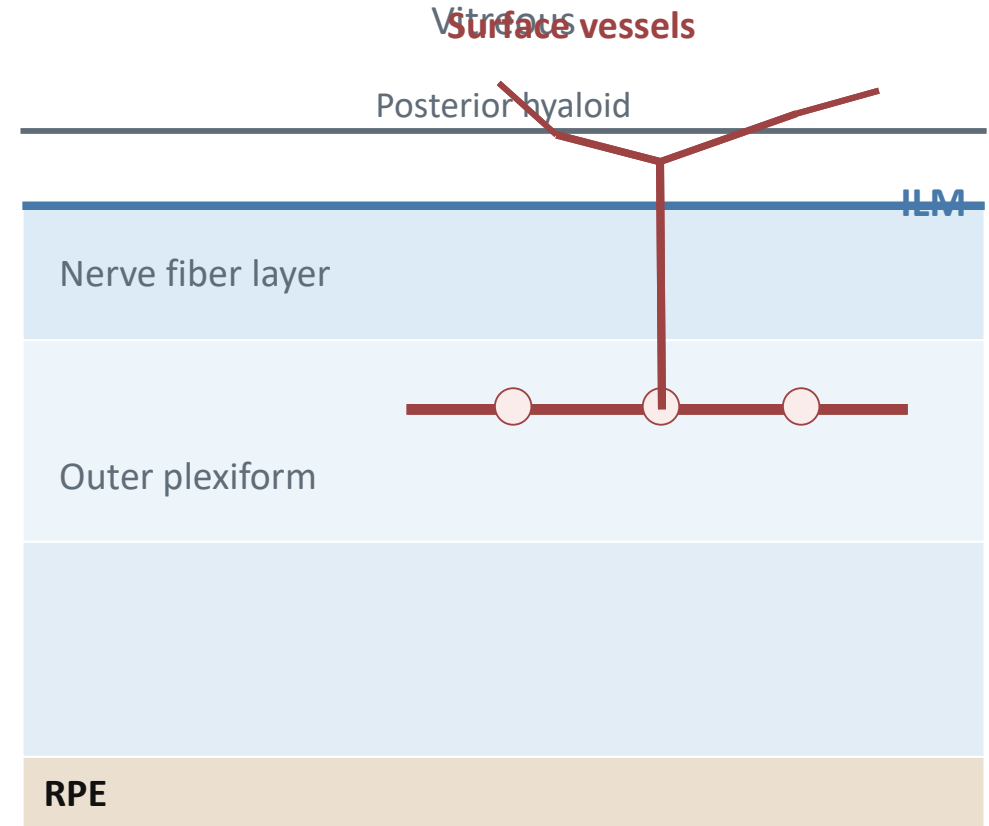


The proliferative transition crosses the ILM

Pathologic new vessels extend through the retinal internal limiting membrane.

They grow on the retina or optic disc surface.

This crossing—rather than edema or exudate—defines proliferative retinopathy.

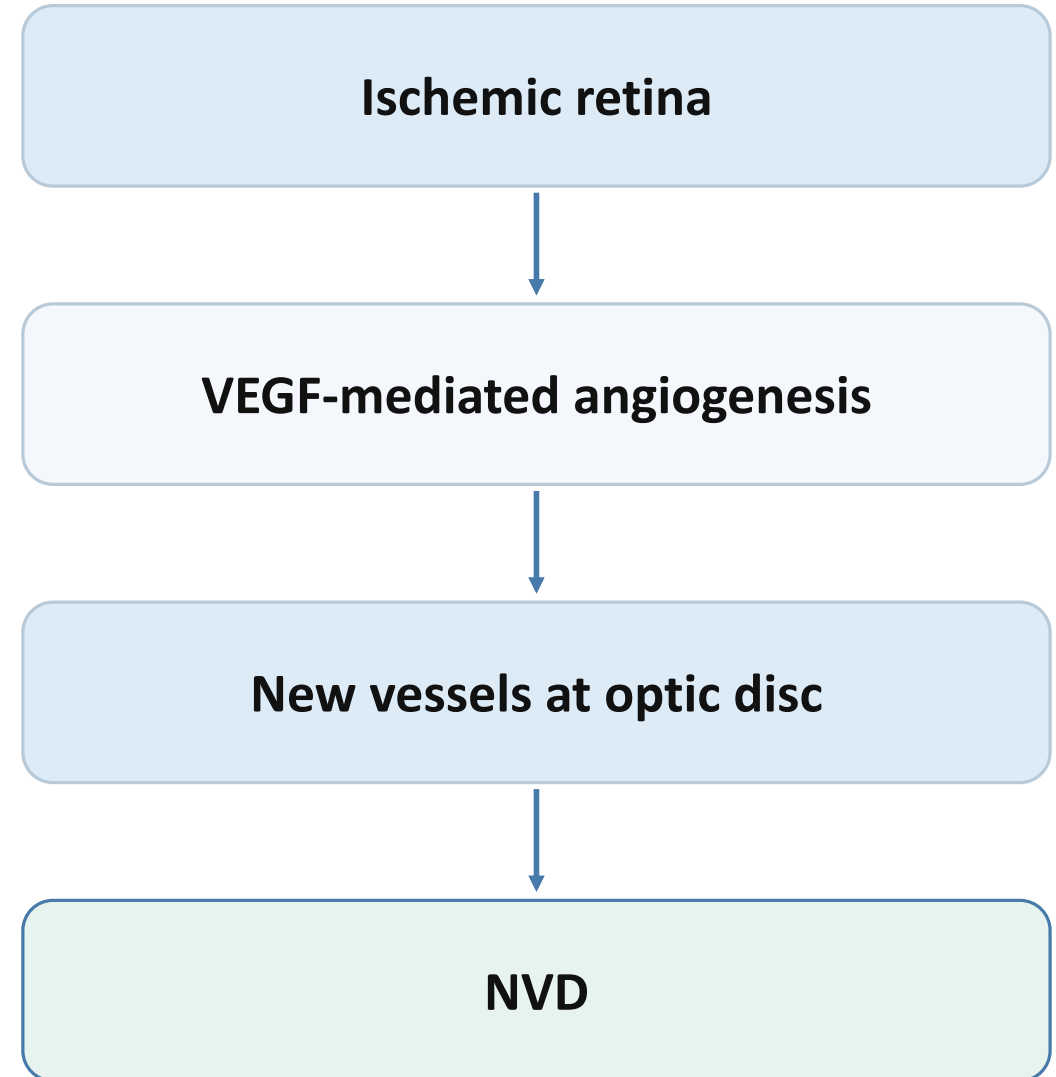


NVD: Neovascularization of the optic disc

NVD refers to new vessels arising on the optic nerve head surface.

The optic disc is a distinct anatomic site for proliferative growth.

The site and amount of neovascularization influence ophthalmic management.

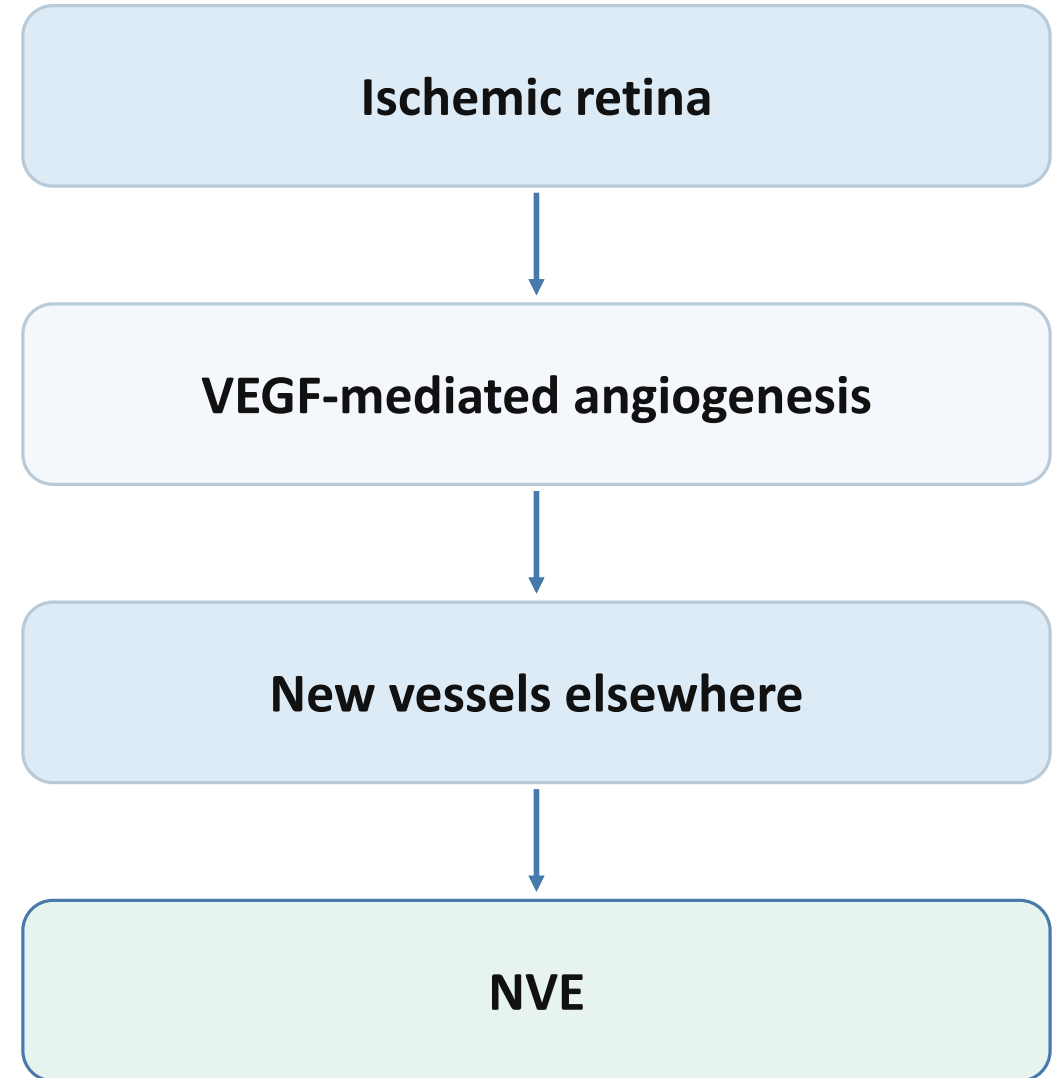


NVE: Neovascularization elsewhere

NVE describes new vessels along the retinal surface away from the disc.

Both NVE and NVD are surface-neovascular phenomena.

Location and extent of new vessels contribute to management decisions.



NVD and NVE: Different sites, shared biology

NVD

Optic nerve head surface

Disc location

NVE

Retinal surface outside disc

Elsewhere location

A neovascular membrane contains more than vessels

An angiogenic membrane contains newly formed vascular channels.

Fibrous or glial supporting stroma may be substantial or minimal.

Its stromal component is important for organization and traction.

Abnormal new vessels



± fibrous / glial stroma



Neovascular membrane



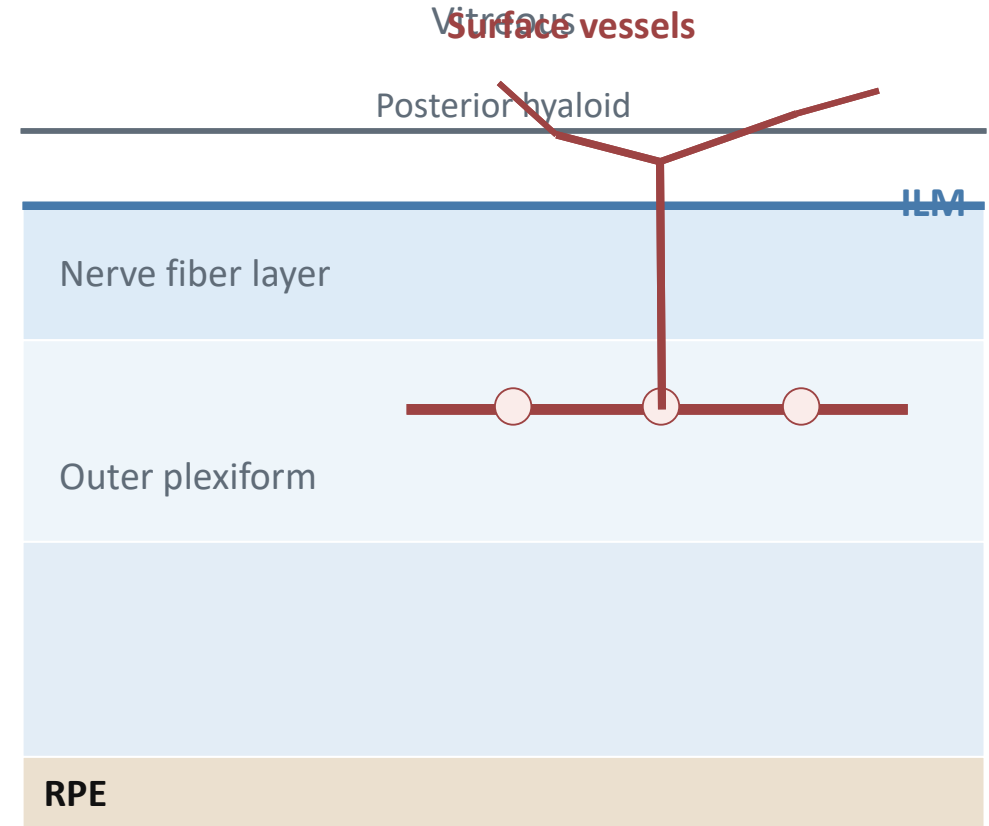
Bleeding / fibrosis risk

The ILM breach changes mechanical relationships

Intraretinal vessels are embedded within retinal substance.

Preretinal membranes grow into the interface with the vitreous.

Abnormal tissue in this interface becomes vulnerable to traction during vitreous movement.

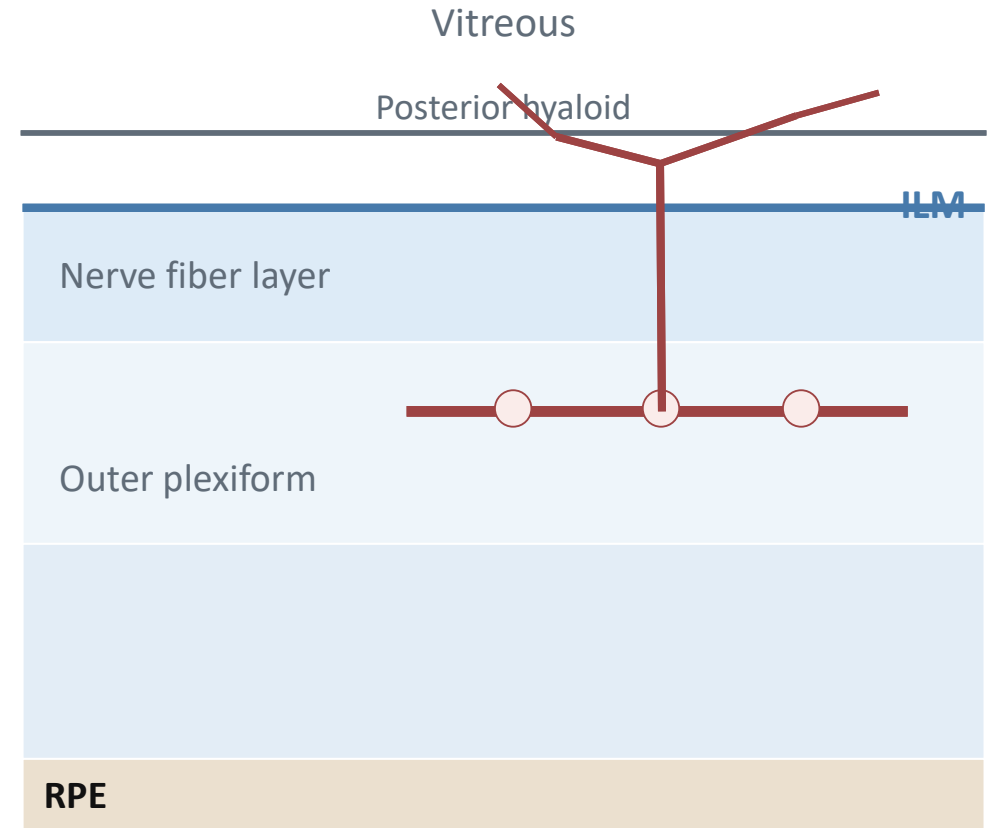


The posterior hyaloid borders the preretinal space

The posterior hyaloid is the posterior boundary of vitreous humor.

A potential plane lies between posterior hyaloid and retinal ILM.

With the hyaloid intact, fibrovascular membranes may extend along this plane.



Posterior vitreous detachment can disrupt new vessels

The vitreous may later separate from the ILM.

Attached abnormal vessels may be pulled or torn during separation.

The result can be extensive vitreous hemorrhage.

Preretinal fibrovascular membrane



Posterior vitreous separation



Vessel disruption



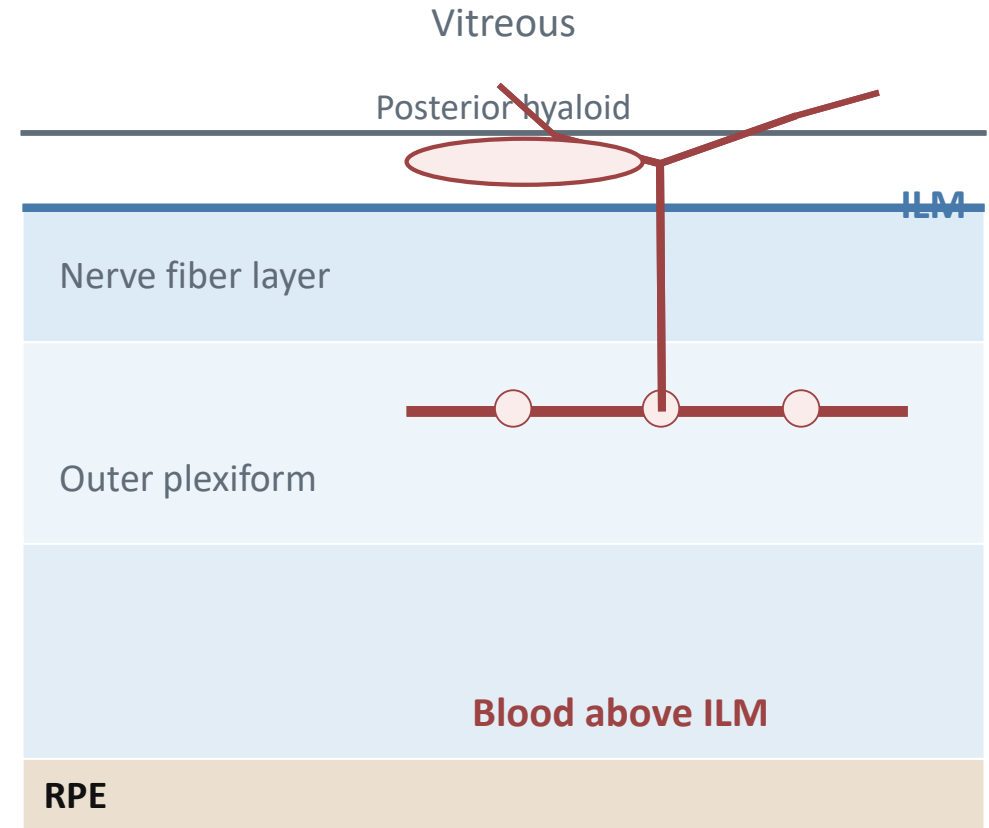
Vitreous hemorrhage

Preretinal hemorrhage occupies a superficial plane

Blood may collect beneath the posterior hyaloid and above the ILM.

This is distinct anatomically from hemorrhage within retinal layers.

The relation to neovascular tissue explains the superficial location.

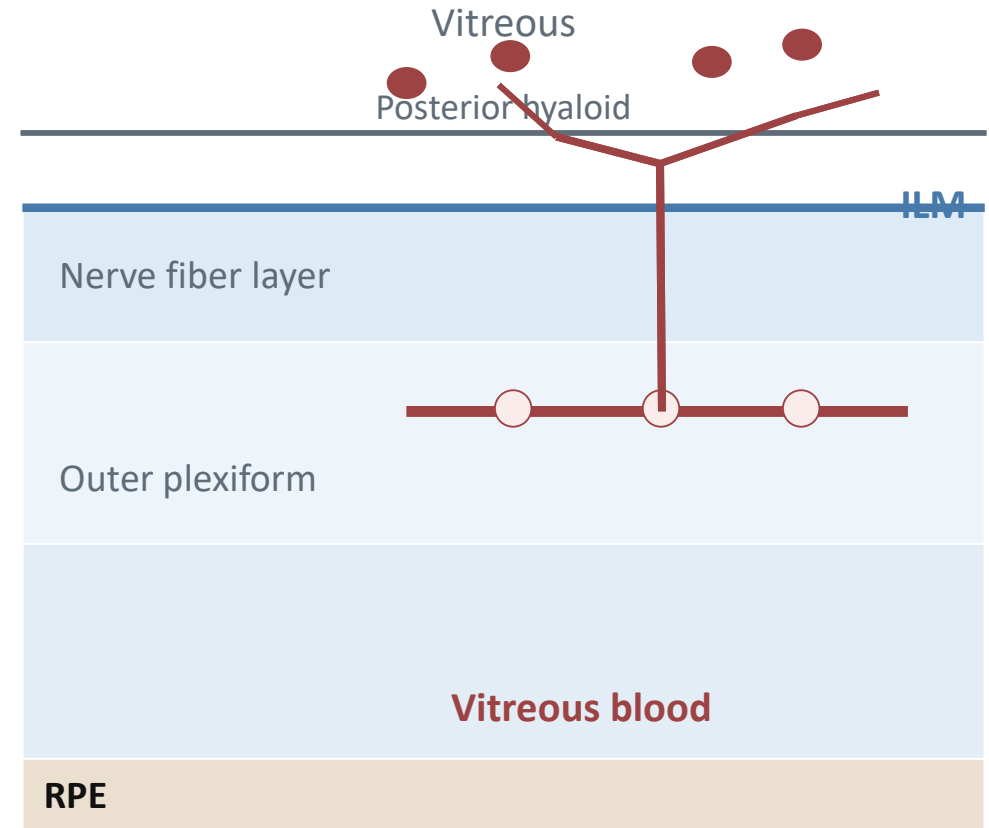


Vitreous hemorrhage follows rupture of fragile membranes

The abnormal neovascular network can be disrupted mechanically.

Blood enters the vitreous cavity and may interfere with visual transmission.

The source of blood lies at the retinal–vitreous interface, not necessarily within the retina.

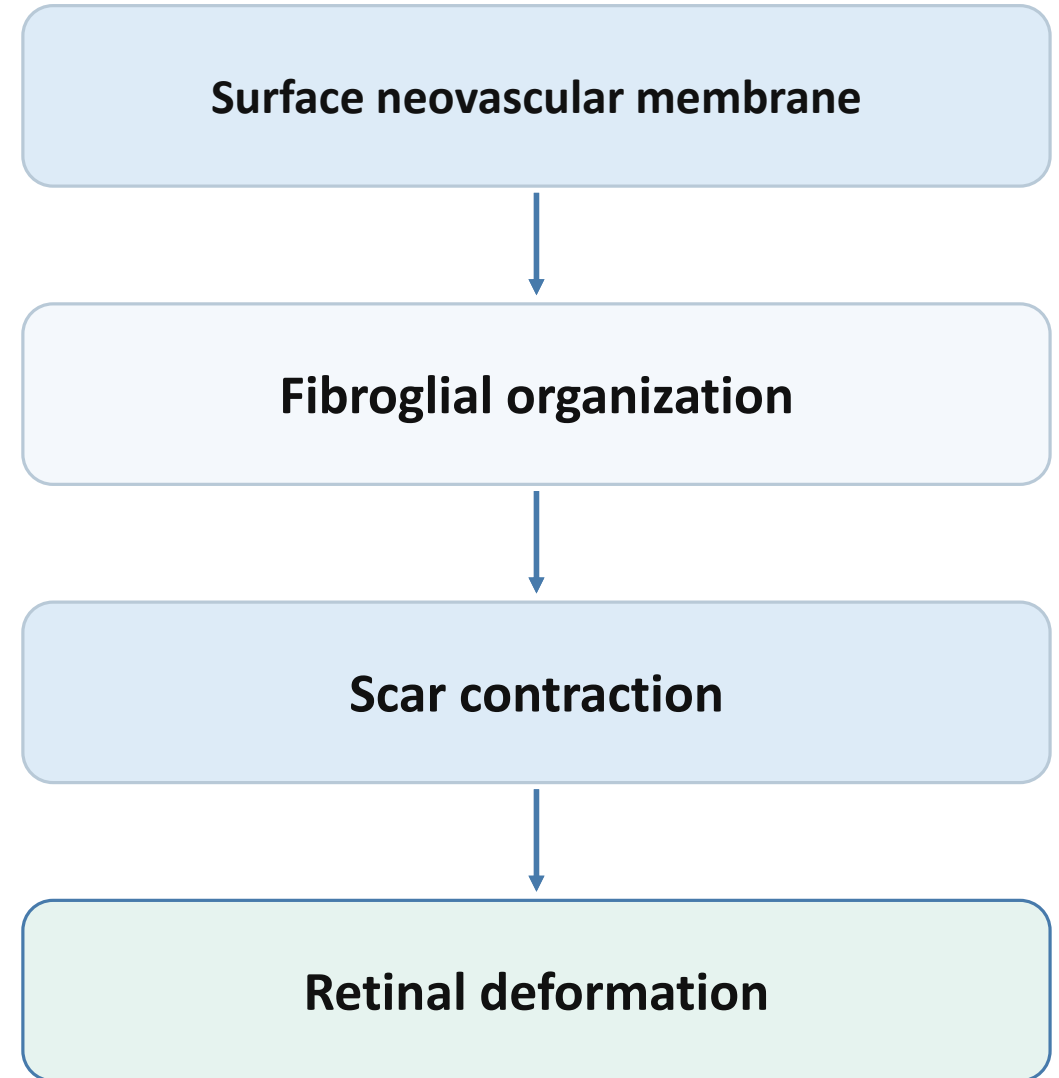


Neovascular membranes can organize into scars

Fibrovascular tissue may undergo organization and contraction.

Scarring exerts force along retinal and vitreous interfaces.

The clinical consequence depends on retinal deformation and traction.

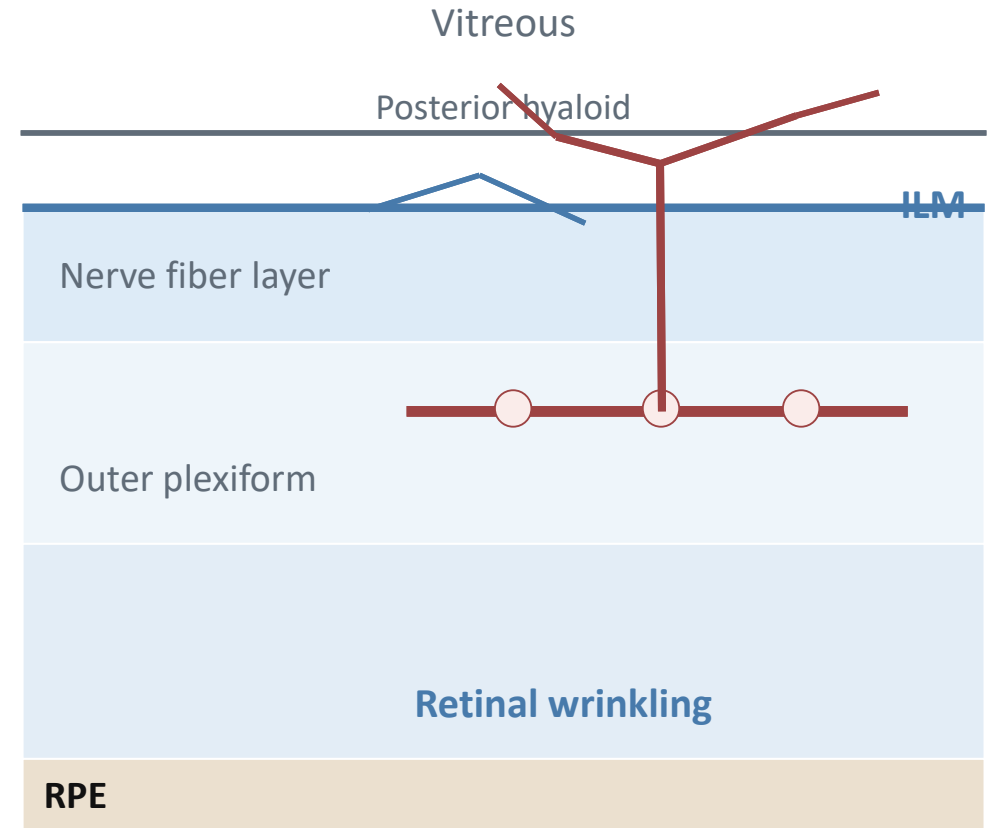


Retinal wrinkling distorts photoreceptor alignment

Contraction can wrinkle the retina.

Disrupted alignment of retinal photoreceptors can distort vision.

Vascular disease therefore causes visual impairment through a mechanical pathway as well as edema.

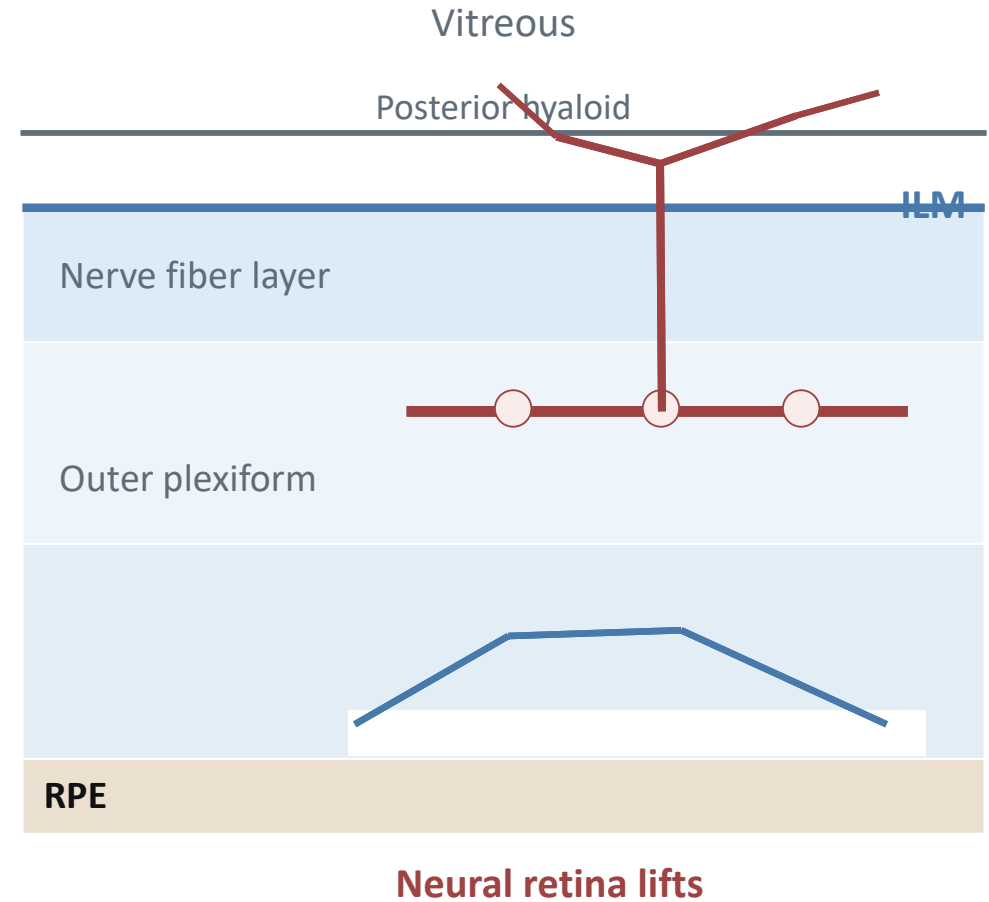


Contractile force can lift neurosensory retina

Fibrovascular contraction exerts traction on the underlying retina.

Sufficient traction separates neural retina from the RPE.

This is tractional retinal detachment.



Tractional detachment need not involve a retinal break

NONRHEGMATOGENOUS

No retinal break required

Contractile traction

RHEGMATOGENOUS

Full-thickness retinal break

May follow severe traction

Severe traction may eventually tear the retina

Traction may progress from elevation to retinal tearing.

Once a tear develops, a rhegmatogenous component is present.

Robbins explicitly describes this progression in advanced diabetic disease.

Membrane contraction



Tractional lifting



Retinal tear



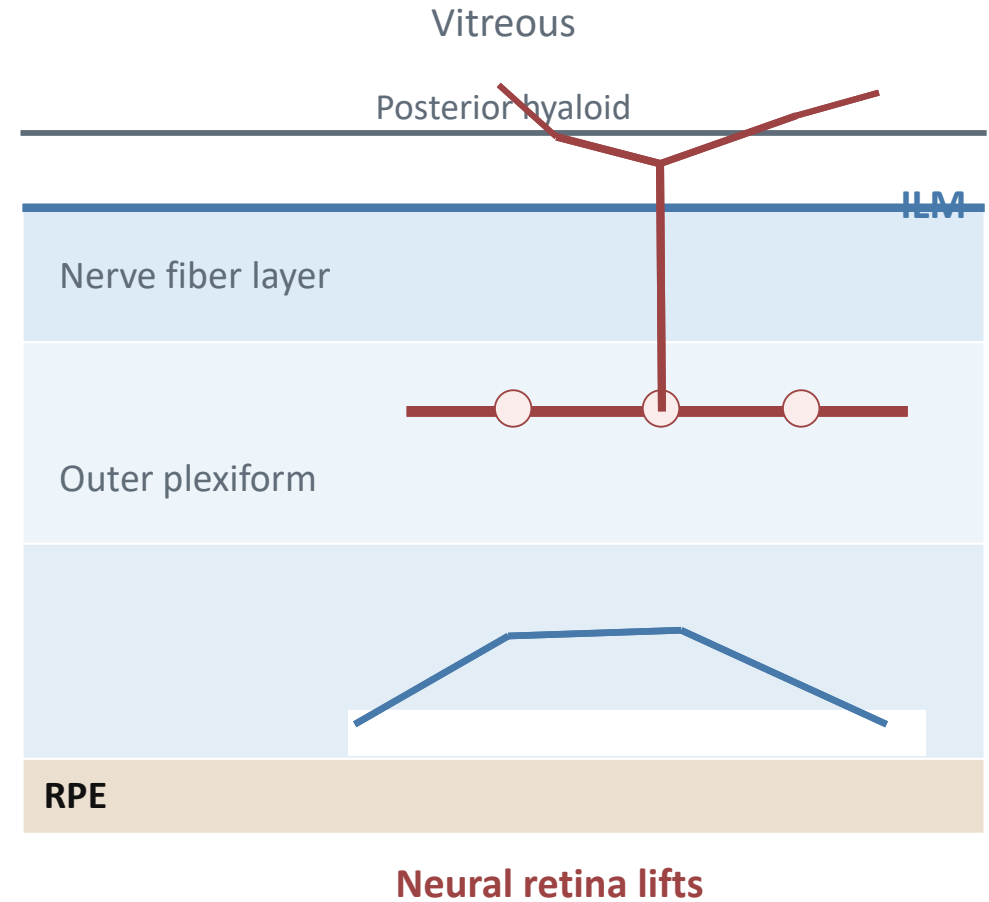
Combined traction + break

Retinal detachment disrupts the RPE interface

Neurosensory retina normally lies apposed to retinal pigment epithelium.

Detachment separates those layers.

The resulting alteration threatens normal photoreceptor support.



Proliferative disease creates two injury mechanisms

HEMORRHAGIC

Neovascular vessel disruption

Preretinal / vitreous blood

TRACTIONAL

Membrane organization

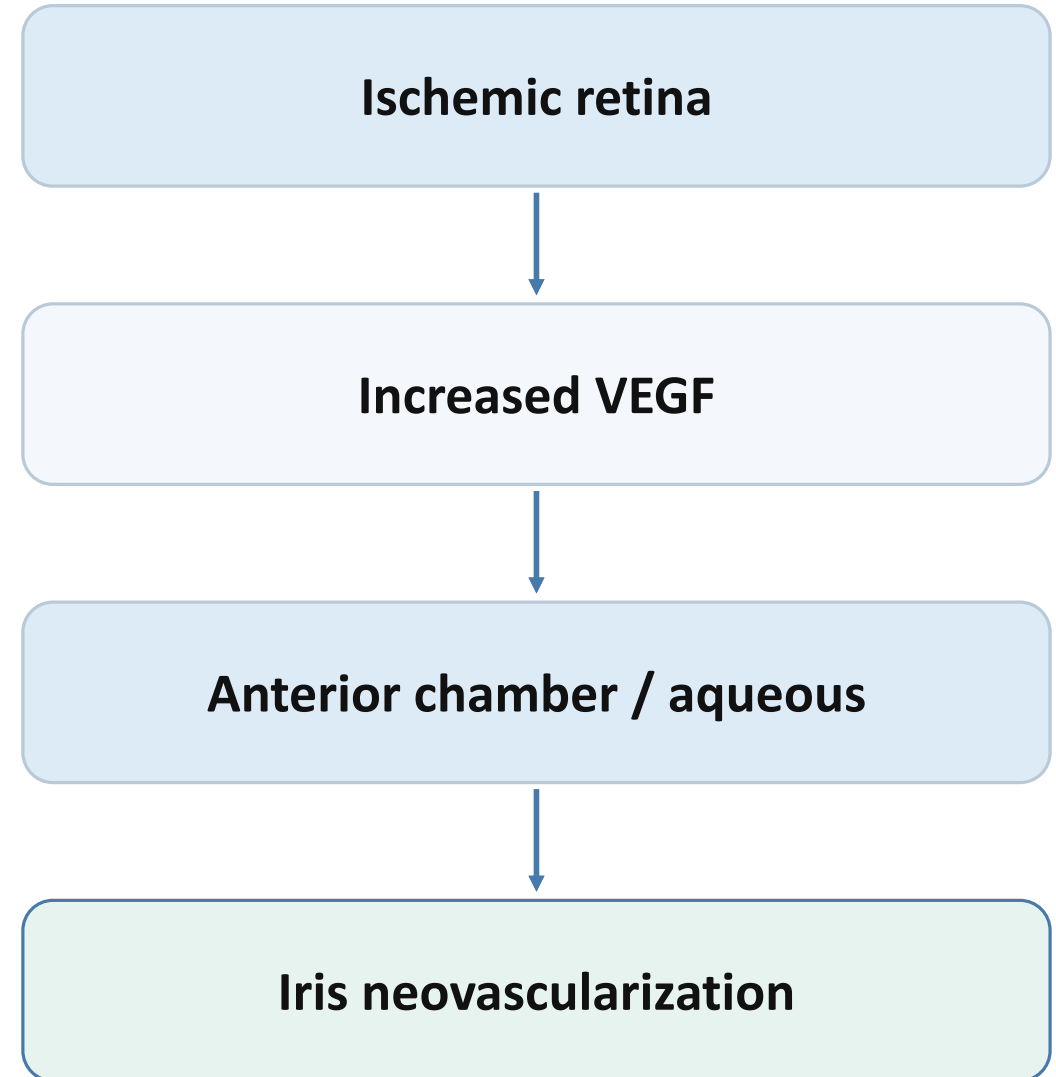
Wrinkling / retinal detachment

Ischemic retina can signal the anterior segment

Retinal hypoxia increases VEGF.

VEGF in aqueous humor is implicated in iris-surface neovascularization.

Thus a posterior-segment vascular lesion can produce anterior-segment disease.

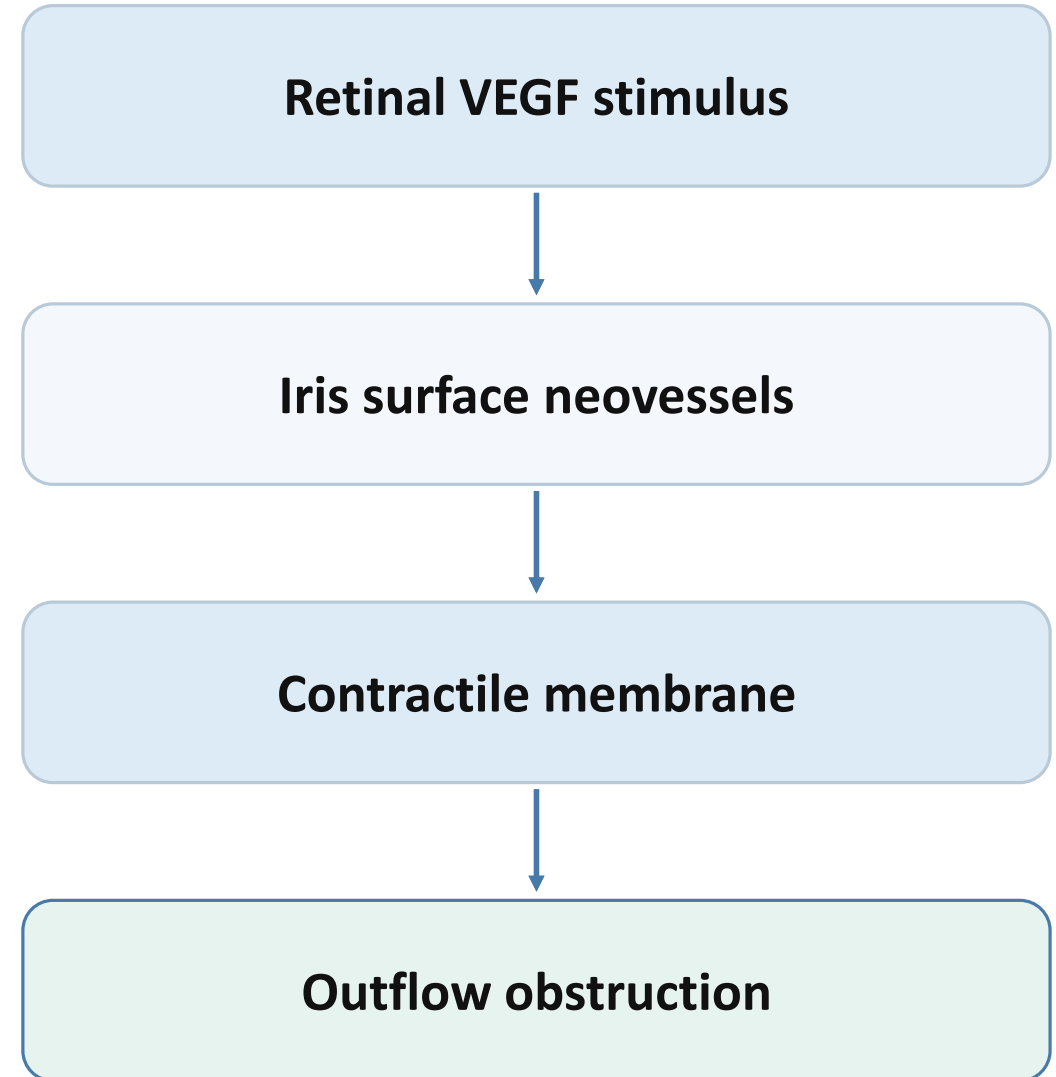


Iris neovascularization adds an abnormal membrane

New vessels and associated membrane may grow over the iris surface.

The lesion is driven indirectly by retinal ischemic signaling.

Surface membrane contraction can compromise normal aqueous outflow.



Anterior synechiae obstruct aqueous drainage

Contracting iris neovascular membrane promotes iris–trabecular adhesions.

These anterior synechiae impair access to the trabecular meshwork.

A major aqueous outflow pathway becomes mechanically compromised.

Iris fibrovascular contraction



Anterior synechiae



Trabecular outflow blocked



Elevated intraocular pressure

Neovascular glaucoma is an ischemic consequence

An iris neovascular membrane can lead to angle closure.

Outflow impairment elevates intraocular pressure.

The resulting neovascular glaucoma is therefore downstream of retinal vascular ischemia.

Retinal nonperfusion



VEGF-driven iris vessels



Synechial angle closure



Neovascular glaucoma

Posterior and anterior neovascular disease differ

RETINAL NEOVESSELS

Retinal / optic disc surface

Vitreous bleeding and traction

IRIS NEOVESSELS

Iris surface and angle

Anterior synechiae / glaucoma

Locate every lesion before naming the complication

Intraretinal microvascular lesion →
nonproliferative compartment.

Cross-ILM membrane → proliferative retinal
compartment.

Iris-angle membrane → neovascular glaucoma
pathway.

Within retina

At vitreoretinal interface

At iris–angle interface

Visual loss can result from distinct mechanisms

Macular edema disturbs central retinal tissue architecture.

Vitreous hemorrhage impairs clear visualization through the media.

Retinal deformation or detachment disrupts normal photoreceptor position.

Macular edema

Vitreous blood

Retinal traction / detachment

Fluorescein tests permeability and perfusion

LEAK

Permeability defect

Macular edema association

NONPERFUSION

Occlusion / ischemia

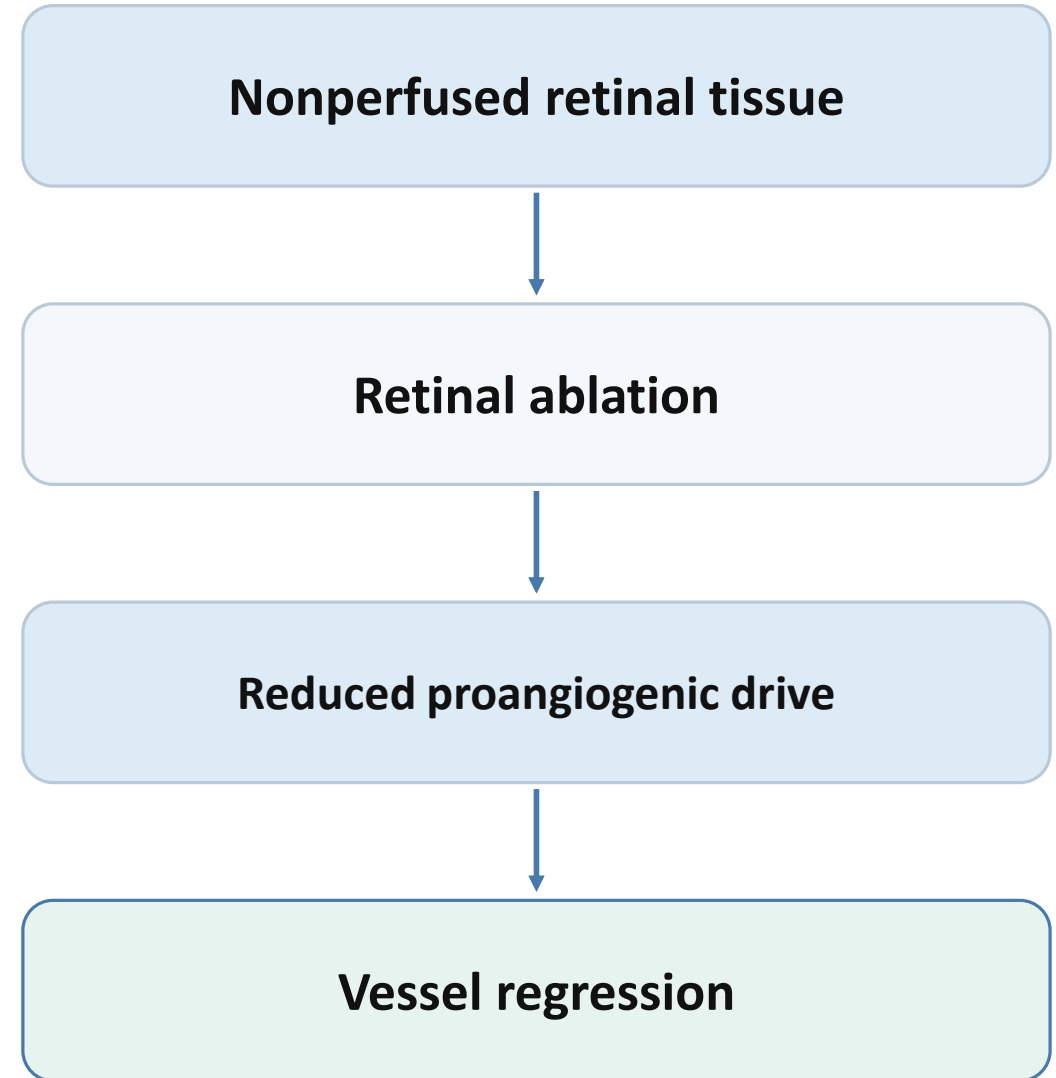
VEGF-driven angiogenesis

Retinal ablation can reduce angiogenic signaling

Laser photocoagulation or cryopexy to nonperfused retina may induce regression of neovascularization.

Retinal and iris vessel regression supports ischemia as the driving stimulus.

The pathology principle is suppression of the hypoxia-driven neovascular response.

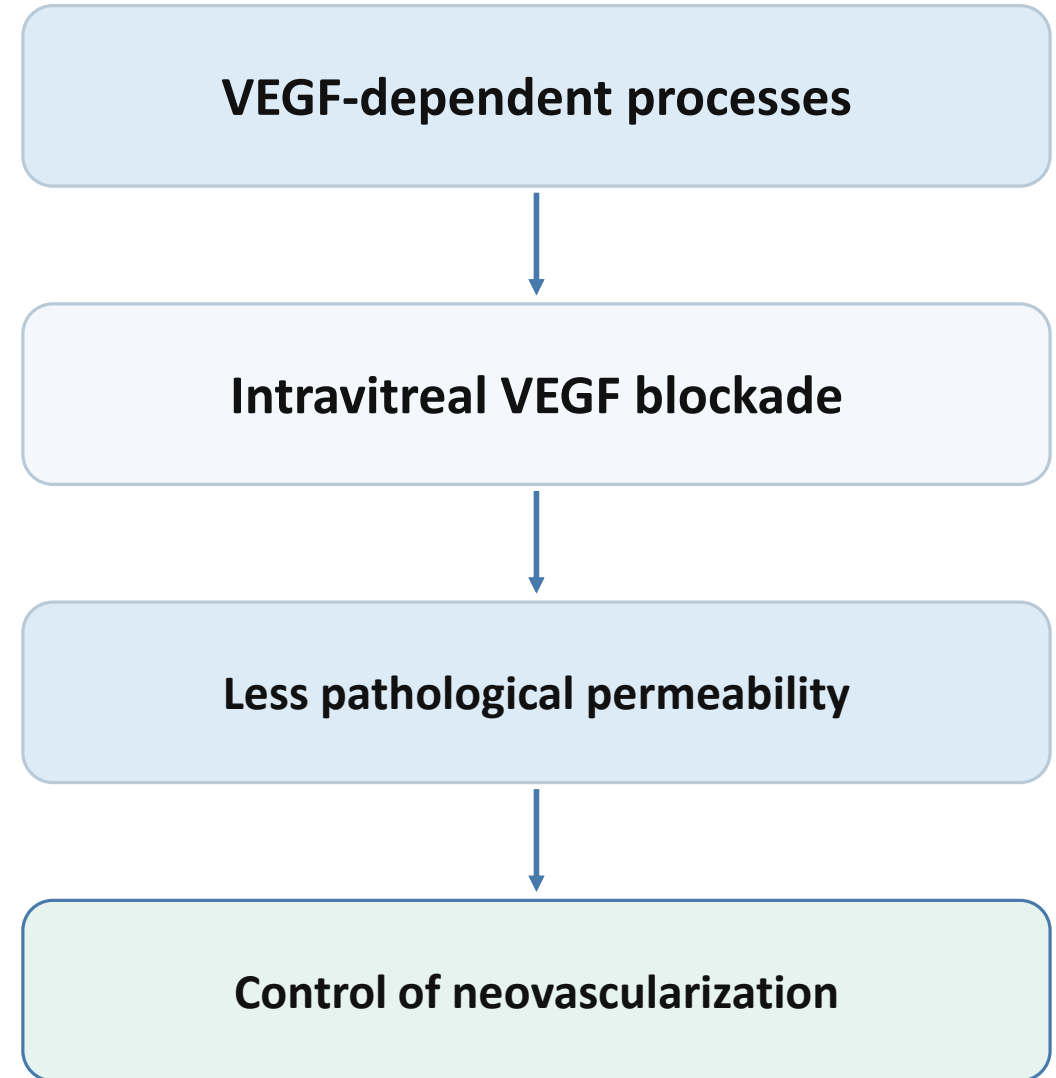


Intravitreal VEGF inhibition targets a defined mechanism

VEGF contributes to vascular permeability and neovascularization.

Intravitreal VEGF inhibitors are used for diabetic macular edema and retinal neovascularization.

Targeted therapy follows from the pathological VEGF mechanism.



Morphologic classification guides interpretation

NPDR

Intraretinal changes

Edema / hemorrhage / ischemia

PDR

Preretinal membrane

Hemorrhage / traction / detachment

Diabetic and hypertensive retinopathy can overlap

DIABETIC

Pericyte reduction; Microaneurysms

Leakage $\pm$ neovascularization

HYPERTENSIVE

Arteriolar narrowing / sclerosis

Arteriovenous crossing change

Teaching vignette: Edema without proliferation

A diabetic retina has leakage, exudates, and macular thickening.

No vessels are described crossing the ILM.

Interpret the visual threat and the retinopathy category separately.

Identify the leakage lesion

Identify the boundary

Explain visual impairment

Teaching vignette: Intraretinal angiogenesis

A capillary bed shows nonperfusion and abnormal new channels within the retina.

No vascular membrane is present above the ILM.

What prevents classification as proliferative disease?

Localize the channels

Identify the ILM

State why IRMA $\neq$ PDR

Teaching vignette: Surface neovascularization

New vessels are seen extending onto the optic disc surface.

The adjacent retina shows zones of nonperfusion.

Classify the lesion and explain its angiogenic stimulus.

Recognize NVD

Link ischemia to VEGF

Predict possible hemorrhage

Teaching vignette: Progressive vitreoretinal traction

A fibrovascular membrane is followed by posterior vitreous separation.

Hemorrhage and retinal wrinkling develop.

Identify the two distinct mechanical complications.

Membrane disruption → bleeding

Scar contraction → traction

Potential retinal detachment

Teaching vignette: Neovascular glaucoma pathway

Advanced retinal nonperfusion coexists with iris neovascularization.

Peripheral iris–trabecular adhesions are present.

Explain why intraocular pressure may rise.

Retinal ischemia → VEGF

Neovascular iris membrane

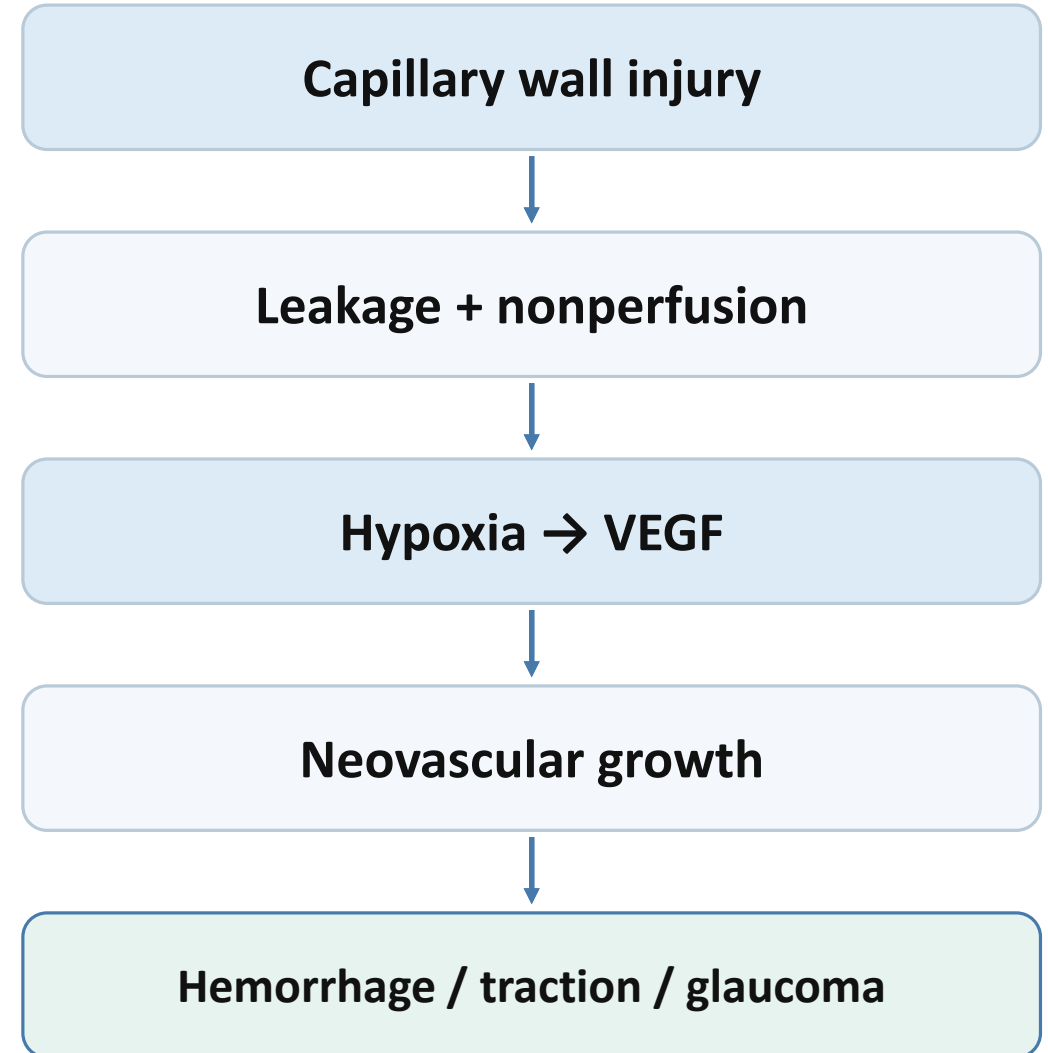
Synechial angle obstruction

Integrated sequence: Capillary injury to complications

Microangiopathy produces leakage and/or retinal nonperfusion.

Ischemia drives VEGF and may generate retinal and iris surface neovascular membranes.

Edema, bleeding, traction, detachment, and glaucoma are mechanistically distinct endpoints.



Essential structural checkpoints

Basement membrane thickening and relative pericyte loss characterize diabetic microangiopathy.

The ILM is the boundary used to distinguish retinal neovascularization from intraretinal disease.

Posterior hyaloid interaction explains bleeding and traction; Iris-angle scarring explains glaucoma.

Capillary wall

ILM / hyaloid

Iris / angle

References and source boundaries

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026). Chapter 29, The Eye: Diabetes Mellitus, pp. 1201–1203.

Adjacent anatomical context: Retina and Vitreous, pp. 1198–1201; associated figures and captions on pp. 1202–1205.

All retinal diagrams in this lecture are original editable schematics, not photomicrographs, fundus photographs, or reproduced textbook figures.

The source-based therapeutic discussion explains mechanisms; it is not a current clinical treatment guideline.