Vitamin D Deficiency - What the Primary Care Physicians Needs to Know

Saturday, June 18, 2011
Madrid I ~ 8:00am - 8:45am

Robert Heaney, MD
Creighton University
601 N 30th St., Suite 4841
Omaha, NE 68131
Tel: 402-280-4029
Fax: 402-280-4751
Email: rheaney@creighton.edu

Objectives

- Distinguish between the targets of the IOM recommendations and the advice physicians give their patients
- Cite evidence of skeletal benefit at serum 25(OH)D concentrations above 20 ng/mL
- Describe the cell-biologic basis of vitamin D action
- Recall several nonskeletal conditions aggravated by low vitamin D status

Faculty Disclaimer

The OAFP has selected all faculty appearing in this program. According to OAFP policy, all relationships between speakers and proprietary entities will be disclosed.

*The speakers returned a disclosure indicating that they or an immediate family member **does not have** a significant financial interest in or affiliation with a commercial supporter of this educational activity and/or with the manufacturer(s) of commercial products and/or providers of any commercial services discussed in this educational presentation/material.*

They listed (if applicable) commercial enterprises and the nature of relationship with each, e.g. research grants, stock or bond holdings, speakers' bureau, employment, ownership or partnership, consulting fees, other remunerations (honoraria, travel expenses):

Corporate Organizations	*Financial Interests/Affiliations*
None	

The content of this/these material(s)/presentation(s) in this CME activity **will not** include discussion of unapproved or investigational uses of products or devises.

VITAMIN D DEFICIENCY

WHAT THE PRIMARY CARE PHYSICIAN NEEDS TO KNOW

Robert P. Heaney, M.D.
Creighton University Osteoporosis Research Center

CU ORC

DISCLOSURES

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

CU ORC

2

SCOPE OF PRESENTATION

- what are some of the manifestations of vitamin D deficiency?
- how common is vitamin D deficiency?
- what is the biologic basis for the effects of vitamin D in the body?
- how should the PCP approach the prevention and treatment of vitamin D deficiency?

CU ORC

3

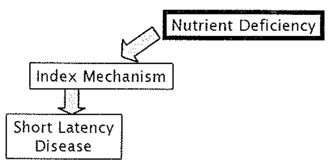
Working definition:

- a deficiency is any condition in which inadequate intake of a nutrient results in significant dysfunction or disease

– or –

- deficiency is a nutrient status below the lower limit of some measurement

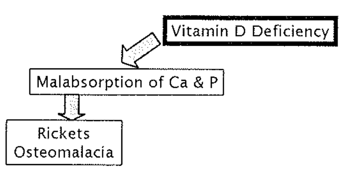
RETHINKING DEFICIENCY DISEASE



CU ORC

5

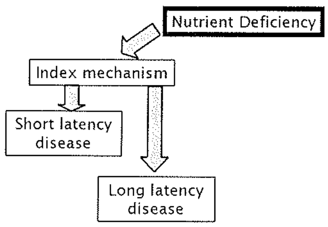
RETHINKING DEFICIENCY DISEASE



CU ORC

6

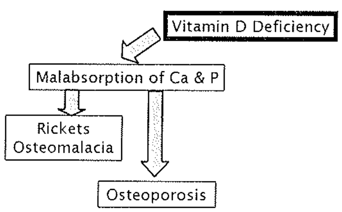
RETHINKING DEFICIENCY DISEASE



CU ORC

7

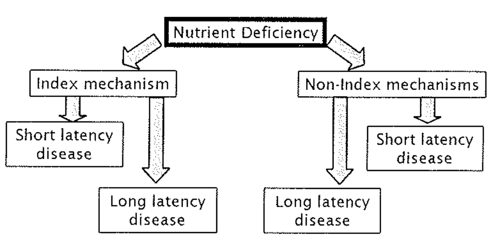
RETHINKING DEFICIENCY DISEASE



CU ORC

8

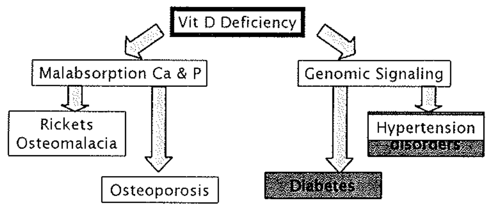
RETHINKING DEFICIENCY DISEASE



CU ORC

9

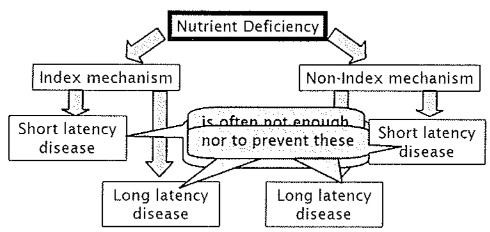
RETHINKING DEFICIENCY DISEASE



CU ORC

10

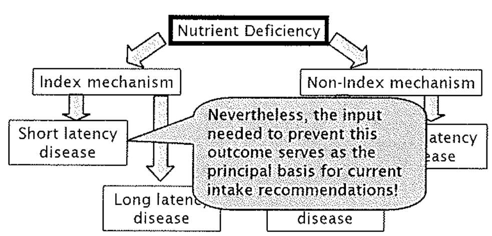
RETHINKING DEFICIENCY DISEASE



CU ORC

11

RETHINKING DEFICIENCY DISEASE



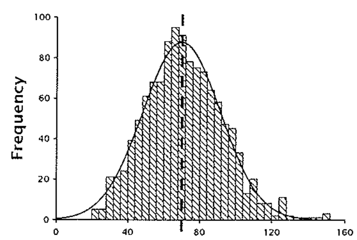
CU ORC

12

Prevalence

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

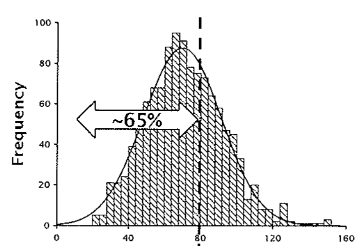


*Lappe et al., JACN 2006

14

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

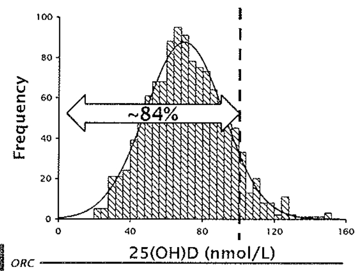


*Lappe et al., JACN 2006

15

25(OH)D IN OLDER WOMEN*

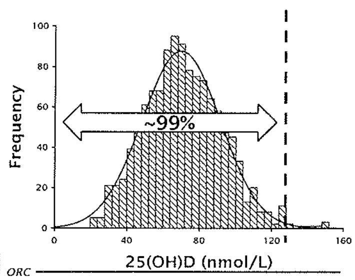
- 1168 women aged 55 & older
- latitude 41° N
- 25(OH)D values adjusted for season
- median vit D supplement dose = 200 IU



*Lappe et al., AJCN 2008 CU ORC

25(OH)D IN OLDER WOMEN*

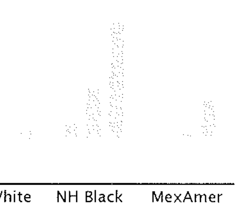
- 1168 women aged 55 & older
- latitude 41° N
- 25(OH)D values adjusted for season
- median vit D supplement dose = 200 IU



*Lappe et al., AJCN 2008 CU ORC

VIT D DEFICIENCY IN CHILDREN

- NHANES 2001-2004
- girls
- n=3012
- Kumar et al. Pediatrics 2009



CU ORC

All studies, in virtually all nations, irrespective of latitude, show that the majority of the world's population has inadequate vitamin D status.

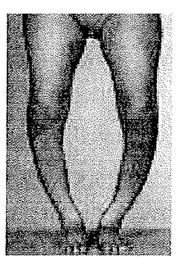
Rickets/Osteomalacia – Mechanism

- inadequate concentrations of Ca and P in blood to mineralize growth cartilage or newly formed bone matrix
- additionally, low serum Pi impairs chondroblast & osteoblast function

CU ORC

CANONICAL VIT D DEFICIENCY

- rickets in children
- osteomalacia in adults



CU ORC

INFANT VIT D INTAKE*

- 2008 AAP infant recommendation 400 IU/d
- using data from Infant Feeding Practices Study, investigators found that:
  - fewer than 1 in 7 were given any vitamin D, overall
  - formula-fed: 20-37% met AAP recs**
  - breast-fed: 5-13% met AAP recs
  - mixed-fed: 9-14% met AAP recs

CU ORC

* Perrine et al. 2010, *Pediatrics* 125:627-32
** Rates vary by age

INFANT VITAMIN D INTAKE*

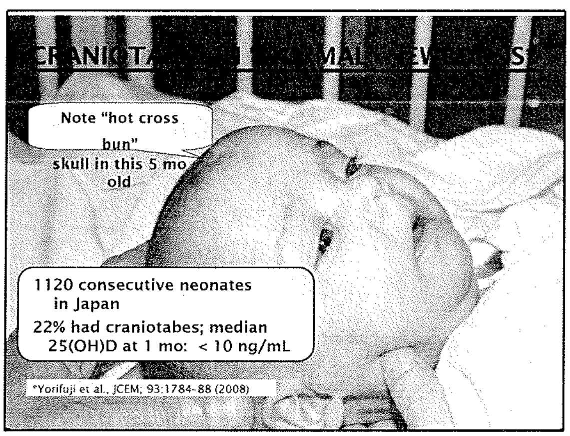
- *Infant Feeding Practices Study*
- > 33,000 infants
- 2005-2007
- Intakes (1 mo):
  - breast - 43%
  - formula - 26%
  - mixed - 32%

2008 AAP recommendation

CU ORC

* Perrine et al. 2010, *Pediatrics* 125:627-32

23



Manifestations/Consequences

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
- ↑ risk of schizophrenia

the IOM confined its recommendations to this group of outcomes

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
- ↑ risk of schizophrenia

for these it reported that there was not enough information to permit setting an intake requirement

RECOMMENDED FOR WHOM?

- myself — required level of evidence: *low*
- my patients & clients — required level of evidence: *moderate*
- the general public — required level of evidence: *high*

CU ORC

28

RECOMMENDED FOR WHOM?

- myself
- my patients & clients — level where we M.D.s & N.P.s function
- the general public — level where the IOM functions

CU ORC

29

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

for others vit D will be critical; they will show the biggest effects

CU ORC

30

VITAMIN D IN NATURE

- vitamin D exists in two chemically distinct forms:
  - vitamin D2 – ergocalciferol
  - vitamin D3 – cholecalciferol
- cholecalciferol is the natural form in animals; it is what we make in our skins on exposure to UV-B light

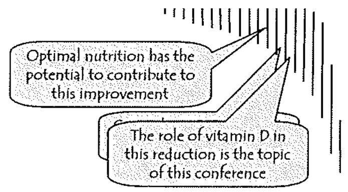
CU ORC

31

THEORETICAL MORTALITY CURVE

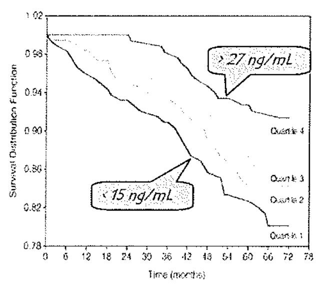
THEORETICAL MORTALITY CURVE

SQUARING THE MORTALITY CURVE



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



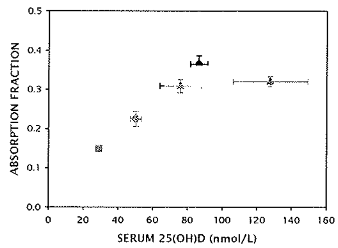
* Semba et al. (2009) Nutr Res 29:525-530

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)

CU ORC

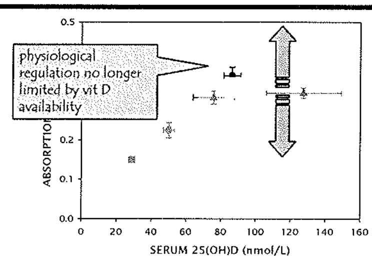
A VITAMIN D THRESHOLD



CU ORC

37

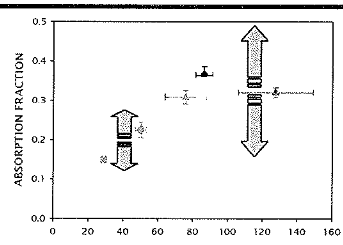
A VITAMIN D THRESHOLD



CU ORC

38

A VITAMIN D THRESHOLD

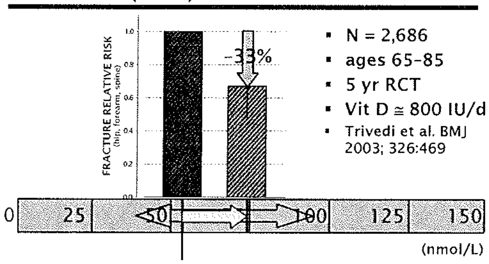


CU ORC

39

Skeletal outcomes

THE 25(OH)D CONTINUUM

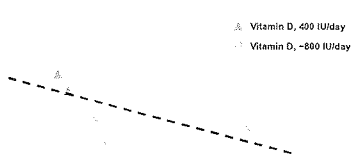


- N = 2,686
- ages 65-85
- 5 yr RCT
- Vit D ≅ 800 IU/d
- Trivedi et al. BMJ 2003; 326:469

CU ORC

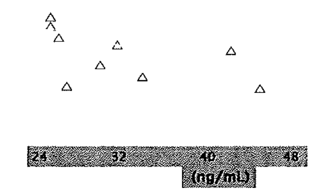
41

ACHIEVED 25(OH)D & HIP FRACTURE*



*Redrawn from Bischoff-Ferrari et al. *JAMA*. 2005;293:2257–2264

ACHIEVED 25(OH)D & NON-VERT FX*



* Redrawn from Bischoff-Ferrari et al. (2009) Arch Int Med; 169:551–561

VITAMIN D & OSTEOMALACIA

- 675 autopsy cases
- static histo-morphometry on iliac crest
- osteoid volume evaluated as a function of vitamin D status
- Priemel et al., JBMR 2010; 25:305-12

osteoid accumulation is the histological hallmark of

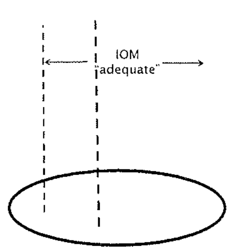
normally osteoid is mineralized within few days of its deposition; if it accumulates that means there is a mineral deficit

CU ORC

44

VITAMIN D & OSTEOMALACIA

- autopsy cases
- N = 675
- static histo-morphometry
- osteoid volume evaluated as a function of vitamin D status
- Priemel et al., JBMR 2010; 25:305-12

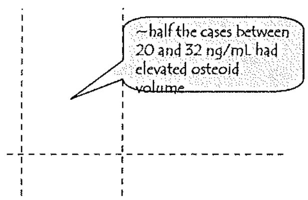


CU ORC

45

VITAMIN D & OSTEOMALACIA

- autopsy cases
- N = 675
- static histo-morphometry
- osteoid volume evaluated as a function of vitamin D status
- Priemel et al., JBMR 2010 25:305-12



CU ORC

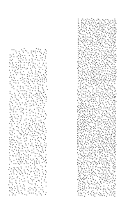
VITAMIN D & OSTEOMALACIA

- 121 postmenopausal women
- S. Australia
- seasonal differences in dynamic histomorphometric variables
- Need et al., JBMR 2007; 72:757-61

CU ORC

VITAMIN D & OSTEOMALACIA

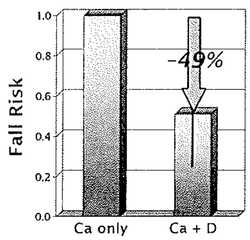
- 121 postmenopausal women
- S. Australia
- seasonal differences in histomorphometric variables
- Need et al., JBMR 2007; 72:757-61



CU ORC

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



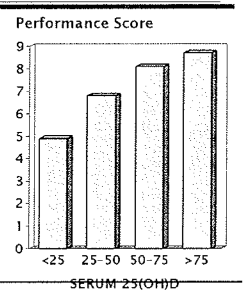
CU ORC

*Bischoff et al. *JBMR* 2003:18:343-351

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

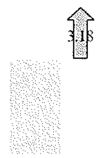


*Wicherts et al. JBMR 2006 CU ORC

Cardiovascular outcomes

VIT D & BLOOD PRESSURE*

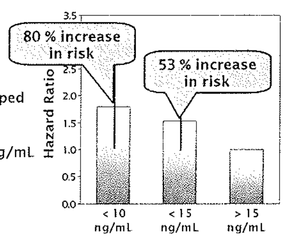
- 1811 men & women with measured 25(OH)D levels**
- 4 yrs' observation
- 97 cases of incident hypertension
- RR computed for 25(OH)D <15ng/mL vs. >30 ng/mL



*Forman at al., 2007;Hypertension 49:1063
** Health Profs Follow-up Study & Nurses Health Study

VIT D & CARDIOVASCULAR DISEASE

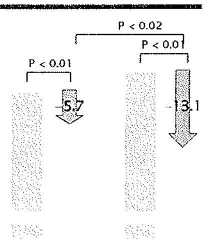
- 1739 Framingham Offspring members
- age: 59 yrs
- follow-up: 5.4 yrs
- 120 individuals developed a CV event
- HR calculated against 25(OH)D values > 15 ng/mL
- *Wang et al. Circulation 2008*



CU ORC

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



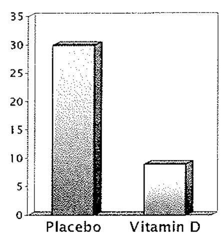
*Pfeifer et al., JCEM 2001; 86:1633-37

CU ORC

Immune system outcomes

VITAMIN D & INFLUENZA*

- 208 African-American, postmenopausal women
- 3 yr DB-RCT
- placebo or vit D_3
  - 800 IU/d - 2 yrs
  - 2000 IU/d - 3rd yr
- basal 25(OH)D: 18.8 ± 7.5
- P < 0.002



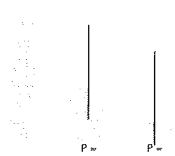
CU ORC

*Aloia & U-Ng (2007) Epidemiol & Infect

56

VITAMIN D & INFLUENZA*

- DB-RCT
- winter 2008-2009
- 334 Japanese school children, aged 6-15
- mean wt: 35.5 kg
- 1200 IU D_3/d in addition to self-supplementation



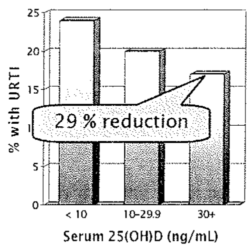
CU ORC

*Urashima et al., AJCN 2010

57

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

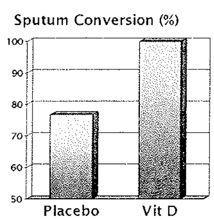


CU ORC

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

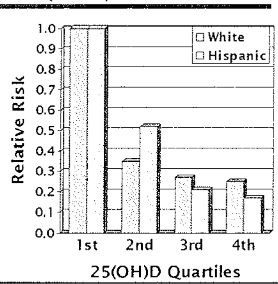


CU ORC

*Nursyam et al., Acta Med Indones 2006

DIABETES & 25(OH)D

- Scragg et al., 2004 Diabetes Care 27:2813-18
- NHANES-III
- 6,228 adults
- plasma glucose independently predicted by BMI & serum 25OHD (fasting and 2 hr post load)

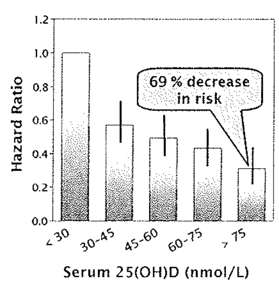


CU ORC

Cancer outcomes

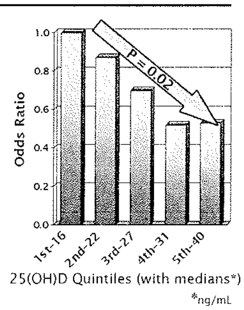
BREAST CANCER RISK

- Case-control study
  - 1394 cases
  - 1365 controls
- Odds ratio for CA inversely associated with vit D status [25(OH)D]
- *Abbas et al., Carcinogenesis (2008) 29:93-99*



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*

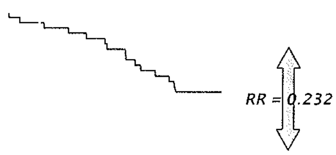
- 1179 healthy women
- aged 66.7 ± 7.3
- four year trial
- 1032 finished (87.5%)
- baseline 25(OH)D: 28 ng/mL ± 8
- three treatment groups:
  - control
  - Ca (1400-1500 mg/d)
  - Ca plus D_3 (1100 IU/d)
- achieved 25(OH)D: 38 ng/mL ± 9

CU ORC

*Lappe et al. AJCN 2007

64

VITAMIN D & CANCER*



*Lappe et al AJCN 2007

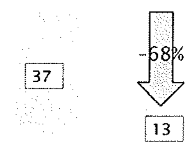
CANCERS BY TREATMENT (YRS 2-4)

Site	Placebo (n=266)	Ca+D (n = 403)
Breast	7 (2.6%)	4 (1.0%)
Colon	2 (0.7%)	0 (0.0%)
Lung	3 (1.1%)	1 (0.2%)
Marrow/Lymphoma	4 (1.5%)	2(0.5%)
Other	2 (0.7%)	1 (0.2%)
Total	18 (6.8%)	8 (2.0%)*

* P < 0.05

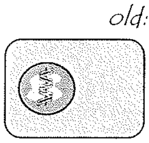
CANCER RISK (ALL)

- N = 1,179
- ages 55-85
- 4 yr RCT
- Vit D ≅ 1100 IU/d
- median achieved serum 25(OH)D = 29 ng/mL
- Lappe et al. AJCN 2007



How is it that a single nutrient could have such diverse effects in so many body systems?

CELL MODELS



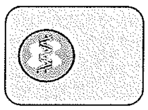
old: DNA in somatic cells functions mainly to make faithful copies for tissue repair or replacement

new: DNA functions constantly in synthesis of needed cellular apparatus

CU CRC

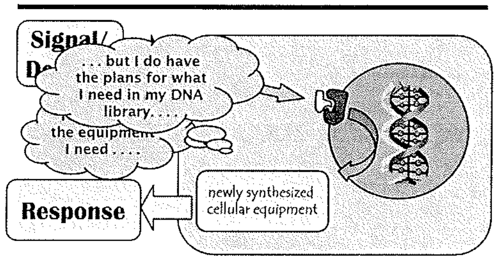
CELL MODELS

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

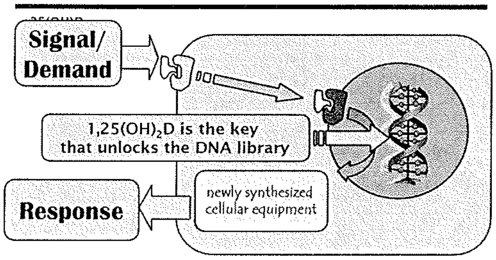


new: cell/tissue differentiation meant that only certain genes can be accessed in each tissue

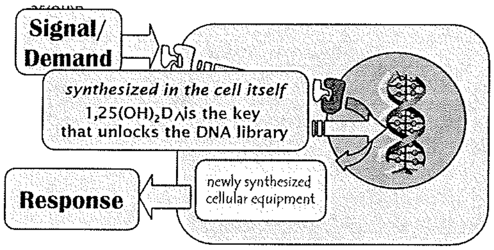
HOW A CELL RESPONDS



HOW A CELL RESPONDS



HOW A CELL RESPONDS



CU ORC

73

VIT D – CANONICAL SCHEME

skin liver kidney gut

D_3 ⇒ 25(OH)D_3 ⇒ 1,25(OH)$_2$D$_3$ ⇒ CaBP

- the functional indicator of vit D status
- a principal storage form of the vitamin

CU ORC

74

OLD VIT D – CANONICAL SCHEME

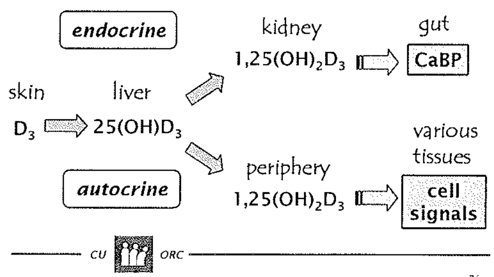
skin liver kidney gut

D_3 ⇒ 25(OH)D_3 ⇒ 1,25(OH)$_2$D$_3$ ⇒ CaBP

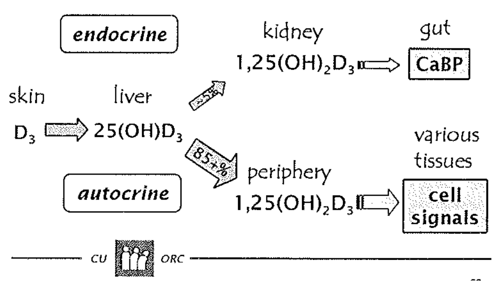
CU ORC

75

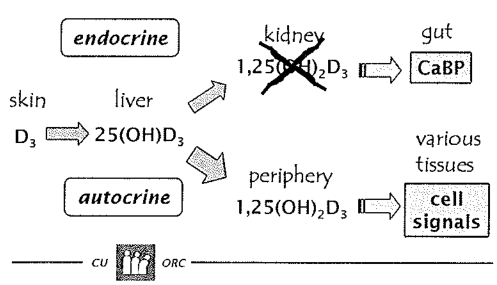
VIT D – EXPANDED SCHEME

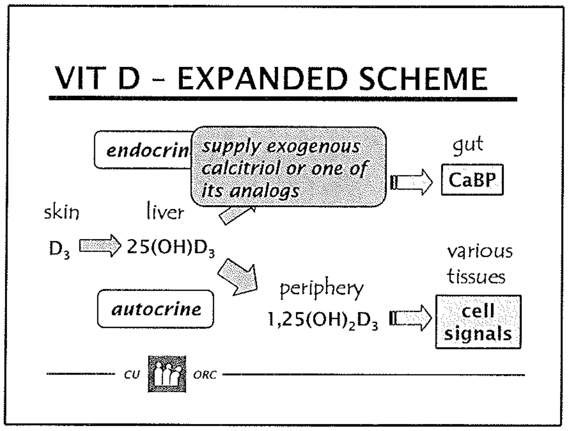


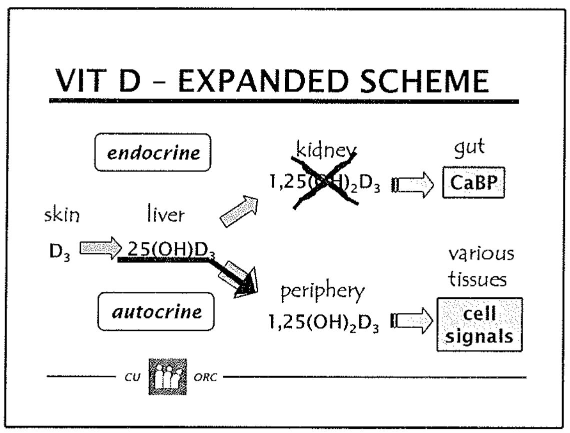
VIT D – EXPANDED SCHEME

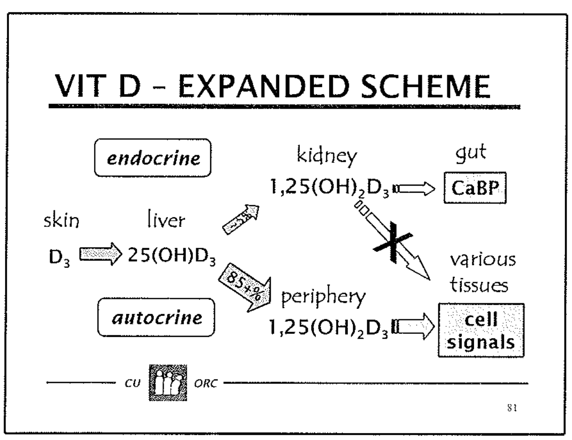


VIT D – EXPANDED SCHEME

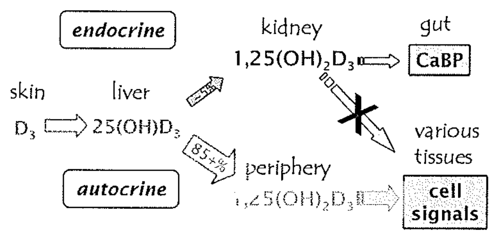



VIT D – EXPANDED SCHEME
endocrin
supply exogenous calcitriol or one of its analogs
gut
CaBP
skin
liver
D3
25(OH)D3
various tissues
periphery
autocrine
1,25(OH)2D3
cell signals
CU
ORC


VIT D – EXPANDED SCHEME
endocrine
kidney
1,25(OH)2D3
gut
CaBP
skin
liver
D3
25(OH)D3
various tissues
periphery
autocrine
1,25(OH)2D3
cell signals
CU
ORC


VIT D – EXPANDED SCHEME
endocrine
kidney
1,25(OH)2D3
gut
CaBP
skin
liver
D3
25(OH)D3
85+%
various tissues
periphery
autocrine
1,25(OH)2D3
cell signals
CU
ORC
81

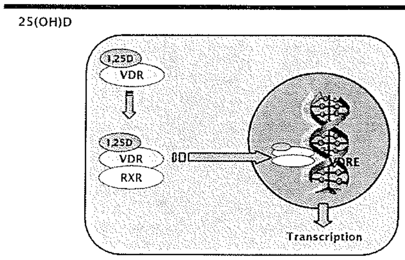
VIT D – EXPANDED SCHEME



CU ORC

82

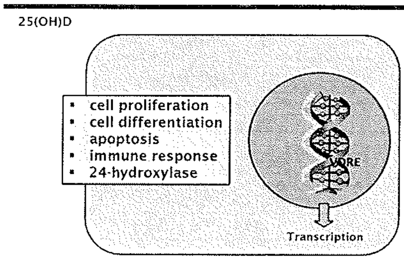
AUTOCRINE ACTION



CU ORC

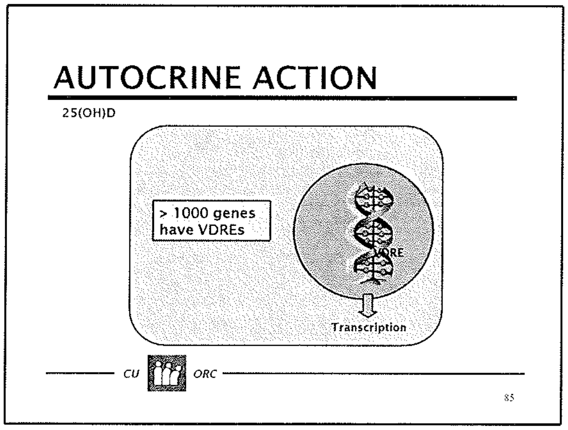
83

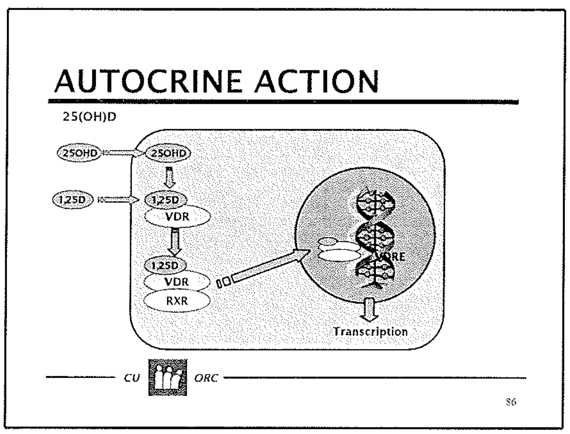
AUTOCRINE ACTION

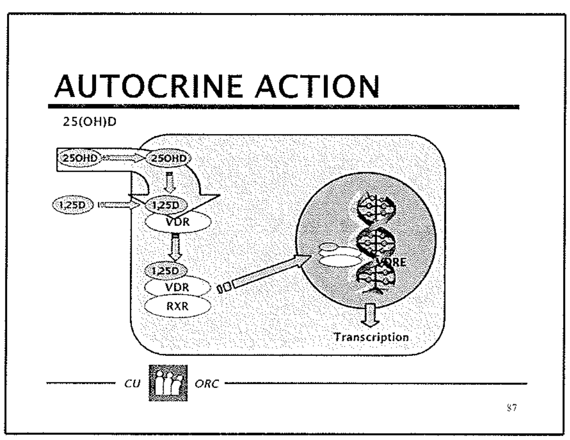


CU ORC

84


AUTOCRINE ACTION
25(OH)D
> 1000 genes have VDREs
VDRE
Transcription
CU ORC
85


AUTOCRINE ACTION
25(OH)D
25OHD
25OHD
1,25D
1,25D
VDR
1,25D
VDR
RXR
VDRE
Transcription
CU ORC
86


AUTOCRINE ACTION
25(OH)D
25OHD
25OHD
1,25D
1,25D
VDR
1,25D
VDR
RXR
VDRE
Transcription
CU ORC
87

This scheme means that each tissue

- has the amount of $1,25(OH)_2D$ it needs
- when it needs it
- and is not dependent upon a "one-size-fits all" systemic level of circulating $1,25(OH)_2D$

Management

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 $1,25(OH)_2D$ does not measure vit D status (instead, it measures Ca need)

CU ORC

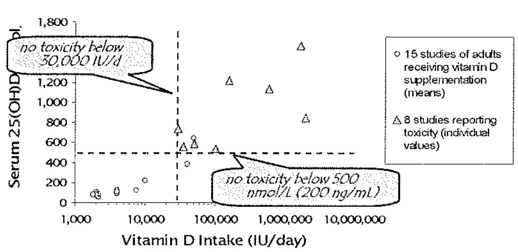
AN APPROACH TO VIT D REPLETION

- aim for serum 25(OH)D of 40 to 60 ng/mL
- as a first approximation assume a ***total*** needed input (all sources) of 75 IU/kg/d
- but: know that individual response varies hugely (6-fold range!); so monitor effect at ~120 day intervals
- many MDs prefer to use larger doses at the outset of treatment (e.g., 3X the expected daily dose daily for the 1st 3 weeks)

CU ORC

Safety

VITAMIN D INTAKE & TOXICITY*



* Hathcock JN et al. *Am J Clin Nutr.* 2007;85:6–18.

CONCLUSIONS

- serum 25(OH)D levels below 32 ng/mL are not adequate for any body system
- levels of as high as 50 ng/mL may be closer to optimal
- inputs from all sources combined (needed to sustain 32 ng/mL) are in the range of ~4,000 IU/d and higher
- in most healthy adults, 2000-3000 IU/d, in addition to all other inputs, will usually suffice

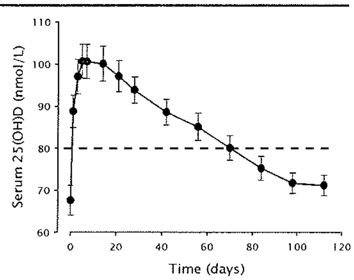
CU ORC

94

Thank you

25(OH)D RESPONSE TO LARGE DOSES*

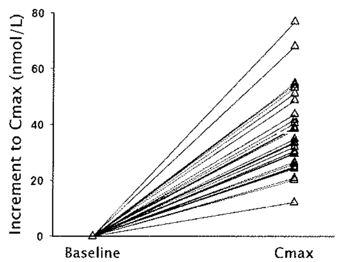
- 100,000 IU D_3, by mouth, once



*Ilahi, Armas, & Heaney (in press)

VARIABILITY OF 25(OH)D RESPONSE*

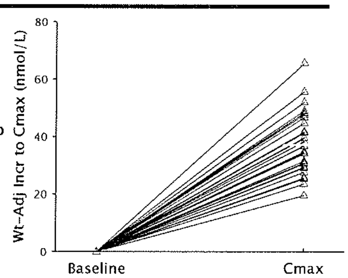
- Δ 25(OH)D to C_{max} ranged from +12 nmol/L to +76 nmol/L
- ~half of the variability due to body size



*Ilahi, Armas, & Heaney (AJCN 2008)

VARIABILITY OF 25(OH)D RESPONSE*

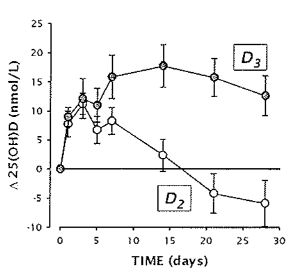
- Wt-adjusted Δ 25(OH)D to C_{max} ranged from +20 nmol/L to +66 nmol/L



*Ilahi, Armas, & Heaney (in press)

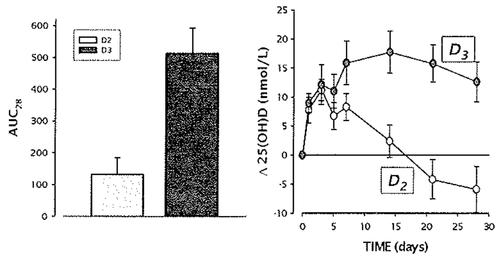
D_2 vs. D_3*

- single oral dose
- 50,000 IU
- D_2 or D_3
- n = 10 in each group



*Armas et al., 2004

D_2 vs. D_3* - AUC



*Armas et al., 2004