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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 D_2 to fortify foods with vitamin D, as unlike vitamin D_3, D_2 can be consumed by vegetarians and vegans[(1)]. However, recent research has indicated that vitamin D_2 has a lesser effect on raising total vitamin D (25(OH)D) status compared to vitamin D_3 and could result in a decrease in 25(OH)D_3 concentrations[(2–4)]. Furthermore, only vitamin D_3 and not vitamin D_2 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 D_2 via a tablet/capsule or via a food fortification vehicle, and to compare concentrations of measured serum 25(OH)D_3 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 D_2 in human adults, had a clear control/placebo comparison group and had measured serum concentration of 25(OH)D_3 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)D_3 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 D_2 supplementation led to a mean difference (MD) in serum 25(OH)D_3 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)D_3 when subjects were supplemented with vitamin D_2 as opposed to a control group.

This meta-analysis indicates that overall, supplementation of vitamin D_2 decreased serum 25(OH)D_3 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 D_2 on 25(OH)D_3. Further research is urgently required to understand fully the molecular mechanisms underlying this drop in 25(OH)D_3 levels, as well as the long-term implications of vitamin D_2 supplementation on health outcomes and mortality.

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