Proteinuria 2006

Family practice resident version

Proteinuria-Systemic versus Renal

Proteinuria may be due to:

- Specific renal diseases or multisystem autoimmune diseases
- Metabolic dysfunction

The latter is much more common!

- When proteinuria is due to specific renal diseases it may be associated with renal dysfunction, hematuria, nephrotic syndrome, nephritic syndrome, or rarely it is isolated and/or transient
- When proteinuria is due to metabolic dysfunction proteinuria is often less than nephrotic range (microalbuminuria), usually isolated and is commonly associated with endothelial/cardiorenal dysfunction/hypertension

Metabolic Syndrome: an Evolving Concept

- In the 80s: Reaven syndrome or syndrome X
  - -insulin resistance
  - -hypertension
  - -hyperuricemia
  - -hypercoagulability (PAI deficiency)
  - -high triglycerides, low HDL
- In the 90s: endothelial dysfunction
  - -nitric oxide
  - -inflammation, cytokines, CRP
  - -sleep apnea
  - -CRF as cardiovascular risk factor
- Now:
  - -fat tissue as endocrine organ
  - -MPO as cardiovascular event predictor
  - -proteinuria as cardiorenal predictor

Cardiovascular Risk and Proteinuria

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII)

Major Cardiovascular Risk Factors:

-Hypertension
-Cigarette Smoking
-Obesity (BMI>30)
-Physical Inactivity
-Dyslipidemia
-Diabetes Mellitus
-**Microalbuminuria or Estimated GFR<60**
-Age (>55 for men, >65 for women)
-Family history of premature coronary artery disease (men<55, women<65)

Advanced Renal Failure- Millions at Risk

Third National Health and Nutrition Examination Survey:

-19.2 million have Chronic Kidney Disease (11%)
-7.6 million have Stage III Chronic Kidney Disease (4.3%)
-0.7 million have Stage IV and End Stage Renal Disease (0.4%)

Definition of:
-Chronic Kidney Disease =**GFR<60 ml/min/1.73 m^2** **or persistent albuminuria**

-Stage III Chronic Kidney Disease=GFR 20-39 ml/min/1.73 m^2

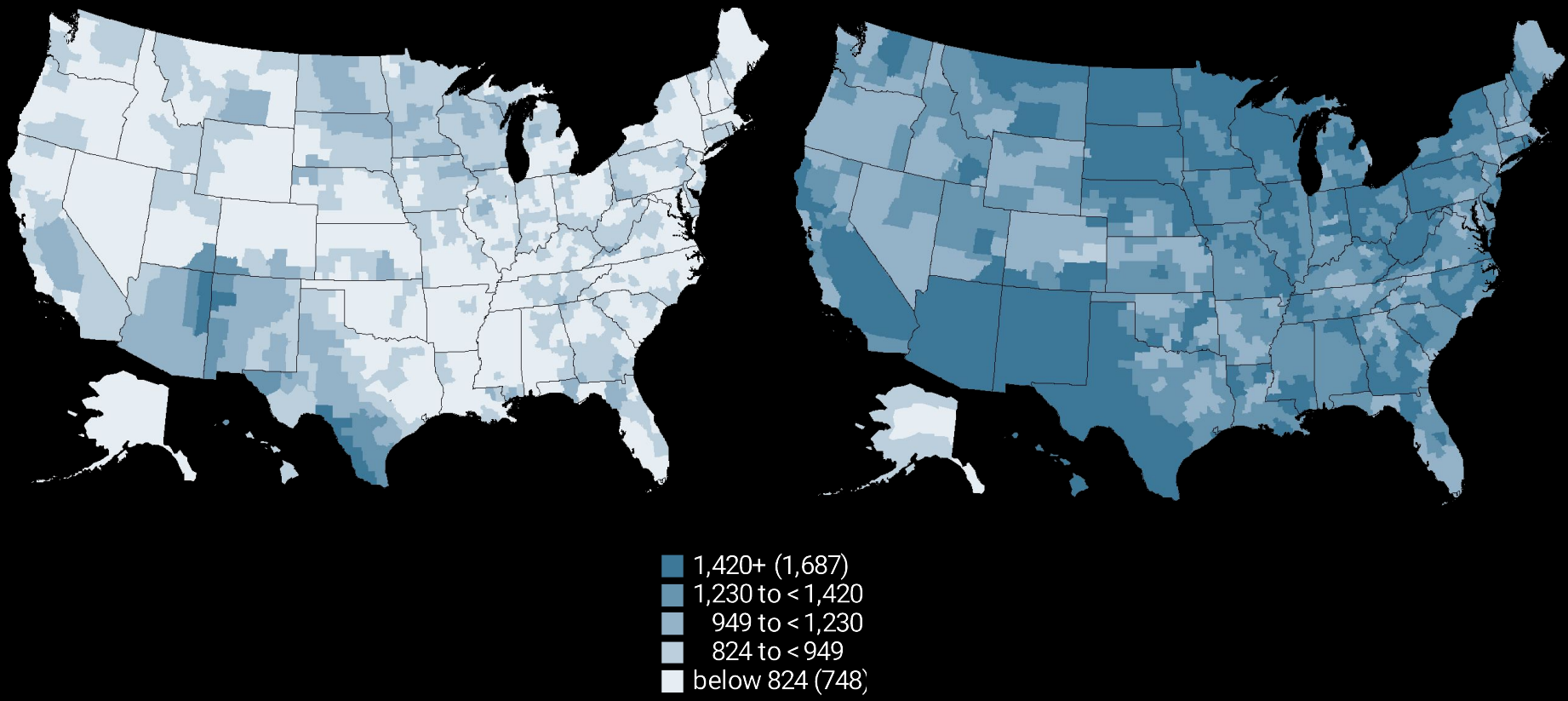
American Journal of Kidney Diseases Vol 41, No 1, 2003: pp1-12

NHANES III on Prevalence of Albuminuria

- 8.3 percent of 14,622 adults had microalbuminuria
- 1 percent had macroalbuminuria (>300 mg/24h)
- Albuminuria 1:3 in Diabetes Mellitus
- Albuminuria 1:7 in Hypertension but no Diabetes
- Albuminuria 1:6 >60 years

Prevalence of ESRD: 1991 versus 2001

(per million population)



Proteinuria is made worse by overeating…..

High protein diets:

1. Splanchnic blood flow
2. Glomerular pressure
3. Tubular protein trafficking

High salt diets:

1. Hypervolemia
2. Blood pressure

Obesity:

1. Blood pressure
2. Glomerular filtration
3. May lead to obesity-related glomerulomegaly/FSGS/ Diabetic Nephropathy

Proteinuria versus Microalbuminuria: definition

Table 15. Definitions of Proteinuria and Albuminuria

	Urine Collection Method	Normal	Microalbuminuria	Albuminuria or Clinical Proteinuria
Total Protein	24-Hour Excretion (varies with method)	<300 mg/day	NA	>300 mg/day
	Spot Urine Dipstick	<30 mg/dL	NA	>30 mg/dL
	Spot Urine Protein-to-Creatinine Ratio (varies with method)	<200 mg/g	NA	>200 mg/g
Albumin	24-Hour Excretion	<30 mg/day	30–300 mg/day	>300 mg/day
	Spot Urine Albumin-Specific Dipstick	<3 mg/dL	>3 mg/dL	NA
	Spot Urine Albumin-to-Creatinine Ratio (varies by gender[a])	<17 mg/g (men) <25 mg/g (women)	17–250 mg/g (men) 25–355 mg/g (women)	>250 mg/g (men) >355 mg/g (women)

[a] Gender-specific cut-off values are from a single study.[19] Use of the same cut-off value for men and women leads to higher values of prevalence for women than men. Current recommendations from the American Diabetes Association define cut-off values for spot urine albumin-to-creatinine ratio for microalbuminuria and albuminuria as 30 and 300 mg/g, respectively, without regard to gender.[8]

- These definitions are methodical: microalbuminuria originally defined as albumin not detectable by dipstick
- Clinically: a continuous rather than categorical variable as:
1. Any proteinuria is bad
2. More proteinuria is worse
3. Above applies even in specific renal diseases such as nephrotic syndrome even at high ranges

Proteinuria: Presentation and Diagnosis

- Most cases of sub-nephrotic proteinuria: asymptomatic, higher ranges: nephrotic syndrome
- Proteinuria is often diagnosed by screening: on urinalysis confirmed/quantified by 24 hour urine collection or random spot urine protein or albumin/creatinine ratio
- The ratios are the preferred method (NKF)
- Diagnosis of persistent proteinuria requires at least 2 consecutive tests being positive
- Transient proteinuria is usually benign: includes orthostatic, exercise-induced, artifacts common-especially in women

False tests- to decrease chance repeat and think

Table 61. Common Causes of False Results in Routine Measurements of Urinary Albumin or Total Protein

	False Positive	False Negative
Fluid Balance	Dehydration increases concentration of protein in the urine	Excessive hydration decreases concentration of protein in the urine
Hematuria	Hematuria increases amount of protein in the urine[a]	
Exercise	Exercise increases the excretion of protein in the urine, especially albumin	
Infection	Urinary infection may cause production of proteins from the organism and the cellular reactions to them	
Urine proteins other than albumin		These proteins usually do not react as strongly as albumin with the routine methods for measuring protein on dipsticks
Pharmaceutical agents*	Extremely alkaline urine (pH >8) may react with the reagent pads on dipsticks to yield a color falsely indicating protein	

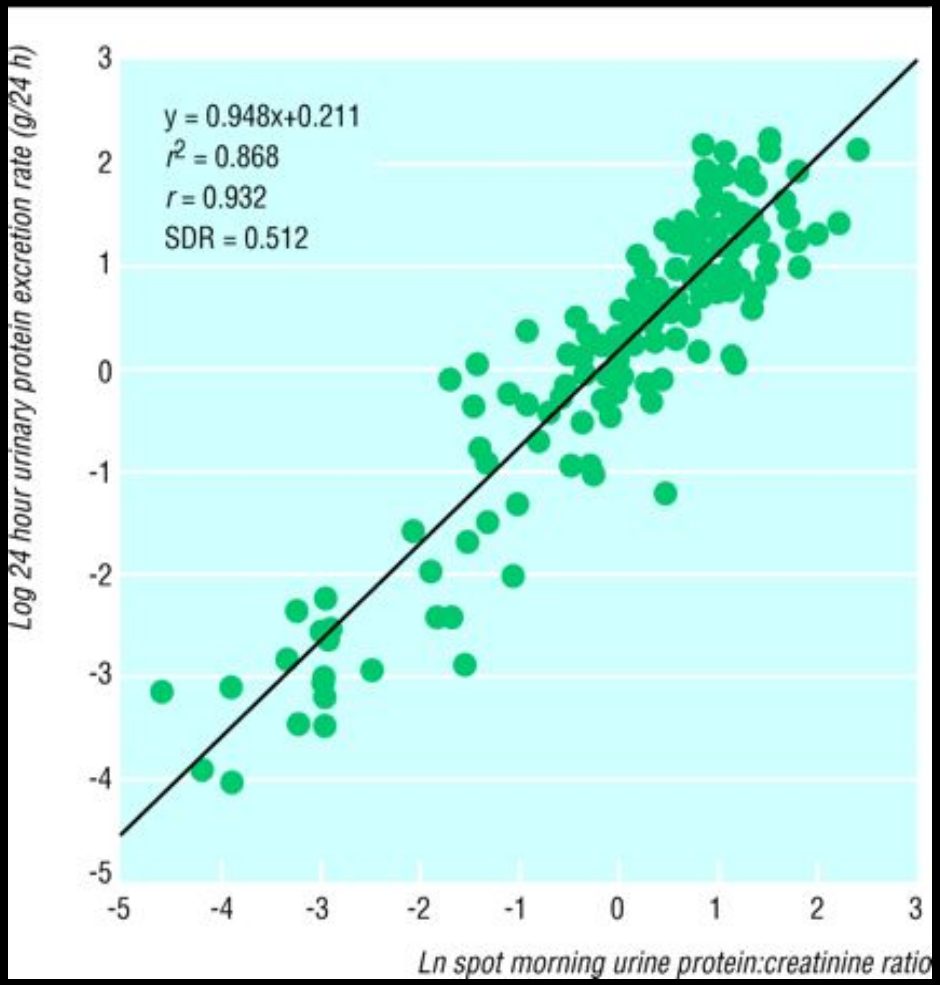
* Or other circumstances causing markedly increased alkalinity of the urine

[a] Hematuria is associated with the presence of proteins that may be measured by the sensitive methods (e.g., those measuring low levels of albumin). Dipsticks that have multiple reagent pads will often have a measurement of hemoglobin, thereby indicating hematuria as the cause of increased albuminuria/proteinuria.

The Ratios versus 24h collection

- 24 hour collection depends on patient compliance
- Under- or over-collection common
- The Ratios have been extensively validated in clinical trials in various age, ethnic groups, disease states

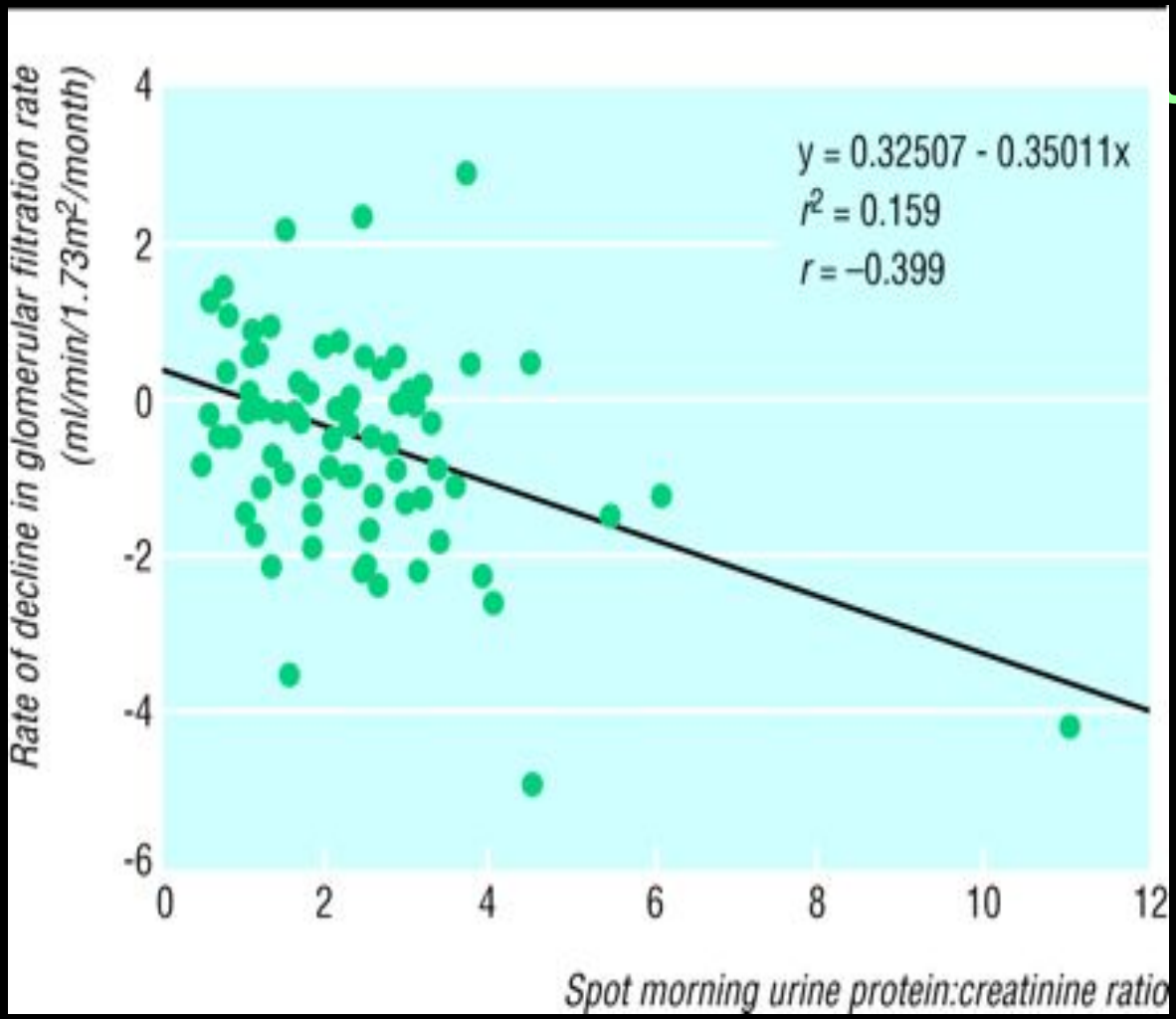
Protein:creatinine ratio and 24 h protein excretion are closely related



Ginsberg (NEJM 1983) – proposed

Ruggenenti et al (1998) study of 177 non-diabetic patients with nephropathy

Protein/creatinine ratio correlates well with renal decline



- The ratio (r=-0.399) is a better predictor of progression than 24 h excretion (r=-0.27) ***Ruggenenti et al 1998***

The Ratios: Methods

- Protein/creatinine ratio: originally described as substitute for 24 hour collection
- Protein/creatinine ratio is not precise below 200 mg/24h estimated protein excretion rate
- Albumin/creatinine ratio: more precise at microalbuminuria range
- Albumin/creatinine ratio requires albumin-specific dipstick
- Albumin/creatinine ratio more predictive at early stages of diseases where predominantly albumin excretion is expected (i.e. most cases; otherwise perform urine protein electrophoresis)

Methods II

- Protein or albumin/creatinine ratio: order protein or albumin random urine concentration and creatinine random concentration
- The ratio is used to normalize urinary protein concentration for measure of urinary dilution

- Attention: units are expressed in mg/g!!!! so calculate:

  Albumin or protein in mg/L →convert to mg/dL

  Creatinine mg/dL → convert to g/dL

Screening I: Common sense

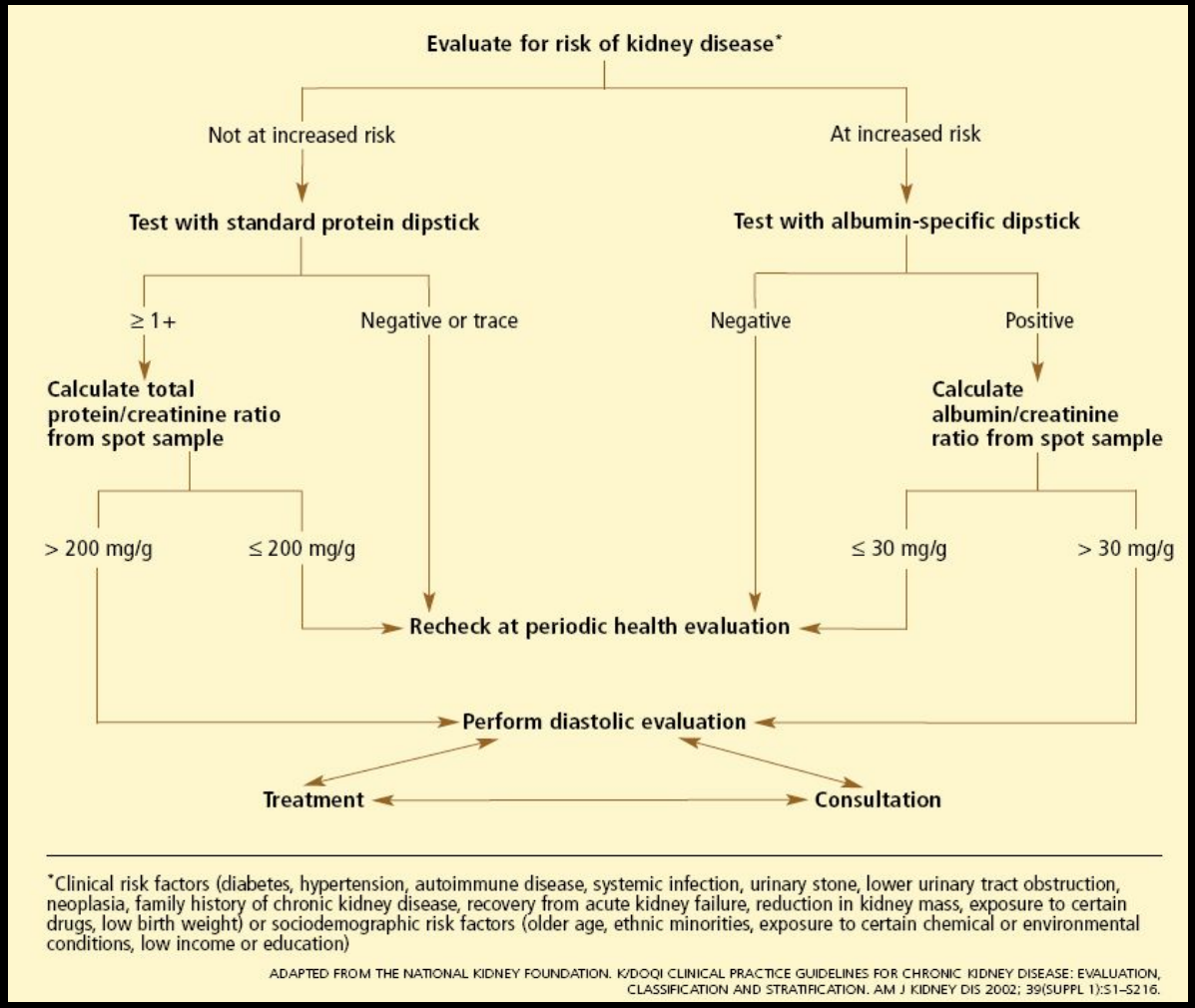
- Hypertension because:
  - -proteinuria suggests end organ damage
  - -presence of proteinuria changes the target of pressure control (125/75 or lower)
- Diabetes Mellitus because:
  - -proteinuria predicts cardiac and renal prognosis
  - -proteinuria is a major therapeutic target
- Any renal dysfunction because:
  - -proteinuria is both a good predictor of course and it is pathogenic

Screening II: NKF Recommendations

- High-risk groups that should be screened for chronic kidney disease include patients who have a

1. Family history of the disease
2. Diabetes mellitus
3. Hypertension
4. Recurrent urinary tract infections
5. Urinary obstruction
6. Systemic illness that affects the kidneys (lupus, vasculitis etc)

Screening Strategy



- Screening of all adults for microalbuminuria is now considered
- Patients with proteinuria are considered as at risk for both renal failure and cardiovascular events
- Proteinuria is a treatment target even at low stages

Proteinuria: what to do next...

1. Check blood pressure
2. Establish volume status
3. Physical exam: look for clues of systemic autoimmune disorders (lupus, vasculitis etc) and atherosclerotic signs: carotid bruits, S4, absent or diminished peripheral pulses
4. Sexual history may be important (HIV,HCV)
5. Evaluate metabolic parameters: BMI, blood sugar, lipids

Proteinuria: Differential Diagnosis

- Hematuria, rapidly advancing renal dysfunction, hypertension: think nephritic syndrome
- Hypertension, edema, hyperlipidemia, hypercoagulability, anemia, possibly hematuria: think nephrotic syndrome
- These can coexist; both need renal evaluation including biopsy
- Hematuria, proteinuria without rapidly worsening renal dysfunction: renal referral and renal ultrasound for evaluation of primary renal diseases (glomerulonephritis, especially IgA nephropathy, ADPKD etc) or urinary tract infection
- Isolated persistent proteinuria: usually of metabolic origin or early phase of nephrotic syndrome

Physical Exam: if you suspect Nephrotic or Nephritic and Nephrotic syndrome

Search for clues for associated diseases:

- -obesity for diabetic nephropathy and ORG
- -ethnicity for FSGS, IgA nephropathy
- -age for MCD, lupus, dysproteinemias etc
- -muscle wasting for malignancy
- -rash, synovitis: lupus, vasculitis
- -GI bleed: HSP, vasculitis
- -CHF, GI amyloid: amyloidosis

Additional workup for Proteinuria if Nephrotic or Nephritic Syndrome are suspected

- Anemia workup
- Serologic testing: appropriate clinical setting
  - -young African American women: ANA
  - -associated nephritic syndrome: ANCA
  - -sexual history: HIV, HCV, HBV
  - -transfusions: HCV
- Renal ultrasound: clue for chronicity (not always)
- Renal biopsy is usually needed unless diagnosis obvious (diabetes, MCD in children)

Nephrotic Range Proteinuria: Etiology

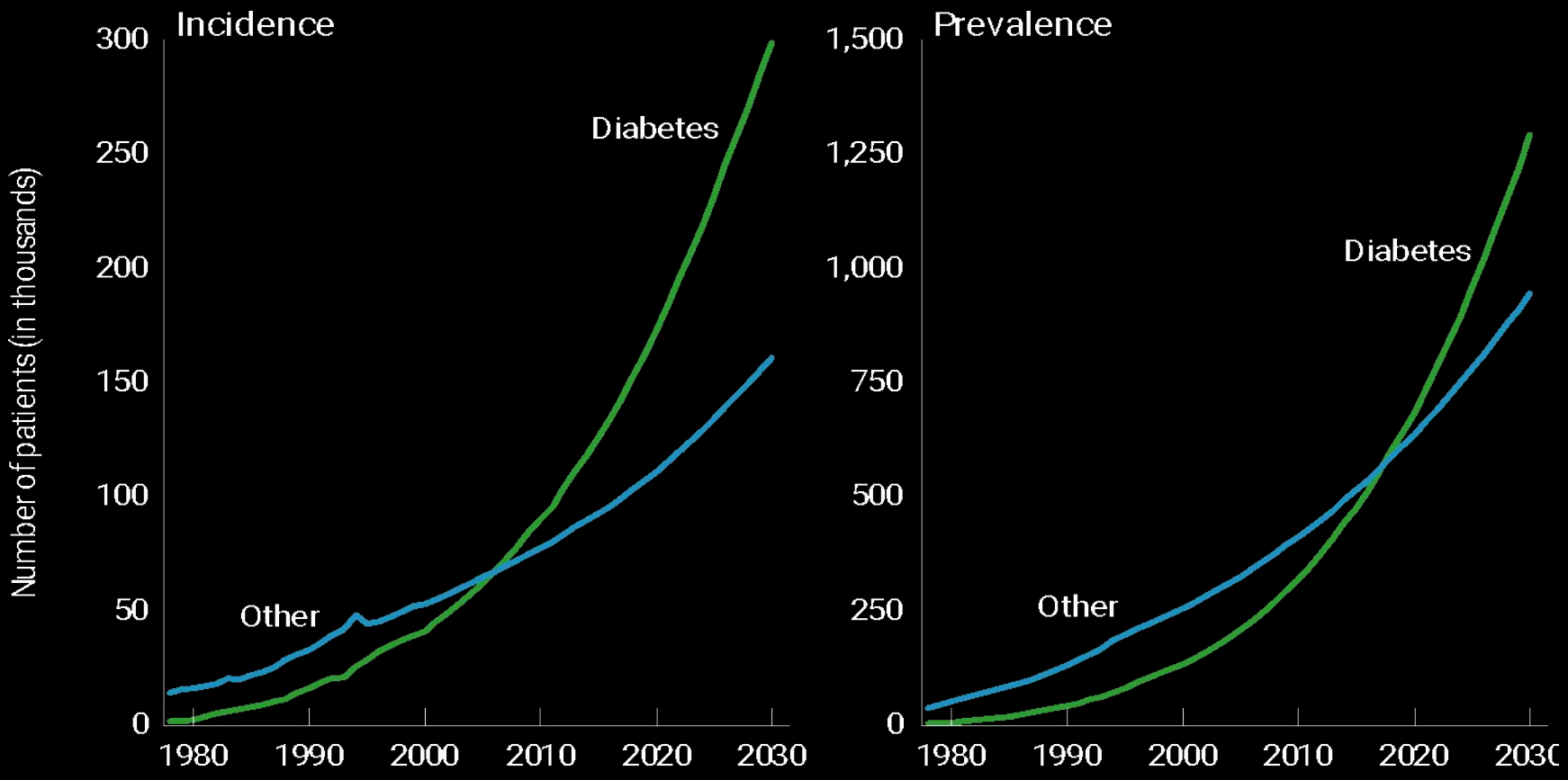
Primary (cause unknown, not associated with systemic illness):

- Minimal Change Disease (MCD)
- Focal Segmental Glomerulosclerosis (FSGS)
- Membranous Nephropathy (MN)
- Membranoproliferative Glomerulonephritis (MPGN)
- Fibrillary/immunotactoid Glomerulonehritis
- others

Secondary/ multisystem illnesses:

- NSAIDS
- Other medication-induced
- Infections: endocarditis, HBV, HCV, HIV, malaria, toxoplasma, parvovirus B19, schistosomiasis
- Malignancy: GI, lung, Hodgkin's, dysproteinemias (especially multiple myeloma)
- Multisystem diseases: SLE, HSP, Amyloidosis
- Metabolic: Diabetes Mellitus, ORG
- Others: Pregnancy (preeclampsia), Transplant Glomerulopathy

End Stage Renal Failure-Etiology



Diabetic Nephropathy-Pathogenesis

- Obesity and organomegaly common; early stages are associated with hyperfiltration
- Pathogenesis: glomerular hypertension, stretch of mesangial cells, consequent scarring: sclerosis in glomeruli
- Pathogenesis: protein trafficking through tubular cells: tubulointerstitial injury, fibrosis

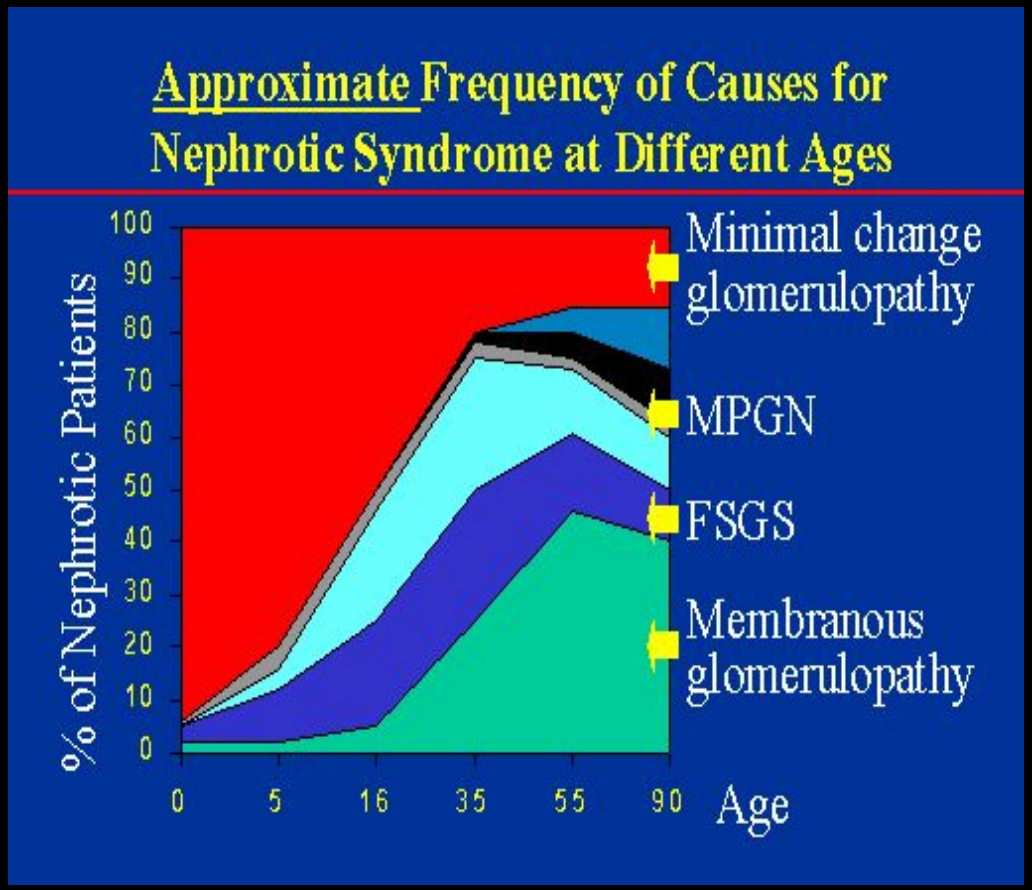
Diabetic Nephropathy-Clinical Characteristics

- Hypervolemia→hyporeninemic hypoaldosteronism and hypertension
- Hematuria may be present
- Nephrotic range proteinuria, hyperlipidemia, edema, hypercoagulability commonly associated
- Often therapy resistant at late stages
- Extremely high prevalence of atherosclerotic problems: macroangiopathy

Diabetic Nephropathy: Therapy

- Weight loss
- Decreased protein, salt, sometimes potassium, carbohydrate and lipid intake (so what should we eat???.....that is the point!)
- ACEI and/or AIIRB
- Statins
- Baby aspirin
- Diuretics (especially if K is a problem....)
- Smoking cessation
- Upcoming: aldosterone and renin blockers

Renal biopsy for nephrotic range Proteinuria: common patterns of histology by age



- Treatment is commonly based on histological pattern of disease, especially if etiology is primary
- Certain patterns are typical of certain systemic diseases

  -MCD: NSAIDS, malignancy;

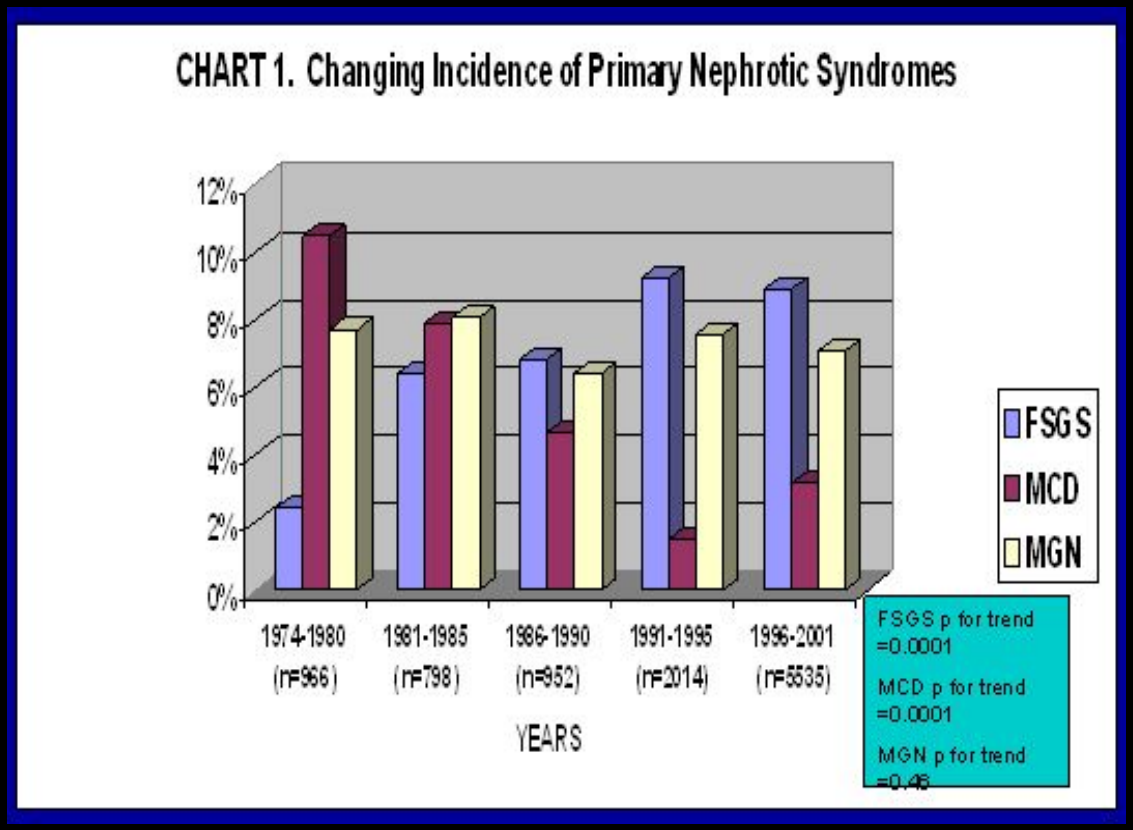
  -MN: malignancy, HBV

  - FSGS: HIVAN, parvovirus, heroin, common pathway of chronic renal injury

  -MPGN: HCV with cryoglobulins

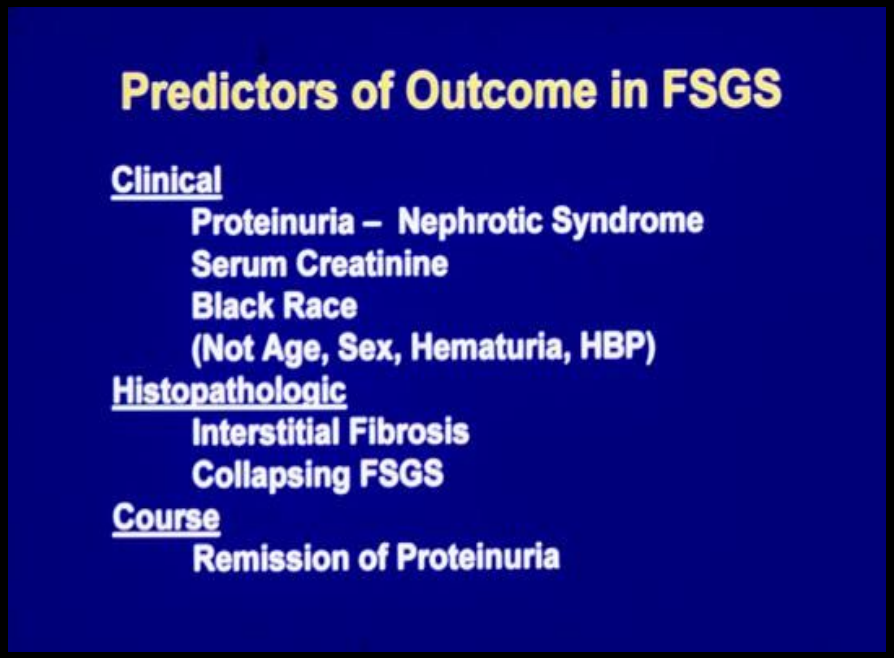
  -all: SLE

The Prevalence of FSGS is increasing



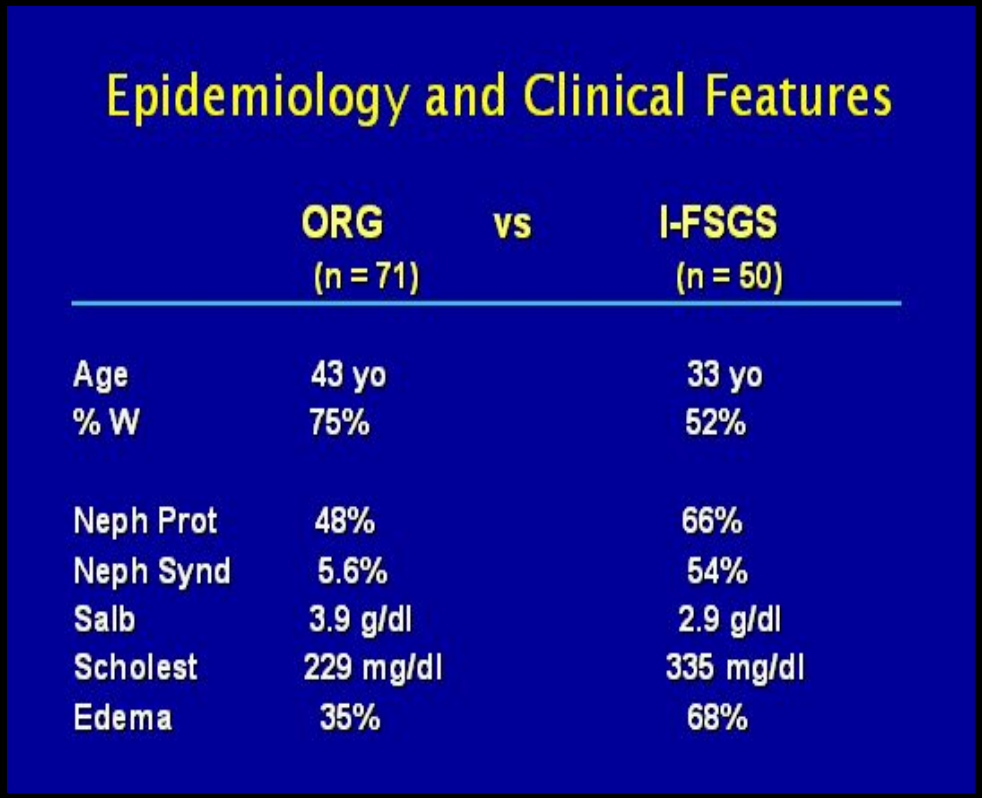
- Study done in Columbia University of New York
- Many adult African Americans
- FSGS is probably more recognized now than in the past
- May still be under-diagnosed

FSGS-predictors



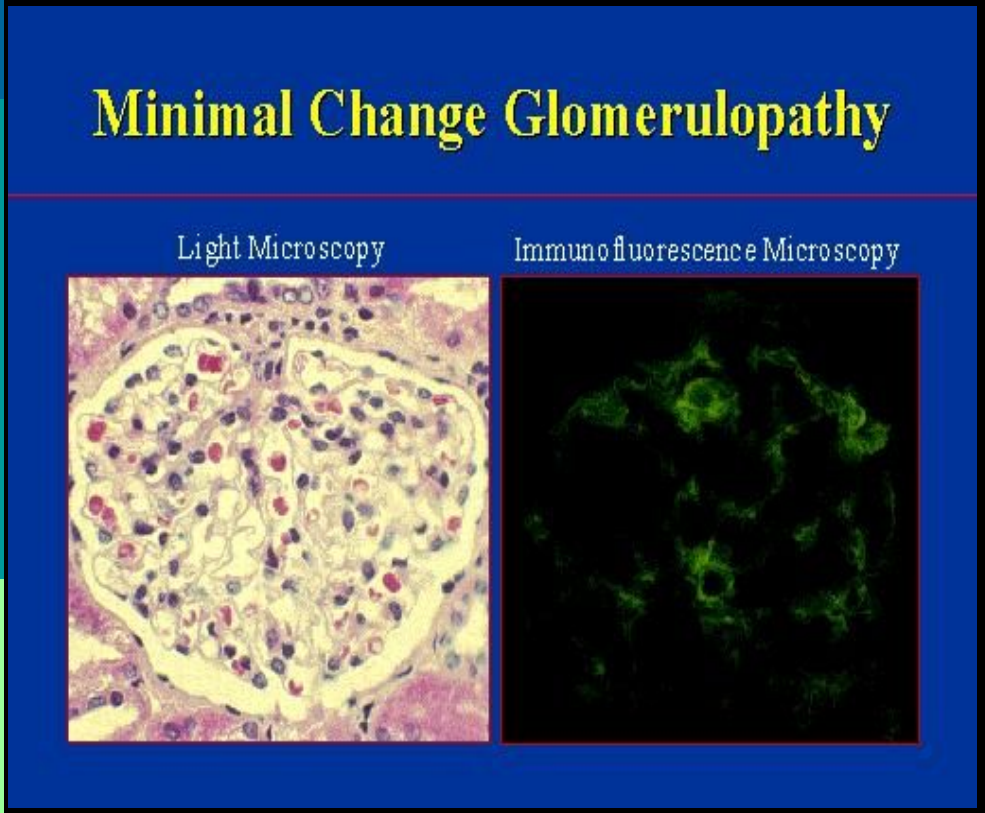
- Predictors in most renal diseases: serum creatinine at presentation, hypertension control, proteinuria
- In Primary FSGS immunosuppressive therapy, in secondary FSGS: ACEI/AIIRB, blood pressure control

Obesity-related glomerulopathy as an independent syndrome



- Histology: glomerulomegaly
- Function: hyperfiltration
- Example: kidney donors in Louisiana
- Treatment: Acei, decreased Na and protein intake, possibly cyclosporine and…..weight loss

Minimal Change Disease

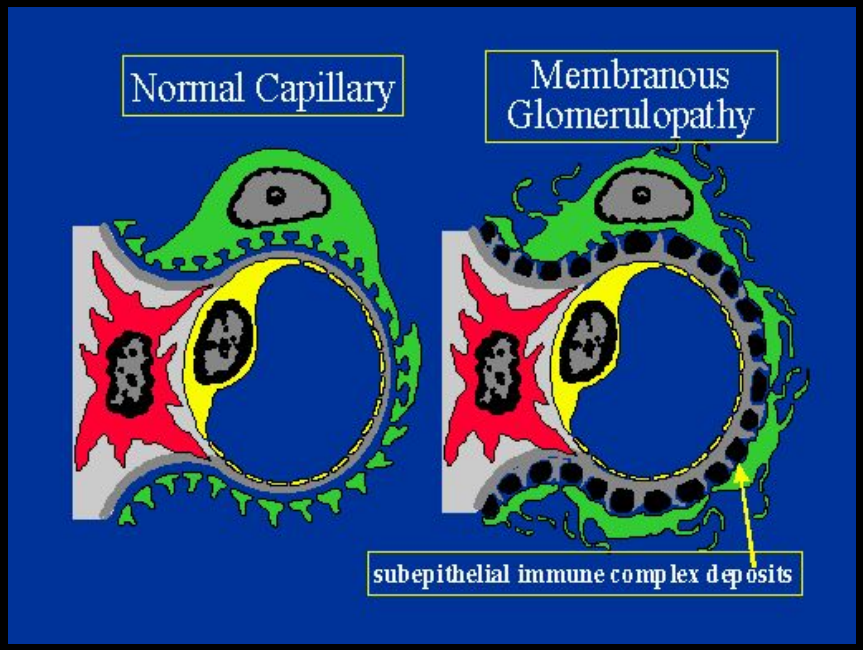


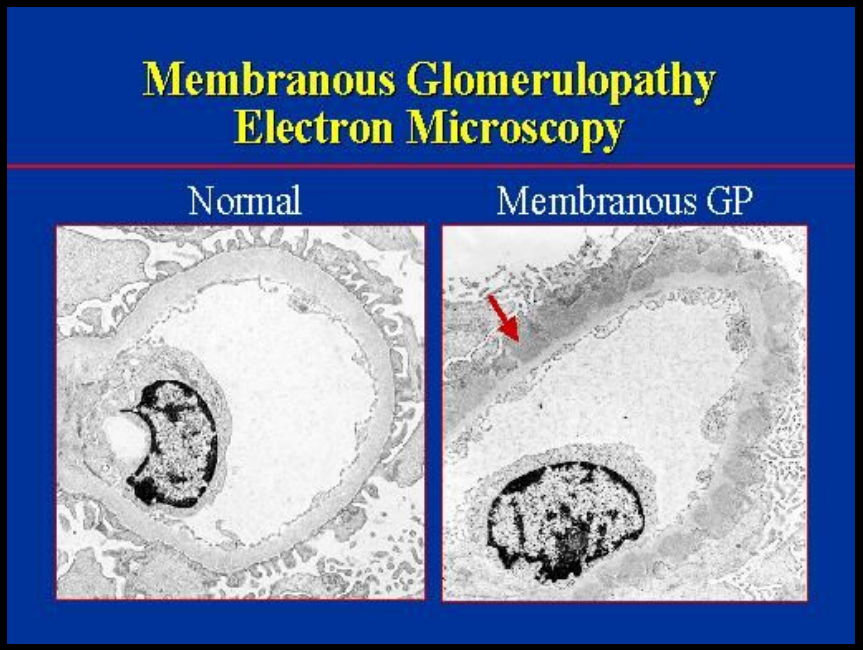
- Common in children and young adults, abrupt onset, male predominance
- Most commonly idiopathic
- May present with ATN especially in adults- this often resolves with diuresis
- Usually responds to steroids- if not, suspect undiagnosed FSGS or malignancy

Minimal Change Disease- prognosis

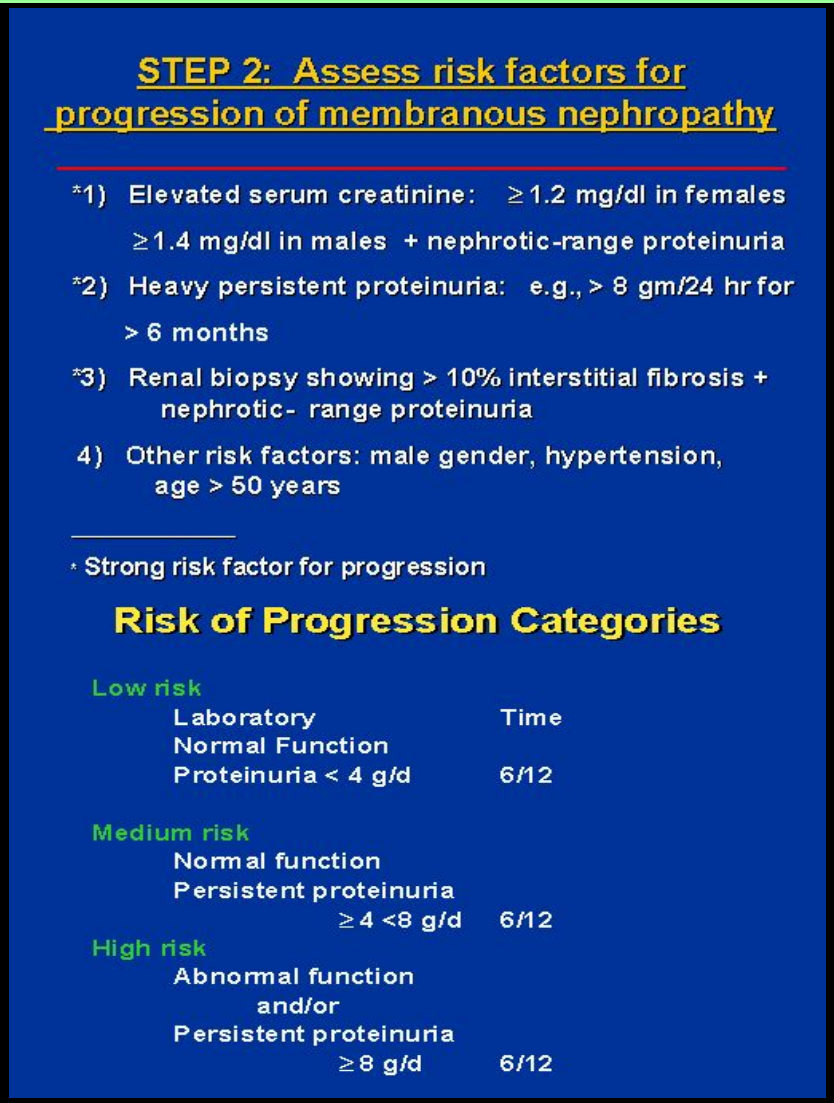
- Progression occurs more in the elderly who present with renal insufficiency
- Thrombotic or infectious complications may occur- more so when not treated promptly
- Early referral is key to avoid complications

Membranous Nephropathy-pathology



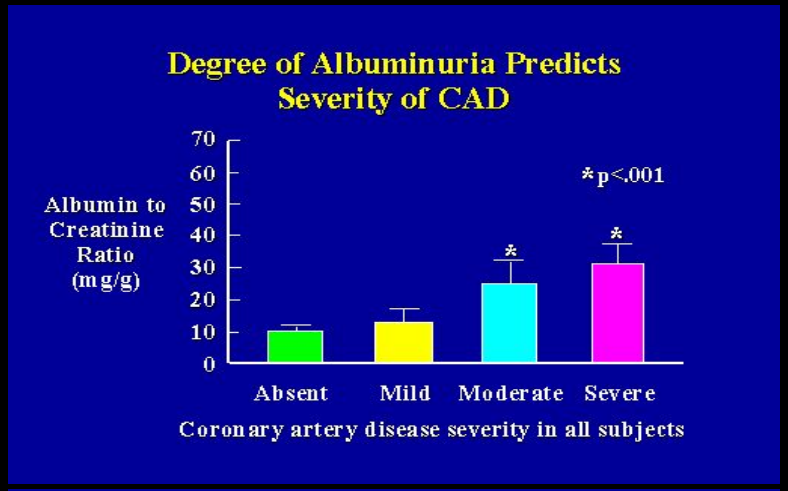


Membranous Nephropathy-Risk Factors



- Membranous nephropathy may be primary or secondary
- Common secondary forms include cancer and lupus
- Risk factors for membranous nephropathy demonstrate the idea that nephrotic range proteinuria is still part of a continuum

More protein means more cardiovascular risk



The Risk of Coronary Artery Disease in the Nephrotic Syndrome

Patients (n=157)

Membranous nephropathy	30%
Glomerulonephritis	19%
Minimal change	13%
Focal glomerulosclerosis	8%

Relative Risk vs. Controls

Coronary artery disease death	5.5
All coronary artery disease	2.5
Myocardial infarction	5.3

JD Ordonez et al, Kidney Int 37:243, 1990

- No matter if proteinuria is nephrotic or subnephrotic range: more protein means more risk
- Risk starts at very low range and highest at nephrotic range

1. HOPE: 1.9 mg/g
2. LIFE: 2.2 mg/g
3. PREVEND: 29%increased risk for 2x increase in albuminuria

Proteinuria: Significance of Treatment

- Goal: decrease cardiovascular and renal risk
- Reduction of proteinuria decreases cardiovascular risk:

1. Steno Diabetes Center data in type I diabetics
2. RENAAL data type II diabetics
3. LIFE in hypertensive patients
4. AASKD in non-diabetic kidney disease

show that degree of reduction in proteinuria is directly related to the lowering of cardiovascular risk

- Numerous studies show that reduction of proteinuria is related to lowering risk of renal decline in diabetic or non-diabetic kidney disease

Treatment Overview

- Blood pressure reduction in all cases
- Diuretics in some cases (volume, K)
- RAS blockade in all cases
- Reduction of protein, salt and caloric intake in most cases
- Immunosuppressive treatment in primary diseases or autoimmune/systemic illnesses
- Antiviral therapy in HIV nephropathy and HCV-related MPGN/cryoglobulinemia

Treatment of proteinuria: blood pressure

- Blood pressure reduction improves proteinuria: target **<125/75 as tolerated**
- Blood pressure reduction decreases cardiovascular risk even in the normotensive range
- Blood pressure reduction by RAS blockade has specific advantages by directly targeting glomerular pressure
- Combination treatment (with CCB or BB or clonidine) often necessary because hypertension is typically difficult to control
- Some CCB have been shown to increase proteinuria by decreasing afferent arteriolar tone (hence autoregulation) but: often necessary as they are potent blood pressure medicines (joke: AASKD study….)

Specific effects of RAS inhibitors

- Reduce LVH
- Improve survival after AMI
- Decrease blood pressure
- Decrease glomerular blood pressure
- Block pro-fibrotic agents (TGFβ) in the kidney
- Decrease insulin resistance
- May potentiate the action of diuretics
- Almost all newer agents have 24h action

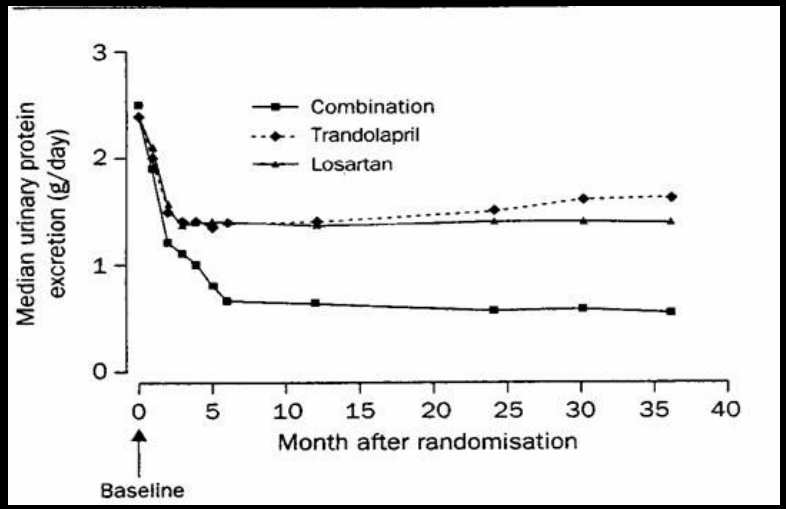
Adverse effects of RAS inhibitors

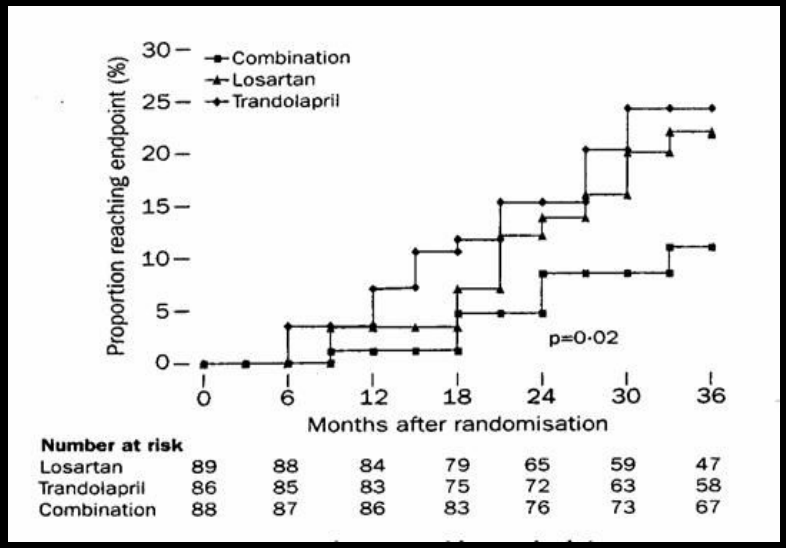
- May decrease GFR in bilateral renal artery stenosis and dehydration
- Hyperkalemia (usually in RAS or dehydration or hyporeninemic hypoaldosteronism)-may respond to diuretics!
- ACEI: cough
- Enhance effect of overdiuresis
- Other side effects (angioedema, excessive BP lowering) are rare

ACEI versus AIIRB

- Most effects of ACE inhibitors were replicated in clinical studies using AII receptor blockers
- AIIRB do not cause cough but share all other adverse effects and are more expensive
- Combination treatment may lead to more RAS blockade

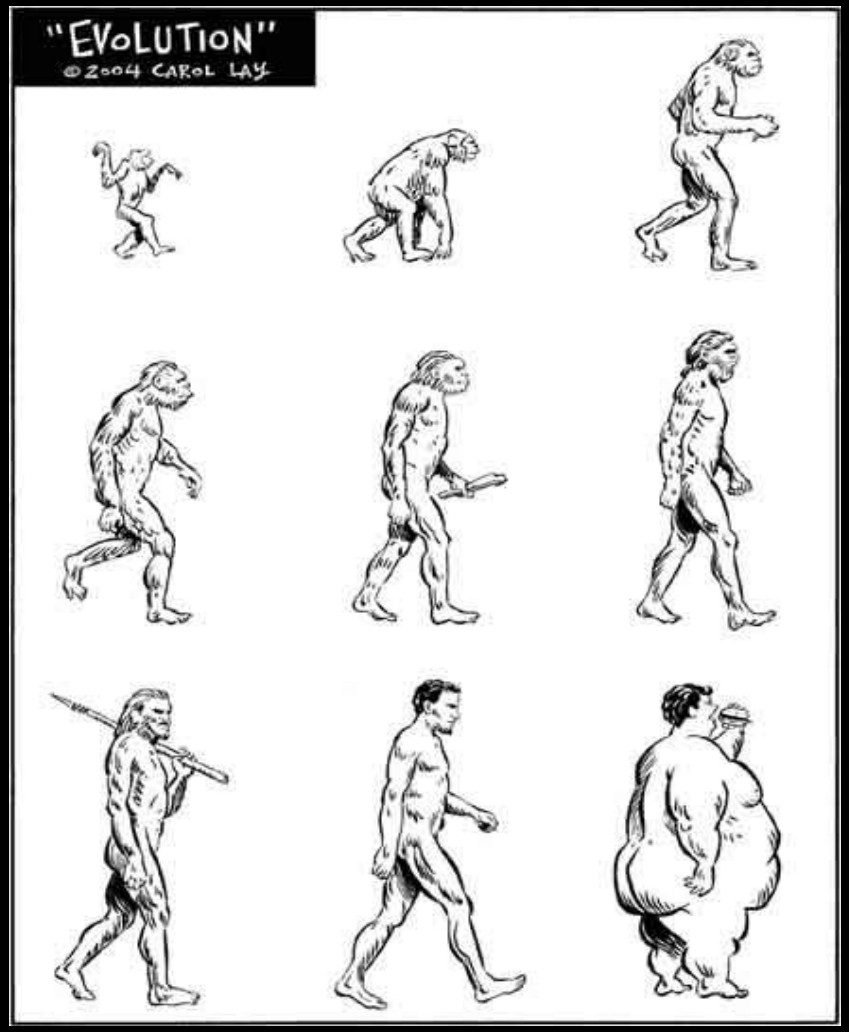
Treatment of Proteinuria: Combination RAS blockade





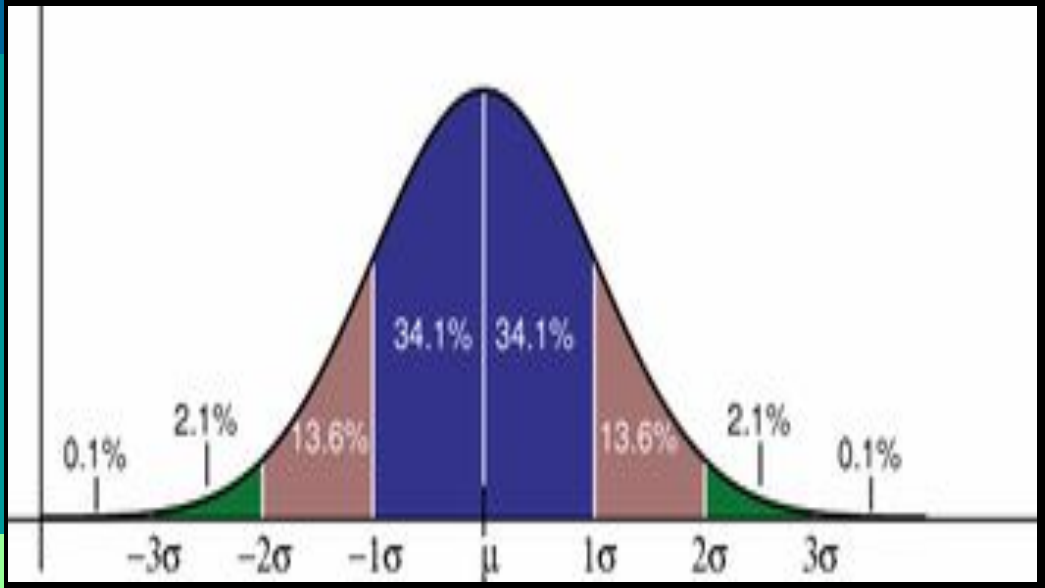
- Combination of ACEI+AIIRB may work better
- Side effects are relatively rare
- Combination with diuretics- works well in practice

Evolution of *Homo Sapiens* toward *Homo Consumans*



- Hunter-gatherers (tens of thousands of years): more potassium, less salt, less animal and heavy-grain protein (acid), less fat, more exercise, less caloric intake, fiber, fresh food
  =very low blood pressure, very low cholesterol and no proteinuria
- Modern man (neolithicum, agriculture, a few millennia): diet loaded with animal-, wheat-, rice-derived protein (acid); salt, excessive calories, mass-produced sugar and industrial chemicals, congested in small urban areas
  =“normal” or high blood pressure, “normal” or high cholesterol and some proteinuria

Have we out-consumed our genetic heritage?



- Laboratory medicine: population average ±2SD=normal but is normal optimal?
- Increasing obesity, diabetes, renal disease: do you really want to be normal?
- Evidence emerging: blood pressure, cholesterol, proteinuria: population at large is not normal because lower is better
- Re-adjust *Homo Consumans** back to *Sapiens*** by lowering metabolic parameters to an ancient baseline (Forman, Brenner 2006) alias cogitare non consumare: cogito ergo sum non consumo ergo sum !

**consumans* =consuming
***sapiens*=thinking

Conclusions I.

- Proteinuria is an important predictor of both cardiovascular and renal risk.
- Spot random samples are the preferred method of diagnosis.
- The degree of proteinuria correlates with the degree of risk at a wide range starting from sub-microalbuminuria to the supra-nephrotic.
- The most common cause of proteinuria is metabolic dysfunction.
- When proteinuria is associated with hematuria or rapidly worsening renal function or if it is nephrotic range evaluation must be done for primary renal or systemic autoimmune diseases including a renal biopsy.

Conclusions II.

- Proteinuria is an important therapeutic target.
- Reduction of proteinuria is associated with decreased cardiovascular and renal risk.
- Blood pressure control, dietary intervention and RAS blockade are the mainstay of treatment in most cases.
- Primary renal or autoimmune diseases also require immunosuppressive treatments.
- Due to the importance of proteinuria screening, currently indicated in high risk populations, may be extended to all adults in the future.