VITAMIN D: How Research Informs Public Health Policy

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Overview

• What is the science telling us about vitamin D?
  ▪ Evidence for the importance of vitamin D in health
  ▪ Scientific gaps: What are the key issues?
  ▪ Who is doing what to fill the gaps?

• Challenges and strategies to address them
  ▪ Key partners /stakeholders and their roles
Vitamin D: Nutrient of the Day

Vitamin D: The Silver Bullet Against Chronic Disease for African Americans
Wednesday, April 16, 2008 by: Paco Tabachinski. NaturalNews.com

Vitamin D deficiency linked to tuberculosis
Nächste Meldung 09.04.2008

Vitamin D found to guard against artery disease
Thu Apr 17, 2008 1:54am IST

Low Vitamin D Levels Linked to Leg Artery Blockages
But doctors are divided on whether supplements are a good option
By Ed Edelson, Posted 4/16/08, US News World Report

Vitamin D Proven to Lower the Risk of Breast Cancer
FeelGoodforLife.com Examines Women’s Health Breakthrough

Science News
High Blood Levels Of Vitamin D Protect Women From Breast Cancer, Study Suggests
Science Daily (Apr. 22, 2008)
Vitamin D: Nutrient of the Day ???

Vitamin D -- Let’s Get Back to the Evidence Base
Reid IR, Intl Bone and Mineral Society, July, 2010

Vitamin D: A Place in the Sun?
Grey A, Arch Intern Med, July 12, 2010

Anticancer Vitamins de Jour ---The ABCED’s So Far

Vitamin D Supplementation in the Age of Lost Innocence
Guallar E, Ann Intern Med, March 2, 2010
Vitamin D and Health

• Clear effect of vitamin D on measures of bone health
• Low vitamin D levels associated with increased risk for other health outcomes
  ▪ Various cancers
  ▪ Cardiovascular disease
  ▪ Autoimmune disease (e.g., multiple sclerosis)
  ▪ Dementia
  ▪ Diabetes
  ▪ Glucose intolerance
• Associations primarily based on ecologic/observational studies
• Cause and effect has not been proven for most of the associations
<table>
<thead>
<tr>
<th>Age</th>
<th>Males and Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–50 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>
</tr>
<tr>
<td>Pregnant and lactating females</td>
<td>200 IU/day</td>
</tr>
</tbody>
</table>

Tolerable Upper Intake Level (UL) for all groups >1 year is 2000 IU/day
Vitamin D Intake from Foods and Dietary Supplements
NHANES 2003–2006, Males

Above adequate intake, percentage

Age (Years)

1–3
4–8
9–13
14–18
19–30
31–50
51–70
≥71

Supplements

Foods

78
80
66
54
49
59
36
24

72
67
53
50
39
45
7
1
Measuring Vitamin D Status

- Biomarker: Serum 25(OH)D
- Methodology: Radioimmunoassay (RIA)

Serum 25(OH)D Cutoff Values

- < 27.5 nmol/L: Level defined by the 1997 IOM report
- < 50 nmol/L
- < 80 nmol/L: Levels defined by others in research community
Prevalence of Low Levels of Serum 25(OH)D (nmol/L), NHANES 2000-2004

Yetley EA. Am J Clin Nutr 2008;88:558S-64S.
Changes in the DiaSorin RIA Over Time

- **Change from the original RIA to the reformulated RIA**
  - Resulted in 12% lower biomarker levels

- **Reformulated RIA fluctuated over time**
  - Between 2000 and 2006, the assay performed for some extended periods 5–10% higher or lower than expected

- **Impact of assay changes on population levels**
Impact of Assay Changes on Population Levels

A. Observed difference

- Men: 18.3 nmol/L*
- Women: 10.3 nmol/L*

B. After accounting for assay difference**

- Men: 7.1 nmol/L*
- Women: 0 nmol/L*

Observed mean for NHANES III
Predicted mean for NHANES III assuming reformulated DiaSorin RIA was used
* Non-Hispanic whites, 20–50 years, examined April-October

**The difference in age-standardized 25(OH)D means was reduced by 10–11 nmol/L after correcting for assay changes
Current Status

• NHANES is valuable source of information on Vitamin D
• Based on the current IOM criteria
  ▪ **Intake**: Fewer than 1/3 of older people meet the recommended adequate intake for vitamin D based on total intake (supplements included)
  ▪ **Serum levels**: Fewer than 6% of the U.S. population have 25(OH)D levels generally considered inadequate
    o A subject of current and intense discussion
• **Serum levels decreased slightly from the late ‘80s/early ’90s to NHANES 2003-2004, most likely in response to altered behavior**
  ▪ Increase in body mass index (BMI)
  ▪ Decrease in sun exposure; decrease in milk consumption
Vitamin D Initiative

• Coordinated by the NIH Office of Dietary Supplements
  ▪ Involves partners from DHHS (CDC, NIH, FDA, AHRQ), NIST, DoD, USDA, and Health Canada

• Goals
  ▪ Improve measurement of vitamin D in foods and supplements
  ▪ Improve measurement of vitamin D status in NHANES
  ▪ Identify and fill research gaps

• Outcomes
  ▪ Systematic reviews, publications, conferences
  ▪ Inform public policy
Systematic Reviews of Vitamin D Status and Health Outcomes

- Agency for Healthcare Research and Quality (AHRQ)
  - Evidence-Based Practice Center Network (www.ahrq.gov/clinic/epc)
  - Systematic reviews inform policy, research, guidelines

- Two Reviews of Vitamin D
    - Sponsored by NIH/ODS to inform a public meeting, 2007
    - Sponsored by U.S. and Canadian governments to inform Dietary Reference Intakes Panel of the Institute of Medicine, 2009
Findings from the First Systematic Review

- Evidence that vitamin D supplementation reduces falls, fractures, and bone loss in men and women >60 years
- Sparse data on other age and gender groups
- Not possible to separate the effect of vitamin D from Ca supplementation
  - Typical amounts used were 700-800 IU vitamin D/day and 500-1,200 mg Ca/day
- Difficult to identify a specific blood level of 25-hydroxyvitamin D indicative of optimal bone health in all population subgroups: Lack of data

Vitamin D and Colorectal Cancer: Observation

Test for overall effect, p=0.02

Garland 1989
Bostick 1993
Kearney 1996
Martinez 1996
Pritchard 1996
Marcus 1998
Pietinen 1999
Jarvinen 2001
McCollough 2003
All

Odds ratios and 95% confidence interval
Vitamin D and Cancer Incidence: Intervention

1179 Healthy women, 66±7 yrs, 4-year study, Ca (1400 mg/d), Vitamin D₃ (1100 IU/d)

Fraction cancer-free vs Time (Years)

RR = 0.232

Findings from the Second Systematic Review

• Infant growth: Most studies find no effect
• Cardiovascular disease
  ▪ Randomized controlled trials: No effect
  ▪ Cohort studies: Variable association
• Body weight: No effect
• Cancer: No effect
• Infectious diseases: No effect
• Pregnancy outcomes: Inadequate data
• All-cause mortality: Inconsistent data
• Hypertension: Inconsistent data

Women’s Health Initiative

- NIH-sponsored: http://www.nhlbi.nih.gov/whi/
- Largest intervention trial in history: >160,000 women
- One of the sub-studies randomized women to vitamin D and calcium for a 7-year period to examine potential effects on hip fractures
Trial Results after 7 Years

- Hip fractures: 12% decrease, not significant
  - 21% decrease for women aged 60-80 years at baseline
  - 29% decrease among women who took ≥ 80% of pills

- Improved hip bone density

- Other fractures (self-reported vertebral, lower arm/wrist, total): No differences

- Kidney stones: Significantly increased 17% (5 per 10,000/year)

Serum 25(OH)D and All-Cause Mortality

Examples of Ongoing NIH-supported Research

- NCI and others: Vitamin D and Omega-3 Trial (VITAL) to examine the role of vitamin D and Omega-3 fatty acids in primary prevention of cancer and CVD
- NIA and others: Dose response for vitamin D in elderly
- NCI: Replication of cancer incidence study
- Many NIH Institutes and Centers: Intermediary metabolism
- ODS and others: Incorporation of analytical tools into measurement of vitamin D status
  - Standard reference material for 25(OH)D in plasma
  - Reference methods developed by NIST and NCEH
In 2009, ODS and NCHS sponsored a roundtable on vitamin D issues in NHANES and recommended:

- Future methodology should be LC-MS/MS
- A subset of the samples analyzed with the DiaSorin RIA will be re-analyzed by LC-MS/MS to bridge the past and the future
- Data generated previously with the DiaSorin RIA need to be adjusted for the assay changes to avoid incorrect interpretation of trends
NIST SRM 972 Vitamin D in Human Serum

- Four levels, each containing 1.0 mL serum
- Certified and reference values for 25(OH)D₂, 25(OH)D₃, and 3-epi-25(OH)D₃
- Value assignment by isotope-dilution LC-MS and LC-MS/MS using data from NIST and CDC

- Metabolite concentrations reported in ng/mL and nmol/L
- COA does not provide data from other analytical techniques
Dietary Reference Intakes for Vitamin D and Calcium

Activity Description

An IOM committee has been named to undertake a study to assess current relevant data and update as appropriate the DRIs for vitamin D and calcium. The review will include consideration of chronic and non-chronic disease indicators. The study will also incorporate, as appropriate, systematic evidence-based reviews of the literature and an assessment of potential indicators of adequacy and of excess intake. Indicators for adequacy and excess will be selected based on the strength and quality of the evidence and the demonstrated public health significance, taking into consideration sources of uncertainty in the evidence.
• Most recent Dietary Reference Intakes (IOM, 1997)
  ▪ Adequate Intake (AI): 200/400/600 IU/day
  ▪ Upper Limit: 2000 IU/day

• Ongoing IOM Review of Recommended Intakes
  ▪ Expected release: Fall 2010

• Dietary Guidelines Advisory Committee Report (USDA-DHHS, 2010)
  ▪ Meet AI via food; some may require supplements
  ▪ http://www.cnpp.usda.gov/dietaryguidelines.htm
Recommendations Made by Professional Groups

- **American Academy of Pediatrics** [www.aap.org/healthychildren/09s_bts/Vitamin%20D.pdf](http://www.aap.org/healthychildren/09s_bts/Vitamin%20D.pdf)
  - 400 IU for children

- **Canadian Paediatric Society** [www.cps.ca/english/statements/ii/fnim07-01.htm](http://www.cps.ca/english/statements/ii/fnim07-01.htm)
  - Weight-based intake for children
  - Up to 2000 IU for pregnant and lactating women

  - More from supplements, not more sun exposure

- **National Osteoporosis Foundation** [www.nof.org/prevention/vitaminD.htm](http://www.nof.org/prevention/vitaminD.htm)
  - 400-800 IU for adults <50 yrs; 800-1000 IU >50 yrs
Vitamin D Challenges

• Exposure
  ▪ UV exposure
  ▪ Foods, including fortified foods
  ▪ Dietary supplements

• Health outcomes
  ▪ Enormous interest based on case reports, observational studies
  ▪ Inconsistent findings from controlled studies
  ▪ Safety must be addressed

• Measurement of status
  ▪ Potential for incorrect interpretation of status measurement, especially when assessing trends over time
• Continued monitoring of status to assess impact of public health recommendations for vitamin D intake
• Dose-response relationships
• Research into basic mechanisms
• Ongoing partnerships among agencies in US and Canada: CDC, NIH, NIST, USDA and Health Canada