Diabetic nephropathy= persistent albuminuria (>3 g/day or 200 µg/min) + ↓GFR + ↑ BP + ↑ cardiovascular M & M

- It can be diagnosed clinically if the following additional criteria are fulfilled:
    1) Presence of diabetic retinopathy
    2) Absence of clinical or laboratory evidence of other kidney or renal tract disease.
- Microalbuminuria usually appears 5–10 years after the onset of diabetes. Although within 1–2 years morphologic changes (**thickening** of the GBM (very sensitive), expansion of the mesangium (diffuse diabetic glomerulosclerosis), nodular glomerulosclerosis (Kimmelstiel-Wilson nodular lesions), changes in podocyte number and morphology, and arteriolar hyalinosis).
- Test patients with DM1 for microalbuminuria 5 years after diagnosis of DM → yearly thereafter. If glucose levels are poorly controlled, screening should be 1 year after diagnosing DM1.
- Test patients with DM2 at the time of diagnosis of DM → yearly thereafter.

The deterioration of renal function in patients with diabetes typically occurs like this: hyperfiltration → microalbuminuria → overt nephropathy +/- the nephrotic syndrome → ESRD

Hyperfiltration: GFR above the upper normal range. Intensified insulin and glucose levels control reduce GFR toward normal levels within days -weeks. No albuminuria or HTN.

Microalbuminuria: urinary albumin is between **0.3 g and 3 g/24 hr**. in at least two out of **three** consecutive non-ketotic sterile urine samples. Urinary albumin/creatinine ratio is 0.3 to 3 g /g creatinine. Elevated filtration both at rest and during exercise.

Patients with DM1 have a **higher risk** for developing **DN** than patients with DM2. However, decline rate of GFR is the same in both types. In DM1, the onset of microalbuminuria typically coincides with the development of hypertension. More than 90% of patients with DM1 and nephropathy have diabetic retinopathy so the absence of retinopathy in DM1 with proteinuria should prompt consideration of a diagnosis other than diabetic nephropathy. Only 60% of patients with DM2 with nephropathy have diabetic retinopathy.

Microalbuminuria is a strong predictor of total and cardiovascular M & M.

The 1st sign of DN? Albuminuria (between**0.3 g and 3 g/24 hr**)

The 1st symptom of DN? Peripheral edema

Macrovascular disease (e.g., stroke, carotid artery stenosis, coronary heart disease, and peripheral vascular disease) are two to five times more common in patients with diabetic nephropathy.

(1) **Puberty**, (2) poor glycemic control and (3) poor lipid control are independent risk factors for microalbuminuria .

Renal biopsy is the gold standard. However, you should assume diabetic nephropathy and delay taking a biopsy (1) if there's macro albuminuria (>300 mg/24 hours), microalbuminuria (30-300 mg/24 h) with retinopathy, microalbuminuria in patients with diabetes for more than 10 years.

It's not diabetic nephropathy if there's hematuria, nephrotic range proteinuria at the time of diagnosis of diabetes, the presence other systemic diseases (e.g., autoimmune disease, HCV, HIV) → require a renal biopsy to diagnose.

Tx.

- Goal: 1. Glycemic control 2. Blood pressure control (target a blood pressure of **130/80** mmHg) 3. RAAS inhibition
- Monotherapy with either an ACE inhibitor or ARB.
- Sodium glucose cotransporter 2 inhibitors (SGL2 Inhibitors) for glycemic control.
- Diuretics. Thiazides → limited to whose **GFR is >40 mL/min**. Loop diuretics are better for patients whose **GFR is < 40ml/min**.
- Low sodium diet, smoking cessation
- For hypertensive patients, Beta adrenergic antagonists may be indicated in patients with arrhythmias, CHF, and CAD. Calcium channel blockers if there're no such conditions.

Lupus nephritis is histologically evident in most patients with SLE within 5 years of diagnosis (patient is 21 to 40 y/o)

- Some anti-dsDNA antibodies cross react with the glomerular basement membrane. Also, higher-affinity autoantibodies (e.g., cationic antibodies) may form intravascular immune complexes, which are deposited in glomeruli. Additionally, autoantibodies of certain isotypes (IgG-1 and IgG-3)readily activate complement.
- 35% of patients have clinical evidence of nephritis at time of diagnosis, and 50–60% develops nephritis during the first 10 years of disease.
- ALL (100%) patient who develops LN has positive anti-dsDNA, and proteinuria.
- 40% has class IV LN.
- Lupus nephritis is the most common secondary GN.
- Can be asymptomatic. Symptoms related to active nephritis may include peripheral edema secondary to hypertension (in 15%) or hypoalbuminemia. Hypertension symptoms (headache, dizziness, visual disturbances, and signs of cardiac decompensation) are usually evident. Hyperkalemia is present in 15% of LN patients.
- C-reactive protein (CRP) level may be normal, but erythrocyte sedimentation rate (ESR) is almost always increased.
- Anti-C1q antibodies are increased but are less sensitive then anti dsDNA, and more specific.
- When to take a biopsy? any of the following
    1. Increasing creatinine without an obvious cause (such as sepsis, hypovolemia, or medication).
    2. Confirmed proteinuria of 1.0 gm per 24 hours.
    3. Proteinuria (>= 0.5 g/day) + hematuria (>= 5 RBCs per hpf) ← confirmed in at least 2 tests done within a short period
    4. Proteinuria (>= 0.5 g/day) + cellular casts ← confirmed in at least 2 tests done within a short period
    5. All patients with clinical evidence of active LN (e.g., edema, HTN, hyperkalemia…).

Classification category	Features
Class I: minimal mesangial	Normal/minimal proteinuria, normal creatinine Earliest and mildest form of glomerular involvement
Class II: mesangial proliferative	Microscopic haematuria +/– proteinuria Hypertension uncommon and nephrotic syndrome plus renal insufficiency rarely seen
Class III: focal lupus nephritis	Haematuria, proteinuria, hypertension, reduced eGFR +/– nephrotic syndrome
Class IV: diffuse lupus nephritis	Most common and severe form of lupus nephritis Clinical features as for class III but also significantly low C3 and high dsDNA, especially in active disease
Class V: membranous nephropathy	Nephrotic syndrome, microscopic haematuria, hypertension, normal/high creatinine Can present without other clinical or serological manifestations of SLE but electron microscopy features will distinguish it from the idiopathic form
Class VI: advanced sclerosing lupus	Slowly progressive renal failure with proteinuria and bland urine sediment

Adapted from Bomback AS, Appel GB. UpToDate: 2018.[12]
Abbreviations: dsDNA = double-stranded DNA; eGFR = estimated glomerular filtration rate; SLE = systemic lupus erythematosus.

Tx.

Goal: normalize renal function or to prevent progressive loss of renal function.

- Induction/initial therapy: corticosteroids, combined with either cyclophosphamide or MMF. (immunosuppression)
- Maintenance therapy: azathioprine or MMF ± low-dose oral corticosteroids. (immunosuppression)
- Calcineurin inhibitors with low-dose corticosteroids be used for maintenance therapy in patients who are intolerant of MMF and azathioprine.
- Relapse/flares is around ¼ at 5 y and ½ at 10 y. Types of renal flares: (1) proteinuric (↑proteinuria), and (2) nephritic (↑>30% of serum creatinine and/or active urine sediment). Flares are associated with RBC or WBC casts, low C3 and C4 and rise in ds DNA.
- Transplantation: ensure that the patient does not have active SLE disease at the time of transplantation. A 3-month period of dialysis is usually prudent because 3.3% of patients on RRT get their kidneys recovered. Recurrent lupus nephritis <2% after transplantation.
- Patients should avoid pregnancy because it may aggravate renal disease. Also, pregnant patients with lupus nephritis are prone to preeclampsia. Preexisting hypertension and antiphospholipid antibody syndrome are the two most common predisposing factors to preeclampsia.