From A to Zinc: the evolving concept of micronutrient supplementation

Turning patients into baywatchers: extra-skeletal effects of vitamin D, from diabetes to ICU

R. Rizzoli (CH)
Vitamin D: Extraskeletal Multiple Benefits?

René Rizzoli MD

Division of Bone Diseases
Geneva University Hospitals and Faculty of Medicine
1211 Geneva 14, Switzerland
Vitamin D Deficiency ->
Impaired Bone Mineralisation

Impaired Mineralisation: **Rickets** versus **Osteomalacia**
Vitamin D metabolism

UV light → Skin
Diet → Vitamin D (cholecalciferol)

1,25(OH)₂D₃ → Target organs

- Specific Nuclear Receptors
- PTH
- Hypocalcemia
- Hypophosphatemia
- IGF-I
MÖLLER'S COD-LIVER OIL

Gained the ONLY FIRST PRIZES at the Great Exhibitions of LONDON, PARIS, Etc.

It is now universally conceded that the quality of Cod-Liver Oil depends upon the condition of the Fish. The Lofoten Waters in Norway are the only known district where the Cod migrates for spawning, and in excellent condition. Hence the well-known superiority of Lofoten Oil; many reject the light brown on account of its unpleasant taste, usually from being improperly prepared. In the case of Moller's Oil, however, prepared at Lofoten, a Pure Oil, distinctly different to the Pale Norwegian, retaining all the curative virtues with a remarkably pure smell and taste.

The late Physician to the North London Consumptive Hospital, Abbott Smith, M.D., M.R.C.P., affirms that Moller's Oil is readily retained by delicate persons and more efficacious.

The Medical Society of Norway has, through its leading members, testified that Moller's Oil is preferred for its medicinal properties.

Dr. L. A. Levee, Professor of Orthopedic Surgery in Bellevue Hospital Medical College, New York, says: "In three years it has been almost impossible to get any Cod-Liver Oil that patients can digest, owing to the objectionable taste of procuring and preparing the fish. * * Moller's Oil, which is perfectly pure, and, in every respect, all that can be wished." Dr. L. A. Levee, before Academy of Medicine, See Medical Record, Dec. 1889, p. 641.

Dr. J. M. Mason, D.S.O., says: "For many years I have given up the use of Cod-Liver Oil altogether, but since my attention was called to Moller's Oil, I have prescribed it almost daily, and have every reason to be perfectly satisfied with it."

SOLD BY DRUGGISTS.

W. H. Schaeffer & Co., 170 & 172 William Street, New York,
SOLE AGENTS FOR THE UNITED STATES AND CANADAS.
Causes of Vitamin D Deficiency

1. Reduced Skin Synthesis
   Sunscreen, Veil, Aging, Season, Skin Pigment

2. Decreased Availability
   Malabsorption, Obesity

3. Increased Catabolism / Loss
   Anticonvulsants, HAART, Nephrotic Syndrom

4. Breast-feeding

5. Decreased 25-OH-D Synthesis
   Liver Failure

6. Decreased 1,25-(OH)2-D Synthesis
   CKD, Vitamin D-dependent Rickets
   X-Linked Hypophosphatemia,
   AD Hypophosphatemia, Oncogenic Osteomalacia
25-OH-D Levels: Definitions

1. **Deficiency** (< 25 nmol/l) -> Mineralization Defect
2. **Insufficiency** (< 50 nmol/l) -> Increased Bone Turnover and/or PTH
3. **Sufficiency (Suboptimal)** (50-75 nmol/l) -> Neutral Effect (General Population)
4. **Optimal** (> 75 nmol/l) -> Desiderable Benefits on Falls & Fracture (Osteoporotic Patients)
Risk Factors for Vitamin D Inadequacy
Serum 25(OH)D <75 nmol/l (multivariate analysis)

- Race (Asian)
- Race (Other)
- BMI (>30 kg/m²)
- Latitude (non-equatorial)
- Inadequate Vit D Supplement Use (<400 IU daily)
- Inadequate Vit D Supplement Use (none)
- General Health (Poor/Fair)
- No MD discussion about vitamin D
- Difficulty tanning
- No recent travel to sunny area

Rizzoli et al, 2006
Threshold Assessment for the Risk of Fracture, According to Quartile of Baseline 25-Hydroxyvitamin D Level

4383 participants ≥ 65 yrs with baseline 25-OH-D levels

Baseline serum 25-OH-D ≥ 61 nmol/l vs < 30 nmol/l:

- ↓ 37% risk of hip fracture (HR, 0.63; 95% CI, 0.46 to 0.87)
- ↓ 31% risk of any nonvertebral fracture (HR, 0.69; 95% CI, 0.57 to 0.84)

After adjustment for study, group assignment (treatment or control), age group, sex, and type of dwelling

Bischoff-Ferrari et al. NEJM 2012
Meta-analysis of Combined Calcium and Vitamin D Effects on Fracture Risk

12 Randomized Controlled Trials:

RR = 0.88 (0.79 – 0.99)

For the US Preventive Services Task Force

Chung et al Ann Int Med 2011
FIGURE 1. Plots of the cumulative incidence of fractures, redrawn from the studies of Chapuy et al (17) (right) and Dawson-Hughes et al (18) (left). In both cases, the upper line represents the placebo control subjects and the lower line represents the subjects treated with calcium and vitamin D. The shaded zones represent the reduction of fracture risk, which, as can be readily seen, starts with the beginning of treatment. (Copyright Robert P Heaney, 2004. Used with permission.)
In situ Detection of VDR in Human Muscle Tissue

Number of VDRs decreases with age among 32 women age 21 – 91 yrs with hip or spine surgery (p = .047)

Bischoff-Ferrari HA et al. JBMR 2004

Human muscle:
Brown staining in muscle nuclei indicate presence of VDR
Lack of Vitamin D Receptor in Rat/Mouse Muscle

Wang & DeLuca Endocr 2011

Rat

Duodenum (D6)

Skeletal Muscle (D6)

Skeletal Muscle (IgG)

Skeletal Muscle (D6 + DAPI)

Mouse Muscle

A

WT: D6/DAPI

E

WT: 9A7/DAPI

B

KO: D6/DAPI

F

KO: 9A7/DAPI

C

WT: IgG/DAPI

G

WT: IgG/DAPI

D

WT: DAPI

H

Kidney: D6
Dose-response for 25-OH-D and function

NHANES III: n = 4100 community-dwelling older individuals age 60+

8-Foot walk

Repeated sit-to-stand

Effect was similar between more or less active individuals, men or women, calcium intake

Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials

H A Bischoff-Ferrari, director of centre on aging and mobility,12 B Dawson-Hughes, director of bone metabolism laboratory,3 H B Staehelin, professor emeritus,4 J E Orav, associate professor of biostatistics,5 A E Stuck, professor of geriatrics,6 R Theiler, head of rheumatology,7 J B Wong, professor of medicine,8 A Egli, fellow,1 D P Kiel, associate professor of medicine,9 J Henschkowsk, fellow16

**High dose vitamin D**

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prince et al(^{w3})</td>
<td>1.10 (0.89 to 1.35)</td>
</tr>
<tr>
<td>Broe et al(^{w1})</td>
<td>1.20 (0.97 to 1.47)</td>
</tr>
<tr>
<td>Flicker et al(^{w4})</td>
<td>1.00 (0.71 to 1.42)</td>
</tr>
<tr>
<td>Bischoff-Ferrari et al(^{w2})</td>
<td>1.10 (0.71 to 1.67)</td>
</tr>
<tr>
<td>Pfeifer et al(^{w5})</td>
<td>1.10 (0.71 to 1.67)</td>
</tr>
<tr>
<td>Bischoff et al(^{w6})</td>
<td>1.10 (0.71 to 1.67)</td>
</tr>
<tr>
<td>Pfeifer et al(^{w7})</td>
<td>1.10 (0.71 to 1.67)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.81 (0.71 to 0.92)</td>
</tr>
</tbody>
</table>

**Low dose vitamin D**

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broe et al(^{w1}) (200 IU D(_2)/day)</td>
<td>1.10 (0.71 to 1.67)</td>
</tr>
<tr>
<td>Broe et al(^{w1}) (400 IU D(_2)/day)</td>
<td>1.10 (0.71 to 1.67)</td>
</tr>
<tr>
<td>Broe et al(^{w1}) (600 IU D(_2)/day)</td>
<td>1.10 (0.71 to 1.67)</td>
</tr>
<tr>
<td>Graafmans et al(^{w8})</td>
<td>1.10 (0.71 to 1.67)</td>
</tr>
<tr>
<td>Combined</td>
<td>1.10 (0.89 to 1.35)</td>
</tr>
</tbody>
</table>

**Dose of vitamin D\(_2\) or vitamin D\(_3\) (IU)**

**Fall prevention by 25-hydroxyvitamin D\(_3\) level**

**25-hydroxyvitamin D\(_3\) serum concentration (nmol/l)**
Causality in Biological Systems

1. Strength of the Association
2. Consistency of the Results
3. Dose-Response Relationship
4. Understanding of the Mechanisms
5. Experimental Verification

Hill, 1965; Potischman 1999; Weed 2000
Accuracy of 25-hydroxyvitamin D Assays (vs isotope dilution/solid-phase extraction liquid chromatography/mass spectrophotometry)

According to the assay:
- slope different from 1.0
- intercept different from 0.0
- values are patients-dependent

<table>
<thead>
<tr>
<th></th>
<th>Elecsys vs Mass Spect.</th>
<th>Slope</th>
<th>Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Individuals</td>
<td></td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Dialysis Patients</td>
<td></td>
<td>0.8 *</td>
<td>- 1.6</td>
</tr>
<tr>
<td>Intensive Care Patients</td>
<td></td>
<td>0.9</td>
<td>- 6.2 *</td>
</tr>
</tbody>
</table>

*Heijboer et al Clin Chem 2012*
Garland et al 2009

Vitamin D for Cancer Prevention: Global Perspective

Breast Mortality

- RR = 0.28
- p < 0.05

Colon

- RR = 0.44
- p = 0.02

Odds ratio breast cancer

58% reduction in breast cancer risk associated with 38 ng/ml serum 25(OH)D

Odds ratio colorectal cancer

55% reduction in colorectal cancer risk associated with 38 ng/ml serum 25(OH)D
Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial\textsuperscript{1,2}

Lappe et al, 2008

N=1179
Breast
Colon
Lung
Leukemia
MM

Calcium: 1400-1500 mg/d, Vitamin D: 1000 IU/d

RR: 0.40
0.53
# Relationship between the Risks of Colorectal, Prostate and Breast Cancer, and 25-OH-D Levels

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nested Case-Control Studies</th>
<th>Number of Subjects</th>
<th>Adjusted OR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal Cancer</td>
<td>9</td>
<td>1127 vs 1122</td>
<td>0.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>8</td>
<td>2399 vs 3210</td>
<td>1.01</td>
<td>0.35</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>4</td>
<td>2363 vs 2363</td>
<td>0.99</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Per 10 nmol/l

For the US Preventive Services Task Force

Chung et al Ann Int Med 2011
Systolic Blood Pressure and Vitamin D Status

Judd et al, AJCN 2008
Systematic Review: Vitamin D and Cardiometabolic Outcomes

Anastassios G. Pittas, MD, MS; Mei Chung, MPH; Thomas Trikalinos, MD; Joanna Mitri, MD; Michael Brendel, BA; Kamal Patel, MPH; Alice H. Lichtenstein, DSc; Joseph Lau, MD; and Ethan M. Balk, MD, MPH
Relationship of 25-hydroxyvitamin D with all-cause and cardiovascular disease mortality in older community-dwelling adults

All-Cause Mortality

Cardiovascular Disease Mortality

Semba et al 2010

1006 ≥ 65 Yrs InChianti Study
<table>
<thead>
<tr>
<th>Study parameters</th>
<th>Study design</th>
<th>Type of subjects studied (age at study)</th>
<th>Study results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D intake via supplementation for the first year of life</td>
<td>Case-control</td>
<td>Infancy (&lt;5 years)</td>
<td>Reduced risk of childhood-onset type 1 diabetes (OR=0.83)</td>
<td>[53]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Childhood (5–9 years)</td>
<td>Reduced risk of childhood-onset type 1 diabetes (OR=0.81)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Childhood (10–14 years)</td>
<td>Reduced risk of childhood-onset type 1 diabetes (OR=0.47)</td>
<td></td>
</tr>
<tr>
<td>Vitamin D intake via use of cod-liver oil 10 μg for ≥5×/week for the first year of life</td>
<td>Case-control</td>
<td>Childhood (&lt;15 years)</td>
<td>Reduced risk of childhood-onset type 1 diabetes (OR=0.74)</td>
<td>[52]</td>
</tr>
<tr>
<td>Vitamin D intake via supplementation ≥2,000 IU/day during the first year of life</td>
<td>Case-control</td>
<td>Infancy till early adulthood (1–31 years)</td>
<td>Reduced risk of childhood-onset type 1 diabetes (OR=0.12)</td>
<td>[54]</td>
</tr>
<tr>
<td>Rickets during the first of life</td>
<td>Case-control</td>
<td>Infancy till early adulthood (1–31 years)</td>
<td>Increased risk of childhood-onset type 1 diabetes (OR=2.6)</td>
<td>[54]</td>
</tr>
<tr>
<td>Vitamin D intake via food continuous variable IU during pregnancy</td>
<td>Case-control</td>
<td>Infancy (&lt;5 years)</td>
<td>Reduced risk of insulin auto-antibodies in offspring (OR=0.49)</td>
<td>[55]</td>
</tr>
</tbody>
</table>

*OR* odds ratio
Type II Diabetes

- In the NHANES III, including 6228 adults age 20 years and older, there was a dose-dependent inverse association between serum 25(OH)D concentration and risk of diabetes. For 25(OH)D levels of 81 nmol/l or higher compared to 43.9 nmol/l or lower, the OR was 0.25 (95% CI 0.11-0.60) (Scragg R et al. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. Diabetes Care. 2004;27(12):2813-8)

- in the same cohort, serum 25(OH)D concentrations were inversely associated with insulin resistance (HOMA-IR), with best levels observed in the top quartile of 25(OH)D of 81 nmol/l or higher.

# Cardiovascular System and Vitamin D

**Table 3** Meta-analyses of intervention studies testing effect of vitamin D analogues on cardiovascular disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Focus</th>
<th>Main finding</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witham</td>
<td>Blood pressure reduction</td>
<td>3.6 mmHg reduction in systolic blood pressure (95% CI, −0.7 to 8.0); 3.1 mmHg reduction in diastolic BP (95% CI, 0.6−5.5) in studies with mean baseline systolic BP &gt; 140 mmHg</td>
<td>Eight RCTs included; no effect seen in 4 RCTs with mean SBP &lt; 140 mmHg</td>
</tr>
<tr>
<td>Wu</td>
<td>Blood pressure reduction</td>
<td>2.4 mmHg reduction in systolic BP (95% CI, 0−4.9). No change in diastolic blood pressure (95% CI, −4.0 to 4.0 mmHg)</td>
<td>Four RCTs included</td>
</tr>
<tr>
<td>George</td>
<td>Glycemic control</td>
<td>Small reduction in fasting glucose (0.32 mmol/l; 95% CI, 0.07−0.57) and small improvement in insulin resistance (standard mean difference 0.25, 95% CI, 0.03−0.48). No improvement in glycated haemoglobin</td>
<td>Effect confined to those with diabetes or impaired glucose tolerance (6 RCTs)</td>
</tr>
<tr>
<td>Wang</td>
<td>Lipids</td>
<td>No effect on total cholesterol, HDL or triglycerides. LDL cholesterol increased by 0.08 mmol/L (95% CI, 0−0.15)</td>
<td>Eleven RCTs</td>
</tr>
<tr>
<td>Elamin</td>
<td>CVS events</td>
<td>Hazard ratio for myocardial infarction 1.02 (95% CI, 0.93−1.13); hazard ratio for stroke 1.05 (0.88−1.25)</td>
<td>Population derived from osteoporosis trials</td>
</tr>
<tr>
<td>Wang</td>
<td>CVS events</td>
<td>Relative risk 0.90 (95% CI, 0.77−1.05)</td>
<td>Two RCTs included comparing vitamin D vs placebo</td>
</tr>
<tr>
<td>Pittas</td>
<td>Blood pressure</td>
<td>Systolic BP lower by 1.9 mm Hg (95% CI, −4.2 to 0.4 mmHg); no difference in diastolic BP</td>
<td>Ten RCTs</td>
</tr>
<tr>
<td>Cheng</td>
<td>CVS events</td>
<td>No reduction in endocrine/cardiovascular adverse events (RR, 1.07; 95% CI, 0.84−1.36)</td>
<td>Population with CKD taking paricalcitol. Combined endocrine/cardiovascular endpoint included for safety, not efficacy</td>
</tr>
<tr>
<td>Kandula</td>
<td>CVS events</td>
<td>No data found on CVS events</td>
<td>Population with CKD (5 RCTs); compared vitamin D_2/D_3 with placebo</td>
</tr>
<tr>
<td>Palmer</td>
<td>Mortality</td>
<td>No reduction in mortality (relative risk, 1.34; 95% CI, 0.42−4.26)</td>
<td>Population with CKD; comparison of 1 alpha hydroxylated vitamin D vs placebo. Three studies with mortality data included</td>
</tr>
</tbody>
</table>

**N = 10 Meta-analyses**  
*Beveridge & Witham Osteoporos Int 2013*
Conclusions: Cardiovascular System and Vitamin D

1. Cross-sectional Studies: Associations between Low 25-OH-D and Stroke, Myocardial Infaction, Diabetes Mellitus, Hypertension and Heart Failure

2. Longitudinal Studies: Associations between Low 25-OH-D and Incident Hypertension and Cardiovascular Events

3. Intervention Studies: Modest Effects on Hypertension, Insulin Resistance and Fasting Glucose, but no Effects on Blood Lipids

-> Need for Large Trials with Cardiovascular Events as Primary Outcome before Recommending Vitamin D as a Therapy for Cardiovascular Disease
Inflammatory Bowel Diseases and Vitamin D

- 72'719 Women -> 1’492’811 patient-year
- 25-OH-D at Baseline
-1986-2008: 122 Crohn’s Diseases & 123 Ulcerative Colitis

-25-OH-D Q4 vs Q1
0.54 for CD (p=0.02)
0.65 for UC (p=0.17)

Ananthakrishna et al Gastroenterology 2012
1. Vitamin D Deficiency and Increased Risk of Respiratory Infection

2. Vitamin D Appears Capable of Inhibiting Pulmonary Inflammation Response while Enhancing Innate Defense Mechanisms against Respiratory Pathogens

3. An Association of Serum Vitamin D Concentrations < 40 nmol/l with Acute Respiratory Tract Infection in Young Finnish Men

4. Randomized Trial of Vitamin D Supplementation to Prevent Seasonal Influenza A in Schoolchildren (RR=0.58, p=0.04) (Urashima et al 2010)

Absence from Duty for Respiratory Infection

Laaksi et al 2007
Association Between Serum 25-Hydroxyvitamin D Level and Upper Respiratory Tract Infection in the Third National Health and Nutrition Examination Survey

Upper Respiratory Tract Infection in the Past Few Days

Ginde et al 2009
Vitamin D and multiple sclerosis

Alberto Ascherio, Kassandra L Munger, K Claire Simon

Figure 5: 25-hydroxyvitamin D concentration and MS risk among young, white adults in the US military

Figure 6: Multiple sclerosis risk and supplemental vitamin D intake among women in the Nurses Health Studies
Higher Serum vitamin D Levels are Associated with Better Cognitive Test Performance in Patients with Alzheimer’s Disease

Oudshoorn et al, 2008
## Risk of Depression and 25-OH-D Levels

<table>
<thead>
<tr>
<th>Number of Studies</th>
<th>Type of Studies</th>
<th>Number of Patients</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Cross-sectional</td>
<td>43’137</td>
<td>0.96</td>
<td>0.94 – 0.99</td>
</tr>
<tr>
<td>5</td>
<td>Cohort</td>
<td>12’648</td>
<td>0.92</td>
<td>0.87 – 0.98</td>
</tr>
</tbody>
</table>

*Per 25 nmol/l*

*Ju et al JNHA 2013*
Conclusions

1. 25-Hydroxyvitamin D Levels > 50 nmol/l are Sufficient to Normalize Calcium and Bone Homeostasis

2. As far as Extraskeletal Systems are Concerned, Modest Reduction of Falls are Observed with ≥ 800 IU / day (RCT)

3. From Association Studies, Colon Cancer, Infections, Cardiovascular and Metabolic Diseases are more Likely in Subjects with 25-Hydroxyvitamin D Levels < 50 nmol/l

-> Target: 25-Hydroxyvitamin D Levels > 50 nmol/l
## Vitamin D Recommendations for Adults (µg)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>IOM (RDA)</th>
<th>US Endocrine Society *</th>
<th>DACH</th>
<th>Dutch Health Council</th>
<th>Belgian Health Council (RDA)</th>
<th>Nordic Dietary Recommendations</th>
<th>Swiss Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 - 50</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>10-15</td>
<td>10-15</td>
<td>7.5</td>
<td>15</td>
</tr>
<tr>
<td>51 - 60</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>10-15</td>
<td>10-15</td>
<td>7.5</td>
<td>15</td>
</tr>
<tr>
<td>61 - 70</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>10-15</td>
<td>10-15</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>&gt; 70 Yrs</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Pregnancy / Lactation</td>
<td>15 µg/d</td>
<td>15 µg/d</td>
<td>15 µg/d</td>
<td>15 µg/d</td>
<td>15 µg/d</td>
<td>15 µg/d</td>
<td>15 µg/d</td>
</tr>
</tbody>
</table>

* 37-50 µg/d for vitamin D deficient patients (< 25nmol/l)  
10 µg = 400 IU
Vitamin D status in adults

Wahl et al Arch Osteoporos 2012