Vitamin D: Bone Up For Winter

The "Vitamin D Winter" is coming. In this webinar we will learn about this important molecule and how you can get the vitamin D you need to help maintain more than just healthy bones.

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Disclosure – I have no conflicts of interest or financial relationships involving vitamin D.

Overview

What is vitamin D and where do we get it?

How does it work and why do we need it?

How much do we need?

How can vitamin D help fight infections?

What is Vitamin D?

Is it a vitamin?

An organic substances that are present in natural foodstuffs

Or a hormone?

A product of living cells that circulates in body fluids

What is Vitamin D?

Mid 1600s

Rickets identified

Early 1800s

Industrial Revolution

Rickets epidemic in northern Europe and US

Rickets attributed to lack of sun exposure

Cod liver oil used to prevent rickets

Early 1900s

Mellanby shows cod liver oil cured rickets in dogs, but attributes it to vitamin A

McCollum designates the antirachitic factor in cod liver vitamin D

UV light effective against rickets

Huldschinsky and Hess and Unger - irradiated rats and their food prevented rickets

In 1970s, Holick et al., and Esvelt et al., showed that irradiation of 7-DHC in skin produced vitamin D3

Vitamin D: A brief history

Where do we get Vitamin D?

Skin

Vitamin D (Cholecalciferol)

Diet

25(OH)-Vitamin D (inactive)

Liver

Kidney

Other Tissues

What you store in your body (and measure in the blood)

1,25(OH)2-Vitamin D (active)

What is active in your cells
Vitamin D₃ synthesis in skin

7-dehydrocholesterol → UV or sunlight → Vitamin D₃ (cholecalciferol)

Conversion to the biologically active form in the body

Liver: CYP2R1 → 25-hydroxyvitamin D₃ (25-(OH)D₃)

Kidney: CYP27B1 → 1,25-dihydroxyvitamin D₃ (1,25-(OH)₂D₃)

Best source of vitamin D

Time need to spend outside at noon to make 1,000 IU vitamin D:

- April 27th (scattered clouds): 11 min
- June 27th (clear skies): 5 min
- August 27th (clear skies): 8 min
- December 27th (overcast): 24 hours

Corvallis: 44.6° N (darker Caucasian)
- 25% skin exposure (head, arms and legs)

Find out how much sunlight you need where you live:
http://nadir.nilu.no/~olaengfaarl/VitD-ez_quartMED.html

What factors affect synthesis by skin and serum levels of 25(OH)D?

- Climate & Weather
  - Season
  - Geographical location
- Skin color
  - Clothing
  - Sunscreen
- Age
  - Cholesterol content of skin
  - Mobility
- Diet and supplement usage
  - Vitamin D content of foods, breast-fed babies
  - Multivitamin or vitamin D pills

Is diet a good source of vitamin D?

http://www.vitaminnday.net/
Light (UV)-treated Mushrooms

Vitamin D₂ synthesis in fungi

Conversion to the active Vitamin D₂ form in the body

Ergosterol

UV or sunlight

Plant/fungi

Vitamin D₂

Ergocalciferol

Ergocalciferol

Liver

CYP2R1

25-hydroxyvitamin D₂

1,25-dihydroxyvitamin D₂

Kidney

CYP27B1

25-hydroxyvitamin D₃

1,25-dihydroxyvitamin D₃

Vitamin D and fortification was a big deal in the 1930s as it is now.

Got Milk?

Beer
Dietary Sources of Vitamin D

<table>
<thead>
<tr>
<th>Food</th>
<th>Amount per serving</th>
<th>Percent DV (600 IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cod liver oil, 1 tablespoon</td>
<td>1,360 IU</td>
<td>230%</td>
</tr>
<tr>
<td>Salmon (sockeye), cooked, 3 ounces</td>
<td>794 IU</td>
<td>130%</td>
</tr>
<tr>
<td>Mushrooms that have been exposed to UV light, 3 ounces</td>
<td>400 IU</td>
<td>67%</td>
</tr>
<tr>
<td>Mackerel, cooked, 3 ounces</td>
<td>388 IU</td>
<td>65%</td>
</tr>
<tr>
<td>Milk, fortified, 1 cup</td>
<td>100-124 IU</td>
<td>17-22%</td>
</tr>
<tr>
<td>Orange juice fortified with vitamin D, 1 cup</td>
<td>100 IU</td>
<td>17%</td>
</tr>
<tr>
<td>Yogurt, fortified, 6 ounces</td>
<td>80 IU</td>
<td>13%</td>
</tr>
<tr>
<td>Liver, beef, cooked, 3.5 ounces</td>
<td>46 IU</td>
<td>8%</td>
</tr>
<tr>
<td>Ready-to-eat cereal, fortified, 0.75-1 cup</td>
<td>40 IU</td>
<td>7%</td>
</tr>
<tr>
<td>Egg, 1 whole (vitamin D is found in yolk)</td>
<td>25 IU</td>
<td>4%</td>
</tr>
<tr>
<td>Cheese, Swiss, 1 ounce</td>
<td>6 IU</td>
<td>1%</td>
</tr>
</tbody>
</table>

*IUs = International Units.

Dietary sources of Vitamin D

RDA 400 IU

Sun exposure calculated at http://zardoz.nilu.no/~olaeng/fastrt/VitD_quartMED.html

Limited sources of significant vitamin D in the diet, especially compared to sunlight.

Vitamin D3 is preferred over D2

Armas, et al., JCEM, 2004

Change in 25(OH)D levels after one 50,000 IU dose of vitamin D

Vitamin D3 clears from the blood more rapidly than Vitamin D2

Vitamin D2 is used by the body, but may need to use daily as a supplement rather than a high dose once per week or once per month as vitamin D3 can be used

Summary

• Best source of vitamin D is sunshine, but not in winter north or south of 35-40° latitude
  – If your shadow is shorter than you, you’re likely getting enough sun to make vitamin D
  – Want to minimize skin damage caused by excessive sun exposure, but maximize vitamin D
• Some dietary sources, but supplements are most reliable
• Vitamin D3 is preferred by the body over Vitamin D2, although both have vitamin D activity

Overview

What is vitamin D and where do we get it?

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How can vitamin D help fight infections?
How does Vitamin D work or mediate its effects?

Steroid-hormone nuclear receptors

VDR: Vitamin D Receptor

Classical (Renal) Activities
- Normal bone growth and mineralization

These recommendations primarily address bone and muscle health in the general population

US Institute of Medicine (IOM):
Recommended Dietary Allowance (RDA):
- <1 year: 400 IU per day
- 1-70 years: 600 IU per day
- >70 years: 800 IU per day

The IOM concludes that these dosages will ensure that 97.5% of the population will maintain adequate levels of serum 25-hydroxyvitamin D [25(OH)D] above 20 ng/ml.

US Endocrine Society’s Clinical Practice Guideline:
- <1 year old: 400-1000 IU per day
- 1-18 years: 600-1000 IU per day
- >19 years: 1500-2000 IU per day

Maintain serum vitamin D levels above 30 ng/ml.

Patients with malabsorption conditions, obese patients, and patients taking certain medications may need two to three times more vitamin D to sustain their vitamin D status.

How much vitamin D do you need?

The Linus Pauling Institute recommends that generally healthy adults take 2,000 IU (50 mcg) of supplemental vitamin D daily.

Infants should have a daily intake of 400 to 1,000 IU (10 to 25 mcg) of vitamin D, and children and adolescents should have a daily intake of 600 to 1,000 IU (15 to 25 mcg) of vitamin D. Supplementation may be necessary to meet these recommendations.

Daily supplementation with 2,000 IU (50 mcg) of vitamin D is especially important for adults over the age of 50 because aging is associated with a reduced capacity to synthesize vitamin D in the skin upon sun exposure.

The Endocrine Society’s Clinical Guidelines, 2011.
Cut-offs for serum 25(OH)D and optimal levels are controversial

Institute of Medicine are as follows:
- Deficiency - ≤12 ng/mL (30 nmol/L)
- Insufficiency - 12-19 ng/mL (30-49 nmol/L)
- Sufficiency - 20-50 ng/mL (50-125 nmol/L)

US Endocrine Society:
- Deficiency ≤20 ng/mL (50 nmol/L)
- Insufficiency - 21-29 ng/mL (51-74 nmol/L)
- Sufficiency - 30-100 ng/mL (75-250 nmol/L)

GrassrootsHealth: http://www.grassrootshealth.net/
- Recommends – 40-60 ng/ml

Additional recommendations
- In a retrospective, observational study, Dorup and colleagues in 2012 reported a J-shaped association of all-cause mortality with serum vitamin D (247,574 subjects).
- Serum vitamin D levels of 50–60 nmol/liter (equivalent of 20-24 ng/ml) was associated with the lowest mortality risk.
- Authors warned that caution must be used when blood levels are above 125 nmol/liter (50 ng/ml).

Vitamin D Deficiency: A major health risk for young and old
- Estimated 1 billion worldwide – Deficient or Insufficient
- 40-100% of US and European elderly (not in nursing homes) deficient
- 70% of US children insufficient; 10% deficient

Toxicity – hypercalcemia or buildup of calcium in your blood
- Symptoms can include:
  - Nausea
  - Loss of appetite
  - Feeling very thirsty
  - Passing urine often
  - Constipation or diarrhea
  - Abdominal pain
  - Muscle weakness or pain
  - Feeling confused
  - Feeling tired

Leads to vascular and tissue calcification – with subsequent damage to the heart, blood vessels and kidney

25(OH)D levels >150 ng/ml are considered potentially toxic

The IOM considers levels greater than 50 ng/ml dangerous

Can vitamin D levels be too high?

In a retrospective study in 24,094 adults, Amrein and associates, found that blood vitamin D levels below 20 ng/ml or above 60 ng/ml (before hospitalization began) was associated with an increased odds of death within 90-days of admittance.

Authors pointed out that a precise relationship between high vitamin D and death cannot be inferred, but cautioned in using very high doses of vitamin D for long periods of time.
However, increased blood levels of vitamin D have not corresponded with increased reports of clinical toxicity.

Incidence of kidney stones (calcium oxalate) does not increase when blood vitamin D levels are between 20 to 100 ng/ml.

Summary
- Associations between low vitamin D levels and numerous health outcomes are known.
- Large numbers of people are not getting enough vitamin D.
- The optimal level is not known, but evidence supports levels higher than 30 ng/ml and perhaps >40 ng/ml.
- It remains to be determined what upper levels are safe, but 30-50 ng/ml is a conservative range to aim for.

Vitamin D and the immune system

Vitamin D is important for a balanced immune response. Keeps inflammation down and increases proteins involved in killing pathogens like antimicrobial peptides. Affects both the innate and adaptive immune responses.

Sources of Vitamin D “cured” TB

Late 1800s
- Niels Ryberg Finsen, København: Gyldendalske Boghandels Forlag (1902)
- http://www.mnwelldir.org/docs/uv_light/uv_light1.htm

1900s
- Prue H. Hart, Shelley Gorman & John J. Finlay-Jones, Nature Reviews Immunology 11, 584-596 (September 2011)

1940-1950
- Children with tuberculosis sunning at a Canadian hospital. Heliotherapy, using sunlight as a medical therapy, was used for tuberculosis.
Role of Vitamin D in Innate Immunity

- Vitamin D insufficiency or deficiency correlates with increased susceptibility to bacterial infection (e.g. Mycobacterium)
- Activated macrophages (a type of white blood cell) metabolize the inactive vitamin D (25-(OH)) to active form (1,25-(OH)\(_2\))
- The active form of vitamin D confers increased ability to engulf pathogens and anti-mycobacterial activity to macrophages

Vitamin D increases bactericidal protein expression

- Induction of Cathelicidin Anti-Microbial Peptide or CAMP (also called hCAP18) by the active form of vitamin D\(_3\)

Macrophages that encounter a pathogen convert vitamin D to the active form (1,25(OH)\(_2\)D) that increases antimicrobial peptide expression to enhance bacterial killing

A number of studies into protecting against respiratory tract infections using vitamin D

Random controlled trials (RCTs)
1. Li-Ng, et al., 2009: 162 adults, 2,000 IU/day for 3 months: no effect
2. Urashima, 2010: 430 children, 1,200 IU/day for 4 months: reduced Influenza A infections, but overall no effect when all influenza strains considered
3. Laaksi, J, 2010: 164 adults, 400 IU/day for 6 months: near significant effects
4. Manaseki-Holland, 2010: 224 children with pneumonia, 100,000 IU taken once protected against repeat pneumonia, but a follow up study in Lancet, 2012 did not replicate results (study design different)

Overall, initial supplementation experiments with vitamin D to reduce rates of infection were not particularly promising

Additional studies

Camargo (2012): Parents reported a significant 50% reduction in the rate of acute respiratory infections in 9-year-old children in Mongolia. Daily dosing of fortified (300 IU daily) versus non-fortified cow’s milk in the winter (Jan-March).

Important note: Serum vitamin D levels at baseline were 7 ng/ml, and increased to 19 ng/ml in the fortified group.

Bergman (2012): Significant 23% decrease in combined infection score (which included five factors) in adults with immunodeficiency from Sweden given a daily dose of 4,000 IU vitamin D\(_3\) for 12 months or a matched placebo.

Important note: Serum vitamin D levels at baseline were 20 ng/ml and increased to >50 ng/ml in the individuals that received vitamin D.

These recent studies are showing promising effects in treating infections with vitamin D. Need to selecting populations with low vitamin D levels and use the right dosing schedule to significantly raise serum vitamin D levels!

Renewed interest in using vitamin D to treat tuberculosis

Martineau, et al., 2011: Tuberculosis patients receiving standard antibiotic therapy and a 100,000 IU dose of vitamin D\(_3\) every two weeks showed accelerated recovery if they possessed a particular genotype of the vitamin D receptor as compared with placebo.

Coussens, et al., 2012: Vitamin D supplementation accelerated resolution of inflammation during tuberculosis treatment.

Salahuddin et al., 2013: randomized, placebo-controlled clinical study showed that 600,000 IU vitamin D\(_3\) once per month for two months in tuberculosis patients led to a significant increase in average weight gain and lower residual disease by chest x-ray.

Studies with tuberculosis have shown some promise, but a number of studies have not. Again the amount of vitamin D and the dosing schedule are probably critical.
Summary

Several clinical trials indicate that vitamin D supplementation can benefit infections by reducing rates or improving outcomes. Design of future experiments will be important as this may explain why some studies are negative. Determination of dose, frequency and serum level will be important.

Questions?

Additional Vitamin D Resources:

Linus Pauling Institute Micronutrient Information Center: http://lpi.oregonstate.edu/mic
GrassrootsHealth: www.grassrootshealth.net
Vitamin D Council: www.vitamindcouncil.org
National Institutes of Health: https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/