REVIEWING THE SCIENCE
VITAMIN D2 AND VITAMIN D3

The case for equivalency in meeting the shortfall of this important nutrient

INTRODUCTION

Although there have been published comparisons of ergocalciferol (Vitamin D2) and cholecalciferol (Vitamin D3) indicating advantages of D3 (oftentimes using very high/pharmacological levels of the vitamins), there are a number of recent reports providing evidence of equal 25-hydroxyvitamin D [25(OH)D] production, which is considered the serum biomarker of Vitamin D status. These studies have been conducted using nutritional levels of Vitamin D intakes that are closer to the FDA daily value (DV), so are more physiologically relevant than the very high levels used in some of the studies showing advantages of the D3 form over D2. The following are a series of objections that appear frequently in media stories about Vitamin D2 and Vitamin D3, with an analysis of the science underlying these positions.
**OBJECTION:** Vitamin D3 is the only ‘natural’ Vitamin D

**CONTROVERSIAL STATEMENT:** Cholecalciferol (Vitamin D3) is a natural by-product of animal origin that is created from exposure to the sun, while ergocalciferol (Vitamin D2) is a synthetic by-product of plant origin.

**RESPONSE:** This statement is misleading to the point of being false. There are no ‘synthetic’ forms of Vitamin D – all are natural. Both Vitamin D2 and D3 are formed through ultraviolet exposure of precursors, ergosterol for D2 and 7-dehydrocholesterol for D3. It is true that most forms of D3 are animal-based. On the other hand, the available non-animal forms (yeast, mushrooms, lichen) are actually based on the fungus kingdom and are primarily D2. A more salient issue to consider when choosing a ‘natural’ Vitamin D source is the manner in which these are processed and prepared as ingredients. Are they highly processed in a mass production facility? Are they extracts? What is the extraction process and what are the residuals in the final product? What substances are added to create a viable, stable final product form?

"There are no ‘synthetic’ forms of Vitamin D – all are natural."

**OBJECTION:** Vitamin D3 is more stable than Vitamin D2 with a longer shelf-life

**CONTROVERSIAL STATEMENT:** In addition to its lower bioefficacy, Vitamin D2 is considerably less stable than Vitamin D3, particularly when in a crystalline powder form that is subjected to varying temperatures, humidity levels and even storage methods.

**RESPONSE:** In her article from 2006, Houghton surmised that Vitamin D3 is more potent than D2 in humans but does so by relying on older data from a variety of non-human species. In further support of this conclusion, Houghton references data from Armas and Trang, both of whom studied the impact of D2 and D3 supplementation on 25(OH)D serum concentrations at doses of 50,000 IU/d and 4,000 IU/d, respectively. As discussed in detail below, this is weak evidence for lower bioefficacy of Vitamin D2 compared to D3. In addition, differences in stability are suggested by Houghton and Vieth in their 2006 commentary which relies on data from a 1943 publication. Analytical methods as well as purity of D2 and D3 preparations over 70 years ago call into question the relevance of these concerns.

In fact, recent work from the Vitamin D, Skin and Bone Research Laboratory at Boston University Medical Center evaluated a newer food source of Vitamin D - mushrooms exposed to UVB light, which provide a significant source of D2. In this study, it was determined that healthy adults who ingested 2000 IUs of Vitamin D2 from mushrooms daily for 3 months were able to raise and maintain their total 25(OH)D concentrations similarly to healthy adults who ingested supplements containing either 2000 IU of Vitamin D2 or D3.

"Analytical methods... of over 70 years ago call into question the relevance of these concerns."
OBJECTION: Vitamin D3 is better than D2 at raising Vitamin D levels in people

CONTROVERSIAL STATEMENT: According to a recent 2012 meta-analysis of randomized controlled trials that compared the effects of Vitamin D3 and D2 supplementation, Vitamin D3 is more efficacious than Vitamin D2 at raising concentrations of serum 25-hydroxyvitamin D (the functional indicator of Vitamin D status). In fact, clinical studies have shown that Vitamin D3 is twice as potent as Vitamin D2 in increasing and maintaining higher serum concentrations of 25-hydroxyvitamin D.

RESPONSE: There are several important considerations regarding the Tripkovic meta-analysis. First, the study was published in 2012, which is significant, because since that time, several important studies were conducted comparing the ability of the D2 and D3 vitamers to raise serum concentration of 25(OH)D when supplemented at more physiological (nutritional) levels. These studies (reviewed below) were not included in the meta-analysis, but show that both forms of Vitamin D at 400, 1000 or 2,000 IU resulted in similar increases in respective serum 25(OH)D concentrations.

Secondly, the authors of the meta-analysis make the statement in their publication that the frequency of dosage had no effect on the efficacy of either ergocalciferol (D2) or cholecalciferol (D3) supplementation. However, the actual data suggest differently. When supplementation was given at 50,000-300,000 IU weekly or monthly, a statistically significant advantage was observed for D3 over D2 in raising serum 25(OH)D levels. But when analysis was focused on daily supplementation with doses of 1,000 IU – 4,000 IU/d, no significant difference in serum 25(OH)D levels was observed. This is relevant, because very high pharmacological doses can force physiologic changes that would not occur at typical nutritional levels of consumption or supplementation.

The authors do acknowledge that in the studies included in their analysis, doses given exceeded the currently recommended RDA of 600 IU and that:

“these studies offered little information for lower doses, which are more realistic in terms of what individuals are likely to be able to consume within their daily diet and gain from sunlight exposure and the concentrations of ergocalciferol and cholecalciferol available in commercial supplements.”

Additionally, the authors conceded that there were many other limitations to their study, not the least of which were diversity with respect to the dosages used; frequency of supplementation, method of administration (i.e., oral vs. intramuscular) and small, underpowered sample sizes that also contributed to heterogeneity in the results. While making bold conclusions about what their analysis represents, the authors stated the need for additional research to clarify significance of this research across various doses of Vitamin D.

The frequently cited Heaney study, ascribing a value of 87% greater potency in raising and maintaining 25(OH)D concentrations to Vitamin D3 compared with D2, should also be considered with caution due to the pharmacological dose used in this study. Indeed, the two vitamers were dosed at 50,000 IU/week (7143 IU/d) for 12 weeks. This intake represents 11 times the current RDA of 600 IU/d and 18 times the current DV of 400 IU/d. The Tolerable Upper Intake level established by the Institute of Medicine is 4,000 IU/d for individuals over 9 yrs old. As noted above, the physiological changes in metabolism or handling of Vitamin D at these pharmacological levels, or levels exceeding those which are considered to be well above the upper intake level, are not known and do not indicate handling of the vitamin at nutritional levels.
OBJECTION: Vitamin D3 is better at promoting human health than Vitamin D2

CONTROVERSIAL STATEMENT: Overall, given the scientific evidence on the superior bioavailability of Vitamin D3 and its efficacy for the treatment and prevention of Vitamin D insufficiency, Vitamin D3 may be the preferred form.

RESPONSE: In fact, the scientific evidence does not support superior bioavailability or efficacy for D3 over D2 at levels that are consistent with those consumed. When controlled studies were conducted to assess D2 vs. D3 at nutritional rather than pharmacological levels, it has been repeatedly shown that the two vitamers are similar in their ability to raise and maintain the serum biomarker of Vitamin D status (25(OH)D). It is interesting to note that these studies, including the work from a well-regarded expert in Vitamin D nutrition, Dr. Holick, are consistently ignored in the D2 v. D3 discussion.

Further supporting the similarity in response between D2 and D3 consumption, a recent Clinical Practice Guideline developed by the Endocrine Society recommends treatment with either Vitamin D2 or D3 for individuals with low serum (25(OH)D) levels. Notably, the two scientists representing opposite sides of the D2 vs D3 debate (Heaney and Holick) are co-authors of this recommendation.

"When controlled studies were conducted to assess D2 vs. D3 at nutritional rather than pharmacological levels, it has been repeatedly shown that the two vitamers are similar..."
CONCLUSION

As is evident from the material discussed in this overview, the science relative to forms of Vitamin D is evolving. The fact that the key publications referred to by those who favor D3 over D2 pre-date some of the very recent work showing equivalency at nutritional intakes demonstrates how quickly the science is developing. Further study will and should take place to understand how this incredibly important nutrient functions in the human body. This is particularly the case as new sources of Vitamin D become available in the marketplace.

It is, however, probably more important to realize that this ‘evolution’ is taking place within an urgent context: a recognition that over 90% of North Americans do not get enough Vitamin D, and that it is considered a ‘shortfall nutrient’ by the USDA. Underscoring the significance of this is the recent FDA proposal to include Vitamin D on the Nutrition Facts Panel to aid consumers in recognizing and choosing Vitamin D-containing foods.

From the material presented here, it is clear that Vitamin D2 is up to the task of helping consumers meet their Vitamin D shortfall and has been shown to be equivalent to Vitamin D3—at the levels (400 to 2,000 IU/day) typically consumed by people. As members of the scientific and nutrition community, it may be best for us to focus on addressing the shortfall in whatever way we can instead of focusing on the D2 versus D3 controversy or predictions of how the science may one day turn out.

REFERENCES CITED


STUDIES THAT SUPPORT D2 EQUIVALENCE TO D3

<table>
<thead>
<tr>
<th>Study</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum concentrations of 1,25-dihydroxyVitamin D2 and 1,25-dihydroxyVitamin D3 in response to Vitamin D2 and Vitamin D3 supplementation. Biancuzzo RM (2013) J Clin Endocrinol Metab 98(3): 973-979</td>
<td>Supplementation with 1000 IU Vitamin D2 or D3 resulted in similar increases in respective serum 25(OH)D concentrations and did not alter serum concentrations of 1,25(OH)2 D3 or total 1,25(OH)2 D.</td>
</tr>
<tr>
<td>Fortified Malted Milk Drinks Containing Low-Dose Ergocalciferol and Cholecalciferol Do Not Differ in Their Capacity to Raise Serum 25-HydroxyVitamin D Concentrations in Healthy Men and Women Not Exposed to UV-B</td>
<td>Supplementation with low dose Vitamin D2 or D3 in a milk-based drink resulted in dose-dependent increases in their respective metabolites. Vitamin D2 supplementation did not influence serum levels of Vitamin D3 metabolite.</td>
</tr>
<tr>
<td>The Change in Plasma 25-HydroxyVitamin D Did Not Differ between Breast-Fed Infants That Received a Daily Supplement of Ergocalciferol or Cholecalciferol for 3 Months Gallo S et al. (2013) J Nutr143: 148-153</td>
<td>Supplementation of breastfed infants with 400 IU Vitamin D2 or Vitamin D3 for 3 months showed that the increases in serum concentrations of 25(OH)D did not differ between the two groups.</td>
</tr>
<tr>
<td>Vitamin D2 Is as Effective as Vitamin D3 in Maintaining Circulating Concentrations of 25-HydroxyVitamin D Holick M et al (2008) J Clin Endocrinol Metab 93(3): 677-681</td>
<td>Supplementation with 1000 IU Vitamin D2 was as effective as 1000 IU Vitamin D3 in maintaining serum 25(OH)D concentrations.</td>
</tr>
<tr>
<td>Photobiology of Vitamin D in mushrooms and its bioavailability in humans Keegan R-J (Holick Lab) et al (2013) Dermato-Endocrinology 5:1, 165–176</td>
<td>Bioavailability of 2000 IU Vitamin D2 in mushrooms vs. 2000 IU Vitamin D3 in mushrooms was determined by evaluating ability to raise and maintain serum 25(OH)D concentrations.</td>
</tr>
</tbody>
</table>