Does the “D” in Vitamin D stand for Diabetes?

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Experts: Paucity of vitamin D is a crisis

Low levels linked to diabetes, arthritis, cancer, experts say
Study: Exercise, tea and vitamin D to ward off dementia

The Miracle of Vitamin D: Sound Science, or Hype?

By TARA PARKER-POPE
• This may be sitting on your waiting room table right now!
• Our patients are also interested in the possible relationship between vitamin D and diabetes
The “Sunshine” Vitamin

- Fat-soluble vitamin; cholesterol derived pre-vitamin in dermis
- Created in skin when 20% of skin is exposed to UVB radiation 5-15 minutes per day –
- Natural food sources: fatty fish, egg yolks, beef liver
- Fortified foods: milk, cereal, energy bars
What is “Vitamin” D?

• Vitamins
  – Essential substances derived from the diet
  – Cannot be synthesized by the human body

• Hormones
  – Naturally occurring substances
  – Synthesized by special cells within the body
  – Affect functions of other cells that possess a receptor for that hormone

• Vitamin D – both a vitamin and a hormone
  – Is obtained from the diet, but also made by the skin
  – Its structure and receptor activity resemble those of steroid hormones
Foods with Vitamin D

Salmon
3 oz = 794 IU

Fortified cereal
1 cup = 40 IU

Fortified milk
1 cup = 120 IU

Egg yolk
40 IU

How many of your patients eat 3 ounces salmon a day?
UVB

Cutaneous Formation of Vitamin D

7-DHC, provitamin D₃

SKIN

Vitamin D₃

KIDNEY

VitD-25-hydroxylase

25(OH)VitD

LIVER

1-α hydroxylase

1,25(OH)₂ Vitamin D
35th Latitude – significant vitamin D deficiency is likely to occur 8-9 months of the year in more northern regions
Clinical Manifestations of Osteomalacia

<table>
<thead>
<tr>
<th>Presenting Symptom</th>
<th>Percent</th>
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<tbody>
<tr>
<td>Bone pain</td>
<td>94%</td>
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<tr>
<td>Muscle weakness</td>
<td>94%</td>
</tr>
<tr>
<td>Fracture</td>
<td>76%</td>
</tr>
<tr>
<td>Waddling gait</td>
<td>24%</td>
</tr>
<tr>
<td>Difficulty walking</td>
<td>12%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>12%</td>
</tr>
<tr>
<td>Cramps</td>
<td>12%</td>
</tr>
<tr>
<td>Tingling/numbness</td>
<td>6%</td>
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</table>
Pseudofractures in osteomalacia  Looser-Milkman pseudofractures of the pelvis and left femoral neck (arrows) in a patient with osteomalacia. Courtesy of CJ Menkes, MD.
Vitamin D Fracture Prevention Meta-analysis

• Pooled all double-blind RCT’s that studied vitamin D supplementation
• Must include hip and nonvertebral fracture data with followup of at least one year
• Mean age ≥60
• Must include 25(OH)vitD measurement
• Most studies included calcium in control and treatment groups

Bischoff-Ferrari et al, May 11, 2005, JAMA 293(18)2257-2264
Vitamin D Results
Meta-analysis of 7 RCT’s

25(OH)VitD ng/mL

Control
Baseline: 14.72
Follow-up: 15.3

Treatment
Baseline: 14.72
Follow-up: 31.68

Bischoff-Ferrari et al, May 11, 2005, JAMA 293(18)2257-2264
Significant Fracture Reduction

Bischoff-Ferrari et al, May 11, 2005, JAMA 293(18)2257-2264
Fracture Reduction with Vitamin D

- Significant reduction only observed in the studies where treatment dose was 700-800IU/day
- Greater fracture reduction was achieved with higher serum 25(OH)vitD levels
  - 26% reduction in hip fractures
  - 23% reduction in non-vertebral fractures
- 35% reduction in falls with improvement in muscle strength
Intestinal Calcium Absorption

Compiled from Bischoff et al, Heaney et al, Barger-Lux et al
What about the rest of the body?

- VDR (vitamin D receptor) found in almost every system – so it must have role in those cells, right?
- Links to vitamin D in the literature:
  - Prostate and colon cancer
  - Dementia
  - Multiple sclerosis
  - Rheumatoid arthritis and fibromyalgia
  - Immune function and influence on cytokines
  - Cardiovascular disease
  - Type 1 and Type 2 Diabetes
  - And many others
Vitamin D and the β cell and insulin receptors

- Pancreatic β cells express the VDR but also 1-α-hydroxylase enzyme
- Insulin secretion is calcium-dependent
  - Calcium or vit D def may decrease glucose-mediated insulin secretion – rat studies
  - Vitamin D suppl improved insulin release in a few small studies
- Vitamin D may have effect on insulin action by stimulating expression of insulin receptor
  - Obs studies show inverse relationship between vitamin D status and insulin resistance
Observational Human Studies

• The role of vitamin D in Type 1 and 2 DM is suggested by multiple observations:
  – Control is worse in the winter – also a time of hypovitaminosis D
  – Nurse’s Health Study: women who took in avg of 1200mg calcium and 800 IU D daily had 33% lower risk of developing Type 2 DM than those who took the lowest amount of calcium and vitamin D (<400uD)
  – NHANES: Vitamin D had inverse relationship with both diabetes prevalence and measures of insulin resistance (HOMA-R)
    • Not seen in blacks
Observational studies, cont

- Study of 10,000 Finnish Children
- Those taking 2,000IU daily associated with 80% reduction in Type 1
- Children with Rickets had the highest rate of type 1 DM
Calcium intake and Type 2 DM

• WHI – calcium intake was inversely associated with the prevalence of metabolic syndrome
• Nurses Health Study – calcium intake was inversely associated with incidence of Type 2 DM
• Both adjusted for vitamin D intake
• Calcium repletion alone normalized glucose tolerance and insulin secretion in vitamin D deficient rats
• In one small study of diabetics, an oral calcium load augments glucose-induced insulin secretion
But . . .

• Observational studies don’t always adjust for education, activity level, generalized interest in being healthy
• Wintertime is also when we exercise less and eat more and celebrate the holidays
• Increased adiposity causes great sequestration of vitamin D with varying vitamin D requirements for sufficiency
• Should only serve as a springboard upon which to hypothesize and then plan randomized, controlled trials
Preclinical Type 1 DM Trials

- Calcitriol has been found in some studies to prevent lymphocyte proliferation and cytokine production.
- In NOD mouse calcitriol protects against insulinitis.
Type 1 DM and Vitamin D

- Pathogenesis of type 1DM: autoimmune destruction of pancreatic islet cells
- This process may be initiated by the release of self-reactive T cells, which then promote a progression which includes cytokine involvement in pancreatic islet destruction
- There’s an important genetic influence, however:
  - Low concordance among identical twins
  - Those with genetic predisposition frequently do NOT develop Type 1 DM
  - People in Finland are 400x more like to develop diabetes than those in Venezuela
  - Therefore, there must be an environmental factor
Vitamin D and immunomodulation

• Interacts with vitamin D response elements in the promoter region of cytokine genes to interfere with nuclear transcription factors implicated in cytokine generation
• Found to down-regulate nuclear factor κβ, which promotes proinflammatory cytokines
• Interferes with cytokine generation by up-regulating expression of calbindin – this protects against cytokine-induced apoptosis
EURODIAB Study

• Multicenter study in Europe
• Case/control study – included pts with onset of diabetes before age 15 and controls without diabetes
• Assessment of dietary intake of vitamin D using questionnaires and interviews
• Result: increased exposure to vitamin D in infancy resulted in an OR of 0.67 for the development of Type 1 DM

EURODIAB, cont

- Relied on mother’s recollection of supplements given to their children in the first year of life – the average age of the child was 11
- No 25(OH)vitamin D levels were known
- Time of onset of DM not reported
- Type/amount of vitamin D not quantified

2008 Meta-analysis

- 5 observational studies looking at use of vitamin D in infancy to reduce type 1 DM
- All based upon interviews & questionnaires
- One study from Norway did note a sig reduction in use of cod liver oil 5x per week versus <5x/week, OR 0.81

Zi[its CS, Akobeng AK, Arch Dis Child 2008;93:512-517
Does vitamin D supplementation improve Type 2 control?

- 36 subjects with Type 2 DM, age 21-75 with DM for at least one year, treated with metformin + hs basal insulin
- Randomized to vitamin D 40,000 units once a week x 6 months or placebo

<table>
<thead>
<tr>
<th></th>
<th>Baseline values</th>
<th>Change from baseline after 6 months (delta values)</th>
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<tbody>
<tr>
<td></td>
<td>Vitamin D group</td>
<td>Placebo group</td>
</tr>
<tr>
<td>Males/females</td>
<td>9/7</td>
<td>9/7</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.7 ± 9.7</td>
<td>54.8 ± 5.9</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>25.0</td>
<td>18.8</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>32.8 ± 6.8</td>
<td>31.3 ± 6.3</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>1.01 ± 0.08</td>
<td>0.99 ± 0.08</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>138.1 ± 14.0</td>
<td>132.6 ± 13.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79.4 ± 9.0</td>
<td>81.5 ± 9.1</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>9.8 ± 3.1</td>
<td>9.2 ± 2.4</td>
</tr>
<tr>
<td>Serum insulin (pmol/L)</td>
<td>376 ± 454</td>
<td>372 ± 539</td>
</tr>
<tr>
<td>Serum C-peptide (pmol/L)</td>
<td>1,163 ± 581</td>
<td>1,035 ± 478</td>
</tr>
<tr>
<td>Serum fructosamine (µmol/L)</td>
<td>267 ± 51</td>
<td>269 ± 34</td>
</tr>
<tr>
<td>HbA&lt;sub&gt;1c&lt;/sub&gt; (%)</td>
<td>8.0 ± 1.3</td>
<td>7.9 ± 1.1</td>
</tr>
<tr>
<td>HOMA–Insulin secretion [(pmol/L)/(mmol/L)]</td>
<td>229 ± 252</td>
<td>258 ± 496</td>
</tr>
<tr>
<td>HOMA–Insulin resistance [(pmol/L) × (mmol/L)]</td>
<td>27.6 ± 34.3</td>
<td>25.0 ± 30.7</td>
</tr>
<tr>
<td>Serum calcium (mmol/L)</td>
<td>2.35 ± 0.06</td>
<td>2.39 ± 0.09</td>
</tr>
<tr>
<td>Serum PTH (pmol/L)</td>
<td>3.9 ± 3.6</td>
<td>4.0 ± 1.6</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>63.4 ± 12.8</td>
<td>66.2 ± 8.4</td>
</tr>
<tr>
<td>Serum 25(OH)D (nmol/L)</td>
<td><strong>60.0 ± 14.0</strong></td>
<td><strong>58.5 ± 21.0</strong></td>
</tr>
<tr>
<td>Serum cholesterol (mmol/L)</td>
<td>4.5 ± 1.1</td>
<td>4.8 ± 0.9</td>
</tr>
<tr>
<td>Serum triglycerides (mmol/L)</td>
<td>1.6 ± 0.7</td>
<td>1.5 ± 0.6</td>
</tr>
<tr>
<td>Serum HDL-cholesterol (mmol/L)</td>
<td>1.3 ± 0.3</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>Serum LDL-cholesterol (mmol/L)</td>
<td>3.0 ± 1.0</td>
<td>3.3 ± 0.8</td>
</tr>
<tr>
<td>24 h urinary calcium excretion (mg)</td>
<td>5.1 ± 3.0</td>
<td>5.3 ± 2.9</td>
</tr>
</tbody>
</table>

<sup>a</sup> Vitamin D group versus placebo group regarding delta values.
Glucose Tolerance and vitamin D

- 33 adults without diabetes (12 with metabolic syndrome, 21 with normal glucose metabolism) with vitamin D insufficiency were given two doses of 100,000 u cholecalciferol 2 weeks apart
- There was a significant increase in vitamin D from baseline
- No significant difference seen in blood glucose, insulin levels or insulin sensitivity as assessed by an oral glucose tolerance test

Tai K et al, Nutrition 2008;24:950-956
Vitamin D and Type 2 DM

- Ljunghall randomized 65 middle-aged men with IGT or mild DM and sufficient vitamin D levels at baseline (avg 38) to 0.75mcg calcitriol vs. placebo for 3 mo
  - No effect on fasting or stimulated glucose tolerance
- In another crossover trial, 20pts with Type 2 DM and vitamin D deficiency were treated for 4d with 1ug/d of calcitriol
  - No change seen in glucose, insulin or c-peptide concentrations
What should we recommend?

• There is currently no clear evidence that vitamin D supplementation reduces the onset of Type 1 DM, Type 2 DM or the severity of disease in a current diabetic

• Vitamin D supplementation is recommended in infancy, especially to breast-fed infants, to improve skeletal growth and formation

• Large, randomized, double-blind, placebo controlled trials would be needed to more definitively establish a role of vitamin D in the setting of diabetes prevention
Recommended vitamin D supplementation

- Current recommendations include calcium 1200mg qd for adults over 50 yr
- Vitamin D: adults 51-70, 400 units/day; for those over 70 – 600 units per day
- The main consensus is that optimal vitamin D blood levels for bone health and fall prevention is 30-40 ng/mL
  - This typically requires a maintenance daily vitamin D intake of 800 units

Vitamin D goals:

- Deficiency: <10-12
- Insufficiency: <30-32
- Goal: 32 – 80 or 100
- Potential toxicity: >100 – 110
- Vitamin D sufficiency is indicated to prevent secondary hyperparathyroidism, potentially to reduce fractures and to improve muscle strength/reduce falls
Hopefully our Buckeyes are all Vitamin D Sufficient!