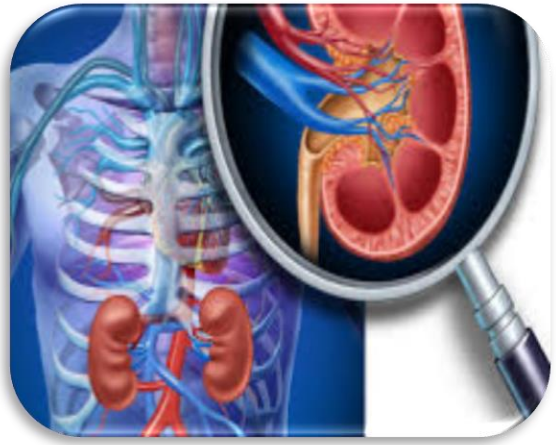
In The Name of God

Ophthalmology and the Kidney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Introduction

- The Association between **renal disease and blindness** was first reported in the middle of the **nineteenth century**.

- Although the causes for the link were not known, it is now appreciated that there are **several causes** for this association.

Arch Ophthalmol. 2012;130:1136–44.
Primer on Nephrology2022

causes

- **Disturbances in Embryogenesis** can lead to **anatomic and functional** abnormalities in the **two organs**.

- The period of **organogenesis** for both the **eyes and the kidneys** spans the **fourth to sixth weeks of gestation**.

- **Dysfunction of Multiple Proteins** that are of importance in both organs.

- **Storage Disorders**, where **accumulation of a metabolite** can cause both renal and ocular dysfunction.

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Clin Kidney J. 2014;7(4):337-8.

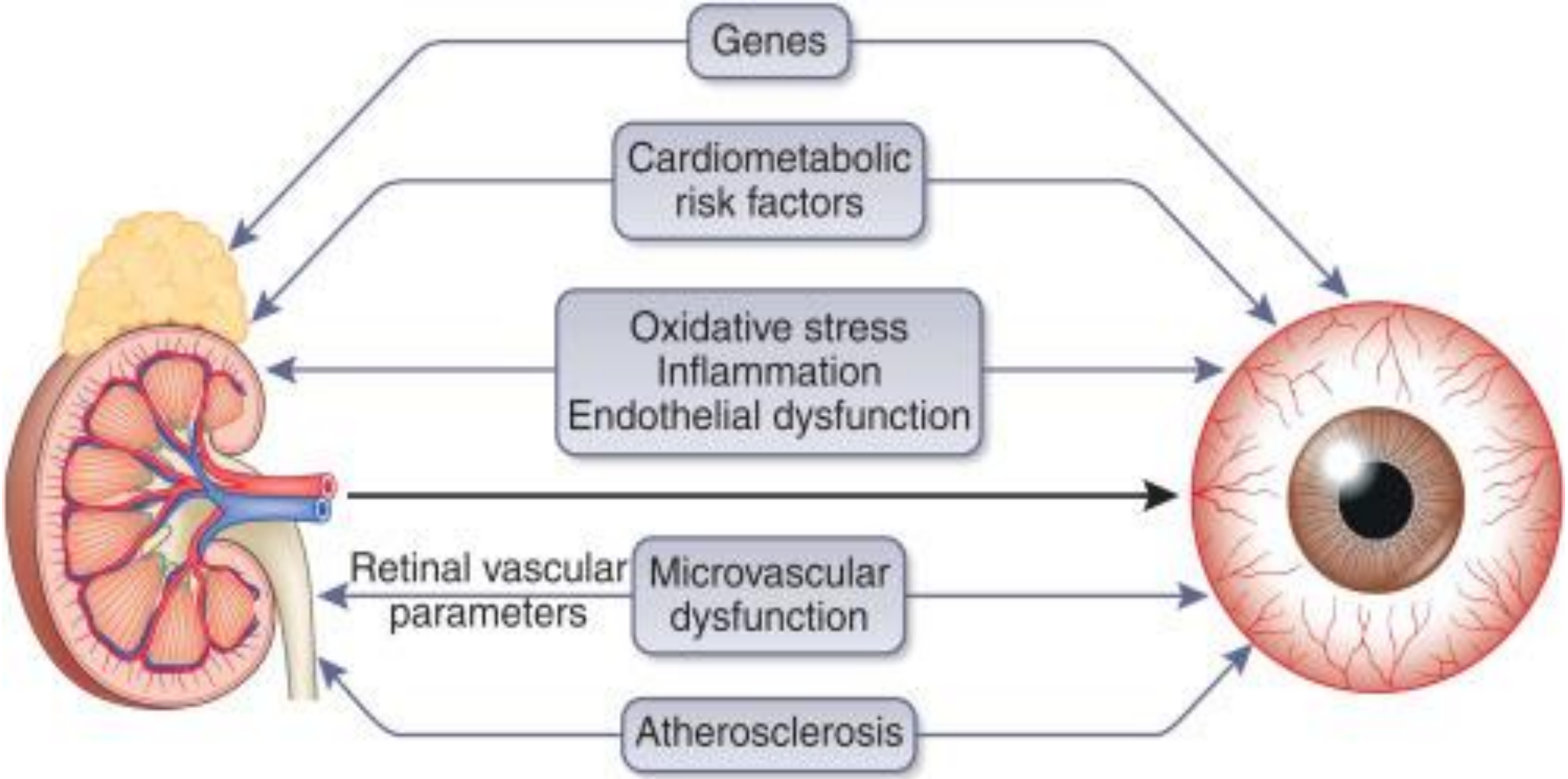
Causes…

- **Retinal microvascular disease has been shown to be predictive of CKD development .**

Conversely,

- Patients with **CKD** are at higher risk for **age-related macular degeneration (AMD), diabetic retinopathy, glaucoma and cataract.**

- **Hypertensive retinopathic** changes can be particularly severe in **renal failure** with accelerated hypertension.



Common pathogenetic mechanisms underlying renal and retinal diseases.

Kidney International2014

“Acquired Eye Disease”

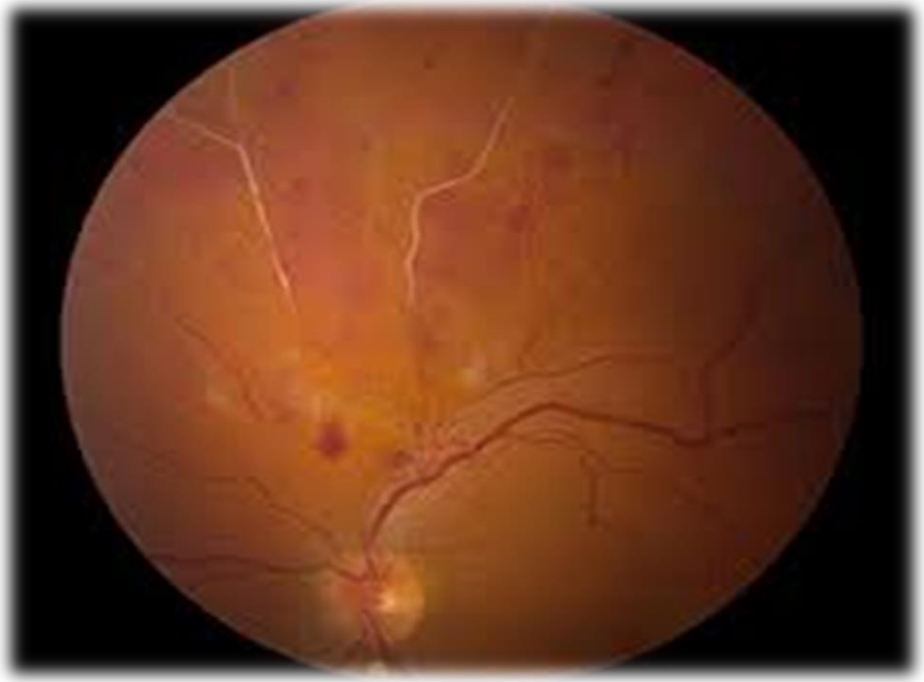
- Hypertensive Retinopathy
- Diabetic Retinopathy
- Inflammatory Diseases of the Eye

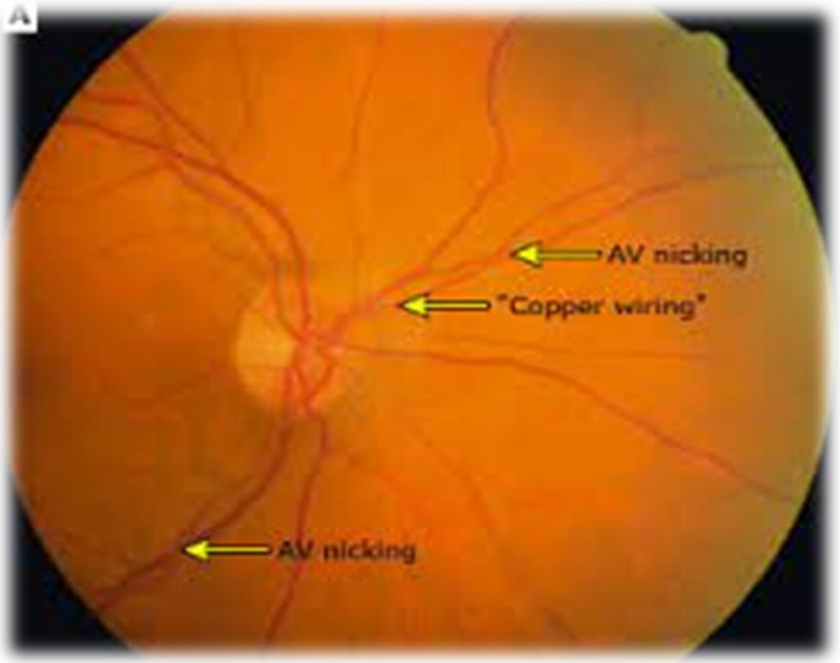
Hypertensive Retinopathy

- The initial response to elevated blood pressure is diffuse and **localised vasospasm of the retinal arterioles with generalised and focal arteriolar narrowing.**

- These changes that eventually lead to sclerosis compress adjacent venules resulting in **arteriovenous nicking and alterations in the arteriolar light reflex (‘copper wiring’).**

copper wiring





Retinal arterioles appear orange or yellow instead of red

Hypertensive Retinopathy…

- **Retinal microvascular abnormalities are associated with renal dysfunction**, suggesting that common **systemic microvascular processes** may underlie the development of **microvascular damage in the eye and kidneys.**

- **Renal Physicians** could consider **retinal morphology** when assessing **cardiovascular disease risk** in people with **CKD**.

- **CRIC Study**, found that worsening of **hypertensive retinopathy** was associated with an **increased risk of incidence of CVD** .

Br J Ophthalmol. 2020; bjophthalmol-2019-315333.

Epidemiology

- Hypertensive retinopathy is seen in **6–15% of non- diabetic adults aged older than 40 years.**

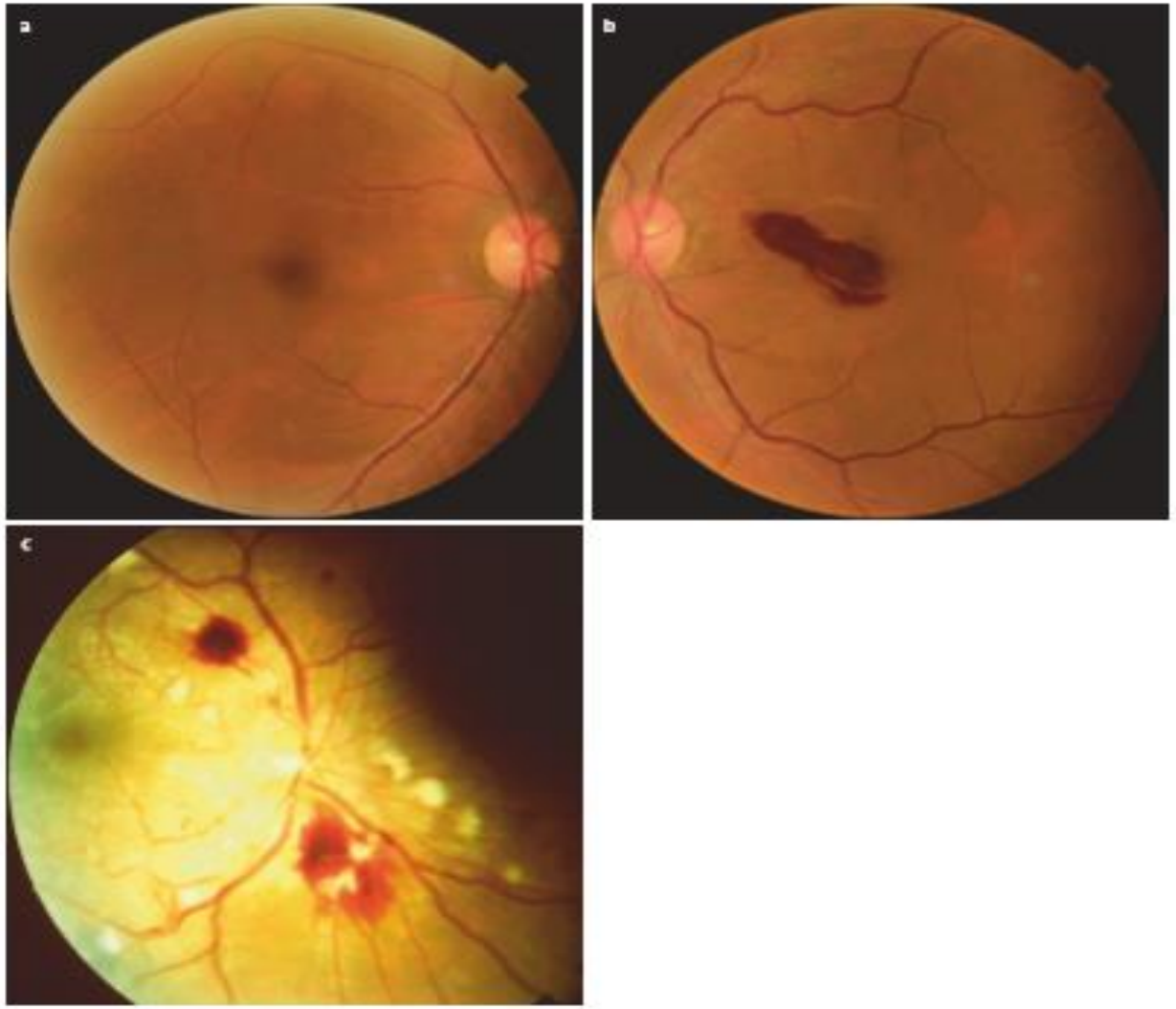
- **Isolated retinal haemorrhages and/or microaneurysms are the most commonly observed signs** (5.7–8%) with presence of **cotton wool spots** being **relatively uncommon** (0.2%).

- The **strongest evidence** of the usefulness of an **evaluation of hypertensive retinopathy** for risk stratification is based on its association with **stroke and CAD**.

Pathophysiology

- Changes manifest in the retina as **microaneurysms, haemorrhages, hard exudates and cotton wool spots.**

- **Swelling of the optic disc** may occur at this time and usually indicates severely elevated blood pressure.



Fundus photograph showing copper wiring' of vessels **a** with haemorrhage **b** in the left eye. **c** **Grade IV** hypertensive retinopathy with retinal haemorrhages, cotton wool spots and **papilloedema**.

Aetiology

- ✓ Demographic factors
- ✓ Systemic medical conditions
- ✓ Inflammation
- ✓ Nitric oxide-dependent endothelial dysfunction
- ✓ Lifestyle factors (smoking)
- ✓ Genetic factors

Surv Ophthalmol. 2009;54:74–95.
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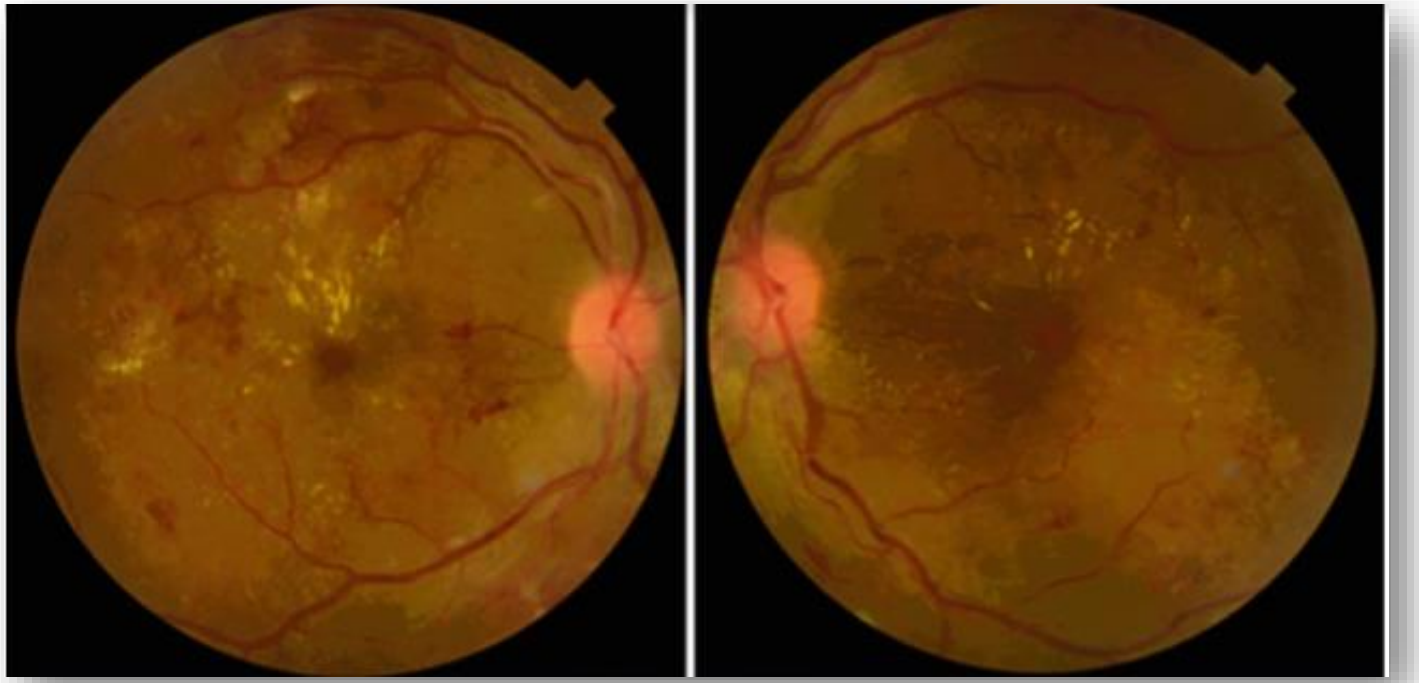
Diabetic Retinopathy

- **Diabetic retinopathy** is the **most common** ophthalmic complication of DM.
- The **initial** response to **hyperglycaemia** is **dilatation of the retinal blood vessels.**
- Diabetic **macular oedema** is the main cause of **visual loss** in patients with diabetic retinopathy.
- **Early-stage disease** is **reversible** or can be stabilised with improved systemic **control of hyperglycaemia and blood pressure**.
- **Late- stage disease** management will include combinations of **intravitreal injections of pharmacologic agents.**



Fundal Photograph showing **Advanced Proliferative Diabetic Retinopathy** with **visible microaneurysms, haemorrhages, hard exudates and neovascularisation**.

Macular oedema is likely to be present on a 3D examination of the eyes

Risk Factors

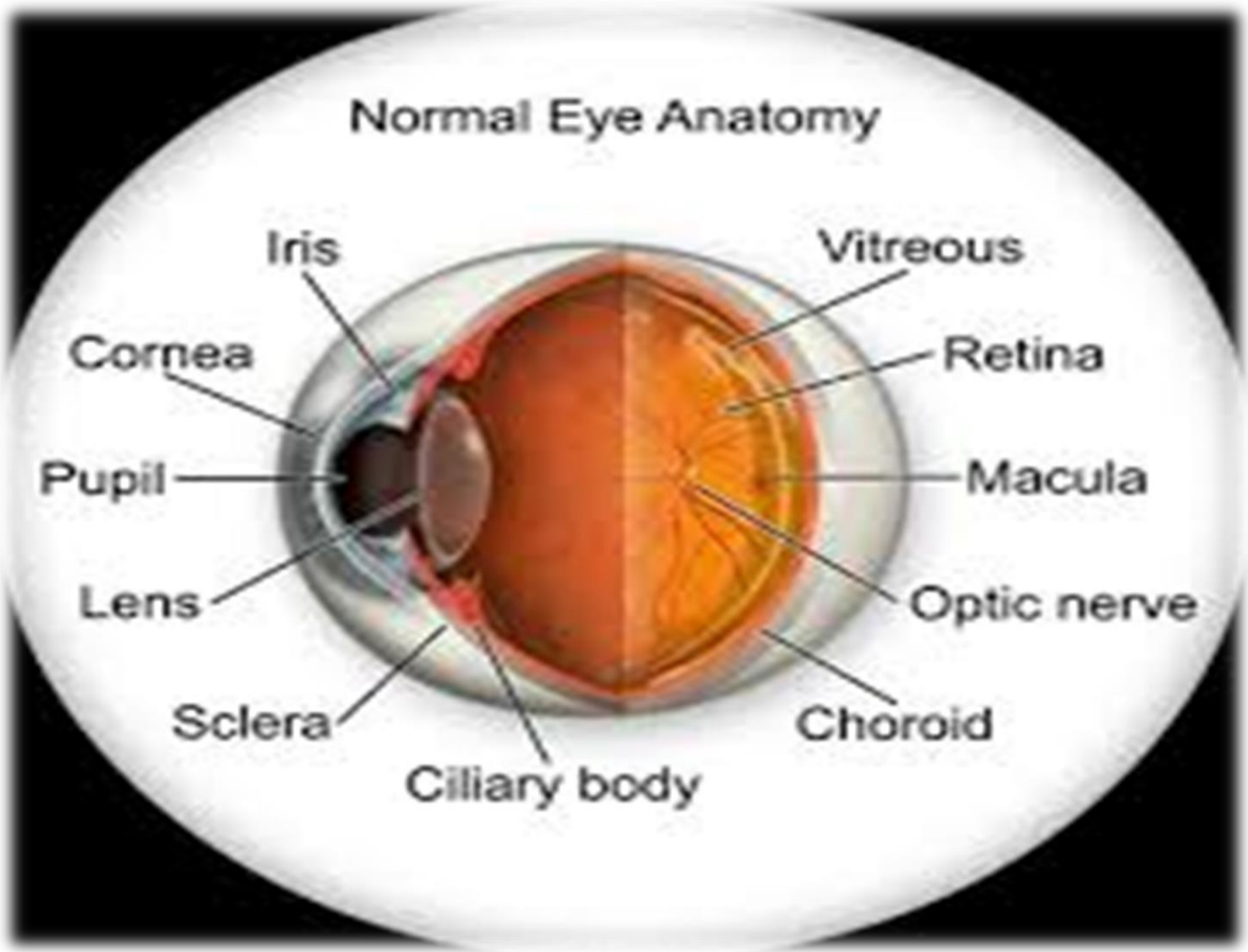
- **In T1DM, Higher HbA1c, HbA1c variability, Age of onset of T1DM and Total cholesterol were independently associated with the risk of DR** and a **protective association** was found for **HDL cholesterol**.
- **Mean HbA1c and presence of Albuminuria were associated with progression of DR.**

- **In T2DM, Age and Duration of diabetes are associated with DR** development whereas **modifiable** risk factors include the **obesity, hypertension, renal function and total cholesterol.**

Acta Ophthalmol. 2018;96:459–64.

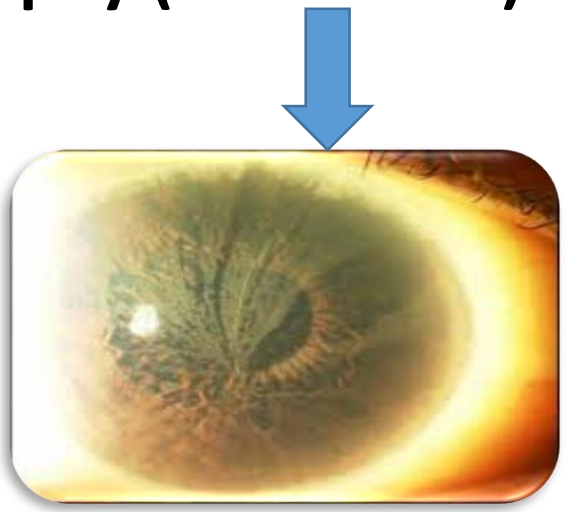
Inflammatory Diseases of the Eye

- Systemic Autoimmune Disease
- Infection (usually in the context of immunosuppression)
- Syndromes
- Allergy (usually drug)
- Toxicity Related


Normal Eye Anatomy
Iris
Vitreous
Cornea
Retina
Pupil
Macula
Lens
Optic nerve
Sclera
Choroid
Ciliary body

Keratitis

- **Keratitis** (inflammation of the cornea) for nephrologists occurs in the **immunocompromised, most commonly related to herpes simplex**.
- The cornea is also involved as part of the **sicca syndrome** in **Sjogren's syndrome and sarcoidosis.**
- **Corneal dystrophy (verticillata) in Fabry disease**.



Episcleritis

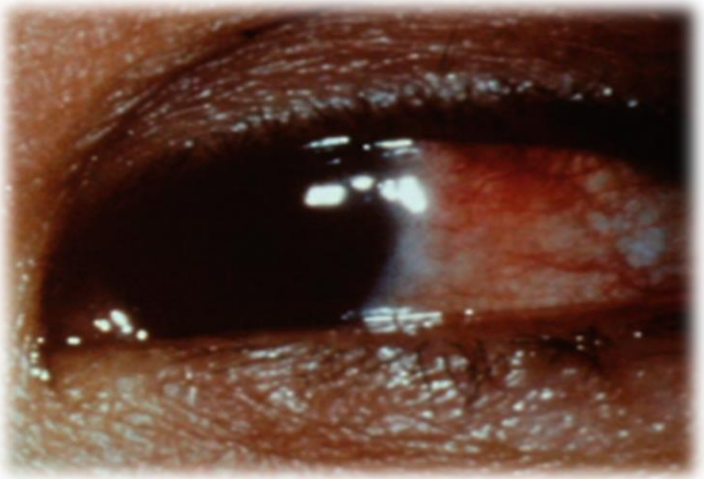
- **Episcleritis,** typically presents with a **red eye** (**inflammation of superficial vessels** and some discomfort).

- This clinical sign **usually occurs in isolation**, but in a **small percentage** of cases can be a manifestation of **vasculitis** (**micropolyangiitis or granulomatous polyangiitis**).

Scleritis

- Scleritis is more likely to be **painful**, has a **greater risk of progressing to loss of vision and is more strongly associated with an underlying systemic illness .**

- Typically, **rheumatological conditions and, in the context of renal disease, vasculitis and less commonly SLE.**



Scleritis as the presenting feature in a patient with a flare of micropolyangiitis

OXFORD JOURNALS NDT Plus

NDT Plus. 2010 Oct; 3(5): 453–455.
Published online 2010 Jun 2. doi: 10.1093/ndtplus/sfq103

PMCID: PMC4421692
PMID: 25984051

IgA nephropathy in a patient presenting with scleritis

Catarina Teixeira,[1,*] Ana Miguel Quintas,[2,*] José António Lopes,[1] Margarida Miranda,[2] and Edgar de Almeida[1]

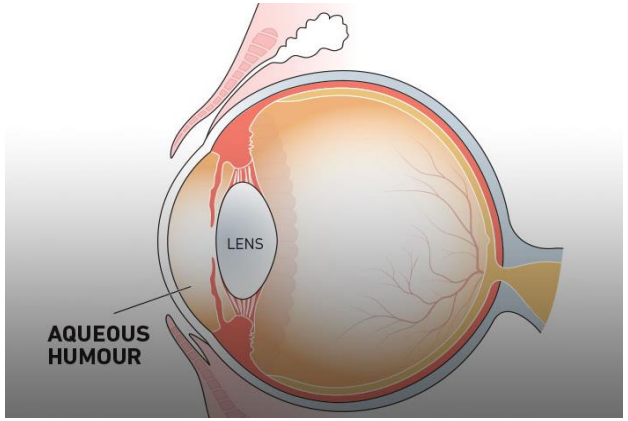
- **Scleritis can occur in association with IgAN.**
- **In patients with scleritis and asymptomatic urine abnormalities, IgAN should be considered and properly investigated.**

Uveitis

- **Anterior** (involving the iris/ciliary body) which may have symptoms of **pain and photosensitivity** and is associated with **redness at the limbus and cells in the aqueous**.

- **Intermediate** (involving the vitreous/ciliary body).

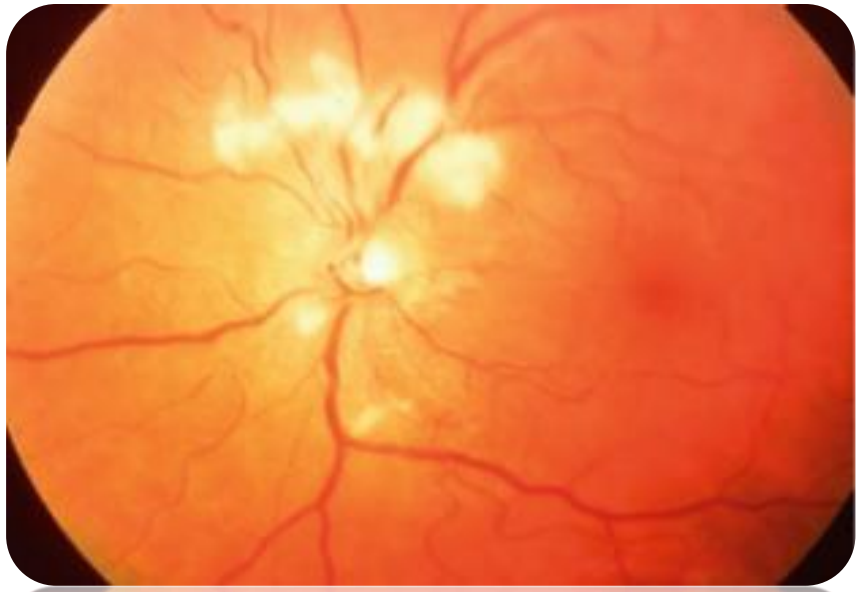
- **Posterior**, involving the choroid/ retina.



Posterior uveitis…

- **Posterior uveitis is more commonly painless**.
- It is associated with **systemic inflammatory** conditions in roughly **40%** of cases.
- Most commonly the underlying diagnoses are **spondyloarthritidies**, such as **ankylosing spondylitis and Behcet's syndrome**, but from the renal perspective, sarcoidosis, tubulo-interstitial nephritis and uveitis and vasculitis .
- **Occasionally Sjogren's syndrome and SLE are underlying diagnoses.**

Uveitis…



Retinal image of **retinal vasculitis** in a patient with **granulomatous polyangiitis** who presented with multiple symptoms, including loss of vision.

Infectious causes of uveitis

Infectious causes of uveitis are myriad, most notably **CMV and herpetic viruses** such as **HSV and HZV** in the **immunocompromised** and **syphilis and tuberculosis**.

Granulomatous polyangiitis

Granulomatous polyangiitis can also present as **proptosis** secondary to a retro-orbital mass or vasculitic involvement of **optic and orbital nerves.**

Goodpasture's syndrome

- The target antigen in **Goodpasture's syndrome** is the **alpha 3 chain of type IV collagen,** which is present in the **GBM, the alveoli and the eye**.

- **Eye involvement in this 'pulmonary renal syndrome'** is **rarely reported**, being limited to **non- rheumatogenous** retinal detachments **subretinal neovascularisation and lesions related to hypertension.**

Nephron. 1994;68(1):52–6. https://doi.org/10.1159/000188087.
Primer on Nephrology2022

“Inherited Eye Disease”

- Developmental Disorders
- Disorders of Structure and Function
- Metabolic Disorders

Developmental Disorders

Mutations in transcription factors important for normal development of **both organs**, such as **PAX2 and LMX1B**.

- **PAX2** plays an important role in **early renal development** and mutations are associated with **renal malformations**, especially **hypoplasia**.
  - **Typical Eye Manifestation is coloboma** .

- **LMX1B** is involved in the **organisation of the GBM** and mutations (e.g. **nail-patella syndrome**) manifest with **nephrotic range proteinuria, whereas the ocular manifestation is typically open-angle glaucoma.**

Pediatr Nephrol. 2017;32(10):1845–50.

Coloboma, **maldevelopment of the iris** which may be associated with CHARGE syndrome (CHD7 mutations) or papillorenal syndrome.

- Environmental factors, such as drinking alcohol during pregnancy, may also increase a baby's risk for coloboma.

Pediatr Nephrol. 2017;32(10):1845–50.

Disorders of Structure and Function

- **Ciliopathies** commonly affect the **kidney and eye** due to the important role of cilia in both organ systems.

- **Ciliopathies** are commonly associated with **retinopathies**, such as **retinitis pigmentosa** in **Bardet- Biedl syndrome**.

- Common Renal manifestations of **ciliopathies** include **cystic kidney disease, including nephronophthisis and cystic dysplasia.**

Transl Sci Rare Dis. 2019;4(1–2):97–115.
Curr Opin Genet Dev. 2019;56:49–60.

Disorders of Structure and Function…

- **Lowe syndrome**, also known as **oculocerebrorenal** syndrome.

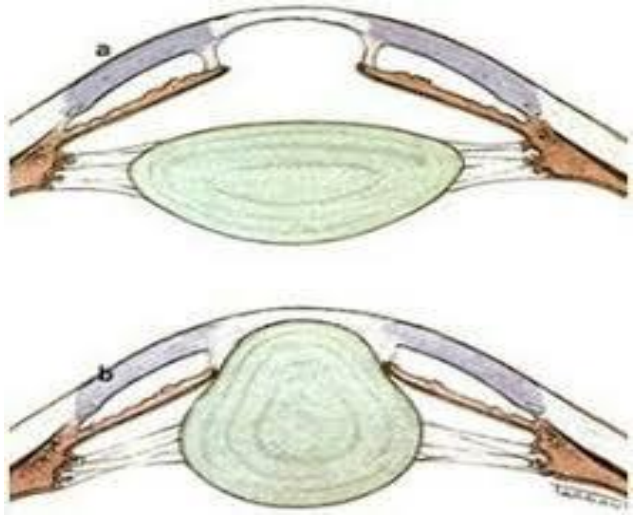
Ocular manifestations include **congenital cataracts and glaucoma**, the **renal phenotype** is characterised by a **proximal tubulopathy and progressive CKD**.

- **Alport syndrome** and related type 4 collagenopathies an important structural component in the **GBM , as well as of the lens, cornea and retina**.

Clinical manifestations in the **eye** include **lenticonus, corneal dystrophy and maculopathy**, whereas in the **kidney glomerular dysfunction predominates, typically haematuria and proteinuria.**

Clin J Am Soc Nephrol. 2015;10(4): 703–9.

Anterior lenticonus

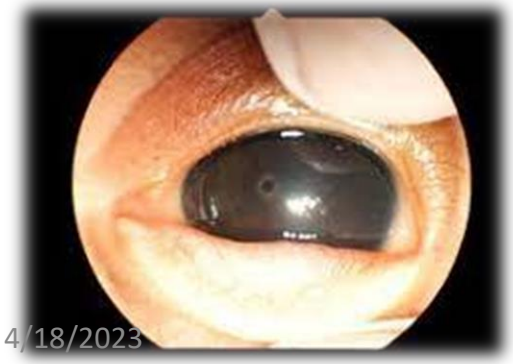


Disorders of Structure and Function…

- **Pierson syndrome** is caused by mutations in **LAMB2**, encoding laminin ß2, another important structural component of the **GBM**.

- **Renal manifestations** : **glomerular dysfunction**, especially **congenital nephrotic syndrome.**

- **LAMB2** is also expressed in neuromuscular junctions and the **typical ocular manifestation is microcoria due to dysplastic ciliary muscles .**



Am J Ophthalmol. 2008;146(4):602–11.

Metabolic Disorders

Accumulation of a substrate can affect multiple organ systems, including the kidney and eye.

- **lysosomal storage disorders**
- **Cystinosis**
- **Fabry disease**

Cystinosis

- **Ocular manifestation** includes **photophobia and keratopathy. but later also retinopathy.** often have **red irritable eyes**.

- **Renal manifestation includes Fanconi syndrome and progressive CKD.**

- **Cystine crystals cannot normally be seen with the naked eye or with an ophthalmoscope.**

- **Slit lamp Examination** demonstrating and monitoring **cystine deposition in the cornea**.

Pediatr Nephrol. 2012

Fabry disease

- Mutations in GLA, encoding alpha-galactosidase A.

  Dysfunction of the enzyme can lead to **corneal dystrophy**, whereas **renal manifestations are characterised by proteinuria and progressive CKD.**

Skin Therapy
Lett. 2018;23(2):4–6.

Primary hyperoxalurias

- Eye manifestation is typically only seen in the **most severe form, PH1**.
- Renal manifestations are **primarily** in the form of **urolithiasis**, but in **more severe** cases **ESRD** can ensue.
- Oxalate deposition in the eye can lead to **crystalline retinopathy and optic neuropathy.**

Nature reviews. Nephrology, 2012

“CKD and the eye”

Table 42.2 Chronic kidney disease and the eye

Haemodialysis	
Conjunctival erythema	Red eyes of uraemia — high plasma phosphate levels induce corneal and conjunctival precipitation of calcium pyrophosphate
Metastatic calcification	Band keratopathy — calcium deposition across the anterior surface of the cornea. Associated with elevations of the serum concentration of calcium or calcium-phosphate product (see Fig. 42.8)
Uraemic amaurosis/ transient cortical blindness	Profound uraemia in association with preserved pupillary contraction on light exposure and normal fundoscopic findings. This abnormality clears within 24–48 hours of initiating dialytic therapy
Raised intraocular pressure	Removal of urea and other solutes reducing serum osmolality more rapidly than ocular osmolality, steep gradient in the presence of ocular-blood barrier
Anterior ischaemic optic neuropathy	Intradialytic hypotension and anaemia

“CKD and the eye”

Kidney transplantation	
Opportunistic ocular infections	A variety of infections can involve the eye in patients who are immunosuppressed for renal conditions such as glomerular disorders or transplantation. Most commonly herpes simplex virus and ophthalmic involvement of varicella zoster but potentially CMV, HHV8, listeria, nocardia, mycobacteria, fungi such as *Cryptococcus neoformans*, candida and aspergillus infections, as well as parasites such as toxoplasmosis

“CKD and the eye”

Medications used in CKD	
Hydroxy-chloroquine	Retinopathy with 7.5% prevalence in individuals with more than 5-year exposure
Cyclospo-rine and interferon	Evanescent cortical blindness
Cidofovir for BKV	Anterior uveitis
Corticoste-roids	Posterior subcapsular cataract
Sulphadi-azine	Shock of wheat crystals
Steroids	Elevated intra-ocular pressure, ‘development of steroid cataract’ is dose and duration dependent (15 mg of oral prednisolone for a year)

Risk factors of CKD	Associated eye diseases
Age	Cataract, AMD, DR, glaucoma, retinal vascular damage
Smoking	AMD, cataract
Diabetes mellitus	Cataract, DR, AMD, glaucoma, retinal vascular damage
Hypertension	AMD, DR, retinal vascular damage, glaucoma
Obesity	AMD, DR, cataract
Hyperlipidemia	AMD, DR

Kidney International June 2014, Pages 1290-1302

Table 2. Common pathogenic mechanisms underlying both CKD and eye diseases

Mechanisms of CKD	Associated eye diseases
Atherosclerosis	Cataract, AMD, DR, glaucoma, retinal vascular damage
Endothelial dysfunction	AMD, cataract
Oxidative stress	Cataract, DR, AMD, glaucoma, retinal vascular damage
Inflammation	AMD, DR, retinal vascular damage
Renin–angiotensin system dysfunction	DR, retinal vascular damage, glaucoma
Genetic polymorphisms	AMD, retinal venular diameter
Klotho	AMD, cataract, retinopathy

Kidney International June 2014, Pages 1290-1302

Managing the Patient with CKD and Visual Impairment

- Service levels agreements between nephrology and ophthalmology, such as **screening for hydroxychloroquine retinopathy**, should be straightforward to establish.

- Some units off joined **clinics** for patients with **vasculitis and other oculo-renal** conditions such as **VHL syndrome**.

Managing the Patient with CKD and Visual Impairment…

- A **nephrologists** should discuss systems for **screening urine** in patients in ophthalmology clinics with **chronic or aggressive uveitis or scleritis to exclude renal involvement** and a **robust system** for **rapid renal referral** in the face of an abnormal urine deposit.

- **Annual diabetic retinopathy screening**; offering ophthalmology review in haemodialysis units would likely improve communication and offer a more patient-focused service.

- The **ocular manifestations of kidney disease** can be a result of the **disease** itself, or its **treatment** and **ophthalmoscopy are an important but often neglected part of clinical assessment in nephrology.**

- **Fundoscopy as a part of new patient assessment is critically important.**

- **Systemic immunosuppression** can lead to **eye-threatening complications** including **opportunistic ocular infections**; awareness of this and the need for **rapid ophthalmology assessment** are an important parts of **patient/staff education.**

- ✓ The **eye** offers a **unique window** onto the body's **microcirculation** that can aid **both diagnosis and monitoring of common conditions**.

- ✓ There is potential to **improve the patient pathway** between our **two specialties** and **expedite diagnosis and treatment**.


Have a
GREAT
Day!