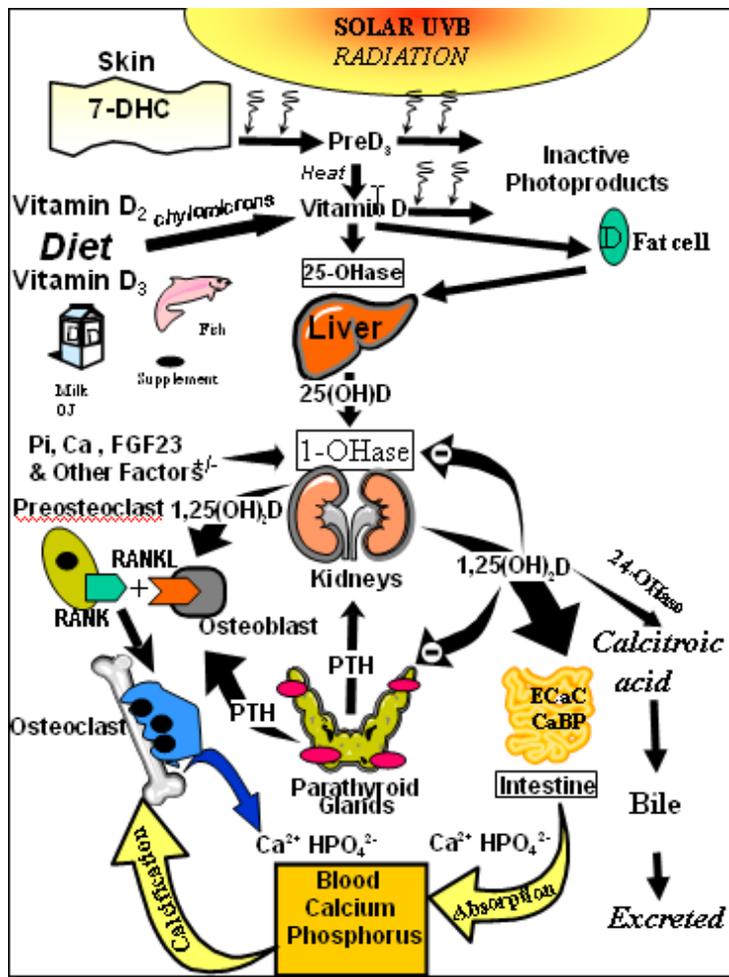


## **Role of Vitamin D in Muscle Strength and Function**

Michael F. Holick, PhD, MD

It was well documented at the turn of last century that one of the physical findings associated with rickets was severe muscle weakness. Children with rickets had a difficult time standing and were at higher risk for upper respiratory tract infections due in part to poor muscle tone of their diaphragm and accessory muscles for breathing.<sup>1</sup> 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, that it was vitamin D's effect on calcium metabolism that was important for maximizing muscle strength.<sup>1</sup>

In the early 1970s it was realized that vitamin D that was made in the skin or came from the diet required two obligate hydroxylations before it became active on regulating calcium and phosphorus metabolism and maintaining bone health (Fig 1).<sup>2</sup>



**Fig 1. Schematic representation of the synthesis and metabolism of vitamin D for regulating calcium, phosphorus, and bone metabolism.** During exposure to sunlight 7-dehydrocholesterol in the skin is converted to previtamin D<sub>3</sub>. Previtamin D<sub>3</sub> immediately converts by a heat dependent process to vitamin D<sub>3</sub>. Excessive exposure to sunlight degrades previtamin D<sub>3</sub> and vitamin D<sub>3</sub> into inactive photoproducts. Vitamin D<sub>2</sub> and vitamin D<sub>3</sub> from dietary sources are incorporated into chylomicrons and transported by the lymphatic system into the venous circulation. Vitamin D (D represents D<sub>2</sub> or D<sub>3</sub>) made in the skin or ingested in the diet can be stored in and then released from fat cells. Vitamin D in the circulation is bound to the vitamin D binding protein, which transports it to the liver where vitamin D is converted by the vitamin D-25-hydroxylase to 25-hydroxyvitamin D [25(OH)D]. This is the major circulating form of vitamin D that is used by clinicians to measure vitamin D status. (Although most reference laboratories report the normal range to be 20-100 ng/mL, the preferred healthful range is 30-60 ng/mL.) It is biologically inactive and must be converted in the kidneys by the 25-hydroxyvitamin D-1 $\alpha$ -hydroxylase (1-OHase) to its biologically active form 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D]. Serum phosphorus, calcium fibroblast growth factors (FGF-23), and other factors can either increase (+) or decrease (-) the renal production of 1,25(OH)<sub>2</sub>D. 1,25(OH)<sub>2</sub>D feedback regulates its own synthesis and decreases the synthesis and secretion of parathyroid hormone (PTH) in the parathyroid glands. 1,25(OH)<sub>2</sub>D increases the expression of the 25-hydroxyvitamin D-24-hydroxylase (24-OHase) to catabolize 1,25(OH)<sub>2</sub>D to the water soluble biologically inactive calcitroic acid, which is excreted in the bile. 1,25(OH)<sub>2</sub>D enhances intestinal calcium absorption in the small intestine by stimulating the expression of the epithelial calcium channel (ECaC) and the calbindin 9K (calcium binding protein; CaBP). 1,25(OH)<sub>2</sub>D is recognized by its receptor in osteoblasts, causing an increase in the expression of

receptor activator of NFκB ligand (RANKL). Its receptor RANK on the preosteoclast binds RANKL, which induces the preosteoclast to become a mature osteoclast. The mature osteoclast removes calcium and phosphorus from the bone to maintain blood calcium and phosphorus levels. Adequate calcium and phosphorus levels promote the mineralization of the skeleton.

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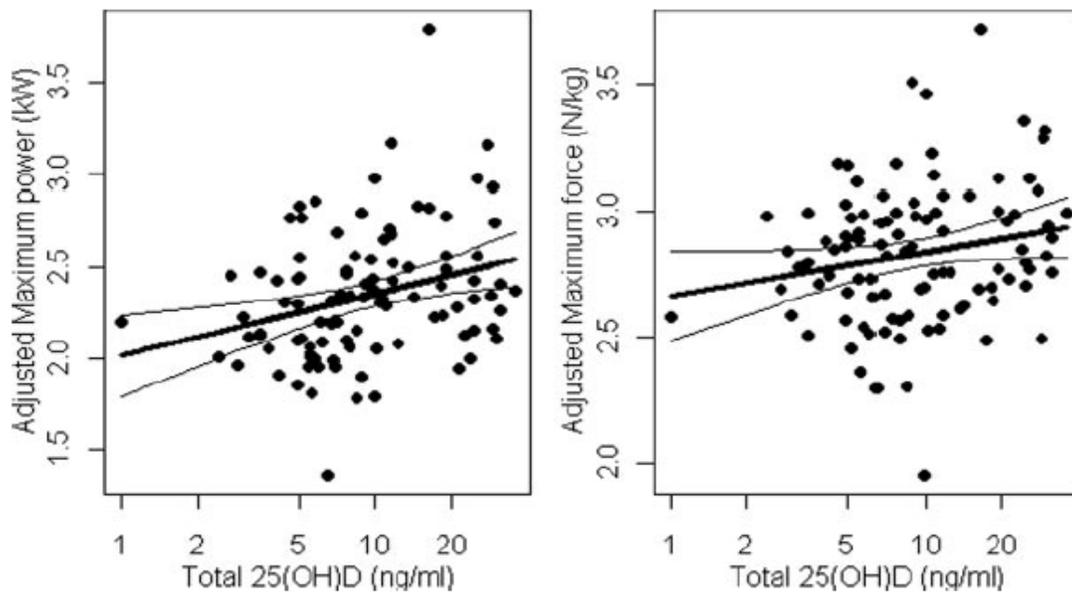
Vitamin D first enters the liver where it is hydroxylated to form the major circulating form of vitamin D, 25-hydroxyvitamin D [25(OH)D]. 25(OH)D travels to the kidneys where it is converted to its active form, 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D].<sup>2-4</sup> 1,25(OH)<sub>2</sub>D enters the bloodstream and travels to its target tissues, where it interacts with a nuclear vitamin D receptor (VDR) to alter gene expression. In the small intestine 1,25(OH)<sub>2</sub>D enhances the efficiency of intestinal calcium absorption to about 30% to 40% and phosphorus absorption to ~80%.<sup>2</sup> In the skeleton 1,25(OH)<sub>2</sub>D interacts with its nuclear receptor in osteoblasts increasing the expression of receptor activator of NFκB ligand (RANKL), which binds to the preosteoclast's RANK, which in turn induces the formation of mature osteoclasts (Fig 1).<sup>2,5</sup> Once formed osteoclasts release enzymes and hydrochloric acid (HCl) to dissolve the matrix and mineral, resulting in the release of calcium and phosphorus into the circulation.

### **Vitamin D and Muscle Function**

In the 1980s it was recognized that embryonic chick skeletal muscle had a vitamin D receptor (VDR).<sup>6</sup> Immunohistochemical evaluation of human skeletal muscle revealed the presence of a VDR<sup>7</sup> and researchers observed a significant reduction in the VDR with increased age from 21 to 91 years.<sup>8</sup> Mice that were genetically engineered to have no VDR had small and variable muscle fibers that were demonstrated to be independent of calcium and phosphorus levels.<sup>9</sup> The muscle phenotype in these mice that lacked VDR also had a persistence of immature muscle gene expression during adult life.<sup>10</sup> These abnormalities persisted even when the mice were placed on

a high-calcium diet so that their calcium metabolism was corrected. VDR genotype was associated with muscle strength in non-obese older women, with a 23% difference in quadriceps strength between bb and BB genotype for the VDR.<sup>11</sup> 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 phosphorus metabolism.

El-Hajj Fuleihan et al<sup>12</sup> reported on bone health and lean body mass in 170 girls ages 10-17 years who were randomized to receive weekly oral vitamin D<sub>3</sub> doses of 1400 IU or 14,000 IU in a double-blind placebo-controlled 1-year study. In the overall group of girls lean body mass increased significantly but not grip strength. The blood levels of 25(OH)D reached  $38 \pm 31$  ng/mL in the group that received an equivalent of 2000 IU of vitamin D<sub>3</sub> a day compared to  $17 \pm 6$  ng/mL in the group that received an equivalent of 200 IU of vitamin D<sub>3</sub> a day. The researchers concluded that vitamin D supplementation for 1 year resulted in substantial increases in lean body mass as well as bone area and bone mass in girls ages 10-17 years without any toxicity. An evaluation of serum 25(OH)D in 99 post-menarchal 12-14 year old females revealed a positive relationship with jump velocity, jump height, and power. A 75% reduction in power was observed in girls who had a blood level of 25(OH)D <15 ng/mL (Fig 2).<sup>13</sup>



**FIG. 1.** The positive relationship between 25(OH)D status and muscle power (*left panel*;  $P = 0.003$ ) and force (*right panel*;  $P = 0.05$ ), after adjustment for weight as a quadratic term.

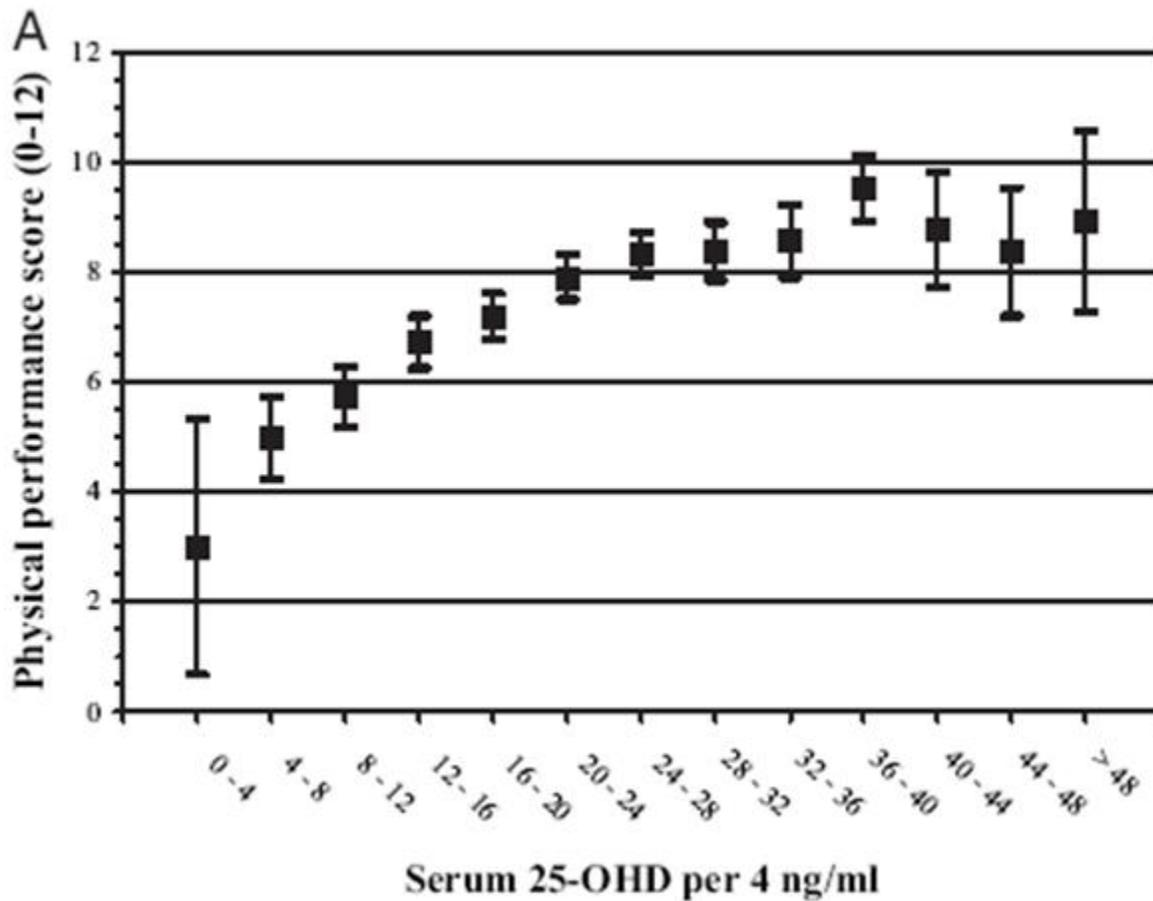
**[designer: delete legend above and change ng/ml to ng/mL]**

**Fig 2.<sup>13</sup>** The positive relationship between 25(OH)D status and muscle power (*left panel*,  $P = 0.003$ ) and force (*right panel*,  $P = 0.05$ ), after adjustment for weight as quadratic term.

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These data are consistent with a longitudinal aging study from Amsterdam that reported a 30%-50% reduction in grip strength and loss of appendicular skeletal muscle mass in elders who had a serum 25(OH)D <20ng/mL.<sup>14</sup> Stewart et al<sup>15</sup> evaluated 231 healthy postmenopausal women ages 45-65 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.<sup>2</sup> They observed that 25(OH)D was a common contributor to physical fitness indices including androidal fat mass, whole body lean mass, and balance and in grip strength in healthy postmenopausal women.

The observations that human skeletal muscle had a VDR and that it decreased with age<sup>8</sup> 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 NHANES III revealed a dose response relationship between serum 25(OH)D levels and improvement in the ability to walk 8 feet or to get from sitting to standing position.<sup>16</sup> In the 4100 ambulatory adults 60 years and older the poorest muscle function was observed when their 25(OH)D was <20 ng/mL. Improvement in muscle function was observed in the reference range of 9-37 ng/mL.<sup>7</sup> These association studies were followed by several double-blind randomized controlled trials demonstrating that increased vitamin D intake to 800 IU/d improved muscle strength and balance and reduced risk of falling by as much as 72%.<sup>8,17</sup> A meta-analysis of five high-quality trials demonstrated that 400 IU of vitamin D a day did not appear to have any benefit and that the threshold for improvement of skeletal health was observed when the vitamin D intake was at least 800 IU of vitamin D a day.<sup>16</sup> An evaluation of physical performance in older people revealed a more than 200% improvement in physical performance when 25(OH)D levels were between 28-32 ng/mL (Fig 3).<sup>18</sup>



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**Fig 3.<sup>14</sup> Physical performance in 1234 older people in relation to 25(OH)D. Shown are CI for the mean. Adjusted for age, gender, number of chronic diseases, degree of urbanization, BMI, and alcohol consumption. CI=confidence interval, BMI=body mass index, 25(OH)D=25-hydroxy vitamin D**

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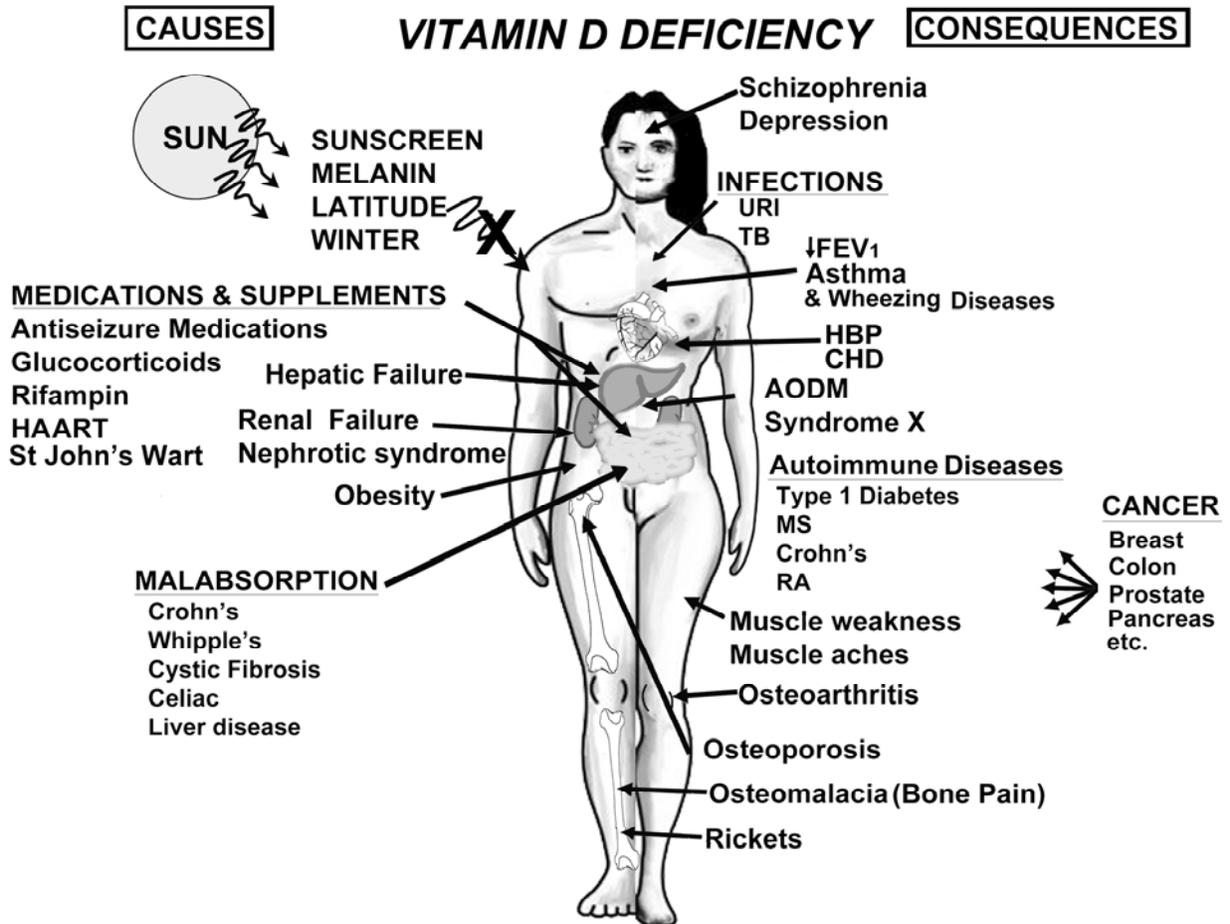
### Vitamin D Deficiency Pandemic and Other Health Consequences

Vitamin D deficiency is now being recognized as one of the most common if not most common medical conditions worldwide. It has been estimated that 30%-100% of children, young, middle-aged, and older adults are vitamin D deficient [25(OH)D <20 ng/mL] or insufficient [25(OH)D = 21-29 ng/mL].<sup>2</sup>

Fifty million teenagers in the United States were found to be vitamin D deficient or insufficient<sup>19</sup> and have a 240% increased risk of having high blood pressure, high blood sugar, and blood biochemistries consistent with metabolic syndrome (pretype 2 diabetes).<sup>20</sup> Vitamin D deficiency has been associated with a 50% increase risk of developing and dying from prostate, colon, breast, and other deadly cancers.<sup>21-24</sup> Vitamin D deficiency and insufficiency have also been linked to hypertension and heart disease.<sup>25-27</sup> There is a 50% increased risk of having a heart attack and more than 100% increase risk of dying from a heart attack if the patient is vitamin D deficient.<sup>28,29</sup> An evaluation of peripheral vascular disease revealed an 80% reduced risk when the 25(OH)D was >29 ng/mL. Autoimmune diseases including multiple sclerosis, rheumatoid arthritis, Crohn's disease, and type I diabetes as well as type II diabetes also have been associated with vitamin D deficiency.<sup>30-34</sup> Men and women who ingested more than 800 IU of vitamin D and 1000 mg of calcium a day reduced their risk of type 2 diabetes by 33%.<sup>34</sup>

### **Treatment and Prevention of Vitamin D Deficiency**

There are a multitude of causes of vitamin D deficiency with devastating health consequences (Fig 4).<sup>2</sup>



**Fig 4. Schematic representation of the major causes of vitamin D deficiency and potential health consequences.** HAART=highly active retroviral therapy, URI=upper respiratory (tract) infection, TB=tuberculosis, FEV=forced expiratory volume, HBP=high blood pressure, CHD=coronary heart disease, AODM=adult onset diabetes mellitus, MS=multiple sclerosis, RA=rheumatoid arthritis

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It has been estimated that for every 100 IU of vitamin D/d ingested the serum level of 25(OH)D increases by 1 ng/mL.<sup>35</sup> Vitamin D<sub>2</sub> and vitamin D<sub>3</sub> are equally effective in raising and maintaining blood levels of 25(OH)D when given to children and adults.<sup>36,37</sup>

To treat vitamin D deficiency 50,000 IU of vitamin D<sub>2</sub> once a week for 8 weeks is effective in raising the blood levels to >30 ng/mL in non-obese children and adults.<sup>36-39</sup> Recurrence of

vitamin D deficiency can be prevented by giving 50,000 IU of vitamin D<sub>2</sub> once every 2 weeks.

We observed after 6 years on this medical regimen that blood levels were maintained between 40 and 60 ng/mL without any toxicity.<sup>39</sup>

## **Conclusion**

Fractures in the elderly are a major problem that has huge economic and health consequences.<sup>40</sup>

Men and women who fracture a hip have a 20% risk of dying within the first year and 50% never have the quality of life they once had. It is estimated that 50% of hip fractures is due to falling.

Vitamin D deficiency causes proximal muscle weakness, making it more difficult to stand from a sitting position and increases risk of sway. Therefore vitamin D deficiency not only precipitates and exacerbates osteopenia and osteoporosis but increases risk of fracture due to decreased muscle strength and imbalance.

Now that vitamin D deficiency has been linked with so many chronic illnesses a major effort is needed to re-educate both health care professionals and the public about the beneficial effects of sunlight and vitamin D supplementation for health.<sup>2,41</sup> Based on the most recent literature 1000 IU of vitamin D a day will not maintain blood levels of 25(OH)D >30 ng/mL in healthy adults who are not exposed to vitamin D producing sunlight.<sup>36</sup> Thus adults need at least 1500-2000 IU of vitamin D a day. Children require at least 400 IU of vitamin D a day and preferably 1000 IU of vitamin D a day to improve their overall health and well-being, including muscle strength.

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## Q&A

**Q:** Dr Holick, can you comment on the vitamin D receptor? Is there resistance in the receptor that can determine the effectiveness of the supplementation of vitamin D?

**Dr Holick:** The most dominant factor that may be related to vitamin D status probably is the polymorphism for the vitamin D binding protein. You probably are aware that the vitamin D binding protein is an alpha globulin, and it is a major component of the protein makeup of the blood. It looks as if the polymorphism for it helps determine vitamin D status much more so than almost anything else. Vitamin D receptor polymorphism studies have been interesting but often have not had enough subjects to show what is going on. Thus, there have been a lot of studies positive and negative for the various polymorphisms. So we do not yet have good enough data to be able to say that vitamin D receptor polymorphism is related to vitamin D status. Vitamin D binding protein polymorphism certainly does.

**Q:** We talk about vitamin D deficiency in muscle weakness, but given that all cells have the receptor, do we know whether this is a cell-autonomous event or something on the bone cell that is somehow cross-talking to the muscle? Also, if the receptor is in the muscle, is it regulating mitochondrial genes or other genes that prevent that weakness?

**Dr Holick:** The vitamin D receptor knockout mouse shows significant structural abnormalities in the skeletal muscle, implying that vitamin D is playing some role in skeletal muscle itself. We do not know at a molecular level how vitamin D is playing a role in muscle function or in muscle strength. It has been suggested that hypocalcemia or, more importantly, hypophosphatemia in a person with vitamin D deficiency might be the major cause of muscle dysfunction. However, studies in rodents show that if you correct calcium and phosphorus metabolism by putting the animals on a high-calcium and high-phosphorus diet, that you still can see some of these defects.

**Q:** But research with a knock out still would not address what is happening in the actual cell, correct? It could happen in another cell and you could just be missing another factor. So has anyone done even simple experiments on cultured cells to show that if you deplete this receptor and then give the cell vitamin D, you do lose something?

**Dr Holick:** Research from Argentina, mainly in muscle cells from chicks, has suggested that if you culture them and you do not have 1,25-dihydroxyvitamin D they do not grow and function as well.

**Q:** That is strength, myofibrillar content, or what?

**Dr Holick:** It is thymidine incorporation and protein synthesis.

**Q:** That could be proliferation. Was that done on differentiated muscle or flat myoblasts?

**Dr Holick:** Myoblasts.

**Q:** We have sick people in the hospital who stay there and do not get outside. Sometimes they stay in the ICU for 6 or 8 weeks. We try to include vitamin D in some of the formulas, but to be honest, patients are on a lot different things. Do you know what vitamin D levels are likely in hospitalized patients? Is there some relationship between vitamin D levels and, say, falls or in-hospital mortality?

**Dr Holick:** The half-life of 25-hydroxyvitamin D in the circulation is about 2 weeks. So you could pretty much predict levels. One research group studied inpatients and found that most of them were vitamin D deficient. The problem is that most of the population is vitamin D deficient. We do know that people who are vitamin D deficient have increased risk of mortality, and I suspect that in an ICU, vitamin D deficiency probably plays a significant role in weakness, infirmity, and general health outcomes. It is unfortunate that people have not realized that giving them vitamin D is a simple fix.

**Q:** Would you suggest that anybody who goes into the ICU or even just the hospital should get 50,000 units of vitamin D automatically? We measure vitamin D on everybody coming out of our ICU. I think I have seen a level of 20 once, and that is the highest I have seen. If the ICU people would get the message, we could at least fix these patients as they come into the hospital.

**Dr Holick:** Absolutely. Even more frustrating for us is that the orthopedic surgeons will send these patients out after repairing a hip fracture and never think about their vitamin D status. We and others have shown that they are all vitamin D deficient coming in, and they are all vitamin D deficient going out.