Vitamin D and Musculoskeletal Health: What’s new?

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https://www.cimauk.org/
Outline

1. Review recent systematic review and meta-analyses
2. Recent Public Health Recommendations for vitamin D
3. Emerging trends in vitamin D enriched foods
4. Emerging evidence in very old adults (> 85 years)
Biosynthesis and metabolism of vitamin D

Holick (2004)
Vitamin D and muscle

Review recent systematic review and meta-analyses
Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis

Mark J Bolland, Andrew Grey, Alison Avenell

Interpretation Our findings suggest that vitamin D supplementation does not prevent fractures or falls, or have clinically meaningful effects on bone mineral density. There were no differences between the effects of higher and lower doses of vitamin D. There is little justification to use vitamin D supplements to maintain or improve musculoskeletal health. This conclusion should be reflected in clinical guidelines.

Lancet Diabetes Endocrinol
2018; 6: 847–58
Study heterogeneity

- Season
- Dietary intakes
- Sunlight exposure
- Assay variation in measuring vitamin D status
- Vitamin D status of participants at baseline

<table>
<thead>
<tr>
<th>Baseline 25-hydroxyvitamin D concentration</th>
<th>4/72 (6%)</th>
<th>41/72 (57%)</th>
<th>71/72 (99%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 nmol/L</td>
<td></td>
<td></td>
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<tr>
<td>&lt;50 nmol/L</td>
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<tr>
<td>&lt;75 nmol/L</td>
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</table>
Assessment of research waste part 1: an exemplar from examining study design, surrogate and clinical endpoints in studies of calcium intake and vitamin D supplementation

Mark L. Rolland, Allison Averill and Andrew Grey

Table 1 Classification of endpoints in 547 randomised controlled trials of vitamin D supplementation

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Number of RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical endpoints</td>
<td></td>
</tr>
<tr>
<td>Fracture</td>
<td>18</td>
</tr>
<tr>
<td>Falls</td>
<td>17</td>
</tr>
<tr>
<td>Respiratory (e.g. asthma, COPD, URTI)</td>
<td>14</td>
</tr>
<tr>
<td>Musculoskeletal symptoms/Pain</td>
<td>11</td>
</tr>
<tr>
<td>Pregnancy outcomes</td>
<td>9</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>8</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>7</td>
</tr>
<tr>
<td>Mood</td>
<td>6</td>
</tr>
<tr>
<td>SLE/Rheumatoid Arthritis</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>41</td>
</tr>
<tr>
<td>Surrogate endpoints</td>
<td></td>
</tr>
<tr>
<td>Bone mineral density</td>
<td>57</td>
</tr>
<tr>
<td>25OHD only</td>
<td>49</td>
</tr>
<tr>
<td>HbA1c or measures of glycaemia</td>
<td>42</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>38</td>
</tr>
<tr>
<td>Basic biochemistry</td>
<td>37</td>
</tr>
<tr>
<td>Bone turnover markers</td>
<td>31</td>
</tr>
<tr>
<td>25OHD, vitamin D metabolites and/or PTH only</td>
<td>24</td>
</tr>
<tr>
<td>Muscle Strength</td>
<td>16</td>
</tr>
<tr>
<td>Body weight</td>
<td>15</td>
</tr>
<tr>
<td>Physical performance tests</td>
<td>14</td>
</tr>
<tr>
<td>Vascular properties</td>
<td>7</td>
</tr>
<tr>
<td>Hepatitis C viral load</td>
<td>5</td>
</tr>
<tr>
<td>Lung function tests</td>
<td>4</td>
</tr>
<tr>
<td>Lipids</td>
<td>4</td>
</tr>
<tr>
<td>Other laboratory tests/assays</td>
<td>51</td>
</tr>
<tr>
<td>Other endpoints</td>
<td>16</td>
</tr>
</tbody>
</table>

Fig. 1 Number of publications over time of calcium intake with bone mineral density (left panels) or fracture (right panels) as endpoints by study design over time.
Recent Public Health Recommendations for vitamin D
## International recommendations

<table>
<thead>
<tr>
<th></th>
<th>IOM</th>
<th>SACN</th>
<th>EFSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum-linked reference value 4</td>
<td>EAR: 16 ng/mL RDA: 20 ng/mL</td>
<td>EAR (cannot establish) RNI ≥10 ng/mL</td>
<td>AR (cannot establish) PRI (cannot establish) AI: 20 ng/mL</td>
</tr>
<tr>
<td>Intake reference value 4</td>
<td>EAR: 400 IU (10 μg) RDA: 600 IU (15 μg)</td>
<td>RNI: 400 IU (10 μg)</td>
<td>AI: 600 IU (15 μg)</td>
</tr>
<tr>
<td>Selected Outcome</td>
<td>Skeletal health</td>
<td>Musculoskeletal health</td>
<td>Musculoskeletal health</td>
</tr>
<tr>
<td>Components of Selected Outcome</td>
<td>Integrated BMC/BMD, rickets, osteomalacia, calcium absorption, fractures</td>
<td>Rickets, osteomalacia, bone health indicators, fractures, falls, muscle health</td>
<td>Consideration of increased risk of adverse musculoskeletal outcomes</td>
</tr>
</tbody>
</table>
Evidence for the proposed benefits of vitamin D on non-musculoskeletal health outcomes is drawn mainly from observational studies so findings might be due to reverse causality (i.e., low 25(OH)D concentration is a consequence of the illness rather than the cause) or confounding by other factors associated with a specific health outcome.

There is limited RCT evidence for some non-musculoskeletal health outcomes and the findings are inconsistent.

The evidence overall suggests that the risk of poor musculoskeletal health is increased at serum 25(OH)D concentrations < 25 nmol/L.
New RNI’s

• The RNI was estimated by modelling data from individual RCTs in adults (men & women, 20-40 y and 64+ y) and adolescent girls (11 y). The RCTs had been conducted in winter so that dermal production of vitamin D was minimal.

• An RNI of 10 μg/d is proposed for the UK general population aged 11-64+ y. The RNI assumes minimal sunshine exposure because the studies used to derive this figure were conducted in winter. This is the amount needed to achieve a serum 25(OH)D concentration ≥ 25 nmol/L during winter in 97.5% of the population.
Vitamin D intakes are well below national recommendations

- Vitamin D deficiency has adverse consequences for musculoskeletal health across all stages of the lifecycle.\(^{(1)}\)
- In July 2016, a new RNI of 10\(\mu\)g/day was introduced for people aged 4 years and above.\(^{(1)}\)

Figure 1. Mean intakes of vitamin D from food sources (NDNS 2008/09 – 2011/12).\(^{(2)}\)
Vitamin D deficiency in Europe: pandemic?1,2


Am J Clin Nutr 2016;103:1033–44.

Key findings

• Using an NIH led international Vitamin D Standardization Program (VDSP) protocol for standardizing 25(OH)D values from 14 national health/nutrition surveys showed that 13.0% of the 55,844 European individuals sampled had serum 25(OH)D concentrations <30 nmol/L on average in the year, with 17.7% and 8.3% in those sampled during extended winter (Oct–Mar) and summer (Apr–Nov) periods, respectively.

• The suggests that vitamin D deficiency is widespread across Europe and at prevalence rates that meet the criteria of a pandemic (definition of a pandemic: “an epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people”
Emerging trends in vitamin D enriched foods
Food sources of vitamin D

Foods which provide the daily requirement of 10µg (400IU)

- 6 egg yolks
- 1 salmon fillet
- 6 x UV-exposed mushrooms
- 125g (5oz) margarine
- 6 x 100g pots

<table>
<thead>
<tr>
<th>Naturally present</th>
<th>‘Fortified’ foods</th>
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</table>
Vitamin D fortification of eggs for human health

Linda C Browning and Aaron J Cowieson

EFSA limits on vitamin D in hen feed = 3000IU vitamin D3/kg feed OR 75µg 25(OH)D /kg feed OR a combination not to exceed 3000IU/kg feed (1µg = 40IU)

8 of these 9 treatment groups exceed current EFSA limits
Relative effectiveness of oral 25-hydroxyvitamin D₃ and vitamin D₃ in raising wintertime serum 25-hydroxyvitamin D in older adults¹–⁴

Kevin D Cashman, Kelly M Seamans, Alice J Lucey, Elisabeth Stöcklin, Peter Weber, Mairead Kiely, and Tom R Hill

As nmol/L increase per μg compound, 25(OH)D₃ is 4.2 to 5-times as effective as D₃.⁹

Advantages of eggs as a fortificant

- Eggs naturally contain vitamin D and some 25(OH)D$_3$ depending on animal feeding practices.
- Eggs are a suitable food vehicle due to their relative sustainable production systems.
- Eggs are an inexpensive protein source and a nutritious and versatile food and ingredient.
- Eggs have been largely exonerated from CVD risk - no recommended limit on how many eggs people should eat.\(^{(6)}\)

UK annual egg consumption has increased from ~160 to 189 eggs/capita over the last 10 years.
'Sunshine Egg': A novel and healthier vitamin D enriched food (Innovate UK, Agri-Tech Catalyst Project) 2015/2016

Commercially focused Research. The Catalyst offers funding for private sector/academic collaborative research and development projects, to deliver innovation in agriculture and food systems.

Largest egg business in the UK owning approximately 40% of the national flock with eggs being produced both on company-owned farms and under contract.

A global science-based company in feed and supplement innovations for human and animal health

One of the UK’s leading centres for research into all aspects of poultry science, human nutrition and consumer behaviour.

Innovate UK
Initial exploitation and impact

September 21st 2018:

• Initial exploitation plans have included the recent reformulation and launch of Noble Food’s leading egg brand Happy Egg, containing nearly 30% more vitamin D than standard eggs at no additional cost to the consumer.
• The brand is the UK’s market leader in free-range eggs with 15% of the market share.
• Produces circa. 350 million eggs per year.
• Bought by 5.9 million households in the UK.
• Candidate REF impact case study developing from the work. Focus on research publication and gathering the appropriate supporting business statements and evidence needed to build a strong case.
New project to begin January 2019 will explore:

- Storage, cooking and processing effects on egg vitamin D content
- Impact of enriched egg consumption on vitamin D status and musculoskeletal health in a RCT
- Impact of wider egg enrichment with vitamin D on population intakes through stochastic modelling (Using NDNS data)
- Consumer acceptability of wider egg enrichment
Emerging evidence in very old adults
(> 85 years)
Factors Influencing Health Trajectories in very old Age

- Genes
- Nutrition
- Health
- Lifestyle
- Environment
- Socioeconomic status
- Attitude

These factors and their interactions have been studied in the **Newcastle 85+ Study**; a 6-year prospective study in more than 1000 individuals born in 1921 of the biological, clinical and psychosocial factors associated with healthy ageing. [http://research.ncl.ac.uk/85plus/](http://research.ncl.ac.uk/85plus/)
Cohort recruitment profile

Newcastle and North Tyneside General practices
(53/64 participated)

Invited to participate (n=1459)

Contact made (n=1409)

Declined (n=358)

Recruited (n=1042)

HA assessment only (n=3)

HA+GPRR (n=849)

GPRR only (n=188)

GPs declining similar to those agreeing on QoF etc

HA, HA+GPRR, GPRR, refusers compared: slightly more females in GPRR and refusers
HA+GPRR similar to Census

A quarter of men and a sixth of women have no important functional limitation at age 85.

Vitamin D Deficiency is common in the Newcastle 85+ participants

<table>
<thead>
<tr>
<th>25 (OH) D (nmol/l)</th>
<th>&lt;10</th>
<th>&lt;25</th>
<th>&lt;30</th>
<th>&lt;40</th>
<th>&lt;50</th>
<th>&lt;60</th>
<th>&lt;70</th>
<th>&lt;80</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of cohort</td>
<td>2</td>
<td>25</td>
<td>33</td>
<td>51</td>
<td>63</td>
<td>73</td>
<td>82</td>
<td>88</td>
</tr>
</tbody>
</table>

Institute of Medicine DRI’s

Deficiency = 30 nmol/l
EAR established at 40 nmol/L
RDA established at 50 nmol/L

All seasons

Use of vitamin D containing preparations (both supplements and medications) appeared to be the strongest predictor of 25(OH)D concentrations in these very old adults.

In the Newcastle 85+ Study (n = 845), we aimed to determine the association between 25(OH)D season-specific quartiles (hereafter SQ1–SQ4), grip strength (GS) and physical performance decline (Timed Up-and-Go Test, TUG) over 5 years using mixed models.

In the time-only models with linear and quadratic slopes, SQ1 and SQ4 of 25(OH)D were associated with weaker GS initially in men (SQ1: (SE) = -2.56 (0.96); SQ4: -2.16 (1.06)) and women (SQ1: -1.10 (0.52); SQ4: -1.28 (0.50)) (all p < 0.04).

In the fully adjusted models, only men in SQ1 had a significant annual decline in GS of 1.41 kg which accelerated over time (-0.40 (0.1)), (both p < 0.003) compared with those in combined middle quartiles. Only women in SQ1 and SQ4 of 25(OH)D had worse TUG times initially, but the rate of TUG decline was not affected.

Low baseline 25(OH)D may contribute to muscle strength decline in the very old and particularly in men.
The association between vitamin D and musculoskeletal health is consistent with a 'cause and effect' relationship.

The confusion in the literature is related to what the ultimate goal of supplementation is: i.e. Clinical benefit (classical pharmacological) V's Promotion of population health (classical Nutrition approach).

Vitamin D shouldn't be written off yet! Clinical science should target those most likely to benefit from vitamin D treatment.

Maintaining population vitamin D status above 25 nmol/L needs to be a priority. Given that 1 in 5 British adults fall below this threshold, strategies to increase dietary intakes such as food fortification should be a priority.
Acknowledgements

• Newcastle 85+ study participants
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• Newcastle 85+ Study academic stakeholders
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• National Health Service organizations
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  - Prof Carol Jagger
  - Dr Antoneta Granic
  - Mr Nuno Mendonca (PhD Student)
  - Prof John Mathers
  - Dr Mario Siervo
  - Dr Karen Davies
  - Dr Wendy Wrieden