Vitamin D and Inflammation

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Liver

Vitamin D

25(OH)D

storage form

nmol/l=ng/ml x 2.5
Renal 1,25(OH)$_2$D Production

25(OH)D

\[ \rightarrow \]

1,25(OH)$_2$D

*active form*
Extra-Renal $1,25(OH)_2D$ Production

25(OH)D $\rightarrow$ 1,25(OH)$_2$D active form
Vitamin D and Inflammation: Cell and Animal Studies

Good evidence that 1,25(OH)$_2$D contributes to regulating the immune response and inflammation

- VDR in immune system cells and 1,25(OH)$_2$D$_2$ hydroxylase in dendritic cells and macrophages suggest autocrine/paracrine actions at site of inflammation

- Cell culture evidence suggests that 1,25(OH)$_2$D can down regulate production of pro-inflammatory cytokines by immune cells

- VDR KO mice develop chronic inflammation in GI tract

Yu et al. PNAS 105:20834-20839, 2008
Flores M. Nutr Res Rev 18:175-82, 2005
Vitamin D and Inflammation: Human Studies

• Much less direct evidence in human studies

• **Extensive** evidence from observational studies that vitamin D influences risk for conditions having an inflammatory component

• BUT uncontrolled confounding is a possibility because many third factors are associated with both vitamin D levels and disease risk, e.g. obesity, time spent outside, age

• Limited and often flawed trial data
Evidence from Human Studies of Vitamin D Associations with Autoimmune and Inflammatory Conditions

- multiple sclerosis
- rheumatoid arthritis
- inflammatory bowel disease
- Crohn’s disease
- systemic lupus erythematosus
- periodontal disease
- hypertension/arteriosclerosis/other CVD
- type 2 diabetes mellitus
Changes in Markers of Inflammation

- 38 vitamin D deficient Bangladeshi-British adults age 35-65
- 25(OH)D
  - pre: 8.6 ng/ml (21 nmol/l)
  - post: 14.1 ng/ml (35 nmol/l)
- 1 year supplementation with 3-monthly vitamin D injection
- no control group
- (n=24-38)
Inflammatory Bowel Disease

Retrospective study in 504 patients with inflammatory bowel disease

50% deficient, 11% severely deficient

In Crohn’s disease and ulcerative colitis, vitamin D deficiency associated with higher disease activity and poorer quality of life.

Presented by A. Ulitsky at 2009 meeting of the American College of Gastroenterology
PERIODONTAL DISEASE: Adj. B (mm) for Periodontal Attachment Loss by Quintile of 25(OH)D (relative to Q5)

NHANES III

NHANES III linked to mortality files
3408 adults age 65+ followed median 7.3 years

Risk of CVD and Non-CVD Mortality by 25(OH)D

Ginde AA et al., JAGS 57:1595, 2009
Women’s Health Initiative\(^1\)

36,282 women age 50-79 randomized to placebo or 1000 mg/d Ca + 400 IU/d D3 followed for 7 years

Lappe et al.\(^2\) estimate 25(OH)D increase to have been \(\approx 2\) ng/ml

\(^1\)Margolis KL et al., Hypertension 52:847-55, 2008.

Women’s Health Initiative

33,951 women age 50-79 randomized to placebo or 1000 mg/d Ca + 400 IU/d D3 followed for 7 years

Per-protocol results above.
ITT results, $P=0.72$

de Boer et al., Diabetes Care 31:701-7, 2008.
The Association of Vitamin D with Physical and Cognitive Function

- good evidence from observational studies and some trials
- effects may be due to actions of vitamin D that are independent of its anti-inflammatory role
60 older men and women

--- adj. age, sex, hs-CRP
----- unadjusted

--- adj. age, sex, 25(OH)D
----- unadjusted

Boxer RS et al., JAGS 56:454, 2008
Prevalence of Dementia, AD, and Stroke by 25(OH)D Status

J.S. Buell
Patient Populations

• Few studies except in chronic kidney disease

• Many effects may be more pronounced in patient populations due to
  – more profound D deficiency
  – potential need for greater 25(OH)D substrate
264 Hospitalized Alzheimer’s patients mean age 72 yrs Japan, latitude 32° N (≈ San Diego)

Sunlight exposure for 15 min. per day on clear days vs.
Usual low sun exposure (83% had none)

Sato et al., J Bone Miner Res, 2005
Vitamin D in Chronic Kidney Disease

• 1,25(OH)_2D declines in kidney disease due to reduced renal mass for conversion of 25(OH)D and also because of increased fibroblast growth factor-23

• Large observational studies demonstrate reduced mortality with administration of 1,25(OH)_2D or analogs
  – Tentori, Kidney Int 70:1858, 2006

• It may also be desirable to supplement these patients with 25(OH)D as substrate for autocrine/paracrine functions – this has received much less research attention
Association of Calcitriol Treatment with Mortality in CKD

520 male US veterans, mean age 69.8
CKD stage 3-5, not yet receiving dialysis

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Evidence from Observational Studies</th>
<th>Evidence from Vitamin D Intervention Studies</th>
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</thead>
<tbody>
<tr>
<td>Vitamin D affects immune response and inflammation in cells, animals</td>
<td>--</td>
<td>strong – many, varied studies</td>
</tr>
<tr>
<td>Vitamin D affects markers of inflammation in human studies</td>
<td>limited – few studies</td>
<td>limited – few studies</td>
</tr>
<tr>
<td>Vitamin D affects markers/precursors for diseases with inflammatory component</td>
<td>moderate – many studies, some large</td>
<td>limited – few studies, most small</td>
</tr>
<tr>
<td>Vitamin D affects prevalence/incidence of diseases with inflammatory component</td>
<td>moderate – many studies, some large</td>
<td>limited except for bone &amp; falls</td>
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<tr>
<td>Vitamin D affects patient survival</td>
<td>good for CKD patients, otherwise limited</td>
<td>very limited to non-existent</td>
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Ongoing Trials

Trials of vitamin D supplementation in older adults are now underway to look at effects on

- Cardiovascular Disease
  - Hypertension
  - Hypercholesterolemia
  - Metabolic Syndrome

- Type 2 Diabetes Mellitus
  - Insulin Resistance
  - Glucose Intolerance

- Systemic Lupus Erythematosus

- Asthma

- Chronic Obstructive Pulmonary Disease

Clinicaltrials.gov
Considerations for Future Intervention Studies

- Lack of effect in prior studies may often have been due to inclusion of subjects with relatively high baseline 25(OH)D – focus should be on those with known or suspected deficiency
- Lack of effect also results from inadequate 25(OH)D step up – critical to choose high enough dose and attain high adherence rates
- Frail, ill elderly are the most likely to benefit but have been little studied except with respect to bone and falls
## Multiple Sclerosis Risk

<table>
<thead>
<tr>
<th>Vitamin D levels (nmol/L)</th>
<th>OR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>15.2 – 63.2</td>
<td>1.0</td>
</tr>
<tr>
<td>63.3 – 75.3</td>
<td>0.57 (0.30-1.07)</td>
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<tr>
<td>75.4 – 84.8</td>
<td>0.57 (0.30-1.07)</td>
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<tr>
<td>84.9 – 99.1</td>
<td>0.74 (0.40-1.36)</td>
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<tr>
<td>99.2 – 152.9</td>
<td>0.38 (0.19-0.75)*</td>
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Case Control: 148 cases, 296 controls

*P = .006

White men & women only. Black & Hispanic: not significant (potentially due to lower numbers of cases).

RCT: Calcium, Vitamin D and Cancer Incidence

- **Ca + 1100 IU vit D / day**
  - RR=0.23

- **1400-1500 mg Ca / day**
  - RR=0.59

- Placebo
  - reference

1179 healthy postmenopausal women

Lappe JM et al., Am J Clin Nutr 2007:1586
Meta-Analysis of Vitamin D and Falls

Iowa Women’s Health Study:
Adj. RR of Rheumatoid Arthritis

Merlino LA et al., Arthritis and Rheumatism 50:72, 2004
Health Professionals Follow-Up Study

Adj. RR of Myocardial Infarction

P-trend 0.02

Nested case-control in 18,225 men followed for 10 years

Giovannucci et al, Arch Int Med 2008
Falls

- Considerable trial data supports protective effect of vitamin D supplementation ≥ 800 IU/d on falls in elderly
  - Bischoff-Ferrari JAMA 293:2257, 2005 (meta-analysis)

- No effect seen in some large, well-conducted studies possibly due to
  - low baseline risk of falls
  - small 25(OH)D step-up due to high starting value, low dose or poor compliance (e.g. RECORD Trial: Grant, Lancet 365:1621, 2005)
Obesity and Vitamin D Status

381 healthy adults >= 65 yrs
adjusted for sex, age, vitamin D intake, season, sun exposure

Harris SS & Dawson-Hughes B, JCEM 2007:3155
Meta-Analysis:
RCTs of oral vitamin D supplementation
Adults age 65+

Bischoff-Ferrari et al. JAMA 2005
NHANES III: Time to Stand