

Vitamin D in 2010: “Here Comes the Sun” ?

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1

Vitamin D:

- Calcium and bone metabolism:
- Enhances intestinal absorption of both calcium and phosphorus into circulation.
- Promotes mineralization of bone:
- Calcium incorporation into cartilaginous bone matrix.

2

Vitamin D deficiency:

- Severe Vit. D deficiency: rickets.
- Osteomalacia (“soft bones”):
 - “Saber shins:” bowing of lower legs, due to inadequate bone mineralization in childhood.
 - Prevented by levels of 25-hydroxy-Vit. D > 10 ng/ml.
- Also caused abnormal spine curvature with exaggerated lumbar lordosis, and flattening of pelvis (decreased AP diameter), interfering with birth canal. History: this was the original reason for development of the C-section procedure.

3

Vitamin D deficiency:

- Milder Vit. D deficiency:
- Appears asymptomatic.
- Limited ingestion/absorption of calcium or Vit. D → normal physiologic increase in PTH (parathyroid hormone) → increased resorption of bone → maintain normal serum calcium, but at expense of bone density (secondary hyperparathyroidism).
- Exacerbates osteoporosis.

4

“Not Just Your Mother’s Vit. D Deficiency”:

- Recent research shows Vit. D also important in:
- Neuromuscular function: strength and coordination, risk of falling.
- Myalgias: chronic pain in elderly improved with Vit. D supplementation; fibromyalgia.
- Immune function -- Infections:
 - TB: cathelicidin production in macrophages.
 - Influenza: flu season occurs in spring, after winter, when population’s Vit. D levels are lowest.
 - Enhances innate immunity, first line of defense against invading pathogens.

5

Nonclassic Actions of Vit. D:

- Immune function – Autoimmune diseases:
 - Dampens adaptive immunity, T and B cells which recognize and attack specific antigens.
 - Vit. D deficiency associated with increased rates of:
 - Type 1 diabetes
 - Rheumatoid arthritis
 - Multiple sclerosis
 - Asthma
 - Rejection of transplanted organs

6

Nonclassic Actions of Vit. D:

- Cancer prevention: enhances regulation of cell proliferation and differentiation, affects cancer growth.
 - Evidence best in colorectal cancer; mixed for breast and prostate cancer.
- Type 2 diabetes:
 - Vit. D stimulates insulin production
 - Decreases insulin resistance (by HOMA measurement).
 - In people with IFG (impaired fasting glucose), saw significant decrease in progression to overt T2DM when treated with Vit. D 700 IU/day and calcium 500 mg/day.

7

Nonclassic Actions of Vit. D:

- Renin production in kidney:
 - Increased in Vit. D deficiency.
 - Increased angiotensin, aldosterone, and vascular tone.
 - Increased HTN and LV hypertrophy.
- Cardiovascular disease:
 - Increased frequency of MI and sudden cardiac death when serum levels of 25-hydroxy-D were low.

8

Vit. D Metabolism:

- Sunlight on skin produces Vit. D from cholesterol precursors. Balance with risk for skin cancer.
- Food sources (limited): Vit. D-fortified milk, cod liver oil. Supplements often needed.
- Requires hydroxylation (addition of -OH group) at 2 places on Vit D molecule:
 - 1) Liver: 25-hydroxy-D (or 25-OH-D)
 - 2) Kidney: 1,25-dihydroxy-D (or 1,25-diOH-D)
 - Then "active" Vit. D can bind to the Vit. D receptor.
- A few other tissues are capable of producing 1,25-diOH-D locally (immune cells); importance of Vit. D action beyond bone metabolism.

9

Vit. D: How Much is Enough?

- What do you measure? Serum 25-OH-D.
- This level is mostly dependent on availability of substrate Vit. D.
- Could be low in chronic liver disease, but only if severe.
- Long serum half-life, therefore stable serum level.

10

Vit. D: How Much is Enough?

- Don't measure 1,25-diOH-D:
- This level may remain adequate even when Vit. D is deficient. Secondary hyperparathyroidism will develop, then PTH increases renal hydroxylation of Vit. D; therefore this level may not be a good reflection of adequate Vit. D availability.
- Short serum half-life; variable serum level; may not accurately reflect physiologic status.

11

Normal Range:

- Past: defined as average level obtained at Mayo Clinic in Rochester, Minn. in winter.
- 25-OH-D > 10 ng/ml will prevent rickets, but is not sufficient for additional actions of Vit D.
- "Desirable" level currently being defined:
 - > 20 ng/ml will probably prevent secondary hyperpara.
 - Current consensus: > 30 ng/ml
 - Possibly >40 ng/ml for some functions

12

Normal Range:

- Toxic effects probably won't occur unless $> 100 - 150$ ng/ml.
 - Hypercalcemia may occur at lower levels in people with primary hyperparathyroidism, or with uncontrolled granulomatous disease (sarcoidosis).
- Measured in ng/ml in US; nmol/L elsewhere.
 - Factor of 2.5:
 - $30 \text{ ng/ml} = 75 \text{ nmol/L}$

13

Vit. D Therapy:

- Vit. D ubiquitous in living world:
 - D₂ in plant kingdom; ergocalciferol.
 - D₃ in animal kingdom; cholecalciferol.
- D₃ binds more tightly to animal (human) Vit. D receptor, vs. D₂.
- D₂ binds to human receptor, but doesn't stay bound as long; effective duration of action of each dose is shorter.
- If giving daily dose, D₂ vs. D₃ probably doesn't matter.
- Most OTC supplements now are D₃.

14

Vit. D Therapy:

- If giving large doses of Vit. D intermittently, the duration does matter.
- Prescription Vit. D (Drisdol) is D₂ 50,000 I.U., in bright green capsule (generic ~ \$2.70/capsule).
- New pharmacologic D₃ preparation (Replesta) OTC, 50,000 I.U. in orange-flavored wafer (~ \$4/wafer).
- After single dose of D₂ 50,000 IU, serum 25-OH-D is back to baseline after 2 weeks.
- After single dose of D₃ 50,000 IU, serum 25-OH-D stays up for 1 month or more.

15

Vit. D Therapy:

- To correct significant deficiency, consider D₂ 50,000 IU once weekly x 3 months, then lower dose of OTC D₃ daily after that. Or try the new D₃ 50,000 IU when fully available, for the first 3 months.
- It takes 1,000 IU daily of Vit. D administration to raise serum 25-OH-D by 10 ng/ml.
 - If baseline 25-OH-D were 19 ng/ml, you'd want to raise it by 10-20 ng/ml. Therefore, need 1,000-2,000 IU of Vit. D daily.
 - Even after a 3-month course of pharmacologic Vit. D, it will wear off. Serum level will return to baseline if maintenance therapy not given.

16

Vit. D Therapy:

- Don't give very high doses at very long dosing intervals:
- Study (JAMA, May, 2010): Gave D₃ 500,000 IU (50,000 IU daily x 10 days) as "single" annual dose in community-dwelling older women, in fall or winter, for 3-5 yrs.
- Higher rate of falls and fractures in the high-dose Vit. D group vs. placebo: RR 1.26 for fractures, 1.15 for falls. Fractures and falls occurred esp. in first 3 months after giving the annual dose.
- Don't give prescription D₂ 150,000 IU q. 3 months.

17

Vit. D Therapy:

- It's best not to assume that everyone needs megadose Vit. D.
- Intake of both calcium and Vit. D vary at baseline.
- Absorption of both calcium and Vit. D also vary; decreased in elderly.

18

Vit. D Therapy:

- Measure 25-OH-D in those at risk:
 - Older adults
 - Limited sun exposure (mobility, skin Ca, clothing, latitude)
 - Bariatric surgery
 - Dark skinned persons
 - Obesity (larger requirement?)
 - Diabetes

19

Vit. D Therapy:

- In primary hyperparathyroidism:
- Vit. D deficiency will make PTH go even higher; more bone resorption.
- Try to restore normal level of 25-OH-D, and give adequate calcium intake, unless hypercalcemia actually does worsen.

20

Vit. D in Chronic Kidney Disease

- May have impaired renal hydroxylation, low 1,25-diOH-D.
- But measuring 1,25-diOH-D generally still not helpful.
- CKD patients are just as likely as general population to be deficient in “conventional” Vit. D.
- Measure serum 25-OH-D. Bring up to goal level with “conventional” Vit. D supplements.
- In CKD (eGFR < 60 ml/min), measure PTH. If not elevated, Vit. D analog therapy is not yet needed.

21

Vit. D in Chronic Kidney Disease

- Cont’d:
- If PTH doesn’t come down, then Vit D. analog might be needed. OR, person might be calcium deficient. Check calcium intake. Measure 24-hr urine calcium; goal 100 – 300 mg/day.
- In advanced CKD, avoid excessive correction of PTH, due to higher risk of calcification of vascular plaque, and higher CVD rates. See Table, next slide. (At kidney.org, KDOQI Guidelines, Bone Metabolism and Disease in CKD, Eval. of Calcium and Phosphorus Metabolism, Table 15.)

22

PTH Goals in CKD:

CKD	PTH (pg/ml)	PTH (pmol/L)
Stage 3: GFR 30 – 59 ml/min	35 – 70	3.85 – 7.7
Stage 4: GFR 15 – 29 ml/min	70 – 110	7.7 – 12.1
Stage 5: GFR < 15 ml/min or dialysis	150 – 300	16.5 – 33.0

23

Vit. D: Clinical Perspective

- Caveat: Although some of the information about Vit. D benefits has been shown in interventional studies, much of the information about benefits of Vit. D is observational, not yet confirmed in randomized controlled clinical trials.
- Given failure of B-vitamins and antioxidants to show clinical benefit for CVD (or cancer), maintain some caution in our enthusiasm.

24

Vit. D: Clinical Perspective

- Goal of 25-OH-D 30-60 ng/ml for most people is probably sound.
- New national guidelines: Vit. D 800 – 1,000 IU daily for adults, and 400 IU daily for children. This is still a conservative position. Vit. D 2,000 IU daily is recommended for pregnant women.
- For many adults, 2,000 IU daily may be a good idea.
- Some people may need even higher doses; depends on 25-OH-D level.

25

Case: Mrs. O.

- 75 y/o white woman has DEXA with T-score -2.5 at lumbar spine.
- Serum calcium is 9.4 mg/dl. PTH is 120 ng/ml (< 65).
- Refer to ENT surgeon for parathyroidectomy?

26

Mrs. O.:

- 3 inch height loss over past 20 yrs.
- Recent rib fracture when fell into dining room table.
- Had mild CVA a few yrs ago; developed seizure disorder; takes phenytoin/Dilantin.
- Lives alone, doesn't get out much due to arthritis and mild gait difficulty; uses walker.
- What else would you like to know?

27

Mrs. O.:

- 25-OH-D is 15 ng/ml.
- Dilantin interferes with hepatic hydroxylation of Vit. D. She also has limited sun exposure.
- She takes a multivitamin with Vit. D 400 IU daily.
- She takes calcium 1 pill daily. Her pill is calcium citrate; label indicates 500 mg calcium, but "serving size" is 2 pills. She gets only 250 mg calcium daily.
- How would you treat her?

28

Mrs. O.:

- Fracture studies do not show benefit for Vit. D doses of 400 IU daily or less.
- Try Vit. D₃ 2,000 IU daily to raise her 25-OH-D into 30's ng/ml.
- Consider initial "loading dose" of Vit. D₂ 50,000 IU once weekly for 3 months, followed by daily dose above.
- Increase calcium citrate to 2 pills TID (1,500 mg calcium daily).
- Recheck 25-OH-D and 24-hr urine calcium later on.

29

Mrs. O.:

- Studies in elderly show benefit when Vit. D and calcium are both given; possibly less benefit if only 1 of these nutrients is given.
- Benefits:
 - Reduced fractures
 - Reduced falls
 - Reduced overall mortality, whether a fracture occurs or not.

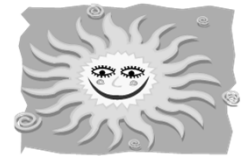
30

Mrs. O.:

- Don't give teriparatide/Forteo until Vit. D and calcium deficiencies are corrected, and PTH is back to normal. Forteo is contraindicated in uncorrected secondary hyperparathyroidism as well as primary hyperparathyroidism.
- Bisphosphonates won't be effective until Vit. D and calcium are sufficient.
- Also consider strengthening program, gait training, and assessing home for fall risk.

31

THANK YOU !!!



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32