Glomerular diseases

MB 2017

The kidneys:
• eliminate metabolic waste products
• regulate fluid and electrolyte balance
• influence acid-base balance
• product the following hormones:
  – prostaglandins (which affect salt and water regulation)
  – erythropoietin (which stimulates red cell production)
  – 1,25-dihydroxycholecalciferol (which enhances calcium reabsorption from the gut)
  – renin (which increases vascular tone)

Glomeruli

• filtrate about 800 litres of plasma each day (180 litres of filtrate, most of which is reabsorbed in the tubules)

• components of the capillary wall (endothelial and epithelial cells, basement membrane) contribute to the filtration barrier

Glomeruli –molecular architecture of the filtration barrier

• Nephrin – a transmembrane protein, the major component of the slit diaphragms between adjacent foot processes; plays a critical role in maintaining the selective permeability of the basement membrane

• Mutation in nephrin are associated with abnormal leakage of plasma proteins, giving rise to the nephrotic syndrome

Normal glomerulus

Clinical terminology

• proteinuria - protein in the urine
• hematuria - blood in the urine
• urinary casts, formed in tubules - hyaline (protein loss), granular (inflammatory cells), red cells
• azotemia - elevated blood urea nitrogen (BUN) and creatinine; reflects a decreased glomerular filtration rate GFR

From Rubin’s Pathology
Lippincott Williams & Wilkins 2005
Clinical terminology

When azotemia give rise to clinical manifestations and biochemical abnormalities, it is termed uremia.

- **uremia** - renal failure (clinical syndrome of azotemia with secondary endocrine, GI (uremic gastroenteritis), cardiovascular (uremic fibrinous pericarditis) dysfunction

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Nephritic syndrome

- Results from glomerular injury
- Acute onset of usually grossly visible **hematuria** (red blood cells and red cell casts in urine)
- Mild/moderate proteinuria
- Oliguria
- Oedema and hypertension

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Nephrotic syndrome

- A glomerular syndrome characterized by heavy **proteinuria** (excretion of greater than 3.5 g of protein/day in adults)
- Hypoalbuminemia
- Hyperlipidemia and lipiduria
- Severe oedema

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Clinical terminology-cont.

- **acute renal failure** - rapid onset of decreased glomerular filtration (oliguria or anuria); it can result from glomerular injury (glomerulonephritis), vascular injury (thrombotic microangiopathy) or tubular injury
- **chronic renal failure** – characterized by prolonged symptoms of uremia, results from progressive scarring in the kidneys, with GI symptoms like nausea, vomiting, GI bleeding; **polyuria**
- **ESRD** - end-stage renal disease

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Polyuria is a condition usually defined as excessive or abnormally large production of urine (at least 2.5 L over 24 hours in adults)
Glomerular diseases

- detailed examination of the glomerulus by:
  - light microscopy MI
  - immunofluorescence IF
  - electron microscopy EM
  - close correlation with clinical information

Routine studies on biopsy specimens

- H&E and other special stains help to classify the type of glomerular disease
- Immunofluorescence identifies patterns and type of protein deposition (linear in antiGBM disease; granular—indicates immunocomplexes deposition)
- Electron microscopy detects submicroscopic defects (fusion of podocytes, damage to visceral epithelial cells)

There are three complementary classifications of glomerular diseases

- aethiological,
- immunological and
- morphological

Morphological nomenclature of glomerular injury

- diffuse: a lesion affecting all glomeruli
- focal: " involving some glomeruli
- global: " the whole glomerulus
- segmental: only part of the glomerulus
- crescentic: florid proliferation of the epithelial cells of Bowman’s capsule and infiltration of monocytes, compressing the glomerulus

Crescent glomerulonephritis

- Compressed glomerulus
Pathogenesis of glomerular disease may be categorized as follows:

• damage to the podocyte (effacement of the foot processes)
  – minimal change disease MCD
  – focal segmental glomerulonephritis FSGS
  – HIV nephropathy
• disorders of the glomerular basement membranes
  – Alport’s disease
  – diabetic nephropathy

Pathogenesis of glomerular disease may be categorized as follows (continued):

• in situ immune complex deposition (binding of antibodies to an intrinsic glomerular antigen)
  – anti-GBM nephritis
  – membranous nephropathy
• deposition of circulating immune complexes in the glomerulus and secondary inflammation
  – post-infectious glomerulonephritis
  – membranoproliferative glomerulonephritis
  – IgA nephropathy
  – lupus nephritis

Each disease: potential for overlap of pathologic features shared with other glomerular diseases

Pathogenesis of glomerular disease may be categorized as follows (continued):

• T-cell production of cytokines (cytokines cause the GMB to lose its negative charge)
• Example – minimal change disease

The glomerulus

• Consists of an anastomosing network of capillaries invested by two layers of epithelium (visceral, composed of podocytes and parietal, lining the Bowman space)
• Bowman space (urinary space) – the cavity in which plasma ultrafiltrate first collects

Glomerulus

From Rubin’s Pathology
Lippincott Williams & Wilkins 2005
The normal glomerular filtration system

- Is permeable to water and almost completely impermeable to molecules of the size and molecular charge of albumin (a 70000 kDa protein)
- This selective permeability is called "glomerular barrier" function
- The characteristics of normal barrier depend on the complex structure of the capillary wall and integrity of the basement membrane
- The podocyte is crucial to the maintenance of barrier function

Glomerular diseases presenting with nephrotic syndrome

Normal cellularity of the glomerulus and lack of immune deposits

- Minimal change
- Focal segmental glomerulosclerosis
- Membranous glomerulopathy
- Diabetic glomerulosclerosis
- Amyloid nephropathy
- Light and heavy chain deposition diseases

GLOMERULAR DAMAGE

Nephrotic syndrome

- Increased permeability of capillaries to protein
  - Proteinuria (3.5 g/24 hr)
  - Hypoproteinemina (albumin < 3 g/100 ml)
- Plasma oncotic pressure
- Compensatory synthesis of proteins and lipoproteins by liver
- Hyperlipidemia
- Fluid escapes into tissues
- Low plasma volume
- Aldosterone secretion
- Fluid retention
- Edema

Minimal change

- 65-90% of the nephrotic syndrome in children
- Idiopathic
- Associated with allergy or lymphoid neoplasm
- Pathogenesis: # a disorder of T cells (they elaborate cytokines – loss of epithelial foot processes) # mutations in the nephrin gene?
- A normal appearance under the light microscope

Minimal change

- EM: an effacement of podocyte foot processes
- There are also epithelial cell vacuolization and focal detachments
- A normal appearance under the light microscope

Minimal change

Clinical course:

- The insidious development of the nephrotic syndrome
- No hypertension
- Selective proteinuria (alb>glob)
- More than 90% of patients respond well to corticosteroids
**Minimal change**

From *Rubin’s Pathology*, Lippincott Williams & Wilkins 2005

**Focal segmental glomerulosclerosis (FSGS)**

- Common in children (causes 10% of nephrotic syndromes) and adults (15%)
- Focal (some glomeruli) and segmental (portion of single glomerulus) scarring or sclerosis
- Increased matrix or adhesion to Bowman’s capsule
- Primary - idiopathic
- Secondary (e.g., diabetes, HIV, heroin abuse)
- Poor prognosis: commonly progresses to chronic renal failure (CRF); 50% ESRD

**Membranous glomerulopathy**

- Slowly progressing; form of chronic immune complexes nephritis (85%)
- M:F
- Idiopathic (15%) or secondary to autoimmune or infectious diseases (malaria, hepatitis B), heroin abuse, lymphomas, SLE
- Accumulation of the immune complexes in the subepithelial zone
- MI: capillary wall thickening without inflammation
- IF, MI: projections of the BM around deposited complexes (IgG and C3)
- Variable prognosis: 25-40% of patients progressing to ESRD

**Diabetic nephropathy**

- A long-term, insidious complication of diabetes mellitus. It is characterized clinically by the onset of microalbuminuria, progressing to overt nephrotic-range proteinuria, and a steady decline in the glomerular filtration rate and elevation of systemic blood
Diabetic nephropathy

- It is the most common cause of chronic renal failure in the United States and accounts for more than one-third of patients enrolled in long-term dialysis.

Diabetic glomerulosclerosis DG

- Diabetes produces vascular sclerosis of small vessel throughout the body.
- Half of diabetic patients develop DG.
- One third of all patients with DG develop chronic renal failure.

Diabetic glomerulosclerosis - pathogenesis

- Glycosylation -of the basement membranes (increases cells permeability to proteins); - of the arterioles (arteriolosclerosis).
- Osmotic damage to endothelial cells (glucose is converted into osmotically active sorbitol-water enters the cells causing damage).
- Increased deposition of type IV collagen in mesangium and glomerular and tubular cells membranes.

Diabetic glomerulosclerosis DG

MI:

- diffuse global thickening of the glomerular basement membrane and matrix expansion.
- Kimmelstiel-Wilson nodules: hyaline round accumulation in glomeruli.
- Exudative lesions: capsular drops and fibrin caps.
- Additional changes: chronic pyelonephritis (inflammation, fibrosis, thyroidization, presence of protein material within renal tubules).

In diabetes, basement membranes of majority of capillaries in the body are thickened by deposits of nonenzymatic glycosilated proteins (diabetic microangiopathy): retinopathy, coronary arteries, and peripheral vessels.

- The deposits appear diffusely on the basement membranes of capillary loops of the glomeruli, as well as on basement membranes of tubules and arterioles.
In nodular diabetic glomerulosclerosis, PAS-positive nodular deposits (containing mucopolysaccharides, fibrils and collagen) may appear in the mesangial space, at the periphery of the glomerulus, pushing the capillaries. The lesion is focal (glomeruli are not entirely affected), and some of them are spared. This pattern is also called Kimmelstiel-Wilson lesion.

The specific glomerular lesions associated with diabetes mellitus were first recognized by Kimmelstiel and Wilson in 1936, and since then, they are referred to as Kimmelstiel-Wilson (KW) nodules.

Nodular glomerulosclerosis - the Kimmelstiel-Wilson lesion of diabetes mellitus. Nodules of pink hyaline material form in regions of glomerular capillary loops in the glomerulus. This is due to a marked increase in mesangial matrix from damage as a result of non-enzymatic glycosylation of proteins.

Ovoid or spherical, hyaline, sometimes laminated deposits of mucopolysaccharides, lipids, and fibrillar proteins. They are located in mesangium in periphery of glomerular tuft.

Exudative lesion - capsular drops: accumulations between Bowman’s capsule and the parietal cells. Occasionally seen in hypertension.
Fibrin caps (exudative lesions)

- deposits of condensed leaked plasma proteins overlying peripheral capillaries between endothelial cell and basement membrane
- (also occur in non-diabetic disease)
- exudative lesions (fibrin caps, capsular drops) do not correlate with renal failure

„thyroidization”

Diabetic nephropathy

Chronic pyelonephritis: inflammation in the interstitium, fibrosis, atrophy of the renal tubule (”thyroidization”).

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Tubulointerstitial nephritis TIN

- A group of inflammatory diseases that primarily involve the interstitium and renal tubules. The glomeruli are spared or affected late in the course
- In most cases the renal pelvis is involved – ”pyelonephritis” (bacterial)
- „interstitial nephritis” – reserved for cases of TIN that are nonbacterial in origin (drugs, viral, immune)

TIN

- Acute pyelonephritis – suppurative inflammation caused by bacterial infection
- Chronic pyelonephritis – interstitial inflammation and scarring/deformity of the pelvicalyceal system
ESRD

- Gross - diffuse fine granularity of cortical surface (nephrosclerosis)
- Microscopic - globally sclerotic glomeruli, dilated tubules resembling thyroid follicles, interstitial fibrosis

**Amyloid nephropathy**

- renal involvement in 80 - 90% of cases of secondary amyloidosis
- amyloid deposits involve the glomerulus, arteries, interstitial areas
- AL amyloid - plasma cells - chemotherapy
- AA amyloid - colchicine
- MI:
  - eosinophilic deposits involving mesangium, capillary walls
  - PaS and silver negative

**Glomerular diseases presenting solely with hematuria**

- Hereditary nephritis (Alport syndrome)
- Thin glomerular basement membrane nephropathy = Benign familial hematuria
Hereditary nephritis (Alport syndrome)

A basement membrane nephropathy caused by a defect in type IV collagen, which leads to a progressively sclerosing glomerular disease

- Mutation of the alpha-5 chain of type IV collagen (COL4A5 gene)
- Inherited in an X-linked fashion
  - Males develop end-stage renal disease (ESRD) by age 40
  - Females develop hematuria
- Additional findings: ocular and ear defects

Histology:
- Hypercellularity of the glomeruli to sclerosis
- Accumulation of foamy macrophages,

Symptoms:
- Chronic proteinuria, ESRD

EM diagnosis:
- Thickening of the GBM

Management of syndrome: treatment of symptoms

ESRD

Sclerotic glomerulus filling the entire Bowman's space

PaS stain

Thin glomerular basement membrane nephropathy

- Hereditary GBM disorder
- Asymptomatic microscopic hematuria
- Various mutations in collagen genes
- Diagnosis: EM

Glomerular diseases presenting with nephritic syndrome

- Acute postinfectious glomerulonephritis
- Type I membranoproliferative glomerulonephritis
- Type II membranoproliferative glomerulonephritis (Dense Deposit Disease)
- Lupus nephritis
- IgA nephropathy (Berger disease)
Acute postinfectious glomerulonephritis
The most common childhood renal disease caused by infection with group A (beta-hemolytic) streptococci or other bacteria
• Patients demonstrate pharyngeal or skin infections before the onset of renal symptoms
• Immune complex deposition in the kidney:
  – entrapment of circulating preformed complexes or
  – antibody reaction to bacterial antigens trapped in the glomerulus

MI: hypercellular glomeruli (proliferation of mesangial cells and matrix), influx of neutrophils, narrow Bowman space
IF: deposits of IgG and C3 along the capillaries and in the mesangium
EM: subepithelial „humps”

Treatment of symptoms, the majority of patients recover within months

Hypercellularity with many neutrophils

Membranoproliferative glomerulonephritis MPGN
it’s not a ONE disease: it’s a description of a pattern of reaction to a variety of causes, like bacterial endocarditis or osteomyelitis, systemic connective tissue disorders, drugs or unknown
Membranoproliferative glomerulonephritis MPGN Type I
- 5-10% of cases of idiopathic nephrotic syndrome in children and young adults
- Immune complexes formation against foreign antigens that subsequently localize to the mesangium and subendothelial region
- MI: hypercellular, hyperlobulated glomerulus, duplication of the GBM
- The prognosis is poor: 20% of patients develop crescentic disease
- 50% ESRD after 10 years

Membranoproliferative glomerulonephritis MPGN Type II
Dense deposit disease
- Extensive localization and activation of the complement in the GBM
- MI like type I
- Overall worse prognosis

Dense deposit disease
Mesangial expansion and double contour of capillaries

Lupus nephritis (secondary glomerular disease)
- Immune complexes in SLE damage basement membranes
- **PROGNOSIS:**
  - 25% of overall patients progressing to ESRD within 5 years
**Lupus nephritis**

**CLASSIFICATION**
- class I: gl appear normal
- class II: subendothelial immune complexes
- class III: focal proliferative GN
- class IV: diffuse proliferative GN (>$50\%$ of glomeruli - the most common type)
- class V: membranous GN
- class VI: chronic sclerosis disease

**WHO Classification of Lupus Nephritis**

<table>
<thead>
<tr>
<th>CLASS</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Minimal Mesangial Glomerulonephritis - histologically normal on light microscopy but with mesangial deposits on electron microscopy</td>
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<tr>
<td>II</td>
<td>Mesangial Proliferative Lupus Nephritis - typically responds completely to treatment with corticosteroids</td>
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<tr>
<td>III</td>
<td>Focal Proliferative Nephritis - often successfully responds to treatment with high doses of corticosteroids</td>
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<tr>
<td>IV</td>
<td>Diffuse Proliferative Nephritis - may respond to corticosteroids and immune suppressant drugs</td>
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<tr>
<td>V</td>
<td>Membranous Nephritis - characterized by extreme edema and protein loss</td>
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<tr>
<td>VI</td>
<td>Glomerulosclerosis</td>
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**IgA nephropathy (Berger disease)**

- One of the most common causes of recurrent microscopic or gross hematuria and the most common glomerular disease revealed by renal biopsy worldwide
**IgA nephropathy (Berger disease)**

- deposition of IgA in the mesangium with complement activation
- the mechanism is unknown
- affects children and young adults (15-30)
- Frequently occurs after respiratory or GI tract infection in genetically susceptible individuals;
- gross or microscopic hematuria

**PROGNOSIS:**

- Slow progression to chronic renal failure occurs in 25-50% of cases over a period of 20 years

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**Chronic glomerulonephritis**

- The unfortunate outcome of various types of glomerular diseases
- Advanced scarring (HYALINIZATION AND OBTURATION) of the glomeruli