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Vitamin D Supplementation Improves Physical Performance in Athletes and Healthy Aging in Physically Active Adults

Johannes Hirsch [1], Gabriel Cismaru [1,2,*], Radu Rosu [1,2], Gabriel Gusetu [1,2], Horatiu Comsa [1,2], Bogdan Caloian [1,2], Diana Irimie [1,2], Florina Fringu [1,2], Raluca Tomoaia [1,2,] Dana Pop [1,2]

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1 "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca;
2 Fourth Department of Internal Medicine, Cardioloy-Rehabilitation, Cluj-Napoca, Romania;

* Correspondence: Gabriel Cismaru, gabi_cismaru@yahoo.com

Abstract: Vitamin D deficiency is a significant global public health issue, even in regions with all year sun exposure. Currently, the scientific community has not yet reached a unanimous agreement regarding the optimum levels of vitamin D and the precise threshold values. Additional efforts are required to standardize the evaluation of vitamin D insufficiency and deficiency and to provide uniform treatment guidelines. Epidemiological studies have identified a broad spectrum of estimated prevalences in athletes. Their performance when participating in sports. depend on their muscles, heart and lung function. It seems that athletes have significantly lower levels of vitamin D compared to the general population. However, there is a lack of comprehensive studies and systematic reviews on this subject, making it challenging to reach conclusions due to variations in laboratory techniques and cut-off values. While there is an abundant of research on the supplementation of vitamin D and its benefits, it is challenging to provide general recommendations for athletes due to the limitations of extrapolation. However, there is a rather high occurrence of Vitamin D deficiency among individuals who engage in regular physical activity. Supplementing with Vitamin D helps prevents osteoporosis, bone fractures, enhances muscle strength, avoids lung infections, heart failure, and arrhythmias. It is generally safe when used in appropriate quantities, given its wide therapeutic range. Athletes can decrease the occurrence of training dropouts caused by infection, arrhythmias, muscular weakness and potentially prevent the inability to participate in competitions through correct nutrition and vitamin D supplementation.

Keywords: vitamin D; sports; muscle; heart, athletes rehabilitation, vitamin D, ventricular premature contractions, physical activity

1. Introduction

Vitamin D deficiency is a global public health challenge also affecting countries with all-year sun exposure. Currently there is still no consensus about optimal levels of vitamin D and definitive cut-off values among the scientific community. Further efforts are needed to standardize assessment of vitamin D deficiency and to establish common treatment recommendations. Epidemiological studies found a wide range of estimated prevalences. Numbers are considerably high across all European countries. Correction by oral supplementation can be reached easily and very inexpensively. Side effects are rare but can be severe in cases of chronic overdosing. Attention should be paid to growing sales numbers of OTC vitamin D preparations. Prior to intake medical advice should always be sought. Physicians also are recommended to consider vitamin D deficiency in persons at risk (e.g. homebound, inactive persons or inhabitants of nursing homes) [1-3].

Vitamin D is a crucial hormone for maintaining bone health in full-grown individuals but especially during periods of rapid growth in infants and adolescents. In the absence of sufficient vitamin D calcium absorption decreases and bone mineralization is disturbed. This can lead to severe health conditions named `rickets` in children and `osteomalacia` in adults potentially causing irreversible deformations of bony structures. Another disease that is complicated by vitamin D deficiency or insufficiency is osteoporosis, a disease very prevalent among the (female) population after the 6th decade of life. It predisposes to fractures after very mild traumas that is followed by complicated bone healing. Pharmaceutical therapy of osteoporosis usually includes oral vitamin D supplementation besides other medication [4-5].

The rationale of the influence of vitamin D on athletic performance as a singular mechanism is insufficient. On one hand, vitamin D stimulates myogenesis and synthesis of muscle protein leading to an increase in the proportion of fast action muscle cells. This particular fiber type is responsible for generating power, facilitating rapid muscular contraction, and promoting muscle growth.

Apart from the skeletal effects vitamin D also acts on non-skeletal tissues as muscle, lung or heart. Athletes and physically active persons need to rely on the ability of those structures when performing sports activity. Non-skeletal health is influenced by many factors with vitamin D being only one of many. As described later, vitamin D seems to be involved in the regulation of skeletal and cardiac muscle growth. Supplementation therefore could be beneficial in athletes and physically active persons [1-3].

2. Methodology for searching and criteria for article selection

To perform our evaluation, we set particular criteria for selecting research publications. Our primary focus was on randomized controlled trials (RCTs), followed by nonrandomized controlled trials (such as observational studies, retrospective analyses, and case reports), systematic reviews, and meta-analyses that investigated the effects of vitamin D insufficiency and supplementation in athletes. We only included articles written in English that had the full text available.

To gather relevant literature, we conducted thorough searches on databases such as Web of Science, Scopus, PubMed, Medline, Embase, and Cochrane Library. The evaluation of the included studies was of extreme importance. The assessment of systematic reviews and meta-analyses was carried out following the PRISMA guidelines and employing a meticulous methodology.

Two independent reviewers (JH, GC) conducted evaluations, resolving discrepancies between research through dialogue and disagreement or requesting guidance from a third expert reviewer. This meticulous process ensured the inclusion of high-quality evidence that is relevant to vitamin D supplementation in athletes.

3. Vitamin D mechanism and function

3.1 Synthesis and Metabolism

The term vitamin D encompasses a family of steroid hormones which are involved in calcium homeostasis. Under normal circumstances approximately 4/5 of vitamin D is produced endogenously while the remaining 1/5 is taken up in the form of nutrition. Endogenous formation of the final product 1,25-dihydroxycholecalciferol (or 1,25-(OH)2D) takes place in several steps at different sites within the human body. Synthesis is initiated in the skin where 7-dehydrocholesterol is transformed into cholecalciferol (vitamin D3) by UVB sun light. Dietary vitamin D is represented by cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) but also 25-hydroxycholecalciferol (25-OHD) and 1,25-(OH)2D in trace amounts. Only a few foods are relevant sources of vitamin D.

Examples include fish, egg yolk or fortified milk products (mainly vitamin D3) and some wild grown mushrooms or mushrooms artificially exposed to UV rays (primarily vitamin D2). There is little literature on potential absorptive mechanisms and factors involved. It is assumed that vitamin D is taken up in a similar manner as triglycerides by micelles and then carried to the liver inside chylomicrons. Oral bioavailabilities of vitamin D3 and vitamin D2 are estimated to be similar but in terms of effects cholecalciferol seems to be more powerful. It is the preferred substance for supplementation. Both exogenous and endogenous vitamin D is then converted to 25-hydroxycholecalciferol (25-OHD2 and 25-OHD3 respectively) in the liver. The kidneys play the most important role in activation by further hydroxylation to 1,25-(OH)2D in the proximal convoluted tubule under the regulation of parathyroid hormone (PTH). Hydroxylation also takes place extra-renally, e.g. in myocytes, respiratory epithelium and immune cells which will be discussed later. This last step is crucial since it significantly potentiates effectivity. 1,25-(OH)2D is considered the most potent form of vitamin D. Being one of the 4 liposoluble and hydrophobic vitamins it needs binding proteins for transportation in the bloodstream. Linked to vitamin D-binding protein (DBP), albumin and lipoproteins less than 1% of vitamin D is freely present in plasma. Vitamin D is stored in the liver and adipose tissue in amounts sufficient for up to 4 months without oral uptake or sun light exposure whereas 25-OHD only persists for some weeks. 1,25-(OH)2D has the shortest half-life of around 4 hours. Breakdown of vitamin D takes place in the kidney primarily by hydroxylation at the 24th carbon atom and followed by excretion into the bile. [4–13].

3.2 Mechanism of action

1,25-(OH)2D is the active form of vitamin D and has different effects all over the body. Its main physiological role is to increase the absorption of calcium and phosphate. Affinity of 1,25-(OH)2D for vitamin D receptor (VDR) is estimated to be around 1000-fold higher than that of 25-OHD.

Being a liposoluble molecule vitamin D can easily pass cellular membranes. Analogously to steroid hormones its receptors are mainly located in the nuclei where effects are elicited by upregulation of certain genes. VDR is present in almost every cell and tissue. After vitamin D binds to VDR it complexes with the retinoid-X receptor (RXR) to interact with vitamin D-responsive elements (VDREs) within the targeted genetic region promoting transcription. In the small intestine 1,25-(OH)2D upregulates the formation of a protein called calbindin located in the brush border of the intestinal lining. Its function is to transport calcium from the intestinal lumen into the cell. There is a linear relationship between calbindin concentration and calcium uptake. Besides calcium absorption vitamin D also seems to cause increased phosphate influx across the epithelium although the exact mechanism is still unknown. Besides this genomic mechanism vitamin D and VDR also have direct effects on cellular membranes and calcium influx inside the myocardial cell. At the level of the kidney vitamin D diminishes loss of calcium and phosphate into the urine by enhancing reabsorption. Healthy bone metabolism largely depends on vitamin D and parathyroid hormone (PTH). PTH is released by the parathyroid gland where calcium-sensing receptors are very sensitive to minimal decreases in calcium plasma concentration. PTH secretion is rapid and is strongly regulated by negative feedback. Vitamin D acts on VDRs in osteoblasts and together with PTH it increases transcription of receptor activator of nuclear factor κB ligand (RANKL) to stimulate differentiation of progenitor osteoclasts into mature osteoclasts. Apart from bone resorption, Vitamin D is essential for PTH to regulate bone remodeling because it is needed for intestinal calcium and phosphate absorption and regulation of transcellular transport. On the other hand adequate PTH levels are needed for vitamin D to be activated by 1-α-hydroxylase in the kidney. The importance of vitamin D on the immune system is

demonstrated by the fact that activation of 25-OHD to 1,25-(OH)2D was demonstrated to occur locally in macrophages, lymphocytes, dendritic cells and the respiratory epithelium itself. 1,25-(OH)2D released in response to pathogens is involved in protecting the body from infection. Precise mechanisms are still poorly understood and mostly approximated theoretically or by in vitro studies. Regulation of immune responses is rather complex but overall vitamin D appears to increase the defensive capacity by promoting pathogen recognition and elimination. Because it also may prevent excessive inflammatory changes vitamin D can be considered an immunomodulator. At the level of the muscular system vitamin D effects include the upregulation of a multitude of genes. A prominent example is the enzyme 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) pathway that usually activates the transformation of cortisol to the active substance cortisone and vice versa. Increased levels of 25-OHD suppress the enzymatic activity and thus decrease local intracellular cortisone levels. This may be beneficial for muscle growth and function. [12–19].

4. Prevalence of vitamin D deficiency

4.1. Vitamin D deficiency in European countries

Among the scientific community there is no consensus about defining clear cut-offs for vitamin D deficiency. Basically, there are two distinct concepts: the National Academy of Medicine (Institute of Medicine, IOM) and the Endocrine Society (ES) which both have postulated different cut-off values. There are several assays with different detection techniques available. Details will be explained later but all the commercial assays currently in use focus on 25-OHD levels to diagnose vitamin D deficiency. Vitamin D levels in general underly seasonal changes and largely depend on the degree of sun exposure in countries off the equator. The so called `vitamin D winter` begins when UVB rays fall below levels where cutaneous conversion is not possible anymore. Most of continental Europe lies within latitudes between 40°N and 55°N with vitamin D winter duration ranging from 2 to maximum 5 months. Cashman et al. conducted a trans-European retrospective study to approximate the prevalence of vitamin D deficiency. Levels of 25-OHD were analysed in stored blood samples of more than 55,000 individuals in accordance with the NIH Vitamin D Standardization Program (VDSP) that exclusively uses LC-MS (see later). Participants from all age groups were included (ranging from 2 years up to around 80 years of age) in representative numbers. Overall, 13.0% met the IOM criteria for vitamin D deficiency (<30 nmol/l) and 40.4% fulfilled the ES criteria (<50 nmol/l). As expected, prevalence range among childhood population was calculated to be higher in countries >47°N of latitude than in countries located <41°N (5-20% vs. 4.7-6.9%). Surprisingly, this trend could not be demonstrated in adults and older adults. Prevalence in these age groups was lower in Norway, Iceland and Finland as prevalences in UK, Ireland, Netherlands and Germany. This can be explained by higher vitamin D uptake in the form of fish oil or supplements in up to 60% of the studied Icelandic population (Steingrimsdottir et al.) and is supported by a study assessing a vitamin D food fortification policy in Finland (Jääskeläinen et al.). A more recent review by Lips et al. included additional prevalence studies and also assessed preventive public health measures. The authors concluded that vitamin D status ranged from adequate levels in Scandinavian countries (prevalences of deficiency up to 8.4%) to severe in Western Europe (prevalences up to 30.7%) and to very poor in Southern (no standardized data available but mean serum 25-OHD < 50 nmol/l) and Eastern Europe (certain studies exceeding 50% prevalence). A direct relationship between increasing age and decreasing serum 25-OHD levels was found by a large U.S. study. The amount of time spent outside usually decreases with age and reaches its minimum in the elderly who often are completely homebound. Moreover, there seem to be differences in levels of vitamin D between cultural or ethnic

groups. Several studies found significant lower levels of total 25-OHD in black Americans than in white Americans where darker skin impedes with vitamin D transformation. Prevalence of vitamin D deficiency was also higher in countries of the Middle East where presumably people cover their skin due to religious and cultural reasons. It is still unclear whether those variations have pathological consequences or if they could also be regarded as physiologically and evolutionary. [12,13,20–27].

4.2. Vitamin D deficiency among Athletes

There are plenty of studies regarding baseline vitamin D status (serum 25-OHD) and potential benefits of supplementation. A large systematic review included 23 studies with more than 2300 athletes mostly from North America and Europe. A very high prevalence of 56% for vitamin D `inadequacy` was calculated. Because of the different primary study designs the authors used the variable `inadequacy` that considered both traditional categories (deficiency and insufficiency, i.e. 25-OHD <80 nmol/l). Apart from northern latitude and seasonality the risk for insufficient vitamin D levels was significantly higher in athletes performing indoor sport activities, especially for latitudes >40°N. Numerous single studies conducted more recently also confirmed the assumed prevalence range. Examples include 44% (<75 nmol/l) of 70 Caucasian male handball players measured in July (of which 7% < 50 nmol/l), 65% (<75 nmol/l) in 20 professional US basketball players and 43% of 131 young male Russian football players (age 15.6 ± 2.4 years) with levels <75 nmol/l (of which 23% < 50 nmol/l). Apparently, on paper vitamin D levels in athletes appear to be even lower as compared to the general population but the number of larger studies and systematic reviews is still sparse and extrapolation is difficult due to the different laboratory methods and cut-offs. [28–31]

5. Assessment of vitamin D deficiency by lab tests

Determination of total 25-hydroxycholecalciferol (25-OHD) levels is still considered the gold standard indicator for investigating vitamin D status. It assesses both the oral uptake and the dermal synthesis with 25-OHD2 and 25-OHD3 measured together. One of the most important advantages over 1,25-(OH)2D is the longer half-life of 25-OHD (~4 hours vs. ~15 days) that makes it less vulnerable to variation. Current guidelines recommend against general screening across healthy population since no strong relationship between 25-OHD levels and bone health indices could yet be demonstrated. 25-OHD assessment should only be performed in individuals with health conditions (e.g. chronic kidney disease, malabsorption syndromes) or medication (antiepileptics as phenytoin or barbiturates) known to predispose to vitamin D deficiency or if vitamin D deficiency is suspected (e.g. in case of low-traumatic fractures). Correct and comparable measurements of 25-OHD still are a great challenge for laboratories and physicians. To begin with, 25-OHD is highly protein bound and needs to be isolated first. This is a complex procedure because of the two different dissociation constants of 25-OHD2 and 25-OHD3. Several assays can be used to then determine the total level of 25-OHD. In the beginning of vitamin D testing radio-immunoassays (RIA) were commonly used. In contrary, automated assays nowadays rely on enzyme immunoassays (EIA) using chemical luminescence or liquid chromatography + mass spectrometry (LC-MS). The CDC recommends the use of a high-performance liquid chromatography (HPLC) together with tandem mass spectrometry (MS) as a reference method. Due to lack of standardization, there is large inter-method variability between the vast number of available assays. Despite this variety, current test results are still interpreted compared to the traditional 25-OHD cut-off values of either 50 or 75 nmol/l which were derived from radio-immunoassays (RIA) decades ago. There is an ongoing debate about cut-off levels for diagnosis of vitamin deficiency. Two opposing US guidelines both rely on 25-OHD levels for diagnosis but have no common understanding regarding reference range of sufficient

vitamin D serum levels. The Endocrine Society (ES) defined insufficiency as levels <75 nmol/l and deficiency as values <50 nmol/l in their 2011 guideline. The National Academy of Medicine (formerly Institute of Medicine, IOM) on the other hand considered levels ranging 50-75 nmol/l sufficient, values less than 50 nmol/l as insufficient and deficiency starting below 30 nmol/l. Some authors stress the fact that the IOM guideline only focuses on vitamin D levels required for bone health ignoring non-skeletal vitamin D requirements which might only be fully met at higher levels. Further efforts to standardize assays and set comparable cut-offs are needed. Some authors also suggest reviewing the common cut-off values regarding different ethnicities and degree of latitude to respect differences between different cultural or ethnic groups. Present-day research is conducted on additional and more reliable biomarkers for vitamin D status. Examples include bioavailable vitamin D, 24,25-(OH)2D and possible ratios but their use is yet limited due to analytical obstacles. To conclude, genetic testing (single nucleotide polymorphisms, SNPs) may be considered in the future to find individuals at risk of vitamin D deficiency. [4,9–11,14,24,27,32–36].

6. Levels of 25OH-vitamin D for Bone Health, Muscle Health and Cardiac Health

Requirements of vitamin D vary throughout life. For example, higher amounts are needed before the age of 3 years and during adolescence when demands are increased because of rapid bone growth. There are several concepts to appreciate the daily requirements of vitamin D as the estimated average requirement (EAR) or recommended dietary allowance (RDA). The EAR is defined as the amount of intake necessary to meet the needs of half of the healthy population. The RDA on the other hand describes the dose needed to fulfil the requirements of 97.5% (or EAR + 2 SD) individuals. As described earlier, there are also different views on serum target levels of 25-OHD. A review from Cashman aimed to approximate the EAR and RDA for a given target 25-OHD level. According to his review, for a target value of 50 nmol/l (IOM) the EAR and RDA were estimated to be 8.8 μg/day and 12.7 μg/day, respectively. Converting it into International Units (IU) this corresponds to ca. 350 and 500 IU/day. Women above the age of 60 years are recommended to ensure intake of minimum 800 IU according to osteoporosis experts as explained in detail later. In general, optimum levels of vitamin D are still defined based on its skeletal effects. Deeper understanding of the non-skeletal functions of vitamin D in recent history has led to the assumption that these outcomes might require adaption of the current requirements. A RCT by Rejnmark et al. assessed the relationship between 25-OHD serum levels and non-skeletal health outcomes. They found a significantly increased risk for respiratory tract infection if levels are below 75 nmol/l which could indicate higher requirements for reasons of non-skeletal outcomes. Findings from Charoenngam et al. and Rosen et al. were suggestive for a `beneficial range` of 100-150 nmol/l.

Still, most calculations of ´optimal´ vitamin D levels and requirements studies are extrapolated from investigations that are designed to improve specific diseases or syndromes in the ill or elderly. Although numerous studies on vitamin D can be found on databases as PubMed, little is known about vitamin D requirements in otherwise healthy individuals. Further efforts are needed to investigate a potential dose - effect relationship for non-skeletal health effects of vitamin D to decide whether supplementation should be recommended and if yes which doses are reasonable [37–43].

7. Vitamin D and normal body function

7.1. Bones and Fractures

Body movement and posture relies on the resistance and strength of the bony skeleton. However, bone tissue is remote from simply being a solid structure. It is rather undergoing constant remodeling to keep up the demands of weight-bearing and protection of the body against external forces. To simplify, the cellular part is represented by osteoblasts and osteocytes that are responsible for new formation of bone and osteoclasts which serve in bone resorption. The extracellular matrix (ECM) is made from both organic and inorganic structures. Mineral salts provide stability when deposited next to the organic components, mainly collagen fibers. Calcium and phosphate serve as the two basic ingredients to form hydroxyapatite, the main bone mineral. Any imbalance in the level of substrates or disturbances of regulating factors will lead to either increased bone breakdown or increased precipitation of minerals taking place even in non-osseous structures. As explained earlier, vitamin D deficiency causes hypocalcemia mainly by less intestinal absorption of calcium. PTH is released in response to low calcium levels. This also leads to low levels of phosphate. Adults with chronic vitamin D deficiency can develop a condition called ´osteomalacia`. Here, the ECM is poor in minerals and thus bone strength is decreased. Insufficient levels of calcium during periods of rapid bone growth causes children to have `rickets` that particularly interferes with endochondral bone formation in short bones. A more common condition affecting bone health particularly in post-menopausal women is osteoporosis. It is defined as a decrease in bone density. Fragility and immobility due to a significant higher likelihood of fractures in persons with osteoporosis pose a clinically relevant problem. Pathogenesis of osteoporosis is much more complex than that of rickets or osteomalacia where defects are directly related to vitamin D deficiency. While studies show a clear benefit of vitamin D supplementation in rickets or osteomalacia patients, results in osteoporotic participants are more reserved. Apart from vitamin D treatment of osteoporosis usually is based on a multimodal therapy including calcium supplementation, estrogens/selective estrogen receptor modulators (SERM) or bisphosphonates and recommended regular exercise. High prevalences of vitamin D deficiency among post-menopausal women can be assumed since numbers usually rise with age if no public health measures are present to e.g. fortify dairy products. There is growing evidence that intake of sufficient amounts of vitamin D together with calcium can prevent osteoporotic hip fractures. On the other hand, monotherapy with vitamin D does not seem to favor bone density in osteoporotic persons. Compared to the hormonal therapy or therapy with bisphosphonates, vitamin D and calcium supplementation are less likely to cause side effects if taken in moderate to high doses. Therefore the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) recommends supplementation in women aged 60 years or more. According to Rizzoli et al. “the greatest impact on fracture” is reached by 800-1000 IU/day if 25-OHD levels are below 75 nmol/l. Designing studies to assess whether positive results on bone health can be seen in athletes and physically active persons on supplementation is more difficult. One potential endpoint to compare could be the occurrence of stress fractures or stress bone injuries. Lawley et al. concluded that vitamin D levels should be optimized in athletes that are at high risk (e.g. positive history) to prevent stress fractures and to facilitate bone healing once injuries have occurred. Unfortunately there are few other studies aiming to explore the effects of vitamin D on bone health in athletes and no clear conclusions can be drawn [2,44–52].

7.2. Muscle Strength.

Although little is known about the mechanisms of action on muscle cells, vitamin D was proved to positively influence muscle growth and strength by several proposed ways including impact on protein biosynthesis, energy production and mitochondrial function. Deficiency of vitamin D is suspected to play a role in the pathogenesis and evolution of (neuro-)muscular atrophies for example by increasing reactive oxygen species (ROS) or disturbing the mitochondrial metabolism. Complete knock-out of VDR in mice leads to significantly reduced development of muscle mass. Lack of vitamin D may consequently cause changes in muscle morphology in the form of disarranged myofibrils or a modified Z line. Agergaard et al. aimed to assess changes in muscle quality when introducing supplementation of vitamin D. After 12 weeks of resistance training together with vitamin-D supplementation the young men subgroup showed a significantly increased gain in type IIa muscle fiber percentage (indicating successful endurance training) and reduced myostatin mRNA expression, a TGF β protein that inhibits muscle growth. Two large meta-analysis from 2011 (Stockton et al.) and 2019 (Han et al.) concluded that there was no significant increase on muscle strength in neither trained nor non-trained adults with a baseline of ≥25 nmol/l serum 25-OHD. On the other hand, people with serum levels <30 nmol/l seemed to benefit from supplementation and presented significantly important results of muscle strength (Beaudart et al.). A systematic review with meta-analysis compared the effects of vitamin D supplementation between athletes and non-athletes aged 18-40. A significant effect on upper limb muscle strength was found in the intervention group that received oral vitamin D. Other studies also suggested that supplementation could accelerate recovery after muscular exhaustion even in non-deficient athletes. This could be explained by the presence of 1-α-hydroxylase in muscle cells which allows them to convert 25-OHD into the 1,25-(OH)2D, the most active and potent form of vitamin D. Apparently, there is no tendency to generally recommend supplementation for muscular reasons across scientific literature and further studies are needed for clarification. [17,18,53–64].

7.3. Lung Function

As mentioned earlier, vitamin D plays a role in protective mechanisms of the immune system. This is suggested by lower incidences of influenza infections in vitamin D sufficient adults. Some authors also consider lower levels of vitamin D during the winter and spring months as one of many other explanations for the seasonal predominance of respiratory viral diseases. Apart from the beneficial effects of vitamin D in infectious pulmonary diseases there are several studies suggesting a direct relationship between serum 25-OHD levels and different lung function parameters. Animal models found a significant smaller thoracic gas volume in plethysmography (TGV of 18% less in females, 28% less in males) in mice with vitamin D-depleted diet and housed in an UVB-free environment versus normally grown control mice after correction for body size variability.

A cross-sectional study conducted by the U.S. National Center for Health Statistics with almost 12,000 subjects demonstrated a direct positive association between serum 25-OHD levels and lung function markers (FVC and FEV1) in both smokers and non-smokers. Nevertheless, deficiency of vitamin D appears to be no risk factor for the development of chronic pulmonary diseases as asthma, chronic bronchitis or emphysema but further research is needed for confirmation. Still, on the long term (mortality) vitamin D deficient smokers with COPD or asthma benefitted from supplementation after correction of serum levels in an in study by Sluyter et al. Most importantly, athletes with sufficient levels of vitamin D are less likely to drop out of training due to respiratory infections. This surely is an advantage particularly for professional athletes because any

interruption from exercise can lead to training deficits and poor performance at competitions. [65–71].

7.4. Cardiac Function

Another body system necessary for performing physical activity is the cardiovascular system. As described earlier for skeletal muscle tissue, there is growing evidence that vitamin D is involved in involvement and growth of cardiac muscle aswell. Vitamin D exerts direct effects on various cell types by interacting with the vitamin D receptor. There is an increasing amount of information indicating that vitamin D is essential for the structure and function of the heart. Vitamin D deficiency in animal models leads to substantial alterations in contraction and relaxation rates, finally leading to arrhythmias [72].

The VDR has been identified as a nuclear steroid receptor that regulates gene transcription when it binds to its ligand, vitamin D. In addition to controlling gene expression through the nuclear VDR, vitamin D has been demonstrated to have rapid, nongenomic effects. The available information suggests that the prompt reactions to vitamin D in cardiac muscle cells are mediated by the entry of calcium ions through voltage gated calcium channels, which is facilitated by the activation of G protein-coupled second messenger systems. The inflow of calcium through calcium channels determines the speed and strength of myocardial contraction, as well as the occurrence of arrhythmias. These channels are mainly situated at the t-tubules in cardiac myocytes [73,74].

Animal studies found significant cardiac hypertrophy in mice with VDR knockout (increase of heart/body ratio by 41% as compared to the control group). In contrast, artificially induced hypertrophic cardiac muscle cells displayed increased expression of VDR. Because of this, some authors consider the VDR/vitamin D system a negative feedback loop which can suppress excess cardiac muscle growth. In addition, in vitro experiments showed an inverse relationship between vitamin D and renin and angiotensin II (AT II) production. VDR was shown to interact directly with the gene promoter region for brain natriuretic peptide (BNP), a cardiac hormone released in response to atrial and ventricular stretching. It counteracts the actions of AT II by increasing diuresis and dilating the blood vessels. Another factor contributing to cardiovascular disease is PTH if concentrations are chronically elevated as in chronic kidney disease (CKD) for example. A meta-analysis by Dibaba on the effect of vitamin D intake on serum lipid profile suggested a benefit for individuals with hypercholesterolemia. In clinical practice, RCTs aiming to assess skeletal outcomes in elderly subjects however could not show any significant effect on overall cardiovascular events and mortality when taking vitamin D supplements. Intake of very high dosed vitamin D together with calcium might even increase the risk for stroke. Possible mechanisms include vascular calcifications, initiation of atherosclerosis or simply a hypercoagulable state. As demonstrated, avoidance of overdosing is crucial. Allison et al. conducted a study to specifically assess vitamin D effects on an athlete´s heart. They echocardiographically analysed the hearts of 506 national-level athletes and 244 control participants and compared it to their serum 25-OHD levels. Severely deficient athletes (<25 nmol/l) seemed to have significantly smaller cardiac structures, e.g. left ventricular mass (LVM) or left ventricular internal diameter during diastole (LVIDd). Besides that, positive associations were found between 25-OHD and IVSd (interventricular septum during diastole, LVIDd, posterior wall thickness during diastole, LVM, and LVvolD in the athlete subgroup. Further similar studies are needed since to our knowledge this is the only study of its kind up until now. To conclude, there are several mechanisms by which vitamin D influences cardiac performance. It seems to play a role in adaption to training

but also underlies a complex homeostatic regulation. An universal recommendation to supplement vitamin D in all athletes to promote cardiac health cannot be made. [72–82].

8. How to supplement vitamin D in Athletes ?

First, onetime assessment by an authorized laboratory is recommended to determine the severity of deficiency. Compared to other assays or equipment the costs are relatively little. Measurement results can be used to guide the attempt to correct. A rule of thumb was reported from practice which claimed that supplementation of 800 - 1000 IU/day increases 25-OHD levels by 25-35 nmol/l. A steady state is usually reached after 3 months and serum 25-OHD levels may be checked again. A loading dose can shorten the time to reach steady state but no benefit is reported for this approach. Since toxicity rarely results from low-dose intake experts only recommend testing before initiation of supplementation although follow-ups would be helpful for scientific purposes. Nevertheless every person receiving vitamin D supplements should be informed about potential adverse events and health risks. Intoxication is rare but side effects often tend to occur late after a latent asymptomatic interval. Aside from iatrogenic mistakes, ignorance and over-eager behaviour some cases of severe intoxication are described where OTC supplements were mislabeled. As the sale numbers of such poorly controlled OTC sales of vitamins and other supplements grow, awareness of side effects of overdosing needs to be raised. The estimated threshold of total 25-OHD for clinical signs of toxicity is estimated to be around 750 nmol/l. Although the therapeutic index of vitamin D is wide, chronic intake of high doses can lead to severe hypercalcemia and hypercalciuria with subsequent nephrocalcinosis. Other consequences of hypercalcemia are nausea & vomiting, abdominal cramping or cardiac arrhythmias. The commonest way to supplement vitamin D is by oral preparations. There are tablets and liquids in different concentrations available on the market. Intake can be done daily or weekly depending on the dosages selected. Usually dosages of tablets for daily administration range from 400 – 2000 IU whereas weekly regiments rely on tablets starting at 20,000 up to 50,000 IU. Although the term `vitamin D´ is broadly used for all substances of the vitamin D family, vitamin D supplements solely contain cholecalciferol (vitamin D3). Cholecalciferol is more stable than ergocalciferol (vitamin D2) for storage and cooking and thus more suitable. Absorption capacity was found to increase with dose up to high levels (1250µg of D3 per day) without saturation allowing for weekly administration of high doses instead of daily application especially when deficient. There is no literature on whether supplementation should be done all throughout the year or only to cover the `vitamin D winter`. Professional and semi-professional athletes usually follow personalized nutrition plans. Food rich in vitamin D could be added to meet requirements without the need of additional pills. Examples include canned tuna (~2 IU/gr), fresh and wild salmon (~6-10 IU/gram), fortified milk (~0.5 IU/ml) and sun-dried shiitake mushrooms (~16 IU/gram). It needs to be emphasized that vitamin D in the latter is represented by ergocalciferol. Thus, these mushrooms are best consumed in the raw state without processing. Currently, a global initiative of researchers started a second attempt to establish fortification of food with vitamin D (Pilz et al.). The first effort to address the high rates of rickets at the beginning of the 20th century in industrialized countries was terminated after several children with heart problems and mental retardation were reported. Of note, fortification at that time was done rather zealously. Almost all food products were enriched with vitamin D including dairy products, soda, beer so that overdosing was almost inevitable. Theoretically, vitamin D levels could also be corrected by exposing the body to UVB light. This method is obsolete since UV radiation is known to significantly increases the risk for skin cancer and cannot be recommended from a medical point of view. As both UVA and UVB rays are harmful, there is no benefit of specialized lamps over natural sun light. [51,83–92].

9. Standardization of Vitamin D levels

To date there are 2 ways of reporting 25OH vitamin D levels: ng/ml and nmol/l. Based on 25OH vitamin D concentrations, four states can be defined: deficiency, insufficiency, normal values and toxicity. However, different medical societies propose different values for the 4 states, without clear consensus between them. Currently, there are two basic types of assays in use for measurement of 25OH vitamin D levels: an automated immunoassay, which is commercially developed and marketed; and a chromatography-based assay, which is primarily laboratory-developed using HPLC/ Based on these 2 techniques, different assays for the determination of serum 25OHD levels are in use, and they provide disparate results. Without the standardization of assays, the results obtained from different studies cannot be compared [93].

In 2012 the Endocrine Society defined deficiency, insufficiency, sufficiency and toxicity based on the following values: < 20 ng/ml, 21-29 ng/ml, 30-100 ng/ml, and > 100 ng/ml. These values correspond in nmol/l to: < 50 nmol/l, 52.5-72.5 nmol/l, 75-250 nmol/l, > 250 nmol/l. [94]

10. Ethical and Safety considerations

Vitamin D studies demonstrate diversity in the utilization of placebo groups, rising ethical problems. There are 2 types of control groups: active control without the use of a placebo group or placebo control with different dosage of vitamin D [95].

Active control groups are implemented in vulnerable populations, such as pregnant women newborns and elderly with risks of falls. The absence of a placebo group may result in statistically insignificant outcomes and restrict the study's capacity to identify a substantial impact of the vitamin D. Exposing participants to even minimal risks would be therefore considered less ethical if the study is unlikely to yield substantial results.

Nonetheless, restricting the consumption of vitamin D in the placebo control group may potentially put participants who are deficient in vitamin D at risk. One possible answer to this ethical dilemma is to let participants access to supplements in order to potentially address vitamin D insufficiency. Failure to provide sufficient supplementation presents an unnecessary health hazard to participants, particularly those who have a recognized deficiency.

Vitamin D toxicity, is an uncommon although potentially severe illness that arises from the excessive consumption of vitamin D. rather than from dietary sources or sun exposure. The reason is that body regulates the synthesis of vitamin D through sun exposure, while fortified foods do not contain substantial quantities of vitamin D. Vitamin D toxicity primarily results in hypercalcemia, characterized by symptoms such as nausea, vomiting, weakness, and increased frequency of urination. Excessive intake of Vitamin D can lead to the development of pain at the level of the bones due to abnormal calcium deposits and renal calcifications [96].

However, given that the human body has been shown to produce up to 25,000 IU of vitamin D3 per day when exposed to sufficient sunlight, it can be hypothesized that consuming daily vitamin D3 supplements at dosages up to this amount could be considered safe.in the study of Mc Cukllogh et al. daily high doses of vitamin D 20.000 to 60.000/day for 2 to 6 yeards period did not induce adverse effects. Blood calcium and parathyroid hormone remained in normal limits. [97]

11. Future Research Directions

Individuals with arrhythmias, such as a high burden premature ventricular contractions (PVCs), have decreased athletic performance. Case reports have indicated that vitamin D may reduce the burden of PVCs or even eliminate them. Additional

randomized studies are required to assess the impact of vitamin D in reducing arrhythmia burden and enhancing athletic performance in patients with ventricular arrhythmias that participate in competitive activities.

While earlier research indicates that supplementing athletes with Vitamin D may improve athletic performance, greater doses of Vitamin D supplementation could potentially yield more pronounced results. Further investigation is required, with randomized double-blinded studies to evaluate the effects of higher doses of Vitamin D that increase blood 25OHvitamin D levels above 100 mg/dl in athletes.

12. Limitations

To offer athletes and coaches a thorough understanding of the impact of vitamin D on physical performance, we conducted a comprehensive analysis including both randomized and non-randomized studies in our review. The studies have different designs and varying results. The potential of presenting inconclusive findings regarding vitamin D, without precise knowledge of the direction and extent of the impact on the physical performance, applies to both nonrandomized and randomized studies. However, the likelihood of bias and confounding is likely to be greater in the nonrandomized studies.

13. Conclusions

Although there is plenty of data on vitamin D supplementation and its effects extrapolation of a general recommendation for athletes is difficult. Nevertheless, Vitamin D deficiency is relatively prevalent among physically active persons. There is a noticeable tendency in the sports community to currently optimize training conditions and to always seek for improvements in diet, training methods or equipment. The decision to orally supplement vitamin D is a very individual question. It should be based on personal risk factors (e.g., geographic location, ethnicity, outdoor vs. indoor sport, nutrition). The major science-based advantage of sufficient 25-OHD levels is the protective effect on the immunity against respiratory pathogens. As mentioned earlier, by supplementation athletes may reduce the rate of dropouts from training due to infection and sometimes prevent inability to participate at competitions. If taken in reasonable amounts supplementation normally is safe due to the broad therapeutic index of vitamin D. Additional research is necessary to reach consensus on whether supplementation in all athletes or physically active persons can generally be recommended because of other non-skeletal health effects of vitamin D.

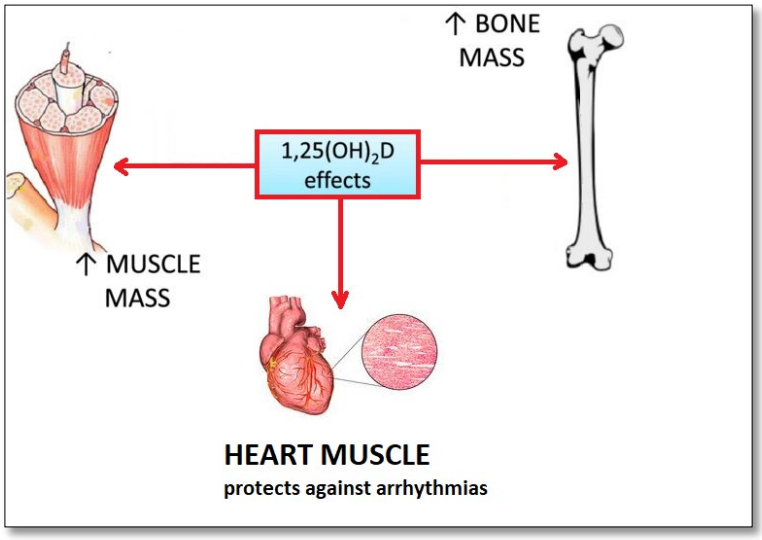

Figure 1. General Effects of Vitamin D

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