An Update on Vitamin D and Calcium

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Disclosure
• No actual or potential conflict of interest in relation to this program or presentation

Learning Objectives
• Explain Vitamin D and calcium physiology, and discuss pathophysiology and sequelae of their deficiencies
• Describe benefits of Vitamin D and calcium supplementation
• Design and select best treatment plan to correct and prevent Vitamin D and calcium deficiencies
• Develop monitoring plans to assess efficacy and toxicity of different Vitamin D and calcium therapies
Presentation Overview

- Overview of Vitamin D and Calcium
- Physiological roles of Vitamin D and Calcium
- Prevalence and risk factors for developing vitamin D deficiency and subsequent calcium deficiency
- Vitamin D and calcium supplementation
- Monitoring of treatment efficacy and toxicity
- Take home messages

What is Vitamin D?

- Fat-soluble vitamin
- Derived from either diet or synthesize in skin through sun exposure
- Available in 2 forms
  - D₃ from UV irradiation of yeast sterol ergosterol (naturally found in sun-exposed mushrooms)
  - D₂ from diet of oily rich fish or synthesized in skin
- Vitamin D₂ or D₃ is biologically inert and requires further metabolism to be converted to active or "hormonal form"

Vitamin D Metabolism

- 25-OHase
- 1α-Hydroxylase
- 1,25 Dihydroxyvitamin D₃ (1,25 (OH)₂ D₃)
**Biological Functions of 1,25 (OH)\(_2\)D**

<table>
<thead>
<tr>
<th>Calcium Regulating</th>
<th>Non-calcium Regulating</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Small intestine</td>
<td>• Inhibit cellular</td>
</tr>
<tr>
<td></td>
<td>proliferation and induce</td>
</tr>
<tr>
<td></td>
<td>terminal differentiation</td>
</tr>
<tr>
<td>• Kidney</td>
<td>• Inhibit angiogenesis</td>
</tr>
<tr>
<td></td>
<td>• Inhibit renin production</td>
</tr>
<tr>
<td>• Bone</td>
<td>• Stimulate insulin production</td>
</tr>
<tr>
<td></td>
<td>• Stimulate macrophage</td>
</tr>
<tr>
<td></td>
<td>cathelicidin production</td>
</tr>
</tbody>
</table>


**What is Calcium?**

• Major mineral component of skeletal muscle
  – Skeletal growth and repair
• Essential nutrient required for
  – Nerve conduction
  – Muscle contraction
  – Hormone and enzyme secretion
  – Blood clotting

**Sources of Calcium**

• Dietary sources
  – Diary products
  – Fortified juices
  – White beans, sardines, fortified cereals
  – Kale, broccoli, Chinese cabbage
• OTC calcium supplements
• Skeletal tissues breakdown
  – Through bone resorption
Benefits of Calcium/Vitamin D

- Promote bone health and prevent fracture
- Improve muscle function and prevent fall
- Vitamin D may potentially reduce risk for
  - Cancer
  - Autoimmune dz (e.g., type 1 diabetes)
  - Infection
  - Cognitive disorder
  - Pain
- Decrease risk for mortality

Vitamin D with Calcium Reduces Mortality:
Patient Level Pooled Analysis of 70,528 Patients from Eight Major Vitamin D Trials

Which of the following is/are good source(s) of Vitamin D?

- a. Diet rich in oily fish
- b. UV conversion of γ-dehyrocholesterol in skin
- c. Fortified dairy products
- d. All of the above
- e. A and B only
Prevalence of Calcium/Vitamin D Deficiency

- Vitamin D Deficiency
  - Overall rate in US 41.6%
  - More than 90% of world’s population is at risk
  - Continues to be undiagnosed and undertreated
  - S&S are insidious or non-specific

- Calcium Deficiency (Chronic)
  - 32% US adults meet adequate calcium intake through diet
  - Prevalence closely linked with osteoporosis
  - Drop in serum calcium is rare due to body’s ability to maintain calcium homeostasis in setting of inadequate calcium intake
  - 98% of calcium is stored in skeletal tissue, which serves as reservoir when serum calcium drops

Calcium Homeostasis

Decrease Serum Calcium

Release of PTH

Ca²⁺ reabsorbed from kidney

Ca²⁺ and Phosphate released from bone

Increase in 1,25 (OH)₂ D

Increase gut calcium absorption

Below recommended levels of calcium intake over time can lead to decreased bone mass (osteopenia) and increased risk of osteoporosis

Common Manifestation of Calcium/Vitamin D Deficiency

- Bone pain or discomfort (often throbbing) in lower back, pelvis, lower extremities
- Impaired physical function
- Muscle aches
- Proximal weakness
- Symmetric lower back pain in women
- Increased risk of fall
- Development of osteopenia and osteoporosis
High Risk Individuals for Developing Calcium/Vitamin D Deficiency

- Older adults/elderly patients
- Institutionalized individuals
- Poor health status or sedentary lifestyle
- Low HDL
  - May be due to decreased 7-dehydrocholesterol
- None milk consumption (lactose and tolerant)
- Limited sun exposure
- Obese

Obesity (BMI >30 kg/m²) and Vitamin D Deficiency

Body is able to maintain calcium homeostasis short term when serum calcium decreases via which mechanism?

- a. Increase parathyroid hormone release
- b. Breakdown of skeletal tissues via osteoblast activity, resulting in calcium and phosphate to be released
- c. Increase calcium excretion via renal tubules
- d. Increased gut absorption of vitamin D
Screening for Vitamin D Deficiency
What is considered appropriate screening?

- Cost of screening
  - Out-of-pocket cost $100 - $200
  - Institutional $27.00
- High risk group
  - Osteoporosis, hx of falls or high risk of falls, malabsorption (e.g., celiac disease, radiation enteritis, bariatric surgery), liver dz
- Musculoskeletal symptoms such as
  - Muscle pain, myalgias, generalized weakness
  - Maybe misdiagnosed as fibromyalgia vs hypovitaminosis D
- Medication that known to lower vitamin D
  - Anticonvulsants
  - Weight loss medications that inhibit/limit absorption of fat soluble vitamins (e.g., Xenical®/Alli® (Orlistat))
  - Glucocorticoids

Interpreting Laboratory Data on Diagnosing Low Vitamin D

- Total 25(OH)D is best to assess body stores of Vitamin D
- 25(OH)D, facilitates treatment monitoring
- Timing of blood draw is not restricted

Definition of “Low Vitamin D”

- No definitive cut off point
- Based on prevention of secondary increase in parathyroid hormone (PTH)
- Studies have shown that PTH level plateaus when 25 (OH) D approaches 30 ng/mL and symptoms of secondary PTH are observed when 25 (OH) D falls below 20 ng/mL
- Vitamin D deficient adult
  - < 20 ng/mL (50 nmol/L)
- Vitamin D insufficient adult
  - 20 – 30 ng/mL (50 – 75 nmol/L)
Hypocalcemia

- Define as calcium <8.5 mg/dL (normal 8.5 to 10.5 mg/dL)
- Serum calcium
  - Total bound and ionized calcium
  - Predominantly bound to albumin
  - Ionized calcium pharmacologically active
- Common causes
  - Hypoparathyroidism, chronic kidney disease, and vitamin D deficiency

Consequences of Calcium/Vitamin D Deficiency

- Osteomalacia/rickets
- Osteopenia & Osteoporosis
- Secondary hyperparathyroidism
- Falls and fracture
  - Muscle weakness and pain
- Sudden drop in serum calcium
  - Neuromuscular irritability (e.g., tetany), electrocardiographic changes, and seizures

Hypovitaminosis D and insufficient calcium intake are associated with increase risk for?

a. Hyperlipidemia
b. Falls and fractures
c. Postmenopausal symptoms
d. Resistant hypertension
Calcium/Vitamin D Supplementation

UVB/Sun Therapy
- Free and easy to do
- Associated with skin cancer
- Unreliable
- Difficult to recommend
  - No clear recommendation on duration/amount of sun exposure
  - Differences in skin pigmentation, season, latitude, time of day, sunscreen use, and amount of body surface exposed

Differences in UVB Irradiation Based on Location, Time of Day, and Season

UVB and Intentional Sun Exposure

SPF 30 sunscreen reduces vitamin D synthesis by 95%

Common Food with Vitamin D

<table>
<thead>
<tr>
<th>Source</th>
<th>Approximate vitamin D content*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forfitted sources</td>
<td></td>
</tr>
<tr>
<td>Cereal</td>
<td>100 IU per serving</td>
</tr>
<tr>
<td>Milk</td>
<td>100 IU per 8 oz</td>
</tr>
<tr>
<td>Orange juice</td>
<td>100 IU per 8 oz</td>
</tr>
<tr>
<td>Nonforfitted food sources</td>
<td></td>
</tr>
<tr>
<td>Breast milk</td>
<td>20 IU per l</td>
</tr>
<tr>
<td>Cod liver oil</td>
<td>400 IU per teaspoon</td>
</tr>
<tr>
<td>Egg yolk</td>
<td>20 IU</td>
</tr>
<tr>
<td>Mackeral (canned)</td>
<td>250 IU per 1.5 oz</td>
</tr>
<tr>
<td>Salmon (canned)</td>
<td>300 to 600 IU per 1.5 oz</td>
</tr>
<tr>
<td>Salmon (fresh, farmed)</td>
<td>100 to 250 IU per 1.5 oz</td>
</tr>
<tr>
<td>Salmon (fresh, wild)</td>
<td>600 to 1,000 IU per 1.5 oz</td>
</tr>
<tr>
<td>Sardines (canned)</td>
<td>300 IU per 1.5 oz</td>
</tr>
<tr>
<td>Tuna (canned)</td>
<td>220 IU per 1.5 oz</td>
</tr>
</tbody>
</table>


OTC Vitamin D Products
Vitamin D Medications

- Ergocalciferol (D₂) - comes from irradiation of yeast and plant sterol ergosterol
  - Drisdol® oral capsule 50,000 IU/cap
  - Drisdol® or Calciferol® oral solution 8,000 IU/mL
- Cholecalciferol (D₃) – comes from oily fish
  - 400 IU, 800 IU, 1000 IU, 2000 IU, 5000 IU, 20,000 IU, and 50,000 IU oral capsules/tablet/solution
- Vitamin D analogs
  - Calcitriol, Dihydrotachysterol, Calcitriol
  - Not indicated to treated vitamin D deficiency

Treatment Strategies for Vitamin D Deficiency

- High risk with 25(OH)D < 20 ng/mL
  - 50,000 IU once weekly of vitamin D₂ or D₃ for 6 to 8 weeks OR
  - 6,000 IU daily of vitamin D₂ or D₃
- Followed by maintenance therapy
- High risk with 25(OH)D 20 – 30 ng/mL
  - 600 – 800 IU daily of vitamin D₂ or D₃ to maintain current level 25(OH)D level of 20 – 30 ng/mL

Usual Recommended Daily Allowance (RDA) for Vitamin D

<table>
<thead>
<tr>
<th>Life stage group*</th>
<th>Institute Recommendations (IU)</th>
<th>Endocrine Society Recommendations (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-11 months</td>
<td>400</td>
<td>1000</td>
</tr>
<tr>
<td>12 months</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td>1-3 years</td>
<td>600</td>
<td>1000</td>
</tr>
<tr>
<td>4-8 years</td>
<td>700</td>
<td>1000</td>
</tr>
<tr>
<td>9-11 years</td>
<td>800</td>
<td>1000</td>
</tr>
<tr>
<td>12 years and older</td>
<td>900</td>
<td>1000</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>1000</td>
<td>1500</td>
</tr>
<tr>
<td>Pregnant or lactating women 18-19 years</td>
<td>1500</td>
<td>10,000</td>
</tr>
</tbody>
</table>

* Includes normal healthy infant and women unless otherwise specified.
* Assumes mean serum normal value for 25(OH)D levels above 20 ng/mL.
* Assumes no risk associated with normal levels for healthy adults. 1 IU of vitamin D is equivalent to 0.25 mcg.
* Assumes serum value (before morning sun exposure) 25(OH)D level in a group of healthy individuals and is the Institute of Medicine recommended level for vitamin D status instead of recommended intake, since serum value is established.

Special Consideration

- Malabsorption (e.g., Gastric bypass)
  - 6,000 IU – 10,000 IU/d of D₂ or D₃
  - Doses up to 50,000 IU/d of D₂ or D₃
  - Followed by maintenance dose of 3,000 – 6,000 IU/d of D₂ or D₃
- Obese OR on medications that that affect metabolism of vitamin D
  - 6,000 IU – 10,000 IU/d to correct deficiency
  - Followed by maintenance dose of 3,000 – 6,000 IU/d of D₂ or D₃
- Tube feeders
  - Avoid ergocalciferol capsules containing D₂ in oil, as it can clog feeding tubes
- Parenteral nutrition
  - 200 IU of IV vitamin D is sufficient to maintain normal vitamin D levels, but not sufficient to correct vitamin D deficiency

Vitamin D Recommendation for CKD Stage 3 and 4

<table>
<thead>
<tr>
<th>Serum 25(OH)D (ng/mL)</th>
<th>Ergocalciferol Dose (Vitamin D₂)</th>
<th>Duration (months)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>50,000 IU/d every 4 to 6 weeks, then monthly</td>
<td>6 months</td>
<td>Measure 25(OH)D levels after 6 months</td>
</tr>
<tr>
<td>10-19</td>
<td>500,000 IU/d as single 100,000 IU dose</td>
<td>4 weeks</td>
<td>Ensure patient adherence, measure 25(OH)D at 6 months</td>
</tr>
<tr>
<td>20-29</td>
<td>50,000 IU/d every 4 weeks, then 50,000 IU/month monthly</td>
<td>6 months</td>
<td>Measure 25(OH)D levels after 6 months</td>
</tr>
<tr>
<td>≥30</td>
<td>50,000 IU/month monthly</td>
<td>6 months</td>
<td></td>
</tr>
</tbody>
</table>

Monitoring for Vitamin D Status After Initiation of Treatment

- Monitor 25 (OH)D every 4 to 6 months
  - Take 3 – 6 months for serum 25(OH)D to plateau following initiation of supplementation
Vitamin D Toxicity

- Rare due to kidney’s ability to limit production of active calcitriol
- Should NOT be diagnosed solely based on 25(OH)D level
- Accompanied by hypercalcemia and hypercalciuria
- No clear cut definition of which level is considered “toxic”
- Variability in laboratories reporting of toxic level
  - Above 80 ng/mL vs. >100 ng/mL
- Published vitamin D toxicity cases report hypercalcemia due to vitamin D intoxication were associated with 25(OH)D concentration of >88 ng/mL

Counseling Points for Monitoring for Vitamin D Toxicity

- Hypercalcemia
  - Nausea, dehydration, constipation
- Hypercalciuria
  - Polyuria, kidney stones
- Headache
- Metallic taste
- Vomiting

What would be the best treatment recommendation for a high risk patient with a vitamin D level of <20 ng/mL?

a. 50,000 IU once weekly for 2 months
b. 500,000 IU once a year
c. 1,000 IU daily for 3 months
d. 50,000 IU once a month for 6 months
**Recommended Calcium Daily Allowance**

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Recommended Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 6 months</td>
<td>200 mg</td>
</tr>
<tr>
<td>Infants 7–12 months</td>
<td>260 mg</td>
</tr>
<tr>
<td>Children 1–3 years</td>
<td>700 mg</td>
</tr>
<tr>
<td>Children 4–8 years</td>
<td>1,000 mg</td>
</tr>
<tr>
<td>Children 9–13 years</td>
<td>1,300 mg</td>
</tr>
<tr>
<td>Teens 14–18 years</td>
<td>1,300 mg</td>
</tr>
<tr>
<td>Adults 19–50 years</td>
<td>1,000 mg</td>
</tr>
<tr>
<td>Adult men 51–70 years</td>
<td>1,000 mg</td>
</tr>
<tr>
<td>Adult women 51–70 years</td>
<td>1,200 mg</td>
</tr>
<tr>
<td>Adults 71 years and older</td>
<td>1,200 mg</td>
</tr>
<tr>
<td>Pregnant and breastfeeding</td>
<td>1,300 mg</td>
</tr>
<tr>
<td>Teenage and older adults</td>
<td>1,000 mg</td>
</tr>
</tbody>
</table>


**Dietary Sources of Calcium**

<table>
<thead>
<tr>
<th>Type of Food</th>
<th>Serving Size</th>
<th>Elemental Calcium per Serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dairy products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plain low-fat yogurt</td>
<td>6 oz</td>
<td>448 mg</td>
</tr>
<tr>
<td>Low-fat yogurt with fruit</td>
<td>8 oz</td>
<td>384 mg</td>
</tr>
<tr>
<td>Mozzarella, part-skim milk</td>
<td>5 oz</td>
<td>133 mg</td>
</tr>
<tr>
<td>Cheddar cheese</td>
<td>1.5 oz</td>
<td>167 mg</td>
</tr>
<tr>
<td>1% Low-fat milk</td>
<td>8 oz</td>
<td>293 mg</td>
</tr>
<tr>
<td>Low-fat cottage cheese</td>
<td>1 cup</td>
<td>209 mg</td>
</tr>
<tr>
<td>Fruits and vegetables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium-fortified orange juice</td>
<td>9 oz</td>
<td>261 mg</td>
</tr>
<tr>
<td>Pear half</td>
<td>1 cup</td>
<td>108 mg</td>
</tr>
<tr>
<td>Rose kish</td>
<td>1 cup</td>
<td>74 mg</td>
</tr>
<tr>
<td>Rose分数线</td>
<td>1 cup</td>
<td>43 mg</td>
</tr>
<tr>
<td>Canned fish</td>
<td>5 oz</td>
<td>125 mg</td>
</tr>
<tr>
<td>Spinach</td>
<td>5 oz</td>
<td>125 mg</td>
</tr>
<tr>
<td>Pea soup</td>
<td>5 oz</td>
<td>181 mg</td>
</tr>
<tr>
<td>Cereals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farro, ready-to-eat</td>
<td>3 cup</td>
<td>100–150 mg</td>
</tr>
<tr>
<td>Farro, cooked with chicken</td>
<td>1 cup</td>
<td>87 mg</td>
</tr>
<tr>
<td>Commercially prepared whole wheat</td>
<td>1 piece</td>
<td>87–117 mg</td>
</tr>
</tbody>
</table>


**Calcium Supplements**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dose</th>
<th>Elemental Calcium Content</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium carbonate</td>
<td>400 mg tablets taken three times daily with meals</td>
<td>40 mg</td>
<td>Least expensive and most commonly used supplement; should be taken with meals, since acidity impacts absorption, can cause constipation</td>
</tr>
<tr>
<td>Calcium citrate</td>
<td>210 mg tablets taken three times daily</td>
<td>210 mg</td>
<td>Less dependent on acidity for absorption, so it does not need to be taken with meals, may be used with agents for long-term patient and suppressor</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>500, 648, or 922 mg</td>
<td>500 mg</td>
<td>Easily used for fracture prevention</td>
</tr>
<tr>
<td>Calcium lactate</td>
<td>130 mg</td>
<td>130 mg</td>
<td>Primarily contains calcium carbonate but may contain detergent food and should be avoided during pregnancy</td>
</tr>
</tbody>
</table>

Factors that Influence Calcium Absorption

- Low vitamin D levels
- Gastric pH
  - Elderly with decrease gut acid (achlorhydria)
- Drug-drug interactions
  - Quinolone antibiotics
  - Phenytoin
  - Acid suppressive medications (Proton pump inhibitors, H2Blockers)
- Glucocorticoids

Adverse Effects of Calcium

- Constipation
- Dyspepsia
- Nephrolithiasis
  - Dose dependent

Contraindications to Calcium/Vitamin D Supplementation

- Granulomatous disease
  - Sarcoïdosis
  - Tuberculosis
- Metastatic bone disease
- Calcium metabolism abnormalities
- Williams syndrome
  - Genetic syndrome manifesting with endocrine abnormalities including hypercalcemia and hypercalciuria
What is the recommended daily allowance of calcium for a 65 y/o female?

- 600 mg/day
- 900 mg/day
- 1,000 mg/day
- 1,200 mg/day

Cardiovascular Risk with Calcium/Vitamin D

- Hypothesis
  - Transient calcium/vitamin D supplemental-related increases in serum calcium precipitate in arrhythmias and promote vascular calcification
- Conflicting data
- Inconsistent findings
- Verdict is still up

Cardiovascular Risk with Calcium/Vitamin D

- Women’s Health Initiative Investigator evaluated risk of coronary and cerebrovascular events in women receiving calcium plus vitamin D supplement
  - 36,282 post-menopausal women (50 – 79 y/o) randomized to calcium carbonate 500 mg with vitamin D 200 IU twice daily or placebo
Results: Women’s Health Initiative Investigator
Calcium/Vitamin D Supplementation and
Cardiovascular Events

**Cardiovascular Risk**

"Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women’s Health Initiative limited access dataset and meta-analysis”


- Objective: To investigate the effects of personal calcium supplement use on cardiovascular risk in the Women’s Health Initiative Calcium/Vitamin D Supplementation Study (WHI CaD Study), using the WHI dataset, and to update the recent meta-analysis of calcium supplements and cardiovascular risk.

Results: Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women’s Health Initiative limited access dataset and meta-analysis

Calcium Supplementation and the Risks of Atherosclerotic Vascular Disease in Older Women: Results of a 5-Year RCT and a 4.5-Year Follow-up

- Enrolled 1,460 women 75.1 ± 2.7 years
- Received 1,200 mg of calcium carbonate or identical placebo
- Primary endpoint was atherosclerotic event causing either death or hospitalization (combined endpoint)

Lewis JR, et al., J Bone Miner Res. 2011;26:35-41

Minimize Potential Risk of CVD with Calcium/Vitamin D

- Do not exceed RDA for calcium and vitamin D
- If possible, encourage dietary intake of calcium to achieve RDA without use of supplemental calcium
Take Home Message

- Vitamin D and calcium have multiple health benefits that go beyond bone health
- Close relationship between calcium deficiency and hypovitaminosis D
- Prolonged inadequate calcium intake or absorption secondary to low vitamin D level lead to poor bone health and fall risk
- Best sources of vitamin D and calcium are dietary sources
- Vitamin D and calcium supplements should only be considered in patient who cannot maintain adequate intake from dietary sources
- Cardiovascular risk associated with calcium and vitamin D supplementation remains unclear
- When recommending additional calcium and vitamin D supplementation, must account for dietary intake

Thank You

References

References