

Can Vitamin D Reduce Total Mortality?

THE ANTIRACHITIC PROPERTIES OF VITAMIN D, the “sunshine vitamin,” are generally well recognized, and the role of vitamin D in calcium and phosphorus homeostasis is well established.¹ In the last several decades, many studies have documented nontraditional roles of vitamin D, as well as adverse consequences of vitamin D deficiency for a range of conditions, including bone health, cancer, cardiovascular disease, glucose intolerance, high blood pressure, some infectious diseases, multiple sclerosis, and type 2 diabetes mellitus.² Except for effects on bone health, which are established in randomized clinical trials,³ the evidence for most of the other potential benefits is generally considered to be less definitive. Nevertheless, an impressive body of in vitro, animal, clinical, and epidemiologic evidence supports the evidence.

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An article in this issue of the *Archives* adds a new chapter in the accumulating evidence for a beneficial role of vitamin D on health.⁴ From the literature, Autier and Gandini⁴ identified 18 randomized trials of vitamin D intake that reported results for total mortality and conducted a meta-analysis for total mortality. All these studies had been conducted for other primary end points. The results are remarkable; individuals who were randomized to vitamin D had a statistically significant 7% reduction in mortality from any cause. The reduction was 8% for studies for which the intervention was at least 3 years and was also 8% for those studies with a placebo control group.

The meta-analysis was skillfully done, but several caveats are important to consider. While the results were statistically significant and no evidence for publication bias was evident, the upper bound 95% confidence interval of the relative risk was 0.99, so chance could still be a possibility. A statistically significant benefit was not observed in any of the individual studies, but each of the 5 largest studies found a nonsignificant lower risk similar in magnitude to the overall result. Importantly, this analysis essentially excludes any negative surprises from vitamin D intakes at the doses given in the trials, which varied from 300 to 2000 IU/d. The study size–adjusted mean daily intake of vitamin D was 528 IU, and vitamin D doses ranged mostly from 400 to 800 IU/d.

One should also consider the nature of the subjects in the trials, which can be seen in Table 1 of the article.⁴ The groups included generally healthy people, but most of the studies were based on subjects at high risk for fractures, and one small study was designed to examine survival in patients with congestive heart failure. Most of the people were middle-aged or elderly, the baseline 25-hydroxyvitamin D levels (when available) ranged from 8.8 to 30.1 ng/mL. Compliance varied from 47.7% to 95%, and when measured, the difference in the 25-hydroxy-

vitamin D levels between the treated and control group ranged from 1.5- to 5.2-fold. Mean follow-up ranged from 6 months to 7 years, with a study size–adjusted mean of 5.7 years' duration. Given the many differences among the studies, the result of no statistical heterogeneity among the studies' results is somewhat surprising, although tests generally may be underpowered to detect heterogeneity.

The analysis was not able to consider the specific causes of death. To have a measurable effect on total mortality for a middle-aged to elderly group, an effect on some of the major causes of death, such as cardiovascular diseases and cancer, would be expected. Given the generally short time courses of the studies, the observed effects likely would be on causes of death with relatively short latencies. For example, if vitamin D were preventing seasonal deaths from pneumonia or influenza, an effect would be almost immediate.⁵ If vitamin D had an additional effect on the development of chronic diseases, which tend to have long latencies, these studies would have underestimated the total benefit of vitamin D supplementation. For cancer, there is some evidence for an influence of vitamin D on both incidence and survival.⁶ The results from this meta-analysis may be more relevant for any benefits on survival and would likely underestimate any ultimate benefit on reducing mortality if vitamin D was also important in influencing cancer incidence. Also, this analysis would not capture the proposed benefits of vitamin D on conditions that develop early in life, such as on type 1 diabetes⁷ and multiple sclerosis.⁸

Should it be surprising that vitamin D has such a wide array of health benefits and influences mortality? Also, why do the results for vitamin D appear to be in contrast to recent trials of micronutrients, including vitamin E and beta carotene, which showed no benefits on mortality and perhaps even adverse effects?⁹ Vitamin D may be distinct in one important way. Proposed benefits of vitamin E and beta carotene were premised on the dubious notion (with the benefit of hindsight) that providing a nonphysiologic dose of a single “antioxidant” would prevent an array of conditions attributable to oxidative stress. In contrast, by increasing vitamin D intake, we may be correcting a deficiency caused primarily by a lack of the natural source of vitamin D, which is from sun exposure. Through evolution, vitamin D has become integrated into many cellular functions. Vitamin D is used in numerous endocrine, autocrine, and perhaps paracrine systems, acting as an important regulator of gene expression. For example, vitamin D appears to be important in the regulation of cell proliferation and differentiation; thus, deficiencies could contribute to carcinogenesis. Also, vitamin D has been shown to be critical for innate immunity¹⁰ and the production of antibiotic peptides, such as cathelicidin, and thus deficiency could contribute to diseases such as tuberculosis.¹¹

The Achilles' heel of the intricate vitamin D system is that the precursor molecule, cholecalciferol, is entirely dependent on sun exposure or dietary intake. As a species, we do not get as much sun exposure as we used to, and dietary sources of vitamin D are minimal. Throughout most of human evolution when the vitamin D system was developing, the "natural" level of 25-hydroxyvitamin D was probably around 50 ng/mL or higher.¹² In modern societies, few people attain such high levels, and levels below 10 or 15 ng/mL are not uncommon. Efforts to avoid excessive sun exposure, especially among lightly pigmented children and adolescents, remain important, but the extreme avoidance of sun exposure may have inadvertently contributed to widespread vitamin D deficiencies. Owing to the UV-B blocking abilities of melanin, most darker-skinned individuals in temperate climates have vitamin D levels that do not come close to what may be optimal levels. The fact that African Americans, who generally have poor vitamin D status,¹³ have a disproportionate incidence of numerous conditions attributed to vitamin D deficiency could be coincidental but should be cause for concern.

In recent years, an increasing number of researchers from various fields have been arriving at the conclusion that the levels of vitamin D in many people are inadequate for optimal health.^{2,12,14} The results from this meta-analysis provide additional evidence from randomized trials of the dire consequences from vitamin D deficiency. Perhaps just as important, the analysis by Autier and Gandini⁴ largely precludes any appreciable chance of some unanticipated adverse effect with long-term use of vitamin D, at least at intakes up to 800 IU/d. The often excessive concern for hypercalcemia may be misplaced; a recent review concluded that the upper limit for vitamin D consumption for adults should be 10 000 IU/d.¹⁵ Individuals can make up to 20 000 IU/d of vitamin D from sun exposure,² and no case of sun-induced vitamin D toxic effects have ever been documented.

Given the high probability of benefit for at least some of the many conditions that have been associated with vitamin D deficiency, and the low likelihood of harm, it seems prudent that physicians measure 25-hydroxyvitamin D levels in their patients. Although the optimal level of 25-hydroxyvitamin D is not established, based on multiple end points, 30 to 40 ng/mL is a reasonable target for adequate levels.¹⁶ Of note, based on the mean 25-hydroxyvitamin D levels achieved in the interventions (see Table 2 of the article by Autier and Gandini⁴), many if not most individuals taking supplements of even 800 IU/d of vitamin D would not achieve a goal of 30 ng/mL. Sun exposure greatly influences the required intake; an individual with substantial sun exposure (eg, a lifeguard) may not require additional oral vitamin D supplementation, whereas an individual with minimal sun exposure (eg, a nursing home resident) may require 1000 to 2000 IU/d to achieve levels of 30 to 40 ng/mL. A potential feasible approach to correct serious deficiency is to provide concentrated forms during a limited period.² Ideally, the form of vitamin D used should be cholecalciferol (vitamin D₃) rather than ergocalciferol (vitamin D₂), which may not be as effective.¹⁷ Most of the studies in the meta-analysis by Autier and Gandini⁴ used cholecalciferol.

As with any good study, some questions are answered in this meta-analysis but more have arisen. Would even a greater reduction in mortality accrue than that suggested in this meta-analysis if intakes of vitamin D were higher, if compliance was improved, if higher levels of 25-hydroxyvitamin D were attained, and if the duration of supplementation was longer? Which causes of death mostly accounted for the reduced mortality? Was the reduced mortality primarily in the winter months when vitamin D levels typically plummet and when excess mortality occurs? Research on vitamin D should be continued to clearly elucidate the specific benefits and optimal intakes and levels of vitamin D. Nonetheless, based on the total body of evidence of health conditions associated with vitamin D deficiency, abetted with the results from this meta-analysis, a more proactive attitude to identify, prevent, and treat vitamin D deficiency should be part of standard medical care. From a broader public health perspective, the roles of moderate sun exposure, food fortification with vitamin D, and higher-dose vitamin D supplements for adults need to be debated.

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Financial Disclosure: None reported.

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