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New Insights into Vitamin D Supplementation in Athletes

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Abstract

Nowadays, we are observing a growing tendency for spending longer periods of time indoors and, as such, a lower solar exposure. This tendency is highlighted by several studies which depict worrying levels of vitamin D inadequacy both in athletes and in general population. Moreover, older people or people with darker skin might be more susceptible to vitamin D inadequacy. 25-hydroxyvitamin D [25(OH)D] serum level is a reliable biomarker that is considered the best determinant of vitamin D status.

Vitamin D may be implicated in several pathologies, and lower levels of vitamin D have been even associated with a higher risk of all-cause mortality. Owing to such, its supplementation may potentially play a key role in prevention and treatment of a wide number of pathologies, such as cardiovascular and autoimmune diseases and cancer as well. Beyond all these benefits, supplementation with vitamin D in athletes may exert beneficial effects on muscle function, increase maximal aerobic capacity and reduce stress fractures. Thus, in athletes the supplementation with vitamin D may have ergogenic effects and reduce the risk of injury with a consequent decrease in the withdrawal time from training and competition.

Supplementation with vitamin D is considered safe when the recommended doses are fulfilled. In addition, vitamin D supplementation should be made in the form of vitamin D3, while vitamin D2, due to its shorter shelf-life should not be considered neither for fortification nor supplementation.

Keywords: Athletes; Cholecalciferol; Supplementation; Lesion prevention; Ergogenic effects; Sports medicine

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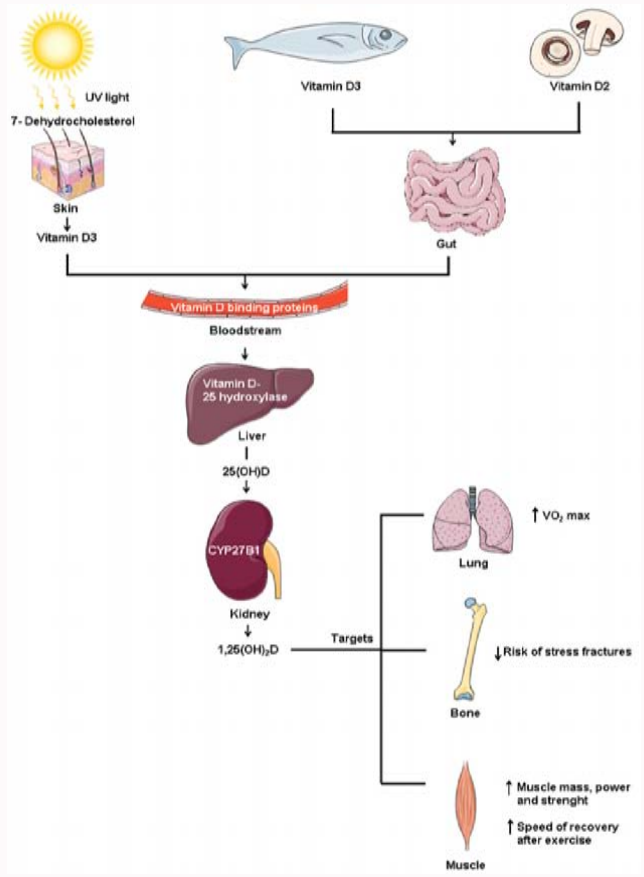
Introduction

Vitamin D, also designated by calciferol, constitutes a group of fat-soluble seco-sterols. In the early 20th century, vitamin D was first considered as a lipophilic vitamin, but it is currently recognized as a pro-hormone [1].

Vitamin D exists in several forms. The two main biologically inactive forms are vitamin D3 or cholecalciferol, and vitamin D2 or ergocalciferol. Cholecalciferol is synthesized after ultraviolet-B exposure from light reaction with 7-dehydrocholesterol. Additionally, it can be obtained through the intake of animal-based foods, particularly fatty fish like herring and mackerel. Ergocalciferol is not produced by humans, being obtained in sunlight-exposed mushrooms [1,2]. The differences between the two aforementioned vitamin D forms are located in their side chain structure [3].

In physiological conditions, vitamin D binding proteins transport both cholecalciferol and ergocalciferol to the liver, where those are hydroxylated (25-hydroxylase) into the inactive form (25-hydroxyvitamin D, also known as 25(OH)D). A further hydroxylation is required, however, to form the active bio-available form. This further step takes place in the kidney, where 25(OH)D is hydroxylated by the cytochrome P450 enzyme 1α-hydroxylase (CYP27B1), forming the biologically active 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) [4,5]. The existence of CYP27B1 in additional tissues such as breast, prostate, colon, bone and even immune cells has been documented. However, the functional impact of this peripheral conversion remains to be fully demonstrated [6]. A major difference with important implications exists in the pharmacokinetics of 25(OH)D and $1,25(OH)_2D$.



Graphical Abstract

The former has a long half-life, approximately 2-3 weeks, serving as a reservoir. This inactive form can be further hydroxylated, depending on the need. The active $1,25(OH)_2D$ form has a considerably short half-life of merely 4-6 hours [7].

The primary and active metabolite of vitamin D ($1,25(OH)_2D$) is then transported throughout bloodstream by vitamin D binding proteins and lipoproteins. In the bloodstream, vitamin D metabolites are bound to vitamin D binding protein, which has a very similar structure to albumin. This binding protein has high affinity to 25(OH) D, $24,25(OH)_2D$ and $1,25(OH)_2D$ [3]. This transporting process enables vitamin D of being able to exert a large range of skeletal and extra-skeletal effects [8].

The $1,25(OH)_2D$ metaboliteis able to reach target tissues responsible for the homeostasis of calcium and phosphorus: intestine, parathyroid glands, bone and the kidney itself. Thereby, $1,25(OH)_2D$ plays the role of a crucial pivot, inducing genomic and non-genomic responses [7].

The nuclear vitamin D receptor (VDR), product of a gene located on chromosome 12, mediates the genomic actions of $1,25(OH)_2D$. Gene transcription is ultimately mediated by the DNA binding domain of the VDR, a process subjected to the interference of co-repressors and co-activators. At the end, repression or activation of target gene expression constitute the final consequences of complex series of events, enhancing calcium absorption [9].

The intestinal cell is a core element of action of $1,25(OH)_2D$. Here, two pathwaysexist to transport calcium absorption in the intestine: transcellular transport and paracellular transport (Figure 1).

Transcellular transport of calcium from the brush border of the apical membrane to the basocellular membrane is saturable and occurs against a concentration gradient. Its entrance in the intestinal cell is made by the transient receptor potential vanilloid type 6 (TRPV6) protein, highly expressed in the intestine; the transient receptor potential vanilloid type 5 (TRPV5), highly expressed in the kidney; and a channel known as CAv1.3. The latter interacts with TRPV6 protein to enhance calcium absorption [10]. Once in the intestinal cell, calcium binds to proteins with high affinity, called calbindins, specifically CB9k. These may act as facilitators in the TRPV6-mediated calcium influx, while also interfering with paracellular tight junctions. Therefore, they are thought to play a pivotal role between transcellular and paracellular pathways. Calbindins might also have anti-apoptotic effects. Calcium exits the gut cell through a plasma membrane protein, PMCA1b and an exchange, NCX1. PMCA1 plays a dominant role, while NCX1 is responsible for only 20% of calcium exit transport [10,11].

Paracellular transport is considered non-saturable, occurs in function of calcium gradient and is present throughout the majority of the intestine. In tight junctions, claudins 2, 12 and 15 are responsible for this type of transport. As it is dependent of calcium gradient, it is only relevant when calcium intake is adequate or high. This paracellular pathway predominates in distal regions of the intestine [10].

$1,25(OH)_2D$ interacts with TVRV6, TVRV5 and CB9k to potentiate calcium transport through the intestine. Paracellular consequences of Vitamin D were also demonstrated in the past, but still remain to be fully addressed. Stimulus such as parathyroid hormone (PTH), thyroid-hormone, growth hormone, prolactin and estrogen may increase transcellular transport. The last two might also enhance paracellular transport in high demanding conditions such as lactation and pregnancy. Pharmacologic doses of long-term glucocorticoids impair transcellular pathway in mice. The aging process does not reduce the number of intestinal VDR. However, the expression of TRPV6 and calbindin-D9k decline over the years [10,12,13].

In the kidney, the same calcium-sparing action is observed, reducing the urine calcium excretion. The bone also contributes to the maintenance of calcemia, since osteoclastic activity and osteoclastogenesis are enhanced by $1,25(OH)_2D$ [9].

PTH works in strict collaboration with $1,25(OH)_2D$ to make sure that calcium and phosphate are always available. When plasma ionized calcium decreases, PTH is synthesized by the parathyroid glands. As expected, vitamin D deficiency and poor calcium intake or absorption stimulate PTH synthesis [14].

Furthermore, Vitamin D shows pleiotropic effects. Almost all cells respond to the presence of $1,25(OH)_2D$, as VDR are almost ubiquitously present. A stunning number of 3% of all human genome is directly and/or indirectly influenced by vitamin D. This widespread function suggests that there is a lot to be discovered on this subject [15].

This review is an outstanding overview about vitamin D physiology and the potential benefits and risks of vitamin D supplementation particularly on athlete's population. We will focus on potential health effects of vitamin D in general population and particularly on athlete's population. Beyond health benefits, we also detail several mechanisms certainly responsible for ergogenic effects

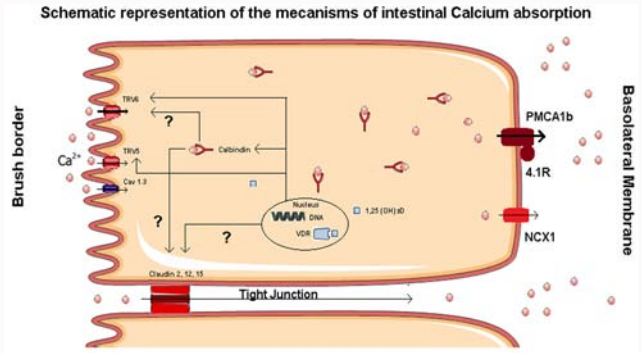


Figure 1: Schematic representation of the mechanisms of intestinal Calcium absorption.

that may ultimately lead to increased sports performance. To finish, we will discuss potential risks of vitamin D supplementation and also the dosages in which these risks may occur.

Vitamin D Sources and Subtypes

Humans obtain most of the vitamin D upon exposure of the skin to the ultraviolet B radiation [16]. However, with current lifestyle, people activities are predominantly performed indoors, posing the problem of an insufficient solar exposure. In addition, vitamin D synthesis can be affected by several factors, like skin pigmentation [17], severe air pollution [18], clothing [3], and topical application of sunscreens [19], depending on its layer thickness [20]. The impact of aging process on Vitamin D depends on the source. An age dependent decrease in 7-dehydrocholesterol was already demonstrated. This lacking substrate may be responsible for a greater than two-fold decrease on the skin capacity to produce vitamin D [21]. Differently, the absorption of dietary vitamin D remains high at all stages of life. A significant part of elderly subjects might fail to produce $1,25(OH)_2D$ due to age-related loss of renal function [22].

In terms of natural availability, vitamin D can be found in a confined range of natural dietary sources. In the case of vitamin D3, these sources include eggs, butter, milk, offal and some fatty fish, especially in the fish liver. Vitamin D2, in turn, can be found on mushrooms [23]. Vitamin D content does not seem to be much influenced after animal food cooking [24,25].

Fortification of everyday foodstuffs with vitamin D provides, naturally, an extra dietary source for vitamin D assimilation (e.g. milk and cereals) [26]. Diet and supplementation-derived vitamin D consist of both vitamin D forms: cholecalciferol and ergocalciferol. Cholecalciferol consists in the source of endogenous vitamin D. It is synthetized after sunlight exposure (290–315 nm), as a result of ultraviolet B radiation interaction with 7-dehydrocholesterol, the precursor compound that is kept within cutaneous cells plasma membranes [27].

Marked differences in the metabolic pathways between cholecalciferol and ergocalciferol are reported and, thereby, they must be taken into consideration. The differences on the side chains between ergocalciferol and cholecalciferol lead to different sites of hydroxylation and production of unique metabolites. These differences affect crucial stages on the activation of vitamin D, such as the conversion to serum 25(OH)D and the affinity to vitamin D binding protein and VDR. The lower affinity of ergocalciferol towards vitamin D binding proteins results in a shorter half-life comparing with cholecalciferol. Moreover, unlike cholecalciferol, ergocalciferol is synthetically produced and evidences a lower stability to varying temperatures and humidity, which can lead to differences between the effective vitamin D content and the labeled content [28]. Additionally, the results of a meta-analysis depicted that cholecalciferol might be more effective in raising serum 25(OH) D concentrations than ergocalciferol [29]. Similar results were obtained recently by a study carried out by Shieh and collaborators, in which cholecalciferol enhanced 25(OH)D levels to a larger extent in comparison toergocalciferol, emphasizing the therapeutic superiority of cholecalciferol [30]. Thereby, the aforementioned body of evidence pinpoints the advantage of vitamin D supplementation by administrating cholecalciferol rather than ergocalciferol, highlighting the fact that the latters hould not be considered as appropriate for food fortification or supplementation.

The effectiveness of cholecalciferol supplementation using daily, weekly or monthly administrations is overlapping. Thus, the frequency of administration can be adjusted according to the convenience and therapeutic adherence [31].

Vitamin D Deficiency and Insufficiency

The serum concentration of 25(OH)D constitutes a robust and a reliable biomarker, considered to be the best determinant of vitamin D status [32]. The Endocrine Society defines vitamin D deficiency as 25(OH)D values below 50nmol/L (20ng/mL), and insufficiency for specific 25(OH)D concentrations comprised between 52.5nmol/L (21ng/mL) and 72.5nmol/L (29ng/mL). Vitamin D sufficiency is defined for 25(OH)D levels ranging between 30ng/mL and 100ng/mL[33].

Vitamin D deficiency in Europe is nowadays considered pandemic. A recent study, which combined the results of over 55000 people in Europe, 13% had Vitamin D deficiency. This result meets the criteria of a pandemic that goes far beyond international borders [34]. A systematic review analyzed data from 195 studies with more than 168000 participants on the status of Vitamin D and showed that over 88% of the samples had mean 25(OH)D values below 75nmol/L, evidencing great variability between them [35].

Moreover, a study conducted by Priemel et al attempted to investigate the relationship between structural histomorphometric parameters of iliac crest bone biopsies and serum 25(OH)D levels. Notwithstanding, according to obtained data, the authors could not define minimum 25(OH)D levels associated with mineralization defects, as these occur in patients with 25(OH)D serum levels below 30ng/mL. No pathologic accumulation of osteoid in patients with serum 25(OH)D levels above 30ng/mL was reported. This study emphasizes, thus, the recommendations of the Endocrine Society, which claim that people should reach the minimum threshold of 25(OH)D serum levels above 30ng/mL[36].

Not only risk groups, like pregnant women, children and older persons, but also general population evidence a high prevalence of vitamin D deficiency. Contrary to the expectations, people of the Middle East, especially women, exhibit a high prevalence of vitamin D deficiency that is probably related with clothing. Moreover, higher levels of vitamin D occur prevalently on northern Europe rather than in Mediterranean countries. This evidence can be related to the high intake of fatty fish and cod liver oil on northern countries, as well as skin pigmentation and sun avoidance characteristic behaviors of Mediterranean countries [37].

Despite having the same capacity to produce vitamin D as white people, black individuals require longer exposure times to UV light due to increased melanin content in their skin. This could easily explain interracial vitamin D metabolism differences[38].

More recently, a meta-analysis combining 23 studies with 2313athletes revealed that athlete population is also at risk for hypovitaminosis D, evidencing a prevalence of vitamin D inadequacy of 56% in this group. It was also demonstrated that vitamin D inadequacy was higher in winter, in higher latitudes and for indoor sports practitioners. Significant differences were also stated for different geographic locations [39].

Athletes and Vitamin D

It is known that vitamin D receptors exist in human skeletal muscle [40], and supplementation with vitamin D results in increased VDR gene expression in human skeletal muscle [41], evidencing the direct effect of vitamin D upon skeletal muscle activity.

A recent meta-analysis suggested an association between low serum 25(OH)D levels and lower extremity stress fractures in military personnel [42]. Moreover, a study performed by Lappe et al found a 21% decrease of fractures through supplementation of female navy recruits with 2000mg of calcium and 800 IU of vitamin D daily [43]. Thus, adequate serum concentrations of vitamin D might be necessary for the prevention of stress fractures amongst active individuals, such as military personnel or athletes [44] .

An inverse relationship between vitamin D levels and body mass index (BMI) was established. Consequently, obesity is associated with vitamin D insufficiency presumably because of the decreased bioavailability arising from deposition in fat compartments [45,46].

Another study showed there was a significant decline of vitamin D levels after a 6-week training exercise with intensity of 60-70% maximal oxygen uptake (VO_2max), which was not verified in the absence of exercise. This fact can be related with the spent of vitamin D at a muscular level that increases with higher levels of muscle activity. The exercise group also experienced the lowering of BMI. It could be expected an increase of vitamin D levels with the lowering of the BMI, due to the inverse relationship between vitamin D levels and BMI. This data reinforces the hypothesis of vitamin D expenditure at muscular level [47].

Ardestani et al. showed that vitamin D is positively associated with maximal oxygen uptake in healthy adults independently of their age, gender, BMI and level of physical activity. The authors have also demonstrated that adequate vitamin D serum levels could potentially pursue a greater benefit on cardiac remodeling and maximal oxygen uptake among individuals with lower levels of physical activity [48]. On the one hand, this study goes in favor of a greater benefit of people with lower physical activity, but, on the other hand, with the level of competition of professional athletes, even small ergogenic effects can make the difference on sport results.

Hypovitaminosis D myopathy is a prominent symptom of vitamin D deficiency, allowing for severely impaired muscle function even before biochemical signs of bone disease development [49]. The vitamin D benefits at the muscular level are favored by studies in the elderly population, demonstrating an improvement in the balance and muscular function, which results, ultimately, in a decrease of falls with the supplementation of vitamin D [50,51]. A 25(OH)D concentration of at least 24ng/mL is required for fall prevention [52]. Hypovitaminosis D constitutes a reversible cause of myopathy, and the awareness of this condition may improve mobility and quality of life [53,54].

Vitamin D may also improve recovery after exercise in a healthy and modestly active population. Supplementation with vitamin D improved the recovery in peak isometric force after exercise protocol and it appeared to be less harmful for the muscle as biomarkers representing muscle damage showed a lower increase [55].

Thereby, vitamin D might have ergogenic effects on several different mechanisms such as: increasing muscle mass, power and strength, increasing VO_2max and the ability to recover faster. This may reduce also the time of withdrawal from the competition, by lowering the risk of stress fractures [56].

Other Potential Vitamin D Benefits

Beyond the beneficial effects of vitamin D amongst bone and muscle functions, vitamin D is implicated in a broader range of pathologies. The vitamin D receptor regulates the expression of numerous genes involved in calcium/phosphate homeostasis, immune response and cellular proliferation and differentiation.

Although the pathophysiology of multiple sclerosis is not fully understood, it is known that this disease arises from a combination of genetic predisposition and environmental exposures such as Epstein Barr virus infection, smoking, season of birth and vitamin D deficiency [57]. The importance of vitamin D deficiency in multiple sclerosis is supported by a meta-analysis that supports a significant association between multiple sclerosis and latitude [58]. Moreover, higher levels of serum 25(OH)D levels on a population of patients with multiple sclerosis demonstrated a lower degree of activity, magnetic resonance imaging (MRI) lesion load, brain atrophy and clinical progression over 5 years of follow-up [59].

Pancreatic tissue also holds vitamin D receptors. Vitamin D may contribute for maintaining insulin secretion and many studies support the role of vitamin D on type 1 and type 2 diabetes. This evidence is substantiated by the higher incidence of hypovitaminosis D in diabetic patients [60].

Another pathology in which vitamin D might be implicated is rheumatoid arthritis. Vitamin D deficiency is highly prevalent in patients with rheumatoid arthritis and it may be involved on the severity and activity of the disease [61].

Beyond the potential beneficial effects in auto-immune diseases, vitamin D can also have beneficial effects in infectious diseases. Supplementation with vitamin D can lead to a decrease of events of respiratory tract infections. This decrease can be caused by the increased production of natural antibodies, inducing monocyte differentiation, inhibiting lymphocyte proliferation and enhancing phagocytic activity of macrophages [62]. The same mechanisms might be involved in other infectious diseases. A recent study also showed a decrease in urinary tract infection (UTI) with a supplementation of 20000 UI per week. The effect on UTI was more evident in males [63].

Vitamin D supplementation might have an effect in decreasing cancer and all-cause mortality, but further studies will need to be undertaken to support these assumptions [64]. In this regard, in the general population, levels of serum 25(OH) D lower than 17.8ng/mL were associated with a higher risk of all-cause mortality [65].

Hence, adequate levels of vitamin D might perform several

beneficial effects on athletes, being responsible for increasing health and reducing the risk of diseases, and, consequently, the risk of withdrawal from training and competition.

Vitamin D Toxicity and Side Effects

One of the roles of vitamin D consists in the enhancement of serum calcium by stimulating intestinal calcium absorption, calcium mobilization from the bone and calcium reabsorption in the renal distal tubule. For that reason, one of the potential side effects of vitamin D supplementation is hypercalcemia.

A well-established causal relationship exists between hypervitaminosis D and hypercalcemia. However, the reported cases of toxicity come from errors in manufacturing, formulation and prescription of vitamin D with intake levels far above of the recommended and the supplementation doses used in previous studies [66]. One example of a report of vitamin D intoxication was a 2 year-old boy that ingested 600000UI/day for 4 days. Although no renal, cardiac or neurologic complications were reported, the hypercalcemia persisted for 14 days and it was complicated by persistent hypertension [67].

Many studies indicate mean serum calcium levels do not increase in healthy adults with high doses of vitamin D up to 100000 UI per day or with vitamin D levels up to 257ng/mL. These levels are far above the recommended levels for accomplishment of vitamin D benefits [68]. However, it seems to exist a risk of hypercalcemia with calcium supplementation without vitamin D [69].

A study in adults with multiple sclerosis, patients were given 1200 mg of elemental calcium and progressive increasing doses of vitamin D3 from 28000 UI to 280000 UI/weekly for 28 weeks. Patients 25(OH) D levels attained two-fold the physiologic range without evoking hypercalcemia or hypercalciuria [70].

After skin conversion of 15% of 7-dehydrocholesterol into vitamin D, a plateau is attained and vitamin D inactive forms, such as lumisterol and tachysterol, are produced [71]. Another reason for the practically non-existent toxicity of vitamin D is that $1,25(OH)_2D$ stimulates its own destruction. This occurs through metabolization of 25(OH)D and $1,25(OH)_2D$ into water-soluble inactive forms by 25-hydroxyvitamin D-24-OHase (CYP24R) [33].

When the decision to prescribe vitamin D supplementation is taken, it is primordial to assess the baseline level of 25(OH)D before supplementing. It is just as important to assess 25(OH)D levels 3-6 months after the first administration, in order to adjust the dose as appropriate. Provided that all safety measures are taken, vitamin D supplementation is safe and may be even safer in a near future, as more studies on this matter arise [71].

The objectives of the present study were to evaluate the basal serum levels of 25(OH)D and calcium in high competition athletes on the latitude 40˚N, concluding the prevalence of insufficiency and inadequacy; to evaluate the relationship between serum 25(OH) D levels and skin type based on the Fitzpatrick scale; to evaluate the effects in 25(OH)D serum levels following supplementation of 1667UI/day of cholecalciferol during a period of 8 weeks; evaluate potential toxicity effects arising from supplementation of athletes with cholecalciferol.

Conclusions

Several studies have evidenced a lack of vitamin D, not only in the general world population, but within athletes. Vitamin D is notably important for many biological processes and may play an important role in several pathologies, including diabetes, cancer, infections, autoimmune and cardiovascular diseases.

Beyond this, it is known that the muscle expresses vitamin D receptors and it seems to occur a muscle consumption of vitamin D, leading to the need of a greater input. As a matter of fact, it is particularly difficult to compensate the greater demand of vitamin D with recourse solely to the diet, due to the limited range of food containing it. Adequate levels of serum vitamin D can contribute to an increasing muscle mass, power and strength, increasing VO_2max and the ability to recover faster after exercise, potentiating the achievement of maximal athletic performance. Besides, vitamin D can help reducing the time of withdrawal from the training and competition, by the avoidance of lesions, such as stress fractures or infectious diseases.

Supplementation with vitamin D is safe. Hypercalcemia may occur solely at much higher doses than the therapeutic recommended doses and in the presence of supplementation of calcium associated with vitamin D. Cholecalciferol has higher affinity to VDRs and a longer shelf-life, which contrasts to ergocalciferol which is characterized by a lower shelf-life. Such body of evidence supports, thus, that supplementation with vitamin D should be performed in the form of cholecalciferol, and ergocalciferol should not be considered for fortification or supplementation.

Athletes with a darker skin may need greater doses of vitamin D supplementation than athletes with lighter skin. Athletes with more advanced ages may also show a higher necessity of greater doses of vitamin D supplementation, as their endogenous vitamin D production will be lower than young athletes. Athletes and general population should also make an effort to privilege outside activities instead of indoor activities if possible in the geographical area.

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