Vitamin D2 versus D3 - Scientific Evidences

Vitamins D3 and D2 are chemically different. In contrast to vitamin D3, vitamin D2 has a double bond between carbons 22 and 23 and a methyl group on carbon 24 in its side chain. Irrespective of their chemical differences, the human body uses the same enzymatic pathways to transform these vitamins to their pro-hormone (conditional vitamins) and hormone forms. There are ongoing debates in the literature and among the health and scientific communities as to the comparative potency or effectiveness (i.e., bioavailability) of these two chemical forms of vitamin D. However, both forms are recognized worldwide and in the U.S. as acceptable sources of this vitamin for foods and supplements (FDA 21 CFR 184.1950 and 21 CFR 172.379).

The bioavailability of a nutrient or drug is primarily used to describe that fraction of an administered dose that remains unchanged or activated as is the case for vitamin D and maintained in the systemic system. When vitamins D3 and D2 enter the circulatory system they are changed to 25(OH)D3 and 25(OH)D2, respectively. While serum levels of 25(OH)D are the standard for assessing both vitamin D bioavailability and status, the measurement of this prohormone does not differentiate between 25(OH)D3 and 25(OH)D2; the serum value is the sum of both.

There remain differences of opinion regarding the comparative effectiveness of vitamin D2 compared to vitamin D3. Fundamentally this difference concerns the serum levels of 25(OH)D resulting among two groups of individuals that are given equivalent doses of the two forms of the vitamin, D2 and D3. Among individuals given vitamin D2, their resulting serum 25(OH)D2 levels, measured as 25(OH)D, are usually lower. There are two proposed explanations for these lower levels of serum 25(OH)D2. The first is that 25(OH)D2 is cleared faster from the blood (IOM, 1997), and alternatively the rate of hydroxylation of ergocalciferol to 25(OH)D2 is slower than the rate of hydroxylation cholecalciferol to 25(OH)D3 (Guo et al., 1993).

Two reports (Trang et al., 1998; Armas et al., 2004) and one review (Heaney, 2008) are frequently cited that indicate vitamin D2 is not as potent as vitamin D3. A report entitled: Vitamin D and Calcium: A Systematic Review of Health Outcomes was prepared in 2009 for the IOM by the Agency for Healthcare Research and Quality, through its Evidence-based Practice Center (later in the text referred to as ARHQ, 2009). This report makes reference to the higher potency of vitamin D3. However, Holick et al. (2008) directly addressed this issue of non-equal potency between vitamin D2 and vitamin D3. In a randomized, placebo-controlled, double-blinded study, 68 healthy adults between the ages of 18 and 84 years received placebo, 1000 IU vitamin D3, 1000 IU vitamin D2, or 500 IU vitamin D2 plus 500 IU vitamin D3 daily for 11 wk at the end of the winter. The circulating levels of 25(OH)D (mean ± SD) increased to the same extent in all three (3) groups. Among groups fed vitamin D2, there was no effect on serum
25(OH)D3 levels. On explanation offered by the authors for the difference in bioavailability between the two forms of the vitamins is the possible effect the carrier (i.e. ethanol vs. oil vs. lactose) that vitamin D2 and vitamin D3 are dissolved in influence either their bioavailability or catabolism. However, the issues of 25(OH)D2 being formed at a slower rate, or metabolized at a faster rate, both resulting in lower serum 25(OH)D levels, deserves additional study. The recent Letter to the Editor by McKiernan and Wiley (2008), although only having two subjects, gives an excellent report of the shorter half life of 25(OH)D2 compared to 25(OH)D3.

While there will remain some controversy regarding the difference in potency of vitamin D2 compared to vitamin D3 in maintaining serum 25(OH)D levels, vitamin D2 has been the primary source for the prevention and treatment of vitamin D deficiency in children and adults over the past 50 years (Eliot and Park, 1938; Holick, 2007). Is has been demonstrated that as little as 100 IU vitamin D2 is effective in the prevention of rickets (Eliot and Park, 1938; Jeans, 1950; Holick, 2006). The number of studies reporting on the potency and effectiveness of vitamin D2 for a number of health issues is numerous (AHRQ, 2009). Furthermore, vitamin D2 supplementation is most commonly used in randomized controlled trials among infants and pregnant or lactating women, compared to vitamin D3 supplementation. Vitamin D2 significantly increased 25(OH)D concentrations in infants, lactating mothers and in cord blood (AHRQ, 2009).

Both the chemical forms of vitamin D3 and vitamin D2 are inactive but are subsequently converted into 25 hydroxy vitamin D3 or 25 hydroxy vitamin D2 [25(OH)D3; 25(OH)D2] in the liver and then to 1,25 dihydroxy vitamin D3 or 1,25 dihydroxy vitamin D2 [1,25(OH)2D3; 1,25(OH)2D2] in the kidney. This sequence of biochemical transformations has provided a mean for monitoring vitamin D status. While the 1,25(OH)2D is the active form of the vitamin, it has a very short half life of about 4 to 6-hours, and therefore presents a challenge to assess its homeostatic presence. Also, the serum concentrations of 1,25(OH)2D are closely regulated by parathyroid hormone, calcium, and phosphate. These factors prevent the dihydroxy form of vitamin D to be used as a measure for vitamin D status. On the other hand, the half life of 25(OH)D, the pro-hormone, is approximately 15 days; it is therefore a more suitable biomarker of vitamin D status. However, there are some limitations with 25(OH)D as marker of vitamin D status, including the fact that serum 25(OH)D level does not indicate the amount of vitamin D stored in other tissues of the body and it reflects the combined amounts of vitamin D ingested and produced in the skin (from sunlight).

References: