Vitamin D Deficiency

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Objectives
- Review vitamin D physiology
- Review recent guidelines
- Discuss deficiency
- Examine dosing
  - Maintenance
  - For deficiency
- Vitamin D toxicity

Key Questions?
- What is the optimal vitamin D level?
- How much vitamin D should we advise our patients to take?
- Did you know?
  Chemically Vitamin D is a steroid (hormone) not a vitamin!

Nomeclature
- Calciferol
- Calcidiol
- Cholecalciferol
- Calcitriol
- Ergocalciferol
- 7-dehydrocholesterol
- 25-hydroxyvitamin D
- 1,25-dihydroxyvitamin D
Vitamin D: Summary

- Vitamin D2 and D3: Precursors
- 25-Hydroxy vitamin D$_3$ (25(OH)D)
  - Storage form of vitamin (~3 months storage in liver)
- 1,25-dihydroxy vitamin D$_3$
  - Active form of vitamin D

  - Functions
    - Calcium metabolism: enhances Ca absorption in the gut & renal tubules.
    - Phosphorus: enhances PO$_4$ absorption in the gut & kidney.
    - Cell differentiation: particularly of collagen & skin epithelium.
    - Immunity: important for cell mediated immunity & immune response.
    - Regulation of gene expression: multiple tissues

Vitamin D Deficiency Causes

- Inadequate intake
- Low exposure to sunshine
  - Inside
  - Dark skin pigmentation
  - Sunscreen
- Diseases and Drug:
  - Liver and renal diseases
  - Gastrointestinal diseases (malabsorption)
  - Antiepileptic medications
  - Glucocorticosteroid

Vitamin D Receptor Sites

- Skin
- Brain
- Spinal cord
- Pituitary
- Salivary glands
- Nasal–oral mucosa
- Teeth
- Parathyroid
- Thyroid
- Thymus
- Lung
- Heart
- Spleen
- Pancreas
- Adrenal
- Kidney
- Esophagus
- Stomach
- Pylorus
- Small intestine
- Large intestine
- Testes
- Prostate
- Bone
- Others

Relative Risk for Cause Specific Mortality

Epidemiology: Other Cardiovascular Risks Associated with Low Vitamin D Levels

- Hypertension (NHANES)
- Peripheral artery disease (NHANES)
- Heart failure and sudden death
  J Clin Endocrinol Metab. 2008;93:3927-3935.
- Stroke
Vitamin D and Immunity

- Epidemic influenza and vitamin D.
  - 1,25(OH)2D acts as an immune modulator
  - Examines seasonal variability of incidence and morbidity of influenza and vitamin D levels

- Association between serum 25-OH D level and URI in the 3rd NHANES.
  - 25(OH)D levels inversely associated with recent URI

1,25(OH)2D acts as an immune modulator

Respiratory Infections and Vitamin D Levels

Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use

Vitamin D Adequacy (or Deficiency)

<table>
<thead>
<tr>
<th>Definitions (units: ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-OH D</td>
</tr>
<tr>
<td>UK</td>
</tr>
<tr>
<td>Deficiency</td>
</tr>
<tr>
<td>Insufficiency</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Optimal</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Possible toxicity</td>
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</tbody>
</table>

Vitamin D Adequacy (or Deficiency)

- Methods used to define: optimal 25(OH)D
  - Level that maximally suppresses PTH secretion
  - Level that results in maximal intestinal calcium absorption
  - Level at which 1,25(OH)2D does not increase with administration of extra vitamin D
  - ? Non-skeletal health outcomes

Studies Demonstrating PTH Plateaus at Various Serum 25OHD Levels

- < 12 ng/dL: one
- < 20 ng/dL: 4 Level defined as deficient (IOM)
- < 30 ng/dL: 3
- ~ 35 ng/dL: 1
- 40 – 50 ng/dL: 2
- No plateau or no relationship: 3

2011 IOM Report on Vitamin D
2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine

- Intake requirements determined based on skeletal health
- Evidence insufficient to address requirements for extraskeletal outcomes.
- Recommended Dietary Allowances (RDAs)
  - Meets requirements of at least 97.5% of the population
- Tolerable upper intake level (UL)
  - Highest daily that is likely to pose no risk
- Adequate Intake (AI)
  - Insufficient evidence to establish RDA or estimated average requirement (EAR)

For calcium and vitamin D, the RDAs and AI are based on the needs of the population. The UL is the highest intake level that is unlikely to cause adverse effects.

Major Differences Between IOM and Endocrine Society Guidelines

- Target 25(OH)D level
  - IOM: above 20 ng/mL
  - ES: above 30 ng/mL

“A clinical approach of targeting a higher 25(OH)D value seems prudent in that improving vitamin D status should reduce multiple adverse consequences of vitamin D deficiency at extremely low cost with minimal toxicity risk.”

Vitamin D Intakes Recommended by the IOM and the Endocrine Practice Guidelines Committee

For infants, children, adults, and pregnant or lactating women, the RDA, AI, and UL for vitamin D intake are provided. The IOM and the Endocrine Society guidelines are generally aligned, with slight differences in recommended intake levels.

Sun exposure

Dietary intake

Supplementation
  - Infants (nursing)
  - Children
  - Adults

What should be the target daily intake?
Sunshine

- How much is needed?
  - Exposure time to release 10,000 – 20,000 IU/day
    - “full body exposure”
    - 4 – 10 minutes: pale skin
    - 60 – 80 minutes: dark skin
- Factors affecting
  - Season of the year
  - Skin pigmentation
  - Latitude
  - Use of sunscreen
  - Clothing
  - Amount of skin exposed
  - Age

Breastfed Infants

- Average vitamin D content of breast milk: < 25 – 78 IU/L
- A supplement of 400 IU per day of vitamin D is recommended for all breastfed infants.
  - American Academy of Pediatrics, November 2008
- ES Guideline: “All infants and children aged 0-1 yr require at least 400 IU daily.”

Breastfeeding: Maternal Supplementation

- RDA supplementation (600 IU)
- High dose supplementation (up to 6400 IU daily)
  - Vitamin D content of breast milk increased to 873 IU/L
  - No maternal vit D toxicity
  - Infants D level increased from 15 to 46 ng/mL
- ES Guideline: “at least 600 IU/d and recognize that at least 1500-2000 IU/d may be needed to maintain 25(OH)D above 30 ng/ml; (4,000-6,000 IU/d if infant not on D supplement)”

Vitamin D in Formula

- Infant formulas
  - Regular (term):
    - Most contain 400 IU/32 oz
    - FDA requires: 258-666 IU/1000 ml
    - Enfamil Premium Newborn: 50 IU/100 ml (400 IU/27 oz)
  - Special (preterm): contain 30-50 IU/100ml
- “All nonbreasted infants, as well as older children who are ingesting <1000 mL/day of vit D-fortified formula or milk should receive 400 IU/day”
  - American Academy of Pediatrics, November 2008

Milk

- Cows milk
  - Fortified with D3
  - 1 Quart provides 400 IU
- Fortified milk: Almost all milk sold commercially in the United States
  - Pasteurized Milk Ordinance (PMO) Fortification with vitamins A and D is optional for whole milk, but is required for all milks where fat is removed (e.g., 2%, 1%, skim).
- Unfortified
  - 1 Quart provides 35-70 IU
Natural Sources of Vitamin D

- **Fatty fish:**
  - Catfish, (3 oz) provides 425 IU
  - Salmon, cooked, (3.5 oz) provides 360 IU
  - Mackerel, cooked, (3.5 oz), 345 IU
  - Sardines, canned in oil, drained, (1.75 oz), 250 IU
  - Tuna, canned in oil, (3.5 oz), 235 IU
  - Eel, cooked, (3.5 oz), 200 IU
- **Egg** provides 20 IU (if egg weighs 60 g)
- **Beef liver,** cooked, (3.5 oz), provides 15 IU
- **Cod liver oil,** 1 Tsp provides 400 IU
- **Mushrooms** are the only vegan source of vitamin D:
  - 100g provides: (regular) 14 IU
  - (exposed to UV) 500 IU

Fortified Foods

- **Breakfast cereals**
  - 40 IU per regulatory serving
- **Milk substitutes**
  - 400 IU per liter
- ** Yogurt**
  - 200 IU per 6 oz
- **Cheese**
  - 40 IU per regulatory serving
- **Juice**
  - 400 IU per liter
- **Spreads**
  - 60 IU per regulatory serving

Estimated Vitamin D Intake (IU/Day)

<table>
<thead>
<tr>
<th>Sex/Age Group</th>
<th>Mean Intake (food and dietary supplement)</th>
<th>Mean Intake (food source only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M 1 - 3 year olds</td>
<td>364</td>
<td>288</td>
</tr>
<tr>
<td>F 1 - 3 year olds</td>
<td>336</td>
<td>272</td>
</tr>
<tr>
<td>M 4 - 8 year olds</td>
<td>372</td>
<td>256</td>
</tr>
<tr>
<td>F 4 - 8 year olds</td>
<td>316</td>
<td>216</td>
</tr>
<tr>
<td>M 9 - 13 year olds</td>
<td>300</td>
<td>224</td>
</tr>
<tr>
<td>F 9 - 13 year olds</td>
<td>308</td>
<td>208</td>
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<tr>
<td>M 14 - 18 year olds</td>
<td>276</td>
<td>240</td>
</tr>
<tr>
<td>F 14 - 18 year olds</td>
<td>200</td>
<td>148</td>
</tr>
<tr>
<td>M 19 - 30 year olds</td>
<td>264</td>
<td>200</td>
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<tr>
<td>F 19 - 30 year olds</td>
<td>232</td>
<td>140</td>
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<tr>
<td>M 31 - 50 year olds</td>
<td>316</td>
<td>216</td>
</tr>
<tr>
<td>F 31 - 50 year olds</td>
<td>308</td>
<td>176</td>
</tr>
</tbody>
</table>

IOM Report: Bone Health in Children

- "Observational studies suggest a correlation between higher 25(OH)D concentrations and baseline BMD and change in BMD or BMC indices for older children and adolescents".
- "Thus far results from RCTs of vitamin D supplementation (maximum dose 2,000 IU per day) have not confirmed a consistent benefit on BMD or BMC across sites and age groups".
- Only one RCT with an outcome measure (fracture) identified as significant in young adult females.
  - Can this be used to guide care of adolescents?

Calcium and Vitamin D Supplementation Decreases Incidence of Stress Fractures in Female Navy Recruits

- 5201 female recruits (age 17-35)
  - 800 IU vitamin D and 2000 mg calcium/day
  - Placebo
- Outcome after 24 months
  - 21% lower incidence of stress fractures in the supplemented group


Vitamin D Deficiency

- **25 (OH) D**
  - Best indicator of supply
  - Definition debated?
  - **25 (OH) D level:**
    - < 30 ng/mL (“insufficiency”)
    - < 20 ng/mL
  - Multiple treatment regimens exist
Groups at Risk

- Older people with low sunlight exposure
- Patients with osteopenia/osteoporosis
- Dark skinned
- Obese
- Gastrointestinal malabsorption disorders
- Gastric bypass
- Medications:
  - Antiepileptic medications
  - INH
  - Rifampin

Vitamin D Deficiency: Symptoms

- Moderate to mild vitamin D deficiency
  25(OH)D between 15 and 20 ng/mL
    - Asymptomatic
    - PTH level elevated in up to 40% of pts
    - Decreased bone mineral density
- Prolonged, severe vitamin D deficiency
  25(OH)D level <10 ng/mL
    - Bone pain and tenderness
    - Muscle weakness
    - Fracture

Which Vitamin D is Best?

- Vit D₂ (ergocalciferol) vs Vit D₃ (cholecalciferol)
- 2012 Meta-analysis (7 studies): D₃ more efficacious at raising 25(OH)D level when given as a bolus dose
- D₃ 5 times more effective in raising 25(OH)D in older adults in winter
- For every 100 units (2.5 mcg) of added vitamin D₃, serum 25(OH)D concentrations increase by approximately 0.7 to 1.0 ng/mL
- Most efficiently absorbed when consumed with foods containing fat
- Uptodate This topic last updated: May 02, 2016
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Vitamin D Formulations

<table>
<thead>
<tr>
<th>Common Name/ Brand Name</th>
<th>Available doses</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>D₃-Vi-Sol</td>
<td>Ergocalciferol</td>
<td>400 IU/mL</td>
</tr>
<tr>
<td>Drisdol</td>
<td>Cholecalciferol</td>
<td>8,000 IU/mL (400 IU in 2 gtt)</td>
</tr>
<tr>
<td>Carlsson Baby Drops</td>
<td>Cholecalciferol</td>
<td>1,000 IU/gtt</td>
</tr>
<tr>
<td>Carlson Ddrops</td>
<td>Cholecalciferol</td>
<td>2,000 IU/gtt</td>
</tr>
<tr>
<td>Replente (waffer)</td>
<td>Cholecalciferol</td>
<td>4,000 IU/gtt</td>
</tr>
<tr>
<td>Rocaltrol *</td>
<td>Calcitriol</td>
<td>0.25 mcg/mL</td>
</tr>
<tr>
<td>Zemplar **</td>
<td>Calcitriol</td>
<td>1 mcg/mL</td>
</tr>
</tbody>
</table>

Therapy in Pediatrics

Dosage for infants and children 0-18 with deficiency

- D₂ or D₃
- 2,000 IU/d for at least 6 weeks or
- 50,000 IU/week for a least 6 weeks
- Followed by maintenance:
  - Age 0 – 1 year
    - 400- 1,000 IU/d
  - Age 1 – 18 years
    - 600- 1,000 IU/d

Endocrine Society Clinical Practice Guideline 2011

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Endocrine Society Clinical Practice Guideline 2011
Vitamin D Deficiency: Treatment of Adults

- Significant heterogeneity among studies
- Difference is of uncertain clinical significance
- Dosing frequency at intervals up to once monthly appears to be less important than cumulative amount

Vitamin D Toxicity

- Highest attainable level from sun exposure:
  - 70 to 80 ng/mL (in general)
  - 100 ng/mL in sunbathers and lifeguards
- Review of published toxicity cases:
  - All cases > 88 ng/mL
  - Hypercalcemia associated with levels > 150 ng/dL
  - "Excess" > 250 ng/dL
  - "Intoxication" > 375 ng/dL

Vitamin D Toxicity

- Case studies in children 1931-2005
  - Lowest vitamin D dose to cause toxicity: 30,000 IU/day for 8 months
  - Randomized control trials (adults)
    - "The starting point for the current UL for vitamin D was 10,000 IU/d, because lower intakes have not been linked to hypercalcemia or acute toxicity."

Institute of Medicine 2011

Meta-Analysis: Effect of Vitamin D on Falls

- Dose response for vitamin D intake versus final serum 25-hydroxyvitamin D [25(OH)D] concentration reported

Vieth, R. Am J Clin Nutr 1999;69:842-856

Effects of Vitamin D on 25(OH)D Concentration in Children and Adolescents

J Clin Endocrinol Metab 2008;93:2693-2701

J Clin Endocrinol Metab 2011;96:2997-3006
### Calcium Intake and Increased Risk of CVD?

- Calcium intake and CVD is complex
- Risk may depend on source of calcium
  - Dietary calcium: protective
  - Supplemental calcium: ↑ risk
    - 22% increase in incident coronary artery calcification (RR=1.22 [1.07-1.39])
    - 
    - J Am Heart Assoc 2016;5:e003815.

### Therapy: Summary

- To avoid toxicity!
  - Use the correct formulation for infants
  - Avoid high concentration formulations
    - Example: D3 = 2,000 units/drop
  - Avoid confusion: provide written Rx
- Prevention is best!
  - Vitamin D testing should be unnecessary

### Special Considerations

- “At least two to three times more vitamin D needed to satisfy vitamin D requirement for”
  - Obese children and adults
  - Use of anticonvulsant medications
  - Glucocorticoids
  - Antifungal
  - AIDS medications

ES Clinical Practice Guideline 2011