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

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Disclosures

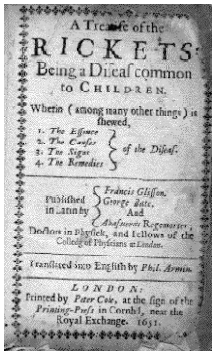
Financial: None

Conflicts of Interest: None

Strong Opinions: Many

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)


A Treatise of the
RICKETS
Being a Disease common
to CHILDREN.
Wherin (among many other things) is
shewed,
1. The Essence
2. The Causes
3. The Signs
4. The Remedies
of the Disease.
Published in Latin by Francis Glisson, George Bate, And Abdiah Cooke Regiomontes, Doctors in Physick, and Fellows of the College of Physicians at London.
Translated into English by Phil. Armin.
LONDON:
Printed by Peter Cole, at the sign of the Printing-Press in Cornhil, near the Royal Exchange. 1651.

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 Glisson and contributors provided a clear description of rickets.

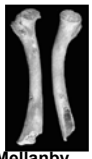
They did not recognize that diet played a role in the etiology of the disease.

Rickets


Edward Mellanby


E. V. McCollum

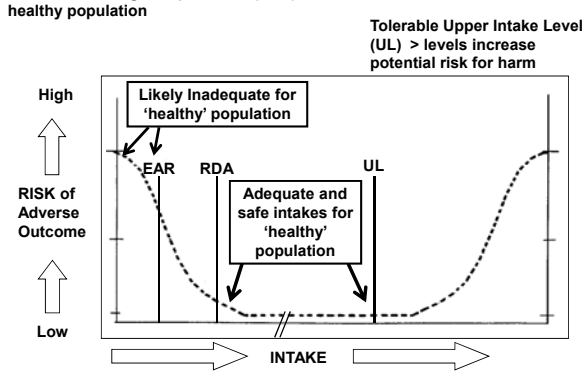

Harry Steenbock



- 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 antirichetic 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.

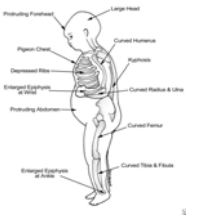
Recommended Dietary Allowance (RDA) – meets the needs of 97.5% of healthy population

Estimated Average Requirement (EAR) – meets the needs of 50% of healthy population



Dietary reference Intakes(DRIs)

The Dramatic Reduction in Rickets



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

REPORT BRIEF | NOVEMBER 2010

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For more information visit www.iom.edu/vitamind

Dietary Reference Intakes for Calcium and Vitamin D

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

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 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

Agency for Healthcare Research and Quality: AHRQ

Number 183

Vitamin D and Calcium:
A Systematic Review of Health Outcomes

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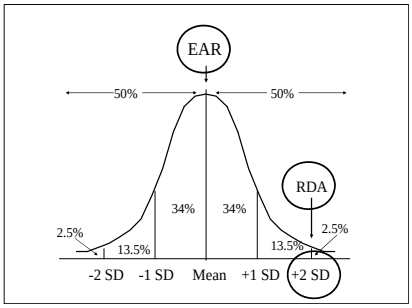
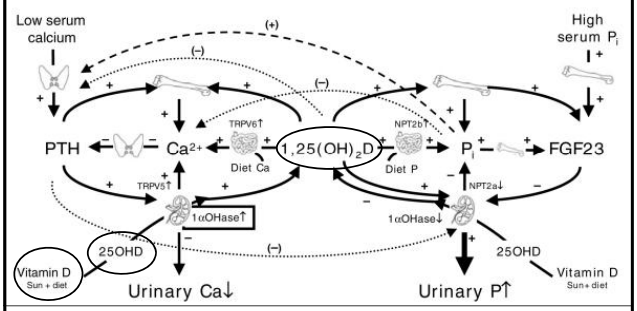
August 2009

Picture Worth 1000 Words
Frequency Distribution of Requirements



Interrelationship of Calcium, Phosphate and Vitamin D



Prentice A. ***Proc Nutr Soc. 2007; 66(4): 512–521***

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**

Vitamin D: 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

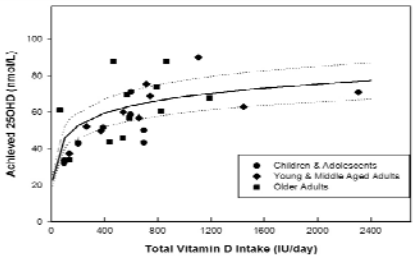
- **Step 2 – Determine how much intake to achieve designated serum level**
  - **<u>Assumption</u> of minimal sun exposure**
  - **Integration of studies conducted in winter in northern latitudes (many recent studies)**
  - ***Simulation of dose-response curve***

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

Ages (yrs)	Recommended Dietary Allowance (RDA)[a]	Tolerable Upper Intake Level (UL)[b]
1 – 3	600	2500
4 – 8	600	3000
9 – 70	600	4000
>70	800	4000

<u>Adequate intakes</u> **for infants are 400 IU/d and ULs are 1000-1500 IU/d [a]Covers the needs of ≥97.5% of the population [b]Level above which there is risk of adverse events**

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



Calcium ERA and DRI

	EAR (mg/day)	RDA (mg/day)
1-3 years	500	700
4-8 years	800	1000
9-18 years	1100	1300
19-5 0 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**

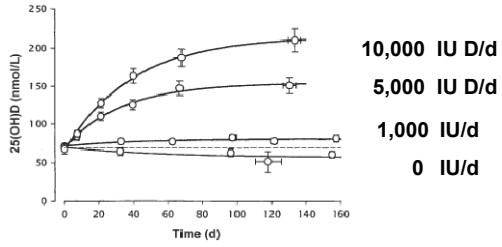
Derivation of Upper Limit: Adults

- 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)

	Vitamin D (IU/day)
Infants 0 to 6 mos	1000
Infants 6 to 12 mos	1500
1-3 years	2500
4-8 years	3000
9-18 years	4000
19-50 years	4000
51-70+ years	4000
Preg/Lac 14-18	4000
Preg/Lac 19-50	4000

Extended Oral Dosing of Vitamin D



10,000 IU D/d
5,000 IU D/d
1,000 IU/d
0 IU/d

*Heaney et al., AJCN 2003

Vitamin D and Bone Health: Where we are in 2012

Laura E. Ryan, MD
Clinical Assistant Professor
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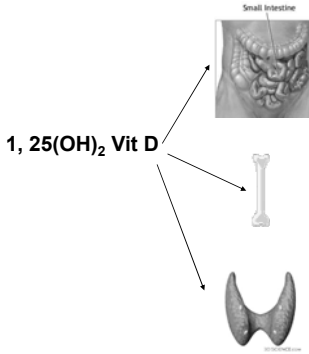
The Ohio State University Wexner Medical Center

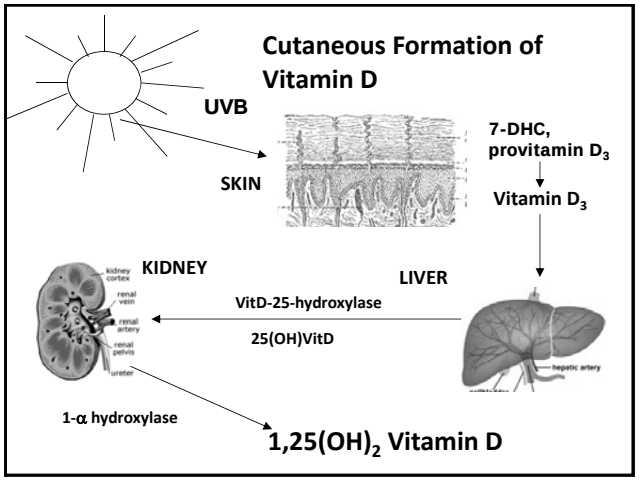
55yo Postmenopausal Woman

- 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?

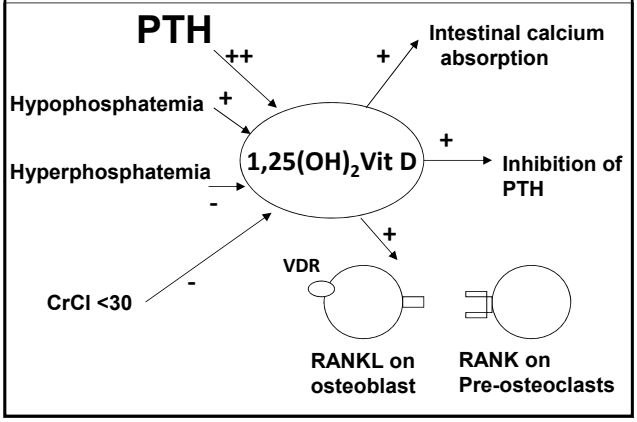
Actions of $1,25(OH)_2D$



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



Normal Activated Vitamin D Physiology



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

Dietary Reference Intakes for Calcium and Vitamin D

Life Stage Group	Calcium: Estimated Average Requirement (mg/day)	Calcium: Recommended Dietary Allowance (mg/day)	Calcium: Upper Level Intake (mg/day)	Vitamin D: Estimated Average Requirement (IU/day)	Vitamin D: Recommended Dietary Allowance (IU/day)	Vitamin D: Upper Level Intake (IU/day)
Infants 0 to 6 months	*	*	1,000	**	**	1,000
Infants 6 to 12 months	*	*	1,500	**	**	1,500
1–3 years old	500	700	2,500	400	600	2,500
4–8 years old	800	1,000	2,500	400	600	3,000
9–13 years old	1,100	1,300	3,000	400	600	4,000
14–18 years old	1,100	1,300	3,000	400	600	4,000
19–30 years old	800	1,000	2,500	400	600	4,000
31–50 years old	800	1,000	2,500	400	600	4,000
51–70 year old males	800	1,000	2,000	400	600	4,000
51–70 year old females	1,000	1,200	2,000	400	600	4,000
>70 years old	1,000	1,200	2,000	400	800	4,000
14–18 years old, pregnant/lactating	1,100	1,300	3,000	400	600	4,000
19–50 years old, pregnant/lactating	800	1,000	2,500	400	600	4,000

*For infants, Adequate Intake is 200 mg/day for 0 to 6 months of age and 260 mg/day for 6 to 12 months of age.
**For infants, Adequate Intake is 400 IU/day for 0 to 6 months of age and 400 IU/day for 6 to 12 months of age.

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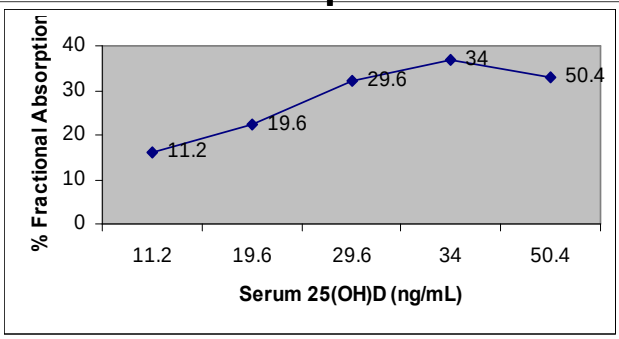
IOM Dietary Reference Intakes for Calcium and Vitamin D. November 2010.

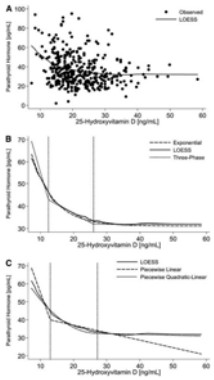
Intestinal Calcium Absorption



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

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



Durazo-Arvizu R A et al. J. Nutr. 2010;140:595-599

WHI Calcium + D trial

Table 2. Odds Ratios of Risk for Hip Fracture*

25-Hydroxyvitamin D Level		Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)†
Per 2.5-nmol/L decreaset		1.03 (1.01–1.05)	1.03 (1.01–1.05)
Per 25-nmol/L decrease		1.30 (1.07–1.58)	1.33 (1.06–1.68)
Quartile (according to control group)			
First (9.2–47.5 nmol/L)	3 – 19 ng/mL	1.73 (1.13–2.66)	1.71 (1.05–2.79)
Second (47.6–60.1 nmol/L)		1.08 (0.72–1.63)	1.09 (0.70–1.71)
Third (60.2–70.6 nmol/L)	24-28 ng/mL	0.78 (0.50–1.20)	0.82 (0.51–1.31)
Fourth (70.7–121.5 nmol/L)	28.2 – 48.6 ng/mL	1.00 (reference)	1.00 (reference)

- 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

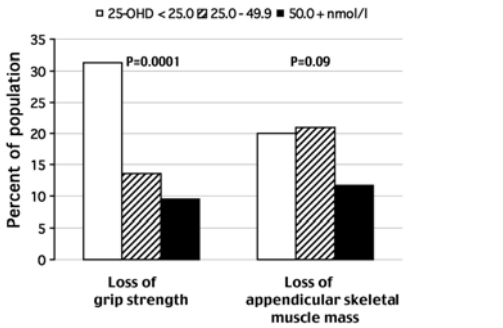
Fracture Prevention

- Trevedi, 2003: 2686 partcipants, 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

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

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

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

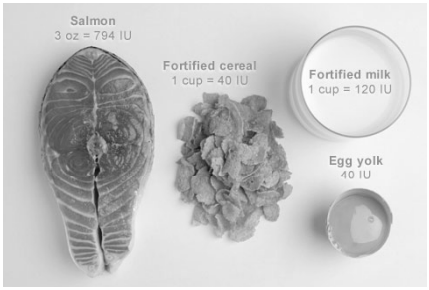


Image from: www.article-answers.com/best-sources-of-vitamin-d-in-foods/

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

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**
  - **Tripkovic L, Lambert H et al. Am J Clin Nutr. 2012; 95:1357**

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

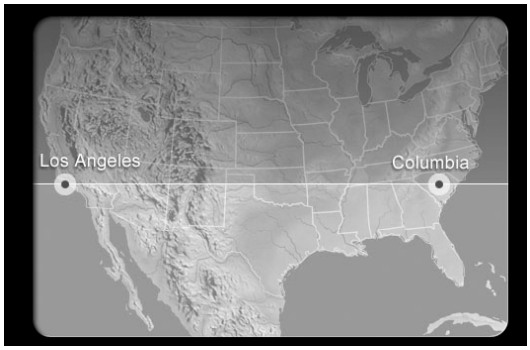


Image from www.menopause.org

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)
- Albumin
- Magnesium, phos
- BUN/creat
- Alk Phos
- 25(OH)vitamin D
- PTH
- TSH
- DXA

- 9.2 (8.6 – 10.0 mg/dL)
- 3.8 (3.4 – 4.8 g/dL)
- 1.8, 3.2
- Creat 0.92 (0.6 – 1.1 mg/dL)
- 76 (50-120 U/L)
- 23 (30 – 100 ng/mL)
- 81 (14.0 – 72.0 pg/mL)
- 1.67 (0.55 – 4.78 mIU/mL)
- 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**?

Women 50 -70
Men
Women >70

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

- 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

Treatment of Osteomalacia: *Calcium and Vitamin D_3 Prevent Hip Fractures*

- 3270 women, 69 to 106 years
- Nursing homes / Apartments
- Ambulatory
- Follow-up 18 month
- Vitamin D deficient

	Number of Fractures by Prescription Group		
	Placebo	CaD	p
Hip	110	80	< 0.001
Non-vertebral	215	160	< 0.004

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

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 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

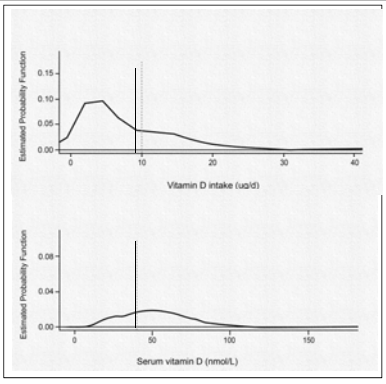
- A serum level of 25(OH)vitamin D of ≥ 20ng/dL is important for bone health
- Not everyone needs to have a vitamin D level checked
- Cholecalciferol may be more effective at raising and maintaining vitamin D stores, but is not widely available and has not been proven to be superior in preventing fractures
- Optimal vitamin D supplementation regimen is not well established and range from daily, weekly to monthly dosing
  - yearly dosing with 500,000IU 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

Vitamin D and Health

Steven K. Clinton, MD, PhD
Professor
Department of Internal Medicine
Division of Medical Oncology
The Ohio State University Wexner Medical Center

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

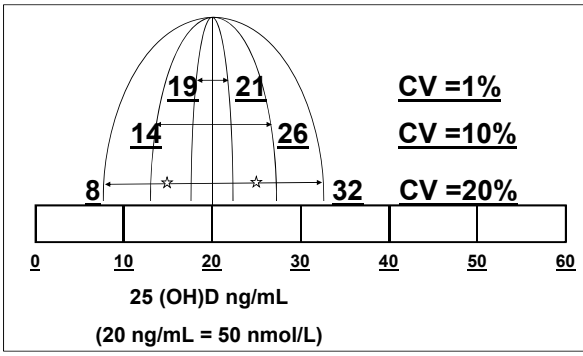


Intakes <400 IU/d (10 µg/d): 71%

Serum 25(OH)D <40 nmol/L: 19%

Vitamin D Assay.

Impact of Assay CV on A 25 (OH) Vitamin D Result



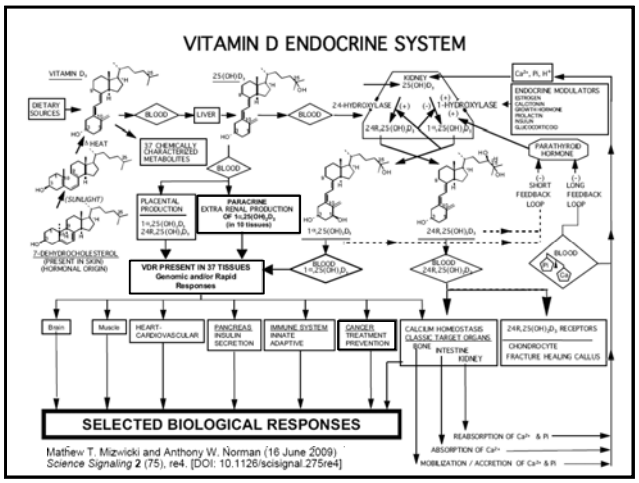
Vitamin D Assays

- 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.

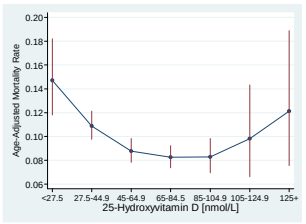
What is the evidence?

Is it sufficient for "public health" guidelines?

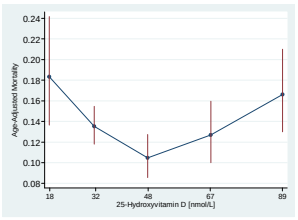


Committee analysis of NHANES data: Confirmed published U-Shaped Relationship

(Melamed, Arch Int Med 2008)



NHANES African Americans, IOM Analysis, unpublished data



Health Outcomes Evaluated: Indicators

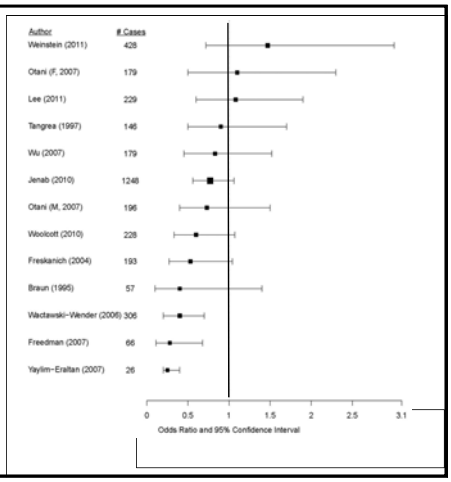
- Cancer / Neoplasms
  - All cancers (overall cancer risk)
  - Breast Cancer
  - Colorectal Cancer/Colon Polyps
  - Prostate Cancer
- Cardiovascular Diseases and Hypertension
- Diabetes (Type 2) and Metabolic Syndrome (Obesity)
- Falls
- Immune Functioning
- Asthma
- Autoimmune Disease
- Infectious Diseases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

Observational Studies



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

Randomized Intervention Trial

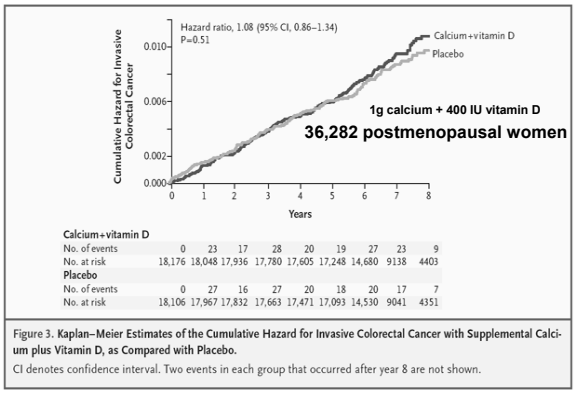


Figure 3. Kaplan–Meier Estimates of the Cumulative Hazard for Invasive Colorectal Cancer with Supplemental Calcium plus Vitamin D, as Compared with Placebo.
CI denotes confidence interval. Two events in each group that occurred after year 8 are not shown.

J Wactawski-Wende et al. NEJM, 2006

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

Funded
- Cognitive Function
- Diabetes/Glucose Tolerance
- Hypertension
- Autoimmune Disorders
- Asthma/Respiratory Diseases
- Diabetic Nephropathy
- Fractures
- Mood Disorders/Depression
- Infections

Pending
- Macular Degeneration
- Colorectal Adenomas
- Non-invasive Vascular Imaging
- Bone Microarchitecture