Diabetic Nephropathy

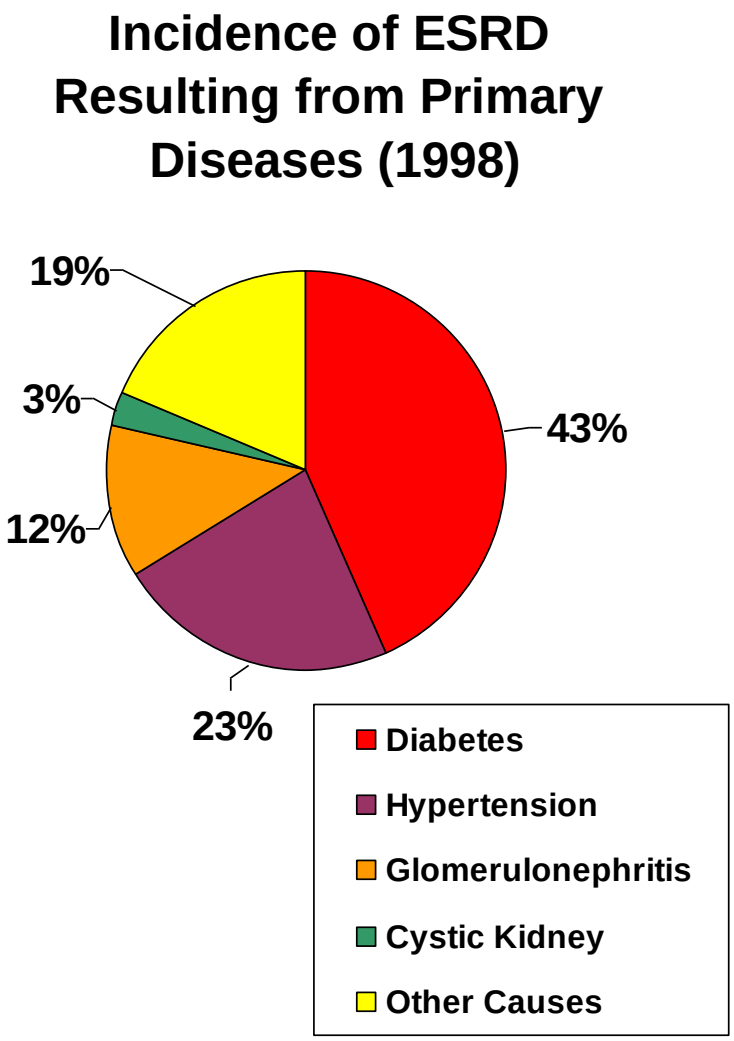
Diabetic nephropathy

Is a clinical syndrome characterized by the following:

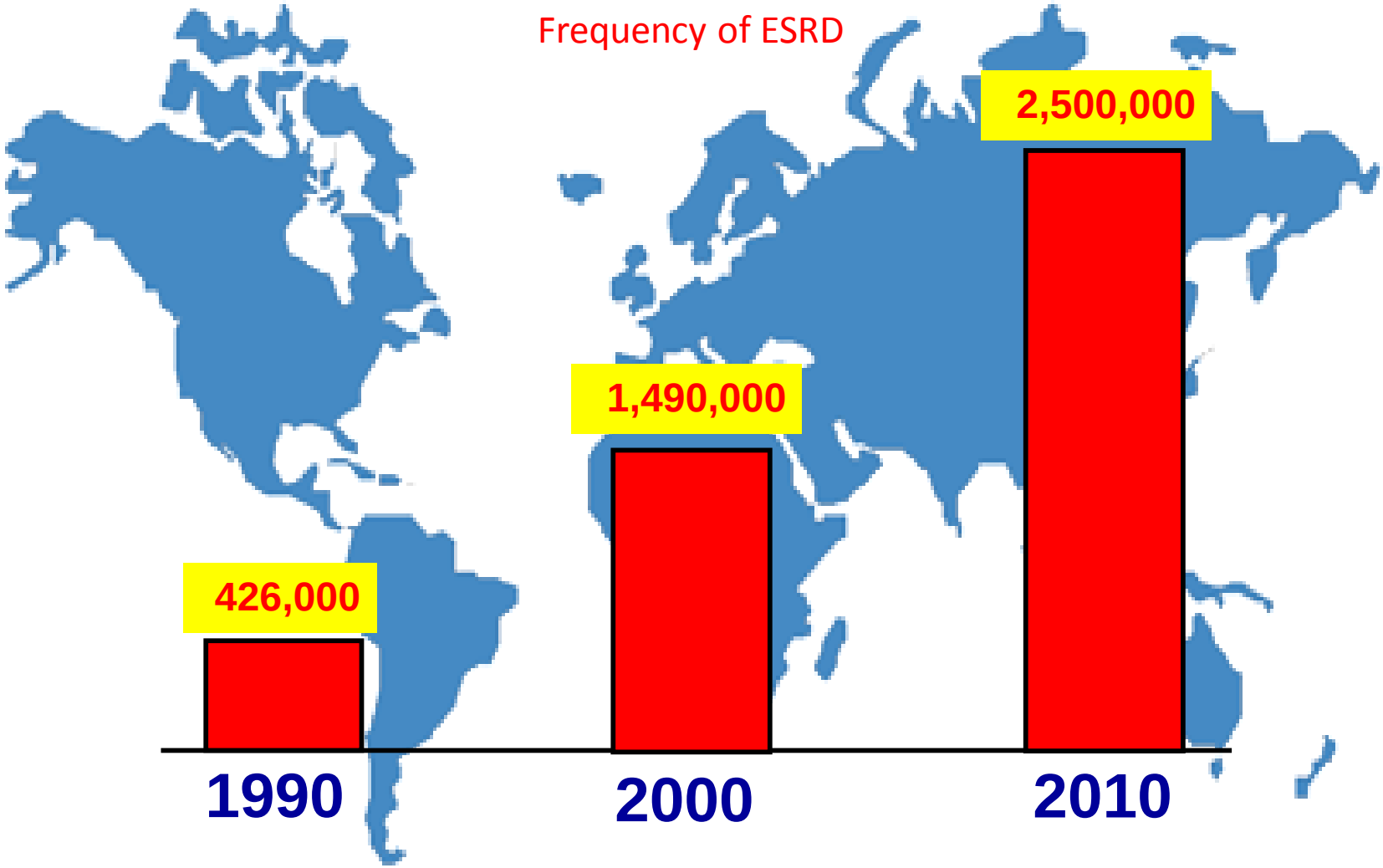
- Persistent albuminuria (>300 mg/d or >200 µg/min) that is confirmed on at least 2 occasions 3-6 months apart
- Progressive decline in the glomerular filtration rate (GFR)
- Elevated arterial blood pressure

Diabetic Nephropathy

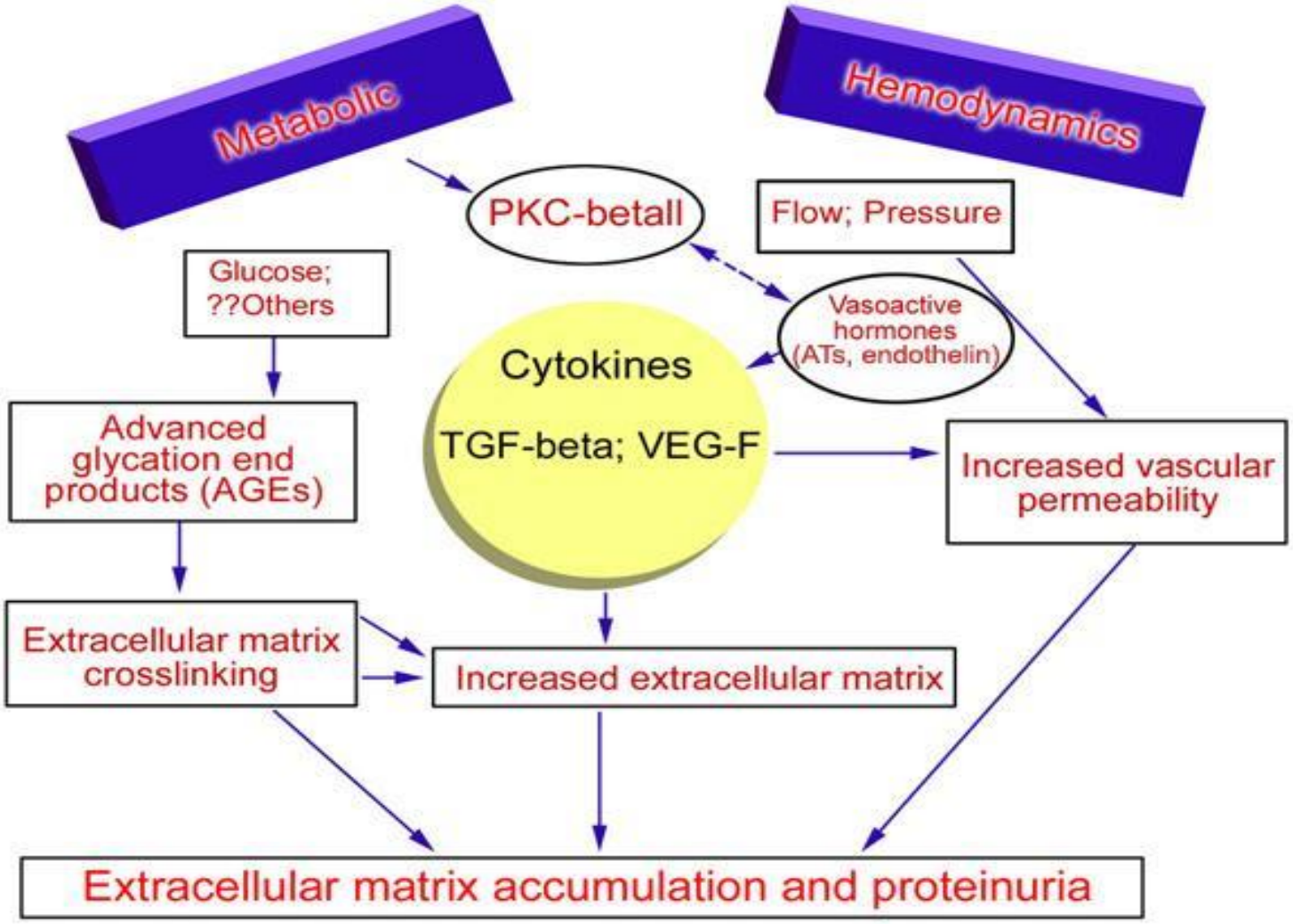
- Over 40% of new cases of end-stage renal disease (ESRD) are attributed to diabetes.
- In 2001, 41,312 people with diabetes began treatment for end-stage renal disease.
- In 2001, it cost $22.8 billion in public and private funds to treat patients with kidney failure.
- Minorities experience higher than average rates of nephropathy and kidney disease



ESRD is increasingly common worldwide



Lysaght, J Am Soc Nephrol, 2002


Metabolic
Hemodynamics
PKC-betaII
Flow; Pressure
Glucose;
??Others
Vasoactive
hormones
(ATs, endothelin)
Cytokines
TGF-beta; VEG-F
Advanced
glycation end
products (AGEs)
Increased vascular
permeability
Extracellular matrix
crosslinking
Increased extracellular matrix
Extracellular matrix accumulation and proteinuria

Potential Regulators of Hyperfiltration

- Glucose and AGEs both increase GFR
- Growth Hormone and glucagon
- Insulin Vasoconstricts preglomerular arteriole
- Renal prostaglandins - excess preglomerular vasodilatation
- Thromboxane - excess postglomerular vasoconstriction

Potential Regulators of Hyperfiltration

- Renin Angiotensin Axis
  - Renin activity is suppressed or normal
  - No discernible pattern
  - Angiotensin II binding is abnormal
- Nitric Oxide
  - Predominantly causes preglomerular arteriolar dilation
  - Vasculature more sensitive to NO in DM
  - Inhibition of NO eliminates hyperfiltration

Risk Factors

1 .Genetic Susceptibility:

Increased incidence if Diabetic sibling or father had nephropathy

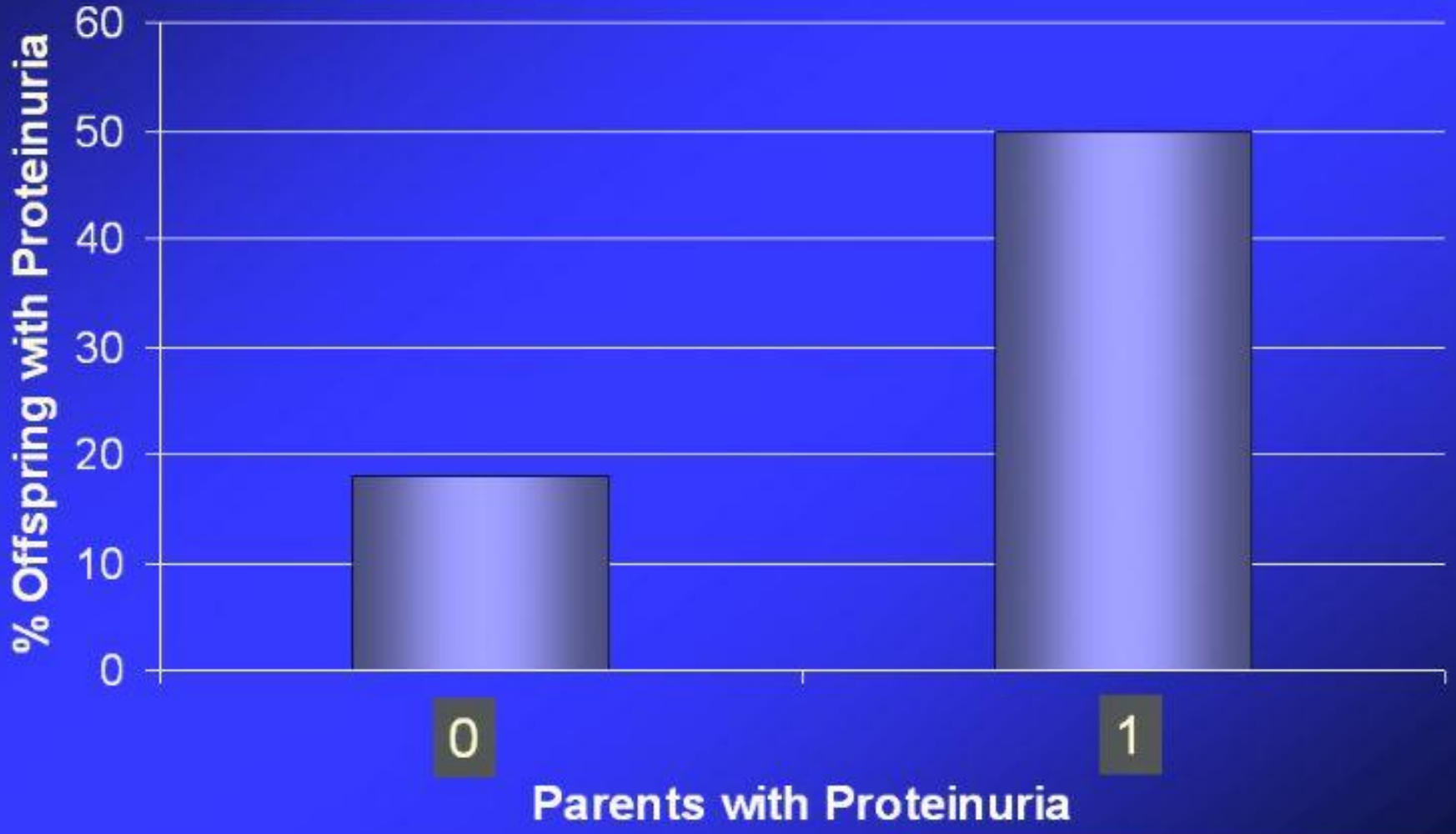
ACE gene of DD polymorphism is risky more than DI or II.

2. Uncontrolled Blood pressure
3. 50 % of type I pts have GFR 25-50 % above normal within first 5 yrs, this is risky

Genetics

- Nephropathy occurs in families
  - Risk of nephropathy increases 5 fold if a sibling has nephropathy
  - Family history of hypertension increases risk
  - Predisposition to diabetic nephropathy can be traced to polymorphism in angiotensinogen and angiotensin receptors

Risk of Diabetic Nephropathy in Caucasian Families With a History of Nephropathy

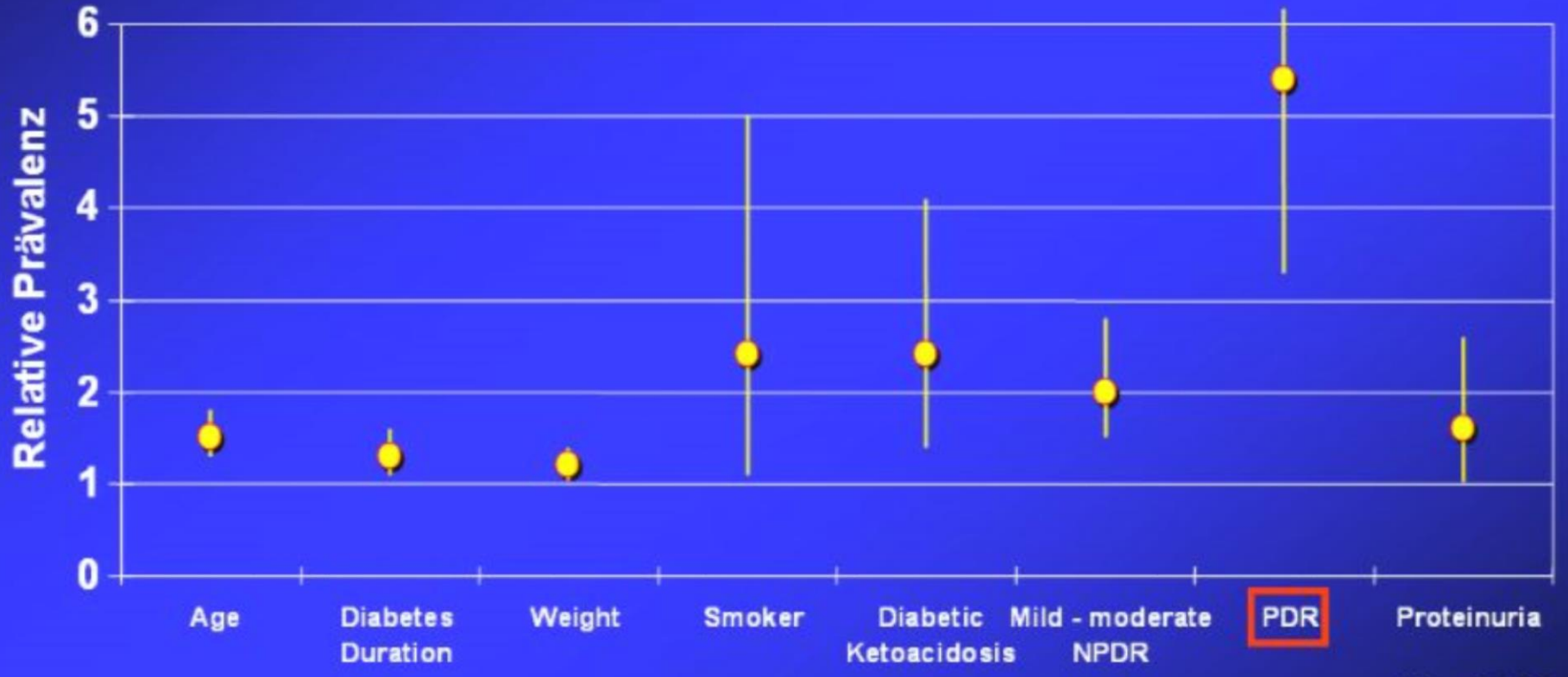


Fava S, et al. *Am J Kidney Dis.* 2000;35(4):708-12.

Risk Factors 2

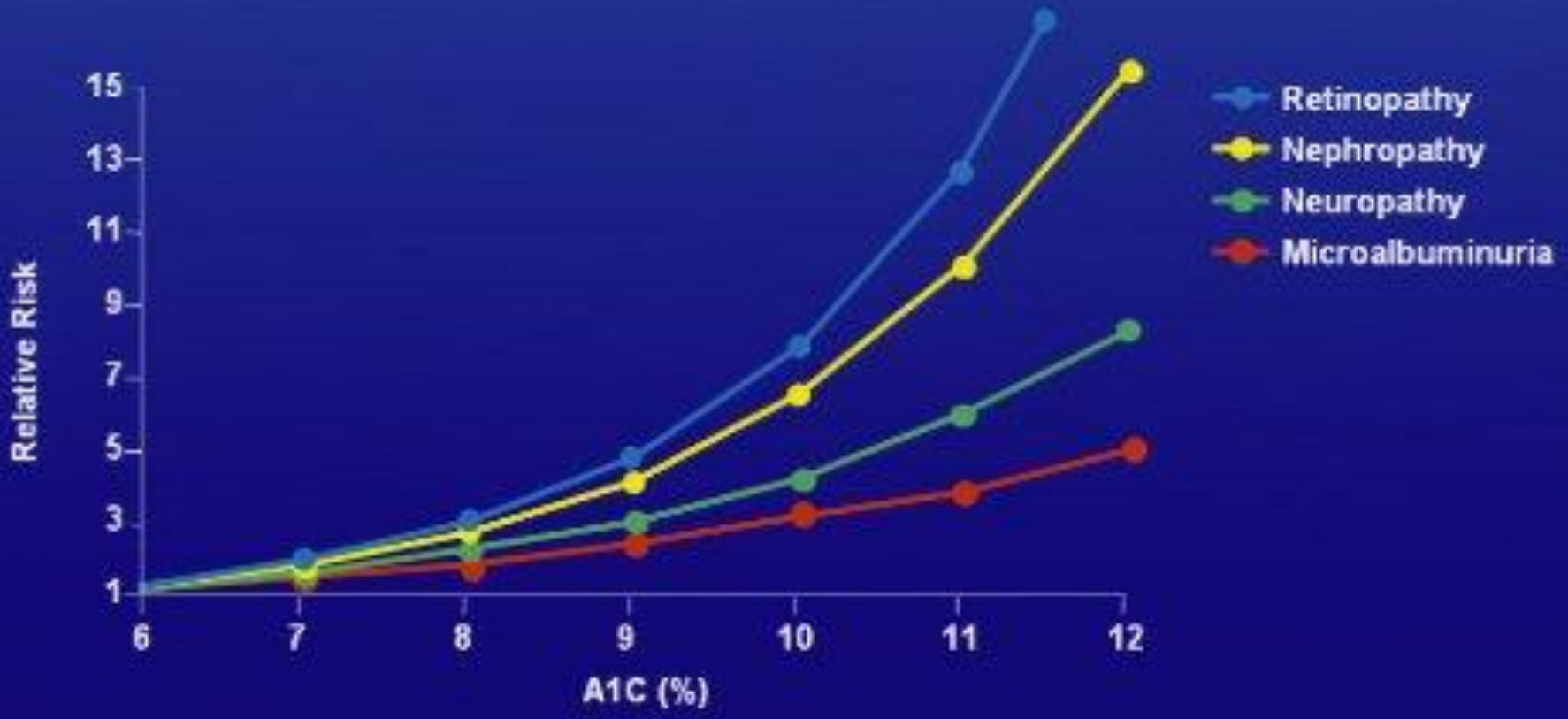
- Glycemic control , higher sugar more risky.
- Race: Blacks, Mexican-Americans, Pima Indians higher incidence.

Independent Predictors of Diabetic Nephropathy (EURODIAB Study)

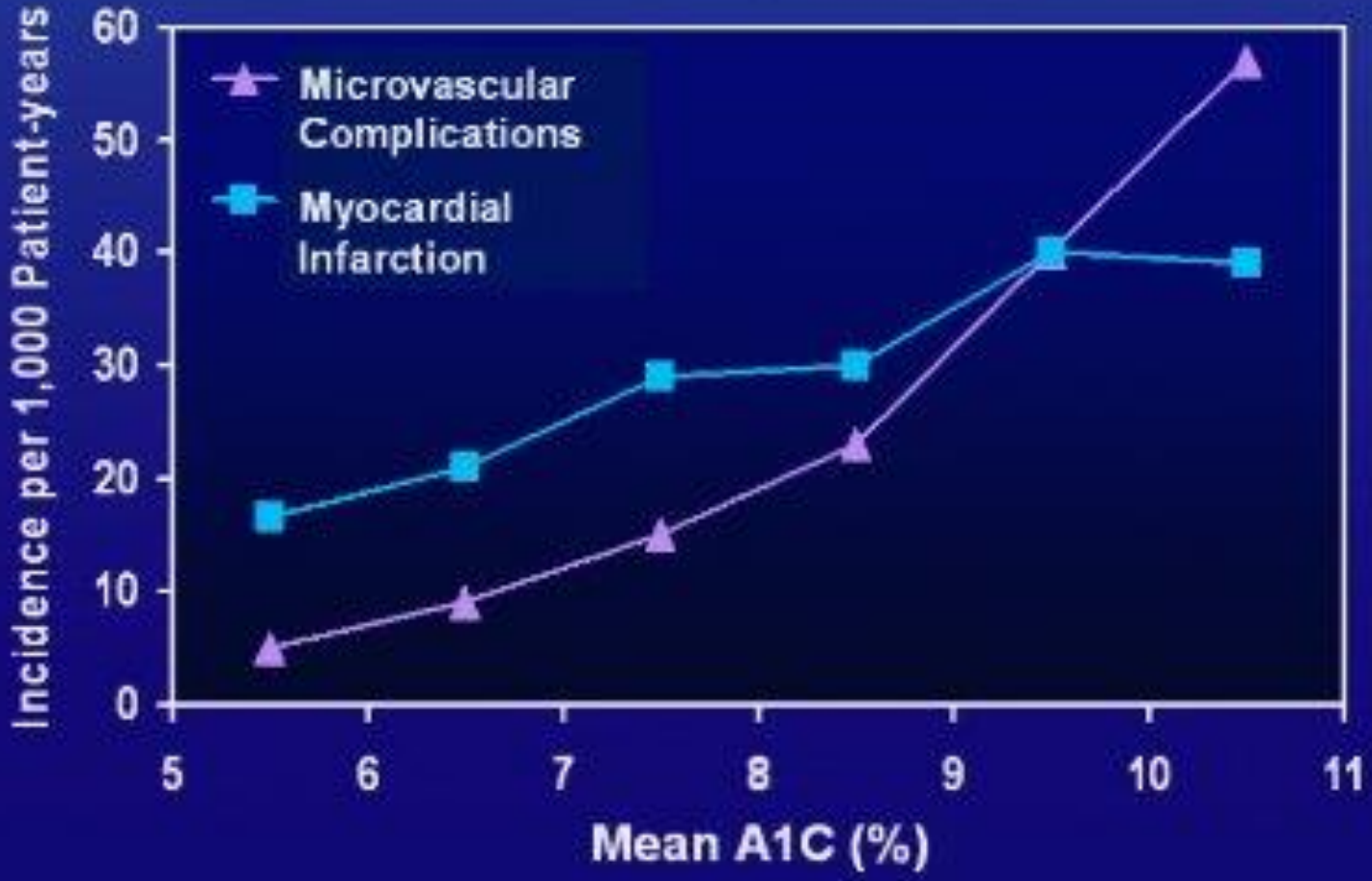


Tesfaye S, et al. *Diabetologia.* 1996;39(11):1377-84.
Giorgino F, et al. *Diabetologia.* 2004;47(6):1020-8.

Relationship of A1C to Risk of Microvascular Complications (DCCT)



Relationship of A1C to Incidence of Complications (UKPDS)



Adapted from Stratton IM, et al. *BMJ*. 2000;321:405-412.

Microvascular Complications: Risk Reduction Per 1% Decrease in A1C

Study	Retinopathy	Nephropathy	Neuropathy
DCCT	27-38%	22-28%	29-35%
Kumamoto	28%	50%	↑NCV
UKPDS	19%	26%	18%

NCV = Nerve Conduction Velocity

Davidson JA. *Endocr Pract.* 2002;8(suppl 1):13-14

Smoking

- Increases risk of nephropathy by factor of eight.
- Increases rate of progression
- Increases cardiac mortality by factor of one hundred.

Diabetes and Renal disease

- Peak onset of Nephropathy is between 10-15 years after the onset of disease.

- Those without proteinuria after 20-25 yrs of the disease have a risk of 1% per year of developing nephropathy.

Diabetic Nephropathy

- Proteinuria developes 17+/-6 years from start of IDDM , and ESRD occur at 22+/- 6 years.

- Rate of decline in GFR averages 1ml/min per month with 50% of patients reaching ESRD 7-10 yrs after onset of proteinuria.

- Decline in GFR is affected by diabetic complications as neurogenic bladder, UTI, and papillary necrosis.

	Rate of Decline in Glomerular Filtration Rate (mL/min/year)	
	Type I	Type II
Normoalbuminuria	1.2 - 3.6	0.96
Microalbuminuria	1.2 - 3.6	2.4
Overt Nephropathy	9.6 -12	5.4 - 7.2

Natural History of Diabetic Nephropathy

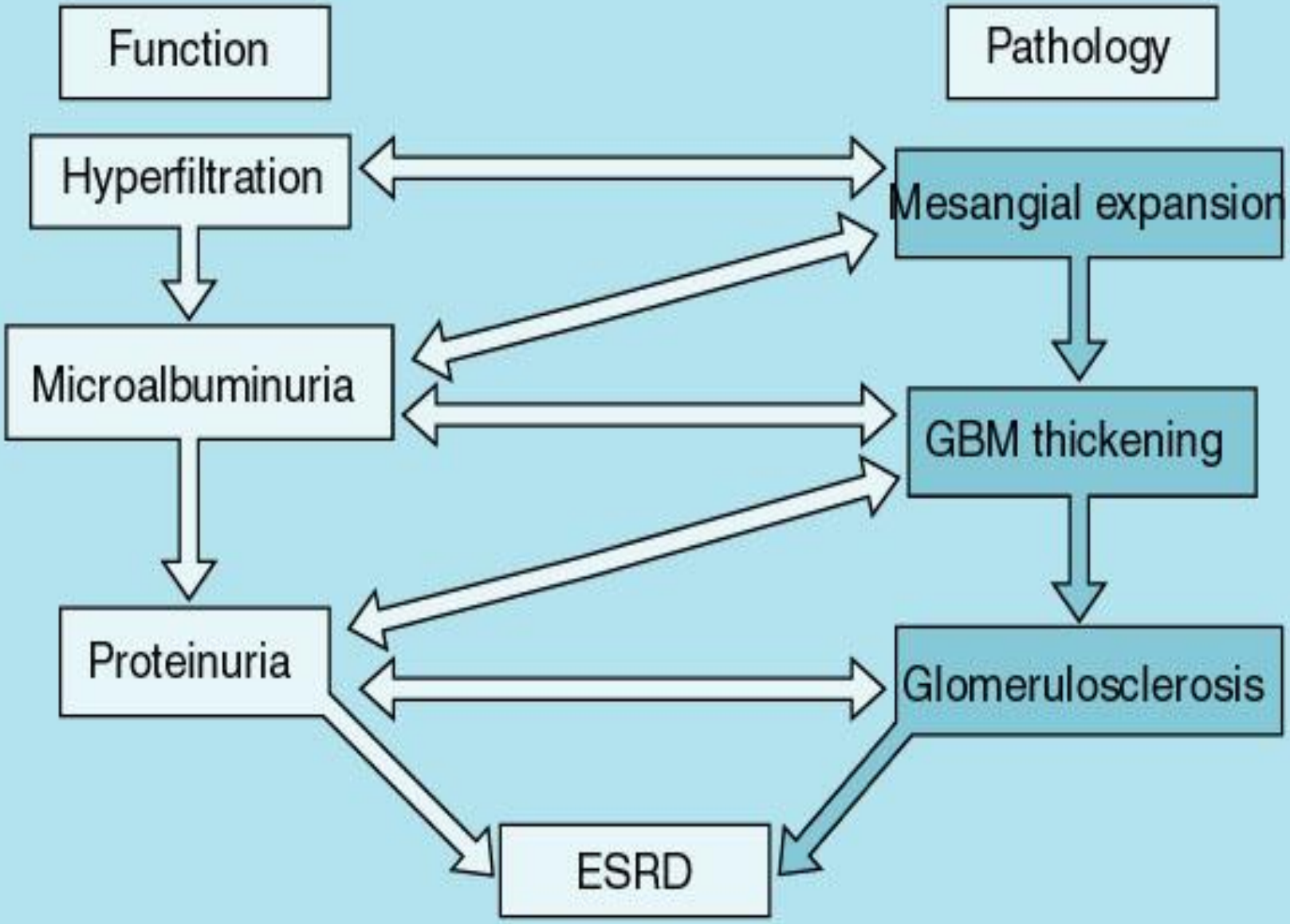
	Designation	Characteristics	GFR (ml/min)	Albumin Excretion	Blood Pressure
Stage 1	Hyperfunction and Hypertrophy onset	Glomerular Hyperfiltration	Increased in Type 1 and Type 2	May be increased	Type 1 normal Type 2 normal - hypertension
Stage 2	"Silent" stage 2-10 years	Thickened BM Expanded Mesangium	Normal	Type 1 normal Type 2 may be < 30 – 300 mg/24hr	Type 1 normal Type 2 normal - hypertension
Stage 3	Incipient Diabetes 10-15 years	Microalbuminuria	GFR begins to fall	30 – 300 mg/24 hr	Type 1 increased Type 2 normal - hypertension
Stage 4	Overt Diabetic Nephropathy 15-20 years	Macroalbuminuria	GFR below Nl	> 300 mg/24 hr	Hypertension
Stage 5	Uremia 20-25 years	ESRD	0 - 10	Decreasing	Hypertension

Diabetic Nephropathy

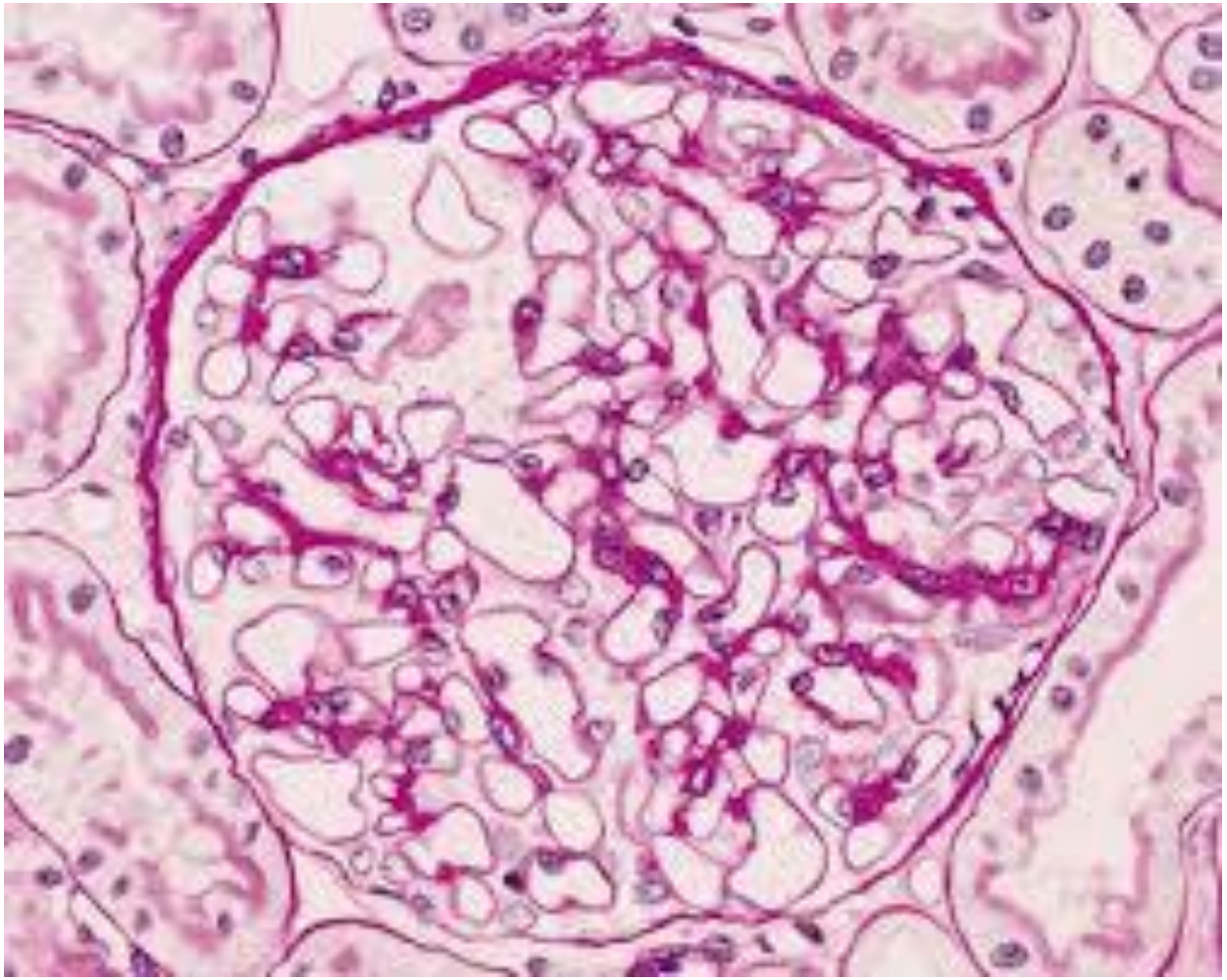
- 50% of deaths in diabetics under 40 related to end stage renal disease
- Type I diabetes
  - 30-40% develop nephropathy
- Type 2 diabetes
  - Renal disease less common (20-30%)
    - But increasing!!!

Diabetic Nephropathy

- When in ESRD insulin requirements decrease, partly because the kidney is responsible for 30-40% of the catabolism of insulin, also due to loss of appetite with Renal Failure.


Function
Pathology
Hyperfiltration
Mesangial expansion
Microalbuminuria
GBM thickening
Proteinuria
Glomerulosclerosis
ESRD

Normal Glomerulus



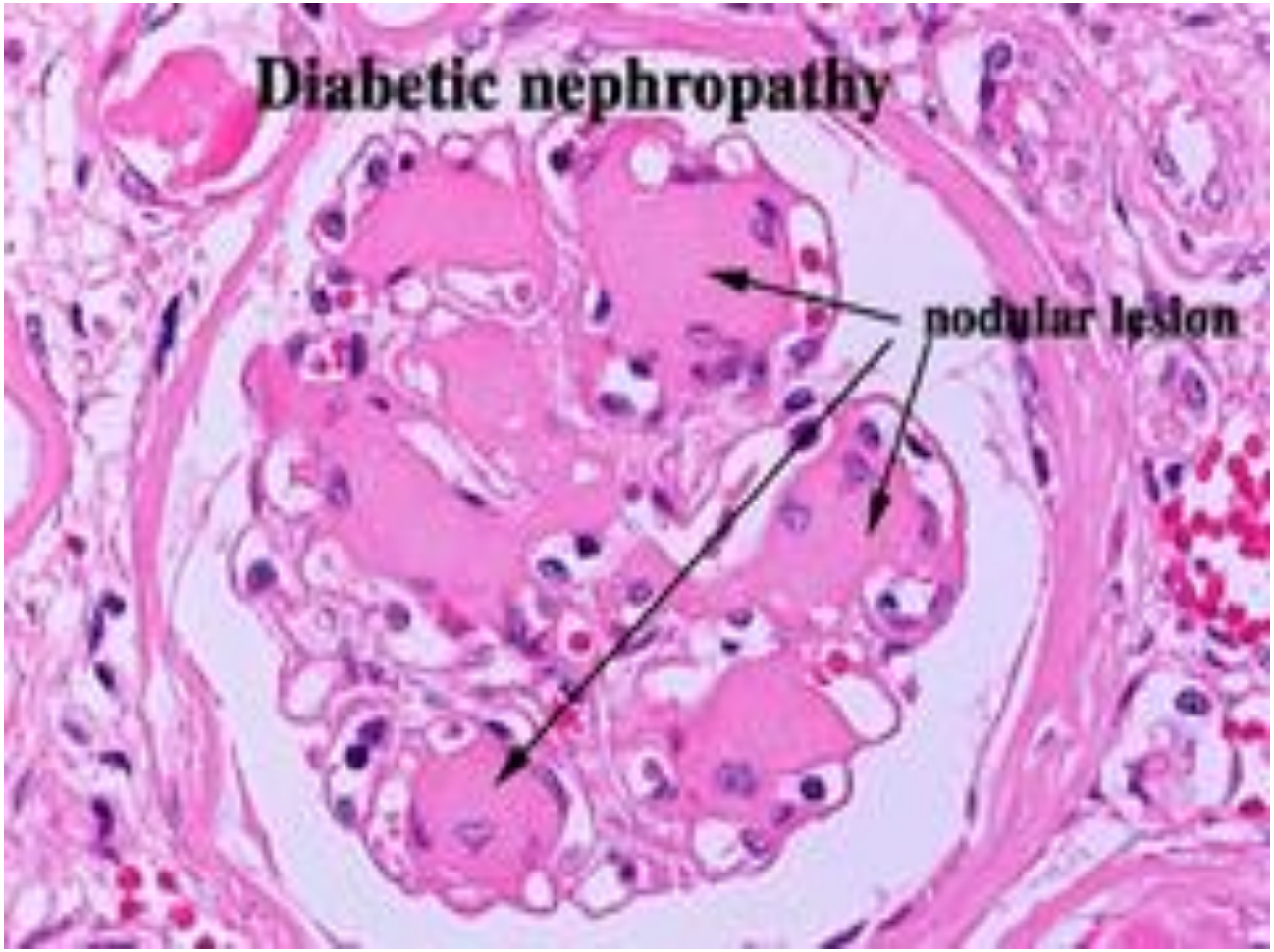


Fig 2. Diabetic nephropathy is one of the causes of nodular glomerulosclerosis, illustrated here, with large nodules of matrix within mesangial areas with lesser increase in mesangial cellularity. The glomerular basement membrane is thick without apparent deposits. (Periodic acid-Schiff stain, original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

Diabetic Nephropathy: Screening Guidelines

- Perform an annual test for microalbuminuria in:
  a) Type 1 diabetic patients of >5 years duration
  b) All type 2 patients starting from diagnosis

- If positive for microalbuminuria, exclude UTI and repeat. Serum creatinine and BUN should also be measured

- Blood pressure should be measured at every visit for diabetes assessment

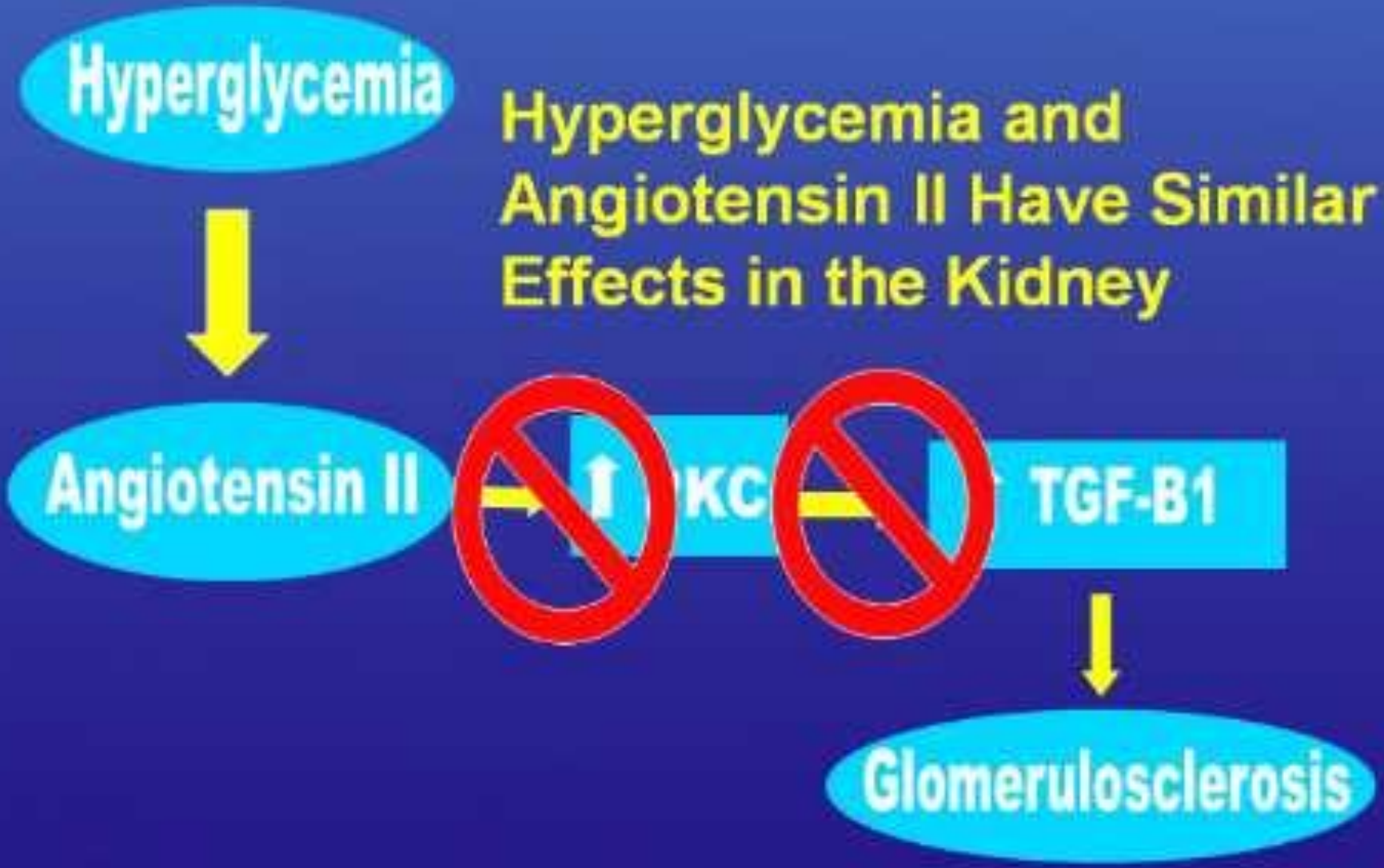
ADA Position statement. *Diabetes Care*. 2005;28(suppl 1):S4-S36.

Definition of Microalbumiuria

Stage	24-h collection μg/mg creatinine	Timed collection μg/mg creatinine	Spot collection μg/mg creatine
Normal	<30	<20	<30
Micro-albuminuria	30-299	20-199	30-299
Clinical Albuminuria	≥300	≥200	≥300

Molitch ME, et al. *Diabetes Care*. 2004;27(Suppl 1):S79-83.

Hyperglycemia and Angiotensin II Have Similar Effects in the Kidney



Lenman R, Schleicher ED. *Clin Chim Acta*. 2000;297:134-144.
Mogensen CE. *Heart*. 2000;84(suppl 1):i26-28.
Leehey DJ. *Kidney Int Suppl*. 2000;77:S93-S98.

Treatment Targets for Diabetic Renal Disease With Hypertension

GLUCOSE

BP

LIPIDS

Goal BP Recommendations for Patients with DM or Renal Disease

Organization	Year	Systolic BP	Diastolic BP
American Diabetes Association	2001	<130	<80
National Kidney Foundation	2000	<130	<80
Canadian Hypertension Society	1999	<130	<80
British Hypertension Society	1999	<140	<80
WHO & International Society of Hypertension	1999	<130	<85
Joint National Committee (JNC VI)	1997	<130	<85

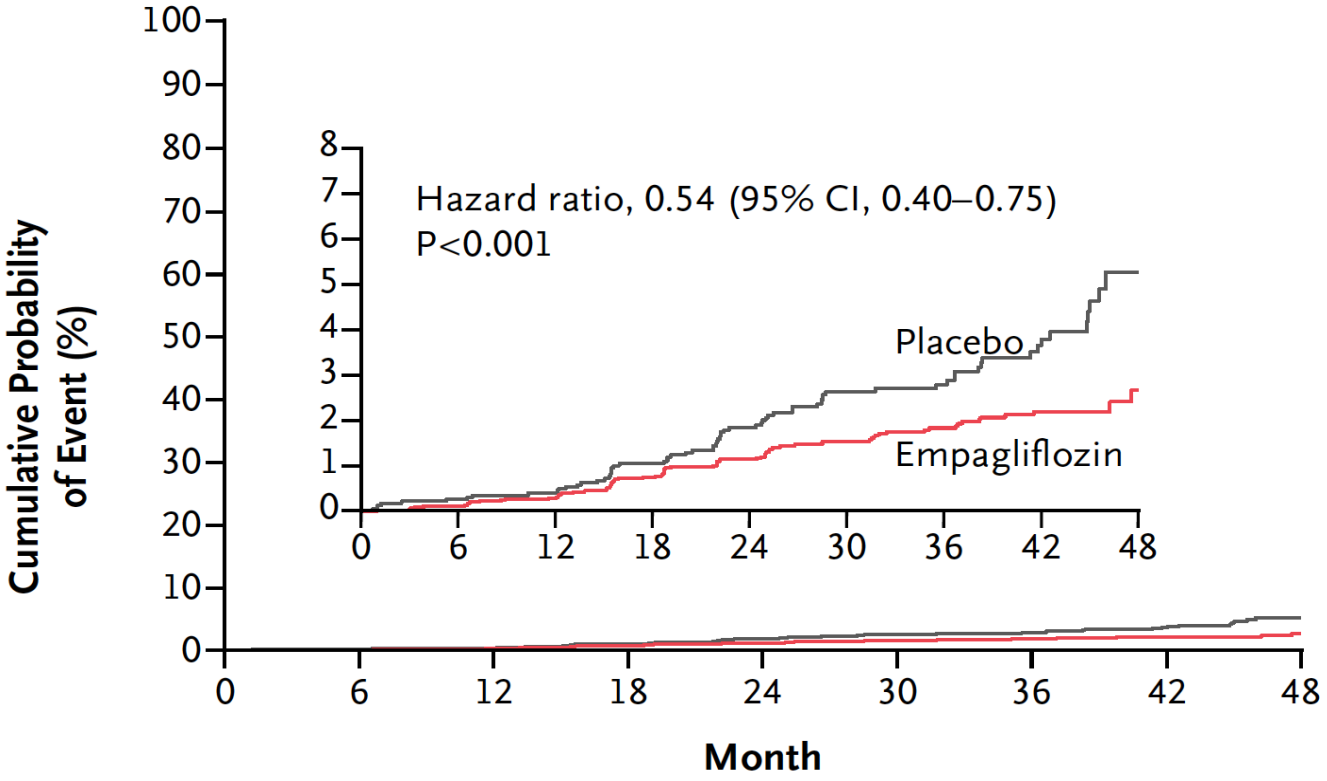
Principles in Detection and Prevention

- Early detection “microalbuminuria”
- Strict Glycemic Control
- Low Protein diet
- Smoking Cessation
- Treat Hypertension aggressively

How Can You Prevent Diabetic Kidney Disease?

- Maintain blood pressure <130/80 mm/Hg
- Maintain preprandial plasma glucose 90-130 mg/dl
- Maintain postprandial plasma glucose <180 mg/dl
- Maintain A1C <7.0%

Empagliflozin reduced doubling of serum creatinine*, initiation of renal replacement therapy, or death due to renal disease



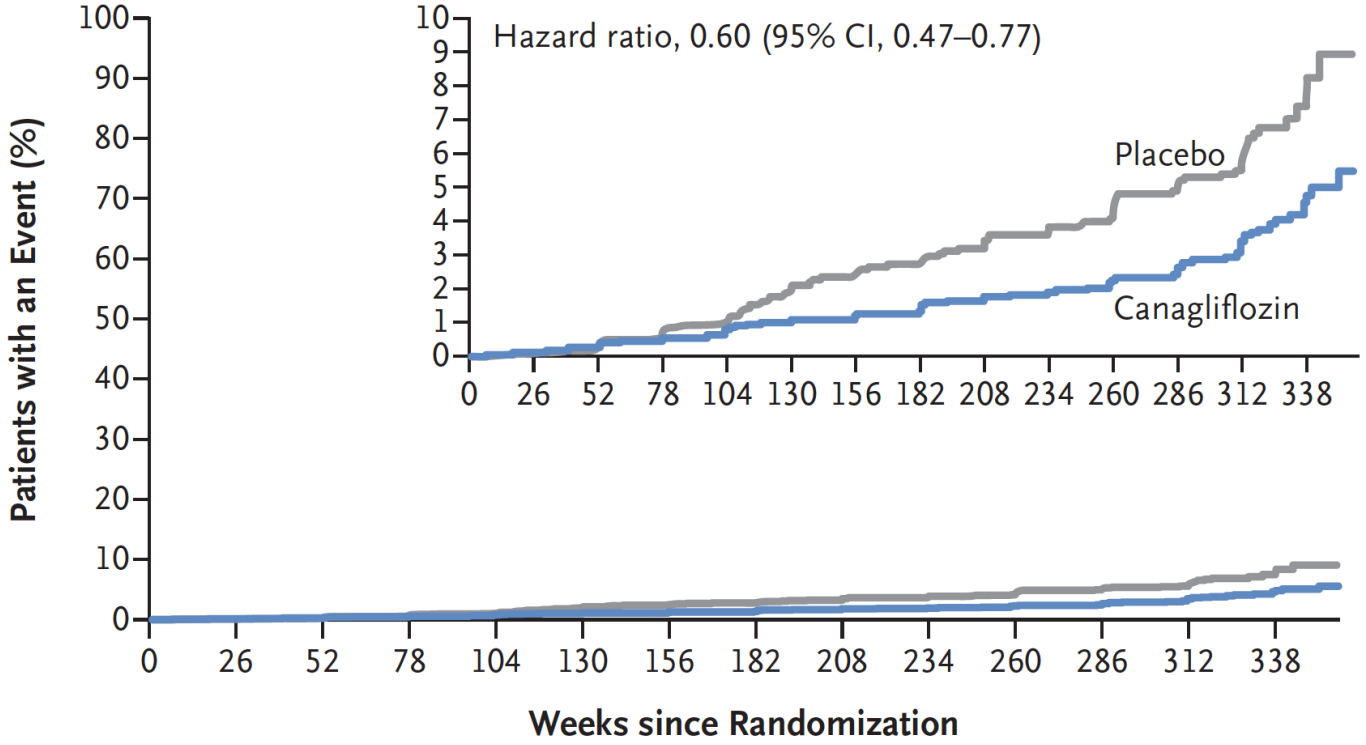
No. at Risk

Empagliflozin	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2323	2229	2146	2047	1771	1289	1079	680	144

Hazard ratios are based on Cox regression analyses. *Accompanied by eGFR [MDRD] ≤45 ml/min/1.73m^2.
HR, hazard ratio; CI, confidence interval. *Post-hoc* analyses.

Wanner et al. N Engl J Med 2016; ৬৭:৩২৩-৩৩৪

Canagliflozin reduced composite endpoint of 40% reduction in eGFR, requirement for renal replacement therapy or death from renal causes



No. at Risk

Placebo	4347	4287	4227	4151	3029	1674	1274	1253	1229	1202	1173	1148	819	229
Canagliflozin	5795	5737	5664	5578	4454	3071	2654	2623	2576	2542	2495	2450	1781	493

Neal B et al. N Engl J Med 2017

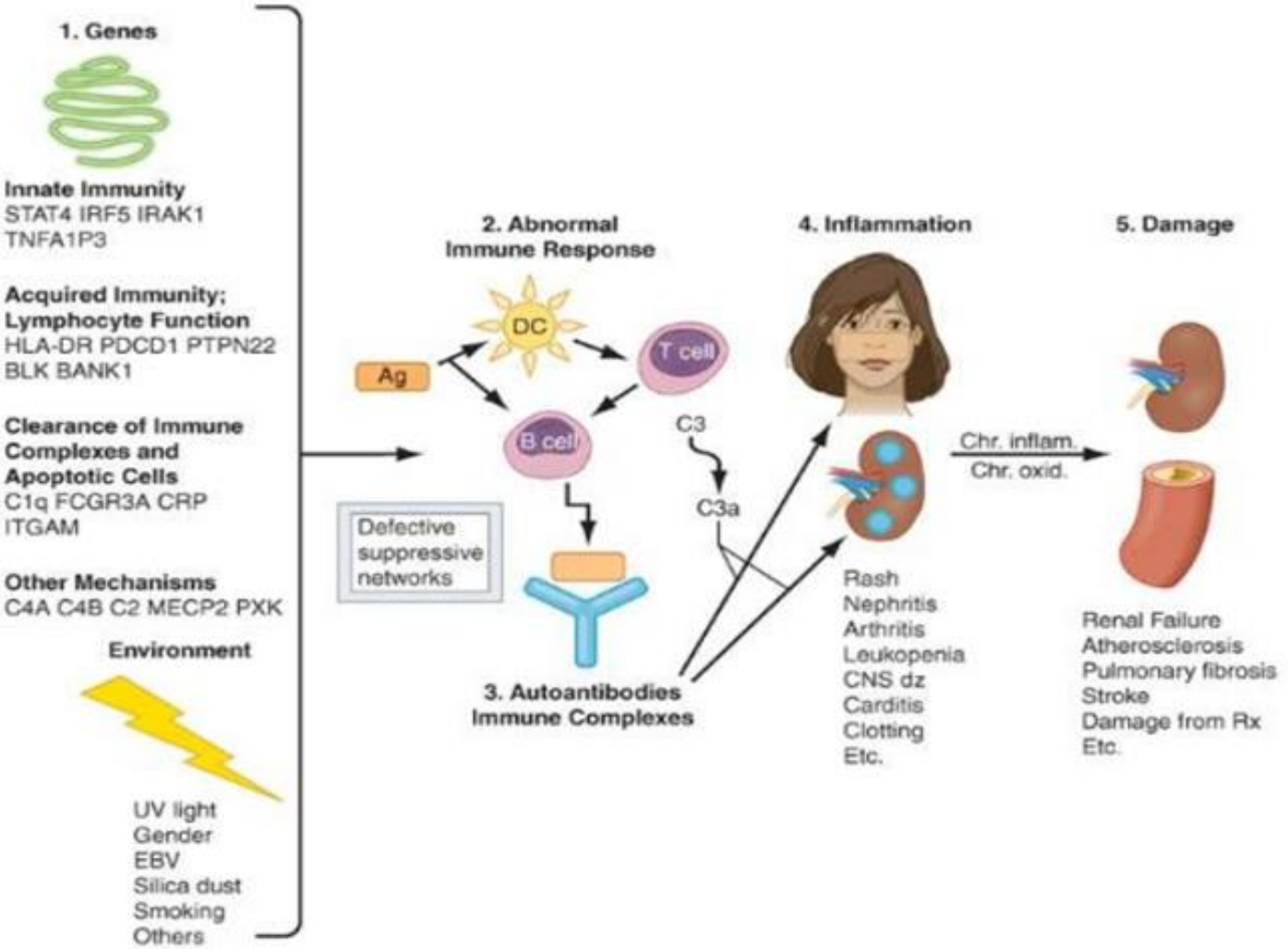
Lupus Nephritis

Ayman Wahbeh, MD, MSc, FACP, FRCP
University of Jordan

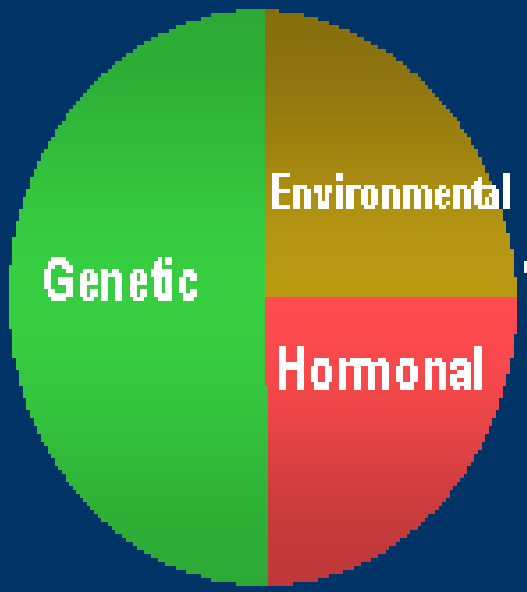
Epidemiology

- SLE incidence: approx. 1 in 500 in the U.S.
- Prevalence: 4-250 per 100,000
- Female/Male: 9/1.
- Age: peak incidence in 30s.
- Race: Black > White.
- Pediatric vs adult rates of renal involvement approx. the same.

Etiopathogenesis



Pathogenesis of SLE



Ag

T HELPER

B

B and T Cell Hyperactivity

Defective Immune Regulation

Autoantibodies

Immune Complexes

Tissue Damage

Clinical Associations of Autoantibodies in SLE

Antigen Specificity	Clinical Associations
dsDNA	Marker for active disease; titers fluctuate with disease activity
ssDNA	Non-specific
Ro/SSA	Cutaneous lupus (75%), photosensitivity, neonatal lupus
La/SSB	With La, low prevalence of renal disease, neonatal lupus (75%)
Sm	Marker for disease; may be associated with CNS disease
RNP (U1-RNP)	MCTD, required for diagnosis
Phospholipids	Hypercoagulable state in some, no significance in others; thrombocytopenia, later trimester abortions
Histones	> 95% in drug-related lupus; present in RA. SLE, systemic sclerosis with pulmonary fibrosis
KU	SLE, MCTD (Europeans/Americans); scleroderma/myositis overlap (Japanese)

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

Tests of SLE disease activity

- Disease activity can be evaluated with **anti-dsDNA**, complement determinations (**C3, C4, and CH50**), and erythrocyte sedimentation rate (**ESR**) or C-reactive protein (**CRP**).
- Generally, elevated ESR and anti-dsDNA, **anti c1q**, and low C3 and C4 levels are associated with active nephritis, especially focal proliferative and diffuse proliferative lupus nephritis.
- Clinically relevant lupus nephritis is associated with a 30% decrease in creatinine clearance, proteinuria of greater than 1000 mg/d, and a renal biopsy showing active lupus nephritis.

WHO Class I: Normal

- LM, EM, IF all normal
- Rare incidence

WHO Class II: Mesangial

- LM: mesangial widening or mild hypercellularity
- EM, IF: mesangial deposits, +/- subendothelial deposits
- Subclass A/B depending on degree of hypercellularity

WHO Class II (cont.)

- 10-20 % of cases
- Prognosis excellent
- No therapy indicated

WHO Class III: Focal proliferative

- LM: Diffuse mesangial hypercellularity, Focal/segmental necrosis and proliferation, hyaline thrombi
- EM: Mesangial and subendothelial deposits
- IF: Granular mesangial and capillary Ig, C3
- Subclassed depending on degree of necrosis and sclerosis

WHO Class III (cont.)

- 10-20% of cases
- Variable prognosis
- May represent one end of spectrum with Class IV
- Prognosis: with < 25% of glomeruli involved, < 5% progress @ 5 years. With 40-50% involved, 15-25% progress to renal death @ 5 years.

WHO Class IV: Diffuse proliferative

- LM: Diffuse hypercellularity, mesangial and endocapillary proliferation, crescents, leukocytic infiltration
- EM: mesangial, subendothelial, subepithelial deposits
- IF: Mesangial and capillary Ig, C3. Extraglomerular deposits.
- Subclassed based on degree of necrosis and sclerosis

WHO Class IV (cont.)

- Most common form, around 40-50%
- Associated with worse prognosis: 5-year renal death rate 10-40%.
- Poor prognosis: African-American, Cr > 2.4 mg/dl, crescents, tubulointerstitial disease, vascular disease
- General indication for considering cytotoxic therapy

WHO Class V: Membranous

- LM: diffuse membranous thickening, mesangial prominence
- EM: Epi/intramembranous deposits, mesangial deposits
- IF: Peripheral granular IgG, C3

WHO Class V (cont.)

- Prognosis variable. May have partial or complete remission with stable creatinines for 5 years or more.
- Overall 5-year renal death rate 10-30%.
- Therapy generally recommended for florid nephrosis or deterioration in renal function.

WHO Class VI

- Characterized by completely or segmentally sclerotic glomeruli as primary abnormality.
- May be considered as either end-stage or arrested disease and not necessarily as separate class.

WHO Classes

- Transformation rate between classes: 10-40%.
- Any transformation possible.
- Most common Class III to Class IV.
- Also common: II to III, II to IV, III to V, IV to V.
- Not predictable from clinical presentation.

Extraglomerular Disease

- Vascular
- Tubulointerstitial

Vascular Disease

- Hypertensive arterial lesions: intimal protein accumulation, endothelial cell damage, luminal narrowing or occlusion by precipitates
- Rarely, may have necrotizing vasculitis which may be assoc. with ANCA.
- May have poorer renal prognosis with vascular disease, mortality unchanged.

Tubulointerstitial Disease

- Mostly found with proliferative GNs.
- May see deposits in tubule basement membrane, interstitium, peritubular capillaries, Bowman's space, but do not corrleate with degree of inflammation.
- Inflammation does correlate with glomerular lesions and with active disease markers.
- Associated with worse prognosis

Treatment options for Lupus Nephritis

Controlled Studies

- Plasmapheresis
- Steroids
- Cyclophosphamide
- Azathioprine
- Mycophenolate mofetil

Uncontrolled Studies

- Chlorambucil
- Nitrogen mustard
- Methotrexate
- Adenosine analogues
- Total lymphoid irradiation
- Monoclonal antibodies
- Cyclosporine A
- Thromboxane inhibitors
- Ancrod venom
- IV gamma globulin
- Marrow ablation/reconstitution

ADJUNCTIVE TREATMENTS

Drugs	Cause
Hydroxychloroquine [Max 6–6.5 mg/kg body weight]	All SLE patients with; unless there is a contraindication: • Lower rates of Flare • Reduced renal damage • Less clotting events
ACEi/ARBs	Patients with proteinuria >0.5 gm/day • Reduces proteinuria by 30%, and • Significantly delays doubling of serum creatinine • Delays progression to ESRD
Antihypertensive	Target of ≤130/80 mmHg • Significant delay in progression of renal disease
Statin therapy	Patients with LDL >100 mg/dl • 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, and
  - Improved quality of life and survival.

CLASS II LN (MESANGIAL-PROLIFERATIVE LN)

- May require treatment if proteinuria is greater than 1000 mg/day.
- Consider prednisone in low-to-moderate doses (ie, 20-40 mg/day) for 1-3 months, with subsequent taper.

CLASS III LN (FOCAL) AND CLASS IV LN (DIFFUSE)

- At high risk of progressing to ESRD
- Require aggressive therapy.
- Therapy for class III and IV LN has 2 phases:
  - Initial/Induction phase: to rapidly decrease kidney inflammation
  - Maintenance phase: to consolidate treatment over a longer time.

REGIMENS FOR INITIAL THERAPY IN CLASS III/CLASS IV LN [INTERNATIONAL SOCIETY OF NEPHROLOGY- KIDNEY DISEASE IMPROVING GLOBAL OUTCOME]

Regimen	A. NIH	B. Euro-Lupus	C. Oral cyclophosphamide	D. MMF
Cyclophosphamide	i.v. cyclophosphamide 0.5–1 g/m^2; monthly for 6 months	i.v. cyclophosphamide 500 mg; every 2 weeks for 3 months	Oral cyclophosphamide 1.0–1.5 mg/kg/d (maximum dose 150 mg/d) for 2–4 months	—
MMF	—	—	—	MMF up to 3 g/d for 6 months
Benefit shown by RCT in proliferative LN	Yes	Yes	Yes	Yes
Benefit shown by RCT in severe proliferative LN	Yes	Untested	Untested	Untested
Comments	Effective in whites, blacks, Hispanics, Chinese	Effective in whites. Untested in blacks, Hispanics, Chinese	Effective in whites, blacks, Chinese; easy to administer and lower cost than i.v. cyclophosphamide	Effective in whites, blacks, Hispanics, Chinese; high cost

LN, lupus nephritis; MMF, mycophenolate mofetil; RCT, randomized controlled trial.

All regimens include corticosteroids:

- Oral prednisone, initial dose up to 0.5–1 mg/kg/d, tapering over 6–12 months according to clinical response.
- i.v. methylprednisolone is sometimes added initially for severe disease.

OTHER INITIAL REGIMENS

Regimens	
Rituximab	• When treatment failed with MMF/CYC
Azathioprine	• 2nd line protocol • Less effective than CYC
MPA	• Less nausea & diarrhea than MMF • Should measured 1 hour after a dose
Cyclosporine	• (4–5 mg/ kg/d) was used for 9 months, and then tapered over the next 9 months. • No differences in responses, relapse rate, Infections and leukopenia with CYC. • ACR guideline preferred it for maintenance therapy.
Tacrolimus	• Equivalent to high-dose IV CYC in inducing complete and partial remissions of LN

Relapses

- Relapse is around 25% at 5 y and 46% at 10 y.
- 2 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.

Pregnancy

- Fetal wastage up to 40%, but fetal survival up to 88-100% if in remission > 6 months before conception. If active disease, it is 50-85%.
- IgG anticardiolipin ab's correlate with high spontaneous abortion rate of 59%
- Heart block fo the newborn due to endocardial fibrosis ass with Ro(SSA).
- Severe flares during pregnancy may cause acute renal failure and maternal and fetal death.
- Closely monitor pregnant patients with SLE, aggressively treat exacerbations, and carefully avoid administering teratogenic drugs.