

See corresponding article on page 613.

A call for action: standard of care guidelines to assess vitamin D status are needed for patients with hip fracture

MF Holick

Section of Endocrinology, Diabetes, Nutrition and Weight Management, Department of Medicine, Boston University Medical Center, Boston, MA, USA

In this issue of the Journal, Hao et al. (1) report a secondary analysis of a multicenter study on a large cohort of patients who had a hip fracture requiring surgical intervention to determine the influence of vitamin D status and the Geriatric Nutritional Risk Index on mortality rates and ability to ambulate. They conclude that patients who had a serum 25-hydroxyvitamin D [25(OH)D] of ≥ 12 ng/mL had higher rates of self-reported walking at 30 and 60 d postoperatively compared with patients with a 25(OH)D < 12 ng/mL. On the other hand, poor nutritional status was observed to have a marginal effect on reduced mobility at 30 d but not at 60 d. They also found no association of vitamin D status nor nutritional status on mortality at these 2 time points. This editorial begins with a brief summary of previous studies providing insight about the controversy associated with vitamin D supplementation recommendations for improving muscle function. It then discusses the merits of the study by Hao et al. (1) and its health implications not only for elderly with hip fractures but also for all children and adults.

By the turn of the 20th century, rickets was a pandemic in most industrialized cities throughout the world (2). The most obvious clinical manifestations were skeletal deformities and growth retardation. However, it was also recognized that children with skeletal manifestations of rickets presented with proximal muscle weakness especially in the hip girdle region (2). Because severe vitamin D deficiency can cause hypocalcemia and hypophosphatemia, it was thought that the muscle weakness was associated with deficiencies of these minerals, which were considered to be essential for maximum skeletal muscle function. Correction of vitamin D deficiency in these children rapidly improved muscle function, whereas improvement in the skeletal abnormalities required a longer duration of therapy.

What is the role of vitamin D for skeletal muscle function? Does it have a direct effect on maintaining maximum skeletal muscle function, or are the associated alterations in calcium and phosphate metabolism more likely to affect skeletal muscle function? Vitamin D deficiency results in a decrease in the efficiency of intestinal calcium and phosphorus absorption. In response to the decrease in the body's ability for acquiring calcium from the diet, the parathyroid glands increase the production and release of parathyroid hormone (PTH) into the circulation. In the kidneys, PTH conserves calcium by increasing tubular reabsorption of calcium from the ultrafiltrate. PTH also

causes the internalization of the sodium phosphate cotransporter, resulting in a loss of phosphate into the urine and a decrease in serum phosphate concentrations. PTH also takes advantage of the skeletal stores of calcium by stimulating the production of receptor activator of NF- κ B ligand (RANKL) in osteoblasts. This ligand interacts with its receptor RANK on monocytes, inducing them to amalgamate into multinucleated osteoclasts. The mature osteoclasts release HCl and collagenases, causing the release of skeletal calcium into the circulation. PTH also stimulates the kidneys to convert 25(OH)D to 1,25-dihydroxyvitamin D [1,25(OH)2D]. 1,25(OH)2D interacts with its nuclear vitamin D receptor (VDR) in the intestine to increase the efficiency of intestinal calcium absorption. It interacts with its VDR in osteoblasts, resulting in the production of RANKL, which like PTH increases the production of osteoclasts. The net effect is for PTH to maintain a normal serum calcium while reducing serum phosphate concentrations. The consequence is a reduced calcium phosphate product, resulting in a mineralization defect of newly laid down collagen matrix and thus resulting in rickets in children and the painful muscle and bone disease, osteomalacia, in adults (2, 3).

Vitamin D exerts multiple effects on skeletal muscle health. Evidence suggests that skeletal muscle has a VDR and the ability to convert 25(OH)D to 1,25(OH)2D (2, 3). It has been proposed that 1,25(OH)2D has both genomic and nongenomic effects, including calcium signaling in skeletal muscle cells (2). Previous studies illustrate that vitamin D plays a pivotal role in muscle cell proliferation and differentiation as well as improving muscle mitochondrial activity, functional capacity, and having a protective effect on muscle fat accumulation and mitochondrial dysfunctions (2, 4). Lower extremity function, proximal muscle strength, and physical performance have been

The author reported no funding received for this study.

MFH is a consultant for Ontometrics, former consultant for Quest Diagnostics, and Speaker's Bureau for Abbott.

Address correspondence to MFH (e-mail: Mfholick@bu.edu).

Abbreviations used: DBP, vitamin D-binding protein; PTH, parathyroid hormone; RANKL, receptor activator of NF- κ B ligand; VDR, vitamin D receptor; 1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D.

First published online July 25, 2020; doi: <https://doi.org/10.1093/ajcn/nqaa202>.

positively associated with serum concentrations of 25(OH)D. A randomized controlled multidose study of vitamin D revealed that supplementation of 800 IU/d lowered the adjusted incidence rate ratio of falls by 72% compared with that of those taking a placebo over 5 mo (5). A meta-analysis of 26 studies that enrolled 45,782 participants, a majority of whom were elderly women, revealed vitamin D use was associated with a statistically significant reduction in the risk of falls. The study also found that the effect was most prominent in patients who were vitamin D deficient at baseline and in studies in which calcium was co-administered with vitamin D (6). Nonetheless, the US Preventive Services Task Force (7) recommends against routine vitamin D supplementation to prevent falls in the elderly.

Here, some sobering facts about muscle weakness and consequences of falls in those aged ≥ 50 y are presented. The CDC reports 1 out of 5 falls results in serious injury and 3 million older people are treated in emergency departments for fall injuries, with $>800,000$ being hospitalized because of a head injury or hip fracture. More than 95% of hip fractures are caused by falling, usually by falling sideways. In 2015, the total medical costs for falls was estimated to be more than \$15 billion (8). Each year, $\sim 300,000$ elders, 75% of whom are women, are hospitalized for hip fracture. Hip fracture among older patients is a devastating injury because it profoundly affects the physical, mental, functional, and social balance that patients had pre-injury. Although a small study reported that 50% of patients with hip fracture died within 6 mo, most studies have reported a 20–30% mortality after 1 y, which is twice the mortality rate for this age population (8–11). Those who survive do not recover their baseline independence and function; 10% never return home and continue to suffer pain and loss of mobility. In recent decades, the increase in life expectancy after age 60 y has led to an exponential growth in hip fractures (8). Major acute complications include sepsis and pulmonary embolus, as well as complications from comorbidities, including cardiovascular heart disease. Long-term consequences of immobilization include bedsores, urinary tract infections, pneumonia, and deep venous thromboses. In addition, immobility leads to significant loss of muscle mass and function, increasing risk for falls and additional fractures including of the unaffected hip (8–11).

In addition to causing pain, a hip fracture results in a loss of physical function, decreased social engagement, increased dependence, and worse quality of life (8–11). Hao et al. (1) reported that 43% and 30% of their fracture patients were unable to walk without assistance at 30 and 60 d, respectively. Those who were unable to walk without assistance had lower 25(OH)D concentrations compared with those who could walk. Interestingly, they observed that it was only the preoperative blood concentration of 25(OH)D that related to the patient's ability to walk after 30 d; postoperative blood concentrations were not related. This could be due to several factors. They observed postoperatively that the albumin concentrations were lower, and this also related to increased risk for mortality. Lower blood concentrations of albumin are also associated with lower blood concentrations of GC protein, which is the vitamin D-binding protein (DBP). Therefore, decreased DBP could result in increased free concentrations of 25(OH)D, which in turn may have improved muscle function (12). We also do not know whether either at the time of admission or at some point in time during the hospitalization some of the patients may have received supplemental vitamin D.

What evidence is there that 25(OH)D may have a direct effect on skeletal muscle performance independent of nutrition, especially as it relates to imbalances in calcium and phosphate metabolism associated with vitamin D deficiency? Hao et al. (1) observed a 56–64% increased rate of walking in patients with a blood concentration of 25(OH)D of ≥ 12 ng/mL compared with only 35% for patients able to ambulate 10 ft 30 d after hip fracture. However, both patient groups had similar blood concentrations of calcium (the investigators did not report serum phosphate concentrations). Shirvani et al. (13) reported an unusual case of a male with a granulomatous disorder who had severe vitamin D deficiency [i.e., 25(OH)D < 5 –10 ng/mL]. The patient's degree of vitamin D deficiency was associated with such severe proximal muscle weakness that he was wheelchair-bound because he could not get up from a sitting position and he was unable to lift his head. He had an elevated serum calcium and relatively normal serum phosphate concentrations at the time of the presentation of the symptoms. All symptoms resolved after he received a small amount (i.e., 400 IU) of vitamin D-3, which quickly raised his 25(OH)D to ~ 15 ng/mL. Therefore, these observations support numerous other reports suggesting that vitamin D has a direct effect on skeletal muscle function and performance.

The take-home message is that patients aged ≥ 50 y presenting with fractures, especially those with hip fracture, should be evaluated at intake for their vitamin D status. Consideration should be made to provide vitamin D supplementation if dietary/supplemental intake or blood concentrations of 25(OH)D suggest deficiency. There are a wide variety of multivitamins containing varying amounts of vitamin D, and there are also a variety of over-the-counter vitamin D supplements containing up to 5000 IU. However, the only pharmaceutical form of vitamin D for adults in the United States is vitamin D-2 at a dose of 50,000 IU. The Endocrine Society's practice guidelines on vitamin D recommend that an effective method for treating and preventing recurring vitamin D deficiency is to give a patient 50,000 IU vitamin D-2 or vitamin D-3 once a week for 8 wk followed by a maintenance dose of 50,000 IU vitamin D-2 or vitamin D-3 once every 2 wk thereafter (14). A 6-y study following this protocol without obtaining a baseline blood concentration of 25(OH)D reported not only that the patients maintained blood concentrations of 25(OH)D of ≥ 30 ng/mL but also, more importantly, that no untoward toxicity was observed (15).

The data from Hao et al. (1) suggest that it is prudent to institute as standard of care vitamin D status assessment and possible supplementation for all patients presenting with hip fracture. It is important to note that other fragility fractures associated with osteoporosis may present similarly. This simple strategy could potentially significantly reduce morbidity and mortality associated with vitamin D deficiency.

The sole author was responsible for all aspects of this manuscript. The author reports no conflicts of interest.

References

1. Hao L, Carson JL, Schlüssel Y, Noveck N, Shapses SA. Vitamin D deficiency is associated with reduced mobility after hip fracture surgery: a prospective study. *Am J Clin Nutr* 2020;112(3):613–8.
2. Wacker M, Holick MF. Vitamin D—effects on skeletal and extraskeletal health and the need for supplementation. *Nutrients* 2013;5:111–48.
3. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266–81.

4. Chang E, Kim Y. Vitamin D ameliorates fat accumulation with AMPK/SIRT1 activity in C2C12 skeletal muscle cells. *Nutrients* 2019;11:2806.
5. Broe KE, Chen TC, Weinberg J, Bischoff-Ferrari HA, Holick MF, Kiel DP. A higher dose of vitamin D reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. *J Am Geriatr Soc* 2007;55:234–9.
6. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, Wong JB, Egli A, Kiel DP, Henschkowski J. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ* 2009;339:b3692. doi:10.1136/bmj.b3692.
7. US Preventive Services Task Force. Interventions to prevent falls in community-dwelling older adults. *JAMA* 2018;319(16):1696–1704 [Internet]. Available from: <https://jamanetwork.com/journals/jama/fullarticle/2678104>.
8. CDC. Home and recreational safety: important facts about falls. [Internet]. 2017. Available from: www.cdc.gov/homeandrecreational/safety/falls.
9. Negrete-Corona J, Alvarado-Soriano JC, Reyes-Santiago LA. Hip fracture as risk factor for mortality in patients over 65 years of age: Case-control study. *Acta Ortop Mex* 2014;28(6):352–62.
10. Schnell S, Friedman SM, Mendelson DA, Bingham KW, Kates SL. The 1-year mortality of patients treated in a hip fracture program for elders. *Geriatr Orthop Surg Rehabil* 2010;1(1):6–14.
11. Downey C, Kelly M, Quinlan JF. Changing trends in the mortality rate at 1-year post hip fracture: a systematic review. *World J Orthop* 2019;10(3):166–75.
12. Bikle DD, Schwartz J. Vitamin D binding protein, total and free vitamin D levels in different physiological and pathophysiological conditions. *Front Endocrinol (Lausanne)* 2019;10:317.
13. Shirvani A, Palermo NE, Holick MF. Man of steel syndrome: silicone and mineral oil injections with associated hypercalcemia, hypophosphatemia, and proximal muscle weakness. *J Bone Miner Res* 2019;3(10):e10208. doi:10.1002/jbm4.10208.
14. Holick MF, Binkley N, Bischoff-Ferrari HA, Gordon CA, Hanley DA, Heaney R, Murad MH, Weaver C. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011;96(7):1911–30.
15. Demetriou ETW, Trivison TG, Holick MF. Treatment with 50,000 IU vitamin D2 every other week and effect on serum 25-hydroxyvitamin D2, 25-hydroxyvitamin D3 and total 25 hydroxyvitamin D in a clinical setting. *Endocr Pract* 2012;18(3):399–402.