


10:45 – 11:30 am

Vitamin D Deficiency

SPEAKER
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The following relationships exist related to this presentation:

- ▶ Frank J. Domino, MD: No financial relationships to disclose.

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Vitamin D Deficiency

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Objectives

- 1. Summarize the basics of Vitamin D metabolism.
- 2. Identify who to screen for Vitamin D Deficiency.
- 3. Assess when to recommend Vitamin D Supplementation.
- 4. Recognize outcomes improved by Vitamin D Deficiency treatment.

Theories: Vitamin D Deficiency

1. Sunscreen
2. Fluorescent Lights
3. H. Pylori
4. Milk Intake
5. Unknown

Why Is Everyone Vitamin D Deficient?

- Theories:
- ↓ Milk Consumption
- Fat Soluble → Need larger amount

Why is everyone Vitamin D Deficient?

- Theories:
- ↓ Milk Consumption
- Obesity
- Sun Exposure:
Sunscreen, Windows, Walking

Why Is Everyone Vitamin D Deficient?

- Theories:
- ↓ Milk Consumption
- Obesity
- Sun Exposure
- PPI Use:
PPI → ↑ pH → ↓ Ca Absorption → ↑ PTH

Physiology of Vitamin D

- NOT a Vitamin; but rather a *hormone*
- Fat Soluble
- Vitamin D “job”: to maintain Serum Calcium
- Obtained from Diet or Sun Exposure
- UV B converts 7 dehydrocholesterol to D3
- Dietary Vitamin D3 & D2 thru. Intestine
- Both bound to Vit D3 binding protein.

Glossary

- Vitamin D —Calciferol; group of chemicals related to Vitamin D
- Cholecalciferol (D3) In animal foods and supplements
- Ergocalciferol (D2) from Plant sources
- Calcidiol (25 Hydroxy D3) *** Serum Level
- Calcitriol (1, 25 Hydroxy D3) Active Form

Vit D Recommendations

	<u>USDA 1999</u>	<u>IOM 2011</u>
■ 19-50 years	200 IU/Day	600 IU
■ 51-70 years	400 IU/Day	600 IU
■ 71- up	600 IU/Day	800 IU
■ Pregnancy	(PNV 400)	600 IU
■ Infants (Breastfed)	200 IU/Day	400 IU**
■ Children (< 16 oz milk)	200 IU/Day	600 IU
■ http://dietary-supplements.info.nih.gov/factsheets/vitamin_d.asp#h3		
■ USPSTF: 65 Years	>= 800 IU/Day	

2011: Newborns 400 IU/Day

- American Academy of Pediatrics updated their 2003 recommendation
- “all children should be give 400 IU/day *within a few days of birth.*”
 - This is a doubling of their previous recommendation.

www.cdc.gov/breastfeeding/recommendations/vitamin_d.htm

Dietary Sources

Dietary Supplement Fact Sheet: Vitamin D - Microsoft Internet Explorer

Address: <http://dietary-supplements.info.nih.gov/factsheets/vitaminD.asp#t2>

Table 1: Selected food sources of vitamin D [10-12]

Food	International Units (IU) per serving	Percent DV*
Cod liver oil, 1 Tablespoon	1,360	340
Salmon, cooked, 3½ ounces	360	90
Macaroni, cooked, 3½ ounces	345	90
Tuna fish, canned in oil, 3 ounces	200	50
Sardines, canned in oil, drained, 1½ ounces	250	70
Milk, nonfat, reduced fat, and whole, vitamin D fortified, 1 cup	98	25
Margarine, fortified, 1 Tablespoon	60	15
Pudding, prepared from mix and made with vitamin D fortified milk, ½ cup	50	10
Ready-to-eat cereals fortified with 10% of the DV for vitamin D, ½ cup to 1 cup servings (servings vary according to the brand)	40	10
Egg, 1 whole (vitamin D is found in egg yolk)	20	5
Liver, beef, cooked, 3½ ounces	15	4
Cheese, Swiss, 1 ounce	12	4

*DV = Daily Value. This is reference numbers developed by the Food and Drug Administration (FDA) to help consumers determine if a food contains a lot or a little of a specific nutrient. The DV for vitamin D is 400 IU (10 µg) for adults. Most food labels do not list vitamin D content unless a food has been fortified with this nutrient. The percent DV (DV%) listed on the table.

Centrum Silver 500 IU

*Who is at RISK for VitD D

- ?Women at Menopause
- Dark Skinned Individuals
- Veiled
- Seniors/Nursing Home
- Multiple Fractures
- **Pregnant/Lactating/PMS**
- Malabsorption
- Seizure Meds

Vitamin D testing: Coding

- Pre Menstrual Synd 625.4
- Arthralgias 719.49
- Fatigue 780.79
- Diabetes (T2) 250.00
- Malabsorption 579.8
- Irritable Bowel Synd 564.1
- Menopausal Disorder 627.8

How to Test

- **25 Hydroxy (OH) Vitamin D level**
 - Most sensitive measure of body stores
- 1,25 Vitamin D active form, but varies
- Interpretation: **IOM (PTH)**
 - WNL: 20-100 ng/ml
 - Deficient < 20 ng/ml
- No need for PTH and Calcium *except*:
 - Serious Cardiac Arrhythmias
 - Renal Insufficiency
 - Malignancy

A Statistical Error in the Estimation of the RDA for Vitamin D.

- IOM did NOT include Pts Vit D taking > 2400 IU/day
- Recalculate RDA using all data →
- ~7000 IU/day from all sources → IOM's goal of >20 ng/mL as the lower level of sufficient
- *All-source* intake of 7000 IU/day is below the no observed adverse effect level (NOAEL) of the IOM

Nutrients 2014, 6, 4472-4475

Case of the A Family

- Osama A. 51 y/o male from Sudan; 4 children
- 25 Vit D: 20-100 WNL, < 20 ng/mL Deficient **25 Vit D**
- Oldest son Ahmed, tears ACL Soccer 12 ng/ml
- Youngest Son, Osman, fx Ulna cross St 9 ng/ml
- Second Son, Ayman, Fx Tib/Fib Soccer 15 ng/ml
- Daughter, Amal, Fx wrist PE @ school Undetect
- Osama (Dad) Fx wrist tripping on curb 12 ng/ml

Treatment

<u>25 Vitamin D*</u>	<u>Status</u>	<u>Treatment</u>
■ 20 – 100 ng/mL	Sufficient	800-4,000 IU D3/Day
■ < 20 ng/mL	Deficient	50,000 IU D2/week (Ergocalciferol) x 12 Wk Then 2,000 D3/Day
■ ????	Calcium	

IOM/ES: Tolerable Upper Intake Level (UL) **4,000 IU/d**

D2 vs D3: Cochrane 2014

- “Vitamin D in the form of vitamin D(3) seems to decrease mortality in predominantly elderly women who are mainly in institutions and dependent care.
- Vitamin D(2), had no statistically significant effect on mortality (small, short RCT’s).
- Vitamin D(3) combined with calcium significantly increased nephrolithiasis
- Cochrane Database Syst Rev, 2014 Jan 10;1:CD007470

Caution with Vitamin D Supplementation

- Sarcoid
- Tuberculosis
- Lymphoma
- Vitamin D + Ca++ → Renal Calculi

Why not just take extra Calcium? Ca Does NOT↓ Osteoporotic Fractures

- Cohort Study of 61,000 women x 19 years
- Influence of Ca intake and Fracture
- Ca Intake beyond 700 mg did NOT reduce Fx Risk
BMJ 2011; 342: d1473

2010 Calcium Without Vitamin D Increases Risk of MI

- Meta Analysis of 15 trials, ~20,000 patients
- Age > 40 yr; > 1 year, Men & Women
- Median F/U > 3.5 years
- Ca alone ↑ MI (RR = 1.27; 95CI 1.02-1.67)
- NNH ~125

BMJ 2010; 341: c3691

2011 Ca + Vit D in Women ↑ CHD RISK

- Reanalysis of WHI data
- Meta Analysis of subset of data (28,000)
Ca + Vit D Supp →
RR MI/CVA 1.15(1.03-1.27)
- HOLD the Ca+

BMJ 2011; 342: d2040

Instead: Dietary Sources of Calcium

- Dairy (Milk, Yogurt) (300mg)
- Green leafy vegetables: broccoli, collards, kale, mustard greens, turnip greens, and bok choy
- Salmon & sardines canned (w/bones)
- Nuts & Beans: Almonds, Brazil nuts, sunflower seeds, tahini, and beans

What Outcomes are influenced by Vitamin D?

2012 Vitamin D (>800 IU/Day) Reduces Hip and Non-Vertebral Fractures in Community Dwelling Adults aged ≥ 65 Years

- **Meta-analyses on 800 IU Vitamin D & fracture**
- 11 RCT; 31,000 patients aged > 65 years of age
- **30% reduction risk of hip fracture**
(HR: 0.70; 95% CI, 0.58 to 0.86) and
- **4% reduction in risk of any nonvertebral fracture** (HR: 0.86; 95% CI, 0.76 to 0.96).

N Engl J Med 2012;367:40-9.

Osteoporosis Treatment

- **Osteoporosis:**

Most studies of Rx (Bisphosphonates, etc.) ALSO include **Vitamin D, Calcium and Weight Bearing Exercise**

-

"Based on relationship between 25(OH)D, bone mineral density, bone turnover, lower extremity function, & falls, supplementation should aim to increase 25(OH)D levels" > 30 ng/ml range

Clin Endocrinol (Oxf). 2009 Sep 10

Vit D Def in Pregnancy : ↑ Gest DM, Pre-Eclampsia & SGA, BV, LBW

- Systematic Review & Meta Analysis of 31 Observational Studies
- **Vitamin D Insufficiency (< 30 ng/ml):**
 - ↑ Gestational diabetes OR = 1.49
 - ↑ Pre-eclampsia OR = 1.79 ,
 - ↑ Small for gestational age infants OR = 1.85.
 - ↑ Bacterial vaginosis & Lower birth weight infants

BMJ 2013;346:f1169

Vit D Def ↑ Risk: Peds: Gastroenteritis and OM

- Observational Study: 475 Children (x=8.9 Yrs)
- 25 OH VD and daily morbidity diary
- **Vitamin D Deficiency:**
- Diarrhea w/Vomiting RR = 2.05
- Ear Ache/Discharge/Fever RR = 2.36
- Cough w/Fever not sig.

Pediatr Infect Dis J. 2013; 32(6): 585

Vit D Supplementation Reduces Risk of Recurrent Pediatric Otitis Media

- RCT 116 children (age 1-5 yr) w/Recurrent OM (≥ 3 in 6 months or ≥ 4 in 12 months)
- 1,000 IU Vit D/Day vs placebo x 4 months
- ≥ 1 OM 26 vs 38; $p = 0.03$
- Risk of OM reduced when $25\text{ OH} > 30\text{ ng/ml}$

Pediatr Infect Dis J 2013; 32: 1055

2008 RCT of vitamin D to prevent influenza A in schoolchildren

- 2008 Small RCT Vitamin D(3) (1200 IU/d) vs placebo schoolchildren on of Influenza A:
- Influenza A in 10.8% in vitamin D(3) vs 18.6% in placebo RR=0.58; 95% CI: 0.34-0.99; $P = 0.04$
- Asthma attacks occurred in 2 children vitamin D(3) vs 12 in placebo (RR: 0.17; 95% CI: 0.04-0.73; $P = 0.006$).
- This study suggests vitamin D(3) supplementation in winter may reduce the incidence of influenza A

Am J Clin Nutr. 2010 May;91(5):1255-60

Vit D & Pediatric Atopic Dermatitis

- RCT Mongolian children w/winter atopic dermatitis.
- 1000 IU per day of cholecalciferol vs. placebo x 1 month+ emollient and patient education.
- Vitamin D \rightarrow improved Eczema score (-6.5 vs. -3.3, $p=0.04$) & global assessment ($p=0.03$).
- Conclusion: Vitamin D in Mongolian children improved atopic dermatitis patient & evaluator scores.

J Allergy Clin Immunol 2014;134:831-5.

Obesity

- 2 Year Vit D Weight Loss Trial, 300+ Patients
- Baseline; Higher BMI \rightarrow Lower 25 OH Vit D
- After 2 Years & Adjusting for age, sex, baseline BMI, total fat intake, and diet group assignment
- **Highest D intake lost additional 5.6 Kg x 2 yrs**
- ? Fecal Fat Excretion
- Higher Intake Vit D \rightarrow Greater Wt Loss

Am J Clin Nutr. 2010 Nov;92(5):1017-22

Obesity & Depression

- Cross Sectional, then **RCT** of Vit D on Depression in Obese Patients
- 440+, BMI: 28-47, $\sqrt{25\text{ VD}}$ & Beck Dep Inventory
- Subjects with Low Vit D \rightarrow Higher Beck scores
- RCT: D3--40K, 20K/week vs Placebo x 1 Yr
- 1Yr: \downarrow Beck in 40K & 20K D3, \downarrow PTH; No Δ Placebo
- **Treat patients with Depression with Vitamin D**
- Jorde: *J Intern Med* 2008; Dec;264(6):599-609

Multiple Sclerosis & VDD

- **Strong Epidemiologic data that Poor Vitamin D status increases risk for MS**
- Observational data \rightarrow VDD may predict poor clinical course in those with MS
- MS patients higher risk of falls & Osteoporosis
- **Initial Clinical trial data of MS patients + high dose Vitamin D pending**
- **Suggested serum goal of 30-60 ng/mL**

Expert Rev Neurother. 2012 Sep;12(9):1101-12

Vitamin D Deficiency Increases Risk of Dementia & Alzheimer disease

- 1,658 elderly adults W/O dementia, CV disease, and stroke
- 25 (OH)D vs. all-cause dementia & Alzheimer disease x 5 yr

All-cause Dementia Alzheimers

- Severe VDD (<10 ng/ml)
2.25 (1.23–4.13) 2.22 (1.02–4.83)
- Deficient (10-20 ng/ml)
1.53 (1.06–2.21) 1.69 (1.06–2.69)

- Conclusion: Vitamin D deficiency is associated with an ↑risk of all-cause dementia and Alzheimer disease.

Neurology® 2014;83:920–928

Pre Menstrual Syndrome

- PMS is related to cyclic decrease in Calcium and increase in PTH
- Nurses' Health Study II Case/Control 1000+
- Highest Vit D (~700 IU/D) RR of PMS of 0.59
- Similar trend with Calcium Intake

Vit D and Calcium MAY reduce PMS

■ Journal of the American College of Nutrition. 19(2):220-7, 2000 Apr
■ Arch Intern Med. 2005 Jun 13;165(11):1246-52 .

Vitamin D & Cancer

1. 2006 Sys. Review of 63 **Observation** Studies

Adequate Vit D Levels -> ↓ Risk

- 30 Colon Cancer (20/30)
- 13 Breast Cancer (9/13)
- 26 Prostate Cancer (13/26)
- Low VD Level → ↑ Ovarian Cancer (7)

Am J Public Health. 2006 Feb;96(2):252-61

2014 AHRQ Umbrella Review Vitamin D and Cancer –

- Colorectal cancer – **low** serum 25 OHVD concentrations increased risk of colorectal cancer. No data on supplementation and risk change.
- Breast cancer – some relationship between **low** 25 OH vitamin D levels and a risk for breast cancer.
- Pancreatic cancer – **high** vitamin D concentration (≥ 40 ng/ml) in an increased risk of pancreatic cancer.
- Prostate cancer – **no** new data association between 25 OHVD concentration and risk for prostate cancer.

BMJ 2014;348:g2035

HTN & Vitamin D: ~ NaCl Restriction

1. Hypertension NHANES III data (IOM Ob)
 2. **BP lower in highest Quintile of 25 VD v lowest.**
- Elevations of Blood Pressure were highest in Non-Hispanic Blacks compared to Whites.

Am J Hypertension 2007; 20:713

2. HTN: **Vit D. Suppl. (8-12 weeks) → ↓ BP**

Average ↓: Systolic > 5 mmHg (NNT=3),
Diastolic > 5 mmHg (NNT=7)

■ J Clin Endo Met 2001; 86(4): 1633

Low Vit D -> Increased Risk of MI

- Case Control study of 18,000+ Men
- If Deficient (<= 15 ng/mL) → RR=2.09
- If Insufficient (<=) 30 ng/mL → RR=1.6

after adjusting for:

FHx CAD, BMI, EtOH, Activity level,
Diabetes mellitus, HTN, Ethnicity, LDL

Vitamin D Def increases risk of MI

Giovanucci, et al. Arch Intern Med 2008; 168(11): 1174-80

VDD & CHD: Kansas

- Cohort Study of ~ 11,000 found VDD:
- Associated w/ HTN, CAD, and DM ($p < 0.05$).
- **VDD Strong predictor of all-cause death** (odds ratios 2.64, 95% CI 1.901 to 3.662, $p < 0.0001$) adjusting for multiple clinical variables.
- **Vitamin D supplementation conferred 'substantial survival benefit'** (OR death 0.39).

Am J Cardiol. 2011 Nov 7

2008 Vitamin D Deficiency & ↑ Risk of All Cause Mortality

- Melamed: Cohort 13,000 NHANES
- **Lowest quartile of 25 OH Vitamin D → ↑ Risk of All Cause Mortality**
- **Mortality RR=1.26 (95% CI 1.08 - 1.46)**
Arch Intern Med. 2008;168:1629-1637.

2014: Meta Analysis Vit DD ↑ Risk of Cardiovascular, Cancer, and Other Causes of Death

- Systematic review & meta analysis ~ 900,000
- Top vs. Bottom Third of serum 25 OH VD: LOW →:
 - CV Mortality RR=1.35 (CI=1.13-1.16),
 - Cancer Mortality 1.14 (1.01-1.29),
 - Non-vasc/non-cancer death 1.30 (1.07-1.59)
- All Cause Mortality 1.35 (1.22-1.49)**

BMJ 2014; 348:g1903.

What Decreases Risk of All Cause Mortality?

- Seatbelts
- Clean Water
- Vaccines
- Exercise

2007 Vit. D Supplementation Decreases of All Cause Mortality

- Meta Analysis: 18 studies of 57,000+ Adults
- Examined Risk of Death Any Cause in **RCT** Vitamin D Supplementation
- Average dose
- > 500 IU/D
- **Vit D Supplementation Decrease in All Cause Mortality (RR = 0.93)**
- Autier: *Arch Int Med* 2007;167(16): 1730

2011 Systematic Review on VD Supplementation

- Cochrane Systematic Review: **50 trials, 90,000+**
- Vitamin D Supp →
 - **DECREASE ALL CAUSE MORTALITY**
 - Vitamin D decreased mortality → RR 0.97
 - Subgroup Analysis: **Older women best outcomes**

Cochrane Database of Systematic Reviews 2011, Issue 7. Art. No.: CD007470

What Didn't Improve in RCT of Vitamin D Supplementation

- Chronic Myalgias/Fibromyalgia
- Upper Respiratory Tract Infections
- "Cure" Psoriasis (? Maybe oral for Tx....)
- Seasonal Affective Disorder
- Treat Osteoarthritis pain
- COPD exacerbations
- Academic Achievement in Adolescents
- Diabetes Prevention

Is this Real?

- **MOST data is *observational* research, rather than RCT's**
- Reference Range of 25 OH Vitamin D based loosely on suppressing PTH
- VDD Association with poor health status
- OTC Drug-- little initiative to study
- Analogous to Treating ↑ Homocysteine or Vitamin E and CHD

Data Summary

SR Data:

- **Lower Risk of Falls/Fx**
- Lower Risk of Some **Cancers**
- **↓ All Cause Mortality**

Intermediate Data:

- PMS, Pregnancy
- CHD Risk, HTN, Dementia

Benefit:

Osteoporosis, Depression, Obesity

2,000-4,000 IU/Day

Summary: Tomorrow

- **Screen ONLY at risk:** Seniors, Menopause, Dark Skinned, Veiled, Home Bound & NH, DM, Multiple Fx , Pregnant, Malabsorption, CHD, Depression
 - Test: 25 OH Vitamin D
 - Treat according to status
- **Prevention** for all: 2-4,000 IU/Day + ?Ca
 - Weight Bearing Exercise