**Vitamin D Deficiency**

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**Clinical Case**

BD is a 67-year female with PMHx of HTN, hyperlipidemia, OA and varicose veins. She presents for her medicare wellness. She has a negative falls screening. She has a BMI of 28.2 and otherwise negative exam. She had a DEXA at age 65 which showed t-score of -1.1. She has been tired of late with aching muscles and requests for all her vitamins to be checked.
Normal Vitamin D Physiology

7-Dehydrocholesterol → Cholecalciferol (Vitamin D3) → LIVER → Calcidiol (25-hydroxyvitamin D) → KIDNEY → Calcitriol (1,25-dehydroxyvitamin D) → Inactive metabolite (24,25-dihydroxyvitamin D)

Calcitriol (1,25-dehydroxyvitamin D)

- Increases intestinal absorption of calcium
- Increases bone resorption of calcium
- Decreases renal calcium excretion
### Definitions of Normal and Deficiency

- **Low** < 20
- **Optimal** - ???
  - 20-40 ng/mL - IOM,
  - 30-50 ng/ml - ENDO, NOF, AGS, IOF
- **Undetermined safe upper limit**
- **Racial differences**
Definitions of Normal and Deficiency- criteria to define optimal levels

- Maximal suppression PTH
- Adequate intestinal calcium absorption
- Fracture prevention

- Maximal suppression PTH = 27.5 to 30 ng/mL
- Adequate intestinal calcium absorption = 4.4 ng/mL
- Fracture prevention = 28-40 ng/mL
Prevalence of Vitamin D

- NHANES data
- Mean Vitamin D 25 (OH) in ng/mL

Symptoms of Deficiency
<table>
<thead>
<tr>
<th>Symptoms of Deficiency</th>
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<tbody>
<tr>
<td><strong>Overt:</strong></td>
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<tr>
<td></td>
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<tr>
<td><strong>Subclinical</strong></td>
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<td><strong>Nonskeletal</strong></td>
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<td><strong>Overt:</strong></td>
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<tr>
<td>Hypocalcemia</td>
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<tr>
<td>Rickets</td>
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<tr>
<td>Osteomalacia</td>
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<tr>
<td><strong>Subclinical</strong></td>
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<tr>
<td>Osteoporosis</td>
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<tr>
<td>Muscle pain/weakness, fatigue, falls</td>
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<td><strong>Nonskeletal</strong></td>
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</table>
Symptoms of Deficiency: Muscle pains

- MayoClinic Proc 2003
- Prevalence of severe hypovitaminosis D in patients with persistent nonspecific musculoskeletal pain
- 150 patients presented consecutively between February 2000 and June 2002 with persistent, nonspecific musculoskeletal pain to the Community University Health Care Center, a university-affiliated inner city primary care clinic in Minneapolis, Minn (45° north). Ages 10-65. 6 ethnic groups

Symptoms of Deficiency: Muscle pains

- 93% (140/150) <20 nl/mL in all
- 100% below 20 ng/mL
  - African Americans, East Africans, American Indians
- Levels of vitamin D in men were as deficient as in women ($P = .42$)
- not seasonal
Effects of Deficiency - Nonskeletal

• VitaminD receptor (VDR) - expressed in all nucleated cells
• 3% of human genome is under control of 1,25 dihydroxyvitamin D
• 10 tissues other than kidney express 1-alpha-hydroxylase

Effects of Deficiency - Nonskeletal

• Falls
• Cancer
• CV system
• Diabetes
• Immune System
• MS
• Asthma
• URI
• mortality
<table>
<thead>
<tr>
<th>Effects of Deficiency- nonskeletal Falls</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Several metanalysis decrease risk as high as 20%</td>
</tr>
<tr>
<td>• Metanalysis not showing reduction falls in community-dwelling adult</td>
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</tbody>
</table>

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<tr>
<th>Symptoms of Deficiency: Falls</th>
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<tbody>
<tr>
<td>• Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA 2010;303:1815</td>
</tr>
<tr>
<td>• Effect of four monthly oral vitamin D supplementation fracture and mortality in men and women living in the community: randomized double blind controlled study. BMJ 2003;326:469</td>
</tr>
</tbody>
</table>
Effects of Deficiency - Cancer

- Colon Cancer
- Breast Cancer

Effects of Deficiency - Cancer

- Colon Cancer
- WHO
  - for each 4nl/mL increase in pre-diagnosis serum 25(OH)D concentration, there was a 6% reduction colorectal cancer risk. ANN INTer Med 2011;155:827
- can elevate risk of pancreatic cancer if >40 ng/ml
### Effects of Deficiency - Cancer

- Breast Cancer
  - Observational studies: inconsistent
  - Prospective studies: possibly
  - Meta-analysis showed inverse relation between cancer risk between 27 and 35 ng/ml in post- but not pre-menopausal women. Medicine (Baltimore) 2013; 92:123

### Effects of Deficiency - Cardiovascular

- Blood pressure: observational studies show inverse associated between 25 OH D and blood pressure. No effect with supplementation
- CV events: Prospective meta-analysis with inverse relationship between 25(OH)D and CVD. No effect with treatment
### Effects of Deficiency - Immune system

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prospective studies</th>
<th>Randomized control trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Asthma</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>URI</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>COPD exacerbation</td>
<td>-</td>
<td>-</td>
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</table>

### Effects of Deficiency - Nonskeletal Endocrine

- **Diabetes type 1:** mixed results suggesting link
- **Diabetes type 2:** prospective meta-analysis showed inverse relation between 25 (OH)D and risk of diagnosis. Interventional studies negative or limited beneficial effects of supplementation

Effects of Deficiency - Mortality

High Risk Groups for Deficiency

- darker skin
- obese
- meds that accelerate vitamin d metabolism
- hospitalized on gen med service
- institutionalized
- limited sun exposure
- osteoporosis
- malabsorption
### Whom to test

**USPSTF 11/2014:** In community-dwelling, nonpregnant, asymptomatic adults age 18 years and older, the USPSTF concludes that the current evidence is insufficient to assess the balance of benefit and harms of screening for vitamin D deficiency.

**High risk groups**

### Laboratory testing

- Vitamin D 25 (OH)
- Vitamin D 1,25 (OH)
- Total Vitamin d = 25 (OH) and 1,25 (OH)
Normal Vitamin D Physiology

7-Dehydrocholesterol

Diet/Supplements

Cholecalciferol (Vitamin D3)

Ergocalciferol (Vitamin D2)

LIVER

Calcidiol (25-hydroxyvitamin D)

KIDNEY

Calcitriol (1,25-dehydroxyvitamin D)

Inactive metabolite (24,25-dihydroxyvitamin D)

Laboratory testing

• Vitamin D 25 (OH)
• Vitamin D 1,25 (OH)
Laboratory testing

- Vitamin D 25 (OH)
- Vitamin D 1,25 (OH)
- if vitamin D25 is less 10=
  Calcium, phosphorus, iPTH, alkaline phosphatase, BUN/Cr, TTG, DEXA

Treatment
Treatment

- Prevent deficiencies
- Treat deficiencies
- With what?

- Vitamin D3/Cholecalciferol
- Vitamin D2/ergocalciferol
- Calcitriol (1,25 dihydroxyvitamin D)
- Calcidiol (25 dihydroxyvitamin D)
- ultraviolet B exposure
**Normal Vitamin D Physiology**

7-Dehydrocholesterol

Diet/Supplements

Cholecalciferol (Vitamin D3)

Ergocalciferol (Vitamin D2)

LIVER

Calcidiol (25-hydroxyvitamin D)

Calcitriol (1,25-dehydroxyvitamin D)

KIDNEY

Inactive metabolite (24,25-dihydroxyvitamin D)

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**Treatment-D3 versus D2**

- *Am J Clinical Nutrition 2012* "Comparison of Vitamin D2 and Vitamin D3 supplementation in raising serum 25-hydroxyvitaminD status: a systematic review and meta-analysis"

Any randomized intervention trials that involved human adults (men and women) that directly compared the effects of vitamin D2 and vitamin D3 supplementation and used serum 25(OH)D concentrations as a primary outcome were initially included for consideration.

3030 studies to 10 studies for systematic review, 7 for met analysis

followup 14 days to 6 months

Systematic review 8 studies showed d3 with increase in 25 oh measurements. two showed equal effect

Metanalysis: 15.23 ng/ML increase with D2
Treatment-D3 versus D2

- Daily food supplementation with 15ug vitamin d2 compared with vitamin d3 to increase wintertime 25-hydroxyvitamin D status in healthy south Asians and white European women
- America Journal of Clinical Nutrition July 5, 2017
- n=335 in Surrey, United kingdom
- given place, supplemented juice or biscuit for 12 weeks

Rate of increase of 25OH vitamin D with D3 supplementation in biscuit and Juice
Treatment-Prevention

- AGS/NOF: 800-1000 IU
- IOM: adults 600-800 IU of cholecalciferol (vit d3)
  - >18, pregnant=600 IU
  - Older >70=800 IU

## Treatment-deficiency

<table>
<thead>
<tr>
<th>Preparation</th>
<th>DOSAGES AVAILABLE</th>
<th>TYPICAL DOSING</th>
<th>POPULATION</th>
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</thead>
<tbody>
<tr>
<td>VitD3 cholecalciferol</td>
<td>400,800,1000,2000,5000,10000, 50,000 IU IM</td>
<td>increased 0.7 to 1.0 for every 100 IU given</td>
<td>Most recommended</td>
</tr>
<tr>
<td>VitD2 ergocalciferol</td>
<td>400,50000 IU liquid IM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcitriol</td>
<td>0.25, 0.50 mcg</td>
<td>0.25-0.5 mcg daily to bid</td>
<td>GFR&lt;30 ml/min, type 1 vitamin d- dependent rickets</td>
</tr>
<tr>
<td>Calcidiol</td>
<td>25, 50 mcg</td>
<td>50-200 mcg daily</td>
<td>Liver disease</td>
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<tr>
<td>ultraviolet exposure</td>
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<td></td>
<td>Malabsorption patients</td>
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**Guidelines**

- USPSTF: final recommendation statement on Vitamin D deficiency in adults-screening 2014
- USPSTF: final recommendation statement on vitamin supplementation to prevent cancer and CVD-preventive medication 2014
- Choosing Wisely: Don’t perform population based screening for 25-OH vitamin D deficiency 2013
- Choosing Wisely: Don’t routinely measure 1,25-dihydroxyvitamin D unless the patient has hypercalcemia or decreased kidney function 2013

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**Guidelines**

- Endocrine Society: clinical practice guideline on evaluation, treatment and prevention of vitamin D deficiency 2011
- ACOG: Committee opinion on vitamin D screening and supplementation during pregnancy 2011, reaffirmed 2015
Clinical Case

- BD is a 67-year female with PMHx of HTN, hyperlipidemia, OA and varicose veins. She presents for her medicare wellness. She has a negative falls screening. She has a BMI of 28.2 and otherwise negative exam. She had a DEXA at age 65 which showed t-score of -1.1. She has been tired of late with aching muscles and requests for all her vitamins to be checked.

Clinical Case

- Vitamin D 25(OH)- 17.7
- What do you recommend?
Summary

• Increasing in incidence
• Do not test all
• Treat with cholecalciferol
• Monitor for vitamin D repletion