The health benefits of vitamin D greatly outweigh the health risks

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In his recent essay, Trevor G. Marshall explores how vitamin D supplementation may be contributing to the current epidemics of obesity and chronic disease[1]. Unfortunately, he has overlooked many important papers that disagree with his hypothesis. This letter points out some of the omissions.

The health benefits of vitamin D3 have been reviewed recently[2]. The benefits for bone health have been known for nearly a century. Benefits for cancer, infectious diseases, autoimmune diseases, and metabolic diseases have been identified in the past three decades.

Starting in the 1980s, largely observational evidence mounted that solar ultraviolet-B (UVB) irradiance and vitamin D reduce the risk of many types of cancer[3]. Based on observational studies, it is estimated that 1500 and 3600 International Units (IU) of vitamin D3 are required daily for a 50% reduction in risk of colorectal and breast cancer, respectively[4]. A recent randomized, double-blind, placebo-controlled clinical trial that studied post-menopausal women in Nebraska found a 77% reduction in all-cancer incidence between the ends of the first and fourth years[5], adding strong support to the observational studies.

Vitamin D enhances innate immunity through induction of human cathelicidin, LL-37[1]. LL-37 helps control both bacterial and viral infections. A recent post-hoc analysis of vitamin D3 supplementation for post-menopausal women living in New York State found substantial benefits in reducing the common cold and influenza for 800 IU/day, and very strong benefits for 2000 IU/day[6]. Benefits also appear to be strong for septicaemia [Grant, submitted] and enteric viral infections such as norovirus [Grant, submitted], both of which are more frequent in winter than in summer.

Many autoimmune diseases appear to arise from an improper immune response to viral infections. Since LL-37 reduces the risk of viral infections, it may also influence the risk of autoimmune diseases such as multiple sclerosis. The well-known increase in prevalence of multiple sclerosis with increasing latitude is consistent with this hypothesis.

There is also a growing body of literature that low vitamin D status is a risk factor for many metabolic diseases, including hypertension, type 2 diabetes, and cardiovascular disease[2]. A recent observational study found that vitamin D deficiency is associated with incident cardiovascular disease[7].

There are some diseases where vitamin D supplementation may be contraindicated. These include granulomatous diseases such as sarcoidosis where local production of 1,25-dihydroxyvitamin D (calcitriol) in response to the disease can leak into the serum and dysregulate calcium metabolism[8].

The current vitamin D3 fortification of food in the United States contributes an average of 250-300 IU/day to the American diet. This amount is too low to have a substantial beneficial effect on risk of cancer. Intake or production of vitamin D3 of 1000-2000 IU/day seems now appears to be required for optimal health, and typically will raise serum 25-hydroxyvitamin D (calcidiol) levels to 40-60 ng/mL[4,6,9].

It is possible that there have not been more clinical trials of vitamin D supplementation clinical trials since there is little income in selling vitamin D3 (a year's supply of 1500 IU/day costs less than $20 U.S.), and such trials are expensive.

The rising prevalence of obesity in the United States can be traced to two primary factors: replacing fat with simple carbohydrates in processed food and subsidy programs, in particular for growing corn and soybeans, that encourages overproduction of energy-dense foods and their sale at low cost[10]. While these issues are addressed, increased vitamin D3 supplementation and fortification of foods will provide substantial health benefits, including reduced incidence of many serious diseases.

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Comment on "Vitamin D discovery outpaces FDA decision making"

"Before you let the sun in, make sure it wipes its shoes."*Dylan Thomas, Under Milk Wood. 1954*

It is always wise to consider evidence from points of view other than those that are current 'received wisdom' so that we can see clearly what we are really looking at. Thus, the above review is of considerable interest [(1)]. The author postulates that circulating hormonal [activated] vitamin D (calcitriol) concentration is more important than circulating 25-hydroxyvitamin D [25-(OH)D] in the determination of tissue functions that are modulated by vitamin D. He also appears to suggest that changes in circulating 25-hydroxy vitamin D reflect changes in calcitriol formation and uptake rather than availability of vitamin D and that circulating calcitriol concentration tells us about vitamin D effectiveness. This would indeed be the case is all tissues depended on uptake of calcitriol from the circulation for their supplies of hormonal vitamin D. However, many tissues express the hydroxylase activating vitamin D and several have been confirmed as producers of calcitriol in situ.[(2-4)] Such tissues must use circulating 25-(OH)D, the substrate for activation by 25-hydroxyvitamin D 1-alpha-hydroxylase. Thus, for example, in the placenta, calcitriol is produced in large amounts from early in pregnancy with increases in circulating maternal calcitriol and reductions in maternal circulating 25-(OH)D [(4)]. However, to suggest that all variation on serum 25-(OH)D concentrations in different disease processes reflects changes in local tissue vitamin D activation to the exclusion of variations due to the amount of vitamin D in the body would be to ignore the massive changes in serum 25-(OH)D seen within hours of exposure to UVb, without any changes in circulating calcitriol [(5)] and would not explain the remarkable seasonal variations in serum 25-(OH)D seen with variation in available effective UVB from sunlight, with variations in dietary intake of vitamin D and with supplement use. In Sweden for example, in a group of 116 women in the winter, an average serum 25(OH)D of 69 nmol/l was accounted for by the following; daily intake of normally fortified Swedish foods, 6.2 nmol/l; 3 fish meals/week, 25.5 nmol/l; regular vitamin supplement use, 11.0 nmol/l and a vacation in the sun within the last 6 months, 14.5 nmol/l leaving 11.8 nmol/l of 25-(OH)D to be accounted for the balance between incoming vitamin D and the amount of 25-(OH)D being consumed by local vitamin D activating tissues [(6,7)]. In addition, however much ultraviolet B effective for induction of vitamin D synthesis [effUVb] one is exposed to vitamin D toxicity does not develop because of feed-back mechanisms in the skin itself [(8)]. Similarly, feed back mechanisms ensure that circulating calcitriol is virtually unchanged in the face of reductions in serum 25-(OH)D in the circulation until there is clinically obvious vitamin D deficiency with bone disease such as rickets or osteomalacia when calcitriol does eventually fall though even then, in some case, serum calcitriol is found to be increased. [(9)] These findings challenge the argument that vitamin D modulation of tissue function depends predominantly on circulating calcitriol and explain why vitamin D repletion continues to be judged at present by circulating concentrations of the storage adduct, 25-(OH)D, acting as it does as the substrate for local tissue activation throughout the body and not just in the kidney. In support of this position it is well known that measurement of circulating calcitriol [hormonally active 1,25dihydroxyvitamin D] is unhelpful in the

assessment of vitamin D repletion since its concentrations are normally so tightly regulated across a wide range of concentrations of 25-(OH)D. [10] Finally, the fact that vitamin D activation has been demonstrated in several of the extra-renal human tissues known to express specific vitamin D activating 1-alpha hydroxylase supports the view that assessment of substrate availability of vitamin D, as reflected by serum 25-(OH)D, is likely to be of importance in the assessment of vitamin D repletion in humans.

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