EDITORIALS

Sunlight and Vitamin D

Both Good for Cardiovascular Health

Fahrleitner et al.[1] report that patients with severe peripheral artery disease (PAD) had a high prevalence of vitamin D deficiency. The authors should be congratulated for realizing that many of the non-specific symptoms associated with PAD and immobility, i.e., muscle pain and weakness, bone aches and pains, and fatigue are also indicative for vitamin D deficiency. They found that 71% of patients with severe PAD had serum 25-hydroxyvitamin D [25(OH)D] levels that were below 9 ng/mL. Remarkably, 13% had serum calciums below the normal range and 40% had overt secondary hyperparathyroidism. The serum calcium levels are usually normal, but can be low in severe, chronic vitamin D deficiency. The hallmark for vitamin D deficiency is the measurement of a low or undetectable level of 25(OH)D in the blood.[2] Although the lower limit of the normal range was 9 ng/mL, as noted by the authors, there is strong evidence that blood levels of less than 20 ng/mL lead to secondary hyperparathyroidism.[2,3] Thus, if the authors had used 20 ng/mL as their cutoff, it is likely that essentially 100% of their patients were vitamin D insufficient or deficient. The clinical signs and symptoms of vitamin D deficiency are extremely subtle or nonspecific. Vitamin D deficiency causes a decrease in the efficiency of intestinal calcium absorption, which in turn, leads to an increase in the production of parathyroid hormone (PTH). PTH stimulates the kidney to produce 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], which increases the intestinal calcium absorption and with PTH stimulates osteoclast precursors to become mature osteoclasts, which in turn mobilize calcium stores from the skeleton. The increase in osteoclastic activity can precipitate and exacerbate osteoporosis. The more subtle effect, however, is that PTH also causes phosphaturia and hypophosphatemia. As a result, the calcium x-phosphate product in the blood is inadequate for normal mineralization of the bone collagen matrix resulting in osteomalacia. In adults, it is not possible to distinguish osteoporosis and osteomalacia, either by x-ray examination or by bone densitometry. Osteoporosis, i.e., holes in the bones does not cause bone pain. In contrast, osteomalacia can cause isolated or generalized bone aches and pains. Although the mechanism for bone pain is not well understood, it is possible that the unmineralized collagen matrix becomes hydrated and expands, causing outward pressure on the periosteal covering, which is innervated by pain fibers. On physical examination the application of minimum pressure with the thumb on the sternum, anterior tibia or radius and ulna will often elicit pain and discomfort, which is a helpful diagnostic sign for osteomalacia. Vitamin D deficiency also causes muscle weakness and muscle aches and pains. Glerup et al.[4] reported that 88% of Danish women of Arab decent who presented with muscle pains and weakness (symptoms similar to fibromyalgia) were severely vitamin D deficient.

The authors commented that most European countries do not fortify milk with vitamin D and that this was a contributing cause for the vitamin D deficiency seen in their patients. It is well documented that elderly, frail patients in both North America, where milk is fortified with vitamin D, and Europe are at a high risk for vitamin D deficiency.[5–8] Recently, Nesby-O'Dell et al.[9] and Tangpricha et al.[10] made us aware that vitamin D deficiency is also prevalent in young, healthy adults. They reported that 42% of African-American woman of childbearing age (15 to 49 years) in the United States, and 36% of healthy young men and women of Caucasian decent in Boston aged 18 to 29 years were vitamin D insufficient, respectively. There is a multitude of reasons that vitamin D deficiency has become an epidemic in most industrialized countries. Very few foods naturally contain or are fortified with vitamin D. Most, i.e., 80% or more, of our vitamin D requirement comes from exposure to sunlight.[2] Increases in skin pigmentation and zenith angle of the sun markedly diminish the production of vitamin D_3.[2] During the winter at latitudes above 35 degrees North and South, very little, if any, vitamin D can be produced in the skin. For example, in Boston (42°N) no vitamin D is produced from November through February. In Edmonton, Canada and Bergen, Norway, vitamin D production is halted between the months of October and April.[2] Thus, there is a relatively short window of opportunity to produce vitamin D_3 in the skin. Once produced, the excess amount is stored in the body fat and released during the winter to maintain 25(OH)D levels. The strong promotion of limiting sunlight exposure because of increased risk of skin cancer has resulted in the widespread use of sunscreens. Although sunscreens are very beneficial in reducing skin damage to excessive exposure to sunlight, they also can markedly reduce the photosynthesis of vitamin D_3 in the skin. When used properly a sunscreen with a sun protection factor of 8 reduces the skin's ability to produce vitamin D_3 by 97.5%.[2]

How do you prevent vitamin D deficiency? I encourage judicious limited exposure to sunlight as the best method to prevent vitamin D deficiency. Since the cutaneous production of vitamin D_3 is dependent on so many factors, including season, time of day, latitude, and the person's sensitivity to sunlight (i.e., amount of skin pigmentation), no one recommendation can be made. If a person knows that he/she will develop a mild sunburn minimum erythemal dose (MED) after 30 minutes of sun exposure, then exposure of the face, arms, hands, and legs for 20% to 25% of that time (i.e., 6 to 8 minutes) 2 to 3 times a week is more than adequate to satisfy the body's requirement. A sunscreen with a sun protection factor of 15 can then be applied to prevent the damaging effects of excessive sun exposure. We observed that adults in a bathing suit exposed to 1 MED of tanning bed radiation raised their blood levels of vitamin D to levels equivalent to those achieved by ingesting between 10,000 and 25,000 international units (IU) of vitamin D.[2] The adequate intake for vitamin D as recommended by the Institute of Medicine in 1997 is 200, 400, and 600 IU of vitamin D for ages up to 50 years, 51 –to 70 years, and 71+ years, respectively.[11] However, in the absence of any exposure to sunlight, there is mounting evidence that at least 800 to 1,000 IU of vitamin D is required daily to prevent vitamin D deficiency.[2,12,13]

How do you efficiently treat vitamin D deficiency? The vitamin D tank is empty and therefore recommending a multivitamin containing 400 IU of vitamin D a day is inadequate. To fill the tank quickly and establish vitamin D sufficiency, a dose of 50,000 IU of vitamin D_2 once a week for eight weeks will raise blood levels of 25(OH)D by more than 100% and usually corrects vitamin D deficiency.[2] A blood level of at least 20 ng/mL should be achieved before vitamin D deficiency is considered to be corrected. It usually takes several weeks to several months before there is improvement in the symptoms. For individuals not able to be exposed to sunlight and who are prone to vitamin D deficiency, giving them 50,000 IU of vitamin D once every 2 to 4 weeks has been effective in preventing recurrence of vitamin D deficiency.

There are other compelling reasons for identifying vitamin D deficiency and aggressively treating it. Vitamin D deficiency not only causes an imbalance in calcium homeostasis and bone metabolism, but also has been associated with increased risk of hypertension,[14] autoimmune disorders including type 1 diabetes,[15] and increased risk of dying of breast, colon, ovarian and prostate cancer.[16–19] It is now recognized that most tissues in the body, including brain, skin, breast, prostate, colon, etc. not only have a vitamin D receptor, but also have the enzymatic machinery to convert 25(OH)D to $1,25(OH)_2D$.[2] $1,25(OH)_2D$ is one of the most potent inhibitors of cellular proliferation and has a multitude of subtle effects on the immune system. There is compelling evidence that $1,25(OH)_2D$, through its receptor in the kidney, is a potent negative regulator of the renin-angiotensin system.[20] This is why patients with vitamin D deficiency have a higher risk of hypertension.[14] In addition, the vitamin D receptor is present in cardiac muscle.[21] Animal studies have shown that vitamin D deficiency causes increased cardiac contractility and myocardial hypertrophy.[19] In addition, it has been observed that vitamin D deficiency increases vascular muscle contractility that appears to be caused by the hypocalcemia associated with vitamin D deficiency. The authors observed that 13% of the patients had hypocalcemia, which could have exacerbated the PAD symptoms by this mechanism.

The authors also observed that 40% of the patients had secondary hyperparathyroidism and they were surprised that it was not higher. Although 40% of the patients had elevated PTH levels, it is likely that most of the patients had higher PTH levels than their homeostatic level due to their vitamin D deficiency. Malabanan et al.[3] demonstrated marked decreases in PTH levels after 50,000 IU of vitamin D_2 once a week for 8 weeks, even in patients who were considered to have normal PTH levels. Vascular smooth muscle cells produce parathyroid hormone–related peptide (PTHrP) and have a receptor for PTH/PTHrP.[22] It is well known that PTH lowers blood pressure, and it is believed that this is due to its effect on vascular smooth muscle, which mimics the PTHrP effect on relaxing vascular smooth muscle and desensitizes vessels to further pressor activity of angiotensin II and other vasoconstrictive agents.[22] It is possible that the increased PTH levels in the vitamin D deficiency alter vascular tone similar to PTHrP and thereby could exacerbate muscle aches and pains associated with PAD.

Thus, physicians should be alert to vitamin D deficiency. The strong association with elevated blood cholesterol levels and cardiovascular disease has made physicians, as well as the public, aware of their blood cholesterol levels. A similar emphasis should be placed on diagnosing and preventing vitamin D deficiency. Patients should have a blood level of 25(OH)D tested once a year, ideally at the end of the Fall season, to ensure that they are not vitamin D deficient before Winter. This will prevent many of the complications associated with vitamin D deficiency.—**Michael F. Holick, MD, PhD,** *Vitamin D Laboratory; Section of Endocrinology, Diabetes, and Nutrition; Department of Medicine, Boston University Medical Center, Boston Mass.*

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