Chronic Kidney Disease Update

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Objectives

- Define CKD
- Discuss patients at risk
- Identify the stages of CKD
- Understand the consequences of CKD
- Learn how to treat the sequelae of CKD
- Apply above knowledge to daily practice

Definition

- Kidney damage or decreased function for > 3 mos
- Damage could be based upon imaging, biopsy or urinary markers
- Decreased function is usually noted by the eGFR
- Doesn't identify a cause
- Doesn't imply symptoms

Introduction

- Disproportionate financial resources consumed by ESRD patients
- NIH and Surgeon General's Office are attempting to educate the public
- Nephrology work force shrinking
- Burden of work up and management falls on PCP's

KDOQI

- Kidney Disease Outcome Quality Initiative 1997, mgd by the NKF (www.kidney.org)
- Evidence based clinical practice guidelines
  - Mgmt of CKD
  - Mgmt of related consequences of CKD
- Updated periodically
- www.kdoqi.com

KDIGO

- Kidney Disease Improving Global Outcomes, 2004
- Global non-profit organization mgd by NKF
- promotes coordination & collaboration to develop & implement practice guidelines
- 2012 released comprehensive set of guidelines
- www.kdigo.com

Patients at Risk

- Advanced age
- DM
- HTN
- + Family History
- Hx of ARF
- Obesity
- Smokers
- HIV
- Most minorities
- NSAID users
- Low income/education
- Reduced kidney size
- Hepatitis C
- Metabolic syndrome
- CT diseases

Symptoms

- Usually asymptomatic
- Edema/fluid retention
- Urinary symptoms occassionally
- Arthralgias, rash
- Vascular symptoms (angina, claudication)
- Wt loss, paresthesias, back pain
- Uremic symptoms

Detection of CKD

- New onset HTN
- Urinalysis with blood or protein
- "routine" labs with abnormal BUN and creatinine
- Imaging study showing abnormal renal anatomy

Serum Creatinine

- Wide range of normal
  - interpret in the clinical context
- 10% lab error in serum creatinine depending upon calibration of serum creatinine assays
- Used to calculate the GFR

Creatinine Clearance

- Inulin is the gold standard
  - Impractical
- Radionuclide and radiocontrast markers
  - ^{123}I-orthoiodohippuran
  - radioiodinated hippuran
  - Iohexol
  - ^{99m}Tc-DPTA or ^{99m}Tc-MAG_3

24 Hour Urine Collections

- Cumbersome, fraught with patient error, noncompliance
- Utility in select patients (where formulae are inaccurate):
  - Extremes of age and body size
  - Severe malnutrition or obesity
  - Diseases of skeletal muscle
  - Para/quadriplegia
  - Vegetarian diet

GFR

- Glomerular filtration rate = GFR
- GFR doesn't equal creatinine clearance
- Multiple formulae
  - MDRD
  - CKD-EPI
- Formulae have limitations

MDRD

- 1999, new version 2007
- Requires steady state
- Falsely elevated in states of malnutrition (nephrosis, liver disease, vegetarian diet), high meat diet
- Less accurate in extremes of disease (high GFR and low GFR), extremes of body size and age

CKD-EPI

- 2009, CKD Epidemiology Collaboration Eq
- Slightly more precise & accurate, esp GFR > 60
- Should reduce over reporting of CKD
  - reduces prevalence of CKD 45 y/o
  - increases prevalence of CKD > 65 y/o
- No African Americans included in studies (done in Europe)

Diagnostic Studies

- Serology
- Urine studies
- Renal US (doppler if indicated)
- Determine CrCl (know limitations)

Serology

- BMP, phos, albumin, total protein, chol
- CBC
- Serum immunofixation if > 50yrs
- Intact PTH if GFR < 60
- Further serology may be warranted

Urine Studies

- Urinalysis
  - Assume: quality sample, no infection
  - Evaluate: sp gr, pH, blood, protein
- Urine sediment: WBC, RBC, crystals, casts
- Urine immunofixation if > 50 years

Proteinuria

- Urine dipstick
  - Misses light chains, microalbumin
  - Concentration dependent
- Urine microalbumin
  - Qualitative or quantitative
- Spot urine for total protein to creatinine ratio **
  - First morning sample is preferred

Proteinuria

- 24 hour collection
  - Assure specimen adequacy by creatinine secretion (varies with gender and age)
  - Largely being replaced by spot tests
- > 3 gms/day suggests glomerular in origin
  - Specifically epithelial cell
- < 1 gm/day suggests tubular origin

Renal Ultrasound

- R/O obstruction
- Assess kidney size
- Cortical thickness
- Cortical echogenicity
- Evaluate for PCKD

Renal Artery Dopplers

- Asymmetric kidneys
- Cortical thinning
- Hypertension
- PVD, bruits or high suspicion

CT Scan

- Imaging of choice in the setting of nephrolithiasis
- May be beneficial in setting of other diseases to identify more anatomy
- Obvious limitation of contrast

Table 63. Interpretation of Abnormalities on Imaging Studies as Markers of Kidney Damage

Imaging Modality/Feature	Associated Kidney Disease
Ultrasonography	
General appearance	May show nephrocalcinosis or discrete stones, hydronephrosis, cysts or masses.
Increased echogenicity	May indicate cystic disease or "medical renal disease."
Small, "hyperechoic" kidneys	Generally indicate chronic kidney disease.
Large kidneys	Generally indicate tumors, infiltrating diseases or diseases causing nephrotic syndrome.
Size disparities and scarring	Suggest vascular, urologic or tubulointerstitial diseases due to stones or infection.
Doppler interrogation	May be useful in investigation of venous thrombosis, less so in arterial stenosis.
Intravenous pyelography (IVP)[a]	May reveal asymmetry of kidney size or function, presence of obstructing stones, tumors, scars, or dilated collecting ducts in medullary sponge kidney.
Computed tomography (CT)[b]	May show obstruction, tumors (e.g. angiomyolipoma), cysts or ureteral calculi. Helical CT with contrast may show sites of anatomic renal artery stenosis.
Magnetic resonance imaging (MRI)	May show mass lesions, renal vein thrombosis, cysts, etc. MR angiography using gadolinium may be useful in patients with decreased kidney function.
Nuclear scans[c]	May reveal asymmetry of kidney size or function, functional evidence of renal artery stenosis, acute pyelonephritis, or scars.

[a] This modality has been largely supplanted by computed tomography, although it remains useful to describe fine detail in the collecting system.

[b] With or without contrast

[c] Captopril renography, mercaptoacetyltriglycine (MAG3), dimercaptrosuccinic acid (DMSA)

Stages of Chronic Kidney Disease

National Kidney Foundation–Kidney Disease Outcome Quality Initiative

Stage	Description	GFR (ml/min)
1	Kidney damage w/ normal GFR	>90
2	Mild decrease in GFR	60-89
3a	"early" moderate kidney dysfunction	45-59
3b	"late" moderate kidney dysfunction	30-44
4	Severe kidney dysfunction	15-29
5	Kidney failure	< 15

Stages of CKD

- Cut-offs are arbitrary, based upon informed opinion
- Progression of kidney disease varies depending upon disease entity and patient

Consider the Causes

- Diabetic kidney disease
- Nondiabetic kidney disease
  - Tubulointerstitial diseases
  - Vascular diseases
  - Glomerular diseases
  - Cystic diseases

Initiation factors

- Diabetes mellitus
  - Classic presentation
- Hypertension
  - Other end organ damage
- CHF, global ischemia
- ASVD, hyperlipidemia
- Autoimmune diseases
- OSA
- Urinary tract infections
  - recurrent
- Nephrolithiasis
- Obstruction (BPH)
- Drug toxicity (NSAIDS)
- Systemic infections (HIV, hepatitis)

Exposures

- Occupation
  - Lead (soldering), mercury or cadmium
- Cigarette use
- Alcohol, particularly moonshine
- STD's or IVDA
- NSAIDs (particularly combination)
- ACE-I, ARBs, diuretics (reversible)

Exposures

- Herbal remedies (aristolochic acid, Ma Huang or Ephedra, ayurveda)
- Arsenic #1 heavy metal contaminant in over 50% of about 250 randomly sampled chinese herbs (Australia), mercury, Cd, Pb all present
- Complementary and alternative medication use soaring (40% btwn 30-70)

Promoters of Progression

- Higher levels of proteinuria (nephrotoxic)
- Poorly controlled blood pressure
- Poorly controlled sugars
- Elevated cholesterol
- Cigarette smoking
- Nephrotoxins
- High protein diets ?

Slow Progression

- Control HTN
- Avoid nephrotoxins, adjust medications
- Early treatment of obstruction, infections
- Tight sugar control in diabetics
- Protein restriction?
- Cholesterol control?

Clinical Consequences

- Fluid Overload
- Hypertension
- Electrolyte abnormalities
- Metabolic acidosis
- Hyperparathyroidism
- Anemia
- Accelerated CV disease
- Malnutrition

Clinical Consequences

- Prevalence increases significantly once GFR < 45 ml/min
- CKD stages 3b, 4, 5

Fluid Overload

- Ability to excrete salt and water is limited
- Restrict oral salt intake
- Because thiazide diuretics alone are often ineffective in CKD, high doses of loop blocking diuretics are required
- Goal is a negative salt balance
- Lasix best dosed b.i.d.

Hypertension

- Both a cause and complication of CKD
- Diuretics, fluid mgmt are the cornerstone
  - Often mediated by volume retention
- ACE-I or ARBs if no renovascular disease
- BP goal (KDOQI/KDIGO):
  - < 130/80 mmHg if proteinuric (> 500mg/day)
  - < 140/90 mmHg if not proteinuric

Hypertension

- Conservative measures
- Individualize the treatment depending upon clinical scenario

Hyperkalemia

- Maintain K^+ homeostasis until GFR < 25 ml/min
- ACE-I, ARBs, NSAIDs, K sparing diuretics, non-selective beta-blockers, digoxin
- Treat metabolic acidosis
- Limit oral intake
- Loop diuretics
- Exchange resins

Metabolic Acidosis

- Once GFR < 25 ml/min
- Impaired renal NH3 production
- Reduced bicarbonate reabsorption

Metabolic Acidosis

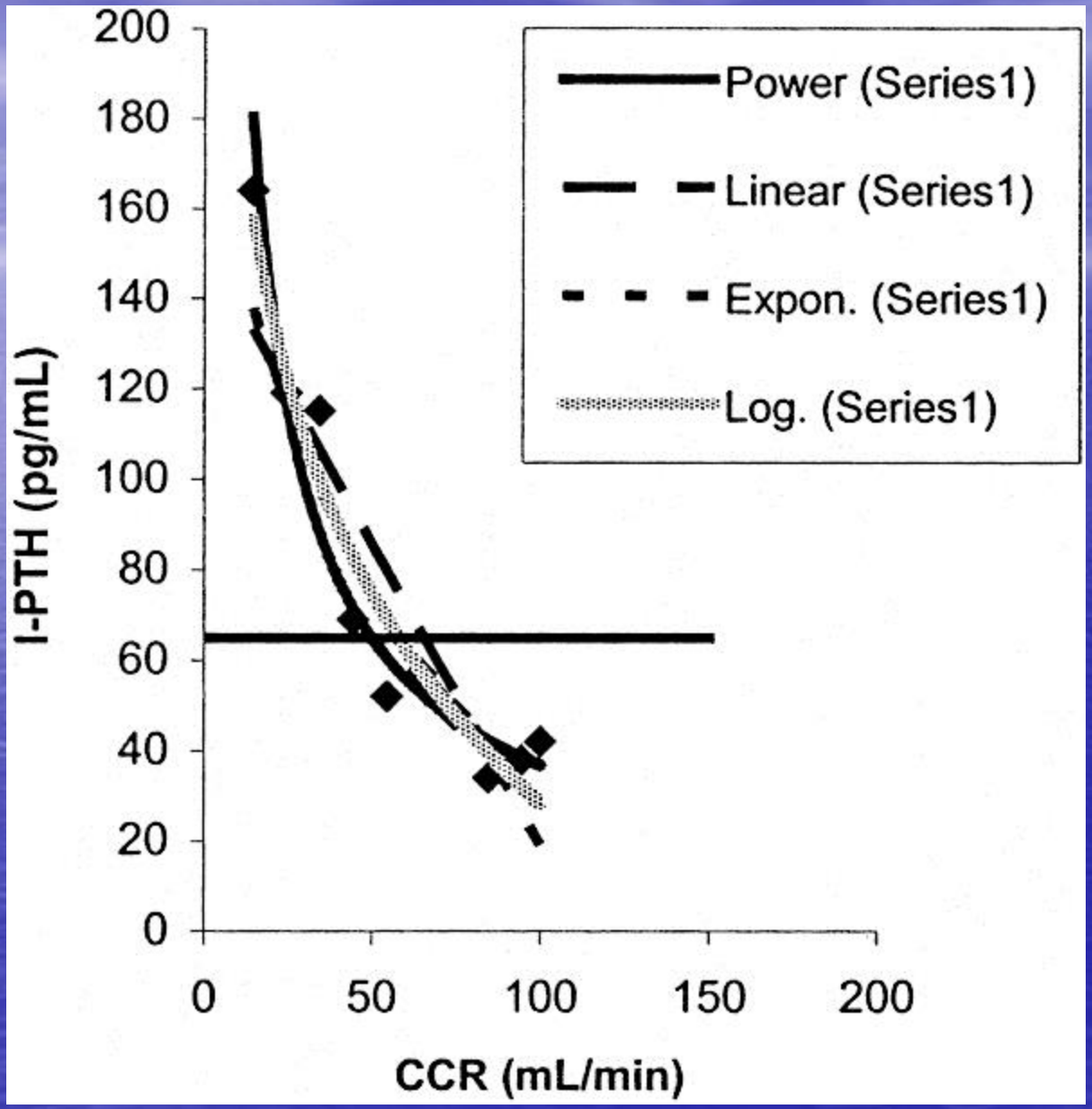
- Treat with oral alkali
  - Maintain serum CO_2 normal
  - 1 meq/kg maintenance
- Options: $NaHCO_3$, baking soda, NaCitrate
- New studies suggest treating may reduce progression of CKD
- Less fluid overload with $NaHCO_3$ in recent study

Metabolic Bone Disease

- Manifest as bone pain, pathologic fractures and ? decreased bone density
- Hyperphosphatemia
  - From decreased GFR
  - Reduced renal synthesis of 1,25-dihydroxy D3
- Hypocalcemia
  - From vitamin D deficiency

Metabolic Bone Disease

- Elevation of PTH may start in Stage 2 CKD
  - Secondary hyperparathyroidism (HPTH)
- Many forms of metabolic bone disease
- Diagnose by bone bx (rarely done)
- High turnover bone disease (HPTH) requires treatment


200
180
160
140
120
100
80
60
40
20
0
I-PTH (pg/mL)
0
50
100
150
200
CCR (mL/min)
Power (Series1)
Linear (Series1)
Expon. (Series1)
Log. (Series1)

PTH Goal

CKD Stage	KDOQI iPTH target (pg/mL)	KDIGO iPTH target (pg/mL)
3	35-70	
4	70-110	
5	150-300	2-9 X ULN

HPTH Treatment Options

- Vitamin D receptor agonists:
  - Calcitriol 0.25mcg/day starting dose
  - Doxercalciferol 0.5mcg/day starting dose
  - Paracalcitriol 1mcg/day starting dose
- Repeat iPTH, calcium and phos in one month after starting therapy
- Watch for hypercalcemia, stop therapy if CaxPhos > 80

Calcium and Phosphorous

	KDOQI	KDIGO
Calcium	8.4-9.5 mg/dL	Normal range
Phosphorous	2.7-4.6 mg/dL in CKD stage 3-4	Normal range CKD stage 3-5
Calcium intake	< 2000 mg/day including supplements in CKD stage 5	
Phosphorous intake	800-1000 mg/day in CKD stage 5	

Hyperphosphatemia

- Low phosphorous diet, 800-1000mg/day
- Phosphorous binders with meals if dietary intervention ineffective
  - Tums, Phoslo 667mg, Renagel 800mg, Renvela 800mg, Fosrenol 500mg (all with meals)
  - Aluminum and magnesium binders avoided
- Ca x Phos product < 55 mg/dL

Calcimimetic Therapy

- Cinacalcet (*Sensipar*)
- Binds to transmembrane domain of the calcium sensing receptor in the parathyroid gland and renal tubules
- For the treatment of HPTH
- Ca and Phos levels decline (as opposed to vitamin D therapy)

Vitamin D

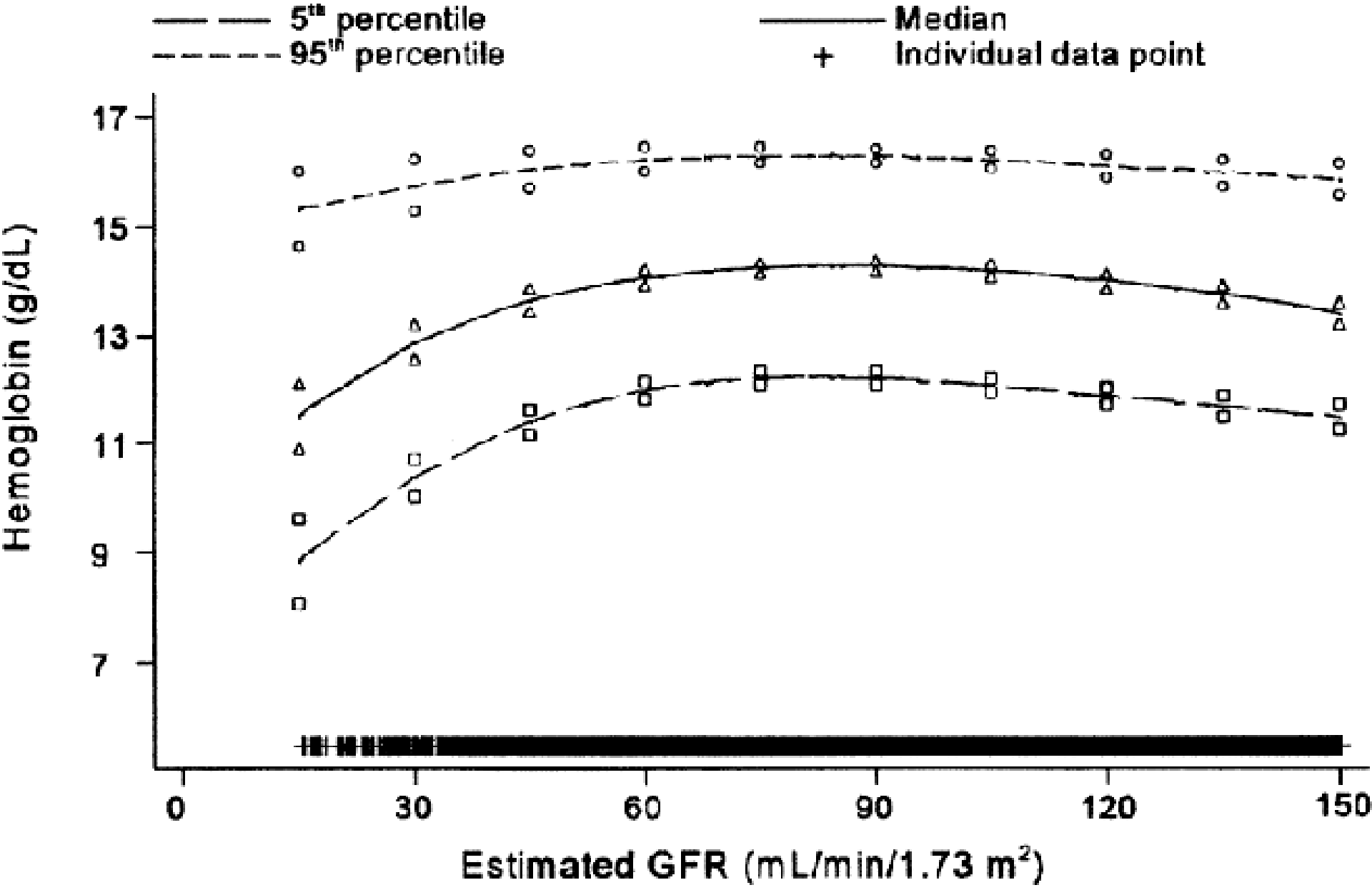
- 25-hydroxyvitamin D level should be monitored initially if PTH elevated
- Supplement if < 30 ng/mL with Ergocalciferol (KDOQI guideline) in stages 3-4
- Recommendation based upon opinion

Anemia

- Normocytic normochromic anemia
- Reduced erythropoietin production from interstitial cells
- Shortened RBC survival, iron and folate deficiencies contribute
- Clinical manifestations include fatigue, dyspnea, depression, etc.

Anemia

- Exclude other causes first
- Treatment with ESAs:
  - Recombinant human erythropoietin 80-120U/kg/week, other options now available darbopoeitin, etc
  - Essentially all require iron supplementation
- Watch blood pressure with procrit therapy
- Goal Hgb 10-11 g/dL


5th percentile
95th percentile
Median
Individual data point
Hemoglobin (g/dL)
17
15
13
11
9
7
0
30
60
90
120
150
Estimated GFR (mL/min/1.73 m²)

Erythropoeitin Stimulating Agents

Risks

- Exacerbation of HTN
- Thromboembolism
- CV events

Benefits

- Reduction in transfusions (important prior to transplant)
- Surveys show improved QOL

CV disease

- Abnormal lipids can be treated with:
  - Dietary intervention
  - Achieve desirable body weight
  - HMG CoA reductase inhibitor
- CKD accelerates CV disease
- Proteinuria is a risk factor for CV disease

CV disease

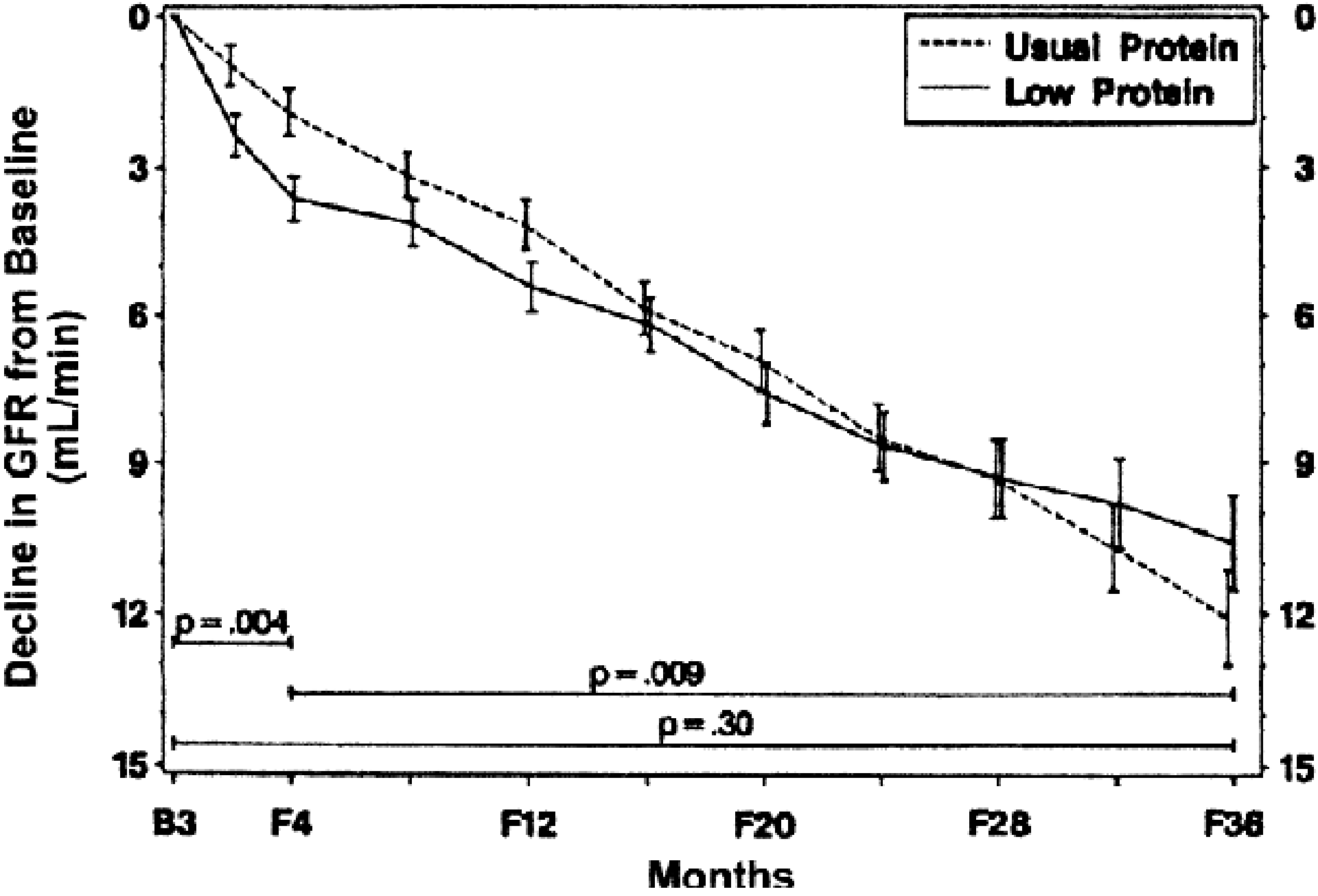
- ESRD patients are at 20x the risk of CV disease as age matched controls
- CV disease accounts for ~ 50% of deaths of ESRD patients
- 15% of ESRD patients have normal LVs (by echo)

Malnutrition

- Multiple serum markers of nutrition: albumin, cholesterol, SGA, nPCR
- *Serum albumin correlates with mortality in ESRD patients*
- CKD patients benefit from regularly seeing dietitians

Protein Restriction

- Studies vary, controversial
- NIH guidelines suggest:
  - GFR 25-55 ml/min 0.8 g/kg/day
  - GFR 13-25 ml/min 0.6 g/kg/day
- Proteinuric patients may benefit most
- Must be done under guidance of RD
- Correlation of low albumin with mortality


Usual Protein
Low Protein
Decline in GFR from Baseline (mL/min)
0
3
6
9
12
15
p = .004
p = .009
p = .30
B3
F4
F12
F20
F28
F36
Months

Nephrotoxins

- Contrast dye
- NSAIDs and COX-2 inhibitors
- OTCs (herbals, supplements)
- Select antimicrobial and antifungal agents
  - Aminoglycosides, amphotericin B
- Immunomodulators
  - Cyclosporine, tacrolimus

Cholesterol

- Statins are agents of choice
  - May reduce proteinuria
  - Mesangial cell modifications
  - No strong data to suggest preservation or improvement in GFR
- LDL < 100 is goal
- Some data suggest that fasting triglycerides ≥ 500 should be treated

Management

- Identify reversible causes of CKD
- Control known factors that lead to progression of CKD
- **Many aspects of treatment are not specific to the cause of the renal disease**

Clinical Action Plan for CKD

Stage	GFR (ml/min)	Plan
1	>90	Diagnosis and treatment Slow progression CVD risk reduction
2	60-89	Estimating progression
3	30-59	Evaluating and treating complications
4	15-29	Preparation for RRT
5	<15	RRT if uremic

Nephrology Referral?

- NIH suggested to refer when Scr > 1.5 mg/dL in women and > 2.0 mg/dL in men
- VHA suggests to refer if CrCl < 25 ml/min or Scr > 4 mg/dL
- Clinical practice guidelines suggest referral when GFR < 30 ml/min or stage 4 CKD
- Lower threshold for referral when nephrotic (pathology changes mgmt 86%)

Nephrology Referral?

- Risk factors for progression:
  - Proteinuria > 500 mg/day
  - Uncontrolled or difficult to control progression
- Identify trend in creatinine, stability may allow for monitoring without referral

Early Referral

- Avoids:
  - urgent dialysis
  - severe metabolic abnormalities
  - fluid overload
  - catheter access
  - delay in transplant referral
- Provides:
  - lowers initial hospital cost
  - patient choice of modality
  - lower 1 year mortality
  - Education on modality
  - Access placement

Conclusions/Summary

- Qualify & quantify primary renal disease
- Slow the progression
- Identify the clinical consequences
- Prevent and or treat the clinical consequences
- Modify the diet
- Watch medications, avoid nephrotoxins

Questions?