What does Vitamin D prevent in older People?

Update

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Conflict of interest

Investigator – initiated trial support from WILD, DSM, Becin
Speaker invitations by Sandoz, Sanofi, Roche Diagnostics, Nestlé, Pfizer, MSD
What does Vitamin D prevent in older People?

• Muscle mass, function
• Sarcopenia
• Falls
• Loss of autonomy
• Hip Fractures
• Mortality
Dual action of Vitamin D

**Muscle**
- Direct effect on muscle mass and function

**Bone**
- Calcium Absorption
- Anti-resorptive benefit on bone

**Falls**
- Fragility Fractures

Primer of Metabolic Bone Diseases 2015. Bischoff-Ferrari et al.: Chapter Falls
Mechanistic Evidence that links Vitamin D to Muscle Health

VDR (-I-) mice have small Muscle Fibres

Phenotype of VDR Knock-out Mice

- Small and variable muscle fibers
- Hypertension
- Left ventricular hypertrophy and failure
- Mineralization defects of bone tissue
- Decreased Insulin secretion

Wild type

VDR (-I-)

Bouillon R, Bischoff-Ferrari HA, Willett WC.; 2008 JBMR
Vaidya A et al.; 2012 Metabolism
VDR present in human muscle tissue and declines with age

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

Bischoff-Ferrari HA, et al. JBMR 2004 replicated by Ceglia L and Dawson-Hughes et al. Journal of Molecular Histology 2010 for several anti-bodies including Santa Cruz 6
Muscle mass:
Vitamin D supplementation has been shown to up-regulate VDR expression and Type II muscle fibre

4-month RCT of 4000 IU vitamin D3 vs placebo
21 postmenopausal women
Significant increase in the number and diameter of Type II fast muscle fibres and

at 4 months mean 25OHD was 52.5 nmol/l in placebo vs 80.0 nmol/l in vitamin D group

preferentially Type II fast muscle fibers
25(OH)D status and prospective risk of sarcopenia

% with > 40% grip strength decline
% with > 3% ALM decline

N = 1008

25(OH)D at baseline

- < 10 ng/ml
- 10-20 ng/ml
- > 20 ng/ml

LASA Study

Visser M et al.; The Journal of Clinical Endocrinology & Metabolism 2003
Muscle quality: 25(OH)D concentrations associated with CT measures of muscle fat infiltration

90 postpubertal females, aged 16–22 yr

<table>
<thead>
<tr>
<th>25OHD (ng/ml)</th>
<th>β</th>
<th>SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle fat (%)</td>
<td>-2.94</td>
<td>0.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-0.65</td>
<td>0.20</td>
<td>0.001</td>
</tr>
<tr>
<td>Inactivity (h/wk)</td>
<td>-0.29</td>
<td>0.25</td>
<td>0.254</td>
</tr>
</tbody>
</table>

Independent of BMI and activity level

Gilsanz V et al.; J Clin Endocrinol Metab. 2010
Muscle quality is a predictor of hip fracture risk

Health ABC case-cohort study (n = 2941, age 70-79; FU 6.6 years):

- MRI-based Intra-muscular fat increased risk of hip fracture by 58% (Q1/4) [RR1.58; 95% CI1.10–1.99], adjusting for BMD, age, race, gender, BMI, and percentage fat.

- Independent of muscle mass and function (SPPB)

Further exploration!
**Muscle function:**

**Meta-Analysis of RCTs Adults Age 60+: Effect of vitamin D on muscle function**

**13 RCTs**

vitamin D supplementation yielded a standardized mean difference of -0.20 (95% confidence interval (CI) = -0.39 to -0.01, P = 0.04) for reduced postural sway.

-0.19 (95% CI = -0.35 to -0.02, P = 0.03) for decreased time for Timed Up and Go Test.

**Timed Up and Go Test**

**17 RCTs**

- **no significant effect** of vitamin D supplementation in adults with 25(OH)D levels > 25 nmol/l.

- **large effect of vitamin D supplementation** on hip muscle strength among those with 25(OH)D levels < 25 nmol/l (SMD 3.52, 95%CI 2.18, 4.85).

Uusi-Rasi et al. JAMA Intern Med. 2015

*Exercise and vitamin D in fall prevention among older women: a randomized clinical trial.*

Stockton KA et al.; OP Int 2011
Falls: Meta-Analyses of vitamin D trials on fall prevention

All but one* peer-reviewed meta-analyses of RCTs with vitamin D showed significant benefits on fall prevention

2004  Bischoff-Ferrari HA et al.; JAMA  - double-blind RCTs -  - 22%
2007  Jackson C et al; QiM  -  - 12%
2008  O’Donnel S et al.; Bone Mineral Metab (Active D)  -  - 34%
2008  Richy F et al.; Calcif Tissue Int (Active D)  -  - 21%
2009  Bischoff-Ferrari HA et al.; BMJ  - double-blind RCTs -  - 19%
2010  Kalyani RR et al.; J Am Ger Soc  -  - 14%
2010  Cameron ID et al.; Cochrane Database Syst Rev  -  - 28%
2011  Michael YL et al.; Ann Intern Med  -  - 17%
2011  Murad MH et al.; J Clin Endocrinol Metab  -  - 14%
2014  Bolland M et al.; Lancet Endocrinology  -  - 5%*

*
Vitamin D Dose and Fall Reduction

8 RCTs (n = 2426) sorted by dose given

All: sig. 27% reduction

700 to 1000 IU vitamin D / d
sig. 34% reduction of falls

200 to 600 IU/d
no reduction

200 to 1000 IU vitamin D / d
higher dose is better?

Benefits of daily vitamin D on falls and fractures may not translate to bolus doses: Zurich Disability Prevention Trial

Objective: To determine the effectiveness of high dose vitamin D in improving lower extremity function and lowering the risk of falling

Design, Participants: 1-year double-blind randomized-controlled trial. Participants were 200 community-dwelling men and women age ≥ 70 with a prior fall – at least 1 fall in the preceding 12 months

Interventions: Three randomly allocated study groups with monthly treatments

- **referenceD** (24’000 IU vitaminD3) -- control
- **highD** (60’000 IU vitaminD3)
- **combinedD** (24’000 IU vitamin D3 plus 300 μg calcifediol)

Bischoff-Ferrari HA et. al. JAMA Internal Medicine 2016
Results 1

Intent-to-treat analyses showed*:

- highD and combinedD were significantly more effective than referenceD in reaching 25(OH)D levels of 30+ ng/ml ($p = 0.001$) at 12 months

  - referenceD: 15% BL --- to 55% M12
  - highD: 19% BL --- to 81% M12
  - combinedD: 12% BL --- to 83% M12

- lower extremity function did not differ among treatment groups ($p = 0.26$) over time

  however, best within group improvement was in referenceD at 12 month: change SPPB $+0.38$; $p = 0.01$

*Analyses adjusted for age, gender and bmi

Bischoff-Ferrari HA et. al. JAMA Internal Medicine 2016
121 seniors fell during 12 month follow-up reporting 275 falls (141 in the first and 134 in the second 6 months of observation)

Intent-to-treat analyses showed*:

• Both in highD and combinedD a higher percentage of seniors fell compared to referenceD (p = 0.048)

  **referenceD** (24’000 IU): 48%; 95% CI: 36-60%
  **highD** (60’000 IU): 67%; 95% CI: 54-78%
  **combinedD** (24’000 IU + calcifediol): 66%; 95% CI: 54-77%

• A similar pattern was found for the mean number of falls (p = 0.09)

  Higher monthly doses of vitamin D did not improve fall prevention
  Best improvement in lower extremity function and reduction of falls with current recommended dose of 24’000 IU/month (800 IU/day)
  Optimal fall reduction seen between achieved 20 to 30 ng/ml 25(OH)D
Vitamin D Status and Loss of Autonomy: admission to nursing home

Higher BL 25(OH)D was associated with a lower risk of nursing home admission.

LASA
Age 65+
N = 1260
FU = 6 yrs
In 4383 persons 65 years of age or older:

- Seniors with 25(OH)D levels > 24 ng/ml achieved 37% hip fracture reduction as compared with persons with baseline levels of less than 30 nmol per liter

- Seniors with 25(OH)D levels > 24 ng/ml achieved 31% non-vertebral fracture reduction

Adjusting for assignment (treatment or control), age group, sex, and type of dwelling

Evidence Double-Blind RCTs in Seniors age 65+ at risk of D-deficiency

Vitamin D 800 IU/d

30% ↓

Hip fracture

14% ↓

Any Non-vert fractures

19-34% ↓

Falls

8 RCTS

12 RCTs / 11 pooled RCT > 30'000 seniors

Bischoff-Ferrari HA et al. Archives of Internal Medicine 2009
Bischoff-Ferrari HA et al. NEJM 2012
Meta-analysis: effect of vitamin D Supplementation on Mortality from clinical trials

4% significant reduction of mortality including all clinical trial data on vitamin D supplementation

Bolland et al. Lancet Endocrinology 2014
Summary
-- What does Vitamin D prevent in older People?

There are several lines of evidence that link vitamin D to several components of the instrument library of sarcopenia
- including muscle mass, muscle strength, function and muscle quality
and key consequences of sarcopenia
- including falls, hip fractures, loss of autonomy and mortality

- Based on the current literature these components may improve most among seniors with vitamin D deficiency
- The vitamin D dose with best evidence for fall and fracture prevention is 800 IU per day (24,000 IU/month)

- Evidence from large RCTs that tests the benefit of vitamin D in the prevention of sarcopenia and frailty is missing to date
Update  DO HEALTH

For the DO-HEALTH investigators

and all partners and collaborators of DO-HEALTH
Main objectives

To improve healthy ageing in European seniors

To reduce healthcare costs via the implementation of effective and broadly applicable disease prevention interventions

Specific objectives

To establish whether vitamin D, omega-3 fatty acids, and a simple home exercise program will prevent disease at older age

To assess comparative effectiveness and cost-benefit of the interventions
DO-HEALTH map

Vitamin D3 - Omega3 - Home Exercise – HeALTHy Aging and Longevity Trial

- Funded by the European Commission Framework 7 research program and University of Zurich.
- Support by industries: Nestlé Health Science, DSM, Roche, Pfizer, Streuli.
- Europe’s largest healthy aging study.
- 2157 healthy seniors recruited at 7 centres in 5 countries.
3 DO-HEALTH Interventions - Background

3 promising interventions to improve multiple organ functions

- Vitamin D
- Omega-3 Fats
- Exercise

Evidence from large clinical trial is missing
Inclusion criteria

- Community-dwelling seniors
- 40% of seniors were targeted to be enrolled based on a fall in the year prior to enrollment

To target relatively healthy seniors, the following inclusion criteria were defined:

- MMSE > 24; Mobile to come to the examination center without help

The following participants were excluded:

- in the last 5 years: history of cancer (except non-melanoma skin cancer), myocardial infarction, stroke, transient ischemic attack, angina pectoris, or coronary artery intervention
DO-HEALTH - Study Design

2x2x2 factorial design, 2157 seniors 70+ -- FU 3 years
with yearly visits and 3-monthly phone calls in all participants
DO-HEALTH – Primary Endpoints

- Incidence of non-vertebral fractures: Bone
- Functional decline: Muscle
- Systolic & diastolic blood pressure changes: Cardiovascular
- Cognitive decline: Brain
- Rate of infection: Immunity
DO-HEALTH – Secondary Endpoints

**Bone**
- Risk of hip / vert. / total fractures
- BMD at spine and hip
- Functional recovery after fracture / Fracture healing

**Muscle**
- Rate of falling
- Reaction T / grip str.
- Muscle mass upper and lower extremities
- Musculoskeletal pain
- Sarcopenia / Frailty

**Cardiovascular**
- Risk of incident hypertension

**Brain**
- Mental health decline and incidence of depression
- Dual tasking gait variability – speed

**Immunity**
- Rates of any upper respiratory infection, incident flu-like illness, incident severe infections that lead to hospital admission

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DO-HEALTH – Secondary Endpoints

- Prevalent and incident symptomatic knee OA
- Severity of knee pain
- Rate of knee buckling
- N of joints with pain
- NSAID use in knee OA

Bone/cartilage

- Decline in oral health
- Tooth loss

Dental

- Gastro-intestinal symptoms (ROME III)

Gastro-intestinal

- Fasting blood concentration of glucose and insulin
- Body composition and fat mass

Glucose-metabolic

- Decline in kidney function

Kidney

- Quality of life
- Incident frailty
- Risk of disability
- Nursing home adm. rate of acute hospital admissions, mortality

Global Health

OA: osteoarthritis
DO-HEALTH – Biomarker Endpoints

**Bone, CV, Immunity, GI, Glc-metabolic, Kidney, Global Health:**
- serum phosphate, serum calcium, intact PTH, ß-CrossLaps serum, P1NP (total), Troponin T, NT-proBNP, homocysteine, CK, cholesterol, HDL-cholesterol, triglycerides, CRP, IL6, ALT, AST, GGT, alkaline phosphatase, bilirubin, fasting glucose, insulin, serum creatinine, calcium urine, albumin urine, creatinine urine, urea, uric acid, total proteins, sodium, potassium, chloride, magnesium, albumin, ferritin, soluble transferrin receptor, TSH, fT4, fT3, cortisol, folic acid, vitamin B12, 25(OH)D

**Inflammation and Immunity:**
- TNF-α, IL-10, IL-8, IL-6, IL-1ß, Percentage T reg

**Bone and Muscle:**
- Myostatin and sclerostin

**Adherence:**
- Serum 25(OH)D, Plasma PUFA (EPA, AA, DPA, DHA)
<table>
<thead>
<tr>
<th>Baseline</th>
<th>Total (n=2157)</th>
<th>Men (n=828)</th>
<th>Women (n=1329)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>74.9</td>
<td>75.2</td>
<td>74.8</td>
<td>0.07</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>26.3</td>
<td>26.6</td>
<td>26.2</td>
<td>0.03</td>
</tr>
<tr>
<td>MMSE Score</td>
<td>28.5</td>
<td>28.5</td>
<td>28.5</td>
<td>0.33</td>
</tr>
<tr>
<td>25(OH)D levels</td>
<td>24.3</td>
<td>23.8</td>
<td>24.7</td>
<td>0.02</td>
</tr>
<tr>
<td>% Vit D deficient (&lt;20 ng/ml)</td>
<td>34.1</td>
<td>37.6</td>
<td>32.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Gait speed (m/s)</td>
<td>1.12</td>
<td>1.09</td>
<td>1.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Healthy ager (NHS definition)</td>
<td>41.8</td>
<td>42.0</td>
<td>41.7</td>
<td>0.89</td>
</tr>
<tr>
<td>% Prefrail (Fried definition)</td>
<td>41.1</td>
<td>24.3</td>
<td>51.7</td>
<td>&lt;0.0001</td>
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<tr>
<td>% Frail (Fried definition)</td>
<td>2.7</td>
<td>0.5</td>
<td>4.1</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Preliminary Baseline Data
% of Healthy Agers and Vitamin D Status

% Healthy Agers by 25(OH)D Status

- VitD <10: 26.6%
- 10-20: 36.9%
- 20-30: 44.2%
- 30+: 46.7%
Many thanks and invitation to Zurich in March 2018