Bone Health July 2017

Prescribing....

- ViDA, a randomised controlled study conducted in New Zealand, found that monthly high-dose vitamin D3 supplements did not reduce the risk of falls and fractures vs placebo.
- It found that vitamin D3 did not reduce the primary outcome of incident cardiovascular disease and death vs placebo.
- Strontium ranelate will be withdrawn by the manufacturers in August 2017, as safety restrictions have led to reduced sales.
- Community pharmacists report that calcium & vitamin d supplements are often returned unused, so prescribers are requested to review the use of supplements regularly.

ViDA Study

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 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".

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 the study 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.

What did the evidence add ?
ViDA is a large scale study which looked at good quality patient-oriented outcomes over a number of years. It was publically-funded by the Health Research Council of New Zealand and the Accident Compensation Corporation of New Zealand. Therefore its results , as follows, are likely to be credible.
It 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.

1. Falls were self-reported by participants - a method of data collection open to recall bias.
2. The study also had low statistical power for the fracture outcome, particularly for sub-groups of interest (e.g. people with vitamin deficiency).
3. 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 in the UK and locally, and may have a lower fracture risk.

Strontium ranelate
There has been confusion about the availability of strontium ranelate, but colleagues are advised that the company will definitely cease production in August 2017. This agent was extensively promoted in 2007 as "the first dual action bone agent" and "the only drug to increase bone formation and decrease bone resorbtion". These claims were however based on biochemical markers of bone formation rather than the more definitive bone biopsies. In 2014 the drug's often-questioned safety profile led to restrictions on its indication and new monitoring requirements by the EMEA of its risks and benefits. The subsequent reduced demand contributed to the company's decision to withdraw it on commercial grounds. There are 161 patients on the islands and 28,500 in England who will now need to be reassessed and alternative options considered.

Calcium and Vitamin D Supplements on prescription
Community pharmacists report that calcium & vitamin d supplements are often returned unused, so prescribers are earnestly requested to review their use regularly.

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