Aging, Vitamin D, and Physical Function

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“Classical” actions of vitamin D

- Intestinal calcium and phosphorous absorption
- Bone formation and resorption

Rickets

Osteoporosis
Causes of vitamin D deficiency and observed associations with health consequences

Adapted from Holick MF et al., Am J Clin Nutr 2008
Classification of vitamin D status: the 25(OH)D continuum controversy

“Deficiency”  “Insufficiency”  “Sufficiency”

0 10 20 30 40 50 60

(ng/mL)

2010 IOM cut-point (for bone)

Holick MF et al., J Clin Endocrinol Metab 2011;
Rosen CJ et al., J Clin Endocrinol Metab 2012
Prevalence of vitamin D deficiency and insufficiency among older adults in the U.S.

NHANES 2000-04; Looker AC et al., Am J Clin Nutr 2008
Risk factors for vitamin D deficiency/insufficiency in older adults

- Decreased exposure to sunlight
- Decreased capacity of the skin to produce vitamin D
  - decreased 7-dehydrocholesterol in the skin
- Inadequate dietary intake
  - vitamin D is found naturally in very few foods (e.g., fatty fish like salmon, tuna, and sardines)
  - fortified foods (milk, milk products, some juices, and cereal) are the major foods sources in the U.S.

Vitamin D intake from diet and diet plus supplements: NHANES 2005-06

RDA: 19-70 yrs, 600 IU; 71+ yrs, 800 IU

Bailey RL et al., J Nutr 2010
Potential roles of vitamin D on physical function
Vitamin D and physical function

- **Muscle contraction**: modulates the activation of protein kinase C and the release of calcium into the cytosol for muscle contractility
- **Muscle cell proliferation/differentiation**: regulates cell proliferation and induction of terminal differentiation into mature muscle fibers
- **Muscle growth**: increases the size of type 1 and II muscle fibers
- **Neuromodulation**: protective effects on central and peripheral neurophysiologic properties
- **Inflammation**: may play a role in the inflammatory response by inhibiting the production of inflammatory cytokines (e.g., IL-6, TNFα)
- **Associated with many of the same chronic conditions that are related to the development of functional limitations**

Are 25(OH)D concentrations sufficient to maintain bone health adequate for optimal physical function in older adults?
NHANES III: 25(OH)D status and physical performance

Older adults with lower 25(OH)D concentrations had slower walk speeds and sit-to-stand times

Serum 25(OH)D, nmol/L
(1 nmol/L = 0.4 ng/mL)

Bischoff-Ferrari HA et al., *Am J Clin Nutr* 2004
Health ABC: 25(OH)D status and physical performance

Older adults with low 25(OH)D concentrations had lower physical performance scores and slower gait speed.

**Health ABC PPB score (0-4)**

- **P for trend, 0.04**

- **<20 ng/mL**
- **20 - 30 ng/mL**
- **30+ ng/mL**

**400-m walk (m/sec)**

- **P for trend, <0.001**

- **<20 ng/mL**
- **20 - <30 ng/mL**
- **30+ ng/mL**

* P<0.05 from 30+ ng/mL

PPB = physical performance battery

Houston DK et al., *Am J Epidemiol* 2012
CHS All Stars: 25(OH)D status and muscle strength

Older adults with low 25(OH)D concentrations had weaker grip strength.

Graphs showing the relationship between 25(OH)D concentration and muscle strength, with a statistically significant trend for grip strength.

Houston DK et al., *J Am Geriatr Soc* 2011
Is there a 25(OH)D concentration threshold for physical function?
Is there a 25(OH)D threshold for physical function?

- 25(OH)D concentrations of 30-32 ng/mL (75-80 nmol/L) have been suggested as optimal for various health outcomes (Bischoff-Ferrari HA et al., *Am J Clin Nutr* 2006)
- In NHANES III, most of the increase in walk speed and sit-to-stand time occurred in individuals with 25(OH)D concentrations between 9 and 16 ng/mL (22.5-40 nmol/L) (Bischoff-Ferrari HA et al., *Am J Clin Nutr* 2004)
- Other studies have shown a threshold at higher 25(OH)D concentrations (Wicherts IS et al., *J Clin Endocrinol Metab* 2007; Houston DK et al., *Am J Epidemiol* 2012; Janssen HC et al., *J Am Med Dir Assoc* 2013; Sohl E et al., *Osteoporosis Int* 2013; Sohl E et al., *J Clin Endocrinol Metab* 2015)
25(OH)D threshold for physical performance

SPPB score (0-12)

Serum 25(OH)D (nmol/L)
(1 nmol/L = 0.4 ng/mL)

26 ng/mL

SPPB = short physical performance battery

Sohl E et al., Osteoporosis Int 2013
# Health ABC: 25(OH)D thresholds for physical performance and strength

<table>
<thead>
<tr>
<th>Measure</th>
<th>25(OH)D threshold (95% CI)</th>
<th>Slope below threshold</th>
<th>Slope above threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( \beta ) (SE) *</td>
<td>P-value</td>
</tr>
<tr>
<td>SPPB score</td>
<td>28.6 (21.9-34.4)</td>
<td>0.10 (0.03)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Health ABC PPB score</td>
<td>30.0 (24.7-35.3)</td>
<td>0.04 (0.01)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>20-m gait speed, m/sec</td>
<td>33.1 (27.1-39.1)</td>
<td>0.01 (0.003)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>400-m gait speed, m/sec</td>
<td>30.0 (21.6-38.4)</td>
<td>0.01 (0.004)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Grip strength, kg</td>
<td>25.9 (16.8-35.0)</td>
<td>0.36 (0.14)</td>
<td>0.01</td>
</tr>
<tr>
<td>Knee extensor strength, Nm/kg</td>
<td>21.9 (10.3-33.6)</td>
<td>0.17 (0.14)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

* per 4 ng/mL increment in 25(OH)D.

SPPB = short physical performance battery; PPB = physical performance battery

Houston DK et al., *Am J Epidemiol* 2012
Is there a 25(OH)D threshold for physical function?

- 25(OH)D levels of 75-80 nmol/L (30-32 ng/mL) have been suggested as optimal for various health outcomes (Bischoff-Ferrari HA et al., *Am J Clin Nutr* 2006)

- Data from Health ABC and other studies suggest that the 25(OH)D concentration threshold for physical performance and muscle strength is between 24 and 32 ng/mL (60 to 80 nmol/L)
Are low 25(OH)D concentrations associated with greater declines in physical function in older adults?


25(OH)D concentrations and change in physical function

• Longitudinal studies are mixed showing both no effect (Verreault R et al., J Am Geriatr Soc 2002; Faulkner KA et al., Osteoporos Int 2005; Bartali B et al., JAMA 2008; Michael YL et al., J Womens Health 2011; Houston DK et al., Am J Epidemiol 2012) and greater declines in muscle strength and physical performance with deficient/insufficient 25(OH)D concentrations (Visser M et al., J Clin Endocrinol Metab 2003; Wicherts IS et al., J Clin Endocrinol 2007; Dam TT et al., Osteoporos Int 2009; Sohl E et al, Osteoporosis Int 2013)
Older adults with low 25(OH)D concentrations had poorer physical performance over 4 years of follow-up… but low 25(OH)D concentrations were not associated with a faster rate of decline.
Rancho Bernardo Study: 25(OH)D status and change in physical performance

Women in the lowest 25(OH)D quartile (≤32 ng/mL) had an accelerated rate of decline in physical performance.

- **TCS = timed chair stands**
- **TUG = timed up and go**

Dam TT et al., *Osteoporosis Int* 2009
25(OH)D status and physical function: observational studies

• Possible explanations for inconsistent results in observational studies:
  – Differences in study populations (e.g., at risk vs. replete, baseline functional status, men vs. women, young old vs. old old, US vs. European)
  – Different assays used to measure serum 25(OH)D
  – Different cut-points used to define 25(OH)D deficiency/insufficiency
  – Different measures of physical performance
  – Differences in adjustment for potential confounders (e.g., season, BMI, physical activity)
  – Differences in duration of follow-up
Does 25(OH)D status alter the disability trajectory?

![Diagram showing the relationship between 25(OH)D status and disability trajectory over time. The graph compares optimal and insufficient 25(OH)D with respect to performance and disability threshold over time.]
Vitamin D insufficiency was associated with an increased risk of mobility limitation over 6 years of follow-up.

Houston DK et al., *J Gerontol: Med Sci* 2012
Does vitamin D supplementation improve physical function?
Vitamin D supplementation and physical performance and strength

Vitamin D supplementation and physical performance and strength

Balance/Sway

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Vitamin D supplementation Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bunout 2006</td>
<td>119.8</td>
<td>38.3</td>
<td>24</td>
<td>134.7</td>
<td>31.9</td>
<td>24</td>
<td>11.4%</td>
<td>-0.42 [-0.99, 0.16]</td>
</tr>
<tr>
<td>Dhesi 2004</td>
<td>0.0899</td>
<td>0.046</td>
<td>62</td>
<td>0.0999</td>
<td>0.057</td>
<td>61</td>
<td>29.8%</td>
<td>-0.19 [-0.55, 0.16]</td>
</tr>
<tr>
<td>Pfeifer 2009</td>
<td>81</td>
<td>32</td>
<td>121</td>
<td>86</td>
<td>30</td>
<td>30</td>
<td>58.8%</td>
<td>-0.16 [-0.41, 0.09]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>207</strong></td>
<td></td>
<td><strong>206</strong></td>
<td><strong>260</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>-0.20 [-0.39, -0.01]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.64$, df = 2 ($P = 0.73$); $I^2 = 0$
Test for overall effect: $Z = 2.02$ ($P = 0.04$)

Timed Up & Go

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Vitamin D supplementation Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bunout 2006</td>
<td>13.8</td>
<td>2.5</td>
<td>24</td>
<td>15.2</td>
<td>4.7</td>
<td>24</td>
<td>8.6%</td>
<td>-0.37 [-0.94, 0.21]</td>
</tr>
<tr>
<td>Pfeifer 2009</td>
<td>7.5</td>
<td>3.4</td>
<td>121</td>
<td>8.3</td>
<td>5.1</td>
<td>121</td>
<td>44.0%</td>
<td>-0.18 [-0.44, 0.07]</td>
</tr>
<tr>
<td>Zhu 2010</td>
<td>8.1</td>
<td>3.9</td>
<td>129</td>
<td>9</td>
<td>7</td>
<td>132</td>
<td>47.4%</td>
<td>-0.16 [-0.40, 0.09]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>274</strong></td>
<td></td>
<td><strong>277</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>-0.19 [-0.35, -0.02]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.43$, df = 2 ($P = 0.81$); $I^2 = 0$
Test for overall effect: $Z = 2.19$ ($P = 0.03$)

Lower extremity strength

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Vitamin D supplementation Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhesi 2004</td>
<td>204</td>
<td>92.4</td>
<td>62</td>
<td>198</td>
<td>79.7</td>
<td>61</td>
<td>19.7%</td>
<td>0.07 [-0.28, 0.42]</td>
</tr>
<tr>
<td>Pfeifer 2009</td>
<td>236</td>
<td>75</td>
<td>121</td>
<td>224</td>
<td>83</td>
<td>121</td>
<td>38.6%</td>
<td>0.15 [-0.10, 0.40]</td>
</tr>
<tr>
<td>Zhu 2010</td>
<td>176.5</td>
<td>49</td>
<td>129</td>
<td>179.5</td>
<td>54</td>
<td>132</td>
<td>41.7%</td>
<td>-0.06 [-0.30, 0.18]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>312</strong></td>
<td></td>
<td><strong>314</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.05 [-0.11, 0.20]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 1.39$, df = 2 ($P = 0.50$); $I^2 = 0$
Test for overall effect: $Z = 0.60$ ($P = 0.55$)

Vitamin D supplementation and physical function

- Randomized controlled trials of vitamin D have been inconsistent showing both no effect and improvements in muscle strength and physical performance.

- In a subset of the Women’s Health Initiative randomized controlled trial of calcium (1,000 mg/d) and vitamin D (400 IU/d), vitamin D supplementation was not beneficial in protecting against declines in physical performance or strength in older women over ~7 yrs of follow-up (n=3,137; Brunner RL et al., J Am Diet Assoc 2008)
Vitamin D supplementation and physical function

- Possible explanations for inconsistent results in randomized controlled trials:
  - Small sample sizes (<100 participants)
  - Insufficient vitamin D dose (<800 IU/d)
  - Type and frequency of vitamin D supplementation
  - Lack of baseline measures of 25(OH)D and response to vitamin D supplementation
  - Inadequate trial duration (≤6 mo)
  - Sample heterogeneity (at risk vs. replete populations, community-dwelling vs. nursing home, falls clinic, or stroke patient populations)
  - Secondary outcome in trails primarily designed to examine falls and fractures
Vitamin D: Knowledge gaps and research priorities

- Observational data suggest that 25(OH)D concentrations greater than those needed for skeletal health may be optimal for non-skeletal outcomes
  - Is 25(OH)D an appropriate biomarker?
  - How do physiological factors (e.g., age, BMI) affect the 25(OH)D response to dietary intake or endogenous production of vitamin D?
  - Are similar associations observed in minorities?
  - Will increasing 25(OH)D concentrations above the current IOM cut-point of 20 ng/mL improve physical function?

- Lack of convincing evidence for non-skeletal health outcomes from sufficiently powered randomized controlled trials
  - Large RCTs underway that include primary outcomes related to physical function (DO-HEALTH, n=2,158; STURDY, n~1200; EVIDENCE, n~200); secondary outcome in VITAL (n=25,874)
Vitamin D: Implications for dietary guidance in older adults

• Current recommendations (RDA) based on skeletal health (600 IU/d for 1-70 yrs; 800 IU/d for >70 yrs)
  – Corresponds to 25(OH)D concentrations of 20 ng/mL
  – Current vitamin D intake from dietary sources ~200 IU/day
  – Most older adults are not able to meet the current RDA through diet alone

• If RCTs show vitamin D supplements / higher 25(OH)D concentrations are beneficial / optimal for non-skeletal health outcomes, higher vitamin D intakes will be needed
  – 1800-2200 IU/d if 30 ng/mL is optimal for physical function and other non-skeletal health outcomes
Acknowledgements

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