Kidney disease and Hypertension in Diabetes

Dr. Hoofar Rafiee

Nephrologist

Department of Internal Medicine

Shahrood University of Medical Sciences

Why is important?

- ***Diabetic Nephopathy (DN)*** is the most common cause of end-stage kidney disease in worldwide.
- Kidney disease secondary to diabetes mellitus, termed as diabetic nephropathy (DN), accounts for over 40% of end-stage kidney disease (ESKD).
- Ten years after the diagnosis of type 2 diabetes, about 25% patients have DN.
- It is estimated that **20-40%** of all diabetic patients will develop diabetic nephropathy.

Diagnosis

- While the **gold standard for diagnosis** of diabetic nephropathy is defined by **histology of the kidney**, the majority of patients do not undergo kidney biopsy, as they are presumed to have diabetic kidney disease **based upon clinical history and laboratory evaluation.**

- This clinical practice is based in part upon **the desire to avoid an invasive procedure** that may not alter treatment, as well as the notion that there is a uniform clinical disease presentation, a traditional belief based upon observational studies performed several decades ago.

Diagnosis

- **Persistent albuminuria**
  - 30-300 mg/d = microalbuminuria
  - 300 mg/d = macroalbuminuria
- **eGFR decreasing**

❖ **Note:**

- Kidney size usually is increased, unlike other cause of CKD.
- Kidney biopsy often is not recommended for diagnosis.

What is Diabetic Nephropathy?

Clinical syndrome

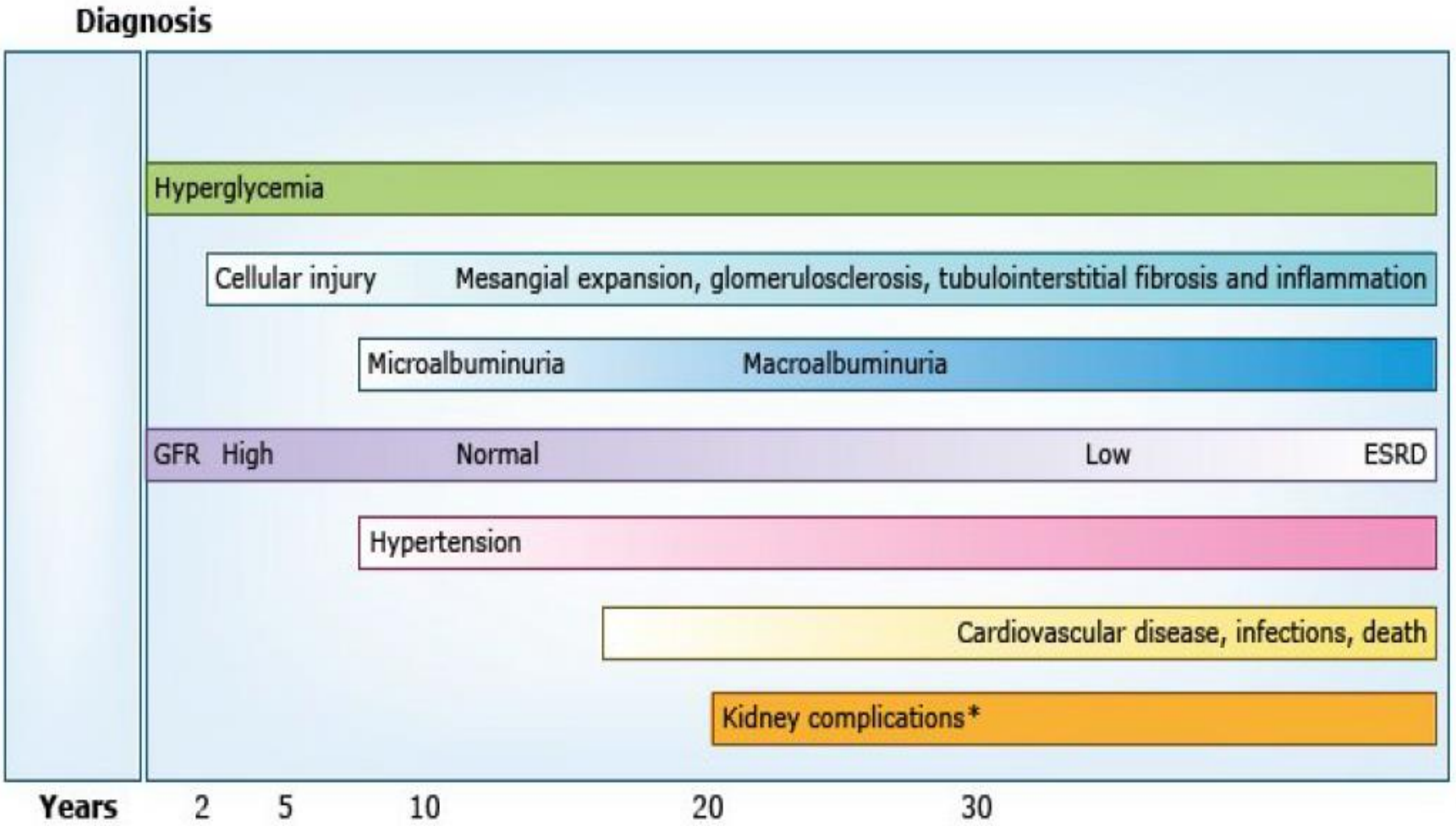
- Persistente proteinuria
- Hypertension
- Progressive decline in renal function

Pathologic renal lesions

- Diabetic microangiopathy – ↑ of basement membrane (BM) material
- Difuse glomerulosclerosis – difuse ↑ in mesangial matrix and thickening of the capillary walls
- Nodular glomerulosclerosis – Kimmelstiel-Wilson lesions
- Insudative lesions – hyalinosis
- Atubular glomeruli
- Difuse linear reaction for IgG along the BM

Natural history of diabetic nephropathy

1. Silent clinical phase, Hyperfiltration, Increased GFR
2. Microalbuminuria (30 – 300 mg/d) ➡ ↑ CVD
3. Macroabuminuria(> 300 mg/d) ➡ **Clinical nephropathy**
4. End-stage kidney disease


Diagnosis
Hyperglycemia
Cellular injury
Mesangial expansion, glomerulosclerosis, tubulointerstitial fibrosis and inflammation
Microalbuminuria
Macroalbuminuria
GFR
High
Normal
Low
ESRD
Hypertension
Cardiovascular disease, infections, death
Kidney complications*
Years
2
5
10
20
30

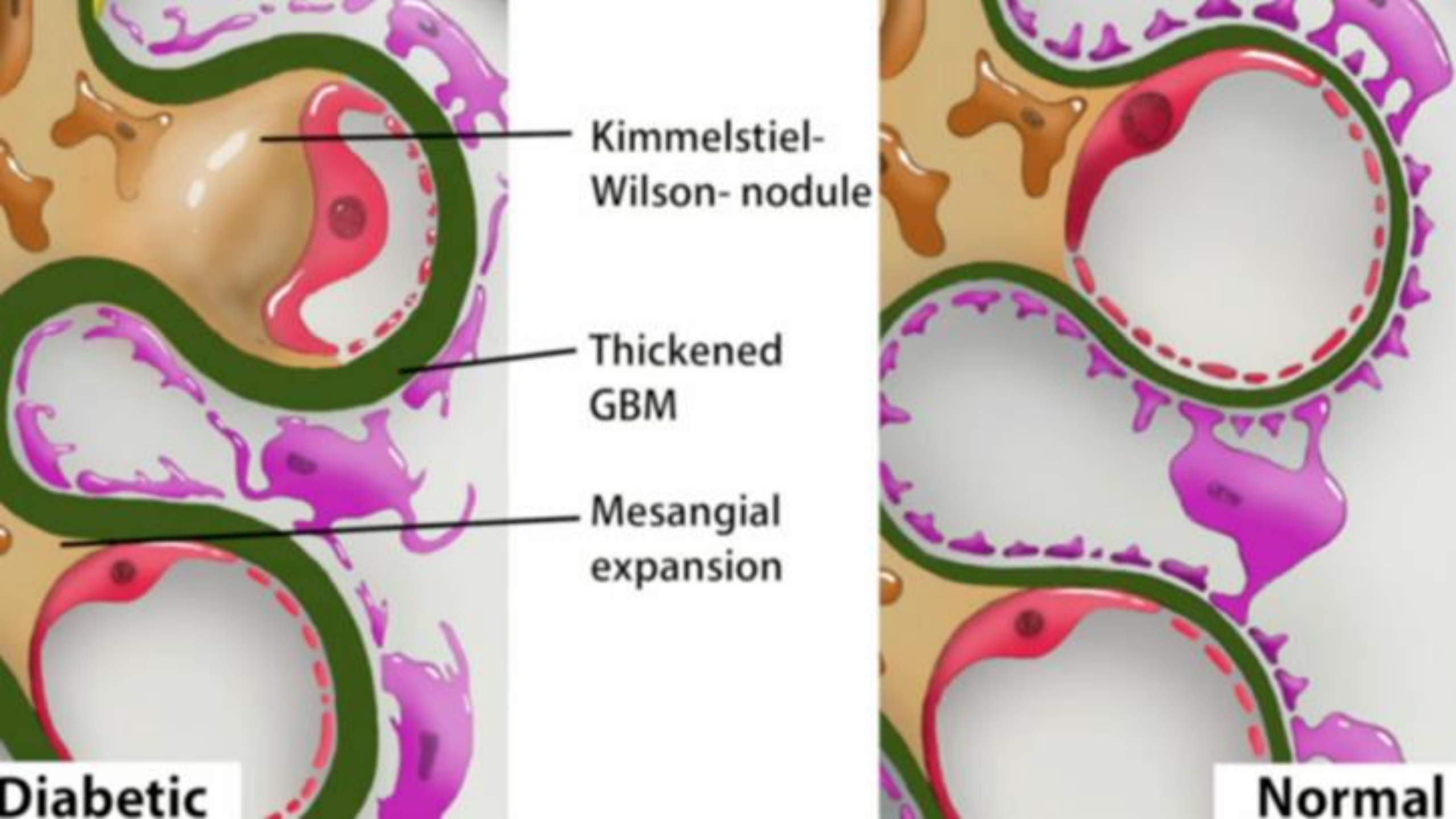
Diagnostic histopathologic lesions

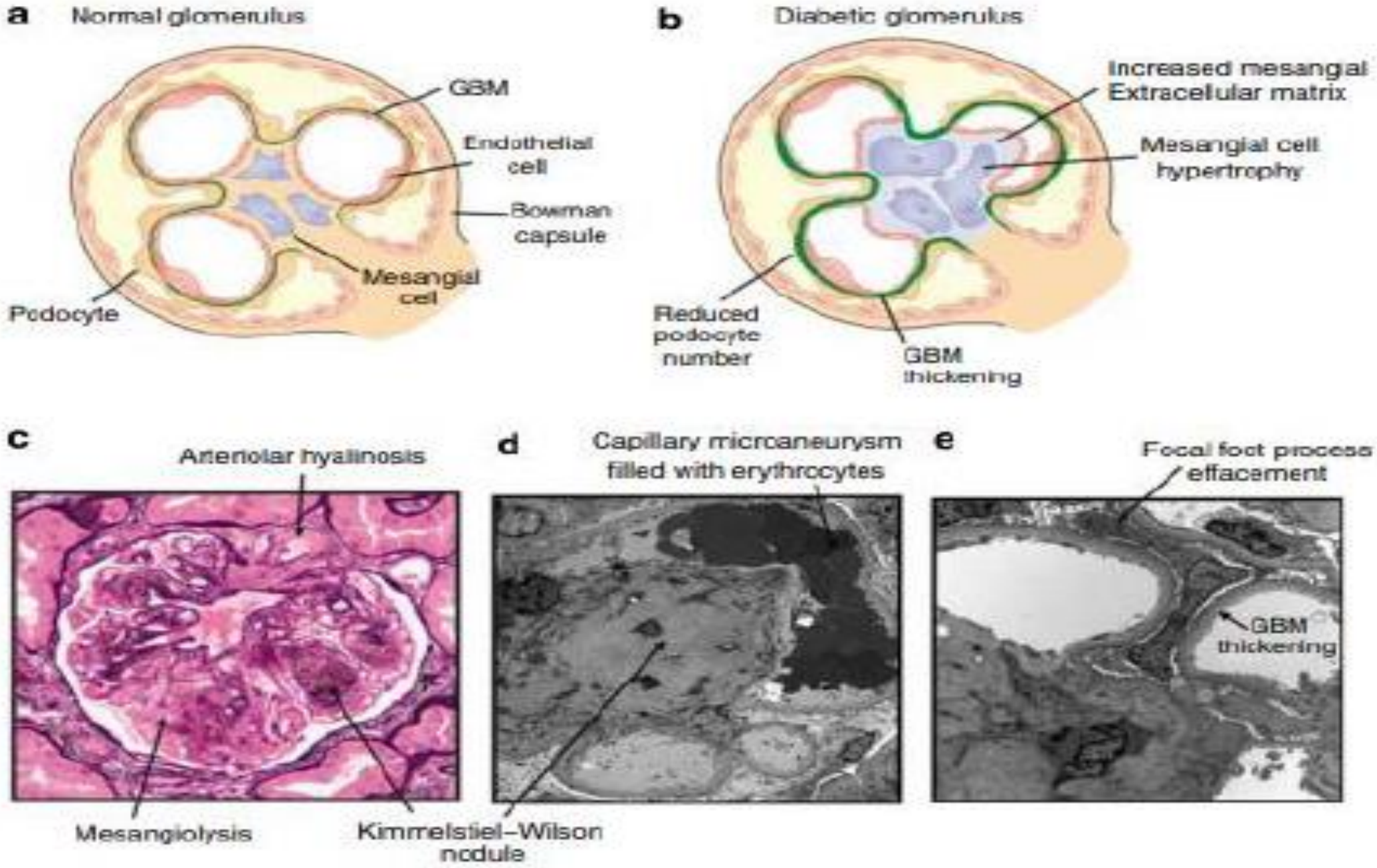
Glomerular

- Thickening of glomerular basement membrane (GBM)
- Mesangial expansion
- Nodular glomerulosclerosis (Kimmelstiel-Wilson lesions)

Interstitial

- Thickening of tubular basement membrane (TBM)
- Arteriolar hyalinosis


Kimmelstiel-
Wilson- nodule
Thickened
GBM
Mesangial
expansion
Diabetic
Normal


a
Normal glomerulus
GBM
Endothelial cell
Bowman capsule
Mesangial cell
Podocyte
b
Diabetic glomerulus
Increased mesangial Extracellular matrix
Mesangial cell hypertrophy
Reduced podocyte number
GBM thickening
c
Arteriolar hyalinosis
Mesangiolysis
Kimmelstiel–Wilson nodule
d
Capillary microaneurysm filled with erythrocytes
e
Focal foot process effacement
GBM thickening

RISK FACTORS

- Hypertension
- Hyperglycemia
- Dyslipidemia
- Obesity
- Smoking
- Genetic susceptibility

RELATION BETWEEN DIABETIC NEPHROPATHY AND RETINOPATHY

- Patients with nephropathy and **DM1** almost always have other signs of diabetic microvascular disease, such as retinopathy and neuropathy.
- But not true for type 2.
- >90% of Ptients with DM1 & nephropathy have **retinopathy**
- But only 60% of patients with DM2 & nephropathy have **retinopathy**

NONDIABETIC RENAL DISEASE

- Onset of proteinuria less than five years from the documented onset of type 1 diabetes.
  - since the latent period for overt diabetic nephropathy is usually at least 10 to 15 years. The latent period is probably similar in patients with type 2 diabetes, but the time of onset is often difficult to ascertain.
- Presence of an active urine sediment containing red cells and cellular casts.
- In **type 1 diabetes**, the absence of diabetic **retinopathy** or neuropathy.
- Rapidly decreasing glomerular filtration rate. (more than 5 cc/min/year)
- Rapidly increasing protein excretion or acute onset of nephrotic syndrome.

NONDIABETIC RENAL DISEASE(continue)

- Refractory hypertension.
- Active urine sediment. (eg, hematuria and red cell or other cellular casts)
- Signs and/or symptoms of another systemic disease.
- More than a 30 percent reduction in glomerular filtration rate after initiation of therapy with an ACE inhibitor or angiotensin II receptor blocker.

Treatment of diabetic nephropathy

- Glycemic control
- Control of BP
- Lifestyle modification(healthy eating , regular exercise , weight loss if needed & smoking cessation)
- Lipid lowering
- Angiotensin inhibition
- SGLT2 inhibitors in Type 2 Diabetes

Glycemic control

- Reverse the **glomerular hypertrophy and hyperfiltration**
- Delay the development of **elevated albumin excretion**. Intensive therapy to near-normal glycemia reduces the onset or progression of diabetic nephropathy for years after less intensive therapy.
- Stabilize or decrease **protein excretion** in patients with increased albumin excretion, although this effect may not be apparent until relative normoglycemia has been maintained for two years.

Control of BP

- A reduction in blood pressure to less than 140/80 mmHg.
- Lower systolic pressure may be more effective in slowing progressive renal disease in patients with a spot urine total protein-to-creatinine ratio ≥ 1000 mg/g
- *Caution: The diastolic blood pressure should not be lowered below 75 mmHg in patients with active coronary disease, and the systolic blood pressure should not be lowered to below 110 mmHg in any patient.*

Control of BP:
Pathogenesis of HTN in DM

1. Diabetic kidney disease :

- The BP typically begins to rise within the normal range at or within a few years after the onset of **microalbuminuria** and increases progressively as the renal disease progresses.

2. Exteracellular volume expansion:

- The excess filtered glucose is reabsorbed in the proximal tubule via a **sodium-glucose cotransporter** ➡ parallel rise in sodium reabsorption ➡ **sodium retention and volume expansion**.

3. Increaced arterial stiffness:

- ↑ Protein glycation & atheromatous disease ➡ **vascular stiffness**
  The **reduction in arterial distensibility**, which is seen with both impaired glucose tolerance and overt diabetes, can contribute to the **rise in systolic pressure** and is associated with mortality risk.

Control of BP:
GOAL BLOOD PRESSURE (Uptodate recommendation)

- Goal systolic pressure:
  - 120 to 125 mmHg with automated oscillometric BP(AOBP)
  - 125 to 130 mmHg with manual ausculatory BP
- Goal diastolic pressure:
  - <80 mmHg.

Goal blood pressure according to baseline risk for cardiovascular disease and method of measuring blood pressure

	Routine/conventional office blood pressure (manual measurement with stethoscope or oscillometric device)*	Unattended AOBPM, daytime ABPM, or home blood pressure¶
Higher-risk population△		
▪ Known ASCVD◊ ▪ Heart failure ▪ Diabetes mellitus ▪ Chronic kidney disease ▪ Age ≥65 years§ ▪ Calculated 10-year risk of ASCVD event ≥10%¥	125 to 130/<80	120 to 125/<80
Lower-risk‡		
▪ None of the above risk factors	130 to 139/<90	125 to 135/<90

Control of BP:
CHOICE OF ANTIHYPERTENSIVE DRUGS

The choice of antihypertensive agents in diabetic patients is based upon their ability to do the following:

- Prevent mortality
- Prevent adverse cardiovascular events
- Prevent the progression of renal disease, if present

Control of BP:
CHOICE OF ANTIHYPERTENSIVE DRUGS

Choice

➨ Angiotensin inhibitors(ACEI & ARB)

Advantages:

- Lower the **blood pressure**, although no drug is likely to be sufficient as monotherapy.
- No specific **toxicity**, except for cough and hyperkalemia.
- No adverse effects on **lipid metabolism**.
- Lower the **plasma GLU concentration** by increasing responsiveness to insulin.
- Protection against the progression of **albuminuria**.
- May slow the progression of **retinopathy**.
- Reduction **cardiovascular mortality** & LVH regression.

Avoid combination renin-angiotensin system inhibition(ACEI+ARB)

Control of BP:
CHOICE OF ANTIHYPERTENSIVE DRUGS

- **Thiazide diuretics:**

  disadvantages:

  - Hyperglycemia
  - Hyperlipidemia
  - Hyperuricemia
  - Hypokalemia
  - Increase in CV risk

Control of BP:
CHOICE OF ANTIHYPERTENSIVE DRUGS

- **Calcium channel blockers**
  - Dihydropyridine: Amlodipine
  - Nondihydropyridine: Diltiazem ,Verapamil

  - No metabolic adverse
  - Adverse effect on heart failure
  - Best choice for **combination therapy** with ACEI & ARB

Control of BP:
CHOICE OF ANTIHYPERTENSIVE DRUGS

- **Beta blockers**
  - Hypoglycemic symptoms masking & worsening of glysemic control
  - possible exacerbation of peripheral artery disease
  - Prevention against microvascular disease

  - **Carvedilol** is a combined nonselective beta and alpha-1 adrenergic antagonist:(best choice)
    - ✓ Improves survival in patients with heart failure
    - ✓ No changes in A1C compare with metoprolol
    - ✓ Decrease albuminuria

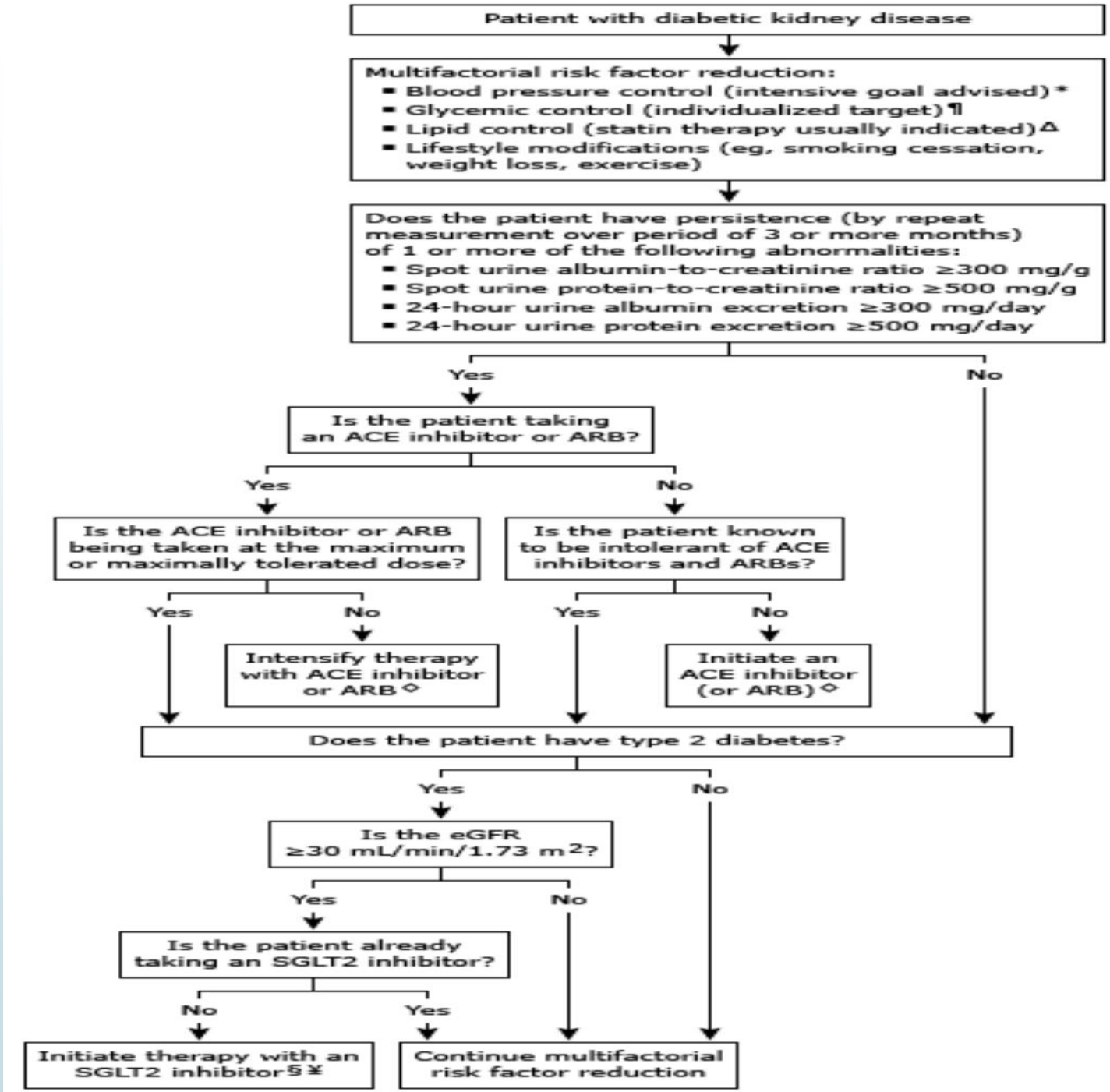
Lipid lowering

- Most patients with DKD are at high cardiovascular risk and should therefore be treated with a **statin**.
- If **statin** therapy is initiated in patients with reduced kidney function, **atorvastatin** or **fluvastatin** are often preferred because they do not require dose adjustment based upon the GFR.
- However, **statins** do not reduce the risk of cardiovascular events or mortality in patients with **ESKD** and should not be initiated in such patients

SGLT2 inhibitors in Type 2 Diabetes

- In patients with type 2 diabetes who have DKD and **severely increased albuminuria** despite angiotensin inhibition, treatment with a SGLT2 inhibitor is recommend.
- Contraindications:
  - Initiating in GFR<30 cc/min (although they can likely be continued among patients whose eGFR ultimately falls below this threshold)
  - Prior lower extremity amputation or current threat of amputation
  - Patients with a prior history of or risk factors for genital infections
  - DM type1

Approach to patient with diabetic kidney disease



Monitoring

- Patients with DKD should ideally be monitored **every 3-6 months**, with:
  - Assessments of blood pressure
  - Volume status
  - eGFR
  - Serum potassium
  - Hb A1C
  - Evaluation of urine albumin or total protein excretion (usually a random urine ACR)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