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Controversies in Vitamin D Supplementation

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Introduction

Upon discovering the curative effect of vitamin D in rickets - a childhood disorder involving softening and weakening of the bones, enterprising American suppliers realized it would be advantageous to market milk that had been fortified with vitamin D (1). Since the 1940's, vitamin D has been added generously to milk, margarine, cereals, breads, pasta, rice, meat, poultry, and multivitamin supplements. In 1973 alone, over three million dollars worth of vitamin D was manufactured and sold in the United States (2). Concurrent with this rise in vitamin D ingestion in Canada, United States, Sweden, Israel, and England were the epidemic onsets of atherosclerosis and osteoporosis, which led Moon et al. to hypothesize that chronic vitamin D excess contributes to the development of these two illnesses (1). Moon and colleagues supported their postulate by citing 37 studies, some dated as early as 1945, which documented cardiovascular and skeletal effects similar to atherosclerosis and osteoporosis in humans and laboratory animals after high vitamin D intake. Subsequently, Haddad et al. showed in seven healthy human volunteers that while endogenously synthesized dermal vitamin D is transported on vitamin D binding protein and causes a more sustained increase in serum 25-hydroxy vitamin D, the orally administered vitamin D is absorbed from the intestinal tract via chylomicrons and carried in the circulation by lipoproteins such as VLDL and LDL, which may end up in the artery wall (3, 4). This finding supports Fraser's earlier speculation that the toxicity of orally acquired vitamin D might be due to its unnatural route through the body and, consequently, it is less finely regulated than endogenously synthesized dermal vitamin D (5).

Dangers of High Vitamin D Intake

A recent study by Rebsamen and colleagues found that vitamin D induced a dose-dependent increase in vascular smooth muscle cell migration in rat aorta, suggesting a possible mechanism of vitamin D in atherosclerosis and vascular remodeling (6). They showed that vitamin D-induced migration is a rapid, non-transcriptional response that requires the activation of phosphatidylinositol 3-kinase pathway, which concurs with the role of phosphatidylinositol 3-kinase in cell migration processes previously shown in numerous cell types including vascular smooth muscle cells. The validity of these results is enhanced by the fact that Rebsamen et al. performed all the experiments in triplicates and obtained comparable results each time. Moreover, the investigators reported statistically significant differences ($P<0.05$) between the vitamin D and control groups, using the unpaired, 2-tailed Student's *t* test. The major limitation of this study, however, is that it was performed *in vitro* on rat aortic smooth muscle cell cultures, which may not be translatable to human subjects *in vivo*.

In another study, nine breeding pairs of Sprague–Dawley rats and their offsprings were fed either normal chow (control), modified chow supplemented with low-dose vitamin D, or modified chow supplemented with high-dose vitamin D (7). Norman et al. found that increased exposure to vitamin D during gestation and early life significantly reduced the aortic elastin content and force generation in these rats. This result is alarming since prior studies have indicated that reduction in the elastin content and increased aortic wall stiffness might be predispositions to aneurysm and hypertension (8, 9). Based on the fact that reduced elastin expression was associated with an increase in elastic lamellae in the aorta (10), Norman et al. proposed that the reduction in elastic lamellae associated with vitamin D was mostly likely due to vitamin D's effect on proteins involved in the synthesis and/or catabolism of elastic fibrils, rather than fetal or

neonatal elastin gene expression. The graded reduction in aortic force generation with increasing exposure to vitamin D found in this study was consistent with the findings of Weishaar et al. who previously demonstrated that chronically vitamin-D deficient rats had increased aortic force generation (11). Since there is evidence that vitamin D crosses the placenta (12, 13), excessive maternal vitamin D intake also means excessive fetal exposure. Norman et al. found this to be disturbing because they believe that Western countries have been consuming excessive vitamin D since the discovery of preventive effect of cod liver oil in rickets in 1919 (14). The validity of these results have been most strongly questioned by Reinhold Veith, who believes that Norman et al. have supplemented the rats' diet with the more potent, vitamin D-derived hormone, 1,25(OH)2D, instead of vitamin D (15). Furthermore, he contends that "modern adults are not consuming physiologically meaningful amounts of vitamin D through foods or vitamin pills."

Support for Vitamin D Supplementation

On the basis of the most commonly used definition of vitamin D insufficiency (16), Rucker and colleagues found that 34% of the 188 healthy Canadians whom they tested had less than 40 nmol/L of serum 25-hydroxy vitamin D at least once out of the four sampling times (17). Furthermore, by using a serum 25-hydroxy vitamin D level of 80 nmol/L as the threshold value for vitamin D insufficiency as suggested by several investigators, Rucker et al. found that 97% of their volunteers would be considered vitamin D insufficient at least once out of the four sampling times (18, 19, 20). They observed lower levels of mean serum 25-hydroxy vitamin D in the fall (52.9 nmol/L) and winter (57.3 nmol/L) months and higher levels of mean serum 25-hydroxy vitamin D in the spring (62.9 nmol/L) and summer (71.6 nmol/L) months. Rucker and colleagues believed that the volunteers in this study had higher levels of serum 25-hydroxy vitamin D than their counterparts because these volunteers lived in Calgary, an area with more sunshine hours and higher elevation than most other Canadian locations (18, 21, 22). Thus, Rucker et al. concluded that the observed seasonal decline in serum 25-hydroxy vitamin D and, thus, prevalence of vitamin D insufficiency underestimated those of Canadians living outside of Calgary. They proceeded to propose a "more aggressive vitamin D supplementation, particularly for elderly people and especially during the fall and winter months." In response to the results of this study, Veith recommended a daily supplement of 1000 IU of vitamin D_3 for all adults in order to prevent vitamin D insufficiency (23). This proposed amount is 2.5 – 5 times greater than the current Adequate Intake value, which is based on inadequate exposure to sunlight (24).

However, it is questionable to recommend supplementation when the supposedly vitamin D insufficient individuals were declared "healthy" and did not exhibit any symptoms. As there is circadian variation, it is not inconceivable that there might be seasonal variations in the amount of serum 25-hydroxy vitamin D that the body needs. Thus, while 40 nmol/L of serum 25-hydroxy vitamin D might be necessary during some periods of the year, a lower level might be appropriate during other times of the year. Furthermore, since less than 3% of the subjects had identified themselves as members of an ethnic minority, this study does not reflect the ethnic diversity and the potential physiological diversity that exist in America. Hence, this is one of the limitations of the study that must be taken into account when generalizing these results to determine the appropriate amount of vitamin D for "all adults."

In a recent study conducted by Chapuy et al., 583 ambulatory institutionalized women with a mean age of 85.2 years were randomized to receive daily calcium and vitamin D supplements or

placebo (25). The women who ingested 1200 mg of calcium and 800 IU of vitamin D had increased serum 25-hydroxyvitamin D and decreased serum parathyroid hormone. Moreover, while femoral neck bone mineral density decreased in the placebo group, it remained unchanged in women who took the calcium and vitamin D supplements. Chapuy and colleagues concluded that "calcium and vitamin D in combination reverse senile secondary hyperparathyroidism and reduce both hip bone loss and the risk of hip fracture in elderly institutionalized women." Thus, they recommended supplementing patients who have low levels of calcium and vitamin D. The strength of this study derives from the fact that it was a 2-year, multicenter, double-blinded randomized controlled trial. The major limitation of this study is that one cannot discriminate the effects of calcium from vitamin D and vice versa. The reduction in hip bone loss and the decreased risk of hip fracture may be simply due to the calcium supplementation alone. In fact, other long-term randomized controlled trials have shown that although vitamin D supplementation increased the subjects' serum 25-hydroxyvitamin D concentration, it by itself did not decrease the incidence of hip fractures and other osteoporotic fractures in elderly individuals (26, 27).

Veith advocated increasing vitamin D intake by highlighting epidemiologic studies that correlated higher serum 25-hydroxy vitamin D levels or environmental ultraviolet light exposure with lower rates of breast, ovarian, prostate, and colorectal cancers as well as multiple sclerosis and hypertension (28). However, in the majority of the studies that he cited, the increased serum 25-hydroxy vitamin D was due to ultraviolet light exposure rather than oral vitamin D supplementation. As mentioned above, the endogenously synthesized vitamin D, which is produced by exposure of the skin to ultraviolet light or sunlight, is transported and regulated differently in the body than the orally administered vitamin D. This might explain the greater toxicity of orally administered vitamin D and the increased incidence of atherosclerosis and osteoporosis in humans and laboratory animals after high oral vitamin D intake. In addition, correlations from epidemiologic studies are not sufficient to justify increasing vitamin D supplementation. Long-term, double-blinded randomized controlled trials are needed to evaluate these potential health benefits before they can be considered as objectives in nutritional guidelines.

Conclusions

Although the research on vitamin D supplementation is still inconclusive, the potential association between high vitamin D ingestion and diseases such as atherosclerosis provides ample reason for caution. Since 15 minutes of exposure to ambient sunlight three times a week is sufficient to produce the body's requirement of vitamin D, there is really no need for healthy individuals to take vitamin D supplements (29). Moreover, there is a simple blood test that measures serum 25-hydroxy vitamin D level, which accurately reflects vitamin D stores in the body (30). Physicians should give this test to patients who they feel might be vitamin D deficient before prescribing the appropriate amount of vitamin D supplementation. Physicians can also use this test to determine if a patient is consuming excess vitamin D and, thus, will know to reduce the patient's risk for toxicity as well as adverse drug and nutrient interactions (31).

Much more research is needed, especially in elucidating the biochemical differences between the orally administered vitamin D and the endogenously synthesized vitamin D *in vivo*. In addition,

as scientists gain a better understanding of the body's requirement of vitamin D, the current practice of rampant fortification of milk and foods with vitamin D should be reevaluated.

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