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Effectiveness and safety of vitamin D in relation to bone health.

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Abstract

OBJECTIVES: To review and synthesize the literature in the following areas: the association of specific circulating 25(OH)D concentrations with bone health outcomes in children, women of reproductive age, postmenopausal women and elderly men; the effect of dietary intakes (foods fortified with vitamin D and/or vitamin D supplementation) and sun exposure on serum 25(OH)D; the effect of vitamin D on bone mineral density (BMD) and fracture or fall risk; and the identification of potential harms of vitamin D above current reference intakes.

DATA SOURCES: MEDLINE(R) (1966-June Week 3 2006); Embase (2002-2006 Week 25); CINAHL (1982-June Week 4, 2006); AMED (1985 to June 2006); Biological Abstracts (1990-February 2005); and the Cochrane Central Register of Controlled Trials (2nd Quarter 2006).

REVIEW METHODS: Two independent reviewers completed a multi-level process of screening the literature to identify eligible studies (title and abstract, followed by full text review, and categorization of study design per key question). To minimize bias, study design was limited to randomized controlled trials (RCTs) wherever possible. Study criteria for question one were broadened to include observational studies due to a paucity of available RCTs, and question four was restricted to systematic reviews to limit scope. Data were abstracted in duplicate and study quality assessed. Differences in opinion were resolved through consensus or adjudication. If clinically relevant and statistically feasible, meta-analyses of RCTs on vitamin D supplementation and bone health outcomes were conducted, with exploration of heterogeneity. When meta-analysis was not feasible, a qualitative systematic review of eligible studies was conducted.

RESULTS: 167 studies met our eligibility criteria (112 RCTs, 19 prospective cohorts, 30 case-controls and six before-after studies). The largest body of evidence on vitamin D status and bone health was in older adults with a lack of studies in premenopausal women and infants, children and adolescents. The quality of RCTs was highest in the vitamin D efficacy trials for prevention of falls and/or fractures in older adults. There was fair evidence of an association between low circulating 25(OH)D concentrations and established rickets. However, the specific 25(OH)D concentrations associated with rickets is uncertain, given the lack of studies in populations with dietary calcium intakes similar to North American diets and the different methods used to determine 25(OH)D concentrations. There was inconsistent evidence of an association of circulating 25(OH)D with bone mineral content in infants, and fair evidence that serum

25(OH)D is inversely associated with serum PTH. In adolescents, there was fair evidence for an association between 25(OH)D levels and changes in BMD. There were very few studies in pregnant and lactating women, and insufficient evidence for an association between serum 25(OH)D and changes in BMD during lactation, and fair evidence of an inverse correlation with PTH. In older adults, there was fair evidence that serum 25(OH)D is inversely associated with falls, fair evidence for a positive association with BMD, and inconsistent evidence for an association with fractures. The imprecision of 25(OH)D assays may have contributed to the variable thresholds of 25(OH)D below which the risk of fractures, falls or bone loss was increased. There was good evidence that intakes from vitamin D-fortified foods (11 RCTs) consistently increased serum 25(OH)D in both young and older adults. Eight randomized trials of ultraviolet (UV)-B radiation (artificial and solar exposure) were small and heterogeneous with respect to determination of the exact UV-B dose and 25(OH)D assay but there was a positive effect on serum 25(OH)D concentrations. It was not possible to determine how 25(OH)D levels varied by ethnicity, sunscreen use or latitude. Seventy-four trials examined the effect of vitamin D(3) or D(2) on 25(OH)D concentrations. Most trials used vitamin D(3), and the majority enrolled older adults. In three trials, there was a greater response of serum 25(OH)D concentrations to vitamin D(3) compared to vitamin D(2), which may have been due to more rapid clearance of vitamin D(2) in addition to other mechanisms. Meta-analysis of 16 trials of vitamin D(3) was consistent with a dose-response effect on serum 25(OH)D when comparing daily doses of <400 IU to doses >/= 400 IU. An exploratory analysis of the heterogeneity demonstrated a significant positive association comparable to an increase of 1 - 2 nmol/L in serum 25(OH)D for every 100 additional units of vitamin D although heterogeneity remained after adjusting for dose. Vitamin D(3) in combination with calcium results in small increases in BMD compared to placebo in older adults although quantitative synthesis was limited due to variable treatment durations and BMD sites. The evidence for fracture reduction with vitamin D supplementation was inconsistent across 15 trials. The combined results of trials using vitamin D(3) (700 - 800 IU daily) with calcium (500 - 1,200 mg) was consistent with a benefit on fractures although in a subgroup analysis by setting, benefit was primarily in elderly institutionalized women (fair evidence from two trials). There was inconsistent evidence across 14 RCTs of a benefit on fall risk. However, a subgroup analysis showed a benefit of vitamin D in postmenopausal women, and in trials that used vitamin D(3) plus calcium. In addition, there was a reduction in fall risk with vitamin D when six trials that adequately ascertained falls were combined. Limitations of the fall and fracture trials included poor compliance with vitamin D supplementation, incomplete assessment of vitamin D status and large losses to follow-up. We did not find any systematic reviews that addressed the question on the level of sunlight exposure that is sufficient to maintain serum 25(OH)D concentrations but minimizes risk of melanoma and non-melanoma skin cancer. There is little evidence from existing trials that vitamin D above current reference intakes is harmful. In most trials, reports of hypercalcemia and hypercalciuria were not associated with clinically relevant events. The Women's Health Initiative study did report a small increase in kidney stones in postmenopausal women aged 50 to 79 years whose daily vitamin D(3) intake was 400 IU (the reference intake for 50 to 70 years, and below the reference intake for > 70 years) combined with 1000 mg calcium. The increase in renal stones corresponded to 5.7 events per 10,000 person-years of exposure. The women in this trial had higher calcium intakes than is seen in most post-menopausal women.

CONCLUSIONS: The results highlight the need for additional high quality studies in infants, children, premenopausal women, and diverse racial or ethnic groups. There was fair evidence from studies of an association between circulating 25(OH)D concentrations with some bone health outcomes (established rickets, PTH, falls, BMD). However, the evidence for an association was inconsistent for other outcomes (e.g., BMC in infants and fractures in adults). It was difficult to define specific thresholds of circulating 25(OH)D for optimal bone health due to the imprecision of different 25(OH)D assays. Standard reference preparations are needed so that serum 25(OH)D can be accurately and reliably measured, and validated. In most trials, the effects of vitamin D and calcium could not be separated. Vitamin D(3) (>700 IU/day) with calcium supplementation compared to placebo has a small beneficial effect on BMD, and reduces the risk of fractures and falls although benefit may be confined to specific subgroups. Vitamin D intake above current dietary reference intakes was not reported to be associated with an increased risk of adverse events. However, most trials of higher doses of vitamin D were not adequately designed to assess long-term harms.

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