Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

ScriptSwitch™ Rapid Update 2 – August 2017

Monthly high-dose vitamin D: no reduction in falls and fractures found in large randomised controlled trial

A randomised controlled trial (RCT) involving over 5,000 people aged between 50 and 84 years found that monthly high-dose vitamin D3 supplements did not reduce the risk of falls and fracture compared with placebo. These findings support those of a 2014 Cochrane review and the Scientific Advisory Committee on Nutrition (SACN) report on vitamin D. These results may be a reason to review the use of monthly high-dose vitamin D to reduce falls and fracture in the general older population.

Reference: Khaw K, Stewart AW, Waayer D *et al.* Effect of monthly high-dose vitamin D supplementation on falls and non-vertebral fractures: secondary and post-hoc outcomes from the randomised, double-blind, placebo-controlled ViDA trial. The Lancet Diabetes & Endocrinology. 2017 Volume 5, Issue 6, Pages 438–447

What do we know already?

- Vitamin D regulates calcium and phosphate levels and is needed for healthy bones and muscles. Public Health England recommends that all people in the UK should consider taking a daily 10 microgram (400 IU) vitamin D supplement during autumn and winter. People who have a higher risk of vitamin D deficiency are advised to take a supplement all year round. At risk groups include people who have no or limited exposure to the sun, people over 65 years, children aged less than 5 years and individuals with darker skin.
- Vitamin D deficiency, generally defined as a serum 25(OH)D concentration below 25 nmol/L, can lead to rickets and osteomalacia. Although there has been much discussion in the scientific literature around 'adequate' and 'optimal' vitamin D levels, no studies have demonstrated a clear clinical benefit of maintaining high vitamin D levels.
- Vitamin D supplements are often prescribed to reduce fracture risk and improve 'bone health', although clinical trials on vitamin D for fracture prevention has reported conflicting results. In 1992, a randomised controlled trial (RCT) found that vitamin D3 (800 IU) plus calcium (1.2 g) reduced the risk of hip and other non-vertebral fractures in women living in nursing homes (Chapuy *et al*, 1992). However, other studies have reported less promising results. Sanders *et al*. (2010) found that a single high dose of vitamin D3 (500,000 IU) given to older, community-dwelling women once a year increased their risk of falls and fracture. A 2014 Cochrane review (Avenell *et al*. 2014) concluded that vitamin D alone is unlikely to prevent fractures, although supplements containing vitamin D plus calcium may prevent fractures. In 2016 the Scientific Advisory Committee on Nutrition (SACN) published the 'Vitamin D and health report', which stated "data in adults ≥ 50 years are mixed but, on balance, suggest that vitamin D supplementation does not reduce fracture risk".

What does this evidence add?

- This RCT found that monthly high-dose vitamin D3 supplements did not reduce the risk of falls and fractures in adults aged between 50 and 84 years.
- It's important to note that fractures and falls were secondary or post-hoc outcomes of a study designed to investigate cardiovascular events. Scragg *et al*. (2017) have reported the cardiovascular outcomes of this study, finding that monthly vitamin D did not reduce incident cardiovascular disease and death compared with placebo.
- This study has some limitations. Falls were self-reported by participants - a method of data collection open to recall bias. The study also had low statistical power for the fracture outcome, particularly for sub-groups of interest (e.g. people with vitamin deficiency). Only around 1.4% of the study population had osteoporosis. The Clinical Knowledge Summary on osteoporosis states that approximately 2% of women aged 50 years have osteoporosis, increasing to almost 50% by 80 years. The population in this study may not be representative of the general population and may have a lower fracture risk.

Study details

Participants:

- The Vitamin D Assessment (ViDA) Study is a New Zealand-based, double-blind RCT involving 5,110 community-based people aged between 50 and 84 years (mean age 65.9 years).
- More men were included in the study (58%), and nearly half the participants (47%) had a history of fracture. Only 1.4% of participants had a history of osteoporosis.
- Levels of 25(OH)D were adjusted for natural seasonal variation ('deseasonalised'). The mean baseline deseasonalised 25(OH)D was 66 nmol/L. Only around 2% of participants had vitamin D deficiency (defined as serum 25[OH]D <25 nmol/L).

Intervention and comparison:

- Participants were randomised to vitamin D3 (colecalciferol) 100,000 IU each month (following a single 200,000 IU loading dose, n=2,558) or placebo (n=2,552).
- This equates to a vitamin D3 daily dose of 3290 IU (83 micrograms), approximately 8-times higher than the recommended daily intake for this vitamin.
- The mean duration of study treatment was 3.4 years.

Outcomes and results:

- The primary outcome of the ViDA study was incident cardiovascular disease. Non-vertebral fractures and respiratory infection were secondary outcomes. Rate of falls is reported as a post hoc outcome. Adverse events were reported by the participants using a questionnaire.
- Approximately 6% of participants in the study had a non-vertebral fracture during follow-up. Monthly high-dose vitamin D did not reduce the risk of non-vertebral fracture compared with placebo (hazard ratio [HR] 1.19, 95% confidence interval [CI] 0.94 to 1.50 after adjustment for sex, age, ethnic origin, history of recent fall, physical activity and baseline 25[OH]D).
- There was no significant difference in the number of people reporting at least 1 fall in the vitamin D3 group (52%) compared with placebo (53%, adjusted HR 0.99, 95% CI 0.92 to 1.07).
- All-cause mortality did not differ significantly between treatment groups (65 deaths in vitamin D group *vs.* 58 in placebo group).

Level of evidence:
Level 1 (good quality patient-oriented evidence) according to the SORT criteria.

Study funding:
The ViDA study was funded by the Health Research Council of New Zealand and Accident Compensation Corporation of New Zealand.