OBJECTIVES

- Normal kidney
- Diabetic nephropathy.
- Nephrotic syndrome.
- Nephritic syndrome.
- Rapidly progressive GN.
- Chronic GN.
- Acute /chronic renal failure

The glomerular capillary wall consists of

1- Endothelial cell
   Single cell for each capillary with fenestrated cytoplasm.

2- Epithelial cell
   The visceral layer of Bowman’s capsule with foot processes.

3- Mesangial cell
   in the centre of the glomerulus. They secrete mesangial matrix.

Natural History of Diabetic Nephropathy

Classification of Kidney Diseases: etiology

Glomerular

vascular

Tubulo-Interstitial

Primary

Systemic

Hereditary

SLE, DM, amyloid, PAN, Wegener’s

H-S Purpura
DIABETIC NEPHROPATHY

GENERAL
- The kidneys are prime targets of diabetes.
- Diabetic nephropathy is the leading cause of chronic renal failure in the industrialised world.
- It is also one of the most significant long-term complications in terms of morbidity and mortality for individual patients with diabetes.

Over 40% of new cases of end-stage renal disease (ESRD) are attributed to diabetes.

LESIONS
- glomerular lesions.
- renal vascular lesions, mainly arteriolosclerosis.
- pyelonephritis, including necrotizing papillitis.

RISK FACTORS
1. DM Type & Duration
   - 20% of Type I after 20 years
   - 40% of Type II any duration
2. Poor diabetic control
3. Hypertension
4. Smokers
5. Family history

STAGES OF CHRONIC KIDNEY DISEASE

<table>
<thead>
<tr>
<th>STAGE</th>
<th>GFR ml/min/1.73m²</th>
<th>Glomerular Filtration Rate</th>
<th>Stage 1 Kidney damage normal function</th>
<th>Stage 2 Kidney damage mild ↓ function</th>
<th>Stage 3 Kidney damage moderate ↓ function</th>
<th>Stage 4 Kidney damage severe ↓ function</th>
<th>Stage 5 Kidney failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;90</td>
<td>130</td>
<td>Slight kidney damage w normal/↑ filtration</td>
<td>Mild ↓ in kidney function</td>
<td>Moderate ↓ in kidney function</td>
<td>Severe ↓ in kidney function</td>
<td>Kidney failure</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>15</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

STAGE I
(Very early diabetes)
1. ↑ demand → ↑ (GFR).
2. Hyperglycemia leads to ↑ kidney filtration
   - osmotic load
   - toxic effects of ↑ sugar levels on kidney cells
3. enlarged kidneys

STAGE II
(Developing diabetes - clinically silent phase)
- Continued hyper filtration & hypertrophy
- GFR remains elevated or returned to normal.
- Glomerular damage progress to significant microalbuminuria (small but above-normal level of the protein albumin in the urine).
- Significant microalbuminuria will progress to end-stage renal disease (ESRD).
- All diabetes patients should be screened for microalbuminuria on a routine basis.

STAGE III
(overt, or dipstick-positive diabetes)
- Glomerular damage has progressed to clinical albuminuria.
- BM thickening due to AGEP
- The urine is "dipstick positive," containing more than 300 mg of albumin in a 24-hour period.
- Hypertension typically develops during stage

STAGE IV
(late-stage diabetes) - GFR has fallen to <10 ml/min.
- Renal replacement therapy is needed.
   - haemodialysis
   - peritoneal dialysis
   - kidney transplantation

STAGE IV
ESRD
- Glomerular damage continues, with ↑ protein albumin in the urine.
- Kidneys’ filtering ability began to decline steadily; BUN and creatinine began to ↑
- GFR ↓ about 10% annually.
- Almost all patients have hypertension at stage 4.

**PATHOGENESIS**

**I. GLOMERULAR HYPER FILTRATION**

- Glucose provides an osmotic diuretic effect
  - Result is ↑ renal filtration, leading to **glomerular hypertrophy**
- Glomerular pressure ↑
- Kidney responds with hypertrophy of epithelium & endothelium
- Accelerates glomerular cell failure
- Result is premature glomerulosclerosis

**II. METABOLIC CHANGES**

- Oxidant Stress - related to abnormal metabolism
- Non-enzymatic glycosylation of macromolecules - particularly basement membrane (BM)
  - ↑ type IV collagen
  - ↓ proteoglycans
- Both changes:
  - ↓ the permeability of capillaries
  - disturb leukocyte diapedesis, oxygen diffusion, nutrition and metabolic waste removal.

**III. HUMORAL IMBALANCES**

- Insulin Deficiency
- ↑ Glucagon Concentrations
- ↑ Transforming Growth Factor (TGF)-β
- ↑ angiotensin II
- Abnormally regulated thromboxanes & endothelins

1. Stimulates extracellular matrix synthesis
2. Inhibits extracellular matrix degradation
3. Up regulates protease inhibitors
4. down regulates matrix degrading enzymes
5. Stimulates synthesis of integrins (matrix receptors)
6. Key role in basement membrane thickening, & mesangial matrix expansion

**Role of TGF-β**

7. TGF-β ultimately increases extracellular matrix proteins.
8. TGF-β stimulates production of several growth factors including
  - basis fibroblast growth factor (bFGF)
  - platelet derived growth factor (PDGF)
  - that stimulate the formation of extracellular matrix (ECM) proteins.

**Major histologic changes occur in the glomeruli of persons with diabetic nephropathy.**

1. Mesangial expansion
2. GBM thickening throughout their entire length.
3. Glomerular sclerosis due to intraglomerular HTN (renal VD and ischemic injury induced by hyaline narrowing of the vessels supplying the glomeruli).
1. **NEPHROTIC SYNDROME**

**CLINICAL PICTURE**

1. Proteinuria (more than 3.5 gm/day).
2. Hypoproteinemia (less than 3gm/dl).
3. Hypercholesterolemia.
4. Edema: massive generalized oedema. It may be associated with ascitis and pleural effusion.
5. Hyperlipidaemia and hyperlipiduria
   - due to ↑ hepatic synthesis of lipoproteins
   - Accompanied by
     - sodium & water retention
     - anemia
     - vulnerability to infection
     - thrombotic complications.

**PATHOGENESIS**

Site of the lesion: Wall of the glomerular capillary especially the basement membrane leading ↑ permeability to plasma proteins.

**CAUSES**

<table>
<thead>
<tr>
<th>Primary glomerular diseases</th>
<th>Secondary glomerular diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Foot process disease.</td>
<td>• Amyloidosis.</td>
</tr>
<tr>
<td>2. <strong>Minimal change</strong></td>
<td>• Diabetic glomerular disease.</td>
</tr>
<tr>
<td>glomerulopathy.</td>
<td>• Systemic lupus erythematosus</td>
</tr>
<tr>
<td>3. Focal-segmental</td>
<td>• Drugs</td>
</tr>
<tr>
<td>glomerulosclerosis.</td>
<td>• Infections</td>
</tr>
<tr>
<td>4. Membranous</td>
<td>• Malignancy</td>
</tr>
<tr>
<td>glomerulopathy.</td>
<td></td>
</tr>
<tr>
<td>5. Membranoproliferative</td>
<td></td>
</tr>
<tr>
<td>glomerulonephritis</td>
<td></td>
</tr>
</tbody>
</table>

**Minimal change G.N**

- Most common cause of nephrotic syndrome in children.
- No changes by ordinary microscope.
- By E/M there is fusion of foot processes of podocytes

**Membranous Glomerulonephritis**

- Most common cause of nephrotic syndrome in adults.
- There is thickening of the basement membrane with subepithelial deposits of IgG and C3 and fusion of the epithelial foot processes.
2. NEPHRITIC SYNDROME
Damage of the glomerular capillary wall with ↓ filtration and escape of red cells with urine

<table>
<thead>
<tr>
<th>CAUSES</th>
<th>URINARY CHANGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Primary glomerular diseases</td>
<td>1. Oliguria</td>
</tr>
<tr>
<td>✓ Acute diffuse proliferative (post streptococcal) glomerulonephritis</td>
<td>2. Dark (smoky, coca cola) urine.</td>
</tr>
<tr>
<td>2. Secondary glomerular diseases</td>
<td>3. High specific gravity (1035 or more)</td>
</tr>
<tr>
<td>✓ Systemic lupus erythematosus</td>
<td>4. Contains RBCs and pus cells.</td>
</tr>
</tbody>
</table>

3. RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS
Site of the lesion:
Epithelial proliferation of the parietal layer of Bowman’s capsule forming crescents.

It is severe, rapid onset of
- Hematuria
- Oliguria or anuria
- Hypertension
- Variable proteinuria & edema

4. CHRONIC GLOMERULONEPHRITIS
It is the end stage of most glomerular diseases.

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>GROSSLY</th>
<th>M/E</th>
</tr>
</thead>
</table>
| 1. Moderate HT               | ✓ Kidney is contracted, ✓ Firm, ✓ Adherent capsule.  
| 2. Hypertensive retinopathy  | Finely granular Surface with small cysts.  
| 3. ↑ blood urea and creatinine | ✓ Cortex and medulla are not demarcated   
| 4. Normocytic anemia         |                                             | • Glomeruli: Some are fibroed and hyalinized & others show compensatory hypertrophy
|                              |                                             | • Tubules: Tubular atrophy               
|                              |                                             | • Interstitium: Interstitial fibrosis & chronic inflammatory cellular infiltration.  
|                              |                                             | • Blood vessels : hypertensive changes   

[Diagram of glomeruli and Bowman’s capsule with crescent formation]
5. RENAL FAILURE

**DEFINITION**

<table>
<thead>
<tr>
<th>UREMIA</th>
<th>AZOTEMIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>The clinical signs &amp; symptoms of renal failure (especially, the clinical problems associated with chronic renal failure.)</td>
<td>means ↑ urea and/or creatinin in blood from any cause.</td>
</tr>
<tr>
<td>When kidney function falls below 10% of normal, uremia becomes apparent</td>
<td></td>
</tr>
</tbody>
</table>

**ACUTE RENAL FAILURE (ARF)**

- **SUDDEN AND SEVERE REDUCTION** in previously normal renal function, may result from primary renal disease.
- Frequently have:
  - Metabolic acidosis
  - Hyperkalemia
  - Secondary effects on other organ systems
  - Disturbance in body fluid homeostasis

**CHRONIC RENAL FAILURE (CRF)**

- **GRADUAL & PROGRESSIVE REDUCTION** in renal function.
- Failure may occur over weeks, months or even years.

<table>
<thead>
<tr>
<th>CAUSES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal (Primary Kidney Disease)</td>
<td>Pre-renal (inadequate blood supply)</td>
</tr>
<tr>
<td>• Congenital</td>
<td>• Heart failure – low cardiac output</td>
</tr>
<tr>
<td>• Acquired (glomerular/tubulointerstitial)</td>
<td>• Low renal perfusion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EFFECTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CARDIOPULMONARY</strong></td>
<td><strong>GASTRO-INTESTINAL</strong></td>
</tr>
<tr>
<td>• High blood pressure with its problems</td>
<td>1. Nausea and vomiting</td>
</tr>
<tr>
<td>• Fibrinous pericarditis</td>
<td>2. Gi bleeding</td>
</tr>
<tr>
<td>• Accelerated atherosclerosis</td>
<td>→uremic gastritis</td>
</tr>
<tr>
<td></td>
<td>→pinpoint bleeds in the stomach mucosa, uremic colitis.</td>
</tr>
<tr>
<td></td>
<td>3. Pancreatitis</td>
</tr>
<tr>
<td></td>
<td>4. Poor appetite &amp; altered sense of smell (everythg smells bad).</td>
</tr>
<tr>
<td></td>
<td>5. Alterations in sense of taste (low serum zinc)</td>
</tr>
</tbody>
</table>

**Pathways Leading To Progressive Renal Failure**

- Renal growth factor & cytokine activation
- Glomerular hypertension
- Transdifferentiation of renal cells to fibroblast phenotype
- Fibrogenesis
- Influx of monocytes and macrophages
- Progressive Loss of Filtration Surface Area
- Renal injury
- GFR
- Systemic hypertension
- T Tubulotubular protein uptake
- Renal microvascular injury
- Thyg's

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www.hypertensiononline.org