VITAMIN D DEFICIENCY: A PRACTICAL GUIDE

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Disclosures
- None

Learning Objectives
- Understand the pathophysiology of Vitamin D metabolism, when to suspect deficiency and how to test for it.
- Be familiar with the controversies surrounding different Vitamin D guidelines.
- Have a practical guide to approaching the patient with low levels.
There is a lot of disagreement about what the benefits are of supplementation, who is deficient and what target levels should be. This a field in flux!

Outline

- Vitamin D physiology
- Definition and epidemiology of Vitamin D deficiency
- What are the data for skeletal and non-skeletal benefits of Vitamin D?
- What level should we target?
- How much and what type of D should we give to get there?
What is striking about her bone density?

- Very low T and Z scores
- Look for a secondary cause

Secondary causes of low bone density

- Hypogonadism
  - Premature/Surgical menopause
  - Pituitary tumors
  - Anorexia
  - Turner's/Klinefelter's
- Glucocorticoid excess
- Immobilization
- Thyrotoxicosis
- Renal hypercalciuria
- Decreased calcium absorption
  - Celiac, surgery
  - Mastocytosis
- Primary Hyperparathyroidism
- Osteomalacia
- Myeloma
- Osteogenesis Imperfecta

More info?

- She is complaining of diffuse bone pain.
  - H/o Crohn's disease that dates to 1981
  - Says she underwent gastric bypass surgery at the same time as her bowel resection due to weight gain from prednisone.
  - Her weight from 285—128 lbs in one year.
  - Taking MVI and B12, but no specific Ca/D
  - S/p TAH/BSO, on estrogen
- Physical exam
  - 105 lbs
  - Fissures on her tongue
  - Tenderness on long bones

- H/o Crohn's disease that dates to 1981
Secondary work up: Lab results

- Serum Ca=8.5 mg/dl
- PTH=206 pg/mL
- PO4=3.7 mg/dl
- 24 hour urine Ca=90 mg
- Urine NTX=100
- 25-OH Vit D=<10 ng/dl
- Femur films were consistent with osteomalacia

Review of pathophysiology: Calcium is TIGHTLY regulated

[Image of bone and calcium regulation pathway]

Action of PTH

- Increase calcium reabsorption
- Increase phosphate excretion
- Increase calcitriol synthesis

NET EFFECT:
- PLASMA CA INCREASED
- PHOSPHATE SAME/DECREASED

GUT
- Increased calcitriol leads to increased Ca absorption

Consequences of Vitamin D deficiency

- Decrease in efficiency of calcium and phosphorus absorption
- PTH rises
- Calcium must be mobilized from bone and excreted from kidney
- Osteoclasts are activated
- Mineralization defects

Factors leading to Vitamin D Deficiency

- Decreased intake
- Decreased absorption
- Decreased sunlight
- Skin pigmentation
- Sequestration
- Defects in 25 hydroxylation
  - Liver disease
  - Anticonvulsants
- Defects in 1-25 hydroxylation
  - Hypoparathyroidism
  - Renal disease
  - Vitamin D dependant rickets

Adapted from M. McDermott
How prevalent is Vitamin D deficiency?

- Depends some on the definition.
  - Mean 25 OH D went from 30 to 24ng/mL
  - Prevalence of D<10 ng/mL went from 2% to 6%.
- NHANES 2005-2006
  - 41.6% of adults had levels below 20ng/mL

Ginde et al Arch Intern Med 2009,
B Dawson Hughes UpToDate 2013

Vitamin D deficiency in pregnant women in South Carolina

Johnson et al, Amer J Perinatal 2011 (epub July 2010)

Is some of this an assay issue?

Johnson et al, Amer J Perinatal 2011 (epub July 2010)

Ginde et al Arch Intern Med 2009,
B Dawson Hughes UpToDate 2013

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BMI affects Vit D levels in offspring.
Who should be screened?
- Osteoporosis
- Kidney disease
- Liver disease
- Malabsorption syndromes
- Hyperparathyroidism
- High risk populations
  - African American adults
  - Hispanic adults
  - Pregnant women
  - Adults with falls
  - Obese children and adults
- Medications:
  - Anti-seizure
  - Glucocorticoids
  - HAART
  - Anti-fungals
  - Colestyramine
- Granulomatous disorders

Endocrine Society Guidelines 2011

What to measure
- 1,25(OH)D is the active metabolite
  - Extremely variable due to regulation by PTH
    - PTH can fluctuate over minutes – even response to a calcium ingestion
    - 1,25(OH)D can be “normal” even in VD deficiency due to shuttling of any remaining 25(OH)D to 1,25(OH)D by PTH (i.e. in CKD)
- For determination of D levels/stores, always measure 25(OH)D

Now the data...
Nursing home residents with a mean level of 14 with
- 800 IU of D and 1200 mg of Calcium → 25% risk reduction in hip and non vertebral fractures. ¹

WHO² study compared
- Vitamin D3 400 IU and Calcium 1000mg without improvement
- However women who were most consistent with their Ca and D had a 29% risk reduction

RECORD³ trial showed no improvement (levels went to 24.8 ng/dl)

¹ Chapuy et al RMJ 1994
³ Grant A Lancet 2006

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**Mixed results on Fracture Risk**

<table>
<thead>
<tr>
<th>Study</th>
<th>Calcium Dosage</th>
<th>Vitamin D Dosage</th>
<th>Fracture Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHI</td>
<td>400 IU</td>
<td>1000 mg</td>
<td>0%</td>
</tr>
<tr>
<td>RECORD</td>
<td>2500 IU</td>
<td>1000 mg</td>
<td>29%</td>
</tr>
</tbody>
</table>

2. Jackson et al, NEJM 2006

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Too much at once is not good: 500,000 Units Yearly
Most recent meta-analysis data on D for Fracture Prevention

<table>
<thead>
<tr>
<th></th>
<th>Hip Fracture Events (N=12,5)</th>
<th>Non-Hip Fracture Events (N=464)</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>5.4%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>4.7%</td>
<td>2.4%</td>
</tr>
<tr>
<td>P-value</td>
<td>0.001</td>
<td>0.015</td>
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Subgroup Benefits at the Highest Actual Intake Level of Vitamin D (792–2000 IU per Day), as Compared with Control Group.

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What about non-skeletal effects?

- Kidney: Decreases renal levels and lowers blood pressure
- Parathyroid, Bones, and Intestine: Improves calcium homeostasis and bone density
- Pancreas: Increases basal insulin secretion
- Breast and Other Cancer Cells: Differentiates proproliferative terminal
- 1-25 Dihydroxy Vitamin D: Increases (D levels)
- Periodontal Tissues: Decreases tooth loss in aging
- Skeletal Muscle Receptors: Improves strength, reduces falls, improves muscle pain syndromes
- Immune Cells: Decreases specific, production, and lymphocyte proliferation
- Heart and Blood Vessels: May decreases risk of congestive heart failure and stroke

Hines et al Nutrition 2010
What level should we target?

- Evidence for >30mg/ml
- Postmenopausal women who increased for 20-32ng increased calcium absorption by 45-60%. (1)
- However not directly measured and study by Hansen et al did not show this(2)
- Does PTH normalization matter?

Heaney et al 2003
Hansen et al 2008

PTH AND VITAMIN D:
Where did the target of 30mg/ml come from?
IOM 2010 Recommendations

<table>
<thead>
<tr>
<th>Life Stage Group</th>
<th>Recommended Daily Calcium (mg)</th>
<th>Recommended Daily D (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-15</td>
<td>1200</td>
<td>600</td>
</tr>
<tr>
<td>Pregnant and lactating 19-50</td>
<td>1000</td>
<td>600</td>
</tr>
<tr>
<td>19-50</td>
<td>1000</td>
<td>600</td>
</tr>
<tr>
<td>51-70 female</td>
<td>1200</td>
<td>600</td>
</tr>
<tr>
<td>70+ female</td>
<td>1200</td>
<td>800</td>
</tr>
</tbody>
</table>

Raised concern for risk for harm at:
>2000 mg Ca per day
>4000 IU D per day

Endocrine Society Guideline 2011 Recommendations

<table>
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<th>Age</th>
<th>Suggested dose of Vitamin D</th>
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<tr>
<td>Infants 0-1</td>
<td>400-1000 IU</td>
</tr>
<tr>
<td>Children 1-18</td>
<td>600-1000 IU</td>
</tr>
<tr>
<td>Adults 19-50</td>
<td>600 IU</td>
</tr>
<tr>
<td>Adults 50+</td>
<td>600-800 IU</td>
</tr>
</tbody>
</table>

But they note that to raise blood level to >30 ng/dl may take 1500-2000 IU
Bottom line

- Levels around 20ng-30 ng/ml seem to be optimal for bone health
- The optimal level for non-bone effects is unknown
- Some concerns for levels>50 by IOM report

How to supplement

- If level is <20ng/mL, replete. Many will do this with 50,000 IU weekly for 6-12 weeks and then start a maintenance dose.
- The dose will depend on patient factors and how hard you think it will be to keep level up.
- If the level is 20-30ng/mL, many people treat with 600-2000 IU daily.
- D3 may be better than D2.

B. Dawson-Hughes from Up To Date
Micol Rothman, personal experience

Patients received 50K units of ergocalciferol once/week for 8 weeks

Ann Epidemiol 2009;19:75–79
J Clin Densitometr. 1998;1:201–204
Sources of Vitamin D

Solar UV-B (sunlight)
- Pinkness=10,000-25,000 ingestion

Naturally occurring food sources
- Salmon 400 IU/3.5 oz
- Cod liver oil 400 IU/tsp
- Egg yolks 20 IU

Fortified foods in US
- Milk 100 IU/serving
- Cereal 100 IU/serving
- Orange juice 100 IU/serving
- Yogurt 100 IU/serving

Random-effects meta-analysis comparing the effects of daily and bolus supplementation of D3 with that of D2 on net changes in serum 25(OH)D concentrations.

Limited resources: What if you can’t check levels?
- 68 nursing home patients received a minimum of 5 months of daily 2000 IU vitamin D(3) supplementation.
- 94.1% had a 25(OH)D(3) level in excess of 80 nmol/L after a minimum of 5 months of daily 2000 IU vitamin D(3) supplementation.
- No residents had 25(OH)D(3) levels in a toxic range.
Due to her malabsorption, has required 50,000 IU 3 times a week.
Clinical sx and bone density improved

FIG. 1. Serum 25OHD levels are unchanged despite a marked increase in vitamin D intake after RYGB

FIG. 3. Change in BMD 1 yr after RYGB, presented as percent change (and SEM) in BMD from preoperative baseline at each measurement site
QUESTIONS?
Thank you for this invitation
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