**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**
- **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)

Calcitriol (1,25-dehydroxyvitamin D)

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

<table>
<thead>
<tr>
<th>Definitions of Normal and Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Low &lt;20</td>
</tr>
</tbody>
</table>
| • 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

<table>
<thead>
<tr>
<th>Definitions of Normal and Deficiency - criteria to define optimal levels</th>
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<tbody>
<tr>
<td>• Maximal suppression PTH = 27.5 to 30 ng/mL</td>
</tr>
<tr>
<td>• Adequate intestinal calcium absorption - 4.4 ng/mL</td>
</tr>
<tr>
<td>• Fracture prevention - 28-40 ng/mL</td>
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</table>
Prevalence of Vitamin D

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

![Graph showing mean Vitamin D 25 (OH) levels from 1998 to 2006.]

Symptoms of Deficiency

- Overt:
  - Hypocalcemia
  - Rickets
  - Osteomalacia
- Subclinical:
  - Osteoporosis
- Nonskeletal:
  - Muscle pain/weakness, fatigue, falls
  - Nonskeletal

Symptoms of Deficiency

- Overt:
  - Hypocalcemia
  - Rickets
  - Osteomalacia
- Subclinical:
  - Osteoporosis
- Nonskeletal:
  - Muscle pain/weakness, fatigue, falls
  - Nonskeletal
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

Symptoms of Deficiency: Muscle pains

- Muscle pains
- 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

Effects of Deficiency- nonskeletal

- Immune System
- MS
- Asthma
- URI
- mortality
<table>
<thead>
<tr>
<th>Effects of Deficiency-nonskeletal Falls</th>
<th>Symptoms of Deficiency: Falls</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Several metanalysis decrease risk as high as 20%</td>
<td>• Annual high-dose oral vitamin and falls and fractures in older women: a randomized controlled trial. JAMA 2010;303:1815</td>
</tr>
<tr>
<td>• Metanalysis not showing reduction falls in community-dwelling adult</td>
<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>

<table>
<thead>
<tr>
<th>Effects of Deficiency-Cancer</th>
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</tr>
</thead>
<tbody>
<tr>
<td>• Colon Cancer</td>
<td>• Colon Cancer</td>
</tr>
<tr>
<td>• Breast Cancer</td>
<td>• WHO</td>
</tr>
<tr>
<td></td>
<td>• for each 4ng/mL increase in pre diagnosis serum 25(OH)D concentration, there was a 6% reduction colorectal cancer risk. ANN INTer Med 2011;155:827</td>
</tr>
<tr>
<td></td>
<td>• can elevate risk of pancreatic cancer if &gt;40 ng/ml</td>
</tr>
</tbody>
</table>
**Effects of Deficiency-Cancer**

- Breast Cancer
  - observational studies: inconsistent
- Prospective studies: possibly
- metanalysis 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>
</tr>
</tbody>
</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

- darker skin
- obese
- meds that accelerate vitamin D metabolism
- hospitalized on gen med service
- institutionalized
- limited sun exposure
- osteoporosis
- malabsorption

High Risk Groups for Deficiency

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

- Vitamin D 25 (OH)
- Vitamin D 1,25 (OH)
- total Vitamin d= 25 (OH) and 1,25 (OH)

Laboratory testing

Whom to test

- Laboratory testing
Normal Vitamin D Physiology

7-Dehydrocholesterol → Cholecalciferol (Vitamin D3) → Ergocalciferol (Vitamin D2) → LIVER → Calcidiol (25-hydroxyvitamin D) → KIDNEY → Inactive metabolite (24,25-dihydroxyvitamin D) → Calcitriol (1,25-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 dihydroxyvitaminD)
- ultraviolet B exposure

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**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)

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**Treatment-D3 versus D2**


Any randomized intervention trials that involved human adults (men and women) that directly compared the effects of vitaminD2 and vitamin D3supplementation and used serum 25(OH)D concentrations as a primary outcome were initially included for consideration.

30% 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-deficiency

<table>
<thead>
<tr>
<th>Preparation</th>
<th>DOSAGES AVAILABLE</th>
<th>TYPICAL DOSING</th>
<th>POPULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>VitD3 cholecalciferol</td>
<td>200, 400, 1000, 2000, 5000, 10000, 50,000 IU</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, 50,000 IU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcitriol</td>
<td>0.25, 0.50 mcg</td>
<td>0.25-0.5 mcg daily or bid</td>
<td>GFR&lt;30 ml/min, type 1 vitamin d-dependent rickets</td>
</tr>
<tr>
<td>Calciol</td>
<td>50, 100 mcg</td>
<td>50-200 mcg daily</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Ultraviolet exposure</td>
<td></td>
<td></td>
<td>Malabsorption patients</td>
</tr>
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</table>
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

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?
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<tbody>
<tr>
<td>• Increasing in incidence</td>
</tr>
<tr>
<td>• Do not test all</td>
</tr>
<tr>
<td>• Treat with cholecalciferol</td>
</tr>
<tr>
<td>• Monitor for vitamin D repletion</td>
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