Vitamin D deficiency: The new hidden diagnosis?

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Outline

• Metabolism and biology
• Assessing vitamin D status
• Vitamin D supplementation
• Evidence for association between vitamin D and disease

Metabolism and biology

Where does vitamin D come from?

• Not really a vitamin: a prohormone
• Sources
  – Dietary:
    • two forms: vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol)
    • fatty fish; fortified milk, cereal; supplements
  – Sunlight:
    • only vitamin D₃ synthesized in humans
    • Synthesis from 7-dehydrocholesterol in the skin with UVB exposure
    • Higher skin pigmentation leads to reduced synthesis of vitamin D₃

Vitamin D metabolism

Key Steps

• Vitamin D₂, D₃ converted to 25(OH)D in the liver by 25-hydroxylase
• 25(OH)D is the major circulating metabolite (not active)
• 1α-hydroxylase (1α-OHase) in kidneys converts 25(OH)D to active form, 1,25(OH)₂D
• Extrarenal production of 1,25(OH)₂D is common

Main physiologic function: regulation of calcium metabolism

• 1,25(OH)₂D acts to regulate calcium (Ca²⁺) and phosphate (HPO₄²⁻)
  – Increases calcium absorption in intestine
  – Regulates mineralization of the skeleton
    • via RANK pathway induces preosteoclasts → mature osteoclasts
    • Mature osteoclasts remove Ca²⁺ and HPO₄²⁻ from bone to maintain Ca²⁺ and HPO₄²⁻ blood levels
    • Adequate Ca²⁺ and HPO₄²⁻ blood levels promote mineralization of the skeleton
  – PTH can stimulate the activity of 1α-OHase; 1,25(OH)₂D can lower PTH levels

A word about PTH

• Trend toward higher PTH levels with lower 25(OH)D
• 25(OH)D level at which PTH levels stabilize is suggested to be “optimal” or “sufficient” level
  – Estimates range from 10 ng/ml to 30 ng/ml and higher

Non-skeletal vitamin D metabolism

• 10 tissues express 1α-OHase:
  – Osteoclasts, skin, macrophages, placenta, colon, brain, prostate, endothelium, parathyroid glands
• 37 tissues express vitamin D receptor (VDR):
  – Adipose, adrenal, bone, bone marrow, brain, breast, cancer cells, cartilage, colon, hair follicle, intestine, kidney, lung, lymphocytes …
Assessment of vitamin D status

- Conventional measurement in ng/ml
  - SI units are nmol/l
  - To convert ng/ml to nmol/l, multiply by 2.5
- Vitamin D status is assessed by measuring \(25(OH)D\) in the serum
  - Only use \(25(OH)D\) to assess status!
  - \(25(OH)D = 25(OH)D_2 + 25(OH)D_3\)
  - Study reported that 25% of health care providers may incorrectly use \(25(OH)D_2\) or \(25(OH)D_3\) levels to identify and treat "deficiency"

Assay problems for 25(OH)D?

- Most common methods
  - Antibody based-assays (DiaSorin)
  - LC/MS (Gold standard; Quest, research labs)
- In early 2009, lab reported problems with assays for previous ~2 years
  - Quest Diagnostics had erroneously high readings from LC/MS
- Standard reference material is becoming available
  - National Institute of Standards and Technology and the Office of Dietary Supplements plan to make this available to laboratories sometime in 2009

Prevalence of vitamin D deficiency

- Geographical variation in 25(OH)D
  - Generally higher latitudes have lower 25(OH)D levels, especially in winter
  - Can be offset by fatty fish consumption (Scandinavia)
- Seasonal variation in 25(OH)D
  - At higher latitudes, decrease in 25(OH)D during winter
    - Boston: No vitamin D₃ synthesis Nov – Feb
    - Edmonton: No vitamin D₃ synthesis Oct - Mar

Serum concentrations of 25(OH)D in the United States

- NHANES 2000-2004: Adjusted mean serum level
  - Southern latitudes (35 °N) collected Nov – March; Northern latitudes (35 °N) April–Oct

Causes of vitamin D deficiency

- Reduced skin synthesis
  - Sunscreen use, skin pigment, aging
- Decreased bioavailability
  - Malabsorption, obesity (sequestration of vitamin D in fat)
- Decreased synthesis of 25(OH)D
  - Liver failure, mild to moderate liver dysfunction
- Decreased synthesis of 1,25(OH)₂D
  - Chronic kidney disease
Vitamin D supplementation

Current Dietary Reference Intakes

- Only Adequate Intakes have been established for vitamin D
  - 1 ug = 40 IU
  - Assumes no sunlight exposure
  - No special recommendations for pregnancy, lactation
  - Tolerable upper limit
    - Birth – 1 year: 1000 IU/day; > 1 year: 2000 IU/day

<table>
<thead>
<tr>
<th>Age</th>
<th>Adequate Intakes</th>
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</thead>
<tbody>
<tr>
<td>Birth – 50 years</td>
<td>200 IU/day</td>
</tr>
<tr>
<td>51 – 70 years</td>
<td>400 IU/day</td>
</tr>
<tr>
<td>71+ years</td>
<td>600 IU/day</td>
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</tbody>
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Adequate intakes used when insufficient evidence to establish an RDA. Level assumed to ensure nutritional adequacy.


Highest safe dose of vitamin D?

- Sun exposure does not lead to toxicity
  - Only through supplements, over-fortification of foods
- No systematic studies to establish toxic levels, mostly case series

Vitamin D toxicity: outbreak

- Outbreak of hypercalcemia due to over-fortification of milk
  - Boston area home-delivery dairy bought 30-35 times vitamin D needed to supplement milk
  - 11,000 households exposed
  - 41 hospitalizations and 2 deaths due to hypercalcemic state
  - Average 25(OH)D level: 224 ng/ml in cases
  - Age strong risk factor for hypervitaminosis D: decline in renal function?

Vitamin D toxicity

- Women’s Health Initiative: calcium (1 g/day) + vitamin D (400 IU/day)
  - 17% increased risk of kidney stones over 7 years
  - Prevalence of stones 2.4% in txt group vs. 2.1% in placebo
- Toxic level?
  - Serum 25(OH)D concentration consistently >200 ng/mL
  - Some suggest as high as 300 ng/mL

Highest safe dose of Vitamin D?

Data suggests 10,000 IU/day may be safe

- Circles: mean values from studies without toxic levels
- X’s: single values from people reported to be intoxicated with vitamin D
- Arrow: lowest dose reported as causing hypercalcemia

High dose (>~1500 IU/day) vitamin D has not be evaluated for safety or harm in a large RCT

Supplements: vitamin D₂ or vitamin D₃ better?

- Considerable controversy about this topic!
  - Some studies suggest vitamin D₂ is about one-third as effective in raising 25(OH)D levels than vitamin D₃ (Armas 2004, Trang 1998)
  - AHRQ report suggests D₃ more effective than D₂
  - Others suggest vitamin D₂ and vitamin D₃ are equally effective (Holick 2008)
- Most over the counter supplements contain vitamin D₃; vitamin D₃ not approved as a pharmaceutical agent in the U.S.
- Prescription for 50,000 IU is for vitamin D₂
High dose vitamin D3: coming to a computer near you …


Daily or monthly?

- Daily adherence may be poor …
- Long half life of 25(OH)D (~3 weeks)
- Provides opportunity other dosing schedules

Daily or monthly?

- New Zealand study: three groups receiving vitamin D₃
  - 500,000 IU loading dose
  - Loading dose + 50,000 IU/month
  - 50,000 IU/month
- All three groups had increased 25(OH)D
- When the levels in each group reached a plateau …
  - The loading dose + 50,000 IU/month had the highest levels (36 ng/ml)
  - The loading dose alone group had the lowest levels (28 ng/ml)
  - The monthly dose had intermediate levels (32 ng/ml)
- Safety: no significant increase in serum calcium

Relation between vitamin D and disease

Bacon CJ et al. Osteoporos Int. 2008 In Press
Rickets and osteomalacia

- Both conditions are the result of defective mineralization of the bone
- 25(OH)D level below which disease occurs is unclear
- Children:
  - Exclusively breast-fed infants with dark skin and no sun exposure born to vitamin D deficient mothers are at high risk
- Adults:
  - Institutionalized elderly with no sun exposure and those without exposure to supplemented foods (lactose intolerant) are at high risk

A cautionary tale …

- Beta-carotene
  - Serum levels of beta carotene associated with reduced risk of cancer
  - Biological explanations found (antioxidant “radical trapping”)
  - Randomized trial
    - 22,000 participants
    - NO differences in mortality, cardiovascular disease, cancer

Another cautionary tale …

- Selenium and Vitamin E
  - Secondary analyses of previous RCTs suggested a beneficial effect of both selenium, vitamin E for prostate cancer
  - SELECT study
    - Randomized controlled trial
    - 200 ug/day selenium, 400 IU/day vitamin E
    - 35,533 men, $121 million
    - NO differences in prostate cancer

More reasons to be cautious …

- Multivitamins and cancer, death in women (observational WHI study)
  - No association
- Vitamin C and cancer in men (Physician’s Health Study II)
  - No association
- Folate and prostate cancer in men (Aspirin/Folate Polyp Prevention Study)
  - More incidence in treatment group
Osteoporosis, Falls and Fracture

- Probably the most researched area
- Mostly focused on older adults (>65 years)
  - Observational studies
    - Low 25(OH)D associated with increased falls (fair evidence)
    - Positive association, 25(OH)D and BMD (fair evidence)


Meta-analyses for vitamin D supplementation and fracture

- Mixed results from meta-analyses
  - Analyses that do not incorporate adherence generally do not see an association between supplementation and reduce fracture risk
  - Analyses that incorporate adherence generally see a risk reduction of about 20% for non-vertebral and hip fractures
- Summary: dose needed is probably >>400 IU/day
  - Large RCT with good adherence and little loss to follow-up is needed


Osteoporosis, Falls and Fracture

  - Randomized trials
    - Vitamin D3 and calcium: small increases in BMD
    - Inconsistent evidence: Vitamin D supplementation and fractures and falls
      - Limitations of studies: poor compliance, incomplete assessment of 25(OH)D status; large loss to follow-up
      - Little evidence from randomized trials that vitamin D above current reference intakes is harmful


Cardiovascular disease

- Coronary angiography patients
  - 3,299 patients followed for 7.7 years
  - 25(OH)D deficiency (<10 ng/ml) vs. higher levels (>30 ng/ml)
    - 3x higher risk of heart failure death
    - 5x higher risk of sudden cardiac death
- Health Professionals Follow-Up Study
  - 454 MI and fatal coronary heart disease, 900 matched controls, all men
  - Deficient (<15 ng/ml) were 2.4 times more likely to have an MI than those who were sufficient (>30 ng/ml)

Cancer

• Strongest evidence for vitamin D and prevention of colorectal cancer
  – Meta-analysis: 25(OH)D concentrations >32.8 ng/ml had 50% lower incidence, compared to those with ≤12 ng/ml
• Secondary analysis of RCT: vitamin D plus calcium supplementation reduced cancer incidence (all types) by > 75%
  – Nebraska, 1179 community dwelling women


Cancer

• Limited support for other cancer types
• Suggestion of an association between higher 25(OH)D levels and increased risk of pancreatic cancer
  – Finnish smokers: 3-fold increased risk of pancreatic cancer, highest (>26.2 ng/ml) vs. lowest (<12.8 ng/ml) 25(OH)D levels
  – Results not confirmed in subsequent study: only seen in people with low UVB exposure


Overall mortality

• NHANES III data
  – Recruited 1988-1994, followed for 8.7 years (median)
  – 13,331 participants, 1806 deaths
  – 26% increased risk of mortality for those in the lowest (<17.8 ng/ml) vs. the highest (>32 ng/ml) quartile of 25(OH)D
• Meta-analysis of RCTs with mortality data: 7% reduced risk of all-cause mortality
  – Death was secondary endpoint, cause of death not determined
  – Doses ranged from 300 IU to 2000 IU/day
• WHI Randomized trial
  – Vitamin D3 (400 IU) + calcium (1 g/day) vs. placebo
  – No effect of supplementation of total mortality in 36,282

Auer and Gandra, Arch Intern Med. 2007;167(16):1730-1737
Mohamed et al. Arch Intern Med. 2006;166(15):1629-1637

Other diseases

• Osteoarthritis
• Schizophrenia
• Depression
• Lung Function
• Autoimmune diseases (MS)
• Diabetes
• Peridontal disease
• Athletic performance
• Infectious disease/TB
Other populations

• Infants and young children
  – Vitamin D deficiency occurs in breastfed infants with high levels of skin pigmentation, no vitamin D supplementation and little sun exposure
  – Functional outcomes of vitamin D inadequacy (aside from frank disease) is not well studied in this age group

• Adolescents
  – Key time period for bone development
  – 25(OH)D level for optimal bone health unknown in this age group
  – U.K. study found that 25(OH)D positively related to muscle strength and jumping

Summary

• Vitamin D likely to have multiple effects
  – VDR, 1α-OHase found in many tissues

• Use total 25(OH)D for vitamin D status
  – Consider supplementation for those below 20 ng/ml; certainly for those below 10 ng/ml

• Levels up to 10,000 IU/day may be safe, BUT …
  – Robust data from large RCTs of higher dose vitamin D supplementation is lacking
  – Data suggest 1500 IU/day is needed for “sufficiency”
  – Monthly dosing of vitamin D₃ may also be effective

Summary

• Vitamin D and health outcomes
  – Fracture prevention
    • Most studied outcome: suggestion of a benefit for supplementation above 400 IU/day
    • Results have been inconsistent to date
  – Limited randomized trial data for higher doses of vitamin D (>1000 IU/day)
    – Additional RCTs with good adherence and little loss to follow-up are needed