WHAT’S A VITAMIN D DEFICIENCY?
OVERVIEW, ACTIONS

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DISCLOSURES

- Robert P. Heaney, M.D.
  - no personal financial relationships to disclose
OBJECTIVES

- define nutrient deficiency
- define how vitamin D status is assessed
- define the low end of the vitamin D sufficiency range
- describe how vitamin D can work in so many different tissues & organ systems
Working definition:
- a deficiency is any condition in which inadequate intake of a nutrient results in significant dysfunction or disease
- conversely, nutrient adequacy is the situation in which further increases in intake produce no further reduction in dysfunction or disease
RETHINKING DEFICIENCY DISEASE

Nutrient Deficiency → Index Mechanism → Short Latency Disease
In the early days of nutrition as a science, short latency of the disease/dysfunction was necessary in order to recognize the connection between cause and effect.
RETHINKING DEFICIENCY DISEASE

Vitamin D Deficiency

Malabsorption of Ca & P

Rickets
Osteomalacia
RETHINKING DEFICIENCY DISEASE

Nutrient Deficiency

Index mechanism

Short latency disease

Long latency disease
RETHINKING DEFICIENCY DISEASE

Vitamin D Deficiency
Malabsorption of Ca & P
Rickets
Osteomalacia
Osteoporosis
RETHINKING DEFICIENCY DISEASE

Nutrient Deficiency

Index mechanism

Short latency disease

Long latency disease

Non-Index mechanisms

Short latency disease

Long latency disease
RETHINKING DEFICIENCY DISEASE

Vit D Deficiency

Malabsorption Ca & P

Rickets
Osteomalacia

Rickets
Osteomalacia

Malabsorption Ca & P

Osteoporosis

Genomic Signaling

Hypertension disorders

Diabetes

Cancer

Immune disorders

Hypertension

Periodontitis

Diabetes
RETHINKING DEFICIENCY DISEASE

Nutrient Deficiency

Index mechanism

Short latency disease

Non-Index mechanism

Long latency disease

is often not enough nor to prevent these

Short latency disease
RETHINKING DEFICIENCY DISEASE

Nutrient Deficiency

Index mechanism
- Short latency disease
- Long latency disease

Non-Index mechanism
- Short latency disease
- Long latency disease

Nevertheless, the input needed to prevent this outcome serves as the principal basis for current intake recommendations!
What is the right endpoint?
What is the operative model for nutrition?
WHAT IS THE OPERATIVE MODEL?

- for the media?
- for regulators?
- for nutritional policy makers?
- for nutritional physiologists?
WHAT IS THE OPERATIVE MODEL?

- for the media and for regulators
  - nutrition is about killing yourself with a fork
  - it’s about avoiding risks
  - it’s about warnings & cautions
### Nutrition Facts

**Serving Size:** 1 cup (228g)  
**Serving Per Container:** 2

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calories</strong> 250</td>
<td>Calories from Fat 110</td>
</tr>
<tr>
<td><strong>Total Fat</strong> 12g</td>
<td>18%</td>
</tr>
<tr>
<td>Saturated Fat 3g</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Cholesterol</strong> 30mg</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Sodium</strong> 470mg</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Total Carbohydrate</strong> 31g</td>
<td>10%</td>
</tr>
<tr>
<td>Dietary Fiber 0g</td>
<td>0%</td>
</tr>
<tr>
<td>Sugars 5g</td>
<td></td>
</tr>
<tr>
<td><strong>Protein</strong> 5g</td>
<td></td>
</tr>
</tbody>
</table>

- **Vitamin A** 850 IU  
- **Vitamin C** 10%  
- Calcium 20%  
- Iron 4%

*Percent Daily Values are based on a 2,000 calorie diet. Your Daily Values may be higher or lower depending on your calorie needs.

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>2,000 Calories</th>
<th>2,500 Calories</th>
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</thead>
<tbody>
<tr>
<td>Total Fat</td>
<td>Less than 65g</td>
<td>Less than 80g</td>
</tr>
<tr>
<td>Sat Fat</td>
<td>Less than 20g</td>
<td>Less than 25g</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Less than 300mg</td>
<td>Less than 300mg</td>
</tr>
<tr>
<td>Sodium</td>
<td>Less than 2,400mg</td>
<td>Less than 2,400mg</td>
</tr>
<tr>
<td>Total Carbohydrate</td>
<td>300g</td>
<td>375g</td>
</tr>
<tr>
<td>Dietary Fiber</td>
<td>25g</td>
<td>30g</td>
</tr>
</tbody>
</table>

For a package of macaroni & cheese

http://vm.cfsan.fda.gov/~dms/foodlab.html
Limit these nutrients

Get enough of these nutrients

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</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Vitamin A:</td>
<td>4%</td>
</tr>
<tr>
<td>Vitamin C:</td>
<td>2%</td>
</tr>
<tr>
<td>Calcium:</td>
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<tr>
<td>Iron:</td>
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*Percent Daily Values are based on a 2,000 calorie diet.
Your Daily Values may be higher or lower depending on your calorie needs.
MEDIA REPORTING

- the overwhelming majority of media reports about nutrition emphasizes harm and risk
- while the explanation is partly that harm is more newsworthy than benefit (and the media battens on controversy)
- still the impression unwittingly conveyed to the general public is one of concern and danger
WHAT IS THE OPERATIVE MODEL?

- *for nutritional policy makers*

- nutrition is about determining the least one can get by on without suffering overt disease of a specific type
- (once called MDRs)
WHAT IS THE OPERATIVE MODEL?

- *for nutritional physiologists*

- adult nutrition is about preventive maintenance of tissues and organs
- it’s about keeping them from wearing out or breaking down prematurely
- its referent is the intake that prevailed when human physiology evolved
THE PREVENTIVE MAINTENANCE MODEL

*foundational premises:*

- all tissues need all nutrients
- shortages impair the functioning of *all* body systems
- premature organ/system “wearing out”, as a consequence of nutrient deficiency, will vary from person to person, depending on variable genetic composition; and
- therefore, expression of nutrient deficiency will usually be pluriform – both between and within individuals
THE INTAKE REFERENT

- it is sometimes argued that primitive intakes may be ill-suited to modern conditions
- but lacking specific evidence to that effect, the presumption ought to tip toward the primitive intake
  - what is the justification for privileging the status quo?
- the burden of proof should fall on those who claim that primitive intakes are unsafe or that lower intakes are adequate
THE PREVENTIVE MAINTENANCE MODEL

• also recognizes that:
  ➢ the organism will work perfectly well without maintenance – *for a while* . . .

• it thus reconciles the seeming paradox that an organism can be “deficient” without being clinically “sick”
  – *for a while* . . .

• it’s also about squaring the morbidity/mortality curve
THEORETICAL MORTALITY CURVE

AGE (yrs)

SURVIVAL (%)
SQUARING THE MORTALITY CURVE

Certainly, NCEP and DGA take this for granted. Optimal nutrition has the potential to contribute to this improvement. The role of vitamin D in this reduction is the topic of this conference.
ALL-CAUSE MORTALITY*

- 714 community dwelling women
- aged 70–79
- Baltimore Women’s Health & Aging Studies I & II
- median follow-up: 72 months
- risk adjusted for age, race, BMI, & other factors associated with mortality

THE RESPONSE THRESHOLD

VITAMIN D STATUS

EFFECT

Rickets?
THE RESPONSE THRESHOLD

VITAMIN D STATUS

EFFECT

Falls risk?
THE RESPONSE THRESHOLD

Blood pressure? Immune response?

VITAMIN D STATUS

EFFECT
RESPONSE HETEROGENEITY

- different tissues within an individual
- and different individuals within a population
- will have varying threshold 25(OH)D response levels
- *hence*, inadequate vitamin D status will manifest itself differently from patient to patient and from population to population
choosing the rightmost inflection point ensures adequate coverage of all endpoints
CELL MODELS

old: DNA in somatic cells functions mainly to make faithful copies for tissue repair or replacement

new: DNA functions constantly in synthesis of needed cellular apparatus
Signal/Demand

... but I do have the plans for what I need in my DNA library... the equipment I need....

Response

newly synthesized cellular equipment
HOW A CELL RESPONDS

1,25(OH)_2D is the key that unlocks the DNA library

newly synthesized cellular equipment
HOW A CELL RESPONDS

Signal/Demand

synthesized in the cell itself

1,25(OH)\textsubscript{2}D \^ is the key that unlocks the DNA library

Response

newly synthesized cellular equipment
OLD
VIT D – CANONICAL SCHEME

\[
\begin{align*}
\text{skin} & \quad \text{liver} & \quad \text{kidney} & \quad \text{gut} \\
D_3 & \quad \rightarrow & \quad 25\text{(OH)}D_3 & \quad \rightarrow & \quad 1,25\text{(OH)}_2D_3 & \quad \rightarrow & \quad \text{CaBP}
\end{align*}
\]
VIT D – EXPANDED SCHEME

**Endocrine**

- Skin
- Liver
- D₃ → 25(OH)D₃

**Autocrine**

- Kidney: 1,25(OH)₂D₃ → periphery: 1,25(OH)₂D₃ → various tissues: cell signals

- Gut: CaBP

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CU ORC
VIT D – EXPANDED SCHEME

**Endocrine**
- Skin
- Liver
- D₃ → 25(OH)D₃
- 85% autocrine

**Autocrine**
- Kidney
- 1,25(OH)₂D₃
- Various tissues
- 1,25(OH)₂D₃
- Gut
- CaBP
- Cell signals
VIT D – EXPANDED SCHEME

- **endocrine**
  - skin
  - liver
  - 25(OH)D$_3$ → 1,25(OH)$_2$D$_3$

- **autocrine**
  - periphery
  - D$_3$ → 25(OH)D$_3$ → 1,25(OH)$_2$D$_3$

- **kidney**
  - 1,25(OH)$_2$D$_3$

- **gut**
  - CaBP

- **various tissues**
  - cell signals

- **cell signals**
VIT D – EXPANDED SCHEME

**endocrine**

skin → liver  
D₃ → 25(OH)D₃

**autocrine**

periphery  
1,25(OH)₂D₃  
→ various tissues  
→ cell signals

kidney  
1,25(OH)₂D₃  
→ gut  
→ CaBP
AUTOCRINE ACTION

25(OH)D

1,25D
VDR

1,25D
VDR
RXR

VDRE

Transcription
AUTOCRINE ACTION

25(OH)D

- cell proliferation
- cell differentiation
- apoptosis
- immune response
- 24-hydroxylase

Transcription

VDRE
AUTOCRINE ACTION

25(OH)D

> 1000 genes have VDREs

Transcription
AUTOCRINE ACTION

25(OH)D

25OHD  25OHD
1,25D  1,25D
    VDR
    1,25D
    VDR
    RXR

VDRE

Transcription

CU ORC
AUTOCRINE ACTION

25(OH)D

25OHD

1,25D

1,25D

VDR

VDR

RXR

VDRE

Transcription

CU ORC
This scheme means that each tissue
- has the amount of $1,25(\text{OH})_2\text{D}$ it needs
- when it needs it
- and is not dependent upon a "one-size-fits-all" systemic level of circulating $1,25(\text{OH})_2\text{D}$
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

the Vit D 1-α hydroxylase

Cyp27B1
VDR

the Vit D receptor

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

25(OH)D
- human monocytes in fetal calf serum
- fetal calf serum is low in both 25(OH)D & 1,25(OH)₂D

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

25(OH)D
- human monocytes in fetal calf serum
- add 1,25(OH)_2D to the system

*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*
human monocytes activated with *M. Tuberculosis* and incubated in human serum

- African-American
- White
- African-American with added 25(OH)D

*Cathelicidin mRNA*

- serum 25(OH)D: 78 nmol/L
- serum 25(OH)D: 22 nmol/L

*Liu et al., Science 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
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

*Sursyam et al., Acta Med Indones 2006
ASSESSING VITAMIN D DEFICIENCY

- serum total 25(OH)D is the:
  - functional indicator for vit D status
  - an important storage form of vit D at typical inputs
- serum 25(OH)D$_2$ is of no value unless the MD is following treatment with vit D$_2$
- serum 1,25(OH)$_2$D does not measure vit D status (instead, it measures Ca need)
A VITAMIN D THRESHOLD

![Graph showing absorption fraction vs. serum 25(OH)D levels]

- Absorption Fraction
- Serum 25(OH)D (nmol/L)
A VITAMIN D THRESHOLD

physiological regulation no longer limited by vit D availability
A VITAMIN D THRESHOLD

SERUM 25(OH)D (nmol/L) vs. ABSORPTION FRACTION
The evidence to be presented in the papers of this meeting points to a requirement for serum 25(OH)D that is above 80 nmol/L* (and perhaps as much as 100-125 nmol/L**).

* 32 ng/mL
** 40–50 ng/mL
THE 25(OH)D CONTINUUM

"deficiency"

"insufficiency"

"normal"

0 25 50 75 100 125 150 (nmol/L)
THE 25(OH)D CONTINUUM

"deficiency"

"insufficiency"

"normal"

0  25  50  75  100  125  150 (nmol/L)
THE 25(OH)D CONTINUUM

“deficiency”

0 25 50 75 100 125 150

(normal)

(nmol/L)

CU ORC
25(OH)D & SERUM iPTH*

290 consecutive pts. on a general medical ward – MGH

*after Thomas et al., 1998 NEJM;338:777–783
25(OH)D IN OLDER WOMEN*

- 1168 women aged 55 & older
- Latitude 41° N
- 25(OH)D values adjusted for season
- Median vit D supplement dose = 200 IU

*Lappe et al., JACN 2006

62%
NHANES–III

- women aged 60–79
- summer, northern states
VIT D DEFICIENCY IN CHILDREN

- NHANES 2001–2004
- girls
- n=3012
What would this distribution look like if the entire population were to be supplemented with vitamin D? – say, with 2600 IU/d?
NHANES–III* + THE TUIL

NHANES–III* + 2600 IU/D

- 2600 IU/d would raise 25OHD by ~46 nmol/L
- ~2.5% of population still below 80 nmol/L
- thus 2600 IU/d ≈ the RDA for women >60 yrs
- *but, that’s over & above all current inputs*

NHANES–III* + 2600 IU/D

- what about those already 2 SD above the mean?
- the rise with an extra ~2600 IU/d would be predicted to bring them to no more than 180 nmol/L – well below the toxic range

“stones” are self-reported AEs
not a pre-planned outcome variable
not adjudicated
vit D dose $\approx$ 200 IU/d
KIDNEY STONE RISK

STONE INCIDENCE
(per 100,000/yr)
in brief, the WHI stone numbers are so out of line with all other stone data they cannot be accepted as real

nor could they plausibly be attributed to the small dose of vit D used in WHI
CONCLUSIONS

- serum 25(OH)D levels below 80 nmol/L are not adequate for any body system
- levels of as high as 120 nmol/L may be closer to optimal
- inputs from all sources combined (needed to sustain 80 nmol/L) are in the range of ~4,000 IU/d and higher
- in most healthy adults, 2000–2600 IU/d, in addition to all other inputs, will usually suffice
OBJECTIVES

- define nutrient deficiency
- define how vitamin D status is assessed
- define the low end of the vitamin D sufficiency range
- describe how vitamin D can work in so many different tissues & organ systems

- disease or dysfunction due to low intake
- serum 25(OH)D concentration
  \[ \geq 80 \text{ nmol/L (32 ng/mL)} \]
- the key that unlocks the DNA library in most tissues
Thank you