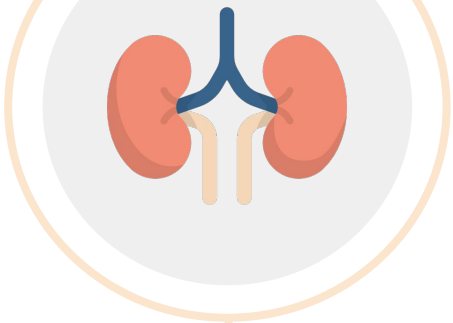
Diabetic nephropathy



Amazing video by osmosis

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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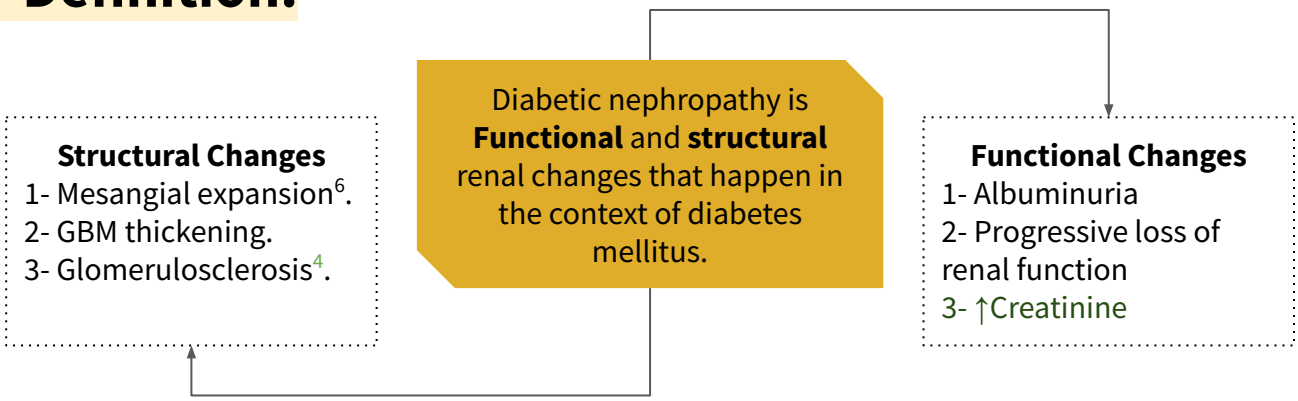
Introduction to Diabetic Nephropathy

◄ 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:

Creatinine: 1 g = 10 mmol

	Microalbuminuria[1]	Macroalbuminuria
Albumin (Normal: < 30 mg/day).	30-300 mg/day. (Moderately increased albuminuria)	> 300 mg/day. (Severely increased albuminuria)
Albumin to creatinine ratio (ACR)[2,3]	**30-300 mg/g** Creatinine **or** **> 3-30 mg/mmol** creatinine (30:1) *to convert g → mmol divide it by 10	**>300 mg/g** creatinine **or** **>30 mg/mmol** creatinine (300:1)
Urine dipstick	Can't be detected[5].	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: it's difficult to collect 24h urine sample as it has several limitations. so urine spot is much easier to use. why ACR? albumin levels vary depending on urine concentration, hence Albumin concentration alone isn't reliable in a urine spot. it must be correlated to creatinine.
4: Late in the course of the disease.
5: (You must screen for microalbuminuria) Urine dipstick can only detect albumin >300. Hence, the name micro for what's less than that.
6- Due to increased deposition of extracellular matrix . High glucose levels cause mesangial cell hypertrophy , which results in a large amount of mesangial matrix .

Epidemiology & risk factors

◀ Importance

1) **a leading cause of End Stage Renal Disease (ESRD) in our society**[4]
2) **Diabetic nephropathy is a risk factor for cardiovascular disease**[3] **(Ischemic heart disease)**

◀ Epidemiology

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 diabetic nephropathy in DM Type II

Saudi Arabia:
10.8 %[1] - **31.8%**[2] (more representative)

11.5% in UK
43.9% in Thailand

Prevalence of ESRD in Diabetics

Type I: 7-10% (ESRD developing after 20-30 years)

Type II: 1.5%[1] **- 5%**[2] (15% of diabetic nephropathy)[6]
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 (in general is risk factor for Kidney diseases).
6. **Age** Agings process weakens the kidney tissue (wear-and-tear)
7. Race (e.g. Asians, Pima Indians, black Americans)
8. Genetic factors (Family history of Diabetic Nephropathy)
9. **Retinopathy**[5] → evidence 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), So diabetes and hypertension account for 80% of the causes of ESRD in our society
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 is 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 a kidney biopsy.
6- **Why only 5% of diabetic patients develop ESRD?** Because many of them are died from cardiovascular events before they reach ESRD. (Diabetic nephropathy doesn't mean always ESRD or needing to dialysis).

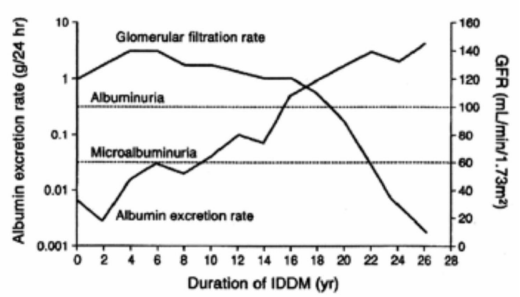
Natural History in Type 1 DM

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 & ↑creatinine.

In Type II DM:
it follows the same course of type I, but the problem is that we do not know when did DM exactly started.



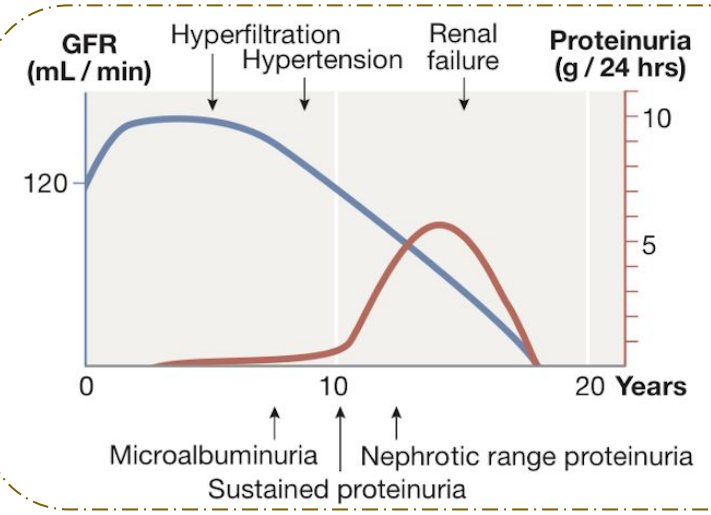


Figure explanation

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.

Pathophysiology

Thickening of the glomerular basement membrane → **Accumulation of matrix material in the mesangium** → **Nodular deposits** → **Glomerulosclerosis worsens (heavy proteinuria)** → **Glomeruli are progressively lost and renal function deteriorates.**

Pathophysiology *(cont.)*

1 Hyperfiltration & thickening of glomerular basement membrane[1]

Hyperfiltration (↑GFR[2] &↓Creatinine)
afferent arteriole becomes vasodilated to a greater extent than the efferent glomerular arteriole[2]

Expression of Growth factors
→mesangial cell hypertrophy and increased secretion of extracellular mesangial matrix material

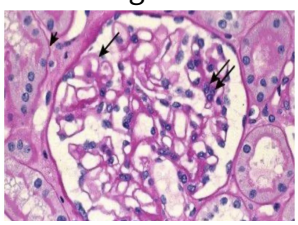
01 → 02 → 03 → 04 → 05

Hyperglycemia and AGEs

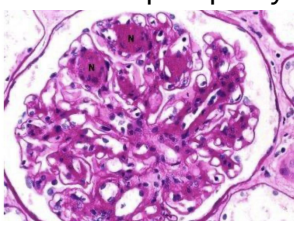
increased intraglomerular filtration pressure→
increased albumin filtration

Thickened GBM, Mesangial expansion leading to Nodular Glomerulosclerosis

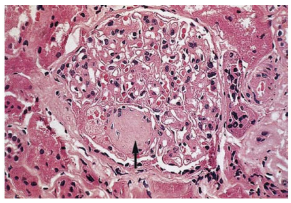
Normal glomerulus



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)

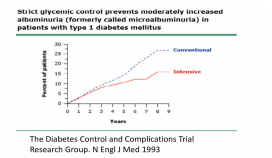
4 Hyperglycemia increases the expression of transforming growth factor-beta (TGF-beta)

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: Afferent arteriole dilated due to effect of Prostaglandin, Efferent arteriole constricted due to effect of Angiotensin II
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** or ARBs)[2]	**independent of BP[3]**
Lowering lipid	LDL < 2.0 mmol/L	-
Decreasing proteinuria	-	dietary restriction of proteins
Lifestyle modification	-	diet restrictions (↓Na), weight loss and exercise.
Dialysis		should be considered in ESRD, and if there is complete failure consider renal transplant

◄ Screening and investigations:

- ➔ The urine of all people with diabetes should be checked regularly (at least annually) for the presence of 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

1: 7.5% in elderly because they are more prone to hypoglycemic events.
2: Associated with better renal outcomes. **Why? 1-** Because when we block Angiotensin II, The efferent arteriole will dilate and intra-glomerular pressure will decrease, **So the proteinuria will be less.** When we have less proteinuria that is protective to the kidney. **2.** They found out it inhibit TGF-beta (one of the growth factors that can cause structural changes).
3: to dilate efferent arterioles →↓ intraglomerular pressure → ↓albumin excretion → ↓ Albuminuria 2) to protect from CVD events 3) inhibit the expression of Growth factors

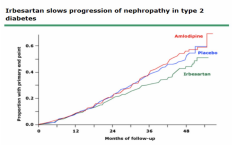
Management of diabetic nephropathy

◄ Management:

- aggressive reduction of blood pressure
- aggressive reduction of cardiovascular risk factors
- optimisation of glycaemic control

1st line therapy

ACE inhibitors OR angiotensin 2 receptor blockers (ARBs)



We give the patient who has diabetic nephropathy regardless the BP

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.

2nd line therapy

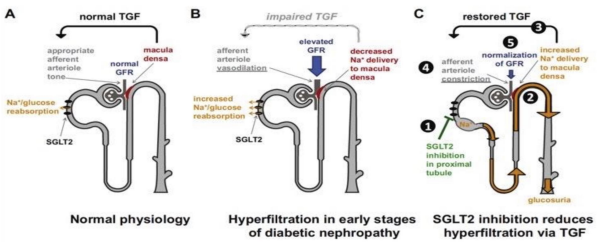
addition of a diuretic and/or salt restriction

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

3rd line therapy

Renal transplantation

New agent: SGLT inhibitor



Only used in type II DM. (Not given to type I because of the risk of Euglycemic diabetic ketoacidosis DKA) **MCQ**
Mechanism : SGLT2 transport Na^+ and Glucose from the tubule into blood (reabsorption) and when the filtrate reach the macula densa the sodium will be low because of the reabsorption, and the macula densa will send the feedback to the glomerulus that's no much sodium so dilate the afferent arteriole.
in case of SGLT2 Inhibitor it will block the transporter so the macula densa sense more sodium and glucose in the urine and get a feedback (Tubuloglomerular feedback) tubule will get a feedback to the glomerulus causing constriction of afferent arteriole and decrease in the intraglomerular pressure and that will decrease the proteinuria. Possible Complication is recurrent UTI. 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

Cases (mentioned by the Dr)

◄ Case study 1:

18-year- old male diagnosed with DM 3 years ago, presented with significant proteinuria of 2.5 g(2500 mg). does he have diabetic nephropathy?

Answer: No, it doesn't follow the time frame. Macroalbuminuria is expected after 10 years of diagnosis. most likely kidney disease of another causes. preform a biopsy.

◄ Case study 2:

70-year-old female who's known to have diabetes for 20 years. in addition to HTN and IHD. referred to you for elevated creatinine of 150 µmol/L and proteinuria of 2g (2000 mg). Urinalysis is otherwise normal, no hematuria. she states that she's experiencing photocoagulation because of retinopathy. does this patient have diabetic nephropathy?

Answer: Yes, it follows the time frame.

◄ Case study 3:

60-year-old male. diagnosed with DM type II 10 years ago. presented with elevated creatinine = 120 µmol/L and albuminuria = 1.2g (1200 mg) is his kidney disease a related diabetes? and what is the next step to confirm your diagnosis?

Answer: Yes, even though it doesn't follow the time frame. his disease might have been developed years before the diagnosis (>10 years) .perform a fundoscopy, if it is +ve confirm the diagnosis. if it is -ve then do a kidney biopsy.

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!

GOOD LUCK !

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