Chronic Kidney Disease

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Outline

- Care of the CKD patient is shared between the GP and the CKD clinic
- The important aspects of this shared care include:
  - Preventing the progression of kidney disease
  - Reducing CV risk factors
  - Managing anemia
  - Treating CKD mineral and bone abnormalities
  - Planning for renal replacement therapy if needed
CKD

• CKD clinic
  – Multidisciplinary
    • Nephrologist
    • Nurse
    • Dietician
    • Pharmacist
    • Social worker
  – Works with the GP to manage complex renal patients
Preventing Progression of CKD
Treatment of HTN

• Diabetics or nondiabetics with albumin/Cr > 30 mg/mmol
  – ACE I or ARB
  – < 130/80

• Nondiabetics with no Proteinuria
  – ACE I, ARB, thiazide, β blocker (in pts < 60 years old), or a long acting calcium channel blocker

• Large-vessel renovascular disease
  – ACE I, ARB, thiazide, β blocker in pts < 60, or long acting calcium channel blocker
  – Be careful with ACEI or ARB
Preventing Progression of CKD
Treatment of DM

- \( \text{HbA}_1\text{C} < 7\% \)
  - \( \text{HbA}_1\text{C} \) unreliable in HD patients
- Fasting glucose 4-7
- Discontinue metformin when eGFR < 30, ARF, or pt at increased risk of ARF (unwell, starting NSAIDs, IV contrast etc)
- Choose short acting sulfonylureas such as gliclazide
Preventing Progression of CKD
Treatment of Proteinuria

• Microalbuminuria is associated with a 2 – 4 fold increased risk of CVD

• Does not necessarily indicate CKD. It is also a marker of endothelial dysfunction or chronic inflammation

• Overt albuminuria/proteinuria, particularly plus HTN is a significant marker for progressive kidney disease, particularly proteinuria of > 1 gm/daily
Preventing the Progression of CKD
Treatment of Proteinuria

• Inhibition of RAAS with
  – ACE I or ARBs – not both
    • Reduce proteinuria by 35 - 45%
    • Accept an increase in Cr of 30 - 35%

• Nondihydropyridines
  – diltiazem/verapamil

• Aldosterone antagonists
  – Can be added to ACE or ARB
    • Meta-analysis of 11 trials, 991 pts with CKD
    • Further reduce proteinuria (mean decrease of 800 mg/d)
    • 3.1 RR of hyperkalemia at nonmaximal ACE or ARB doses
    • No data on mortality, CV or renal outcomes

Sankar D. Navaneethan, Sagar U. Nigwekar, Ashwini R. Sehgal, Giovanni F.M. Strippoli Aldosterone
Antagonists for Preventing the Progression of Chronic Kidney Disease: A Systematic Review and Meta-analysis,
CJASN (3) March 2009, 542-55
CVD in CKD

• Most individuals with kidney disease die of cardiovascular disease before they ever developing ESRD

• CKD is associated with chronic inflammation, endothelial dysfunction, activation of the renin-angiotensin system, insulin resistance, vascular calcification, volume overload, anemia, and excess sympathetic tone
Cardiovascular Risk According to Stage of CKD

<table>
<thead>
<tr>
<th>Stage of CKD</th>
<th>Odds ratio of having CV disease</th>
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<tbody>
<tr>
<td>1</td>
<td>Depends on proteinuria</td>
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<tr>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>3</td>
<td>2 to 4</td>
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<tr>
<td>4</td>
<td>4 to 10</td>
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<tr>
<td>5</td>
<td>10 to 50</td>
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<tr>
<td>ESRD</td>
<td>20 to 1000</td>
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Microalbuminuria increases the odds of CVD 2 to 4 fold

Cardiovascular Disease in CKD

- LVH
- Atherosclerosis
- Arteriosclerosis
LVH

• Caused by volume and pressure overload
• Present in:
  – 30% of CKD 3
  – 45% of CKD 4
LVH

• Echocardiograms done in cohort of 433 incident ESRD hemodialysis patients
  – 73.9% had LVH
  – 35.5% had LV dilatation
  – 14.8% had systolic dysfunction
  – Only 15.5% were free of LVH, LV dilatation, or systolic dysfunction

CKD

• Thus, care of CKD patients must focus on decreasing their cardiovascular risk factors
Lifestyle Management

- Diet
- Exercise

- BMI 18.5 - 25
- Waist circumference < 102cm for men, < 88cm for women
- Smoking cessation
- Protein restriction 0.8-1 gm/kg/day
- Sodium intake < 1.5 gm/day
- Correction of metabolic acidosis
Lipids

- **Stage I-III CKD**
  - Same goals as general population
- **Stage IV CKD**
  - Goal LDL < 2.0 mmol/L
  - Goal TC/HDL < 4.0 mmol/L
- Statin first. Measure CK & ALT every 3 mths in CKD stage IV or V
- Gemfibrozil or Niacin for low HDL
- For triglycerides > 10
  - Gemfibrozil
  - Niacin
- In CKD IV do not coadminister fibrate & statin
Lipid Profile in CKD

- As CKD progresses
  - Decreased HDL
  - Increased triglycerides
    - Diminished clearance due to
      - Change in the composition
      - Decreased lipoprotein lipase
  - Increased Lp(a)
  - Increase in the oxidative metabolism of LDL
  - Slowed clearance of postprandial chylomicrons
Lipid Profile in CKD

• In the general population
  – Increased total cholesterol, LDL and triglycerides, and decreased HDL are associated with increased mortality

• As CKD progresses
  – A significant number of studies have found that low rather than high cholesterol is associated with increased mortality
  – Secondary to chronic malnutrition inflammation
ALERT Trial

- RCT of fluvastatin or placebo
- 2,102 kidney transplant patients, 85% who did not have established CV disease
- Mean followup 5.1 years, mean Cr ~145 umol/L
- Fluvastatin lowered LDL 32%
- 17% reduction in primary composite endpoint of cardiac death, nonfatal MI, or coronary revascularization procedure not statistically significant (CI 0.64 - 1.06)
- 35% reduction in secondary endpoint, cardiac death and nonfatal MI (CI 0.48 – 0.88)

SHARP Trial

- SHARP Trial (Study of Heart And Renal Protection)
  - 9,438 pts in 18 countries randomized to placebo vs ezetemibe/simvastatin
    - 3,056 were on dialysis (HD or PD)
    - 6,382 had CKD (eGFR > 150 umol/L in men and > 130 umol/L in women)
  - RR of major vascular events 0.83 (CI 0.74-0.94, P=0.0010)
  - Similar reduction in risk of atherosclerotic events in all subgroups, including dialysis pts
  - No difference in the rate of progression of kidney disease

SHARP trial website and ASN presentation in Denver Colorado 2010
SHARP: Major Atherosclerotic Events

Risk ratio 0.83 (0.74 – 0.94)
Logrank 2P=0.0022

Proportion suffering event (%) versus Years of follow-up
Statins in HD Patients

• 4 D Trial
  – 1255 HD pts with DMII and elevated LDL randomized to lipitor 20mg/d vs placebo
  – Mean LDL decreased from 3.1 to 1.9 mmol/L after 1 mth
  – Median follow up 4 years
  – No difference in the incidence of the primary composite outcome (CV death, nonfatal MI or stroke)
  – Reduction in CV events but increase in stroke

• AURORA
  – 2776 HD pts randomized to Crestor 10 mg/d vs placebo
  – Mean LDL decreased from 2.6 to 1.5 mmol/L over 3 mths
  – Mean follow up 3.8 years
  – No difference in the incidence of the primary composite outcome (CV death, nonfatal MI or stroke)


Anemia

• Caused by decreased erythropoietin production, decreased red cell survival, and decreased erythropoietin responsiveness

• Most often develops when GFR < 30, but can develop at < 60 in some pts

• 90% of pts with GFR < 25

• Normocytic, normochromic
Anemia

• Untreated anemia leads to:
  – Fatigue, weakness, lethargy
  – Decline in cardiac function
  – Decreased cognition and mental acuity
  – Reduced exercise tolerance
Anemia

- R/O other causes of anemia
- Treat iron deficiency
- Diagnosis of iron deficiency in CKD is different than in individuals with normal renal function

- Defined by demonstration of enhanced erythropoiesis in response to iron supplementation
  - Ferritin < 10 in non CKD
  - compared to ferritin < 100 in CKD
  - compared to ferritin < 200 in dialysis

- ? Secondary to the chronic inflammatory state in kidney disease
Iron Therapy

• **IRON SALTS**
  - Ferrous sulphate 300 mg tid (60 mg elemental iron/tablet).
  - Ferrous fumarate 300mg (100 mg elemental iron/tablet)
  - Ferrous gluconate 300mg (35 mg elemental iron/tablet)

• **HEME IRON POLYPEPTIDE**
  - Proferrin (11 mg elemental iron/tablet)
  - Improved well being within several days
  - Maximal reticulocytosis within 7-10 days
  - Hgb begins to rise in 1-2 weeks

• **IV IRON**
  - If unresponsive to oral iron
Anemia

- Multiple retrospective studies and registry studies suggested an inverse relationship between Hgb and risk of hospitalization and death related to cardiovascular complications
Anemia

• CREATE (CKD)
  – 603 pts in 22 countries with CKD stage 3 or 4 and a hgb of 110-125 gm/L
  – Randomized to ESA for goal Hgb of
    • 130-150
    • or placebo
  – Primary outcome composite of 8 CV endpoints
  – No difference in CV events but improvement in QOL

Anemia

• CHOIR (CKD)
  – 1432 predialysis pts with Hgb < randomly assigned to Hgb of 113 or 135 g/L
  – Composite primary endpoint of death, MI, stroke, or hospitalization for heart failure
  – Terminated early for significantly higher number of events in the high Hgb group (HR 1.34, CI 1.03-1.74)
  – Secondary post hoc analysis suggested that the increased endpoints may be related to the dose of epo rather than the hgb level reached

Anemia

• TREAT (CKD)
  – Randomized, double blinded placebo controlled trial in 623 sites, 24 countries
  – 4,038 pts with CKD, anemia, and DM randomized to darbepoetin for goal Hgb of 130 or placebo
  – Event driven trial - follow up continued until 1203 endpoints occurred

TREAT Trial

• At median f/u of 29 months trial reached the endpoint number
  – No difference in primary endpoints
    • Death or ESRD
    • Death or a CV event (MI, heart failure, stroke)
  – Incidence of stroke was twice as high in darbepoetin group (5% vs 2.6%, p < 0.001)
  – QOL outcome mixed with greater improvement in mean FACT fatigue score in darbepoetin group but no difference in the Short Form General Health Survey
  – Decrease in transfusions by 50% in the darbepoetin group
  – In pts with cancer
    • More pts in EPA group died (14 of 188 compared to 1 of 160, P=0.002)

Current Iron/Anemia Goals

- Ferritin goal > 100 pm/L in CKD
- TSAT goal > 20%
- Iron therapy in CKD initiated prior to ESA because otherwise the iron deficiency will limit the erythropoiesis response and drive up the required dose of ESA
- Epo started at hgb <100 g/L for goal hgb 100-120 and not greater than 130 g/L
Chronic kidney Disease-Mineral Bone Disorder (CKD-MBD)

- As kidney function declines, there is a progressive deterioration in mineral and bone homeostasis.
CKD-MBD
Chronic kidney Disease-Mineral Bone Disorder

• Abnormal mineral metabolism
  – Ca, PO4, PTH, Vitamin D metabolism

• Abnormal bone
  – Turnover, mineralization, volume

• Abnormal extraskeletal calcification
  – Vascular or other soft tissue calcification
CKD-MBD
Abnormal Mineral Metabolism

– Tendency toward increased PO4 starts in early in CKD
– Compensatory increase in secretion of:
  • PTH which triggers
    – Increased bone resorption with release of Ca and PO4
    – Decreased renal PO4 reabsorption
  • FGF-23 which leads to
    – Decreased renal PO4 reabsorption.
– In normal renal function 80-95% of filtered PO4 is reabsorbed. By CKD stage 5, only 15% of PO4 is reabsorbed
– Thus, serum PO4 remains in the normal range until GFR is < 25-40 ml/min
Abnormal calcium, PO4 and iPTH

Abnormal Vitamin D and iPTH

Phosphate and Mortality

Phosphate and Mortality in Normal Renal Function

Vascular Calcification

• Not passive precipitation of calcium and phosphate in a supersaturated serum
• Active cellular process
  – Upregulation of inducers
    • In the presence of high phosphate, uremia, dyslipidemia, DM vascular smooth muscle cells differentiate into an osteoblast like phenotype
  – Downregulation of inhibitors
    • Fetuin-A, matrix Gla protein, osteoprotegerin, pyrophosphates
Extraskeletal calcification

ARTERIOSCLEROSIS

Calcification is in the media, as opposed to the intima
Elevated pulse pressure, increased pulse wave velocity leading to LVH, dysfunction and failure
ATHEROSCLEROSIS

Calcification is in the intima, as opposed to the media
Present in > 95% of atherosclerotic plaque
Associated with MI, angina, stroke
Vascular Calcification and Mortality

Soft Tissue Calcification

- Medial calcification of small cutaneous arteries, calciphylaxis

- Valvular calcification
CKD-MBD
Abnormal Bone

- Mineralization
- Volume
- Turnover

KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) KI; 2009 (76) Supplement 113
CKD-MBD
Abnormal Bone

• Osteitis fibrosa
  – Increased PO4, PTH
  – ALP
  – Decreased 1-25(D)
  – Variable calcium
  – Increased vascular calcification
CKD-MBD
Abnormal Bone

• Adynamic Bone
  – Low PTH
  – Calcium and phosphate levels are variable (adynamic bone ceases to buffer dietary calcium and phosphate)
  – Increased vascular calcification
**CKD-MBD**

**Abnormal Bone**

**Osteomalacia**

- Decreased vitamin D, calcium and PO4
- Increased PTH

Pseudofractures in osteomalacia
- Retrospective cohort study
- 1272 dialysis pts over 10 years
- Incidence of nonpathologic hip fracture compared with general population matched for age, sex, race
- Standardized hip fracture ratio in the dialysis pts was 17.4 times greater than that of the general population
- 1 year mortality post hip fracture in a dialysis patient was 64% as compared to the 20% 1 year mortality post hip fracture in the general population
- Average age at the time of hip fracture 64 yrs in males and 61 yrs in female dialysis patients as compared to 80 yrs in male and 74 years in female pts in the general population

Treatment of CKD-MBD

- Ca and PO4 kept within normal limits
  - Restrict dietary PO4 to 800-1000mg/day
  - Calcium based PO4 binders
- iPTH may be elevated. Target level currently unknown
  - Vitamin D analogues
  - Chemical parathyroidectomy
  - Parathyroidectomy
CKD and Osteoporosis

- Many of the same risk factors for osteoporosis in the CKD patient as the general population
  - Older age, female
  - Low BMI
  - History of fracture
  - Diabetes, CVD, PVD
  - Low albumin
- Coexists with CKD-MBD
- Difficult to diagnose in CKD stage III to V
- Accurate diagnosis in CKD requires bone biopsy showing low volume, disrupted microarchitecture but normal mineralization and turnover
CKD and Osteoporosis

• BMD in pts with CKD
  – It may not predict fracture risk. Many fractures on CKD pts occur in pts with normal BMD
  – It does not predict the type of renal osteodystrophy
  – It does not predict the bone quality
  – Artifactual increase in BMD due to soft tissue calcification
  – KDIGO recommends not doing BMD in CKD 3-5

BMD Scan?

- Recent meta-analysis of cross sectional observational studies done by Jamal

- Dialysis pts with fractures have lower BMD at the lumbar spine and radial sites compared with hemodialysis patients without fractures.

- However:
  - there was significant heterogeneity in the meta-analysis
  - only 1 study was from North America and it showed no association between BMD and fracture risk

- In summary, low BMD may or may not be associated with an increased risk of fracture in dialysis patients

Treatment of Osteoporosis in CKD

- Estrogen/testosterone
- Selective estrogen receptor modulators (SERMs)
- Bisphosphonates
- Parathyroid hormone
- Diet and Lifestyle
  - Physical activity, nutrition, fall prevention
Bisphosphonates

- KDIGO suggests bone biopsy prior to initiation of bisphosphonates

- Less than 1% of oral dose absorbed

- 40-60% binds to hydroxyapatite in bone where it remains for up to 10 years causing osteoclast apoptosis and decrease in bone resorption.

- Remaining 40-60% is renally excreted

- Minimal data in CKD but what is available suggests halving the dose or doubling the interval

- Initial increase in bone mass

- Concern in patients with adynamic bone disease is decreased bone remodeling, reduced repair of microcracks and impaired bone strength
BISPHOSPHONATES

- Post hoc analysis of pooled data from 9 RCTs of 8996 post menopausal women with CKD followed for up to 3 yrs
- Risidronate vs placebo. Intention had been to exclude pts with CKD but exclusion was based on Cr. When eGFR was calculated many participants had CKD stage 1-3
  - 7%(572) with GFR < 30, 45% (4071) with GFR 30 – 59, and 48% (4353) with GFR 60-79.
- PTH, PO4, Ca, ALP, Vit D levels were normal

Hormones/Osteoporosis

- Premenopausal women with advanced CKD stage 4/5 have a greater risk of premature and persistent amenorrhea which contributes to accelerated bone loss

- 54% of men with CKD stage 4/5 have low or low normal testosterone which also contributes to accelerated bone loss

- Small studies show improvement in osteoporosis with hormone replacement. There is inhibition of bone demineralization and improved BMD

- Due to altered pharmacokinetics of estradiol in CKD lower doses are required


SERMS and Osteoporosis

- Some evidence of benefit for Raloxifene in CKD
- Post hoc analysis of the MORE trial
  - Multicenter RTC trial
  - 7705 postmenopausal women with osteoporosis
  - Looked at the effect of raloxifene over 3 yrs on:
    - the rate of change BMD
    - incidence of fractures
    - adverse events by stage of CKD
- Decrease in vertebral fractures (OR 0.57, CI 0.47-0.69)

Blackwell, I.A. Ensrud KE. The effect of raloxifene treatment in postmenopausal women with CKD, JASN, 19(7) 2008
Nitrates and Osteoporosis

- Some evidence for nitrates in non CKD and nitrates safe and commonly used in CKD
  - Secondary analysis of the prospective Canadian Multicentre Osteoporosis Trial
  - ~ 4000 pts, looked at annual percent change in BMD of the hip and spine in pts on nitrates vs no nitrates
  - Pts on daily nitrates had a statistically significant increase in BMD

Planning for Renal Replacement Therapy

- Renal Replacement therapy vs Conservative management
Conservative Management

• Average lifespan of an 80 yr old starting dialysis is 12 months
• Will pts started on dialysis
  – Live longer?
  – Feel better?
  – Function better?
Change in Functional Status with Dialysis

- National data base of all US nursing home residents who started dialysis between June 1998 and October 2002

- 3902 pts identified, 3702 had at least one measure of functional status as a baseline prior to starting dialysis
Change in Functional Status with Dialysis

- MDS Activities of Daily Living (ADL) score administered every 3 months and after discharge from hospital
- Uses a scale of 0-4 to rate 7 activities. Maximum score is 28 with higher score indicating poorer functional status
  - 0 independent
  - 1 needs supervision
  - 2 limited assistance
  - 3 extensive assistance
  - 4 dependent
- Defined a change in functional status as a decline of 2 or more points on the ADL scale
- Mean age 73, mean eGFR 10.5 ml/min
- 95% started HD

Kurella Tamura M., Chertow G.M. et al., Functional Status of Elderly Adults before and after initiation of Dialysis; NEJM; 2009; 361:1539-1547.
87% of patients had either a decline in functional status, or death, in the year following initiation of dialysis.

Kurella Tamura M., Chertow G.M. et al., Functional Status of Elderly Adults before and after initiation of Dialysis; NEJM; 2009; 361:1539-1547.
Trajectory of Functional Status and Mortality

Kurella Tamura M., Chertow G.M. et al., Functional Status of Elderly Adults before and after initiation of Dialysis; NEJM; 2009; 361:1539-1547.
Single centre retrospective cohort study
97 Canadian community dwelling pts 80 years or older initiating dialysis
90% had been seen by a nephrologist prior to initiation, 47% initiated PD

Jassal SV et al., Loss of Independence in Patients Starting Dialysis at 80 Years of Age or Older; NEJM; 2009; 361: 1612-1613
Conservative Management

• Multidisciplinary team broadens to include
  – GP, nephrologist, CKD nurse/SW/dietician
  PLUS
  – spiritual care, palliative care

• Focus is on symptom management,
  psychological care,
  spiritual care
Planning for Renal Replacement Therapy

- Types of Renal Replacement therapy
  1. Pre-emptive transplant if possible
  2. Home therapy
     1. PD
     2. Home Hemodialysis
  3. Community Dialysis
  4. Incenter Hemodialysis
Access Planning
Initiation of dialysis

- No evidence at which eGFR dialysis should be initiated
- Symptoms of uremia
- Refractory metabolic abnormalities (metabolic acidosis, hyperkalemia, hyperphosphatemia, anemia)
- Refractory volume overload (edema, CHF or HTN)
- Decline in nutritional status (wt loss, decreasing albumin, Subjective Global Assessment)
CKD: Take Home Points

- Most CKD patients have CVD and will die of CV events prior to ever reaching ESRD therefore require aggressive CV risk factor reduction
- Once reaching ESRD the options include both renal replacement therapy or conservative management
- Regardless of the option chosen, CKD patients are complex, sick, require multidisciplinary care, and GP continued involvement is key