DIABETIC NEPHROPATHY

DIABETIC KIDNEY DISEASE

DKD

Diabetic kidney disease = Diabetic nephropathy

Diabetic nephropathy occurs:

- in type 1 (formerly called insulin-dependent or juvenile onset),
- type 2 (formerly called non-insulin-dependent or adult onset) DM,
- in other secondary forms of diabetes mellitus, for example after pancreatitis or pancreatectomy,

duration of diabetes has to be long-enough and level of glycemia high enough to result in complications, including DN

Diabetic kidney disease = Diabetic nephropathy

In most diabetic patients CKD should be attributable to diabetes if:

- **macroalbuminuria is present (albumin excretion>300mg) or**
- **microalbuminuria is present (albumin excretion 30-300 mg)**
  - **In the presence of diabetic retinopathy**
  - **In type 1 diabetes of at least 10 years duration**

Clinical diagnosis

- **GFR< 60 ml/min/1,73 m2**
- **Hypertension (90%)**
- **Absence of clinical or laboratory evidence of other kidney or urinary tract disease**
- **Biopsy confirmation diagnosis is rare**

(NKF K/DOQI Clin. Guidelines, Am. J. Kidney Dis. 2007)

Kidney Disease Oucomes Quality Initiative

Epidemiology of DN

Data suggest that the renal risk is currently equivalent in the two types of diabetes.

- in type 1 diabetes DN rarely develops before 10 years' duration
- in type 2 diabetes 3% of newly diagnosed patients have overt nephropathy

At 10 years following diagnosis:

- the prevalence of microalbuminuria: 25%
- macroalbuminuria: 5%
- elevated plasma creatinine concentration (defined as ≥175 µmol/L [2.0 mg/dL]) or requirement for renal replacement therapy: 0.8%

Epidemiology of DN type 1

- 20-30% pts with DM 1 developes microalbuminuria after a mean duration of diabetes of 15 years.
- <50% of pts with microalbuminuria progresses to overt nephropathy; (microalbuminuria may regress or remain stable in a substantial proportion, probably related to glycemic and blood pressure control).
- 7% of pts with type DM1 and normal GFR developes ESRD after 16 years of follow-up.
- >2% of the intensively-treated subjects develop renal insufficiency (serum creatinine > 2.0 mg/dL or renal replacement therapy) over an average 30 years of diabetes duration

Epidemiology of DN type 2

- **The most common cause of ESRD in Europe and USA**
  - **25-45% of all patients enrolled in ESRD program**
- **30% of all patients with DM**

Diabetic *vs* Nondiabetic kidney disease in diabetic patients

- **With the restricted biopsy policy:**
- 29% pts. have diabetic nephropathy alone
- 38% have another glomerular disease superimposed on diabetic nephropathy
- remaining pts. Have either nephrosclerosis or nondiabetic glomerular disease.
- **With the unrestricted policy,**
- 51% pts. have diabetic nephropathy alone
- 22% have another glomerular disease superimposed on diabetic nephropathy
- remaining pts. have either nephrosclerosis or nondiabeticglomerular disease.
- **The most common nondiabetic glomerular diseases are:**
  - membranous nephropathy,
  - IgA nephropathy,
  - postinfectious glomerulonephritis
  - and minimal change disease/FSGS

Nondiabetic glomerular disease in diabetic patients

The major clinical clues suggesting the presence of nondiabetic glomerular disease are:

- **The onset of proteinuria <5 years from the documented onset of DM1**

- 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.

- **The acute onset of renal disease**. DN is a slowly progressive disorder characterized by increases in protein excretion and the serum creatinine concentration over a period of years.
- **The presence of an active urine sediment containing red cells (particularly acanthocytes) and cellular casts**. However, hematuria and red cell casts can also be seen with diabetic nephropathy alone.
- **In DM1 diabetes, the absence of diabetic retinopathy or neuropathy**.

In contrast, lack of retinopathy in type 2 diabetes does not preclude diabetic nephropathy.

- **Signs and/or symptoms of another systemic disease**.
- **Significant reduction in the glomerular filtration rate (>30 percent) within two to three months of the administration of ACE inhibitors or angiotensin II receptor blockers**

Other (than DN) causes of CKD should be considered in the presence of any of the folllowing circumstances in diabetic patient

- **Absence of diabetic retinopathy**
- **Low or rapidly decreasing GFR**
- **Rapidly increasing proteinuria or nephrotic syndrome**
- **Refractory hypertension**
- **Presence of active urinary sediment**
- **Signs or symptoms of other systemic diseases**
- **>30% reduction in GFR within 2-3 months after initiation of an ACE inhibitor or ARB**

Nephrosclerosis – a common component of CKD in diabetic patients

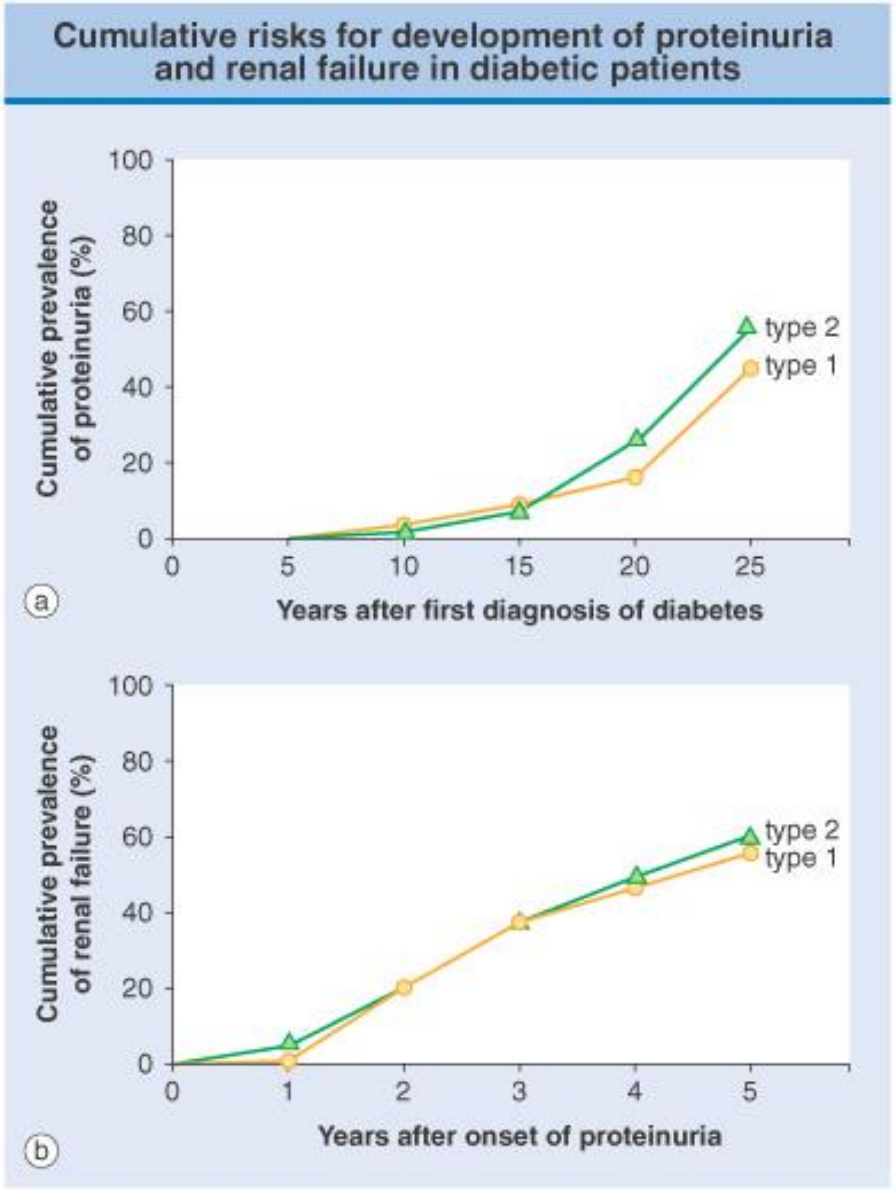


Figure 29.3 Cumulative risks for development of proteinuria and progression to renal failure in patients with type 1 and type 2 diabetes.

Microalbuminuria

- **it is below the level of clinical albuminuria (obtained with Albustix)**
- **it is a marker of incipient DN**
- **it predicts the development of diabetic nephropathy**
- **it predicts the cardiovascular mortality and morbidity**
- **marker of endothelial dysfunction**
- **renal histology: normal or DN**

Transient microalbuminuria

- **hyperglycemia, poor glycemic control**
- **hypertension**
- **massive obesity**
- **heavy exercise**
- **various acute and chronic illnesses, fever**
- **cardiac failure**
- **pregnancy**

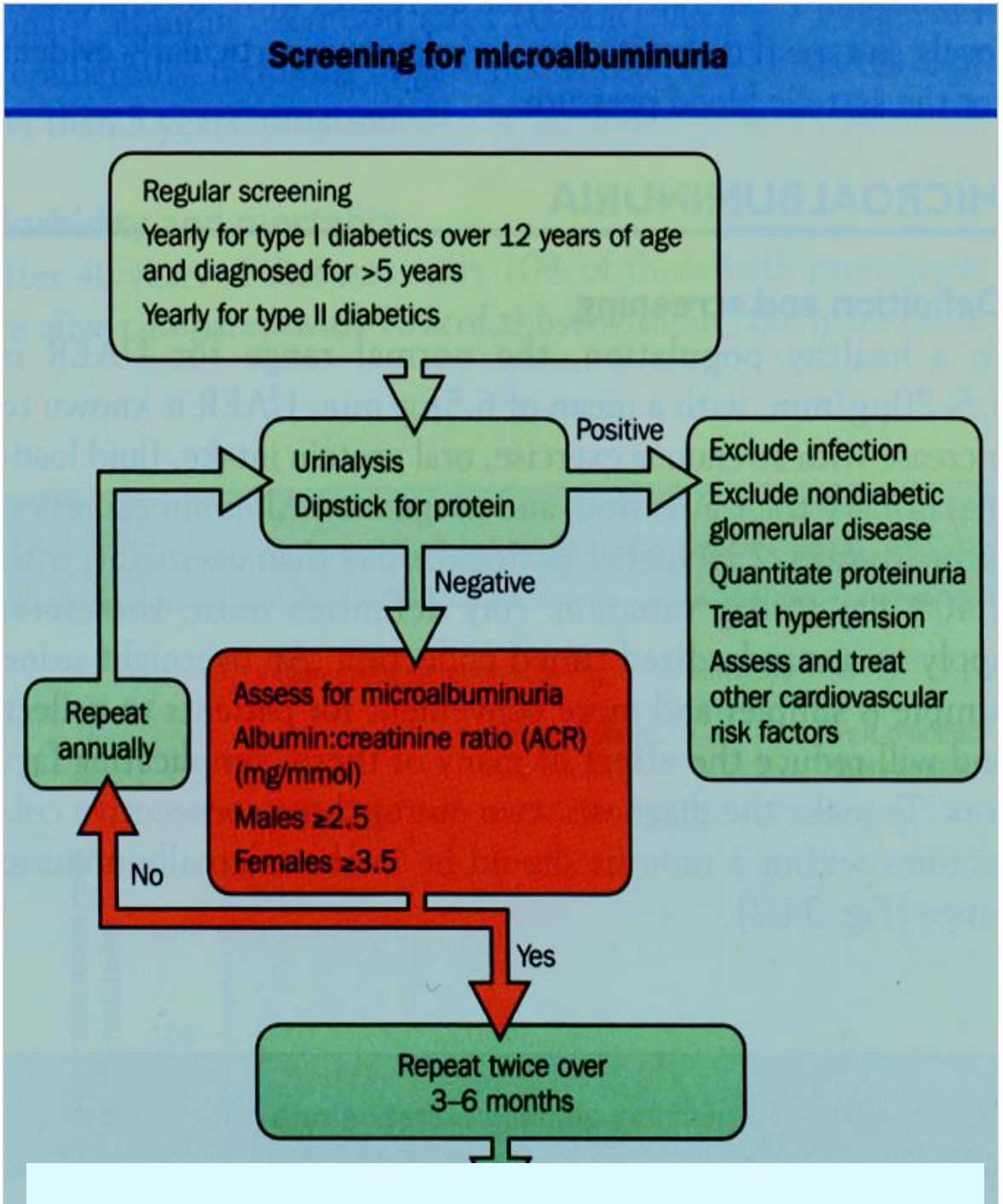
Screening for MA

type 1 DM:

- **after the first 5 years: yearly**

type 2 DM:

- **at diagnosis**

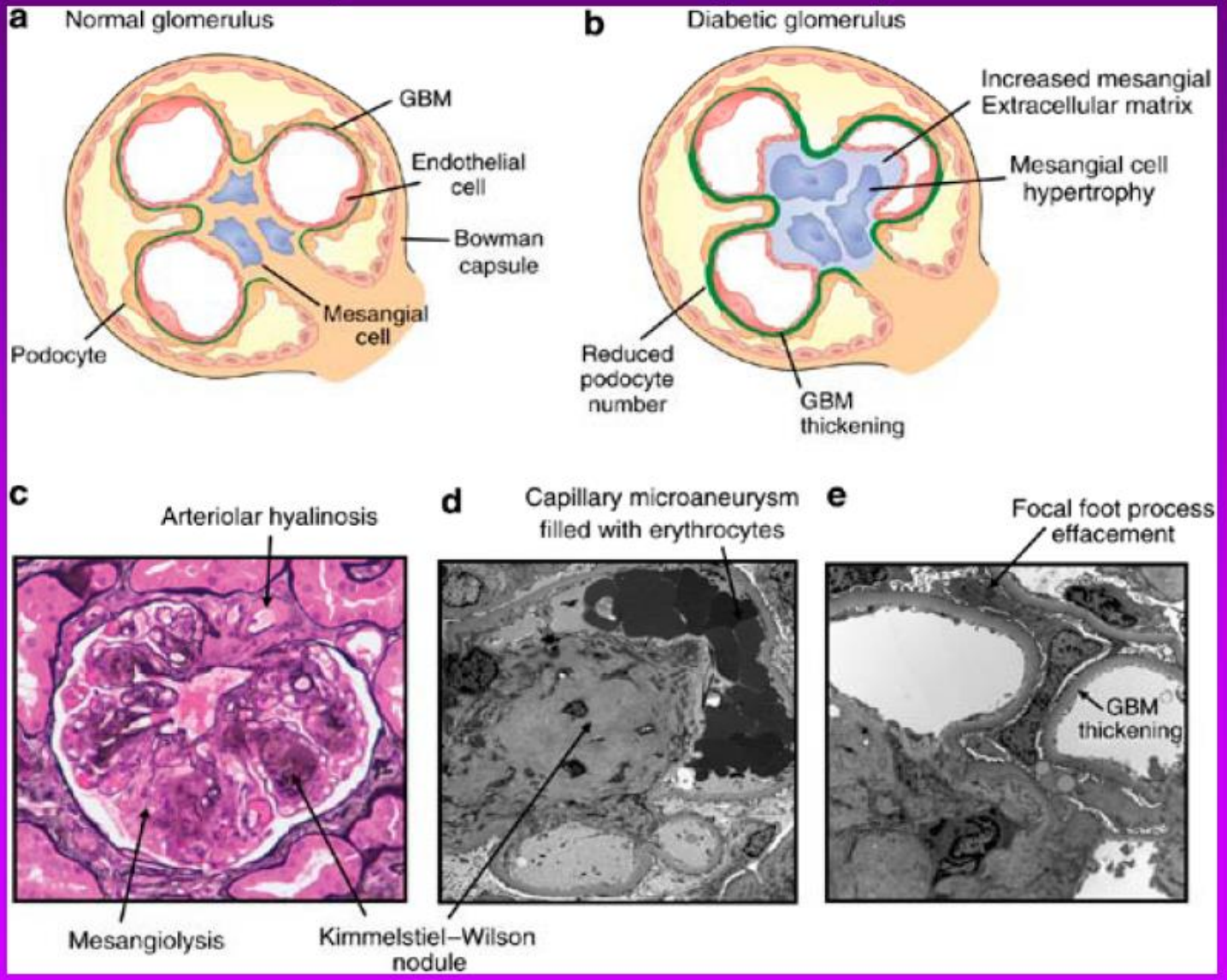

Screening for microalbuminuria
Regular screening
Yearly for type I diabetics over 12 years of age and diagnosed for >5 years
Yearly for type II diabetics
Urinalysis
Dipstick for protein
Positive
Exclude infection
Exclude nondiabetic glomerular disease
Quantitate proteinuria
Treat hypertension
Assess and treat other cardiovascular risk factors
Negative
Assess for microalbuminuria
Albumin:creatinine ratio (ACR) (mg/mmol)
Males ≥2.5
Females ≥3.5
Repeat annually
No
Yes
Repeat twice over 3–6 months

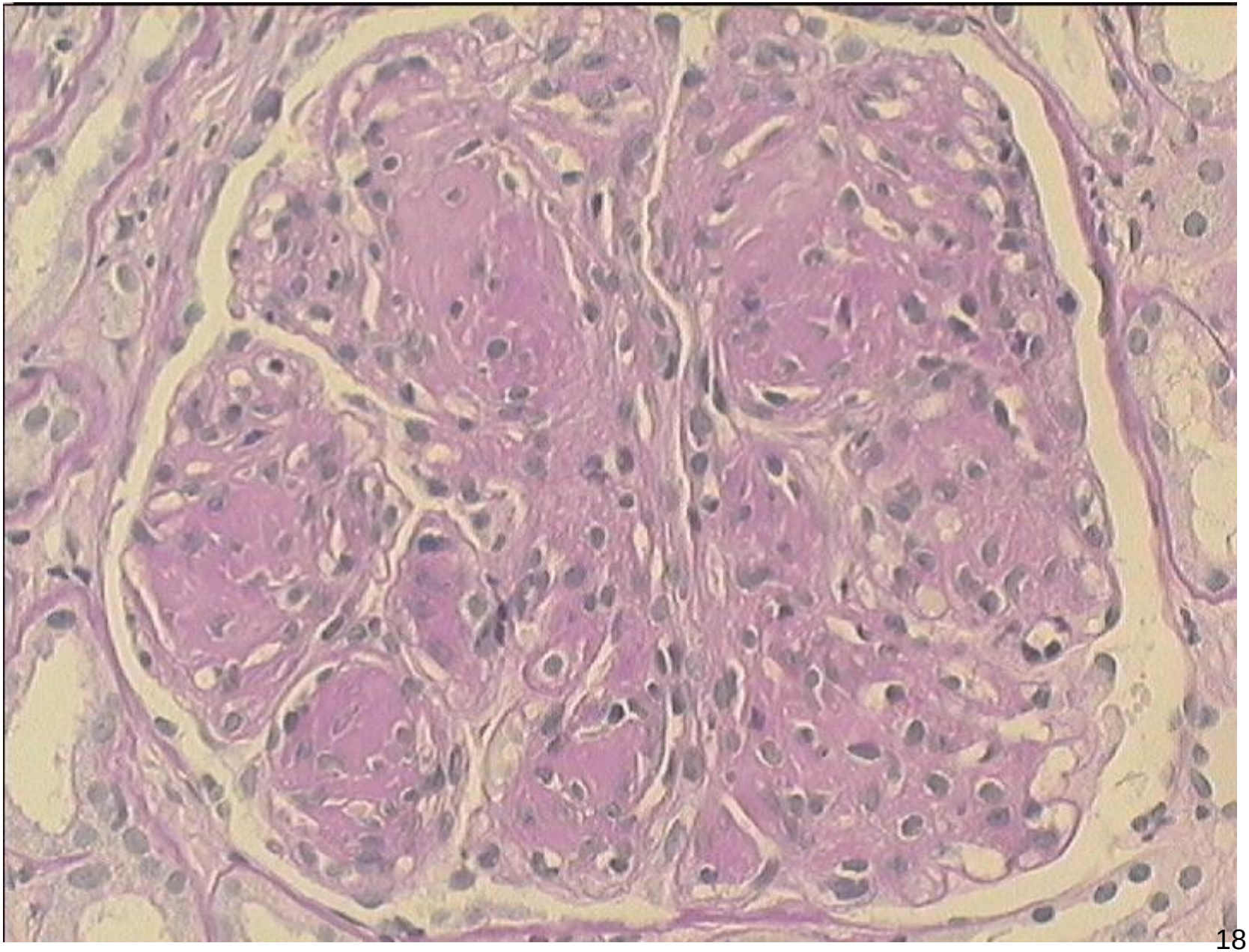
Diabetic nephropathy – pathological picture

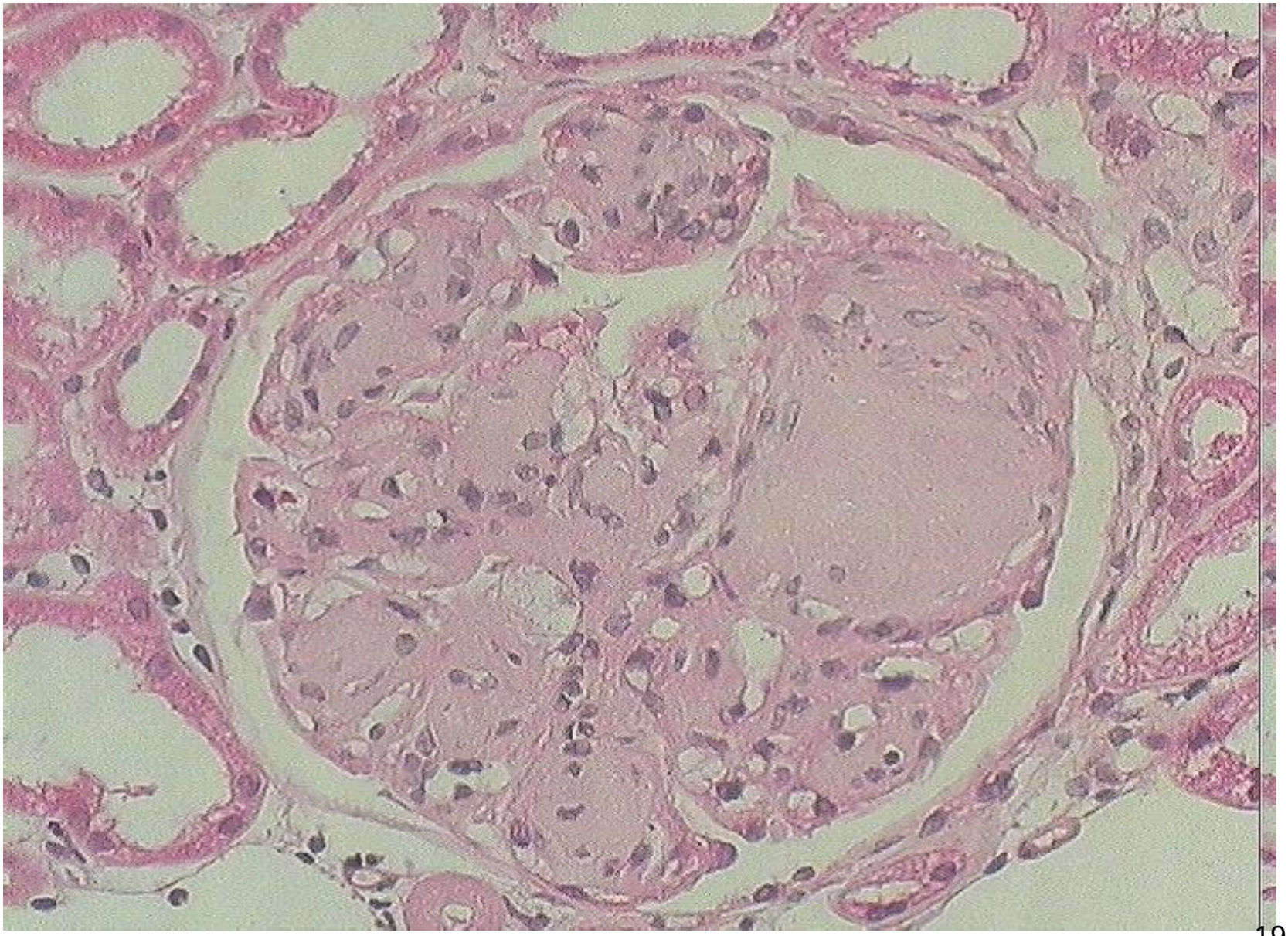
- **diffuse and nodular glomerulosclerosis**
  - **diffuse: widespread increase in mesangial matrix (mesangial expansion), increase in glomerular basement membrane (GBM) width, glomerular hypertrophy**
  - **nodular: hyaline, acellular PAS-positive intercapillary nodules (Kimmelstiel-Wilson lesion)**
- **arteriolar hyalinosis: hyaline deposits in the efferent and the afferent glomerular arterioles**
- **compression and narrowing of the capillary loops → decline in glomerular filtration**

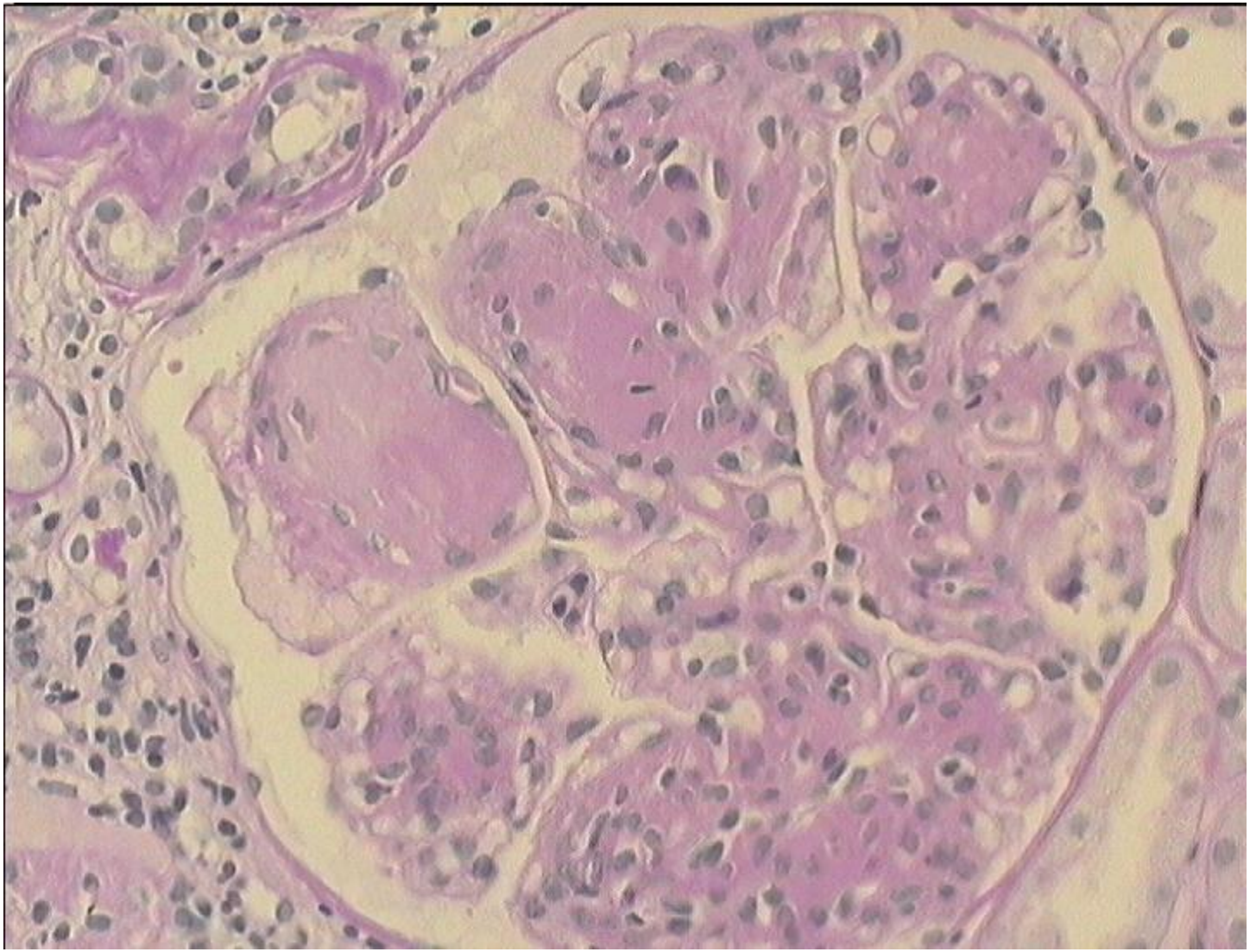
Diabetic Kidney Disease: Glomerular Changes

(Jefferson KI 2008; 74: 22)









Diabetic Kidney Disease:
Cardinal Features

LOCATION	ABNORMALITY	MECHANISM
Mesangial Cell	Expansion Matrix overproduction Hypertrophy	Altered metabolism Collagen depostion Mesangial cell AII synthesis Mechanical stress
Glomerular Basement Membrane	Thickening Matrix deposition Decreased charge	Collagen deposition Protein crosslinking AGEs Loss of heparan sulfate proteoglycans
Podocyte	Effacement Detachment from GBM Reduced number Apoptosis	Nephrin down regulation Mechanical stress
Glomerular Endothelial Cell	Defective autoregulation Microvascular changes Increased permeability Reduced glycocalyx	Afferent vasodilatation Efferent vasoconstriction AII actions VEGF expression Endothelin Reactive oxygen species
Tubulo-Interstitium	Interstitial fibrosis Tubular hypertrophy TBM thickening Inflammation Ischemia	Collagen production Extracellular matrix synthesis Fibroblast proliferation

Early structural and functional lesions

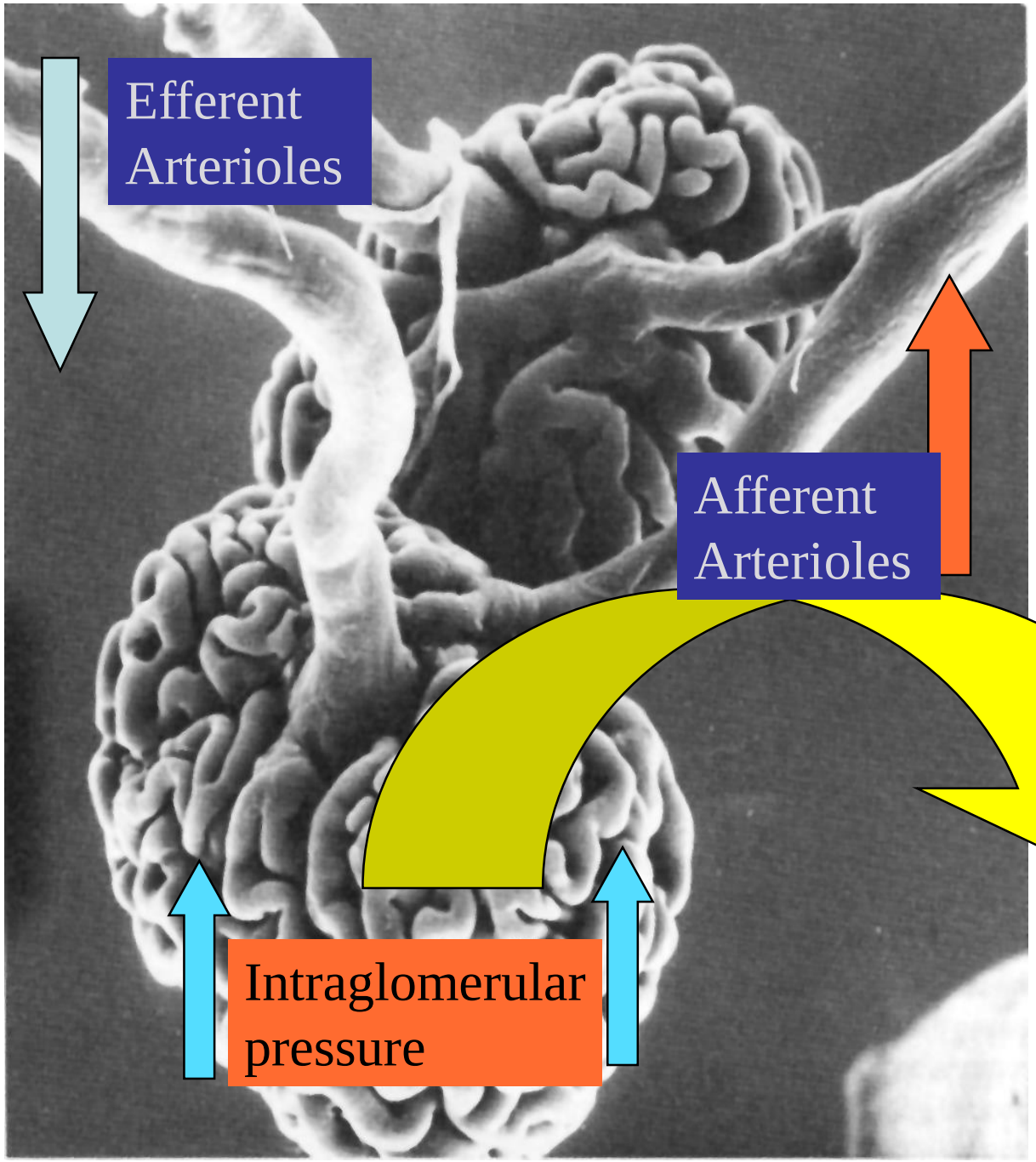
- first few months after the onset of DM: kidney enlargement: tubules, glomeruli (hypertrophy, hyperplasia), increased GFR
- after 2-3 years: thickening of the basement membranes of the tubules and the glomeruli
- after 3-5 years: mesangial expansion of the glomerulus and the tubulointerstitial regions
- **poor prognosis**: mesangial expansion, tubulointerstitial fibrosis, high GFR

Hyperfiltration (increased GFR) in incipent DN - pathophysiology

- **increased renal plasma flow (RPF)**
- **increased glomerular transcapillary hydraulic pressure (intraglomerular hypertension):**
  - **dilatation of the afferent arteriole**
  - **ischemic injury induced by hyaline narrowing of the efferent arteriole**
- **increased glomerular capillary surface area (excessive renal growth)**

Mediators of hyperfiltration in diabetes

- **glucose**
- **ketone bodies**
- **insulin, growth hormone, glucagon**
- **high protein intake**
- **prostaglandins, nitric oxide**
- **atrial natriuretic peptide (ANP)**
- **glomerulopressin**
- **increased sodium/lithium and sodium/hydrogen countertransport**
- **kidney and glomerular enlargement**


Efferent Arterioles
Afferent Arterioles
Intraglomerular pressure
Albuminuria

Mechanisms of Progression: Injury, Insult, and Susceptibility

LOCATION	HEMODYNAMIC INJURY	METABOLIC INSULT	GENETIC SUSCEPTIBILITY
Mesangial Cell	Mechanical stretch Angiotensin stimulates proliferation Renin stimulates TGF-B	Mesangell cell matrix production	
Glomerular Basement Membrane	Angiotensin stimulates type IV collagen	AGE production	RAGE gene
Podocyte	Angiotensin suppresses nephrin	VEGF production	NOS 3 PKC polymorphism
Glomerular Endothelial Cell	Angiotensin stimulates Endothelial cells	↑ VEGF ↓ NO Synthase PKC stimulates vaso-dilatory PGs	ACE genetic polymorphism
Tubulo-Interstitium	Angiotensin stimulates fibroblasts	Glucose exposure increases collagen synthesis Accumulation of ADMA	

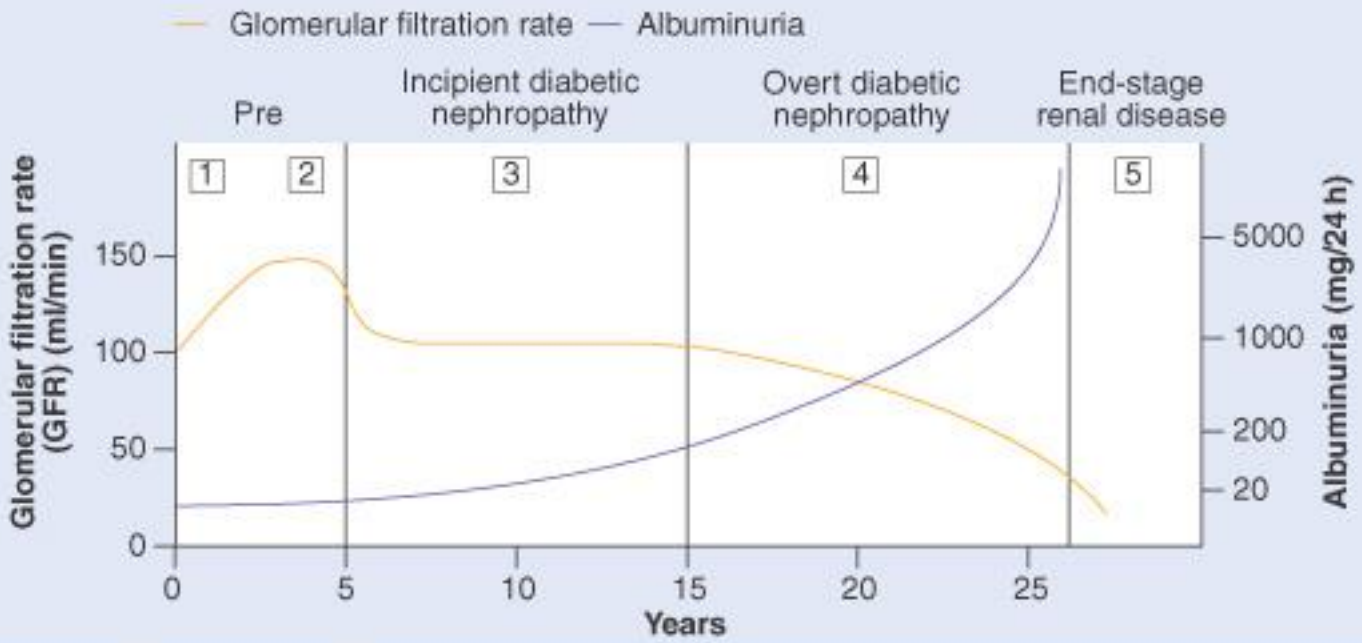
Diabetic nephropathy- risk factors

- **microalbuminuria**
- **genetic factors**
- **sex: M>F**
- **predisposition to arterial hypertension**
- **ethnic conditions**
- **onset of IDDM before age 20 yr**
- **glycemic control**
- **smoking**
- **hyperlipidemia**
- **presence of retinopathy**

Progression of diabetic nephropathy – risk factors

- **hypertension**
- **proteinuria**
- **glycemic control**
- **hypercholesterolemia**
- **high dietary protein intake**
- **smoking ?**
- **genetic**
  - **insertion(I)/deletion(D) polymorphism of ACE gene**
    - **DD genotype worse than ID and worse than II**
  - **aldose reductase gene?**
- **pregnancy ?**

Natural history of type 1 diabetic nephropathy



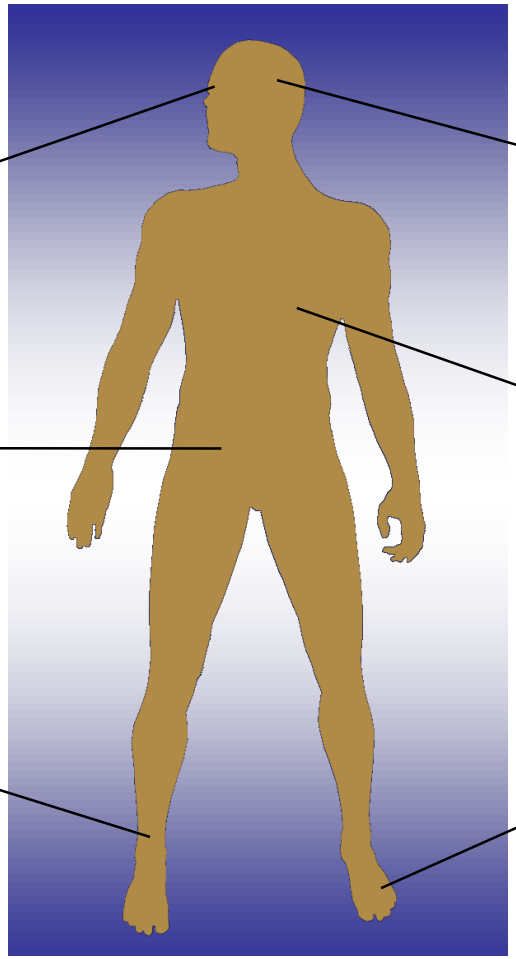
Stage	Pre	Incipient	Overt
Functional	GFR ↑ (25%–50%)	Microalbuminuria, hypertension	Proteinuria, nephrotic syndrome, GFR ↓
Structural	Renal hypertrophy	Mesangial expansion, glomerular basement membrane thickening, arteriolar hyalinosis	Mesangial nodules (Kimmelstiel-Wilson lesions) Tubulointerstitial fibrosis

Figure 29.5 Natural history of type 1 diabetic nephropathy. Functional and structural manifestations of diabetic nephropathy. Numbers 1 through 5 indicate the stages of nephropathy defined by Mogensen.

Extrarenal complications in diabetic nephropathy

- **diabetic retinopathy**
  - **all type 1 diabetic patients with nephropathy**
  - **50-60% proteinuric NIDDM patients**
- **peripheral neuropathy**
  - **almost all patients with advanced nephropathy**
  - **gustatory sweating, impotence, postural hypotension, diarrhea, cystopathy**
- **macroangiopathy: CHD, stroke, carotid artery stenosis, peripheral vascular disease**
- **foot ulcers, sepsis, amputations**

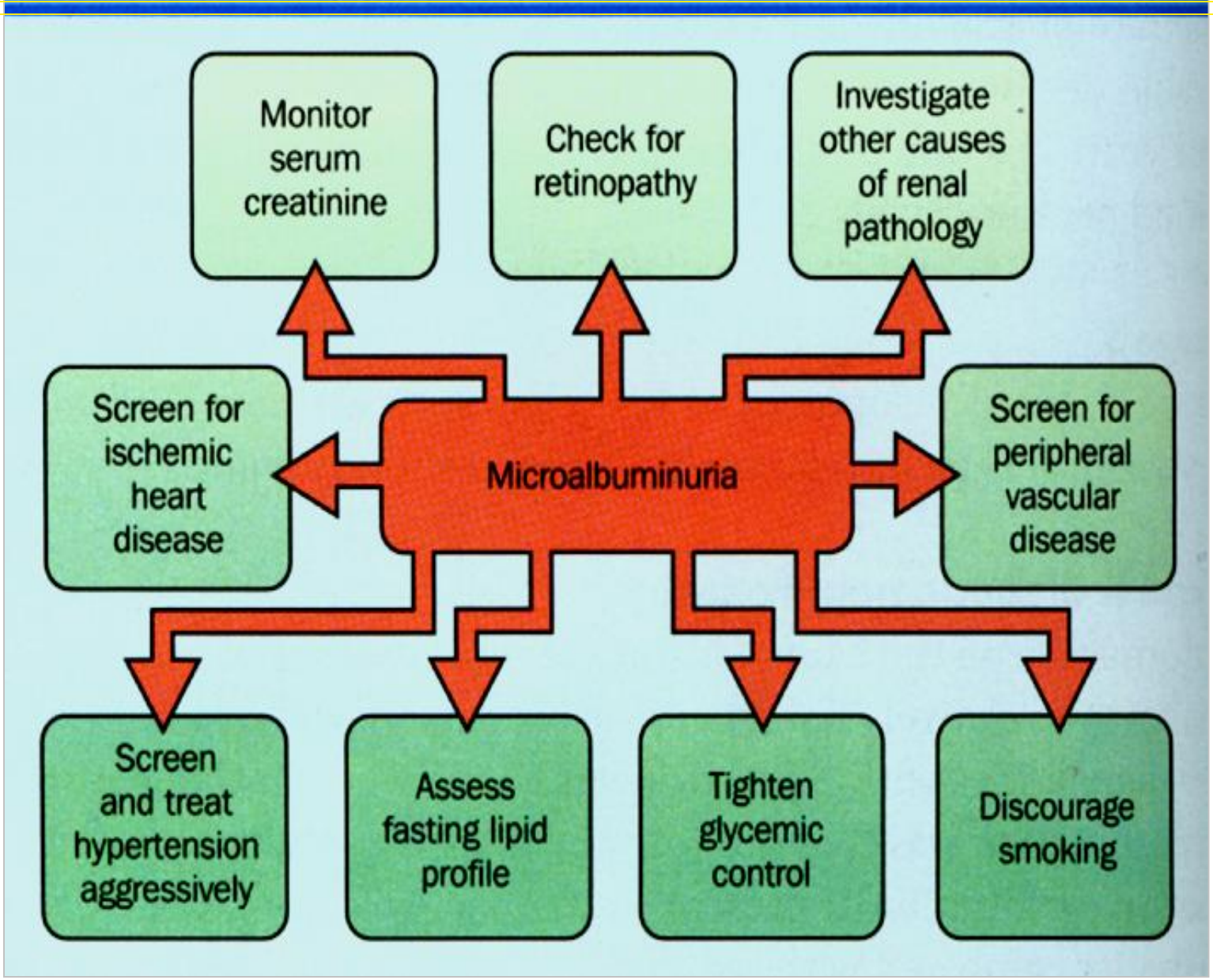
50% of Type 2 Diabetes Patients Have Complications at the Time of Diagnosis



Treatment of MA and DN

- **primary prevention (progression from normo- to microalbuminuria) – „P”**
- **secondary prevention (progression from microalbuminuria to diabetic nephropathy) – „S”**
- **progression from diabetic nephropathy to ESRD – „E”**

Investigation and treatment of microalbuminuria



Treatment modalities

- **intensive blood glucose control**
- **antihypertensive treatment (ACE-Is, ARBs, long-acting dihydropyridine calcium antagonist, β-blokade)**
- **lipid lowering**
- **restriction of dietary proteins (0,8g of high biologic value /kg)**
- **smoking cessation**
- **exercise/ weight control**

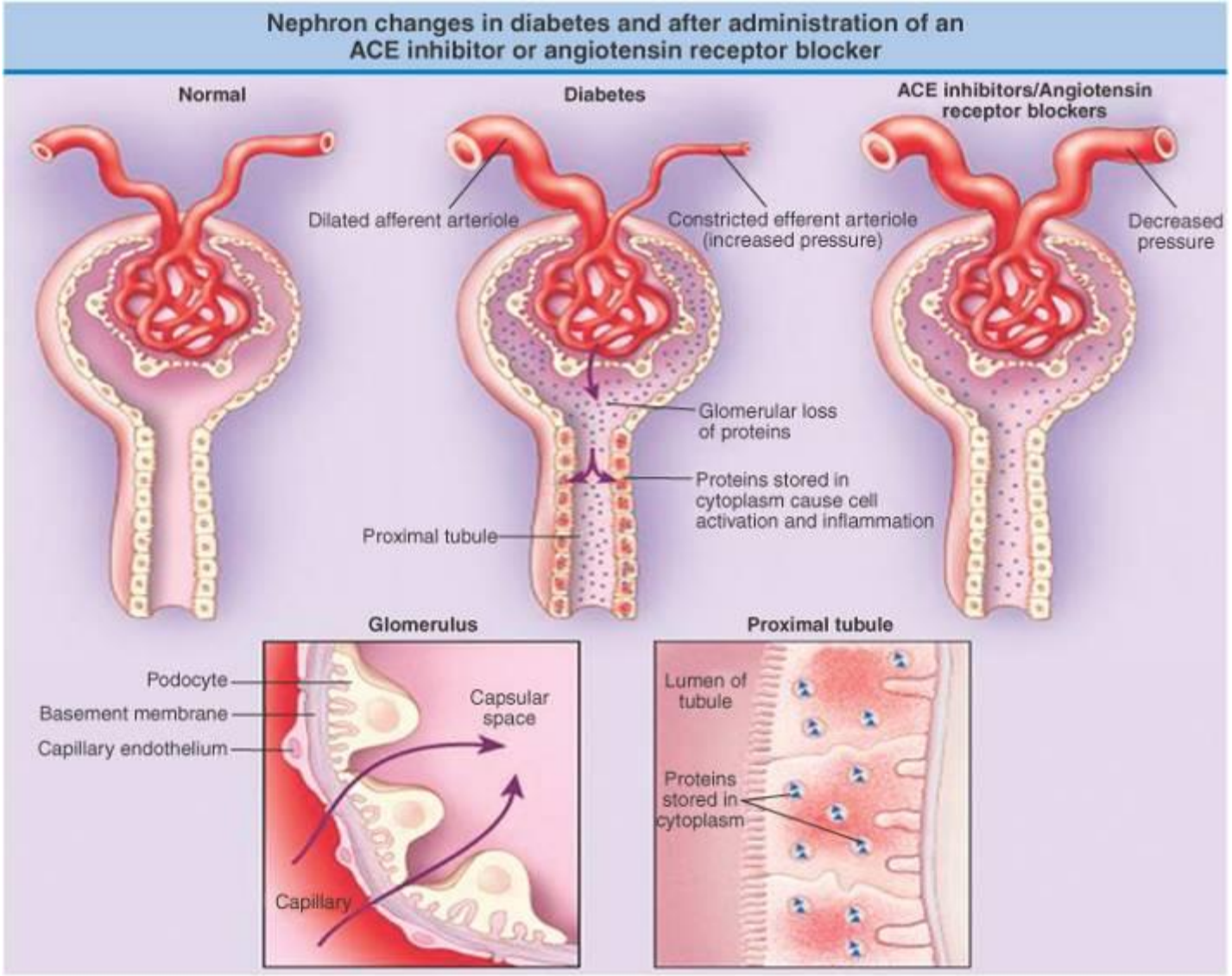


Figure 29.1 Schematic comparison of a normal nephron, a nephron in diabetic nephropathy, and a nephron in diabetic nephropathy after administration of angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB). Note afferent vasodilation and efferent angiotensin II–mediated vasoconstriction in diabetes causing glomerular hypertension, which is relieved by ACE inhibitor/ARB treatment. Note also protein leakage into the filtrate and tubular loading with endocytosed protein causing an inflammatory reaction promoting interstitial fibrosis. This is reversed by ACE inhibitor/ARB treatment.

Antihypertensive treatment – therapeutic goals:

Accoriding to UPtoDate (Jan 2013)

- all patients with diabetes mellitus have a goal blood pressure **less than 140/90 mmHg.**
- a weaker recommendation:
  an attempt to lower the systolic pressure below 130 to 135 mmHg if it can be achieved without producing significant side effects.
- **a goal blood pressure of less than 130/80 mmHg in patients with diabetic nephropathy and proteinuria (500 mg/day or more).** Patients with moderately increased albuminuria are treated similarly to diabetic patients without proteinuria.
- **For patients who fulfill the entry criteria in ACCORD BP (type 2 diabetes plus either cardiovascular disease or at least two additional risk factors for cardiovascular disease), goal systolic pressure of less than 120 mmHg.** Such a goal may be considered in highly motivated patients who would accept more aggressive antihypertensive therapy to further reduce their risk of stroke.

Management of the patient with advanced renal failure

- **hypertension – ACE-I, ARBs, loop diuretics**
- **glucose control**
- **malnutrition**
  - **predictor of mortality**
  - **indication for early start of dialysis**
- **acute and „acute on chronic" renal failure – high susceptibility to ischemic injury**

Management of the patient with advanced renal failure

- **vascular access – consider when GFR 20-25 ml/min**
- **initiation of renal replacement therapy – GFR 15 ml/min**
- **after start of dialysis: protein intake 1,3g/kg/day**

Treatment options for diabetic patient with ESRD

- **transplantation**
  - **kidney**
  - **simultaneous pancreas plus kidney (SPK)**
  - **pancreas after kidney (PAK)**

  the best option: preemptive SPK
- **continous peritoneal dialysis (CAPD)**
- **hemodialysis**
- **CAPD or HD ?**

CAPD (continous peritoneal dialysis)

- **better survival during first 2 years than on HD**

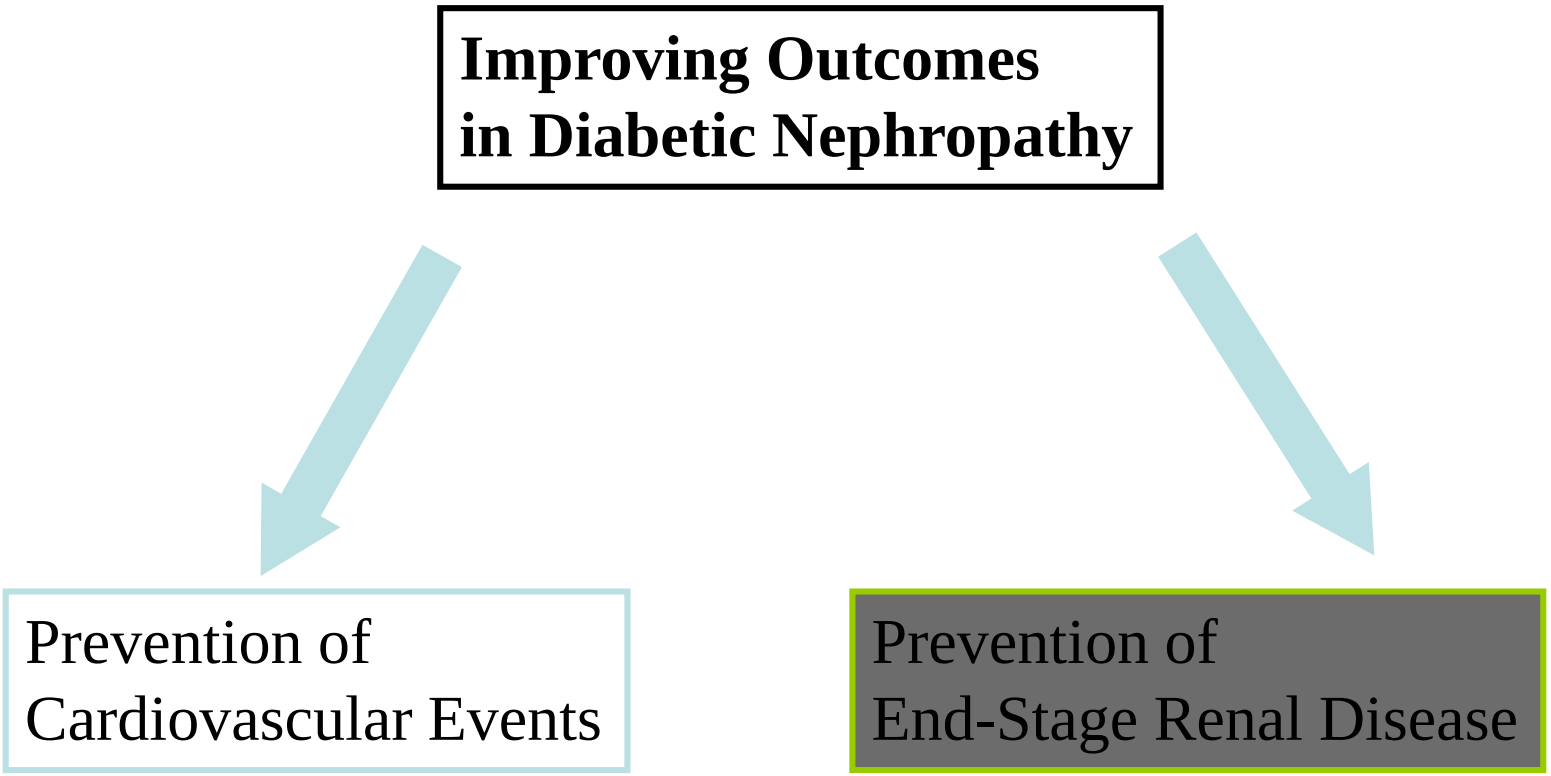
Management of the patient with advanced renal failure

- **transplantation – the treatment of choice**
- **predicted survival**
  - **– on the waiting list – 8 years**
  - **– after transplantation – 19 years**

Urinary tract infection

- more severe and more aggressive than in non-diabetic patients
- pathophysiology:
  - glucosuria
  - defective neutrophil function
  - increased adherence to uroepithelial cells
  - impaired bladder evacuation (detrusor paresis)
- complication: capillary necrosis

Diabetic Nephropathy



SUMMARY

- **Diabetic nephropathy occurs in both type 1 and type 2 DM.**
- **Leading cause of end-stage kidney disease**
- **The risk of progression of diabetic nephropathy has improved over the last several decades, largely due to**
  - **rigorous glycemic control,**
  - **aggressive blood pressure reduction**
  - **the use of angiotensin converting enzyme**
- **characterized by hypertension, proteinuria and progressive loss of kidney function**
- **Cardiovascular complications excessive an increase with worsening kidney function**
- **More likely to die than progress to end-stage**
- **Proteinuria in diabetes mellitus is occasionally due to a glomerular disease other than diabetic nephropathy, or to nephrosclerosis.**
- **The three major histologic changes in the glomeruli in diabetic nephropathy include mesangial expansion; glomerular basement membrane thickening; and glomerular sclerosis. Different histologic patterns have similar prognostic significance.**

Diabetic Nephropathy: Take Home Message

- **Lower blood pressure < 130 / 80 mmHg**
- **Reducing Proteinuria**
- **Inhibition of Renin-Angiotensin System**
- **Multiple risk factor intervention**
  - **Glycemia**
  - **Dyslipidemia**
  - **Physical activity**
  - **Aspirin**
  - **Smoking cessation**