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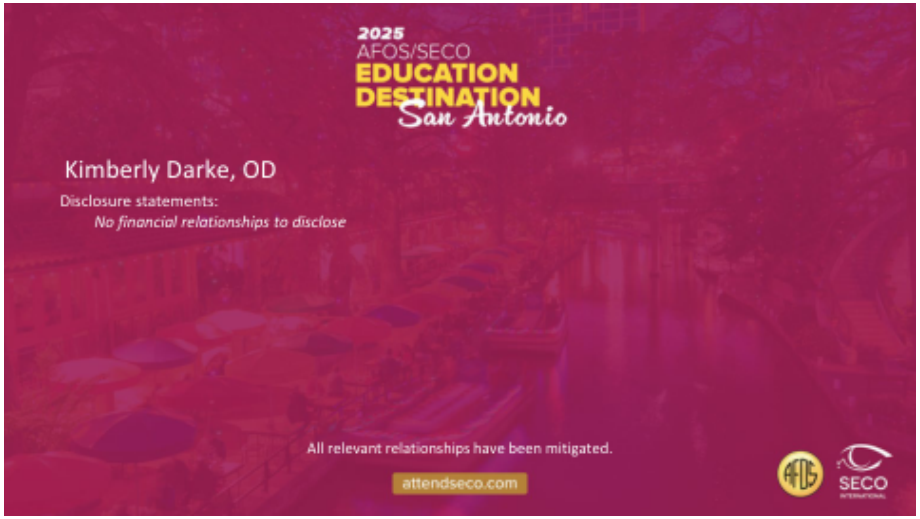

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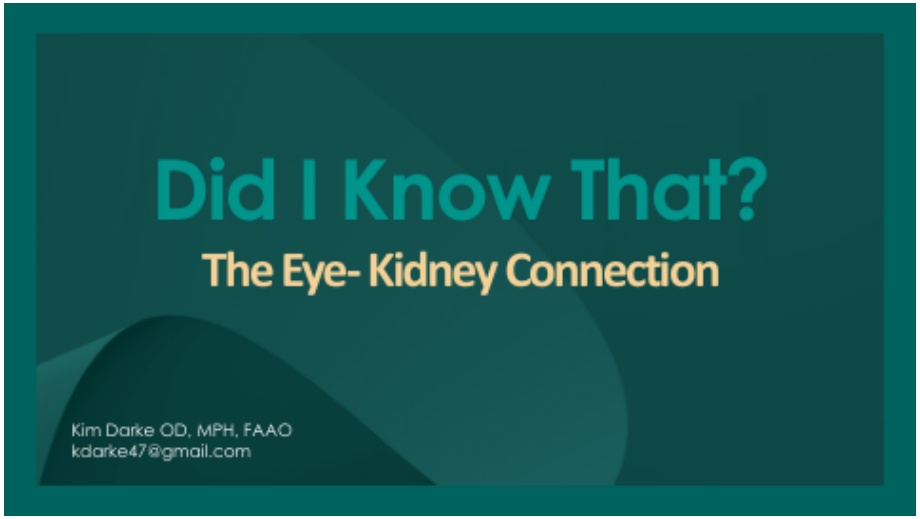

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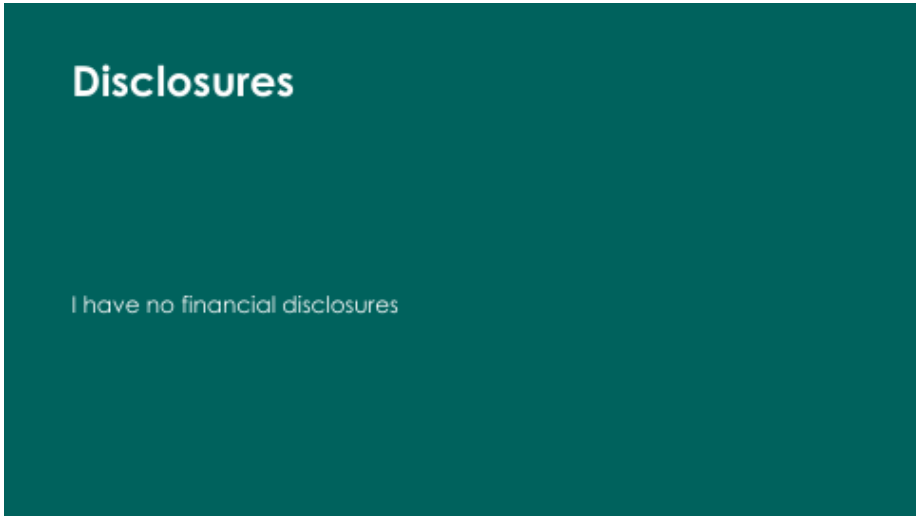
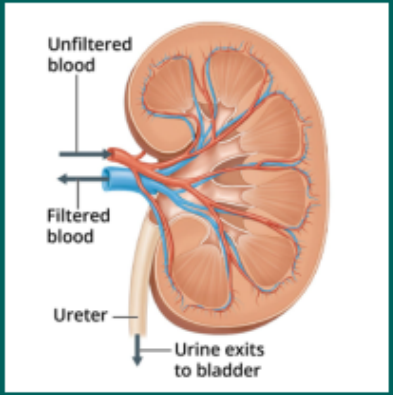


Slide 5

Basic Kidney Anatomy

- Kidneys remove waste and excess fluid from the body
- Kidneys filter on average 150 quarts of blood per day!
- ~1-2 quarts of urine are produced daily
- The functional unit of the kidney is the nephron



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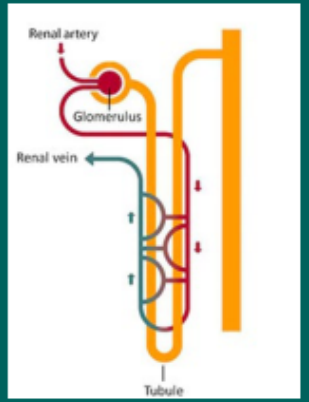
Nephron

Nephron Filtration of Blood

- Glomerulus
  - Filters small particles out of the blood
- Tubule
  - Returns needed substances to the blood stream and removes waste

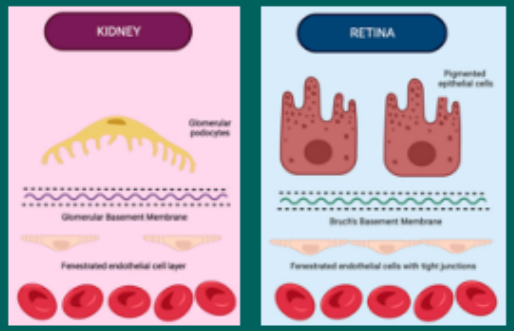


Slide 7

Eye-Kidney Connection

Renal Glomerulus and Choroid

- Highly vascular networks
- Similar blood vessel organization



Slide 8

Major Kidney Functions

- Waste and Drug Excretion
- Nutrient Reabsorption
- Blood Pressure Regulation
- Maintenance of Plasma Osmolarity
- Maintain Important Endocrine Functions

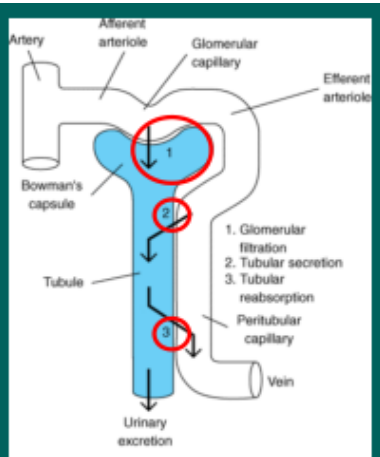
Slide 9

Kidney Physiology

Waste + Drug Removal

3 Routes of Drug Excretion

1. Glomerular Filtration
2. Tubular Secretion
3. Tubule Reabsorption



Source: Eaton DC, Pooler JP: *Vander's Renal Physiology, 7th Edition*. http://www.accessmedicine.com

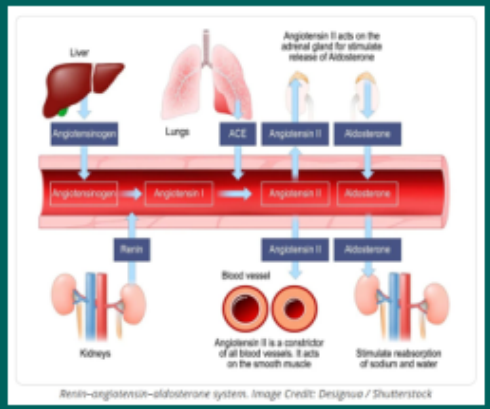
Slide 10

Kidney Physiology

Maintenance of Fluids and Blood Pressure Regulation

Renin-Angiotensin-Aldosterone System (RAAS)

- Systemic
- Tissue Specific



Renin-angiotensin-aldosterone system. Image Credit: Designua / Shutterstock

Slide 11

Reduced Kidney Function Alters RAAS

Chronic Kidney Disease → ⬇ Renal Perfusion → ⬆ RAAS Activation → ⬆ Aldosterone

Increased Aldosterone:

- Promotes inflammation
- Increases oxidative stress
- Accelerates fibrosis
- Increases proteinuria

Slide 12

Potential Ocular Impact

OPEN ACCESS

Retina | July 2018

Aldosterone Exposure Causes Increased Retinal Edema and Severe Retinopathy Following Laser-Induced Retinal Vein Occlusion in Mice

Michael J. Allingham; Nomingerel Tserentsoodol; Peter Saloupis; Priyatham S. Mettu; Scott W. Cousins

July 2018

Increased systemic aldosterone resulted in greater retinopathy and increased severity and duration of retinal edema

Slide 13

Kidney Physiology – Endocrine Functions

The kidneys secrete necessary signaling compounds:

- Renin
- Erythropoeitin
- Activates Vitamin D
- Produces Prostaglandins

Slide 14

Kidney Physiology – Endocrine Functions

Erythropoietin Production

- In response to local or distant hypoxia the kidneys produce the hormone, erythropoietin (EPO)
  - The kidneys are the major producer of EPO
- Erythropoietin signals the bone marrow to begin or increase production of red blood cells

Intraocular Erythropoietin Levels in Patients with Proliferative Diabetic Retinopathy

- EPO levels in the vitreous and aqueous have been found to be higher in diabetic patients compared to non-diabetics

Slide 15

Kidney Physiology- Endocrine Functions

Prostaglandin Synthesis

- Local production and release of prostaglandins helps to combat vasoconstriction in the renal glomerulus
  - ↑ glomerular filtration rate
- Kidney damage can result in reduced renal prostaglandin synthesis which further damages the filtration and regulatory capacity

Slide 16

Acquired Kidney Diseases

- Chronic Kidney Disease
- Diabetic Kidney Disease
- End Stage Renal Disease

Slide 17

Acquired Renal Disease

Chronic Kidney Disease (CKD)

- Occurs when a disease or condition impairs kidney function over a prolonged period of time

Etiologies of CKD	Risk Factors for CKD
Diabetes Hypertension Glomerulonephritis Interstitial nephritis Prolonged urinary tract obstruction	Heart Disease Smoking Family history of CKD Previous Kidney Damage Age

- **Diagnostic Criteria:**
  - Decreased GFR (<60mL/min x 3 months) OR Albuminuria (>30 mg/g)

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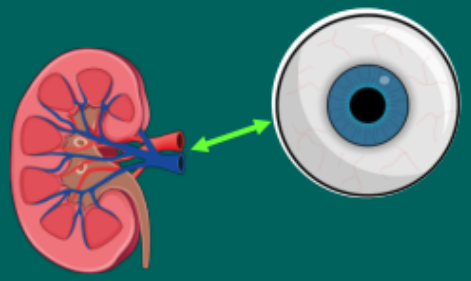
Common SHARED Associations between Kidney Disease and Ocular Pathology

- Age
- Smoking
- Diabetes
- Hypertension
- Obesity
- Hyperlipidemia



Slide 19

Mechanism of CKD	Associated Eye Disease
Atherosclerosis	ARMD Retinal Vascular Damage Choroidal Alterations Diabetic Retinopathy
Endothelial Dysfunction	ARMD
Oxidative Stress	ARMD Retinal Vascular Changes Diabetic Retinopathy
Inflammation	ARMD Retinal Vascular Changes Diabetic Retinopathy
Genetic Mutations	ARMD

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Acquired Kidney Disease

Impacts of Impaired Renal Function

- Reduced drug elimination
- Imbalance of fluid volume
- Reduced blood pressure regulation

Chronic Kidney Disease Staging

- Most common method is based on eGFR
- Important to consider when prescribing certain oral medications

CKD Stage	eGFR
1	>90mL/min/1.73
2	60-89 mL/min/1.73
3a	45-59 mL/min/1.73
3b	30-44 mL/min/1.73
4	15-29 mL/min/1.73
5	<15 mL/min/1.73 Kidney Failure

Slide 21

Acquired Renal Disease

Diabetic Nephropathy / Diabetic Kidney Disease

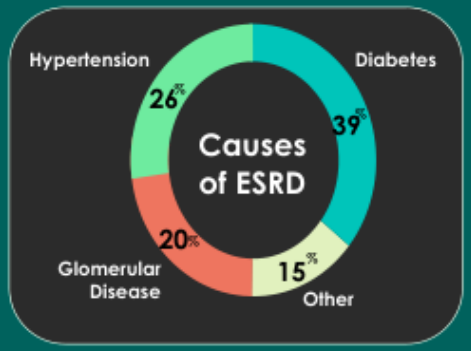
- The leading cause of end-stage renal disease in the United States
- Microvascular damage results in reduced kidney function

Slide 22

Acquired Renal Disease

End-Stage Renal Disease

- Permanent and severe loss of kidney function
- Requires long-term dialysis or kidney transplant to maintain life
- Diagnosed when eGFR <15mL/min



Slide 23

Kidney Function Testing

- Blood Urea Nitrogen
- Estimated Glomerular Filtration Rate
- Serum Creatinine
- Creatinine Clearance
- Microalbumin

Slide 24

Kidney Function Testing

Blood Urea Nitrogen (BUN)

- Measurement of urea nitrogen within the blood
- Elevated blood urea nitrogen may signal poor kidney function
- Obtained as part of a "comprehensive metabolic panel"

Additional Etiologies of Elevated BUN

- Dehydration
- High protein diet
- Age

Normal BUN Range
7-20 mg/dl

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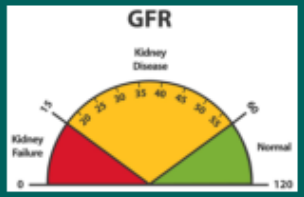
Kidney Function Testing

Estimated Glomerular Filtration Rate (eGFR)

- Blood test ESTIMATES how much blood is filtered through the renal glomeruli each minute
- eGFR is not directly measured, the estimated rate is based on measurement of a serum substance and several patient characteristics (age, sex, race)
- Common serum substances used to measure eGFR:
  - Creatinine
  - Cystatin C
- Used to diagnose and stage kidney disease
- Naturally decreases with age



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Kidney Function Testing

Serum Creatinine

- Creatinine is a byproduct of muscle and protein metabolism that is removed solely by the kidneys
  - Elevated levels of serum creatinine may indicate reduced kidney function

Additional Etiologies of Elevated Creatinine

- Ingestion of cooked meat
- Medications
  - Cimetidine (antihistamine + antacid)
  - Trimethoprim (oral antibiotic)

Normal Serum Creatinine Range
Adult Men: 0.74 – 1.35 mg/dl **Adult Women:** 0.59-1.04 mg/dl

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Kidney Function Testing

Creatinine Clearance (CrCl)

- Volume of blood plasma cleared of creatinine per unit time
- Requires a 24-hour urine sample followed by a blood draw
  - Creatinine level in healthy individuals is higher in urine than in blood
- Decreased creatinine clearance may indicate decreased glomerular function

Normal Creatinine Clearance
Adult Men: 110-150mL/min **Adult Women:** 100-130mL/min

Slide 28

Kidney Function Testing

Microalbumin

- A urine test used to detect very small amount of protein (albumin)
  - Albumin is produced by the liver and in a healthy individual reabsorbed by the kidney
- Helpful in the detection of EARLY kidney damage

Additional Etiologies of Elevated Microalbumin

- Fever
- Urinary tract infection
- Vigorous exercise prior to sample collection

Normal Microalbumin Range
<30 mg/g

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Anterior Segment Manifestations of Kidney Disease

- Periorbital Edema
- Band Keratopathy

Slide 30

Anterior Segment Manifestations of Kidney Disease

Periorbital Edema

- Hypoalbuminemia leads to decrease in the intravascular oncotic pressure and results in the extravascular accumulation of fluid
- Reduced kidney function also alters the sodium balance
  - Increased sodium retention = increased edema

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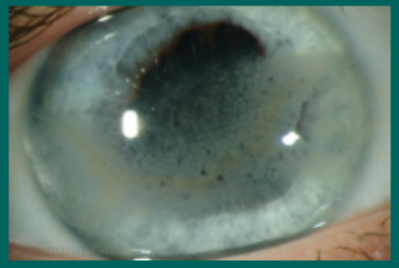
Anterior Segment Manifestations of Kidney Disease

Band Keratopathy

- Decreased renal function leads to increase in serum levels of calcium and phosphorus
- Deposits of calcium and phosphorus in Bowman's layer of the cornea = band keratopathy



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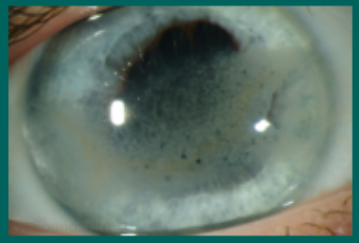
Anterior Segment Manifestations of Kidney Disease

Band Keratopathy

- Phosphate is commonly used as a buffer for topical ophthalmic medications

Should we avoid prescribing phosphate containing therapeutics to patients with preexisting band keratopathy?



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Phosphate Containing Ophthalmic Medications

Steroids
- Dexamethasone
- Prednisolone Acetate 1%
- Fluorometholone

Glaucoma Medications
- Bimatoprost
- Tafluprost
- Latanoprost
- Timolol
- Levobunolol
- Combigan

Slide 34

Retinal Manifestations of Kidney Disease

- Retinal Vascular Alternations
- Diabetic Retinopathy
- Macular Degeneration
- Choroidal Thinning

Slide 35

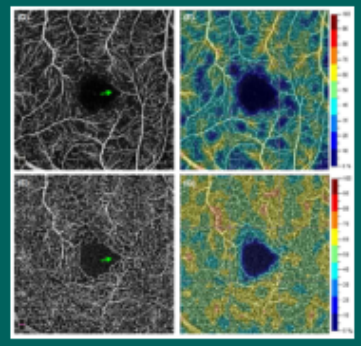
Retinal Manifestations of Kidney Disease

Retinal Vascular Changes
- Dilated fundus examination may provide a noninvasive method for assessing systemic vascular health.
- Chronic kidney disease has been associated with retinal vascular pathology
  - Vascular Sheathing
  - Vascular Density Alternations
  - Arteriole-Venous Ratio Alterations

Slide 36

Retinal Manifestations of Kidney Disease

Vascular Density Alterations
- OCT-A Findings in Asymptomatic CKD Patients
  - Decreased vessel density in superficial> deep capillary plexus
  - Increased size of foveal avascular zone
  - Localized areas of reduced flow signal in superficial plexus



Yeung L. et al (2019)

Slide 37

Retinal Manifestations of Kidney Disease

Arteriole-Venous Ratio Alterations

Narrowing of retinal arteries has been associated with lower eGFR and presence of proteinuria

- Retinal blood supply is autoregulated
  - Relies on complex network of capillary beds and retinal vascular pericytes
- **Endothelin-1**
  - Potent retinal vasoconstrictor
  - Retinal vascular pericytes are influenced by endothelin-1 resulting in vasoconstriction
  - Elevated levels of endothelin-1 are seen in CKD

Slide 38

Diabetic Retinopathy

- Microvascular damage is the root cause of both diabetic retinopathy and vascular kidney damage.

Diabetic Retinopathy	Leading cause of vision loss
Diabetic Kidney Disease	Leading cause of end-stage kidney disease

- Development of retinopathy has been shown to be a predictor of development and progression of CKD

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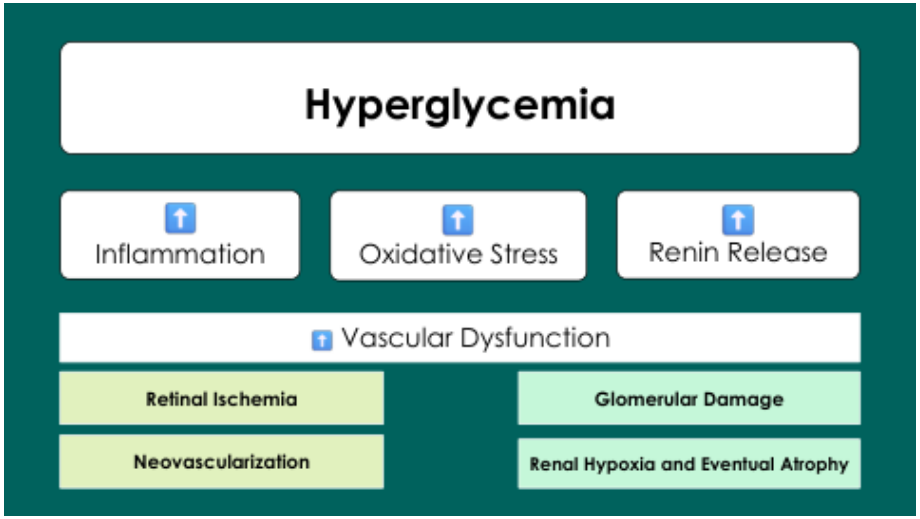

Slide 40

Kidney Impact in Diabetic Retinopathy

Several studies have shown patients with diabetic retinopathy often also have:

- Microalbuminuria
- Lower eGFR
- Greater Serum Creatinine
- Reduced Creatinine Clearance

Diabetic Retinopathy Predicts Progression of Kidney Disease

- Patients with NPDR have a **2.9x** higher risk of CKD progression
- Patients with PDR had a **16.6x** higher risk of CKD progression

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Diabetic Retinopathy

Type 1 Diabetes

- Retinopathy may occur before diagnosis of nephropathy
- Retinopathy is diagnosed based on direct evaluation
- Nephropathy is diagnosed based on functional abnormalities which may be preserved in the early stages of structural damage.

Type 2 Diabetes

- Retinopathy may develop after diagnosis of nephropathy
- Severity of retinopathy may predict future progression of kidney disease

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Macular Degeneration

Macular degeneration is characterized by deposition of lipofuscin and retinal pigmentary changes in the macular region

- **Patients with mild to moderate CKD have a higher risk of developing macular degeneration than patients without CKD**

Do the conditions share disease mechanisms or is the association simply due to common risk factors?

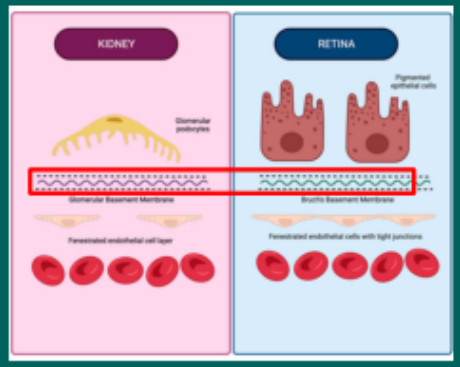
Macular Degeneration and Chronic Kidney Disease	
Shared Risk Factors	**Possible Shared Pathology**
• Advanced Age • Hypertension • Cigarette Smoking	• Increased propensity of atherosclerosis and oxidative stress • Genetic Susceptibility – Complement factor H

Slide 43

Macular Degeneration

Mutation of Complement Factor H

- Mutation results in increased activation of complement cascade
- Dysregulation of the complement system can result in self-attack, local inflammation and tissue damage



Slide 44

Macular Degeneration

Membranoproliferative Glomerulonephritis

- Rare, aggressive kidney disease that impacts glomerular function
- Ocular manifestations resemble bilateral drusen and RPE alterations
  - Patients are generally younger than expected for retinal findings
  - Electron microscopy has demonstrated that kidney deposits and retinal deposits are similar

Pathophysiology: mutations in complement factor H gene

Slide 45

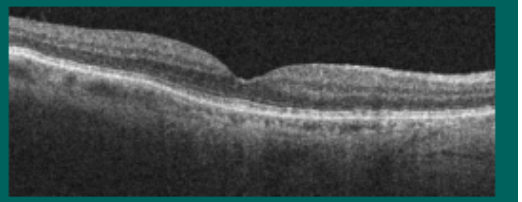
Choroid

Highly vascularized structure responsible for prefusion of outer retinal layers

Choroidal thickness has been show to **thinner** in patient with renal disease

Reduced choroidal thickness is associated with:

- Lower eGFR
- Microalbuminuria



Slide 46

Choroid

Mechanisms present in CKD that may impact choroidal thickness:

- Autonomic nervous system dysfunction
- Oxidative stress
- Subclinical inflammation
- Endothelial dysfunction
- Vascular aging and increased arterial stiffness

Slide 47

Ocular Considerations in End Stage Renal Disease

Hemodialysis

- One of the only treatments for ESRD
- One of the most common adverse events at a dialysis center = HYPO tension
  - Ultrafiltration leads to a rapid reduction in blood volume

Slide 48

Ocular Considerations in Patients Receiving Dialysis

Non-Arteritic Anterior Ischemic Optic Neuropathy (NA-AION)

- **Pathogenesis:** ischemia of the anterior optic nerve due alteration in blood flow through the posterior ciliary artery
- **Examination Findings:** reduced vision, visual field defect, dyschromatopsia, APD (if unilateral or asymmetric), swollen optic nerve with possible splinter hemorrhages

Risk Factors
Crowded Optic Nerve
Older Age
Sleep Apnea
Medication use
Nocturnal Hypotension
Systemic Vascular Disease

Slide 49

Ocular Considerations in Patients Receiving Dialysis

Dialysis- Associated NA-AION

- May occur in younger than expected patients
- Often bilateral at presentation
  - or suffer from bilateral sequential involvement
- At risk for recurrent events if risk factors not addressed

Communication with nephrologist is key in preventing recurrent events!

Slide 50

Ocular Disease Management in Patients with Kidney Disease

- Oral Medication Prescribing
- Iodinated Intravenous Contrast
- Gadolinium Intravenous Contrast

Slide 51

Hydroxychloroquine Retinopathy Monitoring

Hydroxychloroquine

- Disease-modifying antirheumatic agent (DMARD)
- Undergoes partial metabolization
- 40-50% is excreted by the kidneys

Patients with reduced renal function fail to clear HCQ completely which leads to an increased risk of retinal toxicity

Slide 52

Oral Medication Prescribing

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- One of the most common classes of medications used world-wide
- ~2.5 million Americans experience NSAID related renal effects yearly
- NSAIDs exert anti-inflammatory, analgesic and anti-pyretic effects

Mechanism of Action:

- Suppress prostaglandin synthesis
- Inhibiting cyclooxygenase enzymes (COX-1 and COX-2)

Slide 53

Oral Medication Prescribing

NSAID Related Kidney Damage

NSAIDs reduces local prostaglandin production

- ⬇ vasodilation
- ⬆ renal ischemia

Increase inflammatory cell infiltrates

- ⬇ glomerular filtration rate

NSAIDs should be avoided in patients with eGFR<30

Avoid prolonged use in patients with an eGFR between 30-59

Slide 54

Oral Medication Prescribing

Oral Antivirals

- Acyclovir
- Valacyclovir
- Famciclovir

- Renal clearance is the major route of elimination
- Renal impairment reduces clearance and prolongs the elimination of metabolites
  - Increases the risk of undesired effects (neurotoxicity)

Slide 55

Oral Medication Prescribing

Herpes Zoster Oral Acyclovir Dose Adjustments		
Creatinine Clearance (CrCl)	**Normal Dose**	**Renal Adjustment Dose**
0-10 mL/min/1.73m2	200mg 5x per day	200mg q12 hours
0-10mL/min/1.73m2	400mg q12 hours	200mg q12hours
0-10mL/min/1.73m2	800mg q4 hours	800mg q12hours
10-25mL/min/1.73m2	800mg q4hours	800mg q8hours

Normal Creatinine Clearance:
110 to 150mL/min in males and 100 to 130mL/min in females

Slide 56

Oral Medication Prescribing

Herpes Zoster: 1g PO q8hours

Oral Valacyclovir Dose Adjustments	
Creatinine Clearance (CrCl)	**Renal Adjustment Dose**
At least 50 mL/min/1.73m2	No adjustment
30-49 mL/min/1.73m2	1 gram q12hours
10-29 mL/min/1.73m2	1 gram q24 hours
Less than 10mL/min/1.73m2	500mg q24 hours

Slide 57

Oral Medication Prescribing

Herpes Zoster: 500mg PO q8hours

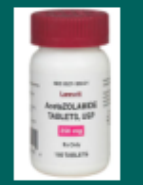
Oral Famciclovir Dose Adjustments	
Creatinine Clearance (CrCl)	**Renal Adjustment Dose**
>60mL/min/1.73m2	No adjustment
40-59 mL/min/1.73m2	500mg q12hours
20-39mL/min/1.73m2	500mg q24 hours
Less than 20mL/min/1.73m2	250mg q24 hours

Slide 58

Oral Medication Prescribing

Oral Carbonic Anhydrase Inhibitors – Acetazolamide

- Impairs resorption of bicarbonate from the kidneys which results in loss of sodium, bicarbonate and water
- Oral acetazolamide is **excreted via the kidneys 100% unchanged**
- Less effective in reducing IOP in patients with end- stage renal impairment
- 1-2% of patients may develop kidney stones secondary to acetazolamide use
  - Increased risk if taken with sodium bicarbonate (antacids)



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Oral Medication Prescribing

Oral Carbonic Anhydrase Inhibitors – Acetazolamide

Normal Renal Function Dose: 250mg q6-12hours

eGFR	Recommended Adjusted Dose
>50 mL/min	250mg q6hours
10-50 mL/min	250mg q12hours
<10 mL/min	Avoid Use

Slide 60

Iodinated Intravenous Contrast

Computerized tomography (CT) scans use density to show intrinsic tissue contrast

- Bone is more dense than organs so bone will be "brighter" on a non-contrast CT

- Water soluble iodine injected intravenously will temporarily increase the density of blood and the structures blood flows through
- Iodinated intravenous contrast is well cleared by dialysis
- Procedures that utilize iodinated contrast:
  - Contrast CTs
  - Angiograms
    - Carotid CTA always request IV contrast

Slide 61

Iodinated Intravenous Contrast

Contrast Induced Acute Kidney Injury

- Defined as a 50% increase in creatinine from baseline within 7 days of exposure to iodinated contrast media
  - Can be temporary and in some very rare cases permanent
- **Symptoms:** increased tiredness, poor appetite, swelling in the feet and ankles, puffiness around the eyes, or dry and itchy skin
- **Risk Factors**
  - eGFR <30 mL/min/1.73m^2
  - eGFR 20-44ml/min/1.73m^2 with additional risk factors
    - Diabetes, proteinuria, volume depletion, exposure to other nephrotoxins

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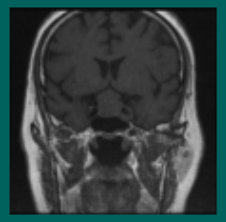
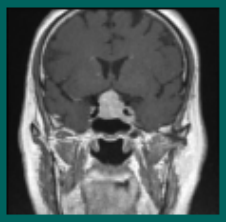
Gadolinium Intravenous Contrast





- Magnetic resonance images are produced by detecting release of energy as protons are realigning with their natural magnetic field
- Introduction of gadolinium affects the local magnetic field, changes the relationship of local hydrogen protons and increases the speed at which the protons realign.

Slide 63

Gadolinium Intravenous Contrast

Nephrogenic Systemic Fibrosis

- Debilitating fibrosing disorder that can affect the skin, connective tissue and in certain cases internal organs
  - Skin is primary/ initial target in most patients – presents with thickening and induration of skin.
  - Presents within weeks to several months after gadolinium contrast exposure
- Reduced risk with newer gadolinium agents
- Most commonly occurs in patients with stage 4 or stage 5 chronic kidney disease or in patients with acute kidney injury
  - Risk is greatest in patients with eGFR less than 30mL/min

Slide 64

Take Home Points

- Ocular and kidney pathology share common disease mechanisms
- Consider kidney health when observing retinal vascular pathologies
- Dilated fundus examinations can provide the entire healthcare team information of systemic vascular health
- Careful consideration is needed when prescribing oral medications to patients

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