MAYO CLINIC

The Death D-fying Vitamin

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In this issue of *Mayo Clinic Proceedings*, Dudenkov et al[1] report on a retrospective study relating vitamin D status (serum 25-hydroxyvitamin D [25(OH)D]) with the risk of all-cause and cause-specific mortality in their patients registered in the Rochester Epidemiology Project. The article reported that vitamin D deficiency was associated with increased mortality. There was a statistically significant inverse relationship with mortality in both white and nonwhite patients, as well as with their serum 25(OH)D level. For white patients who had 25(OH)D levels of less than 12 and 12 to 19 ng/mL (to convert to nmol/L, multiply by 2.496), their unadjusted all-cause mortality hazard ratios (HRs) were 2.6 and 1.3, respectively, when compared with their reference range of 20 to 50 ng/mL. Equally important was the observation that the HR for those who had a 25(OH)D level greater than 50 ng/mL was 1 and thus not different from the reference range. When race was included in the analysis, there remained an increased mortality risk in nonwhite patients, although to a lesser degree when the HR was adjusted. This editorial begins with a brief summary of the history of the relationship of vitamin D and sunlight with mortality before discussing this meritorious study and offers insights into how pleiotropic effects of vitamin D may improve health and reduce mortality.

Vitamin D is the sunshine vitamin. As a result, a multitude of studies have related latitude-associated health outcomes and mortality with vitamin D status. Association studies linking sun exposure with a reduced risk of mortality appeared more than a century ago with the observation that the risk of mortality from cancer increased in those who lived at a higher latitude. In 1941, it was reported that there was an increased risk of cancer mortality in farming communities in northeastern states as compared with those in southern states.[2] In the 1990s, Garland et al[3] observed that colon cancer mortality in the United States inversely correlated with solar radiation, and in a subsequent prospective study, these investigators[3] observed a 3-fold increase in colon cancer risk in people who had a 25(OH)D level less than 20 ng/mL. These studies were advanced by Grant,[4] who reported that premature mortality from various cancers inversely correlated with solar ultraviolet exposure in both men and women. Increases in sun exposure and vitamin D status have been linked to a reduced risk of diverse malignant solid organ tumors.[2] In a Canadian study, the risk of developing breast cancer in women is markedly reduced in those women who were the most sun-exposed in the second decade of life.[5]

Observations relating increased sun exposure, living at lower latitudes (thereby making more vitamin D from sun exposure), and having higher 25(OH)D levels have been associated with improvement in cardiovascular health and reduced risk of cardiovascular mortality.[2] There is an inverse association between latitude and elevation in blood pressure.[6] Vitamin D deficiency has been associated with an increased risk of peripheral vascular disease and myocardial infarction, and mortality from myocardial infarction is markedly increased in the setting of vitamin D deficiency.[7] Type 2 diabetes and obesity are dominant risk factors for cardiovascular diseases; in this regard, there is an inverse relationship with a body mass index (calculated as the weight in kilograms divided by the height in meters squared) greater than 30 kg/m^2 and vitamin D status[2,7]; vitamin D deficiency associates with an increased risk of type 2 diabetes; and the Nurses' Health Study[8] reported a reduced risk of type 2 diabetes in participants with a dietary intake of at least 1200 mg of calcium in conjunction with at least 800 IU of vitamin D per day. Clear evidence also exists in the literature, revealing a substantial association of vitamin D deficiency with hypertension, hyperlipidemia along with peripheral vascular disease, and type 2 diabetes, all of which are risk factors for myocardial infarction, stroke, and mortality.[7] The Ludwigshafen Risk and Cardiovascular Health Study[9] observed that in 1801 patients with metabolic syndrome followed for 7.7 years, marked reduction in all-cause (HR, 0.25; 95% CI, 0.13-0.46) and cardiovascular

disease (HR, 0.33; 95% CI, 0.16-0.66) mortality rates occurred in patients who were relatively vitamin D sufficient as compared with those with severe vitamin D deficiency.

The observation by Dudenkov et al[1] is thus supportive of a multitude of studies worldwide reporting that the maintenance of vitamin D sufficiency can result in substantial reductions in cancer, cardiovascular, and all-cause mortality rates.[2,7] However, is too much of a good thing bad for you? The Institute of Medicine in its report[10] also recognized that there was an inverse relationship of all-cause mortality and serum 25(OH)D levels less than 30 ng/mL. In addition, on the basis of a few studies, the Institute of Medicine raised the concern that when 25(OH)D levels are greater than 30 ng/mL, there is an increased risk of all-cause mortality. They concluded that a blood level of 25(OH)D greater than 50 ng/mL potentially increases the risk of mortality, thereby profiling a J-curve or U-curve phenomenon. More recent studies have challenged this notion of the J or U curve pertaining to serum 25(OH)D levels that are either salutary or potentially injurious. Garland et al[11] in a meta-analysis of 32 studies found a dramatic decrease in all-cause mortality with higher 25(OH)D levels; the maximum benefit was observed when blood levels of 25(OH)D were greater than 30 ng/mL, and this benefit extended above 70 ng/mL. Dudenkov et al[1] in their cohort confirmed that there is no increased mortality risk when blood levels of 25(OH)D are greater than 50 ng/mL.

Dudenkov et al[1] observed that the benefit of improving vitamin D status is not apparent in nonwhite patients as it is in whites. Although the reasons for this lack of an effect of low vitamin D status in nonwhite patients are unclear at present, at least 2 considerations may be germane. First, only about 10% of their cohort was in this group, raising the question of adequate sample size. Second, people of color are at higher risk of vitamin D deficiency, and physicians may thus be more inclined to determine whether vitamin D deficiency exists and/or to recommend vitamin D supplementation. It is conceivable that the observed lack of benefit reflects, at least in part, that a subset of these patients were chronically vitamin D deficient and were subsequently treated for vitamin D deficiency. Kroll et al[12] raised this issue and found that there was evidence that 57% of the patients who had blood levels of 25(OH)D greater than 50 ng/mL were likely being treated for vitamin D deficiency. Therefore, these patients being treated for vitamin D deficiency may be at higher risk of mortality because of their antecedent and presumably long-term vitamin D deficiency.

To attain a blood level of 25(OH)D above 30 ng/mL requires adults to ingest at least 1500 to 2000 IU of vitamin D per day as recommended by the Endocrine Society's practice guidelines on vitamin D.[13] To achieve the preferred range in which the maximum benefit for reduced all-cause mortality has been observed,[2,7,11] which is 40 to 60 ng/mL, would require 4000 to 6000 IU of vitamin D per day. For those who are obese, 2 to 3 times more supplementation is needed.[7,14] Ekwaru et al[14] reported that adults taking up to 20,000 IU of vitamin D per day maintain blood levels of 25(OH)D in the range of 60 to 80 ng/mL and that such dosages of vitamin D were not attended by discernible toxicity. The Endocrine Society's practice guidelines on vitamin D[13] concluded that vitamin D toxicity is not observed until blood levels of 25(OH)D are greater than 150 ng/mL. Vitamin D toxicity, characterized by hypercalcemia, hyperphosphatemia, and suppression of parathyroid hormone, is usually observed when intakes are excessively high, in the range of more than 50,000 to 1 million IU of vitamin D per day and are maintained long-term for several months to years.[7,13]

There is mounting evidence that inflammation caused by various factors including obesity is a major cause for chronic illnesses associated with mortality, including cancer and cardiovascular disease. Vitamin D exerts at least 2 major anti-inflammatory effects. The first anti-inflammatory effect reflects the fact that 25(OH)D is metabolized locally in monocytes and macrophages to 1,25-dihydroxyvitamin D.[2,7] This hormone interacts with its vitamin D receptor in activated B lymphocytes to modulate immunoglobulin synthesis and reduce the production of autoimmunity-related antibodies. 1,25-Dihydroxyvitamin D binds its nuclear vitamin D receptor in activated T lymphocytes, having a dramatic effect on cytokine production and inducing T1 lymphocytes transformation into T2 lymphocytes.[7,15] The second anti-inflammatory effect pertains to the fact that the endothelium is activated and destabilized during

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inflammation, and in this regard, vitamin D has been shown to stabilize endothelial membranes, and with much greater efficacy as compared with equimolar amounts of 25(OH)D.[15]

There is no downside to increasing vitamin D intake and maintaining blood levels of 25(OH)D above 30 ng/mL unless there is an underlying vitamin D sensitivity associated with a granulomatous disorder, some lymphomas, and 25-hydroxyvitamin D-24-hydroxylase deficiency.[7,13] It has been found that at or above this level, maximum bone health is achieved.[7,13] Association studies have suggested that sensible sun exposure and increased vitamin D intake reduce the risk of autoimmune diseases, deadly cancers, infectious diseases, neurological dysfunction, cardiovascular disease, and type 2 diabetes that contributes to all-cause mortality.[2,7] Even nematodes live longer with vitamin D because vitamin D induces beneficial stress response genes and promotes protein homeostasis.[16] The evidence for maintaining a blood level of 25(OH)D of at least 30 ng/mL for maximum bone health and reducing the risk of mortality from chronic illness is robust.

Michael F. Holick, PhD, MD
Section of Endocrinology
Diabetes, Nutrition and Weight Management
Department of Medicine
Boston University School of Medicine and
Boston Medical Center
Boston, MA

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Correspondence: Address to Michael F. Holick, PhD, MD, Section of Endocrinology, Diabetes, Nutrition and Weight Management, Department of Medicine, Boston University Medical Campus, Boston, MA 02118 (mfholick@bu.edu).

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