MY FOCI

- early life
- measuring & assessing 25(OH)D
- other
Early Life
Deficiency – a 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
CLASSICAL VIT D DEFICIENCY

- rickets in children
- caused by poor absorption of calcium
  - leading to high PTH levels,
  - lowered renal phosphate threshold
  - hypophosphatemia
- serum 25(OH)D: < 25 nmol/L
- clinically preventable by 200–400 IU D₃/day
- that dose does not restore full Ca absorptive function nor normal bone histology
RICKETS RISES AGAIN

- decreased sun exposure of babies
- maternal vitamin D deficiency
- failure to supplement infant feedings with vitamin D
- weaning infants to non-milk liquids
Note “hot cross bun” skull in this 5 mo old

- 1120 consecutive neonates in Japan
- 22% had craniotabes
- median 25(OH)D at 1 mo: < 25 nmol/L

*Yorifuji et al., JCEM; 93:1784-88 (2008)
FETAL RICKETS*

- n = 424
- 3D QUS
- splay index at distal femur at 19 & 34 weeks
- (metaphyseal X-sectional area divided by femoral length)
- high ≈ rickets

FETAL RICKETS*

- n = 424
- 3D QUS
- splay index at distal femur

Battered child
or
unrecognized rickets?
UNDIAGNOSED METABOLIC BONE DISEASE

2 month male infant

16 days after starting vit D

slide courtesy of Dr David Ayoub
UNDIAGNOSED METABOLIC BONE DISEASE

hypomineralized zone at edges of skull plates

hypermineralized line typical of healing rickets

slide courtesy of Dr David Ayoub
Cases of apparent child abuse, particularly with little or no evidence of soft tissue injury, must be evaluated for metabolic bone disease before diagnosing abuse!
Patient of Dr. Lyndon Key, MUSC
Her rickets have healed
but –
does she have subtle long-term consequences of early life vitamin D deficiency?
**JUVENILE DIABETES IN FINLAND**

![Graph showing incidence of diabetes from 1960 to 1990 for ages 1-4, 5-9, and 10-14, with separate lines for boys and girls.](image)

This dosage reflects the then common practice in E. Europe of giving 600,000 IU 3x per year during infancy.
JUVENILE DIABETES IN FINLAND*
10,366 northern Finnish children
2000 IU Vit D/d 1st year of life
prevalence of type I diabetes assessed at age 31
RR calculated vs. no supplementation

those who got the recommended amount regularly
those who got it sometimes
those who got it never
those who got little or no vit D at all & were thought to have rickets

*Hypponen et al., Lancet 2001;358:1500–03
**NEONATAL VIT D & DIABETES**

- 10,366 northern Finnish children
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NEONATAL VIT D & DIABETES*

- EURODIAB Study
- 7 European cntrs
- case control 820 cases (~80 % eligible population)
- supplemental Vit D in infancy
- type 1 diabetes < age 15

*Diabetologia 1999; 42:51–54
MS INCIDENCE MAP*

Percent national average incidence:

40–70% 70–100% 100–130% 130–160% 160–190% 190–220%

37° N

*modified from: http://mscenter.ucsf.edu/
MS RISK & BIRTH MONTH*

- 44,045 pts with MS
- populations of Canada, UK, Denmark, & Sweden
- observed cases divided by expected, by birth month

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- observed cases divided by expected, by birth month

INFANT VITAMIN D INTAKE*

- Infant Feeding Practices Study
- > 33,000 infants
- 2005–2007
- Sources (1 mo):
  - breast – 43%
  - formula – 26%
  - mixed – 32%

* Perrine et al. 2010, Pediatrics 125:627–32
These perinatal and early life associations are probably epigenetic in character and are believed to involve the programming of the immune system to distinguish self and non-self – a process in which vitamin D plays an essential role.
VIT D & PREGNANCY OUTCOMES*

- DB–RCT; N = 690 pregnant women
- dosed with 400, 2000, & 4000 IU/d from wk 12 to delivery

*Hollis & Wagner (2009) in press
VIT D & PREGNANCY OUTCOMES*

Serum 25(OH)D (ng/mL)

Visit Number

*Hollis & Wagner (2009) in press
VIT D & PREGNANCY OUTCOMES*

*Wagner & Hollis (2010) in press
VIT D & PREGNANCY OUTCOMES*

- DB–RCT; N = 690 pregnant women
- dosed with 400, 2000, & 4000 IU/d from wk 12 to delivery
- risk of untoward outcomes reduced by half:
  - pre-term delivery (P < 0.01)
  - gestational diabetes, pre-eclampsia, hypertension (P < 0.01)
  - periodontal disease (P < 0.05)
  - neonatal infection (P < 0.05)

*Wagner & Hollis (2010) in press
Other

[Mechanisms]
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
CELL MODELS

old: cell/tissue differentiation meant that each cell type contained different cytoplasmic apparatus

new: cell/tissue differentiation meant that only certain genes can be accessed in each tissue
HOW A CELL RESPONDS

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

CU   ORC
HOW A CELL Responds

25(OH)D

Signal/Demand

1,25(OH)₂D is the key that unlocks the DNA library

synthesized in the cell itself

Response

newly synthesized cellular equipment

CU ORC
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
the Vit D receptor

Cyp27B1 VDR

*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)$_2$D

*Cyp27B1
VDR

* Liu et al., Science 2006
25(OH)D
- human monocytes in fetal calf serum
- add 1,25(OH)₂D to the system

*C 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

*Cathelicidin
*Cyp24
*Cyp27B1
*1,25D
*VDR

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

- 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*
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 $1,25(\text{OH})_2\text{D}$
- every time DNA is expressed, vitamin D is consumed
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
Vitamin D *enables* macrophage function

It does not cause it
INNATE IMMUNITY IN INFANTS

- Infection resistance in infants heavily dependent upon innate immunity
- Human monocytes cultured in cord blood plasma*
  - Macrophage expression of cathelicidin mRNA directly related to cord blood 25(OH)D
  - Low 25(OH)D samples rescued by added 25(OH)D

*Walker et al. JCEM (in press)
Measurement & Assessment
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

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

Vitamin D is an essential component of these mechanisms.

Low vitamin D status impairs this protective/reparative activity.
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
VITAMIN D SHORTAGE

- When vitamin D is in short supply, the various tissues and cells of our bodies cannot make enough calcitriol to open up their DNA libraries adequately.
- Their functioning is thus impaired.
- That, ultimately, is the basis for the multi-system manifestations of vit D deficiency.
A VITAMIN D THRESHOLD

SERUM 25(OH)D (nmol/L)

ABSORPTION FRACTION

CU  ORC
A VITAMIN D THRESHOLD

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

![Graph showing absorption fraction vs. serum 25(OH)D levels, with deficient and adequate thresholds indicated.]

CU ORC
Vitamin D *enables* Ca absorption

It does not cause it
In general vitamin D *enables* tissue response & recovery

It does not cause it
VIT D - CANONICAL SCHEME

<table>
<thead>
<tr>
<th>skin</th>
<th>liver</th>
<th>kidney</th>
<th>gut</th>
</tr>
</thead>
</table>

\[ D_3 \rightarrow 25(\text{OH})D_3 \rightarrow 1,25(\text{OH})_2D_3 \rightarrow \text{CaBP} \]
OLD VIT D – CANONICAL SCHEME

skin        liver        kidney        gut

\[ \text{D}_3 \rightarrow 25(\text{OH})\text{D}_3 \rightarrow 1,25(\text{OH})_2\text{D}_3 \rightarrow \text{CaBP} \]
VIT D - EXPANDED SCHEME

**endocrine**
- skin
- liver
- $D_3 \rightarrow 25(OH)D_3$

**autocrine**
- periphery
- $1,25(OH)_2D_3$

**kidney**
- $1,25(OH)_2D_3$

**gut**
- CaBP

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

endocrine

skin

D_3 → 25(OH)D_3

autocrine

liver

kidney

1,25(OH)_2D_3 → CaBP

≈5%

vast periphery

85+%

cell signals

1,25(OH)_2D_3 → various tissues
VIT D – EXPANDED SCHEME

- **Endocrine**
  - D₃ → 25(OH)D₃ → \(1,25(OH)_2D_3\)
  - Supply exogenous calcitriol or one of its analogs

- **Autocrine**
  - Periphery

- **Gut**
  - \(1,25(OH)_2D_3\) → CaBP

- **Various tissues**
  - Cells signals

- **Skin**

- **Liver**

- **Kidney**
Won’t calcitriol meet the body’s need for vitamin D?

NO!
VIT D – EXPANDED SCHEME

endocrine

skin

D₃

25(OH)D₃

autocrine

liver

kidney

1,25(OH)₂D₃

~5%

~85%

periphery

1,25(OH)₂D₃

gut

CaBP

various tissues

cell signals

CU ORC
Very recent studies have shown that, when serum 25(OH)D is normalized in patients on hemodialysis, serum 1,25(OH)₂D is "normalized" as well.

Bikle showed many years ago that the skin was able to synthesize physiologically meaningful quantities of 1,25(OH)₂D.
How much is enough?
THE RESPONSE THRESHOLD

Ca absorption

VITAMIN D STATUS

EFFECT
THE RESPONSE THRESHOLD

Clinical Rickets?
THE RESPONSE THRESHOLD

Cancer risk?
THE RESPONSE THRESHOLD

Pregnancy outcomes?

EFFECT

VITAMIN D STATUS
THE RESPONSE THRESHOLD

Falls risk?
THE RESPONSE THRESHOLD

Blood pressure? Immune response?

VITAMIN D STATUS

EFFECT
choosing the rightmost inflection point ensures adequate coverage of all endpoints
## HOW MUCH IS ENOUGH?

- **rickets & osteomalacia**
  - clinical: 25 nmol/L
  - histological: 80 nmol/L
- **Ca absorption**: 80 nmol/L
- **fracture risk**: 100 nmol/L
- **pregnancy outcomes**: 120 nmol/L
- **cancer**: 100 nmol/L
- **other**: ????
STATUS OF THE EVIDENCE

- there are now more than 30 randomized controlled trials evaluating a causal connection between serum 25(OH)D levels and various health benefits
  - 13+ osteoporotic fractures
  - 5+ falls
  - 2 hypertension
  - 1 cancer
  - 1 adjuvant tuberculosis therapy
  - 3 respiratory infection/influenza risk
  - 3 pregnancy outcomes
  - 1 periodontal disease
  - 3 insulin sensitivity & diabetes
STATUS OF THE EVIDENCE

- out of this total there are, to be sure, several null trials
- in general these failed trials either –
  - used too low a dose
  - had poor compliance
  - failed to achieve a therapeutic blood level of 25(OH)D
  - failed to optimize co-nutrition
- there is only one negative trial
STATUS OF THE EVIDENCE

- there are, to be sure, several null trials as well
- in general these failed trials either –
  - used too low a dose
  - had poor compliance
  - failed to achieve a therapeutic blood level of 25(OH)D
  - failed to optimize co-nutrition
- there is only one negative trial
Achieved 25(OH)D & Hip Fracture

*Redrawn from Bischoff-Ferrari et al. JAMA. 2005;293:2257–2264
ACHIEVED DOSE & FRACTURE EFFICACY*

25(OH)D RESPONSE TO LARGE DOSES*

- 100,000 IU D₃, by mouth, once

*Ilahi, Armas, & Heaney
VARIABILITY OF 25(OH)D RESPONSE*

- Δ 25(OH)D to C_{max} ranged from +12 nmol/L to +76 nmol/L
- ~half of the variability due to body size

*Ilahi, Armas, & Heaney
VARIABILITY OF 25(OH)D RESPONSE*

- Wt-adjusted Δ 25(OH)D to $C_{\text{max}}$ ranged from +20 nmol/L to +66 nmol/L

*Ilahi, Armas, & Heaney
for some endpoints (e.g., pregnancy, cancer) the data suggest that 80 nmol/L is not high enough
there is huge variability in individual response
the emphasis must be on the achieved serum level, not on the oral dose
levels of 100 – 200 nmol/L are physiological

- given the manifest safety of such levels, we should strive to achieve at least 100 nmol/L in all our patients & clients

- whatever their primary condition, most will be vitamin D-deficient as well

- their recovery will be aided by treating that D deficiency
SUMMARY

- Levels of 100 – 200 nmol/L are physiological.
- Given the manifest safety of such levels, we should strive to achieve at least 100 nmol/L in all our patients & clients.
- Whatever their primary condition, most will be vitamin D-deficient as well.
- Their recovery will be aided by treating that D deficiency.
Thank you . . .