Renal Anatomy and Histology: Gross Structure to Ultrastructure

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Renal Anatomy and Histology: Gross Structure to Ultrastructure

Learning Objectives

By the end of this module, you should be able to:

1. **Describe gross renal anatomy** in terms of cortex, medulla, pyramids, columns, and hilum/renal sinus
2. **Explain the dual blood supply** to the kidney (afferent and efferent systems) and renal portal circulation
3. **Distinguish nephron types** (cortical, juxtamedullary) and their functional specialization
4. **Trace tubular anatomy and histology** from Bowman's capsule through the collecting duct
5. **Analyze glomerular ultrastructure** including podocytes, GBM, and endothelium at the molecular level
6. **Relate structure to function** for each nephron segment

I. Gross Renal Anatomy

A. Overall Dimensions and Location

- **Mass:** 150-170 g per kidney (adult)
- **Dimensions:** ~12 cm length × 6 cm width × 3 cm thickness
- **Location:** Retroperitoneal; T12-L3 vertebral level (left kidney ~1 cm higher than right)
- **Blood supply:** ~20-25% of cardiac output (~1000 mL/min total renal blood flow)

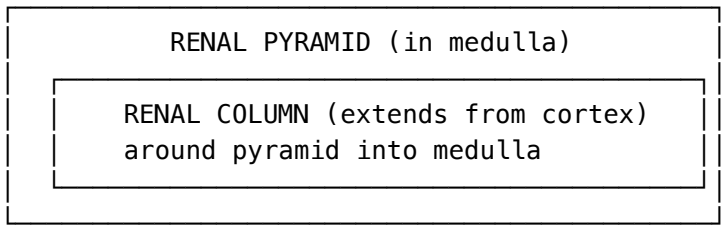
B. External Anatomy

Surface Features: - Smooth, convex lateral surface - Medial border with concave indentation (renal sinus) - Superior and inferior poles; medial and lateral borders

Renal Hilum (Hilus): - Medial concavity where vessels and ureter enter/exit - Anterior-to-posterior order at hilum: **V-U-A** (Vein, Ureter, Artery) - Renal vein most anterior; renal artery behind; ureter most posterior and medial

C. Internal Anatomy: Gross Sectioning

Renal Parenchyma Organization:



Cortex (Outer region): - Contains glomeruli and initial portions of tubules - Pale appearance on cut section - Extends inward between pyramids as renal columns (columns of Bertin)

Medulla (Inner region): - Contains loops of Henle and collecting ducts - Organized into 8-12 renal pyramids - Pyramids visible as striped appearance due to parallel arrangement of tubules - Tips of pyramids (papillae) project into minor calyces

Renal Sinus (Central cavity): - Contains fat and loose connective tissue - Houses the collecting system (calyces and pelvis) - Upper limit of retroperitoneum

Collecting System: - **2-4 major calyces** (anterior and posterior groups) — convergence of minor calyces - **8-12 minor calyces** — receive 1-3 papillae each - **Renal pelvis** — funnel-shaped continuation; transitions to ureter at pelvic brim

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II. Renal Vasculature

A. Arterial Supply

Main Renal Artery: - Arises from abdominal aorta at L1 vertebral level - Right artery crosses posterior to IVC - Each artery divides into anterior and posterior branches at hilum - **No anastomoses between anterior and posterior divisions** (functional end-arteries)

Intrarenal Branching: 1. Segmental arteries (from anterior/posterior branches) 2. Lobar arteries (branch into segments supplied by pyramids) 3. Interlobar arteries (run between pyramids) 4. Arcuate arteries (run along corticomedullary junction) 5. Interlobular arteries (extend from arcuate into cortex) 6. Afferent arterioles (final branches □ glomeruli)

B. The Renal Portal Circulation (Unique to Kidneys)

Concept: The kidney has two capillary beds in series, separated by an arteriole (efferent arteriole).

Pathway:

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Afferent arteriole
        ↓
    GLOMERULUS (1st capillary bed) — filtration site
        ↓
Efferent arteriole
        ↓
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PERITUBULAR CAPILLARIES (2nd capillary bed) — reabsorption/secretion site
        ↓
Venules → Venules → Renal vein
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Functional Consequence: - Glomerular hydrostatic pressure (Pgg) determines ultrafiltration - Peritubular capillary hydrostatic pressure (Pct) is LOW, promoting reabsorption - This arrangement allows independent regulation of filtration and reabsorption

Efferent Arteriole Sensitivity: - Angiotensin II constricts efferent arteriole more than afferent - This increases Pgg (preserves GFR) while decreasing peritubular flow - ACE inhibitors block this effect ☐ decreased GFR when systemically hypotensive

C. Venous Drainage

Intrarenal Drainage: 1. Peritubular capillaries ☐ cortical venules 2. Cortical venules ☐ arcuate veins (follow arteries) 3. Arcuate veins ☐ interlobar veins 4. Interlobar veins ☐ lobar and segmental veins 5. Segmental veins ☐ renal vein (single per kidney; left longer)

Renal Vein Exit: - Left renal vein enters IVC at right angle - Right renal vein enters IVC at oblique angle, shorter course - Left renal vein receives left adrenal and left gonadal veins

D. Lymphatic Drainage

- Follows blood vessels
- Drains to lumbar (aortic) lymph nodes
- Important for tumor staging in renal cancer

III. Nephron Types and Topography

A. Classification by Location

Cortical Nephrons (~85% of total): - Glomeruli located in outer cortex - Short loops of Henle that do not extend far into medulla - Terminate in collecting ducts in outer medulla - More numerous; shorter loops - **Function:** Produce dilute urine; important for water reabsorption regulation

Juxtamedullary Nephrons (~15% of total): - Glomeruli located near corticomedullary junction - Long loops of Henle extending deep into medulla and papilla - Terminate in collecting ducts throughout medulla - Fewer in number; longer loops - **Function:** Create osmotic gradient for concentrating urine; critical for water conservation

B. Functional Significance

Feature	Cortical	Juxtamedullary
Location of glomeruli	Outer cortex	Corticomedullary junction
Loop of Henle length	Short (~2-5 mm)	Long (~12-14 mm)

Feature	Cortical	Juxtamedullary
Vasa recta	Short; minimal branching	Long; extensive branching
Osmolarity gradient generation	Minimal contribution	Critical; generates medullary gradient
Urine concentration capability	Limited	Essential for urine concentration
Plasma oncotic pressure effect	Less important	Critical for concentration

C. Vasa Recta

Definition: Specialized capillary networks associated with long loops of Henle (juxtamedullary nephrons).

Anatomy: - Arise from efferent arteriole of juxtamedullary glomerulus - Form descending and ascending limbs parallel to loop of Henle - Hairpin turns in renal papilla - Return via venules to renal circulation

Function: - Maintain medullary osmotic gradient (countercurrent exchanger) - Deliver nutrients and oxygen to medulla - Remove reabsorbed solutes

Pathophysiology: - Vasa recta collapse in severe dehydration or hypotension - Loss of vasa recta ☐ loss of medullary gradient ☐ polyuria (seen in pyelonephritis, papillary necrosis)

IV. Nephron Anatomy: Tubular Segments

A. Overview and Functions

The nephron consists of seven major functional segments, each with distinct histology and transport properties:

Segment	Length	Location	Primary Function
Glomerulus	N/A	Cortex	Ultrafiltration
Proximal convoluted tubule (PCT)	~15 mm	Cortex	Reabsorption (glucose, amino acids, ions, water)
Proximal straight tubule (PST)	~5 mm	Outer medulla	Continued reabsorption; prepares for countercurrent
Descending thin limb (DTL)	~5-10 mm	Inner medulla	Passive water reabsorption; concentration

Segment	Length	Location	Primary Function
Ascending thin limb (ATL)	~10 mm	Inner medulla	Passive NaCl reabsorption; dilution
Thick ascending limb (TAL)	~10 mm	Outer medulla	Active NaCl reabsorption; dilution (impermeable to water)
Distal convoluted tubule (DCT)	~5 mm	Cortex	Fine-tuning of electrolytes; dilution
Collecting duct (CD)	~20 mm	Cortex through medulla	Final water and electrolyte reabsorption; acid-base handling

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B. Detailed Histology by Segment

1. Proximal Convoluted and Straight Tubules (PCT/PST)

Epithelium: - Simple cuboidal to columnar epithelium - Single layer of epithelial cells with prominent microvilli (brush border) - Brush border increases surface area ~20-fold for reabsorption

Cellular Features: - Abundant mitochondria (high energy demand for active transport) - Extensive basolateral interdigitations with neighboring cells - Large nucleus - Prominent ribosomes and rough endoplasmic reticulum (protein synthesis)

Specialized Transport Proteins: - Apical: SGLT2/SGLT1 (glucose cotransport), PEPT1/PEPT2 (peptide cotransport), amino acid transporters, Na+/H+ exchanger (NHE3) - Basolateral: Na+/K+-ATPase, HCO_3^- /Cl^- exchanger, organic anion transporters - **Function:** Reabsorption of glucose, amino acids, small proteins, electrolytes, water

Junctional Complexes: - Tight junctions (claudins) allow paracellular reabsorption of ions - Relatively "leaky" compared to TAL; allows paracellular solute movement

Clinical Correlate: Diabetes mellitus ☐ glucose exceeds reabsorptive threshold ☐ glucosuria. Medications (SGLT2 inhibitors) block SGLT2 to promote glycosuria and natriuresis.

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2. Descending Thin Limb (DTL)

Epithelium: - Simple squamous epithelium (lowest transport capacity) - Flat cells with minimal mitochondria - Minimal active transport

Permeability Characteristics: - **Highly permeable to water** (aquaporin-1 water channels present) - **Permeable to urea** (UT-A1 urea transporters) - **Less permeable to solutes** (NaCl)

Function: - Passive water reabsorption as osmolarity increases in medullary interstitium - Urea influx from medullary interstitium - Concentration of tubular fluid without active ion transport

Countercurrent Multiplication Role: - Water leaves ☐ osmolarity of tubular fluid increases - Osmolarity gradient drives subsequent segments' function

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3. Ascending Thin Limb (ATL)

Epithelium: - Simple squamous (similar to DTL but different permeability) - Minimal mitochondria

Permeability Characteristics: - **Impermeable to water** (lacks aquaporin) - **Permeable to NaCl and urea** - Passive movement driven by concentration gradients

Function: - Passive NaCl reabsorption (down concentration gradient) - Dilution of tubular fluid - Critical for countercurrent multiplication

Note: ATL permeability varies along its length (proximal portion more permeable to NaCl; distal portion more permeable to urea).

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4. Thick Ascending Limb (TAL)

Epithelium: - Simple cuboidal epithelium - Abundant mitochondria (active transport-dependent) - Minimal or no brush border (some recessed microvilli)

Specialized Transport: - **Apical:** Na-K-2Cl cotransporter (NKCC2) — active transport pump - **Basolateral:** Na+/K+-ATPase, K+ channels (ROMK), Cl- channels - **Paracellular:** Claudins 16 and 19 (tight junctions) — allow cation-selective reabsorption

Characteristics: - **Active NaCl reabsorption** (~25% of filtered load) - **Impermeable to water** — obligate dilution despite osmolyte removal - "Diluting segment" — produces hypotonic tubular fluid - K+ recycling via apical ROMK channels

Clinical Significance: - **Loop diuretics (furosemide):** Block NKCC2 ☐ massive natriuresis - **Bartter syndrome:** Genetic defects in NKCC2, ROMK, or claudin 16 ☐ polyuria, hypokalemia, metabolic alkalosis - **Gitelman syndrome:** (DCT involvement) similar presentation but with hypomagnesemia

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5. Distal Convoluted Tubule (DCT)

Epithelium: - Simple cuboidal epithelium - Fewer mitochondria than PCT or TAL - Minimal brush border

Specialized Segments:

Early DCT (DCT1): - **Apical:** Thiazide-sensitive Na-Cl cotransporter (NCC/HCTZ target) - **Function:** NaCl reabsorption; continued dilution - **Regulatory:** Insensitive to ADH

Late DCT (DCT2) and Connecting Tubule: - **Principal cells:** Sodium channel (ENaC) on apical surface; water channels (aquaporin-2) and K+ secretion - **Intercalated cells:** H+-ATPase and HCO_3- transporters (acid-base regulation)

Function: - Fine-tuning of sodium balance - ADH-responsive water reabsorption - Potassium secretion (principal cells) - Acid-base adjustment

Clinical Correlates: - **Thiazide diuretics:** Block NCC in early DCT - **Familial hypokalemic periodic paralysis:** Gain-of-function CACNA1S or SCN4A mutations ☐ enhanced sodium reabsorption in early DCT - **Pseudohypoaldosteronism (PHA):** Loss-of-function ENaC mutations ☐ inability to reabsorb sodium ☐ polyuria, hyperkalemia

6. Collecting Duct (CD)

Epithelium: - Simple cuboidal; lined with two primary cell types

Principal Cells (~60% of cells): - **Apical:** Epithelial sodium channel (ENaC) — aldosterone-regulated; aquaporin-2 water channels (ADH-responsive) - **Basolateral:** Na+/K+-ATPase, aquaporin-3, aquaporin-4 (water exit) - **Function:** Sodium reabsorption (aldosterone-responsive); water reabsorption (ADH-responsive); potassium secretion - **Regulation:** Aldosterone increases ENaC expression and function; ADH increases aquaporin-2

Intercalated Cells (~40% of cells): - **Type A (α-intercalated cells):** H+-ATPase in apical membrane; HCO3- reabsorption; responsible for urine acidification - **Type B (β-intercalated cells):** HCO3- secretion into urine (bicarbonate wasting); responsible for base excretion

Collecting Duct Function: - **Water reabsorption:** ADH-regulated; allows concentration of urine - **Sodium reabsorption:** Aldosterone-regulated; fine-tunes blood volume and blood pressure - **Potassium secretion:** Aldosterone-stimulated (principal cells); regulated by urine flow and intracellular K+ - **Acid-base balance:** Type A intercalated cells acidify urine (H+ secretion); Type B cells produce alkaline urine (HCO3- secretion)

Osmotic Gradient Creation: - Receiving hypotonic fluid from loop; becomes isoosmotic or hyperosmotic depending on ADH - In presence of ADH: aquaporin-2 inserted into apical membrane ☐ water reabsorption ☐ concentrated urine - In absence of ADH: no water permeability ☐ dilute urine excretion

Clinical Manifestations: - **Central diabetes insipidus:** Lack of ADH ☐ absent water reabsorption in CD ☐ polyuria (dilute urine) - **Nephrogenic diabetes insipidus:** CD unresponsive to ADH ☐ polyuria despite elevated ADH - **Primary hyperaldosteronism:** Excess aldosterone ☐ enhanced ENaC activity ☐ hypertension, hypokalemia - **Pseudohypoaldosteronism (PHA):** ENaC loss-of-function ☐ inability to reabsorb sodium ☐ polyuria, hyperkalemia, metabolic acidosis

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V. Glomerular Ultrastructure: The Filtration Barrier

A. Three-Layer Filtration Barrier

The glomerular filtration barrier consists of three cellular and extracellular components in series:

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│  1. ENDOTHELIUM (fenestrated)    │ ← size selectivity, charge exclusion
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│  2. BASEMENT MEMBRANE (GBM)      │ ← size + charge selectivity
├──────────────────────────────────┤
│  3. PODOCYTES (epithelium)       │ ← size selectivity, mechanical support
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B. Fenestrated Endothelium

Structure: - Continuous capillary endothelium with large pores (fenestrae) - Fenestrae: 60-100 nm diameter (larger than systemic capillaries) - Diaphragms spanning fenestrae composed of glycoproteins (VE-cadherin, VE-PTP)

Composition: - Endothelial cells contain specialized domains: - **Caveolin-1:** Regulatory protein; associated with fenestral formation - **VE-cadherin:** Structural adhesion molecule; forms adherens junctions between endothelial cells - **ZO-1:** Tight junction protein; present at cell-cell junctions

Function: - **Size selectivity:** Fenestrae exclude RBCs and platelets but allow plasma proteins to approach GBM - **Charge selectivity:** Glycocalyx (sialic acid-rich) negatively charged; repels anionic proteins - **Permeability:** Hydraulic conductance ~400× greater than systemic capillaries

Glycocalyx: - Carbohydrate-rich layer on luminal surface - Contains heparan sulfate (negative charge), chondroitin sulfate, hyaluronic acid - Contributes to charge selectivity - Lost in proteinuric diseases (e.g., minimal change disease, diabetic nephropathy)

Clinical Correlate: Electron microscopy shows fenestrated endothelium with intact GBM in minimal change disease (selective proteinuria without ultrastructural changes visible by EM); loss of endothelial glycocalyx correlates with proteinuria.

C. Glomerular Basement Membrane (GBM)

Composition: - **Type IV collagen** (~50% dry weight) — α3α4α5 chains form triple helix - **Laminin** (~15%) — trimeric protein with cross-linking domains - **Nidogen (entactin)** — bridging molecule linking collagen and laminin - **Perlecan (HSPG)** — large heparan sulfate proteoglycan - **Agrin** — basement membrane-associated proteoglycan

Architecture: - Electron-dense layer on transmission EM ("basement membrane") - Three electron microscopic zones: - **Lamina rara interna** (subendothelial zone) — sparse collagen/laminin, rich in proteoglycans - **Lamina densa** (central zone) — electron-dense; α3α4α5 type IV collagen network - **Lamina rara externa** (subepithelial zone) — sparse matrix; anchors to podocytes

Thickness: 200-400 nm; increases with age and in diabetic nephropathy

Function: 1. **Size selectivity:** Pore size ~5-10 nm; excludes proteins >50-60 kDa 2. **Charge selectivity:** Heparan sulfate is negatively charged; repels anionic proteins (albumin, immunoglobulins) 3. **Mechanical support:** Provides structural scaffold for podocytes and endothelium 4. **Filtration:** Combines with endothelium and podocytes for selective ultrafiltration

Molecular Structure of α3α4α5 Collagen IV: - Three chains form a triple helix (Gly-X-Y repeats) - NC1 (non-collagenous) domains at C-terminus form interactions - Mutations cause hereditary nephritis: - **X-linked alport syndrome (85%):** COL4A3 mutations - **Autosomal recessive alport syndrome (15%):** COL4A3 or COL4A4 mutations - **Thin basement membrane disease:** Heterozygous COL4A mutations (usually benign, IgA nephropathy-associated)

Damage Mechanisms: - **Immune complex deposition:** IgG/complement antibodies adhere to GBM; activate complement □ inflammation - **Antibody binding:** ANCA antibodies bind to en-

dothelium; activate complement - **Enzymatic degradation:** Matrix metalloproteinases (MMPs) degrade collagen in active inflammation - **Glycosylation:** Hyperglycemia in diabetes adds glucose groups ☐ non-enzymatic glycation ☐ cross-linking ☐ stiffening - **Hypertension:** Increased glomerular pressure ☐ mechanical stretching ☐ collagen damage and remodeling

Thickening (Basement Membrane Disease): - Seen on electron microscopy as increased electron density and thickness - Causes: Diabetes, membranoproliferative GN, dense deposit disease (C3GN), immune complex GN

Thinning: - Alport syndrome: Progressive thinning then splitting (basket-weave appearance on EM) ☐ rupture - Thin basement membrane disease: Uniformly thin GBM (<250 nm) — usually benign but associated with hematuria

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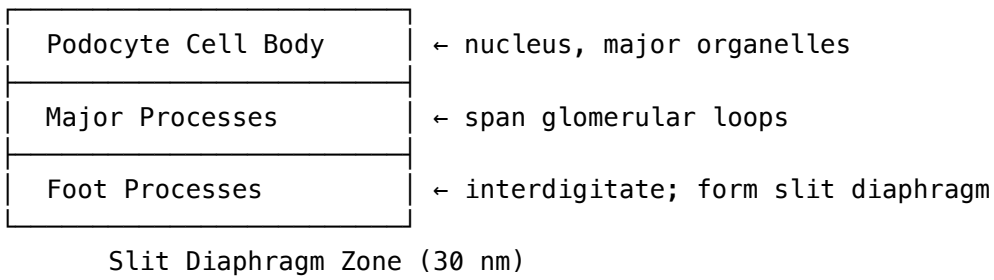
D. Podocytes (Visceral Epithelium)

General Structure: - Large specialized epithelial cells (~6 podocytes per glomerulus) - Cell body resides on Bowman's capsule - Cytoplasmic processes (major processes) extend over glomerular capillaries - Secondary processes (foot processes) interdigitate with adjacent podocytes' foot processes

Architecture:



Slit Diaphragm Proteins (Slit Pore Architecture):

The slit diaphragm is a specialized cell-cell junction between adjacent foot processes. Key structural proteins:

1. **Nephrin (NPHS1)**
   - Transmembrane protein; homophilic adhesion (nephrin-to-nephrin across slit)
   - Contains 8 extracellular immunoglobulin domains
   - Intracellular domain binds podocin and CD2AP
   - Mutations: NPHS1 (congenital nephrotic syndrome of Finnish type)
2. **Podocin (NPHS2)**
   - Stomatin family protein; assembles with nephrin
   - Functions in signaling and filter barrier stabilization
   - Mutations: NPHS2 (autosomal recessive focal segmental glomerulosclerosis, FSGS)
3. **CD2AP (CD2-associated protein)**
   - Adaptor protein; links nephrin/podocin to actin cytoskeleton
   - Links to p130Cas and Sos proteins (signaling)
   - Mutations: CD2AP (FSGS)
4. **ZO-1 (Zonula occludens-1)**

- Tight junction protein; organizes claudins
- Links to actin cytoskeleton via α-actinin
- Provides mechanical integrity

5. **Claudins (claudin-5, claudin-7)**
   - Occludin family proteins; narrow slit opening
   - Seal paracellular pathway
6. **Other Proteins:** α-actinin-4, paxillin, FAK (focal adhesion kinase)

Slit Pore Dimensions: - Width: 30 nm (very narrow) - Diaphragm thickness: ~5-10 nm - Length: ~1-1.5 μm - ~30,000-40,000 slit pores per glomerulus

Size Selectivity at Slit Diaphragm: - Proteins <20 kDa pass freely - Proteins 20-60 kDa partially restricted - Proteins >60 kDa largely excluded - Albumin (66 kDa): Partially excluded (~0.1% filtered)

E. Podocyte Cytoskeleton and Dynamics

Actin Organization: - **Stress fibers:** Bundles of actin filaments in major processes - **Circumferential belts:** Actin rings at the periphery of foot processes - **Dynamic remodeling:** Continuous turnover of actin; enables foot process movement and adaptation

Contractile Proteins: - **α-actinin-4:** Cross-links actin filaments; links to slit diaphragm proteins (CD2AP, ZO-1) - **Myosin II:** Motor protein; generates contraction - **Arp2/3 complex:** Nucleates actin branches; essential for lamellipodial protrusion

Foot Process Dynamics: - Foot processes are not static; exhibit continuous movement (100-500 nm range) - Movement necessary for: - Accommodation to changes in glomerular pressure - Maintaining glomerular permeability - Responding to mechanical and biochemical stimuli

Regulation: - Rho GTPases (Rho, Rac1, Cdc42): Control actin polymerization and contraction - TRPC6 (Transient Receptor Potential channel 6): Ca2+ entry; regulates cytoskeletal dynamics - Phosphatidylinositol-4,5-bisphosphate (PIP2): Links membrane to actin

Clinical Relevance: - **Foot process effacement:** Loss of foot process structure (flattening of podocytes) - Seen on electron microscopy in proteinuric diseases - Minimal change disease: Diffuse foot process effacement; reversible with treatment - Membranous nephropathy: Subepithelial immune deposits with foot process effacement - FSGS: Segmental sclerosis with podocyte foot process effacement - Diabetic nephropathy: Progressive foot process loss correlates with proteinuria

Mutations in Cytoskeletal Proteins: - **ACTA2 (α-smooth muscle actin):** Childhood-onset nephrotic syndrome with FSGS - **TRPC6:** Familial FSGS with progressive renal failure - **INF2 (formin-related protein 2):** Familial FSGS; defective actin nucleation

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F. Podocyte Injury Mechanisms

Proteinuria Mechanisms in Podocyte Injury:

1. **Foot Process Effacement**
   - Loss of slit diaphragm architecture

- Widening of slit pores (normally 30 nm; effaced pores 100-200 nm)
- Loss of size selectivity
- Albumin leak (selective proteinuria ☐ non-selective)

2. **Slit Diaphragm Disruption**
   - Mutations in nephrin, podocin, CD2AP ☐ podocytopenia
   - Immune complex deposition (IgG, C1q) ☐ complement activation ☐ inflammation
   - Podocyte cytoskeletal collapse via TRPC6 hyperactivation (gain-of-function mutations)
3. **Podocyte Apoptosis**
   - Excessive proteinuria ☐ endocytosis of filtered proteins ☐ lysosomal overload
   - Oxidative stress from protein catabolism
   - Loss of growth factors (TGF-β, PDGF in some contexts)
   - Results in permanent nephron loss
4. **Glomerulosclerosis**
   - Podocyte loss ☐ increased burden on remaining podocytes ☐ hypertrophy and hyperfiltration
   - Mesangial proliferation and matrix expansion
   - Permanent scar formation

Triggers of Podocyte Injury: - **Immune:** Antibodies (IgA, IgG, IgM), complement (C1q, C3) - **Metabolic:** Hyperglycemia (glucose toxicity), dyslipidemia - **Hemodynamic:** Hypertension, glomerular hyperfiltration - **Infectious:** Viral proteins (HIV, HBV), immune complex formation - **Toxic:** NSAIDs, ACEi rebound, contrast agents - **Genetic:** Mutations in slit diaphragm or cytoskeletal proteins

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VI. Mesangium and Glomerular Support

A. Mesangial Cells

Location: Central region of glomerulus; between capillary loops

Characteristics: - Modified smooth muscle cells - Contractile proteins (actin, myosin) - Produce extracellular matrix (collagen IV, proteoglycans)

Functions: 1. **Mechanical:** Support capillary loops; control glomerular surface area 2. **Contractile:** Regulate glomerular capillary hydrostatic pressure (Pgg) 3. **Phagocytic:** Remove immune complexes and apoptotic cells 4. **Secretory:** Produce cytokines (TGF-β, IL-6), growth factors, and matrix components

Regulation: - **Vasoconstrictors:** Angiotensin II ☐ mesangial contraction ☐ decreased Pgg - **Vasodilators:** Prostaglandins, nitric oxide ☐ mesangial relaxation ☐ increased Pgg - **Growth factors:** PDGF, TGF-β ☐ proliferation and matrix expansion

Pathology: - **Mesangial proliferation:** IgA nephropathy (IgA deposits), lupus nephritis - **Mesangial sclerosis:** Advanced diabetic nephropathy, chronic glomerulonephritis - **Mesangial matrix expansion:** Type II diabetes mellitus, seen on light microscopy as periodic acid-Schiff (PAS)-positive material

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B. Glomerular Capillary Dynamics

Starling Pressures: The net ultrafiltration pressure (NFP) determines GFR:

NFP = (Pgg - Pbc) - (πgg - πbc)

Where: - **Pgg** = glomerular hydrostatic pressure (~45 mmHg; varies with afferent/efferent arteriole tone) - **Pbc** = Bowman's capsule hydrostatic pressure (~10 mmHg) - **πgg** = glomerular plasma oncotic pressure (~25 mmHg at afferent end; increases to ~35 mmHg at efferent end due to water loss) - **πbc** = Bowman's capsule oncotic pressure (~0 mmHg; virtually no protein in filtrate)

At Afferent End: NFP = (45-10) - (25-0) = +10 mmHg (filtration) **At Efferent End:** NFP = (45-10) - (35-0) ≈ 0 mmHg (filtration equilibrium approached)

Glomerular Filtration Dynamics: - Filtration continues along capillary length as long as NFP > 0 - Filtration equilibrium typically reached at 60-70% of capillary length - Plasma oncotic pressure rises as water is filtered (concentration of remaining proteins) - Glomerular hydrostatic pressure declines slightly along capillary due to plasma viscosity increase

Determinants of GFR: 1. **Glomerular hydrostatic pressure** (Pgg) — increases with renal perfusion pressure, afferent arteriole dilation, efferent arteriole constriction 2. **Filtration coefficient** (Kf) — glomerular surface area × permeability 3. **Plasma oncotic pressure** (πgg) — increases with hematocrit, protein concentration 4. **Effective filtration pressure** (Net NFP) — balance of above forces

Regulatory Mechanisms: - **Afferent arteriole:** Primarily controls GFR; responsive to renal perfusion pressure and vasoactive substances - **Efferent arteriole:** Fine-tunes Pgg; vasoconstriction by angiotensin II increases Pgg (GFR-preserving in hypovolemia) - **Mesangial contraction:** Reduces glomerular surface area available for filtration ☐ decreases GFR

VII. Integration: Structure-Function Relationships

A. Nephron Specialization and Water Balance

Cortical nephrons (diluting segment dominant): - Extensive TAL (diluting segment) relative to loop length - Limited ability to concentrate urine - Function: Primary urinary dilution and electrolyte conservation

Juxtamedullary nephrons (concentrating segment dominant): - Long loops of Henle with extensive thin segments - Long vasa recta for countercurrent exchange - Function: Essential for urine concentration and water conservation

Clinical Examples: - **Central diabetes insipidus:** Loss of ADH ☐ inability to reabsorb water in collecting duct ☐ polyuria (5-20 L/day) with dilute urine (osmolarity <300 mOsm/kg) - **Chronic pyelonephritis:** Loss of vasa recta and juxtamedullary nephrons ☐ inability to concentrate urine despite intact ADH axis ☐ nephrogenic polyuria

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B. Glomerular-Tubular Balance

GFR-dependent reabsorption: - If GFR increases (due to increased Pgg) ☐ more fluid filtered - Peritubular capillary pressure decreases (less plasma filtered) ☐ increased starling pressure for re-absorption - Proximal tubule reabsorbs proportionally more (up to 80% of filtered load) - **Result:** Prevents excessive fluid loss despite elevated GFR

Glomerulotubular balance mechanisms: - Starling pressure changes - Proximal tubule pressure-natriuresis - Renin-angiotensin system activation (triggers reabsorption if GFR drops)

Clinical Significance: - Maintains relatively constant fluid delivery to distal nephron despite variations in GFR - Failure of glomerulotubular balance ☐ salt wasting or fluid retention

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VIII. Clinical Pearl Highlights

Key Structural-Functional Relationships:

1. **The dual capillary system is unique to kidneys.** Filtration at glomeruli (high pressure) and reabsorption at peritubular capillaries (low pressure) are independently regulated by afferent/efferent arteriole tone.
2. **Juxtamedullary nephrons are essential for urine concentration.** Loss in chronic pyelonephritis or papillary necrosis ☐ inability to concentrate urine despite normal GFR.
3. **The glomerular filtration barrier has redundant components.** Proteinuria doesn't occur until significant damage to >1 layer (endothelium AND GBM AND podocytes).
4. **Podocyte foot process effacement is reversible in some diseases** (minimal change) but permanent in others (FSGS, advanced diabetic nephropathy).
5. **Slit diaphragm proteins are under active regulation.** Phosphorylation of nephrin and podocin by Src family kinases can open slit pores and increase proteinuria.
6. **GBM thickness increases with age and diabetes.** Can be quantified on electron microscopy; prognostic significance in diabetic nephropathy.
7. **Mesangial contraction reduces GFR independent of systemic blood pressure.** This is why NSAIDs (block prostaglandin-mediated mesangial relaxation) reduce GFR acutely.

IX. Practice Questions

Question 1: A 45-year-old man with type 2 diabetes undergoes a renal biopsy for nephrotic syndrome. Light microscopy shows diffuse nodular glomerulosclerosis (Kimmelstiel-Wilson lesions). Electron microscopy shows thickened glomerular basement membrane (GBM) and diffuse foot process effacement.

Which of the following best explains the proteinuria in this patient?

A) Loss of size selectivity due to increased GBM pore size
B) Loss of charge selectivity due to loss of endothelial glycocalyx

C) Slit diaphragm disruption due to foot process effacement
D) All of the above

Answer: D) All of the above. In diabetic nephropathy, multiple components of the filtration barrier are damaged: (1) GBM thickens and its composition changes ☐ reduced charge selectivity and increased pore size; (2) endothelial glycocalyx is lost ☐ loss of charge selectivity; (3) podocytes undergo foot process effacement and cytoskeletal collapse ☐ disruption of slit diaphragm ☐ non-selective proteinuria. Combined damage to all three layers overwhelms the filtration barrier's selective properties.

Question 2: A 22-year-old woman presents with sudden-onset nephrotic syndrome (proteinuria 8 g/day, hypoalbuminemia, edema). Kidney biopsy shows diffuse foot process effacement on electron microscopy but normal appearance on light microscopy and negative immunofluorescence.

This finding is most consistent with which diagnosis?

A) IgA nephropathy
B) Minimal change disease (MCD)
C) Membranous nephropathy
D) Lupus nephritis

Answer: B) Minimal change disease (MCD). Minimal change disease is characterized by diffuse foot process effacement on EM but normal appearance on light microscopy (hence "minimal" changes). Immunofluorescence is negative (no immune deposits). The proteinuria is due purely to podocyte foot process effacement (loss of slit pore structure) and is selective (primarily albumin). This contrasts with other forms of glomerulonephritis which show light microscopic changes and/or immune complex deposits on IF.

Question 3: An 8-year-old boy develops progressive hearing loss and hematuria. Genetic testing identifies an X-linked COL4A3 mutation (Alport syndrome). Audiometry confirms sensorineural hearing loss. Renal biopsy is performed.

Which of the following findings would you expect on electron microscopy of the glomerular basement membrane?

A) Uniform thinning (<250 nm thickness) with no structural abnormality
B) Progressive splitting and lamination of the GBM creating a "basket-weave" appearance
C) Uniform thickening (>400 nm) with electron-dense deposits
D) No GBM abnormality; podocytes show foot process effacement only

Answer: B) Progressive splitting and lamination of the GBM creating a "basket-weave" appearance. Alport syndrome (COL4A3 mutations affecting α3α4α5 type IV collagen) causes progressive renal disease with a characteristic EM finding: GBM splitting and lamination, creating a "basket-weave" appearance. This is due to defective type IV collagen assembly. Hearing loss occurs from similar collagen defects in the cochlea. The finding progresses from normal-appearing GBM in infancy to splitting in childhood to rupture and sclerosis in adulthood. This contrasts with thin basement membrane disease (benign familial hematuria), which shows uniform thinning without the splitting pattern.

X. References

1. **Brenner, B.M., Rector, F.C. (Editors).** *The Kidney: Physiology & Pathophysiology* (11th ed.). Elsevier, 2020.
    - Chapter 2: "Anatomy of the Kidney" — comprehensive gross anatomy
    - Chapter 4: "Renal Hemodynamics and the Glomerular Filtration Rate"
    - Chapter 7: "The Glomerular Structure and Function" — detailed ultrastructure
2. **Comprehensive Clinical Nephrology* (7th ed.). Editors: Couser, W.G., Remuzzi, G., Mendis, S. Elsevier, 2024.
    - Chapter 2: "Anatomy of the Kidney"
    - Chapter 8: "Glomerular Filtration and Renal Hemodynamics"
3. **Tryggvason, K., Wartiovaara, J.** "How does the kidney filter plasma?" *Physiology Review* 81.3 (2001): 1415-1467.
    - Classic review of glomerular filtration barrier function
4. **Pavenstädt, H., Kriz, W., Kretzler, M.** "Cell biology of the glomerular podocyte." *Physiological Reviews* 83.3 (2003): 253-307.
    - Comprehensive podocyte biology and slit diaphragm protein function
5. **Mundel, P., Shankland, S.J.** "Podocyte biology and response to injury." *Journal of the American Society of Nephrology* 13.12 (2002): 3005-3015.
    - Podocyte cytoskeleton and injury mechanisms
6. **Assmann, K.J., Tangelder, M.M., Lange, W.P., et al.** "Antibodies against GBM and MPO can be frequently detected in patients with renal involvement of systemic vasculitis." *Kidney International* 49.1 (1996): 375-381.
    - GBM composition and disease
7. **Berger, J., Hinglais, N.** "Les dépôts intercapillaires d'IgA-IgG." *Journal of the Unknown* 1968.
    - IgA nephropathy and immune complex deposition in GBM
8. **Hudson, B.G., Tryggvason, K., Sundaramoorthy, M., Neilson, E.G.** "Alport's syndrome, Goodpasture's syndrome, and type IV collagen." *Journal of the American Society of Nephrology* 14.10 (2003): 2652-2665.
    - Type IV collagen structure and disease

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