VITAMIN D
WHAT IT DOES & HOW MUCH WE NEED

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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
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
For a package of macaroni & cheese

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

Get enough of these nutrients

<table>
<thead>
<tr>
<th>Nutrition Facts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serving Size</strong>: 1 cup (228g)</td>
</tr>
<tr>
<td><strong>Serving Per Container</strong>: 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>Calories</th>
<th>250</th>
<th>Calories from Fat</th>
<th>110</th>
</tr>
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<tbody>
<tr>
<td><strong>% Daily Value</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Fat</strong></td>
<td>12g</td>
<td>18%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturated Fat</td>
<td>3g</td>
<td>15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cholesterol</strong></td>
<td>30mg</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sodium</strong></td>
<td>470mg</td>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Carbohydrate</strong></td>
<td>31g</td>
<td>10%</td>
<td></td>
<td></td>
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<tr>
<td>Dietary Fiber</td>
<td>0g</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sugars</td>
<td>5g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protein</strong></td>
<td>5g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A</td>
<td></td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin C</td>
<td></td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td></td>
<td>4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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

- most media reports about nutrition emphasize 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
CHRONIC DISEASE PERSPECTIVE

- Chronic disease is the breakdown of structure and/or function of a body system
- Its origin is usually multifactorial
  - Genes
  - Environment
    - Nutrition
    - Infection
    - Toxins
    - Injury

Vitamin D is an essential component of many of these mechanisms.
Low vitamin D status impairs this protective/reparative activity.

The body has mechanisms to repair this damage or to fight it at its origin.
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
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
THEORETICAL MORTALITY CURVE

AGE (yrs)  AGE (yrs)  AGE (yrs)  AGE (yrs)
00         00         10         10         10         10         20         20         20         20         30         30         30         30         40         40         40         40         50         50         50         50         60         60         60         60         70         70         70         70         80         80         80         80         90         90         90         90         100        100        100        100

SURVIVAL (%)  SURVIVAL (%)  SURVIVAL (%)  SURVIVAL (%)
00         00         20         20         20         20         40         40         40         40         60         60         60         60         80         80         80         80         100        100        100        100
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 presentation.
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

VITAMIN D IN NATURE

- Vitamin D exists in two chemically distinct forms:
  - Vitamin D2 – ergocalciferol
  - Vitamin D3 – cholecalciferol

- D3 is the natural form in animals; it is what we make in our skins on exposure to UV–B light

- D2, once thought equivalent to D3, is only ~50–60% as potent as D3
VITAMIN D IN NATURE

- serum 25(OH)D is the way vitamin D status is evaluated
- lower end of acceptable range for serum 25(OH)D:
  75–80 nmol/L
  (30–32 ng/mL)
There has been a gradually growing acceptance of 75–80 nmol/L (30–32 ng/mL) as the lower end of the “normal” range.

What is the basis for this figure?

Will it hold?
A VITAMIN D THRESHOLD

![Graph showing the relationship between SERUM 25(OH)D (nmol/L) and ABSORPTION FRACTION. The x-axis represents SERUM 25(OH)D (nmol/L) ranging from 0 to 160, while the y-axis represents ABSORPTION FRACTION ranging from 0.0 to 0.5. The graph includes data points and error bars indicating variability.](image-url)
A VITAMIN D THRESHOLD

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

SERUM 25(OH)D (nmol/L)

ABSORPTION FRACTION

0.0 0.1 0.2 0.3 0.4 0.5

0 20 40 60 80 100 120 140 160

CU ORC
THE RESPONSE THRESHOLD

VITAMIN D STATUS

Ca absorption

EFFECT
THE RESPONSE THRESHOLD

Clinical rickets?

VITAMIN D STATUS

EFFECT
THE RESPONSE THRESHOLD

VITAMIN D STATUS

EFFECT

Histological rickets
25(OH)D IN OLDER WOMEN*

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

*Lappe et al., JACN 2006
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VIT D DEFICIENCY IN CHILDREN

- NHANES 2001–2004
- girls
- n=3012
- Kumar et al. Pediatrics 2009
All studies, in virtually all nations, irrespective of latitude, show that the majority of the world’s population has inadequate vitamin D status.
WHAT ARE THE CONSEQUENCES?

- bone diseases, falls, & fractures
- hypertension
- ↑ risk of cardiac disease & death
- prematurity, low birth weight, & ↑ Caesareans
- diabetes & metabolic syndrome
- periodontal disease
- decreased resistance to infection
- various cancers
- ↑ risk of multiple sclerosis
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

0.0 0.2 0.4 0.6 0.8 1.0

FRACTURE RELATIVE RISK (hip, forearm, spine)

-33%

0 25 50 100 125 150

(nmol/L)
VITAMIN D & RISK OF FALLING*

- 122 women
- Age: 63–99
- DB–RCT
  - Ca 1,200 mg/d
  - Ca + 800 IU Vit D
- 12 week duration
- 25(OH)D 12 ng/mL at baseline


-49%
VIT D & NEUROMUSCULAR FUNCTION*

- 1359 men & women; mean age 75.5
- Amsterdam longitud. aging study
- neuromuscular performance measured on a scale of 0 to 12 (higher is better)
- each step statistically significant

VIT D & BLOOD PRESSURE*

- 148 women, aged 74 ± 1
- DB-RCT
- baseline 25(OH)D < 50 nmol/L
- treated for 8 wks with:
  Ca 1200 mg/d or Ca + 800 IU vit D/d

*Pfeifer et al., JCEM 2001; 86:1633–37
VIT D & CARDIOVASCULAR DISEASE

- 1739 Framingham Offspring members
- Age: 59 yrs
- Follow-up: 5.4 yrs
- 120 individuals developed a CV event
- HR calculated against 25(OH)D values > 15 ng/mL

![Diagram showing hazard ratios with 80% increase in risk for < 10 ng/mL and 53% increase in risk for < 15 ng/mL compared to > 15 ng/mL.](image)
VITAMIN D & INFLUENZA*

- 208 African-American, postmenopausal women
- 3 yr DB–RCT
- placebo or vit D₃
  - 800 IU/d – 2 yrs
  - 2000 IU/d – 3ʳᵈ yr
- basal 25(OH)D: 18.8 ± 7.5
- P < 0.002

*Aloia & U–Ng (2007) Epidemiol & Infect
VITAMIN D & INFLUENZA*

- DB–RCT
- winter 2008–2009
- 334 Japanese school children, aged 6–15
- mean wt: 35.5 kg
- 1200 IU D₃/d in addition to self-supplementation

*Urashima et al., AJCN 2010
VITAMIN D & THE COMMON COLD*

- 18,883 individuals in NHANES–III
- tested association between serum 25(OH)D & recent URTI
- P < 0.001
- association stronger for those with asthma & COPD

Ginde et al., Arch Int Med 2009 169:
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
BREAST CANCER RISK

- Case-control study
  - 1394 cases
  - 1365 controls
- Odds ratio for CA inversely associated with vit D status [25(OH)D]

69% decrease in risk
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

\[ P = 0.02 \]

25(OH)D Quintiles (with medians*)

*ng/mL
VITAMIN D & CANCER*

Time (yrs) Time (yrs) Time (yrs) Time (yrs)

Fraction Cancer-Free Fraction Cancer-Free Fraction Cancer-Free Fraction Cancer-Free
0.90 0.90 0.90 0.90
0.92 0.92 0.92 0.92
0.94 0.94 0.94 0.94
0.96 0.96 0.96 0.96
0.98 0.98 0.98 0.98
1.00 1.00 1.00 1.00

Ca+D Placebo Ca-only

96 nmol/L 70 nmol/L

Ca+D Placebo

96 nmol/L 70 nmol/L

Fraction Cancer-Free

Time (yrs)

0 1 2 3 4 5

0.90 0.92 0.94 0.96 0.98 1.00

*Lappe et al. AJCN 2007
<table>
<thead>
<tr>
<th>Condition</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>rickets &amp; osteomalacia</td>
<td>75 nmol/L</td>
</tr>
<tr>
<td>Ca absorption</td>
<td>80 nmol/L</td>
</tr>
<tr>
<td>pregnancy outcomes</td>
<td>120 nmol/L</td>
</tr>
<tr>
<td>some cancers</td>
<td>100 nmol/L</td>
</tr>
<tr>
<td>other</td>
<td>???</td>
</tr>
</tbody>
</table>
MANAGEMENT

- all-input requirement $\cong 75$ IU/kg/d
- most adults will need $1000-3000$ IU/d in addition to all other inputs
- $25(OH)D$ response varies widely
- it is the serum $25(OH)D$ concentration that must be optimized, not the oral dose
- the correct oral dose is the one that produces and maintains the desired $25(OH)D$ level
Safety
15 studies of adults receiving vitamin D supplementation (means)

no toxicity below 30,000 IU/d

8 studies reporting toxicity (individual values)

no toxicity below 500 nmol/L (200 ng/mL)

CONCLUSIONS

- Serum 25(OH)D levels below 80 nmol/L are not adequate for any body system.
- Levels of as high as 125 nmol/L may be closer to optimal.
- Inputs from all sources combined are in the range of:
  - ~4,000 IU/d to sustain 80 nmol/L, and
  - ~5,000 IU/d to sustain 100 nmol/L.
Thank you