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Editorial

Vitamin D Deficiency: What a Pain It Is

In the current issue of the *Mayo Clinic Proceedings*, Plotnikoff and Quigley¹ report that 100% of African Americans, East Africans, Hispanics, and American Indians in their Minnesota-based study had deficient levels of vitamin D; overall, 93% of the 150 children and adults in the study, which included 6 broad categories of ethnic groups, were vitamin D–deficient. Is this unexpected? No. Is this newsworthy? Yes.

It is inconceivable with all the advances in modern medicine that vitamin D deficiency should be a health concern in the United States. Most physicians assume that vitamin D deficiency, which plagued children from the 17th through 19th centuries, was eradicated with the fortification of milk with vitamin D. Indeed, from the 1930s through the 1950s, a wide variety of foods and beverages in the United States and Europe, including milk, bread, custard, hot dogs, soda, and even beer, were fortified with vitamin D.² However, the outbreak of vitamin D intoxication in a limited number of young children in Great Britain in the 1950s resulted in the banning of vitamin D fortification of dairy products and other foods in most European countries and the removal of vitamin D from most products except some breads, cereals, and milk in the United States.

Plotnikoff and Quigley¹ evaluated both children and adults who reported persistent musculoskeletal pain that did not meet the strict criteria for fibromyalgia defined by the American College of Rheumatology. Elderly patients with nonspecific musculoskeletal pain refractory to usual therapy, including the use of nonsteroidal anti-inflammatory drugs, had a high prevalence of vitamin D deficiency. Although the observation was not unexpected,^{2,3} the extent of vitamin D deficiency in the younger age group is noteworthy. Specifically, 100% of patients younger than 30

years and older than 60 years had vitamin D deficiencies, with the younger group having significantly lower levels of 25-hydroxyvitamin D. The association between nonspecific musculoskeletal pain and vitamin D deficiency was suspected because of a higher prevalence of these symptoms during winter than summer. The study patients ranged in age from 10 to 65 years, and all had symptoms of vitamin D deficiency. Of the more than 90% of patients who were medically evaluated for persistent musculoskeletal pain 1 year or more before screening, none had been tested previously for vitamin D deficiency.

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Most physicians recognize that the elderly population is at risk for vitamin D deficiency.^{2,3} However, it is less appreciated that children, young adults, and middle-aged adults are also at high risk. Nesby-O'Dell et al⁴ reported that 42% of African American women in the United States aged 15 to 49 years were vitamin D–deficient; Tangpricha et al⁵ reported that 32% of healthy young white men and women in Boston aged 18 to 29 years were vitamin D–deficient at the end of winter in 2003. It is now recognized that mothers with darker skin, along with their newborns and young children who receive their total nutrition from breastfeeding, are at high risk of vitamin D deficiency. In Boston, 76% of 50 mother-infant pairs were found to be vitamin D–deficient, as were 69% of infants in the New York area (J. M. Lee, MD, B. L. Phillip, MD, D. S. Hirsch, MD, M. F. Holick, MD, unpublished data, 2003). Sullivan et al⁶ reported that 48% of girls in Maine aged 9 to 11 years were vitamin D–deficient at the end of winter in 2003.

Vitamin D is essential for the efficient utilization of dietary calcium. In a vitamin D–deficient state, the amount of calcium absorbed is inadequate to satisfy the body's calcium requirement,⁷ resulting in an increase in the production and secretion of parathyroid hormone (PTH). Parathyroid hormone conserves calcium by increasing tubular

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reabsorption of calcium in the kidneys, stimulating the kidneys to produce 1,25-dihydroxyvitamin D (the hormonally active form of vitamin D). However, in a vitamin D-deficient state, inadequate amounts of 1,25-dihydroxyvitamin D are produced to maintain intestinal calcium absorption. As a result, the skeleton, through a PTH-mediated process that involves osteoclast activation, serves as the surrogate source of calcium. This results in osteopenia and osteoporosis.^{2,7}

Another effect of PTH on mineral metabolism often goes unappreciated; it induces phosphaturia, which leads to hypophosphatemia. Thus, the calcium phosphate product in the circulation decreases and becomes inadequate to mineralize the bone properly. However, the osteoblasts continue to deposit collagen matrix on both the endosteal and periosteal surfaces of the skeleton, and the resultant rubbery matrix does not provide sufficient structural support. Instead, it hydrates and expands under the periosteal covering, causing an outward pressure on the periosteal covering that is innervated with sensory pain fibers. This is the likely explanation of why patients with osteomalacia often experience a dull unrelenting aching sensation in their bones. These symptoms are either dismissed or misdiagnosed as fibromyalgia by many physicians. A physical examination that includes application of minimal pressure with the thumb or forefinger on the sternum, anterior tibia, or radius and ulna often will elicit pain and discomfort, which is a helpful diagnostic sign for osteomalacia.

Vitamin D deficiency causes muscle weakness and muscle aches and pains in both children and adults. Glerup et al⁸ reported that 88% of Danish women of Arab descent who presented with muscle pains and weakness were severely vitamin D-deficient. Bischoff et al⁹ observed that adults with vitamin D deficiency have muscle weakness and are more likely to fall.

There are a multitude of reasons for why vitamin D deficiency has again become a major health problem for both children and adults of all ages and races. Extremely few foods naturally contain or are fortified with vitamin D. It has been estimated that 90% or more of our required vitamin D comes from exposure to sunlight.² Anything that interferes with the penetration of solar ultraviolet radiation into the skin, such as increased melanin pigmentation and sunscreen use, will diminish the cutaneous production of vitamin D.^{2,7} Thus, as noted by Plotnikoff and Quigley,¹ children and adults with darker skin are at higher risk of vitamin D deficiency. Application of a sunscreen with sun protection factor 8 reduces the capacity of the skin to produce vitamin D by 95%.^{2,10}

In 1997, the Institute of Medicine of the US National Academy of Sciences recommended new adequate intakes for vitamin D.¹¹ The recommendations, based on the assumption that young and middle-aged adults were more

likely than older adults to be exposed to sunlight, are as follows: 200 IU/d for children and adults to age 50 years, 400 IU/d for men and women aged 50 to 70 years, and 600 IU/d for those older than 70 years. However, a minimum of 1000 IU/d of vitamin D is needed to satisfy the body's requirement.¹²⁻¹⁴ Heaney et al¹⁴ estimated that the body uses 3000 to 5000 IU/d of vitamin D. What does the body do with all that vitamin D? Most organs in the body, including the brain, heart, pancreas, skin, and immune system, recognize 1,25-dihydroxyvitamin D.^{2,7} Furthermore, many of these organs also have the capacity to make 1,25-dihydroxyvitamin D.^{2,7} Besides regulating calcium homeostasis, 1,25-dihydroxyvitamin D is a potent inhibitor of cellular growth, stimulator of insulin secretion, modulator of immune function, and inhibitor of renin production.^{2,7} These functions are likely responsible for the numerous epidemiological observations that people who live at higher latitudes and who are more prone to vitamin D deficiency are at increased risk of developing prostate, colon, breast, and other solid tumors¹⁵; autoimmune diseases including multiple sclerosis and type 1 diabetes; hypertension; and cardiovascular heart disease.^{2,7}

The take-home message from Plotnikoff and Quigley's observations is that when patients with nonspecific skeletal-muscular pain are evaluated, their serum 25-hydroxyvitamin D levels should be obtained. Physicians should disregard the laboratory-reported lower limit of the normal range. A serum 25-hydroxyvitamin D level of at least 20 ng/mL is necessary to minimally satisfy the body's vitamin D requirement.^{14,16} Maintenance of a serum 25-hydroxyvitamin D level of 30 to 50 ng/mL is preferred.^{2,7,14,17}

The most cost-effective and efficient method for preventing vitamin D deficiency is to have adequate exposure to sunlight. Some dermatologists advise that people of all ages and ethnicities should avoid all direct exposure to sunlight and should always use sun protection when outdoors. This message is not only unfortunate, it is misguided and has serious consequences, ie, the risk of vitamin D deficiency and increased risk of many chronic diseases. There is little evidence that adequate sun exposure will substantially increase the risk of skin cancer; rather, long-term excessive exposure and repeated sunburns are associated with nonmelanoma skin cancers. The amount of time for adequate exposure depends on time of day, season, latitude, skin pigmentation, and the area of skin surface that has no sun protection. Typically, the sun exposure of a person in a bathing suit of 1 minimal erythema dose (which causes a slight pinkness to the skin) is equivalent to ingesting 20,000 IU of vitamin D.^{2,7} Thus, exposure of hands, face, and arms or arms and legs to 25% of a minimal erythema dose (about 5-15 minutes between 11 AM and 2 PM in Boston) will provide an adequate amount of vitamin D.

Vitamin D deficiency can be treated easily by giving the patient an oral dose of 50,000 IU of vitamin D once a week for 8 weeks.¹⁶ Long-term prevention of vitamin D deficiency can be accomplished by giving 50,000 IU of vitamin D once or twice a month.

Physicians should be alert to vitamin D deficiency, as noted by Plotnikoff and Quigley.¹ Patients should have their vitamin D status, ie, serum 25-hydroxyvitamin D levels, tested once a year, preferably at the end of the fall season, to ensure that they do not become vitamin D-deficient before winter. Prevention of vitamin D deficiency not only preserves bone and muscle health but also may help prevent many chronic diseases and preserve overall health and well-being.

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