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Effect of vitamin d2 supplementation on serum 25 hydroxy-vitamin d3 levels: a systematic review and meta-analysis

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Food manufacturers will often use vitamin D₂ to fortify foods with vitamin D, as unlike vitamin D₃, D₂ can be consumed by vegetarians and vegans⁽¹⁾. However, recent research has indicated that vitamin D₂ has a lesser effect on raising total vitamin D (25(OH)D) status compared to vitamin D₃ and could result in a decrease in 25(OH)D₃ concentrations^(2–4). Furthermore, only vitamin D₃ and not vitamin D₂ has been found to decrease all-cause and cancer mortality⁽⁵⁾.

The objective was to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) that have supplemented with vitamin D₂ via a tablet/capsule or via a food fortification vehicle, and to compare concentrations of measured serum 25(OH)D₃ following supplementation.

A comprehensive electronic search of the EMBASE and PUBMED databases was performed, covering January 1980 to February 2017. Search terms used were as follows: “vitamin D OR 25-hydroxy* OR vitamin D2 OR vitamin D3 OR cholecalciferol OR ergocalciferol OR 25OHD” AND “supplementation” AND “randomized controlled trial OR randomized controlled trial OR RCT”. Studies were also selected via online hand-searches and by examining study bibliographies. Studies were eligible if they had supplemented vitamin D₂ in human adults, had a clear control/placebo comparison group and had measured serum concentration of 25(OH)D₃ in both groups. Studies were then systematically reviewed for inclusion into the final meta-analysis. Out of 11 studies for systematic review, 8 study authors needed to be contacted to request missing data. Subsequently, data from 6 studies were available to be included for meta-analysis. The majority of 25(OH)D₃ concentrations were measured in nmol/L, although one study required conversion from ng/mL (1 ng/mL = 2.5 nmol/L).

A total of 803 participants were included in the 11 studies selected for systematic review. Ages ranged from 18–84 years and in the 9 studies that declared the gender of subjects, the ratio of males to females was approximately 1:3. The studies were undertaken in the UK, Ireland, USA, New Zealand, Germany and Finland and dated from 1999–2016, although all but 1 study were dated within the last 13 years. Of the 5 studies that declared ethnicity of participants, a range of Caucasian (*n* 343), South Asian (*n* 63), African-American (*n* 31), Hispanic (*n* 5), Asian (*n* 8) and Native American adults (*n* 1) were included. The meta-analysis demonstrated that vitamin D₂ supplementation led to a mean difference (MD) in serum 25(OH)D₃ as follows: MD (fixed) = -11.97 (95% CI -13.93 to -10.1; *P* < 0.00001, *p*^(heterogeneity) = 0.36 *I*² = 9%. Therefore, there was an 11.97 nmol/L drop in 25(OH)D₃ when subjects were supplemented with vitamin D₂ as opposed to a control group.

This meta-analysis indicates that overall, supplementation of vitamin D₂ decreased serum 25(OH)D₃ concentration by an average of 12 nmol/L, which was highly significant (*P* < 0.00001). In addition, the findings suggest that those with higher baseline 25(OH)D concentrations may be more susceptible to the lowering effect of vitamin D₂ on 25(OH)D₃. Further research is urgently required to understand fully the molecular mechanisms underlying this drop in 25(OH)D₃ levels, as well as the long-term implications of vitamin D₂ supplementation on health outcomes and mortality.

1) Arya. (2012) *Aust Fam Physician*. 41(5):73–93.

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3) Logan *et al.* (2013) *Br J Nutr*. 109(6):1082–1088.

4) Iitkonen *et al.* (2016) *Br J Nutr*. 115(7):1232–1239.

5) Bjelakovic *et al.* (2011) *Cochrane Database Syst Rev* (7):CD007470.