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Diabetic Nephropathy

★ **Objectives:**

1. Definition
2. Importance/Epidemiology
3. Pathogenesis
4. Natural History
5. Risk factors and prevention
6. Treatment strategies

★ **Resources Used in This lecture:**

Doctor's note , Davidson, clinical step up,Master the boards

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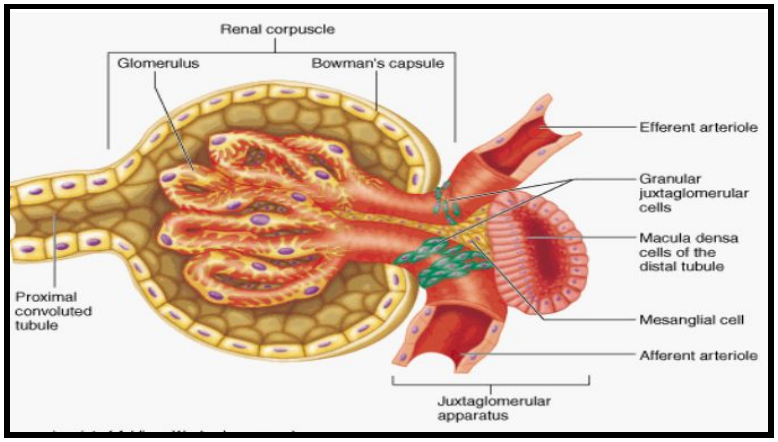
Introduction

- Uriniferous Tubule is the functional unit of the kidney .
- It contains 1- Nephrons 2- Collecting Tubules.
- A normal kidney contains 1.5 nephrons.
- Renal corpuscle in the nephrons contain:

1-Glomerulus: globular shape structure composed of tufted capillaries that are actively involved in the filtration of fluid in the blood to form urine.

2- Bowman's Capsule:Parietal layer→ urinary space and visceral layer or podocytes 3- Mesangial Cells: intraglomerular cells



Epidemiology

Diabetic nephropathy is the second cause of ESRD after HTN In saudi Arabia according to study done in 2015.

- ❏ 40 % of Saudi population between (age 30-70) have abnormal glucose metabolism→ It's Epidemic
- ❏ The prevalence of Diabetic nephropathy in DM2 Saudi population is 31.8 % .
- ❏ The prevalence ESRD in DM2 in SA 1.5- 5%.
- ❏ 7-10 % of type II Diabetic patient in saudi arabia will have ESRD after 20-30 years.

DEFINITION: Nephro= Kidney Pathy=disease (kidney disease caused by diabetes)

The functional and structural renal changes that happen in the context of Diabetes mellitus.

- ❏ Functional (albuminuria and ↑ Cr levels) and structural (Mesangial expansion,GBM[1]thickening and glomerulosclerosis).
- ❏ Diabetic nephropathy is considered microvascular complication of DM.

[1] Glomerular basement membrane

Pathophysiology & Clinical Presentation

<table>
<tr><th>Mechanism</th><th>Clinical presentation</th></tr>
<tr><td>

1- Increase Pressure state

1- Afferent Arteriolar Dilation due to increase the release of PG[2] and NO[3].(Normally NO and PG dilate afferent arteriole)

2-Efferent Arteriolar Constriction due to activation of RAAS.

Since the activation of RAAS usually when there is hypoperfusion to kidneys, Why would efferent constrict when there is already hyperperfusion from afferent arteriole dilatation?

Hyperglycemia results in direct activation of RAAS and increase release of Nitric oxide and prostaglandins.

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1-Increased GFR

Due to increase pressure state and dilation of Afferent arteriole more blood will be filtered.

-First stage is **Asymptomatic.**

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2- Mesangial Expansion

- Due to increased pressure this will result in trauma and damage to the mesangium glomerular.
- Result in secreting Cytokines and oxygen free radicals→ causing inflammation and endothelial dysfunction.

★ **Hyperglycemia and AGEs (Advanced glycation end products) is harmful also participate in this process.**

★ **Hyperglycemia also increase the expression of transforming growth factor-beta (TGF) and vascular endothelial growth factor (VEGF).**

- All will ultimately result in → Thickening of basement membrane (hypertrophy) and matrix accumulation within the mesangium causing→ " mesangial expansion"
- Causing the following outcome:
  1- ↓ surface area of glomeruli for filtration.
  2- Dilation of fenestration between podocyte.

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2- Detectable Proteinuria

-Mesangial expansion will result in damage causing increase space between podocyte in glomerular → leakage of protein.

Depending on progression:

<table>
<tr><th>Microalbuminuria</th><th>Macroalbuminuria</th></tr>
<tr><td>

- Small amount of albumin 30-300 mg/dl
- Creatinine (ACR) ratio : 3 mg/mmol
- Can't be detected by dipstick.
- Glucose control can reverse this stage.
- It takes time 1 to 5 years microalbuminuria to advance to full blown proteinuria

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- >300 mg/dl
- Detected by dipstick
- Glucose control do not significantly affect in this stage.
- Albumin to creatinine ratio (ACR) : 3000 mg/g = 300 mg/mmol.

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3-Nephron Ischemia

Caused by the following previous factors:

1- Constriction of efferent arteriole→ ↓ flow to supply nephron.

2- Cytokine and free radicals not only damaging the mesangium → also cells in the tubules and nephron vasculature.

All resulting in ischemia (cell death) and atrophy of vasculature that support glomerulus.

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3- Last stage is Decrease in GFR

-Due to nephron ischemia → cause one nephron death→ decrease filter of this nepheron→ more nephrons die→ decrease overall GFR→ more than 3 months causes→ chronic kidney disease→ Lastly leading to end stage renal disease(ESRD).

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[2] Prostaglandins
[3] Nitric oxide

Note:

- Nodular glomerulosclerosis⟶ (kimmelstiel-Wilson syndrome) hyaline deposition in one area(usually caused due to efferent involvement of destruction/sclerosis)⟶ common in DM.
- Diffuse glomerulosclerosis⟶ hyaline deposition is global(usually caused due to afferent involvement of destruction/sclerosis)⟶ common among HTN (would commonly lead to renal failure).
- Normal urine excretion of protein about < 150 mg / 24 hours and albumin < 30 mg /24 hours.
- It usually takes 1 to 5 years microalbuminuria to advance to full blown of proteinuria.
- HTN usually develops during transition between microalbuminuria and progressive proteinuria.
- Persistent HTN and proteinuria ⟶ leads to renal insufficiency and eventually ESRD.

Risk Factors:

- ❑ Long Duration of DM
- ❑ Poor glycemic control
- ❑ Age *increases with age.
- ❑ Genetic factors and Race (such british people).
- ❑ Hypertension
- ❑ Smoking
- ❑ Dyslipidemia

- People with Type 1 DM Having diabetic Nephropathy mostly >90%will have diabetic retinopathy.
- People with Type 2 DM Having diabetic Nephropathy 50% will have diabetic retinopathy.

Management and Prevention

- ❑ Control the glucose level.
- ❑ Lower the BP to 130/80.
- ❑ Reduce Cardiovascular risk. (because the atherosclerosis is highly accelerated among DM)
- ❑ RAAS blockade, independent to BP by giving ACEi/ARBs.
- ❑ Lower the LDL level to less than 100 mg/dL ⟶ give statins if needed.
- ❑ Smoking cessation.
- ❑ Lifestyle modification: Weight loss + exercise + diet restriction (Slat + protein).

- Both ARbs and ACEi can cause hyperkalemia, in the presence of renal artery stenosis it might cause marked deterioration in renal function, after initial dose check ⟶ electrolytes and renal function. Non-dihydropyridine calcium antagonist (diltiazem,verapamil)may be good alternatives.
- Dialysis should be considered ⟶ ESRD and if there is complete failure consider renal transplant.
- Once diabetic nephropathy has progressed to proteinuria, glycemic control does not significantly influence on its course. Dietary restriction of protein and ACE inhibitors are recommended.
- Patient with DM should be screened annually for microalbuminuria (since it can't be detected early by dipstick).