Lecture 14

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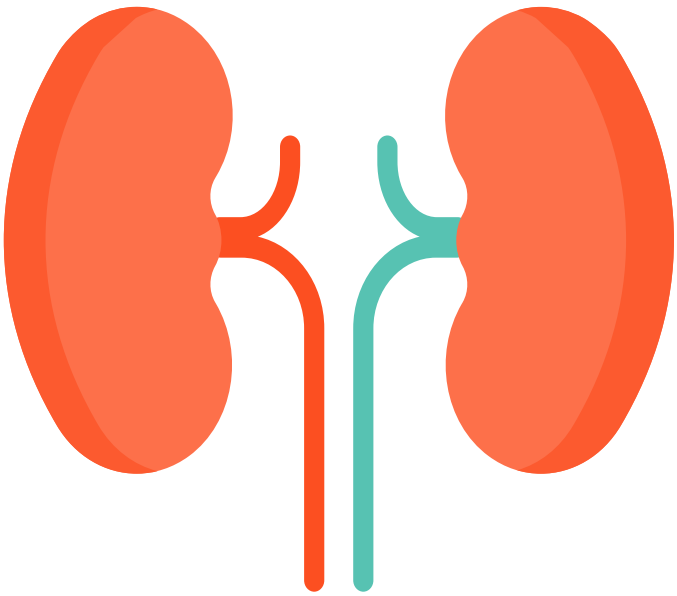

Reviewed By
Noura Alturki
Jehad Alorainy

Diabetic nephropathy

Objectives:

- ★ **Know what Diabetic Nephropathy means.**
- ★ **Know how common Diabetic nephropathy in Saudi Arabia is**
- ★ **To appreciate the huge burden of such a complication.**
- ★ **Know the risk factors of Diabetic nephropathy.**
- ★ **Know how to manage Diabetic nephropathy in general**
- ★ **The role of BP control and the role of ACEI/ARB medications in particular.**

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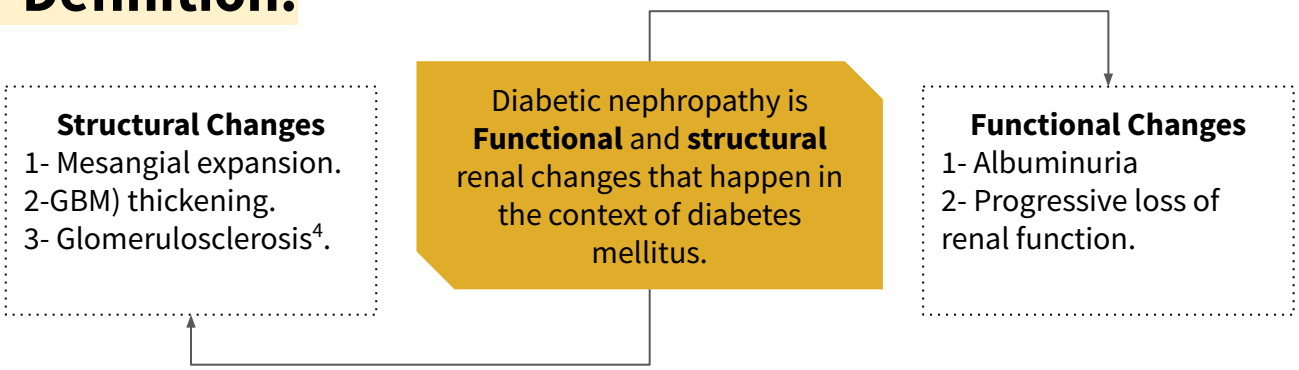
Introduction to Diabetic Nephropathy

◄ Overview:

- 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.
- Microvascular complications are unusual in the first 10 years after the diagnosis of type 1 diabetes but are found in 20–50% of people with newly diagnosed type 2 diabetes as a result of the preceding undiagnosed hyperglycemia.

◄ Definition:



◄ Comparison between Microalbuminuria and Macroalbuminuria:

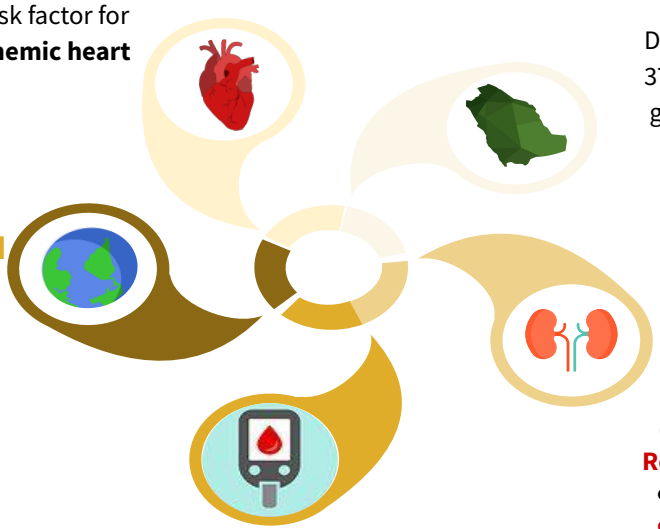
	Microalbuminuria[1]	Macroalbuminuria
Albumin	30-300 mg/day.	More than 300 mg/day.
Albumin to creatinine ratio (ACR)[2]	**> 3 mg/mmol** creatinine (> 30 : 1). (equivalent to **> 30 mg / g** of Creatinine.)	**> 30 mg/mmol** creatinine (> 300 : 1). (equivalent to **> 300 mg / g** of Creatinine.
Urine dipstick	Can't be detected[3].	Detected.

1: Microalbuminuria is present if: Male ACR 2.5–30 mg/mmol creatinine, Female ACR 3.5–30 mg/mmol creatinine
2: The albumin creatinine ratio (ACR) (tested on a mid-stream first morning urine sample) is <2.5 in healthy men, <3.5 mg/mmol in healthy women. An elevated ACR should be followed by a repeat test: There is established microalbuminuria if 2 out of 3 tests are positive, An ACR > 30 mg/mmol creatinine (macroalbuminuria) is consistent with overt nephropathy. Why do we use ACR to evaluate albuminuria ? Plasma creatinine remains fairly constant throughout adult life. despite the concentration of urine, unlike the amount of albumin alone that is affected by the concentration. So using ACR eliminates of variation of concentration and gives a realistic picture of the albuminuria.
3: (You must screen for microalbuminuria) Urine dipstick can only detect albumin >300. Hence, the name micro for what's less than that.
4. Late in the course of the disease.

Epidemiology & risk factors

◀ Epidemiology

Diabetic nephropathy is a risk factor for cardiovascular disease **(Ischemic heart disease)**



Prevalence of diabetic nephropathy in DM type II

- Saudi Arabia
  - 10.8 %[1]
  - 31.8%[2]
- UK
  - 11.5%
- Thailand
  - 42.9%

Prevalence of diabetic nephropathy in type I DM

7-10% (with ESRD developing after 20-30 years)

Prevalence of DM in Saudi Arabia

DM is **an epidemic** in KSA. In total, 37.8% have abnormal glucose metabolism (age 30-70 year):

- 23.7% are **diabetic**.
- 14.1% have **impaired fasting glucose** (Prediabetic state)

Prevalence of ESRD in type II DM[3]

(**DM is a leading cause of End Stage Renal Disease (ESRD) in our society[4].**)

- 1.5%[1]
- 5%[2]

In 10 years:

- 25% of the patient will develop MA (macroalbuminuria).
- 5% will have proteinuria
- 0.8% will have Creatinine ⩾ 175 OR renal replacement therapy.

◀ Risk factors for diabetic nephropathy:

1. Duration of DM
2. Poor glycemic control
3. Hypertension
4. Hyperlipidemia (obesity)
5. Smoking
6. Age (Due to the natural process of wear-and-tear)
7. Race (e.g. Asians, Pima Indians, black Americans)
8. Genetic factors (Family history of Diabetic Nephropathy)
9. Retinopathy[5] → Presence of other microvascular complications

1: By the Saudi National Diabetes Registry (SNDR), Al-Rubeaan et al 2014.
2: (By Alwakeel et al, Ann Saudi Med, 2011).
3: Diabetic nephropathy increases the risk of cardiovascular risk and most people with nephropathy die from cardiovascular disease before progressing to end-stage renal disease.
4: 2nd after hypertension (39% due to hypertension, and 38.8% due to DM)
5: Retinopathy is >90% associated with diabetic nephropathy in type I DM, but only 50% chance to be present in type II DM. and this is helpful in confirming diagnosis. for eg. when you see a case with proteinuria after 10 years of type I DM (which too early for the nephropathy to be developed) → do a fundoscopy to confirm your diagnosis, if it is -ve then it is unlikely to be diabetic nephropathy processed and do kidney biopsy.

Natural History in Type 1 DM

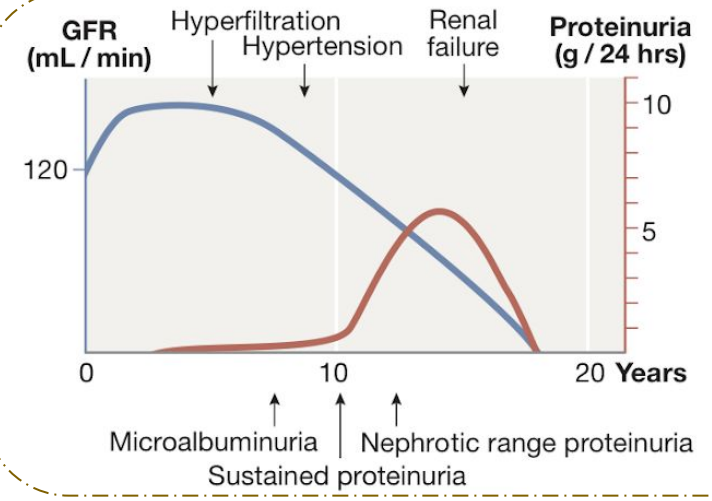
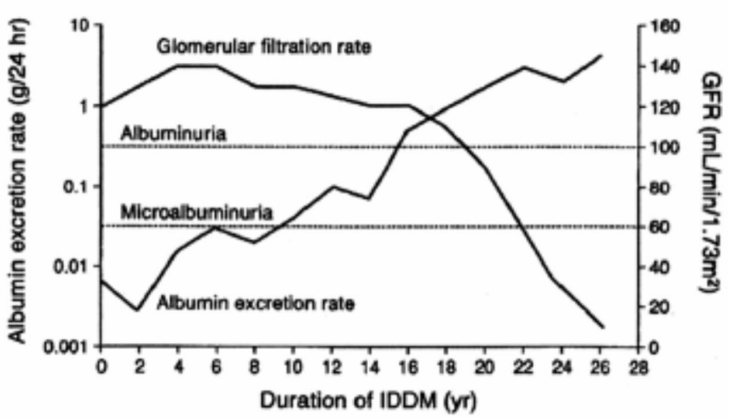


Figure explanation

In the first few years of type 1 diabetes mellitus, there is hyperfiltration, which declines fairly steadily to return to a normal value at approximately 10 years (blue line). In susceptible patients (about 30%), after about 10 years, there is sustained proteinuria, and by approximately 14 years it has reached the nephrotic range (red line). Renal function continues to decline, with the end stage being reached at approximately 16 years.

Dr's explanation



The natural course of developing diabetic nephropathy in type I DM:

Dividing them by 4-5 years:

- First 5 years → Increase GFR leading to hyperfiltration & ↓creatinine.
- 2nd 5 years → Microalbuminuria.
- 3rd 5 years → Macroalbuminuria, Overt nephropathy or diabetic nephropathy.
- 4th 5 years → Decline in GFR

In Type II DM:

Follows the same course of type II, but the problem is that we do not know when did DM exactly started.

Pathophysiology

Thickening of GBM → **Accumulation of matrix material in the mesangium** → **Nodular deposits** → **Glomerulosclerosis worsens (heavy proteinuria)** → **Glomeruli are progressively lost & renal function deteriorates**

Pathophysiology *(cont.)*

1 Hyperfiltration & thickening of glomerular basement membrane[1]

afferent arteriole (leading to the glomerulus) becomes vasodilated to a greater extent than the efferent glomerular arteriole

mesangial cell hypertrophy and increased secretion of extracellular mesangial matrix material

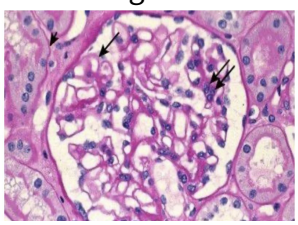
01 → 02 → 03 → 04 → 05

Hyperglycemia

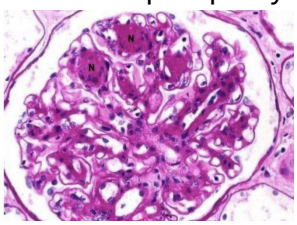
increased intraglomerular filtration pressure, further damaging the glomerular capillaries

Hyperfiltration (↑GFR[2]) & Thickened GBM

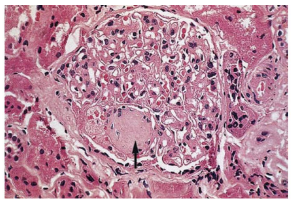
Normal glomerulus



Diabetic Nephropathy



Nodular Diabetic Glomerulosclerosis[3]



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

2 Hyperglycemia and AGEs (advanced glycation end products)

When a wide variety of proteins are exposed to increased glucose concentrations, glucose binds irreversibly to the protein to form AGEs; one example of this is HbA1c, which is used to diagnose diabetes and monitor treatment. AGEs cause tissue injury and inflammation via stimulation of pro-inflammatory factors, such as complement and cytokines.

3 Hyperglycemia Increases VEGF expression (vascular endothelial growth factor)

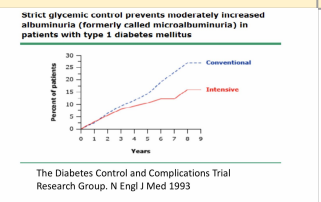
4 Hyperglycemia increases the expression of transforming growth factor-beta (TGF-beta)

When hyperglycemia occurs, excess glucose is metabolized to sorbitol via the polyol pathway. This leads to accumulation of sorbitol and fructose, which cause changes in vascular permeability, cell proliferation and capillary structure via stimulation of protein kinase C & TGF-β.

1: Thickening of the capillary and arteriole basement membrane is the cardinal feature of microvascular complications.
2: GFR > 150 mL/min.
3: Characteristic for diabetic nephropathy
4: Increase expression of TGF-beta and VEGF causes mesangial expansion, thickening of GBM leading to bulky kidney on ultrasound

Treatment

Treatment strategies of Diabetic nephropathy

Strategy	Value	Note/Importance
Glycemic control	HbA1C < 7%[1] 	Strict glycemic control prevents microalbuminuria in patients with type 1 DM
★ **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[2].
Lowering lipid	LDL < 2.0 mmol/L	-
Decreasing proteinuria	-	dietary restriction of proteins
Lifestyle modification	-	diet restrictions (↓Na), weight loss and exercise.
Annual screening for microalbuminuria	➔ Early morning urine is measured for the albumin:creatinine ratio (ACR). Microalbuminuria is present if: ◆ Male ACR 2.5–30 mg/mmol creatinine ◆ Female ACR 3.5–30 mg/mmol creatinine ➔ An elevated ACR should be followed by a repeat test: There is established microalbuminuria if 2 out of 3 tests are positive ➔ An ACR > 30 mg/mmol creatinine is consistent with overt nephropathy	Because it can't be detected early by dipstick
Dialysis	-	should be considered in ESRD, and if there is complete failure consider renal transplant.

1: 7.5% in elderly because they are more prone to hypoglycemic events.

2: due to the antiproteinuric effect of ACEI/ARB

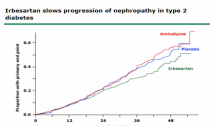
Management of diabetic nephropathy

◀ Management:

1. aggressive reduction of blood pressure
2. aggressive reduction of cardiovascular risk factors
3. optimisation of glycaemic control

1 ★ 1st line therapy

ACE inhibitors OR angiotensin 2 receptor blockers (ARBs)



1. **Effect:** blockade of the renin–angiotensin system arises from a reduction in the angiotensin II-mediated vasoconstriction of efferent arterioles in glomeruli → dilatation of these vessels decreases glomerular filtration pressure and, therefore, the hyperfiltration and protein leak.
   Structural effect: decrease the expression of TGF-beta.
2. **Benefit:** Halving the amount of albuminuria with an ACE inhibitor or ARB results in a nearly 50% reduction in long-term risk of progression to end-stage renal disease
3. **Limitations:** Both ACE inhibitors and ARBs increase risk of hyperkalaemia and, in the presence of renal artery stenosis, may induce marked deterioration in renal function

Note that: If blockade of the renin–angiotensin system is not possible, blood pressure should be managed with standard treatment, such as calcium channel blockers and diuretics.

2 2nd line therapy

addition of a diuretic and/or salt restriction

1. **Benefit:** increase both the anti-proteinuric and antihypertensive effect of angiotensin blockade

3 3rd line therapy

Renal transplantation

New agents: SGLT-2 inhibitors → help in HF and protective effect in kidney disease.

Summary

Diabetic Nephropathy	Functional and structural renal changes that happen in the context of Diabetes mellitus.
Functional: - **Albuminuria** (Microalbuminuria = 30-300 mg\d - ACR> 3mg\mmol creatinine) (Albuminuria => 300 mg\d) - **Progressive loss of renal function**	Structural: - **Mesangial expansion**, **GBM thickening** and **glomerulosclerosis**
Pathophysiology	- Hyperfiltration - Hyperglycemia increases the expression of transforming growth factor-beta (TGF-beta) - Hyperglycemia and AGEs (advanced glycation end products) - Hyperglycemia Increases VEGF expression (vascular endothelial growth factor) - HTN
Risk Factors	- Duration of DM - Age - HTN - Race - Genetic factor - Retinopathy - Smoking, Hyperlipidemia - Poor glycemic control
Treatment Strategies	- Good BP control - BP <130/80 - RAS blockade, independent of BP - Good glycemic control (HgbA1C <7 %) - Lipid lowering agent (LDL-C <2.0 mmol/L) - Diet (protein, sodium)

Natural History in Type 1 DM

First 5 years	Second 5 years	third 5 years	Fourth 5 years
-Hyperfiltration -Normal kidney function	-Microalbuminuria -Normal kidney function	-Macroalbuminuria -Normal kidney function	-Renal function starts to decline -Low GFR

Lecture Quiz

Q1: 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. Serum electrolytes
E. Urine dipstick for glucose

Q2: A 55-year-old woman is seen in clinic, she has a ten-year history of type 2 diabetes treated with glibenclamide. Her blood pressure is 148/93 with new onset proteinuria, her serum results show elevated lipid levels, glycated haemoglobin of 5.5 percent and fasting glucose of 6.0 mmol/L. A renal biopsy shows the presence of Kimmelstiel–Wilson lesions. The most appropriate management is:

A. Increase oral hypoglycaemic dosage
B. ACE II antagonists
C. Start cholesterol lowering therapy
D. Start ACE inhibitors
E. Start renal dialysis

Q3: A 50-year-old diabetic woman presents for follow-up of her hypertension. Her blood pressure is 152/96 in the office today and she brings in readings from home that are consistently in the same range over the past month. Her current medications are amlodipine 5 mg daily and hydrochlorothiazide 25 mg daily. The diuretic was added when she developed peripheral edema on the amlodipine; now she has only trace peripheral edema. A spot urine specimen shows 280 µg of albumin per mg creatinine (microalbuminuria is present if this value is between 30 and 300 µg/mg). What would be the best next therapeutic step in this patient?

A. Add clonidine.
B. Add a beta-blocker.
C. Increase the thiazide diuretic dose.
D. Add an alpha-blocker.
E. Add angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

Q4: What is the range for Microalbuminuria?

A. Albumin > 30 mg\d and ACR >30:1
B. Albumin > 30 mg\d and ACR >300:1
C. Albumin > 300 mg\d and ACR > 30:1
D. Albumin > 300 mg\d and ACR > 300:1

Q5: Which of the following pathologic events occur first in DN?

A. Nephron ischemia
B. Nodular deposits
C. Thickening of glomerular basement membrane
D. Renal function deterioration

Answers: Q1:B | Q2:D | Q3:E | Q4:A | Q5:C

Answers Explanation File!

THANKS!!

This lecture was done by:

- Amirah Alzahrani
- Norah Alharbi

Quiz and summary maker:

- Wejdan Alshamri

Note taker:

- Lama AlZamil

Females co-leaders:
Raghad AlKhashan
Amirah Aldakhilallah

Males co-leaders:
Mashal Abaalkhail
Ibrahim AlAsous

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We are all ears!