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Effects of Vitamin D on Skeletal Muscle and Athletic Performance

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J Am Acad Orthop Surg. 2018;26(8):278-285.

Abstract and Introduction

Abstract

Vitamin D is known to be important for calcium homeostasis and bone metabolism. It also has important direct effects on skeletal muscle. Unlike authentic vitamins, which cannot be synthesized in the body, vitamin D is produced in the skin using sunlight. Through its nuclear receptor (ie, vitamin D receptor) located throughout the body, including skeletal muscle, vitamin D initiates genomic and nongenomic pathways regulating multiple actions, including myocyte proliferation and growth. In some studies, vitamin D supplementation has been shown to increase muscle strength, particularly in people who are vitamin D deficient. Higher serum levels of vitamin D are associated with reduced injury rates and improved sports performance. In a subset of the population, vitamin D appears to play a role in muscle strength, injury prevention, and sports performance.

Introduction

Vitamin D has long been recognized as important in maintaining calcium homeostasis within the body. More recently, vitamin D has been shown to have a direct effect on skeletal muscle through the vitamin D receptor (VDR), leading to the recognition that vitamin D may play a role in muscle function, strength, and recovery and potentially in physical and athletic performance.[1] However, a lack of consensus exists regarding what should be considered normal levels of vitamin D within the blood, what effect vitamin D has on muscle function, and whether higher vitamin D levels can improve athletic performance.

Synthesis and Metabolism

The term vitamin D refers to the organic compound cholecalciferol. The hormonally active form of vitamin D, calcitriol, regulates calcium and phosphate homeostasis and skeletal muscle metabolism and has other physiologic functions throughout the human body.[2] Calcitriol is unique among vitamins in that it is a secosteroid, or a so-called broken ring steroid (Figure 1). Secosteroids are considered a subclass of anabolic steroids because their molecular structure and mechanism of action are similar to those of steroid hormones.[2]

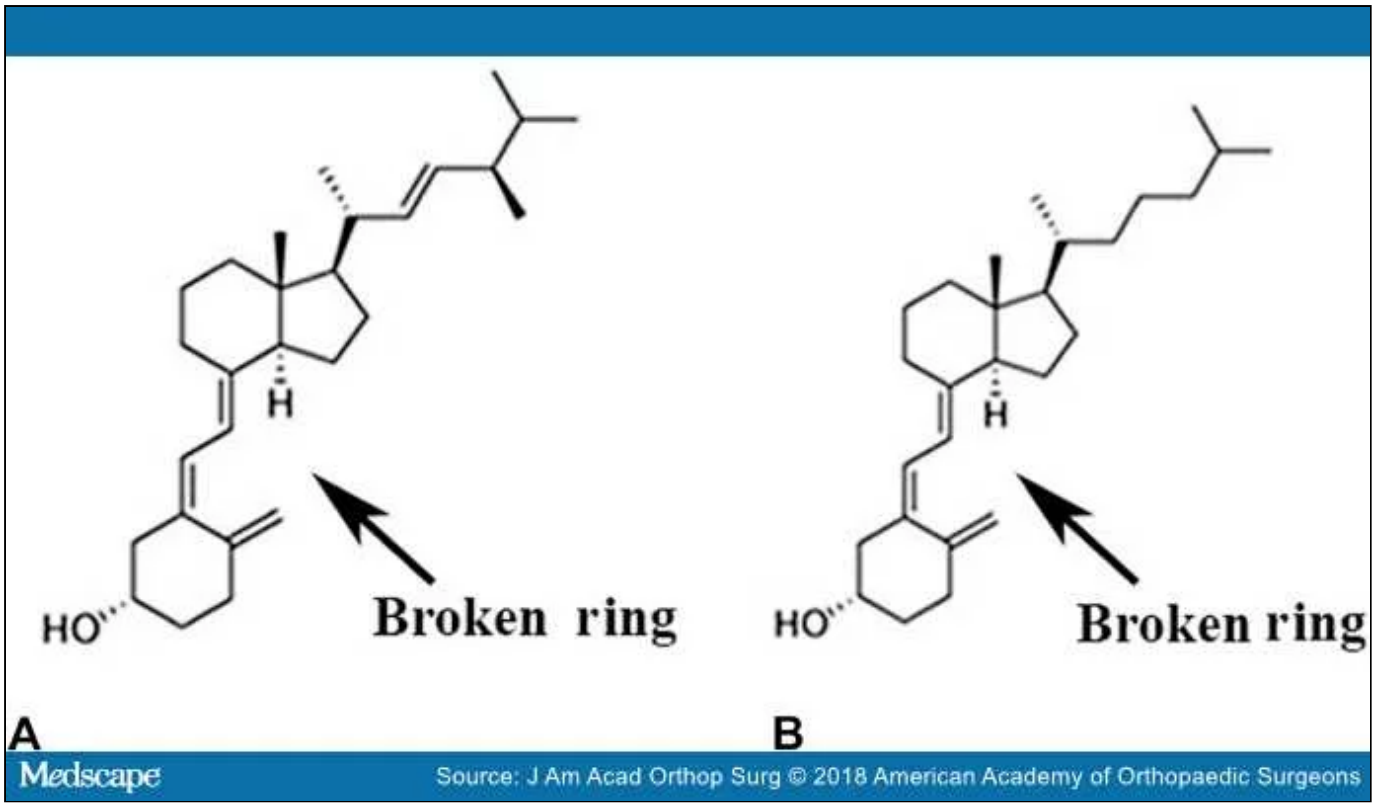

Figure 1.

Diagrams demonstrating the incomplete ring in the chemical structure of vitamin D_2 (A) and vitamin D_3 (B).

In humans, two main forms of vitamin D can be present: cholecalciferol (vitamin D_3, the animal form) and ergocalciferol (vitamin D_2, from plant sources). Although both can be ingested in food or dietary supplements, the synthesis of vitamin D_3 from 7-dehydrocholesterol in the skin (7-dehydrocholesterol is synthesized from cholesterol absorbed in the gut) through sun exposure is the major natural source of the vitamin in animals and humans.[2] Vitamin D_3 undergoes hydroxylation in the liver by the enzyme CYP2R1 to become 25-hydroxyvitamin D_3 (calcidiol). The 25-hydroxylated molecule is relatively inactive and requires further hydroxylation in the kidney and other tissues by the enzyme CYP27B1 to form calcitriol (1,25-dihydroxyvitamin D_3 or $1\alpha,25[OH]_2D_3$), or vitamin D in its biologically active form[2] (Figure 2). The enzyme CYP27B1 is also present in many target cells in the body to allow local synthesis of calcitriol, acting in a paracrine manner in these tissues (Figure 2). Comparable steps can activate ingested vitamin D_2 to a similarly active $1,25(OH)_2D_2$. For simplicity, unless otherwise specified we will use the term 25(OH)D or 1,25(OH)D without the subscript to refer to either the D_2 or D_3 form. Vitamin D blood tests measure the concentration of circulating 25(OH)D molecules. This measure serves as the most commonly accepted marker of overall vitamin D status, in part because the half-life of calcitriol is short. The rate of local synthesis of calcitriol in target cells depends on the circulating concentration of 25(OH)D.

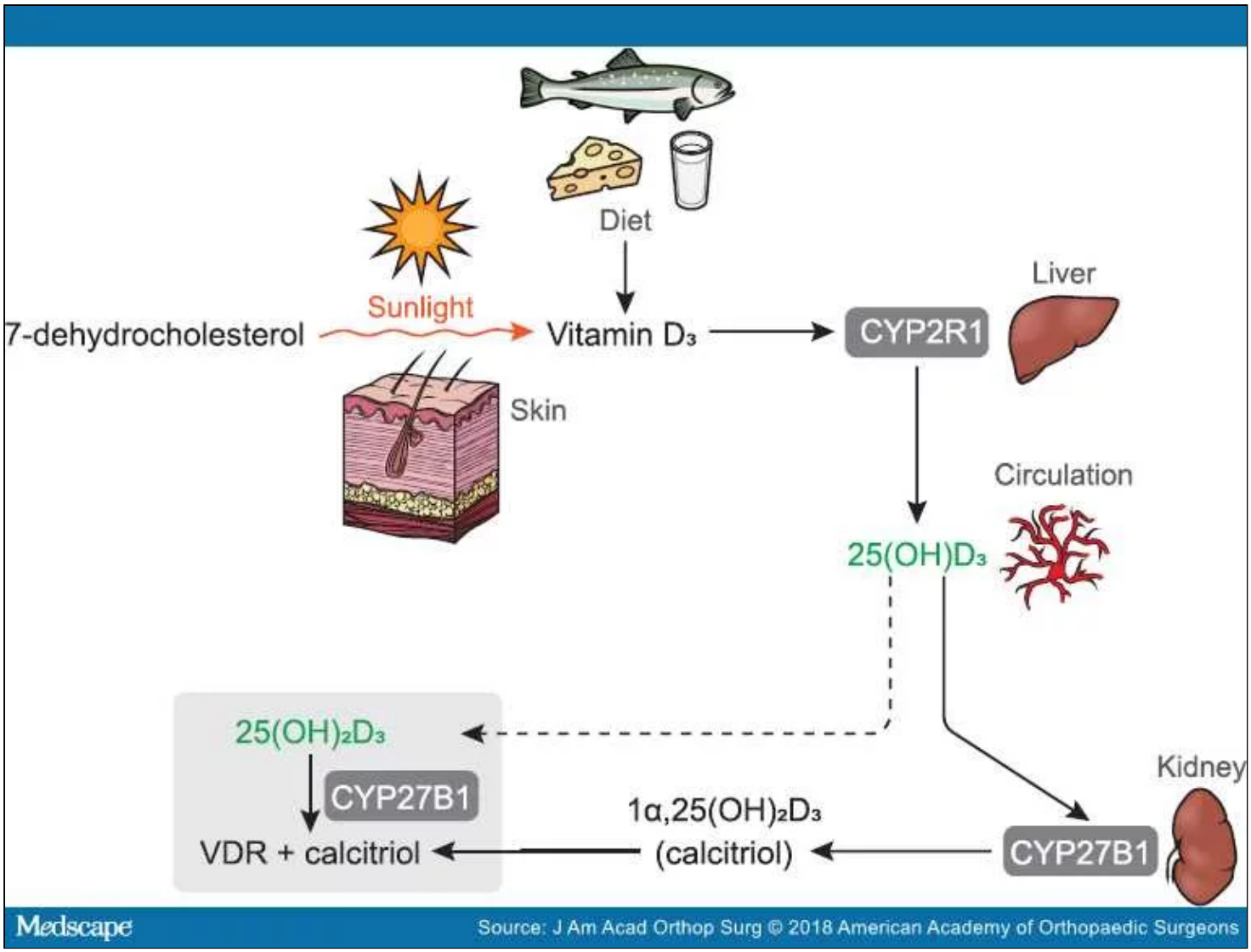

Figure 2.

Diagram depicting the synthesis of vitamin D_3 in the human body. Vitamin D_3 is synthesized from 7-dehydrocholesterol in the skin through sun exposure and can be supplemented with nutritional intake.[1] VDR = vitamin D receptor. (Adapted from Krishnan AV,

Feldman D: Mechanisms of the anti-cancer and anti-inflammatory actions of vitamin D. *Annu Rev Pharmacol Toxicol* 2011;51:311–336.)

Effect on Calcium Homeostasis and Bone Health

The actions of calcitriol are mediated by VDR, a nuclear receptor responsible for the regulation of a multitude of genes and gene products.[2] Historically, the main function of vitamin D was thought to be the maintenance of serum calcium and phosphate homeostasis. Vitamin D stimulates active absorption of calcium and phosphate from the small intestine, whereas in the kidney calcium is reclaimed from the distal renal tubule.[3] Additionally, vitamin D contributes to the mobilization of calcium from bone through osteoclastogenesis resulting from activation of several genes, including the receptor activator of nuclear factor-κ B ligand (RANKL) and the RANKL system.[4]

The vitamin D endocrine system is intimately related to parathyroid hormone (PTH). Together, these hormones tightly regulate serum calcium concentration. In patients with vitamin D deficiency, gastrointestinal absorption of calcium (and phosphate) is reduced, leading to a transient decrease in serum calcium. This decrease results in increased PTH secretion, which stimulates CYP27B1 in the kidney to increase synthesis of $1,25(OH)_2D$ from circulating 25(OH)D, thereby restoring normal calcium levels through increased gastrointestinal absorption, decreased renal excretion, and increased bone resorption of calcium. Chronic vitamin D deficiency leads to secondary hyperparathyroidism. This combination of vitamin D deficiency and elevated PTH level can cause excessive mobilization of calcium from bone to maintain circulating calcium levels at the expense of bone mineral density.[3]

Although vitamin D levels can affect bone mineral density, the role of vitamin D in fracture healing and fracture nonunion is less well understood. A review of >2,000 articles found that vitamin D has been reported to either reduce, increase, or have no effect on the same cytokines in both the inflammatory and soft callus phases of fracture healing.[5] The literature also offers conflicting evidence regarding the effect of vitamin D on osteoblastic differentiation during the hard callus phase.[5] Furthermore, one investigation reported lower serum 25(OH)D levels in patients with fracture nonunion,[6] whereas other studies reported no difference between patients with diaphyseal fracture nonunion and those with normal fracture healing.[7,8]

Molecular Effects on Skeletal Muscle Cells

In addition to the regulation of calcium homeostasis and other extraskeletal pathways by vitamin D, evidence suggests that vitamin D has direct and indirect effects on skeletal muscle through the VDR, which has been shown to be present in muscle cells.[1,9,10] The concept of vitamin D having a direct effect on muscle is supported by observations that mice without functional VDRs have smaller and more variable muscle fiber size as well as lower body weight, size, and coordination levels compared with wild-type mice, even when calcium levels are maintained by special diets with extra calcium.[11]

From a mechanistic standpoint, VDR exerts its downstream effects through two pathways. The first is the genomic (slow or nuclear) pathway, through which the transcription and translation of target genes are modified. One example is the downstream effect of VDR activation on cyclin-dependent kinases, a family of serine/threonine kinases that actively participate in the regulation of the cell cycle.[12,13] A study involving administration of vitamin D to skeletal muscle cells demonstrated a peak of activity in the S (synthesis) phase and an arrest at the G_0 (resting) phase that were dependent on VDR expression and p38 mitogen-activated protein kinase.[13] This finding suggests that vitamin D promotes muscle cell proliferation and differentiation. The second mechanism through which vitamin D may exert effects on muscle is the nontranscriptional membrane-associated signaling (rapid, nongenomic, or membrane) pathway, in which the apparent receptor for $1,25(OH)_2D$ is located in the membrane. This mechanism has been shown to act through several pathways, including via membrane-associated protein disulfide isomerase family A member 3 (Pdia3), which is associated with rapid increases in the activity of phospholipase A_2, the activity of protein kinase C α, and the release of prostaglandin E_2, allowing for modulation of cell function and activity.[12–14] These actions result in enhanced movement of myosin over the actin filaments through augmentation of calcium release from the sarcoplasmic reticulum.[15] Enhanced movement of myosin over actin within the sarcomere can result in greater contractile force of the muscle unit. This calcium influx may also have a role in muscle cell differentiation.[16]

Prevention of Vitamin D Deficiency

Vitamin D_2 and vitamin D_3 are available to humans through a variety of sources. Vitamin D_2 is not synthesized in animals but can be ingested from plant sources or supplements. It is generated both naturally and synthetically from the ultraviolet irradiation of ergosterol in plants, fungi, and yeast. As mentioned previously, vitamin D_3 is synthesized in the skin of most animals, including humans, by the irradiation of 7-dehydrocholesterol, with two further hydroxylations resulting in calcitriol, the hormonally active form of vitamin D.[17] Therefore, humans have access to vitamin D through ambient ultraviolet exposure, dietary intake of egg yolks and oily fish, fortified foods such as milk and some breakfast cereals, and nutritional supplements.

Because dietary sources of vitamin D are limited, even with food fortification, the main source of vitamin D is sunlight-driven synthesis in the skin. In the absence of adequate sunlight exposure, vitamin D deficiency is common; this scenario has been the stimulus for the fortification of food. Nevertheless, vitamin D deficiency remains common in parts of the world far from the equator and in people who have dark skin, use sunscreen, dress in clothing that fully covers the body, are confined indoors, or avoid sun exposure for other reasons. Thus, vitamin D supplementation using either D_2 or D_3 is a critical means of avoiding deficiency.

Vitamin D_2 Versus Vitamin D_3 Supplementation

Although vitamin D_3 and vitamin D_2 undergo similar hydroxylation to be converted to their active form, evidence suggests that they differ in their ability to affect the serum 25(OH)D level, the established marker of overall vitamin D status. Recently, a randomized trial involving healthy volunteers evaluated the effect of 1,000 IU of vitamin D_2, vitamin D_3, or placebo on serum levels of 25(OH)D during winter months, when sun exposure is reduced.[18] After 25 weeks, participants receiving vitamin D_2 or placebo had a considerably lower concentration of circulating 25(OH)D, compared with those receiving vitamin D_3 supplements. Although supplementation with vitamin D_2 led to elevated vitamin D_2 levels, this group had a substantially reduced total 25(OH)D concentration, compared with the vitamin D_3 group.[18] The molecular mechanisms behind these clinical findings are likely complex and may be attributable in part to the difference in binding affinity of vitamin D_2 and vitamin D_3 to vitamin D binding protein (DBP), the carrier protein of vitamin D in the blood.[19]

Genetic polymorphisms of DBP give rise to three major isoforms, the frequencies of which vary depending on race. Prior investigations using monoclonal antibodies to DBP have found lower levels of DBP in persons of African descent, suggesting that levels of free vitamin D (not bound to DBP or albumin) are increased in this population.[20,21]

This finding is contrary to consistent reports of lower mean circulating 25(OH)D in persons of African descent, resulting in unresolved questions and conflicting reports regarding the importance and clinical relevance of free versus total serum 25(OH)D. In a recent investigation of nearly 6,000 participants in the United States, two different polyclonal antibodies were used to detect all isoforms of DBP; consistently lower free and total 25(OH)D levels were found in African Americans compared with white Americans.[22]

Vitamin D Deficiency and Insufficiency

Much debate has centered around the definitions of vitamin D deficiency and insufficiency. In a 2011 consensus statement, the Institute of Medicine concluded that 25(OH)D levels >20 ng/mL (50 nmol/L) were "identified as meeting the needs of at least 97.5% of the [North American] population across all life-stage groups."[23] This requirement could be met by ingestion of 600 IU of vitamin D for most adults and 800 IU for those aged >70 years. The Endocrine Society's clinical practice guideline for the evaluation, prevention, and treatment of vitamin D deficiency defined "deficiency" as 25(OH)D levels <20 ng/mL (50 nmol/L), "insufficiency" as 25(OH)D levels of 21 to 29 ng/mL (50 to 75 nmol/L), and normal levels as >30 ng/mL (75 nmol/L).[24] The Endocrine Society, however, suggested that 600 or 800 IU was not sufficient intake to ensure normal levels in most people. Therefore, they raised the recommended intake to approximately 1,500 IU cumulatively from all sources. Both of these sets of criteria were based on the estimated requirements for maintaining bone health, whereas vitamin D requirements for extraskeletal benefits were not specifically addressed. Because of these differing recommendations, no consensus agreement exists on whether 20 ng/mL or 30 ng/mL and above constitutes a so-called normal vitamin D level.

These consensus statements called specific attention to the increased rates of vitamin D deficiency in persons with dark skin and those who do not receive adequate amounts of direct sunlight, particularly at more northern latitudes. Athletes who participate in sports that mostly occur in an indoor setting may also be at risk of deficiency. A recent systematic review of vitamin D status in >2,000 athletes with a mean age of 22 years found that 56% had vitamin D inadequacy (defined as <32 ng/mL).[25] The risk increased considerably for athletes who played winter and spring season sports, those who played indoor sports, and those at higher latitudes (>40° north). Interestingly, rates of vitamin D insufficiency were substantially higher in the Middle East, possibly because of increased indoor activity in response to extreme outdoor heat, particularly during the summer months. In contrast, Wentz et al[26] investigated serum 25(OH)D levels in a cohort of distance runners in the southeastern United States. They reported that only 5% were vitamin D deficient and 13% were vitamin D insufficient. The authors of the study concluded that training outdoors in a latitude where vitamin D synthesis occurs year-round reduces the risk of vitamin D deficiency. Alternatively, because the study participants were healthy athletes with adequate sun exposure, this finding may suggest that previously defined levels of vitamin D deficiency and insufficiency do not adequately capture the vitamin D status of all persons.

Effect on Muscle Strength

Although vitamin D has been known to affect muscle histochemistry, data have also become available to demonstrate that increased vitamin D levels and supplementation can have a positive effect in otherwise healthy people. One of the first large studies to investigate this association examined nearly 1,000 patients and correlated serum 25(OH)D levels with physical activity and muscle strength.[27] Although the authors found that many study participants were vitamin D deficient, increased 25(OH)D levels were substantially correlated with a higher physical activity metric (short performance physical battery) and with greater hand grip strength. This result was found in participants above and below both the lower (50 nmol/L) and proposed higher (75 nmol/L) thresholds for serum 25(OH)D insufficiency.

These findings were corroborated in a level I meta-analysis of randomized controlled trials investigating the effect of vitamin D supplementation on muscle strength in a young and active cohort.[28] The study examined 310 participants who received either vitamin D_3 or placebo. The participants had a mean baseline serum 25(OH)D of 12.3 ng/mL and an average age of 24 years. Strength metrics for the upper extremity included handheld dynamometer grip strength, one repetition maximum bench press, and assessment with isokinetic dynamometers. Lower extremity strength testing consisted of single-repetition maximum leg press, free weight squats, gastrocnemius-soleus strength isokinetic dynamometer testing, and isometric quadriceps contraction. The

authors found that vitamin D supplementation demonstrated a statistically significant positive effect on both upper and lower limb strength indices. Consistent with prior literature,[29] Tomlinson et al[28] also suggested that daily vitamin D_3 administration would be more effective than weekly or monthly doses at improving muscle strength.

Effect on Sports Performance

Vitamin D is not currently listed as a banned substance by the World Anti-Doping Agency. This fact has led to interest among investigators in examining the effect of vitamin D on sport-specific performance measures. In a recent study, Maroon et al[30] investigated the correlation of vitamin D levels and the ability to obtain a professional contract in a cohort of 80 American professional football players. Although 77% of the athletes studied were characterized as vitamin D "deficient" or "insufficient," a statistically significant correlation was found between lower vitamin D levels and release from the team (because of either poor performance or injury) before the start of the regular season.

In a randomized placebo-controlled trial, the effect of vitamin D (5,000 IU per day over an 8-week period) on sprint times and vertical jumps was assessed in a cohort of athletes, with nearly 70% having baseline serum 25(OH)D levels of <20 ng/mL.[31] The group receiving vitamin D supplementation recorded substantially increased vertical jump heights from the beginning to the end of the study period, whereas no change was observed in the placebo-controlled group. A different randomized controlled trial of postmenarchal women examined the effect of vitamin D supplementation on lower limb muscle force, power, velocity, jumping height, and the Esslinger Fitness Index.[32,33] The authors of the study found that jumping and movement efficiency was substantially increased in the vitamin D group, compared with the control group, a result potentially stemming from improvements in jumping velocity and height.[33]

Effect on Athletic Injury Risk

Because of the important role of vitamin D in bone health, much of the current literature has focused on the association between vitamin D levels and the risk of stress fractures in the athletically active population.[34–39] Davey et al[36] performed a prospective age-matched cohort study of >1,000 Royal Marine recruits in the United Kingdom to evaluate the association between vitamin D levels and stress fracture risk. They identified 92 stress fractures and found that recruits with a baseline serum vitamin D concentration of <50 nmol/L (20 ng/mL) had a 60% higher incidence of stress fracture than recruits with vitamin D concentrations above this threshold had. As would be expected, serum vitamin D levels were found to peak in the summer months, but no association between occurrence of fracture and the time of year could be found.[36] The results of this study were supported by a recent systematic review of eight investigations comprising >2,600 military recruits, which found an association between lower vitamin D levels and increased incidence of stress fracture.[35]

Similar results have been found in a nonmilitary population. In a retrospective review of 124 patients with imaging-confirmed stress fractures at a single center over a 3-year period, Miller et al[37] obtained vitamin D levels near the time of evaluation and reported deficient or insufficient vitamin D levels in 83% of patients. Another investigation found that vitamin D levels were considerably lower in American professional football players with at least one bone fracture, compared with players without a history of fracture.[30]

In contrast, endurance athletes who participated exclusively in an outdoor environment in the southern United States were evaluated for serum 25(OH)D levels, history of stress fracture, bone mineral density, and PTH levels.[26] The authors of that study found low levels of vitamin D deficiency and insufficiency in these athletes and no difference in any outcome measure between the athletes with insufficiency or deficiency and those with adequate levels of serum 25(OH)D.

Adverse Effects

Because vitamin D is a key regulator of calcium homeostasis and many kidney stones are calcium based, some authors have hypothesized an association between vitamin D levels and an increased risk of nephrolithiasis.[40] The evidence regarding whether vitamin D levels and/or supplementation can lead to an increased risk of kidney stones is mixed. In a Women's Health Initiative study, >36,000 postmenopausal women were randomized to receive either 500 mg calcium carbonate plus 200 IU vitamin D_3 twice daily or a placebo, with the main outcome measure being the incidence of urinary tract stones during the 7-year follow-up period.[41] The authors reported that the incidence of self-reported clinically diagnosed urinary tract stones was higher in the experimental group than in the control group (hazard ratio 1.17). More recent studies, however, have not found a positive association between vitamin D and risk of nephrolithiasis. In one investigation, >2,000 patients were followed to determine the incidence of renal stones over a median of 19 months after measurement of serum 25(OH)D levels.[42] The authors of the study concluded that serum 25(OH)D levels of 20 to 100 ng/mL had no association with the formation of kidney stones. Gallagher et al[43] performed a randomized controlled investigation examining the incidence of hypercalciuria and hypercalcemia in 163 vitamin D–deficient women receiving 400 to 4,800 IU/d of vitamin D as well as calcium citrate to achieve a calcium intake of 1,200 mg/d. The authors found no relationship between hypercalciuria and hypercalcemia and vitamin D dose and reported that hypercalciuria was equally common in the treatment and placebo groups. One factor that may influence these findings is the use of calcium carbonate in the Women's Health Initiative study[41] versus the use of calcium citrate in the investigation by Gallagher et al.[43] Because citrate is an inhibitor of stone formation, some physicians advise patients who take both vitamin D and calcium supplementation to use calcium citrate rather than calcium carbonate and to maintain adequate fluid intake. However, many factors other than serum 25(OH)D levels contribute to stone formation, including body mass index, sex, genetics, and diet.

Toxicity

Vitamin D toxicity can result from the ingestion of excessive quantities of vitamin D supplements. No cases of vitamin D toxicity from sunlight or regular dietary intake have been reported. The symptoms of vitamin D toxicity center around the resultant hypercalcemia, leading to an array of symptoms, including anorexia, frequent urination, excessive thirst, nausea, vomiting, and in severe cases, altered mental status and kidney dysfunction. Many cases of vitamin D intoxication are the result of improperly manufactured supplements.[44,45] In one report, a >1,000-fold error was made in the amount of vitamin D in a supplement.[44] Two patients were affected, with both ingesting nearly 1,000,000 IU per day for >1 month, resulting in 25(OH)D levels >1,000 ng/mL. Both patients received supportive treatment with fluids and cessation of vitamin D intake. Diphosphonates were also used to decrease serum calcium levels.

Summary

Vitamin D is a secosteroid hormone that has many important functions, including the regulation of calcium homeostasis and bone metabolism. In addition, VDR has been found in muscle cells, where activation of the receptor has multiple direct effects, including enhanced movement of myosin over the actin filaments through augmentation of calcium release from the sarcoplasmic reticulum. These molecular and cellular changes, as well as other actions in muscle, may be responsible for the findings of decreased fall risk in the elderly, improved muscle strength, lower injury rates, and enhanced athletic performance associated with sufficient 25(OH)D levels. These molecular and cellular changes may even benefit people with adequate vitamin D levels, but particularly improve function and decrease fracture risk in those who are vitamin D deficient.

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