Role of Vitamin D in the Prevention of Falls

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Objectives

1) Review the biochemistry and role of vitamin D in the human body

2) Discuss the important role of vitamin D for muscle functioning

3) Examine the evidence for vitamin D and the risk of falls and fractures in the elderly

4) Illustrate the challenges of establishing optimal vitamin D levels and supplementation doses
Case: Mrs. R.

- 86yo female, resident of assisted living facility
- History of osteoarthritis, osteoporosis, squamous cell carcinoma, hypertension, subdural hematoma, and seizure disorder
- Brought to office by daughter after 3rd fall in past 2 months
- Uses walker for ambulation
- Complaint of legs feeling weak and “bones ache”
- Her daughter is worried about risk for fractures and future falls
- What do you do?
Risk Factors for Vitamin D Deficiency and Fractures

1) Age

2) Assisted Living Facility resident

3) Avoids sun exposure per her dermatologist’s instructions

4) Osteoporosis

5) Phenytoin (Dilantin) for history of seizure

6) Muscle weakness and falls

Am J Geriatr Pharmacother 2010;8:34-46.
Vitamin D Biochemistry

- Vitamin D derived from solar synthesis, food, or supplementation
- Ultraviolet B radiation (wavelength 290 - 315 nm) penetrates the skin, converts 7-dehydrocholesterol to previtamin D, which is rapidly converted to vitamin D
- Decreased solar synthesis is associated with
  - Skin changes associated with aging
  - Sunscreen use and dark skin color
  - Winter
  - Window glass, cloud cover, and air pollution
- Hydroxylation
  - Liver: 25-hydroxyvitamin D (calcidiol)
  - Kidney: 1,25-dihydroxyvitamin D (calcitriol), → active hormone
    - Stimulated by PTH, calcitonin and hypophosphatemia,
    - Inhibited by calcium, phosphorus, and 1,25-dihydroxyvitamin D (feedback)

Vitamin D3 and D2

Vitamin D3
(cholecalciferol)
solar synthesis and animals

Vitamin D2
(ergocalciferol)
derived from plant sterols

- Either can exist in the 25-OH and 1,25-OH vitamin D forms
- There is some debate if D2 is biologically equivalent to D3.
Vitamin D and Muscle Function

- Vitamin D receptor expressed in human muscle tissue and activation promotes de novo protein synthesis

- Proximal muscle weakness and diffuse skeletal pain described with rickets, but also seen in vitamin D deficiency without signs of osteomalacia in adults

- Low serum 25-(OH)D and high PTH associated with sarcopenia (loss of muscle mass and strength)

- Secondary hyperparathyroidism may also affect muscle function (proteolysis and intracellular depletion)

- NHANES III: subjects with low 25-(OH)D (<20 nmol/L) had poorest 8-foot walk test and the repeated sit-to-stand test

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Vitamin D and Risk of Falls

- **Nursing Home Residents (Boston)**
  - ≈ 50% had low baseline 25-(OH)D levels (<20ng/mL)
  - Given 200, 400, 600, or 800 IU vitamin D2 over 5 months
  - 800 IU group had a 72% lower rate of falls than placebo

- **Community-Dwelling Older Women (Australia)**
  - Vitamin D deficient (<24 ng/mL) and history of falls
  - Ergocalciferol (D2) 1000 IU/day
  - Reduced risk for falls 53.0% vs. 62.9% control over 1 year
  - Seasonal effect (Winter/Spring)
Seasonal Variation in Vitamin D Levels

*2.5 nmol/L = 1 ng/mL

242 community dwelling elderly in Germany/Austria
25-(OH) vitamin D levels were <31.2ng/mL
Calcium vs. calcium + vitamin D

Vitamin D reduced first falls
- 27% at 12 months
- 39% at 20 months

Significant findings associated with vitamin D
- Increased quadriceps strength (8%)
- Decrease in body sway (28%)
- Decrease in Timed-Up-and-Go test (11%)

Falls: Dose and Serum Levels

- **Dose of Vitamin D**
  - High (700-1000 IU/day) → 19% risk reduction
  - Low (200-600 IU/day) → No effect

- **25-(OH)D Levels**
  - ≥24 ng/mL → 23% risk reduction
  - <24 ng/mL → No effect

Fracture Risk

- Fractures are a function of both bone strength and falls (trauma)
- Low vitamin D levels associated with higher risk for fracture
- African Americans have lower levels of vitamin D than Caucasians, yet have a lower rate of fractures
- Difficult to isolate the contribution of calcium and vitamin D in trials looking at fracture risk
- With adequate vitamin D supplementation, you might even need lower levels of calcium supplementation

Fracture Risk: Calcium is Important

- **Women’s Health Initiative** *(N Engl J Med 2006;354:669-83.)*
  - Calcium + vitamin D in healthy post-menopausal women
  - Increased bone density of hip, but non-significant 12% reduction in hip fractures
  - Low adherence, and benefit seen in subgroup analysis of adhering women

- **Cochrane Review** *(Cochrane Database Syst Rev. 2009 Apr 15;(2):CD000227.)*
  - Vitamin D not effective in preventing fractures
  - When combined with calcium there is reduction in hip fractures
  - Did not take into account the dose of vitamin D

  - Vitamin D 800 IU daily → 70% probability of being better than placebo for all fractures
  - With calcium: reduced the risk of non-vertebral and non-hip fractures
Other Health Benefits of Vitamin D

- Cancer
  - Colorectal
  - Breast, prostate?

- Immune function

- Tuberculosis

- Autoimmune Disease
  - Multiple sclerosis

- Cardiovascular
  - HTN
  - Mortality

- COPD

- Diabetes

- Pain

- Cognitive impairment?

Am J Respir Crit Care Med. 2009; 179:630-636.
Neurology 2010; 74:27–32.

Measuring Vitamin D

- Most important to measure TOTAL 25-(OH)D
- Variation between radioimmunoassays
- Gold standard was considered HPLC method
- Liquid Chromatography-tandem Mass Spectrometry (LC-MS/MS)
  - Separates 25-(OH)D into D2 and D3
  - Mayo Clinic listed price $187.70
Who should be tested?

- Good question, no good answer
- Supplement without testing?
- Degree of insufficiency or deficiency may influence dosing of vitamin D
- Given data on bone health and falls, testing the elderly (especially institutionalized) is important
- All patients with osteopenia or osteoporosis should have vitamin D levels measured
- Screening younger patients??
What is the optimum vitamin D level?

- No consensus
- Likely varies for different life stages
- Maximal suppression of PTH by vitamin D is one criterion (cluster in the 30 - 32 ng/mL range)
- More than half of the population has vitamin D insufficiency or deficiency (obesity, darker skin pigmentation, elderly)
- Values > 24ng/mL to prevent falls
- **Deficiency** <20ng/mL
- **Insufficiency** 20-30 ng/mL
- **Desirable** >30 ng/mL (>75 nmol/L*)


*1 ng/mL = 2.5 nmol/L
Vitamin D Sources

- **Diet**
  - Fatty fish (tuna, salmon); shiitake mushrooms
  - Since 1930’s, milk is fortified (100 IU/cup)
  - Cereals, margarine, and some orange juice fortified

- **Solar Synthesis**
  - 5 - 30 minutes (between 10 am - 3 pm) twice a week
  - Balancing risk of solar damage and skin cancers
  - Variables: seasonal variations in sun intensity, cloud cover, air pollution, duration of exposure, and body surface area exposed
  - Windows and sunscreen block UV-B

Vitamin D Supplementation

- Food and Nutrition Board (Institute of Medicine): “Adequate Intake” of vitamin D
  - 400 units/day for people 51 - 70 years old
  - 600 units/day for people ≥71 years old
  - Should be revised summer 2010*

- Most “senior” multivitamins contain 400 IU of Vitamin D

- Higher doses appear to be beneficial for fractures and falls; therefore recommendations for 800-1000 IU/day may be more appropriate

- Fat malabsorption and gastric bypass patients have impaired vitamin D absorption and require greater supplementation

- Calcium supplementation is still important

*http://www.iom.edu/Activities/Nutrition/DRIVitDCalcium.aspx
Treating Vitamin D Deficiency

25-(OH) Vitamin D <20ng/mL

- Dosing frequency less important than cumulative amount
- 400 IU vitamin D daily only raises 25(OH)D by 7–12 nmol/L (depending on the starting point). (Am J Clin Nutr 2007;85:649-50.)

- 6-Year safety and efficacy of high-dose oral supplementation*
  - 50,000 IU of ergocalciferol (D2) weekly for 8 weeks and then every other week for maintenance
  - No incidents of kidney stones or evidence of intoxication.

- Monthly maintenance of 50,000 IU has also been suggested**

- Consider rechecking levels 3 months after starting therapy to assess adequacy of repletion and adherence (↑D2)

Vitamin D Toxicity

- Nausea, vomiting, poor appetite, constipation, weakness, and weight loss
- Hypercalcemia and hypercalciuria
- 25-(OH) D levels consistently >150ng/mL likely result in toxicity; animal models suggest >400ng/mL
- Upper limit 25-(OH) Vitamin D of 100ng/mL still gives considerable safety margin
- Excessive sun exposure does not cause toxicity
Return to Case: Mrs. R

- **Exam**
  - Unable to rise from chair unassisted
  - Slow, cautious gait, slightly wide-based
  - Pretibial tenderness, no edema
  - Slightly diminished reflexes; normal sensory exam

- **Laboratory Findings**
  - Serum calcium normal; normal albumin
  - Alkaline phosphatase mildly elevated
  - PTH not measured
  - Total 25-OH Vitamin D = 10 ng/mL
Assessment and Plan

- Diagnosis: Vitamin D deficiency
- Initial Rx: ergocalciferol (D2) 50,000 IU po once weekly for next 2 months
- Maintenance Rx: ergocalciferol 50,000 IU po monthly (or every 2 weeks?)
- Recheck vitamin D level in about 3 months
- Continue calcium supplementation
- Need for continued phenytoin (Dilantin) therapy?
- Physical therapy referral
Key Points: Falls and Vitamin D

1) Vitamin D has a direct effect on muscles and has been associated with increased muscle strength, improved neuromuscular function and improved balance.

2) Vitamin D has been associated with a decreased risk of falling in both community-dwelling and institutional-dwelling elderly. Vitamin D with calcium reduces the risk of fractures.

3) An optimum serum level for vitamin D has not been determined, but levels >30ng/mL are associated with favorable health outcomes.

4) Vitamin D supplementation for elderly patients depends on an individual’s level of insufficiency/deficiency, but supplement doses should be at least 800-1000 IU daily, based on available evidence and since toxicity has never been observed at these doses.

5) Vitamin D deficiency can be treated with high dose oral ergocalciferol (50,000 IU) once weekly for 8 weeks followed by maintenance dosing every 2-4 weeks.