Promoting Excellence in Family Medicine

Essential Knowledge Update 14
Vitamin D evidence update

Introduction

There has been an explosion in research on vitamin D. Wider effects of vitamin D in preventing cancer, cardiovascular disease, multiple sclerosis (and many other illnesses) have been suggested. It isn’t clear what we should do on the ground!

Basic Principles – what is vitamin D?

- "Vitamin D" is actually a group of sterol hormones which control absorption of calcium and phosphate from the gut.
- Receptors in many tissues including brain, immune system and cardiovascular system.
- Two main forms:
  - Ergocalciferol (vitamin D2) is found in plants, fortified foods and supplements.
  - Cholecalciferol (vitamin D3) is made in human skin by the action of ultraviolet light on precursors, and also found in fish, fortified food and supplements.
- Vitamin D deficiency is common in the UK, especially at Northern latitudes and in people with pigmented skin.

Overview

- Source Documents:
  - Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. Theodoraou et al BMJ 2014;348
  - Vitamin D and chronic disease prevention, Welsh P, Sattar N. BMJ 2014; 348
  - Vitamin D: too much do I good thing? Davies J.
  - Basic Principles – what is vitamin D?

- Conclusions from the umbrella review

  The review looked at 3 sorts of studies:
  1. Results from the systematic reviews:
     - There were 76 unique health outcomes identified.
     - Only six of these showed a statistically significant association between vitamin D levels and disease.
     - These conditions were:
       - Rheumatoid arthritis activity,
       - Colorectal cancer,
       - Hypertension in children,
       - Bacterial vaginosis in pregnant women,
       - Falls in older people
       - Rickets in children.
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- Conclusions from the umbrella review continued

2. Results from the meta-analyses of association between vitamin D and specific health outcomes
- Of the 48 meta-analyses identified, 30 reported a statistically significant result.
- The authors narrowed these down to 18 which showed no hint of bias (as tested by a variety of statistical methods).
- They therefore believe that the following findings are reliable. Low vitamin D levels are associated with higher risks of:
  - Cancer (colorectal)
  - Cardiovascular disease (including hypertension and stroke)
  - Depression
  - Cognitive decline
  - Metabolic syndrome and diabetes
  - Small for gestational age babies
  - Gestational diabetes

3. Results from the meta-analyses of randomized controlled trials of vitamin D supplementation
- Of the 57 meta-analyses, 13 showed a statistically significant result.
- Vitamin D supplementation is associated with:
  - Lower total cholesterol
  - Lower risk of low birth weight and higher maternal vitamin D levels at term
  - Higher muscle strength, better balance sway, higher femoral neck density, and fewer falls and non-vertebral fractures
  - Lower risk of dental caries
  - Lower risk of abnormal parathyroid hormone levels and hypercalcaemia in patients with chronic kidney disease.

Conclusions from the NEW meta-analysis and systematic review

- Found 22 randomized-controlled trials of isolated vitamin D supplements (not with calcium) including 30,716 participants.
- They analysed the results separately for the vitamin D3 trials (14 trials) and the vitamin D2 trials (8 trials):
  - Vitamin D3 supplementation trials - relative risk of death 0.89 (0.80 - 0.99)
  - Vitamin D2 supplementation trials - relative risk of death 1.04 (0.97 - 1.11)
- Findings broadly similar for different causes of death (such as cardiovascular disease and cancer)
- So, concludes vitamin D3 supplementation reduces mortality, but vitamin D2 supplementation does not (and may even be harmful).

Why does the new meta analysis not agree with the umbrella review?

BMJ editorial suggests:
- Meta analysis of vitamin D3 trials was based on only 13,000 participants, perhaps it was a chance finding.
- Observational data is always at risk from confounding. The unfit or unhealthy may get out less and so have lower vitamin D levels.
- The different teams are using different statistical approaches.
- The studies in the vitamin D3 analysis which had most impact on the findings had elderly participants. Perhaps a small reduction in fracture risk led to the findings of lower risk of mortality (as these patients then avoided the inherent risks of a hospital stay).
**Vitamin D – What do we do in light of the uncertainty?**

The editorials in the BMJ and BJGP suggest:

- Remaining cautious about interpreting observational studies (as these have misled the medical community in the past).
- Waiting for new primary research (such as the on-going VITAL study due to report in 2017) rather than more reanalysis of old data.
- Avoiding expensive testing of vitamin D levels in asymptomatic patients not in an at risk group for bone disease.
- Prescribing low-cost licensed forms of cholecalciferol when needed rather than relying on over-the-counter or unlicensed supplements.

**Vitamin D – more thoughts on uncertainty (my thoughts!)**

- GPs are good at tolerating uncertainty.
- Should we perhaps share this uncertainty with our patients?
- We could inform patients that, at present, the evidence base on vitamin D is incomplete and seek their preferences.
- Not clear whether skin pigmentation adequately considered in the research.
- Not clear why BJGP editorial is pushing licensed products rather than over-the-counter (free to NHS) or branded products such as ProD3 or Hux-D3 which are what medicines management are largely suggesting.
- Consider weekly/monthly dosing as much the cheapest option.

**NICE update November 2014**

**Vitamin D: increasing supplement use among at-risk groups**

Issued: November 2014

NICE public health guidance 56

[guidance.nice.org.uk/PH56](http://guidance.nice.org.uk/PH56)

**NICE recommendations**

- To offer vitamin D supplementation to the following groups:
  - infants and children aged under 5
  - pregnant and breastfeeding women, particularly teenagers and young women
  - people over 65
  - people who have low or no exposure to the sun, for example, those who cover their skin for cultural reasons, who are housebound or confined indoors for long periods
  - people with darker skin, for example, people of African, African-Caribbean or South Asian family origin.

**A note about vitamin D treatments**

- To treat deficiency aiming for 300,000 U over a few weeks.
- Daily recommended intake is 400-800 U
- Hux D3 widely recommended (£2.66 for 20 capsules of 20,000 U) – this would be a treatment quantity. Beware this is non-Halal. Unlicensed.
- Pro D3 - Halal alternative. Unlicensed. (About £10 for 15 capsules of 20,000)
- Fultium D3 often advised for maintenance (800U) (£3.60 for 30)
- But why use daily dosing if monthly works and is cheaper?

**Learning & Service Needs**

**Learning Needs:**

- Do you know when to test for vitamin D deficiency and when to treat without testing?
- What is your local advice on prescribing vitamin D supplements cost-effectively?

**Service Needs:**

- Is there a local protocol on testing and treating vitamin D deficiency?
- Do you have a leaflet available to give to patients (possibly in a range of languages) to explain the issues around vitamin D, useful lifestyle measures and the role of supplementation?
Further Reading:

Vitamin D and mortality: meta-analysis of individual participant data from a large consortium of cohort studies from Europe and the United States. Schöttker et al. BMJ 2014: 348 http://www.bmj.com/content/348/bmj.g3656


Useful Links:

Information for patients explaining NHS opinion on vitamin D
http://www.nhs.uk/Conditions/vitamins-minerals/Pages/Vitamin-D.aspx

National Osteoporosis society guidance on vitamin D