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EDITORIAL

Vitamin D: the other steroid hormone for muscle function and strength

It was well documented more than 100 years ago that children with rickets had a difficult time standing because of muscle weakness and were at higher risk for upper respiratory tract infections because, in part, of poor muscle tone of their diaphragm and accessory muscles for breathing.[1] In the 1930s, exposure to ultraviolet radiation was used by some Olympic teams to improve the performance of their athletes. At this time, it was thought that because severe vitamin D deficiency caused hypocalcemia, which increased neuromuscular irritability, it was vitamin D's effect on calcium metabolism that was important for maximizing muscle strength.[1]

In 1975, Birge and Haddad[2] reported that intact diaphragms from vitamin D–deficient rats that had received 400 IU of vitamin D_3 had improvement in protein synthesis compared with placebo controls. They also observed an increase in adenosine triphosphate (ATP) content and phosphate uptake in this skeletal muscle. Animals that were nephrectomized and received vitamin D_3 showed the same increase in ATP levels in their diaphragms compared with the placebo group. To eliminate the systemic effects of the vitamin, the epitrochlear muscle of the rat foreleg of vitamin D–deficient rats was maintained in culture and incubated with either 25-hydroxyvitamin D_3 [$25(OH)D_3$], 1,25-hydroxyvitamin D_3 [$1,25(OH)_2D_3$], or vitamin D_3. They reported that the addition of 20 ng/mL of $25(OH)D_3$ enhanced the ATP content of the muscle and increased leucine incorporation into protein, whereas 20 μg/mL of vitamin D_3 and 0.5 ng/mL of $1,25(OH)_2D_3$ were without effect. In the 1980s, investigators began to report that skeletal muscle had a vitamin D receptor (VDR) and that $1,25(OH)_2D_3$ regulated skeletal muscle proliferation and differentiation in vitro.[3,4] Further evidence for a direct action of vitamin D on skeletal muscle function came from the observation that VDR knockout mice lacked muscular development.[5] The muscle phenotype in mice that lacked VDR was smaller, with variable muscle fibers, and there was a persistence of immature muscle gene expression during adult life.[5-7] These abnormalities persisted even when the mice were placed on a high-calcium diet so that their calcium metabolism would be corrected. These observations collectively suggested that vitamin D played an important role in the maintenance of skeletal muscle function that was independent of its effect on regulating calcium and phosphate metabolism.

The observations that human skeletal muscle had a VDR and that it decreased with age[8] set the stage for observational studies demonstrating that higher blood levels of 25(OH)D were associated with improved muscle strength and lower extremity function. An evaluation of National Health and Nutrition Examination Survey III data revealed a dose-response relationship between serum 25(OH) levels and improvement in the ability to walk 8 ft or to get from sitting to standing position.[9] In the 4,100 ambulatory adults 60 years or older, the poorest muscle function was observed when their 25(OH)D was less than 50 nmol/L (20 ng/mL). Improvement in muscle function was observed in the reference range of 24 to 92.5 nmol/L (9-37 ng/mL).[9] These association studies were followed by several double-blind randomized controlled trials demonstrating that increased vitamin D intake improved muscle strength and balance and reduced risk of falling by as much as 72%.[10-13] A meta-analysis of five high-quality trials demonstrated that 400 IU of vitamin D a day did not seem to have any benefit and that the threshold for improvement of skeletal muscle health was observed when the vitamin D intake was at least 800 IU of vitamin D a day.[9]

El-Hajj Fuleihan et al[14] reported on bone health and lean body mass in 170 girls aged 10 to 17 years who were randomized to receive weekly oral vitamin D_3 doses of 1,400 or 14,000 IU in a double-blind, placebo-controlled 1-year study. In the overall group of girls, there was a significant increase in lean mass but not in grip strength. The blood levels of 25(OH)D reached 95 ± 77 nmol/L (38 ± 31 ng/mL) in the group receiving an equivalent of 2,000 IU of vitamin D a day compared with 43 ± 15 nmol/L (17 ± 6 ng/mL) in the group that received an equivalent of 200 IU of vitamin D a day. It was concluded that vitamin D supplementation for 1 year resulted in substantial increases in lean mass as well as bone area and bone mass in girls aged 10 to 17 years without any toxicity.

Stewart et al[15], in this issue of Menopause, evaluated 231 healthy postmenopausal women aged 45.8 to 65 years on the relationship between serum 25(OH)D levels and overall fitness. They found that 19% and 44% of the women were vitamin D deficient and insufficient, respectively, consistent with what has been previously observed in children and adults throughout the United States.[16,17] They observed that 25(OH)D was a common contributor to physical fitness indices, including androidal fat mass, whole body lean mass, balance, and in grip strength, in healthy postmenopausal women.

The major limitation of the study, as noted by these investigators, was that we do not know what the contributions of sunlight and diet were on blood levels of 25(OH)D in these women. However, what is clear is that the women who

had taken vitamin D supplements, presumably containing 400 IU of vitamin D, had a mean 25(OH)D concentration of 73 nmol/L, which is considered to be suboptimal. It has been estimated that for every 100 IU of vitamin D ingested, the blood level of 25(OH)D increases by 2.5 nmol/L (1 ng/mL).[18,19] However, what is curious is that when blood levels of 25(OH)D are below 50 nmol/L, the body responds more robustly to the vitamin D supplementation by increasing blood levels of 25(OH)D by 5 to 7.5 nmol/L for every 100 IU of vitamin D ingested.[20] This may be the explanation why the authors observed a mean baseline value of 65.9 nmol/L in women taking supplements. The small amount of vitamin D from dietary sources, along with exposure to sunlight, was likely responsible for the unsupplemented women having detectable levels of 25(OH)D. The unsupplemented group ingested between 12 and 478 IU of vitamin D, which would have translated to a 25(OH)D level of between 0.75 and 30 nmol/L. Thus, to have achieved a blood level of 43 ± 15 nmol/L would have meant that they were receiving most of their vitamin D from sun exposure and from the small amount of vitamin D ingested, which was then efficiently converted to 25(OH)D in the liver.[20]

Testosterone and its androgen derivatives have always been recognized as being important for the maintenance of muscle function and strength. The observation by Stewart et al,[15] along with the many other studies in children and older adults, provides compelling evidence that vitamin D is indeed the other steroid hormone that is important for muscle function and strength.

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Michael F. Holick, MD, PhD
Boston University School of Medicine
Boston, MA

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