Public Health Impact of Calcium and Vitamin D: What are We Waiting For?

Council of State and Territorial Epidemiologists (CSTE)

2012 CSTE Annual Conference

“Public Health 2012: Stand Up and Be Counted”

Robert R. Recker, M.D.
June 5, 2012
Omaha, Nebraska

Creighton University Osteoporosis Research Center
Scope of Presentation

- History of Vitamin D and Health.
- Measures of Vitamin D Status.
- Clinical Expression of Vitamin D Insufficiency.
- The New Physiology of Vitamin D.
- Determining Vitamin D Need.
- How much is Toxic?
- What ARE WE WAITING FOR?

Creighton University Osteoporosis Research Center
BACKGROUND – 1

- 1919/1920 – rickets developed in dogs reared indoors & fed purified diets; preventable by cod liver oil
- 1936 – active agent identified as cholecalciferol (vitamin D₃)
- the RDA for vitamin D was set at 400 I.U. because that was the quantity in 1 tsp of cod liver oil
WHAT WE KNEW

- vitamin D prevented rickets
- the RDA was sufficient to afford protection
- vitamin D was necessary for Ca absorption
WHAT WE DIDN’T KNOW

- how much vitamin D was needed to optimize Ca absorption
- whether there was a connection between vitamin D status and any other disease
- how one could tell whether a patient had sufficient vitamin D
BACKGROUND – 2

- in its 1997 publication, the FNB defined serum 25(OH)D as the functional indicator of vitamin D status
- evidence did not then exist to allow tying any particular serum 25(OH)D levels to specific health or disease outcomes
BACKGROUND – 3

- the index disease for vitamin D deficiency was rickets/osteomalacia
- absence of rickets/osteomalacia was implicitly considered to be evidence of vitamin D sufficiency
- in setting the requirement, no other disease outcomes were considered
- recent AIs (200/400/600/800 IU) are sufficient to prevent the index disease in most people (AI – Adequate Intake)
THE 25(OH)D CONTINUUM

0  25  50  75  100  125  150
(nmol/L)

CU  ORC
THE 25(OH)D CONTINUUM
THE 25(OH)D CONTINUUM

prevention of rickets/osteomalacia

reference range

0  25  50  75  100  125  150 (nmol/L)

CU  ORC
What is the optimal level of serum 25(OH)D
Increased serum PTH is an indicator of homeostatic adaptation.

The point at which the serum PTH level “bottoms out” defines the point at which adaptation is no longer needed.
25(OH)D & SERUM iPTH*

290 consecutive pts. on a general medical ward – MGH

*after Thomas et al., 1998 NEJM;338:777–783
HOW TO DETERMINE “NORMAL”?  

- the relevant questions:
  - is the Ca economy optimal at 25(OH)D levels below 80? **NO**
  - are the autocrine/paracrine functions of vit D optimal at 25(OH)D levels below 80? **WE DON’T KNOW**
THE 25(OH)D CONTINUUM

- 34 post-menopausal women
- studied twice, one yr apart, in the Spring
- given vitamin D one year & not the other
- (Heaney et al. JACN 2003; 22: 142–6)
THE 25(OH)D CONTINUUM

Ca absorption measured
500 mg Ca load
pharmacokinetic method (AUC)

Ca absorption measured
500 mg Ca load
pharmacokinetic method (AUC)
THE 25(OH)D CONTINUUM

- N = 2,686
- ages 65–85
- 5 yr RCT
- Vit D ≈ 800 IU/d
- Trivedi et al. BMJ 2003; 326:469

FRACTURE RELATIVE RISK
(hip, forearm, spine)

0.0 0.2 0.4 0.6 0.8 1.0

-33%

0 25 50 75 100 125 150
(nmol/L)
Within the reference range there is malabsorption of Ca & preventable fractures . . .

These are as much expressions of nutritional deficiency, as are the bleeding gums of scurvy
Prevalence

Using the 80 nmol/L figure
NHANES–III

- women aged 60–79
- summer, northern states
AGE & SKIN VIT D SYNTHESIS

- whole body exposure of 0.032J/cm² (~1MED)
- young: 20–30
  old: 62–80
- after Holick et al. (1989) Lancet
AGE & CAPACITY TO MAKE VIT D*

- surgically obtained skin samples
- Caucasian pts.

\[ \text{7-DEHYDROCHOLESTEROL (µg/6.25 cm²)} \]

-50% decrease

*McLaughlin & Holick (1985) JCI; 76:1536–38
How much vitamin D does one need to give?
25(OH)D RESPONSE TO ORAL D₃

- 66 males
- aged 38.7 yr (± 11.2 )
- dosed with vit D₃ from October through February
66 males
aged 38.7 yr (± 11.2 )
dosed with vit D₃ from October through February
INCREMENT ESTIMATION

\[
Y = Y_0 + a \cdot (1 - e^{-kX})
\]
equilibrium concentrations of 25(OH)D plotted against actual dose of vit D₃

\[ y = -0.038 + 0.700x \]

\[ r^2 = 0.749 \]
TRANSLATION:

- steady-state serum 25(OH)D concentration rises by 0.7 nmol/L for every 1 μg (40 IU) of vit D₃, given as a daily oral dose

- all recent studies have produced estimates of this slope in the same range, i.e., from 0.6 to 1.2 nmol/L/μg/d
TRANSLATION:

- taking a figure in the middle of that range, e.g., 0.9 nmol/L/μg/d,
- the recommended daily intake for individuals 50–70 (400 IU*) would be expected to raise serum 25(OH)D by only 9 nmol/L (3.6 ng/mL)
- the daily input (all sources) required to maintain a level of 80 nmol/L is in the range of 3500–5500 IU/d

*Prior to the IOM report of 2011
Safety
25(OH)D IN OUTDOOR WORKERS

- 26 male outdoor workers
- 41% body surface exposure for 38 hrs/wk for 14 wks
- varying degrees of skin pigmentation
SAFETY AT HIGH DOSES

- 33 males
- aged 38.7 yr (± 11.2 )
- dosed with vit D₃ from October thru February
- 5,000 & 10,000 IU/d
SAFETY AT HIGH DOSES

- in our experiments, doses of 5,000–10,000 IU/d in healthy adults for 4–5 months have not:
  - elevated serum Ca
  - elevated urine Ca

- further, these doses reproduce 25(OH)D levels frequently found at end of summer in outdoor workers – at which levels no hyperabsorption occurs
Non-bone effects of vitamin D
Vitamin D₃

25(OH)D₃

Circulating blood

1,25(OH)₂D₃

ENDOCRINE

AUTOCRINE/ PARACRINE
Vitamin D

\textit{endocrine} \hspace{2cm} \textit{autocrine}

\begin{itemize}
  \item the Ca economy:
    \begin{itemize}
      \item Ca absorption
      \item bone resorption
    \end{itemize}
  \item the cell cycle:
    \begin{itemize}
      \item cell proliferation
      \item cell differentiation
      \item apoptosis
      \item immune response
    \end{itemize}
\end{itemize}
Vitamin D

**Endocrine**

- 25(OH)D
- 1,25(OH)2D
- 1-\(\alpha\)-OHylase
- 1,24,25(OH)3D

**Autocrine**

- 25(OH)D
- 1-\(\alpha\)-OHylase
- 1,25(OH)2D
- 24-OHylase
- 1,24,25(OH)3D

*Kidney cell*
AUTOCRINE ACTION

- Differentiation
- Specialization
- Apoptosis

1,25(OH)\(_2\)D

~ 1000 genes have Vitamin D Response Elements (VDREs)

1,24,25(OH)\(_3\)D

- Cell proliferation
- Cell differentiation
- Apoptosis
- Immune response
- 24-Hydroxylase
VITAMIN D & INNATE IMMUNITY*

activated Toll-like receptor

*Liu et al., Science 2006
VITAMIN D & INNATE IMMUNITY*

25(OH)D

bactericidal peptide

Cathelicidin

*Liu et al., Science 2006
VITAMIN D & INNATE IMMUNITY*

25(OH)D

- human monocytes in fetal calf serum

*Cyp27B1
VDR

.............

*Liu et al., Science 2006
VITAMIN D & INNATE IMMUNITY*

25(OH)D
- human monocytes in fetal calf serum
- add 25(OH)D to the system

*Liu et al., Science 2006
VITAMIN D & TUBERCULOSIS*

- human monocytes activated with *M. Tuberculosis* incubated in human serum
  - African-American
  - White
  - African-American with added 25(OH)D

*Cathelicidin mRNA*

A-A | W | A-A+25D
---|---|---
0  | 1  | 3
1  | 2  | 4
2  | 3  | 0
3  | 4  | 0

*Liu et al., Science 2006*
VITAMIN D & TUBERCULOSIS*

- 67 pts with pulmonary TB
- standard treatment for all
- in addition, randomized to either vit D 10,000 IU/d or placebo
- \( P = 0.002 \)

*Nursyam et al., Acta Med Indones 2006*
VITAMIN D & TUBERCULOSIS

these experiments show that:

- vit D is an essential mediator in the innate immune response
- serum 25(OH)D is the critical variable
- at least some of the increased sensitivity to infection in vit D-deficiency is due to reduction in response to infectious agents because 25(OH)D is rate-limiting
- the greater tuberculosis susceptibility of blacks is due in part to their low vit D status
The vitamin D autocrine/paracrine system functions in the tissue-level control of the immune response and of cell proliferation and differentiation.
## AUTOCRINE vs. ENDOCRINE

A key difference:

<table>
<thead>
<tr>
<th>Endocrine</th>
<th>Autocrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>- the renal 1-α-hydroxylase is regulated by PTH, and is largely independent of substrate [25(OH)D] concentration</td>
<td>- the tissue level 1-α-hydroxylase operates well below its $K_m$, &amp; hence 1,25(OH)$_2$D synthesis is directly proportional to substrate [serum 25(OH)D] concentration</td>
</tr>
</tbody>
</table>
# Autocrine vs. Endocrine

A key difference:

<table>
<thead>
<tr>
<th>Endocrine</th>
<th>Autocrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>the renal 1-α-hydroxylase is regulated by PTH, and is largely independent of substrate [25(OH)D] concentration</td>
<td>thus adequate serum concentration of 25(OH)D is critical for optimal function</td>
</tr>
</tbody>
</table>
Optimal endocrine and autocrine functions of 1,25(OH)₂D are dependent on sufficient levels of serum 25(OH)D.
THE AUTOCRINE HYPOTHESIS

- maintenance of “normal” serum levels of 25(OH)D will reduce the risk of malignant transformation in tissues that use this system
1,25 dihydroxyvitamin D (1,25(OH)2D):

- markedly inhibits genes responsible for proliferation
- enhances genes that cause apoptosis and regulate cellular differentiation

Feldman et al, 2000; Chen and Holick,
Vitamin D & Mammary Cancer

- Low vitamin D status in rats increases mammary oncogenesis in response to DMBA.\(^1\)

- In mouse mammary gland cultures, 1,25(OH)\(_2\)D decreases the oncogenic response to DMBA.\(^2\)

2. Mehta et al., 1997 JNCI; 89:212–18
BREAST CANCER MORTALITY

- US breast CA deaths (1970 – 1994) vs. solar UV exposure
- Grant, WB. Cancer 2002; 94:1867–75
SOLAR RADIATION & CANCER RISK

- Apperly FL
- Cancer Research Vol 1, No 1 (1941)
- 1934–1938 health statistics

“... relative immunity to cancer is a direct effect of sunlight ...”
THE AUTOCRINE HYPOTHESIS

- maintenance of “normal” serum levels of 25(OH)D will reduce the risk of malignant transformation in tissues that use this system
- 13 yr longitudinal study
- 19,000 men
- 149 cases prostate CA

*Ahonen et al., Cancer Causes & Control 11:847-852 (2000)
VITAMIN D & PROSTATE CA*

- those below the median 25(OH)D level were 70% more likely to develop prostate CA than those above.

*Ahonen et al., CancerCauses&Control 11:847-852 (2000)
COLORECTAL CANCER

- Nurses’ Health Study
- ages 46–78
- nested case-control study
- 193 incident cases
- 25(OH)D measured twice, prior to diagnosis
- Feskanich et al., Cancer Epidemiol Biomarkers Prev 2004 13:1502–08
VITAMIN D & CANCER*

- 1179 healthy women
- aged 66.7 ± 7.3
- four year randomized, placebo controlled trial
- 1032 women finished (87.5%)
- baseline 25(OH)D: 71.8 nmol/L ± 20.3
- three treatment groups:
  - placebo
  - Ca (1400–1500 mg/d)
  - Ca (1400–1500 mg/d) plus D₃ (1100 IU/d)

*Lappe et al. 2006*
**VITAMIN D & CANCER***

*Lappe et al. 2006*
Solar Radiation and Cancer Mortality

An inverse correlation between cancer death rates and sunlight exposure has been found for numerous cancers. Some of them include:

<table>
<thead>
<tr>
<th>breast</th>
<th>ovary</th>
</tr>
</thead>
<tbody>
<tr>
<td>colon</td>
<td>lung</td>
</tr>
<tr>
<td>rectum</td>
<td>pancreas</td>
</tr>
<tr>
<td>prostate</td>
<td>uterus</td>
</tr>
<tr>
<td>stomach</td>
<td>kidney</td>
</tr>
<tr>
<td>bladder</td>
<td>esophagus</td>
</tr>
<tr>
<td>thyroid</td>
<td>multiple myeloma</td>
</tr>
<tr>
<td>non-Hodgkins lymphoma</td>
<td></td>
</tr>
</tbody>
</table>

Grant W. Cancer 2002;94
Holick M.. Prog Biophysics Mol Biol 2006;92:
Giovannucci E. Cancer Causes and Control 2005;16
Annual incidence rate of **Type I diabetes, children**, by latitude of population centroid, reporting countries, Source: WHO data

\[ R^2 = 0.25 \]

\[ p < 0.0001 \]
Multiple Sclerosis Prevalence
55 Global Regions

$R^2 = 0.46$

$p < 0.0001$
Diseases/Conditions with evidence supporting a link to Vitamin D insufficiency

• Falls
• Osteoporotic fracture
• Type 1 Diabetes mellitus
• Multiple Sclerosis
• Autoimmune Diseases
• Infectious Disease
• Cancer of all types
• Cardiovascular Disease
• Hypertension
• Myocardial Infarction
• Asthma
SUMMARY – 1

- Vitamin D serves many functions beyond facilitation of active Ca absorption.
- Absence of rickets/osteomalacia does not constitute vit D sufficiency.
- *Calcium-related* functions are optimal at or above serum 25(OH)D levels of 80 nmol/L (32 ng/mL).
SUMMARY – 2

- Optimal 25(OH)D values for the non-bone effects are not known.
- The RDA/DRI for vitamin D ensures only absence of rickets/osteomalacia.
- Individuals who are dark-skinned, elderly, or living at high latitudes need more than the RDA/DRI for bone health.
IMPLICATION

- If ~80 nmol/L is accepted as the lower limit of healthy normal for 25(OH)D,
- Even above average summer sun exposure at 41° N latitude is not sufficient:
  - to guarantee winter-long sufficiency
  - to ensure even summer sufficiency in dark-skinned individuals
CONCLUSIONS – I

- Most of the vitamin D consumed each day in healthy adults comes from the skin.
- Optimal 25(OH)D levels are >80 nmol/L,
- Persons with 25(OH)D values lower than optimal have inadequate skin input,
- If we are to rectify this situation, we shall have to use oral vit D₃ doses substantially higher than current FNB, or IOM recommendations.
Thus, what are we waiting for?

- The forgoing presentation contained mostly epidemiologic and basic research.
- We need confirmation with clinical trial data to convince scientists and policy-makers.
- Vitamin D deficiency resembles nutritional deficiency in general: The result is very long-latency disease.
- The disease phenotypes appear only after very long periods of time have elapsed.
- Randomized clinical trials are impractical because of the time and expense required to accomplish them.
Options that might be considered

1. Convince scientists and policy-makers that bench science and epidemiologic associations are enough to make a public health decision in this area.

   This may be impossible because of widespread scientific skepticism and safety questions that can only be answered by randomized controlled trials.

2. Conduct a few randomized controlled trials in some disease category that may be doable and practical.

   We have enrolled 2,300 randomly selected subjects into a randomized placebo-controlled trial in eastern Nebraska testing whether calcium supplements of 1,250 mg/d combined with 2,000 I.U./d will reduce the incidence of all cancers over a period of 4 years.
Thank you. . .