Vitamin D
Hormone Du Jour

J R Minkoff MD, FACP
Endocrinology
Clinical Professor of Family and Community Medicine
UCSF

Why Is Vitamin D Important?

Musculo-skeletal effects

Skeletal:
Vitamin D increases efficiency of gut absorption of calcium
Muscular:
- Low vitamin D is associated with muscle weakness
- Low 1,25 diOH function also associated with muscle dysfunction
BUT – little evidence that D treatment makes a difference in strength or symptoms
  - equivocal studies on falls

Musculo-skeletal effects

Possible other effects
- Immunomodulatory effects
- Cardiovascular effects
- Glucose metabolism
- Cellular growth/Regulation - Cancer
Vitamin D factoids

- Not exactly a vitamin (essential exogenous micronutrient)
  - it acts as a hormone and is elaborated endogenously
- Fat soluble
  - Stored in body fat
  - Inverse relationship between BMI and 25OH vitamin D
- Active intracellular hormone is 1,25 diOH vitamin D
  - Works at the Vitamin D Receptor (VDR) in nuclei of many cell types
  - 100 times more potent than 25OH vitamin D

Why calcium?

Essential for neuromuscular activity
  - neurotransmitter release
  - muscle contraction
    - striated
    - smooth
    - cardiac
High priority to maintain calcium balance

99% resides in bone

Vitamin D is Essential for Calcium Homeostasis

Calcium homeostasis is tightly regulated by the Parathyroid glands
Calcium is stored in the bone
Vitamin D is metabolized in the liver to
  - 25 OH vitamin D – T1/2 is 22 days
Activated vitamin is 1hydroxylated mainly in the kidneys
  - 1,25diOH vitamin D – T1/2 is 7 hours
  - 100x more active at the intranuclear receptor
Is calcium either necessary or sufficient for fracture prevention?

- Many studies suggest benefit of adequate calcium intake in post-menopausal women
- The safety of calcium supplements (without vitamin D supplements) has been questioned
- All medication studied include calcium and vitamin D in both placebo and intervention groups

Current knowledge:
- Dietary calcium may be better
- Supplement deficient patients
- Supplement patient you are treating for osteoporosis

Daily Calcium Intake

=Dietary
e=Calcium
All calcium salts are not created equal

**Elemental Calcium** in common products
- 40 percent of calcium carbonate
  - take after meals: need low pH to dissociate
- 21 percent of calcium citrate
  - take any time
- 13 percent of calcium lactate
- 9 percent of calcium gluconate

Aim for 1200-1500 mg TOTAL DAILY ELEMENTAL CALCIUM intake

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Vitamin D

- Physiology
- Basis for defining vitamin D sufficiency
- Data on fractures
- Etiologies for vitamin D deficiency
- Treatment
- Non-skeletal effects

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Vitamin D Levels – Lower in Higher Latitudes
Vitamin D for Muscle and Bone Health

Adequate vitamin D and calcium to prevent falls and fractures

- Multiple studies show fracture prevention with calcium and vitamin D.
- Negative studies had poor compliance (<60%), inadequate doses (< 800 IU) or 25OH D levels < 30 ng/ml
- Many studies showing benefit of treatment in D or Ca deficient patients

High Prevalence of Vitamin D Deficiency

30-50% of children and adults are vitamin D deficient

- Europe
- Middle East
- India
- Australia
Statistics the same for the US

Holick et al. AJCN 2008

Clinical application

When should we think of vitamin D insufficiency?
- Complaints of low back pain, proximal muscle weakness or myalgias with or without weakness
- Fractures in patients 45 or older or fragility fractures
- Chronically ill patients and those who are housebound
- Bariatric surgery patients and those with partial gastrectomy; short bowel syndrome or malabsorption due to other GI disease
Measuring Vitamin D

- 1 ng/mL = 2.5 nmol/L
- 40 ng/mL = 100 nmol/L

One caveat:
- Most clinical assays are inaccurate
  - CV up to 20%
  - e.g. 24 ng/mL could be <20 or over 30

Optimal Vitamin D

Desirable level begins at 30-32 ng/mL
(75-80 nmol/L)

Do my patients need vitamin D?

How much?

Vitamin D and PTH

290 consecutive pts. on a general medical ward
- MGH

Thomas 1998. NEJM
How much Vitamin D should we take in?

New Guidelines recommend:
- **800 IU vitamin D** and **1000 mg calcium** daily for pre-menopausal women
- **800 IU vitamin D** and **1500 mg Calcium** daily for post-menopausal women and men over 50.

Determining Vitamin D Sufficiency

- Relationship between 25(OH)D and PTH
- 25(OH)D and intestinal calcium absorption
- 25(OH)D concentration and certain diseases

Interventional studies of 25(OH)D with or without calcium
- Fracture risks
- Fall risks
- Cancer risks
- Blood pressure, diabetes, CV disease
Vitamin D requirements for Muscle and Bone Health change with AGE

- Metabolism and signaling decrease with age.
  - Decreased skin production
  - Decreased renal mass and 1 hydroxylation
  - Decreased vit D receptor sensitivity equals:
    - Decreased intestinal absorption
- Multiple studies show fracture prevention with calcium and vitamin D.
- Prevents fall and fractures

What Is A Normal Vitamin D Level?

What Is the “Desirable” or “Optimal” Vitamin D level?

Optimal Vitamin D for bone health

- Desirable level begins at 30-32ng/mL (75-80 nmol/L)
- Evidence on fractures tells the story
Impact of calcium and vitamin D supplementation on hip fracture

Studies measuring Serum 25 OH D levels and PTH response:
Adequate D supplements decrease nonvertebral fractures

<table>
<thead>
<tr>
<th>Study</th>
<th>Gender</th>
<th>Dose vitamin D$_3$ (μg)</th>
<th>Published serum 25(OH)D (nmol/l)</th>
<th>Standardized serum 25(OH)D (nmol/l)</th>
<th>Effect on serum PTH (ng/ml)</th>
<th>Preventive effect on non-vertebral fracture (hip and vertebra)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapuy [25, 28]</td>
<td>F</td>
<td>30</td>
<td>108</td>
<td>29</td>
<td>-32</td>
<td>++</td>
</tr>
<tr>
<td>Trout [27]</td>
<td>F, M</td>
<td>15, 30</td>
<td>74</td>
<td>&lt; 20 (μg/ml)</td>
<td>-15</td>
<td>+</td>
</tr>
<tr>
<td>Lips [36]</td>
<td>M, F</td>
<td>10</td>
<td>54</td>
<td>54</td>
<td>NS</td>
<td></td>
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</tbody>
</table>

Table 2 Estimates of the minimum serum 25(OH)D levels optimal for fracture prevention and the doses of vitamin D$_3$ needed to achieve them. From Dawson-Hughes et al. [1], with permission.

<table>
<thead>
<tr>
<th>Vitamin D Research Community</th>
<th>Insufficiency</th>
<th>Deficiency</th>
<th>Sufficiency</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>20-29 ng/mL</td>
<td>&lt; 20 ng/mL</td>
<td>≥ 30 ng/mL</td>
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<tr>
<td>Observer</td>
<td></td>
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<tr>
<td>Lips</td>
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<tr>
<td>Holick</td>
<td>70</td>
<td>50</td>
<td>90</td>
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<tr>
<td>Heaney</td>
<td>75</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>Moxner</td>
<td>75</td>
<td>20</td>
<td>900</td>
</tr>
<tr>
<td>Vieth</td>
<td>75</td>
<td>25</td>
<td>1000</td>
</tr>
<tr>
<td>Dawson-Hughes</td>
<td>75</td>
<td>25</td>
<td>1000</td>
</tr>
</tbody>
</table>

Some pts may need more
**Vitamin D Deficiency – Lab Findings**

- Low 25 (OH) vitamin D
- Elevated PTH
  - Maybe inappropriately normal in the setting of magnesium insufficiency
- Calcium normal or low normal
- Phosphorus normal or low normal
- Elevated Alkaline Phosphatase
- 1,25 (diOH) D may be normal
  - (rarely useful clinically)
- 24 hour urine calcium low (<100mg)

**Severe Vitamin D Deficiency**

- Osteomalacia
  - decreased bone mineralization
  - unmineralized osteoid
- Usually with vitamin D level < 10ng/mL – Ca and P may be low
  - Bone pain
  - Malaise
  - Muscle weakness
  - Muscle aches/pain
- May lead to fractures
  - Physical findings
    - Proximal muscle weakness
    - Increased body sway
    - Bone pain and muscle pain on palpation

**Radiologic Findings**

- Low bone density
  - Osteomalacia simulates osteoporosis
- Pseudofractures (looser zones)
  - Fissure, narrow radiolucent lines
  - Pathogenesis:
    - Stress fractures
    - Erosion from artery pulsation
      - (frequently located in apposition to artery)
Vitamin D Deficiency - Rickets

Defective mineralization of cartilage in the epiphyseal growth plate
- Growth Retardation
- Skeletal deformities
- Knock knees and bowed legs

MDR’s are set to prevent this
Vitamin D and CALCIUM INSUFFICIENCY

How much daily calcium?
- ~ 250 mg daily used for bone metabolism
- Absorption depends on
  - vitamin D
  - intact GI system
  - amount of calcium intake
  - Type of calcium salt
Daily calcium needs in the adult

- 50 + years: 1000 to 1500 mg total intake (diet + supplementation)
- NIH.gov/factsheets/calcium

Vitamin D & Fracture Reduction

Meta-analyses of Vitamin D with or without Calcium

- Trials included for analyses have been different
- Analyses were different
- Conclusions different

Calcium and Vit D are effective for hip fracture risk reduction

Boonen JCEM 2007: 16% risk reduction
- Studies that used higher D 700-800IU with Ca
  - 21% fracture reduction
- Vitamin D alone not effective
  - Tang et al. Lancet 2007: 12% risk reduction
  - More effective if vitamin D ≥ 800 and Ca is ≥ 1200mg

Effects of Vitamin D on fracture reduction is dose dependent

Bischott-Ferrari HA et al.
JAMA 2005 & Arch Int Med 2009

- Effect on hip fracture and nonvertebral fracture reduction is vitamin D dose dependent
- Comparing 482-770 IU vs 400IU (Arch Int Med)
  - 20% reduction in nonvertebral fracture and 18% reduction in hip fracture
- Level of vitamin D achieved important, greater risk reduction with higher 25(OH) D levels
- Assessing compliance/adherence in the studies important to interpret effectiveness of vitamin D
Dose Dependent and 25(OH)D Dependent Hip Fracture Nonvertebral Fracture

Bischoff-Ferrari HA et al. AJCN 2006; JAMA 2005

Treatment – Special Situations
- Patients with osteoporotic fractures
  - prior to and
  - throughout osteoporosis medication treatment
- Treatment of vitamin D deficiency

INCREASE IN BONE MASS AFTER CORRECTION OF VITAMIN D INSUFFICIENCY IN BISPHOSPHONATE-TREATED PATIENTS
Treatment of severe vitamin D deficiency increases BMD significantly

12 pts, mean age 60, with low bone density
Low D average = 9 ng/mL (range 6.7 – 14) with associated secondary hyperparathyroidism
50,000IU twice weekly x 5 weeks (+ 1000mg of Ca)
D level ↑ to mean level of 24ng/mL (6.5-62.2)
PTH lowered significantly
BMD ↑ significantly when repeated after 10 months
Spine: 4.1%
Hip neck: 4.9%

Adams et al. JCEM 1999

Using vitamin D and bisphosphonates

Does vitamin D level effect outcomes of therapy?

1515 women treated for osteoporosis, retrospectively looked at D status:
D deficient < 50 nmol/l (20ng/ml).
Adjusted Odds Ratio for incident fracture 1.77 in D-deficient women (95% CI: 1.20-2.59; p = 0.004) adjusted for age, weight and SES

Adami S et al. 2009 Osteopor 20 239.
In older women with osteoporosis persistence of secondary HPTH due to vitamin D deficiency reduces BMD response to Alendronate


Ensure Vitamin D is Adequate

500 women treated with alendronate with baseline vitamin D levels:
- Deficient ≤ 10 ng/ml, n = 12
- Insufficient ≤ 30 ng/ml, n = 417
- Sufficient > 30 ng/ml, n = 71
- 250 IU vitamin D daily
- Post hoc analysis: No difference in BMD change


Vitamin D deficiency may blunt therapeutic response

Of 39 previously responsive bisphosphonate treated patients who lost BMD 20 were D deficient. 17 responded to 500,000 IU over 5 weeks with BMD gains over the next year.

Table 3: Results of Vitamin D Treatment in 20 Study Subjects With Vitamin D Insufficiency and Significantly Decreased Bone Mass

<table>
<thead>
<tr>
<th>After vitamin D therapy</th>
<th>Change in bone mineral density (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Lumbar spine</td>
</tr>
<tr>
<td>Responders (n = 17)</td>
<td>+3.9 ± 1.5</td>
</tr>
<tr>
<td>Nonresponders (n = 31)</td>
<td>−0.8 ± 3.0</td>
</tr>
</tbody>
</table>

*Significant change after vitamin D treatment (P<0.05)
Treatment—Special Situations

More is likely needed
- Meds that increase metabolism of 25 OH D
  - One strategy: add daily 2, 5, 10K and monitor

Malabsorption
- Gastric bypass, Crohn's, etc
  - May need 50,000-100,000 IU daily and monitor
  - Call for help from endocrinology if needed

Obesity
- Consider: 50K x 12 wks or 50K 2x /week x 8 weeks and monitor

Nephrotic syndrome
- One strategy: twice a week 8-12 weeks and monitor

All need some kind of increases maintenance dose
Might as well start while giving loading dose

Treatment—Special Situations

Cautions are needed
- Renal patients with renal insufficiency
  (especially ≥ stage III)
- Primary hyperparathyroidism
- Pt with granulomatous disease

May Consider Decreasing Calcium
Supplements during pharmacologic vitamin D treatment

Treatment of Vitamin D Deficiency: Labs

25 (OH) D in 2-4 months
Follow Calcium and Creatinine
- PTH may be normal or lowered once D store is replenished
- PTH may not be normal right away
- PTH may be inappropriately low in the setting of D deficiency if Mg++ deficient

Alk phos
- If ↑ at presentation, especially if evidence of osteomalacia

Other Labs to consider:
24 urine calcium
- If PTH is still elevated a few times with normal vitamin D levels
- U_Ca < 100mg usually suggests lack of Ca intake or vitamin D deficiency
Treatment (NJME 2007)

Children, adults, pregnant or lactating women
- 50,000IU/ week x 8 weeks
- Repeat if < 30ng/mL
- Maintenance: 800-2000IU D(3) daily after tx
  - Some pts need more 4000IU daily – monitor
  - Some pts may need 50,000IU 2x/month or 1x
    month for maintenance - monitor

If you measure 25 OH vitamin measure Calcium

If deficient assume you will need higher doses after you replenish levels and to maintain normal levels unless you correct some underlying abnormality

Case Study # 1
42 yo woman w fatigue.
- Patient had bariatric surgery (Roux-en-Y) in her 30’s.
- Diagnosis of ‘fibromyalgia’
- h/o fractures (2 in one year)
- One dose of calcium @hs and a one-a-day vitamin + minerals
- Protonix bid
Work-up

Physical exam unrevealing: difficulty getting up from her chair

Labs:
FBS, hct, transaminases and TSH normal.
Alk phos 138.

Labs (Case Study # 1)
- Calcium 7.8 (8.5-10.3 mg/dL)
- P 0.8 (1.0-1.9 mg/dL)
- Albumin 3.6
- CBC normal save for high MCV
- Creatinine 0.8
- PTH 125 (10-65 pg/mL)
- 25 OH vitamin D 8 (30-100 ng/mL)
Signs and Symptoms
(Case Study # 1)
- Myalgias
- Fractures
- Positive Chvostek’s sign

Treatment (Case Study # 1)
- Started 50,000 IU vitamin D₂ BID
- Calcium citrate for best absorption
- B 12 supplement
- Look for other deficiencies: B1, B2, Vitamin A, E, iron.

Conclusions
- Vitamin D is essential for optimal bone and muscle health
- Optimal vitamin D intake and sun exposure → levels 30-50 ng/ml (75-100 nMol/L)
- Inadequate vitamin D and calcium levels can reduce efficacy of osteoporosis treatment.
- Intervention is warranted in symptomatic (including fractures) patients
- Aggressiveness of therapy should match severity
Why Is Vitamin D Important?

Musculo-skeletal effects

Possible other effects
- Immunomodulatory effects
- Cardiovascular effects
- Glucose metabolism
- Cellular growth/Regulation - Cancer

Cancer

- Epidemiology:
  Low D levels associated with increased colon cancer risk; possible increase risk at high levels
  Normal D levels – lower breast cancer risk in postmenopausal women; not lower with higher levels
  Interventional studies – no benefit

Immune System

MS – higher risk with lower D levels
  - no RCT's looking at prevention or benefit
Asthma – conflicting findings and trials
TB - Deficiency common – no benefit
URI – Rx only effective with very low D
COPD – no benefit unless D is low
CV system

Hypertension – despite association
   – no benefit
CV events – association - no benefit
DM 1 – association – one case control trial suggests benefit in prevention
DM 2 - association – no benefit

Mortality
<10 ng/dL – increased mortality
Calcium + D may improve mortality (meta-analysis)

Conclusions

- Vitamin D is essential for optimal health
  - Musculoskeletal integrity
  - Changes in immunity
  - ? cancer
  - ? cardiovascular risk
- Optimal vitamin D intake and sun exposure → levels 30-50 ng/ml
- Intervention is warranted in symptomatic patients