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.

[Color index : Important | Notes | Extra]

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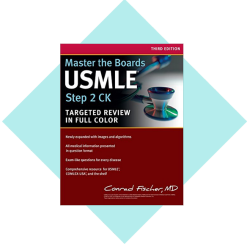
Resources:

- 435 slides



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"Medicine is an art, nobody can deny it."

7 : 36 minutes

❖ Diabetic nephropathy:

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.

Changes in Diabetic Nephropathy:

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

Comparison between Microalbuminuria and Macroalbuminuria:

	Microalbuminuria	**Macroalbuminuria[2]**
Albumin [3]	30-300 mg/dl	More than 300 mg/dl
Albumin to creatinine ratio (ACR)[4]	More than 3 mg/mmol	3000 mg/g = 300 mg/mmol.
Dipstick	Can't be detected so 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.
Notes	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.	
	HTN usually develops during the transition between microalbuminuria and macroalbuminuria, persistent HTN and proteinuria will reduce GFR leading to insufficiency and ESRD. Explains why the use of ACEi is critical in slowing progression to ESRD	

[1] Glomerular basement membrane
[2] Macroalbuminuria is known as Albuminuria and overt
[3] Normally it is less than 30 mg/dl
[4] use the ratio to confirm because the patient could be dehydrated and have concentrated urine

❖ Epidemiology:

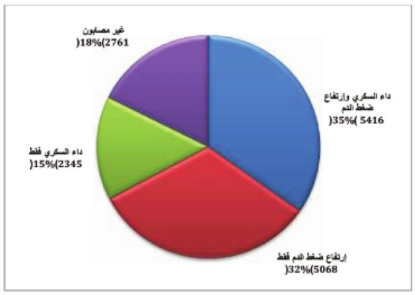
Epidemiological data have indicated that the overall incidence is declining as standards of glycaemic and blood pressure control have improved.

- ➔ 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
- ➔ Prevalence of diabetic nephropathy in **type ll** DM in the UK and Thailand are 11.5% and 42.9%, respectively.
- ➔ Diabetic nephropathy is a risk factor for cardiovascular disease
- ➔ ESRD in **type ll** DM (most of those with diabetic nephropathy die before developing ESRD, usually of cardiovascular complications):
  - ◆ 1.5%[5]
  - ◆ **5%**[6]
  - ◆ After 10 years:
    - 25% MA (macroalbuminuria).
    - 5% proteinuria
    - 0.8% Creatinine ≥ 175 OR renal replacement therapy
- ➔ Prevalence of diabetic nephropathy in **type I** is 7-10% with ESRD developing after 20-30 years

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

سبب الفشل الكلوي	العدد	النسبة المئوية%
إعتلال كلوي بإرتفاع 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%

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



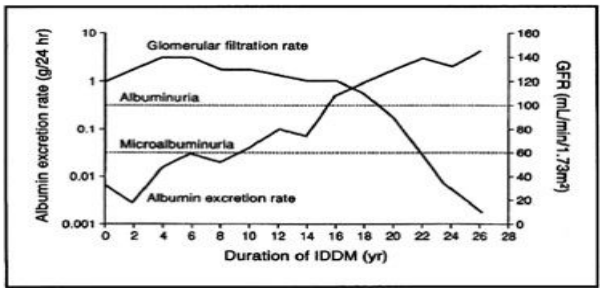
Natural history in type 1 DM:

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)

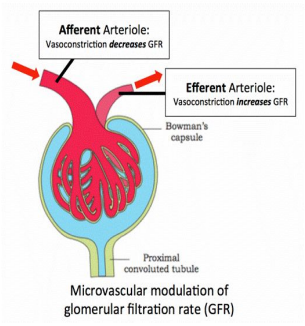
Fourth 5 years (16-20) Renal Functionstarts to decline Low GFR



- In the first few years of type I DM there is hyperfiltration, which declines steadily to return to normal value after 10 years.
- The natural history is the same in type II DM if we know when it started exactly (but this is not usually the case)
- In susceptible patients (30%), after 10 years there will be sustained proteinuria and by approximately 14 years it has reached the nephrotic range. Renal function continues to decline, with the end stage being reached at approximately 16 years.

[5] the Saudi National Diabetes Registry (SNDR), Al-Rubeaan et al 2014.
[6] Alwakeel et al, Ann Saudi Med 2011

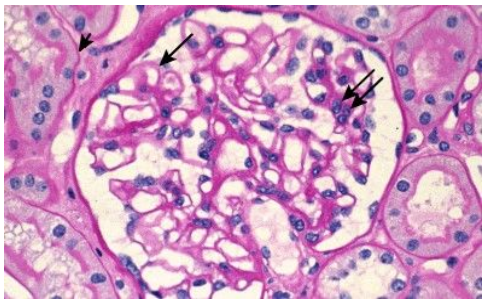
❖ Pathologically, the first changes coincide with the onset of microalbuminuria include ***thickening of the glomerular basement membrane*** *and* ***accumulation of matrix material in the mesangium***. Subsequently, ***nodular deposits are characteristic***, and glomerulosclerosis worsens as heavy proteinuria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

1. Hyperfiltration:
There is no clear single mechanism that causes hyperfiltration but all the following share the same end result of increasing the blood in contact with glomerulus so more filtrates are removed and the GFR is increased
	• Hyperfiltration marks the beginning of the development of diabetic nephropathy, and persists approximately 5 years.
	• Hyperglycemia results in direct activation of RAAS and increase release of Nitric oxide and prostaglandins (**increased pressure state**)
	  ○ RAAS activation increases angiotensin II > **Efferent** arteriolar **constriction** (slows blood out)
	  ○ NO and prostaglandins > **Afferent** arteriolar **dilation** (more blood in)
	• Hyperglycemia increases the expression of transforming growth factor-beta (TGF-beta) causing thickening of the GBM
	• Hyperglycemia and AGEs (advanced glycation end products) (toxic)
	• Hyperglycemia Increases VEGF expression (vascular endothelial growth factor)
	• HTN
	 
	Microvascular modulation of glomerular filtration rate (GFR)

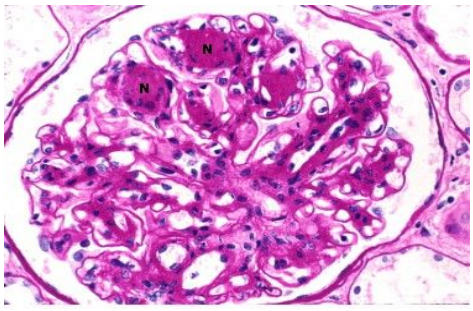
2. Mesangial Expansion:	• Increased pressure will result in trauma and damage to the mesangium
	• Cytokines and O2 free radicals from damage → inflammation and endothelial dysfunction
	• AGEs, VEGF and TGF-beta also affect the mesangium and cause expansion
	• All will ultimately result in thickening of basement membrane (hypertrophy) and matrix accumulation within the mesangium " mesangial expansion"
	• **Outcome:**
	  ○ ↓ Surface area of glomeruli for filtration.
	  ○ Dilation of fenestration between podocyte.
	  ○ Protein leakage

3. Nephron Ischemia:	• Constriction of efferent arteriole will ↓ flow to supply nephron. • Cytokine and free radicals don't only damage the mesangium but also 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 • In 3 months chronic kidney disease will develop and eventually ESRD

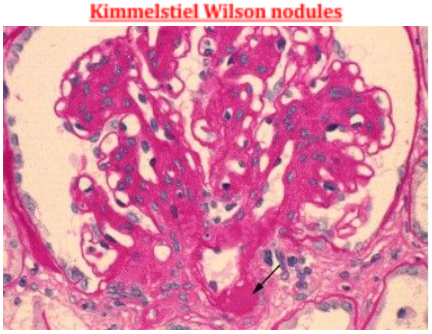
Normal glomerulus



Diabetic Nephropathy



Thickening of mesangium
Thickening of GBM
Kimmelstiel Wilson nodules



Pathologic types:

- **Nodular glomerulosclerosis (kimmelstiel-Wilson Nodules)** (the name could come in MCQ) : hyaline deposition in one area of the glomerulus (usually due to efferent involvement of destruction/sclerosis)→ seen 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).
- Isolated glomerular basement membrane thickening.

Risk Factors

❖ Risk Factors:

- Long Duration of DM.
- Poor glycemic control.
- **Hypertension** (one of the most important risk factors)
- Hyperlipidemia
- Presence of other microvascular complications (for example **Retinopathy**) 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)
- Family history of diabetic nephropathy **(Genetic factors).**
- Family history of hypertension

Microalbuminuria is a good predictor of progression to nephropathy in type 1 DM, it is less reliable in older patients with type II, in whom it may be accounted for by other diseases.

❖ Diabetic Nephropathy and Retinopathy :

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

❖ Prevention and Treatment Strategies :

- Control the glucose level : (HbA1C <7 %)
- Decreasing proteinuria (by dietary restriction of proteins) is very important in slowing the progression of diabetic nephropathy.
- Lower the BP to 130/80
- Reduce Cardiovascular risk. (because the atherosclerosis is highly accelerated among DM patients)
- **RAAS blockade by giving ACEi/ARBs (independent of BP)** Why ACEi/ARBs?
  - Blocking angiotensin II will dilate the efferent arterioles and hence reduce the filtration rate.
  - They also reduce the progression of the disease
  - They reduce the expression of TGF beta (unknown mechanism)
- Lower the LDL level to less than 100 mg/dL (< 2 mmol/L). (give statins if needed)
- Smoking cessation.
- Lifestyle modification: Weight loss + exercise + diet restriction (Salt + protein).

Notes about treatment strategies:

The presence of established microalbuminuria or overt nephropathy should prompt vigorous efforts to reduce the risk of progression of nephropathy and of cardiovascular disease by:

- *Aggressive reduction of blood pressure*
- *Aggressive cardiovascular risk factor reduction*

★ In **type 1 diabetes**, ACE inhibitors have been shown to provide greater protection than equal blood pressure reduction achieved with other drugs , and subsequent studies have shown similar benefits from angiotensin II receptor blockers (ARBs) in patients with **type 2 diabetes.**

(Type **I** = ACE**I** | **Type II** = angiotensin **II** receptor blockers).

➔ This benefit from blockade of the renin–angiotensin system arises from a reduction in the angiotensin II-mediated vasoconstriction of efferent arterioles in glomeruli. The resulting dilatation of these vessels decreases glomeruli filtration pressure and therefore the hyperfiltration and protein leak.

➔ Both ARBs and ACEi can cause **hyperkalemia**, in the presence of renal artery stenosis it might cause marked deterioration in renal function, (What to do ?) after initial dose →check electrolytes and renal function. (Non-dihydropyridine calcium antagonist (diltiazem,verapamil) may be good alternatives)

➔ Dialysis should be considered in **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).