HYPERTENSIVE NEPHROSCLEROSIS

PATHOGENESIS:

1. Renal injury
   a. Atherosclerotic HTN-related vascular lesions: chronic HTN in pre-glomerular arterioles reduces blood flow in the glomerulus → ischemic damage in glomeruli & post-glomerular structures
   b. Glomerular hyperperfusion: remaining (undamaged) glomeruli are working harder (hyperperfusion) → direct damage to these glomerular capillaries
2. Loss of autoregulation: with progressive renal injury there is a loss of autoregulation of RBF and GFR → lower BP threshold for renal damage & steeper slope b/w BP and renal damage
3. Vicious cycle: renal damage & nephron loss → more severe HTN and glomerular hyperfiltration → further renal damage
4. Progression to glomerulosclerosis
5. Renal tubules may also become ischemic & gradually atrophic

DIAGNOSIS:

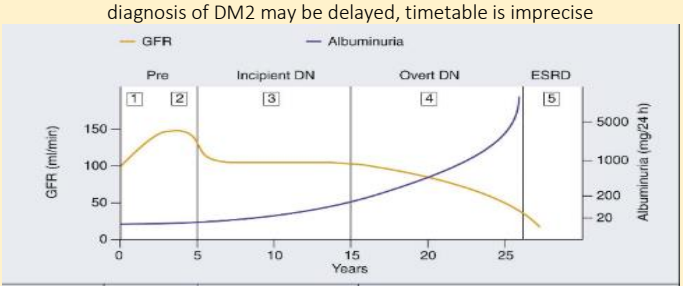
Clinical Presentation	• Hx of HTN • Hypertensive crisis (→ AKI) • Black pts higher risk • Likelihood of progressive renal failure (ESRD) linked to BP control • Often mixed with DM nephropathy
Blood Tests	• Slowly progressive increase in SCr & BUN
Urinalysis	• Mild proteinuria (<1 g/d)
Ultrasound	• Small echogenic kidney (= chronic disease)

TREATMENT: blood pressure management (lectures 13 & 14)

DIABETIC NEPHROPATHY:

PATHOGENESIS: 5 stages

1. GLOMERULAR (adaptive) HYPERFILTRATION & RENOMEGALY: kidney adapts to damage by increasing GFR (up to 140%) to functioning nephrons
   > LONG-TERM: causes damage to glomeruli of remaining nephrons → progressive CKD and proteinuria
   > OTHER HOMEOSTATIC MECHANISMS: help maintain Na, K, Ca, PO4
   > DM2: glomerular hyperfiltration also reported and is positively correlated with development of proteinuria
2. EARLY GLOMERULAR LESION: **expansion** of glomerular mesangial matrix & **thickening** of glomerular basement membrane (2-5 yrs after DM1 onset)
   > DIRECT: hyperglycemia alters growth, gene, protein expression of cells
   > INDIRECT: hyperglycemia forms advanced glycation end-products (AGEs) → enhance expression of collagen, TGF-B & PKC
   - TGF-B (transforming growth factor): inhibits degradation of extracellular matrix (ECM) in glomerular mesangial and epithelial cells → accumulation
   - PKC (protein kinase C): increases production of cytokines, ECM, and endothelin-1
3. MICROALBUMINURIA: UAE = urinary albumin excretion
   > UAE increases by 25 mcg/min/year when GFR normal/elevated
   - When UAE > 70 mcg/min/year → GFR begins to decline
   > BP higher (but not necessarily > 140/90) in pts with micro-albuminuria → combo leads to clinical nephropathy in 5-15 yrs
4. CLINICAL NEPHROPATHY: after several yrs with microalbuminuria, GFR declines below normal for age & gender → macroalbuminuria
   > MACROALBUMINURIA: universal hallmark in diabetic nephropathy
   > NEPHROTIC SYNDROME: DM1 is leading cause in N. America
   > DECLINE IN GFR: 11 mL/min/yr in DM1 and 5.2 mL/min/yr in DM2
5. END-STAGE RENAL DISEASE:
   > DM1: 20-30 years after onset, 30-40% of pts manifest with ESRD
   > DM2: 5-25 years after diagnosis of DM2 pts have ESRD, but since diagnosis of DM2 may be delayed, timetable is imprecise



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

DIAGNOSIS:

Clinical Presentation	• Hx of diabetes (DM1 or DM2) • Increase risk in blacks or natives
Blood Tests	• Increased eGFR with early disease (stage 1) • Increased albuminuria = first sign usually picked up • Rapid drop in eGFR at late stage
Urinalysis	• Hematuria • Proteinuria • Usually no sediment

TREATMENT: (only can slow down progression, can't stop it)

- Weight loss if increased BMI
- Smoking cessation
- Glycemic control
  - Can reverse glomerular hypertrophy & hyperfiltration
    > With intensive insulin therapy, GFR decreases within 8 days of initiation, and falls further during 3 months of insulin txt
  - Can slow down eGFR decline
- Blood pressure control & proteinuria control
  - RAAS inhibitors

PROTEINURIA:

RISK FACTORS:
- Race (non-Caucasian)
- HTN
- DM
- Acute MI
- > 70 y/o

COMPLICATIONS:
- Mortality
- CV mortality
- ESRD
- AKI
- Progressive CKD

PROTEINURIA:
- Small amount of proteinuria is normal
  - Protein < 150 mg/d
  - Albumin < 30 mg/d
- Proteinuria can be due to problems in glomerule, tubule or overflow
- Transient proteinuria is common
  - DAY-TO-DAY VARIATION
  - Exercise
  - Febrile illness (fever)
  - Decompensated CHF
  - UTI
  - Urologic/menstrual bleeding
  - Acute elevation in BP or BG
- Confirm by repeating urine test 1-2 wk later

TREATMENT:
- Identify underlying cause
- CVD risk factor medication
  - Salt restriction (< 2g/day)
  - Quit smoking
  - Exercise
  - Weight control
  - Treat OSA (sleep apnea)
  - Dyslipidemia
- BP control targets (regardless of proteinuria)
  - Non-DM: 140/90
  - DM: 130/80
- Antiproteinuric agents: ACEIs or ARBs

DEFINITIONS:

Terminology (KDIGO 2012)	Old terminology	Urine dipstick	Quantity of albuminuria
Normal to mildly increased albuminuria (A1)	Normal	-ve	< 30 mg/day ACR < 3 mg/mmol
Moderately increased albuminuria (A2)	Microalbuminuria	-ve or + 1	30 – 300 mg/day ACR 3-30 mg/mmol
Severely increased albuminuria (A3)	Macroalbuminuria or overt proteinuria	+ 2 or + 3	300 mg/day ACR > 30 mg/mmol
Nephrotic range proteinuria	Nephrotic range proteinuria	+ 4	3000 mg/day ACR > 300 mg/mmol

ANTIPROTEINURIC AGENTS:

	Proteinuria reduction
ACEI/ARBs (higher doses)	**30 – 40%**
Sodium restriction (< 2 g/day)	30 – 50%
Weight loss (5% reduction)	30%
Add diuretic (HCRZ or furosemide) to ACEI/ARB	30 – 40%

Additive reductions (ex// ACEI + salt reduction = 60-90% proteinuria reduction)

TARGETS FOR PROTEINURIA:
- Observational studies show lower level of proteinuria = decreased CKD progression
- No study looking at target proteinuria level and outcomes = no specific targets identified

ACEI/ARBs AS ANTIPROTEINURIC AGENTS:

MOA: decrease in proteinuria is independent of BP reduction
- Vasodilation of efferent arterioles → decrease in intra-glomerular pressure
- ↓ podocytes apoptosis
- ↓ inflammatory activities in mesangial cells and proximal tubule cells due to high blood sugar

COMBINATION ACEI + ARB:
- Better at reducing proteinuria
- No reduction in CKD progression
- Might increase risk of ESRD
- May increase risk of mortality
- Increased risk of ADR (hypotension, hyperkalemia)

= DO NOT USE COMBINATION ACEI + ARB

WHEN TO USE:
- ACEI/ARBs used regardless of pt's BP, if pt can tolerate it (BP, SCr or K+)
  - No eGFR cutoff to which pt won't benefit from ACEI/ARB therapy
  - Be more cautious with CKD Stage 4 and 5
- Check SCr and K+ within 1-2 wks of starting or uptitrating ACEI/ARB
- May need to stop or decrease ACEI/ARB if:
  - SCr increases by > 30%
  - K+ > 6
- SICK DAY MANAGEMENT: hold ACEI/ARB during period of volume depletion