Chronic Kidney Disease

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NKF Definition of Chronic Kidney Disease

- Kidney damage for 3 or more months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests.

- GFR < 60 ml/min/1.73m² for 3 months or more, with or without kidney damage.
### Staging of CKD Based on GFR

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR ml/min/1.73M²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage w/normal or inc. GFR</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild dec. GFR</td>
<td>60 – 89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate dec. GFR</td>
<td>30 – 59</td>
</tr>
<tr>
<td>4</td>
<td>Severe dec. GFR</td>
<td>15 – 29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt; 15 need for RRT</td>
</tr>
</tbody>
</table>

At increased risk

> 90 w/ risk factors

NKF-K DOQI AJKD 2002;39:S1
GFR Calculators

- Available on Web site
  http://www.nephron.com
Definitions

- **ESRD**
  - GFR <15 ml/min/1.73 m²; stage 5 CKD
  - Pts require renal replacement therapy

- **Uremia**
  - Clinical syndrome

  - Thirst
  - Twitching
  - Fatigue
  - Confusion
  - Pallor
  - Coma
  - Nausea
  - Bone Pain
  - Vomiting
  - Pigmentation
  - Breathlessness
Epidemiology

- Rate of growth of renal disease is 6-7% per year
  - Largest increase seen in:
    - Pts over 65 yrs
    - African American
    - Native American
      - US Renal Data System (USRDS)
Epidemiology

- Life expectancy has increased.
  Reflects:
  - Improved dialysis equipment/procedures
  - Wider acceptance of dialysis
  - Increased graft survival in tx pts
Causes of ESRD

- Diabetes
  - 39% of cases
- HTN
  - 28%
- DM & HTN account for largest increase in ESRD prevalence
- Glomerulonephritis
  - 11%
Causes of Death w/ESRD

- Cardiac diseases
- Infection
- Cerebrovascular disease
- Malignancy
Clinical Manifestations

- Derangement in Na & water
  - Na wasting & dehydration
    - Inability to reabsorb Na
  - Fluid overload
Clinical Events as GFR Declines

- 65 ml/min (Stage 2 CKD)
  - Nocturia, decreased ability to concentrate urine
Clinical Events as GFR Declines

- < 60 ml/min (Stage 3 CKD)
  - iPTH levels begin to rise
  - Begin to see evidence of bone disease at Stage 3 CKD (GFR 30-59 ml/min/1.73m²)

- 50 ml/min (Stage 3 CKD)
  - Anemia

- 15 ml/min (Stage 4 CKD)
  - Decreased K excretion (F&E)
    - K excretion is flow dependent
    - Decreased aldosterone synthesis/effectiveness
Clinical Events as GFR Declines

- 15 ml/min (Stage 4 CKD)
  - Acidosis (Acid-Base)
    - Cannot excrete H ions generated by metabolism of dietary protein
    - Decreased GFR -> decreased filtration of urinary buffers
    - Impaired synthesis of ammonia to titrate H ions
Management of Renal Disease Complications
Renal Osteodystrophy

- Kidney plays impt role in $\text{PO}_4$ excretion and vitamin D activation

- Clinical complications
  - Early manifestation is pruritis
  - Bone pain
  - Increased propensity to fractures
  - Development of metastatic calcifications
    - L/T complication
  - Skeletal abnormalities
Process

- Hypocalcemia -> secretion of parathyroid hormone (PTH)

Causes of hypocalcemia

- Hyperphosphatemia
- Decreased production of 1,25 dihydroxy-vitamin D₃ aka calcitriol
- Peripheral resistance to actions of PTH
Hypocalcemia

- Hyperphosphatemia
  - As GFR falls, 30 ml/min, PO$_4$ is retained because 70% of ingested PO$_4$ is excreted by kidneys
  - PO$_4$ complexes with Ca -> hypocalcemia
Hypocalcemia

- Kidneys are responsible for activation of vitamin D to calcitriol
  - Activation occurs in proximal tubule by mitochondrial P-450 system
  - Enzyme involved in activation is 1-alpha-hydroxylase
  - Decreased renal mass/nephron loss -> decreased ability to produce calcitriol
Calcitriol

- Interacts with intestinal receptors to increase Ca absorption

- 2 effects in renal failure:
  - 1st effect of decreased calcitriol -> decreased Ca absorption
  - 2nd effect of decreased calcitriol -> impaired bone mineralization
Hypocalcemia -> HyperPTH

Nephron Loss

- Impaired Phosphate Excretion
  - Hypocalcemia
    - Increased PTH Secondary Hyperparathyroidism

- Decreased Production Calcitriol
  - Impaired bone mineralization
    - Osteomalacia more later
  - Hypocalcemia
    - Increased PTH Secondary Hyperparathyroidism
Consequences of Hyperphosphatemia

- Increased Ca x P product: Soft-tissue (metastatic) calcifications
- Blocks calcitriol-effect to inhibit PTH secretion
- Direct effect of increased PTH
Hyperphosphatemia and PTH

- Phosphate has a direct stimulatory effect on PTH gland
  - High phosphate diet $\rightarrow$ increased mRNA expression per cell and PTH cell hyperplasia
  - Low phosphate diet $\rightarrow$ post transcriptional decrease in PTH mRNA levels
  - Low phosphate diet decreases serum PTH
    - Observed in rats, dogs
    - Observed in ESRD patients
Normal Effects of PTH

- Physiologic attempt to restore normal [Ca] and [PO₄]
  - Stimulates 1-alpha hydroxylase activity -> increased calcitriol
  - Increased GI absorption of Ca
  - Increased renal Ca reabsorption; decreased renal CL of Ca
  - Decreased renal tubular reabsorption of PO₄; increased renal PO₄ excretion

- Maintains Ca & PO₄ homeostasis until GFR fall to < 25-30% of normal....then
Secondary Hyperparathyroidism

- As renal function worsens,
  - Sufficient production of calcitriol can no longer be maintained -> PTH biosynthesis increases
  - Peripheral resistance (1º) renal to PTH...
  - Persistent hypocalcemia...
  - Leads to REDIRECTION OF PTH TO BONE
    - Sacrifice the integrity of bone in an effort to maintain normal [Ca]
    - Increased bone resorption
2° Hyperparathyroidism

Increased PTH
Secondary Hyperparathyroidism

Increased renal Ca reabsorption

Decreased renal tubular reabsorption of phosphate

Increased Ca mobilization from bone
Classification of Renal Bone Disease

- High turnover lesions
  - Osteitis fibrosa cystica
  - Due to persistently elevated PTH
  - PTH & IL-1, IL-6, IL-11, TNF, GM-CSF, & M-CSF recruit & differentiate osteoclast precursors
- Active bone resorption
  - Increase in number & size of osteoclasts
  - Increase in osteoblastic activity, but normal bone is replaced by fibrous tissue
Osteitis Fibrosa Cystica

- Clinical consequences:
  - Fractures
  - Skeletal deformities
  - Tendon rupture
  - Bone pain
Classification of Renal Bone Disease

- Low turnover lesions
  - Osteomalacia 2° to:
    - Calcitriol deficiency
      - Mineralization of bone depends on an adequate supply of calcitriol
        - Impaired formation of calcitriol -> decreased Ca -> impaired mineralization
    - Persistent metabolic acidosis
      - Bone buffering
  - Aluminum accumulation
    - Aluminum bone disease
Classification of Renal Bone Disease

- Low turnover lesions
  - Osteomalacia cont’d
    - Decreased bone formation & turnover
    - Further impairment in the mineralization of newly formed bone -> unmineralized bone collagen (osteoid)
    - Accumulation of osteoid
    - Prevention of osteomalacia w/ calcium supplementation, calcitriol, correction of acidosis
Classification of Renal Bone Disease

- Adynamic bone disease
  - Overuse/ overtreatment of vitamin D analogues or calcium-containing phosphate binders
Bone Lesions

- A = normal bone
- B = osteitis *fibrosa* cystica
- C = osteomalacia
  - Unmineralized bone
- D = mixed dz
- E = adynamic bone disease
Manifestations of Renal Osteodystrophy

- Pruritis
  - Calcium deposits in the skin
- Osteomalacia
  - Softening of the bones
- Osteoporosis
  - Bone loss
- Osteosclerosis
  - Abnormal bone density/hardening/deposition
Manifestations of Renal Osteodystrophy

- **Calciphylaxis**
  - Calcifications leading to ischemic necrosis of tips of fingers & toes
- **Red eyes**
  - Calcifications of the conjunctivae
- **Band keratopathy**
  - Calcifications of the cornea
Metastatic Calcification

- Occurs when $\text{Ca} \times \text{PO}_4$ product $> 55 \text{ mg}^2/\text{dl}^2$
  - Hyperphosphatemia plays a major role
  - Current K/DOQI recommendations are to maintain product $< 55 \text{ mg}^2/\text{dl}^2$

- Can occur in visceral & nonvisceral tissues
  - Visceral: heart, lungs
  - Nonvisceral: joints, muscle, SQ tissue, tissue near tendons
Massive soft-tissue calcification of the foot of a patient on long-term hemodialysis

Archives of Orthopedic & Trauma Surgery
2003;123(1):51-3
Cardiac calcification

- Occurs when $\text{Ca} \times \text{PO}_4$ product $> 70$ mg$^2$/dl$^2$
- Cardiac calcifications have been reported in 60% of dialysis pts upon autopsy (AJKD 1996; 27:394-401; Nephrol Dial Transplant 1998; 13:2037-40)
  - Found in myocardium, pericardium, conduction system, aortic & mitral valves, myocardial & coronary arteries
  - May lead to arrhythmia, LV dysfxn, aortic & mitral stenosis & regurg, heart block, ischemia, CHF, death
Vascular calcification

- Phosphorus may enter smooth muscle cells of blood vessels
- Phosphorus alters the phenotype of smooth muscle cells causing them to change into osteoblasts (bone-laying cells)
- This begins the process of blood vessel calcification
- Calcification of coronary arteries is associated with increased CV mortality in patients w/Stage 5 CKD (GFR < 15)
Computed tomography (CT) sections from a 27 year old male hemodialysis pt showing calcification in all 3 coronary arteries and aorta.
Metastatic pulmonary calcification after renal transplantation
CXR showing numerous diffuse confluent nodular opacities.
Ref: Eur Respir J 1997;10:1025-7
Metastatic pulmonary calcification after renal transplantation
Computed tomography (CT) scan of the chest.
Ref: Eur Respir J 1997;10:1025-7
Metastatic calcifications

- Factors
  - Elevated PTH
  - Hyperphosphatemia
  - Hypercalcemia
  - Elevated Ca x P product
Hip Fractures

- Incidence of hip fractures in the dialysis population is 4 x general population
- Associated with 1 year mortality 2x that of dialysis patient without hip fracture

Ref: Leinau L et al, Semin Dialysis 2006;19(1):75-9
Detection
<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>GFR ml/min/1.73 m²</th>
<th>iPTH</th>
<th>Ca &amp; PO$_4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>30-59</td>
<td>Q 12 months</td>
<td>Q 12 months</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Q 3 months</td>
<td>Q 3 months</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 or dialysis</td>
<td>Q 3 months</td>
<td>$Q \ monthly$</td>
</tr>
</tbody>
</table>
Management
Hyperphosphatemia

- Need to maintain serum [PO₄] within the *near normal* range
  - CKD Stage 3 & 4 goal PO₄ = 2.7 – 4.6 mg/dl
  - CKD Stage 5 goal PO₄ = 3.5 – 5.5 mg/dl
    - In healthy pts w/ good renal fxn:  2.2-4.2 mg/dl
  - Avoid hypophosphatemia to decrease the risk of osteomalacia (softening of the bones)
- 2 methods: dietary restriction, PO₄ binders
Dietary Restriction

- Limit intake to 800-1000 mg/d in pts on dialysis
  - HD removes 500-700 mg PO\textsubscript{4}/session
  - PD removes 300 mg/day
- Use more severe restrictions in pts not yet on HD
  - Note: Usual daily intake in healthy pts is 1000-1800 mg/d
High PO$_4$ Foods

- **Dairy foods**
  - Milk, eggs, butter, ice cream, cheese
- **Meats**
- **Chocolate**
- **Carbonated beverages**
  - Beer, cola
- **Nuts**
- **Legumes**
  - Beans, lentils, peas, soybeans, soy foods
- **Breads & cereals**
  - Barley, bran, cornbread, whole-grain breads
Phosphate Binders

- Used when pts cannot control $[\text{PO}_4]$ with diet and dialysis alone
- Majority of pts require phosphate binders
  - Calcium-containing binders (L/T use)
    - CaCO$_3$ or Ca acetate
  - Polymer: sevelamer (L/T use)
  - Aluminum-containing binders (S/T use)
    - ALOH: Amphojel, Alternagel, Alu-Tabs/Caps, Basaljel
Guidelines

- Bind dietary $\text{PO}_4$ in the GI tract
  - Decreased $\text{PO}_4$ absorption
  - Increased fecal elimination of bound $\text{PO}_4$
- Administer immediately before or with meals
- Adjust dose to size/timing of meals
- Avoid long-term use of aluminum-containing binders
  - Aluminum accumulation & toxicity
Calcium Carbonate \((\text{CaCO}_3)\)

- Carbonate salt may correct acidosis
- Inexpensive
- Contains a high % of elemental Ca
- Provides Ca supplementation
  - May help correct hypocalcemia – dec. PTH
  - BUT may cause hypercalcemia
- Generic products may have poor dissolution characteristics
Calcium-Containing Products

- Abdominal roentgenogram showing dialysis pt w/poor dissoln of generic Ca-containing binder
Calcium Acetate

- **Claim to fame:**
  - It has twice the binding capacity for PO$_4$ per Ca compared to CaCO$_3$
  - Phoslo 667 mg 2-3 tabs with meals
    - 167 mg of elemental Ca
  - Contains Ca, so can also cause hypercalcemia
Calcium Citrate

- Disadvantages:
  - **Citrate may enhance aluminum absorption**
    - Risk aluminum toxicity
  - Do not use with aluminum-containing binders (incl. Sucralfate)
  - Aluminum-citrate complexes may inhibit bone growth & exacerbate aluminum bone dz
Calcium-containing Binders

- Total dosage of elemental calcium should not exceed 1500 mg/day
- Total intake of elemental calcium (including dietary calcium) should not exceed 2000 mg/day
- Should not be used in HD pts who are hypercalemic (corrected serum Ca >10.2 mg/dl or whose iPTH < 150 pg/ml)
- Pts who have vascular and/or soft-tissue calcifications should use non-calcium containing binders
<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Content</th>
<th>Elemental Ca</th>
<th>Number of Pills to Equal about 1500 mg Elemental Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tums</td>
<td>500 mg</td>
<td>200 mg</td>
<td>7.5</td>
</tr>
<tr>
<td>Tums EX</td>
<td>750 mg</td>
<td>300 mg</td>
<td>5</td>
</tr>
<tr>
<td>Tums Ultra</td>
<td>1000 mg</td>
<td>400 mg</td>
<td>3.75</td>
</tr>
<tr>
<td>Tums 500</td>
<td>1250 mg</td>
<td>500 mg</td>
<td>3</td>
</tr>
<tr>
<td>Brand Name</td>
<td>Content</td>
<td>Elemental Ca</td>
<td>Number of Pills to Equal about 1500 mg Elemental Ca</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------</td>
<td>--------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>PhosLo</td>
<td>667 mg</td>
<td>167 mg</td>
<td>9</td>
</tr>
<tr>
<td>Chooz (gum)</td>
<td>500 mg</td>
<td>200 mg</td>
<td>7.5</td>
</tr>
<tr>
<td>CalciChew</td>
<td>1250 mg</td>
<td>500 mg</td>
<td>3</td>
</tr>
<tr>
<td>CitraCal (citrate)</td>
<td>Not Recommended</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aluminum-containing Binders

- Use aluminum-containing binders when:
  - \( \text{PO}_4 \) is markedly elevated (>7 mg/dl)
  - Double product is elevated > 60-75 mg/dl...
  - Minimize risk of metastatic calcifications
  - Pts who cannot be controlled w/ Ca-containing binders alone
  - Pts who develop hypercalcemia from Ca-containing binder
# Aluminum-containing Binders

<table>
<thead>
<tr>
<th>OTC Product</th>
<th>Usual Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphojel</td>
<td>30-60 ml po with meals</td>
</tr>
<tr>
<td>Alternagel</td>
<td>30-60 ml po with meals</td>
</tr>
<tr>
<td>Alu-Tab 500 mg</td>
<td>1-3 tabs with meals</td>
</tr>
<tr>
<td>Alu-Cap 400 mg</td>
<td>1-3 tabs with meals</td>
</tr>
</tbody>
</table>
Aluminum-containing Binders

- Switch to a Ca-containing binder when serum $[\text{PO}_4] \leq 6 \text{ mg/dl}$
- Use S/T (4 weeks)
- Avoid L/T use
- Situations of aluminum toxicity:
  - Concurrent use of aluminum- & citrate-containing products
  - High [aluminum] in dialysate
  - Rare nowadays: use of deionized water & reverse osmosis to clear aluminum
Aluminum Toxicity – Acute Aluminum Neurotoxicity

- **Features:**
  - Altered consciousness
  - Seizures
  - Coma
  - Usually progresses to death
    - Hi mortality
Aluminum Toxicity – Dialysis Encephalopathy

Features – Subacute syndrome:
- Speech abnormalities
- Altered consciousness
- Seizures
- Often intermittent and worsens transiently after HD
- Usually slowly progressive
Aluminum Toxicity – Bone Disease

- Impaired bone mineralization -> osteomalacia
- Altered bone cell proliferation -> adynamic bone disease

Features:
- Bone pain
- Fractures
- Muscle weakness
Aluminum Toxicity – Microcytic Anemia & Epo Resistance

- Aluminum competes with Fe for the same absorption and cellular uptake pathways
- Decreased erythropoiesis
- Features:
  - Microcytic anemia
  - No evidence of iron deficiency
  - No response to iron therapy
Aluminum Toxicity

- Difficult to treat
- PREVENTION IS KEY
- HD does not remove aluminum
  - Highly bound to transferrin
- Pts with Sx of organ dysfxn should receive chelation therapy (DFO)
  - DFO chelates aluminum, then hi flux or hi efficiency is used to remove chelated product
Magnesium-containing PO$_4$ Binders

- Recommended in textbook BUT NOT USED
  - Risk of hypermagnesemia
  - Egs Maalox, Mylanta
  - Do not use magnesium laxative eg MOM
Non-calcium, non-aluminum, non-magnesium-containing phosphate binders
Sevelamer (RenaGel)

- Nonabsorbable polymer-based PO$_4$ binding agent; forms ionic & to a lesser extent H bonds w/PO$_4$

- Does not contain Ca, Al, or Mg so no accumulation of these ions
  - No risk of hypercalcemia

- 400, 800 mg tabs
  - TID w/meals

- No studies, but manufacturer recommends no other meds 1hr before or 3 hrs after sevelamer dose
Sevelamer vs Ca Acetate

- N=83 adult HD pts (age 54.4 ± 15 yrs)
- Open-label, randomized, crossover study
- 2-week PO$_4$ binder washout period
- Randomized to: sevelamer 465 mg cap 2-4 caps tid wm or Ca acetate 667 mg tabs 1-3 tabs tid wm to achieve serum [PO$_4$] 2.5-5.5 mg/dl x 8 wks
- 2-week washout, then crossed over to other txmt

Ca acetate-treated pts had a higher incidence of hypercalcemia during treatment
Serum $[\text{PO}_4]$ 

Observed a similar decrease in $[\text{PO}_4]$ between sevelamer & Ca acetate
L/T Effects of Sevelamer on CaxPO\textsubscript{4} Product & Lipids

- **Premise:**
  - Non-aluminum-, non-calcium-containing binder so should have no effects on CaxPO\textsubscript{4} product
  - May also have favorable effect on lipid profiles
    - Binds bile acids, resulting in increased fecal bile acid excretion & reduction in LDL

- N=192 adult HD pts
- Received open-label sevelamer
  - Nephrol Dial Transplant 1999;14(12):2907-14
# Results

<table>
<thead>
<tr>
<th>Sevelamer-treated pts</th>
<th>Mean Change in:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Serum [PO$_4$] mmol/L</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Serum [Ca] mmol/L</strong></td>
</tr>
<tr>
<td></td>
<td><strong>CaxPO$_4$ product</strong></td>
</tr>
<tr>
<td></td>
<td><strong>LDL mmol/L</strong></td>
</tr>
<tr>
<td></td>
<td><strong>HDL mmol/L</strong></td>
</tr>
</tbody>
</table>

$P < 0.0001$, all comparisons
Lanthanum carbonate

- **Fosrenol (Shire)**
- **Non-aluminum-, non-calcium-containing binder so should have no effects on \( \text{Ca}_x\text{PO}_4 \) product**
- Trivalent cation found in the environment and seawater
- Binds phosphate in the gut
- \( F < 0.002\% \)
- 250 – 1000 mg chewable tablets
Lanthanum carbonate vs standard therapy: HD pts

- n=1359 chronic HD pts
- 1-3 week washout period
- Pts were randomized to receive lanthanum carbonate initial dose of 750 or 1500 mg/day DD after meals (n=682) or standard therapy w/pre-study phosphate binder (n=277)
- Doses were titrated to achieve serum PO₄ level < 5.9 mg/dl (before the DOQI guidelines of <5.5 mg/dl)
- 6-week dose titration followed by 24 month maintenance phase
- Primary goal: L/T safety of lanthanum vs standard therapy; Secondary goal: efficacy of lanthanum vs standard therapy

Adverse Events

- Treatment related AE occurred in ≥ 15% of total pts
- Most common were GI in both groups (N/V/D, abdominal pain)
- Hypercalcemia:
  - lanthanum 4.3% vs standard tx 8.4%
- Low incidence of biliary/liver disorder:
  - lanthanum 4% vs standard therapy 7%
- No $p$ values reported
Serum Phosphate

![Graph showing changes in serum phosphate levels over study weeks and months, comparing Lanthanum carbonate and Standard therapy.](image-url)
% Pts w/Controlled Phosphate
Serum Calcium

![Graph showing serum calcium levels over study weeks and months, comparing Lanthanum carbonate and Standard therapy.](image)
Serum PTH

Shaded area = desired range
Conclusions

- Similar tolerability
- Similar efficacy
- Lanthanum carbonate maintains serum calcium levels at a lower level than standard therapy.
Calcium Supplementation

- Once PO$_4$ has been controlled, achieve normocalcemia
- Target serum [Ca] 8.4-10.2 mg/dl; 8.4-9.5 mg/dl in CKD stage 5
- Achieved by administering Ca supplements \textit{between} meals
Treatment Failure of \( \text{PO}_4 \) Binders

- Poor compliance
  - GI upset
  - OTC products advertised as antacids or Ca supplements \( \rightarrow \) confusion
    - Educate pt that it is a phosphate binder
- Poor dissoln
- Presence of severe hyperparathyroidism
Questions (not a clicker question)

- How would you prescribe PO₄ binders in the following situations?
  - NPO
  - Continuous enteral tube feedings
  - TPN
  - No breakfast, regular lunch, big supper
  - Pt receiving po Fe supplements
2° Hyperparathyroidism

- Initiated by hypocalcemia
  - Recall, decreased calcitriol & increased PO$_4$ contribute to hypocalcemia -> increased PTH

- Shift in Ca set point
  - Serum [Ca] necessary to suppress PTH is higher (recall, target serum [Ca] 9-11 mg/dl)
    - Parathyroids are insensitive to negative feedback controls
Set Point – Sigmoidal PTH-Ca Relationship n=5 pts

1. $[PO_4] = 8.5 \text{ mg/dl} \rightarrow$ set point $[Ca] = 5.1$
2. $[PO_4] = 7.0 \text{ mg/dl} \rightarrow$ set point $[Ca] = 4.8$
3. $[PO_4] = 5.4 \text{ mg/dl} \rightarrow$ set point $[Ca] = 4.6$

Q: What happens to the set point as $[PO_4]$ increases?

- Abstract JASN 1997; 8:556; Kidney Int 1999; suppl 73:S31-S37
Set Point – Sigmoidal PTH-Ca Relationship  \( n=5 \) pts

- Q: What happens to the set point as \([\text{PO}_4]\) increases?
  - Shifted to right -> need higher [Ca] to suppress PTH
  - Control of \(\text{PO}_4\) results in lower [PTH]

- Abstract JASN 1997; 8:556; Kidney Int 1999; suppl 73:S31-S37
Calcitriol

- Suppresses the synthesis & release of PTH
  - Binds to target cells (VDR = vitamin D receptor) & inhibits PTH gene transcription
  - Directly interacts w/receptors on the PTH gland to inhibit PTH secretion
- Interacts with intestinal receptors -> increased Ca absorption → dec. PTH
When to start therapy

- Achieve normophosphatemia first
  - Serum $[PO_4] < 5.5$ mg/dl (stage 5 CKD)
  - Serum $[PO_4] < 4.6$ mg/dl (stages 3-4 CKD)
- Hyperphosphatemia
  - Causes resistance to the PTH-suppressing effects of vita D analogs
  - Directly stimulates PTH release
  - If Ca increases with vita D analog, then increased risk of metastatic calcifications
# When to start therapy

<table>
<thead>
<tr>
<th>Stage 3 CKD</th>
<th>iPTH pg/ml</th>
<th>Serum Ca mg/dl</th>
<th>Serum PO$_4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR 30-59</td>
<td>&gt;70</td>
<td>&lt;9.5</td>
<td>&lt;4.6</td>
</tr>
<tr>
<td></td>
<td>(target 35-70)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 4 CKD</th>
<th>iPTH pg/ml</th>
<th>Serum Ca mg/dl</th>
<th>Serum PO$_4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR 15-29</td>
<td>&gt;110</td>
<td>&lt;9.5</td>
<td>&lt;4.6</td>
</tr>
<tr>
<td></td>
<td>(target 70-110)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 5 CKD</th>
<th>iPTH pg/ml</th>
<th>Serum Ca mg/dl</th>
<th>Serum PO$_4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR &lt;15</td>
<td>&gt;150</td>
<td>&lt;9.5</td>
<td>&lt;5.5</td>
</tr>
<tr>
<td></td>
<td>(target 150-300)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Vitamin D Analogs

- Use agents that do not require kidney activation such as
  - 1,25-dihydroxy vitamin D₃ (calcitriol)
  - 1-alpha-hydroxy vitamin D₂ (paricalcitol)
Calcitriol

- 2 products
  - Rocaltrol (oral): 0.25, 0.5 mcg caps
  - Calcijex (IV): 1 mcg/ml

- Daily vs Pulse Dosing
Calcitriol po: QD, TIW, or QWK


- N=16 adult CRF pts (51 ± 16 yrs)
- Randomized crossover study:
  - A: 0.5 mcg po qam
  - B: 2.0 mcg po TIW
  - C: 2.0 mcg po q week
- 3 months of each txmt; 1 month wash-out period
- Low PO₄ diet; CaCO₃ for PO₄ > 2mmol/L; AlOH for PO₄ > 5.5 mmol/L
Calcitriol po: QD, TIW, or QWK

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>A (qd)</th>
<th>Basal</th>
<th>B (TIW)</th>
<th>Basal</th>
<th>C (q week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[iPTH] pg/ml</td>
<td>270 ± 136</td>
<td>275 ± 168</td>
<td>283 ± 148</td>
<td>135 ± 76*</td>
<td>274 ± 111</td>
<td>165 ± 121*</td>
</tr>
<tr>
<td>iCa mM/L</td>
<td>1.15 ± 0.06</td>
<td>1.19 ± 0.05</td>
<td>1.16 ± 0.05</td>
<td>1.22 ± 0.06</td>
<td>1.15 ± 0.06</td>
<td>1.18 ± 0.04</td>
</tr>
</tbody>
</table>

\( \text{P} 0.05 \)
Calcitriol po: QD, TIW, or QWK

- TIW pulse dosing significantly reduced [iPTH]
- First data to show efficacy of single po once a week pulse dose
  - No significant modulations in [iCa] or [PO₄] were observed
L/T Effect of IV Calcitriol
Includes Bone Density Studies

- N=15 HD patients (age 18-70 yrs); [iPTH] 10x normal
- 2 week washout period; calcitriol IV 1 mcg TIW x 3 wks, then dose adjusted per [iPTH] & serum [Ca]
- BMD: femoral neck, lumbar spine (baseline & after 1 yr)
- Study duration: 1 year
  - Ref: Am J Nephrol 1997;17:118-123
L/T Effect of IV Calcitriol

- X-axis = time (months)
- Significant reduction in [PTH] associated w/increased [Ca]
## Dual Photon Densitometry

### $g/ cm^2$

<table>
<thead>
<tr>
<th>Site</th>
<th>Pre-txmt</th>
<th>Post-txmt</th>
<th>% increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine*</td>
<td>1.071 ±</td>
<td>1.159 ±</td>
<td>9.3 ± 8.9</td>
</tr>
<tr>
<td></td>
<td>0.23</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Femur**</td>
<td>0.834 ±</td>
<td>0.89 ±</td>
<td>7.43 ±</td>
</tr>
<tr>
<td></td>
<td>0.002</td>
<td>0.09</td>
<td>6.80</td>
</tr>
</tbody>
</table>

* $p < 0.003$; ** $p < 0.001$
Pulse Oral vs IV Calcitriol

- N=20 chronic HD patients
- 4 month run-in phase with no calcitriol
- Randomized to receive calcitriol 0.5 mcg TIW, then adjusted q 2 wks per [iCa]
  - pulse po (n=10) or IV (n=10)
- Study txmt duration = 4 months
  - Ref: Nephron 1997; 77: 267-72
### Pulse Oral vs IV Calcitriol

<table>
<thead>
<tr>
<th></th>
<th>Pulse oral n=10</th>
<th>IV n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.31 ± 0.10</td>
<td>1.35 ± 0.09</td>
</tr>
<tr>
<td>2 mo</td>
<td>1.24 ± 0.05</td>
<td>1.38 ± 0.08</td>
</tr>
<tr>
<td>4 mo</td>
<td>1.25 ± 0.06</td>
<td>1.34 ± 0.08</td>
</tr>
</tbody>
</table>

[iPTH] pg/ml median

<table>
<thead>
<tr>
<th></th>
<th>Pulse oral n=10</th>
<th>IV n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>344</td>
<td>330</td>
</tr>
<tr>
<td>2 mo</td>
<td>200</td>
<td>123</td>
</tr>
<tr>
<td>4 mo</td>
<td>144*</td>
<td>60*</td>
</tr>
</tbody>
</table>

iCa mM/l

<table>
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<tr>
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<th>Pulse oral n=10</th>
<th>IV n=10</th>
</tr>
</thead>
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<td>1.25 ± 0.06</td>
<td>1.24 ± 0.05</td>
</tr>
<tr>
<td>2 mo</td>
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<td>1.35 ± 0.09</td>
</tr>
<tr>
<td>4 mo</td>
<td>1.38 ± 0.08</td>
<td>1.31 ± 0.10</td>
</tr>
</tbody>
</table>

\[P < 0.001, \text{ 0 vs 4 mo.}\]
Pulse Oral vs IV Calcitriol

- Pulse calcitriol (po or IV) significantly reduced [iPTH] in pts w/mild to moderate hyperparathyroidism
- Pulse calcitriol (po or IV) did not significantly reduce [iPTH] in pts w/severe hyperparathyroidism
  - 1157 + 156 vs 807 + 228 pg/ml, p=0.09

IV calcitriol produced the effect sooner (p 1st mo) vs po calcitriol ( p 2nd mo)
Pulse Dosing

- Has a direct effect on PTH gland
  - May be due to supratherapeutic peak

- Greater reductions in PTH concentrations

- Less intestinal Ca absorption
  - Lesser incidence of hypercalcemia

- Typical starting doses for pulse (po or IV):
  - 0.5-2 mcg, with 0.5-1.0 mcg increase based upon [PTH] obtained q 6 months
Hypercalcemia

- Hold calcitriol
  - Risk development of adynamic bone dz
- Restart at a lower dose once hypercalcemia is controlled
  - Hold/adjust doses of Ca-containing binders/supplements; use/switch to sevelamer
  - Use lowest [Ca] in dialysate
Paricalcitol (Zemplar)

- Associated with a low incidence of hypercalcemia with pulse dosing
  - Decreased intestinal absorption of Ca;
    decreased Ca mobilization from bone
- Efficacious alternative to calcitriol w/less hypercalcemia
  - No prospective studies have compared the agents
Paricalcitol (Zemplar)

- IV: 0.04 – 0.1 mcg/kg given as a bolus dose no more frequently than qod at any time during HD
- Injection: 5 mcg/ml (1 ml, 2 ml, 5 ml)
- Oral Capsule, Liquid Filled: 1, 2, 4 mcg
Suppression of PTH by Paricalcitol

- N=71 original pts -> n=35 randomized to study txmts (22 paricalcitol; 13 placebo)
  - chronic HD patients; age 50 ± 16 yrs
- Placebo-controlled, randomized, multicenter trial
- 4 weeks of paricalcitol 0.04 – 0.24 mcg/kg TIW or placebo
  - Different dosing groups: 0.04, 0.08, 0.16, 0.24 mcg/kg
Suppression of PTH by Paricalcitol

- Study endpoint: at least a 30% reduction from maximum baseline \([iPTH]\) for 75% of pts receiving paricalcitol per dosing group
<table>
<thead>
<tr>
<th>Weeks</th>
<th>Placebo</th>
<th>0.04 mcg/kg</th>
<th>0.08 mcg/kg</th>
<th>0.16 mcg/kg</th>
<th>0.24 mcg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-100</td>
<td>-80</td>
<td>-60</td>
<td>-40</td>
<td>-20</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>-100</td>
<td>-80</td>
<td>-60</td>
<td>-40</td>
<td>-20</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>-100</td>
<td>-80</td>
<td>-60</td>
<td>-40</td>
<td>-20</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
</tr>
</tbody>
</table>
% Pts Achieving 30% Reduction in [iPTH] from Baseline

![Bar Chart showing % Pts Acheiving 30% Reduction in [iPTH] from Baseline across different doses of mcg/kg compared to Placebo.](chart.png)
Suppression of PTH by Paricalcitol

- 68% of pts receiving paricalcitol achieved efficacy endpoint regardless of dose
  - 83% of pts in the 0.16 – 0.24 mcg/kg group attained efficacy endpoint
  - 2% in the placebo group attained efficacy endpoint

- No clinically significant differences in [Ca] or [PO₄] between paricalcitol and placebo groups
Paricalcitol Capsule (Zemplar)

- To test the safety and efficacy of oral paricalcitol capsules (F = 0.80) in pts w/ stage 3 and 4 CKD with secondary HPT
- Combined results of 3 prospective, randomized, double-blind, placebo-controlled, multicenter studies
- n=220 pts
- Initial dose 1-2 mcg QD or 2-4 mcg thrice weekly depending on iPTH ≤ 500 pg/ml (lower doses or > 500 pg/ml higher doses)
- Study treatment duration: 24 weeks
Achievement of iPTH Targets

- Paricalcitol (n=101)
- Placebo (n=108)

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Paricalcitol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 consecutive ≥ 30% decreases in iPTH</td>
<td>91%</td>
<td>0%</td>
</tr>
<tr>
<td>4 consecutive ≥ 30% decreases in iPTH</td>
<td>74%</td>
<td>0%</td>
</tr>
<tr>
<td>iPTH &lt;110</td>
<td>75%</td>
<td>12%</td>
</tr>
</tbody>
</table>
Absolute iPTH Values from Baseline

Mean ± SE

$P < 0.001$ found from week 3 thru end of study
Serum Ca & PO4 Levels

Mean ± SE
Paricalcitol-Treated Patients

![Graph showing the change in calcium, iPTH, and phosphorus levels over the weeks post-first dose of study drug.](image)
Conclusions

- Txmt with po paricalcitol
  - Observed significant and sustained iPTH level reduction in patients with stages 3 and 4 CKD
  - Observed minimal or no effect on calcium and phosphorus metabolism
Doxercalciferol (Hectorol)

- **Intravenous Solution**: 2 mcg/ml
  - End of dialysis dosing
- **Oral Capsule**: 0.5 mcg, 2.5 mcg
- **Oral Capsule, Liquid Filled**: 0.5 mcg, 2.5 mcg
  - PreHD po dosing – QD
  - HD po dosing - TIW
- **Dosing based upon iPTH levels**
- **No head-to-head trials w/paricalcitol**
## NKF K/DOQI Goal Conc.

<table>
<thead>
<tr>
<th></th>
<th>CKD Stage 3</th>
<th>CKD Stage 4</th>
<th>CKD Stage 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GFR (ml/min/1.73 m^2)</strong></td>
<td>30-59</td>
<td>15-29</td>
<td>&lt;15 or dialysis</td>
</tr>
<tr>
<td><strong>iPTH (pg/ml)</strong></td>
<td>35 - 70</td>
<td>70 – 110</td>
<td>150 – 300</td>
</tr>
</tbody>
</table>

iPTH = intact PTH
New Assay – Biointact PTH

- Biointact PTH (biPTH)
- Assays different part of PTH molecule
- Target range is 50% that for iPTH
## NKF K/DOQI Goal Conc.

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<tr>
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<td>150 - 300</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>biPTH (pg/ml)</th>
<th>CKD Stage 3</th>
<th>CKD Stage 4</th>
<th>CKD Stage 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.7 - 35</td>
<td>35 - 55</td>
<td>75 - 150</td>
<td></td>
</tr>
</tbody>
</table>

iPTH = intact PTH; biPTH = biointact PTH
<table>
<thead>
<tr>
<th></th>
<th>CKD Stage 3</th>
<th>CKD Stage 4</th>
<th>CKD Stage 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO$_4$ mg/dl</td>
<td>2.7 – 4.6</td>
<td>2.7 – 4.6</td>
<td>3.5 – 5.5</td>
</tr>
<tr>
<td>Ca mg/dl</td>
<td>8.4 – 10.2</td>
<td>8.4 – 10.2</td>
<td>8.4 – 9.5</td>
</tr>
<tr>
<td>Ca x PO$_4$</td>
<td>&lt;55</td>
<td>&lt;55</td>
<td>&lt;55</td>
</tr>
</tbody>
</table>
Corrected Serum [Ca]

- Corrected Serum [Ca] in mg/dl = total serum Ca (mg/dl) + 0.0704 x [34 minus serum albumin (g/L)]
  - Most closely approximates corrected total Ca in CKD pts; R = 0.84 (no p value reported in K/DOQI)

- Corrected Serum [Ca] in mg/dl = total serum Ca (mg/dl) x [4 – serum albumin (g/L)]
  - “For routine clinical interpretation needed for appropriate care of pts w/kidney diseases”
    K/DOQI

Monitoring Vitamin D Therapy

- Serum Ca & PO₄ every month for the 1st 3 months, then every 3 months (opinion)
- PTH every 3 months (opinion)
Vitamin D Dose Adjustments

- If iPTH below target i.e risk of adynamic bone disease (or if serum Ca > 9.5 mg/dl):
  - Hold vitamin D until iPTH increase to above target range (or serum Ca returns to < 9.5 mg/dl), then resume half the dose of vitamin D. If the lowest dose is being used, then reduce to alternate-day dosing (opinion)
Vitamin D Dose Adjustments

- If serum $PO_4$ increases to $>4.6 \text{ mg/dl}$, hold vitamin D therapy, begin or increase dose of phosphate binder until serum $PO_4$ decreases to $< 4.6 \text{ mg/dl}$, then resume prior dose of vitamin D (opinion)
Mortality risk among HD patients receiving different vitamin D analogs

- Mortality rates were similar for paricalcitol vs doxercalciferol.
- Mortality was lower in paricalcitol and doxercalciferol vs calcitriol ($P < 0.05$).
- Mortality was higher in pts not on vita D analogs vs pts on vita D analogs ($P < 0.05$).

Kidney Int 2006;70:1858-1865
What’s new?

Calcimimetic agents
Calcium-Sensing Receptor

- Found in high concentrations on the surface of PTH cells
  - When activated by increased extracellular Ca, the calcium-sensing receptor signals the cell by means of a G-protein transducing pathway to raise the intracellular Ca concentration
  - Modulates PTH secretion
  - Activation by small changes in extracellular [iCa] -> steep inverse relationship w/PTH
Calcimimetics

- Acquired alterations in the expression of the calcium-sensing receptor (CaR) may play a role in the pathogenesis of hyperPTH.

- Calcimimetics
  - Modulate the calcium sensing receptor, making it more sensitive to calcium, leading to suppression of PTH secretion.
  - Enhances the affinity of CaR for Ca and reduces PTH secretion.
Calcimimetics

- In general,
  - Effects occur within 1-2 hours after administration
  - Fall in [PTH] is dose-dependent
  - PTH returns to baseline within 4-24 hours
  - Observe a decline in plasma Ca following decline in [PTH]
    - Can result in clinical symptoms
    - Seen with larger doses
Achieving NKF-K/DOQI Goals with Cinacalcet (Sensipar)

- Data were combined from 3 placebo-controlled, double-blind, 26 wk studies
- n = 1136 HD pts w/secondary hyperparathyroidism
- Randomized to receive traditional therapy with cinacalcet or placebo
  - Initial cinacalcet dose 30 mg po daily (max 180 mg)
- Continued concomitant meds: Vitamin D, phosphate binders, Ca supplements
  - Moe SM et al KI 2005;67:760-71
**iPTH**

- **iPTH** = intact PTH
- **BL** = baseline
- **Shaded region** = K/DOQI target range

![Graph showing iPTH levels over weeks for Cinacalcet and Control groups]

- **Cinacalcet N: 663**
  - Week 2: 547 pg/mL
  - Week 26: 473 pg/mL
- **Control N: 471**
  - Week 2: 410 pg/mL
  - Week 26: 366 pg/mL
Serum phosphorous

- BL = baseline
- Shaded region = K/DOQI target range
Serum calcium

- BL = baseline
- Shaded region = K/DOQI target range
Ca x P

- Ca x P = calcium x PO$_4$ product
- BL = baseline
- Shaded region = K/DOQI target range
## NKF K/DOQI Goal Conc.

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<tr>
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<tr>
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<td>&lt;55</td>
<td>&lt;55</td>
<td>&lt;55</td>
</tr>
</tbody>
</table>
Achievement of K/DOQI Targets:
Study A: 12 week dose titration; 14 week efficacy assessment (US, Canada)
Achievement of K/DOQI Targets:
Study B: 12 week dose titration; 14 week efficacy assessment (Europe, Australia)
Achievement of K/DOQI Targets:
Study C: 16 week dose titration; 10 week efficacy assessment (US, Canada, Australia)
2 targets: \( PTH \leq \) & \( \text{CaxP} < 55 \)
<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Cinacalcet</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ca &lt; 7.5 mg/dl</td>
<td>5%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Low Ca rarely associated w/symptoms &amp; returned to values &gt; 8.0 w/adjustment of all meds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>31%</td>
<td>19%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27%</td>
<td>15%</td>
</tr>
<tr>
<td>Serious events</td>
<td>29%</td>
<td>31% $p &gt; 0.05$</td>
</tr>
<tr>
<td>Study withdrawal (N/V)</td>
<td>15%</td>
<td>8%</td>
</tr>
<tr>
<td>Deaths (all not related to drug)</td>
<td>2%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Parathyroidectomy

- **Indications:**
  - Persistent hypercalcemia
    - Serum [Ca] > 11.5 mg/dl
    - Occurs because of large doses of calcitriol analogs needed to suppress PTH
  - Persistently elevated Ca x PO$_4$ product & progressive soft tissue calcification despite agents to lower PO$_4$
  - Progressive radiographic lesions & Sx of bone dz associated with hyperPTH
Parathyroidectomy

Indications

- Uncontrolled bone dz associated with debilitating sx
- Intractable pruritis
  - Calcifications under the skin
- Syndrome of calciphylaxis (rare)
  - Vascular calcification causing ischemic necrosis of skin, muscle, and or subcutaneous fat
Procedure

- **Subtotal parathyroidectomy**
  - Resection of $3 \frac{1}{2}$ of 4 parathyroid glands
  - Leave 50 g of one viable gland in place

- **Total parathyroidectomy with forearm autograft**
  - Removal of all 4 parathyroid glands
  - Autotransplanting 1 gland into the forearm
    - Accessible site
Post Op

- Marked increase in bone production
  - “Hungry bone syndrome”
  - Hypocalcemia
  - Hypophosphatemia
  - Hypomagnesemia

- Treatment with supplemental calcium and calcitriol may be necessary for week-months