State of the Science: How Does Vitamin D Impact the Health of Older Adults?

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Learning Objectives

Updating the Science: (20-25 mins)
- To provide an updated review of the physiology, disposition, and genomics of vitamin D, and the assessment of its clinical status.
- To compare the clinical pharmacology between ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3).

Interpreting Vitamin D Status in Practice: (10 mins)
- To discuss the current controversy on the definition of vitamin D deficiency and threshold of initiating vitamin D supplementation in older adults.

Bring to the Bedside and Clinic: (25 mins)
- To evaluate the impact on different vitamin D interventions on the major clinical outcomes in older adults.

Looking to the Future: (5 mins)
- To overview the major ongoing clinical trials involving vitamin D interventions in older adults.
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Pre-vitamin D

Negative feedback loop:

- ↑ ionized Ca,
- ↑ Phos

25(OH)D (Calcidiol)

1,25(OH) D (Calcitriol)

• ↑ intestinal calcium absorption
• ↑ bone mineralization
• Calcium homeostasis
• Regulate immune cell differentiation


How Does Vitamin D Impact the Health of Older Adults (Lingtak-Neander Chan), Elder Friendly Futures Conference, September 2016
Vitamin D Cellular Response

Genomic effects vs non-genomic effects

25(OH)D₃: 25-hydroxyvitamin D₃
1,25-(OH)₂D₃: 1α,25-dihydroxyvitamin D₃
1,24,25-(OH)₃D₃: 1α,24,25-trihydroxyvitamin D₃

DBP, vitamin D binding protein;
RXR, retinoid X receptor;
VDR, vitamin D receptor;
VDRE, vitamin D response element
FGF23, fibroblast growth factor 23;
PKC, protein kinase C;
PLC, phospholipase C;
PTHrP, parathyroid hormone-related protein;

Adapted from: Jensen MB. Nature Rev Endocrinol 2014;10,175–186
Epigenetics of Vitamin D Disposition

- Genetic polymorphisms affecting a person’s response to vitamin D have been identified

- Genes regulating vitamin D metabolism:
  - **DHCR7** (7-dehydrocholesterol reductase)
  - **CYP2R1** (25-hydroxylase) – synthetic pathway
  - **CYP24A1** (24-hydroxylase) – catabolic pathway

- Other polymorphisms
  - **GC** (Vitamin D binding protein)
  - **VDR** (Vitamin D receptor)
  - **CASR** (Calcium-sensing receptor)

Vitamin D – Cutaneous Synthesis

- Takes place between 10 AM and 3PM
- Driven by exposure to UV-B radiation, which is affected by the zenith angle of the sun

- Factors affecting cutaneous vitamin D3 production:
  - skin pigmentation,
  - sunscreen use,
  - time of day,
  - season,
  - latitude & altitude,
  - adiposity
  - air pollution (especially ozone)

- Solar photoproducts inactive to calcium metabolism (tachysterol and lumisterol) are produced with prolonged exposure to solar UV-B radiation
Influence of Latitude on the Synthesis ofPrevitamin D3


Comparison of Cutaneous Vit. D Synthesis After UV-B Exposure between Normal Weight and Obese Individuals


- 13 control subjects and 13 obese subjects; all Caucasians
- Subject received 27 mJ/cm² of UV-B radiation after refrain from sun exposure for 24 hrs
- BMI: Control - 22.2 ± 0.04 kg/m²
  Obese - 38 ± 1.7 kg/m²
Vitamin D – Kinetics

- Transporter-mediated intestinal absorption
  - CD36 (Cluster determinant 36)
  - NPC1L1 (Niemann–Pick C1-Like 1)
  - SR-BI (Scavenger receptor class B type I)
  - Unidentified apical efflux transporter

- Passive diffusion
- Facilitate by micelle formation and bile salt

- Bioavailability varies: 55 – 98%
- Max absorption between 4 – 10 hrs

Regional enterocytic content of vitamin D after oral administration in mice


Dietary vitamin D (as cholecalciferol)
25(OH)D - Physiological Characteristics

- 25(OH)D is physiologically active [1/200th of 1,25(OH)D]
- 25(OH)D is VERY HIGHLY protein bound
  - Vitamin D binding protein (VDBP): 80-88%
  - Albumin: 10-15%
  - Free fraction in plasma: 0.03-0.04%
- Free + Albumin bound 25(OH)D is considered the mobile, bioavailable pool for physiological functions
- Highly distributed to adipose tissues
- Likely acute phase response

Distribution of Plasma Vitamin D concentration in Obese Patients Based on Body Mass Index (BMI)

Assessing Clinical Status of Vitamin D

Approaches

- Daily intake

- Plasma vitamin D concentrations
  - Total 25(OH) vit. D (D2 + D3)
  - 25(OH) vitamin D3
  - 1,25(OH) vitamin D

- Other potentially helpful tests

Vitamin D

Precursor compounds

- Cholecalciferol (D3)
- Ergocalciferol (D2)
  - Endogenous compounds & diets
  - Half-life ~ 24 hrs

Prohormone

- 25(OH) vitamin D (Calcidiol)
  - Regarded as “body pool” & storage; weak physiological activities
  - Half-life ~ 15 days

Active hormone

- 1,25(OH) vitamin D (Calcitriol)
  - Most active form as a hormone
  - Half-life 4 to 6 hours
Assessing Clinical Status of Vitamin D

Considerations

- Clinical risk factors
- Timing of sampling
  - Dose
  - Replacement regimen
  - Acute illness or stress response?
- Seasonal variation
  - 1.5 to 4 times more Europeans have below threshold 25(OH)D concentration in winter than summer months
  - Seasonal variation for 25(OH)D in the region:
    - Seattle area: 7 ng/mL (or 30%) in Seattle area
    - Southwestern Alaska: Up to 11.1 ng/mL (43%)


Comparison of 25(OH)D concentrations in British cohorts with different dietary habits

[Results from the EPIC-Oxford Study]

- Meat eaters (n = 1388) 
- Fish eaters (n = 210)
- Vegetarians (n = 420)
- Vegans (n = 89)

# Conversion from nmol/L to ng/mL: divided by 2.5

European Prospective Investigation into Cancer and Nutrition (EPIC)

25(OH) Vitamin D Assays

- Competitive protein binding assay
- Chemiluminescence
- Immunoassays
  - EIA
  - RIA
- Direct UV detection–based HPLC assays
- GC-MS
- Liquid chromatography–tandem mass spectrometry (LC-MS/MS)

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The Numbers Game: D2 vs D3

- Vitamin D3: Cholecalciferol
  - Endogenous vitamin D
  - Meat-based sources, including fish

- Vitamin D2: Ergocalciferol
  - Plant-based sources

D2 vs D3: Are they Clinical Equivalent?

- D2 has shorter serum half-life
- D3 has higher affinity to CYP27B1 than D2
- D3 has higher binding affinity to VDBP
- CYP24A1 metabolite of D3 [1,24,25(OH)₃D₃] has higher affinity to VDR
- Different binding affinity towards VDBP (D2 vs D3) results in different free plasma 25(OH)D₃, which may contribute to different clinical effects
- HOWEVER, because of the regulation (DSHEA), it is almost impossible to determine the difference clinically

Baseline vitamin D2, vitamin D3 and metabolite ratio in a cohort

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 8)</th>
<th>Vit. D2 (n = 17)</th>
<th>Vit. D3 (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH) D2 (ng/mL)</td>
<td>0.9 ± 2.1</td>
<td>3.8 ± 4.9</td>
<td>0.9 ± 2.7</td>
</tr>
<tr>
<td>25(OH) D3 (ng/mL)</td>
<td>17.6 ± 7.8</td>
<td>15.5 ± 6.9</td>
<td>21.3 ± 12.9</td>
</tr>
<tr>
<td>1,25(OH) D2 (pg/mL)</td>
<td>0.0 ± 0.0</td>
<td>2.8 ± 6.7</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>1,25(OH) D3 (pg/mL)</td>
<td>30.3 ± 8.1</td>
<td>30.5 ± 9.0</td>
<td>35.4 ± 13.0</td>
</tr>
</tbody>
</table>

Biancuzzo RM et al, J Clin Endocrinol Metab 2013;98: 973–979

Changes in vitamin D profile after supplementation with placebo, vit D2, or vit D3.


How Does Vitamin D Impact the Health of Older Adults (Lingtak-Neander Chan), Elder Friendly Futures Conference, September 2016
Summary

- Vitamin D is a hormone with broad endocrine, paracrine, autocrine, and intracrine functions.

- The disposition and physiological actions of vitamin D appear to be altered by many factors, including genetic polymorphism.

- There is also an inter-ethnic variance on the disposition of 25(OH)D.

- It is unclear how aging may alter the endogenous synthesis, intestinal transport and absorption, and metabolism of vitamin D.

- It is also unclear how the action of vitamin D, especially its interaction with VDR, is affected by aging.

- A standardized vitamin D assay is needed.

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What is the prevalence of Vitamin D Deficiency in the U.S.?

A. 8.1%
B. 21.0%
C. 41.6%
D. 82.1%

Reported incidence of vitamin D deficiency defined as 25(OH)D level below 20 ng/mL

Clinical Debate: Interpretation of Vitamin D Concentration

<table>
<thead>
<tr>
<th>25-OH(D) Level Cutoff</th>
<th>Opinions of Expert and Professional Bodies About Cutoff Levels</th>
<th>Summary of Previous Research on the Associations Between 25-(OH)D Levels and Risk for Health Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20 ng/mL</td>
<td>Widely used by researchers and available guidelines as indicative of deficiency</td>
<td>Levels ≥50 nmol/L (≥20 ng/mL) have been associated with decreased risk for fractures, CVD, CRC, diabetes, depressed mood, cognitive decline, and death</td>
</tr>
<tr>
<td>20 – 30 ng/mL</td>
<td>Debate about whether these levels represent deficiency</td>
<td>Levels &gt;60 nmol/L (&gt;24 ng/mL) associated with decreased risk for CVD Levels &gt;75 nmol/L (&gt;30 ng/mL) associated with decreased risk for death and CRC Data conflict about whether levels &gt;75 nmol/L (&gt;30 ng/mL) are associated with decreased risk for fractures</td>
</tr>
<tr>
<td>30 – 50 ng/mL</td>
<td>General agreement that these levels do not represent deficiency; however, some recommend targeting 25-(OH)D levels to this range because results of 25-(OH)D testing vary</td>
<td>Levels between 87 and 100 nmol/L (35 to 40 ng/mL) may be associated with decreased risk for death and CRC</td>
</tr>
<tr>
<td>50 – 200 ng/mL</td>
<td>Debate about whether these levels are associated with adverse health outcomes</td>
<td>Possible U shaped association between vitamin D levels and risk for death and pancreatic cancer</td>
</tr>
</tbody>
</table>

Summation of fall prevention by dose and achieved 25(OH)D concentrations

Calcium absorption fraction plotted as a function of serum 25(OH)D concentration

The total fraction of calcium absorption from the intestine appears to reach plateau when serum 25(OH)D approaches 80 nmol/L (~30 ng/mL).

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Distribution of serum 25-hydroxyvitamin D levels by racial/ethnic group in the US population aged 13 years and older, and in dark-skinned, traditionally living peoples in equatorial Africa

Distributions are smoothed by averaging each set of three adjacent data points. The area under each curve represents 100% of that group. Means, standard deviations (SD), and confidence intervals (CI) are shown near the X axis.

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Data interpreted based on 3 studies:
- Barger-Lux & Heaney, J Clin Endocrinol Metab (2002)

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16
Inter-ethnic Variation of Plasma 25(OH)D Concentration Throughout a Calendar Year


Summary

- The prevalence of vitamin D deficiency varies depending on the cut off for 25(OH)D. The cutoff value indicating clinical deficiency may also be specific to race or ethnicity.

- The benefits of routine surveillance 25(OH)D monitoring in lower risk older adults require further investigation.

- The threshold plasma 25(OH)D concentration that warrants routine vitamin D supplementation in older adults has not been determined.

- Despite having lower average 25(OH)D concentration in African Americans, it is unclear whether it consistently translates to increased risks for metabolic bone disease.
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Disease States of Focused Discussion

- Bone health
  - Fracture
  - Fall prevention
  - Functional impairment

- Cardiovascular
  - Stroke/ CVA
  - CVD, CHD

- Others
  - Cancer
  - Mortality
Does Vitamin D Prevent Fractures in post-menopausal women and older men?

- Cochrane Review on RCTs or quasi-RCTs
- Interventions:
  - Vitamin D ± calcium vs placebo
  - Community, nursing home, and hospital settings
- Data captured:
  - 53 trials (total n = 91,791)
  - Vitamin D doses – 400 IU/day to 500,000 IU x1


<table>
<thead>
<tr>
<th>Treatment</th>
<th>Outcomes</th>
<th>Risk Ratio (vs placebo)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D alone</td>
<td>Hip and new fractures</td>
<td>1.12</td>
<td>0.98 to 1.29</td>
</tr>
<tr>
<td>Vitamin D + calcium</td>
<td>Hip fracture</td>
<td>0.84</td>
<td>0.74 to 0.96</td>
</tr>
<tr>
<td>Vitamin D + calcium</td>
<td>Non-vertebral fractures</td>
<td>0.95</td>
<td>0.90 to 0.99</td>
</tr>
</tbody>
</table>

How Does Vitamin D Impact the Health of Older Adults (Lingtak-Neander Chan), Elder Friendly Futures Conference, September 2016
**Exercise and Vitamin D in Fall Prevention Among Older Women – 2-year RCT**

- To determine the effectiveness of exercise training and vitamin D supplementation in reducing falls

- Settings: Finland, 409 home-dwelling women
  - 70 – 80 years old

- Interventions:
  - Placebo
  - Placebo with exercise
  - Vitamin D 800 IU/day without exercise
  - Vitamin D 800 IU/day + exercise

- Vitamin D assay – fasting samples; EIA

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**Hazard Ratios (95%CIs) for Fallers, Injured Fallers, and Multiple Fallers**

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo No exercise</th>
<th>Vitamin D No exercise</th>
<th>Placebo + Exercise</th>
<th>Vitamin D + Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>All fallers</td>
<td>HR = 1.00</td>
<td>HR = 0.77 (0.54 - 1.11)</td>
<td>HR = 0.93 (0.66 - 1.31)</td>
<td>HR = 0.91 (0.64 - 1.28)</td>
</tr>
<tr>
<td>Injured fallers</td>
<td>1.00</td>
<td>0.89 (0.47 - 1.69)</td>
<td>0.47 (0.23 - 0.99)</td>
<td>0.38 (0.17 - 0.83)</td>
</tr>
<tr>
<td>Multiple fallers</td>
<td>1.00</td>
<td>1.07 (0.71 - 1.62)</td>
<td>1.14 (0.76 - 1.71)</td>
<td>1.14 (0.77 - 1.71)</td>
</tr>
</tbody>
</table>
Other Findings

- Mean baseline calcium intake: 1040 – 1125 mg/day
- Femoral neck BMD ↓ in all groups, but greatest in the placebo without exercise group
- Lumbar spine BMD did not change significantly in any group

Vitamin D Status

<table>
<thead>
<tr>
<th>Serum 25(OH)D (ng/mL)</th>
<th>Baseline</th>
<th>Post-study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>27.5</td>
<td>25.1</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>27.5</td>
<td>37</td>
</tr>
</tbody>
</table>

Does Treating Vitamin D Insufficiency Improves Calcium Absorption and Bone Density?

- Goal:
  - Determine if maintaining 25(OH)D levels > 30 ng/mL for 1 year would increase total fractional calcium absorption (TFCA) and BMD more than low-dose vitamin D3 or placebo

- Interventions:
  - Enrollment criteria- 25(OH)D between 14 and 27 ng/mL
  - Loading dose 50,000 IU D3 daily x15 days; then
    - 800 IU/day OR
    - 50,000 IU q 15 days (~ 3,333 IU/day)

- Assessments:
  - BMD, Muscle mass
  - Dual stable calcium isotope methods for TFCA
**Longitudinal Changes in Serum 25(OH)D Concentrations by Treatment Assignment**


Vitamin D Supplementation and Outcomes

- No differences between treatment arms:
  - The absolute or annualized percentage change in lumbar spine, mean total hip, or total-body BMD;
  - Trabecular bone score
  - Muscle mass,
  - Number of falls, or number of fallers
  - C-telopeptide or bone-specific alkaline phosphatase
  - 1-year change in Health Assessment
  - Questionnaire score or Physical Activity for the Elderly score
Annualized Percent Change in Bone Mineral Density by Treatment Assignment


Can High Dose Vitamin D Prevent Functional Decline in Older Adults?

- Goal:
  - To determine if high dose monthly vitamin D prevents functional decline in home-dwelling adults > 70 years old

- Interventions:
  - 24,000 IU vitamin D3 monthly (~800 IU/day)
  - 60,000 IU vitamin D3 monthly (~2,000 IU/day)
  - 24,000 IU vitamin D3 + 300 μg 25(OH)D

- Assessments:
  - Short Physical Performance Battery (SPPB score)
  - Physical examination
  - Appendicular muscle mass (per DEXA)
Clinical Outcomes

- SPPB score did not differ significantly among the treatment groups (P = .26)
- Functional and muscle mass end points were qualitatively similar.

<table>
<thead>
<tr>
<th>Falls Assessment</th>
<th>24,000 IU</th>
<th>60,000 IU</th>
<th>24,000 IU + 25(OH)D</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of falls</td>
<td>47.9%</td>
<td>66.9%</td>
<td>66.1%</td>
<td>0.048</td>
</tr>
<tr>
<td>Adjust mean # of falls</td>
<td>0.94</td>
<td>1.47</td>
<td>1.24</td>
<td>0.09</td>
</tr>
</tbody>
</table>
Vitamin D Supplementation Among Patients With Symptomatic Knee Osteoarthritis (OA)

**Background:**
- Association between Vitamin D supplementation and benefits for knee OA is based on observational trials

**Goal:**
- An RCT to evaluate the effects of 2 years of vitamin D supplementation on knee pain and tibial cartilage volume

**Enrollment:**
- Baseline 25(OH)D between < 60 nmol/L (24 ng/mL)
- Treatment arm: 50,000 IU vitamin D$_3$ monthly x 24 months
- Vitamin D assay: chemiluminescent immunoassays

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### Baseline Characteristics

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<thead>
<tr>
<th></th>
<th>Vitamin D (n = 209)</th>
<th>Placebo (n = 204)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hobart, No. (%)</td>
<td>129 (61)</td>
<td>132 (64)</td>
</tr>
<tr>
<td>Melbourne, No. (%)</td>
<td>80 (38)</td>
<td>72 (35)</td>
</tr>
<tr>
<td><strong>Age, mean (SD), y</strong></td>
<td>63.5 (6.9)</td>
<td>62.9 (7.2)</td>
</tr>
<tr>
<td><strong>Women, No. (%)</strong></td>
<td>106 (50)</td>
<td>102 (50)</td>
</tr>
<tr>
<td><strong>Body mass index, mean (SD)</strong></td>
<td>29.6 (5.4)</td>
<td>29.6 (4.6)</td>
</tr>
<tr>
<td><strong>Serum 25-hydroxyvitamin D, mean (SD), nmol/L</strong></td>
<td>43.7 (11.8)</td>
<td>43.8 (12.7)</td>
</tr>
<tr>
<td><strong>Radiographic osteoarthritis, No. (%)</strong></td>
<td>163 (96)</td>
<td>157 (96)</td>
</tr>
<tr>
<td><strong>Total WOMAC score (0-2400), mean (SD)</strong></td>
<td>687.3 (426.3)</td>
<td>664.7 (390.8)</td>
</tr>
<tr>
<td>Pain (0-500)</td>
<td>137.9 (88.8)</td>
<td>134.7 (83.4)</td>
</tr>
<tr>
<td>Stiffness (0-200)</td>
<td>61.5 (41.5)</td>
<td>61.7 (40.1)</td>
</tr>
<tr>
<td>Function (0-1700)</td>
<td>487.9 (318.1)</td>
<td>467.6 (292.8)</td>
</tr>
</tbody>
</table>

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Jin X et al, JAMA. 2016;315(10):1005-1013

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Bone Health and Fracture: Vitamin D 50,000 IU monthly in OA

Western Ontario and McMaster University Index of osteoarthritis (WOMAC) score

- Assess during walking, using stairs, in bed, sitting or lying, and standing
- Mean changes at 24 months:
  - - 49.9 for placebo,
  - - 35.1 for vitamin D ($p = 0.10$)

Vitamin D and Cardiovascular Outcomes

- Hypertension (60.1 ± 11.3 year old)
  - 2,800 IU vitamin D3 QD x 8 weeks had no effect on SBP, DBP, Renin, BNP, but mild increase in serum triglycerides

- Heart failure (65.9 ± 10.4 years old)
  - NYHA Class II-IV
  - Vitamin D3 50,000 IU weekly for 6 months was not associated with improved peak VO_2, 6MW, and muscle strength
  - Serum 25OHD increased by 42.3 ± 16.4 ng/mL

- CVD, CHD, stroke risks (34.7% > 65 years old)
  - Observational trial showed that 25(OH)D < 20 ng/mL is associated with higher risk

Vitamin D and Stroke

- Acute ischemic stroke (66.2 ± 12.9 year old)
  - 25(OH)D > 30 ng/mL is associated with better functional outcomes (modified Rankin scale (mRS) score of ≥ 3,) at 3 months

- Subclinical CVD per longitudinal MRI
  - 55-72 year-old with no previous clinical stroke
  - Baseline serum 25(OH)D was not associated with white matter hyperintensities on MRI or prevalent subclinical infarcts as seen on serial cerebral MRIs obtained approximately 10 years apart.


Woman Health Initiative – Extension

- Incidence similar between vit.D supplemented group (1,000 IU/day) vs placebo based on WHI data (at 5 year after end of intervention) for:
  - Colorectal cancer
  - Invasive breast cancer
  - CVD
  - All-cause mortality

- In post hoc analyses, the incidence of vertebral fractures, HR= 0.87 (95% CI: 0.76, 0.98) and in situ breast cancers, HR = 0.82 (95% CI: 0.68, 0.99) were lower among women randomized to supplementation.

Summary

- Evidence supporting the clinical benefits of maintaining plasma 25(OH)D concentration > 30 ng/mL in geriatric population is weak.

- The health benefits of routine vitamin D supplementation (> 800 IU/day) in older adults remains unclear.

- Benefits in bone health was observed with concurrent vitamin D and calcium supplementation, but not vitamin D alone.

- Exercise appears to offer stronger impact on bone health and fall prevention than vitamin D.

- Oral dose of > 50,000 IU may be associated with increase fall risk in older adults.

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Major Ongoing Clinical Trials -1

- **BEST-D** (Biochemical Efficacy and Safety Trial of Vitamin D) University of Oxford
  - Study aim: To determine the daily dose of vitamin D needed in older people to maintain blood levels of vitamin D similar to those seen in healthy younger people at the end of the summer months.

- **VDOP** (Vitamin D supplementation in older people) University of Cambridge.
  - Study aim: To examine the relationship between vitamin D supplementation at a range of doses (12,000 IU/month, 24,000 IU/month or 48,000 IU/month, equivalent to 400 IU/day, 800 IU/day and 1,600 IU/day, respectively) and the change in bone mineral density (BMD) in older people living in private households in the North East of England

- **VITAL** (Vitamin D and Omega-3 Trial) Harvard Medical School.
  - Study aim: To determine whether taking daily dietary supplements of vitamin D3 (2000 IU) or omega-3 fatty acids (Omacor® fish oil, 1 gram) reduces the risk for developing cancer, heart disease, and stroke in people who do not have a prior history of these illnesses.

Major Ongoing Clinical Trials - 2

- **D-Health**: A trial of vitamin D for prevention of mortality and cancer in older Australian adults –The University of Queensland, Australia
  - Study aim: To determine whether increasing the mean 25(OH)D concentration in the general population through widespread supplementation would result in improved health outcomes.

- **FIND** (Finnish Vitamin D Trial) The University of Eastern Finland.
  - Study aim: To determine the benefits and risks of vitamin D3 (1600 IU/day, 3200 IU/day, or placebo) in the primary prevention of cardiovascular (CVD) and cancer among 18000 men 60 years or older and women 65 years or older.

- **VIDAL**: Vitamin D and Longevity Trial; The London School of Hygiene & Tropical Medicine.
  - Study aim: To determine if taking vitamin D (100,000 IU/month or placebo) can reduce mortality and morbidity among older adults the general population between the ages of 64-85.
MOVING FORWARD...

- More studies that enroll adults > 80 years of age are needed
- The value of targeted plasma 25(OH)D concentration vs standard oral intake at 800 IU/day should be compared
- Studies should be designed to compare the outcomes based on different targeted 25(OH)D concentration
- The impact of genetic polymorphism of vitamin D disposition on the dosing regimen and clinical outcomes should be investigated
- The reasons behind the increased fall risks with “mega-doses” of vitamin D should be explored.

APPENDIX 1: Recommendation of vitamin D intake

<table>
<thead>
<tr>
<th>Age group</th>
<th>EAR (IU/day)</th>
<th>RDA (IU/day)</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year-old to 70</td>
<td>400</td>
<td>600</td>
<td>2,500 for 1-3 yo, 3,000 for 4-8 yo, 4,000 others</td>
</tr>
<tr>
<td>&gt; 70-year-old</td>
<td>400</td>
<td>800</td>
<td>4,000</td>
</tr>
<tr>
<td>Pregnant/lactating women</td>
<td>400</td>
<td>600</td>
<td>4,000</td>
</tr>
</tbody>
</table>

Institute of Medicine (IOM) 2010 Report

www.iom.edu/vitamind
APPENDIX 2a: Vitamin D replacement “Simple Rule”

- Every 1,000 IU/day of D2 or D3 given orally would raise serum 25(OH)D by 10 ng/mL over a period of 3 to 4 months.

- An "unofficial summary" of the dose-response curve based on many small trials.

- A simplified approach and covariances such as sun exposure, dietary effect, GI symptoms, drug/nutrient interactions are not taken into consideration.


APPENDIX 2b: Vitamin D replacement “The Dutch Sliding Scale”

- A weight-base equation based on the plasma 25(OH)D concentration:

  \[ \text{Total Vit. D dose (in IU)} = 40 \times (75 - \text{current 25(OH)D level}) \times \text{wt(kg)}. \]

- Note that the 25(OH)D level is measured in SI unit (nmol/L). So you need to convert our common unit from ng/mL to nmol/L by multiplying by 2.5.

- You can also rewrite the question to:

  \[ \text{Total vitamin D Dose} = 40 \times (75 - (\text{current 25(OH)D (ng/mL) \times 2.5)}) \times \text{wt (kg)}. \]

- Replace this amount with a weekly dose no more than 25,000 IU.

- The equation assumes that the dose-response relationship is linear, which is not true with increased fat mass. So, this method loses sensitivity in obese patients.