# Diabetic nephropathy and Lupus Nephritis

# Diabetic nephropathy

# Definition

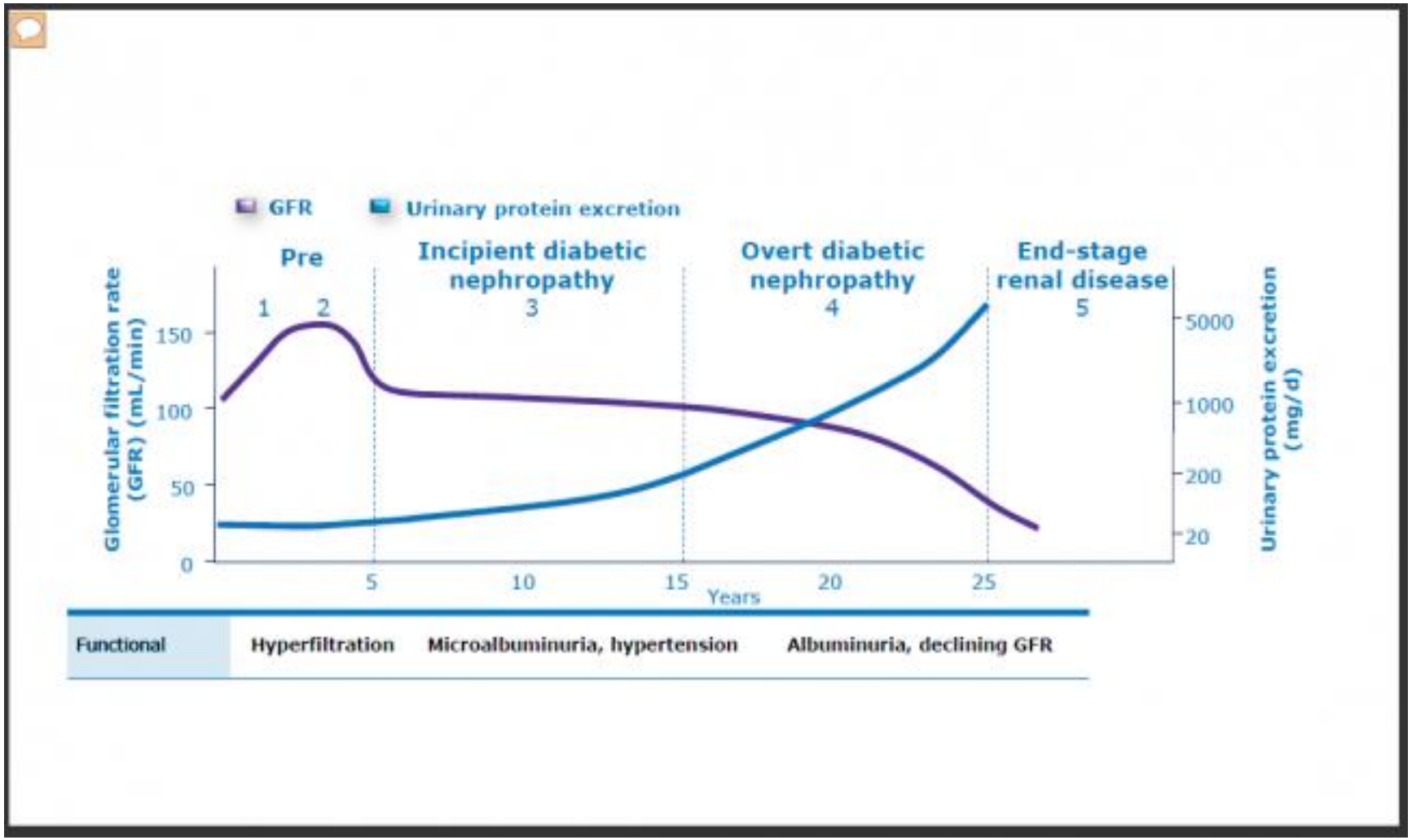
- Persistent albuminuria (>300 mg/24 hr or 200 μg/min) is the hallmark of diabetic nephropathy.

- Can be diagnosed clinically if the following additional criteria are fulfilled:
  - Presence of diabetic retinopathy
  - Absence of clinical or laboratory evidence of other kidney or renal tract disease.

- Clinically, diabetic nephropathy is characterized by a progressive increase in proteinuria and decline in GFR, hypertension, and a high risk of cardiovascular morbidity and mortality.

- Approximately 40% of patients with types 1 or 2 diabetes develop nephropathy, but due to the higher prevalence of type 2 diabetes (90%) compared to type 1 (10%), the majority of patient with diabetic nephropathy have type 2 disease.

# Progression of diabetic nephropathy



- Microalbuminuria appears 5–10 years after the onset of diabetes.
- It is currently recommended
    - To test patients with type 1 disease for microalbuminuria 5 years after diagnosis of diabetes and yearly thereafter
    - To test type 2 patients at the time of diagnosis of diabetes and yearly thereafter

- Within 1–2 years after the onset of clinical diabetes, morphologic changes appear in the kidney. Thickening of the GBM is a sensitive indicator for the presence of diabetes but correlates poorly with the presence or absence of clinically significant nephropathy.

# Pathology

- The composition of the GBM is altered notably with a loss of heparin sulfate moieties that form the negatively charged filtration barrier.
- This change results in increased filtration of serum proteins into the urine, predominately negatively charged albumin

# Pathology

- The expansion of the mesangium due to the accumulation of extracellular matrix correlates with the clinical manifestations of diabetic nephropathy
- The diffuse and generalized process of mesangial expansion has been termed diffuse diabetic glomerulosclerosis .
- Nodular glomerulosclerosis (Kimmelstiel- Wilson nodular lesions) represents areas of marked mesangial expansion appearing as large round fibrillar mesangial zones, often with extreme compression of the adjacent glomerular capillaries
- Afferent and efferent glomerular arteriolar hyalinosis can also be detected within 3 to 5 years after onset of diabetes.

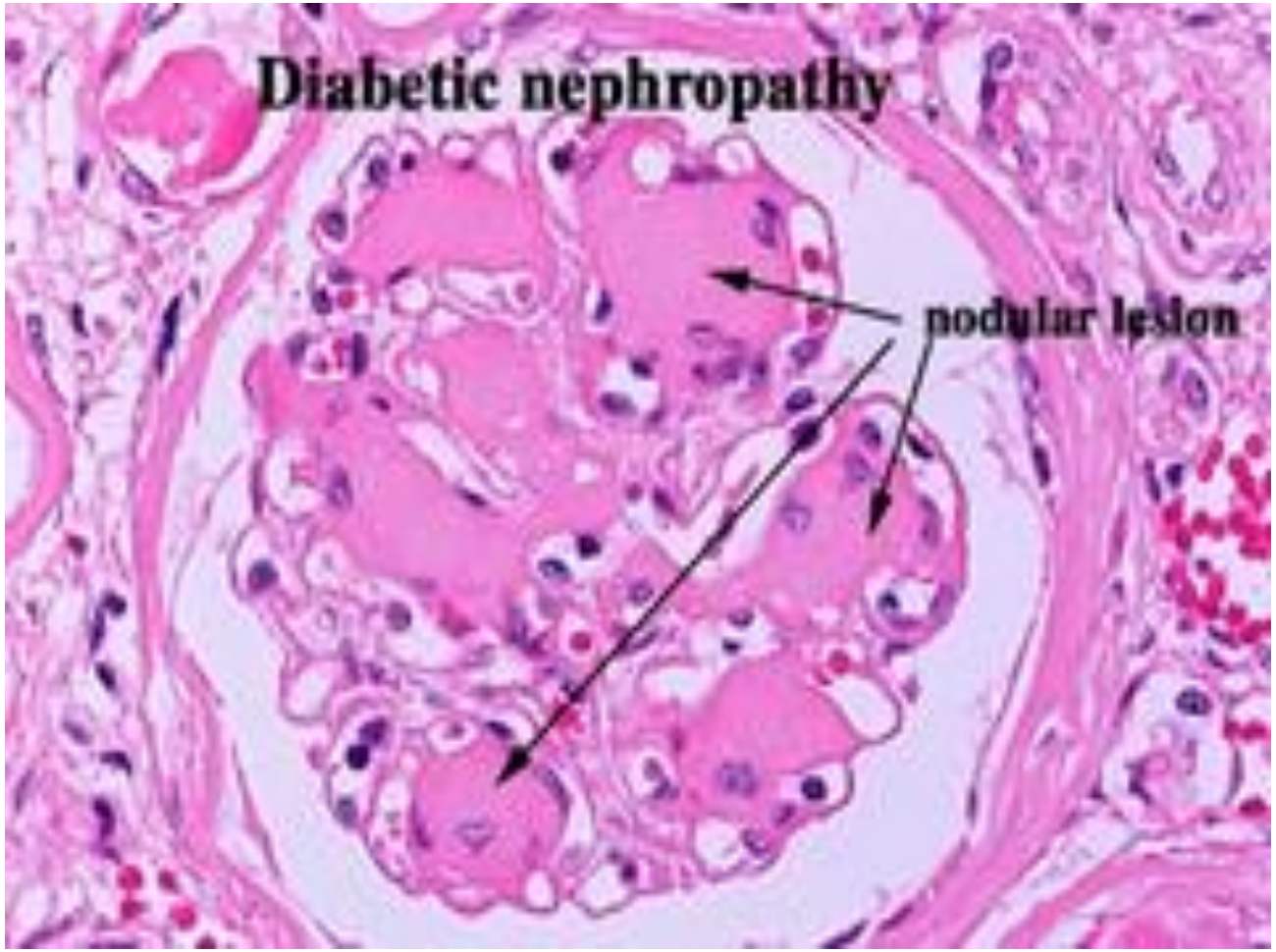
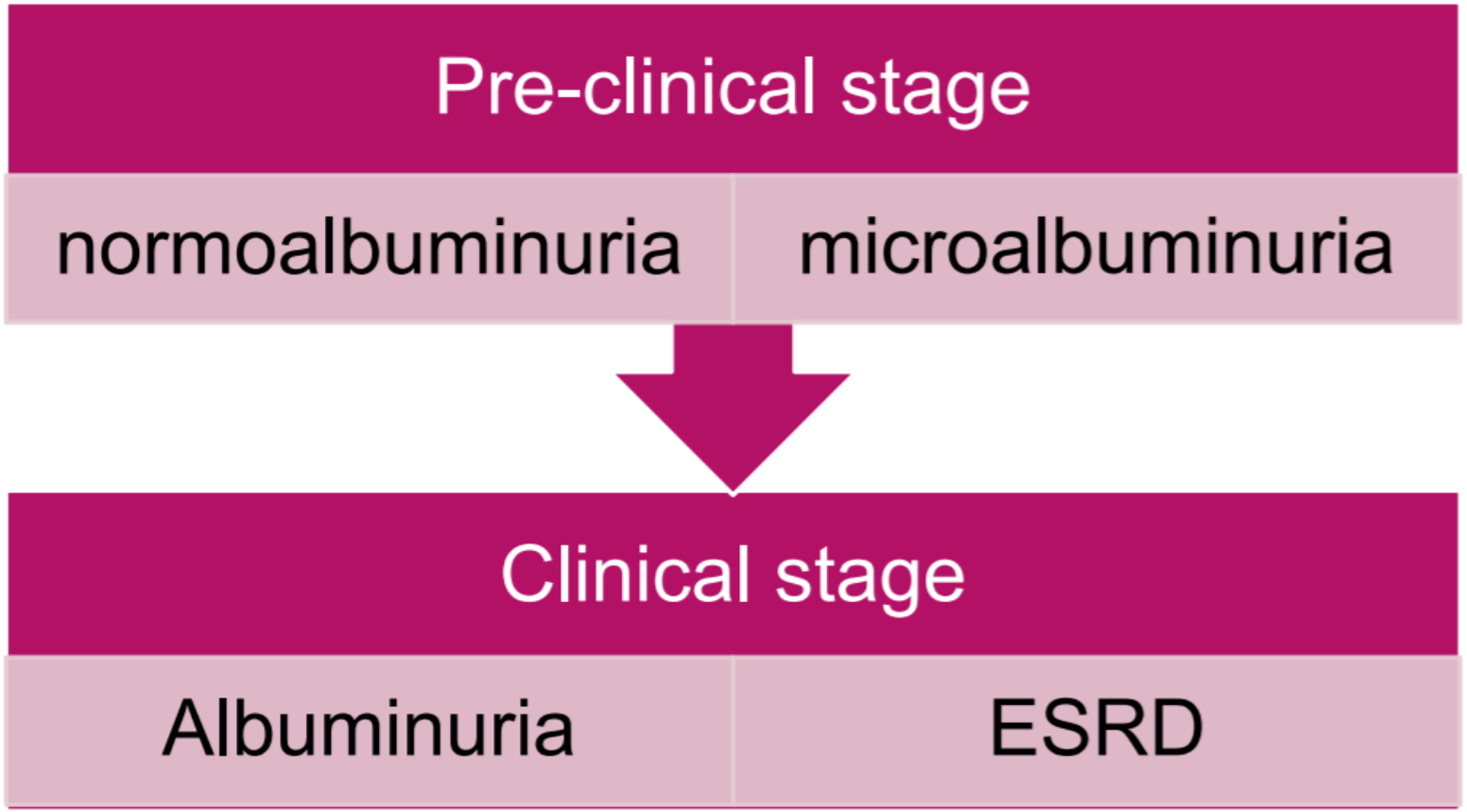



**Fig 2.** Diabetic nephropathy is one of the causes of nodular glomerulosclerosis, illustrated here, with large nodules of matrix within mesangial areas with lesser increase in mesangial cellularity. The glomerular basement membrane is thick without apparent deposits. (Periodic acid-Schiff stain, original magnification X400).

# Clinical course



- The deterioration of renal function in patients with diabetes typically occurs over the course of several phases, which include :

- 1) hyperfiltration.
- 2) microalbuminuria.
- 3) overt nephropathy +/- the nephrotic syndrome.
- 4) ESRD

# Normoalbuminuria with hyperfiltration

- Albuminuria less than 30mg/day Hypertension and albuminuria are typically not present during this phase.
- Characteristic feature is a GFR above the upper normal range for age-matched healthy nondiabetic subjects.
- Intensified insulin treatment and control to near-normal blood glucose levels reduce GFR toward normal levels after a period of days to weeks in both type 1 and type 2 diabetic patients.

- 2.71X it  progress to microalbuminuria in patients with hyperfiltration.

# Microalbuminuria

- Urinary albumin excretion within the microalbuminuric range (30 mg to 300 mg/24 hr) in at least two out of three consecutive nonketotic sterile urine samples is defined as persistent microalbuminuria.
- Urinary albumin/creatinine ratio is measured, and microalbuminuria is defined as 30 to 300 mg/g creatinine.

# Microalbuminuria

- Factors causing microalbuminuria are:
    - Loss of glomerular charge selectivity
    - Changes in podocyte number and morphology.
    - Elevated filtration both at rest and during exercise compared with normal controls
    - Glomerular hypertension with or without systemic hypertension.

# Microalbuminuria as a Predictor of Nephropathy

- Type 1 diabetic patients with microalbuminuria have a median risk ratio of 21 for developing diabetic nephropathy,

- Type 2 diabetic patients with microalbuminuria have medican risk ratio for developing diabetic nephropathy ranges from 4.4 to 21 (median = 8.5) in type 2 diabetic patients with microalbuminuria.

- It has been suggested that 58% of microalbuminuric patients revert to normoalbuminuria with good glycemic control.

- In type 1 diabetics, the onset of microalbuminuria typically coincides with the development of hypertension.

- The presence of hypertension during this phase is more variable among type 2 diabetics.

- Microalbuminuria is a strong predictor of total and cardiovascular mortality and cardiovascular morbidity in diabetic patients.

- Similarly, microalbuminuria predicts coronary and peripheral vascular disease, death from cardiovascular disease and stroke in the general nondiabetic population.

# Diabetic nephropathy

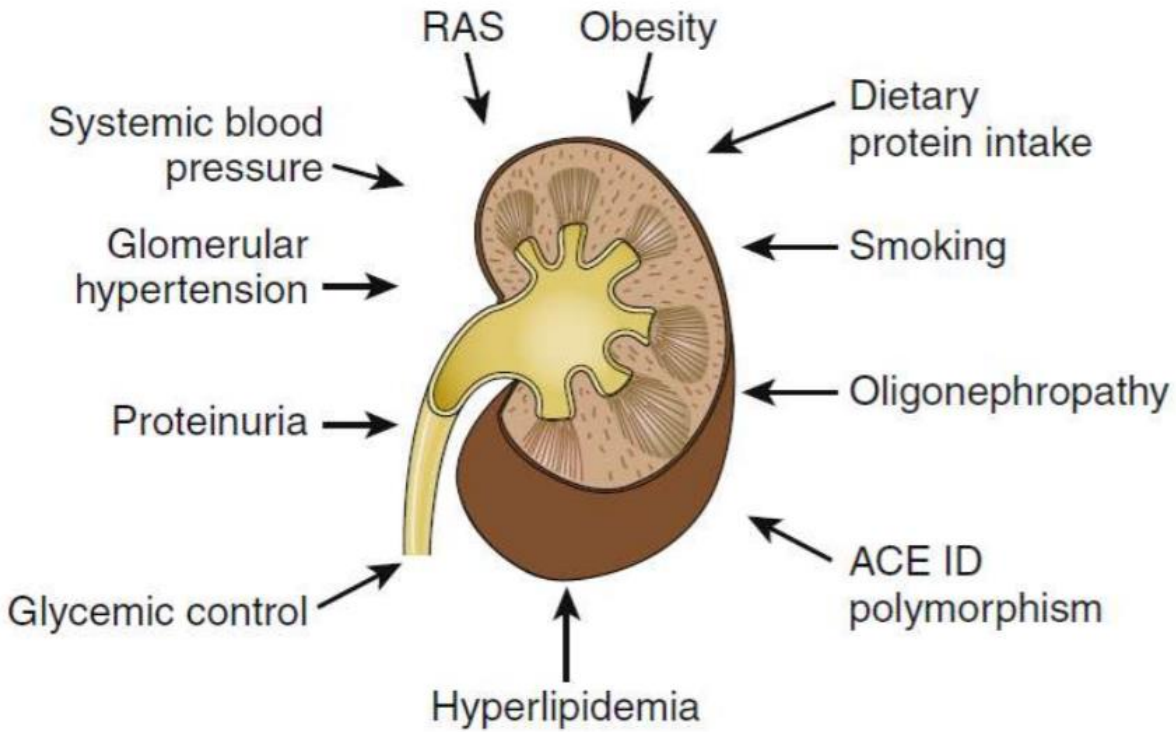
- Diabetic nephropathy is a clinical syndrome characterized by
    - Persistent albuminuria (>300 mg/24 hr, or 300 mg/g creatinine).
    - A decline in GFR.
    - Raised arterial blood pressure.
    - Enhanced cardiovascular morbidity and mortality.

- Albuminuria is the first sign, peripheral edema is often the first symptom of diabetic nephropathy.

- Fluid retention is frequently observed early in the course of this kidney disease; that is, at a stage characterized by well preserved renal function and only a modest reduction in serum albumin level

- Rate of decline in GFR is highly variable across individuals, ranging from 2 to 20 mL/min/yr, with a mean approximating 12 mL/min/yr and is similar in both types of diabetes.

# Factors contributing to progression of DN



- Systemic hypertension lead to hyperperfusion and increased capillary pressure – Glomerular hypertension.

- Impaired or abolished renal autoregulation of GFR and renal plasma flow as demonstrated in type 1 and type 2 diabetic patients with nephropathy increases vulnerability to hypertension or ischemic injury of glomerular capillaries

# Diabetic retinopathy

- More than 90% of patients with type 1 diabetes and nephropathy have diabetic retinopathy

- So the absence of retinopathy in type 1 patients with proteinuria should prompt consideration of a diagnosis other than diabetic nephropathy

- Only 60% of patients with type 2 diabetes with nephropathy have diabetic retinopathy.

# Macrovascular disease

- Macroangiopathies (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.

# SCREENING AND DIAGNOSIS

- Screening for diabetic nephropathy must be initiated
    - Type 2 at the time of diagnosis, since 7% of them already have microalbuminuria at that time
    - Type 1 diabetes, the first screening has been recommended at 5 years after diagnosis

- Puberty, poor glycemic control and poor lipid control are independent risk factors for micro albuminuria .

- Therefore, in type 1 diabetes, screening for micro albuminuria might be performed 1 year after diabetes diagnosis in these patients or patients with poor glycaemic control

- If micro albuminuria is absent, the screening must be repeated annually for both type 1 and 2 diabetic patients

# Diagnosis

- Renal biopsy is the gold standard
- A renal biopsy may be deferred with the assumed diagnosis of diabetic nephropathy in the context of :
    - Macro albuminuria (>300 mg/24 hours) that has developed progressively,
    - Microalbuminuria (30-300 mg/24 h) with retinopathy
    - Microalbuminuria in patients with diabetes for more than 10 years .

# Its not Diabetic nephropathy if :

- Haematuria,
- Nephrotic range proteinuria at the time of diagnosis of diabetes,
- The presence other systemic disease processes including autoimmune disease, hepatitis C, or human immunodeficiency virus warrant the consideration of another potentially treatable condition that would require a renal biopsy to diagnose.

# Treatment goals include:

1. Glycemic control
2. Blood pressure control
3. RAAS inhibition:
    - Monotherapy with either an ACE inhibitor or ARB is currently recommended as first line therapy for diabetic patients with microalbuminuria or diabetic nephropathy.
    - Beyond the impact of blood pressure lowering, inhibition of the RAAS additionally slows the progression of diabetic nephropathy compared to other antihypertensive drugs.
    - The current recommendations outlined by the National Kidney Foundation are to target a blood pressure of 130/80 mmHg in diabetic patients
4. sodium glucose cotransporter 2 inhibitors (SGL2 Inhibitors)

# General recommendations

Patients should adhere to a low sodium diet

The use of diuretics may also enhance the antiproteinuric effects of RAAS inhibition while simultaneously decreasing fluid overload and HTN

The use of thiazide diuretics should be limited to patients whose GFR is >40 mL/min, and loop diuretics dosed at least twice daily are more appropriate for patients whose GFR is < 40ml/min.

Smoking Cessation

# General recommendations

- Patients with diabetic nephropathy frequently require additional antihypertensive drugs, and drugs may be selected according to the comorbidity profile of an individual patient.

- Beta adrenergic antagonists may be indicated in patients with arrhythmias, congestive heart failure, and coronary artery disease

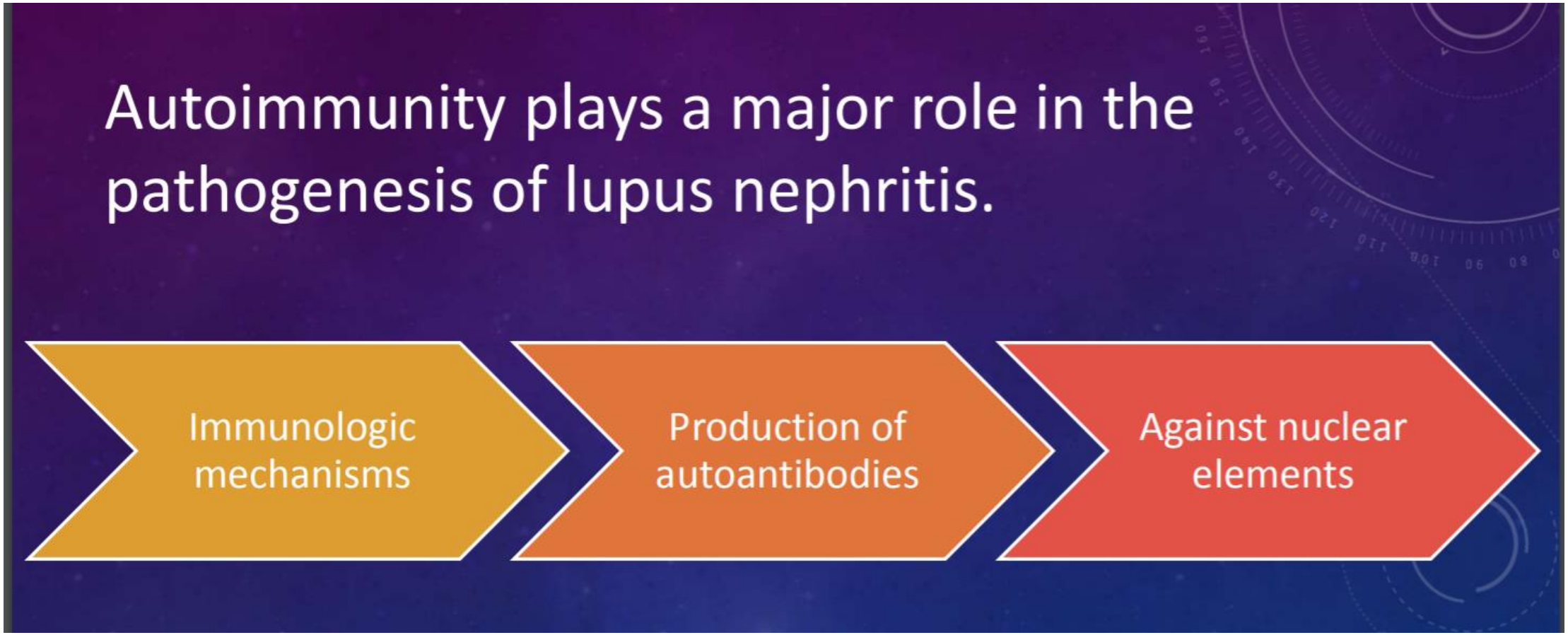
- calcium channel blockers can be preferentially used in patients that lack these conditions.

# Lupus Nephritis

LUPUS NEPHRITIS

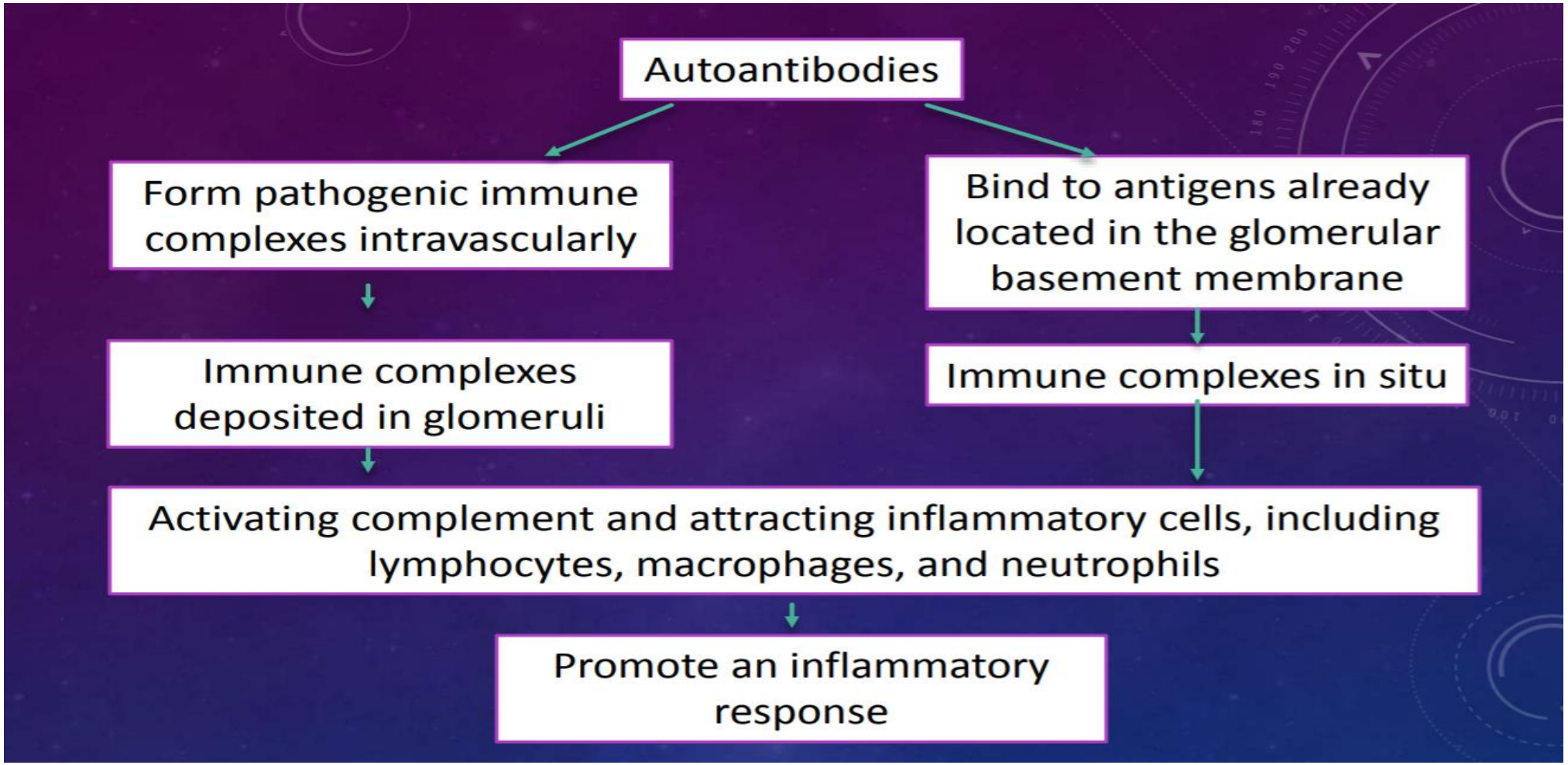
- Lupus nephritis is histologically evident in most patients with SLE.
- One of the most serious manifestations of SLE.
- Usually arises within 5 years of diagnosis.

# PATHOPHYSIOLOGY



# PATHOPHYSIOLOGY

- The characteristics of the nephritogenic autoantibodies associated with lupus nephritis are as follows:
- Antigen specificity directed against nucleosome or double stranded DNA (dsDNA) - Some anti-dsDNA antibodies cross react with the glomerular basement membrane.
- Higher-affinity autoantibodies may form intravascular immune complexes, which are deposited in glomeruli.
- Cationic autoantibodies have a higher affinity for the anionic glomerular basement membrane. iv. Autoantibodies of certain isotypes (immunoglobulin IgG 1 and IgG 3 ) readily activate complement.




The histologic type of lupus nephritis that develops depends on numerous factors, including the antigen specificity and other properties of the autoantibodies and the type of inflammatory response that is determined by other host factors.

- 35% adults having SLE have clinical evidence of nephritis at time of diagnosis.
- 50–60% developing nephritis during the first 10 years of disease.
- Female
- 73.2% between age of 21 to 40 year
- 100% has positive Anti-ds DNA
- 40% Common histological type was Class IV
- Lupus nephritis was the most prevalent among secondary GN

# CLINICAL FEATURES: SYMPTOMS

- Asymptomatic
- Symptoms of active systemic lupus erythematosus (SLE), including fatigue, fever, rash, arthritis, serositis, or central nervous system (CNS) disease.
- Symptoms related to active nephritis may include peripheral edema secondary to hypertension or hypoalbuminemia.
- Other symptoms directly related to hypertension that are commonly associated with diffuse lupus nephritis include headache, dizziness, visual disturbances, and signs of cardiac decompensation

- **TABLE 1** -- Clinical features of patients with lupus nephritis

| Feature of | % of Those with Nephritis |
|---|---|
| Proteinuria | 100 |
| Nephrotic syndrome | 45 to 65 |
| Granular casts | 30 |
| Red cell casts | 10 |
| Microscopic hematuria | 80 |
| Macroscopic hematuria | 1 to 2 |
| Reduced renal function | 40 to 80 |
| Rapidly declining renal function | 30 |
| Acute renal failure | 1 to 2 |
| Hypertension | 15 to 50 |
| Hyperkalemia | 15 |
| Tubular abnormalities | 60 to 80 |

# LABORATORY TESTS

- Blood urea nitrogen (BUN)
- Serum creatinine
- Urinalysis to check for protein, red blood cells [RBCs], and cellular casts)
- A spot urine test for creatinine and protein concentration (normal creatinine excretion is 1000 mg/24 h/1.75 m 2 ; normal protein excretion is 150-200 mg/24 h/1.75 m 2 ; normal urinary protein-to-creatinine ratio is

# LABORATORY TESTS

- ANA [for diagnosis SLE]
- Antibodies to double-stranded DNA (dsDNA), ↑
- Complement (C3, C4, and CH50), ↓
- Erythrocyte sedimentation rate (ESR), ↑
- C-reactive protein (CRP) levels. ↔
- Anti-C1q antibodies ↑ [less sensitive then Anti dsDNA, but more specific]

# INDICATIONS FOR RENAL BIOPSY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

- Increasing serum creatinine without compelling alternative causes (such as sepsis, hypovolemia, or medication)
- Confirmed proteinuria of 1.0 gm per 24 hours (either 24- hour urine specimens or spot protein/creatinine ratios are acceptable)
- Combinations of the following, assuming the findings are confirmed in at least 2 tests done within a short period of time and in the absence of alternative causes:

  - Proteinuria 0.5 gm per 24 hours plus hematuria, defined as 5 RBCs per hpf ,

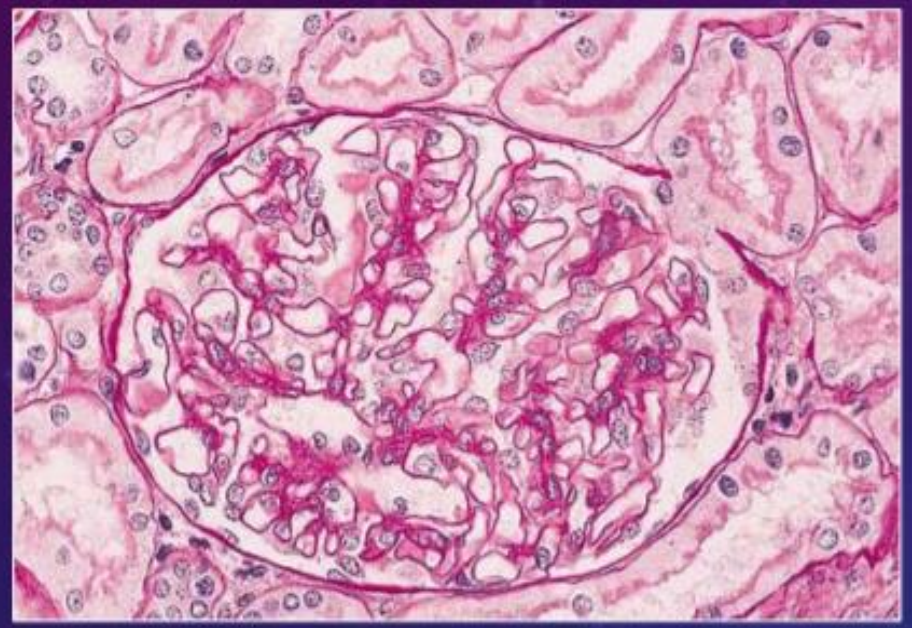
  - Proteinuria 0.5 gm per 24 hours plus cellular casts

# RENAL BIOPSY

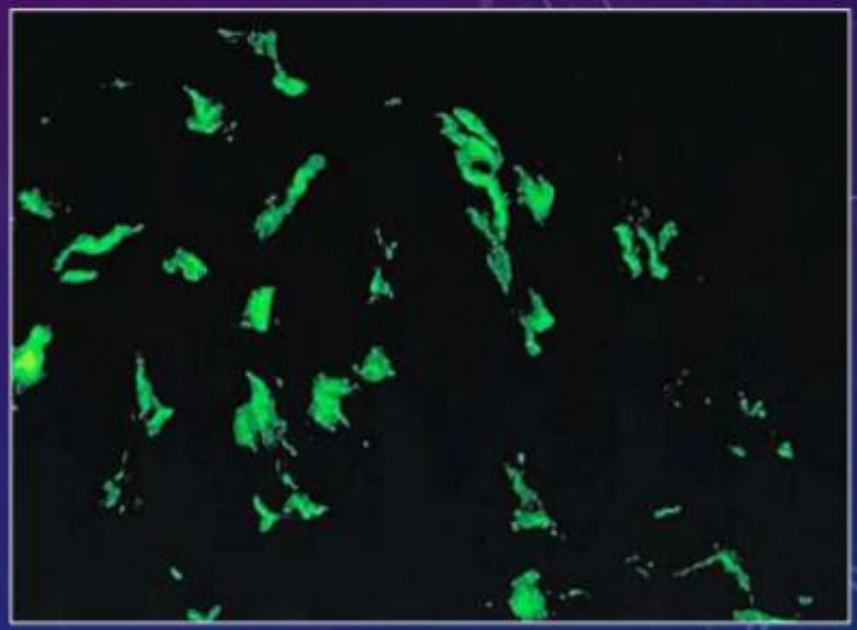
- All patients with clinical evidence of active LN, previously untreated, undergo renal biopsy (unless strongly contraindicated) for
    - Classified by current ISN/RPS classification
    - Disease evaluated for activity and chronicity
    - Identify additional or alternative causes of renal disease
    - Determining prognosis and treatment

| International Society of Nephrology/Renal Pathology Society 2003 classification of LN | |
|---|---|
| Class I | Minimal mesangial LN |
| Class II | Mesangial proliferative LN |
| Class III | Focal LN (50% of glomeruli)<br>III (A): active lesions<br>III (A/C): active and chronic lesions<br>III (C): chronic lesions |
| Class IV | Diffuse LN (50% glomeruli)<br>Diffuse segmental (IV-S) or global (IV-G) LN<br>IV (A): active lesions<br>IV (A/C): active and chronic lesions<br>IV (C): chronic lesions |
| Class V | Membranous LN |
| Class VI | Advanced sclerosing LN (90% globally sclerosed glomeruli without residual activity) |

# CLASS I

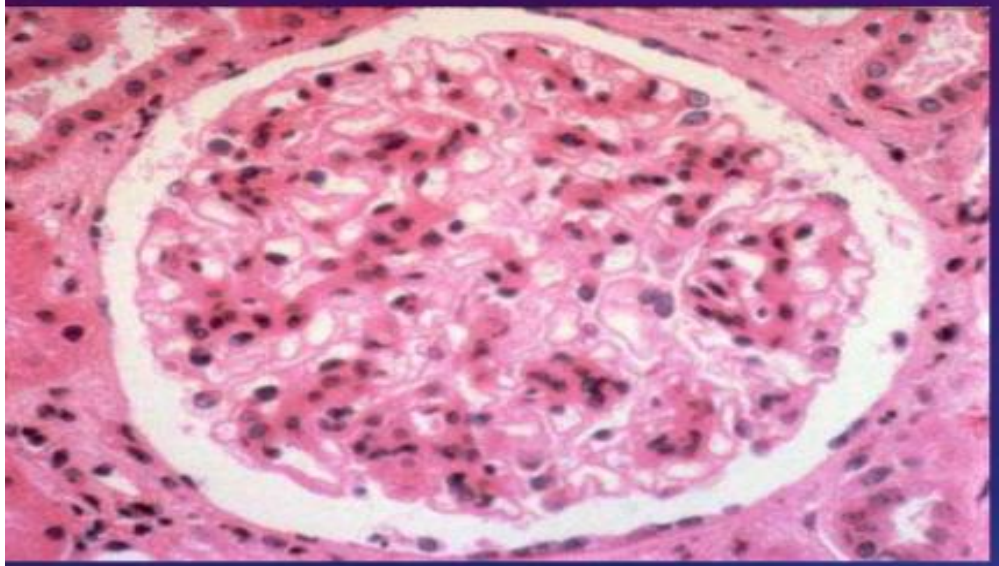


No structural changes by light microscopy

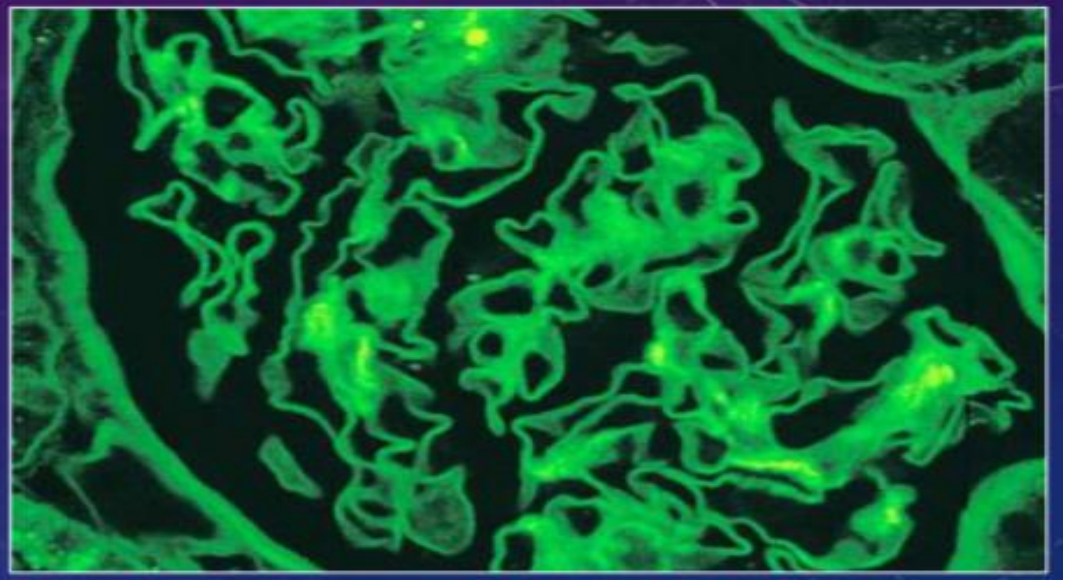


Delicate mesangial positivity for IgG.

# CLASS II

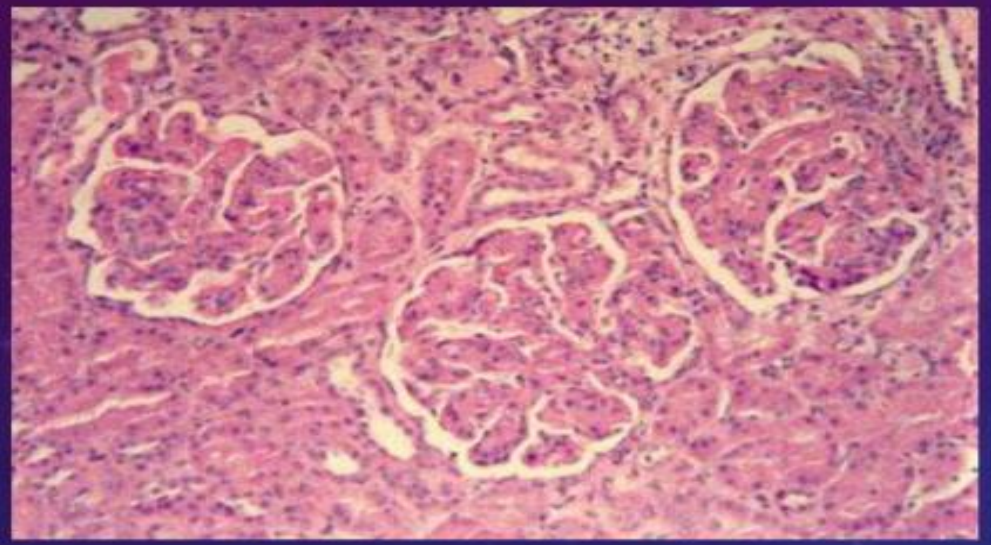


Mesangial cell proliferation, mesangial matrix expansion.

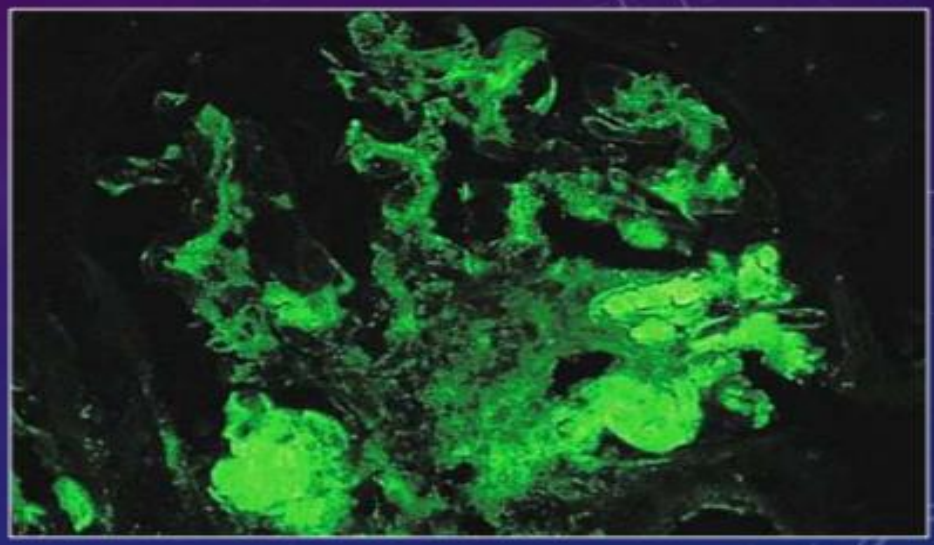


Granular mesangial positivity of all three immunoglobulins and both complements (C1q and C3) ("full house" pattern)

# CLASS III

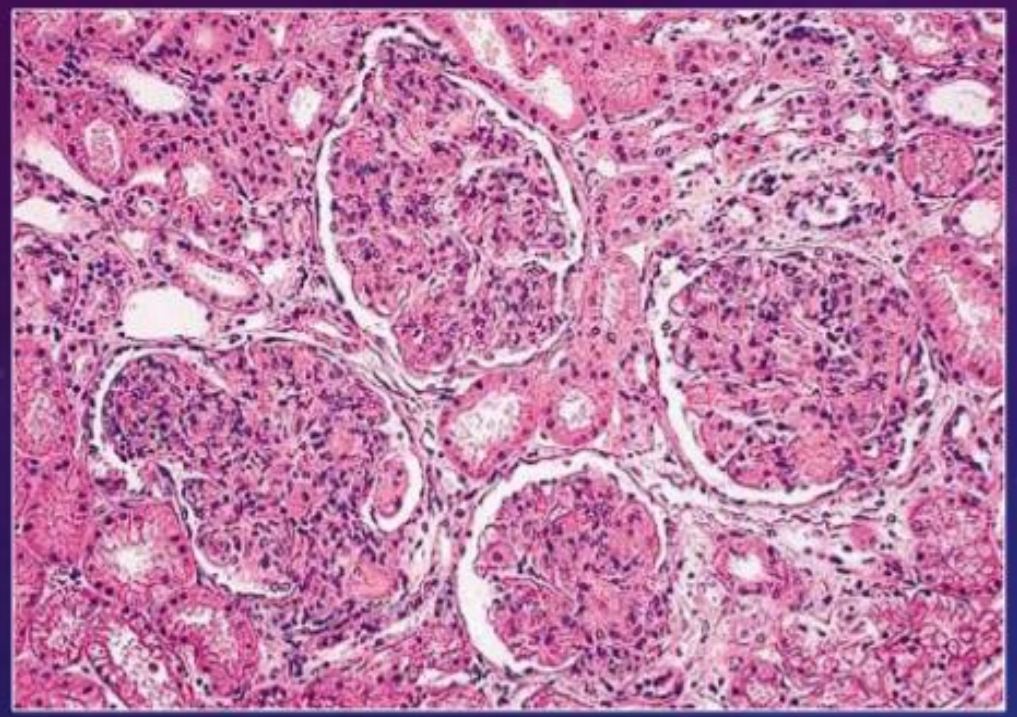


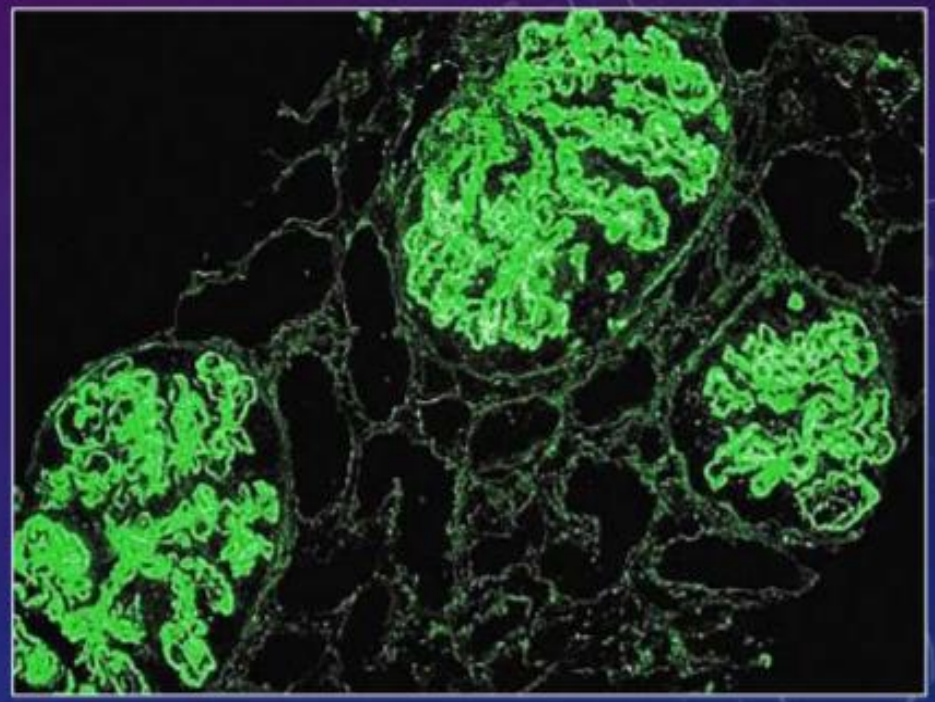
Less than 50% of all glomeruli, segmental or global, swelling and proliferation of endothelial and mesangial cells associated with leukocyte accumulation, capillary necrosis, and hyaline thrombi; extracapillary proliferation, crescents.



Full house pattern as in class II, immune deposits also identified in tubular basement membranes, interstitial capillary walls, interstitial collagen, arterial intima, and media, Fibrinogen positivity

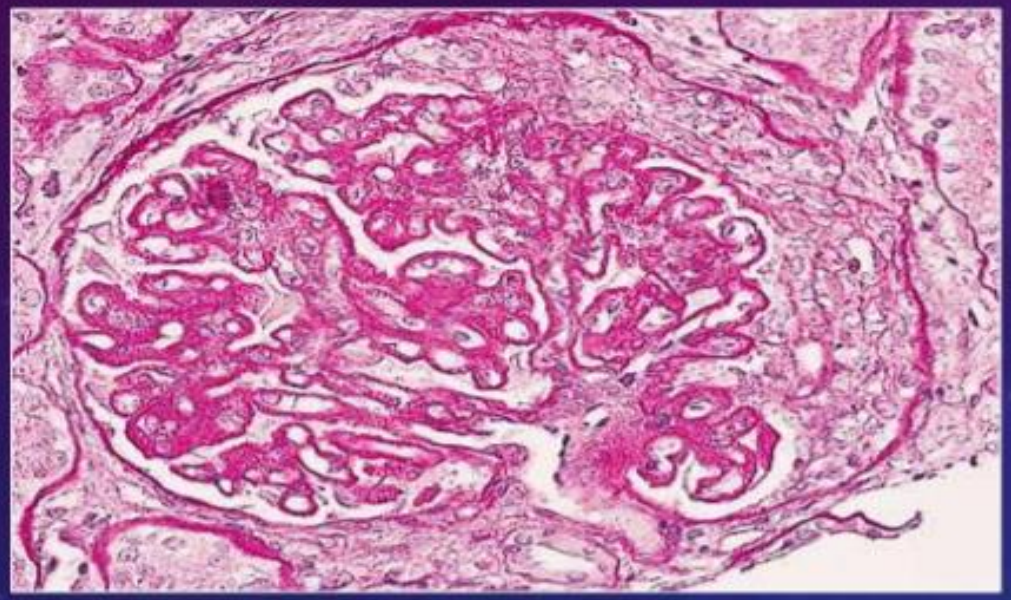
# CLASS IV



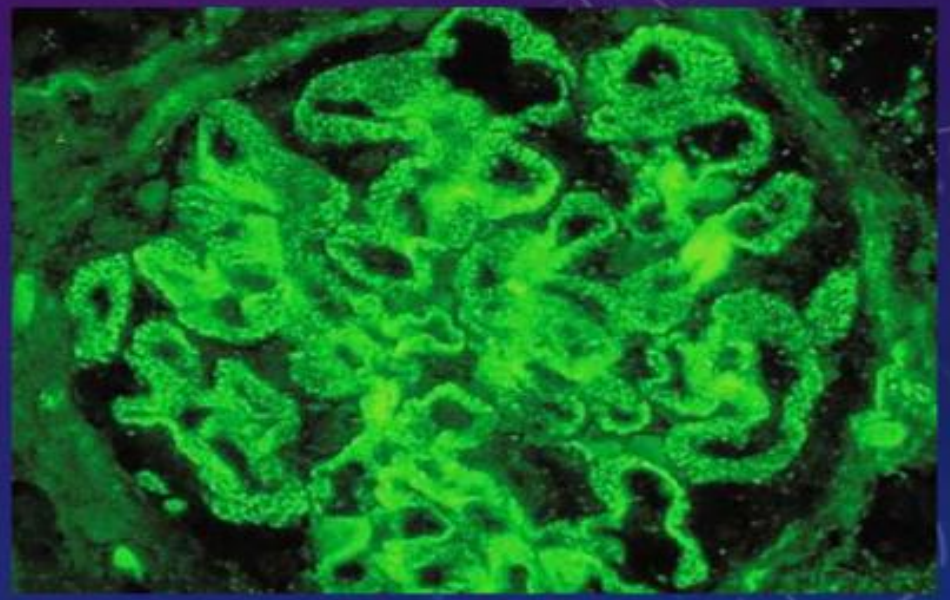


Lesions similar to Class III, but
involves > 50% of glomeruli

# CLASS V

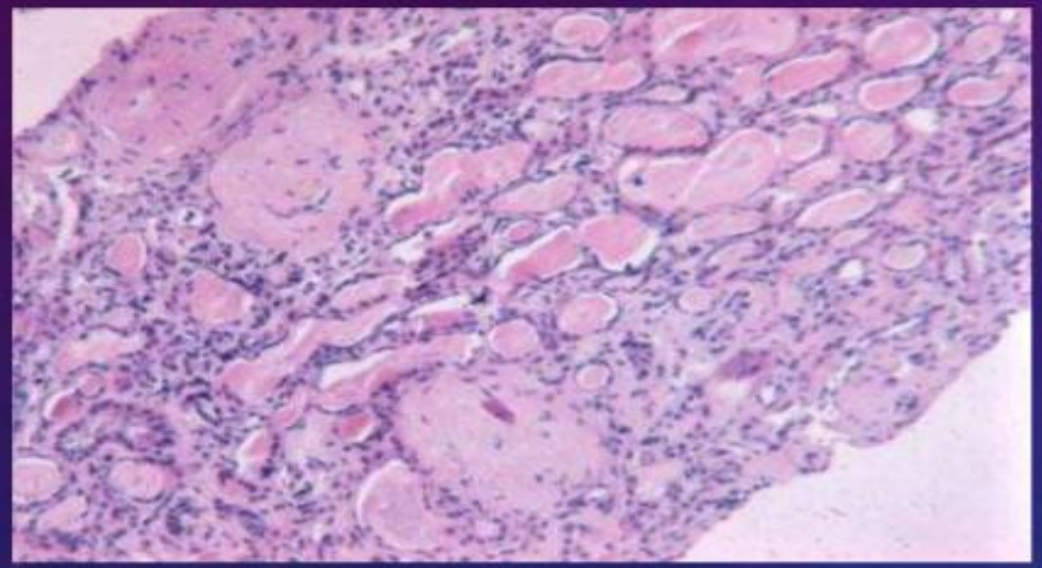


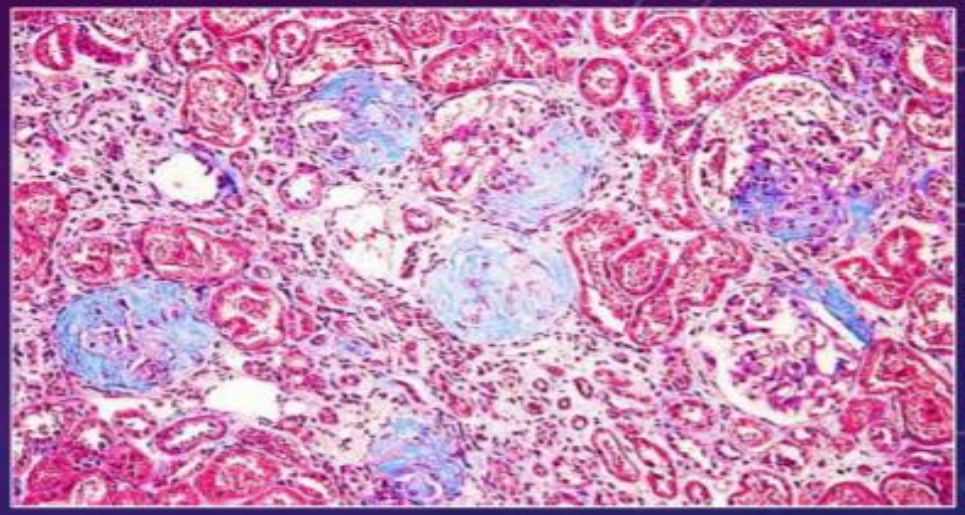
Diffuse thickening of the capillary walls due to deposition of subepithelial immune complexes, increased production of basement membrane-like material

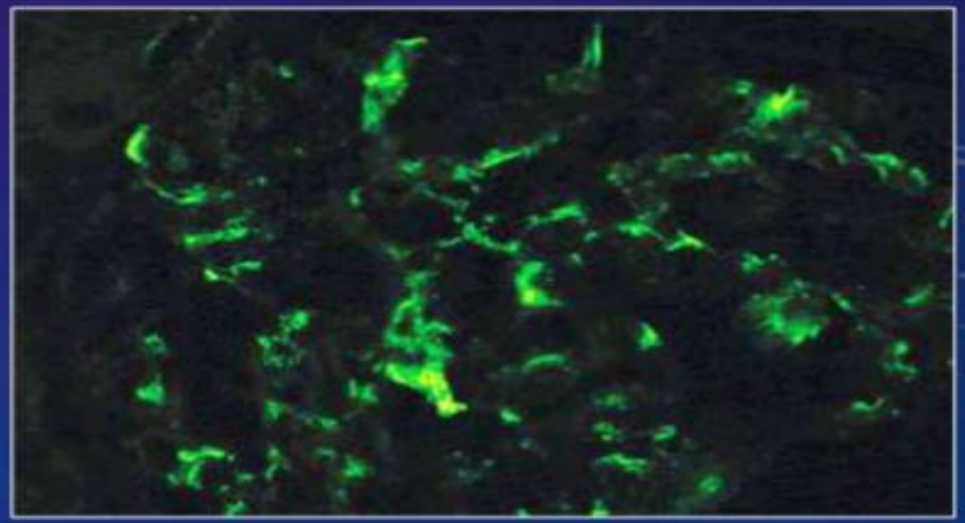


There are delicate subepithelial immune deposits staining for IgG with or without mesangial deposits

# CLASS VI







Sclerosis of more than 90% of the glomeruli, end stage renal disease, severe tubular atrophy, interstitial fibrosis, inflammation.

# TREATMENT

- The principal goal of therapy in lupus nephritis is to normalize renal function or, at least, to prevent the progressive loss of renal function.
- Therapy differs depending on the pathologic lesion. It is important to treat extrarenal manifestations and other variables that may affect the kidneys.
- Adjunctive Treatments
- Primary disease management by immunosuppressive agents Induction Therapy
- Maintenance Therapy
- Lifestyle Changes

## ADJUNCTIVE TREATMENTS

| Drugs | Cause |
| --- | --- |
| Hydroxychloroquine<br>[Max 6–6.5 mg/kg body weight] | All SLE patients with; unless there is a contraindication:<br>• Lower rates of Flare<br>• Reduced renal damage<br>• Less clotting events |
| ACEi/ARBs | Patients with proteinuria >0.5 gm/day<br>• Reduces proteinuria by 30%, and<br>• Significantly delays doubling of serum creatinine<br>• Delays progression to ESRD |
| Antihypertensive | Target of ≤130/80 mmHg<br>• Significant delay in progression of renal disease |
| Statin therapy | Patients with LDL >100 mg/dl<br>• As GFR<60ml/min/1.73m$^2$ & SLE itself accelerated atherosclerosis |
| Calcium supplementation | Prevent osteoporosis if the patient is on long-term corticosteroid therapy |

# IMMUNOSUPPRESSIVE AGENTS

- Depends upon class of LN diagnosed on kidney biopsy along with presence of extra-renal manifestations of SLE
- Goals of immunosuppressive treatment:
- Long-term preservation of renal function,
- Prevention of flares,
- Avoidance of treatment-related harms,
- Improved quality of life and survival

# IMMUNOSUPPRESSIVE AGENTS

- INITIAL/INDUCTION PHASE
    - Corticosteroids , combined with either cyclophosphamide or MMF

- MAINTENANCE THERAPY :
    - Azathioprine (1.5–2.5 mg/kg/d) or
    - MMF (1–2 g/d in divided doses) ± Low-dose oral corticosteroids
    - Calcineurin inhibitors with low-dose corticosteroids be used for maintenance therapy in patients who are intolerant of MMF and azathioprine.
- They may need Dialysis and Kidney transplant

# LIFESTYLE CHANGES FOR LUPUS NEPHRITIS

- Drink enough fluids to stay well hydrated.
- Eat a low-sodium diet, especially if hypertension is an issue.
- Avoid smoking and drinking alcohol.
- Exercise regularly.
- Maintain a healthy blood pressure.
- Limit cholesterol.
- Avoid medications that can affect the kidneys, such as nonsteroidal anti-inflammatory drugs (NSAIDs).

# Relapse

- Relapse is around 25% at 5 y and 46% at 10 y.
- Types of renal flares:
    - Proteinuric (increase proteinuria)
    - Nephritic (increase >30% of Scr and/or active urine sediment).
- Flares are highly predicted by RBC or WBC casts, low C3 and C4 and rise in ds DNA.

# Transplantation

- Patients with SLE account for 3% of all renal transplantations in the United States.
- Ensure that the patient does not have active SLE disease at the time of transplantation.
- A 3-month period of dialysis is usually prudent to ensure that spontaneous renal recovery does not occur. ~3.3% of patients on RRT have functional renal recovery and be off dialysis.
- Recurrent lupus nephritis <2%, and allograft loss due to recurrence is <2-4%.
- Majority of patients has a decline in disease activity with ESRD treatment.

# Pregnancy and lupus nephritis

- Patients should avoid pregnancy because it may aggravate renal disease, especially in the presence of active lupus nephritis, nephrotic syndrome, severe hypertension, or an elevated serum creatinine more than 2 mg/dL.
- Patients with lupus nephritis have a 50-60% chance of renal flare during pregnancy if they conceive during active disease.
- Patients with well-controlled SLE who conceive after a 3- to 6-month period of remission have a 7-10% chance of renal flare.
- Pregnant patients with lupus nephritis are prone to preeclampsia. Preexisting hypertension and antiphospholipid antibody syndrome are the 2 most common predisposing factors to preeclampsia.

Thank you