PUBLIC HEALTH GRAND ROUNDS

August 19, 2010
Overview

- What is vitamin D and why do we need it?
- Which scientific and public health issues make vitamin D one of the most talked about nutritional issues today?
- How is vitamin D status in the U.S. population evaluated through the NHANES survey?
  - Challenges and ways to address them

NHANES

National Health and Nutrition Examination Survey
What is Vitamin D?

- Fat-soluble vitamin that helps the body absorb calcium
- Primarily needed for bone growth and bone remodeling
- Other roles in human health
  - Modulates neuromuscular and immune function
  - Reduces inflammation
Main Sources of Vitamin D

**Sunlight: UVB exposure**
Vitamin D3 – cholecalciferol

**Food**
Vitamin D3 – cholecalciferol, animal sources
Vitamin D2 – ergocalciferol, plants (mushrooms)

**Supplements**
Vitamin D2 and vitamin D3
## Main Dietary Sources of Vitamin D

<table>
<thead>
<tr>
<th>Source</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortified milk</td>
<td>400 IU/quart</td>
</tr>
<tr>
<td>Some yogurts</td>
<td>80 IU/8 oz</td>
</tr>
<tr>
<td>Some fortified cereals</td>
<td>40–100 IU/serving</td>
</tr>
<tr>
<td>Some fortified juices</td>
<td>100 IU/8 oz</td>
</tr>
<tr>
<td>Fatty fish <em>(salmon, mackerel, herring, tuna)</em></td>
<td>200–400 IU/3 oz</td>
</tr>
<tr>
<td>Some calcium and vitamin/mineral supplements</td>
<td>Most often 400 IU</td>
</tr>
</tbody>
</table>
Vitamin D Metabolism

- Vitamin D is rapidly taken up and transported to the liver
- Vitamin D2 and vitamin D3 are metabolized
  - First, in the liver to the circulating form: 25-hydroxyvitamin D or 25(OH)D
  - Then, to the active form: 1,25-dihydroxyvitamin D in the kidney
- The production of 1,25-dihydroxyvitamin D is tightly regulated by parathyroid hormone (PTH)
Groups at Risk of Vitamin D Deficiency

- Breastfed infants
- Older adults
- People with limited sun exposure
- People with dark skin
- People with fat malabsorption
- People who are obese or who have undergone gastric bypass surgery
Vitamin D Deficiency Diseases

- **In children**
  - Low levels of vitamin D (<27.5 nmol/L) have been shown to be associated with a high risk for rickets in children (softening and weakening of the bone)
  - Today, with fortification of milk with vitamin D, cases are extremely rare

- **In adults**
  - Inadequate levels of vitamin D leads to osteomalacia, causing bone pain and muscle weakness and possible fractures (especially in the elderly population)
Vitamin D and Health

- Low vitamin D levels have been associated with increased risk for numerous other health outcomes
  - Various cancers
  - Cardiovascular disease
  - Autoimmune disease (e.g., multiple sclerosis)
  - Dementia
  - Diabetes
  - Glucose intolerance

- These associations are primarily based on ecologic/observational studies
- The cause and effect has not been proven for most of the associations
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
Ian R. Reid, Intl Bone and Mineral Society, July, 2010

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

Anticancer Vitamins du Jour - The ABCED’s So Far
Tim Byers, Am J of Epidemiol, 2010;172:1-3

Vitamin D Supplementation in the Age of Lost Innocence
Eliseo Guallar et al, Annals Intern Med, March 2, 2010
Issues Under Discussion

- **Vitamin D status of the U.S. population**
  - What is it and has it changed over time?

- **Dietary sources**
  - What foods provide vitamin D?
  - Are dietary supplements a significant source of vitamin D?

- **Vitamin D requirements**
  - How much vitamin D do we need?
  - How much is too much?
Sources of Information on Vitamin D

- Clinical research studies
- Randomized clinical trials
- Population-based surveys or surveillance systems

National Health and Nutrition Examination Survey (NHANES)
Assessing the health and nutritional status of adults and children in the United States

www.cdc.gov/nchs/nhanes.htm
## National Health and Nutrition Examination Surveys

<table>
<thead>
<tr>
<th>Survey</th>
<th>Dates</th>
<th>Ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHES I</td>
<td>1959–62</td>
<td>18–79 years</td>
</tr>
<tr>
<td>NHES II</td>
<td>1963–65</td>
<td>6–11 years</td>
</tr>
<tr>
<td>NHES III</td>
<td>1966–70</td>
<td>12–17 years</td>
</tr>
<tr>
<td>NHANES I</td>
<td>1971–75</td>
<td>1–74 years</td>
</tr>
<tr>
<td>NHANES II</td>
<td>1976–80</td>
<td>6 months–74 years</td>
</tr>
<tr>
<td>Hispanic HANES</td>
<td>1982–84</td>
<td>6 months–74 years</td>
</tr>
<tr>
<td>NHANES III</td>
<td>1988–94</td>
<td>&gt; 2 months</td>
</tr>
<tr>
<td>NHANES</td>
<td>1999+</td>
<td>All ages</td>
</tr>
</tbody>
</table>

NHES, National Health Examination Survey
NHANES Provides Data for Many Essential Public Health Functions

<table>
<thead>
<tr>
<th>Reference data</th>
<th>Weight and height charts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition monitoring</td>
<td>Dietary intake</td>
</tr>
<tr>
<td>Disease control</td>
<td>Diabetes</td>
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<tr>
<td>Prevention initiatives</td>
<td>Folate</td>
</tr>
<tr>
<td>Monitor environmental exposure</td>
<td>Lead</td>
</tr>
<tr>
<td>Track health behaviors</td>
<td>Second-hand smoke</td>
</tr>
</tbody>
</table>
Assessment of Vitamin D Status in the U.S. Population

- Vitamin D intake from foods and dietary supplements
- Levels of vitamin D in serum
- Collecting risk factor data previously shown to be associated with vitamin D status
Is intake adequate?
What are the groups of concern?
## Current Guidelines for Adequate Intake for Vitamin D, Institute of Medicine (IOM) 1997

<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>
</tbody>
</table>

Pregnant and lactating females: 200 IU/day

**Tolerable Upper Intake Level (UL)**

For all population groups is 2000 IU/day

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Vitamin D Intake from Foods and Dietary Supplements
NHANES 2003–2006, Males

Above adequate intake, %

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Supplements</th>
<th>Foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3</td>
<td>72</td>
<td>78</td>
</tr>
<tr>
<td>4–8</td>
<td>67</td>
<td>80</td>
</tr>
<tr>
<td>9–13</td>
<td>53</td>
<td>66</td>
</tr>
<tr>
<td>14–18</td>
<td>50</td>
<td>54</td>
</tr>
<tr>
<td>19–30</td>
<td>39</td>
<td>49</td>
</tr>
<tr>
<td>31–50</td>
<td>45</td>
<td>59</td>
</tr>
<tr>
<td>51–70</td>
<td>7</td>
<td>36</td>
</tr>
<tr>
<td>≥71</td>
<td>1</td>
<td>24</td>
</tr>
</tbody>
</table>
Vitamin D Intake from Foods and Dietary Supplements
NHANES 2003–2006, Females

Above adequate intake, %

Age (years)

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

Supplements 70 53 47 32 41 32 44 2 0.3
Foods 76 66 53 24 21 56 22

Bailey RL et al. J Nutr 2010;140:817-822
Assessment of Vitamin D Status in the U.S. Population

- Vitamin D intake from foods and dietary supplements
- Levels of vitamin D in serum
- Collecting risk factor data previously shown to be associated with vitamin D status
Levels of Vitamin D in Serum

- **Biomarker:** Serum 25(OH)D
- **Methodology:** Radioimmunoassay (RIA)
  - Issue: Reformulation of RIA
  - Consequence: Need to bridge the gap between data obtained by different RIA methodologies

- **Serum 25(OH)D cutoff values**

  - < 27.5 nmol/L
  - < 50 nmol/L
  - < 80 nmol/L

Level defined by the 1997 IOM report

Levels defined by others in research community
Prevalence of Low Levels of Serum 25(OH)D (nmol/L) NHANES 2000–04

*Data for age 1-5 available from NHANES 2003–04 only

Yetley EA. Am J Clin Nutr 2008;88:558S-64S.
Current Status

- NHANES is a 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 has 25(OH)D levels generally considered inadequate.
- **Biomarker serum levels decreased slightly from the late ‘80s/early ’90s, most likely as a response to altered behavior**:
  - Increase in body mass index (BMI)
  - Decrease in sun exposure; decrease in milk consumption.
Interpretation and methodological issues

- There are 2 ways to assess vitamin D status in the U.S. population (intake and blood levels)
- Measuring each has methodological challenges
- Correlation of serum levels with adequacy established only at 27.5 nmol/L for children
- Reformulations or changes in laboratory methods complicate the interpretation of trends in status over time
- No agreed-on “cutpoint” for vitamin D deficiency/adequacy
- All issues that may lead to misinterpretation of population levels have to be examined carefully and communicated promptly
Assess current relevant data and update as appropriate the dietary reference intakes for vitamin D and calcium

- Review evidence on indicators of adequacy and indicators of adverse effects from excess
- Give priority to indicators of adequacy for the various age, gender, and life-stage groups to define an Estimated Average Requirement
- Give priority to selecting a critical adverse effect to define a so-called benchmark intake
- Identify research gaps to address the uncertainties identified in the process of deriving the reference values and evaluating their public health implications
Imminent and Next Steps

- The IOM Report on Dietary Reference Intakes for Vitamin D and Calcium expected in late fall of 2010
- Depending on the recommendations (and possible new cutpoints)
  - Further analyses of the NHANES data on vitamin D will likely occur
  - Future programmatic directions and public health guidance for vitamin D will likely be determined
TESTING FOR VITAMIN D BLOOD LEVELS: CHALLENGES AND OPPORTUNITIES

Christine M. Pfeiffer, PhD
Chief
Nutritional Biomarkers Branch
Division of Laboratory Sciences
National Center for Environmental Health
Centers for Disease Control and Prevention
Methodology to Monitor Vitamin D Status

- **Measuring total 25-hydroxyvitamin D, 25(OH)D**
  - In serum
  - Radioimmunoassay (RIA) developed in the mid-1980s
  - NHANES 2000–2006: Reformulated DiaSorin RIA

- **Measuring individual 25(OH)D forms**
  - In serum
  - Liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS)
  - NHANES 2007 and forward
### Issues with Classical Immunoassay Methodology

<table>
<thead>
<tr>
<th>Performance characteristic</th>
<th>Definition</th>
<th>Impact on population monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower precision</td>
<td>Greater variation in laboratory measurements</td>
<td>Difficult to identify small changes in the population over time</td>
</tr>
<tr>
<td>Lower specificity</td>
<td>Compounds other than 25(OH)D may alter results</td>
<td>Difficult to obtain accurate testing results</td>
</tr>
<tr>
<td>Lower robustness</td>
<td>Fluctuations in assay performance over time</td>
<td>Difficult to interpret changes in the population over time</td>
</tr>
</tbody>
</table>
Changes in the DiaSorin RIA Over Time

- The change from the original RIA to the reformulated RIA
  - Resulted in 12% lower biomarker levels

- The 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

NHANES 1988-1994
Original RIA

NHANES 2000-2006
Reformulated RIA
Impact of Assay Changes on Population Levels

A. Observed difference

*Men
- Observed mean for NHANES III: 18.3 nmol/L
- Observed mean for NHANES 2003–2004: 10.3 nmol/L

*Women
- Observed mean for NHANES III: 18.3 nmol/L
- Observed mean for NHANES 2003–2004: 10.3 nmol/L

B. After accounting for assay difference**

*Men
- Predicted mean for NHANES III assuming reformulated DiaSorin RIA was used: 7.1 nmol/L

*Women
- Predicted mean for NHANES III assuming reformulated DiaSorin RIA was used: 0 nmol/L

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

The prevalence of serum 25(OH)D levels of lower than 25 nmol/L (deficient) more than doubled from NHANES III to NHANES 2001–2004.

Potential for Misinterpreting Population Levels

- Rather small changes in the 25(OD)D levels (~10%), as a result of assay changes, can lead to big changes in population levels
- Lack of data adjustment for assay differences can lead to very different conclusions
- Timely and appropriate communication to the scientific community is critical to avoid publication of incorrect information
Outlook to a New Analytical Methodology
Isotope Dilution Tandem Mass Spectrometry Coupled to Liquid Chromatography (LC-MS/MS)

<table>
<thead>
<tr>
<th>Precision</th>
<th>&lt;8% day-to-day variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>Less possibility for compounds other than 25(OH)D to alter results</td>
</tr>
<tr>
<td>Robustness</td>
<td>In-house calibration with 25(OH)D$_2$ and 25(OH)D$_3$, and calibration verification with NIST reference material</td>
</tr>
</tbody>
</table>
In 2009, the NIH Office of Dietary Supplements and the CDC National Center for Health Statistics sponsored a roundtable on vitamin D issues in NHANES

- 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
Importance of Standard Reference Materials in Providing Traceability

- National Institute of Standards and Technology (NIST) and CDC National Center for Environmental Health (NCEH) collaborated in developing the first standard reference materials for 25(OH)D
  - NIST standard reference materials SRM 972 and 2972
  - Improve accuracy of measurements
  - Improve comparability of data across methods and laboratories

- NIST will conduct a commutability study to assess which SRM materials may be used to calibrate immunoassays
Lessons Learned and Way Forward

- Relatively small assay fluctuations can have a large impact on population levels and make interpretation of population data difficult

- NHANES
  - Needs best possible analytical methodologies
  - Standardization, harmonization, and accuracy of analytical methodologies must be supported and strengthened

- Validation of the new LC-MS/MS method and bridging the gap between samples analyzed by different methods is underway
VITAMIN D: HOW RESEARCH INFORMS PUBLIC HEALTH POLICY

Paul M. Coates, PhD
Director
Office of Dietary Supplements
National Institutes of Health
The Dietary Supplement Health and Education Act of 1994 authorized the establishment of the ODS at the NIH (created in 1995)

Mission: Strengthen knowledge and understanding of dietary supplements to foster an enhanced quality of life and health for the U.S. population by

- Evaluating scientific information
- Stimulating and supporting research
- Disseminating research results
- Educating the public

Public Law 103-417, DSHEA
Overview

What is the science telling us?
- 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 the challenges
- Key partners/stakeholders and their roles
Vitamin D Initiative

- **Coordinated by the NIH Office of Dietary Supplements**
  - Involves partners from DHHS (NIH, CDC, 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 research gaps

- **Outcomes**
  - Systematic reviews
  - Publications to inform public policy
Systematic Reviews of Vitamin D Status and Health Outcomes

- Agency for Healthcare Research and Quality (AHRQ)
  - Evidence-Based Practice Center Network
  - Systematic reviews inform policy, research, and guidelines

- 2 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 (Institute of Medicine, 2009)
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 calcium (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(OH)D indicative of optimal bone health in all population subgroups: Lack of data

Findings from the Second Systematic Review

- Infant growth: Most studies found 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

Dietary Reference Intakes for Vitamin D and Calcium

Type: Consensus Study
Topics: Food and Nutrition, Public Health
Boards: Food and Nutrition Board

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.
Vitamin D Challenges

- **Exposure**
  - UVB 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**
  - Incorrect interpretation of status measurement, especially when assessing trends over time
Vitamin D and Colorectal Cancer

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

1179 healthy women, 66±7 years, 4-year study, Ca (1400 mg/d), vitamin D3 (1100 IU/d)

Fraction cancer-free

Time (years)

RR = 0.232

Women’s Health Initiative

- NIH-sponsored: http://www.nhlbi.nih.gov/whi
- Largest intervention trial in history: >160,000 women
- One of the substudies 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**: No differences
  - (self-reported vertebral, lower arm/wrist, total)

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

Jackson RD et al. NEJM 2006;354:669-683
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 serum
  - Reference methods developed by NIST and NCEH
Current Public Health Recommendations

- **Most recent Dietary Reference Intakes (IOM, 1997)**
  - Adequate Intake (AI): 200/400/600 IU/day
  - Upper Limit: 2000 IU/day

- **How can people meet these recommendations?**
  - Most organizations recommend brief sun exposure, although there is no agreement on how much
  - Foods, especially those fortified with vitamin D (e.g., milk)
  - Supplements, especially among the elderly

- **Ongoing IOM review of recommended intakes**
  - Expected release late fall of 2010
Recommendations Made by Professional Groups

- **American Academy of Pediatrics**
  - 400 IU for children

- **Canadian Paediatric Society**
  - Weight-based intake for children
  - Up to 2000 IU for pregnant and lactating women

- **American Academy of Dermatology**
  - More from supplements, not more sun exposure

- **National Osteoporosis Foundation, International Osteoporosis Foundation**
  - 400-800 IU for adults <50 years; 800-1000 IU >50 years

American Academy of Pediatrics: [www.aap.org/healthychildren/09s_bts/Vitamin%20D.pdf](http://www.aap.org/healthychildren/09s_bts/Vitamin%20D.pdf)
Canadian Paediatric Society: [www.cps.ca/english/statements/ii/fnim07-01.htm](http://www.cps.ca/english/statements/ii/fnim07-01.htm)
- 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 the United States and Canada: CDC, NIH, NIST, USDA, and Health Canada