Vitamin D and Pediatric Chronic Kidney Disease

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Objectives

1. Describe vitamin D metabolism and deficiency.

2. Understand disturbances in vitamin D metabolism in Chronic Kidney Disease (CKD).

3. Examine pediatric data.

4. Summarize the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for vitamin D in children with CKD.
Outline

• Overview of Vitamin D
• Vitamin D and Chronic Kidney Disease
• KDOQI Clinical Practice Guideline
  • Bone mineral and vitamin D requirements
• Overview of Vitamin D

• Vitamin D and Chronic Kidney Disease

• KDOQI Clinical Practice Guideline
  • Bone mineral and vitamin D requirements
What is vitamin D?

The body itself makes vitamin D when it is exposed to the sun.

Cheese, butter, margarine, fortified milk, fish, and fortified cereals are food sources of vitamin D.
Why do we need vitamin D?

- Building & keeping strong bones
- Controlling calcium & phosphorus levels
- May have other benefits
  - Increasing immunity
  - Preventing heart disease & cancer
# Recommended Dietary Allowances (RDAs) for Vitamin D

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–12 months</td>
<td>400 IU (10 mcg)</td>
<td>400 IU (10 mcg)</td>
</tr>
<tr>
<td>1–13 years</td>
<td>600 IU (15 mcg)</td>
<td>600 IU (15 mcg)</td>
</tr>
<tr>
<td>14–18 years</td>
<td>600 IU (15 mcg)</td>
<td>600 IU (15 mcg)</td>
</tr>
<tr>
<td>19–50 years</td>
<td>600 IU (15 mcg)</td>
<td>600 IU (15 mcg)</td>
</tr>
<tr>
<td>51–70 years</td>
<td>600 IU (15 mcg)</td>
<td>600 IU (15 mcg)</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>800 IU (20 mcg)</td>
<td>800 IU (20 mcg)</td>
</tr>
</tbody>
</table>
## Selected Food Sources of Vitamin D

<table>
<thead>
<tr>
<th>Food</th>
<th>IUs per serving</th>
<th>Percent DV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cod liver oil, 1 tablespoon</td>
<td>1,360</td>
<td>340</td>
</tr>
<tr>
<td>Swordfish, cooked, 3 ounces</td>
<td>566</td>
<td>142</td>
</tr>
<tr>
<td>Salmon (sockeye), cooked, 3 ounces</td>
<td>447</td>
<td>112</td>
</tr>
<tr>
<td>Tuna fish, canned in water, drained, 3 ounces</td>
<td>154</td>
<td>39</td>
</tr>
<tr>
<td>Orange juice fortified with vitamin D, 1 cup (check product labels, as amount of added vitamin D varies)</td>
<td>137</td>
<td>34</td>
</tr>
<tr>
<td>Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup</td>
<td>115-124</td>
<td>29-31</td>
</tr>
<tr>
<td>Yogurt, fortified with 20% of the DV for vitamin D, 6 ounces (more heavily fortified yogurts provide more of the DV)</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Margarine, fortified, 1 tablespoon</td>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>Sardines, canned in oil, drained, 2 sardines</td>
<td>46</td>
<td>12</td>
</tr>
<tr>
<td>Liver, beef, cooked, 3 ounces</td>
<td>42</td>
<td>11</td>
</tr>
<tr>
<td>Egg, 1 large (vitamin D is found in yolk)</td>
<td>41</td>
<td>10</td>
</tr>
<tr>
<td>Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 0.75-1 cup (more heavily fortified cereals might provide more of the DV)</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Cheese, Swiss, 1 ounce</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>
Sun Exposure

• **Recommendations for sufficient vitamin D synthesis**
  - Approximately 5–30 minutes
  - Between 10 AM and 3 PM
  - At least twice a week
  - To the face, arms, legs, or back without sunscreen
Synthesis and Metabolism of Vitamin D

(1) Dermal Synthesis

(2) Nutrition

(5) Liver:
Vit D → Vit D-25 hydroxylase → 25(OH)D

(6) Determine Status

(4) DBP Transport

(7) Kidney:
25(OH)D → (1α-OHase) → 1,25(OH)₂D (active)

Majority of circulating 1,25
• >99% of circulating 25(OH)D and 1,25(OH)$_2$D are bound

• Proteinuric patients have urinary loss of vitamin D binding protein (DBP) and albumin

• Total serum 25(OH)D levels, the conventional index of vitamin D status, may not reflect free or bioavailable vitamin D in the setting of ↓ serum DBP and albumin

\[
\text{Free 25(OH)D} = \frac{\text{total 25(OH)D}}{1 + (6 \times 10^3 \times \text{albumin}) + (7 \times 10^8 \times \text{DBP})}
\]

Bikle et al. J Clin Endocrinol Metab 1986
Vitamin D Binding Protein

- VitD-DBP complexes are freely filtered by the glomerulus
- VitD-DBP complexes are reabsorbed via megalin/cubilin-mediated endocytosis in the proximal tubule
  - along with numerous other ligands

Other ligands:
- Albumin
- PTH
- Retinol binding protein
- B₂-microglobulin
- α1-microglobulin

Kidney: Phos, Ca, FGF-23 ↓ or ↑ 1,25

Bone:
1,25 anabolic & catabolic actions

catabolic → osteoclasts remove Ca & Phos to maintain serum Ca & Phos

adequate Ca & Phos promote skeletal mineralization

Parathyroid:
PTH stimulates 25 → 1,25 & inhibits 24-OHase

Negative feedback:
↑1,25 → ↓PTH & stimulates 24-OHase to catabolize 1,25 → calcitriol acid

Intestine: Ca absorption by interaction with VDR-RXR → ↑ TRPV6 (Ca Channel) & CaBP

Holick, M. NEJM 2007
Vitamin D promotes the body's absorption of calcium, essential to development of healthy bones and teeth.

DRI: 5 µg
Fat-soluble
• Extra skeletal actions of vitamin D
  - Many cells have the VDR and the 1α-OHase
    • Breast, colon, pancreas, prostate
    • Immune cells (monocyte, macrophage, lymphocyte)
      ✓ **Innate and acquired immunity**
      ✓ **Autoimmune disease (MS, IBD, Type 1 diabetes)**

• Locally produced 1,25(OH)$_2$ vitamin D
  - Does not enter the circulation
  - Is not regulated by PTH
  - Does not affect calcium metabolism
  - Local and intracellular levels may exceed 100-1000 times circulating levels

Holick, M. NEJM 2007
Extra Skeletal Actions of Vitamin D

1,25 (OH)\textsubscript{2}D does not enter the circulation

Required for local synthesis of 1,25 (OH)\textsubscript{2}D
Burden of Vitamin D Deficiency

• 25(OH)D of 20 ng/ml
  - Meets the requirements of ≥ 97.5% of the population

• Based solely on classical skeletal actions

• Stressed that further research is needed to define the requirements for other facets of health
A deficiency of vitamin D or an inability to utilize vitamin D may lead to a condition called rickets, a weakening and softening of the bones brought on by extreme calcium loss.
Nutritional Rickets

• 1st clinical description 350 years ago by Francis Glisson

• Rachitis derived from Greek for spine

• Old English “wrickken” – to twist

• 200 years later cod liver oil and sunlight shown to prevent → 1928 Nobel Prize to Adolf Windaus
Nutritional Rickets

• Development of rickets depends on:
  - Duration and severity of vitamin D deficiency
  - Growth rate
  - Dietary Calcium intake

• Biochemical Findings:
  - Normal Serum Calcium
  - ↓ Serum Phosphorus
  - Normal or ↑ 1,25(OH)₂D
Rickets

Figure 1: Radiograph of wrist showing rickets
Classic features of rickets include cupping, fraying, and spaying of the metaphysis. The ulna (which grows more quickly at its distal end) is more severely affected. Widening of the growth plates is not shown because the secondary ossification centres of the radius and ulna are not yet apparent.

Wharton and Bishop. Lancet 2003

Tiosano and Hochberg. J Bone Miner Metab 2009
Burden of Vitamin D Deficiency

• Highly prevalent in children and adults worldwide

• Adverse effects are now known to extend far beyond bone and mineral metabolism:
  - Mortality
  - Cardiovascular disease
  - Insulin resistance
  - Autoimmune disease
  - Infection
  - Inflammation
Outline

- Overview of Vitamin D
- Vitamin D and Chronic Kidney Disease
- KDOQI Clinical Practice Guideline
  - Bone mineral and vitamin D requirements
CKD MBD

• CKD – Mineral and Bone Disorder (MBD)
  - A systemic disorder of mineral and bone metabolism caused by CKD and manifested by either one or a combination of:
    • Abnormalities of Ca, Phos, PTH, or Vit D metabolism
    • Abnormalities of bone turnover, mineralization, volume, linear growth, or strength
    • Vascular or soft tissue calcification

• Renal Osteodystrophy
  - An alteration of bone morphology in patients with CKD
  - It is one measurement of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy

CKD MBD & Vitamin D

(1) ↓ Dermal Synthesis

(2) Nutritional D Deficiency

(3) ↓ Activation of 25(OH)D → 1,25(OH)₂D

(4) ↑ Phos

(5) ↓ Ca Absorption

(6) ↑ PTH due to (4) and (5)

(7) ↑ FGF23

Holick, M. NEJM 2007
CKD Risk Factors

- **Risk Factors for lower 25(OH)D**
  - Decreased sunlight exposure
  - Less efficient dermal synthesis of Vitamin D$_3$
  - Dietary restrictions
  - Proteinuria – urinary losses of DBP & albumin

- **Risk Factors for lower 1,25(OH)$_2$D**
  - Lower substrate
  - Proximal tubal injury in the kidney
  - Increased FGF 23
- **Inhibits 1-α-OHase activity**
  - Needed to convert 25(OH)D → 1,25(OH)₂D

- **Induces 24-OHase activity**
  - Responsible for catabolism of 25(OH)D and 1,25(OH)₂D

\[ \text{FGF 23} = \text{1-α-OHase activity} \downarrow \text{24-OHase activity} \]
• Extra Skeletal

- Vitamin D deficiency linked to mortality and complications in CKD including:
  • Insulin Resistance
  • Anemia
  • Inflammation

- In prospective studies of adults with CKD, low serum 25(OH)D concentration was an independent predictor of CKD progression and mortality
Vitamin D Renoprotective

• Vitamin D deficiency may also contribute to podocyte injury and development of proteinuria

• Animal studies: treatment with activated vitamin D
  - Inhibited the renin-angiotensin system
  - Prevented podocyte loss and glomerulosclerosis
  - Reduced hypoalbuminemia

Vitamin D Renoprotective

- Normal 25 (OH) D ≥ 50 ng/ml associated with:
  - Decreased Proteinuria
  - Greater preservation of renal function

- Analysis of 3 RCT evaluating safety and efficacy of paracalcitol in CKD stages 3-4
  - Proteinuria

- Subsequent RCT CKD stages 2-3
  - Hypoalbuminemia

Prevalence of Insufficiency

- Insufficiency is common in children with CKD
- **16-30 ng/mL = vitamin D insufficiency**

<table>
<thead>
<tr>
<th>Author/Journal</th>
<th>Year</th>
<th>n</th>
<th>25(OH)D</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menon et al. Peds Neph</td>
<td>2008</td>
<td>57</td>
<td>&lt; 30 ng/mL</td>
<td>77.2 %</td>
</tr>
<tr>
<td>Hari et al. Peds Neph</td>
<td>2010</td>
<td>42</td>
<td>&lt; 30 ng/mL</td>
<td>82.1 %</td>
</tr>
<tr>
<td>Ali et al. Pediatrics</td>
<td>2009</td>
<td>88</td>
<td>&lt; 32 ng/mL</td>
<td>72 %</td>
</tr>
<tr>
<td>Seeherunvong et al. J.Pediatrics</td>
<td>2009</td>
<td>258</td>
<td>&lt; 30 ng/mL</td>
<td>60 %</td>
</tr>
<tr>
<td>Belostotsky et al. Arch Dis Child</td>
<td>2008</td>
<td>143</td>
<td>&lt; 30 ng/mL</td>
<td>83.2 %</td>
</tr>
</tbody>
</table>
## Prevalence of Deficiency

- **Deficiency is common in children with CKD**
- **5-15 ng/mL = vitamin D deficiency**

<table>
<thead>
<tr>
<th>Author/Journal</th>
<th>Year</th>
<th>n</th>
<th>25(OH)D</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menon et al. Peds Neph</td>
<td>2008</td>
<td>57</td>
<td>5-15 ng/mL</td>
<td>21.1 %</td>
</tr>
<tr>
<td>Hari et al. Peds Neph</td>
<td>2010</td>
<td>42</td>
<td>&lt; 16 ng/mL</td>
<td>42.8 %</td>
</tr>
<tr>
<td>Ali et al. Pediatrics</td>
<td>2009</td>
<td>88</td>
<td>&lt; 15 ng/mL</td>
<td>39 %</td>
</tr>
<tr>
<td>Seeherunvong et al. J.Pediatrics</td>
<td>2009</td>
<td>258</td>
<td>&lt; 20 ng/mL</td>
<td>28 %</td>
</tr>
<tr>
<td>Belostotsky et al. Arch Dis Child</td>
<td>2008</td>
<td>143</td>
<td>&lt; 20 ng/mL</td>
<td>58 %</td>
</tr>
</tbody>
</table>
Vitamin D and CKD

• 182 children with CKD vs. 276 healthy controls
  - In children with ↓ 25(OH)D concentration
• No apparent difference in 25 (OH) D concentrations between early –stage CKD and healthy children

Kalkwarf et al. Kidney Int 2012
• Statistically significant interaction between 25(OH)D concentration and CKD stage for predicting 1,25(OH)$_2$D concentrations (p<0.0001)

• For a 1 ng/ml increase in 25(OH)D concentration, 1,25(OH)$_2$D concentrations increased as follows:
  - Healthy 0.4% (n=275, p=0.01)
  - CKD 2/3 0.7% (n=57, p=0.04)
  - CKD 4/5 4.2% (n=14, p=0.006)
  - CKD 5D 2.3% (n=8, p=0.15)

Kalkwarf et al. Kidney Int 2012
25(OH) D
- Positively associated with 1,25(OH)₂D
- Inversely related to Intact PTH & inflammatory markers CRP, IL-6

Conclusion

\[ 25\text{(OH)}D = 1,25\text{(OH)}_2D \uparrow \]

\[ \text{PTH & Inflammation} \downarrow \]
Hypoalbuminemia and glomerular disease were independent risk factors for Vitamin D deficiency
- Adjusted for age, race, season and CKD stage

Adjusted mean 25(OH) D by diagnosis (p<0.0001):

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mean 25(OH) D (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAKUT (congenital abnormalities of the kidney and urinary tract)</td>
<td>24.8</td>
</tr>
<tr>
<td>Systemic inflammatory disease/glomerulonephritis</td>
<td>19.2</td>
</tr>
<tr>
<td>FSGS (focal segmental glomerulosclerosis)</td>
<td>14.6</td>
</tr>
<tr>
<td>Other</td>
<td>25.5</td>
</tr>
</tbody>
</table>

Adjusted mean 25(OH) D by albumin <3 vs. ≥3
- 11.1 vs. 23.5 ng/ml (p<0.0001)
**Vitamin D Supplementation**

- If the serum level of 25-hydroxyvitamin D is less than 30 ng/mL, supplementation with vitamin D$_2$ (ergocalciferol) or vitamin D$_3$ (cholecalciferol) is suggested.

<table>
<thead>
<tr>
<th>Author/Journal</th>
<th>Year</th>
<th>n</th>
<th>Supplement</th>
<th>25 (OH)</th>
<th>PTH</th>
<th>Ca &amp; Phos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menon et al. Peds Neph</td>
<td>2008</td>
<td>22</td>
<td>2000 - 4000 IU D$_2$</td>
<td>n/a</td>
<td>↓</td>
<td>No elevated levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Per day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hari et al. Peds Neph</td>
<td>2010</td>
<td>42</td>
<td>600,000 IU D$_3$</td>
<td>↑</td>
<td>↓</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shroff et al. CJASN</td>
<td>2012</td>
<td>47</td>
<td>50,000 IU D$_2$</td>
<td>n/a</td>
<td>Delayed hyperpara onset</td>
<td>No elevated levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Per KDOQI</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

National Kidney Foundation 2009
• **Cholecalciferol** (D$_3$) is Superior to **Ergocalciferol** (D$_2$)
  - Cholecalciferol appears to have higher bioefficacy than ergocalciferol
  - Greater increases in 25(OH) vitamin D levels with cholecalciferol
  - Cholecalciferol maintains higher levels of 25(OH)-vitamin D over time
  - Greater efficacy may be related to higher affinities to hepatic 25-hydroxylase, DBP, VDR, and differences in deactivation
Vitamin D Supplementation

- **Ergocalciferol (Vitamin D$_2$)**
  - 50,000 IU capsules - 100 capsules
    - $143.40
  - Liquid 800 IU/mL - 60 mL
    - $110.82

- **Cholecalciferol (Vitamin D$_3$)**
  - 10,000 IU capsules - 100 capsules
    - $4.34
  - Liquid 2000 IU per drop – 30 mL
    - $11.39
• FDA does not routinely review the manufacturing of dietary supplements, and therefore cannot guarantee their safety and effectiveness.

• Rely on different certifying organizations:
  - U.S. Pharmacopeial Convention (USP)
    • Products voluntarily submitted → meet stringent testing & auditing criteria
  - NSF or National Products Association
    • Third party organizations → have processes set up for facility & product inspection

• Products not certified by USP → require certificates of analysis (COA)
  - Confirm whether or not the dosage matches label
Vitamin D Supplementation

- Initiate therapy with active vitamin D sterol (calcitriol)
  - CKD Stages 2-4
    - 25 (OH) D >30 ng/mL and serum levels of PTH are above target range for CKD stage
  - CKD Stage 5
    - PTH > 300 pg/mL

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>GFR Range (mL/min/1.73 m²)</th>
<th>Target Serum PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>60-89</td>
<td>35-70 pg/mL (OPINION)</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>35-70 pg/mL (OPINION)</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>70-110 pg/mL (OPINION)</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 or dialysis</td>
<td>200-300 pg/mL (EVIDENCE)</td>
</tr>
</tbody>
</table>
• Use activated vitamin D to decrease PTH
  - Activated Vitamin D
    • Limited by ↑Ca & ↑Phos
      ✓ Calcitriol
      ✓ Alfacalcidol
  - Vitamin D Analogs
    • Minimize intestinal Ca & Phos absorption
      ✓ Paricalcitol
      ✓ Doxercalciferol
  - Calcimimetics
    • Mimics calcium at the CaSR in the parathyroid glands
      ✓ Cinacalcet
Vitamin D Supplementation

- **Calcitriol**
  - 0.25 mcg capsules - 30 capsules
    - $57.59

- **Paricalcitol**
  - 1 mcg capsules – 30 capsules
    - $264.67

- **Doxercalciferol**
  - 0.5 mcg - 50 capsules
    - $366.31

- **Cinacalcet**
  - 30 mg capsules – 30 capsules
    - $1084.83
Outline

• Overview of Vitamin D
• Vitamin D and Chronic Kidney Disease
• KDOQI Clinical Practice Guideline
  • Bone mineral and vitamin D requirements
• Total oral and/or enteral calcium intake from nutritional sources and phosphate binders should be in the range of 100% to 200% of the DRI for calcium for age.

• Intestinal calcium absorption is impaired in CKD because $1,25(OH)_2D$ production decreased

• Stimulate calcium absorption with vitamin D therapy

• Must also worry about excessive calcium load
  - Phosphate binders
  - High doses of calcitriol
  - Absorption from dialysis fluids
### Table 20. Recommended Calcium Intake for Children with CKD Stages 2 to 5 and 5D

<table>
<thead>
<tr>
<th>Age</th>
<th>DRI</th>
<th>Upper Limit (for healthy children)</th>
<th>Upper Limit for CKD Stages 2-5, 5D (Dietary + Phosphate Binders*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mo</td>
<td>210</td>
<td>ND</td>
<td>≤420</td>
</tr>
<tr>
<td>7-12 mo</td>
<td>270</td>
<td>ND</td>
<td>≤540</td>
</tr>
<tr>
<td>1-3 y</td>
<td>500</td>
<td>2,500</td>
<td>≤1,000</td>
</tr>
<tr>
<td>4-8 y</td>
<td>800</td>
<td>2,500</td>
<td>≤1,600</td>
</tr>
<tr>
<td>9-18 y</td>
<td>1,300</td>
<td>2,500</td>
<td>≤2,500</td>
</tr>
</tbody>
</table>

Abbreviation: ND, not determined.

* Determined as 200% of the DRI, to a maximum of 2,500 mg elemental calcium.
Phosphorus

• Suggested to reduce dietary phosphorus intake to 100% of the DRI for age when serum PTH concentration is above target range for CKD stage and serum phosphorus concentration is within normal range for age.

• Suggested to reduce dietary phosphorus intake to 80% of the DRI for age when the serum PTH concentration is above target range for CKD stage and serum phosphorus exceeds normal range for age.

• Monitor serum phosphorus every 3 months in CKD stages 3 to 4 and monthly in CKD stages 5 and 5D.

• In all CKD stages, avoid serum phosphorus levels both above and below the normal reference range for age.
### Table 23. Recommended Maximum Oral and/or Enteral Phosphorus Intake for Children With CKD

<table>
<thead>
<tr>
<th>Age</th>
<th>DRI (mg/d)</th>
<th>High PTH and Normal Phosphorus*</th>
<th>High PTH and High Phosphorus†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mo</td>
<td>100</td>
<td>≤100</td>
<td>≤80</td>
</tr>
<tr>
<td>7-12 mo</td>
<td>275</td>
<td>≤275</td>
<td>≤220</td>
</tr>
<tr>
<td>1-3 y</td>
<td>460</td>
<td>≤460</td>
<td>≤370</td>
</tr>
<tr>
<td>4-8 y</td>
<td>500</td>
<td>≤500</td>
<td>≤400</td>
</tr>
<tr>
<td>9-18 y</td>
<td>1,250</td>
<td>≤1,250</td>
<td>≤1,000</td>
</tr>
</tbody>
</table>
Vitamin D

• When should 25 (OH) D be measured?

    • Only if PTH elevated for CKD Stage

  - KDOQI Ped Nutrition Update (2009)
    • CKD 2-5 Measure annually
• KDOQI Ped Bone Guidelines (2005)
  - CKD Stages 2-4
    • If PTH > target range, serum 25 (OH) D levels should be measured
    • If 25 (OH) < 30 ng/mL → supplement with vitamin D
    • If serum levels of PTH are above the target range for the CKD stage & when serum levels of 25(OH)D are >30 ng/mL → initiate therapy with active vitamin D
  
  - CKD Stage 5
    • If PTH > 300 pg/mL → initiate therapy with active vitamin D sterol
In CKD patients, Stages 2-4, with stable renal function, compliant with visits and medications with serum phosphorus levels < upper target value, calcium <10 mg/dL (2.5 mmol/L), and 25(OH)D ≥30 ng/mL (75 nmol/L)

- Measure serum PTH

  - Is serum PTH >70 pg/mL (7.7 pmol/L) (Stage 2) or >110 pg/mL (12.1 pmol/L) (Stage 4)?
    - No → Monitor according to Guideline 1
    - Yes → See Guideline 9A

  - Hold or reduce vitamin D dose

  - Measure serum P and Ca

  - Is serum Ca <10 mg/dL (2.5 mmol/L)?
    - No → Initiate or increase phosphate binder (Guideline 5) or restrict dietary phosphate (Guideline 4)
    - Yes → Stop or reduce dose of Ca-based phosphate binder (Guideline 6), or reduce Ca supplements

  - Is serum P < upper target value?
    - No → Continue oral dose of vitamin D sterol
    - Yes → Measure serum PTH

- <35 pg/mL (3.85 pmol/L) (Stages 2-3), or <70 pg/mL (7.7 pmol/L) (Stage 4)

- ≥35 pg/mL (3.85 pmol/L) (Stage 3), or ≥70 pg/mL (7.7 pmol/L) (Stage 4)
Table 16. Serum Levels of PTH, Calcium, and Phosphate Required for Initiation of Oral Vitamin D Sterol Therapy, and Recommended Initial Doses in Patients with CKD Stages 2-4

<table>
<thead>
<tr>
<th>Serum PTH (pg/mL or ng/L)</th>
<th>Serum Ca (mg/dL) [mmol/L]</th>
<th>Serum P (mg/dL) [mmol/L]</th>
<th>Dose Oral Calcitriol</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;70 (CKD Stage 2.3)</td>
<td>&lt;10 [2.37]</td>
<td>≤ age-appropriate levels</td>
<td>&lt;10 kg: 0.05 μg every other day</td>
</tr>
<tr>
<td>&gt;110 (CKD Stage 4)</td>
<td>&lt;10 [2.37]</td>
<td>≤ age-appropriate levels</td>
<td>10-20 kg: 0.1-0.15 μg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;20 kg: 0.25 μg/day</td>
</tr>
</tbody>
</table>

Table 17. Initial Calcitriol Dosing Recommendations for Children on Maintenance Dialysis

<table>
<thead>
<tr>
<th>Serum PTH (pg/mL)</th>
<th>Serum Ca (mg/dL) [mmol/L]</th>
<th>Serum P (mg/dL) [mmol/L]</th>
<th>CaXP*</th>
<th>Calcitriol Dose per HD Session</th>
<th>Calcitriol Dose for Patients Receiving PD (TIW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300-500</td>
<td>&lt;10 [2.37]</td>
<td>&lt;5.5 [1.78] for adolescents</td>
<td>&lt;55 for adolescents &lt;65 for infants and children</td>
<td>0.0075 μg/kg (maximum = 0.25 μg/kg) qd</td>
<td>0.0075 μg/kg (maximum = 0.25 μg/kg) qd</td>
</tr>
<tr>
<td>&gt;500-1000</td>
<td>&lt;10 [2.37]</td>
<td>&lt;5.5 [1.78] for adolescents</td>
<td>&lt;55 for adolescents &lt;65 for infants and children</td>
<td>0.015 μg/kg (maximum = 0.5 μg/kg) qd</td>
<td>0.015 μg/kg (maximum = 0.5 μg/kg) qd</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>10.5 [2.50]</td>
<td>&lt;5.5 [1.78] for adolescents</td>
<td>&lt;55 for adolescents &lt;65 for infants and children</td>
<td>0.025 μg/kg (maximum = 1 μg/kg) qd</td>
<td>0.025 μg/kg (maximum = 1 μg/kg) qd</td>
</tr>
</tbody>
</table>

HD  Hemodialysis, thrice weekly (TIW)
Pd  Peritoneal dialysis, thrice weekly (TIW)
*  <65 in children below 12 years of age
- Serum 25-hydroxyvitamin D levels must be measured once per year.

- If the serum level of 25-hydroxyvitamin D is < 30 ng/mL, supplementation with vitamin D₂ (ergocalciferol) or vitamin D₃ (cholecalciferol) is suggested.

- In the repletion phase, it is suggested that serum levels of corrected calcium and phosphorus be measured at 1 month following initiation or change in dose of vitamin D and at least every 3 months thereafter.

- When patients are replete, supplement vitamin D continuously and monitor levels yearly.
Vitamin D

• Levels < 5 ng/mL = severe vitamin D deficiency
  - Osteomalacia
  - Hypocalcemia

• Levels 5-15 ng/mL = mild vitamin D deficiency
  - Increased risk of bone demineralization and fractures

• Levels 16-30 ng/mL = vitamin D insufficiency
  - Hyperparathyroidism
# Vitamin D

## Table 22. Recommended Supplementation for Vitamin D Deficiency/Insufficiency in Children with CKD

<table>
<thead>
<tr>
<th>Serum 25(OH)D (ng/mL)</th>
<th>Definition</th>
<th>Ergocalciferol (Vitamin D$_2$) or Cholecalciferol (Vitamin D$_3$) Dosing</th>
<th>Duration (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>Severe vitamin D deficiency</td>
<td>8,000 IU/d orally or enterally $\times$ 4 wk or (50,000 IU/wk $\times$ 4 wk); then 4,000 IU/d or (50,000 IU twice per mo for 2 mo) $\times$ 2 mo</td>
<td>3</td>
</tr>
<tr>
<td>5-15</td>
<td>Mild vitamin D deficiency</td>
<td>4,000 IU/d orally or enterally $\times$ 12 wk or (50,000 IU every other wk, for 12 wk)</td>
<td>3</td>
</tr>
<tr>
<td>16-30</td>
<td>Vitamin D insufficiency</td>
<td>2,000 IU daily or (50,000 IU every 4 wk)</td>
<td>3</td>
</tr>
</tbody>
</table>
Summary

• Vitamin D is a key player in normal calcium and phosphorus homeostasis that involves a complex interplay between the kidney, parathyroid, intestine, and bone.

• CKD presents unique disturbances in vitamin D metabolism.

• Sufficient Vitamin D prevents skeletal deformities and has extra-skeletal benefits.

• National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for vitamin D in children with CKD are available.
Questions?