Bioavailability of Vitamin D and Its Metabolites in Black and White Adults

Michael F. Holick, M.D., Ph.D.

Vitamin D deficiency has become a global health problem that has been associated not only with metabolic bone disease but also with many chronic illnesses.[1] The definition of vitamin D deficiency has been controversial, in part owing to the interpretation of surrogates associated with vitamin D status. The Institute of Medicine concluded that to maximize bone health, the level of 25-hydroxyvitamin D should be higher than 20 ng per milliliter.[2] Others have relied on parathyroid hormone levels to assess vitamin D status, arguing that such levels reach a nadir and plateau when 25-hydroxyvitamin D levels are 30 to 40 ng per milliliter.[3] One study indicated that a 25-hydroxyvitamin D level of more than 30 ng per milliliter ensured the absence of osteomalacia.[4] Bone mineral density has a positive correlation with serum 25-hydroxyvitamin D levels,[5] and numerous association studies have suggested that the risk of many chronic illnesses is increased with a 25-hydroxyvitamin D level of less than 30 ng per milliliter.[1]

A perplexing paradox is that blacks have a higher bone mineral density but lower 25-hydroxyvitamin D levels than whites.[6] In this issue of the *Journal,* Powe et al.[6] report the evaluation of serum levels of calcium, 25-hydroxyvitamin D, and parathyroid hormone as well as bone mineral density in more than 2000 community-dwelling blacks and whites. The investigation confirmed that blacks had higher bone mineral density and lower 25-hydroxyvitamin D levels than whites. However, when the authors compared two common polymorphisms in the vitamin D–binding protein gene in blacks and whites and then measured vitamin D–binding protein levels and calculated free 25-hydroxyvitamin D, they found that blacks had lower vitamin D–binding protein levels than whites and that their bioavailable 25-hydroxyvitamin D levels were similar to those in whites. The authors concluded that vitamin D deficiency may need to be redefined, to consider not only total but also bioavailable 25-hydroxyvitamin D levels.

The vitamin D–binding protein that is also known as GC-globulin is the approximate size of albumin and has three major polymorphic forms — GC1F, GC1S, and GC2. Vitamin D–binding protein has the highest affinity for 25-hydroxyvitamin D, with 20 times and 100 times less affinity for 1,25-dihydroxyvitamin D and vitamin D_3, respectively. The vitamin D–binding protein variants have different abundances and affinities for vitamin D and these two vitamin D metabolites, with GC1F greater than GC1S and GC1S greater than GC2.[7] GC1F is the most abundant form in persons of African ancestry, whereas GC1S is most abundant in European populations. Albumin also binds 25-hydroxyvitamin D with lower affinity than that of the vitamin D–binding protein. Albumin in the circulation is 15 times more abundant than vitamin D–binding protein; approximately 10% of the total 25-hydroxyvitamin D in the circulation is bound to albumin, which may also be an important component of bioavailable 25-hydroxyvitamin D.[6] Megalin (LRP2), a transmembrane protein, internalizes 25-hydroxyvitamin D bound to the vitamin D–binding protein and albumin.[7] Mice lacking megalin have increased urinary loss of 25-hydroxyvitamin D bound to vitamin D–binding protein and albumin and have a metabolic bone disease that is more severe than that seen in mice lacking vitamin D–binding protein.[7] Thus, the bound 25-hydroxyvitamin D appears to be important for the renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D for calcium and bone metabolism.

It has been hypothesized that during the course of evolution, the most abundant polymorphic form of the vitamin D–binding protein in blacks had an increased affinity for vitamin D_3 and thus was able to transport vitamin D_3 more efficiently from the skin to the liver for its metabolism to 25-hydroxyvitamin D.[8] However, mice lacking vitamin D–binding protein have been shown to metabolize vitamin D_3 to 25-hydroxyvitamin D with increased efficiency, which suggests that free, not bound, vitamin D_3 is what the liver prefers.[7-9]

Maasai warriors living near the equator, who are outside daily, have mean blood levels of

25-hydroxyvitamin D of 44 ng per milliliter.[1,3] As the people in equatorial Africa began migrating farther north and south, their deeply pigmented skin was less efficient in producing vitamin D_3, resulting in rickets due to severe vitamin D deficiency; for women, the flattened, deformed pelvis caused by rickets complicated giving birth. One may speculate that this might have been the evolutionary driver for the mutation of the melanocyte-stimulating hormone receptor gene, leading to skin with little sunscreening pigment to enhance vitamin D_3 production.[10] Is it possible that this loss of pigment may also have led to lower bone density? The higher blood calcium levels observed in blacks as compared with whites may result from higher bioavailable levels of 1,25-dihydroxyvitamin D due to the observed lower levels of vitamin D–binding protein. Bioavailability may be relative regarding vitamin D and its metabolites. Megalin serves to transport the bioavailable 25-hydroxyvitamin D bound to the vitamin D–binding protein and albumin.[7] However, the liver prefers unbound vitamin D_3.[9] Immune and other cells lack megalin and thus may be able to use only unbound 25-hydroxyvitamin D. Therefore, more research is needed to fully appreciate what bioavailable versus total vitamin D status means — for 25-hydroxyvitamin D as well as 1,25-dihydroxyvitamin D. Full elucidation will be important not only for bone health but also for physiological aspects of vitamin D in health and disease.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Department of Medicine, Section of Endocrinology, Nutrition, and Diabetes, and the Vitamin D, Skin, and Bone Research Laboratory, Boston University Medical Center, Boston.

1. Hossein-Nezhad A, Holick MF. Vitamin D for health: a global perspective. Mayo Clin Proc 2013;88:720-55.
2. Institute of Medicine, Committee to Review Dietary Reference Intakes for Calcium and Vitamin D. Dietary reference intakes for calcium and vitamin D. Washington, DC: National Academies Press, 2011.
3. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. J Clin Endocrinol Metab 2012;97:1153-8.
4. Bischoff-Ferrari HA, Dietrich T, Orav J, Dawson-Hughes B. Positive association between 25-hydroxyvitamin D levels and bone mineral density: a population-based study of younger and older adults. Am J Med 2004;116:634-9.
5. Priemel M, von Domarus C, Klatte TO, et al. Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. J Bone Miner Res 2010;25:305-12.
6. Powe CE, Evans MK, Wenger J, et al. Vitamin D–binding protein and vitamin D status of black Americans and white Americans. N Engl J Med 2013;369:1991-2000.
7. Chun RF. New perspectives on the vitamin D protein. Cell Biochem Funct 2012;30:445-56.
8. Kamboh MI, Ferrell RE. Ethnic variation in vitamin D-binding protein (GC): a review of isoelectric focusing studies in human populations. Hum Genet 1986;72:281-93.
9. Safadi FF, Thornton P, Magiera H, et al. Osteopathy and resistance to vitamin D toxicity in mice null for vitamin D binding protein. J Clin Invest 1999;103:239-51.
10. Lalueza-Fox C, Römpler H, Caramelli D, et al. A melanocortin 1 receptor allele suggests varying pigmentation among Neanderthals. Science 2007;318:1453-5.

DOI: 10.1056/NEJMe1312291