Vitamin D, Muscle Function, and Exercise Performance

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Vitamin D is currently a topic of great interest among researchers. Increasing evidence suggests that exposure to a few minutes of sun daily may strengthen the immune system, maintain cardiovascular health, protect against certain cancers, and possibly even enhance athletic performance. Researchers propose that these are among the nonskeletal benefits of vitamin D.[1–6] Recent data also indicate that vitamin D deficiency is pandemic; the healthy and the young are not excluded.[1]

Muscle tissue was among the first nontraditional vitamin D target organs to be identified.[6–8] Much attention has since been paid to the effects of vitamin D on muscle strength, exercise capacity, and physical performance. Numerous studies have reported a correlation between vitamin D and muscle function.[3,6–10] These findings raise many important clinical questions, especially in the area of sports medicine.

If vitamin D does improve muscle function, what implications does this have on the performance of athletes who have vitamin D deficiency? Is routine screening necessary? What is the role of vitamin D supplementation to enhance performance in these athletes? Although the issue of vitamin D deficit may have been recognized, controversy exists regarding what constitutes normal serum levels, the amount of supplementation required to restore normal levels, and the relative effect of such supplementation on our overall health. This review summarizes the current

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understanding of the functions of vitamin D, describes its role in muscle function, and explores the possible implications of its deficiency and supplementation on exercise performance in individuals who are vitamin D deficient and nondeficient.

SEARCH STRATEGY

The authors performed a literature search using PubMed/Medline, Ovid, EMBASE, and ScienceDirect databases indexed under the Medical Subject Heading (MeSH) terms; ''Vitamin D OR Vitamin D supplementation OR Vitamin D deficiency'' combined with the terms; ''athletic performance'' OR ''performance enhancement'' OR ''strength'' OR ''exercise'' OR ''muscle strength'' OR ''muscle function'' OR ''physical performance'' OR ''in normal individuals'' OR ''chronic fatigue'' OR ''myalgia.'' The literature search was limited to articles dating back to January 2000 and written in the English language. All types of articles were reviewed, based on their direct relevance to the aims of this review. In addition, we searched the reference lists of all identified articles, and latest editions of standard texts. Additional sources written before the year 2000 were included for completeness as part of background information on the topic.

THE BASICS ABOUT VITAMIN D

Sources

Vitamin D is a steroid hormone that regulates various tissue processes by way of specific cell receptors.[10,11] 25-Hydroxy vitamin D (25-OHD) is the main storage form of vitamin D, whereas 1,25-dihydroxy vitamin D (1,25-DiOHD or 1,25$(OH)_2$D) is the main biologically active metabolite responsible for calcium homeostasis. The main forms of vitamin D are listed in **Table 1**. The main source of vitamin D in the human body is cutaneous synthesis via the effects of ultraviolet radiation on the vitamin D precursor, 7-dehydrocholesterol. This mechanism is well regulated and accounts for most of vitamin D synthesis in the body. Anything that reduces the number of solar UVB photons penetrating the skin or alters the amount of 7-dehydrocholesterol in the skin affects production of vitamin D_3.[3] Examples of factors that interfere with 1 or both of these processes, thus causing vitamin D deficiency, are listed in **Table 2**. On the contrary, protective mechanisms such as pigment in skin and formation of inactive isomers (luminosterol, tachysterol) prevent its overproduction.

The alternative source of vitamin D is from dietary intake (**Table 3**). However, most modern diets contain inadequate vitamin D; even those rich in fortified dairy or cereal products. Vegetarian and vegan diets are lacking in this regard.[12–14] Thus, whenever sufficient cutaneous production is poor, vitamin D deficiency likely ensues.[15]

Vitamin D Requirements and Normal Levels

The present recommendation for adequate daily vitamin D for all age groups is 400 IU.[16] Despite clear recommendations, there is still controversy about the normal serum level of serum vitamin D. From studies looking at the physiology of the vitamin

Table 1
Main forms of vitamin D

Type of Vitamin D	Source
Vitamin D_2 (ergocalciferol)	Plant
Vitamin D_3 (cholecalciferol)	Animal
Dihydrotachysterol	Synthetic

Table 2
Factors that predispose to vitamin D deficiency

Dark skin
Inadequate sun exposure
Sun exposure at dawn and dusk
Insufficient surface area of skin exposed to sun
Cloudy (typically winter) outdoors
Northern latitudes
Consistent use of sunscreens or sun block lotions
Low dietary intake

D cycle (**Fig. 1**), it is surmised that serum levels of less than 30 ng/mL are consistent with relative vitamin D deficit, whereas levels of 30 ng/mL or more may be considered to be sufficient.[17] Using these guidelines, it is estimated that 50% of children and adolescents have vitamin D deficiency. The importance of adequate vitamin D levels for the maintenance of good bone health and prevention of osteoporosis is clearly

Table 3
Major dietary sources of vitamin D

For Every 100 g (3.5 ounces) of:	IU of Vitamin D:
Cod liver oil (~2 teaspoons)	10,000
Lard (pork fat)	2800
Atlantic herring (pickled)	680
Eastern oysters (steamed)	642
Catfish (steamed/poached)	500
Skinless sardines (water packed)	480
Mackerel (canned/drained)	450
Smoked chinook salmon	320
Sturgeon roe	232
Shrimp (canned/drained)	172
Egg yolk (fresh)	148 (one yolk contains about 24)
Butter	56
Lamb liver (braised)	20
Beef tallow	19
Pork liver (braised)	12
Beef liver (fried)	12
Beef tripe (raw)	12
Beef kidney (simmered)	12
Chicken livers (simmered)	12
Small clams (steamed/cooked moist)	8
Blue crab (steamed)	4
Crayfish/crawdads (steamed)	4
Northern lobster (steamed)	4

Source: United States Department of Agriculture Database.

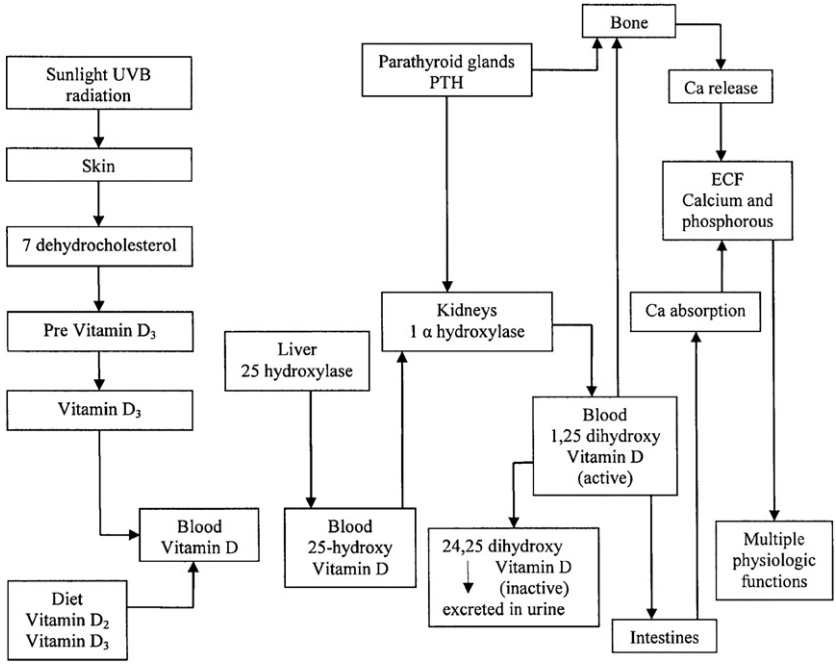

Fig. 1. The vitamin D cycle.

documented.[1,3,4,9,12,18,19] The presence of insufficient vitamin D levels in such a large proportion of the population therefore has significant implications for prevalence of disorders of calcium, phosphorus, bone metabolism, and the resultant pathology.

Mechanism of Vitamin D Action

Vitamin D exerts its effects by binding to the vitamin D receptor (VDR), which is a nuclear hormone receptor.[11,20] VDRs belong to the family of nuclear hormone receptors and are structurally homologous to the other members of the group, including retinoic acid, retinoid X, and thyroid hormone receptors. The VDR acts by forming a heterodimer with retinoid-X receptor, binding to the DNA elements, and recruiting coactivators in a ligand-dependent fashion.[11,21] Vitamin D acts mainly to amplify transcription by way of upregulatory response elements, although some of its effects may also include transcription repression. In addition, the hormone promotes DNA protein interactions of various other transcription factors.[14]

VDRs are found in many tissues and organs, including the small intestine, colon, osteoblasts, activated T and B lymphocytes, pancreatic β islet cells, brain, heart, skin, gonads, prostate, breast, mononuclear cells, as well as skeletal and smooth muscle.[3]

Functions of Vitamin D

Vitamin D has been long-recognized for its calciotropic properties, acting at the level of the kidney, intestine, and bone.[8,11] Vitamin D is a pleiotropic hormone, influencing other body processes in addition to calcium metabolism.[7,9,11] In the last few years, new data have revealed a correlation between vitamin D levels and several significant diseases, including hypertension, diabetes, depression, and cancer.[1,3–5,9,18,22] Studies suggesting a likely protective role of vitamin D in these conditions have placed

it at the frontline of current scientific endeavors, earning it a potential claim to being the new miracle drug.[23]

The concept of vitamin D pleiotropism originated in 1985 with the identification of VDRs outside bone from cultured rat myoblast cells, proving that, in addition to bone, muscle is also a direct target organ for 1,25(OH)2D.[6] The VDR has subsequently been described in tissues such as smooth muscle, heart muscle, liver, lung, colon, gonads, and skin, and was also recently isolated from human skeletal muscle.[3,6,24]

The expanded role of vitamin D was further supported by the discovery of an independent photoendocrine system in epidermal keratinocytes.[22] In addition to synthesizing the prehormone vitamin D destined for kidney activation, epidermal keratinocytes were also found to produce their own, local vitamin D 24-hydroxylase enzyme capable of activating it, as well as epidermal VDRs.[22,25] These findings suggest local paracrine and autocrine effects of vitamin D in addition to its role as an endocrine hormone.[22,25] This intracellular autocrine function has also been identified in various organs including bone, brain, muscle, pituitary gland, and liver. The main functions of vitamin D are summarized in **Table 4**.[11,26–29]

Vitamin D is believed to affect the body's immune system, endocrine system, cardiocirculatory system, neuromuscular performance, and neuropsychological functioning.[1,3,4,9] It is also believed to act as a potent antioxidant protecting against free radical damage, as well as being an inducer of cellular differentiation, protecting against carcinogenesis.[1,3,4,9]

ROLE OF VITAMIN D IN MUSCLE

Vitamin D–deficiency Myopathy

The first associations between vitamin D and muscle function were made from observations of muscle weakness in children with rickets as well as adults with osteomalacia.[8] Vitamin D deficiency has been known to cause muscle weakness, hypotonia, and prolonged time to peak muscle contraction, as well as prolonged time to muscle relaxation.[24,30,31] Varying patterns of muscle weakness, proximal myopathy, generalized musculoskeletal pain, and hypotonia occur in children who have vitamin D deficiency. Muscle weakness and hypotonia, in turn, cause a waddling gait and difficulty in walking, sitting, standing, and climbing stairs.[32]

Ahmed and colleagues[33] studied patients who were treated with statins, vitamin D deficient, and had myalgias, and found that vitamin D supplementation, while continuing statin therapy, reversed the myalgia in 92% of these patients. Sixty-four

Table 4
Main functions of vitamin D

Site	Function
Intestine	Production of calbindin (the calcium-binding protein in the intestine) Promotes calcium and phosphorus absorption in the intestine Regulates gene transcription and cell proliferation in the parathyroid gland
Bone	Role in synthesis of type 1 collagen: evidence is equivocal Stimulates synthesis of osteocalcin Promotes differentiation of osteoclasts
Muscles	Increases amino acid uptake in muscles Alters phospholipid metabolism in muscles Vitamin D deficiency causes myopathy Nongenomic effects on muscles Increases troponin C in muscles

percent of the 128 patients with myalgia had low vitamin D, versus 43% of the patients who were asymptomatic. Of the 82 patients who were vitamin D deficient and myalgic, while continuing statins, 38 received vitamin D (50,000 IU/wk for 12 weeks), with a resultant increase in serum vitamin D and resolution of myalgia in 35 (92%) of them. The study concluded that hypovitaminosis D was associated with myalgia in patients treated with statins, and that this myalgia can be reversed by vitamin D supplementation. These results indicate that vitamin D probably has an advantageous effect on muscle function.

Vitamin D deficiency is also associated with musculoskeletal pain.[34] One study found that 89% of subjects with chronic musculoskeletal pain were deficient in vitamin D.[34] Another study revealed that 93% of patients presenting to a community clinic with nonspecific musculoskeletal pain were found to have vitamin D deficiency.[35] Of these patients, all less than 30 years of age were vitamin D deficient, with 55% being severely deficient.[35] Patients with vitamin D deficiency and musculoskeletal pain may often be misdiagnosed with fibromyalgia, chronic fatigue syndrome, myositis, or other nonspecific collagen vascular diseases.[5] It is estimated that 40% to 60% of patients with fibromyalgia may have vitamin D deficiency.[5]

These observations suggest not only the likely association of vitamin D in muscle functioning but also the importance of vitamin D–deficiency screening and treatment in patients with myalgias. Many of the patients presenting with myalgias are also athletes who may potentially benefit from an intervention as simple as vitamin D replacement.

Molecular Mechanisms of Vitamin D Actions in Muscles

Adequate muscle function and contraction uses genomic and nongenomic actions. Genomic actions are mediated by the nuclear VDRs. Normocalcemia, which is facilitated by vitamin D sufficiency, is essential for normal muscle contraction. Nongenomic actions are performed via VDRs present on cell membranes. The actions of vitamin D on muscle are also believed to be effected by vitamin D–binding protein.[36] Studies have shown that vitamin D facilitates the adenosine triphosphate (ATP)–dependent calcium uptake in sarcoplasmic reticulum, increases the concentrations of phosphorus Y and ATP in the cell, and leads to increased protein synthesis.[37,38] These findings support the manifestation of myopathy and generalized weakness seen in hypovitaminosis D and rickets. In muscle tissue, the genomic pathway is believed to influence muscle calcium transport and phospholipid metabolism.[7]

Nongenomic functions of vitamin D are also being increasingly recognized.[39] These are characterized by rapid effects that do not result from gene transcription. A proposed mechanism of initiation of these rapid effects is the binding of $1,25(OH)_2D$ to another vitamin D–specific receptor; a cell surface receptor.[7] Receptor binding activates a network of second-messenger pathways that transmit the signal to the cytoplasm.[7] This is also believed to direct intracellular calcium regulation in muscle cells.[7] Another speculated effect of vitamin D in muscle cells includes activation of the mitogen-activated protein kinase (MAPK) signaling pathways.[8] In humans, MAPK pathways regulate cell processes such as myogenesis, cell proliferation, differentiation, and apoptosis. In this way, vitamin D is believed to stimulate muscle cell proliferation and growth.[7]

VDR Knockout Mice Model

VDR null mutant mice are characterized by growth retardation, osteomalacia, muscle impairment, and systemic metabolic changes such as secondary hyperparathyroidism and hypocalcemia.[7] VDR null mutant mice have muscle fiber diameters that are 20% smaller and more variable in size than those of wild-type mice at 3 weeks

of age (before weaning).[7] These VDR mutant mice also had abnormally high expression of myogenic differentiation factors compared with wild-type mice, suggesting alterations in muscle cell differentiation pathways resulting in abnormal muscle fiber development and maturation.[7]

VDR Polymorphisms in Muscle

Subtle variations in the DNA sequence of the VDR gene, also known as VDR polymorphisms, are associated with a series of biologic characteristics including muscle strength.[7] *BsmI*, a restriction fragment length polymorphism of the VDR gene, has been associated with muscle performance.[7] In a cross-sectional study of nonobese women, the VDR *BsmI* polymorphism was associated with differences in quadriceps muscle strength, but not in grip strength.[40]

Another recent, population-based cross-sectional study has found an association of the poly A repeat and the *BsmI* polymorphisms with hamstring cross-sectional area, but not with quadriceps or grip strength.[40] Young women with the bb allele, which may be associated with higher VDR activity, were found to have lower fat-free mass and hamstring (but not quadriceps) strength compared with those with the BB allele.[7] Why the allele associated with higher VDR activity would have reduced muscle strength remains unknown.[7]

Vitamin D and Histologic Changes in Muscle

Muscle biopsies obtained in patients with osteomalacia reveal an atrophy of type II muscle fibers with enlarged interfibrillar spaces and infiltration of fat, fibrosis, and glycogen granules.[24,30] In sudden movements, the fast and strong type II fibers are the first to be recruited to avoid falling. Primarily type II fibers are affected by vitamin D deficiency, which probably explains the falling tendency of elderly individuals who are vitamin D deficient.[24,30] Oh and colleagues[41] assessed the role of vitamin D as a factor accounting for fatty degeneration and muscle function in the rotator cuff. Lower serum vitamin D levels were related to higher fatty degeneration in the muscles of the rotator cuff ($P = .001$, $P = .026$, $P = .001$ for supraspinatus, infraspinatus, and subscapularis muscles, respectively).[41] Serum levels of vitamin D were also found to have a significant positive correlation with isokinetic muscle torque.[41]

Vitamin D and Cardiovascular Smooth Muscle Effects

In addition to its effect on skeletal muscles, vitamin D also plays an important role in the functioning of the cardiovascular system smooth muscle. Studies show that 1,25-DiOHD increases active stress generation in arteries, therefore affecting blood pressure.[13,42] In a study of elderly patients, parathyroid hormone (PTH) and 1,25-DiOHD were reported to be independent determinants of blood pressure, and a decrease in blood pressure and heart rate was observed after short term vitamin D and calcium supplementation.[43,44] The specific role of PTH versus 1,25-DiOHD on blood pressure and heart rate has not been clearly elucidated.

Recent data from the long-term National Health and Nutrition Examination Survey (NHANES) findings, which included 3577 adolescents aged 12 to 19 years, show low serum vitamin D to be associated with an increased risk of high blood pressure, high blood sugar, and metabolic syndrome. The average serum level of 25(OH)D was 28.0 ng/mL in whites, 15.5 ng/mL in blacks, and 21.5 ng/mL in Mexican Americans.[22] After adjusting for age, sex, race, body mass index, socioeconomic status, and physical activity, adolescents with 25(OH)D levels in the lowest quartile (<15 ng/mL) were 2.36 times more likely to have high blood pressure, 2.54 times more likely to have high blood sugar, and 3.99 times more likely to have metabolic syndrome than

those with vitamin D levels in the highest quartile (>26 ng/mL).[22] These findings may have important bearings on a young athlete's ability to perform.

VITAMIN D DEFICIENCY (INSUFFICIENCY) IN ATHLETES

Vitamin D deficiency is pandemic, including a high prevalence among the young and the healthy.[1,3,4,15,45–48] Concurrently, vitamin D deficiency is also reported in otherwise healthy athletes.[15,45–48] Because cutaneous synthesis of vitamin D is the main source of adequate vitamin D supply, factors that limit sunlight exposure pose the greatest risk for developing vitamin deficiency, especially in athletes. Therefore, among those at greatest risk are athletes competing in northern latitudes (especially during the winter months), athletes practicing indoors, those who consciously avoid sun exposure or use sunscreen, and those of darker skin pigmentation.[15]

Several studies have documented the high rate of vitamin D deficiency or insufficiency in athletes. A cross-sectional survey of elite gymnasts at the Australian Institute of Sports[49] highlighted the high prevalence of vitamin D deficiency or insufficiency even in elite athletes who otherwise would be assumed to be healthy. Of 18 female, adolescent gymnasts, 13 had low dietary calcium intakes, and 6 had vitamin D levels less than 50 nmol/L (20 ng/mL). This finding underlines the importance of surveillance for vitamin D insufficiency in athletes, especially those who train indoors and have inadequate sun exposure. The study also revealed the high prevalence of stress injuries of bone in these girls in the year before the study. Recommendations for vitamin D supplementation were implemented in this group following the study.[49]

In a group of German gymnasts training predominantly indoors, 77% were found to have vitamin D levels less than 35 mg/mL, with 37% having levels less than 10 mg/mL.[50] Contrary to expectations, a French study also revealed low levels of 25-hydroxyvitamin D in cyclists.[30] A Finnish study reported unequivocal results, with no difference in vitamin D status between a group of cyclists and controls.[51]

Ward and colleagues[45] assessed serum 25(OH)D in girls aged 12 to 14 years, and measured muscle power with jumping monography; a novel outcome sensitive for assessing the muscles most often affected by vitamin D deficiency. Vitamin D levels were significantly associated with muscle power and force in adolescent girls. Vitamin D myopathy is associated with fatigue induction and nonparticipation in physical education or organized sports.[45] A reduced motivation to exercise resulting from vitamin D myopathy may, in turn, alter psychosocial development and health during the adolescence, contributing to low mechanical bone stimulus for bone-mass gain.[22]

Studies in the elderly population provide insights that are important in establishing the role of vitamin D in neuromuscular and skeletal muscle function. A meta-analytical study of the elderly population concluded that vitamin D supplementation appeared to reduce the risk of falls by 20%.[52] Improvement in the musculoskeletal function indicated by a reduction in the number of falls was also documented in a double-blind, randomized, control trial by a 3-month treatment trial with calcium and vitamin D supplementation, in the elderly age group.[53] The role of vitamin D supplementation in improving muscular performance, balance, and reaction time, but not muscular strength, was shown in one study, suggesting a neuromuscular or neuroprotective role of vitamin D.[54] Several studies also show an increase in type 2 muscle fibers and improvement in muscle atrophy with vitamin D treatment.[55–57]

VITAMIN D AND ATHLETIC PERFORMANCE

If vitamin D affects neuromuscular functioning, the logical question is whether it will affect skeletal, muscular, and neuromuscular functioning in athletes, and how much

that would affect their performance levels? The effect of vitamin D levels on athletic performance has rarely been studied. Once vitamin D insufficiency is identified, potential interventions for improvement include dietary supplementation with vitamin D and calcium or increased sun exposure. Exposure to sun is increased by increasing the amount of time spent in the sun, modifying the sun exposure for maximally appropriate ultraviolet radiation exposure, or increasing the surface area of skin exposed to the sun.

UV Radiation and Increased Physical Performance

The athletic benefits of UV radiation were described as early as the 1930s, linking UV exposure to improvements in motor performance, strength, and speed.[15,16,58] In 1938, Russian investigators reported that a course of UV irradiation improved speed in the 100-m dash in 4 students undergoing daily physical training. Mean times improved by 1.7% in the nonirradiated controls versus 7.4% in the irradiated students undergoing identical training.[15] In the late 1960s, American researchers found that even a single dose of ultraviolet irradiation improved the strength, speed, and endurance of college women.[15]

Seasonality of Physical Performance

The seasonality of athletic ability has also been observed.[15] European studies dating back to the 1950s were among the first to analyze changes in fitness associated with the time of the year.[15] Significant seasonal variation in 25(OH)D_3 levels has also been shown.[22] In the northern hemisphere, vitamin D stores peak in the summer, begin to decline by the autumn, and reach their nadir during the winter months.[15,22] Based on our current assumption that vitamin D may increase athletic capacity, the authors expect the results of the early European observational studies to correlate with the pattern of seasonal variability of vitamin D stores. Several such studies revealed a peak in physical performance during the summer months.[5,15,59]

A 1956 study, cited by Cannell and colleagues[15] in their review, attempted to quantify a seasonal variation in the trainability of musculature. The major criticism of the observed seasonality of physical fitness is that people tend to be more active when it is warm outside. For this reason, the study also controlled for the time spent exercising. The researchers found that there was a significant peak in trainability in the summer, followed by a sharp autumn decline, and lowest trainability in the winter.[15] The distinct pattern of increased performance in the summer followed by a sharp decline in the early autumn closely resembles the pattern of seasonal variability of vitamin D, suggesting a possible association between them.

In 1979, a large cross-sectional survey of 1835 healthy Norwegian men (age 40–59 years) also found a small, but significant, overall seasonal variability in physical performance ($P = .04$) with a peak in fitness occurring during the summer ($P<.001$).[59] However, in contrast with the previous study, no difference in physical performance was established between winter and autumn.[59]

Vitamin D Deficiency and Obesity

Factors that perpetuate low vitamin D levels may also significantly hinder athletic performance. Limited mobility and increased storage of vitamin D in fat tissue have been postulated as potential causes, but obesity is a consequence of low vitamin D levels.[22] Moreover, obese individuals only produce half the amount of vitamin D produced by nonobese individuals in response to sun exposure.[22] Vitamin D absorption following oral supplement administration is not impaired in obese individuals. These results suggest a decreased passage of vitamin D formed in the skin into the general circulation due to its subcutaneous accumulation in obese people.[22] As

such, hypovitaminosis D not only impedes muscle function but also contributes to obesity.

SUMMARY

Although there is some evidence that an adequate level of vitamin D is positively correlated with improvement in exercise performance, key questions still remain: How does vitamin D enhance skeletal muscle function? What is the optimal vitamin D level, if any, that will maximize exercise performance? It is generally agreed that persons who have vitamin D deficiency should receive vitamin D supplementation. It is unclear whether vitamin D supplementation by otherwise healthy athletes would be of benefit. The fundamental debate about the optimal daily dietary intake and adequate levels of vitamin D continues. Studies suggest a daily intake ranging between 400 IU and 2000 IU.[60] More research and clinical trials addressing these issues will be important, especially in the pediatric and adolescent population and in athletes.[7]

If vitamin D does improve muscle function, the implications of this on the performance of athletes who may be vitamin D deficient need to be established. Other important questions include whether there is a role for vitamin D supplementation in enhancing performance in such individuals; whether oversupplementation could potentially be used to boost performance in nondeficient athletes; and whether such supplementation would be effective, safe, or fair.

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