Diabetic Nephropathy

Objectives:

- Know what Diabetic Nephropathy means.
- Know how common is Diabetic nephropathy in Saudi Arabia and to appreciate how bad are this complications.
- Know the risk factors of Diabetic nephropathy.
- Know how to manage Diabetic nephropathy in general, and the role of BP control and ACEI/ARB medications in particular.

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- Editing file
- Feedback

Introduction to Diabetic Nephropathy

7 : 36 minutes

❖ Overview:

Functional and structural renal changes that happen in the context of Diabetes mellitus. Diabetic nephropathy is an important cause of morbidity and mortality, and is now among the most common causes of end-stage renal failure in developed countries. About 30% of patients with type 1 diabetes have developed diabetic nephropathy 20 years after diagnosis, but the risk after this time falls to less than 1% per year, and from the outset the risk is not equal in all patients. Indeed, some patients do not develop nephropathy, despite having long-standing, poorly controlled diabetes, suggesting that they are genetically protected from it. Whilst variants in a few genes have been implicated in diabetic nephropathy, the major differences in individual risk remain unexplained.

❖ Definition :

Diabetic nephropathy: is composed of **Functional** and **structural** changes that happen the context of diabetes mellitus.	
Functional changes	• Albuminuria • Progressive loss of renal function.
Structural changes	Mesangial expansion, GBM[1] thickening and glomerulosclerosis.

❖ Comparison between Microalbuminuria and Macroalbuminuria:

	Microalbuminuria **(Moderately increased albuminuria)**	**Macroalbuminuria[2]** **(Severely increased albuminuria)**
Albumin [3]	30-300 mg/dl.	More than 300 mg/dl.
Albumin to creatinine ratio (ACR)[4]	More than 30 mg / g of Creatinine. (> 30 : 1) (The normal ratio is less than 30 mg/g). The normal excretion of creatinine in urine is 1g /day	More than 300 mg / g of Creatinine. (> 300 : 1).
Urine Dipstick	Can't be detected. (You must screen for microalbuminuria) Urine dipstick can only detect albumin >300. Hence, the name micro for what's less than that.	Detected.
Glucose control	Strict glucose control can reverse this stage.	Do not significantly affect in this stage.
Extra	It takes 1 to 5 years microalbuminuria to advance to full blown proteinuria. Note that those who have microalbuminuria have a 50% chance of developing macroalbuminuria.	

We always want the ratio to be: **(albumin / 1 gram of creatinine)** , so if we get from the lab 20 mg / 0.5 g , we will multiply these numbers by 2 to get the ratio (40mg / 1g of creatinine).

[1] Glomerular basement membrane.
[2] Macroalbuminuria is known as Albuminuria and overt.
[3] Normally the albumin in urine is less than 30 mg/dl.
[4] Use the ratio to confirm because the patients could be dehydrated and have concentrated urine thus giving falsely increased albumin or the opposite (diluted urine) thus giving less albumin.

❖ Epidemiology:

The epidemiology of Diabetic Nephropathy reflect how the issue is important.

- Diabetic nephropathy is a risk factor for cardiovascular disease.
- Diabetes Mellitus is an epidemic in Saudi Arabia, with a prevalence of 23.7%.
- 14.1% have impaired fasting glucose. (Prediabetic state)
- In total 37.8% have abnormal glucose metabolism (age 30-70 year).
- A leading cause of End Stage Renal Disease (ESRD) in our society.
- Prevalence of **diabetic nephropathy** in type ll DM is estimated:
  - ➔ 10.8 % by the Saudi National Diabetes Registry (SNDR), 2014.
    Not reliable (Suspecting registration problems)
  - ➔ **31.8%** (By Alwakeel et al, Ann Saudi Med, 2011).

أسباب الفشل الكلوي النهائي عند مرضى التنقية الدموية
بيانات نهاية عام 2015م

سبب الفشل الكلوي	العدد	النسبة المئوية%
إعتلال كلوي بارتفاع ضغط الدم	6081	39%
إعتلال كلوي بداء السكري	6055	38.8%
مجهول السبب	1158	7.4%
إعتلال كبيبات الكلى البدئي	570	3.7%
إعتلال كلوي إنسدادي	364	2%
إلتهاب الأوعية	259	2%
الآفات الكلوية الوراثية	270	1.7%
تشوهات خلقية	214	1.4%
إعتلال أنبوبي خلالي مزمن	129	1%
عوالق الحمل	74	0.5%
أخرى	416	2.5%
المجموع	15590	100%

- Prevalence of diabetic nephropathy in **type ll** DM in UK & Thailand are 11.5% & 42.9%, respectively.
- The prevalence of ESRD in **type ll** DM :
  - ➔ 1.5% By the Saudi National Diabetes Registry (SNDR), Al-Rubeaan et al 2014.
  - ➔ **5%** By Alwakeel et al, Ann Saudi Med 2011

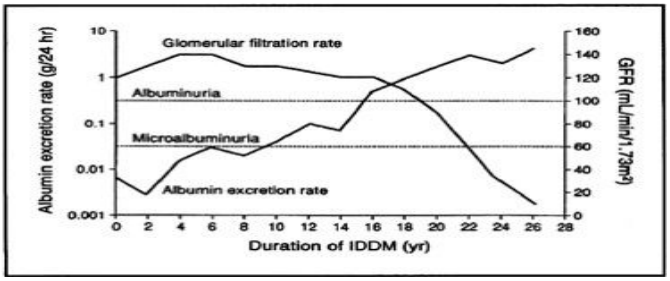
We expect it higher than 5%, but usually they die from cardiovascular complication before they reach ESRD.

- **in type I:** Prevalence of diabetic nephropathy is 7-10% with ESRD developing after 20-30 years
- In **type ll** DM, After 10 years:
  - ➔ 25% of the patient will develop MA (macroalbuminuria).
  - ➔ 5% will have proteinuria
  - ➔ 0.8% will have Creatinine $\geq$ 175 OR renal replacement therapy.

- Diabetic Nephropathy and Retinopathy:

- More than 90% of people with Type 1 DM and diabetic Nephropathy will develop diabetic retinopathy. Type 1 DM patients almost ALWAYS have retinopathy
- 50% of people with Type 2 DM and diabetic Nephropathy will develop diabetic retinopathy.

Natural History in Type 1 DM



First 5 years (0-5): Hyperfiltration (Normal kidney Function) High GFR → **Second 5 years (6-10):** Micaroalbuminuera (Normal Kidney Function) → **Third 5 years (11-15):** Macroalbuminurea (Normal kidney function) → **Fourth 5 years (16-20)** Renal Functionstarts to decline Low GFR

- **The First 5 years** of Type 1 DM there is hyperfiltration and we don't expect to have any albuminuria.
- **The Second 5 years** microalbuminuria start to appear (not detected by dipstick),ratio of albumin to creatinine between 30-300 mg/g.
- **The Third 5 years**, patient will start to have macroalbuminuria or overt nephropathy.
- **The Fourth 5 years**, GFR will be low and creatinine level will start to increase (declining in kidney function) .

So the time frame to ESRD is 20 years (it may be less if blood sugar poorly controlled and if there's high blood pressure).

The natural history is the same in type II DM if we know when it started exactly (but this is not usually the case).

Do we usually perform kidney biopsy to patients with diabetic nephropathy? the answer is no (see next cases)

Why these informations are important?

1- Let's say there's a 28 years old patient with type 1 DM diagnosed 7 years age came to your clinic with albumin : creatinine ratio of 250 mg / g. Do we need to do kidney biopsy?
- No, because he underwent with the natural course of diabetes.

2- If the same patient came to your clinic with proteinuria reaching 1.5g (1500mg), is that because of Diabetic nephropathy?
- No, because he didn't undergo with the natural course, so we will do kidney biopsy to consider the other causes of proteinuria.

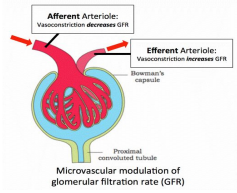
3- A 70 years old gentleman known to have diabetes type 1 for the last 25 years came to my clinic with proteinuria 2.5g and creatinine level of 180mg. Do we need to do biopsy for this patient ?
- No because he underwent with the natural course of diabetes and you not indicate any other problems or other causes of nephropathy.

4- 65 years old gentleman diagnosed to have type 2 DM 8 years ago, he referred to you because creatinine is 130g and proteinuria 2g. So will you expect creatinine and proteinuria will be high in 8 years time? - No, unless he diagnosed with DM before or not discovered.

Do we need to do kidney biopsy in this case ?
- because we don't know when this patient developed the diabetes, we will do fundus examination. If he has retinopathy most likely he will have nephropathy and we don't need to do the biopsy. But if he didn't have retinopathy we have to do kidney biopsy..

Pathogenesis and Risk Factors

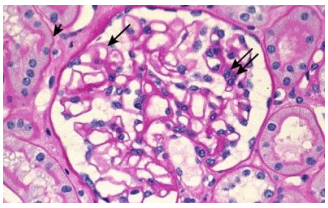
❖ Pathogenesis:



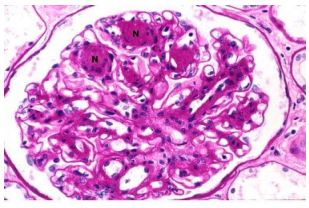
The first changes coincide with the onset of microalbuminuria include thickening of the glomerular basement membrane and accumulation of matrix material in the mesangium. Subsequently, nodular deposits are characteristic, and glomerulosclerosis worsens as heavy proteinuria develops, until glomeruli are progressively lost and renal function deteriorates.

1. Hyperfiltration & GBM Thickening:	- Hyperglycemia results in direct activation of RAAS and increase release of Nitric Oxide and Prostaglandins. - RAAS activation increases angiotensin II → **Efferent** arteriolar **constriction.** (slows blood out) - NO and prostaglandins → **Afferent** arteriolar **dilation.** (more blood in) **- Afferent dilation and efferent constriction will cause Hyperfiltration.** • Hyperglycemia increases the expression of transforming growth factor-beta (TGF-beta). (causing thickening of GBM) • Hyperglycemia and AGEs (advanced glycation end products). (Which are toxic to the kidney) • Hyperglycemia Increases VEGF expression (vascular endothelial growth factor) • HTN. (AGEs, VEGF and TGF-beta play a role in GBM thickening as well as Mesangial Expansion)
2. Mesangial Expansion:	- Chronic Increased pressure will result in trauma and damage to the mesangium → Cytokines and O2 free radicals from damage → inflammation and endothelial dysfunction → **mesangial expansion.** - AGEs, VEGF and TGF-beta also affect the mesangium and cause matrix accumulation within the mesangium " mesangial expansion" **Outcome:** ○ ↓ Surface area of glomeruli for filtration. ○ Dilation of fenestration between podocyte. ○ Protein leakage
3. Nephron Ischemia:	- Chronic Constriction of efferent arteriole will ↓ flow to supply nephron. - Cytokine and free radicals also damage cells in the tubules and nephron vasculature. - All result in ischemia (cell death) and atrophy of vasculature that support glomerulus. - **As more nephrons die, GFR decreases and eventually ESRD developed.**

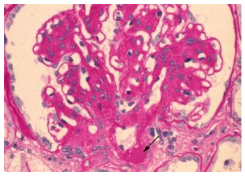
Normal glomerulus



Diabetic Nephropathy



Thickening of mesangium
Thickening of GBM
Kimmelstiel Wilson nodules



- **Nodular glomerulosclerosis (Kimmelstiel-Wilson Nodules)**: Hyaline deposition in one area of the glomerulus (usually due to efferent involvement of destruction/sclerosis)→ seen in DM

❖ Risk Factors for Diabetic Nephropathy:

- Duration of DM. (longer duration of DM → more risk to develop diabetic nephropathy)
- Poor glycemic control.
- Hypertension. (One of the most important risk factors)
- Hyperlipidemia.
- Retinopathy → Presence of other microvascular complications. (Usually precedes diabetic nephropathy)
- Smoking.
- Age. (Risk increases with age) Here age refers to the time at which DM developed, those who get it in their 50s are at a greater risk than those who get it in their 30s.
- Race. (e.g. Asians, Pima Indians)
- **Genetic factors.** (Family history of Diabetic Nephropathy)

Prevention and Treatment

❖ Prevention and Treatment Strategies:

We can prevent and delay the diabetic nephropathy by controlling and reducing the risk factors.

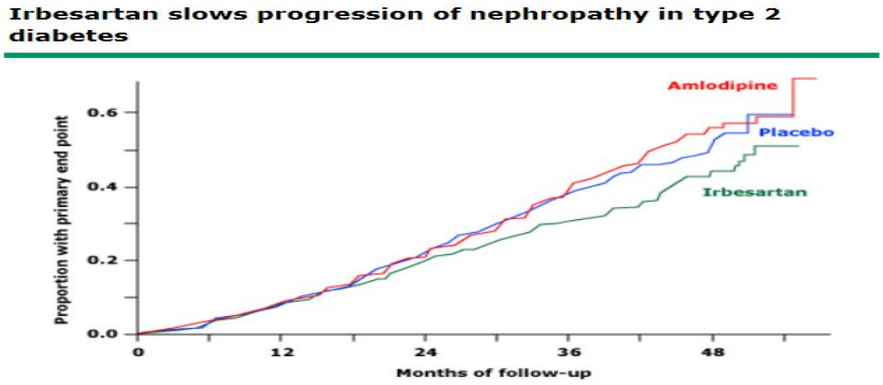
1. Good glycemic control: ($HbA_1C < 7\%$)
2. **Good BP control: BP < 130/80 (If a patient is diabetic and hypertensive and has nephropathy you should control the BP to prevent End Stage Renal Disease!)**
3. **RAAS blockade by giving ACEi/ARBs (independent of BP).**
4. Lipid lowering agent : LDL < 2.0 mmol/L. (Statins)
5. Decreasing proteinuria (by dietary restriction of proteins).
6. Smoking cessation.
7. Lifestyle modification: diet restrictions, weight loss and exercise.

- Patient with DM should be screened annually for microalbuminuria (since it can't be detected early by dipstick).
- Dialysis should be considered in ESRD, and if there is complete failure consider renal transplant.
-

❖ Why ACEi/ARBs?

- ➢ Blocking angiotensin II will dilate the efferent arterioles and hence reduce the filtration rate.
- ➢ They reduce the expression of TGF beta (unknown mechanism).

Therefore, they reduce the progression of the disease.



- The administration of Irbesartan, Angiotensin II receptor blockers (ARBs) in patients with type 2 diabetes will slow the progression of nephropathy in compared with Calcium channel blockers .

- In **type 1 diabetes**, **ACE inhibitors** have been shown to provide greater protection than equal blood pressure reduction achieved with other drugs.

3 Scenario Mentioned by Doctor :

1. **Patient is hypertensive and diabetic but has no nephropathy, do we use ACEi or ARBs?**
   I will use one of them (No evidence support that).

2. **Diabetic patient hypertensive and had albuminuria we will use it?**
   Yes use ACEi or ARBs.

3. **Diabetic patient has albuminuria but normal blood pressure we will use it ?**
   Yes but we should be careful it may cause hypotension that's why we use small doses.

Summary

<table>
<tr><th colspan="3">Diabetic Nephropathy</th></tr>
<tr><td>Definition</td><td colspan="2">Diabetic nephropathy is composed of functional and structural changes that happen in the context of diabetes mellitus.</td></tr>
<tr><td rowspan="2"></td><td>Functional</td><td>Structural</td></tr>
<tr><td>1. Albuminuria:
a. <u>Micro</u>albuminuria → (30 - 300 mg/dl)
b. <u>Macro</u>albuminuria → (> 300 mg/dl)
2. Progressive loss of renal function</td><td>1. Mesangial expansion,
2. GBM thickening
3. Glomerulosclerosis</td></tr>
<tr><td>Epidemiology (Saudi Arabia)</td><td colspan="2">• Prevalence of diabetic nephropathy in <u>type ll</u> DM is estimated 31.8 %
• Prevalence of ESRD in <u>type ll</u> DM : 5%</td></tr>
<tr><td>Natural History</td><td colspan="2">In <u>type 1</u>:
 
</td></tr>
<tr><td>Pathogenesis</td><td colspan="2">Hyperfiltration → GBM thickening → Kimmelstiel-Wilson Nodule</td></tr>
<tr><td>Risk factors</td><td colspan="2">1. Duration of DM
2. Poor glycemic control
3. Hypertension
4. Hyperlipidemia
5. Retinopathy
6. Smoking
7. Age
8. Race
9. Genetic factors</td></tr>
<tr><td>Treatment Strategies</td><td colspan="2">1. Good glycemic control → HbA1C < 7%
2. Good BP control → BP < 130/80
3. ACEi (ex: lisinopril) or ARBs (ex: Irbesartan) → independent of BP
4. Statins → LDL < 2.0 mmol/L.
5. Dietary restriction (protein and sodium).
6. Smoking cessation.</td></tr>
</table>

Examine Yourself !!

1. **Which one of the following is functional changes in diabetic nephropathy?**
    a. Mesangial expansion.
    b. Albuminuria.
    c. GBM thickening.
    d. Glomerulosclerosis.

2. **Which one of the following is histopathological change happen in diabetic nephropathy?**
    a. Duval bodies.
    b. Spindle cell.
    c. Kimmelstiel-wilson nodule.
    d. Amyloid deposition.

3. **Which of the following involve in the pathophysiology of diabetic nephropathy?**
    a. VEGF.
    b. Histamine.
    c. PDGF.
    d. Vitamin C deficiency.

4. **When the Microalbuminuria start to appear in patient with T1DM?**
    a. First 5 years(0-5).
    b. Second 5 years (6-10).
    c. Third 5 years (11-15).
    d. Fourth 5 years (16-20).

5. **Normal Albumin to creatinine ratio is:**
    a. Less than 30 mg/g.
    b. 30-300 mg.
    c. More than 300 mg/g.
    d. All of the above.

6. **Patient came to you and you suspect Diabetic Nephropathy. What is the first step of investigation you will do?**
    a. Do fundoscopic examination.
    b. Do Kidney biopsy.
    c. Start Dialysis.
    d. Give diuretics.

7. **A diabetic patient is evaluated with urine analysis which revealed microalbuminuria. What is the next step in the management of this patient?**
    a. Kidney biopsy.
    b. Start ACE inhibitors.
    c. Give insulin for better glycemic control.
    d. Start ARB with Beta Blockers.

8. **Which of the following is true in dealing with diabetic patient known to have HTN with renal impairment:**
    a. We always confirm the diagnosis of Diabetic nephropathy with renal biopsy.
    b. We start the patient on daily dialysis.
    c. Give ARBs or ACE inhibitors.
    d. Start on antibiotics to prevent complication of Diabetic foot.

9. **Which of the following is true regarding the epidemiology of Diabetes and Diabetic Nephropathy.**
    a. The prevalence of abnormal glucose metabolism in KSA is about 39.8%.
    b. The prevalence of ESRD is less than expected because patient die from cardiac events.
    c. The prevalence of Diabetes in KSA is more than in Thailand.
    d. More than 50% of patients in KSA on dialysis are due to Diabetes.

10. **Which of the following is a modifiable risk factor for Diabetic Nephropathy?**
    a. Age of onset of Diabetes.
    b. Hypertension.
    c. Duration of the Disease.
    d. Family history.

Answers:1-B, 2-C, 3-A, 4-B, 5-A, 6-A, 7-B, 8-C, 9-B, 10-B