Medicine
TEAM 437

MED437
KING SAUD UNIVERSITY

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 particular.

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Resources :

- 437 slides | Same of 436 lecture
- Teamwork 436
- Doctor notes | Dr.Mohammd Alkhowaiter
- Oxford handbook of clinical medicine
- Step-up to medicine

Introduction to Diabetic Nephropathy

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** renal changes that happen in the context of diabetes mellitus.

Functional Changes

1- Albuminuria (presence of albumin in urine)

2- Progressive loss of renal function.

(Increase in creatinine or decline in GFR.)

Structural Changes

1- Mesangial expansion.

2-GBM(glomerular basement membrane) **thickening.**

3- Glomerulosclerosis.

4- Nodular formation.

Comparison between Microalbuminuria and Macroalbuminuria:

How can I estimate number of albumin in the urine ?
By albumin : creatinine ratio in urine .

	Microalbuminuria (Moderately increased albuminuria)	**Macroalbuminuria** (Severely increased albuminuria)
Albumin	30-300 mg/dl.	More than 300 mg/dl.
Albumin to creatinine ratio (ACR)[4]	More than 30 mg / g of Creatinine. > 3 mg/mmol 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.
Note	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).
Normally the albumin in urine is less than 30 mg/dl.
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.

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.

Epidemiology:

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

- Diabetic nephropathy is a risk factor for cardiovascular disease. (Ischemic heart 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 II DM is estimated: Will all the patients with DM develop diabetic nephropathy ?
  - ➔ 10.8 % by the Saudi National Diabetes Registry (SNDR), 2014.

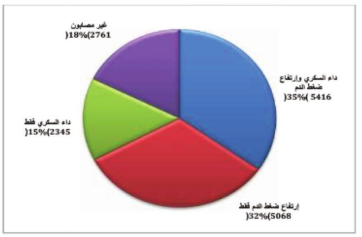
  Not reliable (Suspecting registration problems) underestimated study
  - ➔ **31.8%** (By Alwakeel et al, Ann Saudi Med, 2011).(more reliable)

- 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 ≥ 175 OR renal replacement therapy.

إنتشار داء السكري وإرتفاع ضغط الدم عند مرضى التنقية الدموية
بيانات نهاية عام 2015



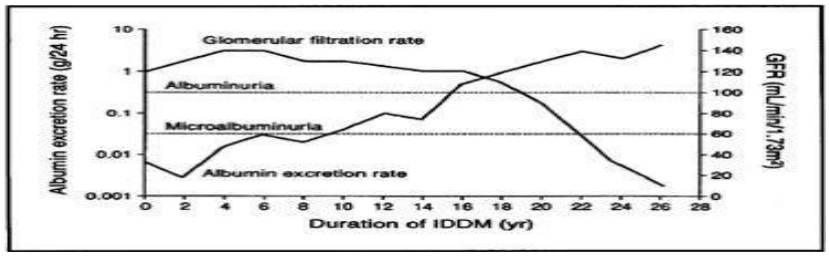
أسباب الفشل الكلوي النهائي عند مرضى التنقية الدموية
بيانات نهاية عام 2015م

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%
الأفات الكلوية الوراثية	270	1.7%
تشوهات خلقية	214	1.4%
إعتلال أنبوبي خلالي مزمن	129	1%
عواقب الحمل	74	0.5%
أخرى	416	2.5%
المجموع	15590	100%

Extra:

Progression in diabetic nephropathy. Strict glycemic control has been shown to slow or prevent progression from microalbuminuria to proteinuria. This is the critical stage (marked by star) once proteinuria develops, glycemic control does little to control the course and will eventually lead to ESRD.

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- Ahmad is 20 years old gentleman,known to have DM type 1, who was diagnosed 5 years ago, he was referred to you because of high creatinine = 170, and the primary care physician asks you if that is due to diabetic nephropathy ? - No, It is not due to diabetic nephropathy. I will need to biopsy the patient, because he is not following the natural history of the disease, so I need to exclude other causes.

2- 65 years old gentleman who is known to have type 2 DM for the last 20 years, he was referred to you for the first time because of high creatinine = 170 and proteinuria is 2000 mg / g , and he ask you " do you think this is due to diabetic nephropathy?"- yes, because of the duration. No need to do kidney biopsy, because it is likely diabetic nephropathy since he is following the natural history of the disease.

3- 30 years old gentleman known to have type 2 DM , he was referred to you 10 years after diagnosis of diabetes, because of albuminuria. His albumin - creatinine ratio is 2000 mg / g and creatinine of 120, when you reviewed his results during the past 10 years you noticed that HbA1c is always more than 10 , 11 , 12 (poorly controlled) , and poorly controlled blood pressure, the diabetologist is a bit concerned about having any other kidney disease .

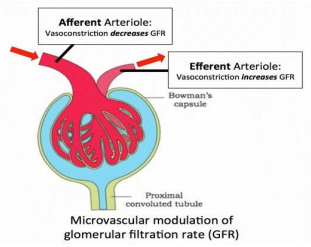
- First I will do fundus examination, if there is retinopathy it is more likely diabetic nephropathy , if there is no retinopathy I will do kidney biopsy, but if the biopsy is in keeping with diabetic nephropathy I won't use it .

- What is the challenge in type 2 DM ? We don't know exactly when did diabetes type 2 started.

Pathogenesis and Risk Factors

Pathogenesis:

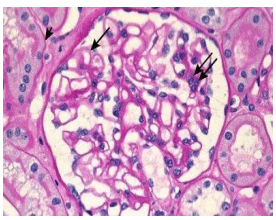
The first changes coincide with the onset of microalbuminuria include thickening of the glomerular basement membrane and accumulation of matrix material in the mesangium. Subsequently, nodular deposits are characteristic, and glomerulosclerosis worsens as heavy proteinuria develops, until glomeruli are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



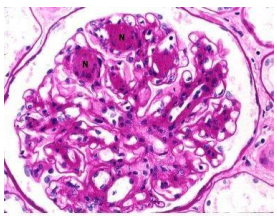
Microvascular modulation of glomerular filtration rate (GFR)

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)
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
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.**

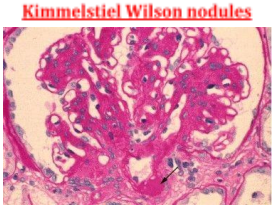
Normal glomerulus



Diabetic Nephropathy



Thickening of mesangium
Thickening of GBM
Kimmelstiel Wilson nodules



- **Nodular glomerulosclerosis (Kimmelstiel-Wilson Nodules) "Important"**: 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 :

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

1. Good glycemic control: ($HbA_1C < 7\%$) Strict glycemic control prevents moderately increased albuminuria (formerly called microalbuminuria) in patients with type 1 DM.
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.

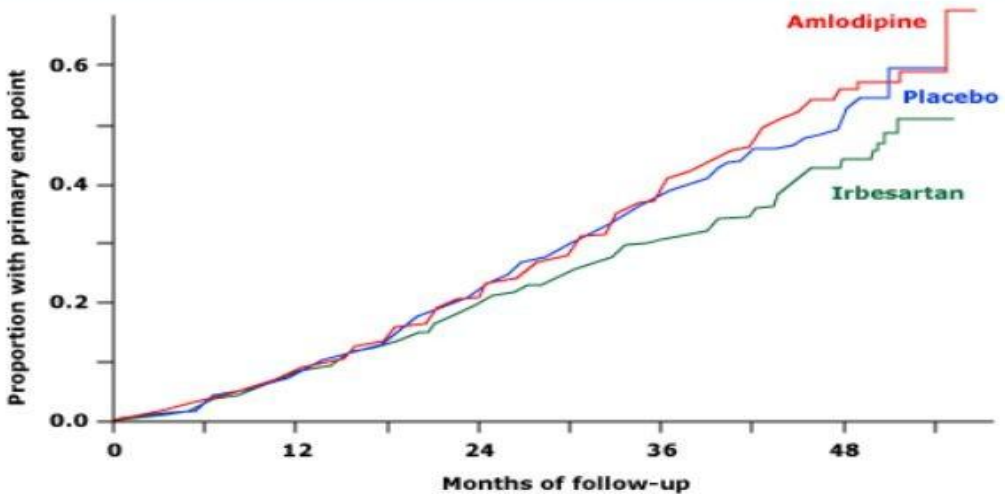
- Patient with DM should be screened annually for microalbuminuria (since it can't be detected early by dipstick).
- Dialysis should be considered in ESRD, and if there is complete failure consider renal transplant.

❖ 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

Irbesartan slows progression of nephropathy in type 2 diabetes



- 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

Diabetic Nephropathy: Functional and structural renal changes that happen in the context of Diabetes mellitus.

Importance	The leading cause of ESRD and risk factor for cardiovascular disease (especially IHD)	
Changes	**Functional**	**structural**
	Albuminuria Progressive loss of renal function ↓ GFR and ↑ creatinine	Mesangial expansion, GBM thickening Glomerulosclerosis (Kimmelstiel-Wilson Nodules)
Caused by	1- HTN 2- Hyperglycemia increases: - expression of transforming growth factor-beta (TGF-beta) - VEGF expression (vascular endothelial growth factor) } Structural changes 3- Hyperglycemia and AGEs (advanced glycation end products) (toxic)	

Natural History in Type 1 DM	First 5 years	Second 5 years	Third 5 years	Fourth 5 years
	Only hyperfiltration No albuminuria	microalbuminuria	Macroalbuminuria (overt nephropathy)	↓ GFR creatinine level will start to increase (declining in kidney function) .
	Normal kidney function			
	ESRD almost takes 20-30 years to develop in DM1 and 10 years in DM2 because they usually diagnosed late.			

Risk Factors		
	Duration of DM	longer duration → more risk
	Age	Risk ↑ with age, Here age refers to the time at which DM developed.
	Retinopathy	◆More than 90% of people with Type 1 DM and DN will develop diabetic retinopathy. DM1 patients almost ALWAYS have retinopathy ◆ 50% of people with Type 2 DM and diabetic Nephropathy will develop diabetic retinopathy.
	Genetic factor - Race – HTN – Smoking – Hyperlipidemia - Poor Glycemic control	

Prevention And Treatment	
	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!)
	RAAS blockade by giving ACEi/ARBs (independent of BP).
	Good glycemic control: HgbA1C <7 %
	Lipid lowering agent : LDL < 2.0 mmol/L. (Statins)
	Decreasing proteinuria (by dietary restriction of proteins).

Summary

	Microalbuminuria (Moderately increased albuminuria)	Macroalbuminuria (Severely increased albuminuria)
Albumin	30-300 mg/dl.	More than 300 mg/dl.
Albumin to creatinine ratio (ACR)	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.	Can be detected.
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.	

436 scenarios

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..

Questions:

1. A 19-year-old man is recently diagnosed with type 1 diabetes and attends your clinic to ask about possible complications in the future. He mentions an uncle who has end-stage renal disease due to poorly controlled diabetes and specifically enquires about testing for early signs of renal impairment. The most appropriate investigation is:

A. Blood pressure.
B. Microalbuminuria.
C. Serum Creatinine.
D. Urine dipstick for Glucose.

2. 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.

3. Which one of the following is histopathological change happens is diabetic nephropathy?

A. Duval bodies.
B. Kimmelstiel-wilson nodule.
C. Spindle cells.
D.Amyloid deposition.

4. **A 54-years-old lady has DM 2 for 9 years in routine clinic visit her HA1c 6.8 Albumin/ creatinine ratio = 228 (year ago was 100) she on glipizide 400 mg and metformin 1000 mg she has 2 brothers ESRD of DM on retinal examination she has retinopathy what is more effective management?**

A. Increase OHD to reach HA1c less than 6%.
B. No change on medication
C. Add ACEl to her medications.
D.Stop medication

5. **Which one of the following is functional changes in diabetic nephropathy?**

A. Mesangial expansion.
B. Albuminuria.
C. GBM thickening.
D. Glomerulosclerosis.

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.

Answers: 1-B / 2- A / 3- B / 4- C / 5- B / 6- A