Epidemic of Vitamin D deficiency: fact or fiction?
Controversies galore!
Neil R. M. Buehler, MD, FRCPE
Metabolic Unit, Oregon Health & Science U.
Portland OR
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I was an external consultant for ZRT Labs

Lecture objectives
At the end of this session attendees should know:
- The basic relationships between vitamin D, PTH, calcium and phosphorus.
- The manifestations of D deficiency in children and differential Dx of rickets.
- The controversy and effect of D supplementation in adult bone disorders.
- The current controversy re D levels and other adult onset disorders.
- The indications for assay of plasma D levels and the normal range.

Vitamin D and Icebergs!
Nutritional rickets & osteomalacia are the visible part
This part sinks the Titanic! osteoporosis etc
Invisible but clinically important?
What did Rumsfeld say??

7-Dehydrocholesterol
Previtamin D 3
UV Light B, [290-315A]
Liver
Kidney *
[Cholecalciferol]
Ergocalciferol D2 [plants]
Diet 200-500IU/day
Supplement 500-2000IU/day
25-OH D3
1,25-diOH D3
inactive metabolites

• -penia: "Not a diagnosis: it describes lack or loss of bone volume and structural quality. Causes: Osteogenesis Imperfecta, inadequate calcium or vit D, immobility (includes osteoporosis).
• -porosis: "Decalcification resulting in loss of bone tissue, enlargement of marrow and Haversian canal spaces, reduced thickness of cortex and structural weakness".
• -malaica: "Failure to calcify due to lack of available Ca, also known as adult rickets, due to vitamin D deficiency".
• Rickets: "Failure to calcify due to lack of available Ca and due to vitamin D deficiency".

Diet
Ca 1000mg, Vit D 400 IU, P 1000mg
Plasma calcium & mineral homeostasis
PTH
TCT
20% absorbed
80% stools
magnesium
80% absorbed
20% stools
pH
**Actions of Vitamin D**

- Works through a standard steroid receptor system
- **Gut**: Increases Ca & P absorption
- **Bone**: Increases Osteocalcin & osteoclasts and new bone formation
- **Kidney**: Increases Ca & P reabsorption

All aimed at maintaining plasma Ca level especially when combined with PTH activity

**Other actions of Vitamin D?**

**Rickets: History**

Known in neolithic & bronze age skeletons
- China 300 BC, Mediterranean 2000 years ago
- Epidemic started in 17th C
- 1822: Rural kids not affected v. city kids
- 1827: Cure by cod liver oil [but not used much]
- 1890: Not common in Orient v. N Europe – Boston 80%, Austria 90%

- 1919: Cure by UV light
- 1930s: D added to milk
- 1950s: “Epidemic” of D toxicity
- 1960s: Biochemistry worked out

The name “rickets” is from the Old English “wrickken”, to twist.

Animals can get rickets too!

Even at the London Zoo!

**Causes of D deficiency - rickets**

- **Environment** – Winter, latitude, pollution, Ca deficiency
- **Personal** – Clothes, exposures, diet, sun phobia
- **Racial** – Color, customs, clothes, diet
- **Maternal** – Poor supply during pregnancy

- Elderly – Indoor living
- GI – Steatorrhea, CF, celiac, surgical
- Hepatic – Alcoholism, chronic liver disease, bile duct abnormalities, Niagil syndrome, bile acid defects, 25-OHylase defect
- Renal – Chronic renal disease, renal Fanconi syndrome, 1-OHylase defect
- Other – Medications, Obesity, Some Malignancies, D-receptor defects, tumoral
Dietary lack of vitamin D

– Of course! But what specifically?
– Unfortified milk feeding
– Milk avoidance [e.g., lactase deficiency]
– Breast feeding
– Cultural differences in food choices [usually migrated populations from tropics]
– Natural food faddists & anti-supplementarians
– Health foods
– Home grown foods

Sunbathing and vitamin D

• UV-A and -B both cause skin aging, malignancy etc
• A MED [Minimum Erythema Dose] of UV-B generates approximately 20,000 IU pro-vitamin D3. In mid-summer, this takes about 15-30 min.
• With dark skin, the time required for this increases by > 5 fold.
• Spf 8 reduces precursor D synthesis by ~85%.
• In Portland, the winter sun is too weak to generate any D precursors in skin.
• UV-A penetrates glass; UV-B does not

Heliophobia!

Afghanistan: 2004
Burkhas and Swaddling

Overt Clinical Rickets

- Growth slowing with swollen metaphyses
- “Rachitic Rosary”
- Hypotonia, slow development [e.g., standing, walking]
- Irritable, often due to bone pain
- Eventually bone malformation
- Frequent infections
- Tetany, “Laryngismus stridulus” [stridor], seizures
- Hot cross bun skull, craniotabes

London 1889
Idaho 1989
Oregon 1970-89

Weight bearing limbs!

Swollen metaphyses

Nutritional Rickets "Rachitic rosary" at costochondral junction

5 mo: note "Hot X bun" skull
Severe rickets
"Bone-within-bone"

Severe Osteomalacia
With pseudofractures
"Looser's nodes"

Vitamin D deficiency due to Medical Causes I
GI Disorders
- Liver diseases [failure of 25-OH-ylase to function]
- Pancreatitis
- Inflammatory bowel disease
- Bypass and Short bowel syndromes [83%]
- Malabsorption:
  - Bile acid secretion problems
  - Cystic Fibrosis [90%]
  - Celiac disease [~70%]

Cantorna MT. Am J Clin Nutr 80:1252,2004

Vitamin D deficiency due to Medical Causes II
- Renal failure
  - Renal tubular damage [1-OH-ylase activity]
  - Special note in Fanconi Syndrome
    - proximal renal tubular damage
    - eg: cystinosis, galactosemia
- Obesity
- Some cancers [eg: Lymphoma]

Medications and vitamin D metabolism
Several medications especially phenobarbital & dilantin [not valproate] stimulate the p450 enzymes that are involved in 25 and 1,25 OH-D synthesis and also in their inactivation
  - Also lovastatin, clarithromycin, cyclosporin, triazolam, diltiazem, estrogens etc

Some caveats also with weight reduction medications, calcipotriene, steroids

Drugs that affect the calcium system such as thiazides, verapamil, Ca channel blockers etc

Absorption of atorvastatin can be reduced
MedlinePlus 2/24/11
Vitamin D deficiency in the tropics: 2006-07
Ethiopia “Rachitic rosary” ? due to Ca & P deficiency not Vit D lack

One-two percent of pediatric admissions to hospital in Addis Abba have active rickets.
In China 65%, Delhi India, 90% the Middle-East, 25-50%, Africa, 30%, New Zealand 80% of women AND CHILDREN have biochemical or clinical evidence of D deficiency.
Active rickets reported in “many infants” admitted to hospitals in India.

Treatment of D deficiency in Children

[1000 IU=25 mcg]
New AAP recommendations [Nov ’08]
DRI (~RDA): Infants and children 400 IU/day

• Infants with low Vit D “Insufficient/Asymptomatic”:
1000-3000 IU/day for several weeks/months till 25-OH D level is normal.

• Active rickets/osteomalacia:
1. 10-20,000 IU/day till all levels normal. Weeks or months
2. 300-400,000 IU IMl if follow up is unlikely.
3. Rocaltrol [1,25 di-OH D] 1-2 mcg/day PO or IV if tetany till stable then D3 3000-5000IU/day.

Hereditary Vit D dependent rickets

Vit D Dependent Rickets Type I due to 1-OHylase deficiency [OMIM 264700]
Severe disease, requires 1,25-OH D₃

Vit D Dependent Rickets due to 25-OHylase deficiency [OMIM 600081]
Very rare, requires 1,25-OH D₃

Vit D Dependent Rickets Type II due to abnormal D receptor[s] [OMIM 277400]
Severe & mild forms, alopecia, little response to Rx [comparable to other steroid receptor defects]

Early effects of vitamin D in rickets ~2 weeks

3 weeks Rx
6 weeks Rx

Cure!
6-10 weeks

Prolonged Overtreatment

Rare cases of hypercalcemia led to decades of worry about potential problems with high doses of Vitamin D

Worries about Vitamin D overdose

- Too high intake could lead to hypercalcemia, renal stones and calcification*.
- In a group of healthy men, increasing Vit D intake from baseline to 40,000 iu/day for 3 months increased the plasma Vit D levels from 35 to >160 ng/mL.
- Neither the plasma calcium nor the urine Ca/Creatinine ratio increased.

*About 1/100 people have “idiopathic hypercalcuria” due to overabsorption of Ca in the gut. This clearly raises the risk of stones in such people

EVEN SO, THIS IS NOT RECOMMENDED!

Plasma 25(OH)D reflects oral Vitamin D$_3$ intake

Calcium and Vit D recommendations

Daily Recommended Intakes [~the old RDAs]

<table>
<thead>
<tr>
<th>Age</th>
<th>Ca mg/d</th>
<th>Vit D IU US*</th>
<th>Canada**</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLBW</td>
<td>210</td>
<td>200</td>
<td>200-400+</td>
</tr>
<tr>
<td>6-12 mo</td>
<td>500</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>1-3 yrs</td>
<td>800</td>
<td>600</td>
<td>600-800</td>
</tr>
<tr>
<td>4-8 yrs</td>
<td>1300</td>
<td>600</td>
<td>800-1200</td>
</tr>
<tr>
<td>Teens</td>
<td>1300</td>
<td>600</td>
<td>800-1200</td>
</tr>
<tr>
<td>Adult/Preg/BF</td>
<td>600-800</td>
<td>2000</td>
<td></td>
</tr>
</tbody>
</table>

* The Institute of Medicine USA: 2010
** Canadian Pediatric Soc. 2007

1000 IU = 25 mcg
### Calcium and Vit D recommendations

#### Daily Recommended Intakes [-the old RDAs]

<table>
<thead>
<tr>
<th>Age</th>
<th>Ca mg/d</th>
<th>Vit D IU US*</th>
<th>Canada**</th>
<th>CA Pediatr.#</th>
<th>Vit D council</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLBW</td>
<td>160-200</td>
<td>200-400+</td>
<td>400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-12 mo</td>
<td>210</td>
<td>400</td>
<td>400+</td>
<td>400</td>
<td>BF1000, F 600</td>
</tr>
<tr>
<td>1-3 yrs</td>
<td>500</td>
<td>400-800</td>
<td>400-4000</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>4-8 yrs</td>
<td>800</td>
<td>400</td>
<td>800-1200</td>
<td>400-4000</td>
<td>1500</td>
</tr>
<tr>
<td>Teens</td>
<td>1300</td>
<td>400</td>
<td>800-1200</td>
<td>400-4000</td>
<td>2000</td>
</tr>
<tr>
<td>Adult/Preg/BF</td>
<td>400-600</td>
<td>1-2000</td>
<td>600-4000</td>
<td>4-6000***</td>
<td></td>
</tr>
</tbody>
</table>

* The Institute of Medicine USA: 2010
** Canadian Pediatric Soc: 2007
# CA Pediatrician 2011
*** 1000 IU/d added should eventually raise plasma 25 OH D levels by ~10ng/mL

### Controversies about Vitamin D

- How do you define deficiency?
- Is there an “epidemic” of deficiency?
- What should be the accepted “normal” level?
- What should the DRIs for infants, children, adults/elderly, pregnancy, lactation etc be?
- Might doses be different for children v. adults?
- How likely is a prolonged high D intake to cause hypercalcemia?
- What is the role of Vit D in other apparently unrelated disorders?

### Normal values of 25-OH Vitamin D

**CAVEAT: Units! 1 ng/mL = 2.5 nmol/L**

- Depends on who you ask!
  - Literature reports? >30ng/mL
  - Population studies? Depends where you are! >15ng/mL
  - Optimal physiological effects? >40ng/mL
- IOM: 2010 >20ng/mL
- US Endocrine Society 2011 >30ng/mL

**Normal lab values in Portland [30ng/mL=75nmol/L]**
- OHSU[ARUP]: Kaiser, Legacy, ZRT Labs. >30 ng/mL
- $90-130

### Increasing plasma level to ~30 ng/mL

- 20 → 35 ng/mL increases Ca absorption by 45-60% / Am Calc Res 2003
- 12 → 30ng/mL increases insulin sensitivity by ~60% / Am J Clin Nutr: 2004
- 15 → 40 ng/mL reduces colon cancer risk by ~50% / Cancer Epidemiol: 2004
  - US Nurse study, 400 IU/day reduced MS risk by 60%
  - Finland: 2000 IU for yrs 0-1 Type 1 JODM reduced by 80% after 30 yrs / The Lancet 2001
  - Several studies: reduced incidence of DM by ~30% / Diabetes Care 2006
  - Low levels associated with increased rates of breast cancer / Breast cancer res 2007

#### The Iceberg & Vitamin D levels

- Rickets/Osteomalacia < 10-15 ng/mL
- Long-term bone problems? <30ng/mL

**If so, over how long and at what age?**

- Maximal Ca absorption minimal PTH levels 35-40 ng/mL
- Sunbathing levels 60-80 ng/mL

**What about all the other associations?**
- Cancer? Diabetes? MS??

### Deficiency “Insufficiency” Normal

<table>
<thead>
<tr>
<th>Plasma Vitamin D levels ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>30</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>60</td>
</tr>
</tbody>
</table>

**Deficiency** "Insufficiency" **Normal**
Plasma 25-OH D was measured in 40 healthy, mostly Black, mother-infant pairs. Although a majority of mothers received a daily prenatal multivitamin, vitamin D deficiency (<12 ng/mL)* was found in 50% of mothers and 65% of their newborn infants, with a positive correlation between maternal and infant plasma 25-OH D concentrations. Maternal vitamin D deficiency may represent an important risk factor for the development of rickets in children.” [USA]

*Note: Normal level is >30ng/mL: 12ng/mL is already low!

Pregnancy and breastfeeding

Pregnancy and breastfeeding – 2007

* Pittsburgh – 54% Afr/Amer and 42% white on prenatal vits. had values <80nmol/L. For their babies, 47 & 56% had low values. [Bodner LM, J Nutr: 137]
* Boston – 50% mums on prenatal vitamins. and 65% offspring had values <30 nmol/L [Lee JM, Clin Pediatr. 46]
* Europe – >50% “Asian women”, 8% European had values <25 nmol/L [Van der Meer, Am J Clin Nutr. 84]
* UK – low values in pregnancy correlate to low bone density in offspring at 9yo. [Javait MK, Lancet: 367]

• Many reports: 5 fold increase in preclampsia with low D levels

Vitamin D in Breast Milk

“Normal” breast milk contains ~25-50 IU/L, infant formulae contain ~ 250-600 IU/L

- "It is a well known fact that human milk is a poor source of vitamin D for the nursing infant”.
- This is wrong! Maternal vitamin D supplementation can satisfy both maternal and infant requirements

- “There does not appear to be an increased need for vitamin D during lactation despite accelerated bone loss” [IOM 2010]

Increased D intake and breast milk D levels

Maternal Supplementation with 6,400 IU Vitamin D3/day (n=6)

<table>
<thead>
<tr>
<th>Vitamin D$_3$ (nmol/L ± SD)</th>
<th>Mother</th>
<th>1 mo</th>
<th>3 mo</th>
<th>6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_0$</td>
<td>11.5 ± 10</td>
<td>80 ± 30</td>
<td>97 ± 67</td>
<td>117 ± 47</td>
</tr>
<tr>
<td>25(OH) D$_3$ (nmol/L ± SD)</td>
<td>Baby</td>
<td>14 ± 6</td>
<td>36 ± 8</td>
<td>115 ± 23</td>
</tr>
<tr>
<td>Milk Activity (IU/L)</td>
<td>90 ± 27</td>
<td>403 ± 173</td>
<td>379 ± 202</td>
<td>782 ± 429</td>
</tr>
</tbody>
</table>

Normal plasma >80-160 nmol/L (~30-60 ng/ml)

Congenital Rickets – China 1994
There is a difference between long-term Vit D and Calcium homeostasis

- For the first ~30 years we try our best to build Ca stores with the aid of D, diet, hormones and exercise.
- For the next 20 years our bodies try and retain Ca using the same approaches.
- Eventually, the loss of Ca and bone protein develops at rates that depend on D, diet, hormones, exercise and genetics.
- Vitamin D levels are pretty much the same throughout life
- Requirements of D to get maximum benefit are not clear, but seem to be much higher than currently recommended.
- If the plan is to stash away as much Ca in the early years then D intake should be more aggressive at that time.
- Attempts to restore Ca levels at advanced ages with Ca, D or any other approach are much less effective.

Adults - Vitamin D deficiency and fracture risk

- Vitamin D insufficiency
  - Serum Ca
  - Raised PTH
  - Bone absorption
  - Muscle weakness
  - Increased falls
  - Increased fracture risk

Vitamin D levels and risk of fracture: 216 people with prior stroke, 2 years

- IOM thinks that there might be some validity in this

WHI Calcium-Vitamin D Study

- 36,000 postmenopausal women ages 50-79 randomly assigned to receive 1000 mg calcium and 400 IU D3 daily or placebo
- With treatment,
  - Total hip BMD increased 1%
  - No effect on hip fracture risk
  - Renal stones increased 17%

- Conclusions
  - Calcium and vitamin supplements of no benefit

Vitamin D deficiency and renal disease: a retrospective study

- 80% had levels <31ng/mL
- Rx 50,000 IU/week/24 weeks
- Results:
  - Plasma 25 OH D 9.0 increased to 25 ng/mL [p=<.0005]
  - HgB A1C fell 6.9-6.0% [p<0.0005]

Vitamin D and Diabetes

Joslin Clinic: 81% JODM had insufficient levels and 15% were severely low (2008).
- D affects the immune system that relates to islet cell functions (Matthieu, 2006).
- 29% reduction in DM after D supplements of 400 IU from infancy for up to 30 years (Epelis, 2009).
- Finland: Higher D levels in men reduced incidence of DM by 70% (Michos, 2009).
- No association between D and JODM (Diabetol. 2011).
- Higher D levels associated with lower Type II severity (Diabetes 2011).
- Association with at least 3 D related genes and JODM (Diabetes 2011).

Vitamin D and immunoregulation

- Many immune cells can convert 25-D to 1,25-D and can use it.
- 1,25-D is Involved in T-cell and suppressor cell activity.

Serum 25-(OH) D levels and risk of Multiple Sclerosis

- >7 million US military personnel.
- Used stored blood samples.
- 300 individuals with MS, 610 Controls.
  - Average age at MS onset was 28 y.
  - 57/30 % White/Black.
  - Elevated 25(OH)D levels in Whites more protective at younger ages.
  - Individuals <20 years old with average 25(OH)D ≥40 ng/mL had 91% reduction in MS risk vs. average <40 ng/mL.
  
JAMA 296, Munger et al. (2006)

- 40% reduction in new MS events with 40,000 IU/DAY X 1 year in 40 patients.
  
Neurology 2011; Burton

Vitamin D and cancer

Early breast Ca: 37% deficient, 38% insufficient.
- Deficiency increased risk of recurrence and death (J Clin Oncol 2009).
- 11 studies: Highest levels reduced rates by ~50%.
- Prostate: 120 men: 40% deficient, 32% insufficient.
- Deficiency increases the risk of death. (B J Urol Int 2009).
- Controls: 31% deficient, 40% insufficient.
- Colon: 33% lower risk with the higher blood levels (J Clin Oncol. 2011).

What does all this mean????????

National Cancer Institute - 2010

- Suggests D intakes LOWER than current recommendations.
- "Tolerable" upper intake ~1000IU/day.
- Colon: Probably but "not proven".
- Breast: No association shown.
- Prostate: No association shown.
- Pancreas: Possible INCREASE with higher levels.
- Hodgkins, ovary, stomach, kidney, endometrium: no associations.

Any associations might be related to genetic variants in the D receptor.

NCI Factsheet 2010

National Institute of Medicine: Dec 1st 2010

The IOM proposes new Dietary Reference Intakes (DRIs) that are based on more information and higher-quality studies than were available when these values were set in 1997. The IOM finds that the evidence supports a role for vitamin D and calcium in bone health but not in other health conditions. Further, emerging evidence indicates that too much of these nutrients may be harmful, challenging the concept that "more is better."
Previous reports of an epidemic of vitamin D deficiency in North America were based on an overestimation of adequacy. Population screening with serum 25OHD is therefore not warranted. Current laboratory reference ranges for serum 25OHD are overestimated and should be revised. Practice guidelines to treat disease should not be applied to the healthy American population where use of the DRI is appropriate.


Only in the past two years have we been able to glimpse at the true role of vitamin D in overall health.

The extra-skeletal health benefits of vitamin D we now know are numerous, ranging from inhibition of smooth muscle cell migration, suppression of vascular calcification, down-regulation of pro-inflammatory cytokines and up-regulation of anti-inflammatory cytokines. Anti-cancer effects involve multiple immunomodulatory properties.

MedlinePlus 2/24/11

Prevalence of hypovitaminosis D in the general population [of the UK] was alarmingly high during the winter and spring, which warrants action at a population level rather than at a risk group level.

[15.5% in winter, 3.2% in summer]

“There is no smoke without fire”!

So what should we be doing?

- Decide which side of the controversy you’re on!
- Decide what levels you would like to see
- Think about levels in your “at risk” populations
- Think about what levels you would like for yourself
- To raise levels by 10ng/mL need to give an additional 1000IU/day for at least 3 months
- To prevent long-term bone etc problems need to give an additional ?????????
### Takeaway points 1
- Vitamin D deficiency/insufficiency is resurgent even in the developed world including the US
- We do not think twice about screening for iron deficiency or even for lead levels – why not for vitamin D status?
- Demand for assay in the US is rising rapidly
- Sales of D3 have increased x10 in the last 10 years
- Practitioners should now consider screening for 25-OH-D levels at least in at-risk populations.
- Shoot for levels at least >30 ng/mL [75nmol/L]

### Takeaway points 2
- Dose required to raise levels >30 ng/mL may be 5-10x higher than the DRI.
- Overt clinical rickets, once recognized by all, is not on most practitioners’ radar and the diagnosis is usually missed.
- D deficiency in adults is usually occult unless found on bone scan or after fracture
- It is high time that Oregon conducted a survey of 25-OH-D levels in its susceptible populations with a plan for subsequent public health action.

### Good references
- AAP FAQs: http://www.aap.org/family/vitdpatients.htm
- NIH, Office of Dietary Supplements: http://ods.od.nih.gov/factsheets/vitamind.asp#h4
- www.grassrootshealth.org: A D-evangelical web site
- Aloia JF. J Clin Endo Metab: 96. 2011, pp. 2987-2996

### What does the Cochrane Group say?
- Where are the RCTs?????
- Synthesizing the literature was challenging!
- Elderly: 6% reduction in mortality using D3
- Pregnancy: possible relation to SGA births
- MS: Unclear

### The end!
The risks for nutritional deficiencies will never die even if we defeat every other disease of mankind. They remain in the wings until our guard is lowered, our awareness is diverted, our nutritional habits are altered and they will then pounce again and again!

### Dangers with Supplements
- Additives considered unsafe: Aconite, bitter orange, chaparral, colloidal silver, coltsfoot, comfrey, country mallow, germanium, greater celandine, kava, lobelia, and yohimbe. The FDA has warned about at least eight of them.
- Always use a product that is USP verified

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**Thankyou**
We may be able to defeat every other disease of mankind, but nutritional deficiencies can never be defeated or forgotten. They remain as specters in the wings until our guard is lowered, our awareness is diverted, our nutritional habits are altered and they will then pounce again and again!

First good descriptions in 17th C

King James VI had rickets

25(OH) vitamin D concentrations according to daily vitamin D intake

Vitamin D and cancer

Early breast Ca: 37% deficient, 38% insufficient.
Deficiency increased risk of recurrence and death

11 studies: Highest levels reduced rates by ~50%

Prostate: 120 men: 40% deficient, 32% insufficient.
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Colon: 33% lower risk with the higher blood levels

What does all this mean???????
A bone of contention?

- What level causes overt bone disease? <10ng/mL
- What level prevents all overt bone disease? >30-35ng/mL
- If so over what period of time? ??????????
- What level maximizes Ca absorption and minimizes PTH levels >35-40ng/mL
- Levels that sunbathers readily achieve suggesting an evolutionary connection with sun exposure and D homeostasis 40-80 ng/mL

Baseline
Calcium only
4,000 IU/d Vit D3
8,000 IU/d Vit D3
16,000 IU/d Vit D3
32,000 IU/d Vit D3

Plasma 25-D ng/ml
12 25 30 36 55 65

Urine Calcium:creatinine Ratio
Baseline
Calcium only
4,000 IU/d Vit D3
8,000 IU/d Vit D3
16,000 IU/d Vit D3
32,000 IU/d Vit D3

Schwachmann Syndrome

Alagille syndrome
AD inheritance, variable expression
Bile duct hypoplasia [Static or progressive]
"Broad forehead, pointed chin, big nose"
Pul. Stenosis & Peripheral Pul. Stenosis
Malabsorption/steatorrhea

Vitamin D deficiency in the tropics: 2006-07 reports
- One-two percent of pediatric admissions to hospital in Addis Ababa have active rickets.
- In China 65%, Delhi India, 90% the Middle-East, 25-50%, Africa, 30%, New Zealand 60% of women AND CHILDREN have biochemical or clinical evidence of D deficiency.
- Active rickets reported in "many infants" admitted to hospitals in India.

Lack of sunlight
- Dark skin, Northern climes, cold weather, city dwelling, air pollution.
- Clothing habits [eg: Burka in Muslims]
- Sun phobia with excessive protection by clothing and high Spf lotions
- Indoor living, as in the elderly
Emerging vitamin D deficiency

- Insufficiency: <30 ng/mL
- Mild deficiency: reduced 25-OH D only [<20 ng/mL]
- Early bone disease: 25-OH D <15 ng/mL + rising PTH
- Moderate: 25-OH D <5 ng/mL, PTH & Alk Phos

- Overt clinical rickets: +/- Ca & PO₄
- Advanced: 25-OH D very low, Ca & PO₄ low
  Alk phos & PTH high

1,25 di-OH D₃ [Calcitriol] Normal: 20-40 pg/ml, 56-112 pmol/L:

**NOTE:** it is usually increased in D deficiency