Vitamin D: The 2011 Dietary Reference Intakes for Vitamin D and Calcium

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Outline

- The 2011 Dietary Reference Intakes for Vitamin D and Calcium (Dr. Clinton)
- Vitamin D and Skeletal Health (Dr. Ryan)
- Vitamin D and Non-Skeletal Outcomes (Dr. Clinton)

Disclosures

Financial: None
Conflicts of Interest: None
Strong Opinions: Many

Francis Gilsson et al.
A Teatise of the Rickets: Being a Disease Common to Children.
London. 1651

This book was one of the first pediatric texts published in England. Francis Gilsson and contributors provided a clear description of rickets. They did not recognize that diet played a role in the etiology of the disease.
Rickets

- It was not until 1918, that Edward Mellanby, experimenting with dogs, showed that diet was the determining factor in rickets, and that cod liver oil could prevent rickets.
- E.V. McCollum later showed that the antirachitic factor was unique and not vitamin A.
- Goldblatt and Soames / Hess and Weinstock showed that UV light produces an anti-rachitic factor. Steenbock patented the irradiation of foods to produce the anti-rachitic factor.
- A. Windaus, University of Gottingen, Germany: The structures of vitamin D and metabolites defined in the 1930s.

The Dramatic Reduction in Rickets

Dietary reference Intakes (DRIs)

Why Revisit DRI for Vitamin D (2010)?

- Previous DRI's established 1997
  - Average Intake & Upper Level
- Scientific Evidence after 1996 until 2010
  - 75% of current published evidence relating dietary vitamin D or serum 25(OH)D to health outcomes
  - Many health outcomes not considered by the 1997 DRI Committee
    - Performance measures (e.g. falls in elderly)
    - Non-bone health outcomes
      - (cancer, cardiovascular, diabetes, etc.)
    - Considerable controversy-discussion about effects of vitamin D and amounts needed
- Calcium included because closely linked to vitamin D
- Sponsors: U.S. and Canadian governments
- IOM- NAS Committee of Experts
  - Closed Deliberations and final External Review
**RECOMMENDED DIETARY ALLOWANCE (RDA):**
Daily requirement which meets the needs of >97.5% of population

**TOLERABLE UPPER LIMIT (TUL or UL):**
Highest average daily intake that is likely to pose NO risk

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**Vitamin D and Calcium: DRIs**

- DRIs reflect a "public health" approach
- DRIs are about populations and the distribution of needs.
  - Need dose-response → median requirement and variance → level akin to requirement of 98.7% of population
- DRIs are not for the medical model
  - diseased individuals, therapy of deficiency syndromes
- The IOM-DRI Committee considered many chronic diseases:
  - as possible "indicators" for establishing RDA-DRI
  - to consider "totality" of evidence
  - quality of studies and strength of the evidence
  - randomized clinical trials (RCT) provide the greatest level of confidence

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**Health Outcomes Evaluated: Indicators**

- **Cancer / Neoplasms**
  - All cancers (overall cancer risk)
  - Breast Cancer
  - Colorectal Cancer/Colon Polyps
  - Prostate Cancer
- **Cardiovascular Diseases and Hypertension**
- **Diabetes (Type 2) and Metabolic Syndrome (Obesity)**
- **Falls**
- **Immune Functioning**
- **Asthma**
- **Autoimmune Disease**
- **Infectious Diseases**
- **Neuropsychological Functioning**
- **Physical Performance**
- **Preeclampsia of Pregnancy**
- **Skeletal Health** (commonly Bone Health)
  - Calcium absorption, Calcium balance, BMC/BMD, Fracture risk, Rickets/Osteomalacia, 24OHD (intermediate), PTH (intermediate)
**Vitamin D: Challenges**

- Vitamin D → Homeostatic regulated hormone
- Sun exposure and synthesis
  - Seasonal changes in serum 25OHD
  - Cannot incorporate readily in DRI considerations
  - Exposure and synthesis not well quantified
  - Risk of skin cancer
- Biomarker of exposure
  - Serum 25OHD
- Most data on health outcomes relate to serum values, not to dietary intake

**Development of Requirement Distribution**

- Step 1 – Link serum levels to distribution requirement
  - 40 nmol/L (16 ng/mL) roughly equivalent to EAR
  - 50 nmol/L (20 ng/mL) roughly equivalent to RDA
- Note:
  - Some studies (bone) suggest 50 nmol/L TOO HIGH for RDA
  - Others suggest 50 nmol/L TOO LOW for RDA
  - Decision was made by the COMMITTEE based on the totality of the highest quality evidence
Vitamin D: Development of Requirement Distribution

- Step 2 – Determine how much intake to achieve designated serum level
  - Assumption of minimal sun exposure
  - Integration of studies conducted in winter in northern latitudes (many recent studies)
  - Simulation of dose-response curve

In the case of this report..... dose-response estimation for vitamin D required integration of data and use of prediction model

Vitamin D: Institute of Medicine (IOM) Dietary Reference Intakes, 2011 (IU/d)

<table>
<thead>
<tr>
<th>Ages (yrs)</th>
<th>Recommended Dietary Allowance (RDA)a</th>
<th>Tolerable Upper Intake Level (UL)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – 3</td>
<td>600</td>
<td>2500</td>
</tr>
<tr>
<td>4 – 8</td>
<td>600</td>
<td>3000</td>
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<tr>
<td>9 – 70</td>
<td>600</td>
<td>4000</td>
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<tr>
<td>&gt;70</td>
<td>800</td>
<td>4000</td>
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Adequate intakes for infants are 400 IU/d and ULs are 1000-1500 IU/d *Covers the needs of ≥97.5% of the population
bLevel above which there is risk of adverse events

Calcium ERA and DRI

- 1-3 years 500 700
- 4-8 years 800 1000
- 9-18 years 1100 1300
- 19-50 years 800 1000
- 51-70 years M 800 1000
- 51-70 years F 1000 1200
- >70 years 1000 1200
- Preg/lac 14-18 years 1100 1300
- Preg/lac 19-50 years 800 1000
- Infants 0 to 6 mos: AI = 200
- Infants 6 to 12 mos: AI= 260
Derivation of Upper Limit: Adults

- Challenging
  - no long-term studies of higher dose supplements
- Serum 25(OH)D levels >125-150 nmol/L have been associated with increased risk for various endpoints
- Prudent not to surpass 125-150 nmol/L for sustained serum concentrations

**Tolerable Upper Intake Levels (ULs)**

<table>
<thead>
<tr>
<th>Vitamin D (IU/day)</th>
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<tbody>
<tr>
<td>Infants 0 to 6 mos</td>
<td>1000</td>
</tr>
<tr>
<td>Infants 6 to 12 mos</td>
<td>1500</td>
</tr>
<tr>
<td>1-3 years</td>
<td>2500</td>
</tr>
<tr>
<td>4-8 years</td>
<td>3000</td>
</tr>
<tr>
<td>9-18 years</td>
<td>4000</td>
</tr>
<tr>
<td>19-50 years</td>
<td>4000</td>
</tr>
<tr>
<td>51-70+ years</td>
<td>4000</td>
</tr>
<tr>
<td>Preg/Lac 14-18</td>
<td>4000</td>
</tr>
<tr>
<td>Preg/Lac 19-50</td>
<td>4000</td>
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</tbody>
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**Extended Oral Dosing of Vitamin D**

<table>
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<th>Vitamin D (IU/day)</th>
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<td>1000</td>
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<tr>
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<td>51-70+ years</td>
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<tr>
<td>Preg/Lac 14-18</td>
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<td>Preg/Lac 19-50</td>
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**Vitamin D and Bone Health: Where we are in 2012**

Laura E. Ryan, MD
Clinical Assistant Professor
Center for Women’s Health
Division of Endocrinology, Diabetes and Metabolism
The Ohio State University Wexner Medical Center
55yo Postmenopausal Woman

- Presents for yearly evaluation – menopause age 51
- Wonders about bone health and need for ‘vitamins’
- Never a fragility fracture or height loss
- + Strong family history of hip fracture in both parents
- Never smoker, no steroid requirement
- ROS is negative, denies bone pain or muscle weakness
- You order bone density
- What do you recommend for vitamin D supplementation in this patient?

Actions of $1,25(OH)_2D$

- Stimulates intestinal calcium absorption
- Stimulates bone resorption at very high levels via osteoclastogenesis
- No evidence that it enhances bone formation directly
- ↓ PTH gene expression

Cutaneous Formation of Vitamin D

UVB → SKIN → 7-DHC, provitamin D$_3$ → Vitamin D$_3$ → LIVER → VitD-25-hydroxylase → 25(OH)VitD → 1α-hydroxylase → $1,25(OH)_2$ Vitamin D

Normal Activated Vitamin D Physiology

PTH

- Intestinal calcium absorption
- Hyperphosphatemia
- Hypophosphatemia
- Hypervitaminosis D

$1,25(OH)_2$Vit D

- Inhibition of PTH
- VDR
- RANKL on osteoblast
- RANK on Pre-osteoclasts

CrCl <30
New Recommendations for Calcium and Vitamin D supplementation, 11/30/2010:

IOM Dietary Reference Intakes for Calcium and Vitamin D: November 2010.

Optimal serum level of 25(OH) vitamin D remains debated:

- 445 healthy volunteers
- Age > 65yo
- Normal kidney/hepatic function
- National Institute on Ageing
- STOP/IT trial


Intestinal Calcium Absorption

Compiled from Bischoff et al, Heaney et al, Barger-Lux et al

WHI Calcium + D trial

- 36,282 postmenopausal women aged 50-69 – baseline BMD unknown/not selected
  - Greater difference likely would have been seen if selected for low bone density or low baseline vitamin D levels
  - Placebo or calcium (1000mg/day) + vitamin D (400 IU/d)
  - Were also allowed to take personal supplementation
  - Varying rates of compliance
  - Risk of hip fracture was not statistically significant between placebo vs. treatment group
  - When analyzed those who were 'very compliant', there was a significant benefit to being on vitamin D

Jackson RD, LaCroix AZ, et al. NEJM 2006; 354:669
Fracture Prevention

- Trevedi, 2003: 2686 participants, 65-85yo, community dwelling
- Given 100,000 IU orally q4mo (average 800IU/day) for 5 years
- Placebo group 25(OH)D: 21.2 ng/mL
- Treated group: 29.6 ng/mL
- 22% reduction in all fractures; 33% reduction in fragility fractures

Prevalence of grip strength loss (defined as loss >40%, study sample n = 1,008) and appendicular muscle mass loss (defined as loss >3%, study sample n = 331) during 3-yr follow-up according to categories of baseline serum 25-OHD concentration.

Visser M et al. JCEM 2003;88:5766-5772

Not everyone needs to have their vitamin D levels checked. Consider in:

- Elderly (age >65-70yo)
- Institutionalized/NH
- Dark skinned individuals
- Obese individual
- Hospitalized on general medicine service
- Patients with osteoporosis
- Fragility fractures
- Meds that increase vitamin D metabolism
- Pregnant women
- Malabsorption
- s/p bariatric surgery

First patient

- 55yo with strong family history hip fracture
- Being evaluated for osteoporosis
- Getting 25(OH) vitamin D level would be reasonable, along with calcium, PTH and albumin levels for physiologic context
- If her 25(OH) level is >20, IOM vitamin D recommendation:
  - 600 IU per day
Foods with Vitamin D

Image from: www.article-answers.com/best-sources-of-vitamin-d-in-foods/

How many of your patients eat 3 ounces salmon a day?
Unlike calcium, dietary vitamin D is often an inadequate source for our daily needs

<table>
<thead>
<tr>
<th>Foods with Vitamin D</th>
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<tbody>
<tr>
<td>Salmon 3 oz = 174 IU</td>
</tr>
<tr>
<td>Fortified cereal 1 cup = 40 IU</td>
</tr>
<tr>
<td>Fortified milk 1 cup = 120 IU</td>
</tr>
<tr>
<td>Egg yolk 1 egg = 4 IU</td>
</tr>
</tbody>
</table>

62yo female with gluten sensitivity and stress fracture of metatarsal

- GI symptoms have completely resolved on gluten-free diet, but she also finds that she might be lactose intolerant and avoids dairy
- Stress fracture of the foot occurred after she had been walking around on Black Friday for 8 hours
  - No other history of fractures
- She doesn’t smoke, no height loss, no family history of fractures
- Takes “burst” of steroids 1-2 x per year for asthma exacerbations, especially in the spring
- Takes one prenatal vitamin daily

Cholecalciferol (D3) vs. Ergocalciferol (D2)?

- Dietary egg yolks and oily fish – mainly have D3
- Fortified foods – mainly have D2
- Most recent meta-analysis of 7 randomized trials found that cholecalciferol (D3) is more effective at both increasing serum vitamin D levels and also maintaining that level in the setting of lower-compliance
  - All of these trials, however, were in the setting of high-dose repletion, rather than daily maintenance
  - Difference only seen in weekly or monthly higher-dosing regimens

Is this debate practical in central Ohio?
- CVS – has no cholecalciferol available
- Walmart does have cholecalciferol in stock
- Target – no cholecalciferol in stock, but could order it

35th Latitude – significant vitamin D deficiency is likely to occur 8-9 months of the year in more northern regions
By the way – our patient does live in central Ohio – sigh . . .
Evaluation of our patient:

- Calcium (total): 9.2 (8.6 – 10.0 mg/dL)
- Albumin: 3.8 (3.4 – 4.8 g/dL)
- Magnesium, phos: 1.8, 3.2
- BUN/creat: Creat 0.92 (0.6 – 1.1 mg/dL)
- Alk Phos: 76 (50-120 U/L)
- 25(OH) vitamin D: 23 (14.0 – 72.0 ng/mL)
- PTH: 81 (14.0 – 72.0 pg/mL)
- TSH: 1.67 (0.55 – 4.78 mIU/mL)
- DXA: LS T-score -1.6
  - TH T-score -1.5
  - FN T-score -2.4

Hypovitaminosis D Osteopathy

- Stage 1:
  - Reduced intestinal absorption of calcium; decreased skeletal calcium reserves
  - Osteoporosis; no biopsy evidence of osteomalacia
- Stage 2:
  - Decreased calcium absorption and bone mass (stage 1, cont)
  - No clinical or lab evidence of osteomalacia
  - Osteomalacia is evident on bone biopsy
    - Increased undermineralized osteoid, decreased mineral apposition rates
- Stage 3:
  - Osteomalacia – clinically, biochemically, histologically

Hypovitaminosis D Osteopathy

- First introduced by Parfitt in 1990
- Highlighting the pathophysiologic change in bone before the development of the definition of osteomalacia
- Three stages, based upon histomorphometric analysis of adult bone samples
- Links the connection of Vit D to osteoporosis

How would you deal with this patient’s low vitamin D and secondary hyperparathyroidism?

- My own practice:
  - PM Women with low bone mass, vitamin D >30: 1000-1200IU/day
  - 25(OH)D level 25-30
    - 2000 IU/day, recheck 3-4mo
    - 18 – 25
      - 50,000 IU weekly x 6weeks
      - 2000IU daily; recheck 3-4mo
      - 12-18
        - 50,000IU 2x/week x 6weeks
        - Likely will need high dose weekly indefinitely
        - Daily 1200 – 2000 units OTC
      - <12
        - See above, but also look for the cause of the malabsorption

Goal: normalize vitamin D, but possibly more importantly, normalize parathyroid hormone.
73 yo female presents with thigh pain and recent pelvic ramus Fx

- Hx Roux-en-Y gastric bypass surgery 18 years ago, with successful weight loss; she now weighs 160 lbs.
- Does take 500mg calcium citrate BID and one MVI daily
- Has had multiple falls over the last couple of years – recently fell down 4 back steps resulting in pelvic pain – to ER
- Admits to a sense of muscle weakness, causing her falls
- All of the bones of her legs hurt: “if my cat walks over my legs I scream in pain”
- Has lost 4” in height; broke wrist after falling onto the grass 2 summers ago

Evaluation

- Calcium 8.2
- PTH 185
- Phos 1.9
- Alk phos 224
  - Normal 38 - 126
- Creat – 0.60
- TSH – 2.1
- Vitamin D – 6
- 1,25(OH)vitamin D: 72
  - Normal 23 – 67

Diagnosis? Osteomalacia

P. van Schoor NM Primer on the Metabolic Bone Diseases, ASBMR, 2008, 329-335.

Treatment of Osteomalacia: Calcium and Vitamin D$_3$ Prevent Hip Fractures

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>CaD</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Hip</td>
<td>110</td>
<td>80</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Non-vertebral</td>
<td>215</td>
<td>160</td>
<td>&lt; 0.004</td>
</tr>
</tbody>
</table>

Chapuy et al. NEJM 1992;327:1637-42.

Treatment of Vitamin D Deficiency in Osteomalacia

- Often requires 50,000 unit capsules dosed up to daily
- May take 12-18 months to reverse whole-body depletion of calcium and vitamin D
- With persistent malabsorption or Roux-en-Y gastric bypass, may need 50,000 units 1-2x per week as maintenance, indefinitely
- Activated forms of vitamin D, calcitriol, are sometimes required
- Endpoint: normalization of alkaline phosphatase, PTH, blood calcium levels, and a normal 24hr urinary excretion of calcium; improvement of BMD by DXA
- Endocrinology consultation is often helpful
Vitamin D and Bone Health

- A serum level of 25(OH) vitamin D of > 20 ng/dL is important for bone health.
- Not everyone needs to have a vitamin D level checked.
- Cholecalciferol may be more effective at raising and maintaining vitamin D stores, but is not widely available and has not been proven to be superior in preventing fractures.
- Optimal vitamin D supplementation regimen is not well established and range from daily, weekly to monthly dosing.
  - Yearly dosing with 500,000 IU may be harmful.
- Vitamin D supplementation in the setting of secondary hyperparathyroidism or osteomalacia often requires much higher doses of vitamin D or calcitriol.

Vitamin D Status: Diet and Sunlight

Prevalence of Low Vitamin D Status: The impact of sunlight.
US Adults (NHANES 2005-2006)

Intakes <400 IU/d (10 µg/d): 71%
Serum 25(OH)D <40 nmol/L: 19%
Vitamin D Assays

- Multiple different systems and changes in assay characteristics over time (Immune, HPLC, LC/MS).
- Quality control inconsistent
- Assay differences are concentration dependent
- Coefficients of Variation can be 10-20%
- We need established standards
  - Performance characteristics: CVs, specificity, sensitivity
  - Performance on external QC programs – e.g., DEQAS
  - Relationship to external reference standards (e.g., NIST SRM)

**Vitamin D: The Panacea for Cancer.**

What is the evidence?

Is it sufficient for "public health" guidelines?
Health Outcomes Evaluated: Indicators

- Cancer / Neoplasms
  - All cancers (overall cancer risk)
  - Breast Cancer
  - Colorectal Cancer/Colon Polyps
  - Prostate Cancer
- Cardiovascular Diseases and Hypertension
- Diabetes (Type 2) and Metabolic Syndrome (Obesity)
- Falls
- Immune Functioning
- Asthma
- Autoimmune Disease
- Infectious Diseases
- Neuropsychological Functioning
- Physical Performance
- Preeclampsia of Pregnancy

Vitamin D and Human Cancer

- Very weak data for dietary intake and most cancers.
- Strongest data is for serum 25OHD and colon cancer
- Few RCT in cancer
  - Studies completed test single dosages of Vit D
  - Studies often provide both Vit D and Calcium
  - Confounding with diet and/or exercise behaviors
  - Baseline status may be critical
  - Lower 25OHD groups may show benefit.
- Potential for U-shaped curve for pancreatic cancer.
- Many cancers have not been studied.
Vitamin D and Human Cancer

- Genetics has not been incorporated.
  - Human genetic variation.
    - Polymorphisms of vitamin D signaling
    - Cancer predisposition genotype
  - Genetic heterogeneity of the cancer
- Additional prospective studies, including consortia
- Deeper investigation into organ site differences
- Controlled trials –
  - multiple dosages over a wider range
  - longer durations
  - starting earlier

Human Studies of Vitamin D and Cancer

- Target populations
  - Cancer risk profile (frequency of outcome)
    - General population
    - Higher risk population
      - Age
      - Ethnicity
  - Genetic predisposition
  - Carcinogen exposure
  - Premalignant condition
  - Cancer present
    - Pre-surgical models
- Exposure Measures
  - Document diet, serum, and tissue metabolites
Vitamin D and Cancer Risk
Vitamin D and Omega-3 Trial

- PI's: JoAnn Manson and Julie Buring, Harvard Medical
- Recruiting ~20,000 women and men
- All cardiovascular disease and cancer
- Combination of vitamin D 2,000 IU + ω-3 1g vs. placebo
- 5 years supplementation

Planned Ancillary Studies in VITAL

<table>
<thead>
<tr>
<th>Funded</th>
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<tbody>
<tr>
<td>Cognitive Function</td>
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<td>Colorectal Adenomas</td>
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<td>Hypertension</td>
<td>Non-invasive Vascular Imaging</td>
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<td>Bone Microarchitecture</td>
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<td>Mood Disorders/Depression</td>
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<td>Infections</td>
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