VITAMIN SUPPLEMENTS AND HEALTHY AGING

F. MICHAEL GLOTH, III, MD
Johns Hopkins University School of Medicine

Objectives:

• Describe the potential harm associated with vitamin A supplementation in seniors.
• Review the impact of vitamin B12 and folate in a frail senior population
• Identify the skeletal and non-skeletal effects of vitamin D

DISCLOSURE
F. Michael Gloth, III, MD does have a significant financial interest or other relationship with manufacturer(s) of commercial product(s) and or provider(s) of commercial services discussed in the presentation.
GSK, Merck, Novartis, Purdue, Roche, Wyeth
Slide 1
Vitamin Supplements and Healthy Aging

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Slide 2
Objectives

1. Participants will recognize the potential problems associated with vitamin A supplementation in a population susceptible to bone loss and fracture.
2. Participants will be able to analyze the need for vitamin B-complex and D vitamins in long-term care residents.
3. Participants will appreciate the usefulness of vitamin D in bone-related and non-bone health for long-term care residents.

Slide 3
Vitamin deficiency:
Hypovitaminosis accompanied by physiological or biochemical abnormalities

Slide 4

3 Questions Before Supplementing Vitamins in LTC

- Is there evidence of widespread deficiency in seniors in LTC?
- Is there evidence that supplementation would be helpful?
- Is there evidence that supplementation would be harmful?

Slide 5

PERCENT BELOW RDA

- BASED ON 3-DAY MONITORED FOOD RECORDS BY LOCATION


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VITAMIN A
Vitamin A

- Is there evidence of widespread deficiency in seniors in LTC?
  - How to measure?
  - No good evidence of widespread deficiency

Vitamin A

- Is there evidence that supplementation would be helpful in LTC patients?
  - Murphy S, West KP Jr, Greenough WB 3rd et al. (Age Ageing. 1992 Nov;21(6):435-9.) showed no benefit in LTC on infections of vitamin A suppl'n
  - No good confirmed studies of benefit to vitamin A supplementation in the LTC setting.

Vitamin A

- Is there evidence of widespread deficiency in seniors in LTC? No
- Is there evidence that supplementation would be helpful? No
- Is there evidence that supplementation would be harmful?
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Vitamin A as Harmful


Slide 11

Vitamin A as Harmful

Diane Feskanich; Vishwa Singh; Walter C. Willett; Graham A. Colditz Vitamin A Intake and Hip Fractures Among Postmenopausal Women. JAMA, Jan 2002; 287: 47 - 54.

<table>
<thead>
<tr>
<th>Quintiles of Consumption</th>
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<th>3</th>
<th>4</th>
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<td>Vitamin A</td>
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<td>Multivariate RR (95% CI)</td>
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<td>2250-3000</td>
<td>1700-2249</td>
<td>1250-1699</td>
<td>&lt;1250</td>
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<td>&lt;0.001 (1.25-2.46)</td>
<td>&lt;0.001 (1.18-2.43)</td>
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<td>1.89 (1.74-2.05)</td>
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Diane Feskanich; Vishwa Singh; Walter C. Willett; Graham A. Colditz Vitamin A Intake and Hip Fractures Among Postmenopausal Women. JAMA, Jan 2002; 287: 287 - 54.

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Vitamin A as Harmful

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Vitamin A

- Is there evidence of widespread deficiency in senior in LTC?  No
- Is there evidence that supplementation would be helpful?  No
- Is there evidence that supplementation would be harmful?  Yes

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Table. Relative Risk for All-Cause Mortality With Antioxidant Vitamins

<table>
<thead>
<tr>
<th>Trials/Agent</th>
<th>Relative Risk of Mortality With Antioxidant Vitamin</th>
<th>95% Confidence Interval</th>
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<tr>
<td>All trials — all agents</td>
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<td>1.02 - 1.08</td>
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<td>Low bias trials — all agents</td>
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<td>High bias trials — all agents</td>
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<td>1.09 - 1.11</td>
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<td>Beta-carotene</td>
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VITAMIN B
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**Vitamin B**

- Is there evidence of widespread deficiency in seniors in LTC?
- Is there evidence that supplementation would be helpful?
- Is there evidence that supplementation would be harmful?

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**Vitamin B**

- Is there evidence of widespread deficiency in seniors in LTC?
  - Perhaps

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**Vitamin B**

- Is there evidence of widespread deficiency in seniors in LTC? Maybe
- Is there evidence that supplementation would be helpful?
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Vitamin B

- Improvements in CV risk by reducing Homocysteine levels (B12 & Folate)
- Improvement in Cognition
- Improvement in Bone and Reduction in Falls/Fractures

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Vitamin B Supplementation Dosing

Oral cyanocobalamin supplementation in older people with vitamin B12 deficiency: a dose-finding trial.


- METHODS: We conducted a randomized, parallel-group, double-blind, dose-finding trial to determine the lowest oral dose of cyanocobalamin required to normalize biochemical markers of vitamin B(12) deficiency in older people with mild vitamin B(12) deficiency, defined as a serum vitamin B(12) level of 100 to 300 pmol/L (135-406 pg/mL) and a methylmalonic acid level of 0.26 mmol/L or greater.

- RESULTS: Supplementation with cyanocobalamin in daily oral doses of 2.5, 100, 250, 500, and 1000 μg was associated with mean reductions in plasma methylmalonic acid concentrations of 16%, 16%, 23%, 33%, and 33%, respectively. Daily doses of 647 to 1032 μg of cyanocobalamin were associated with 80% to 90% of the estimated maximum reduction in the plasma methylmalonic acid concentration.

- CONCLUSION: The lowest dose of oral cyanocobalamin required to normalize mild vitamin B(12) deficiency is more than 200 times greater than the recommended dietary allowance, which is approximately 1 μg daily.

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Vitamin B

- Are there clear improvements in CV risk by reducing Homocysteine levels (B12 & Folate)?


- Summary: No clear benefit in CV Dz
Vitamin B

- Is there improvement in cognition?

- Remains to be seen.

Vitamin B

- Improvement in Bone and Reduction in Falls/Fractures

- Remains to be seen.
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Vitamin B

- Is there evidence of widespread deficiency in seniors in LTC? Some
- Is there evidence that supplementation would be helpful? Perhaps
- Is there evidence that supplementation would be harmful? Very little

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VITAMIN D

Slide 27
Vitamin D

- Is there evidence of widespread deficiency in seniors in LTC?
- Is there evidence that supplementation would be helpful?
- Is there evidence that supplementation would be harmful?
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Vitamin D

• Is there evidence of widespread deficiency in seniors in LTC?

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Age-related Changes in the GI Tract

• Vitamin D absorption is dependent upon vitamin D status
• Vitamin D absorption decreases by 40% (receptors also decrease affecting Calcium absorption) compared to young cohorts
• Acid secretion and gastric emptying are altered by diseases and medications more commonly in seniors


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Age-related Changes (cont’d)

• Older subjects convert 7-dehydrocholesterol to cholecalciferol in the skin at about half the rate of young subjects.
• There is less precursor (7-dehydrocholesterol) per volume of dermal tissue in older subjects
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Risk Factors for Vitamin D Deficiency

- Advancing age
- Celiac disease
- Pernicious anemia
- HGA (heterozygous factor V Leiden or activated protein C resistance)
- Cholecalciferol (vitamin D) deficiency
- Excess use of sunscreen
- Obesity
- Chronic kidney disease
- Low outdoor activity or low UVB exposure
- Pregnancy

The national goal is to achieve vitamin D in the absence of or not requiring vitamin D supplementation.

- 200 IU = dental x-ray
- 400 IU = osteoporosis
- 600 IU = osteomalacia

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2004 Surgeon General's Report: Bone Health and Osteoporosis

You need more vitamin D as you get older.

- Nutritional supplements typically provide 400 IU of vitamin D.
- One cup of vitamin D fortified milk provides 200 IU of vitamin D.
- 300 IU of vitamin D at age 20-30
- 400 IU of vitamin D at age 60
- 600 IU of vitamin D at age 70

Minimum Daily Requirements

- RDI = Recommended Dietary Allowance
- 600 IU (400 IU for women age 70+)
- 300 IU (200 IU for women age 60+)
- 200 IU (100 IU for women age 50+)

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**PERCENT BELOW RDA**

- BASED ON 3-DAY MONITORED FOOD RECORDS BY LOCATION
- RDA for vitamin D was 400 I.U.

[Graph showing data on vitamin D intake by location]


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**The Majority of Americans Are Not Receiving Adequate Levels of Vitamin D**

**Vitamin D Intake**

- [Graph showing vitamin D intake by age group]


*Percent consuming AI or above from diet + supplements significantly different from diet alone, P* < 0.05.

- According to an NHANES III survey of 3,444 women aged 51 and older, over 70% of women 51-70 were estimated not to meet adequate intake guidelines for vitamin D based on daily intake from diet and supplements (400 IU).
- Nearly 90% of women over the age of 70 were estimated not to meet guidelines (600 IU).

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**Vitamin D deficiency:**

**Hypovitaminosis D** accompanied by physiological or biochemical abnormalities

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Low Vitamin D Status and PTH Increase

Gloth et al. JAMA 1995. 274:1683-6

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Relationship Between Serum Intact PTH (iPTH) and 25(OH)D


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Relationship Between Serum 25-(OH)D and PTH in Medical Inpatients
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Vitamin D Status: Impact on Calcium Absorption and PTH

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The 25(OH)D Continuum Controversy

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Existing Assays and Laboratories are Highly Variable and Inconsistent
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**Percent of Subjects with Low Vitamin D Status**

- Low Vitamin D Status: 45%
- Normal Vitamin D Status: 38%
- *Defined as 25-OH D < 15 ng/mL*

Gloth et al. JAMA 1995; 274:1683-6

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**NH vs Community Dwellers**

- Vitamin D intake: 232 ± 378 I.U./day
- PTH level was significantly related to NH LOS


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**Prevalence of Vitamin D Deficiency in Postmenopausal Women Treated for Osteoporosis**

52% of subjects in the study had inadequate levels of vitamin D

Prevalence of Vitamin D Deficiency in a Minimal Trauma Fracture Population


Vitamin D

- Is there evidence of widespread deficiency in seniors in LTC? Yes
- Is there evidence that supplementation would be helpful?

Supporting Data for Vitamin D

- Association with Falls – Stein et al. JAGS '99
- Increased risk in Hip Fracture trials – LeBoff et al. JAMA '99
- Vitamin A (Cod Liver Oil) negatively impacts – JAMA '02
- Muscle strength is associated with vitamin D Status – JAGS '99 & JBMR '97
- Vitamin D Deficiency Pain Syndrome – Arch Intern Med '91
Higher 25(OH)D Levels Are Associated With Better Lower Extremity Function in Ambulatory Women

- 4,100 ambulatory adults included in NHANES III
- 60 to ≥ 90 years
- Functional measurements used to assess lower extremity function:
  - 8-ft walking speed test
  - Timed sit-to-stand test

Reference range of 22.5–94.0 nmol/L (9.0–37.7 ng/mL).
N = 4,100; P < 0.001.

Lower Levels of Vitamin D May Be Associated with the Risk for Falling

- N = 122
- Ages: 63–99
- Randomized, double-blind, controlled trial
  - Calcium 1200 mg/d
  - Calcium 1200 mg/d + vitamin D 800 IU/d
- 12-week duration
- Mean serum 25(OH)D 12 ng/mL at baseline
- Women living in long-term care units

Calcium only (n=44) vs Calcium + vitamin D (n=45):
- 49% reduction in falls, P = 0.01

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Vitamin D May Reduce the Risk for Falling

- N = 199 men; 246 women
- Ages: >65 y.o.
- Randomized, double-blind, controlled trial
  - Placebo
  - Calcium 500 mg/d + vitamin D 700 IU/d
- 3-yr duration
- Mean serum 25(OH)D 32 ng/mL at baseline
- Ambulatory living at home

Cumulative % who fell

0.0 0.2 0.4 0.6 0.8 1.0

Placebo (n=75)
Calcium + vitamin D (n=59)

-46%

Reduction in falls
OR=0.54
CI=0.30-0.97


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Vitamin D has been associated with a 20-30% reduction in fall rates


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HCR ManorCare - Region 4
Fall Trends

% Frequency

July August Sept Oct Nov Dec Jan
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Facility Average Monthly Fall %

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Vitamin D: Fracture Reduction

Hip Fractures

Other Nonvertebral Fractures

P=0.04

P=0.015

Chapuy M, et al. NEJM

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Association of Vitamin D and Risk of Fracture

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Vitamin D, Bone, and Teeth

- Vitamin D supplementation or Vitamin D Loss may have a rapid impact on bone <6 months
- Vitamin D and Calcium also reduces tooth loss
- Adding another fat-soluble vitamin, A, may impair the benefit of vitamin D on Bone (Nurses’ Health Study > 3000 mcg/d retinol equivalents)

Khosla S et al. JAMA. 2002; 288: 47-54

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Vitamin D, Diabetes, and Bone

- Type 1 Diabetes has been associated with bone loss
- Type 2 Diabetes has been associated with better BMD
- Vitamin D Supplementation in infants has been associated with reduced risk of type 1 diabetes
- Vitamin D Deficiency has been associated with glucose intolerance and perhaps insulin resistance

Hypponen E et al. Lancet. 2001; 358: 1500-3

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Nursing Home Vitamin D Deficiency

- Calcium Absorption lower in NH women
- 17% Secondary Hyperparathyroidism
- 1000 I.U. of Vitamin D was inadequate to maintain stores
- 46% of over 200 NH residents on supplements (200-400 I.U. per day) had 25-OH Vitamin D < 15 ng/mL

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Vitamin D and Calcium on PTH, Sway & Falls

- 25-OHD at Baseline 25 nmol/L (10ng/mL)
- Sway frontal & sagittal diam and sway area 8 wks
- PTH at 8 weeks
- Falls at one year


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Vitamin D Deficiency Pain Syndrome

- Excruciating Pain with Light Pressure on Large Muscle Groups
- Pressure Sores Are Painful
- Unresponsive to Opioids or TCA’s
- Marked Improvement or Resolution within 5-7 days of 100,000 I.U. Vitamin D


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Seasonal Affective Disorder

- All patients in a small trial of SAD showed improvement on Hamilton Depression and SIGH-SAD Scales after 100,000 I.U. of Vitamin D statistically significantly better than broad spectrum light with plastic cover.
- Vitamin D status improved significantly more in Vitamin D treated group

Gloth et al. J Nutr Health Aging ’99. 3(1):5-7
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Bringing Vitamin D Deficiency to Light

Gloth et al. J Nutr Health Aging ’99. 3(1):5-7

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Functional Improvement with Vitamin D

- Vitamin D Deficient Subjects Treated with Vitamin D had a statistically significant improvement in FEFA scores
- Functional improvement was linearly associated with change in vitamin D status


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Vitamin D and Infection

- TLR activation of human macrophages up-regulated expression of the vitamin D receptor and the vitamin D-1-hydroxylase genes, leading to induction of the antimicrobial peptide cathelicidin and killing of intracellular Mycobacterium tuberculosis. We also observed that sera from African American individuals, known to have increased susceptibility to tuberculosis, had low 25-hydroxyvitamin D and were inefficient in supporting cathelicidin messenger RNA induction. These data support a link between TLRs and vitamin D-mediated innate immunity and suggest that differences in ability of human populations to produce vitamin D may contribute to susceptibility to microbial infection.

More on Vitamin D and Cancer

  - Total vitamin D intake was weakly associated with reduced risk of distal colorectal adenoma (RR = 0.79, 95% CI: 0.63, 0.99; p(trend) = 0.07), but more strongly with distal colon adenoma risk (RR = 0.67, 95% CI: 0.52, 0.87, p(trend) = 0.004). The combinations of high vitamin D and low retinol intake (RR = 0.55, 95% CI: 0.28, 1.00) further decreased risk of distal colorectal adenoma when compared with the opposite extreme.

Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial.
Vitamin D and Fractures

- Vitamin D has been associated with clinical endpoints
  - Improvement in BMD
  - Reductions in falls
  - Reductions in fractures


Other Chronic Conditions Affected By Vitamin D Levels

<table>
<thead>
<tr>
<th>Condition</th>
<th>Status of Evidence</th>
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<tbody>
<tr>
<td>Low BMD</td>
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</tr>
<tr>
<td>Falls or fracture risk of fracture</td>
<td>++</td>
</tr>
<tr>
<td>Knee pain</td>
<td>++</td>
</tr>
<tr>
<td>Fatigue</td>
<td>++</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>++</td>
</tr>
<tr>
<td>1,25(OH)2 vitamin D</td>
<td>++</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>++</td>
</tr>
<tr>
<td>Periosteal disease</td>
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Vitamin D and Calcium

- 36,282 postmenopausal women 50-79 y.o.
- 1000 mg calcium; 400 I.U. vitamin D
- May take other calcium and vitamin D
- 0.71 Hazard Ratio (CI 0.52-0.97) if adhered
- Significant improvements in hip BMD at all points measured over the 9 year study.
- "...the findings provide evidence of a positive effect of calcium with vitamin D on bone health in older postmenopausal women"
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Vitamin D

- Is there evidence of widespread deficiency in seniors in LTC? Yes
- Is there evidence that supplementation would be helpful? Yes
- Is there evidence that supplementation would be harmful?

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Defining the Upper Limit of Vitamin D Intake

- Cases of vitamin D toxicity have been reported in patients receiving ≥ 10,000 IU/day for at least 1 month.
- No toxic effects were observed in individuals given 4,000 IU/day administered orally for 5 months.1

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What is the Optimal Intake of Vitamin D? How Much is Too Much?

Defining the Upper Limit of Vitamin D Intake:
There is limited information regarding doses of vitamin D associated with toxicity, although intermittent (yearly or twice yearly) single doses of vitamin D as high as 600,000 IU have been given without reports of toxicity.
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**Vitamin D**

- Is there evidence of widespread deficiency in seniors in LTC? Yes
- Is there evidence that supplementation would be helpful? Yes
- Is there evidence that supplementation would be harmful? Very little

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**Who gets supplements and how?**

- > 800 I.U. per day if no sunlight
- Consider 100,000 I.U. once every 3 months or 50,000 I.U. monthly
- Only measure levels when guidance is needed
- Consider measuring for steroid treatment (Vitamin D and Steroids competitively bind for VDRE sites on allele)


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**According to the Surgeon General...**

“Vitamin D is important for good bone health because it aids in the absorption and utilization of calcium. There is a high prevalence of vitamin D insufficiency in nursing home residents, hospitalized patients, and adults with hip fractures.”

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